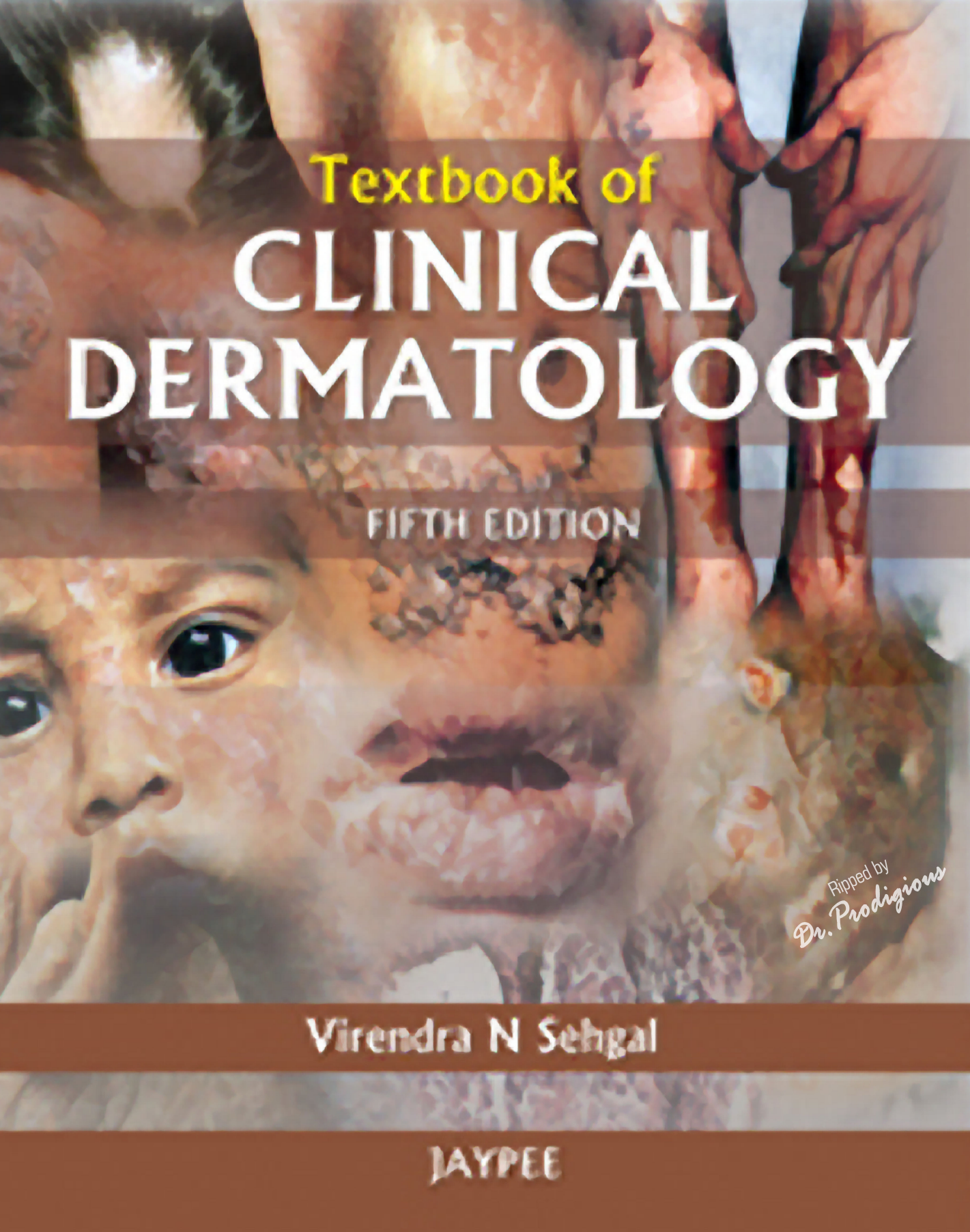

Textbook of
CLINICAL
DERMATOLOGY
FIFTH EDITION
Ripped by
Dr. Prodigious
Virendra N Sehgal
JAYPEE

# Textbook of Clinical Dermatology

# Textbook of Clinical Dermatology

## *Fifth Edition*

**Virendra N Sehgal** MD FNASc FAMS FRAS (London)
Consultant/Practising
Dermato-venereologist
Visiting Professor of Dermatology and Venereology,
Skin Institute and School of Dermatology
Greater Kailash, New Delhi, India

*Former*

Director-Professor and Head
Department of Dermatology and Venereology
Maulana Azad Medical College and associated
Lok Nayak Jay Prakash Hospital, New Delhi, India

Principal/Medical Superintendent/
Director- Professor Dermatology and Venereology
Lady Hardinge Medical College, New Delhi, India

Director- Professor Dermatology/
Venereology/Medical Superintendent
University College of Medical Sciences
and associated Guru Teg Bahadur Hospital
Shahdara, Delhi, India

**JAYPEE BROTHERS MEDICAL PUBLISHERS (P) LTD**

**New Delhi • St Louis (USA) • Panama City (Panama) • London (UK) • Ahmedabad**
**Bengaluru • Chennai • Hyderabad • Kochi • Lucknow • Kolkata • Mumbai • Nagpur**

*Published by*
Jitendar P Vij
**Jaypee Brothers Medical Publishers (P) Ltd**

*Corporate Office*
4838/24 Ansari Road, Daryaganj, **New Delhi** - 110002, India,
Phone: +91-11-43574357, Fax: +91-11-43574314

*Registered Office*
B-3 EMCA House, 23/23B Ansari Road, Daryaganj, **New Delhi** - 110 002, India
Phones: +91-11-23272143, +91-11-23272703, +91-11-23282021
+91-11-23245672, Rel: +91-11-32558559, Fax: +91-11-23276490, +91-11-23245683
e-mail: jaypee@jaypeebrothers.com, Website: www.jaypeebrothers.com

*Offices in India*
- **Ahmedabad,** Phone: Rel: +91-79-32988717, e-mail: ahmedabad@jaypeebrothers.com
- **Bengaluru,** Phone: Rel: +91-80-32714073, e-mail: bangalore@jaypeebrothers.com
- **Chennai,** Phone: Rel: +91-44-32972089, e-mail: chennai@jaypeebrothers.com
- **Hyderabad,** Phone: Rel:+91-40-32940929, e-mail: hyderabad@jaypeebrothers.com
- **Kochi,** Phone: +91-484-2395740, e-mail: kochi@jaypeebrothers.com
- **Kolkata,** Phone: +91-33-22276415, e-mail: kolkata@jaypeebrothers.com
- **Lucknow,** Phone: +91-522-3040554, e-mail: lucknow@jaypeebrothers.com
- **Mumbai,** Phone: Rel: +91-22-32926896, e-mail: mumbai@jaypeebrothers.com
- **Nagpur,** Phone: Rel: +91-712-3245220, e-mail: nagpur@jaypeebrothers.com

*Overseas Offices*
- **North America Office, USA,** Ph: 001-636-6279734, e-mail: jaypee@jaypeebrothers.com, anjulav@jaypeebrothers.com
- **Central America Office, Panama City, Panama,** Ph: 001-507-317-0160, e-mail: cservice@jphmedical.com Website: www.jphmedical.com
- **Europe Office, UK,** Ph: +44 (0) 2031708910, e-mail: info@jpmedpub.com

*Textbook of Clinical Dermatology*



*First Edition:* 1992
*Second Edition:* 1994
*Third Edition:* 2001
*Fourth Edition:* 2004
*Fifth Edition:* **2011**

ISBN 978-81-8448-985-9

Typeset at JPBMP typesetting unit

Printed at

# Preface to the Fifth Edition

The success of preceding edition has prompted me to once again take stock of the contents of the edition. Accordingly, it was thought worthwhile to expand the text by addition of three new chapters, and enrich contents of the miscellaneous by adding new quality photographs besides selective references under further reading, have been added, conforming to Vancouver style. The updates made in the current fifth edition of *Textbook of Clinical Dermotology* should be of help to inquisitive readers.

**Virendra N Sehgal**

# Preface to the First Edition

Dermatology is one of the unique disciplines of medicine, where a disease expresses itself over the skin and/or mucous membrane. The characteristic morphological features, configuration, and distribution is precise enough to make a clinical diagnosis. Accordingly, the text has been profusely illustrated by clinical photographs to add to visual dimension of dermatoses. Furthermore, it has been supplemented by an up-to-date information on the probable etiology of the diseases. Besides, it carries a vital component in the form of current concepts of treatment of the diseases. Clinical Dermatology, therefore, should be able to fill a perceptible void in the speciality. This should not only be useful to the under- and postgraduates, but also to the practising physicians. Certainly, it will be of considerable value to all those who are interested in knowing about the pattern of dermatoses in Indian subcontinent.

**Virendra N Sehgal**

# Contents

# 1 Chapter Drug Reactions

Drug reactions are a legacy of the rapid strides made in the development of pharmaceutical industry worldwide. It is, therefore, imperative to comprehend the mechanism of reactions in order to prevent such episodes in future, and also to create awareness amongst the patients of such an eventuality. The pathogenesis of cutaneous adverse reactions to drugs is varied, and multifactorial. Immunologic, nonimmunologic (pharmacologic), toxic, and genetic factors are some of the mechanisms incriminated. Despite, many drug reactions may remain unaccounted. The clinical patterns of drug eruption may give a clue to the etiologic diagnosis.

## CLINICAL FEATURES

### Exanthems

Macular and maculopapular eruptions are frequently encountered cutaneous manifestation of drug reactions. They may be triggered by any of the common drugs. There is often, a latent period of up to 3 weeks between the administration of the drug and appearance of exanthem. In a susceptible individual, it may occur within 3 days. The eruptions may be accompanied by pruritus and pyrexia. However, this may be attributed to the concomitant illness, for which the medicine has been administered. Eosinophilia, and transient lymphadenopathy may accompany more severe eruptions. The eruptions may last for 1 to 2 weeks. Regression is heralded by desquamation of the skin. This is more evident on the palms and soles. Residual pigmentation may last for a few months.

The maculopapular eruptions caused by drugs vary in size from pinpoint to a coin. The color may be bright red or dull. The lesions are usually livid on the lower extremities. They are discrete; however, minute lesions may express as diffuse erythema. The lesions are almost always distributed symmetrically. The trunk and extremities are most frequent site of affliction. Palms and soles may be spared in mild eruption but are frequently involved in eruptions of moderate severity. The lesions in the intertriginous areas may become macerated.

The exanthemata may either be of the following kinds:

- Scarlatiniform, consisting of punctate, pin-point or pinhead lesions. They have a tendency to coalesce. Scaling may also be evident
- Rubelliform, characterized by isolated lentil sized macules and papules
- Morbilliform eruptions
- Polycyclic and polygyrate erythema
- Reticular eruptions
- Sheet-like erythema
- Papular eruptions
- Diffuse erythema with extensive scaling.

Macular and maculopapular eruptions are manifestation of type IV (cell-mediated) immunologic reaction. They are commonly caused by antibiotics like penicillin, ampicillin, amoxycillin; streptomycin; sulfonamides namely sulfamethoxazole, sulfapyridine, sulfasoxazole, sulfamethoxazole-trimethoprim combination; antirheumatic-antipyretics such as acetyl-salicylic acid, phenylbutazone, diclofenac sodium, indomethacin; antidiabetics like carbutamide, chlorpropamide, tolbutamide, glymidine; cytostatic agents such as bleomycin, daunorubicin; uricosuric agents like allopurinol, and probenecid.

Such exanthematous eruptions are often a bewildering dilemma for the physicians. Viral exanthems closely mimic it. Such eruptions may be caused by viral infections like rubella, rubeola, scarlatina, infectious mononucleosis, roseola, echovirus, and coxsackievirus. Moreover, exanthem may appear in a person suspected to have viral illness and has been administered medicines for it. A probable diagnosis of drug eruption may be entertained if one takes into cognizance the morphology of the lesions, the incubation period, temporal relationship between exposure to the drug and onset of eruptions, history of similar eruption in the past, and the likelihood of that particular drug causing exanthem. Withdrawal of the drug is followed by disappearance of the lesions.

**Figure 1.1:** Demographism urticaria: Wheal formations

## Urticaria

Urticaria is a vascular reaction pattern characterized by transient, erythematous swellings of the skin and the mucous membranes. The swellings represent localized areas of edema, the 'wheals' (Fig. 1.1), in contrast to 'angioedema' where in addition subcutaneous tissue is affected. Urticarial reactions to the drugs occur as a result of either type I (IgE dependent) or type III (immune-complex mediated) reactions or are result of non-immunologic activation of the effector system. These reactions may manifest either as immediate, accelerated or late reaction. Urticarial reactions may either be acute or chronic. Chronic urticaria lasts for more than 6 weeks, and drugs may be responsible for it are aspirin exacerbates. The urticarial reactions, manifesting as IgE dependent type I hypersensitivity reactions, are serious since subsequent readministration could result in anaphylaxis. The drug should be discontinued immediately and further investigation of the patient's sensitivity is imperative. In the type III (immune-complex mediated) drug induced urticaria, the possibility of subsequent life threatening anaphylactic reaction is minimal. This form of urticaria usually occurs 4 to 12 days after chal-

lenge. The urticarial eruptions are associated with serum sickness which may manifest as fever, arthralgia, and hematuria as well as hepatic and neurological symptoms. Certain drugs such as aspirin, nonsteroidal anti-inflammatory agents, radiographic dyes, and opiates may induce urticarial reactions through other mechanisms.

### Photosensitivity

Several drugs are capable of inducing photosensitivity by either photoallergic or phototoxic reactions. The photoallergic contact dermatitis is a cutaneous cell-mediated hypersensitivity reaction (Type IV) to exogenous drugs in the presence of radiant energy. Wavelengths in the ureterovesical angle (UVA) range are responsible for the photoallergic reactions. The electromagnetic energy converts an immunologically inactive form of the photosensitizing compound to its active form. The hapten formed is the stable photoproduct of the drug which combines with a protein in the skin to produce full antigen. However, it has also been reported that the hapten is an unstable photoproduct, which must be in close proximity to the protein at the time of irradiation to form full antigen. In both situations, this elicits a cell-mediated immune response which may result in eczematous dermatitis. The photoallergic reactions do not occur after first exposure to the photoallergen. Phototoxic reactions may occur on first exposure to the phototoxic substances, in an individual, if enough of the chromophore absorbs adequate radiation in reactive tissue. The clinical reaction may begin soon after the systemic chromophore reaches the skin. Whereas in topical photosensitizers, it may begin within a few minutes. The phototoxic reactions may be photodynamic or nonphotodynamic in nature, the difference being that photodynamic reactions require oxygen. The phototoxic reactions resemble to sunburn and are characterized by burning, stinging, erythema, edema, and blister formation followed by desquamation. The photosensitivity reactions are localized to the exposed portions of the body including the face, dorsal aspect of the forearms, V of the neck, and back of the hands. Sulfonamides, sulfonylureas, frusemide, thiazides, phenothiazines, griseofulvin, and nalidixic acid are some of the common photosensitizers. All the known photoallergens are also phototoxic; however, they may elicit only photoallergy and not phototoxicity, since very low energy is required to elicit photoallergic reactions. The phototoxic drugs are halogenated salicylanilides, halogenated phenols, sulfanilamides, sulfonylureas, frusemide, thiazides, phenothiazines, coal tar, psoralens, tetracyclines, griseofulvin, nalidixic acid, thiourea, vinblastine, amantadine, quinidine, and oral contraceptives. However, all phototoxic substances are not photoallergic. The psoralen, and chlorpromazine induced phototoxic reactions are nonphotodynamic ones. Photodynamic processes appear to be responsible for reaction to certain dyes, coal tar, polycyclic hydrocarbons, demethylchlortetracycline, chlorthiazide, griseofulvin, and sulfonylureas. Drugs may also induce photosensitivity diseases. Isonicotinic hydrazide (INH) may cause pellagra.

### Bullous Eruptions

The bullous eruption due to drugs may be of the following kinds:

- Bullous fixed-drug-eruption (FDE)
- Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN)
- Drug induced pemphigus. D-penicillamine

is the most frequent implicated drug. The mechanism of penicillamine induced pemphigus is unknown; however, an increased frequency of HLA-B15 in such patients has been reported, suggesting that D-penicillamine may unmask a genetic predisposition to the development of pemphigus antibodies. The epidermotropism of penicillamine and its ability to cause acantholysis on normal human skin cultured *in vitro* without antibody mediation (biochemical acantholysis) has also been reported. Drugs containing thiol groups in their molecules are most capable of inducing pemphigus, as they interfere with the biochemistry of keratogenesis. Other drugs are piroxicam, penicillin, captopril, rifampicin, thiopronine, α-mercaptopropionylglycine, phenytoin, and phenobarbitone. D-penicillamine induced pemphigus may occur in 3 to 10 percent of the patients. Pemphigus foliaceous is more frequently observed than pemphigus vulgaris

- Phototoxic bullae may be induced by high doses of frusemide and nalidixic acid
- Bullae may arise at pressure points in comatose patients after overdoses of barbiturates, methadone, meprobamate, imipramine, and nitrazepam.

## Vasculitis

Vasculitis is being increasingly diagnosed as a manifestation of cutaneous drug eruption. In most instances, vasculitis is induced by type III (immune-complex mediated) reaction, but type II (cytotoxic) reaction is also incriminated. The drug induced vasculitis may manifest either as urticarial vasculitis, papular and/or purpuric dermatoses. It results from extravasation of red blood corpuscles from the damaged vessels into the dermis. Urticarial vasculitis lasts longer than the urticarial wheals. Vasculitis is more frequent on dependent areas. It may not be limited to the cutaneous vasculature, but also involve the brain, liver, and other viscera. The drugs responsible for vasculitis are allopurinol, salicylates, BCG vaccine, frusemide, hydrochlorthiazide, penicillin, D-penicillamine, thiouracil derivatives, and phenytoin.

## Fixed Drug Eruption

It is characterized by the appearance of round or oval, edematous plaques of sizes varying from coin to a palm, affecting any part of the skin and/or mucous membrane (Fig. 1.2). The lesions are usually preceded or accompanied by itching or burning. Formation of bullae may be an accom-

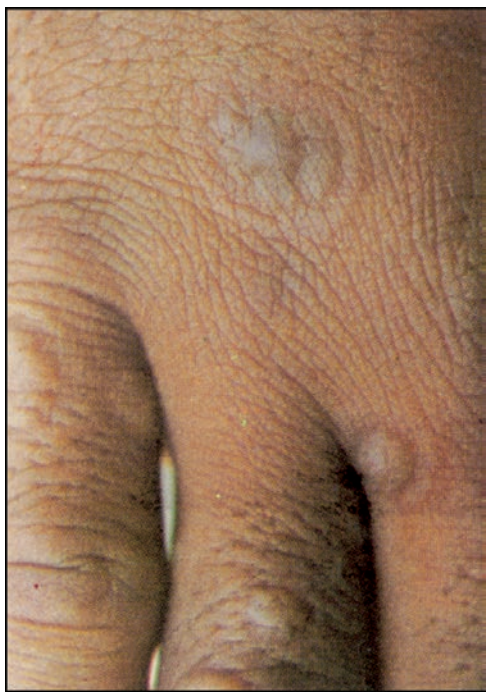


**Figure 1.2:** Fixed drug eruption (FDE): A well-defined bluish macule of FDE positive provocation with a causative drug

paniment in severe cases. The eruption fades, to leave behind dusky-brown macules. However, upon rechallenge with the causative drug the lesions reappear at the same site or there may also be appearance of new lesions elsewhere. This recurrence *in situ* is its diagnostic hallmark. The adults are usually affected, however, it has also been reported in children. The lesions are distributed over the limbs, trunk, lower lip, and genitalia. Mucosal lesion may accompany cutaneous lesions or occur independently. The precise mechanism is unknown, however, type III (immune-complex), type IV (delayed hypersensitivity) and also type II (antibody mediated cytotoxicity) have been documented.

The causes of FDE differ according to the disease pattern of the region and prescribing habits of the medical practitioner. Also the relative frequency with which a drug causes FDE changes frequently as new drugs are introduced in the market. In the developing countries the common offenders are as follows:

- Analgesics; acetylsalicylic acid, oxyphenbutazone, and paracetamol
- Sulfonamides and sulfamethoxazole-trimethoprim combination
- Antibiotics like tetracycline.

In the developed countries, the drugs most frequently associated with FDE are barbiturates, phenazone derivatives, and less frequently tetracycline, sulfonamides, and acetylsalicylic acid.

## Lichenoid Drug Eruption

They are characterized by appearance of flat topped, greyish white or lilac papules, which may coalesce to form plaques. Moderate to severe itching may be its accompaniment. Wickham's striae, however, are usually absent. Lichenoid drug eruptions are not limited to the flexor areas of the skin, but appear as symmetrical eruption over the trunk and extremities. The symptoms begin to recede within days after discontinuation of the drug. The differentiation from classical lichen planus may be attempted by the microscopic pathology of these lesions, and is characterized by focal parakeratosis, focal interruption of granular layer, and cytoid bodies in the cornified and granular layers. Eosinophils are also present. The drugs that have been implicated are streptomycin, ethambutol, para-aminosalicylic acid, quinacrine, chloroquine, hydroxychloroquine, methyldopa, quinidine, phenothiazine, thiazides, heavy metals (gold, bismuth), penicillamine, β-blockers, and captopril.

## Drug Induced Systemic Lupus Erythematosus (SLE)

Drug induced SLE may present as the following:

- Erythematous papules resembling cutaneous vasculitis with an associated positive antinuclear antibodies
- Patients may develop butterfly rash and systemic manifestations like fever, malaise, arthralgia, myalgia, pleuritic pain, pericarditis, hepatosplenomegaly, and lymphadenopathy
- Some drugs may cause systemic symptoms and less often the positive antinuclear antibodies
- Drug like alpha-methyldopa has been shown to induce the formation of antinuclear antibodies but no patient has been reported to develop symptomatic SLE with this drug.

Besides the ARA (American Rheumatic Association) criteria necessary for the diagnosis of SLE, it has been suggested that the following features must be included to make a diagnosis of drug induced SLE:

- The drug must have been administered before the onset of any sign and/or symptom of SLE
- The disease process must reverse itself upon cessation of therapy. Clinical signs and symptoms must begin to clear within days, but laboratory findings may take months to years
- Resumption of drug therapy should result in prompt reappearance of signs and symptoms.

Drug induced lupus erythematosus (LE) differs from idiopathic LE in that renal damage is uncommon, and the severity of the disease is less, particularly concerning fever, cutaneous manifestations, and lymphadenopathy. The disease is usually reversible on withdrawal of the offending drug. Laboratory findings show LE cells, antinuclear antibodies, antinucleoprotein antibodies, antibodies to denatured (single strand) deoxyribonucleic acid (DNA), and deoxyribonucleoprotein and histones.

A number of pathogenetic mechanisms to explain drug induced SLE are known. Some may have genetic predisposition for SLE and this may become manifest after the stimulus provided by the drug. This may be seen with procainamide and hydralazine where slow acetylators are predisposed to SLE.

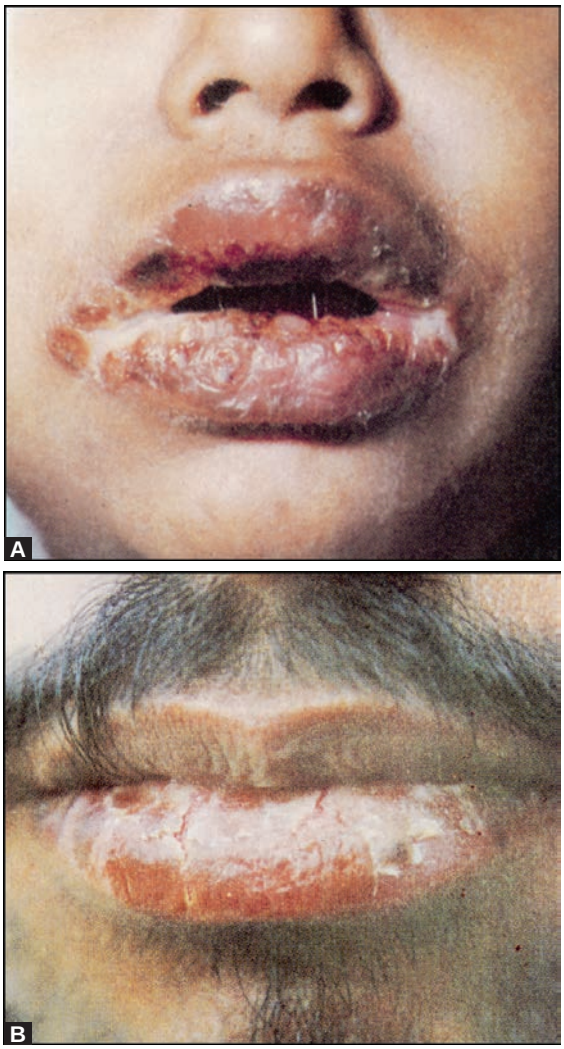
D-penicillamine is most often used in the treatment of collagen vascular diseases. However, it is difficult to be certain whether the SLE produced by it is the result of increased induction or just unmasking of the disease in a patient predisposed to it. It has been hypothesized that all drugs induce SLE through the production of antinuclear antibodies and that these were produced because the drugs were able to form complexes with deoxyribonucleoproteins released through normal catabolic processes. These drug-nucleoprotein complexes represented 'denatured nucleoprotein' that evoked immune response.

Drug induced lupus erythematosus has been reported administration of the following drugs including procainamide, hydralazine, phenytoin, isoniazid (INH), penicillin, streptomycin, sulfonamides, chlorpromazine, practolol, hydrochlorthiazide, D-penicillamine, carbamazepine, ethosuximide, primidone, tridone, barbiturates, phenylbutazone, and cimetidine.

## Erythema Multiforme, Stevens-Johnson's Syndrome and Toxic Epidermal Necrolysis

Erythema multiforme (EM) may occur secondary to the drugs. The minor form of the disease is characterized by typical target (iris) lesions (Figs 1.3A and B) and is a benign condition. However, a much more severe condition, erythema multiforme major or Stevens-Johnson's syndrome (SJS) is associated with mucosal, ocular, and visceral involvement. Toxic epidermal necrolysis (TEN) represents an even more dramatic form of same disease characterized by severe, widespread erythema, blisters, and loss of skin in sheets with denudation of over 10 percent of body area. Nikolsky's sign is positive. Mucous membranes are severely eroded. Destruction of cutaneous barrier produces loss of fluids, electrolytes, and proteins similar to 2nd degree burns. It is the most severe blistering disease with mortality rates between 20 to 66 percent in acute phase and potentially disabling ocular sequelae in survivors. Thus erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis form a spectrum.

Virtually any drug is capable of evoking these conditions, but sulfonamides, sulfamethoxazole-trimethoprim combination; antibio-




**Figures 1.3A and B:** Erythema multiforme: A macules macule-papular lesions of EM, involvement of mucous membranes of the oral cavity

tics like ampicillin, amoxycillin, tetracycline; butazones; nonsteroidal anti-inflammatory drugs; and hydantoins are most frequently incriminated. In developing countries antitubercular drugs are frequently the cause of toxic epidermal necrolysis. Thiacetazone and isoniazid are usually responsible. Rifampicin, pyrazinamide, streptomycin, and ethambutol are relatively safe. The exact pathophysiologic mechanisms for EM, SJS, and TEN are not known. It is presumed that tissue damage is the result of type III (immune-complex mediated) reaction. However, the same pathophysiologic events could result from a type II (antibody dependent cytotoxic) reaction with the blood vessels (endothelial cells and/or basement membrane) serving as hapten. The subsequent immune reaction occurs to the drug, hapten-complex, and results in injury to the blood vessels. The diagnostic criteria for each of these are as follows.

*Erythema Multiforme (EM)*

- Individual lesions—less than 3 cm diameter
- Target (iris) lesions—typical or atypical
- No mucous membrane involvement or only 1 mucous membrane with minimal symptomatology
- Less than 20 percent body area involved in reaction
- Biopsy specimen compatible with EM.

*Stevens-Johnson's Syndrome (SJS)*

- Individual lesion—less than 3 cm in diameter (lesions may coalesce)
- Target (iris) lesions—typical or atypical
- Mucous membrane involvement (at least 2)
- Fever
- 20 percent of body area involved in first 48 hours.

*Toxic Epidermal Necrolysis (TEN)*

- Bullae and/or erosions over—more than 20 percent of body area
- Bullae develop on erythematous base
- Occurs on non-sun exposed skin
- Skin peels off in more than 3 cm sheets

- Frequent mucous membrane involvement
- Tender skin within 48 hours of onset of rash
- Fever
- Biopsy specimen compatible with drug induced TEN.

### Exfoliative Dermatitis

It is regarded as an extreme state of skin irritation affecting the whole or most of the skin surface. There is itching, burning, and redness of the skin. Scales are exfoliated from the body. It is conceived as a secondary reactive process and drugs are an important cause. These drugs may have been used for pre-existing dermatosis or otherwise. The onset of drug induced erythroderma is usually abrupt and florid in contrast to other causes where it is usually insidious. The drugs most often incriminated for erythroderma are sulfonamides like sulfadiazine; antituberculous drugs namely thiacetazone, isoniazid, streptomycin; antirheumatic-antipyretics such as phenylbutazone. Injudicious and increasing use of topical therapy containing sensitizers may also predispose to exfoliative dermatitis. A proportion of psoriatics develop erythroderma because of vigorous use of tar ointment.

### Pigmentation

Pigmentation associated with the drug therapy may be of cosmetic concern to the patient and responsible for noncompliance. Heavy metals like silver, gold are trapped by the macrophages in the skin and impart color to it. Arsenic is responsible for both hypo and hyperpigmentation. It displaces copper from the tyrosinase system and interferes with pigment formation, causing 'raindrops in the dust appearance'. It also gets deposited in the skin producing hyperpigmentation. Clofazimine, an iminiophenazine dye, used as antileprosy drug gets deposited in the skin especially in the lesions, producing a red discoloration. Phenothiazines combine with melanin and get deposited in the skin producing a greyish pigmentation. Antimalarials cause slate gray pigmentation. Oral mucosa may be discolored. Bleaching of the hairs may also result. Tetracyclines and minocycline not only produce hyperpigmentation of the skin but also stain the teeth. Melasma is produced in some women using oral contraceptives. Nails may become pigmented after treatment with cyclophosphamide, doxorubicin, and timolol. Acanthosis nigricans like reaction may occur with nicotinic acid.

### Acneiform Eruption

Drug induced acneiform eruptions are usually papulopustules. Comedones are infrequent. Hormonal preparations tend to produce acne by physiological effect on pilosebaceous apparatus. Isoniazid tends to induce acne in slow acetylators. The mechanism for other drugs is unknown. Acneiform eruptions are induced by corticosteroids ACTH, iodides, bromides, androgens, oral contraceptives, lithium, isoniazid (INH), actinomycin D, danazol, and quinidine. The drug induced acne have certain distinct features:

- It may arise in any age group if the drug is being administered.
- The lesions consist of papules and pustules localized mainly on the trunk. However, comedones are uncommon.
- The lesions often subside on discontinuation of the drug.

## DIAGNOSIS

The diagnosis of cutaneous drug reaction is clinical. Laboratory investigations supplement and not supplant a thorough clinical history

and examination. The first task is to 'suspect' the drug responsible for the eruption, and then an endeavor be made to establish a relationship between the administration of the drug and the appearance of the symptoms, in order to identify the offending drug. The most important step is to obtain a careful and thorough history. Majority have a clear temporal relationship between the drug administration and the onset of an adverse reaction. Thus all drugs that the patient has consumed just prior to the eruption must be identified along with the illness for which taken, the duration of therapy, total dose, and route of administration. Specific questions must be asked about the drugs available over the counter without the prescription. Such medicines include laxatives, oral contraceptives, tonics, and antirheumatic-antipyretics. The patient often forgets or considers them unimportant. If the patient denies any drug intake, specific questions should be asked concerning the last time a tablet was taken and the reason for it. Any history of similar episode in the past or any other adverse drug reaction must be enquired. A knowledge of the likelihood of a drug producing a particular cutaneous reaction helps in correlating the symptoms to the offending drug.

Elimination test: Once the cutaneous drug reaction and the likely drug triggering that reaction is suspected, it must be withdrawn. In most cases, the improvement after discontinuation of the suspected medicine gives further indication of the causal relationship. However, many drug reactions improve only a long-time after discontinuing the therapy as the drug or its metabolite has a long half-life and continues to exert its effect. Also there are a number of reactions that regress even though the therapy is continued, such as the ampicillin induced eruption.

In vivo test: They are useful if the drug reaction is allergic in nature. These include the intradermal test, scratch test, and patch test. Praüsnitz-Kustner test is obsolete and no longer performed. Prick test, scratch test and intradermal test are indicated in drug reactions mediated by Gell and Coomb's type I reaction, and are helpful in urticaria and angioedema caused by the drugs. The drugs are tested as pure substance. Generally, the tests are reliable for high molecular weight substances. The reaction is considered positive if a wheal appears at the test site, 10 to 20 minutes after the test. Intradermal testing is a common procedure to detect hypersensitivity to penicillin before administering the full therapeutic dose.

Patch test: It is performed by dissolving the drug in a suitable, nonirritant solvent and applying it to the skin under occlusion for 48 hours. After this period, the site is inspected for dermatitic reaction. It is useful in a proportion of drug reactions mediated by Gell and Coomb's type IV reaction such as the following:

- Maculopapular eruption
- Fixed drug eruption
- Progressive pigmentary purpura
- Photoallergic reaction.

In vitro test: There are a number of *in vitro* tests to demonstrate hypersensitivity to the drug. However, they require sophisticated laboratory facilities and this reduces their diagnostic usefulness. The radioallergosorbent test (RAST) demonstrates specific IgE antibodies in the serum. Thus, it can be used to detect drug specific IgE antibodies. However, at present

there are tests only for specific IgE antibodies against penicilloyl G, penicilloyl V, insulin, and ACTH. RAST is limited to drugs that are protein in nature.

Histamine release test: It is based on the principle that IgE antibodies produced in response to drugs bind to the surface of the mast cells. If these IgE molecules are cross-linked by an antigen, histamine is liberated from the mast cells, which can be measured. However, this test is limited to benzylpenicillin and penicilloyl polylysine.

Basophil degranulation test: It serves to identify specific antibodies, particularly IgE, by a morphologic evaluation of the basophilic leukocytes, which lose their granules. However, false-positive and false-negative reactions are not infrequent. Thus the value of this test in evaluating drug allergy is limited.

Passive hemagglutination test: It is based on the identification of blastogenesis, a transformation of some of the lymphocytes to lymphoblasts which occurs when the patients lymphocytes are incubated with the suspected drug. This test is useful in evaluating macular, and maculopapular drug eruptions. Positive reactions are found not only in Gell and Coomb's type IV reaction, but also in type I and type III reactions. It is helpful in detecting reactions to isoniazid, sulfonamides, streptomycin, phenobarbital, penicillin, and furosemide.

Lymphocyte and macrophage migration inhibition test: It detects the lymphokine MIF, released from the sensitized lymphocytes on contact with drug antigen. This inhibits the migration of macrophages from guinea pig peritoneal exudate. The technique is complicated and of limited use.

Histopathological examination: It is particularly useful in the diagnosis of lichenoid drug eruptions, erythema multiforme, drug induced vasculitis, erythema nodosum, and toxic epidermal necrolysis.

Provocation test: It should be the last step in a diagnostic progression because, although reliable, it exposes the patient to potential life threatening hazards. It should not be performed in cases of anaphylaxis, toxic epidermal necrolysis or erythroderma. The patient should preferably be hospitalized. He is then administered 1/8th of a tablet, and examined for a similar response as the drug eruption, within a reasonable time after drug administration. If no reaction occurs, the challenge dose is serially increased to ¼, ½, 1 tablet and then the full therapeutic dose.

## TREATMENT

The adverse drug reaction warrants immediate withdrawal of the suspected drug. Antihistamines may be administered orally for milder reactions. Hospitalization may be required for the management of more severe reactions. Patient may then be administered steroids and/or antihistamines either parenterally or orally. Antipruritic lotions may be applied to allay itching and burning.

## RECOMMENDED READING

1. Chan HL, Stern RS, Arndt KA et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol* 1990;126:43-47.

2. Hasan T, Jansen CT. Erythroderma: A Follow up of 50 cases. *J Am Acad Dermatol* 1983;8:836-840.
3. Korman NJ, Eyre RW, Zone J et al. Drug induced pemphigus: Autoantibiotics directed against pemphigus antigen complexes are present in penicillamine and captopril induced pemphigus. *J Invest Dermatol* 1991;96:273-276.
4. Sehgal VN, Gangwani OP. Fixed drug eruptions: Current concepts. *Int J Dermatol* 1987; 26:67-74.
5. Sehgal VN, Srivastava G: Exfoliative dermatitis: A prospective study of 80 patients. *Dermatologica* 1986;173:278-284.
6. Stubb S, Alanko K, Reitamo S. Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989;120:583.
7. Tan EM, Cohen AS, Fries JF *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus (SLE). *Arthr Rheum* 1982;25:1271-1277.
8. Vanden Hante V, Antoone JL, Lachapelle JM. Histopathological discriminant criteria between lichenoid drug eruption and idiopathic lichen planus: Retrospective study on selected samples. *Dermatologica* 1989;179:10-13.
10. Sehgal VN, Srivastava G. Toxic epidermal necrolysis (TEN) Lyell's syndrome. *J Dermatolog Treat*. 2005;16:278-286.
11. Sehgal VN, Srivastava G, Sherma S. Lichenoid (lichen planus-like) interface dermatoses: Clinicopathological fallout. *Int. J. Dermatol*. (In Press).

# 2 Chapter Acne and Acneiform Dermatoses

Acne vulgaris is a follicular disorder affecting susceptible pilosebaceous follicles, primarily of the face, neck, and upper trunk and characterized by both noninflammatory and inflammatory lesions. It is one of the most common dermatoses affecting the teenage population. Boys have a peak incidence between ages of 16 and 19 years and girls between ages of 14 and 16 years. Both sexes are equally affected. Most cases of acne subside completely within a few years of their onset but a small percentage continue to remain active.

Acne vulgaris is a dermatosis of unknown etiology. However, many factors are incriminated in its pathogenesis and aggravation. Androgenic stimulation at puberty is believed to increase the activity of sebaceous glands and sebum production. A change in the process of keratinization of the sebaceous follicle may produce an increased adherence of the horn cells resulting in retention hyperkeratosis. Free fatty acids in the surface lipids are also suspected to be comedogenic. Bacterial colonization of the sebaceous follicle may also contribute in the pathogenesis of acne. *Propionibacterium acnes, Staphylococcus epidermidis,* and *Pityrosporum ovale* colonize the follicle and produce lipases. These lipases hydrolyse the sebum triglycerides to free fatty acids, which contribute to follicular hyperkeratosis. Also biologically active substances produced by *Propionibacterium acnes* seep into dermis and attract neutrophils and activate complement.

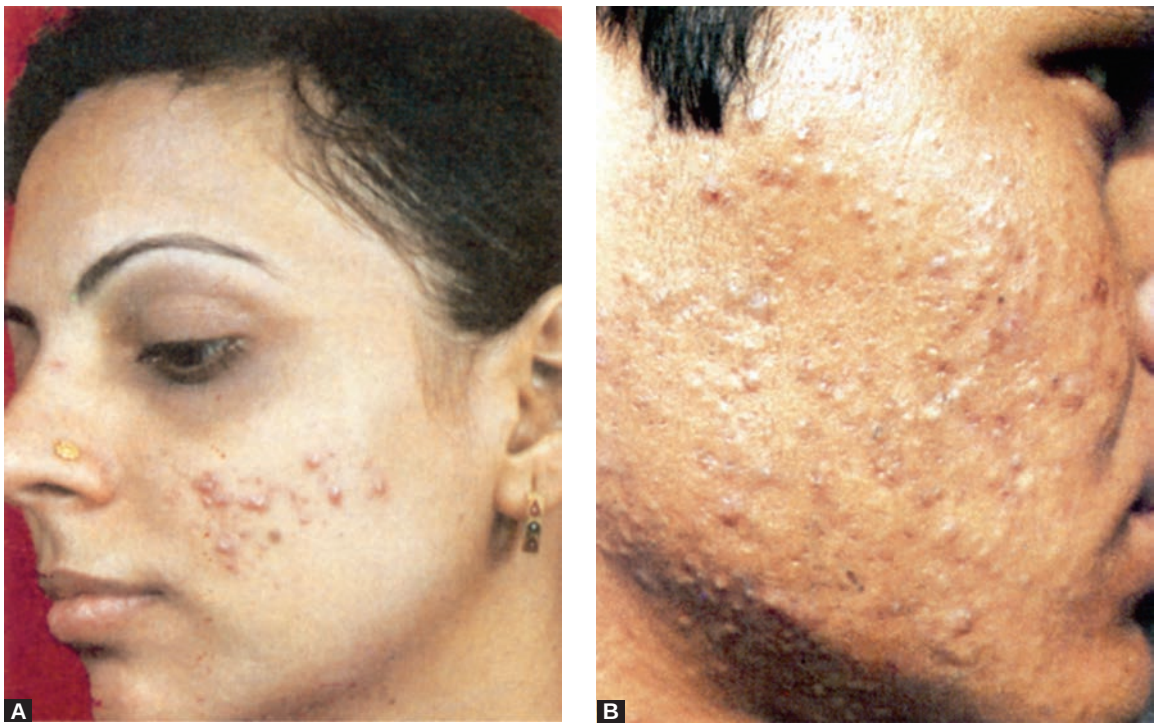
## CLINICAL FEATURES

The comedones, open or closed, are the pathogenic lesions of acne (Figs 2.1A and B). Papules, pustules, nodules, and cysts (Fig. 2.2) may also appear during the course of the disease. The lesions are localized to the face, neck, back, anterior chest, and extremities. The open comedone, also called blackhead, has a widely dilated orifice filled with keratin, lipids, and organisms. Melanin imparts black color to the lesion.

The closed comedone, a whitehead, is a small, flesh colored papule, that has only a microscopic opening, which prevents its contents from escaping. Continued production of sebum and keratin, leads to rupture of the follicular wall, releasing the contents into the dermis and initiating an inflammatory response. This inflammation in the dermis is responsible for the papules, pustules, cysts, and nodules.

## DIAGNOSIS

There are no diagnostic tests for acne vulgaris. Diagnosis is clinical. However, lesions of acne vulgaris need to be differentiated from acneiform dermatoses.




**Figures 2.1A and B:** Acne vulgaris—comedons

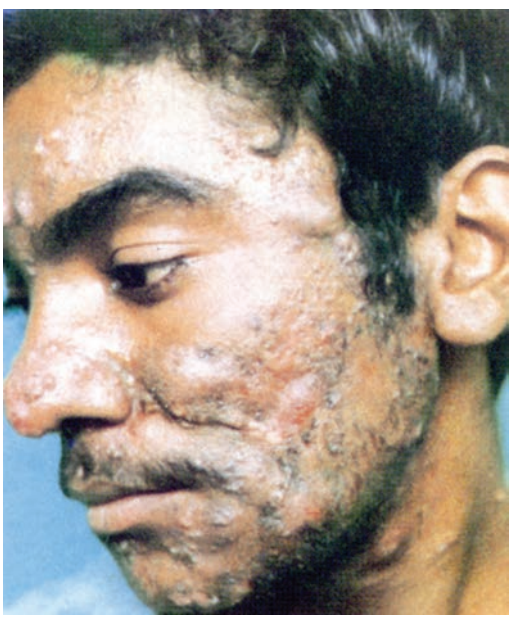


**Figure 2.2:** Acne vulgaris—cystic acne

*Neonatal acne:* It is characterized by the formation of comedones in a newborn. The lesions are localized to the nose and adjacent areas of cheeks. It is due to stimulation of the sebaceous glands by maternal hormones. It clears spontaneously.

*Drug acne:* Prolonged application of topical steroids especially on the face, systemic corticosteroids, adrenocorticoids, iodides, bromides, lithium, and isoniazid may result in acne. The lesions consist of small papules and pustules localized mainly on the trunk.

*Occupational acne:* Several industrial compounds like tar derivatives, cutting oils, chlorinated hydrocarbons may cause acne. The lesions are inflammatory and present as comedones, papules, pustules, large nodules, and cysts. They tend to involve areas covered by clothing

permitting intimate contact between the offending chemical and skin. Face is usually spared.

*Tropical acne:* This develops in tropical climate and is localized to trunk and buttocks. It resembles acne conglobata and presents as deep, large, inflammatory nodules.

*Acne cosmetica:* Certain cosmetics induce acneiform eruption and are responsible for persistent low grade close comedones on the face.

*Pomade acne:* The pomade applied to the scalp may spill to the forehead and cause acne. It is frequently seen in black males. The lesions are multiple, closely packed, closed comedones.

*Rosacea/Acne rosacea:* Rosacea/acne rosacea is a well-conceived fascinating overture. It is a common facial dermatosis, which may have deleterious effects on the patient's psychosocial interactions. It is a disease of the middle age, more prevalent in skin type I and II, than those in darker skin type. It is, therefore, worthwhile to emphasize that the entity is recognized to occur in phases, and may pass through distinct phases namely pre-rosacea (grade 1), vascular rosacea (grade II) and Inflammatory rosacea (grade III). Pre-rosacea (grade 1) is identified by a simple tendency to blush/flush which may progress to a persistent redness in the central portion of the face, occupying the nose in particular. The redness of the face is an outcome of dilation of blood vessels approximating the skin surface. The progression of this phase may trespass into vascular rosacea (grade II). The latter may develope small blood vessels on the nose and cheeks swell and become apparent resulting in telangiectasia. Also the skin may become overtly sensitive. It may also have an accompaniment of oily skin and dandruff. The continuation of the disease may ultimately result in inflammatory rosacea (grade III). Small, red bumps (nodules) or pustules are its salient clinical manifestations, spreading across the nose, cheeks, forehead and chin. Hyperglandular subtypes may lead to different forms of phyma, of which rhinophyma is the most frequent.

Moreover, in view of the natural history of the disease National Rosacea Society Expert Committee on Classification and Staging of rosacea had taken cognizance of subtypes and variants of rosacea and their characteristics, and had made certain recommendations, the briefs of which are replicated in Table 2.1. The clinical features are more or less similar to those described (vide supra), with the only addition of granulomatous rosacea.

The condition seems to be a reaction pattern, and is heralded by remissions and exacerbation. The diagnosis in the current patient conformed to inflammatory grade III rosacea, and had ventured through the well-recognized phases. The microscopic pathology was complementary, and was characterized by dilation of the hair follicle(s), dense perivascular and perifollicular lympho-histiocytic infiltrate and lymphocytic exocytosis and edema, in the follicular epithelium in addition to focal epithelioid cell granulomas. The preceding changes are largely confined to the upper dermis, while lower dermis is relatively free. Nevertheless, it is imperative to take stock of the other clinical conditions which may simulate rosacea/acne rosacea; acne vulgaris, erysipelas, seborrhoeic -and contact eczema as well as systemic diseases like lupus erythematosus, dermatomyositis, scleroderma, sarcoidosis, leukemia, and lupus miliaris disseminatus faciei. Although the precise pathogenesis and pathophysiology 3 of the condition is only speculative yet destruction of

**Table 2.1: Subtype s and variants of rosacea and their characteristics**

| *Subtype* | *Characteristics* |
|---|---|
| Erythematotelangiectatic | Flushing and persistent central facial erythema with or without telangiectasia. |
| Papulopustular | Persistent central facial erythema with transient, central facial papules or pustules or both. |
| Phymatous | Thickening of skin, irregular surface nodularities and enlargement. May occur on the nose, chin, forehead, cheeks, or ears. |
| Ocular | Foreign body sensation in the eyes, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema. |
| Variants granulomatous | Non-inflammatory; hard; brown, yellow, or red cutaneous |

**Table 2.2: Systemic therapy for acne vulgaris**

| *Drugs* | *Trade name* | *Dosage* | *Duration of therapy* | *Other information* |
|---|---|---|---|---|
| 1. *Antibiotics* | | | | |
| a. Tetracycline | Hostacycline | 250 mg four times a day initially.<br>Maintenance with 250–500 mg daily. | 4–5 weeks<br>Several months | Prolonged use may result in gram-negative folliculitis.<br>Also predisposes to monilial vaginitis. |
| b. Erythromycin | Erythrocin | 250 mg four times a day initially.<br>Maintenance with 250–500 mg daily. | 4–5 weeks<br>Several months | Estolate salt may cause cholestatic jaundice. |
| c. Doxycycline | Nudoxy | 100–200 mg daily initially followed by maintenance dose of 50–100 mg daily. | 4–5 weeks<br>Several months | |
| d. Minocycline | | 50-100 mg twice a day. | Several months | High incidence of CNS side-effects. |
| e. Clindamycin | | 150 mg thrice a day. | A few weeks to months | Pseudomembranous colitis. |
| 2. *Estrogens*<br>Ethinyl estradiol | | 100 µg once a day. | A few months | To be used only in females over 16 years with recalcitrant, severe, pustulocystic acne. |
| 3. *Retinoids*<br>Isotretinoin | Accutane | 1 mg per kg per day for facial lesions.<br>2 mg per kg per day for truncal acne. | 15-20 weeks and if required a second course after two months. | To be used only in severe disfiguring cystic acne.<br>Not to be used in pregnancy.<br>Contraception advised during the treatment. |

the dermal vessels and connective tissue seem to be accountable for the development of a chronic inflammation. This may in turn lead to the phenotype of the various grades of rosacea.

### Treatment

The treatment of acne vulgaris may consist of topical therapy, systemic therapy, or a combination of both.

Topical therapy alone is indicated for mild to moderate lesions, and it may consist of the following:

For mild lesions, consisting of only comedones, bacteriostatic agents are indicated. These are as follows:

- Benzoyl peroxide—5 percent gel (pernox gel)
- Topical antibiotics
  - Erythromycin 2 percent lotion (acnesol) and 3 percent cream (acnicin)
  - Clindamycin phosphate 1 percent lotion (cleocin)
  - Tetracycline hydrochloride lotion.

Benzoyl peroxide is administered for comedones, while the papular and pustular lesions respond to topical antibiotics. Clindamycin and erythromycin are equally effective. They not only are bacteriostatic but also supress inflammation. They are applied twice daily and cause mild dryness and erythema.

In moderately severe cases, topical retinoids are advised. Tretinoin 0.05 percent cream (Retino-A, Eudyna) may be used. These preparations are applied once daily to all areas except around the eyes. They should be applied on dried skin. Erythema and peeling are the effects of therapy. Patient should be cautioned about the initial exacerbation of the lesions and also advised to protect the skin from sunlight.

Keratolytics like sulfur, resorcinol, and α-hydroxy acids are irritants and are thus avoided.

*Systemic therapy:* The details of systemic therapy are displayed in Table 2.2.

## RECOMMENDED READING


1. Buxton PK. ABC of dermatology: Acne and rosacea. *Br Med J*. 1988; 296:41-45.
2. Drake LA. American Academy of Dermatology. Guidelines for care of acne vulgaris. *J Am Acad Dermatol*. 1990;22:676-680.
3. Kligman AM. An overview of acne. *J Invest Dermatol* 1974; 6: 268-287.
4. Leyden JT. Retinoids and acne. *J Am Acad Dermatol*. 1988; 19:164.
5. Shalita AR. Acne revisted arch. *Dermatol* 1994;130: 363.
6. Sardana K, Garg VK, Sehgal VN, et al. Efficacy of fixed low dose isotretinoin (20 mg alternate days) with topical clindamycin gel in moderately severe acne vulgaris. *J Eur Acad Dermatol Venereol*. (In Press).
7. Sehgal V, Sharma S, Sardana K. Rosacea/acne rosacea: efficacy of combination therapy of azithromycin and topical 0.1% tacrolimus ointment. *J Eur Acad Dermatol Venereol*. 2008; 22:1366-368.

# 3 Chapter Seborrhea

Seborrhea is a disorder characterized by erythema and yellowish, greasy scales, distributed over the sebaceous sites. It forms a part component of seborrheic diathesis that includes oily skin, acne, rosacea, seborrhea, seborrheic dermatitis, and labile personality. Both the sexes are affected, however, it is more prevalent in males. It tends to affect adolescents and adults. It is rare before puberty and reaches its peak between 18 and 40 years, when the activity of the sebaceous glands is maximum. The seborrheic dermatitis of infancy is an expression of seborrhea, due to the activity of sebaceous glands under the influence of maternal hormones.

The etiology of seborrheic dermatitis is unknown, although it is presumed that:

- Increased secretion and retention of sebum on the skin may act as an irritant and alter the epidermal function following percutaneous absorption. In some cases, however, the sebum production may be normal or reduced. Qualitative abnormalities in the composition of sebum have also been found
- *Pityrosporum ovale* colonizes the scaly epidermis and induces inflammation
- It may be associated with parkinsonism. Treatment with levodopa reduces seborrhea in addition to ameliorating the symptoms of Parkinson's disease
- Seborrhea may be a manifestation of zinc deficiency syndrome
- Severe form of seborrheic dermatitis is a frequent cutaneous manifestation of acquired immunodeficiency syndrome (AIDS).

## CLINICAL FEATURES

It presents as inflammatory, erythematous scaly eruption, the margins of which may be well-defined or indistinct. The scales are yellow in color and greasy in consistency. The disease has a centrocorporeal distribution tending to localize in areas with high density of sebaceous glands, namely the scalp, forehead, eyebrows, paranasal folds, and retroauricular areas. On the trunk it involves the parasternal, interscapular, superior intergluteal folds, and pubic region. Seborrheic dermatitis has the following morphological variants, namely:

### Infantile Seborrheic Dermatitis

- Cradle cap
- Seborrheic dermatitis
- Leiner's disease
- Acne neonatorum.

### Seborrheic Dermatitis of Adults

- *Scalp seborrheic dermatitis*
  - Pityriasis sicca/seborrhea capitis/dandruff
  - Inflammatory seborrheic dermatitis of the scalp.

- *Facial seborrheic dermatitis*
  - Pityriasis oleosa/oily skin
  - Marginal blepharitis
  - Acne vulgaris
  - Rosacea
  - Nasolabial seborrheic dermatitis
  - Seborrheic dermatitis of the beard.
- *Otitis externa*
- *Intertriginous/flexural seborrheic dermatitis*
- *Truncal seborrheic dermatitis*
  - Petaloid seborrheic dermatitis of the chest
  - Pityriasiform/erythematosquamous seborrheic dermatitis
  - Follicular seborrheic dermatitis of the back
- *Exfoliative dermatitis secondary to seborrheic dermatitis.*

Seborrheic dermatitis in the neonates may manifest as cradle cap. It begins in 3rd/4th week of life and presents as erythematous, adherent, waxy scaling of the scalp. It clears spontaneously by 8 to 12 months. The neonate may also develop circumscribed, yellow red, scaly plaques over the trunk, diaper area, and flexural folds. The scales are greasy and greyish white/yellow. Acne neonatorum is another expression. These manifestations of seborrheic dermatitis in infancy are due to the transplacental transfer of maternal androgens to the newborn which stimulate the sebaceous glands. The lesions subside once the maternal androgens are metabolized. Leiner's disease is due to defect in the fifth component of the complement. It presents as seborrheic dermatitis which progresses to erythroderma. Severe pyogenic infections, diarrhea, and failure to thrive are its other features. It may prove fatal.

Adult seborrheic dermatitis may begin as noninflammatory, greasy desquamation over the scalp. It is composed of desiccated sebum which is greyish white, and greasy. It may progress to inflammatory dermatitis. Perifollicular redness and scaling extends to form plaques which may remain discrete or coalesce to involve the entire scalp. It may extend beyond the frontal hairline. Both sides of pinna, the preauricular region, and the sides of the neck may also be involved. There is usually erythema, greasy scales, and crusts. Otitis externa may be its accompaniment. Facial seborrheic dermatitis may be preceded by an oily complexion, 'seborrhea oleosa'. It may progress to erythema, and scaling which involves the 'rosaceous' area. It is accompanied by episodic flushing. Telangiectasia may also develop. Acneiform papules, pustules, and cysts may appear. Rhinophyma may be an associated feature in men. The beard area may be affected and the lesions are similar to those found over the scalp. However, pustulation of the beard follicles may be prominent. Seborrheic blepharitis is an erythematous, scaly, granular inflammation of the lid margins and cilia. On the trunk, seborrheic dermatitis may manifest as either petaloid or pityriasiform dermatitis. The petaloid pattern is seen in men on the front of the chest and interscapular region. It begins as small, yellowish red, follicular papules covered with greasy scales. Extension and confluence of follicular papules give rise to figurate or circinate lesions like petals of a flower. The pityriasiform type present as oval, papulosquamous eruption resembling pityriasis rosea. The lesions, however, are more extensive than pityriasis rosea, involving the neck up to the hair margin. The flexural type of seborrheic dermatitis involves the axillae, groins, anogenital and submammary regions, and umbilicus. The lesions resemble intertrigo and present

as diffuse, sharply marginated erythema, and greasy scaling. Crusted fissures may develop. Sweating and secondary infection predispose to a weeping dermatitis.

## DIAGNOSIS

The diagnosis of seborrheic dermatitis is clinical. However, it needs to be differentiated from the following disorders which may simulate it closely.

*Psoriasis:* Psoriasis of the scalp may simulate seborrheic dermatitis. However, the lesions are wellcircumscribed, erythematous plaques covered with silvery, greyish white, micaceous scales.

*Infective dermatitis secondary to pediculosis:* The scalp should be screened for the lice and the nits.

*Flexural ringworm and candidiasis:* They can be excluded by microscopical examination of the scrapings from the advancing margin of the lesion for the fungus.

*Pityriasis rosea:* This is characterized by 'herald' patch. The lesions are oval, maculosquamous and disposed with their long axis along the lines of body cleavage.

*Drug eruptions:* Methyldopa, chlorpromazine, and cimetidine may produce cutaneous eruptions that mimic seborrhea. However, the history of drug intake is contributory.

## TREATMENT

Seborrheic dermatitis is responsive to topical steroids. One percent hydrocortisone is usually potent enough to provide symptomatic improvement. Seborrheic dermatitis of the scalp responds to tar shampoos, 2.5 percent selenium sulfide, or 2 percent cetrimide shampoo. Systemic ketoconazole improves seborrheic dermatitis; however, it recurs when the drug is stopped.

**Table 3.1: Seborrhea treatment**

| *Diseases* | *Treatment* | *Status* |
|---|---|---|
| Seborrheic dermatitis of the scalp | 1. 2.5 percent selenium sulfide shampoo (Selsun), 2 to 3 times a week.<br>2. 1 percent zinc pyrithione shampoo.<br>3. Tar shampoo.<br>4. Topical application of steroid lotions on the scalp.<br>• Flucinolone acetonide lotion (Flucort scalp lotion)<br>• Betamethosone valerate lotion (Betnovate scalp lotion) | • Inhibits mitotic activity<br>• Kills *Pityrosporum ovale*<br>• Possesses antimicrobial effect<br>• Inhibits epidermal proliferation<br>• Useful in inflammatory and severe seborrheic dermatitis |
| Seborrheic dermatitis of the trunk and face | 1. 1 percent hydrocortisone cream or ointment (Wycort).<br>2. Pragmatar cream containing 3 percent salicylic acid, 4 percent acetyl alcohol coal tar distillate.<br>3. 2 percent sulfur in calamine lotion.<br>4. 200 mg of ketoconazole daily. | • Suppresses seborrheic dermatitis<br>Potential toxicity limits its use |
| Seborrheic blepharitis | 1. Topical application of 10 percent sulfacetamide (Albuceol).<br>2. Topical application of 10 percent sulfacetamide + 0.2 percent prednisolone + 0.12 percent phenylephrine suspension. | • Monitor intraocular tension. |

Also the potential side effects of this drug make it unsuitable for long-term therapy (Table 3.1).

## RECOMMENDED READING

1. Bergbrant IM, Faergemann J. The role of *Pityrosporum ovale* in seborrheic dermatitis. *Semin Dermatol* 1990;9:262-268.
2. Geen CA, Farr PM, Shuster S. Treatment of seborrheic dermatitis with ketoconazole II: Response of seborreic dermatitis of the face, scalp, and trunk to topical ketoconazole. *Br J Dermatol* 1987;116: 217-221.
3. Kligman AM, Leyden JJ. Seborrheic dermatitis. *Semin Dermatol* 1983;2:57-59.

# 4 Chapter

# Rosacea

Rosacea is a chronic disorder of unknown etiology, characterized by hyperemia of the flush area of the face. There are the following two cardinal clinical components of the disease:

- Vascular change consisting of persistent erythema and flush
- Acneiform eruption with papules, pustules, nodules, cyst, and sebaceous hyperplasia.

The disease may be seen at any age in either sex. However, it tends to occur in women frequently between the ages of 30 and 50 years. It is severe in the males. Blepharitis, conjunctivitis, keratitis, and rhinophyma may be associated with rosacea.

## CLINICAL FEATURES

The disease begins as prominent 'flush'. Initially it is limited to lower half of the nose and then extends to involve the blush area of the face, chin, and central forehead. With time the intermittent episodes become long-lasting. Residual erythema may persist. This is accompanied by telangiectasia, blanching on diascopy. This is followed by the greasy appearance over the face and formation of papules, pustules, nodules, and cysts localized to the central one third of the face (Fig. 4.1). Comedones are conspicuous by their absence. Rhinophyma may develop, especially in men in consequence to hyperplasia of the sebaceous glands over the nose. The ocular lesions are often benign and restricted to blepharitis and conjunctivitis. However, iritis, episcleritis, and keratitis may also develop. Keratitis may predispose to ulceration and corneal opacity.

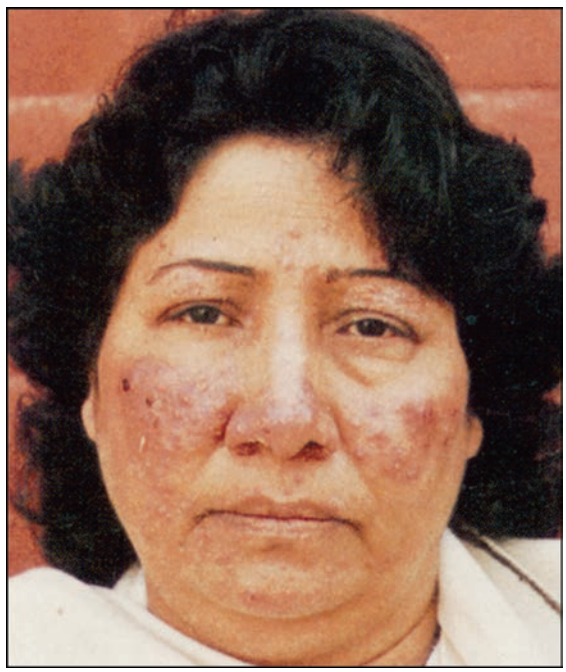


**Figure 4.1:** Erythematous papules/nodules, comedones are conspicuous by their absence. Face and the buttocks are also affected

It usually runs a chronic course. Spontaneous remission is uncommon. However, there may be periods of increased or decreased activity. With time, the intermittent episodes become more persistent. Various hues of ery-

thema may persist instead of return to normal color.

## DIAGNOSIS

The diagnosis is primarily clinical. However, it may be supplemented by histopathology. Hematoxylin and eosin stained section reveals the following:

- Lymphohistiocytic inflammatory infiltrate around upper dermal blood vessels
- Dermal edema
- Dermal elastosis
- Telangiectasia
- Loss of architecture of upper dermis
- Hypertrophy and hyperplasia of sebaceous glands

Rosacea needs to be differentiated from the following.

*Acne:* Comedones, open or closed, the hallmark of acne, are conspicuous by their absence in rosacea. Also, rosacea occurs in older age group and the localization of the lesions to middle third of the face, sparing the other seborrheic areas helps distinguish rosacea from acne.

*Periorificial dermatitis:* It primarily affects young women. It is characterized by discrete, small, erythematous papules, and pustules disposed singly or in clusters, around the mouth. Lesions may spread to involve the nose and malar areas. There is often a persistent erythema of the nasolabial folds. Dry scaling may superimpose on these lesions.

*Seborrheic dermatitis:* It is characterized by erythema, greasy scaling, and at times oozing localized to 'seborrheic' areas such as the scalp, eyebrows, eyelids, nasolabial, and postauricular folds, presternal, and interscapular areas.

*Photodermatitis*: It presents as erythema, edema, vesiculation, and oozing localized to the sun exposed areas. Exposure—withdrawal test is cardinal.

## TREATMENT

Rosacea being a progressive disorder should be intercepted with systemic and topical measures similar to that of acne vulgaris. The drugs used and their mode of administration are displayed in Table 4.1. Large telangiectatic vessels may be

**Table 4.1: Systemic and topical therapy of rosacea**

| *Treatment* | *Status* |
|---|---|
| 1. 250 mg of tetracycline (Hostacycline, Idicycline) four times a day, till symptoms subside. | Decreases acneiform eruptions, diminishes erythema, and clears keratitis |
| 2. 250 mg of erythromycin (Erythrocin, Thromycin) four times a day, till symptoms subside. | —do— |
| 3. 100 mg of minocycline twice a day, till symptoms subside. | Useful in cases resistant to tetracycline |
| 4. 250 mg of ampicillin (Campicillin) four times a day, till symptoms subside. | —do— |
| 5. 200 mg of metronidazole (Flagyl) thrice a day, till symptoms subside. | Useful in papulopustular rosacea |
| 6. Clonidine. | Reduces the flush in menopausal women |
| 7. 0.5 mg/kg/day of isotretinoin for 20 weeks. | Useful in refractory papulopustular rosacea<br>Reduces erythema and telangiectasia.<br>Rhinophyma may improve |
| 8. Topical application of 2 percent erythromycin (Acnecin, Acnesol), preferably at night time. | Supplements the parenteral therapy. |
| 9. Topical application of 2.5 to 5 percent of benzoyl peroxide (Pernox gel). | —do— |
| 10. Topical application of 1 percent of metronidazole. | —do— |

destroyed by argon laser surgery or by electrocoagulation. Rhinophyma may be treated by surgical reduction, laser surgery or dermabrasion.

## RECOMMENDED READING

1. Nielsen PG. Metronidazole treatment in rosacea. *Int J Dermatol* 1988; 27:1-5.
2. Wilkin JK. Rosacea. *Int J Dermatol* 1983;22:393-400.

# 5 Chapter Eczema/Dermatitis

Eczema/dermatitis is a pattern of inflammatory response of the skin, which is characterized by erythema, edema, vesiculation, exudation, and crust formation (Figs 5.1A and B). It is accompanied by itching/burning. It is induced either in consequence to factors working from within (systemic) or from without (extrinsic). Eczema may manifest either as acute dermatitis or with the features of chronic dermatitis, the hallmark of which is lichenification. The latter is a slow, insidious process, formed at the backdrop of incessant scratching and is perceived as pigmentation, thickening, and exaggeration of the skin markings (Table 5.1).

**Table 5.1: Exogenous and endogenous eczemas**

*Exogenous dermatitis*
- Air-borne contact dermatitis
- Photodermatitis
- Phytophotodermatitis
- Irritant contact dermatitis
- Allergic contact dermatitis
- Infectious eczematoid dermatitis

*Endogenous dermatitis*
- Atopic dermatitis
- Seborrheic dermatitis
- Nummular eczema
- Stasis dermatitis
- Pompholyx.

## ENDOGENOUS ECZEMAS

*Atopic dermatitis:* It is a part component of atopic diathesis and is characterized by lowered threshold to pruritus. It may arbitrarily be divided into infantile, childhood/adolescent and adult variants.

In infants it usually appears about the third months of life. The child is usually fair, fat, anxious, with shiny eyes and glassy expression. The face, particularly the cheeks are the usually affected site. The lesions are erythematous and dry or mildly oozing. It is characterized by remission and relapses. However, it usually disappears at the age of 2 years. In a high proportion of patients, the condition recurs in late childhood, adolescence or early adult life. At this time, dermatitis tends to localize in the flexural areas, the antecubital and popliteal fossae, neck, eyelids, and behind the ears. At times the eruption may become generalized. The features are essentially of erythema, edema, vesiculation, and oozing. In the adult phase, the skin may be lichenified.

Several of the patients of atopic dermatitis have atopic diathesis, characterized by history of hay fever, asthma and/or urticaria in the patient or in the family.

*Seborrheic dermatitis:* It is the part component of seborrheic diathesis which includes acne vulgaris, rosacea, seborrheic dermatitis, and labile personality. The dermatitis is characterized by scaly patches, the margins of which are indistinct. The lesion is erythematous with

scales which are greasy and greyish white or yellow in color. It has a centrocorporeal (shower bath) distribution with a predilection for scalp, eyebrows, forehead, paranasal folds, retroauricular areas, presternal, interscapular, and pubic areas. In obese patients, the intertriginous folds of the trunk may also be involved.

*Nummular dermatitis:* It presents with characteristic round, nummular, coin-like lesions, distributed on the extensor surface of the extremities, posterior aspect of the trunk, buttocks, and lower legs. The dermatitis may remain localized as a few small, scaly patches or there may be a gradual relentless appearance of new lesions. Eventually the lesions may involute in 2-3 months time.

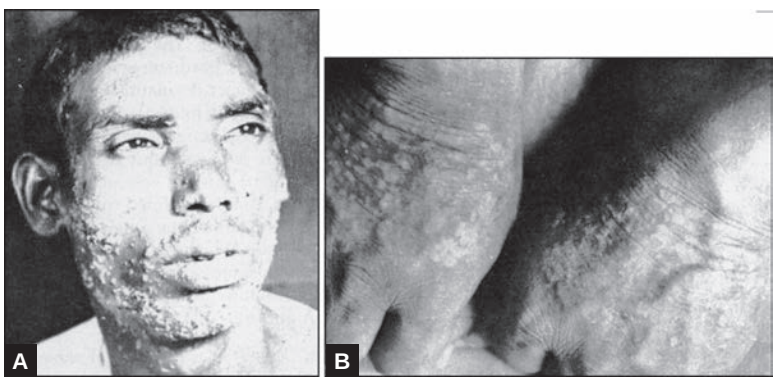
*Stasis dermatitis:* It usually affects persons like teachers, laborers, rickshaw-pullers, athletes, etc. whose work requires long hours of standing. This predisposes to varicose veins with tortuous, dilated veins over the legs. It is followed by stasis of blood on the dependent parts of the legs.

Over a period of time, there is diapedesis of red blood corpuscles into the surrounding tissue and this manifests as petechiae over the skin surface, usually confined to around the ankles. Subsequently, the red blood cells are hemolyzed and hemosiderin is liberated. It is evident as pigmentation over the area. This acts as foreign substance and evokes eczematous response. Also the oxygenation of the part is impaired resulting in ulceration. The ulcer margins may develop pseudoepitheliomatous hyperplasia and subsequent malignant transformation.

## EXOGENOUS ECZEMAS

*Air-borne contact dermatitis:* It is usually encountered in those who work in open and are exposed to dust, pollens, and other particles suspended in the air. The laborers, farmers, industrial workers, gardners are often affected by air-borne contact dermatitis. The particles tend to lodge in body folds. Repeated exposure to the allergen causes sensitization and subsequently there is eczematous response in the form of erythema, edema, vesiculation, oozing and crusting, usually confined to the flexures. On withdrawal from the environment, the eczema subsides. However, when the person returns to the same surroundings, there is a relapse of dermatitis (exposure-withdrawal test) (Figs 5.1A and B).

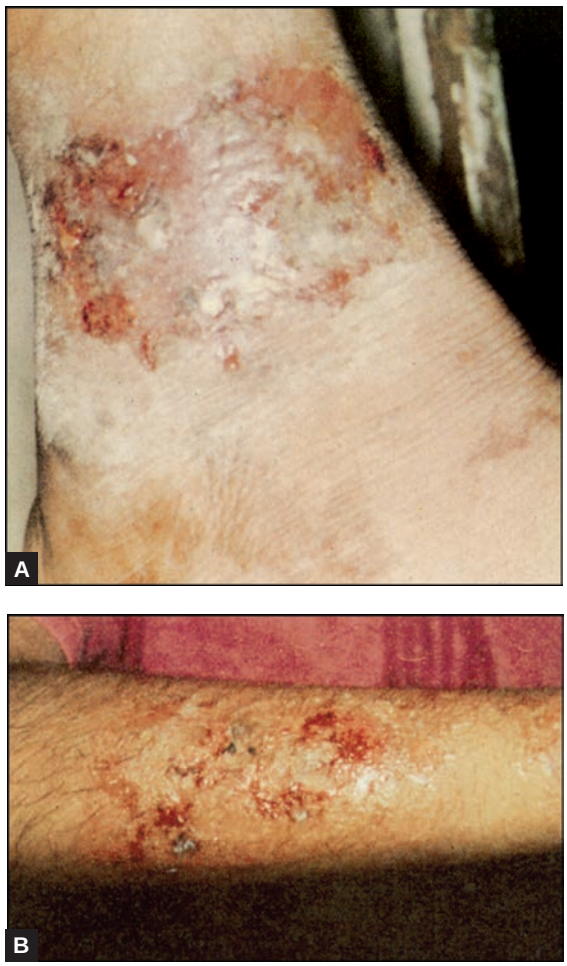
*Photodermatitis:* It is the general name used to define the abnormal eczematous response to the stimulus of light. It is usually evoked in




**Figures 5.1A and B:** Air-borne contact dermatitis: Erythema, edema scaling

association with chemicals which are innocuous to the skin in absence of light exposure. However, when the skin is challenged with appropriate concentration of the agent and the wavelength of the light, dermatitis is produced. These photosensitivity reactions may either be photoallergic or phototoxic, depending upon whether the immune system is participating or not. The photoxic reaction may be elicited in any individual provided there is enough light energy of appropriate wavelength and adequate concentration of the agent. However, in photoallergic dermatitis, the absorbed light energy promotes a photochemical reaction between the chemical and skin proteins resulting in the formation of photoantigen. There is sensitization to this photoantigen and on subsequent exposure, an eczematous response is elicited.

There is usually a prodrome of itching and/or burning on areas exposed to sunlight, namely forehead, butterfly area of the face, tip of the nose, pinna, 'V' of the neck, and extensor aspects of the forearms. This is followed by eczematous response in the form of erythema, edema, vesiculation, and oozing. On healing, these areas may show hyperpigmentation. Exposure-withdrawal test is positive in photodermatitis also. When the patient is withdrawn from sunlight and confined to a darkroom, the eczema subsides. However, re-exposure to sunlight again precipitates the eczematous response. Photopatch test may also be performed by using a blackened X-ray film with a window. This is applied to an area exposed to light. Eczematous response would be elicited on the skin underneath the window which was accessible to light exposure (Figs 5.2A and B).




**Figures 5.2A and B:** Infectious eczematoid dermatitis (IED)

## DIAGNOSIS

The diagnosis of acute eczema is made by the presence of cardinal clinical features of erythema, edema, vesiculation, and crusting, and associated itching. The chronic lichenified dermatitis is characterized by hyperpigmentation, thickening of the skin, and exaggeration of skin markings. The clinical features of respective eczemas (*vide supra*) should help in forming the diagnosis. Office procedures, namely patch test for contact dermatitis, photopatch test for photodermatitis and exposure—withdrawal

**Table 5.2: Treatment of eczema/dermatitis**

| *Types of eczemas* | *Mainlines of treatments* | *Other associated treatments* |
|---|---|---|
| Atopic eczema | A. Topical corticosteroids as creams<br>*Infantile:* Hydrocortisone butyrate (Locoid)<br>*Adolescent:* Bland compresses in exudative stage, followed by application of topical corticosteroids like Betamethasone valerate or Beclomethasone dipropionate (Diplene)<br>*Adult:* Topical corticosteroids, if lichenification has occurred, prefer ointments.<br>B. Antihistamines<br>Phenergan 10 to 25 mg thrice daily<br>Practin 4 mg thrice daily. | Explain regarding the relapses and remission. |
| Seborrheic eczema | Topical corticosteroids like betamethasone-17 valerate (Diplene) applied twice or thrice daily.<br>Oral corticosteroids if dermatitis is severe. | Corticosteroid lotions (Flucort lotion) and cetrimide shampoo. |
| Pompholyx | Oral corticosteroids like decadron (0.5 mg) 2 tabs thrice daily or Prednisolone 40 mg/day. | Treat the focus of infection with suitable antibiotics. |

test for air-borne contact dermatitis (ABCD) are useful supplements in diagnosis.

## TREATMENT

The corticosteroids form the mainstay of treatment. These may be combined with antihistamines. Antibiotics may be indicated in associated secondary infection. Topical bland compresses like potassium permanganate, boric acid or aluminium subacetate are essential (Table 5.2).

## RECOMMENDED READING

1. Sehgal VN, Jain S. Eczema/dermatitis. *J Indian Med Assoc* 1993;91:78-79.

# 6 Chapter Erythroderma/Exfoliative Dermatitis

Exfoliative dermatitis/erythroderma is an extreme state of skin irritation affecting either whole or most of the skin surface. It is conceived as a secondary or reactive process to a host of cutaneous and/or systemic affliction. However, a proportion of cases belong to the idiopathic group.

The etiology of exfoliative dermatitis may show geographical and regional variations. In India, the important causes of it are as follows:

I. *Pre-existing skin dermatoses*

They may give rise to exfoliative dermatitis *per se* or it may be the result of treatment taken for these disorders. In order of frequency, the most common skin dermatoses which may progress to erythroderma are:

- Psoriasis
- Air-borne contact dermatitis
- Phytophotodermatitis
- Staphylococcal scalded skin syndrome (SSSS)
- Seborrheic dermatitis
- Atopic dermatitis
- Photosensitive dermatitis
- Pityriasis rubra pilaris (PRP)
- Stasis dermatitis
- Norwegian scabies
- Ichthyosiform dermatoses.

II. *Drug induced*

In Indian setting, the common drugs responsible are as follows:

- Antituberculous drugs like isoniazid, thiacetazone, and streptomycin
- Antirheumatic-antipyretics like phenylbutazone
- Sulfonamides like sulfadiazine
- Antibiotics like tetracyclines.

III. *Systemic diseases*

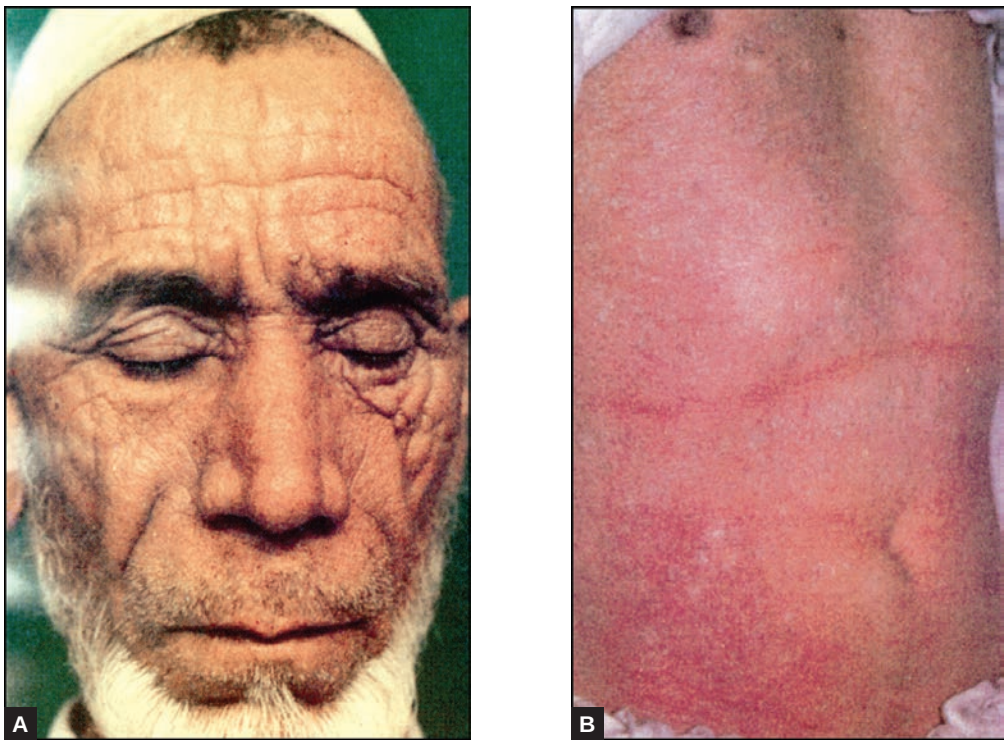
IV. *Malignancy*

- Leukemias
- Lymphomas

However, in India malignancy and systemic diseases are uncommon causes of erythroderma.

## CLINICAL FEATURES

Its evolution is insidious except in SSSS and drug induced erythroderma. The patient may report with itching, burning, and/or generalized redness of the skin. Itching is severe in air-borne contact dermatitis, phytophotodermatitis, and atopic dermatitis. There is generalized exfoliation of scales which may be powdery, flaky or thin papery. In psoriasis the scales are typically shiny, silvery white, brittle, micaceous, and exorbitant. Patient may note bountiful scales on the bed. Palms and soles are usually spared except in Norwegian scabies




**Figures 6.1A and B:** (A) Air-borne contact dermatitis, (B) Generalized erythema, edema and scaling

and pityriasis rubra pilaris. There may also be generalized lymphadenopathy, hypo or hyperthermia, tachycardia, and pedal edema (Figs 6.1A and B).

## DIAGNOSIS

The following investigations are undertaken in exfoliative dermatitis:

- Complete hemogram including hemoglobin concentration, total and differential leukocyte count
- Erythrocyte sedimentation rate
- Total and differential serum proteins
- Serum electrolytes
- X-ray chest
- Skin biopsy, which may show features of the underlying disease responsible for exfoliation or it may be a picture of nonspecific dermatitis
- Lymph node biopsy.

Bronchoscopy, colposcopy, proctoscopy, barium meal studies, and liver scan may be undertaken when indicated by the history and clinical examination.

## TREATMENT

An endeavor should be made to clearly define the cause of exfoliative dermatitis, for which details of history should be formed around the administration of topical or systemic drugs. The morphology of the dermatoses likely to culminate into exfoliative dermatitis should be recorded. Malignancy, though not a frequent cause of exfoliative dermatitis in our

**Table 6.1: Systemic treatment and supportive measures**

| *Corticosteroids* | *Adjuvants* | *Other supportive measures* |
|---|---|---|
| Initiate treatment with prednisolone (Wysolone) 60-80 mg daily in divided doses<br>or<br>Dexamethasone (Decadron 0.5 mg tab) 8 mg daily<br>or<br>Inj Decadron (4 mg/mL) intramuscularly twice daily. Dose may be tapered with clinical improvement | Methotrexate may be required in cases not showing adequate response to corticosteroids alone and in cases secondary to psoriasis and PRP. Test dose of 5 mg orally to be followed by 22.5 mg in three divided doses at intervals of 12 hours every week. | 1. Maintenance of environmental temperature to prevent hypo and hyperthermia.<br>2. Bland emolients like vaseline, paraffin or coconut oil for local application.<br>3. High protein diet.<br>4. Antacids like digene/mucaine/gelusil gel in the dose of 2 tsf thrice daily.<br>5. Potassium chloride 1-2 tsf thrice daily.<br>6. Antibiotics, if required, in adequate dosage for a requisite period.<br>7. Care of the bowel and bladder.<br>8. Monitoring of the blood pressure daily, and weight, blood sugar, and serum electrolytes every week. |

country, should also be suspected, especially in old age. Accordingly, the investigations (*vide supra*) are imperative. Many a times, histopathology may decide the underlying disease.

The patient should be hospitalized. Requisite dosage of prednisolone or its derivatives to be administered are displayed in Table 6.1.

## RECOMMENDED READING


1. Abrahams I, McGarthy JT, Sanders SL. 101 cases of exfoliative dermatitis. *Arch Dermatol* 1963; 87:96-101.
2. Hasan T, Jansen CT. Erythroderma: A follow-up of 50 cases. *J Am Acad Dermato* 1983;8:836-840.
3. Nicoles GD, Helwig EB. Exfoliative dermatitis: A clinicopathologic study of 135 cases. *Arch Dermatol* 1973;108:788-797.
4. Sehgal VN, Srivastava G. Exfoliative dermatitis: A prospective study of 80 patients. *Dermatologica* 1986;173:278-284.
5. Wilson HTH. Exfoliative dermatitis: Its etiology and prognosis. *AMA Arch Dermatol Syphilo* 1983;69:577-588.
6. Sehgal VN, Srivastava G, Sardana K. Erythroderma/exfoliative dermatitis: a synopsis. *Int J Dermatol* 2004;43:39-47.
7. Sehgal VN, Srivastava G. Erythroderma/generalized exfoliative dermatitis in pediatric practice: an overview. *Int J Dermatol* 2006;45:831-839.

# 7 Chapter Atopic Dermatitis

Atopic diathesis is a predisposition to develop hay fever, allergic rhinitis, bronchial asthma, urticaria, and/or atopic dermatitis. The atopic person has a predilection to produce reagin antibodies in abnormally large amounts. The 'reagin' response to allergens is preponderant in such individuals and this is responsible for the type I (IgE-mediated) hypersensitivity manifestations. Atopic dermatitis (AD) an expression of atopic diathesis, in an abnormally reacting skin, may manifest in the form of eczema/dermatitis. Intense pruritus being its hallmark, it usually has its onset between 2 to 6 months. It may pursue a chronic course with varied morphology and localization. It passes through infantile, childhood, and adult phases. Remissions and relapses are cardinal. Spontaneous resolution is frequent, at times; however, its relics are evident as stigma. A number of confirmed and putative activators are responsible for triggering atopic dermatitis. These are stress, aeroallergens like mites, molds, yeast, human dander, foods, irritants, viruses, and staphylococci.

The initial event in the pathogenesis of atopic dermatitis is the release of mediators from the skin mast cells. Various factors have been implicated for it.

- Serum levels of IgE are elevated in approximately 80 percent of patients and correlate with the disease activity
- Neuropeptides such as substance P stimulate histamine release from skin mast cells and may link the central nervous system to cutaneous inflammatory cells
- Abnormal cyclic nucleotide metabolism.

The levels of cyclic adenosine monophosphate (cAMP) in stimulated leukocytes are reduced. This results from excessive hydrolysis by cAMP-phosphodiesterase (PDE). The reduced levels of cAMP may be responsible for the hyper-releasability of mediators of inflammation. Histamine released via these mechanism interferes with cell-mediated immunity through inhibition of $H_2$ receptor bearing lymphocytes. Alternatively or in addition, IgE immune complexes inhibit cell-mediated immunity by blocking lymphocyte proliferation response to antigens. The resulting defective cell-mediated immunity allows enhanced IgE production. Thus a vicious circle is established and cell-mediated immunity is depressed and enhanced IgE production dominates the immune mechanism in atopic dermatitis. The eczematous reaction in atopic dermatitis is the manifestation of IgE-mediated late phase reaction, which are mediated by histamine and characterized by perivascular leukocytic infiltrate.

Abnormalities of other secondary messenger systems, including abnormalities of protein kinase C activity and of inositol activation have been observed in atopic subjects. These may

be a consequence of downregulation of second messenger systems because of chronic exposure to low levels of inflammatory mediators, but these may themselves be responsible for permitting further mediator release. These abnormalities offer a biochemical explanation for increased type I mediated immunity and diminished cell mediated immunity.

Furthermore, these patients have a defect in T-lymphocyte suppressor function. They demonstrate cutaneous anergy to microbial antigens such as candidin and streptokinase-streptodornase, and to a variety of strongly immunogenic haptens such as poison ivy and dinitrochlorobenzene (DNCB). *In vitro* studies demonstrate impaired mitogenic response of lymphocytes to mitogens such as phytohemagglutinin (PHA), concanavalin A, candidin, tuberculin, and herpes simplex virus. Lymphocyte mitogenesis is diminished when dermatitis is active but may normalize with clinical remission. There is a decreased antibody mediated cellular cytotoxicity and a decreased natural killer (NK) cell activity.

The atopic subjects also show altered vascular response to histamine, serotonin, cholinergic, and sympathomimetic agents. The vascular abnormalities manifest as:

- Pallor
- Low finger temperature
- Pronounced vasoconstriction on exposure to cold
- White dermographism
- A reduced reaction to histamine
- White reaction to nicotinic acid esters
- Delayed blanch with acetylcholine

## CLINICAL FEATURES

The primary and predominant symptom of atopic dermatitis is itching. This sets up a vicious cycle. Itching leads to scratching, scratching causes lichenification, and lichenification lowers the threshold for itch (Fig. 7.1). Three phases are recognized in atopic dermatitis, namely:

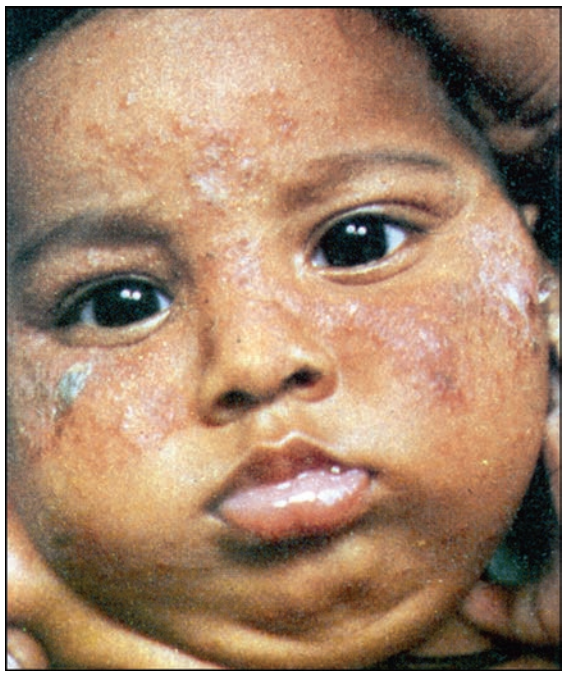
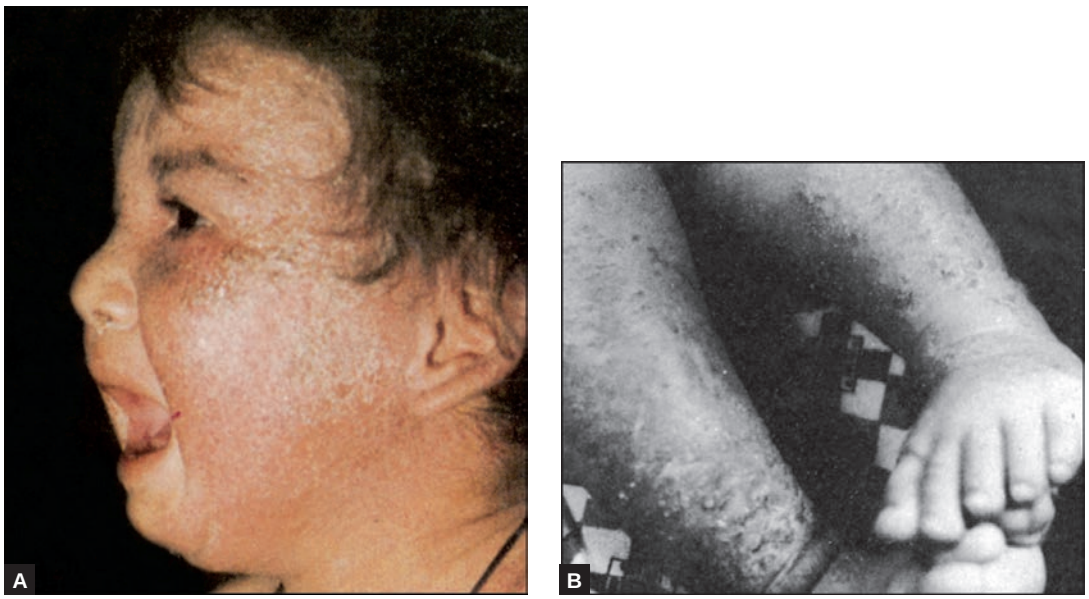


**Figure 7.1:** Atopic dermatitis

*Infantile phase:* The onset is usually in the third month of life. The child is fair, fat, anxious with shiny eyes, and glassy expression. The face, particularly the cheeks are the usual affected site. The skin is erythematous and dry with few papulovesicles and scant oozing (Fig. 7.2A and B). The course is marked by remissions and relapses. However, it usually disappears by the age of 2 years.

*Childhood phase:* The dermatitis recurs between the ages of 4 and 10 years. At this time it tends to localize in the flexural areas, the antecubital and popliteal fossae, neck, eyelids, and behind the ears. The eruption may become generalized.




**Figures 7.2A and B:** Atopic dermatitis: Erythematous, dry scaly lesions over the cheeks, and the legs in a plump child. Bilateral symmetrical

The features are essentially of erythema, edema, vesiculation, and oozing.

*Adolescent and adult phase:* The lesions are dry, lichenified, hyperpigmented plaques in flexor areas, in addition to eruptions elsewhere in the body.

The atopic subject may have stigmata and suffer from complications. A linear transverse fold below the edge of lower eyelids, known as Dennie-Morgan's fold is indicative of atopic diathesis. Thinning of the lateral eyebrows, Hertoghe's sign is sometimes present. Cataract may be an associated finding. The opacities are unilateral in about half of the cases, and the anterior cortex is twice as often involved as the posterior cortex. Superimposed infections such as verrucae vulgaris, molluscum contagiosum, and dermatophytosis are common. *Staphylococcus aureus* dominates the skin flora. It colonizes the eczematous lesions of atopic dermatitis. There is increased susceptibility to generalized herpes simplex infection resulting in Kaposi's varicelliform eruption.

## DIAGNOSIS

The diagnosis of atopic dermatitis is clinical. It is supplemented by eliciting a detailed history of atopic diathesis in self and other members of the family. The following Hanifin and Lobitz criteria help in the diagnosis.

*Must have each of the following:*

- Pruritus
- Typical morphology and distribution:
  - Flexural lichenification in adults
  - Facial and extensor involvement in infancy
- Tendency toward chronic or chronically relapsing dermatitis plus either

**Table 7.1: Mainstay and supportive therapy of atopic dermatitis**

| *Mainstay* | *Supportive* |
|---|---|
| 1. Burrow's (aluminum acetate) or Condy's (Potassium permanganate) compresses for 10 to 20 min, 3 to 4 times a day.<br>2. Topical application of corticosteroids. Ointments are preferable except in exudative lesions localized to flexural areas. Initiate therapy with a potent corticosteroid applied twice a day:<br>• Betamethasone dipropionate 0.05 percent (Diprolene, Diplene)<br>• Flucinolone acetonide 0.025 percent (Flucort)<br>For maintenance, use mild corticosteroids like<br>• Hydrocortisone butyrate 0.1 percent (Locoid)<br>• Betamethasone dipropionate 0.0125 percent (Diprovate RD).<br>3. In case of secondary infection, antibiotics may be combined with steroids for topical application<br>• Dipgenta skin cream<br>• Tenovate G skin cream<br>4. Tar compounds like 5 to 10 percent liquor carbonis detergens in hydrophilic ointment may be applied for lichenified dermatitis, either alone or in combination with steroids.<br>5. Antihistamines to allay anxiety and relieve itching<br>• 25 mg of promethazine hydrochloride (Phenergan) thrice a day. | 1. 40 to 60 mg of prednisolone (Wysolone) or its equivalent of corticosteroids may be administered for short periods only to suppress acute flare ups.<br>2. Avoid excessive bathing and use a bland soap.<br>3. Massage oil on wet skin after bath to trap moisture.<br>4. Treatment with PUVA, sodium cromoglycate, and phosphodiesterase inhibitors are under trial. |

*Must have two or more of the following features:*

- Personal or family history of atopic disease (asthma, allergic rhinitis, atopic dermatitis)
- Immediate skin test reactivity
- White dermographism or delayed blanch to cholinergic agents
- Anterior subcapsular cataracts, or else

*Must have four or more of the following features:*

- Xerosis/ichthyosis/hyperlinear palms
- Pityriasis alba
- Keratosis pilaris
- Facial pallor/infraorbital darkening
- Elevated serum IgE
- Keratoconus
- Tendency to nonspecific hand dermatitis
- Tendency to repeated cutaneous infections

## TREATMENT

The treatment of atopic dermatitis should be undertaken as shown in Table 7.1.

## RECOMMENDED READING

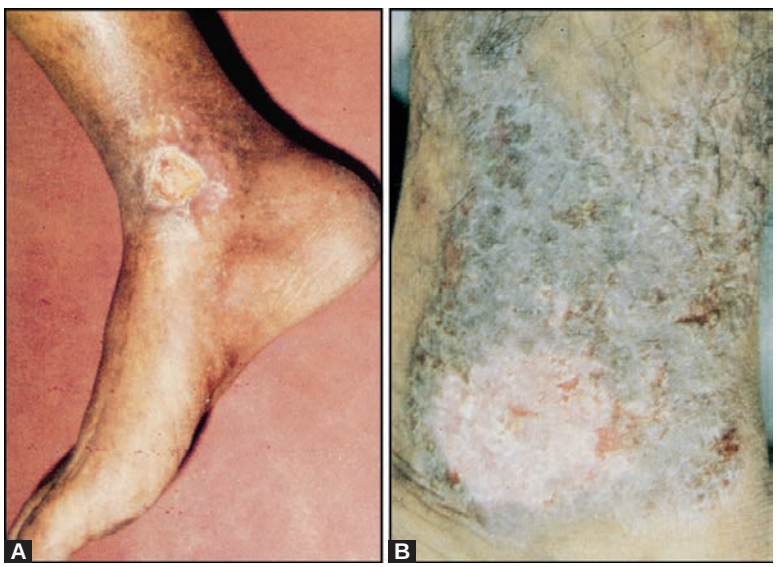
1. Hanifin JM, Lobitz WC Jr. Newer concepts of atopic dermatitis. *Arch Dermatol* 1970;113:663-670.
2. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* (Stockh) 1980; 92(S):44.
3. Hanifin JM. Atopic dermatitis. *J Allergy Clin Immunol* 1984;73:211-226.
4. Rajka G. *Essential Aspects of Atopic Dermatitis.* Berlin: Springer-Verlag 1989.
5. Roth HL. Pathophysiology and treatment of atopic dermatitis. *Int J Dermatol* 1977;16:163-178.
6. Sehgal VN, Jain S. Atopic dermatitis: Nomenclature. *Int J Dermatol* 1993;32:575-576.
7. Sehgal VN, Jain S. Atopic dermatitis: Clinical criteria. *Int J Dermatol* 1993;32:628-637.
8. Sehgal VN, Jain S. Atopic dermatitis: Ocular changes. *Int J Dermatol* 1994;33:11-15.

# 8 Chapter

# Stasis Dermatitis

Stasis dermatitis is a pruritic eczematous reaction that arises secondary to venous hypertension. This may either be in consequence to varicose veins or previous deep vein thrombosis. It is also termed as varicose or gravitational eczema.

Varicose veins are the dilated and tortuous veins (Figs 8.1A and B). This condition commonly affects the veins of the legs. It may either be primary or secondary. The primary varicose veins are associated with a normal deep venous system. They may arise as a result of congenital absence and/or incompetence of the valves, wasting and/or weakness of the muscles, and congenital arteriovenous fistula. Varicosity is also predisposed by abdominal tumors and pregnancy. However, the largest group of primary varicose veins is constituted by those whose work demands standing for long hours such as teachers, porters, and conductors. The secondary varicose veins are associated with deep thrombophlebitis in the past. Persistent obstruction of the deep veins, incomplete recanalization of the thrombosed veins, valvular destruction, and reflux of the blood through incompetent perforators results in high pressure in the superficial venous system. This is followed by the opening up of venous collateral circulation visible as tortuous superficial veins. In either case the valves become incompetent. The return of the blood from the lower limbs to the heart is impeded and there is a high pressure leakage of blood into the superficial venous system. This predisposes to edema and the diapedesis of the red blood cells into the subcutaneous tissue. The fibrin molecules also escape into the interstitial




**Figures 8.1A and B:** Varicose vein resulting in an ulcer, medial malleolus

fluid where they form fibrin complexes around the capillaries. The red blood cells are hemolyzed and there is liberation of hemosiderin. This is responsible for the brownish pigmentation, especially noticeable on the medial side of the lower leg. The hemosiderin molecules are irritant and induce itching. Scratching leads to break in the continuity of the skin and may also implant the pathogenic microorganisms resulting in eczematous dermatitis. The fibrin layer forms a pericapillary barrier and the edema hinder the diffusion of oxygen and other nutrients that are essential for the normal viability of the skin. This impaired oxygenation perpetuates the eczema and also predisposes to the formation of ulcer. Injudicious application of the topical allergic sensitizers further complicates the matter and may result in an exfoliative dermatitis.

## CLINICAL FEATURES

The patient usually complains of tiredness and aching in the lower leg, toward the end of the day. The ankles may swell by evening. There is brownish pigmentation localized usually to the medial side of the lower leg, just above the medial malleolus. The patient also has itching and a desire to rub or scratch the lower leg.

The eczema is characterized by erythema, edema, vesiculation, oozing, and crusting. It is accompanied by features of venous hypertension, namely swelling of the legs, dilated and tortuous superficial veins, purpura, and brownish pigmentation secondary to hemosiderin. The ulcer if present, is localized on the medial side of the lower leg, usually over the medial malleolus. It is vertically oval in shape (Figs 8.1A and B). The base may be red and granulating and the borders punched out. The surrounding skin may get sclerosed. Leashes of dilated venules may form around it. Also small patches of atrophy (atrophie blanche) are occasionally seen in its vicinity. Stasis ulcer may at times cause: (i) hemorrhage, (ii) osteomyelitis, (iii) periosteitis, (iv) calcification of the veins, (v) pseudoepitheliomatous hyperplasia, (vi) carcinomatous change, (vii) talipes equinus, owing to long continued faulty habit of walking on the toes to get relief from pain.

## DIAGNOSIS

It is clinical. It is supplemented by examination of the varices. This is most important because diagnosis depends on the success/failure of treatment. The aim is to locate the site of the incompetent superficial deep valves. This is facilitated by performing the following tests.

*Trendelenburg's test:* This is done to determine incompetency of the valves in the superficial and communicating systems. The patient is first placed in the recumbent position and the veins are emptied by raising the limb and stroking the varicosed veins proximally. The termination of long saphenous vein is compressed with the thumb, and patient's asked to stand up quickly. The pressure is then released. If the varices fill very quickly by a column of blood from above, it indicates the incompetency of the superficial system. This is a positive Trendelenburg's test. Absence of retrograde filling of the saphenous vein signifies a negative Trendelenburg's test. To test the communicating veins, the pressure is not released but maintained for about a minute. Gradual filling of the veins during this time indicates an incompetency of the communicating veins, allowing the blood flow from the deep to the superficial veins.

*Perthes' test*: This is employed to ascertain the status of deep veins. A tourniquet is tied around the upper part of the thigh, tight enough

to prevent any reflux of the blood down the vein, and the patient is asked to walk quickly for a while with the tourniquet in place. If the communicating and deep veins are normal, the varicose veins shrink whereas if they are blocked, the varicose veins become more prominent. The test may be repeated by tying the tourniquet at different levels to find out the levels of the incompetent perforators.

*Schwartz test:* In a prominent varicose vein, an impulse may be felt by the finger at the saphenous opening if the most prominent part of the varicosity is tapped by the finger of the other hand.

## TREATMENT

Treatment of varicose veins is conservative. The patient is advised to change the vocation and avoid long walks and standing. Whenever he is free he should keep his legs elevated during the day and also at night. The latter is achieved by raising the foot off the bed. In case it is difficult to avoid walking or prolonged standing he is educated to tie a crepe bandage after evacuating the veins by elevating the leg. In addition, dermatitis/eczema should be treated in the manner described in Chapter 5. An ulcer of varicose vein is quite chronic and should be treated in a similar manner as any other ulcers. It is imperative to emphasize that the ulcer should be kept clean by bathing it with light pink solution of potassium permanganate. Topical as well as systemic antibiotics may also be administered according to the recovery of organism in culture. In case there is an osteomyelitis, sequestrum may have to be removed surgically. Surgical intervention for varicose veins, though at times advocated is not a very useful procedure because of recurrence of the condition.

## RECOMMENDED READING

1. Burton JL. Venous hypertension, fibrin, leg ulcers. *Br J Dermatol* 1983;109:229-231.

# 9 Chapter

# Hand Dermatitis

Hand dermatitis is a common, chronic, and intriguing disorder that poses a diagnostic dilemma and a threapeutic challenge. The clinical features are not specific and the disorder may be a manifestation of either acrodermatitis continua of Hallopeau, pustular psoriasis of the palms, pompholyx, id eruption, or tinea mannum.

## CLINICAL FEATURES

*Acrodermatitis continua:* It is a superficial, dissecting vesiculopustular eruption, usually affecting the acral portion of the indexfinger of one hand. Local trauma sustained during the household work initiates the disease. The sap and the juice exuding out while peeling the vegetables seeps through the traumatized site and sensitizes the skin. This is often responsible for precipitating and perpetuating the disease. It begins as a group of deep seated vesicles and pustules with moderate inflammation, affecting the digit. Peripheral extension occurs by the separation of stratum corneum and upper layers of epidermis. Removal of the stratum corneum reveals serous/seropurulent exudate over a moderately inflamed base (Fig. 9.1). The disease process is very chronic, resistant, and persistent. It may cause atrophy of the skin, and destruction of the nail and the digit. Clinical improvement occurs after

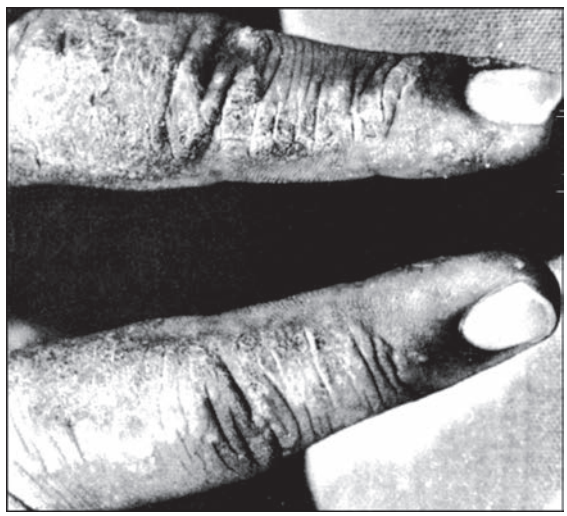


**Figure 9.1:** Acrodermatitis continua

administration of antibiotics and topical and systemic steroids. However, remission is short-lasting. Relapses occur and local trauma and chemical irritants tend to perpetuate the disease.

*Pustular psoriasis of the palms:* It is a chronic, relapsing disorder affecting the mid palm, thenar and hypothenar eminences. The condition is often bilateral and symmetrical. It develops as crops of small, deep-seated pustules and hemorrhagic vesiculopustules developing within areas of erythema and scaling. It is accompanied by moderate to marked itching. During the course, some hyperkeratosis develops. The pustules do not rupture but dry up

in two to three weeks leaving behind punctate brown scabs that are exfoliated. Remissions and relapses are frequent. Some patients ultimately develop typical psoriasis. It is differentiated from acrodermatitis continua by its tendency to involve mid palm and spare the acral portion of the fingers.

*Pompholyx:* It is characterized by the sudden appearance of crops of clear, deep-seated vesicles that appear as 'sago-grains' (Fig. 9.2). Erythema is conspicuous by its absence. However, there may be a sensation of heat over the palms. Moderate to severe itching may precede by the vesicular eruption. The vesicles may become confluent and present as large bullae. The eruption usually subsides spontaneously and resolution with desquamation occurs in 2 to 3 weeks. In a mild case, only the sides of the fingers are affected, but in a severe case the vesicles develop symmetrically over the palms and/or soles. Pompholyx usually occurs in summers and almost invariably there is accompanying hyperhidrosis.

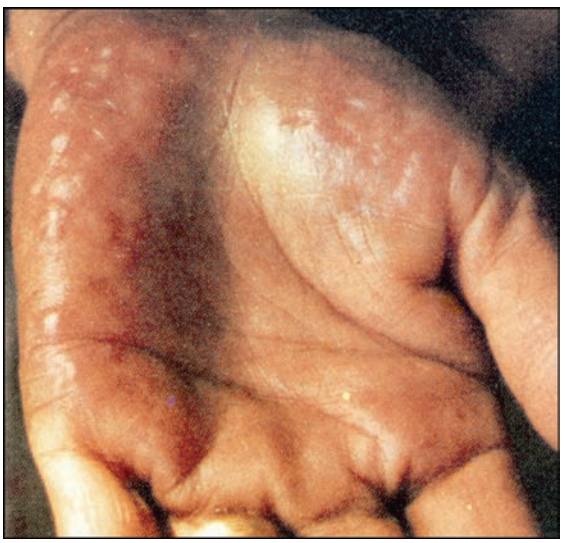


**Figure 9.2:** Pompholyx

Pompholyx is an endogenous eczema. However, it may represent an expression of atopic dermatitis, irritant and/or allergic dermatitis, dermatophytosis or bacterial infection elsewhere in the body, drug eruption, heavy metal ingestion or stress.

*Id eruption:* It is a sensitization reaction associated with a focus of infection elsewhere in the body. The infection may either be bacterial, viral, or fungal. It develops as small, recurrent vesicles or large bullae. The palms and inner sides of the fingers are most markedly involved. The criteria to be fulfilled for presumptive diagnosis of id reaction are as follows:

- A primary focus of infection. Recovery of the causative organism is possible from it
- No organism demonstrable at the id site. Id eruption is sterile
- Resolution of id when the primary infection clears.

*Tinea mannum:* It is the infection of the palms by the dermatophytes. It may manifest either as the following:

- Inflammatory vesicular,
- Noninflammatory squamous eruption,
- Interdigitale infection (Fig. 9.3).

The former is characterized by the eruption of multilocular blisters in cluster over the palms. *T. mentagrophyte* is the usual causative

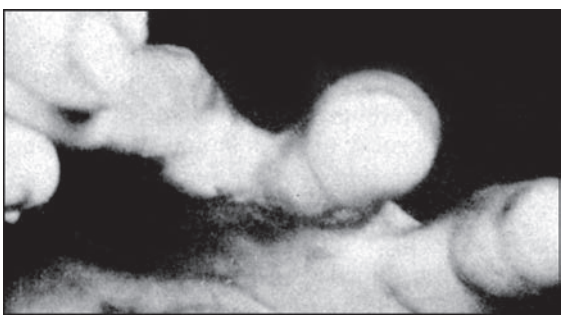


**Figure 9.3:** Tinea interdigitale

organism recovered from the vesicular fluid. The squamous type is caused by *T. rubrum*. The palms and the palmar aspect of fingers are the site of predilection. It presents as diffuse, fine branny, adherent scales especially noticeable in the furrows. The underlying skin is erythematous, but may become markedly thickened and hyperkeratotic with development of painful fissures. In a majority of cases, only one hand is involved.

## DIAGNOSIS

It depends upon the clinical expression of the disease supplemented by the relevant investigations. The synopsis of the diagnosis is shown in Table 9.1.

**Table 9.1: Clinical features, diagnoses and treatment of hand dermatitis**

| *Diseases* | *Clinical features* | *Diagnoses* | *Treatments* |
|---|---|---|---|
| Acrodermatitis continua | Deep vesicles and pustules with moderate inflammation, affecting the acral portion of the fingers. Recurrent and persistant.<br>Atrophy of the skin, nails and digits. Trauma and chemical irritants are the precipitating and perpetuating factors. | Histopathology reveals:<br>1. Spongiform pustule in the stratum malphigii.<br>2. Psoriasiform changes, namely parakeratosis and elongation of rete ridges.<br>3. Upper dermal inflammatory infiltrate. | 1. 30 to 40 mg of prednisolone or its equivalent corticosteroid daily till clinical remission.<br>2. Appropriate antibiotics after culture and sensitivity for a requisite period.<br>3. Wet compresses using 1 in 8000 potassium permanganate.<br>4. Topical application of a corticosteroid antibiotic combination.<br>a. Clobetasol propionate 0.05 percent + gentamicin (Tenovate G)<br>b. Betamethasone dipropionate + gentamicin (Dipgenta) |
| Pompholyx | Eruption of clear, deep seated vesicles resembling sago grains. Accompanying hyperhidrosis. Erythema and inflammation conspicuously absent. Affects palms and sides of the fingers, bilaterally and symmetrically. | Histopathology reveals intraepidermal spongiotic vesiculation and pustulation. | —do— |
| Pustular psoriasis of the palms | Eruption of deep seated pustules and hemorrhagic vesicopustules within areas of erythema and scaling. The pustules dry up leaving behind punctate brown scabs. Affects mid palms, thenar and hypothenar eminences bilaterally and symmetrically. | Histopathology reveals:<br>1. A large intraepidermal, unilocular pustule. Many neutrophils within the pustule.<br>2. Surrounding epidermis shows acanthosis<br>3. Inflammatory infiltrate beneath the pustule.<br>4. Psoriasiform changes conspicuously absent. | 1. Inj Kenacort 40 to 60 mg intramuscular or intralesional every 3 weeks.<br>2. 2 mg per kg per day of etretinate<br>3. 5 to 7.5 mg of methotrexate, 3 doses at 12 hours interval every week<br>4. PUVA therapy. |
| Id eruption | Eruption of small vesicles to large bullae over the palms and sides of finger due to sensitization to a focus of infection. Eruption is sterile. Organism may be isolated from primary focus. | Identification and recovery of causative microorganisms from the primary focus. | Treat the primary focus of infection. |

## TREATMENT

The treatment of hand dermatitis may depend upon its morphological characteristic, the details of which are given in Table 9.1.

## RECOMMENDED READING

1. Epstein E. Hand dermatitis: Practical management and current concepts. *J Am Acad Dermatol* 1984;10:395-424.

10 Chapter

# Lichen Simplex Chronicus

Lichen simplex chronicus is the reaction pattern of the skin which develops at the backdrop of incessant itch that evokes repeated rubbing or scratching. It is common in atopic dermatitis but may also be secondary to other dermatoses. The term lichen simplex chronicus is used when there is no known predisposing skin disorder, whereas if the rubbing is initiated by a pruritic dermatosis, it is termed 'lichenification'. Emotional tension may play an important role in favoring the development of lichenification and ensuring its perpetuation. It is uncommon in childhood and the peak incidence is between 30 and 50 years. However, it may be encountered at any age after adolescence.

## CLINICAL FEATURES

Pruritis is the predominant symptom. It may either be continuous or paroxysmal. It evokes vigorous scratching and rubbing. Initially the skin is red and slightly edematous. However, over a period of time the redness and edema subside and the lesion evolves into a sharply marginated plaque. It is thickened, pigmented, and the normal skin markings are exaggerated over it (Fig. 10.1). The features of acute dermatitis, namely erythema, edema, vesiculation, and oozing are conspicuous by their absence. Surrounding the central plaque is a zone of lichenoid papules and beyond this, an indefinite zone of slight thickening and pigmentation that merges imperceptibly with the surrounding skin. The lesion resembles to the bark of a tree. In most instances, a single area is affected. However, at times, multiple sites may be involved. The sites of predilection are those that are subject to minor irritation and are easily accessible. The occipital and nuchal area of the scalp are the predominant site in women. The plaque may be limited to a small

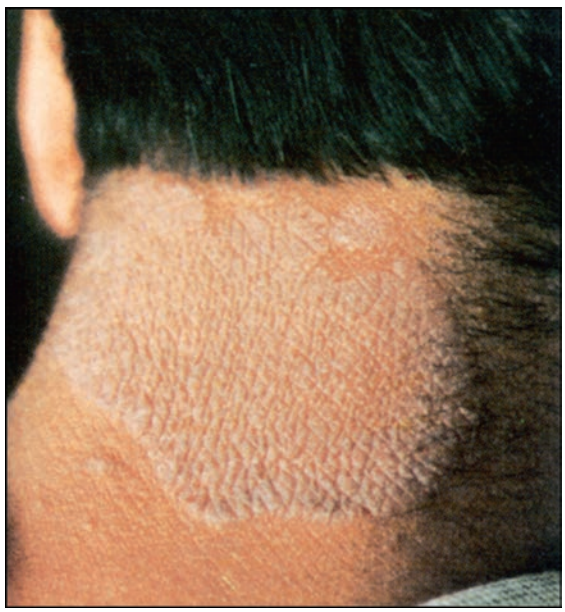


**Figure 10.1:** Pigmentation, thicken, exaggerated skin markings. Incessant itching a hallmark

area around the midline of the nape or may extend to some distance into the scalp. Scaling is often profuse and psoriasiform. Secondary bacterial infection frequently occurs. The retroauricular folds may also be involved. However, scaling crusting, and fissure are quite evident. Other areas of the scalp are less often affected and present as an area of scaling with twisted, broken hair. Ankles and lower leg may also be affected. At these sites the lesions are prone to exhibit a hypertrophic papular response (Fig. 10.2). The extensor surface of the forearms, the upper thighs, and the side of the neck are also frequently involved. The process of lichenification may extend to the vulva, scrotum and perianal region also and may be responsible for pruritus ani and pruritus vulvae.

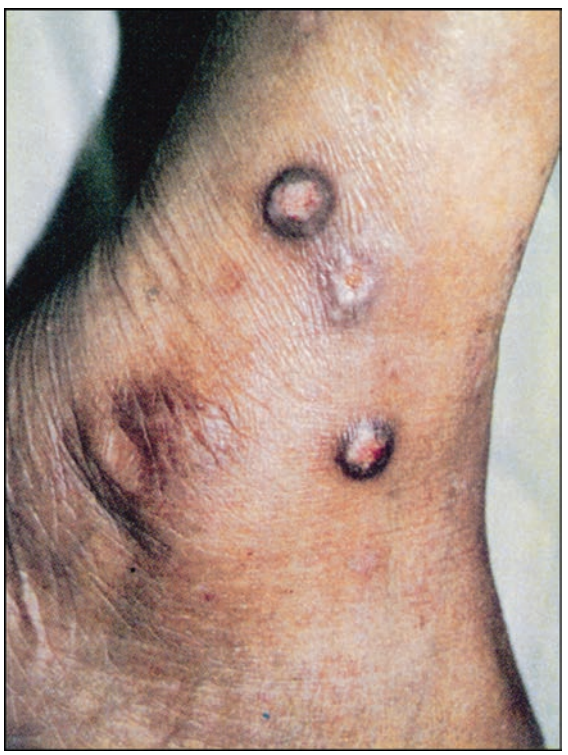


**Figure 10.2:** Prurigo nodularis

Secondary lichenification may complicate various pruritic dermatoses. It develops on the lower legs in the presence of stasis dermatitis, in the flexural folds in atopics. It may also complicate asteatotic eczema, low grade contact dermatitis, and some cases of infection with *Trichophyton rubrum*.

## DIAGNOSIS

The diagnosis of lichen simplex chronicus is clinical. It is based on recognizing the characteristic morphology of the lesion developing at the sites of predilection. It may be supplemented by histopathological examination that reveals the following:

- Marked hyperkeratosis
- Marked acanthosis
- Lengthening of the rete ridges
- Hyperplasia of all components of the epidermis
- Chronic inflammatory infiltrate in the dermis
- Silver impregnation shows proliferation of the Schwann's cells.

An endeavor should be made to detect the primary dermatosis responsible for lichenification. The lesions of lichen simplex chronicus needs to be differentiated from the following:

*Lichen planus:* It is characterized by discrete, polygonal, flat topped, violaceous, greyish white/liac, pruritic papules. The surface is traversed by Wickham's striae. They are distributed over the flexor aspect of the wrist, lumbar region, genitalia, ankles, and anterior aspect of lower legs. Histopathology is characteristic.

*Psoriasis:* It is characterized by erythematoscaly eruptions, single or multiple, disposed primarily on the extensor surfaces of the body. The scales are lamellated and silvary white.

**Table 10.1: Topical and systemic treatment of lichen simplex chronicus**

| *Treatments* | *Status* |
|---|---|
| 1. Topical application of a potent corticosteroids, preferably under occlusion.<br>a. Clobetasol propionate 0.05 percent (Tenovate, Exel)<br>b. Fluocinolone acetonide 0.02 percent (Flucort) | It is the treatment of choice. |
| 2. 0.1 to 0.3 mL of 5 mg/mL of triamcinolone acetonide (Kenacort) intralesional, every week | |
| 3. Oral antihistamines<br>a. 25 mg of promethazine hydrochloride (Phenergan) three times a day.<br>b. 10 mg of hydroxyzine (Atarax) three times a day.<br>c. 25 mg of pheniramine maleate (Avil) three times a day. | It helps to relieve the pruritus. Patients can thus abstain from scratching. |
| 4. Tranquilizers<br>5 mg of diazepam (Calmpose) at bed time | It relieves tension and helps to prevent the compulsive rubbing/scratching. |

Auspitz's sign is positive, evident as pinpoint bleeding on grattage. Histopathology is diagnostic.

*Prurigonodularis:* They develop as persistent, violently pruritic nodules, localized to the extremities, usually in middle aged women. Histopathology is characterized by: (a) Hyperkeratosis, (b) Downward projection of epidermis, so marked that it resembles pseudoepitheliomatous hyperplasia, (c) Dense dermal infiltrate, and d) Schwannomas.

## TREATMENT

The patient should be educated to stop scratching. He must be explained that abstaining from scratching would help the lesion to resolve. However, even moderate rubbing of the skin may be sufficient to perpetuate the changes. Besides, the patient may be administered topical corticosteroids and antihistamines (Table 10.1).

## RECOMMENDED READING

1. Jones RO. Lichen simplex chronicus. *Clin Pediatr Med Surg* 1996;13:47-54.

# 11 Chapter

# Pyodermas

Pyodermas are the infections of the skin and/or its adnexa by pus producing microorganisms. They are fairly common in hot and humid season and account for bulk of dermatology outpatients. They may affect any individual; however, the children are its most common victims. Hot and humid climate, poor hygeine, uncleanliness, circumstances which lower the standard of sanitation and malnutrition predispose to pyoderma.

Pyoderma may manifest as either primary or secondary pyoderma. Primary pyodermas arise in the normal skin, have a characteristic morphology, and are usually caused by a single microorganism. Secondary pyodermas arise over as dermatoses and/or damaged skin as superimposed condition.

Coagulase positive staphylococci (*Staphylococcus aureus*) and betahemolytic *Streptococcus* (*Streptococcus pyogenes*) are responsible for most of the primary as well as secondary pyodermas. However, the already affected skin may also be colonized by gram-negative microorganisms like *Proteus*, *Klebsiella*, *Pseudomonas aeruginosa* and *Escherichia coli*.

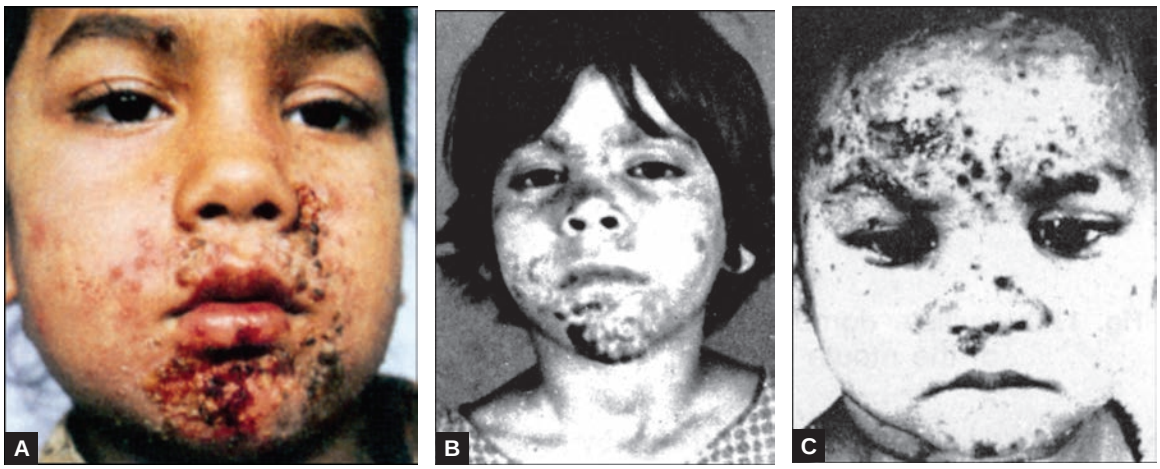
## PRIMARY PYODERMAS

*Impetigo:* It is classified into impetigo contagiosa and impetigo bullosa. Impetigo contagiosa is caused by either *Staphylococcus aureus* or *Streptococcus pyogenes*. Both the microorganisms may be simultaneously isolated from the lesion. It begins as a small, reddish macule which may soon turn into a vesicle. The vesicle has a thin roof that ruptures, leaving a raw, oozing area. The fluid oozing out dries to form a crust, which is thick and honey colored, and has a 'stuck-on' appearance (Figs 11.1A to C). There is a slight erosion under it. The lesion has a predilection for the face and the extremities. Its morphological variants in the form of impetigo circinata, annularis, and follicularis may also be encountered.

Impetigo bullosa is caused by *Staphylococcus aureus* (phage group II type 71). It starts as a vesicle which enlarges to form bulla. The fluid inside the bulla is at first clear, and later turns turbid. The roof of the bulla collapses, collecting the fluid into folds. The fluid then dries to form a thin crust.

*Folliculitis:* It is an infection of the hair follicle that may manifest either as superficial or deep folliculitis.

*Superficial folliculitis:* It is caused most often by coagulase-positive staphylococci (*Staphylococcus aureus*). It starts as a small dome-shaped pustule situated at the mouth of the hair follicle. The pustules rupture, and the pus dries to form small crust. Hair growth is not impaired. Face and the extremities are the sites of predilection (Fig. 11.2).




**Figures 11.1A to C:** Ecthyma—shallow ulcer, after removal of heaped up 'crust'

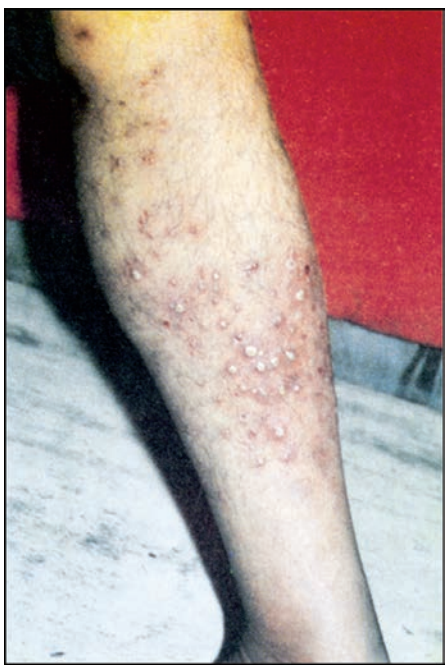


**Figure 11.2:** Multiple dome-shaped papules situated at the mouth of hair follicle(s)

*Deep folliculitis:* The infection extends deeply in and around the hair follicle, the resulting perifolliculitis is resposible for marked inflammatory response. Furuncles, carbuncles, sycosis barbae, stye, and perforating folliculitis of the nose are its morphological variants.

Furuncle or a boil arises in relation to a hair follicle as a deep seated nodule, which is red and painful. It remains tense for a day or two and subsequently softens. A yellowish point forms at the summit of the nodule. It may rupture, with the discharge at the core of necrotic tissue. Furuncles usually arise over hairy areas, exposed to fricion and/or maceration. The buttocks, neck, face and axillae are most often involved by furunculosis (Fig. 11.3).

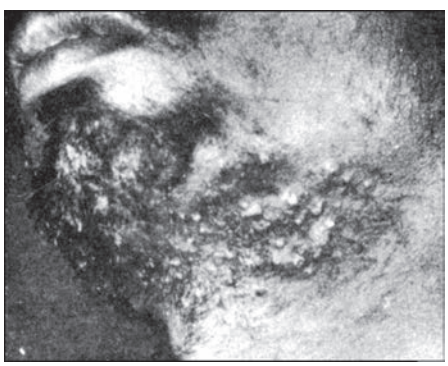


**Figure 11.3:** Furuncle a deep seated nodule in and around the hair follicle

Carbuncle is a deep-necrotizing infection which involves several adjacent, hair follicles. In fact, it may be regarded as an aggregation of furuncles. It drains through a number of sinuses (usually hair follicles) to the surface. Diabetes mellitus predisposes to carbuncles. The patient affected by carbuncle may be toxic and unless properly managed, it may prove fatal.

*Sycosis barbae:* It presents as follicular pustules. The pustules may rupture leading to impetiginization and crust formation. The condition is often persistent and chronic as the individual tends to harbor the pathogenic microoganism (usually *Staphylococcus aureus*) in the nose.

*Ecthyma:* It is initiated by beta-hemolyic streptococci, and begins as a vesicle which arises over an inflamed base. It is followed by formation of dry hard and firmly adherent crust. A shallow ulcer is revealed on removal of the heaped up crust (Fig. 11.4). Healing occurs with scar formation. It affects children and lesions develop on the exposed, trauma prone sites. It is to be differentiated from impetigo in which the crusting is less and there is no ulceration under it.

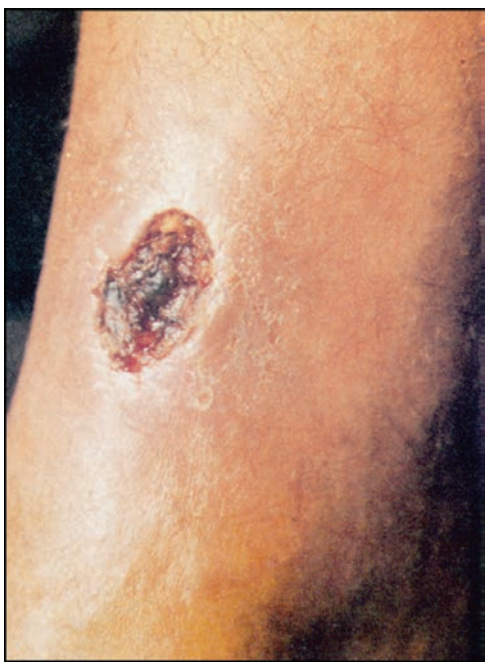


**Figure 11.4:** Ecthyma

*Cellulitis and erysipelas:* Cellulitis is the infection of the subcutaneous tissue, caused by streptococci. The affected area is red, warm and edematous. However, the borders are flat and not sharply circumscribed. Vesicles or bullae, may appear over the area affected by cellulitis. Systemic toxicity may be its accompaniment.

Erysipelas is a type of superficial cellulitis in which there is development of an edematous, brawny, infiltrated, sharply circumscribed plaque that spreads peripherally. The borders are well-circumscribed and distinct. Face and scalp are the favored sites for erysipelas. The hands and genitalia are also frequently involved. The patient may have constitutional symptoms in the form of fever, malaise, and appear toxic.

## SECONDARY PYODERMAS

Infection may complicate any pre-existing cutaneous lesion such as an abrasion, wound, eczematous lesion, ulcer, fungal infection, and scabietic lesions. The morphologic features of the primary lesion may be masked by the superimposed infection.

*Infectious eczematoid dermatitis:* It is a frequently encountered condition. The patient has a primary lesion which is productive of infectious exudate. This may be in the form of a ruptured furuncle, an ulcer or an infected wound. The exudate seeps over the surrounding skin, which becomes sensitized to the exudate and its components. This is followed by the appearance of erythema, edema, and vesicle along the path of flow of discharged exudate. Oozing and crusting appear. Autoinoculation is its hallmark.

## DIAGNOSIS

Laboratory investigations are of limited value. Hemogram may reveal polymorphonuclear leukocytosis. Urine examination is essential in children as they may develop poststreptococcal glomerulonephritis. Culture sensitivity is required only if the patient fails to respond to an apparently adequate treatment.

## TREATMENT

Cleansing and degerming of the skin is of paramount importance. Removal of the bacteria laden crust and debris is essential. Saline or potassium permanganate compresses are effective. Topical therapy is adequate for milder infections. Various topical antibiotics which may be used are as follows:

- Hydroxyquinolines like iodochlorohydroxyquin which exerts broad spectrum antibacterial action
- Neomycin in combination with bacitracin and polymyxin B. Bacitracin is effective against gram-positive organism and polymyxin B against gram-negative organism
- Gentamicin
- Sisomicin (Ensamycin)
- Framycetin (Soframycin)
- Fusidic acid (Fucidin leo skin cream)
- Nitrofurazone (Furacin).

*Systemic therapy:* It is required when:

- There are systemic signs
- The infection is widespread
- Epidemics of pyoderma
- The patients fail to respond to topical therapy
- The children are managed better with systemic therapy.

Staphylococci are usually resistant to penicillin and tetracycline. Betalactamase resistant penicillins, macrolide group of antibiotics,

**Table 11.1: Treatment of pyodermas**

| *Clinical variant* | *Treatments* |
|---|---|
| Impetigo contagiosa and bullosa | 8 to 10 lac units of procaine penicillin, intramuscular, after test dose, daily for a requisite period, or<br>250 to 500 mg of ampicillin (Campicillin) four times a day for a requisite period, or<br>250 to 500 mg of cloxacillin (Klox) four times a day for a requisite period, or<br>250 to 500 mg of erythromycin (Erythrocin, Thromycin) four times a day for a requisite period, or<br>250 to 500 mg of cephalexin (Phexin, Sporidex, Ceff) four times a day for a requisite period. |
| Superficial folliculitis | —do— |
| Furuncles | —do— |
| Ecthyma | —do— |
| Periporitis | —do— |
| carbuncle | 500 mg of cloxacillin, intramuscular or intravenous, four times a day for a few days followed by 500 mg of cloxacillin (Klox) orally four times a day for a requisite period.<br>Diabetes should be monitored if present. |
| Sycosis barbae | 250 to 500 mg of cloxacillin (Klox) four times a day till clinical improvement, followed by 1.2 to 2.4 mega units of benzathine penicillin (Penidure LA) intramuscular, after test dose, once a month. |
| Infectious eczemetoid dermatitis (IED) | 250 to 500 mg of cloxacillin (Klox) four times a day for a requisite period and 30 to 40 mg of prednisolone (Wysolone) every day. |
| Erysipelas and cellulitis | Admit the patient.<br>1 to 2 million units of crystalline penicillin G, intravenous, after test dose, every four hours, for 2 to 3 days followed by 8 to 10 lacs of procaine penicillin, intramuscular, daily for a requisite period. |

cephalosporins and fluoroquinolones are effective against staphylococci. Beta-hemolytic streptococci are sensitive to penicillin (Table 11.1).

## RECOMMENDED READING

1. Feingold DS. Bacterial infections of the skin. *J Am Acad Dermatol* 1989;20:469-475.
2. Sadick NS. Current aspects of bacterial infections of the skin. *Dermatol Clin* 1997;15:341-349.

# 12 Chapter Scabies and Pediculosis

## SCABIES

Scabies, a common cause of itching, is produced by infestation with the mite *Sarcoptes scabiei var hominis*. Poor hygeinic conditions and overcrowding, permitting close body contact, favor the transmission of the disease.

*Acarus scabiei* has four pairs of legs. The female measures 400 μ by 300 μ in size (Fig. 12.1). The male is appreciably smaller. *Acarus scabiei* undergoes its life cycle on the skin surface. The male mite fertilizes the female and dies. The adult female, after impregnation, burrows into the skin and forms a tunnel in the horny layer (stratum corneum). It burrows at the rate of 1 to 5 mm per day. Two days after fertilization, it starts laying eggs along her course in the burrow. Two to three eggs are laid each day. A female *Acarus* lays a total of 10 to 25 eggs during her lifespan of 30 days and then dies at the end of the burrow. The egg hatches in 3 to 4 days producing a larva that moves to the skin surface. It then moults through various stages of octopod nymph into an adult mite in 10 to 14 days.

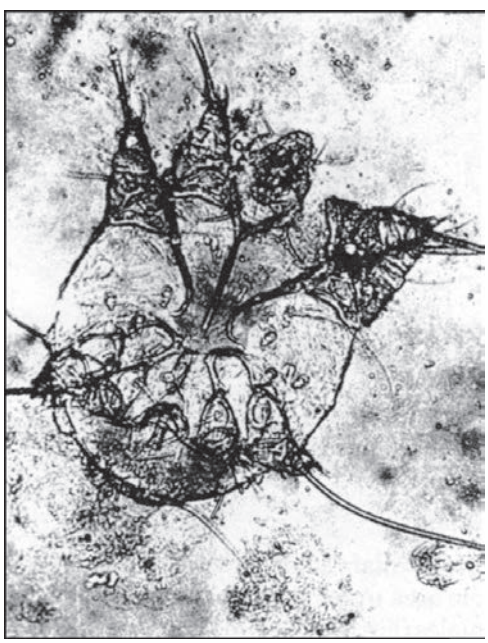
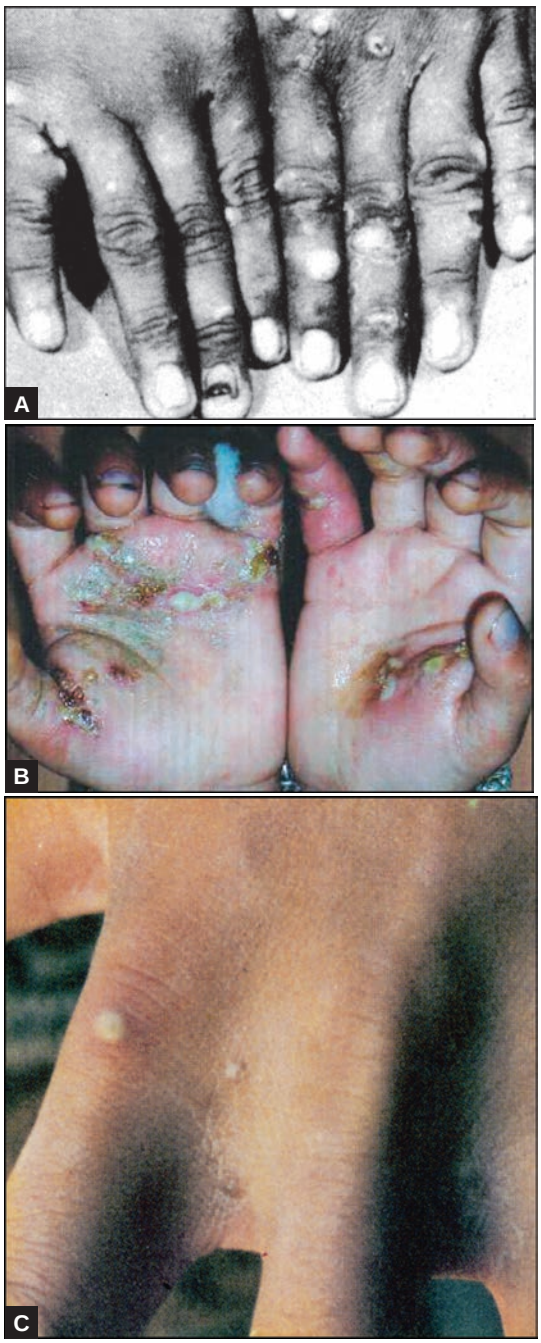


**Figure 12.1:** Sarcoptes scabiei

## CLINICAL FEATURES

In the first attack of scabies, the symptoms do not occur for three to four weeks, till the patient is sensitized to the products of the mite. In subsequent attacks the symptoms may develop within few hours of infestation.

The patient presents with nocturnal itching, most marked when the person is warm in bed. It is associated with burrows, papules, papulovesicles, vesicles or pustules (Figs 12.2A to C). Burrows, though considered pathognomic of scabies, are not frequently encountered in Indian patients. This is because they present late for treatment and by this time the burrows have been excoriated and the secondary bacterial




**Figures 12.2A to C:** Scabies depicting papules and pustules affecting the interdigital spaces and the wrist of the hand

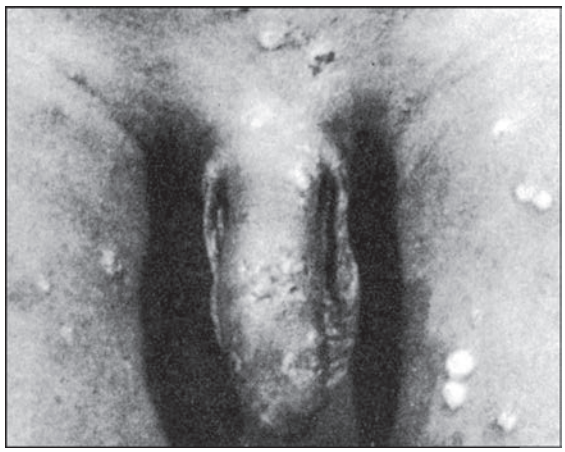


**Figure 12.3:** Scabies: Papular, pustular lesions affecting the genitals

infection has often supervened, resulting in impetiginization. The distribution of lesions is characteristic and the sites of predilection are the interdigital spaces of the fingers, palms, wrists, elbows, anterior axillary folds, lower abdomen, buttocks, nipple area in females, and external genitalia in the males (Fig. 12.3). In infants and small children the scalp, face, palms, and the soles may also be involved. Very often, more than one member of the family may be affected.

## Clinical Variants

A number of clinical variants may be encountered such as the following.

## Classical Scabies (vide supra)

*Norwegian scabies (crusted scabies):* It is encountered in mentally retarded, physically debilitated or immunosuppressed patients. It is characterized by erythematous, scaly eruptions on the hands and feet, harbo ring myriads of mites. There may be associated dystrophy of the nails. It is highly contagious and even a casual contact may transmit the disease.

*Scabies in clean patients:* One or two sites of predilection are affected. Burrows are difficult to find. The mites are often removed by frequent bathing.

*Scabies in infants and children:* It is characterized by atypical sites of affliction namely the head, neck, palms, and soles. The itching is severe resulting in excoriations. Secondary bacterial infection results in pustules, impetigo, ecthyma, and crusting.

*Scabies in the elderly:* It is characterized by severe itching which is frequently attributed to dry skin, anxiety or passed off as senile pruritus. Elderly patients, when bed ridden for a prolonged period, may have involvement of the back.

*Nodular scabies:* Nodules develop as a part of hypersensitivity reaction. They are reddish brown and pruritic and are distributed on covered parts especially male genitalia, groins, and axillae.

*Scabies incognito:* Systemic and topical corticosteroids may mask the signs and symptoms of scabies. However, the infestation persists and may show atypical distribution and unusual extent of involvement.

*Animal scabies:* Close contact with the infested animals is responsible for transmission of scabies from animals to man. The eruption is less severe and the characteristic burrows are not formed.

Various complications may ensue in a case of untreated scabies, such as the following:

- Secondary bacterial infection
- Urticaria
- 'Id' lesions
- Acute poststreptococcal glomerulonephritis in children due to secondary infection with streptococci.

## DIAGNOSIS

It is based on the following:

- History of nocturnal itching
- More than one member of the family affected by it
- The characteristic lesions distributed at the sites of predilection (*vide supra*)
- Recovery of the mite, eggs or scybala from the burrow, if identified.

## TREATMENT

The treatment should be formed around as detailed in Table 12.1.

## PEDICULOSIS

Pediculosis results from infestation with the lice, of which there are two types: (1) *Pediculus humanus* with its two varieties: *Pediculus humanus corporis* and *Pediculus humanus capitis*, (Fig. 12.4) and (2) Phthirus pubis. These infest the body, scalp, and the pubic area, respectively.

The gravid female louse lays a few eggs daily. These eggs are called nits. They are small, oval, greyish white, and 0.5 mm in length (Fig. 12.5). They are firmly glued to the hairs or fibers of the clothing. They moult thrice in a period of 2 to 3 weeks, to attain maturity. Its entire life cycle is of 1 month.

*Pediculosis capitis:* It is the infestation of scalp by *P. capitis*. It localizes in the scalp, favoring the occiput and temporal areas. The adult louse is rarely observed. However, the nits along the hair shafts are easily seen. They are laid close to the scalp surface, at the bottom of the hair. They are carried higher along with the growth of the hair. They are firmly attached to the hair by chitinous sheath and cannot be moved along the shaft.

Itching is the usual presenting complaint. Scratching causes trauma with resultant oozing. Secondary infection usually supervenes resulting in pustulation and abscess formation. Occipital and cervical lymph nodes are frequently enlarged. A recurrent pyoderma

**Table 12.1: Scabies treatment**

| *Scabicidal agents* | *Mode of applications* | *Number of applications* | *Other measures* |
|---|---|---|---|
| 1. 25% Benzyl benzoate for adults 12.5% for children (Ascabiol) | Apply to the whole of skin surface below the neck after a hot scrub bath | 3 applications at 12 hours intervals followed by a bath | Clothes, bed clothes may be laundered. New washed set of clothes should be worn after treatment |
| 2. 1% Gamma benzene hexachloride (Gab, Scarab) | -do- | Single application. Bath after 8 hours. | -do- Avoid application on face and in children as it is an irritant |
| 3. 0.5% Malathion solution | -do- | -do- | -do- |
| 4. 10% Crotamiton | May be applied on whole body including the face | Two applications at 12 hours interval followed by a bath | Usually preferred in infants and small children |
| 5. 10% Precipitate sulfur in pertrolatum | Rarely used | — | Irritant and it stains the clothes |
| 6. Monosulfiram (Tetmesol soap) | To be used as soap prior to applying other scabicidal agents | — | — |
| 7. Topical thiabendazole | — | — | — |

**Figure 12.4:** Pediculosa corporis

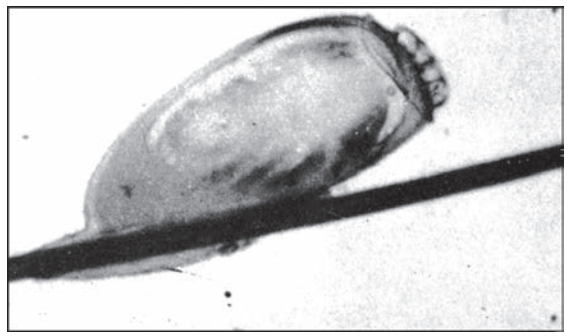


**Figure 12.5:** Nits

of scalp should always arouse a suspicion of pediculosis.

*Pediculosis corporis:* The body louse inhabits the seams of the clothings. The nits remain firmly attached to the fibers and hatch on getting the warmth of the body.

The lice bites the skin to suck blood. During biting, a mild toxin is released which is responsible for producing a purpuric spot and evokes strong itching. This results in excoriations, which are the

**Table 12.2: Treatment of pediculosis**

| *Site of infestations* | *Pediculocidal agents* | *Modes of applications* |
|---|---|---|
| 1. Pediculosis capitis | 1. 1% Gammabenzene hexachloride (Gab)<br>2. 25% Benzyl benzoate (Ascabiol)<br>3. 0.5% malathion | Three applications on consecutive days followed by tying a cloth on the scalp. Shampoo after 7 days. |
| 2. Pediculosis corporis | | Laundering and ironing of clothes, especially the seams. |
| 3. Pediculosis pubis | -do- | Single application is usually sufficient. If necessary, repeat after 3 days. |

hallmark of the disease. They are distributed over the shoulders, trunk, and buttocks. Other lesions which may be encountered are wheals, papules, and exanthematous rashes. Secondary bacterial infection supervenes in neglected cases.

Vagabond's disease results from prolonged neglect of pediculosis and is characterized by dry, scaly, darkly pigmented skin associated with excoriation, eczematization, bacterial infections, and accumulation of crust.

*Pediculosis pubis:* This is the infestation of pubic and perianal hairs by *Phthirus pubis*. It is usually transmitted by sexual contact. The adult louse clings to the hairs with its mouth parts buried in the skin. The adult female lays eggs and nits remain firmly adhered to the pubic hair. The patient complains of itching, which inevitably results in scratching. The hairs may be matted in the thick crust of dried pus, serum, and blood. The patient may also notice tiny blood spots on the underwear. Occassionally, bluish macules, 0.5 cm in diameter may be noticed on the inner aspect of thighs. These are maculae caerulae. They result due to the altered blood pigments of the infested person.

## DIAGNOSIS

The diagnosis is usually suspected on clinical examination and finding the nits or the adult louse on the hair or the fibers in the seams of the clothing. If necessary, the hair or the fiber may be observed under the low power of the microscope.

## TREATMENT

Treatment should be formed around as shown in Table 12.2.

## RECOMMENDED READING

1. Mellanby K. *Scabies*, 2nd edition. Hampton, England: E.W. Classey 1972.
2. Orkin M. Scabies and Pediculosis. Major Probl Clin 1977;19:209-221.
3. Sehgal VN, Rao TL, Rege VL *et al*. Scabies: Study of incidence and treatment methods. *Int J Dermatol* 1972;11:106-111.

# 13 Chapter Tinea (Dermatomycosis)

Tinea/ringworm infection is caused by a distinct class of fungi, the dermatophytes. They thrive in the keratin layer of the epidermis, nails, and hair. However, they do not invade the living epidermis. The serum fungal inhibitory factors in the extravascular space prevent the penetration of the fungi in the living tissue. Several factors such as poor nutrition, unhygeinic conditions, hot and humid climate, vocation promoting sweating and maceration, diabetes mellitus, debilitating diseases, administration of corticosteroids and immunosuppressive agents, atopy, and close and intimate contact with infected persons, animals, and fomites predispose to ringworm infection.

Dermatophytoses are caused by species of the genera *Trichophyton, Microsporum,* and *Epidermophyton*. The common species encountered in the ringworm infection are as follows:

- *Microsporum audouni, M. canis*
- *Trichophyton rubrum, T. mentagrophytes, T. violaceum, T. tonsurans, T. verrucosum,* and *T. schoenleinii*
- *Epidermophyton floccosum*

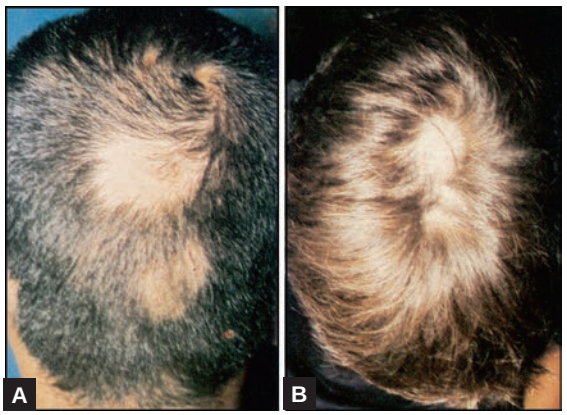
The ringworm infection are classified according to the anatomic area of involvement and thus the fungal infection encountered are tinea capitis, tinea barbae, tinea faciei, tinea corporis, tinea cruris, tinea mannum, tinea pedis, tinea unguium (onychomycosis), and favus.

## CLINICAL FEATURES

### Tinea Capitis

It is a well-known, superficial fungal infection of the scalp hair with varied clinical manifestations. Children up to puberty are susceptible. The infection is transmitted by direct contact and through fomites such as combs, hairbrushes, barbers instruments, and hats. A break in cutaneous barrier is essential to inoculate the fungus. Tinea capitis may present as the following:

- Grey patch, characterized by patch(s) of partial alopecia. The lesions are circular in shape. The hairs are broken at varying lengths and are dull grey in color, due to coating of the surface by arthrospores. Fine scaling and absence of inflammation are characteristic features (Fig. 13.1A). The lesions are usually caused by *T. violaceum* and *T. rubrum*
- Black dot is a distinct entity recognized by the formation of relatively noninflammatory alopecia. It is studded with black dots, as the hair breaks flush to the scalp. Scaling is minimal or absent (Fig. 13.1B). *T. violaceum* is responsible for the black dot variety
- Seborrheic variety is characterized by diffuse erythema, scaling, and mild loss of hair mimicking seborrheic dermatitis. It is caused by *T. violaceum* and *T. rubrum*




**Figures 13.1A and B:** Tinea capitis: Noninflammatory lesion, depicting localize loss of hair, mycelia/ spores were demonstrating in KOH preparation. (A) Grey path, (B) Black path

- Alopecia areata like is characterized by asymptomatic, noninflammatory, nonscarring patches of complete hair loss
- Kerion manifesting as painful, acute inflammatory, boggy, well-circumscribed, bald swelling studded with folliculopustules. It may be caused by *T. mentagrophytes, T. verrucosum, T. violaceum*.

## Tinea Barbae

It is the ringworm infection of the beard and moustache areas of the face with invasion of the coarse hairs. It starts as an itchy, red, follicular papule. The lesion gradually extends to form erythematous, scaly lesion enclosing lusterless hair stumps, broken off close to the skin surface. The periphery is studded with papulovesicles and pustules. There may be numerous patches. The intervening area is apparently normal. Tinea barbae may also present as follicular pustules. The hairs within the affected pustules are loose and easily removed with the forceps without causing pain. Occasionally, it may present as kerion with soft nodular, inflammatory infiltration of the bearded area. *T. mentagrophytes* and *T. verrucosum* are the responsible dermatophytes.

## Tinea Faciei

It is the infection of the glabrous skin of the face with the dermatophyte. It presents as persistent eruption of red macules, papules, and plaques with arcuate border. Itching, burning, and exacerbation after sun exposure are the common complaints. The nondescript presentation of tinea faciei is further modified by injudicious application of corticosteroids. It is caused by *T. rubrum* and *T. mentagrophytes*.

## Tinea Corporis

It is the ringworm infection of the glabrous skin. The fungus invades and proliferates in the stratum corneum and it includes lesions of the trunk and limbs excluding specialized sites such as the scalp, feet, and groins. It may manifest as the following:

*Classical ringworm:* It starts as an erythematous, itchy papule which progresses to form a circinate lesion. It is studded at the periphery with papules and/or papulovesicles. The lesions are scaly, showing clear or apparently normal looking centers (Fig. 13.2). Such lesions are caused by *T. rubrum* and *M. canis*.

*Eczematous annular ringworm:* It presents as circinate, erythematous, scaly, mildly infiltrated plaques. Central clearing, however, is lacking.

*Crusted type:* Scutula and crusted masses similar to those occurring in favus, develop on the glabrous skin.

*Herpetiform type:* It is the inflammatory vesicular type of ringworm caused by zoophilic species. The primary lesion is a plaque of grouped vesicles, which rupture to leave a red erosion. This is subsequently covered by crust.

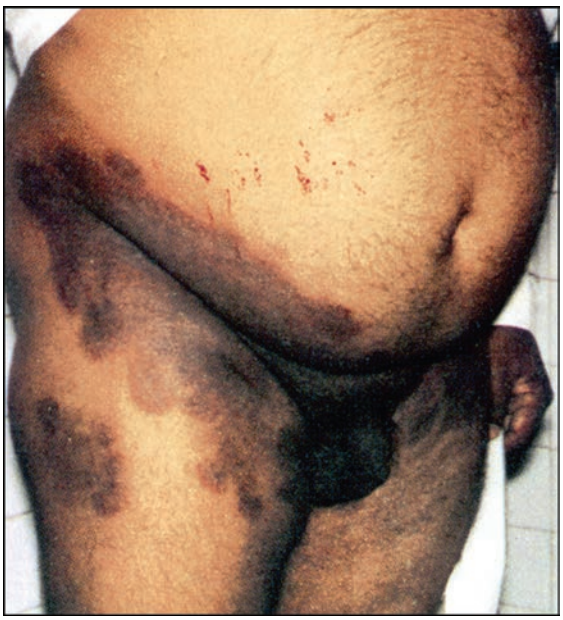


**Figure 13.2:** Tinea corporis: Classical ringworm

New vesicles develop at the periphery. Hyphae are abundant in the vesicular fluid.

*Plaque type:* Chronic extension and lack of spontaneous clearing in the center leads to the formation of large erythematous, scaly plaques. They enlarge eccentrically producing annular pattern. Diabetes mellitus, leukemia, and topical application of corticosteroids predispose to the formation of plaques. *T. rubrum* is responsible for such lesions.

*Tinea profunda:* It manifests as inflamed, elevated, sharply circumscribed, boggy tumor with bright red, granulating surface studded with pustules. It may undergo suppuration and become fluctuant. The lesion may undergo spontaneous healing with scarring. It is caused by zoophilic fungi. *T. verrucosum* and *T. mentagrophytes* are often responsible for it.

*Majocchi's granuloma:* It is granulomatous folliculitis associated with perifolliculitis. It presents as plaque studded with nodules. The nodules are slightly raised and often less than one cm in diameter. It is encountered in women who shave their legs. The primary infection is mycotic folliculitis over the lower leg. On shaving, a fragment of infected hair along with the fungal elements is driven into the corium. This initiates the foreign body reaction resulting in the formation of granuloma. *T. rubrum* is its etiologic agent.

### Tinea Imbricata

This distinct variety of ringworm infection is encountered in tropical countries and is caused by *T. concentricum*, an anthrophilic dermatophyte. The infection begins as an annular plaque with a collarette of scales. The lesion shows central clearing. However, within this area of central clearing a second wave of scaling rises. This process is repeated to produce numerous concentric rings. Confluence of separate lesions may produce bizzare, polycyclic patterns. Pruritus is intense and may induce lichenification.

### Tinea Pedis

Ringworm of the feet may present in either of the following forms:

- Hyperkeratotic, dry squamous inflammation
- Intertriginous inflammation
- Vesicular and bullous eruption simulating pompholyx.

The squamous tinea pedis is characterized by chronic noninflammatory, diffuse, fine branny scales covering the entire plantar surface and extending partially over the sides of the foot in a 'moccasin distribution'. The scale is adherent and silvery white. It is most marked in the skin furrows. There may be associated intertriginous involvement of toes. Changes in toenails may subsequently develop slowly with thickening

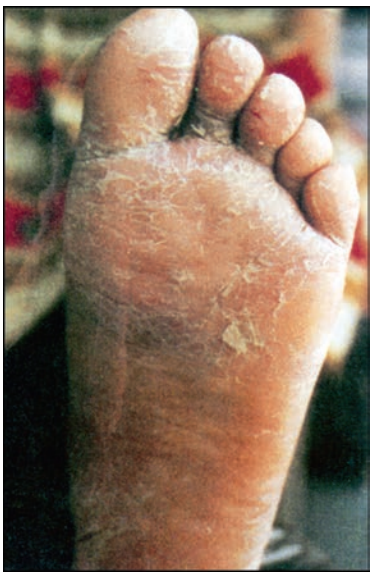


**Figure 13.3:** Tinea pedis: Characteristic maceration, scaling/peeling

and curling of the distal border. *T. rubrum* is responsible for the squamous ringworm of the feet.

The intertriginous ringworm usually develops in the interspace between 3rd and 4th and 4th and 5th toes, due to the small intertriginous space which predisposes to occlusion, moisture retention, and maceration. It develop as maceration, sogginess, scaling, and pruritus (Fig. 13.3). Hyperhidrosis and warm weather predispose to the intertriginous infection. It is caused by *T. mentagrophytes, T. rubrum,* and *E. floccosum*. It requires to be differentiated from bacterial and monilial intertrigo.

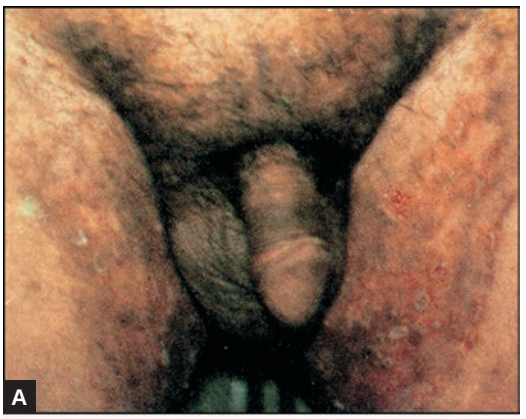
The vesicular ringworm of the feet begins as deep seated vesicles of variable size and number. These may fuse to form bullae which contain yellowish gelatinous fluid. The deep seated vesicles in the areas of thick stratum corneum may appear papular. Erythema is conspicuous by its absence. The clinical picture, thus, may simulate pompholyx. The vesicles rupture to leave behind erythematous erosions or may resolve with desquamation of the skin. Fungi are easily demonstrated in the vesicular fluid. *T. mentagrophytes* is the fungus frequently incriminated. However, *T. rubrum* and *E. flocossum* may also be recovered. Besides pompholyx, it needs to be differentiated from dermatophytid which is a sensitization reaction to fungal infection present elsewhere. There is often a primary focus of fungal infection elsewhere in the body and the fungi is demonstrable from it. The dermatophytid occurs as a sensitization to this and fungi are conspicuous by their absence in these lesions. The trichophyton reaction is positive and the Id' reaction subsides when primary focus heals.

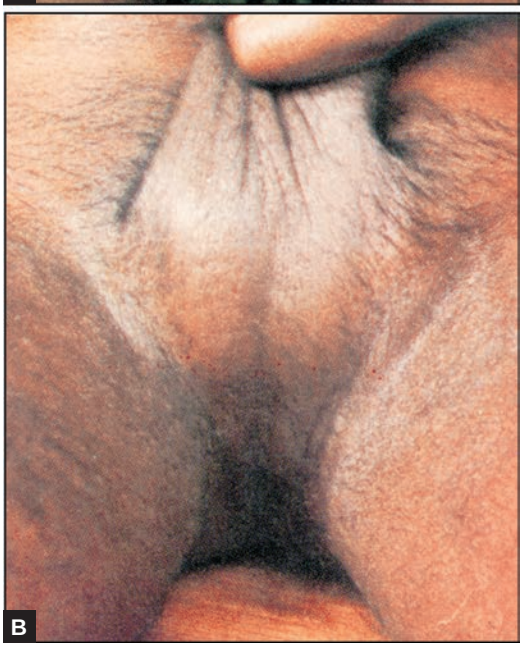
### Tinea Mannum

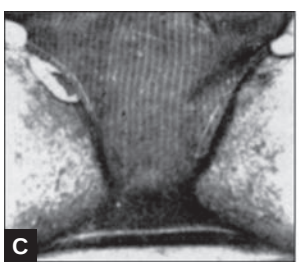
It is the superficial fungal infection of the hands. The morphology of the lesions is similar to tinea pedis.

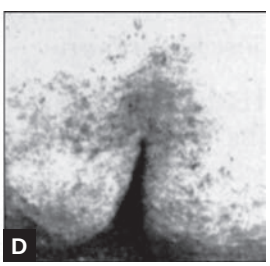
### Tinea Cruris

It is the intertriginous ringworm infection localized to the groins, perineum, and perianal region. It is frequently encountered in obese men during the summer time. It is a common disorder in the tropics and subtropics. Heat, friction, and maceration predispose to it. The lesions affect the groin and crural folds symmetrically and develop as erythematous sharply marginated plaques of semilunar shape (Figs 13.4A to D). The scales covering the plaque are moist due to imbibement of the sweat. The periphery may be studded with papulovesicles and vesicles. The inflammed intertriginous areas rub against each other and induce itching, burning, and discomfort. *Epidermophyton floccosum* and species of *Trichophyton* are responsible for it.




**Figures 13.4A to D:** Tinea cruris: Well-demarcated macerates lesions showing extension from crural area bilateral/asymmetrical, associated with intense itching

## Tinea Unguium (Onychomycosis)

It is the ringworm infection of the nails. It is recognized as the following:

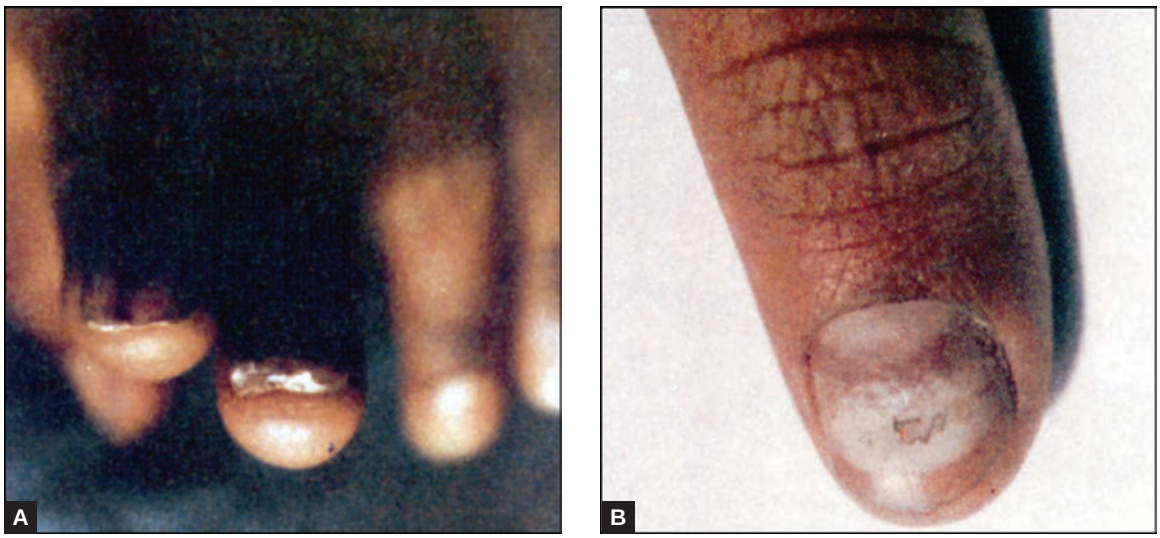
*Distal subungual onychomycosis:* The fungus invades the nail from the distal lateral nail groove on the free margin of the nail. It induces the nail bed to produce soft keratin and proliferates in it. Initially the nail becomes discolored and then thickened, distorted, and crumbly and is lifted from the nail bed due to accumulation of subungual keratin and debris (Figs 13.5A and B). It is brittle and friable. The patient is concerned, not only because the nail is cosmetically embarrassing but also because it catches and pulls on the clothing. *T. rubrum* is the usual causative agent.

*White superficial type:* It is characterized by the primary involvement of the surface of the nail plate which displays small superficial white patches. *T. mentagrophytes* and species of *Acremonium, Cephalosporium*, *Aspergillus*, and *Fusarium* are recovered from these nails.

*Proximal subungual onychomycosis:* It is characterized by the invasion of the nail plate from the proximal nail fold. A white area appears from beneath the proximal nail fold, extends distally and eventually covers the whole nail. *T. rubrum* and *E. floccosum* are responsible for it.

*Total dystrophic type:* It may result from any of the previously mentioned forms. There is severe destruction of the nail leaving only small remnants of keratinous material.

*Favus:* It is a severe type of chronic ringworm infection of the scalp localized to places with cold climate. It is characterized by the formation of a dense mass of mycelium and arthrospores which form a cup-shaped crust, surrounding the hair, the 'scutulum'. This type of infection results in permanent alopecia. *T. schoenleinii* is responsible for it.




**Figures 13.5A and B:** (A) Onychomycosis (tinea unguium): Initial lesion at the distal margin of nail plate, (B) White superficial onychomycosis

## DIAGNOSIS

The diagnosis of superficial mycoses is clinical. It may be supplemented by scraping to demonstrate the fungus and culture. Scraping is an office procedure. About 2 to 3 drops of 10 percent KOH are taken on a clean glass slide. With the help of a blunt knife, the surface and the border of the lesion are scraped. The scrapings are transferred to the slide. It is then covered with the cover slip and allowed to stand for about 10 to 15 minutes, the time required for the keratin to dissolve. The slide may be warmed to hasten the dissolution of the keratin. However, care should be taken to avoid overheating and drying of KOH. It is then viewed under the microscope and scanned for the mycelia and spores. The fungus may also be cultured on Sabouraud's agar medium. This may be required not only to confirm the diagnosis but also to identify the species of the causative fungus.

## TREATMENT

Superficial dermatophyte infections are treated with topical and/or systemic antifungals (Table 13.1). Topical antifungals alone may suffice for the treatment of localized ringworm. Any of the topical antifungal preparations from the following group mentioned may be selected, namely:

- Imidazole derivatives—miconazole, clotrimazole, econazole, ketoconazole
- Triazole—terconazole, itraconazole, fluconazole (Tables 13.2 and 13.3)
- Pyridone-ethanolamine salt—ciclopirox olamine
- Trichlorophenol—haloprogin
- Allylamine derivatives—terbinafine and naftifine.

Widespread, extensive lesions may require griseofulvin in addition to topical antifungal. Griseofulvin is active against *Trichophyton, Microsporum*, and *Epidermophyton* species. It binds to intracellular microtubles inhibiting

**Table 13.1: Treatment of dermatomycosis**

| *Fungal infections* | *Treatments* | *Supportive measures* |
|---|---|---|
| 1. Tinea capitis | 10 mg per kg of ultra-microsize griseofulvin daily in two divided doses, preferably with milk or fatty meal for 6 weeks. An average sized adult requires 500 mg of ultramicrosized griseofulvin (Idifulvin, Demonorm). | 2.5 percent selenium sulfide shampoo for scalp wash 3 to 4 times a week<br>5 mg/mL of triamcinolone acetonide (Kenacort) intralesional once a week or 1 mg/kg of prednisolone daily hastens the cure of kerion. |
| 2. Tinea barbae | Griseofulvin, administered as above for 3 to 4 week. | Topical application of any one of the following:<br>1. Clotrimazole 1 percent W/V solution (Surfaz, Canesten-lotion)<br>2. Tolnaftate 10 mg/mL solution (Tinaderm)<br>3. Miconazole 2 percent lotion (Zole) |
| 3. Tinea corporis | Griseofulvin, administered as above, for a requisite period, usually 4 to 6 weeks and/or topical antifungals. | 1. Miconazole 2 percent gel (Daktarin)<br>2. Miconazole 2 percent ointment (Zole)<br>3. Miconazole 2 percent cream (Micogel)<br>4. Econazole nitrate 10 percent W/W + Cincochane HCl 1.1 percent (Ecoderm)<br>5. Clotrimazole 1 percent, 10 mg per gm (Canesten, Imidil)<br>6. Ciclopirox olamine 10 mg per g (Laprox, Batrafen)<br>7. Tolnaftate 10 mg per mL solution or cream (Tinaderm) |
| 4. Tinea pedis: | | |
| • Intertriginous | Ultramicrosize griseofulvin, administered as above, for a requisite period. | 1. Rest and separation of the toes with cotton or gauze pads<br>2. Dilute acetic acid soak, 2 to 4 percent for 20 min, thrice a day<br>3. Topical antifungal lotion as above<br>4. Topical application of Castellani's paint as an alternative to topical antifungal |
| • Vesicular | —do— | 1. Evacuate the contents of the vesicle by pricking with sterile needle<br>2. Treat as for intertriginous infection |
| • Dry squamous | —do— | Topical application of antifungal creams as above. |
| 5. Tinea mannum | Same as tinea pedis | Same as tinea pedis |
| 6. Tinea cruris | Griseofulvin, for 2 to 4 weeks | Topical application of antifungal creams |
| 7. Tinea unguium | Ultramicrosize griseofulvin, administered as above for 6 to 12 months or 200 mg of ketoconazole once a day for a requisite period. | 1. Surgical avulsion of the affected nail followed by curretting of nail bed and lateral folds to remove debris and topical application of antifungal agents.<br>2. Chemical avulsion of the nail by topical application of 40 percent urea under occlusion. |

mitosis, which accounts for its fungistatic effect. It also causes stunting and curling of hyphae growing *in vitro* and was initially called 'the curling factor.' It enters the epidermis by diffusion from extracellular fluid and from sweat and reaches higher concentration in stratum corneum than serum. Gastrointestinal absorption of griseofulvin is variable and incomplete but is enhanced by taking the drug with a fatty meal. Microsize griseofulvin is produced by a special process that fractures the particles into minute crystals of irregular shape that offer a

**Table 13.2: Fluconazole: dosage schedule**

| *Indications* | *Initial dose (Dose on day 1)* | *Subsequent daily dose* | *Duration of therapy* |
|---|---|---|---|
| Candidal balanoposthitis | 150 mg | | Single oral dose |
| Vaginal candidiasis | 150 mg | | Single oral dose |
| Tinea corporis | | | |
| Tinea cruris | | | |
| Tinea pedis | | 150 mg | |
| | | Once-a-week | Up to 4 weeks |
| Cutaneous candidiasis | | 150 mg | |
| | | Once-a-week | Up to 4 weeks |
| Onychomycosis | | 150 mg | |
| | | Once-a-week | Upto 6-12 months |
| Tinea versicolor (Pityriasis versicolor) | 400 mg | | Single oral dose |
| Systemic candidasis (Candidiama, disseminated candidiasis) | 400 mg | 200 mg OD | Minimum of 3 weeks and for at least 2 weeks after the symptoms have resolved |
| Urinary tract candidiasis | | 50 mg OD | Minimum 30 days |
| Cryptococcal meningitis | 400 mg | 200 to 400 mg OD | For initial therapy |
| Maintenance therapy | | 200 mg OD | For 10-12 weeks after the CSF is sterile |
| Immunocompromized patients at risk of fungal infections | | 50 to 100 mg OD | |

**Table 13.3: Itraconazole: Dosage**

| *Indications* | *Dose* | *Duration* |
|---|---|---|
| Fungal keratitis | 200 mg. o.d. | 21 days |
| Onychomycosis | 200 mg, o.d. | 3 months |
| *Alternatively* | | |
| Onychomycosis (pulse therapy) | 200 mg, b.i.d. | 1 week per month for 3 months |
| Pityriasis versicolor | 200 mg, o.d. | 5-7 days |
| Dermatomycosis | 100 mg, o.d. | 15 days |
| Highly keratinized regions as in plantar tinea pedis and palmar tinea manus require an additional treatment of 15 days at 100 mg daily. | | |
| Oral candidiasis | 100 mg, o.d. | 15 days |
| In some immunocompromized patients, e.g., neutropenic, AIDS or organ transplant patients, the oral bioavailability of itraconazole may be decreased. Therefore, the doses may need doubling. | | |
| Fungal keratitis | 200 mg, o.d. | 21 days |
| Onychomycosis | 200 mg, o.d. | 3 months |

* For patients who have responded to Itaspor therapy earlier.

greater surface for increased gastrointestinal absorption. Further processing to achieve ultramicrosize particles doubles the bioavailability. It is oxidized by hepatic microsomal enzymes and excreted in urine. The usual daily adult dosage is 500 mg of ultramicrosize form. Mild side effects include anorexia, nausea, and diarrhea. It also causes urticaria and exanthematous eruptions. Photosensitivity may occur. Both discoid and systemic lupus erythematosus may be produced by griseofulvin. It may precipitate acute intermittent porphyria.

Ketoconazole is recommended only for the recurring and recalcitrant patients of ringworm infection. Furthermore, it is indicated if the species of dermatophyte is resistant to griseofulvin. Its spectrum includes the dermatophytes, *Pityrosporum orbiculare, Candida*, and many deep fungal organisms. It is an imidazole derivative. It inhibits the synthesis of ergosterol, a fungus specific essential component of the plasma membrane. This results in the disruption of the fungal plasma membrane. The usual adult daily dosage for superficial fungal infections is 200 mg. Its common side effects are anorexia, nausea, constipation, pruritus, and exanthems. It inhibits testosterone synthesis and may cause hypogonadism and gynecomastia. It also causes reversible adrenal insufficiency. However, the most important adverse effect of ketoconazole is hepatotoxicity. Asymptomatic elevation of liver enzymes occurs in 11 percent of patients undergoing treatment. Either transaminases, or alkaline phosphatase or both may be increased. This is usually a transient effect, but persistent elevation of liver enzymes may warrant withdrawal of the drug. It induces toxic hepatitis that resembles viral hepatitis. The incidence of clinical hepatitis caused by ketoconazole is 1/10,000 to 1/15,000. This may prove fatal.

## RECOMMENDED READING


1. Cohn MS. Superficial fungal infections: Topical and oral treatment of common types. *Postgrad Med* 1992;91:239-252.
2. Jain S, Sehgal VN. Commentary: Onychomycosis: an epidemio-etiologic perspective. *Int J Dermatol* 2000;39:100-103.
3. Jain S, Sehgal VN. Onychomycosis: Treatment perspective. *Int J Dermatol* 2000;39:10-14.
4. Jain S, Sehgl VN: Terbinafine, a unique oral antifungal: Current perspectives. *Int J Dermtol* 2000; 39:412-423.
5. Odom R. Pathophysiology of dermatophyte infections. *J Am Acad Dermatol* 1993;28:S2-S7.
6. Sanjeev S, Sehgal VN. Itraconazole: An effective oral antifungal for onychomycosis. *Int J Dermatol* 2001;40:1-5.
7. Jain S, Sehgal VN. Terbinafine: A unique oral antifungal: Current perceptions. *Int J Dermatol* 2000; 39:412-423.
8. Sehgal VN, Sanjeev S. Onchomycosis: Clinical perspective. *Int J Dermatol* 2000;39:241-249.
9. Sehgal VN, Saxena AK, Kumari S. Tinea capitis. A clinicoetiologic correlation. *Int J Dermatol* 1985; 24:116-119.

# 14 Chapter Tinea Versicolor

Tinea versicolor is a chronic, noninflammatory, superficial fungal infection of the skin, characterized by maculosquamous eruption of varied color. The lesions are asymptomatic, however, cosmetic changes may induce the patient to seek medical advice. It is caused by *Pityrosporum orbiculare*. In addition to the wide spread yeast phase a few short rods resembling hyphae are also seen in a few normal subjects. In patients with tinea versicolor, *Pityrosporum* becomes dimorphous by forming, in addition to spores, numerous septate hyphae responsible for the pathogenecity. The factors, such as hot and humid climate, sweating, pregnancy, administration of corticosteroids predispose to the condition.

## CLINICAL FEATURES

The lesions are multiple macules of various sizes and shapes. The color of the macules may either be white, fawn, or brown. Scaling is not marked, but scratching produces fine branny scales (*the coup d'angle sign of Besnier*) (Fig. 14.1). They may also be follicular. It affects the upper-trunk, proximal portions of the extremities, lower abdomen, and sometimes the neck. The distribution is aptly described as conforming to a 'Lady's bathing suit'.

The lesions may be easily visualized using a Wood's lamp. This may reveal that the area of involvement is more extensive than visualized on clinical examination. The patches may become conspicuous after exposure to sunlight.

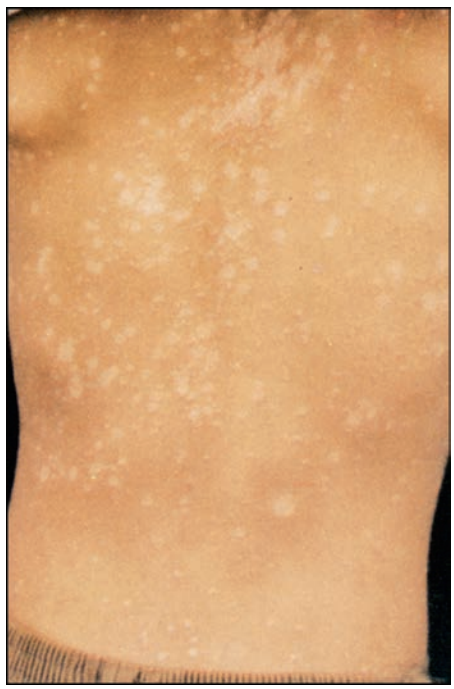


**Figure 14.1:** Hypopigmented, multiple fawn/brown/color with fine scales (the coup d'angle of Besnier)

An explanation for the hypopigmented macules is the formation of $C_9$ and $C_{11}$ dicarboxylic acids such as azelaic acid by *Pityrosporum* organism. These dicarboxylic acids inhibit the tyrosinase activity.

**Table 14.1: Treatment of tinea versicolor**

| *Treatments* | *Modes of application* |
|---|---|
| 1. 2.5 percent selenium sulfide lotion (Selsun). | Apply to the affected areas overnight, twice a week for 4 to 6 weeks. |
| 2. 25 percent sodium thiosulfate lotion. | Apply to the affected areas once a day for 4 to 6 weeks. |
| 3. One percent zinc pyrithione shampoo. | Apply to the affected areas for 5 to 10 min every night for 2 weeks. |
| 4. Topical antifungal cream.<br>Clotrimazole 1 percent cream (Canesten, Imidil)<br>Miconazole nitrate 2 percent cream (Micogel, Zole)<br>Ketoconazole 2 percent cream (Funginoc, Phytoral). | Apply once a day for 4 to 6 weeks. |

## DIAGNOSIS

The diagnosis of tinea versicolor is clinical. It may be supplemented by the following:

- Examination of the scales under the microscope, after dissolving them in 10 to 20 percent potassium hydroxide. This reveals filaments having a tendency to break into short segments of various sizes, and grapelike clusters of budding cells. This appearance of the yeast and hyphal forms is referred as 'spaghetti and meat ball'
- Culture of *Pityrosporum orbiculare* in a lipid rich oil medium. The fungus forms yellowish or creamy colonies
- Histopathological examination of a periodic acid-Schiff stained section reveals hyphae and spores in the horny layer. Furthermore, the hypopigmented areas are characterized by a normal number of melanocytes whose dendrites are filled with small, sparsely melanized melanosomes. Also the number of melanosomes is reduced in many of the keratinocytes. This is explained by an abnormal maturation of melanosomes and partial block in their transfer to keratinocytes.

## TREATMENT

Tinea versicolor responds to the topical application of antifungal creams (Table 14.1). The active infection may be cured within a few days of starting therapy. However to prevent relapse, the treatment may be continued for 4 to 6 weeks. Furthermore, the patient should be explained that pigmentary changes would take few months to resolve.

## RECOMMENDED READING

1. Borelli D, Jacobs PH, Nall L. Tinea versicolor: Epidemiologic, clinical and therapeutic aspects. *J Am Acad Dermatol* 1991;25:300-305.

# 15 Chapter

# Candidiasis

Candidiasis is a superficial fungal infection that may involve almost any of the cutaneous and/or mucosal surface of the body. *Candida albicans* is most often associated with human infections. Other pathogenic strains include *C. guilliermondi, C. krusei, C. tropicalis, C. pseudotropicalis,* and *C. stellatoidea*.

*Candida albicans* is an integral part of the normal flora. It is found as a commensal on the skin surface, oral cavity, and gastrointestinal tract of healthy individuals. However, under certain favorable conditions, it may become pathogenic. Such situations are as follows:

- Physiological—pregnancy, premenstrual, and postnatal periods
- Acquired factors—systemic antibiotic therapy, systemic corticosteroid therapy, immunosuppressive therapy, and oral contraceptives
- Local factors—increased humidity, skin maceration, obesity, and trauma
- Debilitating diseases, defective cellular immunity, diabetes, and other endocrine dysfunctions.

## CLINICAL FEATURES

*Oral candidiasis:* It presents as a sharply defined patch of creamy, crumbly, curd-like white pseudomembrane. Raw erythematous area is exposed on its removal. The membrane comprises of desquamated epithelial cells, fibrin, leukocytes, and fungal mycelia. There may be one or more patches. The buccal mucosa, tongue, gums, and palate are usually affected. In severe cases, it may extend to the esophagus and pharynx. It usually occurs in neonates, premature infants, and debilitated individuals. Oral candidiasis may also develop as chronic hyperplastic candidiasis. There is formation of firm, irregular white plaques, localized to the cheeks, and tongue (Fig. 15.1). The plaque may be surrounded by a rim of erythema. The hyperplastic plaque cannot be easily removed, unlike the pseudomembrane. Median rhomboid

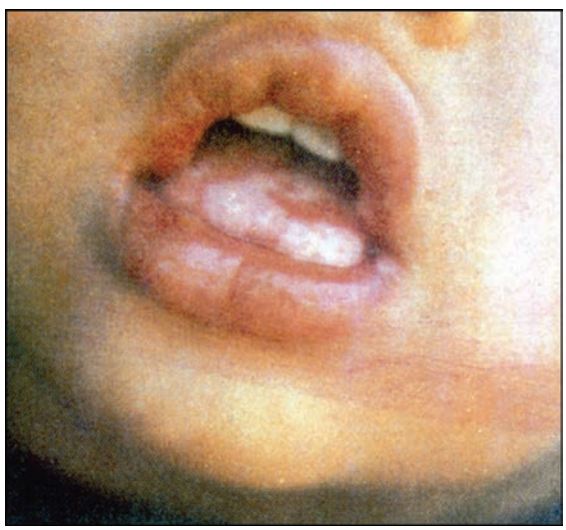


**Figure 15.1:** Firm, irregular, white plaque over the tongue

glossitis is another expression. It is characterized by a diamond-shaped area on the dorsum of the tongue with loss of papillae.

Perlèche or angular cheilitis is characterized by fissures and soreness at the angles of the mouth. This may extend outward to involve the folds in the facial skin. It is an intertrigo, most often caused by *Candida.* Poor nutritional status, lip licking, and excessive salivation predispose to angular cheilitis (perlèche).

*Candidal intertrigo:* It begins as erythematous bright red, scaly, flat topped papules in the depth of the fold and develops into a fringed, irregular edge studded with pustules. These rupture to form erosions. Papular and pustular satellite lesions are distinct. Itching and burning, may at times be intense. It usually affects the skin folds of obese individuals.

*Napkin candidiasis: Candida albicans* is frequently isolated from the moist skin of the buttocks and perineum of the infants. The classical picture of pustules studding the fringed border and the satellite lesions, confined to the area covered by the diaper is diagnostic (Fig. 15.2).

*Candidal paronychia:* The affected nailfold is red and swollen. There is loss of cuticle and the nailfold becomes detached from the nail plate, resulting in 'pocketing'. White pus may be expressed from this 'pocket'. Nail dystrophy with buckling of nail plate and discoloration around the lateral nail fold develops in the later stages (Fig. 15.3). It is usually encountered in the housewives who have to frequently immerse their hands in water.

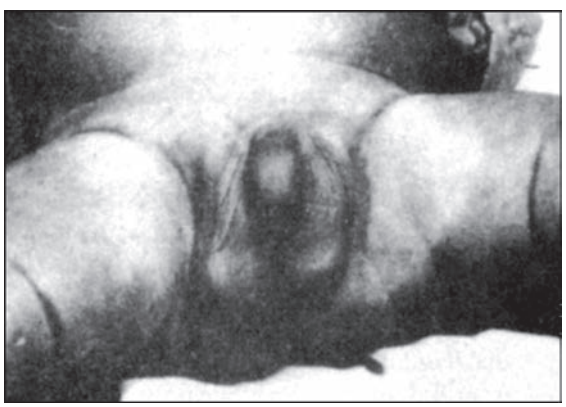


**Figure 15.2:** Diaper rash

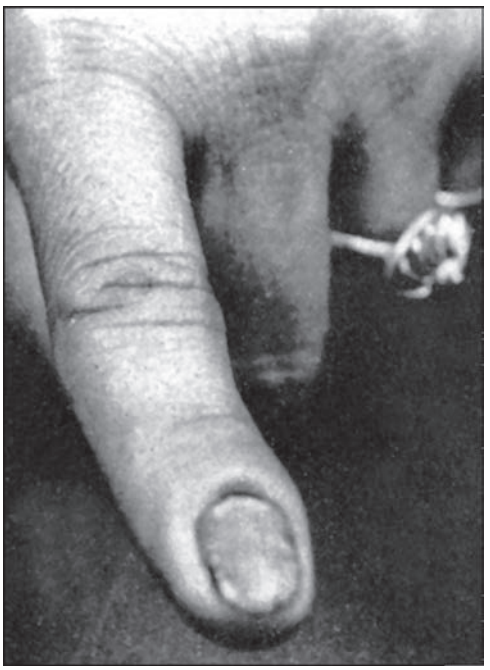


**Figure 15.3:** Swollen and red nail fold with nail dystrophy

*Candidiasis of the genital tract:* It is usually transmitted through sexual contact. Nearly 50 percent of male contacts of women with candidal infection, harbor *C. albicans*. The patient usually complains of intense itching, burning or irritation over the preputial orifice. The prepuce may be difficult to retract and fissured. There is a scant whitish subpreputial discharge. If retraction is possible, the inner surface of the prepuce and glans penis is found to be inflamed. It is erythematous and studded at places with white patches. Erosions may also be present.

Itchy and scaly lesions may be present over the penile shaft and scrotum and may extend to involve the groins also.

Candidiasis of the genital tract may be asymptomatic in females. Some may complain of intense vulval and/or vaginal irritation with or without vaginal discharge. The latter is characteristically white and thick. There may be history of dyspareunia and/or dysuria. Examination of the vulva reveals erythematous and edematous mucosae studded with white curdy patches. Fissures and erosions may be present. Perspeculum examination of the vagina reveals a similar picture on the vaginal mucosa with 'cheese-like' secretions covering the vaginal portion of the cervix. The white

**Table 15.1: Treatment of candiasis**

| *Clinical forms* | *Treatments* |
|---|---|
| 1. Oral thrush | 1. 1 percent gentian violet, applied twice or thrice a day.<br>2. Hamycin lotion, applied twice or thrice a day.<br>3. Imidazole lotions applied twice or thrice a day<br>Miconazole 2 percent lotion (Zole)<br>Clotrimazole 1 percent lotion (Surfaz, Canesten). |
| 2. Perlèche | Topical anticandidal preparations, applied twice a day for 10 to 14 days.<br>1. Clotrimazole 1 percent cream (Canesten, Imidil)<br>2. Miconazole nitrate 2 percent (Micogel, Daktarin)<br>3. Ciclopirox olamine 10 mg perg (Laprox). |
| 3. Vulvovaginal candidiasis | Anticandidal preparation, as pessaries or cream inserted intravaginally. In addition, topical anticandidals may be applied over the vulva. Male partner may need simultaneous treatment.<br>1. Clotrimazole 100 mg vaginal tablet (Imidìl, Surfaz or Canesten vaginal tablet). Insert one tablet high in the vagina, at bed time, for 6 consecutive nights.<br>Or<br>2. Miconazole nitrate 200 mg vaginal pessary (Gynodaktrin ovule). Insert one ovule, high in the vagina for 3 consecutive nights.<br>Or<br>3. Econazole nitrate 150 mg (Econazole vaginal). Insert one tablet in vagina, for 3 consecutive nights.<br>Or<br>4. Nystatin 100,000 Units vaginal tablet (Mycostatin vaginal), 1 to 2 tablets may be inserted in the vagina for 2 weeks.<br>Or<br>5. Miconazole nitrate 2 percent W/W gel (Gynodaktrin) applied intravaginally at bedtime, for 7 to 14 days.<br>Or<br>6. Ciclopirox olamine 10 mg perg cream (Laprox vaginal cream). 5 mg inserted in the vagina at bedtime with applicator for 12 to 14 days.<br>Recalcitrant cases may require the following<br>1. One tablet Nystatin (500,000 Units), four times a day for 2 week.<br>Or<br>2. 200 mg of ketoconazole, twice a day for 5 days. |
| 4. Candidal intertrigo | Topical application of anticandidal cream or lotion, twice a day for 2 weeks. |
| 5. Napkin dermatitis | Same as above |
| 6. Candidal paronychia | 1. Keep the hands dry.<br>2. Avoid contact with detergents.<br>3. 200 mg of ketoconazole, once a day for few weeks.<br>4. Anticandidal lotion may be applied twice a day in nail folds. |

vaginal plaques are difficult to remove and leave bleeding points. The vaginal discharge may be watery and its pH is below 5.

*Chronic mucocutaneous candidiasis:* This form usually arises in those suffering from a spectrum of cellular immunodeficiencies. It develops as persistent *candidal* infection of the oral cavity, the skin, and the nails, refractory to treatment. It may be associated with other cutaneous and systemic infections. The syndrome begins in infancy or early childhood and has the following clinical features namely:

- Persistent oral thrush, recalcitrant to therapy
- Cutaneous candidiasis which usually involves the intertriginous areas but may be widespread and involve the trunk, limbs, hands, and face
- Paronychia, often with nail plate invasion and dystrophy
- Vulvovaginal candidiasis.

## DIAGNOSIS

The clinical suspicion of candidiasis may be confirmed by smear examination and/or culture.

*Candida albicans* is a dimorphic fungus with both yeast and mycelial forms.

- Skin scrapings or other specimens are examined microscopically for budding yeast, pseudohyphae or hyphae after the addition of 10 percent KOH solution to the slide preparation. As *Candida* may be seen on normal skin or mucosa as well, only their abundant presence is significant. Demonstration of mycelial form indicates colonization and tissue invasion and is, therefore, of greater significance.
- Cultures can be obtained readily on Sabouraud's and ordinary bacteriological culture media. Colonies are creamy white, smooth, and have a distinct yeasty odor.
- A rapid method of identifying *C. albicans* is based on its ability to form germ tubes within two hours when incubated in human serum at 37°C (Reynold-Braude phenomenon).

## TREATMENT

Details of the treatment are outlined in Table 15.1.

## RECOMMENDED READING

1. Felman YM, Nikitas JA. General candidiasis. *Cutis* 1983;31:369-377.
2. Ro BI. Chronic mucocutaneous candidiasis. *Int J Dermatol* 1988;27:457-462.
3. Ray TL, Wuepper KD. Recent advances in cutaneous candidiasis. *Int J Dermatol* 1978;17:683-690.

# 16 Chapter Deep Mycotic Infection

## MADUROMYCOSIS

Maduromycosis is a chronic infection of skin and/or subcutaneous tissue resulting in tumefaction studded with sinuses discharging grains. It is caused either by aerobic actinomycetes (actinomycotic mycetoma) or true fungi (eumycotic mycetoma). They are transmitted through accidental injuries in the fields. The organisms differ from one geographic area to other, and are listed in Table 16.1.

**Table 16.1: Causative agents of mycetoma**

| *Fungi* | *Actinomycetes* |
|---|---|
| *Madurella mycetomi* | *Actinomadura madurae* |
| *Madurella grisea* | *Nocardia asteroides* |
| *Phialophora jeanselmei* | *Nocardia brasiliensis* |
| *Allescheria boydi* | *Nocardia caviae* |
| *Pyrenochaeta romeroi* | *Streptomyces somaliensis* |
| *Leptosphaeria senegalensis* | *Streptomyces pelletieri* |
| *Curvularia lunata* | |
| *Neotestudina rosati* | |
| *Cephalosporium corda* | |

After its initial description from India the disease is known as Madura foot/maduromycosis. The term mycetoma is also used to designate it as a fungal tumor. It is common in India, Africa, Mexico, Central America, and in some parts of South American countries. It is usually seen in rural field workers. Men outnumber women by a ratio of 4.5:1. The disease is usually seen between the ages of 20 and 50 years. The portal of entry of this fungus is trivial injury.

## CLINICAL FEATURES

The lesion usually begins as a non-descript, asymptomatic, indolent papule, which in due course enlarges to form nodules and satellite papules. This is accompanied by a globose swelling in and around the primary site. At this point, the nodules may soften, and form discharging sinuses. The suppurative fluid usually displays granules with a hue characteristic of the causative agent. The granules can be recognized with the naked eye. The foot and lower leg are commonly affected. After several years, the foot becomes massively enlarged (tumefaction), with draining sinuses, fibrotic nodules, and irregular contractures (Fig. 16.1). The lesions are usually painless and their evolution, until the grossly deformed limb is formed, is so gradual that the patients seldom report for treatment. By the time the patient applies for therapy, the disease has usually spread to the underlying bones. This is more so in the infections by *S. somalienses*. The lesions do not metastasize, and only spread locally. Other infrequent sites of mycetomas are the hands, shoulders, buttocks, and the head, in that order.

## DIAGNOSIS

In the early stages, the ulcers and sinuses of mycetoma may mimic leg ulcers of other infective etiology. However, chronicity, asymptomatic

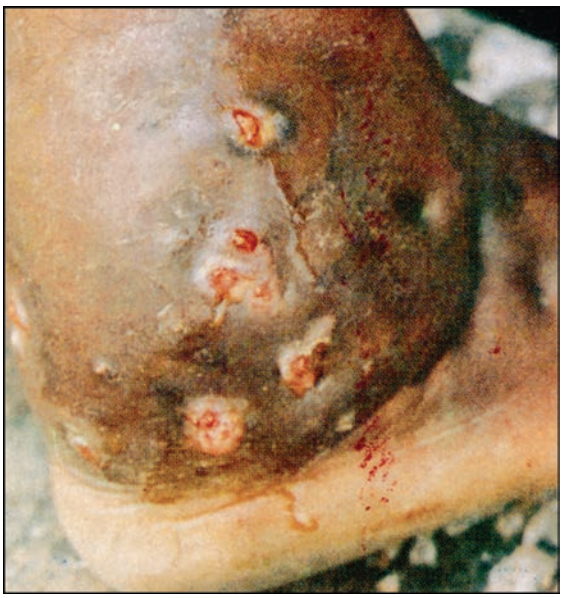


**Figure 16.1:** Madura foot

nature, and absence of systemic signs easily differentiate them. Ulcers induced by venous stasis and arterial insufficiency are bilateral, whereas mycetomas are usually unilateral. Mycetomas also have to be differentiated from elephantiasis of the foot, skin tuberculosis, chromomycosis, chronic osteomyelitis, and sporotrichosis.

The diagnosis is usually based on the chronology of the clinical features, demonstration of various colored granules from the discharged pus, and the culture of the causative organism. It is cultured in Sabourauds' dextrose agar medium, which takes about 1 to 2 months. Histopathological examination of the tissue section reveals numerous chronic granulomas, which may lead to dense scar tissue and local endarteritic changes. These changes are remarkably similar despite their varied etiologic agents. The pathognomonic features, however, are either circular, ovoid, or kidney shaped granules. These granules vary from 0.5 to 2 mm in diameters. Their color varies according to the etiologic agent. They are usually identified in proximity to the abscesses, and are discharged periodically from the wound/sinus. The interwoven colonies of fungal hyphae, with a fibrin shell derived from the host are characteristic. The granules may get fragmented by the suppurative reaction. These fragments may then be carried by the macrophages, producing new colonies. In eumycetomas, the fungus appears ramified and displays 2 to 4 mm vesicular hyphae. *Actinomycosis madurae, Nocardia rosatti, Madurella mycetomi* and *Streptomyces pellitieri* granules in sections show a fairly specific morphology, and are easy to characterize by a mycologist.

## TREATMENT

The response to therapy is variable, and depends chiefly on the etiologic agent and duration of the disease. The treatment principles, thus, differ in different mycetomas. The drug of choice for actinomycotic mycetoma is sulfonamide. It is given as 6 to 8 gm daily in 4 divided doses for several weeks (Table 16.2). Alternative drugs are penicillin, tetracycline, chloramphenicol, and rifampicin. Diaminodiphenyl sulfone has been found to be effective in infections due to *Nocardia brasiliensis*. The eumycotic mycetomas are refractory to treatment. Amphotericin-B shows poor results with a high incidence of side effects, as is ketoconazole. In advanced cases surgical resection with plastic repair may be the only alternative.

## SPOROTRICHOSIS

Sporotrichosis is a chronic, subcutaneous lymphatic mycosis caused by *Sporothrix schenckii* resulting in indolent ulcers along the lymphatic

channels of the limbs. *Sporothrix schenckii* is a dimorphous fungus that grows on decaying vegetable matter such as timbers in underground mines. It is introduced into the skin through minor traumas such as thorn pricks/splinter injuries. The lesion is usually produced after 8 to 30 days of inoculation.

Sporotrichosis is a disease of both tropical and temperate climates. The disease shows seasonal variations, and is more active in a humid environment with temperatures ranging between 16 and 20°C. Initially, it was reported in America; since then it has been reported the world over. The largest number of cases from one single area has been reported from mining area of Johannesburg. It has been reported to affect male farmers, laborers, and horticulturists. Occasionally, it may occur in women and children.

## Clinical Features

Cutaneous lymphatic sporotrichosis, the most common presentation of the disease, forms an important differential diagnosis of leg ulcers. It usually starts as a small papule over the foot or ankle following injury, which soon breaks down to form a shallow ulcer. These are asymptomatic, and recalcitrant to treatment. So-called sporotrichotic chancre persists for several months, followed later by the development of new nodules arising in line with the draining lymphatic channels (Fig. 16.2). The nodules occasionally suppurate, discharging scanty thin pus and forming a shallow circular ulcer. They are characteristically attached to the underlying lymphatic channel, which is firm and nontender. After several years, swollen regional lymph nodes may break down to form sinuses. Occasionally, fixed sporotrichosis of the localized cutaneous variety may be seen. This is due to lack of spread through lymphatics.

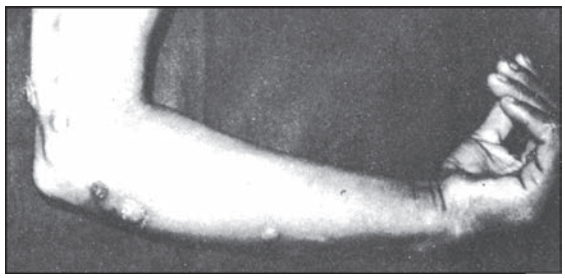


**Figure 16.2:** Sporotrichosis

## Diagnosis

Deep mycoses, syphilis, tularemia, glanders, anthrax, pyogenic lesions, skin tuberculosis, staphylococcal lymphangitis and drug eruption are to be differentiated. Chain of lesions along lymphatic channels, chronicity, and benign nature are its clinical hallmarks. However, its diagnosis is confirmed by harvesting fungus on Sabouraud's dextrose agar, which displays moist, white colonies with a wrinkled surface. The colonies gradually darken to brown or black color. Sporotrichin test is usually positive. Histopathology is unhelpful; nevertheless, it must be done in each case. It reveals minute intraepidermal abscesses within a hyperplastic epidermis. In the dermis, an inflammatory infiltrate is formed by neutrophils, lymphocytes, plasma cells, and small granulomas, and minute abscesses are seen.

## Treatment

Oral iodides are the treatment of choice for cutaneous lymphatic sporotrichosis. An aqueous saturated potassium iodide solution is given as 1 ml, 3 times a day in milk or water. The dose is gradually built to 3 to 4 ml three times a day. It should be continued for 3 to 4 weeks after an apparent recovery. The use of potassium iodide is empirical, as it has been seen that *Sporothrix schenckii* can grow in a medium containing 10 percent potassium iodide.

**Table 16.2: Treatment of deep mycosis**

| *Disease* | *Drug of choice* | *Mode of administration and duration of treatments* | *Other drugs* |
|---|---|---|---|
| Mycetoma | | | |
| • Actinomycotic mycetoma | Sulfonamides | 6 to 8 gm of sulfadiazine or its derivatives is given daily for several weeks after the signs of the disease have disappeared. | Penicillin, tetracycline, and chloramphenicol may be administered along with sulfonamide to ensure a complete cure. |
| | Co-trimoxazole | 800 mg of sulphamethoxazole + 160 mg of trimethoprim daily, for a requisite period | Diaminodiphenyl sulfone (200 to 300 mg) (DDS) is effective in schizomycetomas due to *N. brasiliensis*. |
| • Eumycotic mycetoma | Surgical resection and plastic repair | | Amphotericin B has been tried, though the results are poor. |
| Sporotrichosis | Potassium iodide | An aqueous saturated solution of potassium iodide is given in a dose of 1 mL three times a day in milk or water. The dose is gradually increased to 3 to 4 mL thrice daily, for 3 to 4 weeks after an apparent recovery | Amphotericin B |
| Chromo-blastomycosis | Amphotericin B | In localized lesions, 5 mg/mL in 2 percent lidocaine is injected intralesionally. | Calciferol, iodides, thiobendazole, 5-fluorocytosine. |
| | Ketoconazole | 400 to 800 mg daily for requisite period | |

The application of moist heat and a rubifacient used alone or in combination is also useful. It is reported to cure the lesions in a period of 3 to 16 weeks (Table 16.2).

## CHROMOMYCOSIS

Chromomycosis or verrucous dermatitis is characterized by insidious development of verrucoid, papillomatous excrescences confined to the skin and subcutaneous tissue of the feet and legs. It is caused by species of closely related fungi producing identical morphology. They are *Phialophora verrucosa, Phialophora pedrosoi, Fonsecaea compacta, Phialophora dermatitidis*, and *Cladosporium carrionii*. Soil and wood are their natural habitats. They are introduced traumatically into human tissue. The incubation period varies from a few months to a few years.

It was first reported in Brazil in 1894. It is an uncommon deep mycotic infection confined to the tropics and subtropics—Central, South, and North America, Cuba, Jamaica, and Martinique. Isolated cases have also been found in India, South Africa, Madagascar, Australia, and Northern Europe. Adult male farm workers and laborers, whose occupation brings them into intimate contact with soil, are chiefly affected. However, children and women may also be affected by it. All races are susceptible, although most of the cases have been described in Caucasians of North America. Person-to-person and animal-to-human transmission does not occur.

### Clinical Features

A warty papule develops at the site of inoculation, which gradually ulcerates and/or enlarges

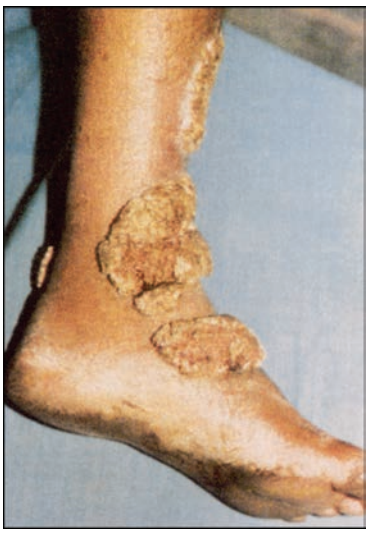


**Figure 16.3:** Chromomycosis

to form a brownish, black verrucous plaque with a raised border. Ulceration occurs in the plaque, discharging scanty serous exudate. Eventually, the lesion becomes a dry, verrucoid, hyperkeratotic mass grossly deforming the foot and accounting for the name 'Mossy Foot' (Fig. 16.3). New crops of satellite warty papules emerge in the vicinity of this plaque. The disease is asymptomatic, but secondary infection may cause some degree of pain and itching. The underlying bone and muscles are not invaded and are spared. However, in extreme involvement, the deeper lymphatics may be affected. Their blockage is responsible for the secondary elephantiasis.

## Diagnosis

The disease is to be differentiated from blastomycosis, which is characterized by a sharply delineated advancing border and central atrophic healing. Tertiary gummatous syphilis, yaws, leishmaniasis, cutaneous tuberculosis, other fungal granulomas, neoplasms, and other causes of chronic leg ulcers are also to be differentiated from chromomycosis.

Diagnosis is clinched by the clinical picture, isolation of the fungus on culture, and its demonstration on a histopathologic tissue section. Microscopic examination of the tissue section reveals features suggestive of foreign body granuloma, within which are areas of abscess formation. Epidermis shows moderate to marked hyperplasia, which may occasionally turn into pseudoepitheliomatous hyperplasia. Keratolytic abscesses may be formed in the hypertrophic epidermis. The dermis shows extensive infiltration with polymorphous granulation tissue, numerous multinucleated giant cells, and neutrophilic microabscesses. Despite areas of tuberculoid formation, there is no caseation necrosis. When infection spreads to subcutaneous tissue, several abscesses lined by fibrous walls are formed. Hematoxylineosin or PAS stains identify the fungus lying either free in the granulomas or within giant cells. Occasionally, transepidermal migration of fungal spores may occur.

## Treatment

Excision followed by plastic repair can be performed in early lesions. Localized lesions may respond to amphotericin B. Recently oral ketoconazole has emerged as the treatment of choice. Calciferol, iodides, thiobendazole, and 5-fluorocytosine have also been tried (Table 16.2).

## RECOMMENDED READING

1. Sehgal VN, Jain S, Sing N. Porotrichosis. *J Dermatol* 1996;23:517-525.

# 17 Chapter Cutaneous Tuberculosis

Cutaneous tuberculosis has recorded an increase in its incidence recently. This has largely coincided with the general decline in pulmonary tuberculosis in developed countries. The current situation in the Indian subcontinent seems to approximate that of developed countries of the temperate regions of the globe. Hence, it is imperative to study the pattern of cutaneous tuberculosis in the tropics, which may not only help in defining its status but also enrich teaching.

## Causative Microorganisms

*Mycobacterium tuberculosis, Mycobacterium bovis,* and *Bacillius Calmette Guerin* occasionally are responsible for cutaneous tuberculosis.

## Route of Infection

It may either be the result of the following:

- Exogenous inoculation
  - Primary chancre, in the absence of hypersensitivity to tubercle bacillus
  - Lupus vulgaris (LV) and tuberculosis verrucosa cutis (TBVC) in a presensitized host.
- Endogenous spread through
  - Contiguous extension (autoinoculation) resulting either in scrofuloderma or tuberculosis cutis orificialis (TBCO)
  - Lymphatics, resulting in lupus vulgaris in previously sensitized individual
  - Hematogenous, resulting in miliary tuberculosis in an immunocompromised host, especially, in children.

## Classification

Cutaneous tuberculosis is a manifestation of cell-mediated immunity. It is divided into the following:

*Primary tuberculosis:* It manifests in an individual not previously infected or who has not acquired a natural or artificial immunity to the tubercle bacillus. It may present either as:

- Primary inoculation tuberculosis (tuberculous chancre), or
- Acute miliary tuberculosis of the skin.

*Secondary tuberculosis:* It develops in an individual who has either been previously infected or has acquired a natural or artificial immunity to the tubercle bacillus. It is perceived as forming a continuous spectrum with lupus vulgaris and tuberculosis verrucosa cutis at one end and scrofuloderma and tuberculosis cutis orificialis at the other. This spectrum takes into account the gradation of cell-mediated immunity of the host from high to low across the spectrum. Secondary cutaneous tuberculosis is conceived either as the reinfection (lupus vulgaris and tuberculosis verrucosa cutis) or reactivation (scrofuloderma and tuberculosis cutis orificialis).

## Clinical Features

### *Tuberculous Chancre*

It results from the inoculation of *Mycobacteria* into the skin or mucosa of a nonsensitized individual. Trauma or any break in the continuity of skin serves as a portal of entry. The sites of predilection are those amenable to trauma. Face and the extremities are commonly affected. Two to four weeks after the initial introduction of the bacilli, forms a nodule that evolves into an indolent, firm, nontender, sharply delimited ulcer (Fig. 17.1). The bacilli reach the regional lymph nodes and produce a painless tuberculous lymphadenopathy about 3 to 8 weeks after the initial infection. Tuberculous chancre, lymphangitis, and regional lymphadenopathy, a prototype of primary inoculation tuberculosis, akin to the Ghon's complex, is produced. The seroconversion to the intradermal PPD coincides with the lymphadenitis. The primary lesion usually heals with scarring, but may persist or terminate in lupus vulgaris or tuberculosis verrucosa cutis. The regional nodes may break down producing scrofuloderma. Occasionally, erythema nodosum may develop.

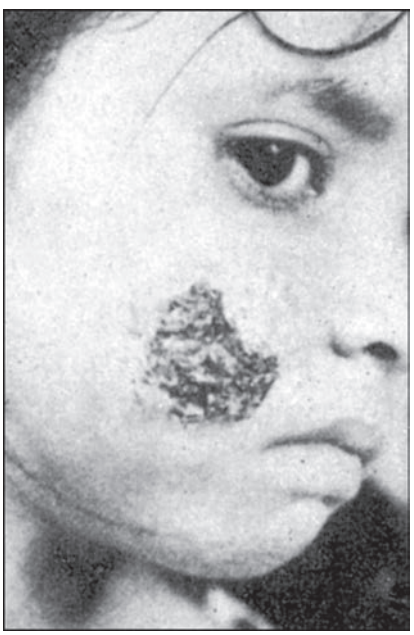


**Figure 17.1:** Tuberculous chancre on the cheek

### *Acute Miliary Tuberculosis of the Skin*

It is an uncommon expression of cutaneous tuberculosis that occurs primarily in infants and children, resulting from the hematogenous dissemination of the tubercle bacilli. The initial focus of infection is either pulmonary or meningeal and it may follow exanthems especially measles or severe infections, that lower the immunologic defence mechanisms. Disseminated lesions occur on all parts of the body, but most frequently on the trunk, thighs, buttocks, and genitalia. They begin as discrete, pin-head sized, bluish-red to brown papules capped by minute vesicles. These vesicles dry up to form crust. Removal of the crust reveals a small umbilication. The lesions heal with the formation of a white depressed scar with a brownish halo. Tuberculin sensitivity is absent because of the overwhelming infection. The disease is usually fatal.

### *Lupus Vulgaris*

It is a reinfection tuberculosis of the skin occurring in previously sensitized host with a high degree of tuberculin sensitivity. Immunity is moderate, and hypersensitivity to PPD is high. It may appear following exogenous inoculation or occasionally, may be the result of either direct extension or lymphatic spread. It may appear over the primary inoculation site, but it usually follows tuberculosis at other site. It may appear over the scar of scrofuloderma or after BCG vaccination. High degree of immunity to

the tubercle bacilli in lupus vulgaris results in slower evolution of the disease.

The lesion is usually solitary. The initial lesion is a small, brownish red papule of soft consistency. 'Apple jelly nodules', though considered as pathognomonic of the disease are infrequently demonstrated. It gradually becomes elevated, infiltrated, and brown in color. It shows gradual peripheral extension and central atrophic areas. The diverse clinical variants of lupus vulgaris are as follows:

*Plaque form:* It manifests as flat plaques with polycyclic or serpiginous configuration. The surface may be smooth or covered with scales. The plaque may show scarring with islands of active lupoid lesion (Fig. 17.2).

*Hypertrophic form:* It may present either as soft tumorous growths with a nodular surface or as hyperkeratotic masses. Edema, lymphatic stasis, vascular dilatation, and elephantiasis may be present.

*Ulcerative form:* Necrosis, ulceration, and scarring predominate in this form. The deeper tissues and cartilage are destroyed producing contractures and deformities.

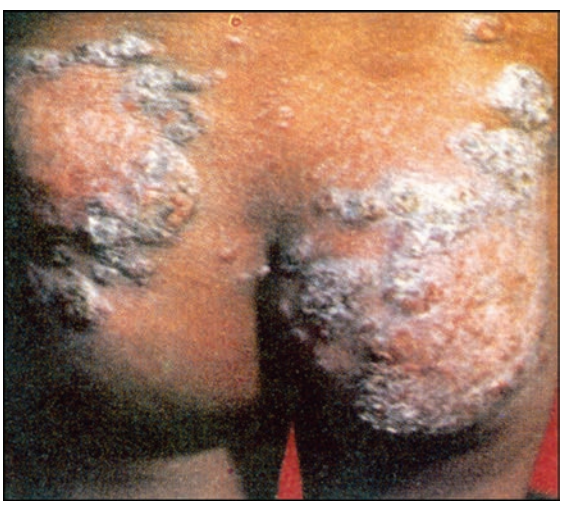


**Figure 17.2:** Lupus vulgaris: A flat plaque, depicting scar with islands of active polycyclic, configuration

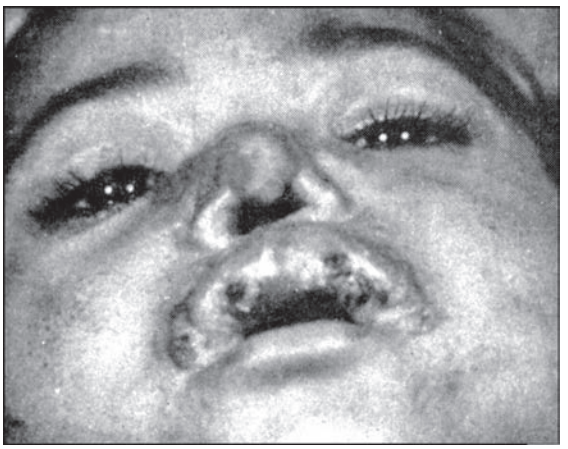


**Figure 17.3:** Lupus vulgaris affecting the lips

*Vegetating form:* It is characterized by marked infiltration, necrosis, and ulceration with minimal scarring.

*Papular and nodular forms:* It has also a special character.

Lupus vulgaris may affect buccal, nasal, and conjunctival mucosae (Fig. 17.3) either primarily or by extension of the cutaneous lesion. The nose is frequently affected with the destruction of its cartilage. Direct extension or lymphatic spread from nasal focus may result in the involvement of the palate, gingiva, larynx, and pharynx.

Scarring is a cardinal feature of healing lupus vulgaris. It may be extensive resulting in the destruction of the underlying tissues and cartilage and subsequent cicatricial changes. This is responsible for the deformities and mutilations such as ectropion, microstomia, contractures, keloids, deformities of soft palate, and laryngeal stenosis. Squamous cell carcinoma and rarely basal cell carcinoma, and sarcoma may complicate.

*Tuberculosis Verrucosa Cutis (TBVC)*

It is a verrucous form of reinfection tuberculosis resulting from exogenous reinfection of skin with tubercle bacilli in a previously infected and/or sensitized individual possessing a moderate to high degree of immunity.

Inoculation occurs at the site of minor abrasion or wounds and areas amenable to trauma are the usual sites of affliction, namely the hands, fingers, and lower extremities. It is an occupational hazard for the physicians, pathologists, forensic experts conducting autopsy, farmers, and butchers.

It starts as an asymptomatic, small papule or a papulopustule with an inflammatory areola, developing at the site of inoculation. It soon becomes hyperkeratotic and warty. By gradual irregular peripheral extension, it develops into a verrucous plaque with horny surface traversed by deep clefts and fissures (Fig. 17.4). The plaque is usually firm, but areas of softening may be present in the center. Pus and keratinous material may be expressed from the fissures. The lesion progresses centrifugally resulting in an annular or serpiginous pattern. Spontaneous resolution may occur at the center. Lymph node enlargement, if associated with TBVC is the result of secondary infection and is not due to the tuberculous process. Classically the lesions of TBVC is solitary, however, multiple lesions have also been recorded.

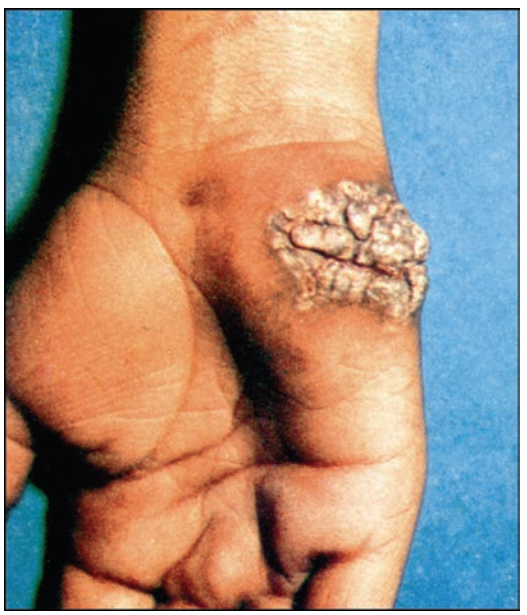


**Figure 17.4:** Tuberculosis verrucosa cutis: Verrucous plaque with horny surface, traversed by deep clefts/fissures

*Scrofuloderma*

It is reactivation tuberculosis occurring as a result of reactivation of the tubercle bacilli introduced during a prior episode of the disease and lying dormant since then. They are reactivated at an opportune time when the cell-mediated immunity of the individual is lowered. Such patients are sensitized to the tubercle bacilli, but possess low cell-mediated immunity to it.

It originates as a tuberculous process of the subcutaneous tissue which subsequently turns into a cold abscess. There is a secondary breakdown of the skin overlying such a tuberculosis focus (Fig. 17.5). The tuberculosis of the lymph nodes, bones, joints, and epididymis is usually responsible for scrofuloderma. Cervical group of lymphnodes are most often involved. However, affliction of axillary, inguinal, parasternal, and epitrochlear lymph nodes are also common. In the neck, the tonsillar, submandibular, preauricular, postauricular, occipital, and supraclavicular lymph nodes are usually implicated.

The initial lesion presents as a firm, subcutaneous or deep cutaneous swelling or nodule, which is freely movable. It later becomes attached to the skin. It then suppurates, softens, and involves the overlying skin with resultant ulceration and sinus formation. Multiple ulcers may

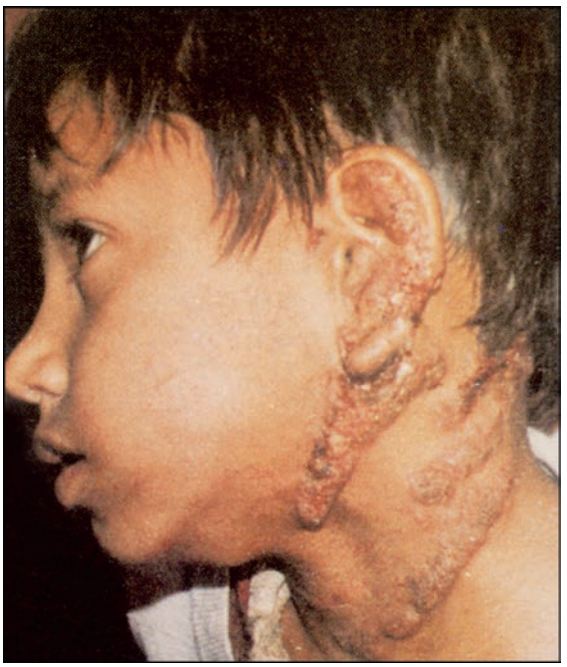


**Figure 17.5:** Scrofuloderma: An ulcer with bluish under -mined edges and soft granulating surface

form which are arranged linearly. These ulcers have bluish undermined edges and soft granulating floors. There is often a watery, purulent or gaseous discharge from the sinuses.

Spontaneous healing occurs but it takes years before it is complete. Cord like keloid scars and localized recurrences are characteristic.

Scrofuloderma is usually associated with manifest tuberculosis elsewhere in the body, usually in the lungs.

### *Tuberculosis Cutis Orificialis*

It is the tuberculosis of the mucous membranes and the skin of the orifices resulting from autoinoculation of tubercle bacilli in patients with advanced visceral tuberculosis. It affects men more often than the women and is most often prevalent in the middle-aged or older individuals. Cutaneous hypersensitivity to tuberculin in these patients is controversial, however, such patients ultimately develop anergy.

The underlying disease is a far advanced pulmonary, intestinal, or genitourinary tuberculosis. Bacilli shed from these foci become inoculated into the mucocutaneous areas of the orifices, at a traumatized site. Ulcerative lesions occur in the oral cavity, perineal, or perirectal areas. The tongue is the most common affected site in the mouth, particularly its tip and the lateral margins. Soft and hard palate, lips, and tooth socket may also be involved. In intestinal tuberculosis the area on and around the anus and in genitourinary tuberculosis vulva, glans penis, and the urinary meatus are involved. The lesion consists of a small, yellowish or reddish nodule, that rapidly breaksdown to form an exquisitely painful, shallow ulcer with bluish undermined edges. The surrounding mucosa is swollen, and the ulcer is covered with pseudomembranous material.

## Histopathology

The histopathologic reactions to *M. tuberculosis* can be organized along an immunopathologic spectrum, as in leprosy. A sequence from non-necrotic epithelioid cell granulomas with no acid-fast bacilli (high immune) through necrotic epithelioid granulomas with some acid-fast bacilli to the position of necrosis with abundant acid-fast bacilli (low immune) can be arranged. Lupus vulgaris typifies the high immune pole, and the patients with TBCO and acute miliary tuberculosis form the low immune pole. The hallmark of the histopathologic diagnosis of cutaneous tuberculosis is the presence of tuberculous/tuberculoid granuloma.

*Primary tuberculous chancre:* The early histologic picture is an acute neutrophilic reaction

punctuated by areas of necrosis and associated with numerous tubercle bacilli. Three to 6 weeks later, coinciding with the conversion of the tuberculin sensitivity, the infiltrate becomes granulomatous and epithelioid cells, giant cells, and lymphocytes appear. Caseation necrosis becomes evident, and the tubercle bacilli become sparse.

*Acute miliary tuberculosis:* Histologic examination reveals focal areas of necrosis and abscess formation, surrounded by a zone of macrophages, containing numerous tubercle bacilli.

*Lupus vulgaris:* Tuberculoid structures composed of epithelioid cells, occasional Langhans giant cell, and mononuclear cells are present, usually in the upper dermis. Of the mononuclear cells, monocytes lie in the immediate periphery of the tubercles, while lymphocytes are located farther away. Occasional foreign body giant cell may be present (Figs 17.6A and B). Caseation necrosis when present is usually minimal, and the tubercle bacilli are difficult to demonstrate. Secondary epidermal changes in the form of atrophy, ulceration, acanthosis, or an occasional pseudoepitheliomatous hyperplasia may be present. A squamous cell carcinoma is an uncommon outcome.

*Tuberculosis verrucosa cutis:* The histologic picture consists of hyperkeratosis, hypergranulosis, acanthosis, and papillomatosis overlying an acute inflammatory infiltrate in the epidermis and microabscesses in the upper dermis. Tuberculoid granulomas with moderate amount of caseation necrosis and few tubercle bacilli are seen in the mid-dermis. At times the dermal infiltrate may be nonspecific altogether. Marked fibrosis, however, occurs consistently.

*Scrofuloderma:* Histopathologic examination of the center of the lesion reveals ulceration and abscess formation. Tuberculoid structures with marked caseation necrosis are present in the lower dermis and at the periphery. Epithelioid cells form the major component with a large number of giant cells. Tubercle bacilli are easily identified. As the lesion gets older and caseation necrosis sets in, however, it becomes relatively more difficult to demonstrate the bacilli. Granuloma formation may not be appreciated and the sections may only show a nonspecific chronic inflammatory infiltrate.

*Tuberculosis cutis orificialis:* The histologic picture is usually nonspecific, showing ulceration and lymph edema. Yet, in most cases, tuberculoid infiltrates with pronounced necrosis are found deep in the dermis. Tubercle bacilli are easy to demonstrate.

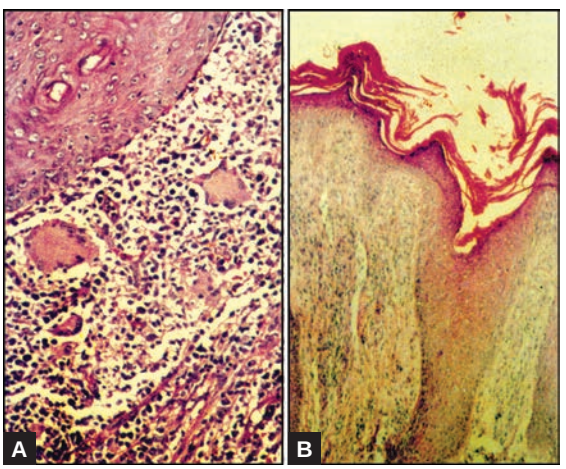



**Figure 17.6A:** Tuberculoid granuloma displaying lymphocytes histiocytes/giant cells (H and E × 100)*, (B) Tuberculosis verrucosa cutis (TBVC)(H and E × 100)* *(*Courtesy:* Blackwell Science INC. Sehgal VN, *et al.* Reinfection (secondary) inoculation cutaneous tuberculosis. Int J Dermatol, 40:205-209;2001)

## Diagnosis

The diagnosis of secondary cutaneous tuberculosis is made on the basis of relevant positive history. In reinfection tuberculosis, it is

imperative to form a history of primary infection or BCG vaccination. The latter, in particular, should be given due consideration, for BCG vaccination forms an important component of immunization program. It may be identified through BCG scar. Primary infection and/or BCG vaccination is responsible for the cellular immunity and sensitization to the tubercle bacillus. Subsequently, infection by another strain of *M. tuberculosis* in such an individual is responsible for reinfection tuberculosis. The evolution of the disease is slow.

In reactivation tuberculosis, a history of acute systemic tuberculosis in the past is usually affirmative which was diagnosed by clinical and investigative procedures, namely lymphocytosis, raised blood sedimentation rate, skiagram of the chest revealing infiltration of the parenchyma producing mottling, or cavitation, or pleural effusion, or enlargement of hilar lymph nodes, positive reaction to Mantoux test, demonstration of the acid-fast bacilli in the smear and its recovery in culture. Futhermore, there is a history of administration of antitubercular drugs in adequate dosage for a requisite period. Subsequent to that the patient recovered and was declared cured. The only evidence of such active systemic disease may be pulmonary scarring, fibrosis and/or calcification as revealed on skiagram. However, some of the tubercle bacilli escape the action of antitubercular drugs and lie in a dormant state as 'persisters' and are reactivated at an opportune time.

Besides the history, the other relative criteria are the morphology of the lesion, and the Mantoux test. The diagnostic value of positive tuberculin test is blurred by BCG vaccination in early life and by exposure to related *Mycobacteria.* However, a very strongly positive Mantoux test is a strong suspicion of active tuberculous infection. A negative reaction is a very strong evidence against any but the miliary tuberculosis. A tuberculous granuloma, characterized by an accumulation of epithelioid cells surrounded by a wall of mononuclear cells, presence of giant cells and caseation necrosis, is diagnostic of tuberculosis. It is also possible to demonstrate acid-fast bacilli in such a granuloma. However, the significance of tuberculoid granuloma, marked by accumulation of epithelioid cells surrounded by mononuclear cells and conspicuous absence of caseation necrosis is relative.

The recovery of *M. tuberculosis* on culture in Lowenstein-Jensen media 4 to 6 weeks after inoculation confirms the diagnosis. However, an effort should be made to exclude atypical *Mycobacteria* by performing niacin test and looking for the formation of pigment on exposure to sunlight. Guinea pig inoculation provides absolute, though delayed proof of pathogenecity. Confirmation, however, is not always possible even by taking into account these relative and absolute criteria. A threapeutic trial is then justified if clinical suspicion is strong. A short-term intensive chemotherapy results in amelioration of the signs and symptoms and appreciable clinical improvement in as short period as 4 to 6 weeks.

## Treatment

The treatment of cutaneous tuberculosis is similar to that of systemic tuberculosis. The objectives of treatment are: (i) to promptly cure the disease, thus reducing its morbidity, (ii) to prevent the emergence of resistant strains and (iii) to prevent the emergence of 'persisters' and hence reduce the possible relapses. In order to achieve the preceding objectives it is imperative to administer antitubercular drugs, the details of which are given in Table 17.1. An intensive short course regimen comprising isonicotinic

**Table 17.1: Antitubercular drugs**

| *Drugs* | *Dosage* | | *Side effects/interactions with other drugs* |
|---|---|---|---|
| | *Adults* | *Children* | |
| Rifampicin | 450 to 600 mg | 10 to 20 mg/kg | *Intermittent dosing* (once/week):<br>Influenza-like syndrome with malaise and headache<br>Acute hemolytic anemia within 2 to 3 hr of dosing<br>Acute renal failure with/without hemolysis<br>Fever, rash, lymphadenitis<br>*Daily dosing*<br>Hepatitis epecially in alcoholics, elderly, and those with liver disease as well. |
| Isonicotinic acid hydrazide (INAH) | 300 mg | 3 to 5 mg/kg | Sensory (and motor) peripheral neuropathy due to pyridoxine deficiency<br>Mental disturbances, incoordination, optic neuritis, convulsions<br>Liver damage<br>Precipitation of epilepsy<br>Inhibition of phenytoin metabolism |
| Ethambutol | 600 to 900 mg | 15 mg/kg | Optic neuritis dose related, partly reversible, affecting one or both eyes<br>Rarely peripheral scotoma<br>Red-green color blindness<br>Decreased urate clearance |
| Streptomycin | 0.75 to 1 gm (Intramuscular) | 30 mg/kg | Increases plasma urine acid by decrease of renal tubular clearance; may cause arthralgia of large, and small joints<br>Neuromuscular block<br>Dose-related renal tubular toxicity |
| Pyrazinamide | 1.5 to 2 gm | 20 to 30 mg/kg | Nephrotoxic<br>Hepatitis with high doses (40 to 50 mg/kg) only<br>Local injection in pleural or peritoneum may cause respiratory paralysis due to curare-like competitive inhibition<br>Different types of skin rashes<br>Drug fever with eosinophilia<br>Contraindicated in liver and kidney disease |
| Paramino salicyclic acid | 10 to 12 gm | 300 mg/kg<br>Crystalluria | Unpleasant taste, gastrointestinal irritation, and nausea vomiting and diarrhea<br>Agranulocytosis and thrombocytopenia<br>Hemolytic anemia<br>Hypothyroidism, goiter diabetes mellitus<br>Hepatitis |
| Thiacetazone | 150 mg | 2 mg/kg | Gastrointestinal symptoms such as nausea, vomiting diarrhea<br>Erythma multiforme<br>Agranulocytosis |
| Ethionamide/ Prothionamide | 375 mg | | Gastrointestinal symptoms |
| Capreomycin | 1gm (Intramuscular) | | Vestibular toxicity |
| Cycloserine | 1gm (Intramuscular) | | CNS toxicity |
| Kanamycin | 1gm (Intramuscular) | | More severe side effects than streptomycin |

**Table 17.2: Treatment regimens for tuberculosis***

| *6-month regimens* | | |
|---|---|---|
| *Drugs* | *Phase 1:2 months* | *Phase 2:4 months* |
| Isoniazid | 5 mg/kg daily | 5 mg/kg daily |
| Rifampicin | 10 mg/kg daily | 10 mg/kg daily |
| Pyrazinamide | 30 mg/kg daily | |
| Supplemented, in areas where resistance to one of these drugs is demonstrated by | | |
| Streptomycin | 15 mg/kg daily | |
| or | | |
| Ethambutol | 25 mg/kg daily** | |
| *8-month regimens* | | |
| *Drugs* | *Phase 1:2 months* | *Phase 2:4 months* |
| Isoniazid | 5 mg/kg daily | 5 mg/kg daily |
| Rifampicin | 10 mg/kg daily | |
| Pyrazinamide | 30 mg/kg daily | |
| Thioacetazole | | 2.5 mg/kg daily |
| together with | | |
| Streptomycin | 15 mg/kg daily | |
| or | | |
| Ethambutol | 25 mg/kg daily** | |

* Unless otherwise indicated, doses are suitable for both adults and children
** 15 mg/kg for children

acid hydrazide (INAH), rifampicin, ethambutol, and pyrazinamide are given together for an initial intensive phase lasting 2 months. This is followed by administration of INAH and rifampicin only for another 4 months in continuation phase. Alternatively, a 9-month treatment can also be given. In this regimen INAH, rifampicin, and ethambutol are administered for an initial intensive phase of 2 months followed by INAH and rifampicin only daily until the end of 9 months (Table 17.2).

Scrofuloderma may require surgical intervention in addition to antitubercular drugs. Similarly, a persistent nodule of lupus vulgaris and lesions of TBVC may have to be excised. In selected cases, the lupoid nodules within the scarred areas may be conveniently destroyed by cryotherapy or electrocautery.

## RECOMMENDED READING


1. Anonymous: WHO Medical Prescribing Information. Drugs used in mycobacterial disease. Geneva: World Health Organization 1991; 12-13.
2. Lever WF, Schaumberg-Lever G. Bacterial Disease. In Lever WF, Schaumberg-Lever G (Eds): *Histopathology of the Skin*. 7th edn. Philadelphia: JB Lippincott 1990.
3. Sehgal VN, Bhattacharya SN, Jain S *et al*. Cutaneous tuberculosis: The evolving scenario. *Int J Dermatol* 1994;33:94-104.
4. Sehgal VN, Jain MK, Srivastava G. Changing patterns of cutaneous tuberculosis: A prospective study. *Int J Dermatol* 1989;28:231-236.
5. Sehgal VN, Wagh SA. Cutaneous tuberculosis: Current concepts. *Int J Dermatol* 1990;29:237-252.

6. Sehgal VN. Cutaneous tuberculosis. *Dermatol Clin* 1994;12:645-653.
7. Sehgal VN, Sardana K, Bajaj P *et al*. Tuberculosis verrucosa cutis: antitubercular therapy, a well-conceived diagnostic criterion. *Int J Dermatol* 2005;44:230-232.
8. Sehgal VN, Sardana K, Sharma S. Inadequacy of clinical and/or laboratory criteria for the diagnosis of lupus vulgaris, re-infection cutaneous tuberculosis: fallout/implication of 6 weeks of anti-tubular therapy (ATT) as a precise diagnostic supplement to complete the scheduled regimen. *J Dermatolog Treat* 2008;19:164-167.

# 18 Chapter Herpes Simplex

Herpes simplex is caused by herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2). It contains a double stranded linear DNA, a surrounding icosahedral protein capsid consisting of 162 capsomers, a tegument composed of fibrillar material (protein), and an impermeable envelop, consisting of lipids, polyamines, and virus specific glycoproteins. The two different serotypes (1 and 2) of HSV can be differentiated by serologic, biologic (tissue culture plaque and neurotropic differentiation), and biochemical (DNA homology) studies.

Humans are the only natural host of HSV. The virus is first introduced into a susceptible host by direct mucocutaneous contact with infectious material. The viral envelop fuses with the plasma membrane. The capsid is uncoated in the cytoplasm, and the core DNA enters the nucleus. Early transcription follows, utilizing the host DNA dependent RNA polymerase. The necessary virus coded enzymes are synthesized and viral DNA replication occurs. The new herpes virus is assembled in the nucleus, and the envelopment takes place at the inner lamella of the nuclear membranes. Subsequently, the virus emerges from the infected cell.

After epithelial inoculation, the virus travels along the sensory nerves to reach the regional sensory ganglia, via retrograde intraxonal transport. This process starts 24 hours after epithelial inoculation. In the ganglia, the virus is dormant. It may be reactivated either by ganglionic or skin trigger. In the former, on reactivation the virus travels down the peripheral nerve to the epidermal cells, producing skin lesions. In the latter, microfoci of infection are continuously produced but are eliminated by the immune defences. However, if the immunity is lowered, these microfoci becomesymptomatic. Reactivation may be triggered by fever, systemic infection, menses, physical trauma, emotional stress, sunburn, and administration of corticosteroids and immunosuppressive drugs.

## CLINICAL FEATURES

It may manifest either as primary or recurrent infection. The primary infection indicates an individual's first exposure to either HSV-1 or HSV-2. This may result in the production of neutralizing antibodies, cytotoxic antibodies, and complement fixation antibodies. The incubation period for primary infection is 3 to 12 days. It runs a clinical course of 1 to 3 weeks. The lesions are usually extensive and accompanied by constitutional symptoms of headache, fever, and malaise. Virus excretion may persist for 15 to 42 days. After primary infection, HSV remains dormant in sensory ganglia and may be periodically reactivated to cause recurrent

episodes. The recurrent lesions are much less severe, restricted to smaller areas and constitutional symptoms are mild or absent. The lesions may heal in 7 to 10 days. Occasionally, the primary infection is asymptomatic. There is only serologic evidence of subclinical primary infection. In such patients, the first clinical manifestation of herpes is known as first episode infection.

### Primary Infection

It begins with a prodrome of severe localized tenderness. It is followed by the eruption of grouped, tense vesicles over an erythematous base. They may later rupture to form polycyclic erosions. The regional lymph nodes are enlarged. They are discrete, firm, and tender. The lesions are accompanied by high grade fever. Purulent, malodorous discharge may accompany oral or vulvovaginal infection. Urethritis may be accompanied by dysuria and/or discharge. Tenesmus and constipation may be associated with anorectal infection.

*Herpetic gingiostomatitis:* It is heralded by high fever, regional lymphadenopathy, and malaise. The vesicles may break to form erosions and ulcers. They affect the oral mucosa, tongue, and tonsils. Tonsilitis and/or pharyngitis may be present. The patient usually has pain, foul breath, difficulty in opening the mouth, and swallowing. This may produce dehydration and acidosis. The herpetic gingivostomatitis needs to be differentiated from streptococcal infection, infectious mononucleosis, thrush, erythema-multiforme, Stevens-Johnson syndrome, Behçet's syndrome, pemphigus vulgaris, and herpangina.

*Inoculation herpes:* It develops on the paronychial region. The virus is inoculated as a result of trauma. There is appearance of grouped vesicles over an erythematous base, the 'herpetic whitlow'. Regional lymph nodes are enlarged and tender.

*Herpetic vulvovaginitis:* It is heralded by marked erythema and edema of the vulva. This is followed by eruption of grouped vesicles over an erythematous base. The vesicles rupture within 24 to 48 hours after eruption to form polycyclic erosions. Regional lymph nodes are enlarged and tender. There may be vaginal discharge. Constitutional symptoms of fever, headache, and malaise precede and accompany herpetic vulvovaginitis. Urinary retention may be a complication. The lesions usually heal within 2 to 6 weeks.

*Herpetic cervicitis:* It is often asymptomatic. However, it is a risk to the fetus in a pregnant woman. Herpes virus, contracted *in utero,* may result in anomalies in the newborn like microcephaly, microphthalmos, encephalitis, chorioretinitis, and intracerebral calcification. Maternal genital herpetic infection may also be associated with abortions, stillbirths, and premature delivery. Seventy percent of neonatal herpes simplex are caused by HSV-2 and acquired as the child passes through the infected birth canal. The neonatal infection may be localized skin infection or systemic and present as encephalitis, hepatitis, pneumonia, and coagulopathy. The risk of infection to the neonate is 3 to 5 percent in recurrent infection and 50 percent in case of primary infection. Herpetic infection during labor necessiates cesarian section before the membranes rupture or within four hours of it.

*Primary herpes genitalis in men:* It starts with pain, burning, and redness over the genitalia. This is followed by the eruption of grouped vesicles, which rupture to form polycyclic erosions (Fig. 18.1). Inguinal lymph nodes are

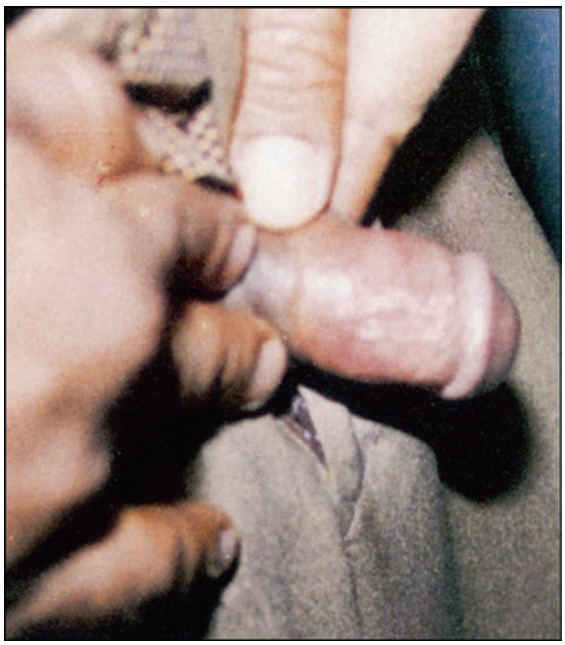


**Figure 18.1:** Herpes progenitalis: Grouped, vesicular lesions over the erythematous base

enlarged and tender. Constitutional symptoms are usually present. Urethral discharge may be an accompaniment.

*Anorectal herpes:* It is characterized by the typical vesicular eruption which subsequently ulcerates. Tenesmus and constipation may accompany anorectal herpes.

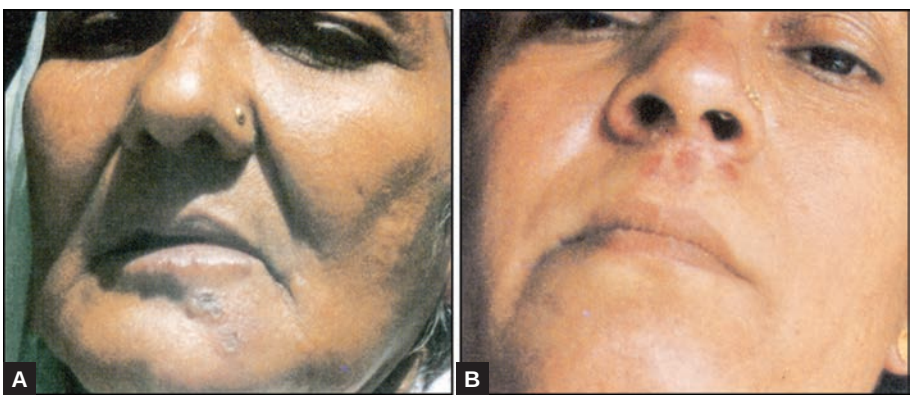
*Disseminated herpes simplex:* This may be encountered in infants and children up to 3 years of age. Malnourishment, kwashiorkor, measles, immunosuppressive drugs, and atopic dermatitis, predispose to disseminated infection. It may also develop in patients with acquired immunodeficiency syndrome (AIDS). The disease begins with gingivostomatitis and then disseminates to involve the liver, gastrointestinal tract, and central nervous system. Viremia may result in death.

## Recurrent Infection

There is a prodrome of mild tenderness, and slight erythematous blush followed by the eruption of grouped vesicles (Figs 18.2A and B). The vesicles, initially clear turn purulent and then dry to form crust. Healing occurs within 7 to 10 days. Tender regional lymphadenopathy accompanies recurrent herpes.

The following complications may develop:

- Herpetic pharyngitis
- Herpetic urethritis
- Aseptic meningitis
- Urinary retention
- Tenesmus and constipation
- Erythema multiforme and Stevens-Johnson syndrome




**Figures 18.2A and B:** Herpes simplex affecting the mucocutaneous junction of the oral cavity

- Dissemination of herpetic infection in immunosuppressed individuals
- Prenatal and neonatal herpes simplex infections
- Women with recurrent herpes progenitalis are prone to cervical carcinoma and advised yearly Papanicolaou smears.

## DIAGNOSIS

The diagnosis of herpes simplex is clinical. It may be supplemented by various diagnostic procedures.

- Cytologic smear of the vesicle reveals large multinucleate giant cells containing 8 to 10 nuclei, varying in shape and size. An intranuclear inclusion body may be identified
- Skin biopsy reveals: (i) an intraepidermal lesion in mid to upper epidermis, (ii) ballooning and/or reticular degeneration of cells, (iii) acantholytic cells, (iv) large, multinucleated viral giant cells. Intranuclear inclusions may be identified in giant cells.
- Virus may be cultured from the vesicle fluid.
- Direct immunofluorescence using monoclonal antibody.
- Identification of the virus under electron microscope.

## TREATMENT

The treatment of herpes simplex may be considered into symptomatic and specific. The antiherpetic drugs are classified as the following (Table 18.1).

*First generation:* (i) idoxuridine, (ii) trifluridine, and (iii) adenine arabinoside.

*Second generation:* (i) acyclovir, (ii) bromovinyldeoxyuridine (BVdU), (iii) Fluoroiodoaracytosine (FIAC), and (iv) phosphonoformate (PFA).

*Third generation:* (i) adenosine arabinoside 5′-monophosphate, (ii) acyclovir analog, namely dihydroxypropoxymethylguanine (DHPG).

*Others:* (i) interferon, (ii) ribaravin, and (iii) isoprinosine.

**Table 18.1: Treatment of herpes simplex**

| *Types of infections* | *Specific treatments* | *Symptomatic treatment* |
|---|---|---|
| 1. Potentially catastrophic infection | 500 mg/m$^2$ of acyclovir, intravenous, every 8 hours | Nil |
| 2. Herpes in immunocompromised host | —do— | —do— |
| 3. Herpes encephalitis | —do— | —do— |
| 4. Eczema herpeticum | —do— | —do— |
| 5. Primary and first episode herpes infection | a. 200 mg of acyclovir 5 times a day for 5 days. Begin treatment within 72 hours of the onset of signs and symptoms.<br>b. Topical application of 5 percent acyclovir ointment (Herperax) every 3 hours | 1. Cool compresses with Burrow's solution for 10 min, 3 to 4 times a day.<br>2. Cleansing mouthwashes with tetracycline suspension or potassium permanganate in herpetic gingivostomatitis |
| 6. Recurrent herpes | 800 mg of acyclovir twice a day or 500 mg five times a day for 5 days. Begin treatment within 48 hours of the onset of signs and symptoms. | 3. Sitz's bath for vulvovaginitis and anorectal herpes.<br>4. Salicylates and other non-steroidal anti-inflammatory drugs<br>5. Topical antibiotics to cure secondary infection. |

Acyclovir is most widely used antiviral agent. It is an acyclic nucleoside analog, with activity against herpes simplex (HSV-1 and 2) and herpes zoster virus. It is a selective substrate for the viral thymidine kinase. The virus specific thymidine kinase concentrates acyclovir in the herpes infected cells by phosphorylating it to monophosphate derivative. Cellular kinase then converts the monophosphate derivative to acyclovir triphosphate. This is a competitive inhibitor of viral DNA polymerase and DNA chain terminator and inhibits viral DNA synthesis. It reduces viral shedding, decreases the time for healing and crusting, and reduces pain. It also prolongs remission; however, recurrence occurs on stopping the drug. The effect of oral acyclovir on recurrent herpes are as impressive as on primary infection provided the treatment is begun within 48 hours of the onset of signs and symptoms. Intravenous acyclovir is used for the management of potentially catastrophic herpes infections. Topical acyclovir has a modest effect on primary and first episode of herpes progenitalis if begun within 72 hours; however, it does not abort recurrent infections.

## RECOMMENDED READING

1. Corey L. First episode, recurrent and asymptomatic herpes simplex infections. *J Am Acad Dermatol* 1988;18:169-172.
2. Fiumara NJ. Herpes simplex. *Clin Dermatol*. 1989; 7:23-36.
3. Flowers FP, Araujo OE, Turner LA. Recent advances in antiherpetic drugs. *Int J Dermatol*. 1988; 27:612-616.
4. Landy HJ, Gossman JH 3rd. Herpes simplex virus. *Obstet Gynecol Clin North Am* 1989;16:405-515.

19 Chapter

# Herpes Zoster

Herpes zoster is caused by varicella zoster virus (VZV). Following a primary infection, the virus lies dormant, residing in the posterior (dorsal) root and/or cranial nerve ganglia. Reactivation of the latent infection in the partial immune host results in zoster. Reactivation may be triggered by various precipitating factors namely physical injuries, mental trauma, febrile illnesses, lymphoproliferative malignancies, leukemia, and UV radiation. Immunosuppressive therapy for lymphoproliferative diseases and transplantation predispose to recurrent and/or disseminated zoster. In patients known to be at risk for acquired immunodeficiency syndrome (AIDS), zoster may herald the depression of cell-mediated immunity. Old age may also predispose to frequent and severe zoster and postherpetic neuralgia.

Herpes zoster is closely related to chickenpox virus on microbiological, and serological basis. It is a medium sized virus that contains DNA and replicates in the cell nucleus. It is icosahedral and contains 162 capsomers surrounded by an envelop. It has a tendency to produce latent infections. Periodic reactivation is its hallmark. Varicella (Chickenpox) is the primary exogenous VZV infection while herpes zoster represents reactivation of an endogenous infection that has persisted in the dormant phase following an earlier primary infection.

## CLINICAL FEATURES

Zoster is heralded by severe continuous pain in the distribution of the affected nerve root. After 3 to 4 days, the skin becomes erythematous. At this time, the patient may also be febrile. This is followed in 3 to 5 days by the eruption of several groups of vesicles on an erythematous and edematous base (Fig. 19.1). The eruption appears in patches of various sizes. The early vesicles contain a clear serum, but after a few days the contents become purulent, and dry to form crust, which fall of within 1 to 2 weeks. Occasionally,

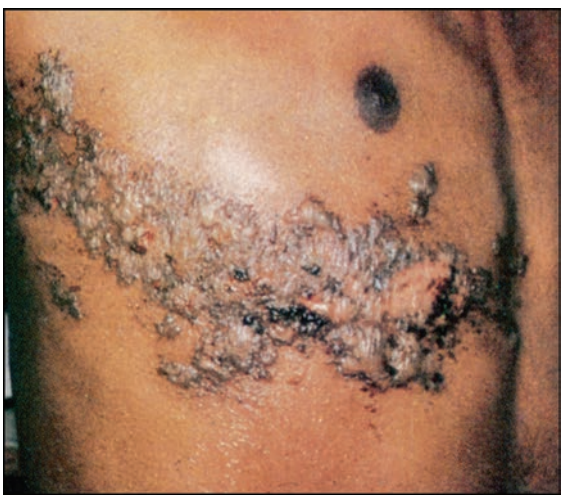


**Figure 19.1:** Unilateral, grouped, vesicles on an erythematous/edematous base, occupying the right thorax

the vesicles may become hemorrhagic or necrotic and may ulcerate. Bullous lesions are unilateral. Any dorsal root ganglion may be affected. However, thoracic (55%), cranial (20%), lumbar (15%), and the sacral (5%) are most commonly involved. Among the cranial nerve ganglia, trigeminal nerve is most often affected. Bilateral and multidermatomal involvement is uncommon. The lesions of zoster erupt for several days. However, it is a self-limiting disorder. It runs a course of 2 to 3 weeks. The pain usually subsides as the eruptions fade, but occasionally, especially in old people, it may be followed by persistent and intractable neuralgia, which may last for several months, the postherpetic neuralgia.

Zoster usually heals without complications. However, the following sequelae may be occasionally encountered:

- Postherpetic neuralgia, an extremely painful, chronic, unremitting pain, encountered in older patients
- Lesions on the tip of the nose herald involvement of the nasociliary branch of the ophthalmic division of the trigeminal nerve. The vesicles may subsequently appear on the cornea, leading to corneal ulceration and keratoconjunctivitis. Scarring and impairment of vision may result (*ophthalmic herpes*) (Fig. 19.2).
- Segmental muscle wasting may occur from involvement of the motor root
- Invasion of the spinal cord and brain may result in myelitis and encephalitis, respectively
- Involvement of sacral root may result in urinary retention
- Ramsay-Hunt syndrome is a zoster of geniculate ganglion. Sensory fibers from VIIth nerve innervate deep facial tissue. Hence jaw pain is present. Vesicles follow ipsilateral sensory fibers to the uvula, palate and auricle. Paresis/paralysis affects muscle of facial expression.

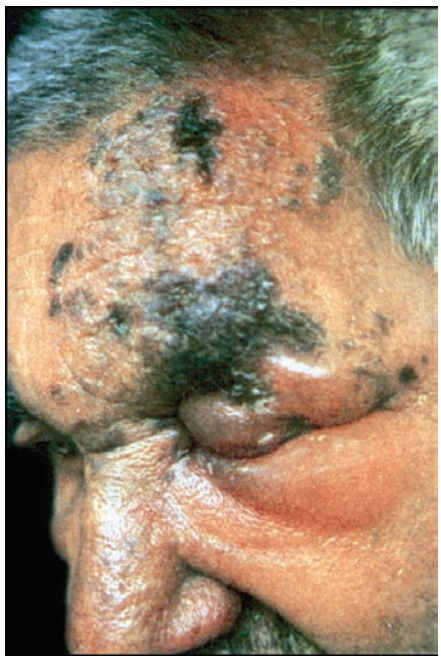


**Figure 19.2:** Herpes zoster ophthalmicus

## DIAGNOSIS

The diagnosis of herpes zoster is clinical. It may be supplemented by various diagnostic procedures.

- Cytologic smear of the vesicle reveals large multinucleate giant cells and ballooning and/or reticular degeneration. The giant cells contain 8-10 nuclei, varying in shape and size. An intranuclear inclusion body may be identified
- Skin biopsy reveals the following:
  - An intraepidermal lesion in mid to upper epidermis
  - Ballooning and/or reticular degeneration of cells
  - Acantholytic cells

**Table 19.1: Treatment of herpes zoster**

| *Clinical types* | *Treatments* | *Status* |
|---|---|---|
| 1. Disseminated zoster | 500 mg/$m^2$ of acyclovir, intravenously every four hours for 7 days. | 1. Aborts dissemination.<br>2. Decreases pain.<br>3. Reduces the time required for healing. |
| 2. Localized herpes zoster | 1. 800 mg of acyclovir, orally, five times a day for 7 days. | 1. Reduces pain.<br>2. Arrests new lesion formation provided the treatment is started within 48 hours.<br>3. Promotes healing. |
| | 2. Cool compresses using 1 in 20 burrow's solution.<br>3. Topical application of 5 percent acyclovir, every 4 hours.<br>4. Application of shake lotions like calamine lotion.<br>5. 400 mg of ibuprofen (Brufen) thrice a day.<br>6. 500-1000 µg of Triredisol-H (vit $B_{12}$) intramuscular, twice a week for 5 weeks.<br>7. 40-60 mg of prednisolone in two equally divided doses at 9 AM and 6 PM for 5 to 7 days and subsequently tapered over 3 to 4 weeks. | 1. Aborts postherpetic neuralgia. |
| Postherpetic neuralgia | 1. Topical application of capsaicin cream (Zostrix), thrice a day.<br>2. 75 mg of amitriptyline four times a day along with 4 mg of perphenazine or 1 mg of fluphenazine hydrochloride four times a day.<br>3. 600 to 800 mg of carbamazepine (Tegretol) or 300 to 400 mg of phenytoin sodium (Dilantin) in two or three divided doses along with 50 to 100 mg of nortriptyline.<br>4. 1000 mg of carbamazepine (Tegretol) every day with 75 mg of cloimipramine. | |

  - Large, multinucleated viral giant cells. Intranuclear inclusions may be identified in giant cells.
- Virus may be cultured from the vesicle fluid
- Direct immunofluorescence using monoclonal antibody
- Identification of the virus under electron microscope.

## TREATMENT

Herpes zoster is a self-limiting condition. The uncomplicated cases should be managed by drying compresses and analgesics to relieve pain. Acyclovir, a purine nucleoside, is effective in localized and disseminated herpes zoster. Post-herpetic neuralgia may be aborted in older patients by administering oral corticosteroids. (Table 19.1).

## RECOMMENDED READING

1. Bernstein JE, Bickers DR, Dahl MV *et al*. Treatment of chronic posthepatic neuralgia with topical capsaicin. A preliminary study. *J Am Acad Dermatol* 1987;17:93-96.
2. Huff JC. Antiviral treatment in chickenpox and herpes zoster. *J Am Acad Dermatol* 1988;18:204-206.

# 20 Chapter

# Warts

Warts are benign epidermal proliferations, caused by infection with human papillomavirus (HPV). Its association with various carcinomas has been recently recognized.

The papillomaviruses are members of the family papovaviridae. It contains double-stranded, circular, supercoiled DNA enclosed in an icosahedral capsid made up of 72 capsomers. The virion has a molecular weight of $5 \times 10^6$ daltons. The virus has no envelop, and is resistant to freezing, and desiccation. The DNA genome of papillomavirus has 8000 base pairs and the capsid diameter is 55 nm. Serologic typing, as applied to some other viruses, is not useful for HPV. Therefore, DNA hybridization has been used as a means of separating different HPV's. Viruses that hybridize by less than 50 percent with other known types are classified as a new type. To date 55 HPV types have been identified. Many of these types have significant clinicopathologic correlation (Table 20.1).

The transmission of HPV occurs by close contact with an infected person. Small breaks in the skin are necessary to inoculate HPV. Autoinoculation is responsible for the local spread of the warts. Many factors are responsible in the infectivity of HPV, including the number of viral particles, the degree and duration of the exposure and the host's defence against HPV infection. Cell-mediated immunity is important in the host defence against HPV.

## CLINICAL FEATURES

The clinical lesions that result from infection with HPV, are classified as cutaneous and extracutaneous.

### Cutaneous Lesions

- Common warts (verrucosa vulgaris)
- Filiform warts
- Flat warts (plane warts)
- Plantar warts (myrmecia and mosaic types)
- Palmar warts
- Anogenital warts
- Bowenoid papulosis.

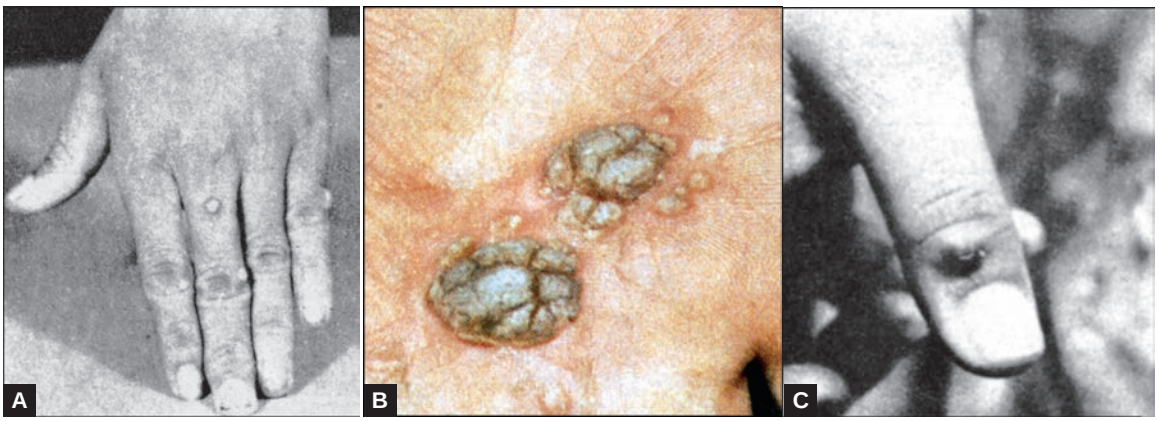
### Extracutaneous Lesions

These are localized to the orificial mucous membranes and include:

- Oral common warts
- Oral condylomata acuminata
- Focal epithelial hyperplasia
- Oral florid papillomatosis
- Nasal papillomas
- Conjunctival papillomas
- Laryngeal papillomatosis
- Cervical warts.

#### *Common Warts*

They are rough keratotic papules that may appear singly or grouped on cutaneous surface. They are commonly located on the dorsal surface of the hands, fingers, and knees




**Figures 20.1A to C:** Common warts: Rough, keratotic papules singly or in groups

(Figs 20.1A to C). Periungual wart may involve the hyponychium and nailbed and may result in nail dystrophy.

### *Flat Warts*

They are slightly elevated, smooth papules, that are less than 5 mm. They may be flesh colored, gray or brown and are usually located over the face, hands, and legs.

### *Plantar Warts*

They have a rough, keratotic surface studded with punctate black dots, representing thrombosed capillaries, and a peripheral rim of thickened skin. Multiple warts may coalesce to form a large plaque, the 'mosaic wart'. The deep endophytic lesions are termed as 'myrmecia'. They are usually located beneath the pressure points such as heel or metatarsal heads, and cause pain on walking.

### *Filiform Warts*

They appear as long, slender, filiform projections.

### *Genital Warts*

They may be either hyperplastic, sessile (papular); verruca vulgaris like or flat warts.

- *Hyperplastic:* They express as single or multiple vegetative lesions. The latter are formed by multiple confluent soft, pinkish or greyish white papillomatous projections. They may occasionally proliferate to form a cauliflower mass. The lesions are usually seen in warm and moist areas and are usually localized to the inner surface of the prepuce, frenulum, coronal sulcus, glans penis or external urinary meatus. In females it occupies vaginal introitus, inner aspect of vulva, vestibule, and vagina.
- *Sessile (papular):* They are usually seen as multiple, small discrete and smooth papules. Shaft of the penis in males and the vulva and/or perianal region in females are its common location.
- *Flat warts:* They are seen as white spots with punctation over uterine cervix and are identified on colposcopy. Pap smears may be performed to demonstrate koilocyte.
- *Verrucosa vulgaris type warts:* They are recognized as single or multiple with rough irregular surface, simulating common warts. They affect the shaft of the penis, outer aspect of labia, perineum, pubis, and groin.

### *Bowenoid Papulosis*

It consists of multiple, small, verrucous or velvety, pigmented papules that involve the anogenital region of young adults. Histopathology reveals changes of carcinoma *in situ* suggestive of Bowen's disease.

### *Epidermodysplasia Verruciformis (EV)*

It is a rare cutaneous disorder characterized by persistent, refractory HPV infection manifesting as disseminated wart like, flat lesions and erythematous hyper or hypopigmented macules. An autosomal recessive pattern of inheritance has been suggested. A deficient CMI predisposes to EV. One-third of the patients may develop malignant degeneration of the cutaneous lesions on sun exposed areas.

### HPV Infection and Carcinoma

The relationship between HPV and human carcinoma has focused mainly on carcinoma of the cervix. Others are the actinically induced squamous cell carcinoma in EV patient, laryngeal and bronchial carcinoma.

## DIAGNOSIS

It is clinical. It may be supplemented by histopathology and detection of HPV.

Microscopic examination of hematoxylin-eosin stained section of common warts reveals: (i) parakeratosis, (ii) hyperkeratosis, (iii) papillomatosis, (iv) acanthosis. The acanthotic reteridges tend to point radially toward the center of the lesion, (v) vacuolated cells, with small basophilic nuclei surrounded by a clear halo and pale cytoplasm (koilocytes) (Fig. 20.2) are found in the upper stratum granulosum. These cells lack keratohyaline granules.

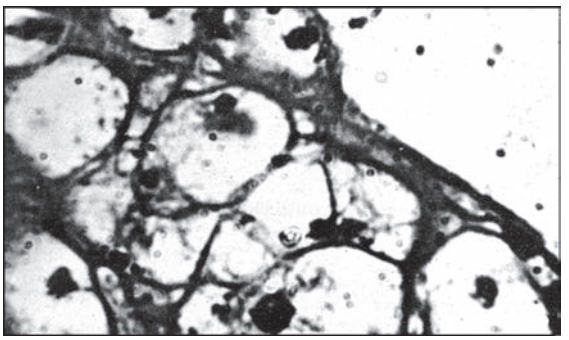


**Figure 20.2:** Koilocyte. Vacuolated cells, small basophilic nuclei surrounded by a clear halo and pale cytoplasm

The flat warts lack the papillomatosis and parakeratosis seen in common warts. Anogenital warts have marked acanthosis and rete ridges display pseudoepitheliomatous hyperplasia.

### Detection of HPV

Recent advances in molecular biology have facilitated the detection of HPV DNA within the tissue. The techniques used are as follows:

- Nucleic acid hybridization, which allows identification of specific DNA or RNA sequences.
- Cleavage of DNA by restriction endonucleases.
- DNA cloning by the use of recombinant molecules. Southern blotting is the technique used to identify HPV DNA
- Polymerase chain reaction, which allows the targeted DNA sequence to be enzymatically amplified before southern blotting. It improves the sensitivity of the test. A single molecule of HPV DNA may be detected in $10^5$ cells by this techniques.

## TREATMENT

Treatment is outlined in Table 20.1.

**Table 20.1: Clinicopathologic correlation of HPV**

| *Clinical type of wart* | | *Type of HPV* |
|---|---|---|
| Painful palmar/plantar warts | : | 1, 4 |
| Common warts | : | 2, 4, 26 to 29 |
| Flat warts | : | 3, 10, 26 to 29, 41 |
| Genital warts | : | 6, 11, 16, 18, 30, 31, 32, 42, 43, 51 to 55 |
| Butcher's wart | : | 7 |
| Oral focal epithelial hyperplasia | : | 13 |
| Epidermodysplasia verruciformis (EV) | : | 5, 8, 9, 12, 14, 15, 17, 19 to 25, 36 to 38, 46, 47, 49, 50 |
| Bowenoid papulosis | : | 16, 18, 31, 32, 34, 39, 42, 48, 51 to 54 |
| Cervical carcinoma | : | 16, 18, 31, 32, 34, 39, 42, 48, 51 to 54 |
| Laryngeal papilloma | : | 6, 11, 43, 44, 55 |

**Table 20.2: Treatment of warts**

| *Types* | *Modalities of treatment* | *Newer therapy* |
|---|---|---|
| 1. Common wart | a. Electrodesiccation and curettage<br>b. Cryosurgery with liquid nitrogen<br>c. Painting the warts with keratolytic paints containing 5 to 20 percent salicylic acid and 5 to 20 percent lactic acid. They are applied at night after cleaning the wart and rubbing it with a pumice stone.<br>d. Topical application of 100 percent trichloroacetic acid every week.<br>e. 25 percent podophyllin resin in compound tincture of benzoin. | |
| 2. Plantar wart | a. Enucleation of the wart by blunt dissection.<br>b. Topical application of keratolytic paints containing 5 to 20 percent salicylic acid + 5 to 20 percent lactic acid after washing and flattening the wart with pumice stone.<br>c. Application of 25 percent podophyllin resin in tincture benzoin overnight.<br>d. Soaks in 3 percent formalin for 15 min every night. | |
| 3. Filiform warts | a. Electrosurgery<br>b. Cryosurgery | |
| 4. Plane warts | a. Topical application of tretinoin (Vitamin A acid) 0.05 percent in cream base every night.<br>b. 5 percent benzoyl peroxide gel<br>c. 5 percent 5-fluorouracil applied twice daily. | |
| 5. Condylomata acuminata | 25 percent podophyllin in compound tincture of benzoin applied every 3rd or 4th day. The surrounding area should be protected by application of vaseline. After the resin has dried, the wart is sprinkled with powder to prevent transfer of podophyllum to apposing skin. Area is washed with water after 3 to 4 hours. | a. Podophyllotoxin 0.5 percent in ethanol applied twice daily for 3 days every week.<br>b. Intralesional injection of interferon alfa 2b in doses of $1 \times 10^6$ IU thrice a week for 3 weeks.<br>c. $1 \times 10^6$ IU/$m^2$ of interferon alfa 2b, intramuscular or subcutaneous. |
| 6. Disseminated warts in immunocompromized patient | 1 mg/kg/day of etretinate orally till warts disappear | |
| 7. Bowenoid papulosis | 1. Topical application of 5 percent 5-fluorouracil<br>2. Surgical removal. | |

## RECOMMENDED READING

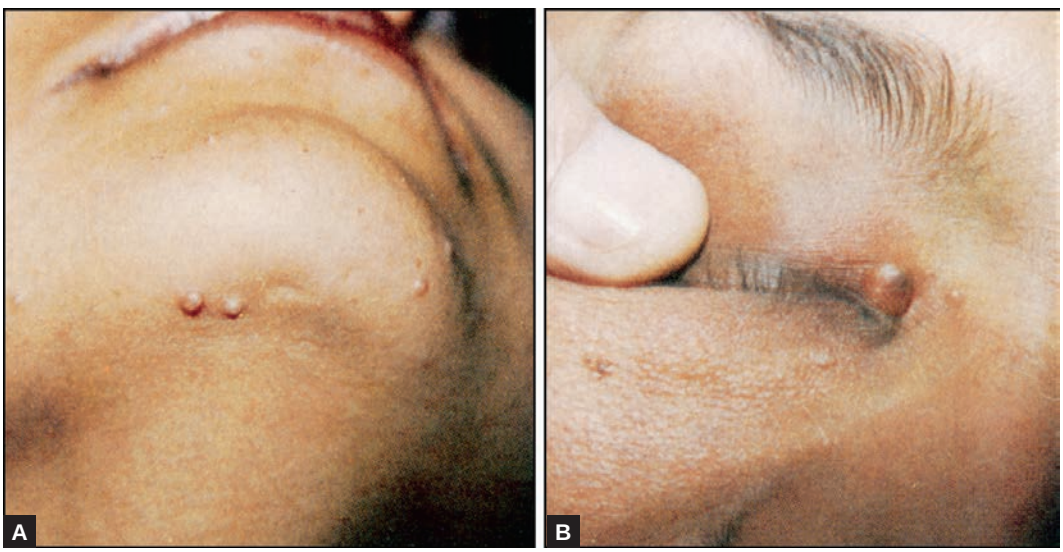
1. Beutner KR. Human Papillomavirus infection. *J Am Acad Dermato* 1989;20:114-123.
2. Cobb MW. Human papillomavirus infection. *J Am Acad Dermatol* 1990;22:547-566.
3. Sehgal VN, Koranne RV, Srivastava SB. Genital warts: Current status. *Int J Dermatol* 1989;28:75-85.

# 21 Chapter Molluscum Contagiosum

Molluscum contagiosum is a viral tumor, caused by a DNA-containing poxvirus. Molluscum contagiosum virus (MCV) is a brick-shaped particle, 300 × 200 × 100 nm in size. It replicates in aggregates within the cytoplasm of the infected cells. Basal cell proliferation and epidermal transit time are increased in infected epidermis.

## CLINICAL FEATURES

Molluscum contagiosum is characterized by dome-shaped, waxy pink papules or nodules 2 to 5 mm in size. Central umbilication is its hallmark. Some lesions may attain a size up to 1 cm. They are at first firm, solid, and flesh colored. However, as they mature, they tend to become softened and pearly white in color (Figs 21.1 A and B). Some lesions may suppurate. They are distributed over the face, hands, lower abdomen, and genitalia. The mucous membranes of the lip, tongue, and buccal mucosa may also be affected. The lesions are usually a few, at times they may be multiple. They are asymptomatic. Gigantic lesions of size 1 cm or more, may occasionally develop inflammation. Rarely the lesions may become horny (molluscum contagiosum carnuatum).




**Figures 21.1A and B:** Pearly-white, umbilicated papules

The disease is contracted by direct contact with infected skin, and by autoinoculation. It may also be transmitted sexually. It affects children, and young adults. Incubation period ranges from 2 to 3 weeks. Immunosuppression secondary to drugs like corticosteroids, methotrexate, and infection with human immunodeficiency virus (HIV) may predispose to widespread and recalcitrant molluscum contagiosum. It usually runs a self-limiting course of 6 to 9 months, but occasionally the lesions may persist for months or years.

## DIAGNOSIS

Pearly-white, dome shaped papule or nodule with central umbilication is distinctive. Diagnosis may be confirmed by incising one of the papules, squashing the contents between two glass slides and staining it with Wright's or Giemsa's stain. Examination under a low power of the microscope reveals ovoid, smooth-walled, homogenous cytoplasmic masses consisting of mature, immature, and incomplete virions along with cellular debris. They measure 25 nm in diameter.

Microscopic examination of hematoxylin—eosin stained section reveals, an acanthoma with downward proliferation of rete-ridges, and envelopment by connective tissue to form a deep crater. The cytoplasm of the prickle cell contains numerous small eosinophilic and later basophilic inclusion bodies called molluscum-bodies, or Henderson-Patterson bodies. Their bulk compresses the nucleus to the side of the cell. A fully developed lesion depicts a crater near the surface, which extends into the lobules. The crater contains the hyalinized molluscum bodies.

## TREATMENT

The following modalities are useful:

- Removal of the lesion with a sharp curette.
- Cryotherapy with liquid nitrogen or dry ice.
- Electrodesiccation.

## RECOMMENDED READING

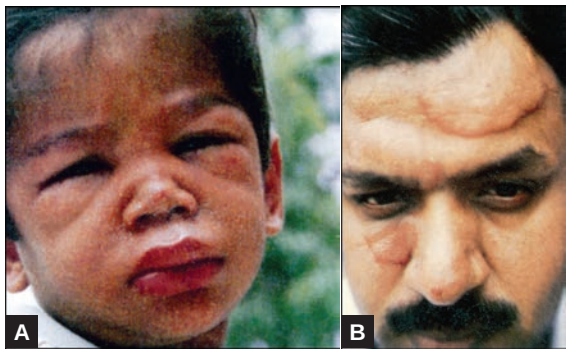
1. Brown ST, Nalley JF, Kraus JF. Molluscum contagiosum: a review, *Sex Transm Dis* 1981;8:227-234.
2. Porter CD, Muhleman MF, Cream JJ *et al.* Molluscum contagiosum: Characterization of viral DNA and clinical features. *Epidemiol Infect* 1987; 99:563-566.
3. Reed J, Parkinson RP. The histogenesis of molluscum contagiosum. *Am J Surg Patho*l 1983;1:161-166.

# 22 Chapter

# Urticaria

Urticaria is a vascular reaction pattern characterized by transient, erythematous swellings over the skin and/or mucous membranes. These swellings represent localized areas of edema, due to extravasation of the protein rich fluid from the dilated blood vessels and are termed wheals. They are usually transient, and resolve in a few hours with the resorption of the extravasated fluid. The wheals vary from pinpoint to fist size or larger. They enlarge by peripheral extension and assume bizzare geographic pattern. They may develop on any part of the body, and may remain localized or become generalized to involve almost the entire skin surface. Involvement of the subcutaneous tissue may be an accompaniment, and is termed angioedema. Prickly sensation often precedes the development of wheals which are usually pruritic and stinging. Involvement of the mucosal surface may result in coryza, respiratory distress, abdominal pain, and hoarseness.

Wheals, the hallmark of urticaria, result from the action of histamine and allied mediators of inflammation on the microvasculature (Figs 22.1A and B). The resultant vasodilatation and increased permeability is responsible for the extravasation of protein rich fluid into the dermis and/or subcutaneous tissue, producing urticaria and angioedema, respectively.




**Figures 22.1A and B:** (A) Acute utricaria/angioedema, (B) Urticaria plaque

## CLINICAL FEATURES

Urticaria may either be acute or chronic. Acute urticaria evolves over a period of days or weeks. History is usually of less than six weeks. Following this short duration, there is complete involution, with no further occurrence. There is often a specific cause responsible for acute urticaria although owing to its self-limiting nature, it may not be always possible to identify it. Chronic urticaria is continuous or persists episodically for at least 6 weeks or longer. The cause may remain unidentifiable even after intensive investigations.

Based on pathophysiologic mechanism, urticaria may be of the following kinds:

- Immune-mediated
- Complement-mediated

- Urticariogenic materials (exogenous)
- Physical urticaria
- Idiopathic

### Immune-Mediated Urticaria

It may be the result of IgE mediated Type I hypersensitivity reaction or may occur independent of IgE, when probably, it is the consequence of cytotoxic (Type II) or immune-complex mediated (Type III) reactions. Type I, IgE mediated reactions are involved in the production of urticaria due to drugs like penicillin, inhalants like pollens, danders, and ingestants like fish, nuts, and mushrooms. Such urticarias are almost always acute in onset. Wheal and flare skin reaction may be diagnostic in some cases of IgE mediated urticarias. Serum sickness, urticarial vasculitis, and transfusion reactions are the examples of non-IgE dependent, immune-mediated urticaria.

### Complement-Mediated Urticaria

It may occur by either immunologic or non-immunologic mechanisms. It involves the activation of complement either through classical or alternative pathways, with the cleavage of $C_{5a}$ and $C_{3a}$ anaphylatoxins from $C_3$ and $C_5$, respectively. These are responsible for the release of histamine from mast cells. Urticaria associated with cryoglobulinemia, connective tissue diseases like SLE, leukocytoclastic vasculitis, viral infections, and certain drugs are examples of complement mediated urticaria. Hereditary angioedema, due to deficiency of CI inhibitor, is also an example of complement-mediated urticaria.

### Urticariogenic Materials

It is mediated by substances that do not act as antigens, but when ingested, inhaled or on contact with the host, produce wheal and flare. They are directly responsible for the release of histamine or allied mediators of inflammation. The various urticariogenic substances are as follows:

- Water
- Chemicals—Tween 80, acacia, tartrazine, radiocontrast media, sodium benzoate
- Drugs—aspirin, nonsteroidal anti-inflammatory agents, cocaine, morphine, codeine, polymyxin-B
- Foods—citrus fruits, strawberries
- Toxins—cobra venoms.

### Aquagenic Urticaria

It is a distinct form of urticaria due to a combination of water and sebum, which produces urticariogenic substance. It is characterized by punctate perifollicular wheals.

### Physical Urticaria

It is a subgroup of chronic urticarias in which wheals are reproducibly induced by a physical stimulus, namely cold, heat, pressure, vibration, light, water, exercise, and increase in core body temperature. The urticarial lesions are produced due to mast cell activation and release of histamine. Some of the common physical urticarias encountered are as follows.

#### *Symptomatic Dermographism*

It manifests as transient wheal and flare response on stroking the skin. It develops within 2 to 5 minutes of stroking and usually lasts for ½ to 3 hours. Delayed dermographism is also encountered and is characterized by the development of deep, tender, linear wheal 3 to 8 hours after the stimulus. It last for 24 to 48 hours.

### *Cholinergic Urticaria*

It is precipitated by the elevation of the core body temperature. The skin lesions appear as 2 to 4 mm pruritic wheals surrounded by extensive areas of macular erythema. The lesions are most pronounced on the uppertrunk and arms. Hypotension, wheezing, gastrointestinal complaints may accompany the urticaria. Symptoms can be reproduced by warming the body by exercise or after a hot bath, that results in an increase in core body temperature by 0.7 to 1°C.

### *Cold Urticaria*

It occurs in both familial and acquired forms. The familial form is transmitted as autosomal dominant disorder and is precipitated by exposure to cold air. It may present either with early onset, within ½ to 3 hours or as delayed onset, 9 to 18 hours after exposure. The lesions are not true wheals but consist of burning, erythematous papules. Headache, arthralgia, fever, myalgia, and chills may be associated.

Acquired cold urticaria is precipitated by exposure to cold followed by rewarming. It presents as pruritic wheals. Swelling of the lips and tongue may occur after ingestion of the cold drinks. Systemic symptoms are usually not present. However, there is a risk of generalized anaphylactic response and syncope, if the patient's entire body is exposed to cold stimulus such as swimming.

### *Heat Urticaria*

Application of local heat followed by urticarial eruption is the hallmark of the disease. In contrast to cholinergic urticaria, exercise and stress do not elicit the urticarial response. Following a contact with hot object, there is development of small papular, pruritic wheals with large flares.

### *Pressure Urticaria*

It occurs 4 to 6 hours after application of sustained pressure. Pressure bearing areas are commonly affected like, foot swelling after prolonged walking, hand swelling after clapping or hammering, shoulder swelling after carrying heavy weight, buttock swelling after sitting and swelling under the belts or tight clothing.

## DIAGNOSIS

The underlying cause(s) of urticaria may be possible to establish only in a few cases. Nevertheless, an endeavor to establish the cause must be made. This requires eliciting the history, correlating urticaria to season, environment, food, drugs, physical activity, heat, and cold. A thorough interrogation into the history of drug intake like aspirin and related nonsteroidal anti-inflammatory drugs, oral contraceptives, antidiarrheal, laxatives and cough mixtures is mandatory.

Specific clinical features on dermatological examination may reveal the diagnosis of urticaria (*vide supra*).

Several provocative tests like stroking the skin (dermographism) application of ice cubes (cold urticaria), localized heat (heat urticaria), exercise and warm bath (cholinergic urticaria), and exposure to water (aquagenic urticaria), may be imperative to perform.

Laboratory investigations such as blood examination (complete hemogram, total and differential leukocyte counts, erythrocyte sedimentation rate), macro and microscopic examination of urine, stool for ova and cysts to rule out parasitic infestations are recommended. Other relevant investigations may be performed as indicated by history and clinical examination.

**Table 22.1: Treatment of acute urticaria**

| *Types of urticaria* | *Drugs* | *Generic names* | *Trade names* | *Dosage* | *Status* |
|---|---|---|---|---|---|
| 1. Acute localized urticaria | $H_1$ receptor antihistamines | | | | |
| | a. Alkylamines | Pheniramine maleate | Avil | 25 to 50 mg thrice daily | Combination of two antihistamines may be given. Practin (4 mg) with Atarax (10 mg) thrice daily is a useful combination. Sedation is the major side effect. |
| | b. Ethanolamine | Diphenhydramine hydrochloride | Benadryl | 25 to 50 mg thrice daily | |
| | c. Ethylenediamine | Triplennamine | | | |
| | d. Phenothiazine hydrochloride | Promethazine | Phenergan | 10 to 25 mg thrice daily | |
| | e. Piperazine | Hydroxyzine hydrochloride | Atarax | 10 to 25 mg thrice daily | |
| | f. Piperidines | Cyproheptadine | Practin | 4 mg thrice daily | |
| | g. Miscellaneous | Astemizole | Histeese<br>Perione<br>Camstem-10<br>Stemiz | 20 to 30 mg initially empty stomach, before breakfast. Then a maintenance dose of 10 mg. | Nonsedating antihistamines. |
| | | Terfenadine | Tofril<br>Terfed | 60 mg twice a day | Nonsedating antihistamine |
| | $H_2$ receptor antihistamine | Cimetidine<br>Ranitidine | Cimetiget<br>Ranitin | 400 mg thrice daily<br>150 mg thrice daily | May be used along with $H_1$ antihistamines in patients who fail to respond to anti-$H_1$ alone. |
| 2. Acute, severe generalized urticaria | Corticosteroid + Antihistamine | Dexamethasone + Promethazine | Decadron + Phenergan | Decadron (1 mL = 4 mg), 1 mL intravenous followed by 25 mg of promethazine hydrochloride (Phenergan) intravenous. If required it may be repeated after 6 to 8 hours. Patient may then be maintained on oral treatment with 0.5 to 1 mg of Decadron and 25 mg of Phenergan thrice a day. | |
| | Adrenaline | — | — | 0.1 to 0.2 mL of 1 in 1000 adrenaline, subcutaneously, every 15 min. | |
| | B-adrenergic receptor agonist | Terbutaline | — | 0.2 mL of terbutaline, subcutaneously, every 15 min till symptoms subside followed by 2.5 to 5 mg of terbutaline orally thrice a day. | |
| | Sympathomimetics | Ephedrine | — | 25 mg of ephedrine, subcutaneously, every 6 hours. | |

## TREATMENT

Avoiding the precipitating cause, if identifiable, is an essential ingredient. $H_1$ antihistamines, the mainstay of treatment of urticaria, compete with histamine for binding sites on the $H_1$ receptor of the effector cell and block the action of histamine. Some individuals possess $H_2$-receptors in addition to $H_1$ in the cutaneous blood vessels. In such patients $H_1$ antihistamines alone may fail to suppress the urticaria. A combination of $H_1$ and $H_2$ antihistamines may then be required. It may also be useful to administer a course of antihelminthic, especially to children. Diethylcarbamazine may be given along with antihistamines in chronic, recalcitrant cases of urticaria. A case of acute urticaria which is generalized and associated with angioedema is

**Table 22.2: Treatment of individual urticaria**

| *Types of urticaria* | *Chemical groups* | *Generic names* | *Trade names* | *Dosage* | *Other measures* |
|---|---|---|---|---|---|
| 1. Symptomatic dermographism | $H_1$-receptor blocker | Hydroxyzine | Atarax | 10 mg thrice daily | Avoid trauma to the skin |
| | or | Cyproheptadine | Practin | 4 mg thrice daily | |
| | $H_1 + H_2$ antagonist | Pheniramine maleate + Cimetidine | Avil + Cimetiget | 25 mg Avil + 400 mg of Cimetiget thrice daily | |
| 2. Cholinergic urticaria | $H_1$-antagonist | Hydroxyzine | Atarax | 10 mg thrice daily | Avoidance of exogenous heat provocation |
| | | Cyproheptadine | Practin | 4 mg thrice daily | |
| 3. Localized Heat urticaria | $H_1$-antagonist | Hydroxyzine | Atarax | 10 mg thrice daily | Induction of tolerance |
| | | Cyproheptadine | Practin | 4 mg thrice daily | |
| 4. Cold urticaria | $H_1$-antagonist | Hydroxyzine | Atarax | 10 mg thrice daily | Avoiding cold exposure |
| | | Cyproheptadine | Practin | 4 mg thrice daily | |
| 5. Aquagenic urticaria | $H_1$-antagonist | Hydroxyzine | Atarax | 10 mg thrice daily | Massage of oils |
| | | Cyproheptadine | Practin | 4 mg thrice daily | |
| 6. Pressure urticaria | Nonsteroidal anti-inflammatory drugs + Corticosteroids | Acetyl salicylic acid + Prednisolone | Aspirin + Wysolone | 600 mg thrice daily + 40 mg daily | |

an emergency which requires prompt attention with parenteral corticosteroids along with antihistamines. Other drugs which may be used to counter such a situation are adrenaline, ephinedrine, and beta-adrenergic receptor agonists like terbutaline (Table 22.1). The treatment of individual urticaria may vary (Table 22.2).

## RECOMMENDED READING


1. Sehgal VN, Jain S: Urticaria. *J Indian Med Assoc* 1992;90:21-23.
2. Lawlor F. Urticaria. *J Eur Acad Dermatol Venereol* 1993;2:35-43.
3. Champion RH. Urticaria: Then and now. *Br J Dermatol* 1988;119:427-436.
4. Elis CN. Current management of urticaria and angioedema. Proceedings of a round table. *J Am Acad Dermatol* 1991;25:145-204.

# 23 Chapter

# Pityriasis Rosea

Pityriasis rosea is a papulosquamous, self-limiting condition, seen usually in adolescents and young adults. The etiology is unknown, however, it may be of viral origin. The lesions usually disappear in 6 to 8 weeks.

## CLINICAL FEATURES

The initial lesion, 'herald' patch, a diagnostic hallmark, is 2 to 6 cm, round, erythematous, scaly plaque. It may not be a presenting feature in a few. In a couple of days, there is appearance of multiple, oval, 1 to 2 cm sized, erythematous, scaly eruptions. The surface is crinkly and the scales are disposed in a collarette fashion. The long axes of the lesions are oriented in the planes of cleavage, running parallel to the ribs. It appears to form an inverted 'Christmas tree'. The lesions are distributed over the trunk and proximal extremities (Figs 23.1A and B). The face, hands, and feet are usually spared. The lesions continue to appear for 7 to 10 days, and disappear in 6 to 8 weeks. Besides the classic appearance, variants may be encountered, namely: (a) inverse pityriasis rosea, (b) papular eruptions, (c) vesicular and bullous eruptions.

## DIAGNOSIS

The diagnosis of pityriasis rosea is clinical. However, it should be differentiated from the following:

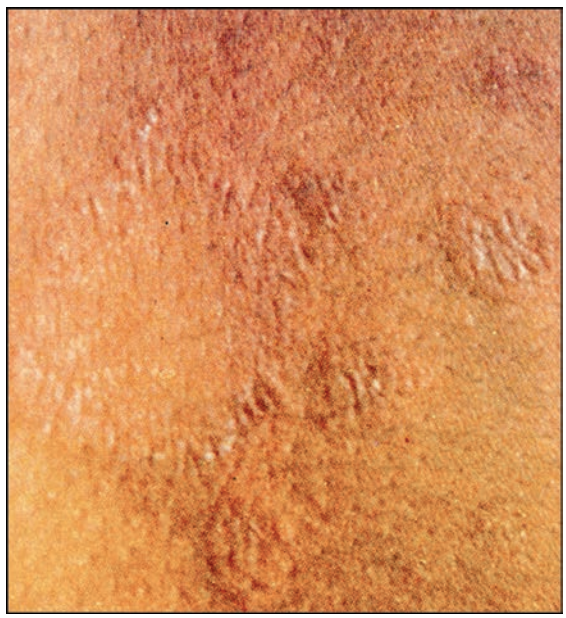


**Figure 23.1A:** Pityriasis rosea: Herald patch, a diagnostic hallmark

*Tinea corporis:* This usually starts as an erythematous, itchy papule which progresses to form a circinate lesion. It is studded at the periphery with papules or papulovesicles. The lesions are scaly, showing clear or apparently normal looking centers. They show seasonal variations, common in hot and humid climate. The demonstration of fungus in 10 percent KOH from the scrapings seen under the microscope and their recovery in Saboraud's agar medium is confirmatory.

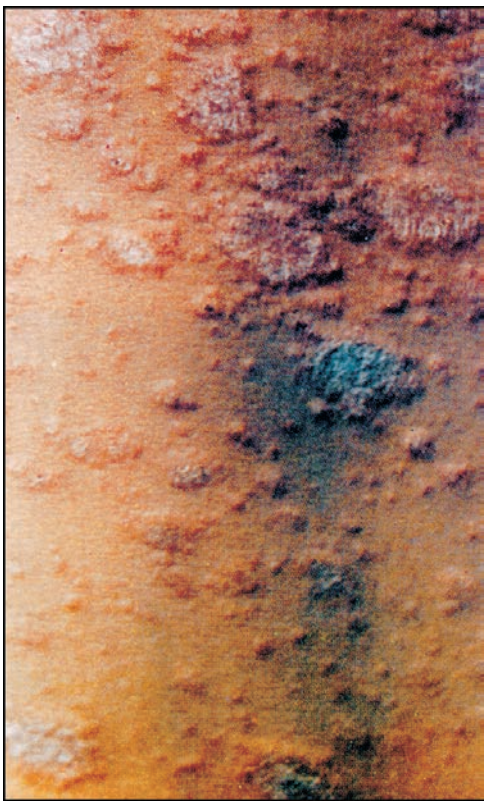


**Figure 23.1B:** Well-defined scaly, ring-like (plaque) lesions in addition to papulosquamous lesions, distributed over the chest along the body cleavages preceded by herald patch

*Psoriasis:* The lesions of this condition are typical—they are erythematoscaly eruptions, single or multiple, disposed primarily on the extensor surfaces of the body. The scales are lamellated and silvery white. Auspitz's sign is positive, evident as a pinpoint bleeding on grattage. Histology is diagnostic.

*Circinate syphilides:* This condition sometimes creates a problem in diagnosis. However, history of sexual exposure, primary chancre or scar on the genitals and polymorphic syphilitic rash is helpful in diagnosis. The diagnosis may be confirmed by the demonstration of *Treponema pallidum* in the lesions and reactive serological tests for syphilis.

*Pityriasis versicolor:* It is characterized by asymptomatic, hypopigmented, mildly scaly, multiple macules distributed on the body surface, largely corresponding to the 'lady's bathing suit'. Seasonal variation is the main feature. The diagnosis could be confirmed by finding of mycelia and spores of *Malassezia furfur* in the scrapings seen under the microscope.

Chronic parapsoriasis or pityriasis lichenoides et varioliform acuta (PLEVA). It should be suspected if the lesions do not resolve in 8 to 12 weeks.

## TREATMENT

It is a self-limiting condition and usually no treatment is required. The patient needs to be explained about the disease and reassured. However, if pruritus is present, antihistamines may be given orally. Topical soothing lotions may be applied.

## RECOMMENDED READING

1. Abdel-Hafez K, Deyab Z. Pityriasis rosea. *Int J Dermatol* 1987;26:231-233.
2. Crissey JT. Pityriasis rosea. *Pediatr Clin North Am* 1956;3:801-809.
3. Parsons JM. Pityriasis rosea: Update: 1986. *J Am Acad Dermatol* 1986;15:159-167.

# 24 Chapter

# Vitiligo

Vitiligo is a common, acquired, idiopathic discoloration of the skin characterized by well-circumscribed, ivory/chalky white colored macules, which are flush to the skin surface in contrast to leukoderma where a cause of such a change is known. The lesion may be surrounded by a ring of tan or intermediate color around which is the normal skin, the 'trichrome'. The hair over the patch may be either normal or white (leukotrichia). Occasionally, vitiligo may be associated with autoimmune disorders like thyroid diseases, diabetes mellitus, pernicious anemia.

The extent of involvement is variable. There may be one, two or a few macules or it may be extensive. Accordingly vitiligo is classified into the following:

- Vitiligo areata (one or two patches) (Fig. 24.1)
- Zosteriform/segmental vitiligo (macules distributed along a dermatome or lines of body cleavage) (Fig. 24.2)
- Acrofacial vitiligo (affecting the face and tips of hands and feet) (Fig. 24.3)
- Vitiligo vulgaris (generalized, involving extensive body areas) (Fig. 24.4)
- Mucosal vitiligo (mucous membrane may be the only site involved or it may be a part component of other variants (Fig. 24.5).

The preceding classification not only helps in diagnosis, but also has prognostic significance.

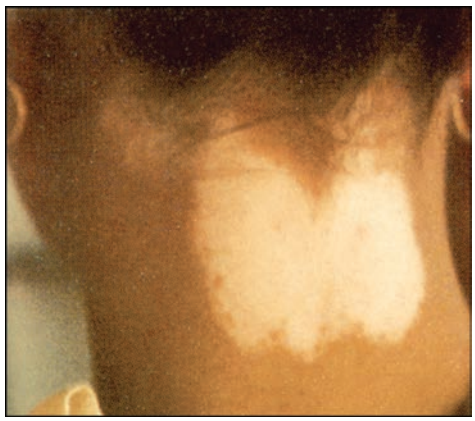


**Figure 24.1:** Vitiligo areata: Well-circumscribed ivory/chalky white color macule(s) surrounded by ring of tan or intermediate color, around which is the normal (trichrome)

**Figure 24.2:** Vitiligo zosteriform/segmental: Macules distributed along a dermatome or line of body cleavage

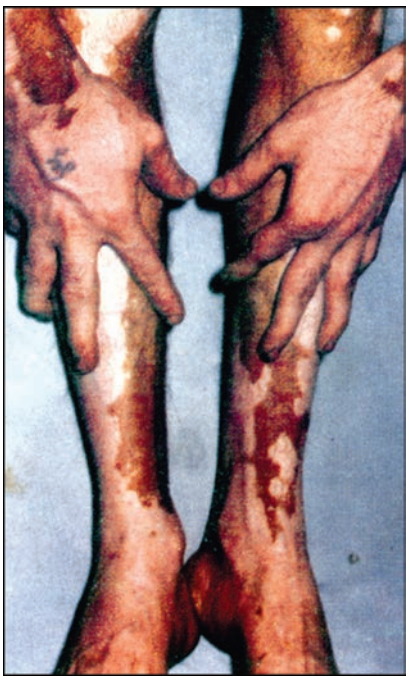


**Figure 24.3:** Vitiligo acrofacialis: Effecting the face/jips of the hands and feet

**Figure 24.4:** Vitiligo vulgaris: Generalized involving extensive areas of the body

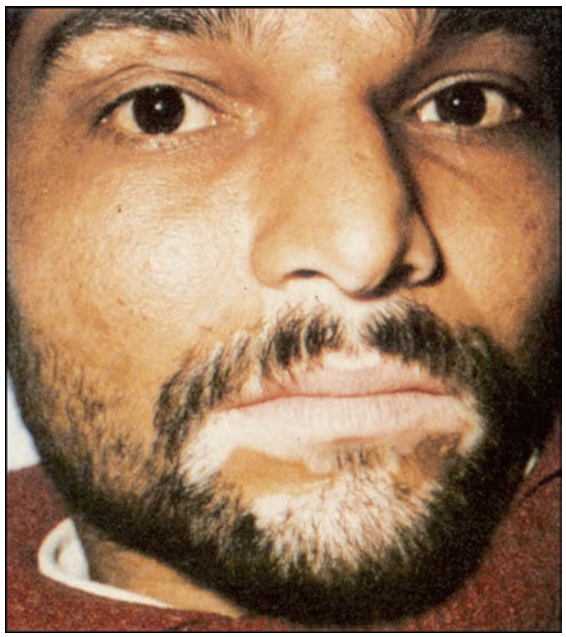


**Figure 24.5:** Vitiligo mucosae: Exclusive mucous membranes affliction, or a part of vitiligo vulgaris

Prognosis, therefore, may be judged by the following:

*Duration of the vitiligo:* Shorter the duration, better the prognosis.

*Age of the patient:* Younger the patient, better the prognosis.

*Leukotrichia:* Its presence carries the poor prognosis.

*Macules over the fleshy areas:* They have better chance for repigmentation in contrast to those over the bony areas.

*Vitiligo areata, and zosteriform vitiligo:* These respond favorably to treatment.

*Dopa reaction:* Positive dopa reaction *in vitro* depicts good prognosis.

## TREATMENT

Psoralens form the mainstay of treatment for vitiligo. Three types of psoralens are in use:

a. Basic psoralen

b. 8-methoxypsoralen
c. 4, 5, 8 trimethyl psoralen.

Treatment may be initiated with any one. Sometimes a patient, refractory to one, may respond to the other.

The precise mode of action of psoralens is unknown. However, it is likely that following absorption, psoralens concentrate in the cytoplasm of the melanocytes. On subsequent exposure to sunlight (PUVASOL) or ultraviolet A (PUVA), it activates the specific enzyme system in the melanocytes, the tyrosinase, concerned with melanin production. Inflammatory response following PUVASOL/PUVA may also initiate repigmentation.

A dose of 0.6 mg/kg is adequate to produce repigmentation. After oral administration, maximum concentration of the photosensitizing drug in the blood is achieved after two hours. In tropical and subtropical countries, maximum UVA radiation from sunlight is available between 9 to 11 AM. Thus to induce maximum photosensitization, it is advisable to take psoralens in the recommended dose after breakfast, followed by exposure of the macule to sunlight at 11.00 A.M. Initially, it is exposed for 15 minutes and then the exposure time is gradually increased to a maximum of 45 minutes (Table 24.1).

**Table 24.1: Duration of exposure in PUVA**

| | *Color of the skin* | |
|---|---|---|
| *Steps of exposures* | *Light* | *Dark* |
| Initial exposure | 15 min | 20 min |
| Second exposure | 20 min | 25 min |
| Third exposure | 25 min | 30 min |
| Fourth exposure | 30 min | 35 min |

In an individual patient, the maximum duration varies with the basic skin color and tolerance. Patients may be encouraged to take longer exposure, provided they tolerate the heat without developing any phototoxic and/or actinic damage. Care should be taken to protect the eyes with sunglasses and the normal surrounding skin by application of para-aminobenzoic acid (PABA) cream or lotion, a UVA light sunscreen.

In favorable cases, persistant erythema, a prelude to repigmentation is noticed usually after a month's exposure. In case the erythema does not appear during this period, the treatment may be abandoned. Subsequent repigmentation starts either from the margins of the macule and/or the hair follicles. These small island of pigmentation may gradually increase and coalesce to form a uniform pigmented macule, a cosmetically favorable outcome. Occasionally depigmentation recurs after stoppage of the treatment. In that event psoralen therapy should be reinforced along with a small dose (20-30 mg) of prednisolone or its equivalent. The latter is more useful in case there is an underlying autoimmune disorder.

## Other Modalities of Treatment

*Topical psoralens:* It is applied early in the morning over the vitiliginous macule, protecting the surrounding area with PABA cream. The areas are immediately exposed to early sun for about 15 minutes and this is gradually increased in subsequent weeks to a maximum of one hour.

### *Topical Corticosteroids*

They are useful in cases of vitiligo areata. Fluorinated steroids (Flucort) and clobetasol propionate 0.5% (Tenovate, Topinate) are used for topical application.

### *Camouflage Creams and Cover masks*

It may be used to hide the patch if other modes of therapy have failed.

### *Skin Grafting*

This is done if there is a patch on an exposed area and is cosmetically disfiguring. However, it should be ensured that the disease has stabilized and not progressing.

### *Monobenzyl ether*

In vitiligo vulgaris, where only a few islands of pigmentation are left 20 percent monobenzyl ether of hydroquinone should be administered topically to these islands, to attain uniform depigmentation.

## RECOMMENDED READING


1. Sehgal VN. Letter: Trioxsalen therapy for vitiligo. *Arch Dermatol* 1974;109:578.
2. Sehgal VN. Effectiveness of oral trioxalen therapy for vitiligo. *Arch Dermatol* 1974;110:957-958.
3. Sehgal VN. A Comparative clinical evaluation of trimethylpsoralen, psoralen and 8-methoxypsoralen in vitiligo. *Int I Dermatol* 1975;14:205-208.
4. Sehgal VN, Rege VL, Mascarenhas F, et al. Clinical pattern of vitiligo amongst India. *J Dermatol* (Japan) 1976;3:49-53.
5. Sehgal VN, Srivastava G. Vitiligo: compendium of clinico-epidemiological features. *Indian J Dermatol Venereol Leprol* 2007;73:149-156.Review.
6. Sehgal VN, Srivastava G. Vitiligo treatment options: An evolving scenario. *J Dermatolog Treat* 2006;17:262-275.
7. Sehgal VN, Srivastava G. Vitiligo. Auto-immunity and immune responses. *Int J Dermatol* 2006;45: 583-590.

# 25 Chapter

# Pemphigus

Pemphigus is well-recognized condition characterized by formation of flaccid bullae affecting skin and/or mucous membranes. It is an autoimmune disorder. Invariably, it is possible to demonstrate tissue bound antibodies at the site of acantholysis by direct immunofluorescence. Circulating pemphigus antibodies in the serum are detectable by indirect immunofluorescence using esophagus of the monkey, guinea pig or the skin. It manifests either as pemphigus vulgaris (pemphigus vegetans) or pemphigus foliaceus (pemphigus erythematoides).

## CLINICAL FEATURES

### Pemphigus Vulgaris

It usually affects the men and women of older age group. Occasionally, youngsters may be affected. An appearance of discrete, flaccid bulla appearing over an apparently normal skin is cardinal (Fig. 25.1). Formation of an erythematous halo around the blister may also be seen. The contents of the blister may either be clear, purulent or hemorrhagic. The blister may break off and its contents may escape. Removal of its roof may reveal raw, exuding angry erosions. In addition, crusting over the erosions may be present. Ultimately flaccid blister may heal leaving behind a hyper or hypopigmentation. The number of blisters may vary from a few to many and may be scattered all over the body. The involvement of the mucous

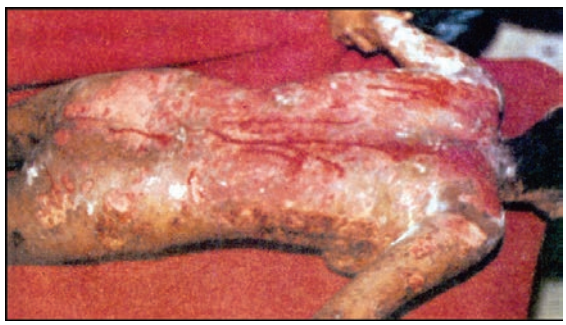


**Figure 25.1:** Pemphigus vulgaris: Flaccid bulla

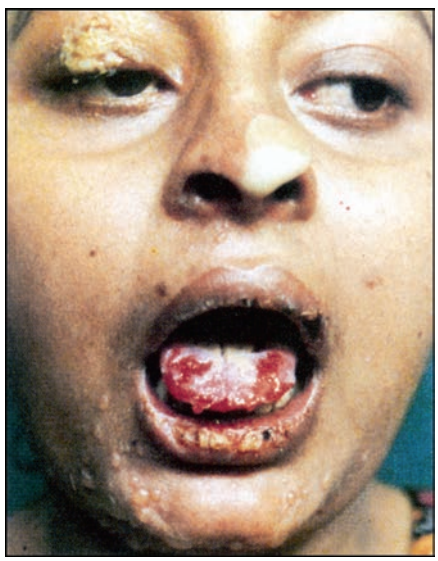


**Figure 25.2:** Pemphigus vulgaris: Oral lesions

membranes may precede or accompany the cutaneous lesions (Fig. 25.2).

### Pemphigus Vegetans

It is a variant of pemphigus vulgaris and is identified by the formation of proliferative and verrucous lesions on the erosions. The vegetations are studded with pustules at the periphery. The condition affects the intertriginous areas, namely the axillae, inguinal region, inframammary and other body folds.

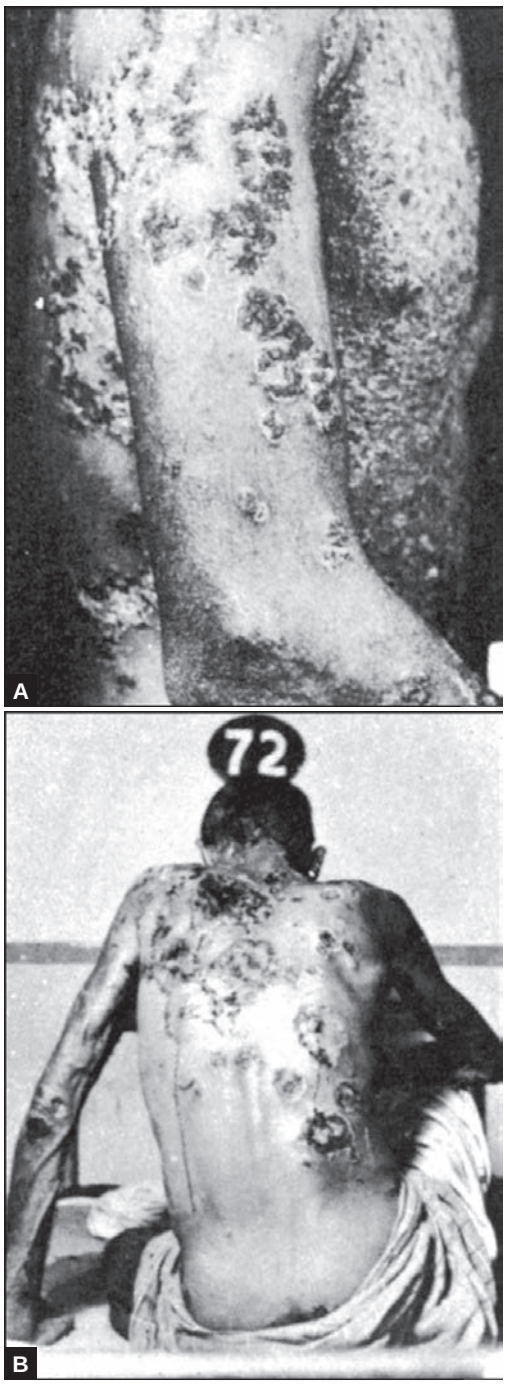
Nikolsky's sign and bulla spread sign are positive. The former is elicited by applying uniform, mild, and tangential pressure with the pulp of the thumb either by the side of the bullae or on an apparently normal skin, preferably over a bony region. This may cause denudation of the skin. The latter is demonstrated by demarcating a fresh blister with a skin marking pencil. Uniform pressure is applied over the fresh blister. The escape of the fluid beyond the limits of the marking indicates positive bulla spread sign.

### Pemphigus Foliaceus

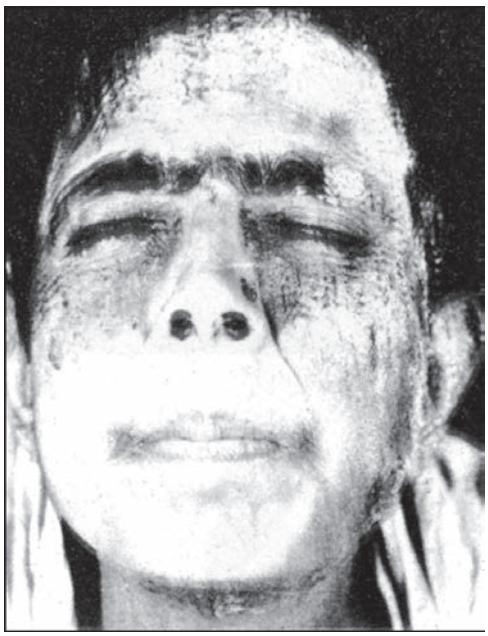
It is a relatively benign condition characterized by appearance of flaccid bullae which arise over an erythematous skin. The bullae are superficial and transitory. The lesion initially appears over the scalp, face, and the trunk. In due course it becomes generalized and the patient may present with a picture mimicking exfoliative dermatitis with crust sticking onto the erythematous background (Figs 25.3A and B).

### Pemphigus Erythematoides (Senear-Usher Syndrome)

It is a localized variant of pemphigus foliaceus. The lesions are confined to the scalp and are




**Figures 25.3A and B:** Pemphigus foliaceus



**Figire 25.4:** Pemphigus erythematoides

evident in the form of diffuse scales. It may appear similar to seborrhea, however, the scales are not greasy. The lesions over the face occupy the butterfly area and may simulate lupus erythematosus (Fig. 25.4).

### Pemphigus Herpetiformis

Pemphigus may present in the form of itchy grouped papules and vesicles over an erythematous base. Initially, histologic picture is devoid of acantholysis, but has spongiosis and eosinophilic infiltrate. Intercellular deposits of IgG are revealed through direct immunofluorescence. There is positive indirect immunofluorescence revealing features of pemphigus. Ultimately, the clinical and histopathological features of pemphigus foliaceous develop.

### Pemphigus in Pregnancy

The occurrence of pemphigus in pregnancy is uncommon. The newborn may either be a stillborn or have clinical, histopathologic and immunologic features of pemphigus. Transplacental transmission of pemphigus antibody is responsible for the entity in neonates.

### Drug Induced Pemphigus

Pemphigus may be induced by drugs. Penicillamine is the most frequent causative agent. It induces pemphigus in 3 to 10 percent of the patients. Pemphigus foliaceus is quite common. An increased frequency of HLA-B15 has been documented suggesting that penicillamine may unmask a genetic predisposition to the development of pemphigus antibodies. The drugs like piroxicam, penicillin, phenobarbitone, phenytoin, rifampicin, captopril, thiopronine and α-mercaptopropionyl glycine, may also be responsible.

## DIAGNOSIS

It is based on the following:

- Cardinal morphological characteristics of pemphigus and its variants.
- Nikolsky's and bulla spread sign are positive.
- Demonstration of acantholytic cells from the fluid or the smear made from the raw surface. A fresh bulla is selected for the purpose. The fluid and/or the material scraped from its floor is transferred to a glass slide and the smear is made. It is fixed and stained with Geimsa's stain. After drying it is scanned under the oil-immersion of the microscope. In pemphigus, acantholytic cells are seen. It is recognized as degenerating, large, prickle cell which has be come rounded. It has a large basophilic nucleus containing nucleoli, a rim of mildly eosinophilic cytoplasm and a densely staining basophilic cell outline (Fig. 25.5).

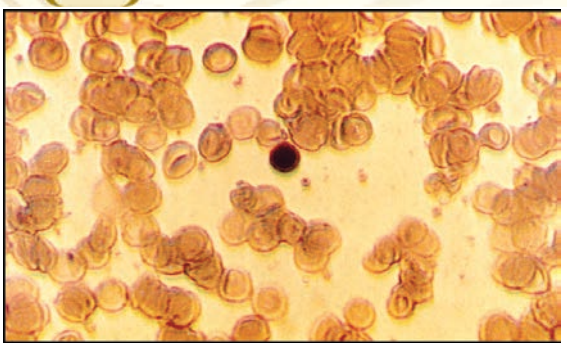
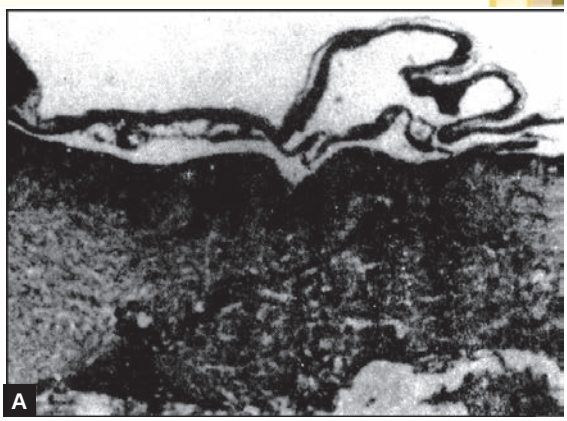


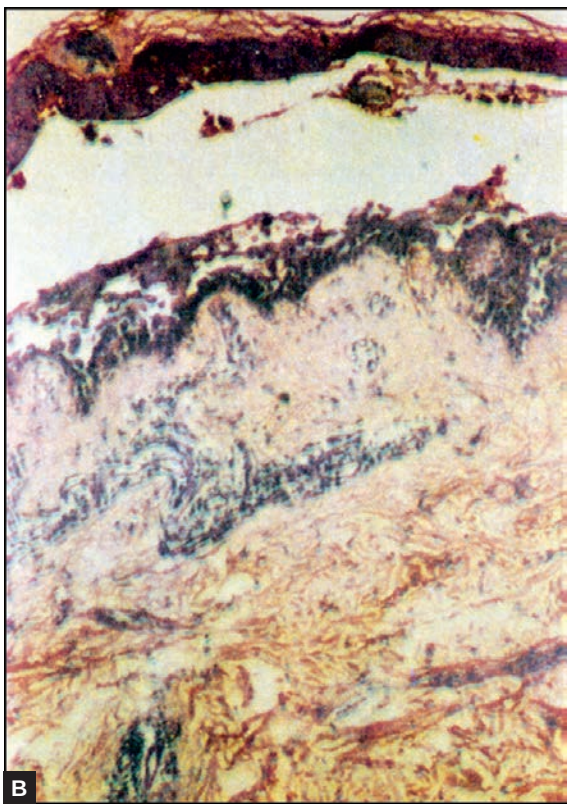
**Figure 25.5:** Acantholytic cell

- Histopathological examination of hematoxylin and eosin stained section (Figs 25.6A and B)
- Diagnosis is confirmed by direct and indirect immunofluorescence (Table 25.1).

## TREATMENT

Corticosteroids are the mainstay of treatment. Sufficiently high doses, either of prednisolone in the range of 80 to 120 mg or its derivaties (dexamethasone/betamethasone) are administered orally/parenterally, to bring the active disease under control (Table 25.2). However, before initiating treatment, it has to be ensured that the patient is fit to take prolonged, high dose, suppressive therapy with corticosteroids. Active tuberculosis and peptic ulcer should be excluded by a detailed history. Blood pressure is recorded to rule out hypertension. Furthermore, complete hemogram, blood sedimentation rate, renal function test, liver function test, blood sugar, serum electrolytes, routine and microscopic urine examination, skiagram of the chest and long bone and electrocardiogram should be done. Also ophthalmologic examination is imperative to exclude cataract. The parameters are required to be periodically reviewed during the course of therapy.




**Figures 25.6A and B:** (A) Pemphigus foliaceous: Subcorneal cleav, (B) Pemphigus vulgaris: Intraepidermal, suprabasal cleavage

**Table 25.1: Laboratory diagnosis of pemphigus**

| *Types* | *Smears* | *Histopathology* | *Direct immunofluorescence* | *Indirect immunofluorescence* |
|---|---|---|---|---|
| 1. Pemphigus vulgaris | Giemsa stained smear from the fluid or base of the bullae reveals acantholytic cells. It is a degenerating cell which has lost contact with surrounding cells. It is large and rounded with a big nucleus occupying nearly 7/8th of the cell. There is condensation of cytoplasm around the nucleus which appears as mild staining eosinophilic rim around the nucleus. The cells wall appears as deeply staining basophilic rim. Nucleus has 3 to 4 nucleoli. | 1. Edema and disappearance of the epidermal intercellular bridges in the lowest level of epidermis.<br>2. Acantholysis, loss of epidermal cell cohesion resulting in formation of suprabasal, intraepidermal cleft.<br>3. Cells in varying stages of acantholysis in the cleft.<br>4. Basal epidermal cells remain attached to the basement membrance forming a 'row of tombstone'.<br>5. Focal collection of eosinophils within the epidermis, eosinophilic spongiosis'.<br>*EM*<br>1. Partial dissolution of the intercellular cementing substance.<br>2. Widening of intercellular spaces.<br>3. Separation of apposing attachment plaques of desmosome.<br>4. Retraction of tonofilaments. | 1. Immunofluorescence at the site of acantholysis.<br>2. Linear IgG deposit in the intercellular space (ICS).<br>3. Deposition of pivotal complement component, $C_3$, in the ICS. | Circulating IgG antibodies directed against intercellular cementing substance |
| 2. Pemphigus vegetans | Same as pemphigus vulgaris | 1. Suprabasal acantholysis<br>2. Pseudoepitheliomatous hyperplasia.<br>3. Papillomatosis.<br>4. Intraepidermal abscesses composed of eosinophils. | Same as pemphigus vulgaris | Same as pemphigus vulgaris |
| 3. Pemphigus foliaceus | Same as pemphigus vulgaris | 1. Subcorneal, acantholytic blister.<br>2. Minimal to moderate eosinophilic infiltrate | Same as pemphigus vulgaris | Same as pemphigus vulgaris |
| 4. Pemphigus erythematoides (Senear-Usher syndrome) | Same as pemphigus vulgaris. | Same as pemphigus foliaceous. | 1. Immunofluorescence at the site of acantholysis, near granular layer.<br>2. Deposition of IgG and $C_3$ in the intercellular space.<br>3. Deposition of IgG and complement at dermoepidermal junction (DEJ). | 1. Antinuclear antibodies<br>2. Pemphigus antibody. |

**Table 25.2: Mainstay of treatment**

| *Treatments* | *Benefits* | *Status* |
|---|---|---|
| Prednisolone 80 to 120 mg daily orally in 2 equally divided doses at 9 AM in the morning and 6PM in the evening till clinical remission, characterized by:<br>• Regression of existing lesions<br>• Absence of new lesions<br>• Healing of the lesions by either hyper or hypopigmentation.<br>Alternatively<br>Decadron (1 mL = 4 mg) 1 to 1.5 mL intramuscular/intravenous, equivalent to 40 to 60 mg of prednisolone in the morning at 9 AM and 1 mL (4 mg) intramuscular or intravenous equivalent to 40 mg of prednisolone in the evening at 6 PM.<br>At remission, reduce corticosteroids to half and add any of the immunosuppressive adjuvant like the following:<br>Cyclophosphamide 100 to 200 mg daily<br>Azathioprine 50 to 150 mg daily<br>Methotrexate 22.5 mg every week<br>Subsequently, reduce daily dosage of prednisolone by 5 to 10 mg or its equivalent every week.<br>Patient may be maintained on 10 to 15 mg of prednisolone. Ideally all treatment may be stopped after the direct and indirect immunofluorescence become negative. | | Mainstay of treatment. |

**Table 25.3: Other modalities of treatment**

| *Treatment* | *Benefits* | *Status* |
|---|---|---|
| 1. Pulse therapy<br>Components.<br>Intermittent high dose (IHD)—intravenous infusion of 100 mg of dexamethasone in 5 percent glucose daily on 3 consecutive days plus 500 mg of cyclophosphamide on day 1 only followed by continuous low dose—50 mg cyclophosphamide.<br>*Phase I:* Relapses of pemphigus warrants reintroduction of pulse, every 2 to 4 weeks. Lesions heal and relapses stop few months after.<br>*Phase II:* Pulse every month for 6 to 9 months.<br>*Phase III:* Administer only 50 mg of cyclophosphamide daily for about year.<br>*Phase IV:* Patient kept under surveillance and is declared cured if he is asymptomatic for 2 years or immunofluorescence is negative on 2 occasions a year apart. | Claims to reduce the side effects of corticosteroids and cyclophosphamide | Not clearly defined. More trials are needed to recommend this treatment for pemphigus on regular basis. |
| 2. Plasmapheresis | Removes the IgG antibodies directed against intercellular substance. Thus attempts to cure rather than suppress pemphigus. | Lowering of plasma proteins evokes rebound synthesis of antibodies. Needs to be combined with corticosteroids and immunosuppressants. |

The high dose of corticosteroids administered at the time of initiating therapy, need to be maintained till clinical remission characterized by regression of existing lesions, absence of appearance of new lesions and healing of existing lesions by hyper or hypopigmentation.

At this juncture, steroids are tapered gradually or reduced to half and adjuvants like cyclophosphamide, methotrexate, or azathioprine added. The steroids are subsequently reduced by 5 to 10 mg of prednisolone every week. The patient may ultimately be maintained in remission by administering 15 to 20 mg of prednisolone. The other modalities of treatment like plasmapheresis, pulse therapy are still under trial (Table 25.3).

## RECOMMENDED READING


1. Bystryn JC. Adjuvant therapy of pemphigus. *Arch Dermatol* 1984;120:941-951.
2. Korman N. Pemphigus. *J Am Acad Dermatol* 1988; 18:1219-1238.
3. Ratnam KV, Phay KL, Tan CK. Pemphigus therapy with oral prednisolone regimens. A 5-year study. *Int I Dermatol* 1990;29:363-367.
4. Sehgal VN, Srivastava G. Paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome. *Int J Dermatol* 2009;48:162-169.

# 26 Chapter

# Pemphigoid

Pemphigoid is a disorder characterized by the eruption of multiple, tense bullae either over an erythematous or normal skin in an elderly patient. The bullae tend to localize in the flexural areas. It affects the elderly usually in their sixth to eighth decade. There is no racial or sex prevalence. Furthermore, there is no association with any specific HLA. It is a self-limiting disorder. Prolonged clinical remissions are the usual outcome of successful therapy. Recurrences are uncommon and the mortality is low.

## CLINICAL FEATURES

It is characterized by the formation of large, tense bullae either over normal or urticarial, or erythematous, or erythrodermic bases. The lesions tend to localize in the flexural areas and the sites commonly involved are the inner aspects of the thighs, flexor surface of forearms, axillae, groins, and lower abdomen. Recurrent crops of blisters may remain localized to one area for many weeks or the blisters may become widespread. The blisters eventually rupture. However, the resulting denuded areas do not increase in size as they do in pemphigus, but show a tendency to heal. About one third of the patients have lesions of the oral cavity. Nasal mucosa may occasionally be involved. Involvement of other mucous membranes, including the anus, vagina, and esophagus is uncommon. It is a self-limiting disorder. The prognosis is good even in the absence of specific therapy with corticosteroids. The disease usually subsides in a few months or years. Mortality is low. Prolonged clinical remission is the usual outcome of a specific therapy and recurrences are uncommon.

## DIAGNOSIS

Bullous pemphigoid may be suspected on the basis of the morphology and distribution of the lesions. Histopathology supplements the clinical diagnosis (Figs 26.1 and 26.2). However, the confirmation is possible only by the immunofluorescene studies (Table 26.1).

There are several clinical variants of bullous pemphigoid. These may, however, represent distinct entities characterized by subepidermal blistering and serology that closely resembles that of bullous pemphigoid. Bullous pemphigoid needs to be differentiated from the following.

### Vesicular Pemphigoid

It is characterized by the eruption of small, tense, sometimes clustered vesicles. However, the grouping is not herpetiform and the skin distribution is random rather than typical of dermatitis herpetiformis. The patients do not

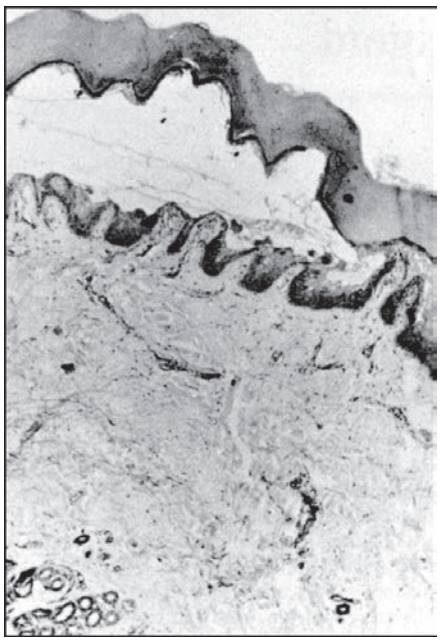


**Figure 26.1:** Bullous pemphigoid (H and E ×50)

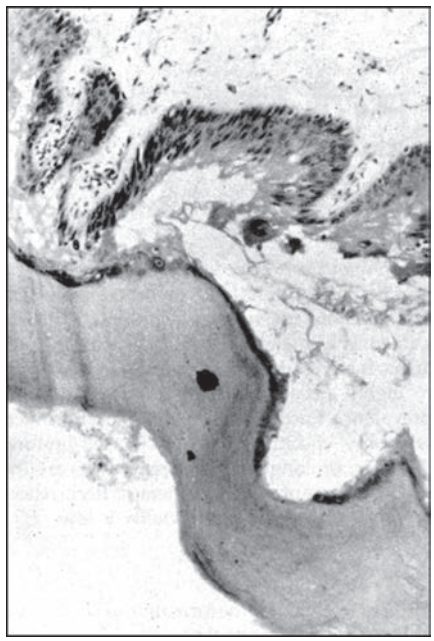


**Figure 26.2:** Bullous pemphigoid (H and E ×100)

**Table 26.1: Diagnosis of pemphigoid**

| *Histopathology* | *Electron microscopy* | *Direct immuno-fluorescence* | *Indirect immuno-fluorescence* |
|---|---|---|---|
| 1. Subepidermal bullae.<br>2. Slight dermal infiltrate in noninflammatory bulla, consisting of scattered eosinophils near the epidermis and within the bullae.<br>3. Dermis shows a sparse perivascular infiltrate consisting of mononuclear cells with a few eosinophils. Inflammatory bulla has extensive dermal infiltrate consisting of eosinophils, intermingled with few neutrophils. Infiltrate is localized around the upper dermal blood vessels in close proximity to the epidermis and in the bulla. | Bulla is localized in the lamina lucida of the basement membrane zone (BMZ). | Linear deposits of IgG and C3 at the lamina lucida of the BMZ. | Circulating IgG anti-BMZ antibodies. |

have malabsorption symptoms or involvement of the jejunal mucosa. On follow-up, they eventually display the tense blisters of bullous pemphigoid.

### Localized Bullous Pemphigoid

At the onset, bullous pemphigoid lesions erupt over a localized area and remain confined at that site for a variable time. After varying intervals of time, they evolve into a generalized bullous eruption. However, in approximately 15 percent of the cases the blisters remain localized at one site only. The disorder is characterized by chronic, recurrent, localized lesions. The isolated sites involved may be the scalp, arms, trunk, and lower extremities. The histologic and serologic features are similar to that of bullous pemphigoid.

### Vegetating Bullous Pemphigoid (Pemphigoid Vegetans)

It is characterized by the development of massive purulent, verrucous, vegetative plaques with fissuring in the groin, axillae, post-auricular region, scalp, and hands. It may be mistaken for pemphigus vegetans. However, the histopathologic examination reveals pseudoepitheliomatous hyperplasia with focal areas of subepidermal bullae. Direct immunofluorescence shows IgG and C3 in linear pattern at the basement membrane zone.

### Nodular/Hyperkeratotic Bullous Pemphigoid

It is characterized by recalcitrant hyperkeratotic nodules, localized over the lower extremities and the extensor surface of the forearms. The lesions are recalcitrant to treatment and may persist for many years. Histopathology reveals subepidermal bullae and serologic features are consistent with bullous pemphigoid.

### Linear IgA Bullous Dermatosis

It is characterized by eruption of blisters intermediate in size between bullous pemphigoid and dermatitis herpetiformis. The bullae are localized over the flexural areas. Of particular relevance is the absence of coexisting enteropathy. Also they do not possess the increased prevalence of HLA-B8. Histopathological examination reveals subepidermal bullae with multiple microabscesses, fibrin, and leukocytoclasis at the tips of dermal papillae. Eosinophils are usually not present; when present, they are in and below bullae but not along the basement membrane as seen in bullous pemphigoid. Direct immunofluorescence reveals deposits of IgA either in the lamina lucida of the basement membrane zone (BMZ) or below the lamina densa. Circulating antibasement membrane zone antibodies are uncommon. The patients usually respond to sulfapyridine that has been found to be superior to dapsone. Refractory cases may be administered prednisolone in combination with either sulfapyridine or dapsone. The distinct features of linear IgA dermatosis are tabulated in the Table 26.2.

### Epidermolysis Bullosa Acquisita

This disorder is characterized by skin fragility and blister formation following trauma to the skin. The lesions have an acral distribution and tend to localize over the extensor aspect of the forearms, hands, and feet. Inflammation is conspicuously absent. Mucous membrane may or may not be involved. Healing occurs with milia formation. Histopathological examination reveals subepidermal blistering disorder. The blister is located below the lamina densa. Immunofluroscence depicts deposition of IgG and C3 in the subbasalar lamina fibril zone, corresponding to the area of attachment of anchoring fibrils to the dermis.

## TREATMENT

Corticosteroids form the mainstay of treatment. However, the dose required to initiate the therapy is usually 40 to 60 mg of prednisolone or

**Table 26.2: Diagnostic criteria for linear IgA dermatosis**

*Clinical*

1. Eruption of blisters intermediate in size between bullous pemphigoid and dermatitis herpetiformis.
2. The bullae localize over the flexural areas.
3. Absence of coexisting enteropathy.
4. Normal prevalence of HLA-B8.

*Histopathological*

1. Subepidermal blister formation.
2. Multiple microabscesses, fibrin, and leukocytoclasis at the tip of dermal papillae.
3. Eosinophils are scant and located in and below the blister but not along the basement membrane as in bullous pemphigoid.

*Immunofluorescence*

1. Deposit of IgA in a linear pattern either at the lamina lucida of the BMZ or below lamina densa.
2. Indirect immunofluorescence reveals lack of circulating antiBMZ antibodies.

*Treatment*

1. Responds to sulfapyridine or dapsone.
2. Corticosteroids may be administered alongwith sulfapyridine/dapsone in refractory cases.

its equivalent corticosteroid, unlike pemphigus vulgaris where very high doses are required. At remission, the corticosteroids are tapered and immunosuppressive adjuvants like cyclophosphamide, azathioprine, or methotrexate added. The patient generally does not require maintenance therapy.

## RECOMMENDED READING

1. Liu HN, Su WP, Rogers RS 3rd. Clinical variants of pemphigoid. *Int J Dermatol* 1986;25:17-24.

# 27 Chapter Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is a chronic, pruritic, papulovesicular eruption, symmetric in distribution, with a predilection to involve the extensor of the extremities, shoulders, and buttocks. Involvement of the mucosae is infrequent. It usually affects the young men and women. Remission and relapses mark the chronic course of the disease. Gluten sensitive enteropathy is its accompaniment. HLA-B8 may be an additional indicator.

The precise etiology is debatable; however, it is presumed that dermatitis herpetiformis represents an allergic state in which the antigen is being presented to a genetically predisposed host via the gastrointestinal tract. The predisposition is through the HLA-B8 linkage. The antigen evokes an immune response producing gastrointestinal lesions and stimulating IgA antibody production. The antigen-antibody complexes, so formed, gain entrance into the systemic circulation, and are deposited in the skin. The IgA-immune complexes activate the alternative complement pathway, generating the inflammatory process resulting in lesions of dermatitis herpetiformis.

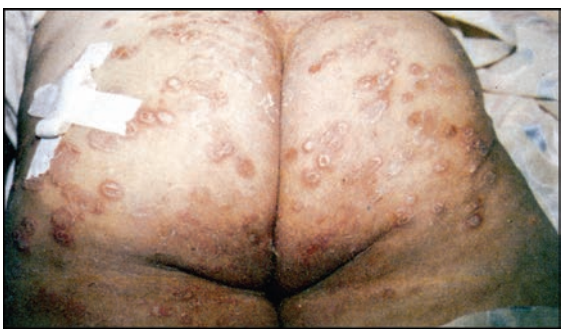
## CLINICAL FEATURES

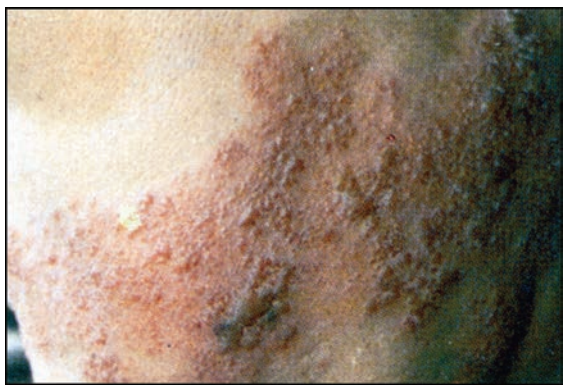
The disease is heralded by an intense itching. This is followed by the eruption of urticarial wheals, erythematous papules, papulovesicles or groups of tiny vesicles. However, they may be excoriated and it may be difficult to find the intact lesions. The vesicles arise on erythematous base and are grouped. Bullae are infrequent. The extensor aspects of the limbs, knees, elbows, buttocks, and the natal cleft are the usual sites of affliction (Table 27.1) (Figs 27.1A and B).

The axillary folds, shoulders, trunk, face, and scalp may also be involved. Mucosae are usually spared. The small bowel disease associated with dermatitis herpetiformis is similar to that seen in adult celiac disease. However, it may be asymptomatic or less severe. Symptomatic steatorrhea occurs in less than 5 percent of DH patients. Chemical evidence of steatorrhea and abnormal D-xylose absorption occurs in less than one-third of the cases. However, 90 percent of dermatitis herpetiformis patients demonstrate histologic evidence of glutensensitive enteropathy. DH has an association with thyroid diseases. Antithyroglobulin and antimicrosomal thyroid antibodies have also been demonstrated. Sporadic association with other autoimmune disorders and malignancies has been recorded. Furthermore, dermatitis herpetiformis may be precipitated by gluten containing diets, namely wheat, barley, rye, oats, iodine; thyroid replacement therapy; and viral illnesses.

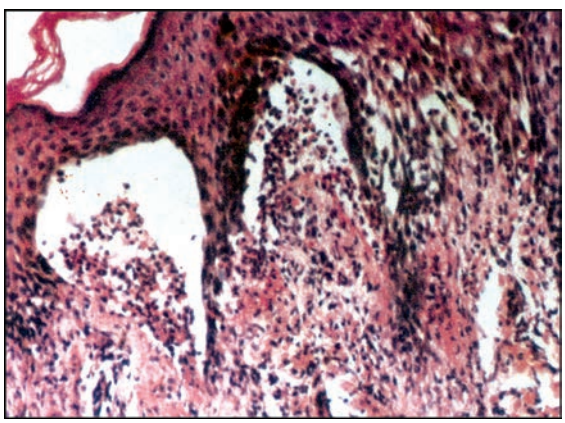
**Table 27.1: Diagnosis of dermatitis herpetiformis**

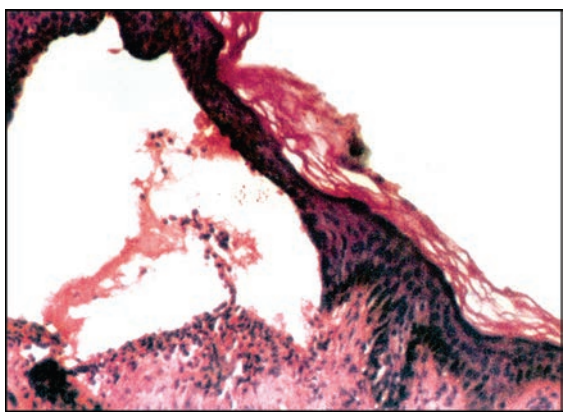
| *Histopathology* | *Direct immunofluorescence* | *Indirect immunofluorescence* |
|---|---|---|
| 1. Accumulation of neutrophils at the tips of dermal papillae forming microabscesses (Figs 27.2A and B). | Granular deposits of IgA at the dermo-epidermal junction of the uninvolved skin. | Circulating IgA antibasement membrane zone antibodies are demonstrable in only 2 percent of the cases. |
| 2. Dermal papilla appears necrotic due to the presence of fibrin. | Pivotal complement component $C_3$ is also demonstrable at the dermo-epidermal junction. | |
| 3. Microabscesses result in the separation of the tips of dermal papilla from the epidermis. Early blisters are multilocular. | Immunoelectron microscopy localizes the granular deposits of IgA at the tips of dermal papilla, beneath the lamina densa, in the area of the anchoring fibrils. | |
| 4. Rete ridges lose their attachment to the dermis. Multilocular blisters become unilocular. | They are closely associated with the bundles of microfibrils of the elastic fibers. | |





**Figures 27.1A and B:** (A) Dermatitis herpetiformis (B) Dermatitis herpetiformis grouped paulo-vesicular eruption over brick red base





**Figures 27.2A and B:** (A) Accumulation of neutrophils at the tips of dermal papillae forming microabscesses (H and E × 40) (B) Higher magnification (H and E × 100)

**Table 27.2: Differential diagnosis of bullous disorders**

| | *Pemphigus* | *Pemphigoid* | *Linear Ig/A dermatosis* | *Herpes gestationis* | *Chronic bullous disease of childhood* | *Dermatitis herpetiformis* |
|---|---|---|---|---|---|---|
| Age of onset | 4th and 5th decade | 6th to 8th decade | Middle age | Pregnant women | Ist decade of life | 3rd decade |
| Morphology | Discrete, flaccid bullae arising over apparently normal skin. Nikolsky/bulla spread sign are positive. Involves scalp, chest and intertriginous areas. | Tense bullae arising over erythematous and/or urticarial plaques. Localize in the flexures. Nikolsky/bulla spread sign are negative. | Bilsters intermediate in size between those of bullous pemphigoid and dermatitis herpetiformis. Localize in flexural area. | Erythematous, edematous papulovesicles and plaques and/or large tense bullae. Lesions may be grouped or coalesce. Abdomen, palms, soles, chest, and face usually involved. | Grouped, tense vesicles and/or bullae. Cluster of jewels arrangement. Localize in the flexures and pelvic region. | Vesicles and/or papulo vesicles of 3 to 6 mm in size. Distribution is symmetrical over extensor surfaces. Elbows, proximal forearms, knees, buttocks, and sacrum involved. |
| Mucosal involvement | Involved in almost all cases. May precede and/or accompany cutaneous lesions. Oropharyngeal, nasal mucosa commonly involved. Laryngeal and vaginal mucosa may also be involved. | Oral lesions in 20 percent cases. Involvement of other mucosae uncommon. | Infrequent | Mucosae spared. | Mucosae spared | Mucosa spared |
| Variants | Pemphigus vulgaris and its variant pemphigus vegetans. Pemphigus foliaceus and its variant pemphigus erythematoides (Senear-Usher syndrome), pemphigus herpetiformis pemphigus neonatorum, drug induced pemphigus. | Classical bullous pemphigoid, localize bullous pemphigoid, Nodular (hyperkeratotic) bullous pemphigoid, vesicular bullous pemphigoid, epidermolysis bullosa acquisita. | Nil | Nil | Nil | Nil |
| Associated features | Nil | Nil | Nil | Nil | Nil | Gluten-sensitive enteropathy |
| HLA association | HLA-A10 HLA-A26 HLA-DRW4 especially in Jews | Nil | Nil | Nil | HLA-B8 | HLA-B8 HLA-DRW3 |
| Precipitating factors | Drugs like D-penicillamine, rifampicin, piroxicam, | Nil | Nil | Pregnancy, usually the 2nd and 3rd trimester. At | Nil | Ingestion of gluten containing diet. Also iodine, thyroid dysfunction and |

*(Contd...)*

*(Contd...)*

| | *Pemphigus* | *Pemphigoid* | *Linear Ig/A dermatosis* | *Herpes gestationis* | *Chronic bullous disease of childhood* | *Dermatitis herpetiformis* |
|---|---|---|---|---|---|---|
| | phenytoin, phenobarbitone, thiopronine, a-mercapto-proprionyl glycine, captopril. | | | times flares up at postpartum period | | thyroid replacement therapy. |
| Location of the blister | Intraepidermal, suprabasal in pemphigus vulgaris. Subcorneal in pemphigus foliaceus. | Subepidermal, in the lamina lucida of the BMZ. | Subepidermal, in the lamina lucida of BMZ | Subepidermal, in the lamina lucida of BMZ | Subepidermal, in the lamina lucida of BMZ | Subepidermal, at the tip of dermal papillae |
| Direct immunofluorescence | Deposition of IgG and pivotal complement component $C_3$ in the intercellular space. | Linear deposition of IgG and $C_3$ at the lamina lucida of the BMZ | Linear deposits of IgA at the (1) Lamina lucida of BMZ or (2) below BMZ | Linear deposits of C3 at the lamina lucida of the BMZ. 30 percent cases also show deposits of IgG at the same site. | Linear deposits of IgA at the lamina lucida of the BMZ | Granular deposits of IgA in the tip of dermal papillae of uninvolved skin |
| Indirect immunofluorescence | IgG pemphigus antibody in the serum. Titers proportional to the severity of the disease. | Serum IgG antibasement membrane zone antibodies in 90 percent cases. | Negative | Serum IgG antibasement membrane zone antibodies in 10 to 20 percent of the cases. | Circulating IgA antibasement membrane zone antibodies. | Negative. |
| Treatment | Corticosteroids in high doses. At remission taper steroids and add immunosuppressive adjuvants. Maintenance dose of steroids required. required. | Corticosteroids in moderately high doses.At remission taper steroids and add immunosuppressive adjuvants. Maintenance therapy not | Dapsone, either alone or in combination with corticosteroids. | Corticosteroids | Dapsone, either alone or in combination with corticosteroids. | Dapsone |

## DIAGNOSIS

A high index of suspicion is required to form the clinical diagnosis of dermatitis herpetiformis. Its pleomorphic manifestation may make it difficult to differentiate this entity from erythema multiforme, pemphigus herpetiformis, neurotic excoriations, scabies, papular urticaria, transient acantholytic dermatoses, pemphigoid, and herpes gestationis. Histopathology, and immunofluorescence are required to confirm the diagnosis (Table 27.1).

## TREATMENT

Diaminodiphenyl sulfone (DDS) is the treatment of choice. Treatment may be initiated with 100 to 200 mg of dapsone. It dramatically improves pruritis and prevents new lesion formation within 24 to 48 hours. An occasional patient may require 300 to 400 mg of dapsone for initial improvement. Strict adherence to a gluten free diet may produce improvement of clinical symptoms, and a decrease in dapsone requirement.

## RECOMMENDED READING


1. Hall RP. The pathogenesis of dermatitis herpetiformis: Recent advances. *I Am Acad Dermatol* 1987;16:1129-1144.
2. Katz SI, Hall RP 3rd , Lawley TJ *et al*. Dermatitis herpetiformis: the skin and the gut. *Ann Intern Med* 1980;93:857-874.
3. Lawley TJ, Yancey KB. Dermatitis herpetiformis. *Dermatol Clin* 1983;1:187-194.
4. Uander Meer JB. Gluten-free diet and elemental diet in dermatitis herpetiformis. *Int J Dermatol* 1990;29:679-692.

# 28 Chapter

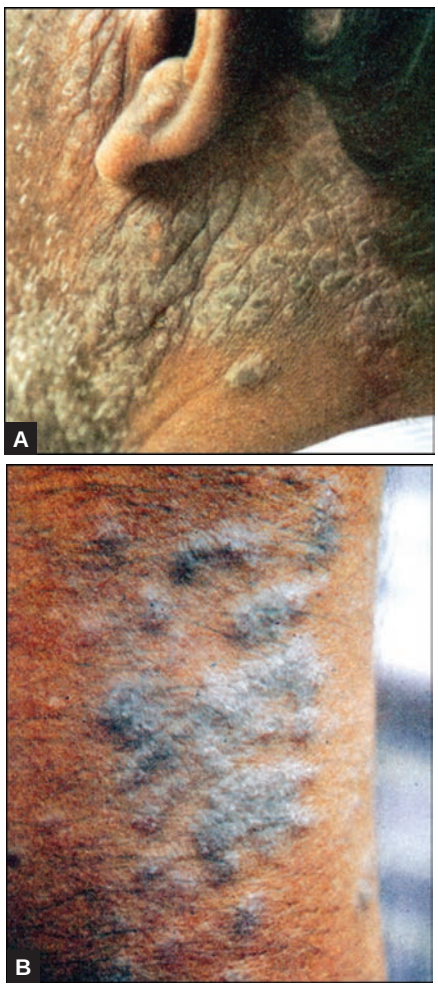
# Lichen Planus

Lichen planus is a papulosquamous disorder of debatable etiology, characterized by the formation of flat topped, polygonal, greyish white, purple/liliac eruptions. Middle age people of both the sexes are its victims.

Its precise etiology is unknown. However, it may either be bacterial or viral in origin. Immunologic factors are also incriminated due to the presence of consistent immunofluorescence pattern. It may also follow bone marrow transplantation or graft versus host reaction. Furthermore, certain individuals are genetically predisposed to it. Also several drugs such as chloroquine, quinacrine, streptomycin, para-aminio salicylic acid (PAS), methyldopa, quinidine, phenothiazine, chlorpropamide, gold, bismuth, levamisole, and penicillamine are incriminated. Exposure to paraphenylenediamine salts encountered in color-photographic developer may also produce these lesions.

## CLINICAL FEATURES

It is characterized by the formation of flat topped, polygonal, greyish white, purple/liliac eruptions (Figs 28.1A and B). Its surface is scaly, and is traversed by fine white lines, 'Wickham's striae' which become prominent after the application of an emolient. The papules may coalesce to form plaques. The papules may be scattered or grouped. They may be linear over the marks




**Figures 28.1A and B:** Flat-topped, polygonal greyish white, purple/iliac scaly eruptions traversed by fine white lines (Wickhams' striate). Papules coalesce to form plaque

of excoriation or trauma (Koebner's phenomenon). They tend to involve the flexor surfaces of the wrist and forearms, lumbar area, ankles, glans penis, anterior aspect of lower legs, and the dorsal surfaces of the hands.

Mucosal surfaces are involved in nearly half the patients. The buccal mucosa and the tongue are most frequently affected but the lips, gums, palate, conjunctivae, larynx, genitalia, and gastrointestinal tract may also be involved. The mucosal lesions consist of lacy, reticulated, white streaks, papules, plaques, and erosions (Fig. 28.2). Chronic erosive oral lichen planus may predispose to squamous cell carcinoma. Nearly 25 percent of the male patients have involvement of genitalia. Lesions are often present over the glans and these may be typical papules in an annular configuration. Occasionally, the glans penis may have erosive lesions.

Nails are affected in 10 percent of the cases and the changes include:

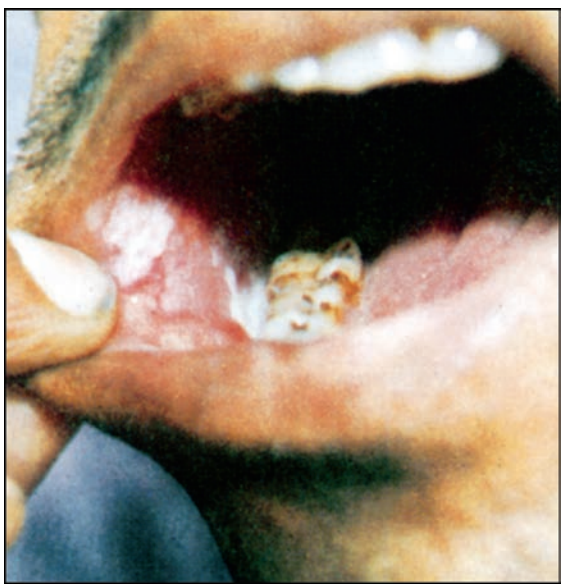


**Figure 28.2:** Mucous membrane: Display lina, reticulate white streaks, papules and erosions

- Thinning of the nail plate
- Longitudinal ridging and splitting
- Subungual hyperkeratosis
- Onycholysis
- Red or brown discoloration of the nail plate
- Pterygium, a hallmark in lichen planus. It results from the fusion of the proximal nail fold with the nailbed resulting in the loss of proximal nail plate.

Acute lichen planus usually resolves in 6 to 18 months. The lesions heal leaving behind hyperpigmentation which may take years to resolve. Chronic lichen planus persists for a long period. Oral lichen planus, hypertrophic lichen planus, and lichen planopilaris tend to be chronic.

Lichen planus may manifest as any of the following variants.

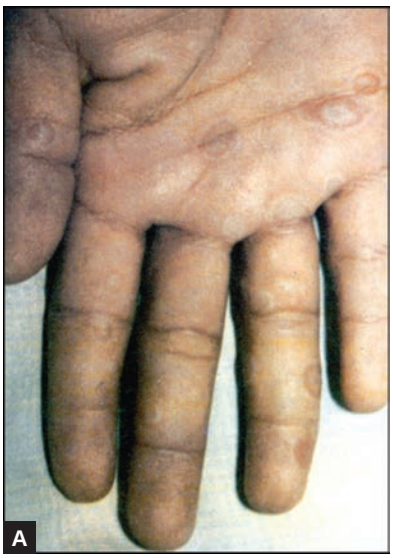
*Annular lichen planus:* It results in a ring of typical lichen planus papules that spread peripherally and produce central clearing (Figs 28.3A and B).

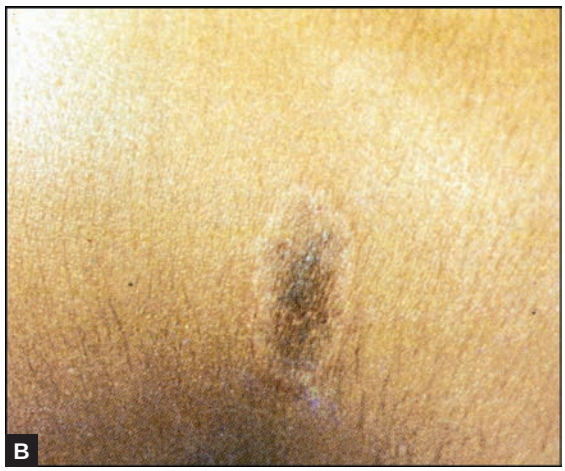
*Linear lichen planus:* It consist of typical lichen planus lesions in a linear fashion. Occasionally, it may be in a zosteriform distribution.

*Hypertrophic lichen planus (lichen verrucosus):* It arises on the shins, ankles, and soles. It consists of intensely pruritic, lichenified, scaly, violaceous, verrucous hyperpigmented plaques. The lesions are often symmetric and chronic (Fig. 28.4).

*Atrophic lichen planus:* It may occur over the mucous membranes. Atrophic lichen planus may produce atrophic white spots which need to be differentiated from lichen sclerosus et atrophicus and guttate morphea.

*Vesiculobullous lichen planus:* It may arise on pre-existing lichen planus lesions or *de novo*. It is the result of separation at the dermoepidermal




**Figures 28.3A and B:** Annular lichen planus

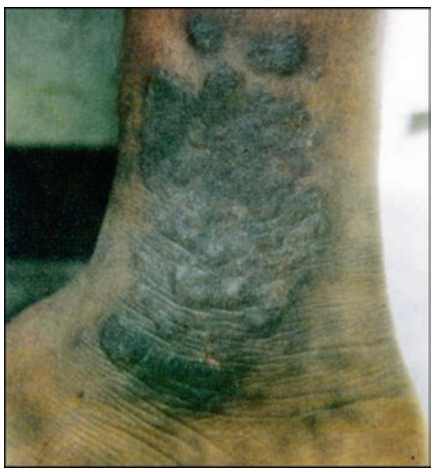


**Figure 28.4:** Hypertrophic lichen planus

**Figure 28.5:** Lichen planus actinicus

junction secondary to basal cell degeneration. It requires to be differentiated, from lichen planus pemphigoides, which is a coexistence of two distinct disease entities and pemphigoid antibodies (IgG) can be demonstrated at the lamina lucida of basement membrane zone by immunofluorescence.

*Lichen planus actinicus:* This variant is usually encountered in tropics, on sun-exposed areas. Lesions are pigmented, dyschromic or granuloma-annulare like and only mildly pruritic (Fig. 28.5).

*Lichen planus erythematosus:* It is observed in older patients and consists of nonpruritic,

soft, red papules, usually located on the forearms.

*Lichen planopilaris:* It presents as acuminate, hyperkeratotic, follicular papules, primarily on the scalp. The affected area may also depict scaling. Alopecia with atrophy may supervene. A variant of lichen planopilaris is Grahm Little-Piccardi-Lassueur syndrome. It consists of cicatricial scalp alopecia (Fig. 28.6), follicular keratotic lesions of the glabrous skin, and noncicatricial alopecia of the axillae and groins.

*Ulcerative lichen planus:* It consists of ulcerations over the soles of the feet and of the buccal mucosa associated with cicatricial alopecia, and loss of toenails. Typical lichen planus lesions may be present over other parts of the body. The lesions over the feet are painful. Squamous cell carcinoma may supervene.

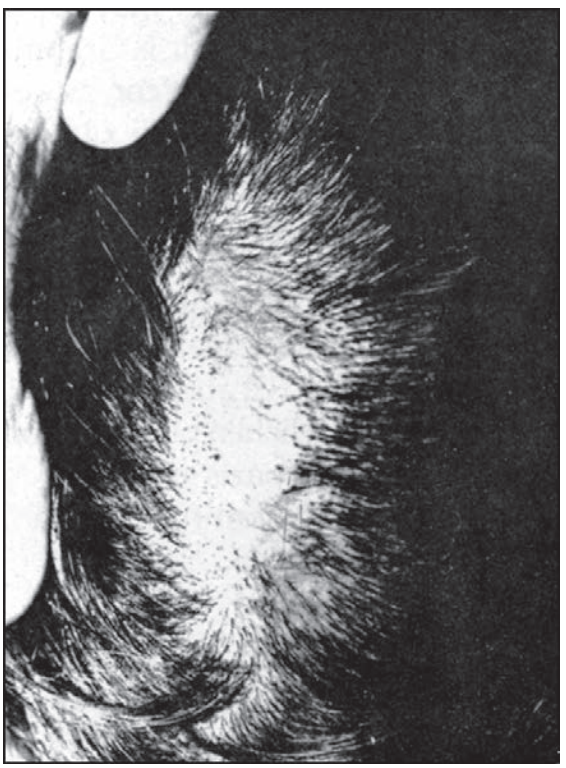


**Figure 28.6:** Lichen planopilaris affecting the scalp

*Twenty-nail dystrophy (TND):* Trachyonychia, a fascinating clinical condition, was brought to focus 25 years ago. Ever since, it has been sparingly reported. Nonetheless, the condition is well recognized, and its diagnosis is made on the basis of clinical features characterized by onset in infancy/childhood, and occasionally in adults. The lesions are fairly representative, and are characterized by the alternating elevation and depression (ridging) and/or pitting, lack of luster, roughening likened to sandpaper, splitting, and change to a muddy grayish-white color. Dystrophy is prominent. Several modes of occurrence have been described including a hereditary component. The confirmation of diagnosis is through microscopic pathology corresponding either to endogenous eczema/dermatitis, lichen-planus like or psoriasiciform. It is a self-limiting condition and may occasionally require intervention.

## DIAGNOSIS

The diagnosis of lichen planus is clinical; however, it may be supplemented by histopathology. Hematoxylin-eosin stained section reveals the presence of: (1) Hyperkeratosis, (2) Focal hypergranulosis, (3) Irregular acanthosis resulting in saw tooth appearance of rete ridges, (4) Liquefaction degeneration of basal cell layer, (5) A band-like upperdermal lymphocytic infiltrate, (6) Incontinence of the melanin, (7) Colloid bodies may be present in the deep dermis, (8) Small separation between dermis and epidermis may be present (Max-Joseph spaces) (Figs 28.7 to 28.9).

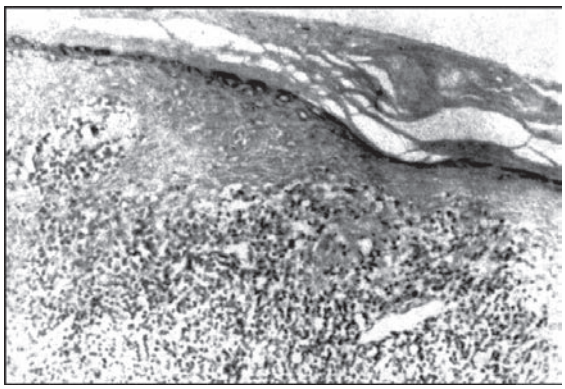


**Figure 28.7:** Lichen planus (H and E × 100)

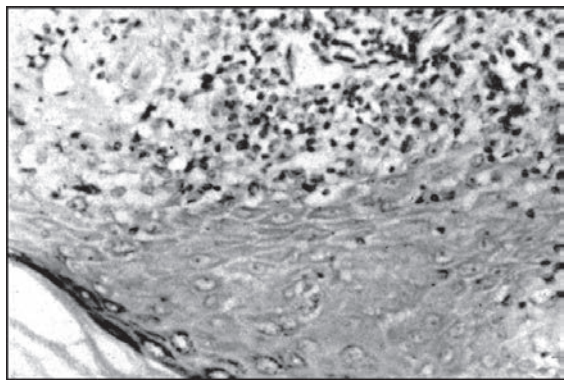


**Figure 28.8:** Lichen planus (H and E × 400)

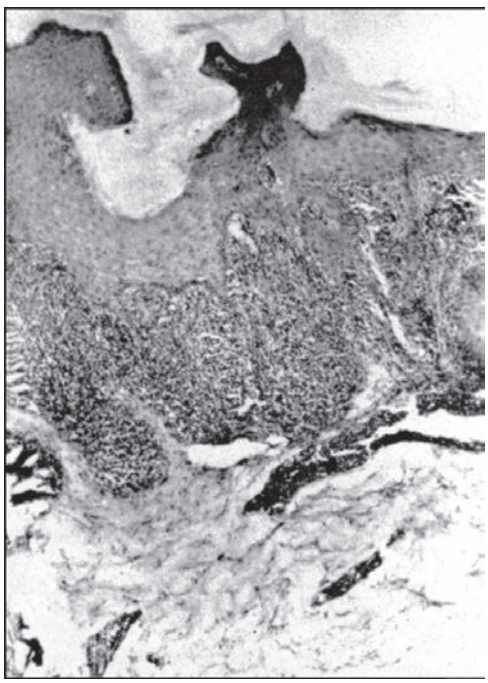


**Figure 28.9:** Lichen planus hypertrophicus (H and E × 50)

## TREATMENT

Lichen planus tends to resolve spontaneously after varying period of time. In mild cases, treatment is symptomatic. Antihistamines may be administered to relieve pruritus. Topical corticosteroids may be applied for their antipruritic and anti-inflammatory effects. Severe, acute, widespread lichen planus may benefit from a tapered course of corticosteroid. Griseofulvin may also be beneficial. Oral lichen planus respond to topical application of corticosteroid in oral protective base. Hypertrophic

**Table 28.1: Treatment of lichen planus**

| *Types of lichen planus* | *Treatment of choice* | *Other modalities of treatment* |
|---|---|---|
| 1. Acute widespread lichen planus | a. 40 to 60 mg of prednisolone every day, tapered off over 2 to 3 months.<br>b. 250 mg of griseofulvin (Idifulvin) twice a day with milk or fatty food. | 1 mg/kg of etretinate every day tapered to a maintenance dose of 25 to 50 mg on alternate days after control |
| 2. Chronic localized lichen planus | a. Antihistamines to relieve itching<br>25 mg of promethazine hydrochloride (Phenergan) thrice a day<br>25 mg of pheniramine maleate (Avil) thrice a day.<br>b. 5 mg of diazepam (Calmpose) at bed time.<br>c. Topical corticosteroids for local application<br>Clobetasol propionate 0.05 percent (Tenovate)<br>Fluocinotone acetonide 0.025 percent (Flucort)<br>Betamethasone valerate 0.12 percent (Betnovate). | |
| 3. Hypertrophic lichen planus | a. Intralesional corticosteroid<br>0.1 to 0.3 mL of triamcinolone acetonide 10 mg/mL (kenacort), intralesional once a week<br>Or<br>b. Topical corticosteroid<br>Clobetasol Propionate (0.05 percent) under occlusion. | |
| 4. Oral lichen planus | Potent steroids in Orabase for local application.<br>Or<br>40 to 60 mg of prednisolone, in divided doses, every day | 200 mg of metronidazole (Flagyl) thrice daily<br>Or<br>100 mg of isotretinoin, once a day |
| 5. Lichen planopilaris | Fluocinolone acetonide 0.025 percent lotion (Flucort) for local application<br>Or<br>Betamethasone valerate 0.1 percent lotion<br>Or<br>0.1 to 0.3 mL of triamcinolone acetonide 10 mg/mL (Kenacort), intralesional, once in two weeks. | |

lichen planus may benefit from intralesional corticosteroids or potent corticosteroids applied under occlusion (Table 28.1).

## RECOMMENDED READING


1. Boyd AS, Neldner KH. Lichen planus. *J Am Acad Dermatol* 1991;25:593-619.
2. Fox BJ, Odom KB. Papulosquamous diseases: A review, *J Am Acad Dermatol* 1985;12:597-624.
3. Sehgal VN. Abraham GJ, Malik GB. Griseofulvin therapy in lichen planus-a double blind controlled trial. *Br J Dermatol* 1972;87:383-385.
4. Sehgal VN. Lichen planus-an appraisal of 147 cases. *Ind J Dermatol Venereol*. 1974; 40: 104.
5. Sehgal VN. Twenty nail dystrophy trachyonychia: an overview. *J Dermatol* 2007;34:361-366.

# 29 Chapter

# Lichen Nitidus

Lichen nitidus is an asymptomatic papulosquamous eruption characterized by numerous, tiny, discrete, flesh colored papules. It affects children and young adults of both the sexes.

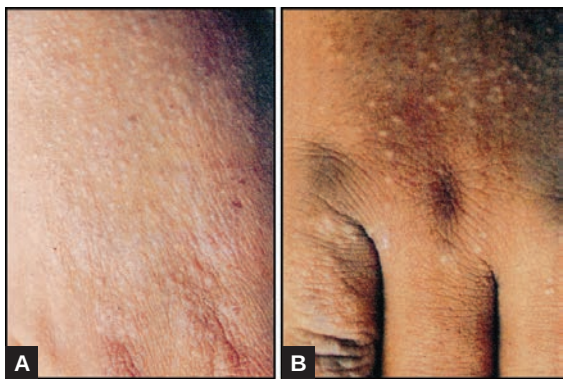
## CLINICAL FEATURES

The lesions are pinheadsized, flat, with a shiny surface. Some lesions are dome shaped and may have a central depression. They are discrete, and occasionally may coalesce to form plaques. Koebner's phenomenon may be elicited. They are distributed over the penis, arms, forearms, and abdomen.

## DIAGNOSIS

It is made clinically and confirmed by histopathological examination. Hematoxylin and eosin stained section reveals (Figs 29.1A and B; 29.2) the following:

- Focal accumulation of inflammatory cells in the widened dermal papilla. The infiltrate consists of epithelioid cells, lymphocytes, and an occasional multinucleate giant cell
- The infiltrate is grasped by elongated, 'claw-like' rete ridges
- Hydropic degeneration of basal cells
- Thin/absent granular layer
- Parakeratotic epidermis over the dermal infiltrate.




**Figures 29.1A and B:** Lichen nitidus. Multiple flesh colored papules over the trunk/dorsum of the hand

The various entities which may occasionally be mistaken for lichen nitidus are verrucaplana, lichen scrofulosorum, lichenspinosum, lichenoid secondary syphilis, lichen planus, lichen amyloidosis, keratosis pilaris, and Darier's disease.

Lichen nitidus was previously considered a variant of lichen planus. Though it shares some features of it, the two are distinct entities (Table 29.1).

## TREATMENT

No therapy is indicated for lichen nitidus and most lesions resolve spontaneously after a few years. Topical corticosteroids may hasten the clearance, and also relieve the pruritus, if any.

**Table 29.1: Differentiation of lichen planus from lichen nitidus**

| *Lichen planus* | *Lichen nitidus* |
|---|---|
| *Morphology* | |
| 1. Papule | 1. Papule |
| 2. Violaceous | 2. Flesh colored |
| 3. Wickham's striae present | 3. Wickham's striae absent |
| 4. Enlarges | 4. Remains tiny |
| *Koebners' phenomenon* | |
| • Present | • May be present |
| *Symptoms* | |
| • Pruritic | • Asymptomatic |
| *Histopathology* | |
| 1. Hydropic degeneration of basal cell is conspicuous | 1. Hydropic degeneration |
| 2. Hypergranulosis | 2. Absent granular layer |
| 3. Lichenoid infiltrate | 3. Granulomatous infiltrate |
| 4. Hyperkeratosis | 4. Parakeratosis |

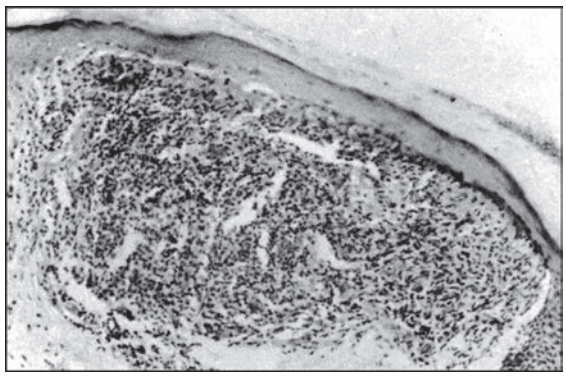


**Figure 29.2:** Numerous, tiny, discrete, flesh colored papules

## RECOMMENDED READING

1. Sehgal VN, Kumar S, Jain S *et al:* Generalised lichen nitidus in a child response to cetrizine dihydrochloride/levamisol. *Australas J Dermatol* 1998;39:60.

# 30 Chapter

# Psoriasis

Psoriasis is a papulosquamous disorder of the skin, characterized by sharply defined erythematosquamous lesions. They vary in size from pinpoint to large plaques. At times, it may manifest as localized or generalized pustular eruption. Besides the skin, it may also affect the joints and the nails. It is universal in occurrence and the incidence is 1 to 3 percent of the world population. It affects members of either sex, usually in the third decade of life. A family history of psoriasis is found in 30 percent of patients. Familial aggregation and the higher concordance rates in monozygotic over dizygotic twin pairs emphasize the pathogenetic importance of heredity in psoriasis. However, the genetic transmission is complex and psoriasis is now considered multifactorial genetic disease that requires both polygenic and environmental factors for its clinical expression. The histocompatibility locus antigens (HLAs) are regarded as the most important genetic markers for psoriasis. HLA-Cw6 is most strongly associated with psoriasis. The presence of HLA-Bw17 has been correlated with a higher familial incidence, more extensive skin involvement, and advanced clinical disease. It has also been reported in those with generalized pustular psoriasis. Those with HLA-B13 appear to have milder, more reversible disease, and often give a history of antecedent streptococcal infection. HLA-B27 shows a strong association with psoriatic sacroilitis and HLA-Bw38 with patients exhibiting psoriasis and distal arthritis.

The pathogenesis of psoriasis is debatable. However, one accepted fact is that the time necessary for a psoriatic epidermal cell to travel from basal cell layer to the surface and be cast off is 3 to 4 days, in contrast to the normal 26 to 28 days. The mechanism underlying this rapidly increased epidermal transit time is still speculated. It is attributed to a shortened cell cycle time (37 hours rather than 163 hours). Alternatively, there is recruitment of the resting cells ($G_0$) into the active cell cycle. In any event, this accelerated epidermopoiesis does not allow normal events of cell maturation and keratinization. This is reflected clinically, histologically, and chemically. Thus, there is production of thick white scales, markedly thickened epidermis with immature nucleated cells in the stratum corneum (parakeratosis), and a reduction of tonofilament formation and keratohyaline granules. Histochemical analysis reveals a high concentration of lipids and phospholipids, an increase in acid mucopolysaccharides, alpha amino acids, and sulphydryl groups, and the retention of taurine along with increased urinary excretion of uric acid.

Alteration in the relative levels of endogenous cyclic nucleotides has been recorded in the psoriatic lesion. There is an increase in the cGMP : cAMP ratio, attributed to the consistent increase in the cyclic GMP in the psoriatic skin. This may be responsible for the epidermal proliferation.

Polyamines, low molecular weight organic amines such as putrescine, spermidine, and spermine have been observed to be higher in the blood and skin lesions in psoriasis. They have been implicated in the regulation of cellular proliferation. Several therapeutic regimens including anthralin, corticosteroids, PUVA, and retinoids lower the polyamine levels.

Polymorphonuclear leukocytes (PMNLs) play an important role in the pathogenesis of psoriasis. Psoriatic scales contain a chemotactic factor for the polymorphs. This has been identified as the complement cleavage product. It has been hypothesized that immune complexes are formed in the stratum corneum by the binding of antistratum corneum antibodies that are detectable in psoriasis. These immune complexes are responsible for fixing the complement. Alternatively, it has been proposed that the psoriatic epidermis contains increased amounts of serine proteinase that are responsible for the activation of the alternative complement pathway.

An increase in the arachidonic acid and 12-HETE has been recorded in the psoriatic scales. There is an inhibition of cyclo-oxygenase, an enzyme required for the conversion of arachidonic acid to prostaglandins. Arachidonic acid is then diverted to the lipoxygenase pathway resulting in the production of leukotriene B4 (LTB4). LTB4 is one of the most potent chemotactic agents.

Psoriatic patients have a decrease in T cells. This is the result of the absence of clones of T suppressor cells. Thus, there is a significant increase in the T helper-suppressor cell ratio. The absence or malfunction of a clone of T suppressor cell allows the recognition of basal cell nuclei as antigen. This results in the formation of antibasal cell nuclear antibodies directed against the nonhistone nuclear protein. The resulting immune response could lead to increased cellular proliferation.

Psoriasis may be precipitated by trauma, infection, endocrine factors, climate, and emotional stress. It may appear at the site of local injury (Koebner's phenomenon). Infection with beta-hemolytic streptococci usually precedes guttate psoriasis. Drugs like chloroquine, lithium carbonate, salicylates, steroids, iodides, nystatin, progesterone, and beta-blockers also precipitate psoriasis.

## CLINICAL FEATURES

Psoriasis is characterized by well-circumscribed, sharply demarcated erythematous papules and/or plaques. These are covered by dry, brittle, silvery or greyish white, loosely adherent, micaceous scales. The scales are disposed in lamellar fashion. Occasionally, a white blanching ring is seen around the psoriatic lesions, known as Woronoff's ring. On grattage, silvery white scales come off in layers. After their removal, a characteristic coherence is observed, as if one scratches on a wax candle (candle grease sign). On further grattage, a thin peel-like membrane, Berkley's membrane, is seen which comes off as a whole. On its removal, a wet surface with multiple pinpoint bleeding is revealed. This is called Auspitz's sign and it is the macroscopic equivalent of the upward proliferation of dermal papillae with vasodilatation. Although no region is exempt from involvement, the sites of predilection are

the elbows, knees, scalp, and lumbosacral area. The localization of the lesions over the extensor surface has been attributed to Koebner's phenomenon, the tendency to reproduce the lesions over the site of trauma. Mucosal surfaces are spared as the turnover of epithelium over them is normally as rapid as in the psoriatic skin. Nail involvement is common and is seen in 30 percent of the cases. However, in psoriatic arthritis nails may be involved in 85 to 90 percent cases. The fingernails are more often involved than the toenails. Nail changes are characterized by the following:

- Thick, brittle, lusterless nails that are difficult to cut
- Pitting of the nail plate. This is the result of involvement of the proximal part of the matrix. The nail pits correspond to the small parakeratotic foci in the matrix. The pits are small
- Subungual hyperkeratosis may be seen under the free edge of the nail. This is the macromorphological equivalent of the parakeratosis formed by the hyponychium
- The nail plate becomes discolored. Brownish red, oval or round lesions can be seen, resulting from an accumulation of parakeratotic material in the nailbed. This is termed as 'Olfleck' phenomenon
- Distal onycholysis is another frequent abnormality. At the free edge a space is formed between the nail plate and hyponychium
- Loss of nail plate.

Psoriasis may present as anyone of the following clinical variants (Table 30.1).

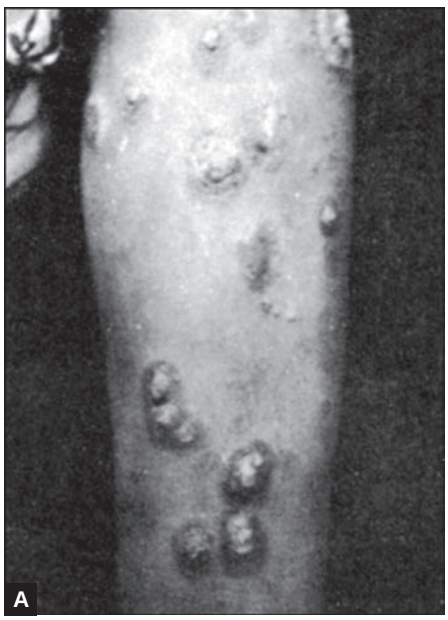
## Chronic Plaque Psoriasis

This is the most common manifestation. It is characterized by sharply defined, erythe-

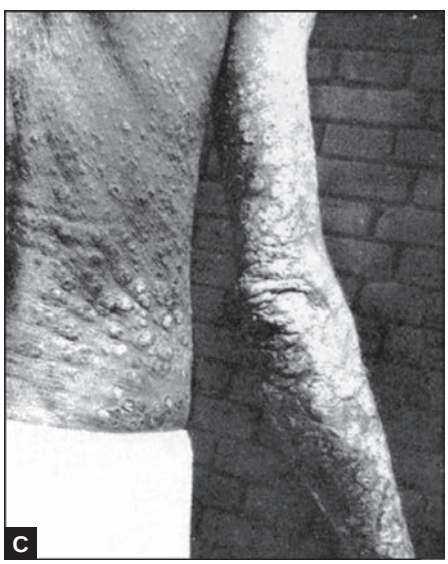
**Table 30.1: Summary of appropriate therapy for various clinical variants of psoriasis**

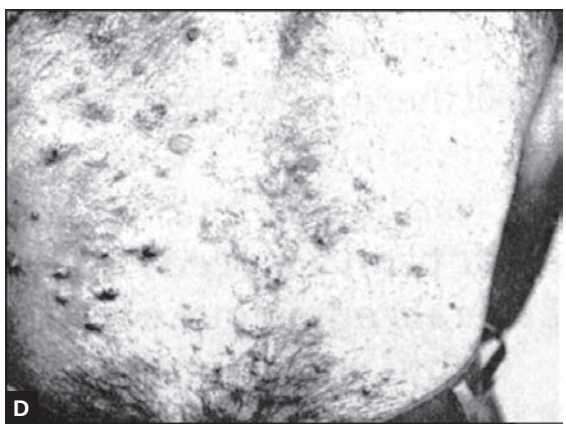
| *Clinical type* | *Treatment of choice* | *Other therapies* |
|---|---|---|
| 1. Localized plaque psoriasis | Phototherapy, and psoriatic ointment/topical corticosteroids. | — |
| 2. Chronic, widespread, plaque psoriasis | PUVA or Goeckerman's regimen or Ingram's regimen | Methotrexate, retinoids, hydroxyurea, cyclosporine A |
| 3. Unstable, extensive psoriasis vulgaris | Methotrexate | Retinoids, PUVA, cyclosporine A |
| 4. Disabling localized psoriasis | PUVA | Methotrexate, retinoids |
| 5. Guttate psoriasis | Systemic antibiotics. Phototherapy and psoriatic ointment/topical corticosteroids | — |
| 6. Palmoplantar psoriasis | PUVA | — |
| 7. Persistent palmoplantar pustulosis | PUVA | — |
| 8. Generalized pustular psoriasis | Retinoids | Methotrexate, corticosteroids |
| 9. Erythrodermic psoriasis | Systemic corticosteroids. At remission taper corticosteroids and add methotrexate | Retinoids |
| 10. Active psoriatic arthritis | Non-steroidal anti-inflammatory agents | Intra-articular steroids |
| 11. Active severe psoriatic arthritis | Methotrexate | Azathioprine, retinoids, gold, penicillamine, and corticosteroids. |
| 12. Nail psoriasis | Injections in the nail matrix with glucocorticoids. | Methotrexate, retinoids. |

matosquamous plaques, usually distributed fairly symmetrically. The size of the lesion may vary from a coin to a palm or larger (Figs 30.1A to G). If the coin-sized lesions predominate, it is termed 'nummular psoriasis' while if palm-sized lesions dominate it is referred as 'psoriasis geographica'. The degree of scaling may also vary considerably. Limpet-like lesions with

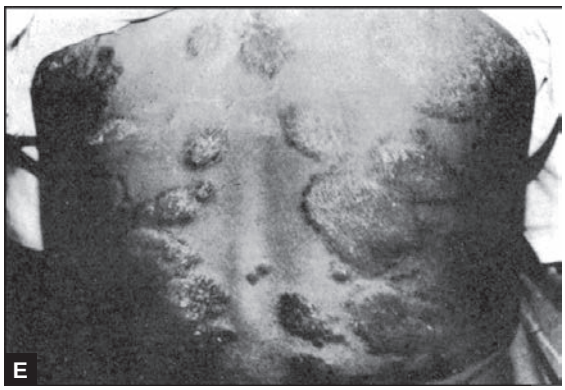


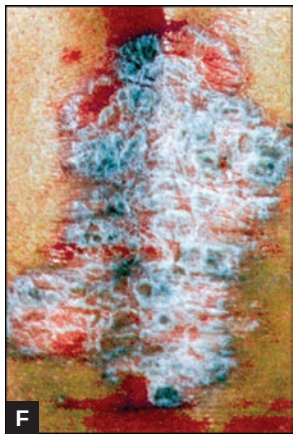


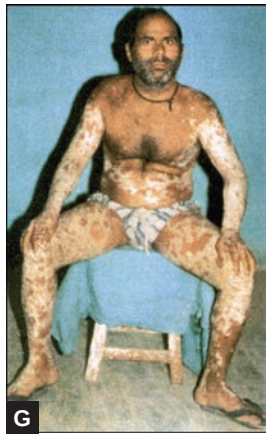



**Figures 30.1A to D**




**Figures 30.1A to G:** Plaque psoriasis: Sharply defined, erythematosquamous plaque(s), covered by dry brittle, silver/greyish white, loosely adherent, micaceous scales disposed in lamellar fashion. Auspitz's sign is positive

scales showing horizontal rather than vertical lamellation are termed rupoid psoriasis or 'ostracea'. Sometimes, psoriatic plaques are surmounted by a massive, thickened horny layer. If dry and cracked, the lesions may be painful. These are termed inveterate or 'elephantine' psoriasis (Fig. 30.2).

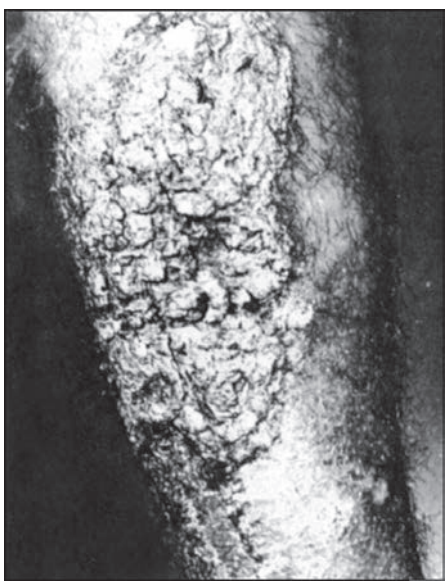


**Figure 30.2:** Psoriasis: Dry, cracked, painful lesions. 'Elephantine' psoriasis

## Guttate Psoriasis (Fig. 30.3)

It is characterized by erythematosquamous papules that are distributed as droplets over the body. The trunk is the site of predilection. Palms and soles are spared. It is common in children and is often preceded by the streptococcal infection of the upper respiratory tract. More

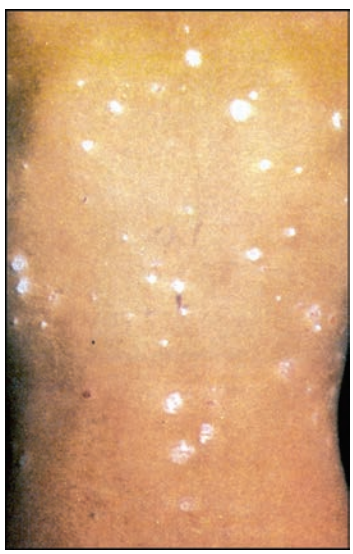


**Figure 30.3:** Guttate psoriasis: Erythematosquamous papules (droplets) over the trunk in a child, preceded by streptococcal upper respiratory tract infection

than half the patients show an antistreptolysin titer higher than 200 units.

### Flexural Psoriasis

The flexures may be exclusively involved or involved along with other sites. The lesions are characterized by poorly demarcated erythematous plaques covered with fine, moist scales. Often a central fissure is present. The lesion tends to localize in the axillae, groins, submammary region, perianal region, and retroauricular region. Seborrheic dermatitis, mycotic infection, and erythrasma need to be excluded.

### Erythrodermic Psoriasis

It is indistinguishable from exfoliative dermatitis secondary to other causes. It may occur spontaneously, follow a systemic illness, vigorous tar or phototherapy or occur as a result of steroid withdrawal. It is characterized by generalized scaling and erythema. Sites that were free of psoriasis are also involved in the totality of the erythroderma. However, often a few areas uninvolved by erythroderma may be present. It may be possible to detect typical erythematosquamous lesions in these areas. Serious systemic dysregulation may occur including hypo- or hyperthermia, protein loss, and water-electrolyte imbalance. Dehydration, renal failure, and cardiac failure may also occur. Erythrodermic psoriasis needs to be differentiated from generalized plaque psoriasis which is characterized by well-circumscribed, erythematosquamous lesions distributed all over the body instead of diffuse erythema and scaling. Also, systemic dysregulation is usually lacking.

### Pustular Psoriasis

It may be precipitated by pregnancy, sudden withdrawal of corticosteroid, hypocalcemia, local irritants, and infections. Distinct subtypes are of it are as follows.

#### *Generalized Pustular Psoriasis of Von Zumbusch*

It is characterized by eruption that starts abruptly with erythema and pustulation. The pustules may coalesce to form lakes of pus. The patient is febrile and the skin is tender. Leukocytosis may be an accompaniment. After a few days, pustulation subsides and gives way to generalized desquamation.

#### *Annular Pustular Psoriasis*

It is characterized by widespread annular lesions. The lesions are erythematous and scaly, with pustules studded at the periphery. They may persist for a few weeks to a few months.

#### *Exanthematous Type*

It is characterized by an acute eruption of pustules. It starts over the palms and soles and spreads abruptly over the whole body. It usually follows an infection and resolves after the infection is cured.

#### *Localized Type*

It is characterized by the appearance of pustules over the chronic plaques of psoriasis. It may be secondary to topical therapies like dithranol and corticosteroids applied under occlusion.

#### *Impetigo Herpetiformis*

It is a rare manifestation of pustular psoriasis that usually occurs during the third trimester of pregnancy. It resembles generalized pustular psoriasis and is associated with severe systemic toxicity. It may result in miscarriage.

### Psoriasis of the Scalp

Scalp may be affected alone or as a part of psoriasis vulgaris. It is characterized by plaque(s)

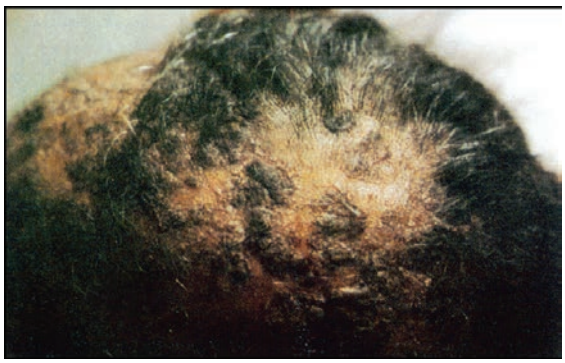


**Figure 30.4:** Scalp psoriasis: Thick, brittle lusterless nail, difficult to cut, proximal pitting, and sublingual hyperkeratosis

over the scalp. The area between the plaques may be free. Scales are similar to those over the skin. Palpation of the scalp gives a 'miniature mountain' feel. It may extend to involve the forehead and form 'corona psoriatica' (Fig. 30.4).

## Psoriasis of the Palms and the Soles

Palmoplantar psoriasis may occur with or without lesions at other sites. The lesions are sharply demarcated plaques with firmly adherent scales. Fissuring may occur.

## Psoriatic Arthritis

It is an inflammatory arthritis, generally with a negative rheumatoid factor, associated with psoriasis. A correlation has been suggested between the psoriatic arthritis and human leukocyte antigens (HLAs). In psoriasis associated with peripheral arthropathy, HLA-B38 is prevalent. Erosive and severe arthritis may be associated with HLA-DR4. Psoriatic arthritis with a prevalently spondylitic involvement is often associated with HLA-B27. Psoriatic arthritis may present in either of the five forms:

### *Asymmetric Oligoarticular Arthritis*

It is the largest group and represents 70 percent of cases. It is characterized by its asymmetry. The joints involved are the distal interphalangeal, proximal interphalangeal, and metacarpophalangeal, but the hip and knee may also be affected. These lesions may be accompanied by tenosynovitis and result in the classic 'sausage finger'.

### *Symmetric Rheumatoid-Like Arthritis*

This represents 15 percent of cases. It is clinically similar to rheumatoid arthritis. Peculiarities include its symmetric nature and negative rheumatoid factor.

### *Classical Psoriatic Arthritis*

This represents only 5 percent of the cases of psoriatic arthritis. Distal interphalangeal joints are predominantly involved.

### *Arthritis Multilans*

It is a severely deforming arthritis with destruction of bones and widespread ankylosis. Osteolysis may cause 'telescoping' of the digits and even complete dissolution of the phalanges. This affects 5 percent of the patients.

### *Ankylosing Spondylitis with or without Peripheral Joint Involvement*

It represents 5 percent of the cases.

The most consistent finding in psoriatic arthritis is the absence of rheumatoid factor. There may be an increase in the nonspecific phlogotic indices like blood sedimentation rate, reactive protein C, alpha-2 globulin, and beta globulin. The radiologic picture of psoriatic arthritis may reveal the following.

- Marginal erosion of the peripheral joints—early erosions appear at the very edge of

the articular cartilage. Later the erosive process may spread to involve the entire joint surface.

- Osteolysis producing whittling of the terminal phalanges and to a lesser extent, metacarpals and metatarsals. This effect produces characteristic morphological appearances including the 'pencil in cup' or 'mushroom' deformity, acro-osteolysis (resorption) of terminal phalanges and in most severe forms, the bones almost disappear 'doigts en lorgnette'. The phalanges may disappear leading to telescoping of the digits and the so called 'hour glass hand.'
- New bone formation — the hypertrophic changes arise as periostitis. These changes contribute to the pencil in cup appearance and if the splaying of the base of distal phalanx is prominent it produces 'fish-tail deformity.'
- Spinal changes are characterized by nonmarginal syndesmophytes. They display various morphological forms, such as 'tear-drop', 'inverted comma' or 'bagpipe shapes'.

## DIAGNOSIS

The diagnosis of psoriasis is clinical. It is based on recognizing the cardinal morphological lesion of psoriasis characterized by erythematoscaly eruptions, single or multiple, disposed primarily on the extensor surface of the body. The scales are lamellated and silvery white. Auspitz's sign is positive, evident as pinpoint bleeding on grattate. It may be supplemented by histopathological examination which reveals the following:

- Parakeratosis.
- Absence of granular layer.
- Regular elongation of the rete ridges with thickening of their lower portions.
- Long edematous and often club-shaped papillae.
- Thinning of the suprapapillary plate.
- Spongiform pustule of Kogoj formed by the intermingling of epidermal cells beneath the parakeratotic stratum corneum with neutrophils.
- The presence of microabscesses in the stratum corneum (Fig. 30.5).

The lesions of psoriasis need to be differentiated from:

*Seborrheic dermatitis:* The usual localization of seborrheic dermatitis is over the scalp, furrows of the face, presternal, interscapular, and flexural areas. The scales are yellowish and greasy.

*Lichen simplex chronicus:* It is a reaction pattern of the skin to prolonged rubbing characterized by thickening, pigmentation, and exaggerated skin markings.

*Syphilis:* Psoriasiform lesions of secondary syphilis may mimick guttate psoriasis. Histopathology and serology are diagnostic.

*Candidiasis:* It may resemble flexural psoriasis. However, it is characterized by collarette scales and pustules at the margin. Demonstration of the fungus is diagnostic.

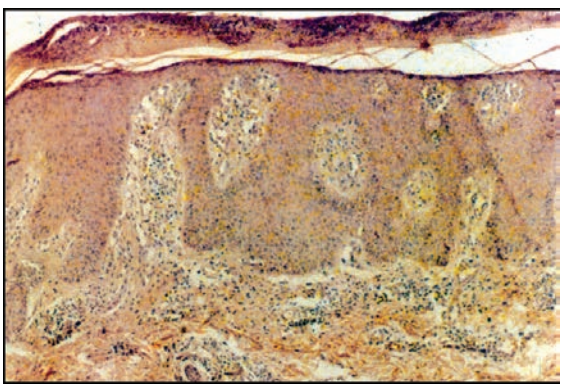


**Figure 30.5:** Psoriasis (Hand E × 40)

*Tinea corporis:* It starts as an erythematous, itchy papule that progresses to form a circinate lesion. It is studded at the periphery with papules and/or papulovesicles. The lesions are scaly showing clear or apparently normal looking center. The demonstration of fungus in 10 percent KOH from scraping seen under the microscope and their recovery in Saboraud's agar medium is confirmatory.

*Pityriasis rosea:* It is characterized by appearance of multiple, oval, well-defined erythematous, scaly eruptions, disposed along the body cleavages, resembling an inverted Christmas tree. The initial lesion a herald patch is the diagnostic hallmark of the disease.

*Parapsoriasis:* It may present as small plaque or large plaque parapsoriasis. The small plaque parapsoriasis is characterized by small to moderate sized plaques that arise on the trunk and proximal part of the extremities. The borders are distinct. The scales are thin, adherent, and do not expose bleeding points on removal. Large plaque parapsoriasis is characterized by oval, poorly defined, plaques more than 5 cm in diameter. They are slightly indurated with fine superficial scales. The trunk and proximal extremities are involved. Auspitz's sign is negative. The diagnosis of parapsoriasis is by exclusion and is further supplemented by histopathology.

*Borderline tuberculoid leprosy:* It is characterized by erythematous/hypopigmented plaques or macules with well-defined, irregular, serrated borders. The surface is dry, bald, and scaly. There is impairment of sensation to temperature, touch, and pain. The nerve feeding or proximal to the patch is thickened and/or tender. The presence of satellite lesions is contributory. The number of lesions varies from 3 to 10. Histopathology is diagnostic.

*Discoid lupus erythematosus:* It is a connective tissue disorder characterized by erythematous plaques covered with thick, adherent scales that dip into the patulous hair follicles. Removal of the scales demonstrates the characteristic 'carpet tack' sign. The lesions heal with central atrophy, scarring, telangiectasia, and depigmentation. Histopathology is diagnostic.

## TREATMENT

Psoriasis is characterized by remissions and relapses. Although it is difficult to cure, yet, topical and systemic therapeutic regimens administered singly or in combination are effective in maintaining the disease in remission. Besides the active therapeutic measures, triggering factors should be identified and their removal attempted. Also, the patient should be explained about the nature of the disease. Explanation that resolution will occur with treatment although recurrences are likely is often rewarding. General measures like reassurance are helpful. The specific treatment varies according to the site, severity, duration, and the clinical variant of psoriasis.

### Phototherapy

Ultraviolet light is an effective treatment of psoriasis. Ultraviolet radiation in the range of 290 to 320 nm (UV B) is optimal. UVR below 300 nm results in more erythema relative to the therapeutic effect and thus lowers the therapeutic index. The radiations above 320 nm have little effect in the absence of photosensitizing agent. The ideal patient for helio/phototherapy is a young adult with a normal reaction to light and having guttate or plaque psoriasis. A history of photosensitive disorder or concurrent treatment with photosensitizing

drug are contraindications to phototherapy. Thick and scaly horny layer of the untreated psoriatic lesion screens most of the incident UVB radiations due to scattering and absorption. Thus it is essential to remove the scales with soap and water prior to exposure to sun or UVB lamp. The application of a topical lubricant improves the therapeutic index further by increasing the transmission of UVB through the psoriatic horny layer. The patient may then be exposed to the midday sunlight daily or undergo UVB exposure thrice a week. Exposure is begun with a dose slightly less than the minimal erythema dose (MED) and each subsequent dose is increased by 20 percent to achieve a mild erythematous response. Heliotherapy/phototherapy remains the safest and an effective means of inducing remission in psoriasis.

### Topical Corticosteroids

Application of topical corticosteroids is useful in treatment of localized plaque psoriasis. Creams are preferred in the intertriginous areas while at other sites ointments are used. Treatment is usually initiated with a potent corticosteroid like clobetasol propionate 0.05 percent (Tenovate) or betamethasone dipropionate 0.05 percent (Diplene). It is applied without occlusion during the daytime. In the evening, it may be applied over the plaques and then the site wrapped with polythene overnight to achieve occlusion. As the lesions flatten and scaling diminish, corticosteroids may be applied intermittently on alternate days. Subsequently, the superpotent topical corticosteroids may be substituted with moderately potent corticosteroids like betamethasone valerate cream (Betnovate).

The steroids are effective in psoriasis and probably act by inhibiting mitosis and inflammation. However, they have a well-recognized potential for side effects like atrophy, striae, telangiectasia, folliculitis, milia, and infection. Also, if used for the treatment of generalized psoriasis, the percutaneous absorption may be significant and cause suppression of hypothalmopituitary adrenal (HPA) axis.

### Coal Tar

Tars inhibit DNA synthesis as well as sensitize the skin to long-wave ultraviolet light (UVA) and hence are effective in psoriasis. Though they do not offer any advantage over lubricants such as petrolatum when used with aggressive UVB treatment, tars provide a beneficial light sparing effect when used with less aggressive UVB regimens. Tar is an integral part of Goeckerman's regimen that is useful in the treatment of plaque psoriasis with moderately extensive involvement. There are many modifications of the Goeckerman's regimen which consists essentially of series of UVL exposure along with the local use of tars to sensitize the psoriatic skin to the ultraviolet light. It should be administered in the following sequence:

- Daily application of 1 to 5 percent crude coal tar or 5 to 10 percent of liquor carbonis detergens in a hydrophilic cream. This is left for 24 hours.
- After 24 hours most of the tar is removed with mineral or vegetable oil.
- This is followed by exposure to ultraviolet light to induce mild erythema. This is equivalent to 20 to 30 minutes of sunlight.
- After the light exposure, patient is given a bath with soap and water to wash off the scales.
- Tar is reapplied after the bath.

### Salicylic Acid

It is a keratolytic agent and in concentrations between 3 and 6 percent causes softening of the horny layers and shedding of the scales. It produces this desquamation by solubilizing the intercellular cement and enhances the shedding of corneocytes by decreasing the cell-to-cell cohesion. It may be combined with corticosteroids or tar. Its keratolytic action supplements the keratostatic effect of these substances. Psoriatic ointment comprising crude coal tar 6 percent, salicylic acid 3 percent, and ammoniated mercury 1 percent is useful in the treatment of psoriasis.

### Anthralin (Dithranol)

It is effective in the treatment of psoriasis. The exact mode of action is not known. However, it probably acts directly on the stem cell population of the epidermis. The release of a hydrogen atom from the 10-methylene group in anthralin initiates the formation of biologically active free radicals. It has been observed that dithranol inhibits key enzymes such as glucose-6-phosphate dehydrogenase, but it may also act by a less specific effect such as depriving the cells of oxygen needed for their proliferating activity. It also has specific effect on mitochondria. Slowing proliferation allows time for the epidermis to form normal keratin. Dithranol forms the integral part of Ingram's regimen that is administered in the following sequence:

- The patient is given tar bath. He soaks and washes himself thoroughly in a 90 liter (20 gallon) bath to which has been added 120 mL (4 oz) of an alcoholic solution of coal tar.
- After drying, the patient is exposed to small doses of UVB, increasing gradually to suberythema dosage.
- Following the light treatment, each lesion is accurately covered by the application of dithranol 0.4 percent in stiffened Lassar's paste (containing salicylic acid 2 percent and hard paraffin 5 percent).
- The lesions are powdered with talc and covered with stockinette dressing.
- The patient returns for treatment after 24 hours.

The regimen is highly effective but suffers from certain disadvantages. The dithranol stains the skin and the dress. Also, it irritates the eyes and thus avoided over the face.

Another approach is the short contact or 'minutes' therapy using higher concentration of anthralin. This technique allows patients to treat themselves at home. Anthralin (0.5 to 2 percent) is applied for 30 minutes to 2 hours and then washed off. This regimen is effective and readily acceptable to the patients.

Systemic therapy is indicated if the patient fails to respond to phototherapy and/or standard topical treatment. Majority of such patients have a widespread disease covering large areas of the body. Some have a localized but disabling psoriasis. The lesions may be cosmetically disfiguring or a hindrance to economically productive employment. The drugs commonly employed for systemic therapy are the corticosteroids, PUVA, methotrexate, and retinoids. A recently introduced drug is cyclosporin A. Such a systemic treatment carries a potential for more serious side effects than the topical therapy. The judgement to use systemic treatment should always be a sound benefit/risk assessment based upon the variables of disease severity, medical fitness of the patient, and provision for administering treatment under supervision with close monitoring of the patient.

## Systemic Corticosteroids

Systemic corticosteroids have no place in the management of plaque psoriasis because of the risk of conversion to pustular form. However, they have a useful role in achieving immediate remission of generalized pustular and erythrodermic psoriasis. Once the patient goes into remission, other definitive treatments like methotrexate or retinoids should be introduced so that the steroids can be withdrawn. Steroids may also be needed for the treatment of acute psoriatic polyarthritis that is threatening severe irreversible joint damage.

## Photochemotherapy (PUVA)

It is an effective way of clearing psoriatic lesions. The therapeutic results of oral and topical PUVA therapy are similar. However, PUVA therapy using topical psoralen is laborious and time-consuming when every psoriatic lesion has to be painted. Thus it is used only for the management of localized disease such as palmar psoriasis. The use of oral PUVA is more simple than topical PUVA and thus more popular. Psoralen forms photoadducts with DNA in the presence of UVA and thus reduces the increased epidermal turnover characteristic of psoriasis.

**Table 30.2: Criteria for the selection and exclusion of patients for PUVA therapy**

| *Candidates for PUVA* | *Exclusion criteria* |
|---|---|
| 1. Severe, extensive psoriasis | 1. Pregnancy |
| 2. Localized pustular psoriasis | 2. History of photosensitivity |
| 3. Persistent palmoplantar pustulosis | 3. Skin malignancies at present or in the past |
| 4. Psoriasis refractory to topical treatment | 4. History of arsenic intake |
| | 5. History of exposure to high dose grenz rays, X-rays or UV-light |
| | 6. Cataracts |
| | 7. Cardiovascular dysfunction |

Administration of PUVA therapy requires judicious selection of the patients (Table 30.2).

The patient is administered any of the psoralen preparations namely: (1) basic psoralen, (2) 8-methoxy psoralen, or (3) 4, 5, 8-trimethyl psoralen. The dose is 0.6 mg/kg body weight. The drug is usually administered at 9.00 AM in the morning with breakfast. Two hours later, at 11.00 AM the patient is exposed to sunlight. Initially the duration of exposure is 15 min. It is gradually increased by 5 minutes. The eyes are protected from sunlight by wearing sunglasses. The average number of exposures required is usually between 20 and 25, and the mean cumulative UVA-dose necessary is 80 to 100 J/cm$^2$.

PUVA, though highly effective modality of treatment, has certain limitations. It may cause acute side effects like nausea, dizziness, headache, pruritus, erythema, burns, and blisters. These are, however, reversible. The main concern is the potential long term risks. Abundant evidence indicates that PUVA is cataractogenic, mutagenic, and causes premature aging of the skin. An increased risk of nonmelanoma skin cancer and especially squamous cell carcinoma is encountered in patients who had previous cocarcinogen therapies like arsenic and ionizing radiations.

## Methotrexate (MTX)

It is a folic acid antagonist, useful in the management of psoriasis unresponsive to the more conventional therapies. Besides having a certain immunosuppressive activity, MTX slows down mitotic activity by reducing DNA-synthesis. It also inhibits granulocyte and monocyte chemotaxis. It inhibits the human $C_{5a}$ induced skin response in psoriatic patients and $LTB_4$ induced

infiltration of granulocytes into psoriatic epidermis. Its anti-inflammatory effect may partially be responsible for its anti-psoriatic action. The important factors in MTX treatment are that the indication should be good and those patients in whom methotrexate is contraindicated, not instituted this treatment. A normal kidney, liver, and bone marrow function is essential before starting MTX therapy. Also active peptic ulcer or infection should not be present. Pregnancy is an absolute contraindication to MTX therapy. Table 30.3 shows the indications and contraindications for MTX therapy.

Methotrexate is administered in 3 doses at 12 hours interval every week. Initially, a test dose of 5 mg is given. If the patient tolerates it, he is given 3 doses of 7.5 mg each at 12 hours interval every week. Patient may develop nausea, abdominal discomfort, vomiting, fatigue, and headache on receiving methotrexate. It may cause bone marrow suppression leading to anemia, leukopenia, and thrombocytopenia. Pneumonitis may develop. However, it is uncommon and resolves rapidly after discontinuation of the treatment. The most serious side effect is the hepatotoxicity. MTX may induce liver damage which may progress to fibrosis and cirrhosis. Thus, it is essential to monitor liver function. However, the noninvasive tests like liver scan with technetium-99m (99mTc), ultrasound, and magnetic resonance do not reveal the true status of liver damage. The most reliable test is the liver biopsy. It should preferably be performed after 1.5 gm of MTX has been administered. The only noninvasive test which might give a clue to MTX induced liver damage is the serum analysis of amino-terminal peptide of type III protocollagen (PIII NP). The investigations shown in Table 30.4 are essential before administering MTX and during the follow-up.

**Table 30.3: Criteria for selection and exclusion of patients for MTX therapy**

| *Indications* | *Contraindications* |
|---|---|
| 1. Severe, extensive psoriasis | 1. Pregnancy |
| 2. Erythrodermic psoriasis | 2. Renal impairment |
| 3. Generalized pustular | 3. Recent hepatitis psoriasis |
| 4. Disabling, localized psoriasis | 4. Liver cirrhosis |
| 5. Disabling, localized pustular | 5. Alcoholism psoriasis |
| 6. Disabling, persistent palmoplantar pustulosis | 6. Refusal to contraception |
| 7. Active pronounced psoriatic arthritis | 7. Active peptic ulcer |
| 8. Psoriasis unresponsive to local treatment and/or PUVA | 8. Severe infections |
| 9. Contraindications to PUVA | 9. Pronounced anemia |
| | 10. Leukopenia |
| | 11. Thrombocytopenia |

**Table 30.4: Laboratory examinations before and during methotrexate treatment of psoriasis**

| *Investigations before therapy* | *Investigations during therapy* |
|---|---|
| Hemoglobin, total and differential leukocyte count, platelet count | Hemoglobin, total and differential leukocyte count and platelet count every week |
| Renal function tests including routine and microscopic examination of urine, blood urea, serum creatinine, and creatinine clearance | Liver function tests including serum bilirubin, SGOT, SGPT, and alkaline phosphatase every week. PIIINP thrice a year |
| Liver function tests including serum bilirubin, SGOT, SGPT, alkaline phosphatase, and if possible PIIINP | Renal function tests including urine examination, blood urea, and serum creatinine every week |
| Skiagram of the chest a year | Skiagram of the chest twice |
| Liver biopsy after a cumulative dose of 1.5 gm of MTX | |

### Retinoids

Etretinate, a synthetic derivative of vitamin A is useful in the management of pustular and erythrodermic psoriasis. The usual dose is 1 mg/kg/day orally to a maximum of 75 mg. The mode of action of etretinate is debatable, though it may involve correction of abnormal polyamine metabolism or leukocyte migration. It also inhibits inflammation, proliferation, and terminal differentiation. Retinoids also have a direct action on keratinocytes.

It is a potentially toxic drug. It causes mucocutaneous dryness leading to cheilitis, dryness of the oral and nasal mucosa, conjunctivitis, thinning and dryness of skin, acral fragility, and hair loss. It also increases triglyceride and cholesterol levels. This may increase the risk for atherosclerosis, and cardiovascular diseases. Thus, it is necessary to monitor the triglyceride and serum cholesterol every month. Also, it should not be administered to patients with obesity, diabetes mellitus, heavy smokers, alcoholics and those having hyperlipidemia and hypercholestrolemia. Though it is less hepatotoxic than methotrexate, it is essential to measure liver transaminases every month. Alkaline phosphatase should also be monitored and if facilities exist, PIIINP should be studied. Another risk is the effect on the skeletal system. It may cause premature fusion of epiphyses, osteoporosis, and calcification of the ligaments. It is teratogenic and is excreted very slowly from the body. Hence, it is unwarranted in women of childbearing age. If administered, patient should be advised contraception for at least 2 years after discontinuation of treatment.

The third generation retinoids, arotinoids, may produce more rapid clearance of psoriasis than etretinate. They are undergoing trial and are not available for clinical use as yet.

### Cyclosporine A

This is the latest drug in the treatment of psoriasis. It selectively inhibits T-helper cell production of interleukin-2 while allowing increase of suppressor T-cell population. Psoriasis is associated with increased T-helper to suppressor cell ratio and decreased suppressor cell activity. Cyclosporine corrects this ratio. However, it has no direct effect on keratinocytes and is not a mitotic inhibitor. It is administered in a dose of 5 to 15 mg/kg. Nephrotoxicity which occurs with prolonged use is its major side effect. Other important side effects are tremor, headache, hypertrichosis, hypertension, parasthesiae, gingival hyperplasia, arthralgia, myalgia, and increased risk of malignancy. It is necessary to monitor renal functions by estimating serum creatinine and EDTA clearance. Also the blood pressure should be periodically recorded.

## RECOMMENDED READING

1. Bickers DR. Position paper-PUVA therapy. American Academy of Dermatology *J Am Acad Dermatol* 1983;8:265-270.
2. Ellis CN, Voorhees JJ. Etretinate therapy. *J Am Acad Dermatol* 1987;16:267-291.
3. Finzi AF, Gibelli E. Psoriatic arthritis. *Int J Dermatol* 1991;30:1-7.
4. Goeckerman WJ. Treatment of psoriasis. *Northwest Med* 1925;23:229.
5. Roenigk HH, Auerbach R, Maibach HI, et al. Methotrexate in psoriasis: Revised guidelines. *J Am Acad Dermatol* 1998;19:145-156.

# 31 Chapter Pityriasis Rubra Pilaris

Pityriasis rubra pilaris (PRP) is an erythematous, papulosquamous disorder characterized by acuminate follicular papules, perifollicular erythema tending to extend to form yellow-pink scaly plaques with islands of normal skin, palmoplantar keratoderma, and pityriasis capitis.

It is an uncommon skin disorder with the average incidence of 1 in 5000 or less. It affects both sexes equally. The peak incidence is recorded in the first and the fifth decades. However, its onset may occur at all ages.

## CLINICAL FEATURES

PRP has been classified into five groups on the basis of age of onset, clinical features, and prognosis. They are: Type I (classical adult); Type II (atypical adult); Type III (classical juvenile); Type IV (circumscribed juvenile), and Type V (atypical juvenile).

*Type I:* It affects the adults and accounts for nearly half the patients of PRP. It starts as small, yellow-pink, acuminate papules caused by follicular hyperkeratosis. At the summit of the papule is a small, broken hair. The zone of follicular hyperkeratosis is surrounded by an erythematous perifollicular halo. Palpation of the lesion reveals a 'nutmeg grater' sensation. Such lesions are almost always located on the dorsal aspect of proximal phalanges. This sign of phalangeal follicular hyperkeratosis is considered pathognomonic of PRP (Fig. 31.1). The interfollicular skin, initially normal, tends to become erythematous and scaly and papules appear to coalesce. The acuminate, follicular papules are lost at this stage except over the dorsa of the phalanges. Erythema and scaling extends to form large, well-demarcated plaques and may involve whole of the skin surface, simulating erythroderma. However, these plaques contain small islands of apparently normal skin, a hallmark of PRP. The scaling is fine and powdery and is likened to the bran of the wheat. It is termed pityriasiform or furfuraceous. Scaling is most marked on the face.

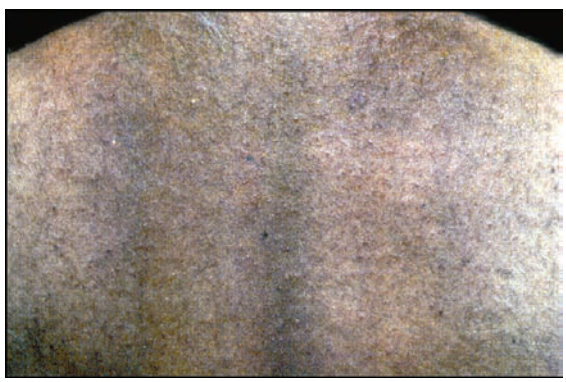


**Figure 31.1:** Pityriasis rubra pilaris. Small yellow pink acuminate papules over dorsum of the hand (Sehgal VN et al: Pityriasis rubra pilaris in Indians. Br J Dermatol 121: 821-22, 1989)

Palmoplantar hyperkeratosis develops early in the disease. It is yellow-orange, thick with painful fissure and may extend to the sides of the feet, producing a 'keratodermic sandal'.

Scalp shows fine and powdery scaling. However, hair loss is uncommon.

Nails may develop longitudinal ridging, subungual hyperkeratoses, and splinter hemorrhages.

Oral lesions may be present, consisting of diffuse, whitish, ground glass appearance, lacy white plaques, white spots and lines, and erosions.

*Type II:* It is characterized by ichthyosiform scaling. Eczematous change may develop over it. The scalp hair is often sparse. Keratoderma is coarse and lamellated.

*Type III:* It resembles classical adult PRP except that its onset is during the first two years.

*Type IV:* It affects prepubertal children and is characterized by erythematous follicular hyperkeratosis localized to the elbows and the knees. It has no tendency to progress to classical PRP.

*Type V:* It begins during the first few years of life and is characterized by erythematous follicular hyperkeratosis and scleroderma-like change in the hands and feet. Most familial cases belong to this group and it tends to run a chronic course.

About 50 percent of the patients remit within 3 years. Prognosis is excellent in classical adult onset (Type I), moderate in circumscribed juvenile (Type IV). Atypical juvenile (Type V) shows no tendency to remit.

## DIAGNOSIS

The diagnosis of PRP is clinical. The histologic changes of PRP, though distinctive, are not diagnostic and only supplement the clinical diagnosis. The histologic features are: (i) follicular keratin plug surrounded by perifollicular parakeratosis, (ii) diffuse hyperkeratosis, (iii) mild irregular acanthosis, (iv) A mild, chronic, perivascular infiltrate in the superficial dermis, (v) liquefaction degeneration of the basal layer (Fig. 31.2).

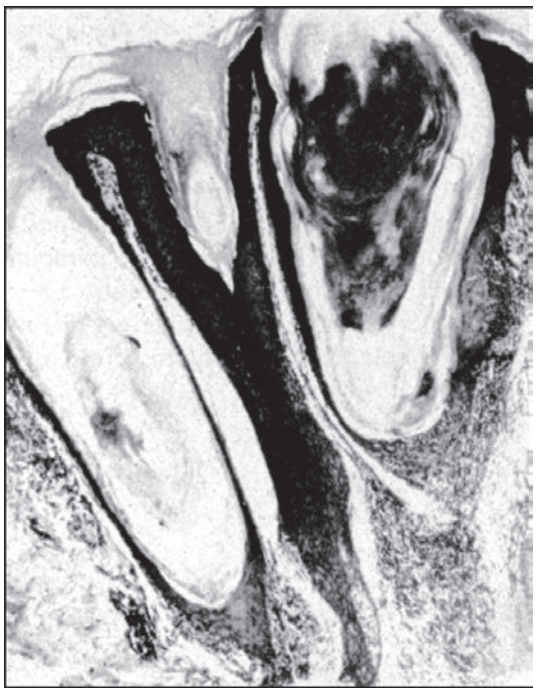


**Figure 31.2:** Pityriasis rubra pilaris(H and E × 50)

The lesions of PRP though characteristic, have to be differentiated from the following: (i) seborrheic dermatitis, (ii) psoriasis, (iii) phrynoderma, (iv) follicular eczema, (v) keratosis pilaris, (vi) Darier's disease, (vii) lichen spinosum.

## TREATMENT

Although many agents have been used in the treatment of PRP (Table 31.1), the results have not been consistent. However, oral vitamin A forms the mainstay of treatment. It is given in a high dose of 150,000 to 500,000 IU daily. Vitamin E, having an apparent synergistic affect,

**Table 31.1: Treatment of PRP**

| *Treatments* | *Status* |
|---|---|
| 1. 50,000 to 300,000 units of vitamin A every day for a prolonged period | It may be combined with 1600 IU of vitamin E to reduce the dose and toxicity of vitamin A |
| 2. 1 million units of vitamin A every day for 5 to 14 days | It is a toxic dose and predisposes to liver toxicity, hypertriglyceridemia, neurologic abnormalities, increases the clotting time, alopecia, arthralgia, bone pain and teratogenecity |
| 3. 0.75 mg/kg of etretinate every day | It useful in erythroderma secondary to PRP |
| 4. 2.5 mg of methotrexate once a day | -do- |
| 5. 1 mg/kg of prednisolone administered in 2 equally divided doses at 9 a.m. and 6 p.m | -do- |
| 6. Topical application of retinoic acid and other keratolytic agents | |

may be combined as an adjuvant to vitamin A. This helps reduce the dose of vitamin A and its potential toxic effect. This may be combined with bland emolients and keratolytic agents. Other agents in vogue for treatment of PRP are: (i) 13-cis-retinoic acid (isotretinoin), (ii) etretinate, (iii) methotrexate, which unlike psoriasis, has to be administered in the daily dosage of 2.5 or 5 mg (iv) aromatic derivatives of retinoic acid such as Ro-10-9459, (v) systemic steroids, (vi) stanozolol, which elevates the reduced levels of retinol binding protein, considered as basic anomaly in PRP.

## RECOMMENDED READING


1. Cohen PR, Prystowsky JH. Pityriasis rubra pilaris: A review of diagnosis and treatment. *J Am Acad Dermatol* 1989;20:801-807.
2. Fox J, Odom RB. Papulosquamous diseases: A review. *J Am Acad Dermatol* 1985;12:597-624.
3. Griffiths WA. Pityriasis rubra pilaris. An historical approach 2. Clinical features. *Clin Exp Dermatol* 1976;1:37-50.
4. Griffiths WA. Pityriasis rubra pilaris: Review. *Clin Exp Dermatol* 1980;5:105-112.
5. Sehgal VN, Bajaj P, Jain S. Pityriasis rubra pilaris (PRP): Report of four cases. *J Dermatol* (Tokyo) 2000;27:174-177.

# 32 Chapter Lupus Erythematosus

Lupus erythematosus is a chronic inflammatory, immune mediated collagen vascular disorder with multisystem involvement. Genetic predisposition, environment, drugs, and immune system interact in the pathogenesis of this multifactorial disorder. The cutaneous presentation in lupus erythematosus may be the primary expression, or part of this multisystemic disease. The skin lesions can be acute, subacute, or chronic. In fact, lupus erythematosus is perceived to form a spectrum with discoid lupus erythematosus and systemic lupus erythematosus as its polar expressions. Discoid lupus erythematosus (DLE) is characterized by the disease activity limited to the skin with minimal or absent systemic/serologic abnormalities. Systemic lupus erythematosus (SLE) is a multisystem disorder, and signs and symptoms of systemic involvement may overshadow the often subtle form of skin changes. The two polar forms are bridged by subacute cutaneous lupus erythematosus (SCLE). It is intermediate in severity between discoid LE and systemic LE. The systemic involvement is usually mild, affecting the musculoskeletal system. Central nervous system and renal system may be mildly affected or spared. Classification of lupus erythematosus and its subsets is outlined in Table 32.1.

**Table 32.1 Lupus erythematosus and its subsets: LE specific skin lesions**

*Lupus erythematosus (LE)*

A. Chronic cutaneous lupus erythematosus (DLE/CCLE)
   1. Localized discoid lupus erythematosus.
   2. Generalized discoid lupus erythematosus (lesions above and below the neck).
   3. Hypertrophic DLE.
   4. Lupus profundus (lupus panniculitis).

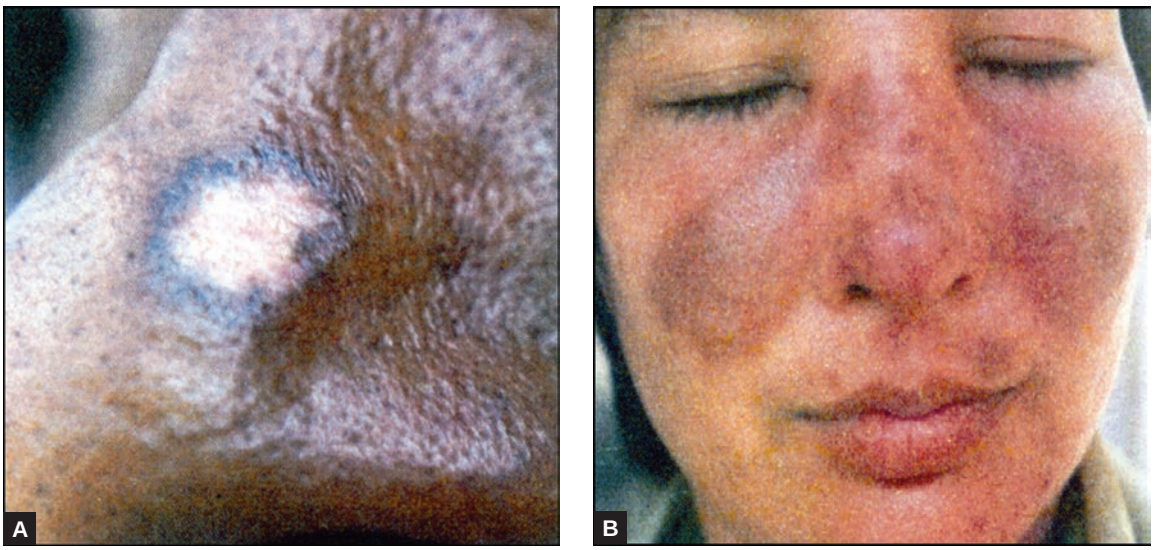
B. Subacute cutaneous LE (SCLE)
   1. Papulosquamous (psoriasiform) SCLE.
   2. Annular/polycyclic SCLE.

C. Systemic lupus erythematosus: Acute cutaneous LE (ACLE)
   1. Facial (malar) erythema.
   2. Widespread erythema of the face, scalp, neck, upperchest, shoulders, extensor surfaces of the arms, and back of the hands.
   3. Bullous or TEN like lesions.

## CLINICAL FEATURES

### Chronic Cutaneous Lupus Erythematosus (CCLE/DLE)

It is a distinctive clinical and histologic lesion that can be localized, disseminated, or verrucous. Discoid lesion, the hallmark of CCLE, are seen only in 20 to 30 percent of SLE patients. They also occur in 15 to 20 percent of the patients with subacute cutaneous LE, and rarely in babies with neonatal LE. Conversely, 5 to 10 percent of chronic cutaneous LE patients may eventually develop systemic disease.




**Figures 32.1A and B:** Discoid lupus erythematosus

The skin lesions of DLE are discrete, erythematosus plaques with well-formed adherent scales that extend into the dilated, patulous, hair follicles. Removal of the overlying scales demonstrates the characteristic 'carpet tack' or langue du chat (cat's tongue) sign. The lesions heal with atrophy, scarring, telangiectasia, and central depigmentation (Figs 32.1A and B). The exposed area, especially the face is involved. Lesions also occur on the neck, back, chest, upperarms, scalp, mucous membranes, and auditory canal. Isolated lesions can occur on the eyelids and lips. Many patients report flare ups during the spring and summer. Spontaneous remissions occur in 25 to 40 percent of the patients.

### *Disseminated CCLE*

Fifty percent of patients with DLE have widespread skin involvement. SLE is more likely to develop in them. A history of unexplained fever, excessive fatigue, joint pains, pleuritic chest pain, and photosensitivity suggests impending SLE in such patients. Besides, on physical examination they may have LE-nonspecific but disease related skin lesions like telangiectasia, thrombophlebitis, Raynaud's phenomenon, chronic ulcers, livedoreticularis, rheumatoid nodules, dermal vasculitis, peripheral gangrene, atrophie blanche, alopecia, mucous membrane lesions, pigmentary changes, sclerodactyly, calcinosis cutis, and/or urticaria. Furthermore, unexplained anemia, leukopenia (lymphocytes < 1000 cells/cu mm), raised blood sedimentation rate (50 mm/hr), positive antinuclear antibody (ANA), hypergammaglobulinemia, and immune deposits at the dermoepidermal junction of clinically normal skin also indicate the progression of the disease toward SLE.

### *Hypertrophic Chronic Cutaneous LE*

It is seen in 2 percent of cases of CCLE. Lesions are localized over the dorsal aspect of hands,

back, and face. Early lesions may resemble hypertrophic lichen planus. Older lesions are nodular and may resemble warts, prurigo nodularis, or keratoacanthoma. Typical discoid LE lesions are often present. Patients with hypertrophic chronic cutaneous LE are predisposed to squamous cell carcinoma.

### *Lupus Panniculitis*

It is a variant of chronic cutaneous LE. It is also referred to as lupus profundus. Two percent of the patients develop panniculitis. Discoid lesions may precede the appearance of lupus panniculitis or it may develop, spontaneously. The characteristic lesion is a movable subcutaneous nodule that arises in apparently normal skin. The lesions are localized over the arms, forehead, cheeks, chin, back, buttocks, thighs, scalp, breast, eyelids, and chest. The overlying skin is usually normal. However, it may also show discoid or poikilodermatous alterations. These lesions infrequently ulcerate and heal with depressed scars. The patient is predisposed to systemic lupus erythematosus.

### *Subacute Cutaneous Lupus Erythematosus (SCLE)*

It is a distinctive subtype of lupus erythematosus and occurs in about 10 percent of the patients of lupus erythematosus. Of the two types of lesions, one is the widespread papulosquamous (psoriasiform) and other is annular (polycyclic) eruption. The lesions are symmetric, widespread, superficial, and nonscarring. Patients with this clinically distinct form of cutaneous LE frequently have a mild systemic illness marked by musculosketetal complaints of arthralgia/arthritis, fever, malaise, and serologic abnormalities. Involvement of central nervous system and renal system is uncommon and mild when present.

The lesions of SCLE are distinct and easily differentiated from DLE. SCLE is nonscarring, the scales are less prominent, follicular plugging is mild, less persistent, and lesions are more widespread. They are less discrete and have a tendency to coalesce, forming large, confluent areas of involvement. The pigmentary changes are reversible. The patients of SCLE develop diffuse, noncicatricial alopecia in contrast to scarring alopecia localized to the lesions of DLE. Photosensitivity is more common in SCLE. Palate is involved in 40 percent of the patients. Livedo reticularis and periungual telangiectasia may be present.

Similar skin lesions may be encountered in ANA negative lupus erythematosus, lupus like syndrome associated with homozygous deficiency of 2nd and 4th component of the complement (C2, C4), neonatal lupus erythematosus, lupus erythematosus/Sjogren's overlap syndrome, and as a complication of thiazide therapy. These patients usually have Ro-positive antibodies. The Ro/SS-A antigen-antibody system is highly specific for connective tissue diseases and helps to confirm the diagnosis of ANA negative lupus erythematosus.

## Systemic Lupus Erythematosus

SLE is a chronic immune disorder characterized by multisystem involvement and clinical exacerbations and remission. Involvement of the skin, serosal surfaces, central nervous system, kidneys, and blood is cardinal. The prevalence of SLE in young women of childbearing age is eight or ten times that in men. The frequency of occurrence of lupus is much higher in the relatives of affected individuals, and the disease concordance rate in identical twins is 50 percent. Complex interrelationships among environmental factors, genetically determined host

immune responses, and hormonal influence are critical in the initiation as well as the expression of the disease. The disease occurs commonly in families with hereditary deficiency of early complement components. HLA-DR2 and HLADR3 are present much more commonly in SLE patients than in controls. Loss of tolerance is central to the pathogenesis of SLE, and genetic tendencies towards the development of autoantibodies, B-cell hyperactivity, and T cell dysfunction are evident. Circulating immune complexes are deposited in the blood vessels, and renal glomeruli, initiating a pathogenic response that damages these tissues.

The 1982 American Rheumatism Association (ARA) revised criteria for classification of SLE are useful in the diagnosis. A patient may be said to have SLE if four or more criteria are satisfied, serially or simultaneously (Table 32.2).

In SLE, the cutaneous manifestations are usually less pronounced and are often overshadowed by the signs and symptoms of systemic disease. Joint manifestations usually precede the cutaneous changes. About 20 percent of SLE patients have cutaneous manifestation at the onset and in about 20 percent, the cutaneous lesions are conspicuous by their absence throughout the course of the disease.

**Table 32.2 ARA criteria for classification of systemic lupus erythematosus (SLE)**

| | *Criteria* | *Definitions* |
|---|---|---|
| 1. | Malar rash | Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds. |
| 2. | Discoid rash | Erythematous, raised patches with adherent keratotic scales and follicular plugging. |
| 3. | Photosensitivity | Skin rash as a result of abnormal reaction to light. |
| 4. | Oral ulcers | Oral or nasopharyngeal ulceration. |
| 5. | Arthritis | Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling and/or effusion. |
| 6. | Serositis | Pleuritis and/or pericarditis. History of pleuritic chest pain, friction rub, evidence of pleural effusion. EKG suggestive of pericarditis. |
| 7. | Renal disorder | Persistent proteinuria exceeding 0.5 g/day or greater than 3+ and cellular cast-red cell, hemoglobin, granular, tubular or mixed. |
| 8. | Neurologic disorder | Seizures and/or psychosis in the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis, electrolyte imbalance). |
| 9. | Hematologic disorder | Hemolytic anemia with reticulocytosis<br>or<br>Leukopenia—less than 4000/$mm^3$ or<br>Lymphopenia, lymphocytes — less than 1500/$mm^3$<br>or<br>Thrombocytopenia, platelets — less than 100,000/$mm^3$ |
| 10. | Immunologic disorder | Positive LE cell preparation<br>or<br>Antibody to native DNA in abnormal titres<br>or<br>Antibody to Sm nuclear antigen<br>or<br>False-positive serologic test for syphilis for at least 6 months |
| 11. | Antinuclear antibody | An abnormal titer of antinuclear antibody by immunofluorescence in the absence of drugs known to induce LE. |

The cutaneous lesions consist of erythema and edema without significant scales. The lesions are ill defined and not sharply demarcated. Butterfly area of the face (malar-region) is the usual site of affliction. However, other areas may also be involved. Occasionally, the lesions show a petechial, vesicular, or ulcerative components. The classic 'discoid' lesions, typical of DLE are seen in 15 percent of the patients. A relatively benign course characterizes SLE when DLE precedes it. The other cutaneous manifestations of SLE are shown in the Table 32.3.

The systemic manifestations of systemic lupus erythematosus include constitutional symptoms like fever, weight loss, malaise, and weakness. Transitory and migratory arthralgia/arthritis is usually the most common and earliest symptom. Arthralgia, deforming arthropathy, and acute migratory polyarthritis may develop. Avascular necrosis of femoral head may develop as a consequence of corticosteroid therapy or due to systemic LE *per se*. Muscular atrophy may accompany extreme weakness and dermatomyositis may be suspected. Pulmonary involvement may manifest as pleural effusion, interstitial lung disease, and acute lupus pneumonitis. Cardiac involvement is indicated by features of either myocarditis, namely cardiomegaly, and gallop rhythm or pericarditis which is the most common cardiac manifestation of SLE. Endocarditis may also occur. Seizures and psychosis are the most common features of CNS involvement. Gastrointestinal involvement may produce symptoms of nausea, vomiting, and diarrhea. Intestinal walls and mesenteric vessels may show features of vasculitis. Lupoid hepatitis is a LE response of serologic antibodies to chronic active hepatitis. LE cells may also be demonstrated.

**Table 32.3: Cutaneous manifestations of SLE**

| |
|---|
| Malar erythema (butterfly rash) |
| Inflammatory periorbital edema |
| Mucous membrane lesions |
| Oral and nasopharyngeal ulceration |
| Alopecia |
| – Fractured frontal hair |
| – Scarring and nonscarring hair loss |
| Raynaud's disease with or without skin changes |
| Cutaneous vasculitis |
| Urticarial lesions |
| Palpable purpura |
| Digital nodules |
| Cutaneous infarcts |
| Leg ulcers |
| Peripheral gangrene |
| Thrombophlebitis |
| Livedo reticularis |
| Periungual erythema and telangiectasia |
| Hemorrhagic bullous lesions |
| Lichen planus like lesions |
| Pernio lesions |
| Lupus profundus |
| Chilblains |
| Sjogren's syndrome |
| Calcinosis cutis |
| Rheumatoid nodules |
| Pigmentary changes |

## DIAGNOSIS

The essentials of morphological characteristics are of paramount significance for diagnosis. Nevertheless, battery of laboratory investigations are imperative to confirm the nature and course of the disease (Table 32.4).

## TREATMENT

Discoid lupus erythematosus, a benign condition, usually runs a chronic course. Its therapy, therefore, is suppressive and has to be administered for a long-time. Patient should be reassured and educated about the nature and prognosis of the disease. He should be advised to protect the skin from sun exposure. Sunscreens which protect against ultraviolet B

**Table 32.4: Morphological characteristics**

| *Histopathology* | *Immunological and hematological parameters* | |
|---|---|---|
| Discoid lupus erythematosus | 1. Hyperkeratosis, with follicular plugging<br>2. Thinning and flattening of the stratum malphigii<br>3. Hydropic degeneration of basal cells<br>4. Patchy, periadnexal lymphocytic infiltrate which may extend up to subcutaneous tissue<br>5. Edema, vasodilatation, and slight extravasation of erythrocytes in the upperdermis (See Figs 32.2 and 32.3)<br>6. Anemia, leukopenia thrombocytopenia in 35 percent cases<br>7. ESR is raised in 20 percent<br>8. LE cell positive in 1.7 percent<br>9 Lupus band test (immune deposit at dermo-epidermal junction of clinically normal, non sun exposed skin) is negative. | Antinuclear antibodies demonstrable in 35 percent cases<br>Anti DNA antibodies in 0-27 percent cases<br>IgM antibodies to ss-DNA in 20 percent<br>Rheumatoid factor in 17 percent cases<br>False positive reaction for syphilis in 20 percent cases |
| Subacute cutaneous lupus erythematosus | 1. Hyperkeratosis is less pronounced<br>2. Hydropic degeneration of the basal cell layer<br>3. A patchy, periadenexal lymphocytic infiltrate in the upperand mid dermis<br>4. Pronounced edema of the upperdermis<br>5. Colloid bodies in lower dermis<br>6. Presence of fibrinoid deposits in lower dermis | 1. Homogenous antinuclear factor in 60 percent<br>2. Anticytoplasmic antibodies: anti-Ro in 60 percent and anti-La in 40 percent<br>3. Lesional subepidermal immuno-globutin deposits in 60 percent<br>4. Lupus band test (immune deposits at dermoepidermal junction of clinically normal, non-sun-exposed skin) is positive in 23 percent |
| Systemic lupus Erythematosus | 1. Nonspecific changes<br>2. Specific changes:<br>a. Hydropic degeneration of basal cells<br>b. Pronounced edema of the epidermis<br>c. Mild perivascular, lymphocytic infiltrate, confined to upperdermis<br>d. Precipitation of fibrinoid material on collagen bundles. Collagen appears thickened and eosinophilic<br>e. Extravasation of erythrocytes<br>f. Colloid bodies may be present<br>g. Epidermis normal or atrophic<br>3. Bullous SLE<br>Clefts may form between epidermis and dermis due to severe hydropic degeneration of basal cells. | 1. Antinuclear antibodies (ANA). Most sensitive. Lacks specificity. Positive in 90 percent of SLE.<br>2. Fluorescent ANA (FANA) at 1: 160 or higher titre with peripheral staining diagnostic of SLE<br>3. Anti-ds DNA antibody, tested with *Crithidia lucitiae*. Specific, not very sensitive. Indicates high risk of renal involvement.<br>4. LE cell test. Specific not sensitive.<br>5. Anti-Sm antibodies. Specific not sensitive. Positive in only 25 percent of SLE<br>6. Anti-ss DNA. Nonspecific.<br>7. Anticytoplasmic antibodies to Ro/SS-A and La/SS-B antigen. Positive in ANA negative SLE cases. Also in 1) SCLE , 2) neonatal LE 3) C2 deficient LE<br>8. Lupus band test (immune deposits at the dermo-epidermal junctions in skin biopsy specimen taken from clinically normal, non-sun-exposed skin) is positive in 55 percent of SLE patients. |

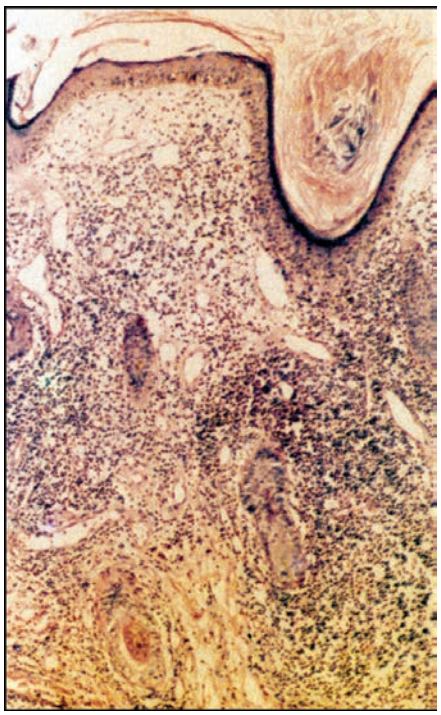


**Figure 32.2:** Discoid lupus erythematosus (H & E × 40)

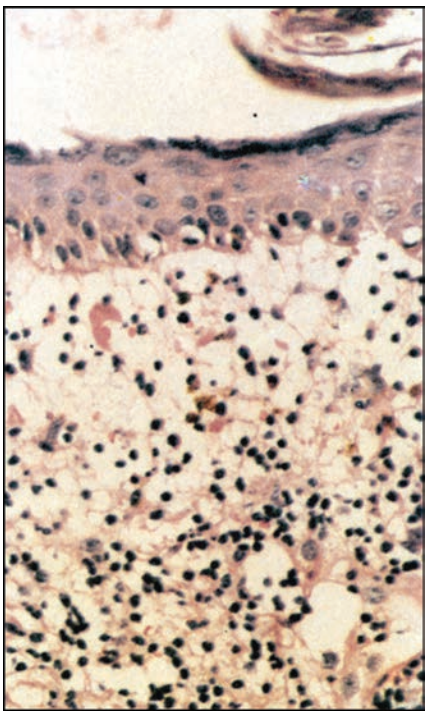


**Figure 32.3:** Discoid lupus erythematosus: Basal cell changes, edema, erythrocyte extravasation, pigment incontinence, colloid bodies (H & E × 200)

and have a sun protection factor of atleast 15 should be used liberally over the sun exposed areas. Topical and/or intralesional steroids are effective form of first line therapy. Patients who are unresponsive to topical corticosteroids and/or have disseminated, progressive disease, require antimalarials like chloroquine diphosphate. Quinacrine may be added if chloroquine alone is ineffective. Vitamin E and clofazimine have been used in patients unresponsive to antimalarials and topical corticosteroids. Retinoids, in conjunction with antimalarials have been used with equivocal results in the treatment of hyperkeratotic DLE. Dapsone has been used as an alternative therapy for the treatment of disease that fails to respond to vitamin E and clofazimine. Thalidomide, although effective in patients unresponsive to traditional therapy, has significant teratogenecity, neurotoxicity, and limited availability. Thus it is not recommended as a treatment (Table 32.5).

Subacute cutaneous lupus erythematosus is a subset of lupus erythematosus, in which only a small percentage are at a risk of developing life threatening complications of SLE. Treatment is based on the extent and severity of the disease, considering carefully the benefits and risks of each modality. Educating the patient is essential. Sun avoidance and the use of sunscreens is necessary. A trial of topical and/or intralesional steroids is warranted for limited cutaneous disease. Antimalarials like chloroquine diphosphate are

**Table 32.5: Treatment of discoid lupus erythematosus**

| *Treatment* | *Status* |
|---|---|
| 1. Protection from the sunlight by wearing full sleeve clothes, using umbrellas and avoiding going out in sun. | |
| 2. Topical application of sunscreens during the day time.<br>Sunscreens that filter out UV-B and have sun protection factor of atleast 15 are preferred.<br>a. 5 percent para-amino-benzoic acid solution (Pabalak) | Provides effective relief from photosensitivity |
| b. Total sun blocks like zinc oxide and titanium dioxide | Required only for extremely photosensitive patients |
| 3. Topical application of corticosteroids of medium potency | Simple and effective therapy. It is suppressive and not curative. |
| i. Betamethasone dipropionate 0.05 percent (Diplene)<br>Or | May cause epidermal atrophy, purpura, and striae. |
| ii. Fluocinolone acetonide 0.2 percent cream (Flucort)<br>Or | |
| iii. 0.1-0.3 mL of 10 mg/mL of triamcinolone acetonide, intralesional, every week. | Useful in the treatment of localized disease. |
| 4. 250 mg of chloroquine phosphate (150 mg of base) (Resochin, Melubrin, Ciplaquin) three times a day in the first week followed by 1 tablet two times a day during the second week and 1 tablet daily from third week onwards. If there is no improvement in 8 weeks, add 100 mg of quinacrine. | Antimalarials possess photoprotective effect, nucleoprotein binding effect, anti-inflammatory properties, and immunosuppressive property. Highly effective in the treatment of DLE. However, clinical improvement begins 4 to 8 weeks after initiating therapy. Relapse rate following discontinuation of treatment is high. Also, antimalarial therapy may cause irreversible retinopathy which may lead to permanent visual loss. Patients are advised ophthalmologic examination before treatment and subsequent examinations every 4 to 6 months. |
| 5. 1 mg per kg of etretinate every day | Alternative therapy for DLE that does not respond to a combination of chloroquine and quinacrine. Effective in the treatment of hyperkeratotic DLE. Potentiates the ineffective antimalarial therapy. It may be used in combination with chloroquine. |
| 6. 100 mg of clofazimine every day | Alternative therapy for the treatment of DLE refractory to conventional treatment. |
| 7. 1,200 to 1,600 IU of tocopherol (vitamin E) every day. | Alternative therapy for the treatment of DLE refractory to conventional treatment. |
| 8. 100 mg of dapsone every day | Alternative therapy for the treatment of DLE when the antimalarials are ineffective or cause adverse reaction. |
| 9. 100 to 200 mg of thalidomide every day | Highly effective in DLE. Improvement begins in 2 weeks and remission occurs within 2 months. Effective in the treatment of DLE refractory to antimalarials and corticosteroids. However, teratogenecity, sensory polyneuropathy are its side effects. Available only for research purpose. |

the first choice for systemic therapy. Systemic steroids should be used only to gain the initial control of relatively severe disease while awaiting the response to antimalarials. They may also be used in a low intermittent dose to suppress antimalarial-resistant disease. Drugs like dapsone, clofazimine, retinoids, and thalidomide have been used with equivocal results in the management of cases unresponsive to antimalarials and corticosteroids. Immunosuppressive adjuvants like azathioprine, cyclophosphamide, methotrexate and also plasmapheresis have been used in severe disease (Table 32.6).

Management of patients with systemic lupus erythematosus is dictated by the severity of the systemic involvement. Treatment of active lupus nephritis and acute cerebritis requires administration of high doses of prednisolone. Patients who fail to respond to corticosteroids are administered immunosuppressive adjuvants. Patients with less aggressive and less life threatening forms of the disease are treated with low dose corticosteroids, antimalarials and/or nonsteroidal antiinflammatory drugs. The latter are useful in the management of fever, pleuritis, pericarditis, and arthritis.

**Table 32.6: Treatment of subacute cutaneous lupus erythematosus (SCLE)**

| *Treatment* | *Status* |
|---|---|
| 1. Avoidance of exposure to sun by wearing full sleeve clothes and using umbrella, and avoiding going out in sun. | |
| 2. Topical application of sunscreens during the day time. Sunscreens that filter out UV-B and have sun protection factor of atleast 15 are preferred. | |
| a. 5 percent para-amino-benzoic acid solution (Pabalak). | Provides effective relief from photosensitivity. |
| b. Total sun blocks like zinc oxide and titanium dioxide. | Required only for extremely photosensitive patients |
| 3. Topical application of superpotent corticosteroid. Clobetasol propionate 0.05% (Tenovate, Clop, Exel) | Monitor for the development of local atrophy, purpura and striae |
| 4. 30 to 40 mg of prednisolone in two equally divided doses at 9 A.M. in the morning and 6 P.M. in the evening for short period. | Reserved only for the treatment of antimalarial resistant cases, or while awaiting the response to antimalarials or if the patients show signs of systemic involvement. |
| 5. 250 mg of chloroquine phosphate (150 mg base) (Resochin, Melubrin, Ciplaquin), three times a day in the first week followed by 1 tablet two times a day during the second week and 1 tablet daily from 3rd week onward. If there is, no response in 8 weeks add 100 mg of quinacrine (Atabrine) | Discussed under DLE. |
| 6. 1 mg per kg per day of etretinate alone or in conjunction with antimalarials | Alternative therapy for the treatment of SCLE. Useful for establishing rapid control of resistant lesions and/or treatment of intermittent acute flare ups |
| 7. 100 mg of dapsone every day | Alternative therapy for the treatment of SCLE resistant to topical potent corticosteroids and systemic antimalarials |
| 8. 100 mg of clofazimine every day to corticosteroid and antimalarial | Alternative therapy for the treatment of SCLE unresponsive |
| 9. 100 to 200 mg of thalidomide every day | Potential to produce clinical improvement in patients of SCLE, unresponsive to conventional therapy. However, its serious side effect namely teratogenecity, precludes its use |

## RECOMMENDED READING

1. Callen JP. Cutaneous manifestations of collagen vascular diseases and related disorders. *Med Clin North Am* 1989;73:1055-1305.
2. Callen JP, Tuffanelli DL, Provost TP. Collagen vascular disease: an update. *J Am Acad Dermatol* 1993;28:477-484

# 33 Chapter

# Scleroderma

Scleroderma is the prototype of the fibrotic skin diseases. It may manifest either as systemic and localized forms. Progressive systemic sclerosis (PSS) is a generalized connective tissue disorder, the fibrotic process affecting not only the skin but also the heart, lungs, kidneys, and the gastrointestinal tract. CREST syndrome, a subset of systemic scleroderma, demonstrates calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia. The visceral involvement is limited or absent in CREST syndrome. Morphea represents the localized form of scleroderma in which the fibrotic changes are confined to the skin. It may be localized or generalized. The localized form of morphea may present as guttate, plaque or linear morphea.

Scleroderma like skin change may be found in association with other connective tissue disorders such as lupus erythematosus and dermatomyositis. This is termed mixed connective tissue disease overlap syndrome. Eosinophilic fascitis, a rapidly developing connective tissue disease is characterized by thickening and induration of the skin, peripheral eosinophilia, and hypergammaglobulinemia. Metabolic and immunological disorders may lead to dermal fibrosis. Scleroderma like changes may develop in graft-vs-host disease, porphyrias, phenylketonuria, and carcinoid syndrome. Drugs and chemicals can induce dermal fibrosis. Bleomycin, an anticancer agent, in addition to pulmonary fibrosis, also lead to dermal fibrosis. Similar cutaneous changes may be induced by pentazocine and polyvinyl chloride. Classification of scleroderma is shown in the Table 33.1.

The overall female to male incidence of scleroderma is 3:1. The average age of onset is 40 to 50 years. In women, however, the average age of onset lies in the child-bearing years of between 30 and 39. Men and older patients with systemic scleroderma tend to have a shorter survival rate and thus a poorer prognosis.

The pathogenesis of scleroderma is related to genetic factors, vascular abnormalities,

**Table 33.1: Classification of scleroderma**

| |
|---|
| *Systemic scleroderma* |
| Diffuse scleroderma |
| Acroscleroderma |
| Acroscleroderma with ascending sclerosis |
| CREST syndrome |
| *Morphea* |
| Plaque |
| Guttate |
| Profundus |
| Nodular or keloidal |
| Pansclerotic |
| Linear; en coup de sabre with/without facial hemiatrophy |
| Generalized |
| *Overlap syndromes* |
| Sclerodermatomyositis |
| Undifferentiated connective tissue disease |
| Mixed connective tissue disease. |

abnormal collagen metabolism, and immunologic abnormalities.

Familial occurrence of scleroderma is unusual. However, chromosomal abnormalities in fibroblasts are more common in scleroderma patients than in general population and have also been noted in familial cases. Variable histocompatibility antigen (HLA) associations have been observed in scleroderma. An increased frequency of HLAB8/DR3,-DRI, and HLA-9 has been noted in systemic scleroderma. An abnormality in collagen gene regulation may be responsible for collagen overproduction.

Vascular abnormalities usually precede the development of fibrosis and may play an important role in the pathogenesis. There are extensive vascular changes, with arteries, veins and capillaries affected. Raynaud's phenomenon occurs in over 90 percent of patients and leads to hypoxia and endothelial cell damage. The endothelial cells appear to be the primary target. A circulating endothelial cell cytotoxic activity has been demonstrated in the scleroderma sera. This produces vacuolization, swelling, and disruption of endothelial cells with large gaps between them. Damage to the endothelial cells leads to platelet aggregation and liberation of platelet-derived growth factor (PDGF), and transforming growth factor-B that promote fibrosis. Endothelial cells, also produce potent vasoconstrictor 'endothelin'.

Another important factor in the pathogenesis of scleroderma is the excessive deposition of collagen. However, the mechanism responsible for this is not precisely known. Recent studies utilizing *in situ* hybridization for detection of type I and VI collagen messenger RNA's in fibrotic disease have demonstrated enhanced collagen gene expression in the vicinity of inflammatory cell present in the lesional skin. The close proximity of fibroblasts demonstrating a collagen-overproduction phenotype, to inflammatory cell infiltrate, suggests that the cytokines elaborated by these inflammatory cells may enhance collagen gene expression. Expression of transforming growth factor-β (TGF-β) is markedly elevated in the lesional skin. This TGF-β upregulates collagen gene expression *in vivo* and *in vitro* and may play an important role in the development of fibrosis. Collagen biosynthesis as measured by C-hydroxyproline and protocollagen proline hydroxylase activity, is markedly increased.

The immune system also participates in the pathogenesis. T cell helperfunction is increased. This may alter fibroblast function. In early stages, lymphocytic perivascular infiltrates are found. Frequent association with other autoimmune diseases is also observed. It has been hypothesized that an increased T helpercell function may stimulate the release of soluble factors that may regulate chemoattraction, the rate of cellular mitosis, and fibroblast collagen synthesis. Interleukin-I has been identified as one of the factors present in activated mononuclear cell supernatants and is considered to modulate fibroblast metabolism. Also, interleukin-2 has been demonstrated to be elevated and correlated with skin involvement. There may be other stimulating and inhibitory mediators originating from mononuclear cells that augment the fibroblast activity in scleroderma. The association of scleroderma like skin changes in chronic graft-vs-host disease emphasizes that PSS is associated with a variety of immunological abbreviations.

Metabolic abnormalities have also been suggested as a possible etiologic factor. The finding of scleroderma-like fibrosis in the skin of patient with malignant carcinoid syndrome

has suggested a dysfunction of serotonin metabolism. Scleroderma patients may also have an abnormality of tryptophan metabolism, characterized by the presence of excessive amounts of kynurenine and other metabolites.

## CLINICAL FEATURES

Systemic scleroderma may involve all connective tissue-containing organs; however, some represent the main target of the disease. These include the skin, gastrointestinal tract, heart, lungs, and kidneys.

### Cutaneous Manifestations

Cutaneous manifestations, are usually early symptoms. They may either proceede or accompany Raynaud's phenomenon. They may be divided into an early edematous phase, sclerotic phase, and late atrophic phase. Initially the skin appears to be thickened, edematous, and may be slightly erythematous. The alterations usually start at acral areas and, later the face, and trunk may be involved. The fingers and hands appear swollen, with nonpitting edema. They are tumid, and cannot be fully extended. Gradually sclerosis develops, with hardening of the skin. It appears to be bound down to underlying structures and cannot be pinched up. Ulcerations, telangiectasias, and atrophy may follow. Hair loss and anhidrosis in affected areas is common. It is secondary to the degeneration of appendages due to the fibrosis. Slow healing and painful ulcers may develop around the fingertips or in areas with underlying calcinosis, and over the knuckles. Secondary infections in these areas may sometimes lead to gangrene, which, together with osseous resorption, can cause severe articular deformities of the hands and even complete dissolution of the terminal phalanges. The American Rheumatism Association has established the clinical criteria for systemic sclerosis (Table 33.2).

**Table 33.2: American Rheumatism Association Scleroderma Criteria Cooperative Study: Preliminary clinical criteria for systemic sclerosis**

1. Proximal scleroderma is the single major criterion, with 91 percent sensitivity and greater than 99 percent specificity.
2. Sclerodactyly, digital pitting, and scar of the fingertips or loss of substance of the finger pad, and bibasilar pulmonary fibrosis contribute the minor criteria.
3. One major or two or more minor criteria are found in 97 percent of patient with definite systemic sclerosis.

Involvement of the feet is similar but less frequent. Sclerosis of the face results in the typical appearance of beaked nose, radial furrowing around the lips, and constricted opening of the mouth. Periungual telangiectasia reflecting dilated nail fold capillaries may also be present. In addition to the sclerotic changes of the skin, marked cutaneous pigmentation may develop, either with mottled or diffuse hyperpigmentation. In some patients skin manifestations remain confined to acral areas for several years. In others, however, sclerosis progresses proximally to the forearms and upperpart of the legs, to upperaspect of the trunk, and finally, involves the whole integument. Occasionally, scleromatous skin changes first appear at the trunk and then spread over the integument within a relatively short period of time. These patients suffer from severe internal manifestations and have a poor prognosis.

#### *Raynaud's Phenomenon*

It occurs in over 90 percent of patients with scleroderma and may be the initial symptom. It is characterized by a triphasic color reaction involving the distal digits. The initial vasoconstriction (white) is followed by cyanosis (blue), and then by hyperemia (red).

### *Gastrointestinal Tract*

Most systemic scleroderma patients may develop dysphagia, regurgitation, peptic esophagitis, and fibrotic strictures. Esophageal involvement can be diagnosed by conventional radiography, manometric measurements, and scintigraphic procedures. Hypomotility is not restricted to the esophagus and may also involve the lower part of the gastointestinal tract. Stomach involvement is uncommon and is characterized by gastric hypomotility and delayed gastric emptying. Small bowel involvement is more common and presents with crampy abdominal pain, diarrhea, and weight loss. Pseudo-obstruction of the small bowel may develop, and at times pneumatosis cystoides intestinalis with perforation may result in benign pneumoperitoneum. Colonic involvement may manifest as bloating, diarrhea, constipation and abdominal discomfort. Colonic diverticuli may develop on the antimesentric border. Chronic constipation leading to rectal prolapse has been reported in some patients. Other manifestations include megacolon, transverse and sigmoid colonic volvulus, stenoses, and diverticular ulcerations. Dysfunction of the small bowel with stagnation often leads to an altered bacterial growth in the intestine. This is mainly responsible for the malabsorption syndrome frequently present in scleroderma patients.

Primary involvement of the liver in scleroderma is uncommon. In most cases altered liver functions are secondary to right ventricular heart disease. Primary biliary cirrhosis, may be present in few cases of the CREST variant scleroderma. Involvement of the pancreas is also uncommon in patients with systemic scleroderma and seems to be much less important for malabsorption than other factors such as intestinal bacterial overgrowth.

### *Heart*

Primary cardiac involvement is common in systemic scleroderma. However, it is frequently overlooked. With the development of more sensitive techniques such as myocardial perfusion scintigraphy, ventriculography, and echocardiography, abnormalities of cardiac function are now detected in the early phases of scleroderma. It usually indicates a poor prognosis and can result in cardiomegaly, congestive heart failure, arrhythmias, myocardial infarction, and sudden death. They are probably caused by endothelial damage of small coronary arteries, myocardial fibrosis, contraction band necrosis, and conduction system fibrosis. Pericarditis is also common and occurs in 10 to 20 percent of the patients. Acute and chronic pericardial effusions may occur. Constrictive pericarditis and cardiac tamponade may also develop.

### *Lungs*

Pulmonary involvement is one of the most important clinical features in systemic scleroderma. In addition to X-ray procedures and functional tests, scintigraphy and the bronchoalveolar lavage have offered new insights into the pathophysiologic events. The disturbance of lung function is characterized by restrictive changes with reduced respiratory volume and impaired diffusion capacity. In addition, obstructive changes involving both large and small airway may be present. The histologic features of scleroderma lung disease include interstitial inflammation, vasculitis, and fibrosis which is indistinguishable from that in idiopathic pulmonary fibrosis. The bronchoalveolar lavage fluid of patients with systemic scleroderma has been shown to contain elevated number of lymphocytes, neutrophils, and circulating

immune complexes. The latter may be responsible for the development of pulmonary fibrosis.

Exertional dyspnea is the most common symptom. It is however, associated with the advanced disease and is rarely the early symptom. The patient may remain stable for many years or rapidly develop acute respiratory failure. Pleuritis and pleural effusion may also develop. Pulmonary hypertension and cor pulmonale secondary to the pulmonary vascular involvement are common late developments in the CREST syndrome. Pulmonary hypertension may run a protracted course or progress rapidly to death.

### *Kidneys*

The presence of renal involvement in scleroderma is regarded as one of the features associated with the poorest prognosis. The clinical criteria for renal disease in scleroderma include persistent proterinuria (> 500 mg/24 hr), hypertension (> 140/90 mm Hg), and azotemia (blood urea nitrogen BUN > 25 mg/100 mL). With these criteria, 15 to 45 percent of scleroderma patients may reveal renal involvement. Renal failure, however, is encountered in only 3 to 5 percent of the scleroderma patients. Extremely high renin levels have been noted in patients who develop acute renal failure.

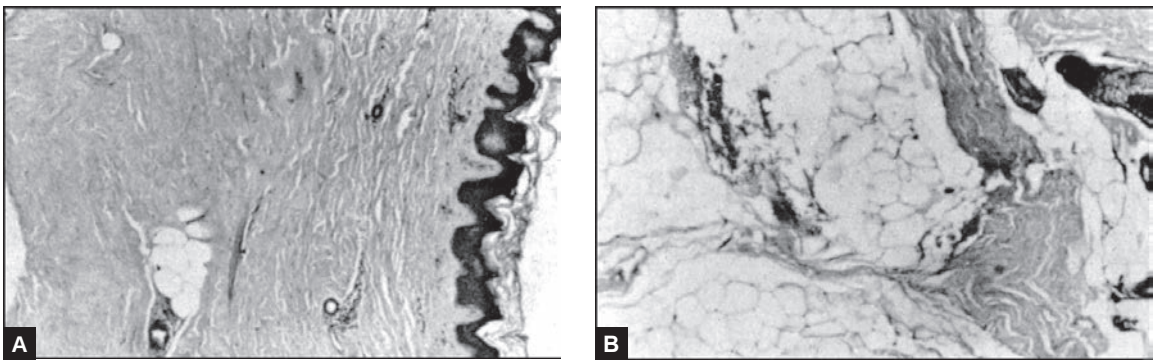
The gross examination of the kidneys of patients with renal scleroderma reveals numerous small infarcts. Histologic changes are similar to those in malignant hypertension. They affect the smaller renal arteries and include marked proliferation with deposition of PAS-positive material, adventitial fibrosis, fibrinoid necrosis, and thrombus formation. These changes may lead to narrowing or even obliteration of the vessel lumina and ultimately to infarction of glomeruli and tubules. Immunofluorescence studies of scleroderma kidney have revealed vascular deposits of pivotal complement components C3 and immunoglobulins (IgM).

### *Joints and Bones*

Joint involvement in systemic scleroderma is frequent and may resemble rheumatoid arthritis. However, it is less destructive. Pain and inflammation with erythema, warmth, and synovial effusions, occur most often in the fingers, wrists, knees, and ankles. Contractures are generally due to sclerotic changes of the overlying skin or surrounding connective tissue, although in some patients a non-erosive hand deformity resembling Jaccoud's arthropathy may be present. The most common roentgenographic abnormalities are resorption of the tufts of the terminal phalanges, juxta articular osteoporosis, periarticular bone erosions, and joint space narrowing. Osteolysis can also occur at other sites, such as feet, ribs, and mandible and is probably related to ischemia.

## Diagnosis

The diagnosis of systemic scleroderma is clinical. It may be supplemented by skin biopsy (Figs 33.1A and B; Figs 33.2A and B). Laboratory examination are helpful in evaluating the activity and prognosis of the disease. A mild normochromic, normocytic anemia is found in one fourth to one third of these patients. In patients with malabsorption, deficiency of vitamin B12 and/or folic acid may cause anemia. Thrombocytopenia and Coombs positive hemolytic anemia may occur but are uncommon and if present suggest an overlap with lupus erythematous. A microangiopathic hemolytic anemia may develop in patients with renal disease and hypertension. A modest elevation of erythrocyte sedimentation rate is




**Figures 33.1A and B:** Scleroderma (H and E × 40)

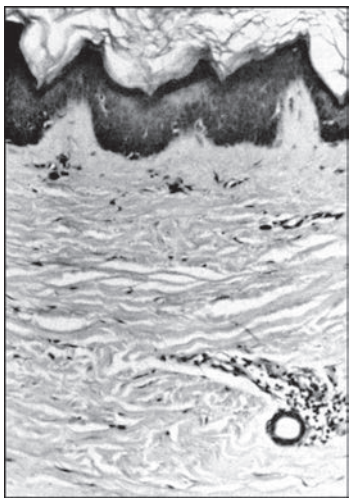


**Figure 33.2A:** Scleroderma (H and E × 100)

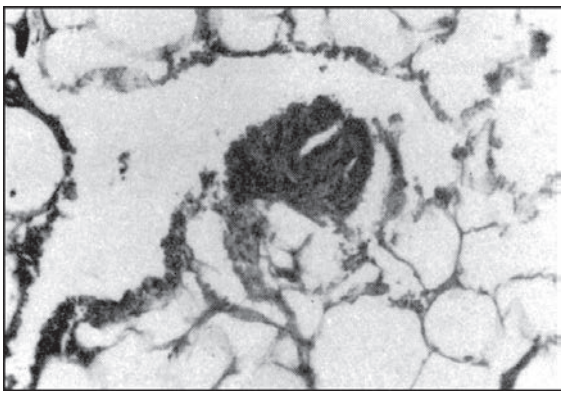


**Figure 33.2B:** Scleroderma (H and E × 100)

common and may relate to the disease activity. Serum immunoglobulin levels are often elevated and circulating immune complexes are demonstrable in 50 percent of the patients with scleroderma.

Antinuclear antibodies of both IgG and IgM class are demonstrable in 40 to 90 percent of cases of scleroderma. The ANA pattern is usually particulate (either thready or finely speckled), but may be nucleolar. In patients with negative antinuclear antibodies, anticentromere antibodies are present. They are considered to be a marker of CREST syndrome and thus imply a good prognosis. The anticentromere antibodies produce a speckled pattern on HEp-2 cells. Another antibody is Scl-70. It is found mainly in patients with diffuse scleroderma and implies a poor prognosis. Patients with acrosclerosis positive for anticentromere antibodies are invariably negative for Scl-70 and thus there are mutually exclusive. Direct immunofluorescence studies of the involved skin may reveal deposition of immunoglobulins or complements within the blood vessel wall. (Table 33.3).

**Table 33.3: Diagnosis of scleroderma**

| *Histopathological changes* | *Immunological changes* | *Hematological changes* |
|---|---|---|
| *Edematous Stage*<br>1. Moderately pronounced inflammatory infiltrate comprising lymphocytes, monocytes, histiocytes, present in the vicinity of the blood vessels and at the interface between the dermis and the subcutaneous tissue<br>2. The trabeculae subdividing the subcutaneous fat are thickened by the presence of inflammatory infiltrate<br>3. Fine, wavy fibers of newly formed collagen appear in the subcutaneous tissue<br>4. Endothelial cell swelling and edema of the vessel wall | 1. IgG and/or IgM antinuclear antibodies in 40 to 90 percent cases. Pattern may be: a. Thready, b. Finely specked, c. Nucleolar<br>2. Anticentromere antibodies, a marker of CREST syndrome. Produces speckled pattern. Indicates good prognosis.<br>3. Scl-70 antibody. Found in patients with diffuse scleroderma. Indicates poor prognosis | 1. Mild normochromic, normocytic, anemia<br>Or<br>Coomb's positive hemolytic anemia<br>Or<br>Microangiopathic hemolytic anemia<br>2. Thrombocytopenia<br>3. Raised erythrocyte sedimentation rate<br>4. Raised serum immunoglobulins<br>5. Circulating immune complexes in 50 percent of the cases. |
| *Sclerotic stage*<br>1. Normal epidermis<br>2. Disappearance of inflammatory infiltrate<br>3. Thick, tightly packed, deeply eosinophilic collagen bundles in the reticular dermis. Collagen appears homogenous in the papillary dermis.<br>4. The eccrine glands appear markedly atrophic. Fatty tissue surrounding them is greatly reduced. The eccrine glands are surrounded and bound down by the newly formed collagen. Also, instead of lying at the dermal-subcutaneous tissue interface, the sweat gland appear pulled up the lie in the papillary dermis.<br>5. The blood vessels in the sclerotic collagen have a fibrotic wall and a narrowed lumen | | |
| *Atrophic Stage*<br>1. Atrophy of the epidermis<br>2. Flattening of rete ridges<br>3. Aggregates of calcium within the areas of sclerotic collagen. | | |

The other investigations may be undertaken to assess the involvement of various systems. Esophageal involvement can be diagnosed by barium swallow, and manometric studies. Recently extremely sensitive scintigraphic procedures and cine esophagram have become

available. They are noninvasive procedures and are helpful for the diagnosis of early esophageal involvement. The involvement of cardiovascular system may be detected by electrocardiogram, echocardiogram, myocardial perfusion scintigraphy, and ventriculography. Pulmonary involvement may be studied by skiagram of the chest and pulmonary function tests. Scintigraphy and the bronchoalveolar lavage have offered new insights into the pathophysiologic events. The bronchoalveolar lavage fluid may contain elevated numbers of lymphocytes, neutrophils, and circulating immune complex. Musculoskeletal involvement may be studied by radiography. The common roentgenographic abnormalities are resorption of the tufts of the terminal phalanges, juxta-articular osteoporosis, periarticular bone erosion, and joint space narrowing. Raynaud's phenomenon may be investigated by measuring the digital blood flow by plethysmography with standardized digit cooling laser—Doppler flowmetry.

## TREATMENT

Treatment of scleroderma may be symptomatic to alleviate the symptoms and specific.

Raynaud's phenomenon is troublesome during the winters. Patient should be advised to avoid excessive cold exposure. Woolen gloves and stocking may be worn to keep the hands and feet warm. Smoking should be avoided. Other drugs that stimulate sympathetic nerves either centrally or peripherally such as caffeine, ergotamine, amphetamines, and pseudoephidrine should not be prescribed. Digital ulceration should be treated with appropriate antibiotics and antiseptic dressings. Topical nitroglycerine may be applied. Musculoskeletal symptoms respond to salicylates and/or nonsteroidal anti-inflammatory agents. They may be combined with physical therapy in the forms of active and passive exercises, warm whirlpool baths, hot water baths, and molten paraffin. Casts and traction splints can help in the correction of digital contractures. Esophageal dysphagia and esophagitis may treated with antacids and histamine H2-receptor antagonists like ranitidine and famotidine. Elevation of the bed and ingestion of small meals in the evening are useful. Esophageal dilatation is of value in patients with incipient strictures. Tetracycline is helpful in the management of malabsorption syndrome. Impotence, a major problem in male patients, may be due to vascular alterations. Attempts may be made to increase the blood flow or the patient may be referred to urologist.

Specific therapy may be: (i) vasoactive, (ii) anti-inflammatory, (iii) those influencing connective tissue metabolism.

Vasoactive agents are useful in patients with Raynaud's phenomenon, acrosclerosis, and digital ulcers. Treatment may be initiated with nicotinic acid, dipyridamole. Calcium channel blocker like nifedipine is also commonly used. However, it may adversely affect esophageal tract function. Ketanserin, a serotonin receptor blocking agent, also decreases the frequency and severity of Raynaud's phenomenon. Low molecular weight dextrans and prostacyclin may be used for the treatment of digital ischemia, ulcers, and gangrene.

Anti-inflammatory agents, commonly corticosteroids are used to ameliorate the systemic involvement. They are useful in patients with debilitating arthritis, myositis, extensive cutaneous edema, and recurring digital ulcers. However, prolonged use of corticosteroids may cause complication. Immunosuppressive agents like cyclophosphamide, azathioprine and cyclosporine have also been utilized.

| Table 33.4: Immunomodulators in the treatment of scleroderma | |
|---|---|
| *Drug* | *Status* |
| 1. 10 to 15 mg of prednisolone daily | Possesses anti-inflammatory effect. Inhibits collagen synthesis. May induce muscular atrophy, hyperglycemia, gastric ulcer, osteoporosis, and hypertension |
| 2. 2 to 4 mg per kg perday of cyclophosphamide | Possesses immunosuppressive-cytotoxic action. May cause gastrointestinal symptoms, diffuse alopecia |
| 3. 1 to 2 mg per kg perday of azathioprine | -do- |
| 4. 2.5 mg per kg day of cyclosporine | Influences the early phase of the immune response by blocking the synthesis and/or release of interleukin-2 from T-helpercells and interleukin-1 from monocytes. May cause renal damage and hypertension |

| Table 33.5: Antifibrotic agents in the treatment of scleroderma | |
|---|---|
| *Drug* | *Status* |
| 1. 150 to 300 mg of d-penicillamine orally, everyday | Formation of a complex between the d-penicillamine and the lysine and hydroxylysine aldehyde groups. This inhibits the synthesis of stable collagen crosslinks |
| 2. 400 mg of cyclofenil, orally, daily | Reduces the *in vitro* synthesis of collagen by fibroblast |
| 3. 1 mg perday of colchicine, orally | Decreases the collagen deposition *in vitro*. Disrupts microtubles which are implicated in the extrusion of collagen from fibroblasts. Increases the activity of collagenases and enhances collagen degradation |
| 4. 750 mg of griseofulvin, daily, orally | Inhibits the proliferation of fibroblast |
| 5. 0.5 to 1 mg per kg perday of 13-cis retinoic acid, orally | Reduces collagen synthesis |

D-penicillamine is capable of decreasing collagen deposition and may arrest the progression and even improve some of the clinical manifestations. Treatment is initiated with a low dose of 125 mg perday and slowly increased to 500 to 1500 mg daily. The primary mechanism of D-penicillamine on collagen metabolism is due to potent inhibition of the formation of certain inter and intramolecular collagen cross-links. This effect is due to the formation of a complex between D-penicillamine and the lysine and hydroxylysine derived aldehyde groups required for synthesis of stable collagen cross-links. Collagen that is not cross-linked is more susceptible to degradation. Thus long term therapy with D-penicillamine results in a net decrease in the total collagen content of the susceptible tissue. However, D-penicillamine does not interfere with preformed collagen cross-links or stable collagen fibers. The toxicity of D-penicillamine may limit its use. Drug eruptions, proteinuria, nephrotic syndrome, thrombocytopenia, and decreased taste acuity are the most common side effects. It may also induce immunologic disorders like lupus erythematosus, myasthenia gravis, dermatomyostitis, and Goodpasture syndrome. It may also cause pemphigus, penicillamine dermatopathy, and elastosis performans serpiginosa. The details of treatment are given in Tables 33.4 to 33.6 for ready reference.

**Table 33.6: Vasoactive agents in the treatment of scleroderma**

| *Drug* | *Status* |
|---|---|
| 2.5 mg per kg of prostacyclin, infused intravenously in 72 hours | Inhibits platelet hyperaggregation and induces vasodilatation. May cause nausea, vomiting, and flushing |
| 2 liters of 10 percent low molecular weight dextran in 0.9 percent sodium chloride infused intravenously in 48 hours. | Inhibits platelet aggregation and enhances fibrinolytic activity. May induce anaphylactic shock |
| 10 mg of stanozolol, orally, daily | Increases the release of the endothelial activator of plasminogen, enhancing fibrinolysis |
| 30 mg of nifedipine, orally, daily | Causes vascular smooth-muscle relaxation. Releases arterial vasospasm. May cause headache, flushing, postural hypotension, tachycardia, worsening of esophageal symptoms |
| 150 mg of captopril, orally, daily | Inhibits the angiotensin converting enzyme |
| 60 mg of ketanserin, orally, daily | Antagonizes the vasoconstricting and platelet aggregating effect of serotonin. |

## RECOMMENDED READING


1. Callen JP, Tuffanelli DI, Provost TT. Collagen vascular disease: An update. *J Am Acad Dermatol* 1993;28:477-484.
2. Perez MI, Kohn SR. Systemic sclerosis. *J Am Acad Dermatol* 1993;28:525-547.

# 34 Chapter Photodermatoses

Photodermatoses refer to adverse reactions to nonionizing radiations. Photosensitive disorders may be considered as: (i) direct disorders that denote those reactions that follow an overexposure or chronic exposure to sunlight alone, (ii) indirect disorders that denote reactions that require participation of endogenous/exogenous photosensitizers in addition to sunlight. A classification of photodermatoses is shown in Table 34.1.

## SUNBURN

It results from a single overexposure to sunlight/UVB emitted from an artificial source. The severity may range from mild asymptomatic redness to an intense erythema, accompanied by tenderness, pain, edema, and vesiculation. Mild reaction begins 6 to 12 hours after exposure and reaches a maximum intensity within 24 hours. It declines over the next 3 to 5 days. The residual tan persists for a few weeks. The intense reaction resembles the milder reaction at the onset. However, the signs and symptoms continue to progress and reach the maximum in 48 hours. Necrosis and sloughing of the skin may occur over the next 24 to 48 hours. Systemic signs and symptoms namely, fever, prostration, nausea, chills, and delirium may accompany severe sunburn.

**Table 34.1: Classification of photodermatoses**

*Direct disorders*

1. Immediate
   a. Sunburn
   2. Delayed
   a. Premature aging/photoaging/dermatoheliosis
   b. Premalignancy
   c. Malignancy

*Indirect disorders*

1. Exogenous/endogenous photosensitizers
   a. Phototoxic reactions
   b. Photoallergic reactions
2. Metabolic and biochemical disorders
   a. Porphyria
   b. Aminoaciduria
   c. Hartnup's disease
   d. Phenylketonuria
   e. Pellagra
3. Idiopathic/immunological
   a. Polymorphic light eruption
   b. Actinic prurigo
   c. Juvenile spring eruption
   d. Solar urticaria
   e. Hydroa vacciniforme
   f. Actinic reticuloid
4. Genetic
   a. Xeroderma pigmentosum
   b. Bloom's syndrome
   c. Cockayne's syndrome
   d. Rothmund-Thomson's syndrome
5. Diseases aggravated/precipitated by sunlight
   a. Lupus erythematosus
   b. Pemphigus erythematoides
   c. Lichen planus actinicus
   d. Rosacea
   e. Herpes simplex
   f. Lymphogranuloma venereum
   g. Varicella

### Diagnosis

It is made on the basis of history of exposure to sunlight, and clinical features. It may be supplemented by histopathological examination that reveals the following: (i) 'sunburn' cells that are the altered epidermal cells characterized by homogenous eosinophilic cytoplasm and pyknotic nuclei, (ii) moderate vascular dilatation, and (iii) mild perivascular mononuclear and polymorphonuclear infiltrate.

### Treatment

Patient should be managed in the similar fashion as a first or second degree burn. On recovery, sunscreens should be applied to prevent sunburn in future (Table 34.2).

## PHOTOAGING

Photoaging refers to those changes in the skin that are induced by repeated exposure to sun. It is also termed 'premature aging' or 'dermatoheliosis'. It is characterized by coarsness, wrinkling, mottled pigmentation, laxity, telangiectasia, purpura, easy bruising, atrophy, and pseudoscars. Ultimately premalignant and malignant neoplasms may develop on the exposed areas. The principal premalignant lesion is actinic or solar keratosis. 25 percent of patients with multiple actinic keratosis develop squamous cell carcinoma in one or more of the lesions. Basal cell carcinoma and melanoma also occur with greater frequency in sun damaged skin. Ultraviolet portion of sunlight,

**Table 34.2: Methods of photoprotection**

| *Methods* | *Status* |
|---|---|
| 1. Avoidance of outdoor exposure during hours of intense sunlight (10 AM to 3 PM) and wearing of protective clothing | Simplest means of achieving photoprotection |
| 2. Application of topical sunscreens | |
| a. physical sunscreens like titanium dioxide, talc, zinc oxide, kaolin, ferric chloride, and icthammol | 1. Cosmetically unacceptable as they are messy and visible<br>2. Easily washed off<br>3. Stain the clothes<br>4. Melt with the heat of sun<br>5. Promote miliaria and folliculitis |
| b. Para-aminobenzoic acid (PABA) and its esters like glyceryl PABA, amyldimethyl PABA, and octyldimethyl PABA | 1. Absorb predominantly in UVB range<br>2. Form hydrogen bonds with stratum corneum and thus afford protection even after bathing proteins |
| c. Benzophenones such as oxybenzone and dioxybenzone | 1. Provide broader UV absorption. Absorb UVB and shorter wavelengths of UVA<br>2. Protect from phototoxic reactions |
| d. Cinnamates such as ethylhexyl-para-methoxy cinnamate | 1. Absorb UVB and shorter UVA wavelengths also<br>2. Do not bind to stratum corneum and thus easily washed away by bathing and sweating<br>3. May cause contact dermatitis |
| e. Butylmethoxylibenzoyl methane (Parsol 1789) | 1. Effective UVA sunscreen<br>2. Poor UVB absorber<br>3. Useful in patients with UVA photosensitivity |
| 3. Systemic sunscreens<br>250 mg of chloroquine (equivalent to 150 mg of active base) (Resochin, Melubrin) thrice a day during the first week, twice a day during second week and once daily during the third week. | |

particularly UVB is implicated in photoaging and photo carcinogenesis. UVA and infrared energy may also contribute.

### Diagnosis

It is clinical. It may be supplemented histopathological examination that reveals the following: (i) thinning of the epidermis, (ii) effacement of the rete ridges, (iii) abnormal keratinocytes in a disorderly arrangement, (iv) impairment of melanin transfer from melanocytes to keratinocytes, (v) progressive degenerative changes in collagen and its replacement by elastic fibrils and finally homogenization and elastosis of the dermis, and (vi) vascular dilatation and ectatic vessels.

### Treatment

The patient should avoid further exposure to sunlight. The premalignant lesions may be treated with topical fluorouracil. Lesions that persist after treatment with fluorouracil are probably invasive. They should be biopsied and treated according to the nature and staging of the malignancy.

## PHOTOTOXICITY

Phototoxic reaction is an indirect photosensitive disorder that can be elicited in all persons with sufficient concentration of the photosensitizing agent and exposure to the offending wavelength of light. The immune system does not participate in these reactions. The action spectrum usually includes the UVA range, though certain substances such as porphyrins and a number of dyes photosensitize to visible light. In addition, a very limited number of chemicals depend on UVB activation Phototoxic reactions may be photodynamic or nonphoto dynamic in nature, the primary difference being that photodynamic reactions require oxygen. Photodynamic process appears to be responsible for reactions to certain dyes, coal tar, polycyclic hydrocarbons, and porphyrin molecules. Photodynamic reactions induce an excited triplet state which reacts with oxygen, forming a singlet oxygen or superoxide anion. This activated oxygen can then damage cell components. Nonphotodynamic reactions have been described for psoralen photosensitization. In this instance, psoralen compounds intercalate into the DNA helix. On photoactivation with UVA radiation, mono and bifunctional adducts may be formed in the DNA depending on the structure of the psoralen molecule and the wavelengths utilized for irradiation. Photoreactions with proteins may also occur.

### Clinical Features

The acute phototoxic reactions are characterized by erythema, edema, and at times blister formation, followed by hyperpigmentation and desquamation. These reactions are confined to the exposed skin. The clinical reaction may begin from a few minutes to several hours after the irradiation and reaches a peak from several hours to several days later. There is no incubation period and even the first exposure to light produces symptoms of phototoxic reaction.

### Diagnosis

The history and clinical examination supplemented by histopathology and phototest are helpful in diagnosis. Histopathological examination reveals the following: (i) epidermal cell degeneration, (ii) dilatation of dermal blood vessels, (iii) minimal inflammatory cell response in the dermis.

### Treatment

Patient should be managed in the similar fashion as a first or second degree burn. Further exposure to the phototoxic agent should be stopped. Topical application of sunscreens is also beneficial (Table 34.2).

## PHOTOALLERGY

Photoallergy is a cutaneous hypersensitivity to exogenous drugs and/or chemicals in the presence of radiant energy. The participation of the immune system is necessary for the response to occur and photons are required along with the chemical for immunologic activation. Although wavelengths within the UVB spectrum have been implicated in some photoallergic reactions, however, in most cases UVA is responsible. The electromagnetic energy converts an immunologically inactive form of the photosensitizing compound into its active form, the hapten. This hapten is a stable photoproduct of the chemical. It combines with a protein in the skin to produce full antigen. This antigen elicits a cell-mediated immune response. The involvement of the immune system is demonstrable by passive transferability. The chemicals responsible for inducing photoallergy are halogenated salicylanilides, halogenated phenols, sulfanilamide, sulfonylureas, thiazides, phenothiazines, griseofulvin, nalidixic acid, 6-methyl-coumarin, and musk ambrette.

### Clinical Features

The initial few exposures to light are asymptomatic which result only in sensitization to the photoallergen. Subsequent exposures result in eczematous eruption characterized by cardinal clinical features of acute eczema, namely erythema, edema, vesiculation, oozing, and crusting. This eruption is localized to areas exposed to the sunlight namely the forehead, nose, malar areas, rims of the ears, sides and back of the neck, V of the chest, and extensor surfaces of the forearms, hands, shins, and feet. The sparing of shielded areas is also characteristic. These areas include the retroauricular areas, the submental region, upper eyelids, back of the neck, nasolabial folds, and the flexor aspects of the limbs, and other deeply recessed body folds.

The photoallergic dermatitis resolves when the exposure to photo allergen is stopped. However, a small number of patients of photoallergic dermatitis continue to display photosensitivity without apparent exposure to the chemical or to a cross-reacting chemical. This is termed as persistent light reaction. The lesions are characterized by chronic eczematous dermatitis localized to the sun-exposed sites. Photopatch test reveals a strongly positive response to a photoallergen. Many hypothesis have been advanced to explain this phenomenon. One is that the patient unknowingly continues to be exposed to the photoallergen or an unsuspected cross reacting substance. Another is that the photoallergen persists in the skin. The third is that a normal skin constituent becomes antigenic and subsequent exposure produces a photoproduct.

### Diagnosis

The history and clinical examination supplemented by histopathology and photopatch test are helpful in the diagnosis. The histopathological examination reveals: (i) intracellular edema in the epidermis (spongiosis) with or without the formation of vesicles, (ii) dense perivascular dermal lymphohistiocytic infiltrate.

For the photopatch test, several common photosensitizers are applied in duplicate to unexposed areas of the skin, most often the

back. All the test sites are covered with an opaque material. After 24 hours, one set of the applied substances is exposed to UVA radiation and then covered again. Both the sets are observed in 48 hours after application. A positive response at the irradiated site, characterized by erythema, edema, and/or vesiculation and the absence of reaction at the photo protected site is diagnostic of photoallergic dermatitis. Photoallergic dermatitis needs to be differentiated from phototoxic reaction (Table 34.3).

### Treatment

The patient is managed as in any acute dermatitis. As soon as the acute dermatitis has resolved, a suitable sunscreen is advised (Table 34.3).

## POLYMORPHOUS LIGHT ERUPTION

Polymorphous light eruption (PLE) is a photodermatoses of unknown etiology. It affects both males and females. The latter are affected frequently. However, there is no absolute restriction of age, sex, or race. The onset of the disease is usually during the early adult life, but the eruptions may at times start in childhood. The action spectrum of PLE is debatable. Ultraviolet A (UVA) is probably most often responsible for eliciting PLE though similar lesions have at times been reproduced with UVB and visible light.

### Clinical Features

PLE is a delayed type of reaction. Lesions appear several hours to a few days after exposure to sunlight. A characteristic sequence of events is often reported by patients following exposure to light. It is heralded by itching, followed by patchy erythema. Subsequently, the lesions distinctive of PLE appear and may remain for a varying period of few hours to days and resolve spontaneously if further exposure to sunlight is avoided. Constitutional symptoms like fever, headache, chills, and nausea may accompany the cutaneous lesions in a few patients. Majority of patients experience seasonal recurrences over many years. Finally

**Table 34.3: Photoallergy and phototoxicity**

| *Features* | *Photoallergy* | *Phototoxicity* |
|---|---|---|
| Prevalence | Low | High |
| Mechanism | Immune-mediated | Direct reaction. May be photodynamic or non-photodynamic. |
| Latent period | Present | Absent |
| Morphology | Eczema/dermatitis | Sunburn |
| Histopathology | 1. Spongiosis<br>2. Dense perivascular dermal lympho histiocytic infiltrate | 1. Epidermal cell degeneration<br>2. Dilatation of dermal blood<br>3. Little inflammatory response in the dermis. |
| Diagnosis | Photopatch test | Phototest |
| Passive transferability | Present | Absent |
| Causative substances | Halogenated salicylanilides, halogenated phenols, sulfanilamide, sulfonylureas, thiazides, phenothiazines, griseofulvin, musk ambrette | Dyes like eosin, rose bengal, halogenated salicylanilide, sulfanilamide, sulfonyl ureas, thiazides, phenothiazine, coal tar, psoralen, griseofulvin, thiourea, tetracyclines |
| Cross reaction | May occur to chemically related substances | Does not occur |

it may resolve spontaneously after many years. There are distinct morphologic variants of PLE. However, the lesions may be monomorphic. These variants are as follow:

*Papular*

This is most common. It is characterized by the formation of small papules or papulovesicles that are disseminated or densely aggregated on a patch of erythema.

*Plaque*

This is the second most common variety characterized by sharply demarcated, erythematous, elevated, often urticarial plaques.

*Vesiculobullous*

It consists of tense vesicles and small bullae on an erythematous base.

*Hemorrhagic*

In this, the papular lesions turn hemorrhagic.

*Erythema-multiforme like*

It shows typical target lesion on sun exposed areas.

*Insect Bite (strophulus)-like*

This is a peculiar, rare variety of the papular type. The lesions are few, scattered, and consist of small urticarial papules topped by a tiny vesicle.

The lesions of PLE are confined to sun exposed sites. However, there are certain sites of predilection even when large areas are sun exposed. These sites are V-neck, dorsa forearms, back of hands, upperarms, face, shoulders, thighs, and lower legs. Occasionally, large parts of trunk may be involved.

### Diagnosis

The diagnosis of PLE is based on the history, evolution of lesions, morphology, histopathology, and provocative phototesting. The histopathologic picture is characterized by: (i) vacuolization of basal cells, (ii) spongiosis in the lower epidermis, (iii) a perivascular lympho cytic infiltrate in the upper and middle corium with subepidermal edema.

The provocative phototesting should be performed preferably before the lesions appear or after the existing lesions have completely subsided. The light source should emit a polychromatic UV light. The usual dose required is 60 to 100 J/cm$^2$ of UVA and/or 2 MED of UVB. The test site should be a previously involved body area. Repeat irradiation on day 1, 2 and 3 may be necessary to elicit PLE.

### Treatment

Patient should be advised to avoid sun exposure. Sun protection may be provided by staying indoors and wearing protective clothing when going out. Preferably, a broad band sunscreen (UVA plus UVB) or physical sunscreens may be applied over the sun exposed areas (Table 34.2). Prophylactic treatment with antimalarials has also been tried, though the results have not been as impressive as in other photodermatosis. Phototherapy and photochemotherapy (PUVA) have also been found effective.

## SOLAR URTICARIA

Solar urticaria is an idiopathic, acquired disorder characterized by itching, erythema, and whealing immediately after exposure to sun light. It is an uncommon disorder and usually manifests in the third or fourth decade. The action spectrum may either be in the

UVB, UVA, or visible light range. The exact pathogenesis of solar urticaria is not known. However, it is considered that the precursor (chromophore) responsible for it exists in the cutaneous tissue fluid in the circulation, whereas in others, it is confined to the skin. A photoallergen is formed from this precursor on exposure to light. Consecutively, an immediate type hypersensitivity develops to this photoallergen. The IgE specific to this photoallergen is synthesized and binds to the mast cells. Subsequent irradiation of the skin results in the cross-linking of the bound IgE antibodies by the photoallergen and the liberation of histamine from the mast cells.

Solar urticaria may either be type I or type II. This distinction is based on the difference in the precursor. It may be an abnormal endogenous substance generated only in the patient or a normal factor present in both the patients and normal subjects.

*Type I*

In this, the precursor is an abnormal endogenous substance present only in the patient. It is converted into photoallergen on irradiation and subsequently the immediate IgE mediated hypersensitivity develops to it. Passive transfer tests are positive in some and negative in other patients with type I solar urticaria.

*Type II*

In this the precursor is a normal constituent of the skin present in both the patient and normal subjects. On irradiation this nonspecific precursor is converted to a photoallergen. However, only the patient develops an immediate hypersensitivity to it. The passive transfer is positive in all cases of type II solar urticaria.

### Clinical Features

It is characterized by the development of erythema and itching within minutes of exposure to sunlight. This is followed by the appearance of wheal and flare reaction. If further exposure is avoided, the skin returns to normal within 30 to 60 minutes. A temporary tolerance may occur after repeated exposure to sunlight. Areas of skin which are irradiated repeatedly show a gradual reduction in urticarial response and ultimately develop a high degree of tolerance (tachyphylaxis).

### Diagnosis

It is based on the history, morphology, and provocative phototesting.

### Treatment

It subsides on withdrawal from light source. Antihistamines and corticosteroids are useful. Further recurrences may be prevented by avoiding sun exposure. Topical sunscreens that block specific activating rays are beneficial (Table 34.2). PUVA has also been used to treat solar urticaria.

## ACTINIC PRURIGO

Actinic prurigo, also termed Hutchison's summer prurigo is an idiopathic photodermatoses that appears during childhood and improves by early adulthood. The action spectrum of actinic prurigo is not known, although UVA is implicated.

### Clinical Features

It is characterized by excoricated papules and lichenification confined to sun exposed areas. The rash persists throughout the year but is aggravated during summers. Cheilitis and involvement of distal third of the nose are

common. Patient may also reveal history of atopy either in the self or the family.

### Treatment

Avoidance of exposure to sunlight is essential. Topical sunscreens are beneficial (Table 34.2). Thalidomide has also been observed to be effec tive in actinic prurigo. However, this drug is not available for clinical use.

## HYDROA VACCINIFORME

It is a photodermatoses with onset in childhood. It usually improves or resolves in early adult life. The pathogenesis is unknown, but abnormal erythema response to UVA radiation is a consistent finding.

### Clinical Features

It is characterized by the appearance of groups of small vesicles that become confluent, necrotic, and crusted. They heal leaving behind a sunken scar. The lesions develop at varying period after sun exposure and are confined to the sun exposed areas.

### Diagnosis

It is clinical. It may be supplemented by histopathology and provocative phototesting. The histological examination reveals: (i) multilocular intraepidermal vesicle, (ii) underlying dermal necrosis, (iii) thrombosis of dermal blood vessel.

### Treatment

The condition responds to antimalarials.

## ACTINIC RETICULOID

It is a photodermatoses of unknown etiology. The action spectrum in actinic reticuloid lies in the UVA range. However, there also exists a marked hypersensitivity to rays in the UVB range. Many patients have a contact allergic sensitivity to oleresin extracts from *Compositae* plants. The eruption is persistent in such cases because of inadvertent contact with airborne plant particles.

### Clinical Features

It is characterized by erythema and lichenfied plaques initially confined to exposed areas. It gradually spreads to cover most of the skin surface and a generalized erythroderma may develop. The skin becomes thickened and the normal furrows are deepened and exaggerated. The appearance of face may resemble leonine facies. There may be a generalized lymphadenopathy. The eruption clears slowly when the patient is withdrawn from light and confined to a darkroom.

### Diagnosis

It is based on the history of chronic sun exposure and the morphology of the lesions. However, histopathology is essential. The histological examination reveals the following: (i) bank-like, dense infiltrate in the upperpart of dermis. The infiltrate is composed of lymphoid cells and histiocytes, with an admixture of eosinophils and plasma cells. The nuclei may be hyperchromatic, (ii) invasion of the epidermis by the inflammatory cells where they may form aggregates resembling Pautrier's abscess. Furthermore, several patients have circulating Sezary cells.

The condition may resemble mycosis fungoides clinically and histologically. In doubtful cases, monoclonal antibodies may be used to characterize the cluster differentiation antigen

on T-lymphocytes. Actinic reticuloid is characterized by infiltration of T-lymphocytes that are predominantly suppressor (CD8), whereas T-lymphocytes in mycosis fungoides or Sezary syndrome are helper T-cells (CD4).

### Treatment

Patient should be withdrawn from light and confined to a dark room. Photochemotherapy is also helpful.

## RECOMMENDED READING


1. Epstein JH. Phototoxicity and photoallergy in man. *J Am Acad Dermatol* 1983;8:141-147.
2. Holzle E, Plewing G, von kries R, *et al*. Polymorphous light eruption. *J Invest Dermatol* 1987; 88(S):32S-38S.
3. Leenutaphong V, Holzle E, Plewig G. Pathogenesis and classification of solar urticaria: A new concept. *J Am Acad Dermatol* 1989;21:237-240.
4. Oltonner JP, Marks R. *Photodamage skin: Clinical signs, causes and management*. Martin Dunitz, Lond, 1st edition 1999.
5. Taylor CR, Stern RS, Leyden JJ, *et al*. Photoaging/photodamage and photoprotection. *J Am Acad Dermatol* 1990;22:1-12.

# 35 Chapter Epidermolysis Bullosa

Epidermolysis bullosa (EB) is a group of disorders, characterized by marked skin fragility and blister formation following seemingly minor or insignificant trauma to the skin. The term 'epidermolysis bullosa' is a misnomer as cytolysis of the epidermis takes place only in some of its subtypes. Hence, it has also been proposed to refer it as mechanobullous disease. The use of electron-microscope has facilitated the classification of the disorder based on the depth of cleavage (Table 35.1).

**Table 35.1: Classification of clinical types of epidermolysis bullosa**

1. *Intraepidermal*
   a. EB simplex, generalized (Koebner)
   b. EB simplex, localized (Webner-Cockayne)
   c. EB herpetiformis (Dowling-Meara)
2. *Junctional (intralamina lucida)*
   a. EB atrophicans generalisata gravis (Herlitz: EB letalis)
   b. EB atrophicans generalisata mitis
   c. EB atrophicans localisata
   d. EB atrophicans inversa
   e. EB progressiva
   f. Generalized atrophic benign EB (GABEB)
   g. Cicatricial junctional EB
3. *Dermolytic or dystrophic (sublamina-densa)*
   Dominant forms
   - Dystrophic EB, hyperplastic variant (Cockayne-Touraine)
   - Dystrophic EB, albopapuloid variant (Pasini)
4. *Recessive forms*
   a. Generalized (gravis or mitis)
   b. Localized
   c. Inverse

## CLINICAL FEATURES

The clinical features, severity, extent of involvement, and the fate vary in different subtypes of epidermolysis bullosa.

### Epidermolysis Bullosa Simplex

The generalized type is inherited as a dominant disorder. It is characterized by formation of vesicles and bullae, over sites prone to trauma, namely the joints of the hands, elbows, knees, and the feet (Figs 35.1A and B). Usually the mucous membranes and the nails are spared. The lesions heal without scarring. The course may be characterized by exacerbations and remissions initially, but with the passage of time, the skin changes subside markedly.

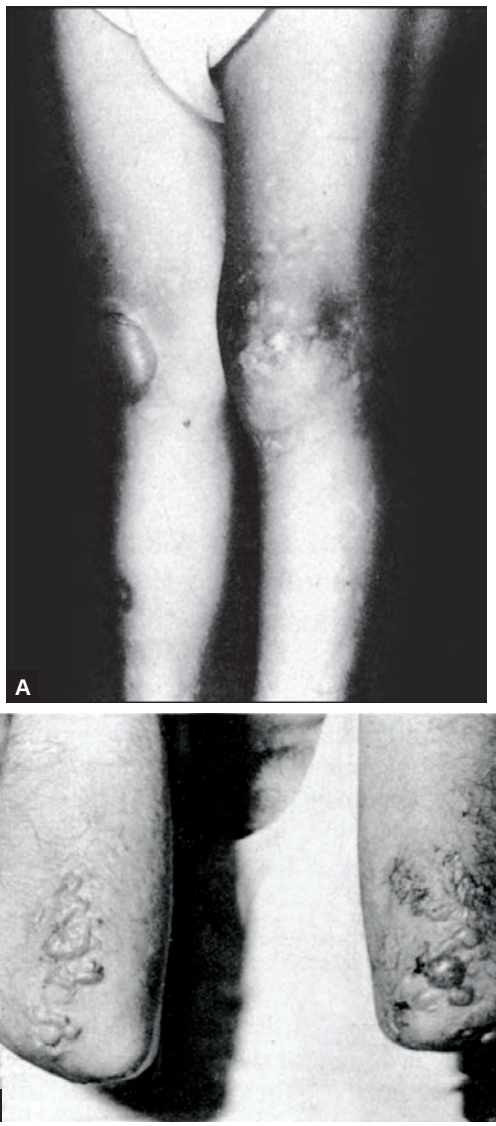
The localized type of EB simplex, also named Weber-Cockayne disease, is inherited as an autosomal dominant disorder. Bullae develop primarily on the palms and soles. Nails may occasionally be lost. Hyperhidrosis may be an associated finding. Usually it develops in adult life following trauma, such as prolonged walking. The lesions exacerbate during hot weather.

### Junctional Epidermolysis Bullosa

It is inherited as autosomal recessive disorder. It may manifest either as the letalis or the benign

form. The letalis type of junctional EB is characterized by severe generalized blistering, which may be present at birth. The newborn may succumb to extensive denudation within a few month of life. However, in some cases erosions may persist for years. Severe oral erosions and dysplastic teeth are common. The dysplasia of the enamel may produce a cobblestone effect on the surface of the teeth. Laryngeal and bronchial lesions may cause respiratory distress and death. In patients who survive infancy, there may be growth retardation. Moderate to severe anemia may also develop.

The benign variety of junctional EB is also inherited as autosomal recessive. It is characterized by onset at birth, with marked skin fragility and generalized blister formation. However, the patient survives to adulthood, instead of dying in infancy as in the letalis form. Skin atrophy is characteristics. Also the nails may be absent or markedly dystrophic. There may be an associated palmoplantar hyperkeratosis and hairs may be lost. A third type termed cicatricial junctional EB has also been observed. In contrast to other reported forms of junctional disease, affected patients of the cicatricial subtypes, develop significant scarring as well as syndactyly and/or contractures, reminiscent of dystrophic EB.




**Figures 35.1A and B:** Epidermolysis bullosa simplex: Vesiculobullous lesions over the extensors of upper extremities and knees

## Dystrophic (Dermolytic) Bullosa

There are two major forms of dystrophic EB differing in mode of transmission and disease severity. Besides, a number of variants exist. The milder one is transmitted as autosomal dominant. It is characterized by the onset at birth or early infancy, marked by appearance of vesicles and bullae over the extensor surface of the extremities. The lesions are localized over the toes, fingers, knuckles, ankles, and elbows. Nikolsky sign is positive and usually the fluid in the bulla may be moved under the skin several centimeters away from the original site. Nails may either be dystrophic or absent. Scalp is usually spared. The mucous membranes may be involved. Recurrent oral blisters and

erosions may develop. However, significant extracutaneous involvement is usually lacking. The lesions heal with scarring and atrophy. Milia are often present on the rims of the ears, the dorsal surface of the hands and on extensor surfaces of the arms and legs. Two additional features may develop in patients with dominant dystrophic EB. In a usually milder form (Cockayne-Touraine variant) healing may lead to hyperkeratotic lesions. In the severe form of dominant dystrophic disorder (Pasini variety) healing leads to atrophic scars. Furthermore, small flesh colored papules (albopapuloid lesions) may be detected on the trunk.

The other type of dystrophic epidermolysis bullosa is inherited as an autosomal recessive disorder. It is the more severe type of the two. It is characterized by onset at birth, and manifests as generalized or acral cutaneous and mucosal blistering. Digital fusion with encasement of fingers and toes in scar tissue, forming a 'mitten-like' deformity is characteristic. Patient may have profound growth retardation and anemia. There is usually a severe involvement of the oral cavity, esophagus, and eyes. Recurrent esophageal blistering may necessiate repeated dilatation. Teeth are frequently dysplastic. Patients with both dominant and recessive forms of dystrophic EB have an increased incidence of developing skin cancers later within areas of chronic blister formation and scarring.

## DIAGNOSIS

Epidermolysis bullosa may be suspected from the morphology and the distribution of the lesions. Family history is also contributory. However, the final diagnosis of EB subtype requires a detailed clinical, genealogic, and histologic analyses. Electron microscopic studies form the mainstay of diagnosis (Table 35.2). In addition to determination of the level of blister formation they also permit evaluation for the possible presence of other associated structural abnormalities including those of tonofilaments, hemidesmosomes, and anchoring fibrils. It is necessary to emphasize the importance of multiple biopsies from both blisters and uninvolved areas of the skin to reach a definite conclusion.

The introduction of fetoscopy and fetal skin biopsy techniques have made prenatal diagnosis possible after 18 to 20 weeks of gestation. A termination of pregnancy is indicated on eugenic grounds in the most severe R-EBD and R-EBA gravis Herlitz cases.

## TREATMENT

The patient should be instructed to prevent trauma. Topical antibiotics like silver sulfadiazine are helpful in wound healing by maintaining a relatively sterile environment. Exudative lesions require wet compresses and dressing. Application of either 20 percent aluminium chloride or a 1 percent glutaraldehyde to the feet may be beneficial to symptomatic patients with EB simplex.

Systemic antibiotics may be administered to treat secondary infection. Phenytoin inhibits collagenase synthesis and appears to be beneficial in patients with recessive dystrophic EB. A few junctional EB patients have also benefitted from this drug. Corticosteroids have been used in emergency situations to prevent strictures. However, it is uncertain whether they can improve the prognosis of fatal forms of EB. Retinoids inhibit collagenase activity *in vitro*. Clinical trials are underway to evaluate their efficacy in this disorder.

**Table 35.2: Diagnosis of epidermolysis bullosa**

| *Types* | *Epidermolysis bullosa* | *Distribution* | *Inheritance* | *Oral lesions* | *Light microscopy* | *Electron microscopy* | *Scarring* | *Prognosis* |
|---|---|---|---|---|---|---|---|---|
| Epidermal | EB simplex | Generalized | dominant | + | Intraepidermal vesiculation Intact BM along the base of the vesicle | Cytolysis of basalar keratinocytes | – | Good |
| | EB localized (Weber-Cockayne) | Hands, feet | Dominant | – | -Do- | Cytolysis of suprabasalar keratinocytes | – | Good |
| Junctional | EB letalis | Generalized | Recessive | + | Uniform separation of epidermis from dermis | Cleavage at lamina lucida. Rudimentary or decreased hemidesmosme | – | Fatal |
| | EB benign | Generalized | Recessive | + | -Do- | -Do- | Atrophy | Good |
| Dermal | EB dystr-dom | Extremities | Dominant | + | Non-inflammatory subepidermal bulla | Cleavage beneath lamina densa. Anchoring fibrils diminished | + | Good |
| | EB dystr-rec | Generalized | Recessive | + | -Do- | Cleavage beneath lamina densa. Anchroing fibril markedly decreased or absent | +++ | Poor |

## RECOMMENDED READING

1. Fine JD, Bauer EA, Briggaman RN, et al. Revised clinical and laboratory criteria for subtypes of inherited epidermolysis bullosa. A consensus report by the Subcommittee on Diagnosis and Classification of the National Epidermolysis Bullosa Registry. *J Am Acad Dermatolol* 1991;24: 119-135.

# 36 Chapter

# Ichthyoses

Ichthyoses constitute a group of genetic and acquired disorders, characterized by accumulation of scales on the skin surface. They are classified on the basis of inheritance pattern, clinical features, and histopathology. Four primary forms of genetic ichthyoses are recognized in which the manifestations are confined only to the skin. In addition, a variety of other disorders of cornification, characterized by multisystem involvement, with cutaneous manifestations forming a part component of symptomatology are termed 'ichthyosiform syndromes' (Table 36.1).

The pathophysiology of ichthyoses is debatable. Lamellar ichthyosis and bullous ichthyosis (epidermolytic hyperkeratosis) are characterized by an increase in the number of cells entering division and a reduced epidermal transit time. These abnormalities are similar to those observed in psoriatic epidermis. The scaling in these disorders is due to failure of desquamation to compensate for an enhanced rate of formation of stratum corneum. In ichthyosis vulgaris and recessive X-linked ichthyosis (RXLI) the mitotic indices and cell transit time are normal/decreased. The primary abnormality in these is greater than normal corneocyte cohesion resulting in a thicker stratum corneum and a decrease in the normal rate of desquamation. Hence, these are also termed as retention ichthyoses.

**Table 36.1: Classification of ichthyoses**

*Primary ichthyoses*
1. Ichthyosis vulgaris
2. Recessive X-linked ichthyosis (RXLI)
3. Epidermolytic hyperkeratosis (bullous ichthyosis)
4. Autosomal recessive ichthyosis (lamellar ichthyosis and nonbullous congenital ichthyosiform erythroderma)

*Related disorders of cornification*
1. Ichthyosis linearis circumflexa
2. Erythrokeratoderma variabilis
3. Harlequin fetus.

*Ichthyosiform syndromes*
1. Chanarin syndrome (neutral lipid storage disease)
2. Sjogren-Larsson syndrome
3. Refsum's disease
4. Rud's syndrome
5. Trichothiodystrophy
6. Keratitis-ichthyosis-deafness (KID) syndrome
7. Ichthyosis hysterix (epidermal nevus syndrome)

*Acquired ichthyoses*
1. Drug induced ichthyosis
2. Essential fatty acid deficiency induced ichthyosis
3. Malignancy-associated ichthyosis
4. Xerosis of hypothyroidism
5. Environmental xerosis
6. Ichthyosis associated with diseases like sarcoidosis, and leprosy.

## CLINICAL FEATURES

### Ichthyosis Vulgaris

It is an autosomal dominant disorder of keratinization. It occurs in about 1 in 300 individuals. Skin changes are not present at birth. They may be noted from early infancy

to teens. Dry skin and prominent keratotic follicles are usually present at ages of 5 to 10 years. Those with ichthyosis vulgaris are predisposed to atopy (atopic dermatitis, rhinitis, asthma, and hay fever) and keratosis pilaris. The disorder is characterized by fine scales that appear 'pasted' over the entire body. Milder forms appear as dryness present only during the winter months. The scales are coarser on the lower extremities than they are on the trunk. The extensor surfaces of the extremities are most prominently involved. Flexors are spared. The scalp is involved, with only slight scaling. Follicular keratotic lesions are frequently found on the back of the hands. Follicular accentuation (keratosis pilaris) may be prominent over the arms, thighs, and buttocks. The palms and soles have accentuation of the dermatoglyphic lines. Keratosis pilaris and dermatoglyphic accentuation are the markers for ichthyosis vulgaris. The course is usually favorable with abatement of signs and symptoms by the time adulthood is reached.

### X-linked Ichthyosis

It is inherited as X-linked recessive disorder and manifests within the first year of life. It is characterized by large, dark colored scales. They are present over the extensor surface of the body. However, flexor surfaces may also be encroached. Face and scalp are relatively spared. Involvement of the palms and soles is uncommon. Keratosis pilaris is not present. The incidence of atopy is not high unlike ichthyosis vulgaris. However, it may be associated with corneal opacities on the posterior capsule and/or Descement's membrane. These are present in the affected males and the female carriers. They do not affect vision but can be demonstrated by slit lamp examination. The link between steroid sulfatase deficiency and recessive X-linked ichthyosis has been demonstrated in many children from diverse ethnic origin and in many tissues including cultured fibroblasts and keratinocytes, hair bulbs, epidermis, stratum corneum, and leukocytes. It is now well-recognized that steroid-sulfatase deficiency is a single nosologic entity which manifests antenatally as placental sulfatase deficiency syndrome with prolonged labor and postnatally as RXLI. Unlike icthyosis vulgaris, RXLI does not improve with age, but gradually worsens in both extent and severity.

Multiple sulfatase deficiency is a distinct syndrome in which the patients display an overlap of steroid sulfatase deficiency (RXLI), mucopolysaccharidosis and metachromatic leukodystrophy. This autosomal recessive disorder is caused by the lack of all known sulfatases.

### Lamellar Ichthyosis

This autosomal recessive form of primary ichthyosis is characterized by presentation at birth as a collodion baby followed by the development of a scaling disorder with involvement of the entire body surface, including the flexures and the face, producing tautness of the skin resulting in ectropion and/or eclabion. Recent metabolic and histochemical studies indicate autosomal recessive icthyosis to represent two distinct genetic disorders, i.e. (i) lamellar ichthyosis, (ii) nonbullous congenital ichthyosiform erythroderma (CIE). Patients with lamellar ichthyosis exhibit a uniformly severe form of ichthyosis with involvement of the entire body surface. The disorder is characterized by the presence of large, dark, plate-like scales. Although erythroderma may develop, it is not a prominent clinical feature. In contrast, patients with nonbullous

**Table 36.2: Differentiating features of nonbullous CIE and lamellar ichthyosis**

| *Features* | *Nonbullous CIE* | *Lamellar ichthyoses* |
|---|---|---|
| Clinical | 1. Fine white scales<br>2. Prominent erythroderma<br>3. Ectropion/eclabion | 1. Thick, dark large scales<br>2. Mild or absent erythroderma<br>3. Severe ectropion/uncommon eclabion |
| Histopathology | 1. Acanthosis<br>2. Thinner stratum corneum<br>3. Marked parakeratosis | 1. Thinner epidermis<br>2. Thicker stratum corneum<br>3. Marked compact hyperkeratosis |
| Cell kinetics | Increased turnover | Normal turnover |
| Biochemical analysis | Marked increase in n-alkanes in the scales | Increase in sterols and fatty acids in the scales |

congenital ichthyosiform erythroderma exhibit finer scales. Although face is involved but the tautness is conspicuously missing. Hence, ectropion and eclabion are uncommon. In many patients, severe erythroderma is a prominent clinical feature. The differentiating features of lamellar ichthyosis from nonbullous congenital ichthyosiform erythroderma are presented in Table 36.2.

### Epidermolytic Hyperkeratosis

It is inherited as autosomal dominant. The disease becomes manifest shortly after birth and is characterized by generalized erythema, scaling, and blister formation. The blisters tend to localize at the sites of trauma. Skin infection also results in blister formation in such subjects. The blisters rupture to produce erosions. The erythema and blistering gradually decrease as the child grows older. Blistering usually resolves completely by the age of 7 and 8 years. Erythema also becomes less prominent after infancy and disappears by middle age. Hyperkeratotic areas begin to appear in late infancy and persist throughout life. They may develop beaded ridges arranged in parallel to form horny patches in the flexures. Severely affected infants may have 'crumpled' ears and ectropion. The palms and soles may be thickened. Hair, nails, and mucosae are usually unaffected.

### Diagnosis

The diagnosis is clinical. It may be supplemented by histopathological examination (Figs 36.1 and 36.2). Features of primary ichthyoses are enlisted in Table 36.3.

## TREATMENT

Ichthyosis vulgaris and X-linked ichthyosis can be managed by daily application of emollients or 40 to 60 percent propylene glycol in water, applied under occlusion overnight, two to three times a week. Moving to a warm, moist climate helps in ameliorating the dryness.

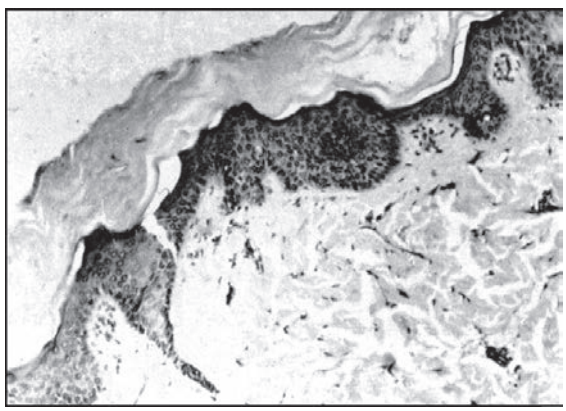


**Figure 36.1:** Ichthyosis vulgaris (H and E × 100)

**Table 36.3: Features of primary ichthyoses**

| *Disorders* | *Mode of inheritance* | *Age of onset* | *Clinical features* | *Distribution transits* | *Courses* | *Histopathologies* | *Epidermal* | *Associations* |
|---|---|---|---|---|---|---|---|---|
| Ichthyosis vulgaris | Autosomal dominant | 1 to 4 years | Small, white, shiny, pasted scales.<br>Keratosis pilaris | Back and extensors<br>Flexures spared | Spontaneous improvement with age | 1. Normal epidermis<br>2. Reduced or absent granular layer<br>3. Sparse dermal infiltrate | 14 days | Atopy |
| X-linked ichthyosis (RXLI) | X-linked recessive | Early infancy | Large, dark brown scales | Front of the trunk, scalp, sides of face, Encroaches on the flexures | Persistent | 1. Acanthosis<br>2. Normal granular layer<br>3. Dermal infiltrate | 14 days | 1. Corneal opacity<br>2. Deficient steroid sulfatase |
| Lamallar ichthyosis | Autosomal recessive | At birth | Polygonal, shield-like adherent scales, state grey or black in color | Entire skin surface | Persistent | 1. Slight epidermal thickening<br>2. Marked hypergranulosis<br>3. Marked compact hyperkeratosis | 4 days | 1. Collodion baby<br>2. Ectropion<br>3. Eclabion |
| Nonbullous congenital ichthyosiform erythroderma | Autosomal recessive | At birth | Fine white scales.<br>Marked erythema.<br>Sparsity of scalp hair | Entire skin | Persistent | 1. Marked epidermal thickening<br>2. Parakeratosis | 4 days | 1. CNS abnormalities<br>2. Immunological abnormalities |
| Epidermolytic hyperkeratosis | Autosomal dominant | At birth or shortly after | Generalized erythema, scaling and blister formation<br>Blistering resolves by 7 to 8 years<br>Erythema resolves by middle age<br>Hyperkeratosis persists throughout life | Trauma prone areas | Persistent | 1. Acanthosis<br>2. Accentuation of rete ridges<br>3. Vacuolar degenerative changes in the upper segment of epidermis. Nuclei appear pyknotic<br>4. Abnormal keratohyaline granules<br>5. Upper dermal edema<br>6. Dermal lympho-histiocytic infiltrate. | 4 days | 1. Ectropion<br>2. Crumpled ears. |

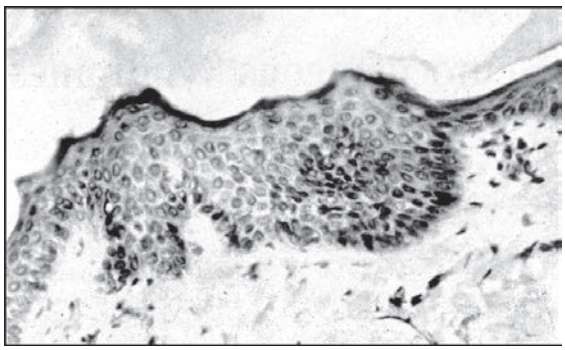


**Figure 36.2:** Ichthyosis vulgaris (H and E × 200)

Lamellar ichthyosis requires topical application of retinoic acid. It may be combined with a corticosteroid. a-hydroxy acid is also effective topical desquamating agent. Oral 13-cis retinoic acid also reduces the scaling.

## RECOMMENDED READING

1. Kumar S, Sehgal VN, Sharma RC: Genodermatosis. *Int J Dermatol* 1996;35:698-699.
2. Rand RE, Baden HP. The ichthyoses: a review. *J Am Acad Dermatol* 1983;8:285-305.

# 37 Chapter Neurocutaneous Syndromes

Neurocutaneous syndromes may manifest as phakomatoses, characterized by nodular retinal excrescences called phakomas. They are constituted by the following: (i) tuberous sclerosis, (ii) neurofibromatosis, (iii) von Hippel-Lindau's syndrome, (iv) Sturge-Weber's syndrome, (v) ataxiatelangiectasia, (vi) basal cell nevus syndrome, and (vii) nevus sebaceous.

## TUBEROUS SCLEROSIS

Tuberous sclerosis is an autosomal dominant disorder, characterized by epilepsy, mental deficiency/low intelligence, and angiofibromas of the face. Hence it is also termed 'epiloia'. The triad may or may not be complete. The angiofibromas consist of numerous small, red, smooth papules in symmetric distribution on the cheeks, nasolabial folds, and the chin (Fig. 37.1). Also, the patient may have subungual and periungual fibromas. The fibromas may also be present over the face and scalp. There may be plaques of slightly thickened, pig-like skin termed as 'Shagreen's patch. The patients may have scattered, hypopigmented, leaf-shaped macules. They are prominently visualized under Wood's light. They are often present at birth and may be the earliest cutaneous sign of tuberous sclerosis.

In addition to the cutaneous lesions, systemic involvement may occur. Multiple tumors may arise in the brain, retina, heart, and kidneys. The cranial tumors are gliomas. They may attain a size of up to 3 cm and are often calcified and visible on skiagram. The retinal tumors are also gliomas and are located peripherally and usually cause no visual disturbance. However, they may extend into the vitreous as mulberry like growths. The cardiac tumors are rhabdomyomas. The renal tumors

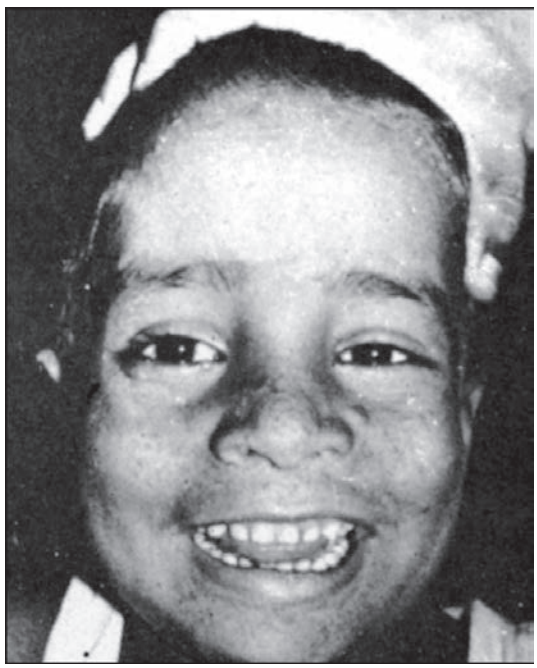


**Figure 37.1:** Angiofibromas in tuberous sclerosis

are angiomyolipomas. They may be solitary or multiple, small or big but are bilateral. They may remain asymptomatic or cause renal failure.

The angiofibromas of tuberous sclerosis need to be differentiated from papular lesions of acne, trichoepitheliomas, and solitary angiofibromas.

### Treatment

The angiofibromas on the face may be destroyed by electrolysis.

## NEUROFIBROMATOSIS

Neurofibromatosis is an autosomal dominant disorder affecting skin, nervous system, and bones. The changes in the skin are characterized by tumors and pigmentation. The cutaneous neurofibromas are flesh colored, semiglobular or pedunculated tumors of soft consistency. They vary in number and size. In some cases, subcutaneous tumors may be present. They are firm, discrete nodules attached to the nerve. In few cases, large pendulous, flabby masses are formed in which numerous thickened, tortuous nerves may be felt (plexiform neurofibromas).

'Cafe'-au-lait' spots are invariably associated. They are coffee brown macules and may appear at birth or soon after. They increase in number and size with age and may precede or accompany cutaneous tumors. Presence of more than six cafe'-au-lait spots of diameter exceeding 1.5 cm is indicative of neurofibromatosis, even in the absence of cutaneous tumors. Freckle like pigmentation may develop in the axilla. It is characteristic of neurofibromatosis and is termed Crowe's sign.

Neurofibromatosis may manifest either as the following.

*Type 1:* Classical neurofibromatosis, with many neurofibromas of varying sizes associated with cafe'-au-lait spots. Central nervous system may be spared. Lisch's nodules are present.

*Type 2:* Central or acoustic neurofibromatosis, characterized by bilateral acoustic neuromas.

*Type 3 (Mixed) and 4 (Variant):* These resemble type 2, but may have more numerous cutaneous neurofibromas, and are at greater risk of developing optic gliomas, neurilemmomas, and meningiomas.

*Type 5:* In contrast to previous four types, arises as a result of postzygotic somatic mutation and is not inherited.

*Type 6:* It has no neurofibromas but only cafe'-au-lait spots.

*Type 7:* It has late onset and manifests in the second decade.

Besides the skin, other systems may be involved. It may involve the endocrine system in the form of acromegaly, cretinism, hyperparathyroidism, myxedema, pheochromocytoma, and precocious puberty. Lisch's nodules are frequent. Bone changes include kyphosis, lordosis, pseudoarthrosis, spina bifida, dislocation, and fractures. Mental retardation, dementia, epilepsy, and brain tumors may also develop.

### Diagnosis

It is clinical. Microscopic examination of hematoxylin-eosin stained section reveals eosinophilic, thin, spindle shaped cells with oval nuclei. Most of the cells are Schwaan cells.

### Treatment

Disfiguring neurofibromas may be surgically excised.

## VON HIPPEL-LINDAU SYNDROME

It is inherited as an autosomal dominant disorder. It consists of angiomas of the retina and

benign hemangioblastomas of the cerebellum. Cutaneous hemangiomas are conspicuously absent. Other features include pheochromocytoma, hypernephroma of the kidney, pancreatic and renal cysts, angiomas of the liver, and polycythemia vera.

## STURGE-WEBER SYNDROME

It is a congenital vascular malformation affecting the vessels of the cortical leptomeninges and skin, usually over the ipsilateral trigeminal distribution. The angiomatous change in the central nervous system is responsible for seizures, contralateral hemiplegia, ipsilateral intracranial calcification, and mental retardation. The skin lesion is a flat nevus flammeus. If cutaneous hemangioma is localized below the palpebral fissure, then intracranial changes do not occur. Skiagram of the skull reveals the characteristic intracranial convolutional calcification. These occur on the same side as the hemangioma and appear as doubly contoured, curvilinear densities resembling a 'tramline'. Eye involvement occurs in one third of the patients and may manifest as glaucoma, buphthalmos, angiomas of the choroid, and hemianopic visual defect.

### Diagnosis

It is clinical. It may be supplemented by radiological examination of the skull.

### Treatment

Control of the seizures, using the anticonvulsants is the objective of the treatment in Sturge-Weber's syndrome. The patient is best managed by a neurologist.

# 38 Chapter Acquired Immunodeficiency Syndrome

The term AIDS (Acquired Immunodeficiency Syndrome) refers to the most severe clinical manifestations of infection with the human immunodeficiency virus (HIV). The infection persists for life and an individual may develop clinical manifestations defining AIDS after a varying interval of time. This progression to AIDS reflects the gradual deterioration of the host's immune system characterized by the depletion of the CD4 helper/inducer lymphocytes. Soon after the person becomes infected, the numbers of CD4 lymphocytes begin to drop from its normal value of about 1000 cells per $mm^3$, at a variable rate of approximately 40 to 80 cells per $mm^3$ per year. This progressive deterioration of the immune system is initially manifested as generalized lymphadenopathy, diarrhea, and weight loss. The AIDS defining conditions develop when the counts of CD4 lymphocytes fall below 200 per $mm^3$.

Center for Disease Control (CDC) had defined AIDS as a disease indicative of a defect in cell-mediated immunity occurring in a person with no cause for immunodeficiency other than HIV. Now it has incorporated the CD4 lymphocyte counts below 200 per $mm^3$ in its revised definition. The major diseases that are considered to indicate a defect in cell-mediated immunity and thus define a person as having AIDS are listed in Table 38.1.

However, extensive investigations of infections and immunity may not be possible in developing countries. To overcome these difficulties, World Health Organisation (WHO) has suggested a case definition for use in these developing countries (Table 38.2).

AIDS in an adult is diagnosed if atleast 2 major and 1 minor signs are present in the absence of known cause of immunosuppression.

The etiologic or causative agent of acquired immunodeficiency virus is retrovirus, i.e. the human immunodeficiency virus (HIV). It was first isolated in 1983 by Luc Montagnies and his colleagues Francois Barre-Sinoussi and Jean-Claude Chermann from an enlarged lymph node. It was termed as lymphadenopathy associated virus. Since then the nomenclature of the virus has been repeatedly changed (Table 38.3).

In 1987, a new retrovirus was identified. It was termed HIV-2 and the original HIV was redesignated HIV-1. The HIV-2 is related to HIV-1 in overall structure and both cause AIDS. However, the pathogenic potential of HIV-2 is not well-established. Furthermore, HIV-2 grows readily in man, monkey, and apes, whereas HIV-1 infects only humans and chimpanzees. Also HIV-2 infection occurs predominantly in West Africa whereas HIV-1 infection predominates in east, central, and southern Africa. The salient features of HIV are summarized in Table 38.4.

**Table 38.1: CDC case definition of AIDS**

- *Protozoal*
  *Pneumocystis carinii* pneumonia (PCP)
  Toxoplasmosis of the brain
  Cryptosporidiosis with diarrhea > 1 month.
- *Fungal*
  Candidiasis—esophageal, tracheal, bronchial or pulmonary (oral thrush alone is insufficient for diagnosis of AIDS)
  *Cryptococcus meningitis* (or other extrapulmonary site).
- *Viral*
  Cytomegalovirus (CMV)—retinitis, pneumonitis, colitis, or encephalitis.
  Herpes simplex-mucocutaneous disease > 1 month
  Progressive multifocal leukoencephalopathy (PML).
- *Bacterial*
  *Mycobacterium avium intracellulare* (MAI) or *M. kansasii* —disseminated.
  *Mycobacterium tuberculosis* (if extrapulmonary and not confined only to lymph glands in a patient who is HIV antibody positive).
  Recurrent non typhoid *Salmonella septicaemia* (if patient HIV antibody positive).
- *Tumors*
  Kaposi's sarcoma : any age if HIV antibody +ve : (< 60 if HIV status unknown)
  Primary CNS lymphoma Non-Hodgkin's lymphoma of B cell type (only if patient HIV antibody +ve).
- *Others*
  HIV encephalopathy (HIV brain and spinal cord disease/AIDS dementia complex—if patient
  HIV antibody +ve) HIV wasting syndrome (Slim disease)—if patient HIV antibody +ve
  Lymphoid interstitial pneumonia (LIP) in a child < 13 years.

**Table 38.2: WHO case definition of AIDS**

*Major Signs*
1. Weight loss > 10% of body weight.
2. Chronic diarrhea > 1 month.
3. Fever > 1 month (intermittent or constant).

*Minor Signs*
1. Persistent cough > 1 month.
2. General pruritic dermatitis.
3. Recurrent herpes zoster.
4. Oropharyngeal candidiasis.
5. Chronic progressive and disseminated herpes simples infections.
6. Generalized lymphadenopathy.

**Table 38.3: Nomenclature of AIDS virus**

| | | |
|---|---|---|
| 1983 | : | Lymphadenopathy associated virus (LAV) |
| 1984 | : | Human T-lymphotropic virus type 3 (HTLV-3): AIDS related virus (ARV) |
| 1986 | : | Human immunodeficiency virus (HIV) |
| 1987 | : | HIV-1 and HIV-2 |

**Table 38.4: Salient features of HIV**

1. It belongs to the *lentivirus* subfamily of retroviruses.
2. The genetic information is encoded in 2 strands of RNA.
3. The RNA is surrounded by 2 protein coats, namely p 18 and p 24.
4. It possesses a spiked envelope. The outer portion of the spike is called gp 120. The stalk that penetrates the envelope is called gp 41.
5. The 3 genes common to all retroviruses are *gag, pol* and *env.*
   *Gag* codes for p 24 and p 18,
   *Pol* codes for the enzyme reverset transcriptase and
   *Env* codes for the synthesis of gp 120 and gp 41.
6. It also contains nonstructural genes *tat, art, 3'orf* .
   *Tat* is essential for viral replication and acts as a transactivating factor, acting both on transcription, and posttranscriptional modification of all viral proteins.
   *Art* acts to enhance the synthesis of viral structural proteins by promoting active translation of viral mRNA.
7. HIV infects cells bearing CD4 receptors. gp 120 virus projections bind to CD4 receptors on T helper lymphocytes.
8. The virus then enters the target cell by fusing directly with host cell membrane.
9. A double stranded DNA (provirus) is formed from viral RNA utilizing the enzyme reverse transcriptase.
10. The provirus integrates into host cell's DNA.
11. The provirus remains sequestered from host immune defences within the CD4 lymphocytes.
12. It may be activated to transcribe mRNA and genomic RNA, leading to protein synthesis, assembly, and new virion formation.
13. Mitogens, antigens, and cytokines such as tumor necrosis factor alpha (TNF-$\alpha$), IL-6, and granulocyte-macrophage colony stimulating factor (GM-CSF) may induce the active replication of the latent virus.
14. New viruses bud out from the host cell membrane.
15. The newly formed gp 120 spikes bind to surrounding CD4 molecules on adjacent cells, and tear holes in their membrane. The punctured cells swell and die.
16. Syncytium may form when the gp 120 of infected cell binds to CD4 receptor on healthy cells. Thus many cells fuse to form the giant cell "Syncytium". Syncytia die soon after formation.

The manifestation of AIDS are secondary to the defects in the cell-mediated immunity. The main cause of the immune defect in AIDS is a quantitative and qualitative deficiency of the helper/inducer lymphocytes. The CD4 (helper/inducer) lymphocyte has been described as the conductor of immunological orchestra and influences the function of many other cells in the immune system. The immune abnormalities in AIDS are summarized in Table 38.5.

AIDS selectively affects "at risk" individuals namely:

- Homosexuals
- Drug abusers
- Haitians
- Hemophiliacs
- Blood transfusion recipients
- Sexual partners of AIDS patients
- Offsprings of AIDS patients

AIDS can be transmitted through the following routes:

- Infected body secretions—semen and saliva
- Infected needles in intravenous drug users
- Factor VIII concentrates prepared from pooled plasma
- Other blood transfusion products
- Transplacental/perinatal/postnatal

Incubation period usually is less than 5 years with a mean of 27.5 months.

## CLINICAL FEATURES

HIV infection is conceived to form a spectrum of clinical manifestations associated with immune dysfunction. This spectrum reflects the progression of HIV infection from the appearance of initial signs and symptoms through a long asymptomatic period with or without development of generalized

**Table 38.5: Immunological abnormalities in AIDS**

I. Defect in T cells
   (a) Lymphopenia
   (b) Reduced CD4 (helper/inducer) lymphocytes
   (c) Interference of the interaction between CD4 molecule and its natural ligand, major histocompatibility (MHC) class II molecule by HIV protein.
   (d) Elevation in the number of CD8 (suppressor/cytotoxic) lymphocytes.
   (e) Inversion of the normal CD4: CD8 ratio.
   (f) Abnormalities in the function of CD8 lymphocytes.
   (g) Decreased or absent delayed hypersensitivity to both recall and new antigens.
   (h) Decreased *in vitro* lymphocyte proliferation responses to
      1. Mitogens
      2. Antigens
      3. Alloantigens

II. Defects in B-cells
   (a) Abnormality of B-lymphocyte function and immunoregulation
   (b) Polyclonal activation of B-cells
   (c) Hypergammaglobulinemia
   (d) Circulating immune complexes (CIC)
   (e) Defective *de novo* antibody response to new antigens.

III. Natural killer cells
   (a) Defective natural killer (NK) cell function that can be restored by *in vitro* addition of interleukin-2.

IV. Monocytes
   (a) Functional abnormalities
      1. Defective chemotaxis
      2. Defective cytotoxic function
      3. Defective presentation of antigens to T-cells
      4. Defective secretion of interleukin-1

V. Others
   (a) Circulating acid-labile alpha interferon
   (b) Nonspecific antilymphocyte antibodies
   (c) Elevated alpha-1 thymosin levels
   (d) Elevated beta-2 microglobulin levels
   (e) Decreased serum thymulin levels
   (f) Increasing soluble interleukin-2 receptor level

lymphadenopathy to the development of AIDS. The CDC classification of HIV disease is shown in Table 38.6.

Another classification for adult patients with HIV infection is the Walter Reed's (WR) classification. The patient is thoroughly examined for the clinical manifestations of HIV disease, screened for antibodies to HIV using ELISA, the positive results of which are then confirmed by Western blot, a T-helper cell count is obtained, and also anergy screen is done by skin testing with mumps, tetanus, trichophyton, and monilial antigens. Patient is then graded on the basis of these results.

WR0: Antibody negative patient with sexual contact with patient with HIV infection.

WR1: Positive culture for, or 2 positive Western blots to HIV.

WR2: 2 positive western blots and chronic lymphadenopathy

WR3: 2 positive western blots and persistent T helper cell depletion.

**Table 38.6: CDC classification of HIV disease**

Group I : Primary HIV Infection
Group II : Asymptomatic Infection
Group III : Generalized lymphadenopathy
Group IV : AIDS
- Subgroup A: Constitutional disease
- Subgroup B: Neurologic disease
- Subgroup C: Secondary infectious disease
  - C-1: Specified infections from surveillance definition of AIDS
    - *Pneumocystis carinii* pneumonia
    - Cryptosporidiosis, chronic
    - Isosporiasis
    - Strongyloidiasis, extraintestinal
    - Candidiasis of esophagus, trachea or bronchi
    - Cryptococcosis, extrapulmonary
    - Histoplasmosis, disseminated
    - *Mycobacterium avium-intercellulare* or *M. kansasii* disseminated
    - Cytomegalovirus infection
    - Herpes simplex, chronic mucocutaneous or disseminated
    - Progressive multifocal leukoencephalopathy
  - C-2: Other specified infectious diseases
    - Hairy leukoplakia, oral
    - Multidermatomal herpes zoster
    - Recurrent *Salmonella* bacteremia
    - Nocardiosis
    - *M. tuberculosis*, extrapulmonary
    - Oral thrush
- Subgroup D: Secondary cancers
  - Kaposi's sarcoma
  - Non-Hodgkin's lymphoma
  - Primary lymphoma of the brain
- Subgroup E : Others

WR4: 2 positive western blots, persistent T helper cell depletion and partial defects in delayed hypersensitivity (DH).

WR5: 2 positive western blots, T helper cell depletion, and either a clinical thrush or persistent energy.

WR6: 2 positive western blots and an opportunistic infection.

The majority of individuals do not experience any sign and symptom at the time of primary infection. However, some may develop fever, rigors, athralgias, myalgias, diarrhea, and aseptic meningitis 3 to 6 weeks after infection. These constitutional symptoms may last for 2 to 3 weeks and then resolve spontaneously.

The acute illness of primary infection is followed by a period of asymptomatic infection. Eight to ten years may elapse before the development of full blown AIDS. Eighty to ninety percent of the infected patients will reveal immunologic deterioration within 3 years of infection, though the clinical symptoms may be lacking. Approximately 75 percent of infected individuals develop some symptoms within the first 7 years.

Certain individuals develop persistent generalized lymphadenopathy (PGL) characterized by enlargement of lymph nodes greater than 1 cm at two or more extrainguinal sites that persists for more than 3 months, in the absence of concurrent illness or condition other than HIV infection to explain the lymphadenopathy.

After the varying interval of 8 to 10 years, the patients develops full blown AIDS. This may be heralded by the following:

- Fever persisting for more than 1 month
- Involuntary weight loss greater than 10 percent
- Diarrhea persisting for more than 1 month.

The constitutional symptoms may be followed by secondary infections. The microorganisms that rarely cause disease in immunologically normal people may be responsible for opportunistic infections in AIDS. The most common sites for such secondary infections are the lungs, pharynx, esophagus, small intestine, bowel, colon, bloodstream, central nervous system, and skin. Systemic manifestations may differ from organ to organ.

*Cutaneous manifestations*: The skin is commonly affected in patients with human immunodeficiency (HIV) infection. Viral, bacterial, fungal, protozoal infections, and ectoparasitic infestation may affect the skin primarily or secondarily. The clinical features are cardinal. However, the lesion bend to be severe, persistent, and resistant to treatment. Unusual inflammatory dermatoses and neoplasms may develop (Table 38.7).

**Table 38.7: Cutaneous manifestations of AIDS**

| | |
|---|---|
| I | Neoplastic |
| | Kaposi's sarcoma |
| | B-cell lymphoma |
| | Squamous cell carcinoma |
| | Basal cell carcinoma |
| II | Viral infections |
| | Herpes zoster |
| | Herpes simplex |
| | *Molluscum contagiosum* |
| | Warts |
| | *Condylomata acuminata* |
| | Cytomegalovirus infection |
| | Oral hairy leukoplakia |
| III | Bacterial infection |
| | Pyodermas, some due to commensal floras |
| | Ulcers (*Pseudomonas* and polymicrobial) |
| IV | Spirochetal |
| | Atypical/malignant syphilis |
| V | Mycobacterial |
| | Disseminated cutaneous tuberculosis |
| | Atypical mycobacterial infection |
| VI | Candidiasis |
| VII | Fungal infection |
| | Dermatophytosis |
| | Pityriasis versicolor |
| | Cryptococcosis |
| | Histoplasmosis |
| VIII | Protozoal |
| | Amebiasis cutis |
| IX | Arthropoid infestation |
| | Scabies (Norwegian) |
| X | Vascular lesions |
| | Vasculitis |
| | Telangiectasia |
| | Thrombocytopenic purpura |
| | Pseudothrombophlebitis, hyperalgisic |
| XI | Papulosquamous |
| | Psoriasis |
| | Seborrheic dermatitis |
| XII | Oral |
| | Apthous ulcers |
| | Gingivitis |
| XIII | Hairs |
| | Premature greying |
| | Telogen effluvium |
| XIV | Nails |
| | Color changes |
| | Deformities |
| XV | Miscellaneous |
| | Exanthems |
| | Xerosis |
| | Ichthyosis |
| | Pruritus. |

*Kaposi's sarcoma:* It presents with one or more asymptomatic faint pink to red macules, papules, blue purple plaques or nodules of variable size. These lesions differ from classic Kaposi's sarcoma by their generally smaller size, tendency to elongate along lines of cutaneous cleavage, and their lack of propensity to involve primarily the lower extremities. Some patients have persistant generalized lymphadenopathy before the onset of the cutaneous lesions. Kaposi's sarcoma in AIDS patiens also has a high incidence of visceral involvment. Chemotherapeutic regimens comprising donorubicin, bleomycin vinblastine have been largely ineffective and have shown complete response in only 15 percent of AIDS Kaposi's sarcoma (Table 38.8).

## DIAGNOSIS

The diagnosis of HIV infection is accomplished by performing a battery of diagnostic tests. The most widely used is a test for HIV antibody employing enzyme-linked immunosorbent assay (ELISA). This sensitive test is useful in screening large number of individuals for HIV infection. More than 95 percent of HIV infected persons will be identified as positive by ELISA within 3 months of infection. Its major disadvantage is the relatively high incidence of false-positive reactions. The rate of false-positive reactions with first generation ELISA, which employs lysates from the HIV infected cells as a source of antigen, has been reduced with second generation ELISA, that utilizes recombinant DNA protein as a source of antigen. All positive ELISA tests should be

**Table 38.8: Differences between classical and epidemic (AIDS) Kaposi's sarcoma**

| | *Classical Kaposi's sarcoma* | *Epidemic (AIDS) Kaposi's sarcoma* |
|---|---|---|
| Risk group | Affects older individuals usually in 6th or 7th decade | Young homosexual men. May also affect intravenous drug users, hemophiliacs. |
| Lesions | Bluish red or dark brown plaques or nodules | Bluish red or dark brown papules, plaques or nodules. |
| Size | Large | Small |
| Number | A few | Multifocal and widespread oval, arranged along lines of body cleavage in mirror image distribution. |
| Location | Lower extremities | Trunk, head, and neck |
| Mucosal involvement | May or may not be present | Adjacent mucosae frequently involved |
| Lymph node Involvement | Involved in only 10 percent cases | Frequent. More than half of the patients have generalized lymphadenopathy at presentation. KS may involve lymph nodes in the absence of skin and mucosal lesion. |
| Visceral involvement | Uncommon | May involve all viscera except brain |
| Histopathology | 1. Vascular formation<br>2. Spindle cell formation containing vascular slits<br>3. Inflammatory reaction resembling 'Granulation tissue' | 1. Dissection of collagen<br>2. Lymphatic vessel like space<br>3. Angiomatoid proliferation<br>4. Premonitory sign<br>5. Spindle cell proliferation |
| Treatment | Surgical excision, radiation therapy, combination chemotherapy | Immune rescue more effective than chemotherapy.<br>1. Human gamma interferon<br>2. Combination chemotherapy |

repeated and if the repeat test is also positive, it should be confirmed by a more specific test for the antibody.

The more specific antibody test used to confirm results of ELISA is the western blot. The western blot assay, expensive and more specific, is a confirmatory test and rules out false-positive results. It identifies antibodies against specific viral proteins such as p24, the major HIV protein, and gp41, gp120, and gp160, the transmembrane and viral envelope proteins. The radioimmunoprecipitation assay (RIPA) is used in research laboratories to further clarify atypical or indeterminate western blot results. However, it presents difficulty in standardization, sensitivity, and specificity.

The above tests rely upon the detection of antibodies to HIV. However, the antibodies do not appear for weeks or months, following infection. Ninety-five percent of infected indivi-duals develop antibodies within 5 months of infection. Occasionally, the antibody response may be delayed for 3 to 4 years. Under these circumstances, demonstration of the virus is necessary for the diagnosis of HIV infection. The test devised include detection of p24 antigen, the major core protein of HIV. It is useful for monitoring the efficacy of the therapy. A latex agglutination test has been developed that detects gp120, the major HIV envelope glycoprotein.

Another highly sensitive test for detecting the virus is the polymerase chain reaction (PCR), which selectively amplifies viral genomeallowing detection of HIV DNA present at very low levels in infected cells.

Viral culture remains the ultimate for diagnosing the HIV infection. The test procedure, however, is technically difficult, and expensive.

A brief summary of the diagnostic tests for HIV infection is given in Table 38.9.

A summary of the evolution of HIV markers following infection with HIV is given in Table 38.10.

Besides the diagnostic test for AIDS, a battery of other investigation should be performed in AIDS (Table 38.11).

## TREATMENT

The goals of AIDS therapy are amelioration of symptoms in 'fullblown' AIDS, prevention of disease progression, and/or treatment of Kaposi's sarcoma and opportunistic infections. There are the following four broad approaches to achieve these goals:

1. Anti-retroviral agents.
2. Immunorestorative therapy.
3. General management.
4. Treatment and or prophylaxis of specific opportunist infections or tumors.

Antiretroviral agents The different stages in the life cycle of HIV present a variety of targets for antiviral agents (Table 38.12).

Zidovudine (3'-azido-3'-deoxythymidine, AZT) has been licensed for use in AIDS. It is a potent chain terminator of HIV reverse transcriptase. It suppresses and not eliminates viral replication in circulating lymphocytes. Circulating HIV antigen (p24) is reduced during treatment. However, it is possible to isolate virus from the cells by cocultivation. If therapy is reduced or discontinued, levels of circulating p 24 antigen rises rapidly. This reinforces the fact that life-long antiretroviral therapy is necessary.

It is well-absorbed from the gastrointestinal tract after oral administration. Its bioavailability is 60 percent and the levels that inhibit HIV replication can be achieved in patients. The half-life of AZT is 1 hour and most of the drug is cleared by hepatic glucuronidation and renal tubular secretion. It also crosses the blood-brain barrier.

**Table 38.9: Diagnostic tests for HIV infection**

| *Tests* | *Advantages* | *Disadvantages* | *Status* |
|---|---|---|---|
| 1. ELISA | | | |
| 1st generation | Sensitive | False-positive reactions | Screening test |
| 2nd generation | Lower incidence of false-positive reactions | Sensitive | Screening test |
| 2. Western blot | Specific<br>Rules out false-positive results of ELISA | Expensive | Diagnostic |
| 3. RIPA | Clarifies atypical or indeterminate Western blots | Not yet standardized | For research |
| 4. Detection of p24 antigen | Useful for monitoring the efficacy of antiviral therapy | p24 may not be detectable during the course of disease in some | Not yet used routinely |
| 5. Latex agglutination test to detect gp120 | Inexpensive, rapid, easy to use | Unstable, unreliable | Not routinely used |
| 6. Polymerase chain reaction (PCR) | Highly sensitive test<br>Detects even non-replicating virus | False-positive results can occur | Not well standardized as yet |
| 7. Viral culture | Most specific test | Technically difficult<br>Expensive | Not for routine use |

**Table 38.10: Summary of evolution of markers for HIV infection**

| *Stages of infection* | *p24 antigen* | *anti-HIV* | *Western blot pattern* |
|---|---|---|---|
| Immediately after infection | — → + | — | — |
| Acute illness | + → — | ± → + | Restricted, often p24 and/or gp120 |
| Carrier, asymptomatic | — | + | Full pattern |
| Carrier, with symptomatic PCL | + | + | Loss of anti-p24 |
| AIDS | + | + | Absence of anti-p24 |

**Table 38.11: Other tests to be performed in AIDS**

1. Hemoglobin concentration
2. Total and differential leukocyte counts
3. Quantitation of CD4 and CD8 lymphocytes
4. Platelet counts
5. Serologic tests for syphilis
6. β-microglobulin level
7. Hepatitis B and toxoplasma serology
8. Skin tests for tuberculosis and one or more control antigens
9. Skiagram of the chest.

**Table 38.12: Sites for antiretroviral activity**

| *Stage in viral replication* | *Antiviral agents* |
|---|---|
| 1. Absorption | Soluble CD4; dextran sulfate; sulphated polysaccharides; peptide T; oligopeptides |
| 2. Entry to cell | Membrane stabilizer AL-721 |
| 3. Uncoating | — |
| 4. Reverse transcriptase | Inhibitors—suramin, phosphono-formate, HPA-23<br>Rifabutin<br>Chain terminators—3'-azido-3' deoxythymidine (zidovidine), 2'-3' dideoxycytidine (dd C), dideoxyinosine (dd I), fluorothymidine |
| 5. Integration | — |
| 6. Activation | Cyclosporin A |
| 7. Transcription | *art* inhibitor-oligonucleotides |
| 8. Translation | Ribaravin<br>*tat* inhibitor<br>pencillamine |
| 9. Post-translation modification | Inhibition of virus-specific protase avorol |
| 10. Glycosylation | Castanospermine deoxynoijmycin |
| 11. Protein kinase C | Xanthote glycryrhizin |
| 12. Assembly | Interferons suramin |
| 13. Budding | Hypericine interferons |
| 14. Syncytial formation | CD4 blocking agents |

It can induce clinical, immunologic, and virologic benefits in patients with severe HIV infection. Patients receiving it have increase in the weight, improved immune function, and decreased incidence of opportunistic infection. The quality of life and survival rate also improves with AZT.

The principal toxicity of AZT is bone marrow suppression. Anemia and leukopenia are frequently observed. Other side effects include headache, nausea, and vomiting. Some patients develop myalgia. Also vitamin $B_{12}$ deficiency has been reported in AIDS patient receiving AZT.

Other dideoxynucleosides such as 2'3'- deodycytidine (dd C) and 2'3'dideoxy adnosine (dd A) are under trial as HIV agents.

The details of zidovudine, dd C and dd A are given in Table 38.13.

## Immunorestorative Therapy

The immunorestorative therapy relies upon the use of: (i) interferons, (ii) interleukin-2, (iii) bone marrow transplantation, (iv) infusion of histocompatible lymphocytes.

Interferons are polypeptides classified into interferon-alpha (1FN-α), interferon-beta (1FN-β), and interferon-gamma (1FN-γ), based upon different antigenic, physiochemical, and biological basis. They were initially regarded as antiviral substances, but their antiproliferative, antitumoral, and immunomodulator properties have been established. Their use in AIDS are summarized in Table 38.14.

**Table 38.13: Antiviral agents in the treatment of HIV infection**

| *Antiretroviral* | *Mode of action* | *Activity* | *Dose* | *Adverse effects* | *Other notes* |
|---|---|---|---|---|---|
| Reverse Transcriptase Inhibitors (RTI)<br>a) Nucleoside RTI<br>1) Zidovudine (AZT) | Nucleoside analogues are structurally similar to the natural dideoxynucleosides that the HIV reverse transcriptase incorporates into a growing, complementary DNA strand. The nucleoside analogues are incorporated into the growing DNA strand and prevent subsequent elongation | 1. Rise in CD4 + count of 50 x $10^6$/liter<br>2. Fall in RNA of about 0.5log<br>3. Initiation of AZT mono-therapy in asymptomatic patient is associated with a reduced progression of disease<br>4. AZT < ddI<br>AZT < AZT + ddI<br>AZT < AZT + ddc | *Adults:* 600 mg/day, either as 200 mg every 8 hours of 300 mg every 12 hours<br>*Pediatric*<br>180 mg/$m^2$ every 6 hour | Neutropenia, and anemia; macrocytosis, nausea, headache, and insomnia<br>Myositis and elevation of cretainine phosphokinase, muscle tenderness and wasting | 1. AZT is glucuronidated in liver to an inactive metabolite that is excreted by kidneys<br>2. Probenecid decrease the renal excretion or inhibits the metabolism of AZT: Concomitant administration of these agents may result in flu like symptoms<br>3. Concomitant administration of agents may increase the toxicity |
| 2) ddC (Zalcitabine) | Nucleoside analogues are structurally similar to the natural dideoxynucleosides that the HIV reverse transcriptase incorporates into a growing, complementary DNA strand. The nucleoside analogues are incorporated into the growing DNA strand and prevent subsequent elongation . Most potent of the antiretroviral nucleoside analogue | AZT + ddC > AZT<br>ddC > ddI<br>Suppression of HIV replication<br>AZT/ddC = AZT/ddI<br>CD4 + cell rise<br>AZT + ddC < AZT + ddI | *Adults* 0.75 mg every 8 hour | Peripheral neuropathy<br>Burning sensation and pain in the distal extremities<br>Pancreatitis, hepatitis, aphthous ulceration of the mouth and esophagus<br>Rash and stomatitis<br>Anemia, leukopenia, and thrombocytopenia<br>Fever, malasie, ototoxicity | 1. ddC should be taken empty stomach<br>2. Magnesium and aluminium containing antacids may decrease the bioavailability ddC. Probenecid increases it<br>3. ddC is eliminated by kidneys and concomitant administration of nephrotoxic drugs may potentially increase the risk of toxicity<br>4. ddC should be used cautiously in combination with drug that may cause peripheral neuropathy or pancreatitis. |
| 3) ddI (didanosine) | Nucleoside analogues are structurally similar to the natural dideoxynucleosides that the HIV reverse transcriptase incorporates into a growing, complementary DNA strand. The nucleoside analogues are incorporated into the growing DNA strand and prevent subsequent elongation<br>ddI is a prodrug for the active intracellular metabolite dd ATP | AZT/ddI > AZT (Both AZT naïve and AZT-experienced patients) | ddI is available as chewable tablet, and powder for oral solution<br>*Adult:* 200 mg every 12 hr for pts ≥ 60 kg<br>125 mg every 12 h for pts ≤ 60 kg | Reversible peripheral neuropathy<br>Pancreatitis, hepatitis<br>Headache, insomnia<br>Uric acid elevation<br>Rash, seizures | ddI is acid labile and is formulated with buffering agents to increase its bioavailability. Concomitant administration of ddI with drugs that require gastric acid for absorption (Ketoconazole, itracona-zole) results in decreased bioavail-ability of these drugs |

*(Contd...)*

*(Contd...)*

| *Antiretroviral* | *Mode of action* | *Activity* | *Dose* | *Adverse effects* | *Other notes* |
|---|---|---|---|---|---|
| Reverse transcriptase | | | | | |
| 4) d 4T (stavudine) | Nucleoside analogues are structurally similar to the natural dideoxynucleosides that the HIV reverse transcriptase incorporates into a growing complementary DNA strand. The nucleoside analogues are incorporated into the growing DNA strand and prevent subsequent elongation | 1. d 4T > AZT (in AZT experienced patients) d4T is<br>a) better tolerated<br>b) produces greater gains in weight<br>c) results in better life quality<br>2. d4 T/ddI results in 1 log fall in HIV load in 50% of patients<br>3. d4T/3TC is well tolerated and is associated with a rise in CD4 and a fall in HIV load of up to 2 log. | *Adults:*<br>Body weight ≥ 60 kg<br>40mg every 12 hours<br>Body weight ≤ 60 kg<br>30mg every 12 hours<br>*Pediatric*<br>0.125 to 2 mg/kg every 12hrs | Peripheral neuropathy<br>Anemia, neutropenia<br>GIT disturbance and pancreatics<br>Elevated hepatic transaminases | d 4T must be used cautiously in combination with other agents that cause peripheral neuropathy (isoniazid and metronidazole) |
| 5) 3 TC (Lamivudine) | Nucleoside analogues are structurally similar to the natural dideoxynucleosides that the HIV reverse transcriptase incorporates into a growing , complementary DNA strand. The nucleoside analogues are incorporated into the growing DNA strand and prevent subsequent elongated | 1. 3 TC monotherapy produces a rapid but transient fall in RNA levels<br>2. Loss of HIV suppression is associated with a rapid development of resistance resulting from a single point mutation at codon 184 of HIV RT<br>3. AZT/ 3TC combination produces a prolonged and sustained CD4+ elevation<br>4. In AZT naïve patients, 3TC/ AZT produces a sustained suppression of HIV RNA at 1year and an increase in CD4 + counts of 80 x $10^6$/liter<br>5. AZT/3TC produces a 30-40 x $10^6$/liter increase in CD4+ and 0.5 log fall in HIV in AZT treated cases | *Adults*<br>Body weight ≥ 50 kg<br>150 mg every 12 hour<br>Body weight ≤ 50 kg<br>2 mg/kg body weight every 12 hours | Elevation of serum amylase Panceratitis peripheral neuropathy | 1. 3 TC may be taken without regards to meals<br>2. 3 TC increase peak serum levels of AZT |
| b)Non nucleoside RTI (NNRTI) | | | | | |
| 1) Nevirapine | NNRTI are structurally dissimilar to the nucleoside RTIs and bind at distinct sites on the RT enzyme | 1. Exerts transient antiretroviral effect that wanes with the development of nevirapine resistance<br>2. AZT/ddI/navirapine (greater viral load suppression at | 200 mg orally, once a day, for 14 days followed by 200 mg twice a day | Skin rash fatigue<br>Diarrhea raised<br>liver function tests<br>Headache and depression | 1. Nevirapine may be taken without regards to meal<br>2. Patients may be instructed to report any skin rash while receiving the drug<br>3. It decrease AZT bioavailability |

*(Contd...)*

*(Contd...)*

| *Antiretroviral* | *Mode of action* | *Activity* | *Dose* | *Adverse effects* | *Other notes* |
|---|---|---|---|---|---|
| | | and more sustained 8 weeks CD4+ rise)<br>3. AZT naïve, asymptomatic patients treated with AZT/ddl/nevirapine experience an increase in CD4+ count of 100 × $10^6$/liter and 50% have viral load suppression to fewer than 20 copies/mL<br>4. Rapid resistance on mono-therapy with nevirapine | | | 4. It induces liver enzymes and has the potential to intact with drug metabolized through cytochrome p 450<br>5. Rifampicin must not be administered commitanly with nevirapine |
| 2)Delaviridine | NNRTI are structurally dissimilar to the nucleoside RTIs and bind at distinct Sites on RT enzyme | AZT/delaviridine = ddl/delaviridine<br>AZT/delaviridine results in<br>a. decrease in viral RNA of 0.5 log<br>b. CD4+ increase of 20-30 × $10^6$/liter | 400 mg thrice a day | Skin, rash Headache fatigue, GI disturbance Elevation in LFT Anemia thrombocytopenia and neutropenia | 1. Delaviridine should be taken with an acidic beverage<br>2. It may be taken without regards to marks<br>3. Patients must be advised to report in case any rash develops<br>4. Drugs that decrease gastric acidity (antacids, $H_2$ receptor antagonist decrease delaviridine absorption<br>5. Concomitant administration of ddI decreases bioavailability of delaviridine<br>6. It is a cytochrome P 450 3A inhibitor |
| Protease inhibitor | | | | | |
| 1) Saquinqvir | Inhibitors of the HIV protease are potent agents with differing structures that bind at distinct sites on the HIV protease active sites. They suppress HIV replication by inhibiting proteolysis of viral gag and gag-pol polyproteins, rendering progeny virus non-infectious. Protease inhibitors may reduce the HIV load by up to 1000-fold (3 log) and may produce a sustained increase in the CD4+ cell count | 1. At standard doses, squinavir exerts a less potent anti-retroviral suppression and has less sustained CD4+ cell response than indinavir and ritonavir , Saquinavir < indinavir, ritonavir<br>2. In AZT naïve patients, the combination of saquinavir and AZT produces<br>a) 1log reduction in HIV load<br>b) 70 × $10^6$/liter rise in CD4+ count<br>3. AZT/3TC/saquinavir causes a peak fall in viral load of over 2log and a peak increase in CD4+ count of 150 x $10^6$/liter | saquinavir is available as 200 mg capsules *Adults:* 600 mg (3 × 200) three times a day *Pediatrics:* Safety of saquinavir in the age group is not established | GI disturbances, elevated liver function test, jaundice, seizures, headache, rash | 1. Patients should be instructed to take saquinavir within 2 hrs of a full meal and each dose should comprise of 3 200 mg capsules<br>2. Saquinavir has low bioavailability and extensive first pass metabolism by liver<br>3. It is metabolized by the hepatic cytochrome p 450. Degradation of saquinavir is inhibited by ketoconazole, and the protease inhibitor ritonavir |

*(Contd...)*

*(Contd...)*

| *Antiretroviral* | *Mode of action* | *Activity* | *Dose* | *Adverse effects* | *Other notes* |
|---|---|---|---|---|---|
| | | 4. In AZT experienced patients the combination of AZT/ddC saquinavir causes a more modest reduction in viral load (0.5 log) and increase in CD4 + cell counts (25 x $10^6$/liter)<br>5. ddC/ saquinavir $\geq$ ddC | | | |
| 2) Ritonavir | Inhibitors of the HIV protease are potent agents with differing structures that bind at distinct sites on the HIV protease active site. They suppress HIV-replication by inhibiting proteolysis of viral gag and gag-pol polyproteins, rendering progeny virus non-infectious. Protease inhibitors may reduce the HIV load by up to 1000 fold (3log) and may produce a sustained increase in the CD4+ cell count | 1. s monotherapy, ritonavir potently suppresses viral load (a 1.2-2 log reduction at 2 weeks) accompanied by an average increase in CD4+ count of 200 × $10^6$/liter<br>2. AZT/ddc/ritonavir combination sustains the above effects for 6 or more months<br>3. In patients with advanced HIV disease with CD4+ well counts below 100 × $10^6$/liter addition of ritonavir to a stable regimen of nucleoside analogue therapy, results in modest effects<br>a) 0.6 log viral load suppression<br>b) 40-50 × $10^6$/liter increase in CD4+ counts<br>Theses effects markedly reduce disease progression and the mortality rate | 600 mg, twice a day with meals | Nausea, diarrhea headache, dizziness circumoral paresthesia vasodilatation, raised hepatic enzymes | 1. Ritonavir should be taken with food<br>2. Ritonavir capsules and solution should be refrigerated<br>3. Caution should be exercised in prescribing ritonavir in patients with hepatic dysfunction |
| 3 ) Indinavir | Inhibitors of the HIV protease are potent agents with differing structures that bind at distinct sites on the HIV protease active site. They suppress HIV-replication by inhibiting proteolysis of viral gag and gag-pol polyproteins, rendering progeny virus non-infectious. Protease inhibitors may reduce the HIV load by up to 1000-fold (3 log) and may produce a sustained increase in the CD4 cell count | 1. Indinavair reduces viral load by 1.5 log at 6 months in previously untreated patients<br>2 Same patients on indinavir monotherapy sustain increase ase of 100 × $10^6$/liter CD4+ cells for more than 1 year<br>3 AZT/indinavir combination therapy shows more marked viral load suppression (1.0-2.6 log), with an average rise in CD4+ count of 100 × $10^6$/liter | *Adults:* 800 mg every 8 hours, taken with water, before or 2 hours after a meal | Nephrolithiasis<br>Asymptomatic indirect hyperbilirubinemia | 1. Patients should be instructed to drink plenty of water to minimize the possibility of nephrolithiasis |

**Table 38.14: Interferons in AIDS**

| *Interferons* | *Doses* | *Effects* |
|---|---|---|
| Alpha-2 interferon | 15 million units/$M^2$ i/v<br>Or<br>1 million units/$M^2$ S/C for 5 days, alternate week for 4 cycles | 1. Augments NK activity<br>2. Useful in Kaposis sarcoma |
| Gamma | 1-10 million units/$m^2$ twice a week by i/v infusion | 1. Augments antibody interferon production<br>2. Increases macrophage tumoricidal activity<br>3. Augments NK activity |

Interleukin-2—it is a glycoprotein released from activated helper T cells in response to either antigen presentation macrophages and Langerhan cells or interleukin-1. It promotes proliferation of activated T cells and promote secretion of lymphokines such as gamma interferon (IFN-γ). It also augments the cytotoxicity of natural killer cells (NK) and lymphocyte activated killer cells (LAK).

It is used either in the natural or recombinant form. The natural form is administered as 24,000 to 1 million units/$M^2$ weekly for 4 weeks. Recombinant interleukin-2 is administered either as 1 million units/kg boiler by infusion or as 3000 to 10,000 units/kg/br by infusion. The immune reconstitution achieved is only temporary.

## RECOMMENDED READING

1. Dover JS, Johnson RA. Cutaneous manifestations of human immunodeficiency virus infection. Part I. *Arch Dermatol* 1991;127:1383-1391.
2. Dover JS, Johnson RA. Cutaneous manifestations of human immunodeficiency virus infection. Part II. *Arch Dermatol* 1991;127:1549-1558.
3. Tappero JW, Conant MA, Wolfe SF, et al. Kaposi's sarcoma. Epidemiology, pathogenesis, histology, clinical spectrum, staging criteria and therapy. *J Am Acad Dermatol* 1993;28:371-395.

# 39 Chapter Mastocytosis

Mastocytosis is a group of disorders characterized by infiltration of the skin and/or internal organs by mast cells. It may present itself either in the form of the following:

I. Cutaneous Mastocytosis
   A. Generalized: Urticaria pigmentosa
      - Maculopapular
      - Telangiectasia macularis eruptiva perstans
      - Diffuse cutaneous mastocytosis.
   B. Localized mastocytoma
II. Systemic mastocytosis
III. Malignant mastocytosis

## CLINICAL MANIFESTATIONS

### Urticaria Pigmentosa (Maculopapular)

It is the most common form of mastocytosis. The onset is in childhood, usually before 2 years of age. There is a symmetric eruption of multiple, small, monomorphic pigmented itchy macules and/or maculopapules over the trunk. Nodules and/or plaques are uncommon. A gentle rubbing/stroking of the lesion produces itching, erythema and whealing. This urticariform reaction, a diagnostic hallmark of mastocytosis is termed Darier's sign. The lesion usually clear by the second decade of life. Occasionally, they may persist into adulthood.

### Telangiectasia Macularis Eruptiva Perstans

It is an uncommon form of mastocytosis, characterized by the eruption of multiple, pruritic, pigmented, telangiectatic macules over the trunk. Urtication on stroking may not be prominent. The lesions are persistent and recal citrant to treatment.

### Diffuse Cutaneous Mastocytosis

It is an uncommon manifestation, characterized by diffuse infiltration of the skin by mast cells. It is associated with generalized intense pruritus. The skin becomes yellowish in color, thickened, leathery and doughy in consistency. Nodules and small tumors may arise over the skin. A generalized erythroderma and/or systemic mastocytosis may develop in some patients.

### Localized Mastocytoma

It is characterized by eruption of single, large cutaneous nodules. Stroking may result in urtication and blister formation. These mastocytoma usually undergo spontaneous resolution.

### Systemic Mastocytosis

It is characterized by infiltration of internal organs by mast cells, with or without cutaneous involvement. Any tissue, except central nervous system may be affected.

Episodic flushing, headache, palpitation, syncope, dyspnea/wheezing, diarrhea, and weight loss are the usual presenting symptoms.

The liver and spleen may be involved, resulting in hepatosplenomegaly. Skeletal involvement may result in vertebral collapse and/or fractures of long bones. Radiological examination may reveal osteoporosis intermingled with osteosclerosis. Mast cell infiltration of small bowel may result in malabsorption and villous atrophy. Hematological abnormalities may be evident as anemia, leukocytosis, and eosinophilia. Mature mast cells may be found in peripheral blood.

The prognosis is guarded in systemic mastocytosis. The disorder tends to persist and the patient's disability depends upon the extent of cutaneous and systemic involvement. Some patients may develop fatal mast cell leukemia.

## DIAGNOSIS

The confirmation of mastocytosis requires demonstration of mast cells in tissue specimens. The biopsy must be taken carefully to avoid urtication and mast cell degranulation. Special stains such as Gram stain, methylene blue, alcian blue, toluidine blue that metachromatically stain the acidophilic granules in mast cell cytoplasm, facilitate the diagnosis. Further investigations such as radiological studies of skeletal and gastrointestinal systems, hematological studies, liver functional test, bone marrow biopsy, urinary estimation of histamine may be undertaken if indicated.

## TREATMENT

It is only symptomatic. Antihistamines may be administered to relieve pruritus. Mastocytomas may be surgically excised.

## RECOMMENDED READING

1. Metcalfe DD. The treatment of mastocytosis: An overview. *J Invest Dermatol* 1991;96:55S-65S.
2. Rothe MJ, Nowak M, Kerdel FA. The mast cell in health and disease. *J Am Acad Dermatol* 1990; 23:615-624.

# 40 Chapter

# Amyloidosis

It is the accumulation of abnormal, fibrillar protein in the tissues. The amyloid proteins may be derived from either: (i) degenerated immunoglobulins or (ii) an acute-phase reactant in serum (amyloid A) or (iii) keratinocytes secondary to epidermal damage. This family of unrelated proteins shares characteristic staining properties and ultrastructural features.

Amyloid proteins may be deposited in multiple organs of the body resulting in systemic amyloidosis. This process may be either primary (in association with underlying occult plasma cell dyscrasia) or secondary (to various chronic diseases). Cutaneous involvement may be a part component of either type. However cutaneous amyloidosis is much more common in primary variant. It manifests as waxy, purpuric papules, nodules and/or plaques. The amyloid protein in such situations is usually derived from immunoglobulin light chains.

Localized amyloidosis may be another manifestation. The amyloid deposits are restricted to a single tissue, and skin may be one such site. The expression of localized cutaneous amyloidosis may either macularamyloidosis, lichen/papular amyloidosis and/or nodular amyloidosis (Table 40.1).

**Table 40.1: Classification**

- Systemic (multiple organs)
  - Primary (occult plasma cell dyscrasia) cutaneous involvement-common
  - Secondary (underlying chronic disease) cutaneous involvement-uncommon
- Localized amyloidosis (single tissue) cutaneous
  - Macular amyloidosis
  - Lichen/papular amyloidosis
  - Nodular/tumefactive amyloidosis

## CLINICAL FEATURES

### Macular Amyloidosis

It manifests as pruritic, grey or dusky brown macules. Rippled and/or reticulated appearance in its cardinal feature. The macules are usually distributed symmetrically over the upper back and the limbs. The lesions tend to persist for many years. The amyloid protein id derived keratinocytes, that undergo filamentous degeneration and apoptosis.

### Lichen Amyloidosis

It is characterized by the appearance of numerous, discrete persisten, pruritic, hyperkeratotic papules. These are usually located over the shins. Occasionally, other sites, namely calves, thighs, feet, arms abdomen and chest may be involved. The amyloid is derived from keratinocytes that undergo filamentous degeneration and apoptosis.

**Table 40.2: Diagnosis of amyloidosis**

| *Types* | *Routine histopathology* | *Confirmation* | *Newer techniques* |
|---|---|---|---|
| Macular amyloidosis | • Amorphous, fissured faintly eosinophilic amyloid deposits in papillary dermis | Special stains | Immunohistochemical studies |
| Lichen amyloidosis | • Amorphous, fissured faintly eosinophilic amyloid deposits in papillary dermis<br>• Irregular acanthosis<br>• Hyperkeratosis | -do- | -do- |
| Nodular amyloidosis | • Diffuse amyloid deposits in reticular dermis and subcutes<br>• Marked plasma cell infiltrate. | -do- | -do- |

### Nodular Amyloidosis

It is an uncommon conditions, characterized by appearance of nodules, that vary from 1 to 3 cm in size. The center may appear atrophic due to involution of the amyloid. The lesions are often localized over the face and the legs. These lesions may be indistinguishable from those of primary and myeloma associated systemic amyloidosis. The amyloid protein is derived from local plasma cell infiltration.

**Table 40.3: Special stains for amyloid proteins**

| *Dyes* | *Examples* | *Appearance* |
|---|---|---|
| 1. Triphenylmethane dyes | Methyl violet<br>Cresyl violet | Metachromasia |
| 2. Cotton dyes<br>Pagoda red | Congo red birefringence under polarized light | Apple green |
| 3. Thiazole dyes | Thioflavine | Fluorescence |

## DIAGNOSIS

The diagnosis of amyloidosis (Table 40.2) may be confirmed by microscopic examination of specially stained tissue sections. The special stains used for the detection of amyloid protein are outlined in Table 40.3.

## TREATMENT

Macular and lichen amyloidosis may be treated with topical corticosteroids. Antihistamines may be administered to relieve pruritus. Nodular amyloids may be surgically excited. Other modes of therapy such as dermabrasion, laser surgery and retinoids and under trial.

## RECOMMENDED READING


1. Blum A, Sohar E. The diagnosis of amyloidosis: Ancillary procedures. *Lancet* 1962;1:721-724.
2. Breathnach SM. Amyloid and amyloidosis. *J Am Acad Dermatol* 1988;18:1-16.
3. Brownstein MH, Hashimoto K. Macular amyloidosis. *Arch Dermatol* 1972;106:50-57.
4. Brownstein MH, Helwig EB. The cutaneous amyloidosis 1: Localized forms. *Arch Dermatol* 1970;102:8-19.
5. Heyl T. Amyloid staining with thioflavine T in dermatopathology. *Trans St Johns Hosp Dermatol Soc* 1966;52:84-87.
6. Tay CH, Dacosta JL. Lichen amyloidosis: Clinical study of 40 cases. *Br J Dermatol* 1970;82:129-136.
7. Yanagihara M, Mehregan AH, Mehregan DR. Staining of amyloid with cotton dyes. *Arch Dermatol* 1984;120:1184-1185.

# 41 Chapter

# Porphyria

Heme porphyrin synthesis is catalyzed by a cascade of enzymes (Fig. 41.1). The defect in the activity of these enzymes, results in the accumulation of its specific substrate, the porphyrin. These porphyrins have a tendency to absorb light in the range of 400-410 nm (Sorets bands). The energy absorbed may be released either directly or indirectly through acceptor molecules. This may result in damage to the tissues.

The porphyrias are classified as shown in Table 41.1 complete detail about it is given in Table 41.2.

## ERYTHROPOIETIC PORPHYRIA (EP) (GUNTHER'S DISEASE)

### Clinical Features

It is inherited as autosomal recessive disorder, and presumed to result from deficiency of the enzyme UROCOSYN III.

It usually has an onset in early infancy; though at times, symptoms may be evident at birth or delayed for a few years. A severe photosensitivity is cardinal and manifests as recurrent painful vesiculobullous eruptions containing pink fluorescent fluid. They rupture

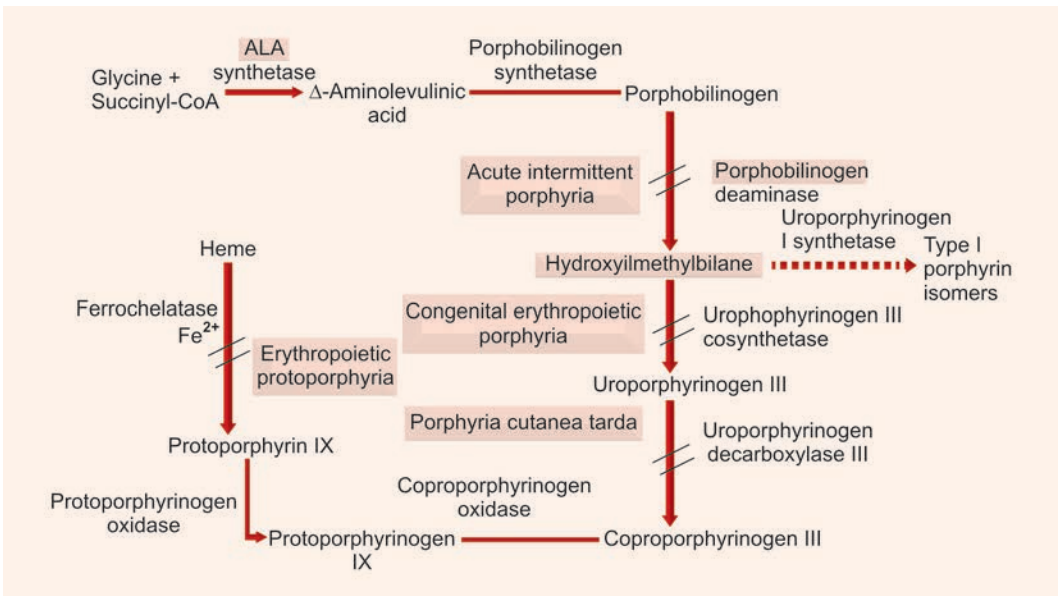



**Figure 41.1:** Heme biosynthesis

**Table 41.1: Porphyria: Classification**

Erythropoietic
- Erythropoietic porphyria
- Erythropoietic protoporphyria
- Erythropoietic corproporphyria

Hepatic
- Acute intermittent porphyria
- Variegate porphyria
- Hereditary coproporphyria
- Porphyria cutanea tarda

Erythropoietic/hepatic
- Hardero porphyria.

to form erosions that heal with scarring, atrophy and depigmentation. Multilating deformities affecting the face, nose, ears and fingers may be sequelae. Hirsutism and/or cicatricial alopecia may be other cutaneous manifestations. Erythrodontia (pink teeth), affecting both deciduous and permanent teeth is common. The teeth may fluoresce pink under Wood's lamp.

The eyes may also be affected in some patients. The ocular changes are characterized by photophobia, keratoconjunctivitis, ectropion and/or symblepheron.

The urine is usually burgundy red in color and may stain the undergarments. It fluoresces red pink under Wood's lamp.

Hematological abnormalities are significant and may manifest as hemolytic anemia with accompanying splenomegaly. An intensely red fluorescence of normoblasts is its hallmark.

### Diagnosis

It may be suspected on clinical examination and confirmed by biochemical investigations that reveal raised uroporphyrinogen I (UROI) and coproporphyrinogen I (COPROI) in urine and feces, respectively.

### Treatment

It is symptomatic. Protection from sunlight is essential. Zinc oxide and titanium dioxide are most suitable sunscreens. Splenectomy may result in marked improvement of hemolytic anemia in some cases.

## ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

### Clinical Features

It is inherited as autosomal dominant and results from deficiency of the enzyme ferrochelatase.

It has an onset in early childhood. Cutaneous photosensitivity, is its constant feature. Exposure to light produces a burning sensation followed by eruption of erythematous, swollen plaques. Blisters are infrequent. The lesions slowly resolve on withdrawl from light source. Repeated episodes of exposure and withdrawl result in atrophic waxy scarring imparting a prematurely aged appearance. These changes are in particular prominent over the knuckles, nose, pinnae, and around the eyes.

Systemic involvement is distinctly uncommon. An occasional patient may develop cholelithiasis and hepatic failure.

### Diagnosis

The elevated levels of protoporphyrinogen in feces, red blood cells, and plasma in a suspected case confirm the diagnosis of erythropoietic protoporphyria. The levels of porphyrins in

**Table 41.2: Details about porphyrias**

| *Porphyrias* | *Inheritance* | *Onsets* | *Cutaneous symptoms* | *Systemic involvements* | *Laboratory investigations* | *Enzyme defects* | *Treatments* |
|---|---|---|---|---|---|---|---|
| Erythro-poietic porphyria | AR | Infancy | Marked photosensitivity<br>Vesicles/bullae/ erosions<br>Scarring with atrophy and mutilating deformities<br>Hypertrichosis | Erythrodontia<br>Ocular changes<br>Hemolytic anemia with splenomegaly. | UROI and COPROI in urine and feces, respectively.<br>Burgundy red urine<br>Fluorescent marrow normoblasts. | UROCO-SYN III | Photoprotection<br>Zinc oxide/ Titanium dioxide<br>Splenectomy |
| Erythro-poietic proto-porphyria | AD | Early child-hood | Erythematous edematous, urticarial plaques on sun-exposed areas.<br>Healing with shallow, waxy scars. Aged wrinkled skin | Cholelithiasis<br>Terminal hepatic failure | Elevated protoporphyrin in feces, and RBC. | Ferro chelatase | Topical and/or systemic beta carotenes |
| Acute intermittent porphyria | AD | 10 to 40 | No cutaneous symptoms<br>Photosensitivity absent | Acute abdominal pain, vomiting, constipation<br>Peripheral neuropathy<br>Biazare psychiatric behavior | Elevated ALA and PBG in urine, during and between attacks | Porphobi-linogen deaminase | Avoid precipitating drugs such as barbiturates estrogens, griseofulvin<br>Exclude surgical emergency<br>Glucose loading<br>Hoeme infusion |
| Porphyria cutanea tarda | AD spora-dic | 3rd or 4th decades | Mild photosensitivity<br>Vesiculo bullous eruptions, erosions on trauma prone areas.<br>Heals with scarring and milia formation.<br>Scarring alopecia<br>Hypertrichosis<br>Sclerodermoid plaques | Impaired liver function | Raised Uroporphyrinogens in urine (URO III> I)<br>Urinary URO:COPRO>3:1<br>Pink fluorescence of urine under Wood's lamp<br>Raised ISOCOPRO excretion in urine and feces | Uroporphy-rinogen decarbo-xylase | Avoidance of precipitants like alcohol, oral contraceptives<br>Phlebotomy and/or chloroquine |

urine are normal. The red fluorescence of erythrocytes under a fluorescent microscope is supplementary.

### Treatment

Protection of the skin from light is essential. Systemic and/or topical betacarotene is an useful adjuvant.

## PORPHYRIA CUTANEA TARDA (PCT)

### Clinical Feature

PCT is a complex, multifactorial disorder that results from inactivation of uroporphyrinogen decarboxylase in liver. It may be either sporadic (PCT type I) or inherited as autosomal dominant trait (PCT type II). It may be induced by drugs such as ethyl alcohol, oral contraceptives, estrogens, hexachlorobenzene, chlorinated phenols, and/or iron.

An increased skin fragility is prominent in PCT. It may manifests as vesiculobullous eruption in areas prone to trauma. Inadvertent trauma may result in peeling of the skin, leaving erosions that slowly heal with scarring and milia formation. Acute photosensitivity, characteristic of erythropoietic porphyria is uncommon, though the lesions worsen on actinic exposure, especially in summers.

Hypertrichosis may yet be another distressing symptom. The hairs may be either coarse or fine in texture and also vary in color. Sclerodermoid plaques may develop over sun-exposed areas.

### Diagnosis

It is essential to corroborate the clinical findings with laboratory investigations.

The total body iron stores are markedly raised in PCT, resulting in increased serum and/or hepatocellular iron. An increased amount of porphyrins is excreted in the urine. Pink-red urinary fluorescence under Wood's lamp is characteristic.

There is an elevation of uroporphyrins (URO) in urine and isocoproporphyrins in urine and stool. The ratio of urinary uroporphyrin to coproporphyrin is greater than 3:1. This helps differentiate PCT from VP, where the ratio is less than 1:1.

### Treatment

Repeated phlebotomy to lower the excessive hepatic iron stores is the treatment of choice. Chloroquine is an alternative therapeutic modality. The mechanism of chloroquine in PCT is debatable. It probably binds to the hepatocellular porphyrins, rendering them water soluble.

## ACUTE INTERMITTENT PORPHYRIA

### Clinical Features

It is inherited as autosomal dominant disorder and probably results from the deficiency of the enzyme porphobilinogen deaminase (PBGD). This enzymes is required for the conversion of porphobilinogen to uroporphyrin I. It usually has an onset in the postpubertal period. Women are affected more often than men.

All the signs and symptoms of AIP are attributable to the autonomic nervous system. Acute attacks with a neurologic visceral symptom complex are its hallmark, and are often precipitated by drugs. Steroid hormones such as estrogens and antimicrobial agents such as griseofulvin, sedative-hypnotics such as barbiturates and anticonvulsants are the usual culprits.

The patients often reports with the complaint of abdominal pain, and accompanying

neurologic and psychiatric symptoms. The pain is intermittent, spasmodic and of varied severity. It may be associated with vomiting and constipation, and may simulate surgical emergency. Peripheral neuropathy is another feature. Its severity may vary from localized paresthesia and weakness to generalized flaccid paralysis. Bizarre neuropsychiatric symptoms may be an accompaniment.

Cutaneous manifestations including photosensitivity, unlike other porphyrias are conspicuously absent.

### Diagnosis

Its manifestations are varied and intriguing. Laboratory investigations are essential to supplement the clinical suspicion. Delta-aminolevulinic acid and porphobilinogen are markedly raised in the urine, both during and after the attack.

Raised PBG levels in urine may be easily demonstrated by a simple office procedure. Exposure of the urine to bright sunlight turn it into a dark red color. Hoesch's and Watson-Schwartz tests are other diagnostic procedure.

### Treatment

The patient should be hospitalized. Surgical emergency should be excluded. Symptomatic treatment may be instituted on confirming the diagnosis. Opiates are useful to relieve abdominal pain, and nausea and vomiting may be controlled by chlorpromazine. Benzodiazepines such as diazepam are safe and may be administered to control seizures. Glucose loading and hematin infusion are also advocated in the management of AIP.

## VARIEGATE PORPHYRIA

### Clinical Features

It is inherited as an autosomal dominant disorder. The exact biochemical abnormality in this disorder is debatable. An increased deltaaminolevulinic acid synthetase (ALAS) or decreased protoporphyrinogen oxidase (PROTOGENO) activities have been proposed as primary enzymatic defects.

It is common in South Africa and usually manifests in the age group of 15 to 30 years. The cutaneous manifestations resemble those in PCT, while the systemic manifestations are similar to AIP.

### Diagnosis

The clinical suspicions may be supplemented by laboratory confirmation. Urinary ALA and PBG are elevated during the attacks but fall to normal in between the attacks. The ratio of URO to COPRO in urine is helpful in differentiating PCT from VP (vide supra). In PCT, the URO: COPRO ratio is 3:1 or more, whereas in VP it is less than 1:1.

### Treatment

Drug avoidance is essential, as it may precipitate VP. Glucose loading and hematin infusion are not so effective in VP. Also phlebotomy and chloroquine are ineffective.

## HEREDITARY COPROPORPHYRIA

It is a very uncommon disorder that results from the defect in the enzyme coproporphyrinogen oxidase. It is characterized by acute episodes of abdominal pain. These may be accompanied by neuropsychiatric symptoms. Some patients may develop photocutaneous lesions resembling those in PCT.

## HEPATOERYTHROPOIETIC PORPHYRIA

It is another uncommon porphyria associated with a defect in the enzyme urophyrinogen decarboxylase. It has it onset in early infancy. The clinical manifestations are similar to erythropoietic porphyria (Gunthers disease) while the biochemical abnormalities are suggestive of PCT.

## RECOMMENDED READING

1. Moore MR, Dister PB. Biochemical diagnosis of the porphyrias. *Clin Dermatol*. 1985;3:24-40.
2. Murphy GM. The cutaneous porphyria: A review of diagnosis and management. *JEADV* 1993;2: 11-17.
3. Petersen CS, Thomsen K. High dose hydroxychloroquine treatment of porphyria cutanea tarda. *J Am Acad Dermatol*. 1992;26:614-619.
4. Young JW, Conte ET. Porphyrias and porphyrins. *Int J Dermatol*. 1991;30:399-406.

# 42 Chapter

# Miliaria

Miliaria denotes a group of disorders characterized by closure of the duct of eccrine sweat glands resulting in sweat retention at various levels. The disorder includes the following:

- Miliaria crystallina (sudamina)
- Miliaria rubra (prickly heat)
- Miliaria profunda (mamillaria).

The variation in clinical expression is based on the level of block of the sweat duct. It may be either within the stratum corneum (miliaria crystallina), deep within the epidermis (miliaria rubra) or at the dermoepidermal junction. The precise pathogenesis is debatable. The raised body/environmental temperature results in sweating, which may not evaporate if the humidity is high. This moisture induces injury to the epidermal cells lining the eccrine duct. This may form an adherent parakeratotic plug within the duct. The eccrine duct ruptures below the level of obstruction producing a sweat retention vesicle. In miliaria crystallina, the superficial plugging within the stratum corneum results in small crystal clear veiscle, the roof of which is formed by stratum corneum. In miliaria rubra, the obstruction is within the epidermis, resulting in rupture of intraepidermal portion of the duct. The injured epidermal cells release enzymes that induce vasodilation and stimulate itch receptors. Whereas in miliaria profunda, the obstruction is at the dermoepidermal junction. The duct may rupture to form sweat vesicle in the dermis.

## CLINICAL MANIFESTATION

Miliaria crystallina usually develops in a febrile patient, as tiny crystalline vesicles on an apparently normal skin. The lesion is largely asymptomatic and is located in the flexural areas.

Miliaria rubra is characterized by eruption of small pruritic/stinging papulovesicles on an erythematous base. The lesions are localized over the trunk and the neck. The itching/burning is paroxysmal and provoked by stimuli that induce sweating.

Miliaria profunda manifests as 1-3 min sized white, asymptomatic papules, usually localized over the trunk. Erythema is conspicuously absent. Compensatory facial hyperhidrosis may be an accompaniment. Numerous eccring glands, may be rendered functionless, if the lesions are widespread. This may impair the cooling action of the sweat. These patients are thus prone to develop weakness, dyspnea, tachycardia, and hyperpyrexia. This is termed 'tropical anhidrotic asthenia.

### Diagnosis

The diagnosis is primarily clinical. In case of doubt, histopathology may be useful.

### Treatment

The patient should be removed to a cool, preferably air-conditioned environment. The soothing shake lotions and prickly heat powders, often advocated are not of much help.

Vitamin C, 1000 mg in divided doses may be administred orally. The condition usually resolves on its own in a few days.

## RECOMMENDED READING

1. Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders II. Disorders of sweat gland function. *J Am Acad Dermatol* 1989; 20:713-726.

# 43 Chapter Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is a malignant tumor, originating from keratinizing cells of the epidermis and/or its appendages. Elderly individuals with fair skin are its victims. Its incidence has gradually increased and is now the second most common cutaneous malignancy. It has a multifactorial etiology and both environmental and host factors may contribute to its pathogenesis.

- Prolonged actinic exposure
- Pre-existing chronic inflammatory lesions
  - Burns scars/chronic ulcers/chronic osteomyelitis
- Premalignancies
  - Actinic keratosis
  - Bowenoid papulosis
  - Erythroplasia of Queryat
  - Leukoplakia
- Infection
  - Human papilloma virus (HPV) Epidermodysplasia verruciformis, a premalignant condition attributed to HPV-5, may progress to SCC
- Carcinogens
  - Arsenic
  - Pitch, tar, soot
  - Hydrocarbons
  - X-rays
- Iatrogenic
  - PUVA (Psoralen + UVA exposure)
- Host factors
  - Color
  - Fair skin individuals, prone to sunburn
  - Xeroderma pigmentosum
- Immunodeficiency
  - Iatrogenic immunosuppression
  - Lymphoproliferative malignancies.

  AIDS *per se* is not a risk factor.

## CLINICAL FEATURES (FIG. 43.1)

SCC begins as a nodule that erodes to form a shallow ulcer. It is surrounded by a wide

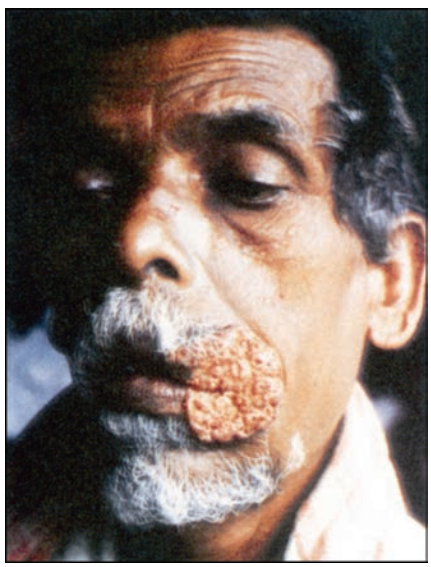


**Figure 43.1:** Squamous cell carcinoma (SCC)

elevated border. The ulcer is covered by crust, that on removal exposes a red granular base. The lesion may arise anywhere on the skin and/or mucous membrane (Fig. 43.1). In addition to the local tissue invasion and destruction, some tumors have a significant potential for metastasis, through the lymphatics.

SCC has following clinical variants:

- Adenoid squamous cell carcinoma
- Mucin producing squamous cell carcinoma
- Invasive squamous cell carcinoma
- Spindle cell squamous cell carcinoma
- Verrucous carcinoma:
  - Verrucous carcinoma of oral cavity
  - Verrucous carcinoma of genitoanal region
  - Plantar verrucous carcinoma.

## DIAGNOSIS

The diagnosis of SCC needs to be confirmed by histopathologic examination. SCC is characterized by irregular masses of epidermal cells that proliferate into the dermis. The proportion of normal to atypical squamous cells varies with the differentiation of the carcinoma. Keratinization with horn pearl formation is a feature of well-differentiated SCC.

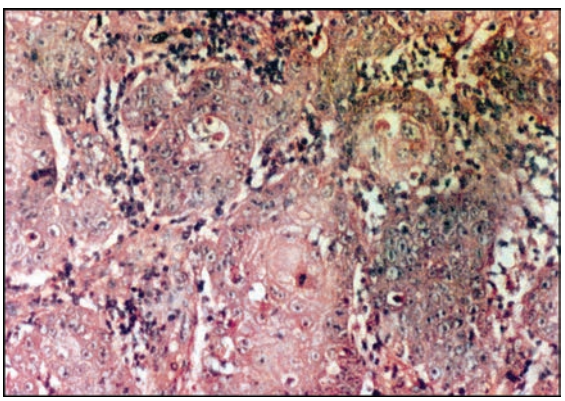


**Figure 43.2:** Squamous cell carcinoma: Horn peals in large number

The depth of invasion, anaplasia and perineural invasion, also determine the malignancy of the tumor. Accordingly, SCC is delineated into 4 different degrees of malignancy (Table 43.1).

Besides the histopathologic assessment of the cutaneous tumor, the following investigations may be undertaken:

- Fine needle aspiration cytology (FNAC) and/or histopathology of the regional lymph nodes
- Skiagram of the chest
- Additional skiagram, ultrasound, magnetic resonance imaging (MRI), and computerized axial tomography (CAT) scan to assess visceral involvement.

## PROGNOSIS

The risk factors associated with biological aggression, local invasion, distant metastasis and recurrences include the following:

- Size > 1 cm
- Rapid growth and ulceration
- Immunocompromised status
- Undifferentiated histopathological pattern
- Adenoid and spindle cell variants
- Deeply invasive SCC
- Perineural and lymphatic infiltration.

## TREATMENT

The details of treatment are outlined in Table 43.2.

**Table 43.1: Grading of squamous cell carcinoma**

| *Grades* | *Depth of penetration* | *Squamous cells* | *Horn pearls* | *Individual cell keratinization* | *Inflammatory reactions* |
|---|---|---|---|---|---|
| i. | Above or up to sweat glands. Intact basal layer at places | Relatively well-differe-ntiated, well-developed intercellular bridges. Few atypical nuclei | Present in large number (Fig. 43.2) | Absent | Marked |
| ii. | Below sweat glands | Relatively atypical cells incompletely keratinized centers | Few in number with | Absent | Sparse |
| iii. | Below sweat glands | Atypical cells, devoid of prickles Numerous atypical mitotic figures | Absent | Present, with dys-keratotic cells, having eosinophilic cyto-plasm and hyperch-romatic nucleus | Absent |
| iv. | Below sweat glands | Atypical, devoid of inter-cellular bridges. Elongated tumor cells, resembling fibrosarcoma | Absent | Present | Absent |

**Table 43.2: Treatment of squamous cell carcinoma**

| *Techniques* | *Indications* | *Status* |
|---|---|---|
| Curettage and electrosurgery | Superficial and *in situ* SCC | Acceptable for low grade malignancy. Poor results in cases of subcutaneous invasion. |
| Excision Entire tumor with 5 mm margin and microscopic assessment of edges, using either frozen or permanent section technique | Primary and recurrent SCC | Acceptable for treatment of SCC with minimal biologic aggressiveness |
| Mohs micrographic surgery. Excision with intra-operative evaluation of horizontally oriented tissue sections. | Large, deeply invasive SCC SCC with neurotropism Poorly differentiated SCC Recurrent SCC | Highest cure rates |
| Cryosurgery | Primary SCC | Reserved for patients with bleeding disorders or other contraindications to surgery |
| Radiotherapy | Adjuvant therapy to surgery in bio logically aggressive tumors with suspected metastasis to lymph nodes Palliative therapy for inoperable tumors | Cure rates have varied in different studies |
| Chemotherapy regimens comprising bleomycin, peplomycin, cisplastin, and methotrexatic | Adjuvant therapy to surgery in biologically aggressive SCC's | Efficacy in the management of SCC with perineural invasion and/or lymph node metastasis is yet to be unequivocally documented |
| Interferons | -do- | Under evaluation |
| Retinoids | -do- | -do- |
| PUVA | -do- | -do- |

## RECOMMENDED READING

1. Anonymous. Guidelines of care for cutaneous squamous cell carcinoma. Committee on Guidelines of Care. Task Force on Cutaneous Squamous Cell Carcinoma. *J Am Acad Dermatol* 1993;28:628-631.
2. Kiva RE, Campana K, Moy RL. Biology of cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 1992;26:1-26.

# 44 Chapter Basal Cell Carcinoma

Basal cell carcinoma (BCC) is a neoplasm of the epidermal basal cells. It usually affects the elderly, fair skinned individuals. The relatively uncommon forms of BCC, namely unilateral basal cell nevus, nevoid basal cell carcinoma, and bazex syndrome may have an early onset.

Several factors may predispose to BCC. Of these, the most significant is a prolonged exposure of a fair complexioned individual to strong sunlight. The actinic predisposition is further enhanced in patients of xeroderma pigmentosum. Radiation therapy with large doses of Roentgen rays, and ionizing radiations is also hazardous. The tumor may also originate in the burns scars.

## CLINICAL FEATURES

It develops as a small painless, waxiform, brownish-red nodule with tiny telangiectatic vessels, prominent on its surface. It slowly increases in size and undergoes central ulceration. The ulcer is well-defined and is surrounded by raised, everted pearly border (Fig. 44.1). It may cicatrize at the center while spreading at the margins. It may deeply invade and destroy the underlying tissue, hence it is termed 'rodent ulcer'. Lymph nodes are usually not involved. The lesion commonly localizes in the upper part of the face above the line drawn from the ear to the angle of the mouth. The inner/outer canthus of the eye is the site of predilection.

The following five clinical types of BCC are well-recognized:

- Nodular basal cell carcinoma
- Superficial spreading basal cell carcinoma
- Morphea form/sclerosing basal cell carcinoma
- Pigmented basal cell carcinoma
- Fibroepitheleioma of the pinkus.

## DIAGNOSIS

The morphology of BCC is characteristic. The diagnosis may be further confirmed by microscopic examination.

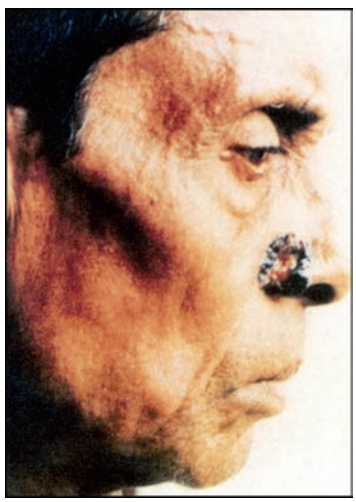


**Figure 44.1:** Basal cell epithelioma
(*Courtesy:* KC Saha, Kolkata)

**Table 44.1: Treatment of basal cell carcinoma**

| *Techniques* | *Indications* | *Advantages* | *Disadvantages* |
|---|---|---|---|
| Curettage and electrodesiccation | Tumors < 2 cm in diameter | High cure rate | Does not provide specimen for microscopic examination |
| Radiation therapy | Tumors localized over eyelids | Tissue preservation<br>High cure rate | Skin atrophy and depigmentation |
| Excision with primary closure | Any BCC>2cm | High cure rate<br>Allows histopathologic examination of resected tissue | Tissue loss may necessitate reconstructive surgery |
| Moh's micrographic surgery | Recurrent tumors<br>Morphea like tumors | High cure rates | Tissue loss may necessitate reconstructive surgery |
| Cryosurgery | If surgery is contraindicated | | Unpredictable cure rates<br>Higher morbidity and scarring |

## TREATMENT

It is essential to completely remove the tumor. The details are outlined in Table 44.1.

## RECOMMENDED READING

1. Gellin G, Kopf A, Garfinkel L. Basal cell epithelioma. A controlled study of associated factors. *Arch Dermatol* 1965;91:38-45.

# 45 Chapter Malignant Melanoma

Malignant melanoma of the skin is a tumor that arises from cutaneous melanocytes. It affects both men and women, usually in fifth to seventh decades of life. However, in the recent past its increasing incidence has been observed in younger individuals. It is a potentially lethal tumor. The therapeutics success rates of advanced malignant melanoma continue to be low. Hence it is imperative to detect the tumor at an early stage. This may be facilitated by screening 'at risk' individuals. These predisposing factors are as follow:

1. Color of the skin—it affects individuals with fair skin, light colored hairs and eyes much more often than darker individual.
2. Skin type.
3. Family history—a family history of malignant melanoma may be forthcoming in 1 to 6 percent of all patients. Such individuals may have younger age of onset, multiple tumors and better prognosis
4. Pre-existing nevi—Junctional nevi have malignant potential. Such a change may be heralded by the following:
   - Change in the color—lightening/darkening
   - Change in shape and size
   - Itching
   - Spontaneous bleeding, erosion, ulceration, and crusting

The asymmetry, border irregularity, color variegation and diameter enlargement (ABCD) of the nevus also indicate malignant transformation.

## CLINICAL FEATURES

Primary cutaneous malignant melanomas have been classified into the following 4 major types. An important distinguishing features is the growth pattern. There is an initial, variable radial growth phase when the melanoma cells remain confined to the epidermis, dermoepidermal junction and/or papillary dermis. Eventually dermal penetration takes place. This is the vertical growth phase (Table 45.1).

### Lentigo Maligna Melanoma

It arises from a pre-existing lentigo maligna, and affects elderly individuals. Women are affected more often than men. It begins as a small pigmented macule that undergoes slow enlargement. It evolves into a irregular patch of variegate color, usually dark brown/black, over a period of 10 to 15 years. At this juncture, malignant transformation may be heralded by an appearance of one or more nodules within the patch. This type is relatively less aggressive with little tendency to metastasize.

**Table 45.1: Malignant melanoma: Clinical features**

| | *Lentigo malignant melanoma* | *Superficial spreading malignant melanoma* | *Nodular malignant melanoma* | *Acral lentiginous melanoma* |
|---|---|---|---|---|
| Percent | 5 | 70 | 15 | 5-10 |
| Age group (years) | 60-80 | 40-60 | 50-70 | 40-60 |
| Site | Predominantly face, other sun-exposed areas | Face, trunk legs, and back | Any site | Palms soles fingers and toes |
| Growth characteristics | Prolonged radial growth phase | Relatively prolonged radial growth phase | Negligible radial growth phase Vertical growth phase from onset | Variable |
| Behavior | Relatively less aggressive and low tendency to metastasize | Variable | Highly malignant | Invasive and highly malignant. |

### Superficial Spreading Malignant Melanoma

It is the most common form of malignant melanoma. Women are its victims more often than men. It begins as a pigmented macule, usually localized over the back of the legs. It undergoes slow enlargement over a period of 5 to 7 years to form an irregular patch of varied hues of black, brown or grey colors. At this juncture it develops one or more nodular eruption, that hearalds the vertical phase of growth.

### Nodular Malignant Melanoma

It affects men more often than women. It arises as a uniformly pigmented raised nodule, often localized over the head, neck or trunk. It undergoes rapid enlargement and ulceration (Fig. 45.1).

### Acral Lentiginous Melanoma

They are uncommon tumors that evolve over the palms, soles, fingers and toes. It begins as a slowly enlarging pigmented patch. The vertical phase of growth may be masked by the skin thickness and thus its detection may be delayed, and thus prognosis is poor.

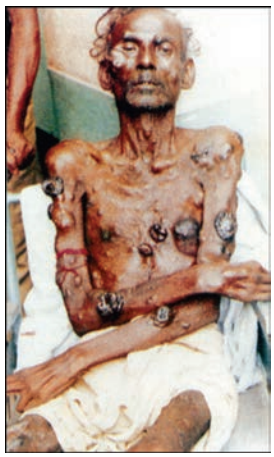


**Figure 45.1:** Malignant melanoma (*Courtesy:* KC Saha Kolkata)

## DIAGNOSIS

Histopathological examination of tissue section forms the mainstay of diagnosis. An excision biopsy with a narrow margin of normal skin may be performed for the purpose. The incisional biopsy may be preferred for larger lesions. The histopathology report should ideally comment upon the following features (Table 45.2):

1. Melanoma and its subtypes.
2. Cellular atypia (present/absent).

**Table 45.2: Histopathology of malignant melanoma**

| *Types* | *Histopathological features* |
|---|---|
| Lentigo malignant melanoma | *Preinvasive*<br>1. Proliferation of atypical melanocytes along the basal layer.<br>2. Cells are singly disposed; minimal tendency to nesting.<br>3. Bank like inflammatory infiltrate in upper dermis.<br>*Invasive*<br>Nesting and nodular collection of melanoma cells in dermis. |
| Superficial spreading malignant melanoma | *Preinvasive*<br>1. Proliferation of nests of atypical melanocytic cell at dermoepidermal junction.<br>2. Small number of tumor cells in the upper dermis.<br>*Invasive*<br>1. Nodular collection of melanoma cells in dermis.<br>2. No preinvasive stage. |
| Nodular malignant melanoma | Nodules of atypical melanocytic cells, extending to varying depths in the dermis. |

3. Lymphocytic infiltration (present/absent).
4. Angiolymphatic invasion (present/absent).
5. Superficial ulceration.
6. Thickness of the lesion (measured in mm from the top of granular layer to the deepest point of the tumor—Breslow measurement).
7. Level of invasion (Clarke's level) (Table 45.3)

## TREATMENT

The treatment of choice for malignant melanoma is surgical excision. For *in situ* melanoma, excision of the lesion with a 0.5 cm margin of clinically normal skin is adequate. The melanoma < 1 mm in thickness may be adequately treated by surgical excision including a 1 cm margin of clinically and histologically normal skin. The adequate margin of normal skin that may be excised for tumors more than 1 mm, is yet not standardized. Elective regional lymph node dissection (E RLND) is usually not indicated. Regional lymphadenectomy may be undertaken in clinically suspect lymph nodes.

**Table 45.3: Clarke's level of invasion**

| *Levels* | *Depth of invasion* |
|---|---|
| Level I | Melanoma cells confined to dermoepidermal junction and epidermis. No dermal invasion. |
| Level II | Melanoma cells invading but not filling the papillary dermis. |
| Level III | Melanoma cells filling the papillary dermis and extending to the junction of papillary and reticular dermis. |
| Level IV | Melanoma cells invading reticular dermis. |
| Level V | Melanoma cells extending into subcutis. |

The role of chemotherapy in the management of malignant melanoma is, yet inconclusive. Dacarbazine is effective for metastatic melanoma. Radiotherapy has been successfully used for the treatment of lentigo maligna in elderly individuals, for palliative treatment of metastasis and for local recurrences. Other modes of therapy, namely melanoma vaccines, monoclonal antibodies, levodopa, dopamine, and immunotherapy are under trial.

## RECOMMENDED READING

1. Anonymous. American Academy of Dermatology. Guidelines of care for malignant melanoma. *Bitt Am Acad Dermatol* 1991;9:3-5.
2. Anonymous. Guidelines of care for malignant melanoma. Committee on Guidelines of Care. Task Force on Malignant Melanoma. *J Am Dermatol* 1993;28:638-641.
3. Grin-Jorgensen C, Kopf AW, Maize JC. Cutaneous malignant melanoma. *J Am Acad Dermatol* 1991; 25:712-716.

# 46 Chapter Cutaneous T Cell Lymphoma

The cutaneous proliferations of neoplastic T cells are termed as cutaneous T cell lymphoma (CTCL). It forms a wide spectrum comprising of the following:

- Mycosis fungoides and Sezary syndrome
- Pagetoid reticulosis (Woringer-Kolopp disease)
- Lymphomatoid papulosis
- Lymphomatoid pityriasis lichenoides
- Actinic reticuloid
- Lymphomatoid granulomatosis
- Adult T cell leukemia.

## MYCOSIS FUNGOIDES (MF)

It is a CTCL, characterized by neoplastic proliferation of predominantly T helper/inducer lymphocytes in the skin. It usually has an onset in 4th to 6th decades and affects men more often than women. It tends to run a protracted clinical course and three stages may be distinct in its evolution. These are the initial eczematous lesions (premycotic stage), followed by irregular, infiltrated plaques of varied sizes and shape (plaque stage) and the final development of nodules and tumors (tumor stage). At times, it may manifest as other characteristic but non specific eruptions such as follicular mucinosis, poikilodermatous atrophic patches, and parapsoriasis of large plaque type. The outcome of MF is variable. In a small proportion the disease may clear spontaneously. In others it may pursue a slow relentless progressive course, while in a few it may rapidly evolve into the fatal tumor stage.

### Clinical Feature

#### *Erythematous (Premycotic) Stage*

It manifests as itchy erythematous, mildly scaly serpiginous macules of variable sizes. Atrophy and telangiectasia may be prominent in some eruptions. The lesions are asymmetric and usually localized over the trunk and the limbs. The morphology is nonspecific and, at times, differentiation from chronic eczema and psoriasis may be difficult.

#### *Plaque Stage*

This is characterized by formation of intensely itchy, erythematous, indurated, oval and/or circular plaques. The surface may be mildly scaly. Individual lesions may coalesce to form polycyclic patterns. These lesions tend to localize over the trunk and buttocks.

#### *Tumor Stage*

In a small proportion of patients, the disease progresses to form tumors and nodules over the plaques. These nodules may ulcerate and are prone to secondary infections. A variant 'tumor de emblee' is characterized by *de novo* appearance of tumors, without a preceding plaque stage.

**Table 46.1: Histopathology of CTCL**

| *Stages* | *Histopathology* |
|---|---|
| Premycotic stage | 1. Nonspecific, upper dermal infiltrate, interspersed with a few atypical mononuclear cells.<br>2. Epidermal infiltration by atypical mononuclear cells, in absence of spongiosis, is characteristic, but uncommon in early CTCL. |
| Plaque stage | 1. Polymorphous, band-like infiltrate in upper dermis, comprising histiocytes, eosinophils, lymphoid cells, plasma cells with a variable number of CTCL cells (10-40 μ sized mononuclear cell with scanty cytoplasm and cerebrifom nucleus termed Lutzner cell).<br>2. Epidermal infiltration either by individual cells or small groups of mononuclear cells surrounded by clear halo-Pautriers abscess |
| Tumor stage | Two histopathologic appearances:<br>A<br>1. A dense, polymorphous infiltrate in dermis extending to subcutaneous fat.<br>2. Epidermotropism or uninolved epidermis.<br>B<br>1. Monomorphous infiltrate of tumor cells in dermis.<br>2. Relatively spared epidermis. |

**Table 46.2: Treatment of CTCL**

| | *Modality* | *Status* |
|---|---|---|
| 1. | Topical steroids + UVB | May produce complete resolution of plaques. |
| 2. | PUVA (Psoralen + UVA) | May produce complete clinical resolution.<br>Histological evidence of persistant atypical<br>T cells necessitates maintenanace therapy. |
| 3. | Topical nitrogen mustard | May result in complete clinical resolution.<br>Histological evidence of persistant atypical<br>T cells necessitates maintenance therapy.<br>Sensitization may be a limitation to its use. |
| 4. | Chemotherapy | Trials with numerous regimens with equivocal results.<br>2-deoxycoformycin, a drug specific for T lymphocytes is under evaluation |
| 5. | Photophoresis | Under evaluation. |

An uncommon presentation of MF is the erythrodermia, characterized by generalized erythema, fine scaling, lymphadenopathy and atypical circulating lymphocytes in the peripheral blood (Sezary syndrome).

## Diagnosis

The morphology of MF may not be characteristic. A thorough clinical examination, supplemented by laboratory studies may be imperative to reach a conclusive diagnosis. The diagnosis approach is outlined below:

- A thorough cutaneous examination, mapping of skin lesions
- Palpation for enlarged lymph nodes
- Skin biopsy (serial sections, if required (Table 46.1)
- Lymph node biopsy (if enlarged)
- Peripheral smear for atypical mononuclear cells
- Skiagram of the chest
- Ultrasound and/or computerized axial tomography (CAT) scan of liver and spleen
- Immunophenotyping to identify the clones of lymphocytes

- Electron microscopy and analysis of nuclear contour index
- DNA cytophotometry.

### Treatment

The details of treatment are outlined in Table 46.2.

## RECOMMENDED READING

1. Edelson RL. Cutaneous T cell lymphoma mycosis fungoides, Sezary syndrome, and other variants. *J Am Acad Dermatol* 1989;2:89-106.
2. Sanchez JL, Ackerman AB. Th patch stage of mycosis fungoides: Criteria for histologic diagnosis. *Am J Dermatopathol* 1989;1:5-26.

47 Chapter

# Acrodermatitis Enteropathica

Acrodermatitis enteropathica (AE) is an uncommon, autosomal recessive disorder. The disorder usually manifests at the time of weaning, the classical AE (Type I), or the disease starts early when the infants are still being exclusively breastfed (AE Type II). In the latter cases, the serum zinc is normal in the mother (60-120 µg/dL), but the breast milk zinc level is low, so the serum zinc level in the infant is decreased. The defect probably lies in the zinc binding ligand in the breast milk. Both clinical variants, however, have identical morphological expressions.

## CLINICAL FEATURES

Morphologically the condition starts as dry, scaly, eczematous plaques on the face, scalp, extremities, and anogenital areas which may worsen to form vesiculobulous pustular and erosive lesions. Hands and feet may become involved. Infection with bacteria or *Candida albicans* may supervene. Diarrhea may also accompany the disorder. Emotional and mental disurbances are commonly associated. Eye complications usually develop and include photophobia and blepharititis. Other manifestations include hypogeusia, anorexia, hypogonadism, anemia, and impaired wound healing (Fig. 47.1).

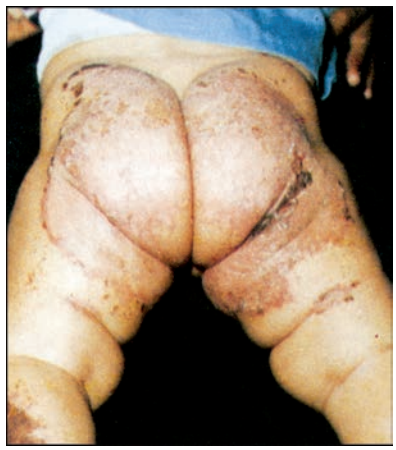


**Figure 47.1:** Acrodermatitis enteropathica

## DIAGNOSIS

It is made on the basis of characteristic morphology, and low serum zinc level (normal in Indian infants, ranges between 60-120 µg/dL).

## TREATMENT

The condition shows dramatic improvement within 48 hours after initiating zinc therapy in the form of zinc sulfate (220 mg; 55 mg Zn) with complete resolution within 7-10 days.

## RECOMMENDED READING

1. Sehgal VN, Jain S. Acrodermatitis enteropathica. *Clin Dermatol* 2000;18:745-748.

# 48 Chapter

# Exanthems

Viral illnesses may be accompanied by eruption of symmetric, erythematous, discrete rash composed of either macules, maculopapules, papules, vesicles, vesiculopustules, or petechiae. Such eruption are termed exanthems. The classic exanthems are still classified in a fascinating way, in the order in which they were described. Accordingly they are as follow:

- First disease — Measles
- Second disease — Scarlet fever
- Third disease — Rubella
- Fourth disease — Duke's disease
- Fifth disease — Erythema infectiosum
- Sixth disease — Erythema subitum

These exanthems have distinct and very characteristic incubation period, primary lesions, and distribution of the eruption and this is helpful in differentiating the exanthems. Amongst these exanthems, measles still has a high incidence, especially in developing countries and is discussed below.

## MEASLES

Measles is an exanthematous viral illness caused by myxovirus. It is spread by droplet infection and has an incubation period of 10 days (the range is 1 to 2 weeks).

### Clinical Features

The onset of measles is usually heralded by a prodrome of fever, malaise, bodyache and mild upper respiratory symptoms, and these represent the first viremia.

The prodrome is followed by invasion phase lasting about 1 week. It is characterized by fever, chills, malaise, sweating, prostration, headache, coryza with mucopurulent discharge, and a dry cough. The fever is classically biphasic. This is followed by the eruption of the characteristic, tiny, bluish white spots surrounded by a bright red, irregular halo, localized on the buccal mucosa, adjacent to the second molars. These are *Koplik's spots*. They rapidly increase in number, extending over the buccal mucosa. They begin to resolve with the appearance of the skin rash.

The exanthem appears 14 days after incubation. It begins as macular eruption in the scalp near the mastoid area, reaching the upper neck in a few hour. Face is involved by the second day. It then extends to the upper extremitites and the trunk. The macules evolve into soft blanchable papules, becoming confluent to form polycyclic bordered plaques. The exanthem fades in the areas of initial involvement first, turning brownish with fine scale.

Systemic symptoms and complications may occasionally complicate the benign course of measles and these include the following:

| | |
|---|---|
| Central nervous system | Non specific EEG change |
| | Encephalitis |
| | Myeloencephalitis |

| | |
|---|---|
| | Subacute sclerosing encephalopathy |
| Pulmonary system | Viral pneumonitis |
| | Bacterial bronchopneumonia |
| Gastrointestinal tract | Diarrhea |
| Others | Otitis media. |

Measles has following clinical variants:

Malignant measles characterized by high fever, hypotension, cutaneous and/or mucosal purpura and neurologic, respiratory and hematologic involvement.

## Differential Diagnosis

Drug eruptions form the main differential diagnosis. These drugs may have been prescribed *per se* or for the constitutional symptoms during the prodrome of measles. Discontinuation of all medicines, prescribed as well as procured over the counter is essential.

## Diagnosis

It is based on cardinal clinical features, the characteristic incubation period, and the distribution of the exanthems. It may be supplemented by Giemsa stained smear of mucopurulent nasal secretion, that reveal the following types of giant cells:

- Giant epithelial cells containing intranuclear eosinophilic granules and reticuloendothelial granules (Warthin-Finkeldey cells).
- Round or irregularly lobed multinucleated giant cells with 60 or more nuclei.
- Microscopic examination of hematoxylin-eosin stained sections of skin biopsy reveals intraepidermal giant cells.
- Electron microscopy to demonstrate intranuclear viral tubular aggregate.

## Treatment

It is supportive. Patients may be administered paracetamol for fever. Antihistamine may be prescribed to allay itch. Soothing shake lotions such as calamine are also useful.

## RECOMMENDED READING

1. Markowitz L, Preblud SR, Orenstein WA. Patterns of transmission in measles outbreaks in the United States, 1985-1986. *N Engl J Med* 1989; 320:75-81.

# 49 Chapter

# Chickenpox

Chickenpox (varicella) is a viral illness caused by varicella zoster virus, an icosahedral, 180 nm encapsulated herpes virus. Varicella is regarded as the primary manifestation of V-Z illness. Following its resolution, the virus lies dormant in the dorsal root ganglion. It may be reactivated at a later period to manifest as herpes-zoster.

## CLINICAL FEATURES

Varicella has an incubation period of 10 to 20 days. It is followed by a prodrome of mild to moderate fever, malaise, myalgia, and body-ache. This is followed by the cutaneous eruption.

The skin lesions begin as 2 to 4 mm sized scralatiniform pink papules, that turn into 3 to 4 mm sized, fragile superficial vesicles, surrounded by an erythematous halo (dew drop on a rose petal). Within a day, the vesicle turns turbid and develops a central umbilication. It then dries to form a crust. The crust is at first firmly adherent, but later on loosens and shed off in 7 to 21 days.

The lesions occur in successive crops and thus all stages of eruption may be visible. The distribution is centripetal. Face, trunk, and proximal extremities are characteristically involved. Palms and soles are spared.

Mucosal lesions may accompany skin eruption. Hard palate, anterior tonsillar pillars, palpebral conjunctiva, vulva, pharynx, and larynx may be affected.

## DIAGNOSIS

It is based on the cardinal clinical features. Dew drop on a rose petal' appearance is rather striking. It may be supplemented by laboratory examination including the following:

- Tzanck smear—reveals multinuclear giant cells with viral inclusion bodies.
- Histopathological examination of skin biopsy (Histologic findings are similar in herpes simplex, herpes-zoster and varicella).

## DIFFERENTIAL DIAGNOSIS

Smallpox was the main differential diagnosis for chickenpox. However, it has now been eradicated worldwide.

- Measles
- Impetigo
- Insect bites
- Smallpox.

## TREATMENT

It is divided into specific therapy and supportive treatment. Acyclovir is the specific antiviral

**Table 49.1: Aciclovir: Dosage schedule (Adults)**

| *Indications* | *Daily dosage* | *Duration* |
|---|---|---|
| Herpes simplex infections (Orofacial Herpes/Genital Herpes) | | |
| First episode | 200 mg × 5 times* | 5-10 days |
| Suppression of recurrent episode | 400 mg × 2 times<br>OR<br>200 mg × 2-5 times | up to<br>12 months |
| Intermittent therapy | 200 mg up to 5 times* | 5 days |
| Herpes zoster | 800 mg × 5 times* | 7-10 days |
| Chickenpox | 800 mg × 5 times* | 7-10 days |

* Every 4 hours while awake

**Table 49.2: Aciclovir: Dosage schedule (Children)**

| *Indication* | *Daily dosage* | *Duration* |
|---|---|---|
| Herpes simplex infections (treatment) | | |
| 2 years and above | Same as adults | |
| Less than 2 years | Half the adult dose | |
| Chickenpox | 20 mg/kg body weight | 5 days |
| Less than 2 years | (up to maximum 800 mg)<br>4 times daily<br>Or<br>200 mg × 4 times | 5 days |
| 2-5 years | 400 mg × 4 times | 5 days |
| 6 years and above | 800 mg × 4 times | 5 days |

agent useful in varicella. It may be administered in a dose of 800 mg, orally 5 times a day, for 7 days (Tables 49.1 and 49.2). Supporting therapy includes antipyretics like paracetamol, antihistamine and application of shake lotion such as calamine.

## RECOMMENDED READING

1. Tarlow MJ, Walters S. Chickenpox in childhood. A review prepared for the UK Advisory Group on Chickenpox on behalf of the British Society for the Study of Infection. *J Infect* 1998; 36:39-47.

# 50 Chapter Skin Structure

Skin is a fascinating organ. Melanin imparts color to the skin, and it adds to the personality of an individual. The color, however, varies according to the environment and the temperature. In cold temperature climate, usually the skin displays fair complexion, while in hot (tropics) the color is wheatish to dark. Protection of skin from ultraviolet rays is directly proportional to the pigment. Texture of the skin too shows variation. It is thick over the palms and soles and transforms itself into nails at the terminal end of the fingers and toes. The skin is thin over the eyelids. Similarly variation in the hair growth is significant. Scalp hair is thick in both men and women while hair growth over the bread area is thick in men only. Pubic and axillary regions are covered with terminal hairs at puberty. The other parts of the body are covered with vellus hair.

There is a transition of skin to mucous membrane at the orifices, the mucocutaneous junctions. Some of the orifices are protected by hair which trap the suspected particles. Thus the skin not only serves to provide mechanical protection, but it also serves the following other functions, namely:

- Barrier function
- Temperature regulation
- Sensory function
- Synthesis of vitamin $D_3$
- Protection from harmful ultraviolet rays
- Protection against pathogenic micro-organisms by resident microflora.

The microscopic structure of the skin is characterized by the epidermis, dermis and adnexa. The two structures, namely epidermis and dermis are fastened together by the highly specialized dermoepidermal junction. Subcutis subserves to insulate these structures.

## EPIDERMIS

It is an outer layer. It varies in thickness from 0.04 mm on the eyelids, to 0.16 mm on the plams. The average thickness is 0.1 mm. It is a stratified squamous epithelum. It takes 28 days for the keratinocytes to move from the stratum basale to stratum corneum. It is composed of the following 4 layers:

*Stratum basale:* It is the deepest layer formed by columnar cells placed perpendicular to the skin surface. The cellular multiplication occurs in this layer.

*Stratum spinosum/Prickle cells layer:* It consists of 5 to 12 layers of polyhedral cells connected to one another by intercellular bridges. Areas of thickened membranes at the point of contact of adjacent keratinocytes are termed 'desmosomes'. There is also intercellular cement like substance that holds the cells together.

*Stratum granulosum:* It lies superficial to the prickle cell layer and is comprised of flat, fusiform cells that contain keratohyaline granules. It is 1 to 3 layers thick.

*Stratum corneum:* This is the most superficial layer that consists of anucleated, flattened, cornified cells.

The cells constituting the epidermis are of the following kinds.

### *Keratinocytes*

They are the principal cells of the epidermis. They originate from ectoderm. They undergo characteristic change as they progressively move upward from the basal to cornified layer. The cytoplasm of basal keratinocytes contains abundant rough endoplasmic reticulum, ribosomes, golgi bodies, and mitochondria. These cells actively synthesize tonofilaments that are precursor of keratinuous protein. As they ascend, more and more tonofilaments aggregate.

Within the cornified layer, aggregates of tonofilaments, rich in free sulphydryl group form a fibrous protein termed as alpha keratin; that is, embedded in the sulphur rich amorphous matrix. The amorphous protein of the matrix is derived from keratohyaline granules. These granules appear in the upper spinous layer and become prominent in the granular layer. Lamellar granules (Odland bodies) also appear in the upper spinous layer. They form bipolar phospholipids, glycoproteins, and acid phosphates. Concurrently, the nuclei and cytoplasmic organelle gradually disappear as the keratinocyte matures into cornified cell.

### *Melanocytes*

They are the dendritic cells, localized amongst basal keratinocytes. They synthesize and secrete melanin containing organelle called melanosomes. They are derived from the precursors in the neural crest. The dendrites of the melanocytes extend in all direction between adjacent keratinocytes. The ratio of the melanocytes to keratinocytes in the basal layer is 1:4 to 1:10. However, overall one melanocyte is associated with an average of 36 keratinocytes. This is termed epidermal-melanin unit. The melanin imparts color to the skin and protects it from harmful effects of sunlight by scattering and absorbing UV rays.

### *Langerhan's Cells*

They are the dendritic cells situated in the mid-epidermis. They originate from the mesenchymal precursors in the bone marrow. They can be stained and detected by peroxidase labeled monoclonal antibody of OKT6. Ultrastructurally they are characterized by a folded nucleus and distinct intracytoplasmic organelles called Langerhan's or Birbeck granules. These granules resemble a tennis racquet. Langerhan's cells play a role in induction of graft rejection, immunosurveillance and in immune reaction of the delayed hypersensitivity type especially allergic contact dermatitis. They also produce interleukin-1 that is required for T cell activity.

### *Merkel's Cells*

They are the dendritic cells that originate in the ectoderm of the neural crest. They are located above the basement membrane and contain intracytoplasmic neurosecretory granules. They are supplied by myelinated nerves that loose their myelin sheaths near the epidermis and continue onward as unmyelinated axons surrounded by cytoplasm and basement membranes of Schwann's cells. The apposition between Merkel's cells and axon terminals

exhibits features of synapses. They function as slow adapting touch receptors.

## Adnexa of the Epidermis

The adnexa of the skin is constituted by the eccrine glands, apocrine glands, and the pilosebaceous apparatus.

### *Eccrine Glands*

These are distributed all over the body except the vermillion border of the lips, nailbeds, labia minora, glans penis, and inner aspect of the prepuce. Their density is maximum on the palms, soles, and axillae. They are composed of three components, viz (i) the secretory portion, (ii) the intradermal duct, and (iii) intraepidermal duct. The secretory portion lies at the interface of the dermis and subcutaneous fat. It is composed of one layer of secretory cells surrounded by a layer of flattened myoepithelial cells. The secretory cells are of 2 types, namely the large, pale, glycogen rich cells and dark staining, smaller cells. The paler cells initiate the sweat formation while the dark cells modify it by actively reabsorbing sodium. The intradermal eccrine duct is composed of two layers of small, cuboidal, deeply basophilic epithelial cells. The intraepidermal eccrine duct extends from the base of the rete ridges to the surface. It has a spiral course. It consist of a single layer of inner or luminal cells and two to three layers of outer cells. The secretory portion produces a precursor sweat that is isotonic with plasma. Subsequently aldosterone acts upon the epithelium lining, the eccrine duct and stimulates resorption of sodium in partial exchange for potassium. However, the duct is relatively impermeable to water. Hence the sweat that is excreted is hypotonic. It has a specific gravity of 1.005 and the pH is 4.5 to 5.5. It contains sodium, chloride, phosphorus, magnesium, iodide, sulfate, iron, zinc, amino acids, and proteins. The major function of sweat is to dissipate heat by evaporation. One liter of evaporated sweat removes 585 kilocalorie of heat from the body. An increase in body temperature of 0.01°C excites hypothalamic stimulation of sweating via the different pathway of the sympathetic nervous system.

### *Apocrine Glands*

Apocrine glands are located in the axillae, areolae, periumbilical, perineal, circumanal areas, prepuce, scrotum, monspubis, labia minora, external ear canal (ceruminous glands) and eyelids (Moll's glands). They are small and nonfunctional till puberty, after which they enlarge. The apocrine gland is composed of (i) a coiled secretory portion located in lower dermis and (ii) a straight excretory and that empties into the infundibulum of the hair follicles above the sebaceous duct. The secretory portion of apocrine gland is lined by a single layer of pale staining columnar cells. The nuclei of these cells is pushed toward the base. These are the secretory cells. Surrounding the secretory cells are (i) a layer of contractile myoepithelial cells, (ii) PAS positive basement membrane, and (iii) type III collagen and elastic fibers. The excretory duct is composed of two layers of cuboidal cells. Apocrine secretions have no function in man. Bacteria present on the skin surface act upon these secretions to produce short chain fatty acid, ammonia, and other adoriferous substances.

### *Hair Follicles*

Hair follicles populate the entire skin surface with the exception of the palsm, soles, dorsa of terminal phalanges of the digits, glans penis,

and mucocutaneous junctions. Hair is different, biologically and morphologically, in different parts of the body. The fine hairs that cover most of the body surface are termed as 'vellus hairs', while the long, coarse, pigmented hairs present over the scalp, eyebrows, eyelashes, beard, moustache, axillae, and pubic region are the 'terminal hairs'. A particular hair follicle may produce different kinds of hair during different stages of life. At puberty, the hair follicles at the axillae, pubes, and beard area start producing terminal hairs in contrast to vellus hairs in the prepubertal period.

During embryogenesis, mesenchymal cells in the fetal dermis collect below the basal layer of the epidermis. Epidermal buds grow down into the dermis at these sites. The developing follicle forms at an angle to the skin surface and continues its downward growth. At the base, the column of cells widens and surrounds the collection of mesenchymal cells forming hair bulb. The hair is formed from cells just above the bulb. Along one side of the follicle, two buds are formed. The upper one develops into sebaceous gland and the lower one into three segmets: (i) the infundibular segment, which extends from the surface opening to the sebaceous duct, (ii) the isthmus which lies between the sebaceous duct and the insertion of arrector pili muscle, and (iii) the maxtrix, which includes the lower most portion of the hair follicle, that lies below the attachment of arrector pili muscle.

The germinative matrix cells of the hair bulb differentiate along the seven separate pathways forming the seven layers. From outside inwards they are: (i) the outer root sheath, (ii) Henle's layer of the inner root sheath, (iii) Huxley's layer of the inner root sheath, (iv) the cuticle of the inner root sheath, (v) the cuticle of the hair shaft, (vi) the cortex of the hair shaft, and (viii) the medulla of the hair shaft.

The growth of the human hair is cyclical. However, each follicle functions as an independent unit and undergoes intermittent stages of activity and quiescence. The growing phase is "anagen". During this phase the cells of the hair bulb actively divide and produce the growing hair. The average duration of anagen is 3 to 10 years. On cessation of this phase, the follicle enters the transitional phase or "catagen". During this phase, the matrix cells stop dividing. The hair develops a brush like zone (club hair). The lower portion of the follicle disappears leaving behind a thin strand of epithelial cells surrounded by a thick basement membrane zone. This phase lasts for 3 to 4 weeks. Next is the resting phase or "telogen". During this phase, the epithelial strand shortens to the level or arrector pili muscle and leaves a small aggregate of epithelial cells exposed to the surrounding dermis. The club hair remains within the shortened follicle until a new anagen hair develops and dislodges it. The telogen lasts about 3 months.

### *Sebaceous Gland*

Sebaceous glands are lipid producing structures that arise as outgrowth from the upper portion of hair follicles. They are distributed throughout the skin except the palms and soles. They are associated with the hair follicle except at certain sites, namely the eyelids (meibomian glands), the buccal mucosa and the vermilion border of the lip (Fordyce spots), the prepuce (Tyson glands), and female areolae (Montgomery tubercles). Microscopically, they are seen to consist of lobules of pale staining, lipid rich cells that are surrounded by an outer layer of

cells resembling basal cells, i.e. the germinative cells. The lipid laden cells arise from the germinative cells. These lipid rich cells gradually disintegrate into an amorphous mass of lipid and cellular debris (sebum); that is, discharged into the sebaceous duct.

### *Nail Unit*

It is comprised of the nail plate and the tissues around and underneath it. The nail plate is hard, convex, rectangular, and translucent. It is about 0.75 mm in thickness and is situated on the dorsal aspect of the distal phalanx of every finger and toe. It is inserted into the grooves in the skin. The grooves are demarcated by folds of the overhaning skin that form the lateral and proximal nail folds. However, the distal edge of the nail is free. The nail plate rests on the nailbed. The nailbed is comprised of epithelium that overlies a richy vascular dermis. The dermis is contiguous with the periosteum of the distal phalanx. The apposing surfaces of the nail plate and nailbed are firmly attached and it is difficult to separate the two. Distal to the nailbed is the hyponychium. It is a narrow zone of skin that merges with the palmar skin and the tip of the digit. Finger nails grow at a rate of 0.1 mm daily. The growth of the toenails is slow. They lengthen by 0.03 mm every day.

The nail unit helps in the appreciation of the fine tactile stimuli. It also protects the terminal phalanges from trauma. Animals use nails for defence by scratching the opponent's skin with them.

## Dermoepidermal Junction (DEJ)

It represents a highly specialized attachment between the basal keratinocytes and papillary dermis. It serves to: (i) attach the epidermis to the dermis, (ii) provides support, and (iii) regulates the permeability across the epidermal-dermal interface. It can be stained by periodic acid Schiff (PAS) stain that reveals the (DEJ) as a thin magenta colored linear band beneath the basal keratinocytes. The ultrastructure study using electron microscopy shows it to be comprised of the following layers:

- The plasma membrane of the basal keratinocytes, which is comprised of the internal and external leaflets. The internal leaflet is studded at regular intervals with electron dense thickenings called "hemidesmosomes". Furthermore, the tonofilaments within the basal keratinocytes are aligned perpendicular to the hemidesmosomes
- Beneath the plasma membrane is an electron lucent band, 30 nm in thickness, termed lamina lucida. It harbors sub-basal dense plaque at regular intervals, usually located beneath the hemidesmosomes. This sub-basal dense plaque is traversed by anchoring filaments
- The basal lamina (lamina densa) lies beneath the lamina lucida. It is electron dense and measures 40 nm in thickness
- Below the basal lamina is a fibrous zone that harbors the anchoring fibrils, type III collagen, and microfibrils.

The dermoepidermal junction is actively affected in various bullous dermatosis, namely the pemphigoid, linear IgA dermatoses, chronic bullous dermatoses of childhood, herpes gestations, and epidermolysis bullosa of the junctional type.

## DERMIS

The dermis rests upon the subcutaneous fat and is 15 to 40 times thicker than the epidermis. It may be divided into two compartments, i.e. (i) a thin zone immediately beneath the

epidermis (the papillary dermis) and around adnexa (the periadnexal dermis) and (ii) a thick zone of reticular dermis. The dermis consists of non-cellular connective tissue composed of collagen, elastic fibers, and ground substance within which are embedded the nerves, blood vessels, lymphatics, muscles and pilosebaceous, apocrine, and eccrine sweat units. The constituents of the dermis are mesodermal in origin except for nerves which are derived from the neural tissue.

Collagen is the major stress resistant material of the dermis and provides a tensile strength to it.

### Reticulum Fibers

They represent a special type of thin collagen fibers that measure 0.2 to 1 μm in diameter. They are not recognizable with routine stains. However, they are argyrophilic and can be impregnated with silver nitrate. Reticulum fibers are the first formed fibers during the embryonic life and in various pathologic conditions associated with increased fibroblastic activity. In the normal skin, even though collagen is continuously replaced, however, the new collagen formed is not preceded by an argyrophilic phase. The reticulum fibers are found around the blood vessels and as basket like capsule around the fat cell. The pathologic conditions associated with reticulum fibers are the tuberculous and sarcoid granuloma, fibroblastic tumors such as dermatofibromas and fibrosarcomas healing wounds.

### Elastic Fibers

They consists of aggregates of protein filaments and elastin. The amino acids desmosine and isodesmosine are unique to the elastic fibers. The elastic fibers in the papillary dermis are fine while those in the reticular dermis are coarse. They play a role in maintaining the elasticity of the skin.

### Ground Substance (Matrix)

It is an amorphous extracellular material that enmeshes the fibrillar and cellular components of the dermis. It is composed of acid mucopolysaccharides, principally hyaluronic acid, chondrotin sulfate and dermatan sulfate, neutral polysaccharides, and electrolytes.

### Vasculature

The dermal vasculature is formed by the superficial and deep plexus. The superficial plexus lies within the papillary dermis. It is parallel to the epidermis and sends capillary end arterioles, and venules to the dermal papillae. The deep plexus is located in the deep reticular dermis, just adjacent to the subcutaneous fat. It is comprised of larger blood vessels. The superficial blood vessels communicate with the deep plexus.

Glomus bodies, specialized aggregates of smooth muscle located between the arterioles and venules, serve to shunt the blood from arterial to the venous side, by passing the capillaries. They are best developed on the digits. They are concerned with temperature regulation.

### Innervation

The skin is supplied by the somatic sensory and autonomic motor nerve fibers. The former mediate the sensations of pain, temperature, light touch, pressure, vibration, proprioception, itch and epicritic sensation. While the latter control the pilomotor activity and the vascular tone.

The sensory receptors of the skin may either be specialized end organs like Vater-Pacini's

corpuscles, Meissner's corpuscles, and mucocutaneous end organs, or they may be 'unspecialized' receptors. Vater-Pacini's corpuscles are located on the weight bearing surfaces in the deep portion of the dermis and in the subcutaneous tissue. They are also numerous in the lips, penis, clitoris, and nipples. They function as mechanoreceptor that detect the sensation of pressure. Meissner's corpuscles are found in the papillary dermis of the volar skin. They are most numerous on the finger tips. They act as rapidly adapting mechanoreceptors that detect the sensation of light touch. Mucocutaneous end organs are located in the papillary dermis of modified hairless skin at the mucocutaneous junction, namely the glans prepuce, clitoris, labia minora, the perianal region, and vermillion border of the lips. Temperature, itch, and pain sensations are transmitted by unmyelinated nerve fibers that terminate in the papillary dermis and around hair follicles. Impulses pass to the central nervous system by dorsal root ganglia.

Postganglionic adrenergic fibers of the autonomic nervous system regulate vasoconstriction, apocrine gland secretion and contraction of arrector pili muscles. Cholinergic fibers mediate sweat secretion.

# 51 Chapter Glossary of Clinical and Histopathological Terms

## Macule

It is a well-circumscribed change in the color of the skin, flush to the skin surface. It is of different shapes and sizes. It may result from hyper or hypopigmentation, vascular abnormalities (erythema), or purpura. They may be associated with fine scales and are then termed as maculosquamous. The common macular eruptions are disseminated, erythematous macules due to viral exanthems or drug eruption, ivory white macules of vitiligo, cafe'-au-lait spots of neurofibromatosis, and maculosquamous eruptions of pityriasis rosea, pityriasis versicolor, and erythrasma.

## Papule

It is a well-circumscribed, solid elevated lesion less than 5 mm or 1 cm in diameter. It projects above the plane of the surrounding skin. It may be the result of the following, such as: (i) metabolic deposits in the dermis, (ii) localized dermal cellular infiltrates, and (iii) localized hyperplasia of cellular elements in the dermis or epidermis. They may have variety of shapes such as acuminate follicular papules *(pityriasis rubra pilaris)*, dome shaped *(molluscum contagiosum)* or flat topped *(lichen planus)*. They vary in color and may be coppercolored *(secondary syphilis)*, lilac *(lichenplanus)*, yellow *(xanthomas)*, hemorrhagic *(cutaneous vasculitis)*, skin colored (adenoma sebaceum and amyloidosis). The surface may be verrucous in warts. Papules covered with scales are referred as papulosquamous, as in psoriasis.

## Plaque

It is a well-circumscribed alteration in the consistency/texture of the skin that may be either raised or depressed below the surface of the surrounding skin. Plaques are often formed by coalescence of papules. Psoriatic plaques are raised, erythematous with layers of silvery scales, disposed in a micaceous fashion. The plaques of lupus erythematosus are erythematous and covered with coarse scales dipping into the patulous hair follicles.

## Lichenification

It is a reaction pattern to repeated rubbing which results in proliferation of the keratinocytes and stratum corneum, in combination with changes in the collagen of the underlying dermis. The lichenified area appears as thickened, pigmented plaque with accentuated skin markings often resembling a tree bark. It is a feature usually associated with chronic itchy eruptions such as *neurodermatitis, atopic dermatitis or chronic eczema*.

### Nodule

It is a palpable, solid, round or ellipsoidal lesion. The depth of involvement and/or substantial palpability, rather than the diameter, differentiates a nodule from a papule. Nodules may be located in the epidermis or extend into the dermis and subcutaneous tissue. Thus the nodules may be of the following kinds:

- Epidermal, *(Keratoacanthoma, basal cell carcinoma)*
- Epidermal-dermal, *(Malignant melanoma, squamous cell carcinoma)*
- Dermal, *(Dermatofibromas, histoid leprosy)*
- Dermal-subdermal *(Erythema nodosum)*
- Subcutaneous *(Lipomas)*

### Wheal

It is a rounded or flat topped elevated lesion that is characteristically ephemeral, disappearing within a few minutes, hours or days. It is an expression of vascular response and is a characteristic feature of acute and chronic urticaria.

### Vesicle

It is a well-circumscribed, elevated lesion that contains fluid. It is less than 5 mm in diameter. The walls of the vesicles are thin and translucent, and the contained serum, lymph, or extracellular fluid is visible through them. A bulla is a bigger vesicle which has acquired a size more than 5 mm. The vesiculobullous eruptions may be epidermal or subepidermal. The epidermal vesicles may arise, secondary to the following, such as (i) spongiosis as in eczema, (ii) acantholysis as in *pemphigus,* (iii) or as a result of ballooning degeneration of epidermal cells as in cases of viral infections e.g. *herpes simplex* or *herpes zoster*. Impetigo is characterized by subcorneal bulla. Subepidermal vesiculobullous eruptions are characteristic of *pemphigoid, linear IgA dermatoses*, and *dermatitis herpetiformis*.

### Pustule

It is a well-circumscribed lesion that contains purulent exudate comprising leukocytes. The exudate may contain the bacteria as in *impetigo*, and *folliculitis* or may be sterile as in *pustular psoriasis*. Pustules may vary in shape, size, and color.

### Furuncles and Carbuncles

A furuncle is a deep necrotizing form of folliculitis with pus accumulation. Several furuncles coalesce to form a carbuncle. Diabetic carbuncle is classic.

### Abscess

It is a localized accumulation of purulent material, so deep in the dermis or subcutaneous tissue that the pus is not visible on the skin surface (*Ischiorectal abscess* or *needle abscess*).

### Cyst

It is a sac that contains liquid or semisolid material and is resilient to touch. Fluctuation is easy to elicit (*Sebaceous cyst).*

### Atrophy

It denotes a diminuition in the size of a cell, tissue, organ, or a part of the body. Epidermal atrophy is the thinning of the epidermis due to the decrease in the number of epidermal cells. The atrophic epidermis is transparent and may or may not retain the normal skin lines. It may be associated with alteration in the dermis. The underlying veins and tendons may become visible. *Senile degeneration, actinic degeneration*, and *discoid lupus erythematosus* may produce epidermal atrophy. Dermal atrophy results from decrease in the papillary and/or reticular dermal connective tissues and manifests as a depression of the skin. Dermal atrophy may occur with or without accompanying epidermal

atrophy. In the former, as in *pregnancy, Cushings disease* or *necrobiosis lipoidica* there may be loss of skin markings, increased translucence, and localized depression of skin. In the latter, the area of skin is normal in color and the skin markings are retained because the atrophic changes are confined to the dermal tissue. Atrophy may be noted in *morphea, chronic discoid lupus erythematosus, scleroderma, dermatomyositis, chronic radiodermatitis, and lipodystrophy*.

### Ulcer

An ulcer is a discontinuity of the epidermis and at least a part of papillary dermis. It, therefore, heals with scarring. An ulcer is described in relation to its location, borders, base, floor, and discharge. It may arise as a result of trauma, tissue infarction, granulomatous inflammation (*Deep mycosis, syphilis, tuberculosis),* a variety of parasitic and bacteriologic disorders, and secondary to neoplasms.

### Erosion

An erosion is a well-circumscribed, moist, depressed lesion that results from loss of all or a portion of the viable epidermis. It heals either by hypo- or hyperpigmentation without scarring (*Pemphigus, erythema-multiforme*, and *traumatic erosions*).

### Scaling

Abnormal shedding or accumulation of stratum corneum in perceptible fleck is called scaling. Scales may develop over macules or papules referred to as maculosquamous and papulosquamous. The nature of the scale may characterize a particular disorder. In *psoriasis*, the scales are thin, dry, brittle, silvery white, and micaceous in disposition. In *seborrhea* they are greasy and greyish white or yellow in color. Fish like scales occur in *ichthyosis.*

### Crust

It develops when serum, blood, or purulent exudate dries on the skin surface and is characteristic of pyogenic infection. 'Stuck on' crusts are feature of *impetigo.*

### Excoriations

They are superficial excavations of epidermis that may be linear or punctate and result from scratching. The classical example of excoriations are *pediculosis, scabies, dermatitis artefacta.* However, they may be produced by any pruritic dermatoses.

### Sclerosis

It refers to a circumscribed or diffuse hardening of the skin. It occurs in *porphyria*. It may result from either dermal or subcutaneous edema, cellular infiltration, or collagen proliferation. *Scleroderma, morphea*, and *porphyria cutanea tarda* are its examples.

### Acantholysis

This refers to the loss of cohesion between neighboring epidermal cells subsequent to the damage in the region of their desmosomes. It may be primary or secondary. Primary acantholysis develops amongst unaltered cells as a result of dissolution of intercellular substance. The individual keratinocyte becomes rounded off and separates from each other, forming an intraepidermal blister. The cells, subsequently, undergo degeneration. Such lesions are encountered in *pemphigus vulgaris, pemphigus foliaceus, benign familial pemphigus,* and *Darier's disease. Secondary acantholysis develops in altered*

*or damaged cells and occurs in viral infections, subcorneal pustular dermatosis*, and *neoplasia of squamous epithelium.*

### Acanthosis

It is a benign, localized increase in the thickness of the spinous layer. It may be encountered in *chronic eczema, lichen planus*, and *psoriasis*.

### Basement Membrane (Basal Lamina)

A homogenous band composed of filaments extending along the undersurface of the epidermal basal cells.

### Basement Membrane Zone

It is located beneath the basal cell layer and consists of basement membrane, lamina lucida, lamina densa, anchoring fibrils, and reticulum fibers. It is visible with periodic-acid Schiff stain.

### Caseation Necrosis

It is characterized by the appearance of pale, eosinophilic, amorphous, finely granular material, and the loss of structural outlines. Some pyknotic nuclei may be visible. It is encountered in *tuberculosis granuloma.*

### Dyskeratosis

It implies premature abnormal keratinization of individual epidermal cells. Benign type of dyskeratosis is encountered in *Darier's disease*, and *chronic benign familial pemphigus*, in both of which a low grade acantholysis occurs. The acantholytic, dyskeratotic cells are represented by corps ronds, which have a central, homogenous, basophilic, pyknotic nucleus surrounded by a clear halo. This is surrounded by a shell of basophilic dyskeratotic material. Neoplastic dyskeratosis, also known as individual cell keratinization, is encountered in Bowen's disease, solar keratosis, and squamous cell carcinoma. It manifests as homogenous, eosinophilic bodies about 10 nm in diameter that may show remnants of their nuclei.

### Hyperkeratosis

It implies an increase in the thickness of stratum corneum. It may be associated with hypertrophy of the granular layer with the sole exception of autosomal dominant ichthyosis where granular layer is diminished. However, it is important to recall that the structure of stratum corneum differs in various parts of the body. It has a dense laminated appearance over the palms and soles whereas it resembles a basket weave over flexible areas such as limbs and the trunk. Hyperkeratosis is encountered in disorders like *chronic dermatitis, occupational callosities, lichen planus*, and *chronic discoid lupus erythematosus.*

### Granuloma

Granuloma is an expression of delayed hypersensitivity reaction (Gell and Coomb *type IV*) to a relatively insoluble or nondegradable material. It is characterized by fairly well-delimited collection of mononuclear cells (lymphocytes and monocytes), in association with either epithelioid cells and/or multinucleated giant cells. *Tuberculosis leprosy, sarcoidosis*, and *deep mycoses* are chronic granulomatous disorders.

### Hydropic Degeneration (Liquefaction Degeneration)

A type of degeneration causing vacuolization of the basal cells. It occurs in *lupus erythematosus, dermatomyositis, lichen planus, poikiloderma atrophicans vasculare, erythema dyschromicum perstans*, and *lichen sclerosis et atrophicans.*

### Lichenoid Tissue Reaction

This reaction is characterized by inflammatory infiltrate in close approximation to the basal cell layer, invading it and obscuring the dermo epidermal junction. This results in cytolysis of keratinocytes and melanocytes leading to the formation of colloid bodies and pigment incontinence. It is a hallmark of *lichen planus, lichenoid drug eruption, lupus erythematosus, lichen melanodermatitis* and *poikiloderma atrophicans vascular.*

### Parakeratosis

Incomplete keratinization characterized by retention of the nuclei in the stratum corneum. The granular layer is often underdeveloped or absent. It is the hallmark of psoriasis. However, it represents a physiological event in the mucous membranes.

### Reticular Degeneration

It results in a peculiar type of intraepidermal blister which is the hallmark of some viral infections, namely, herpes zoster and herpes simplex. The infected keratinocytes become grossly enlarged due to nuclear and cytoplasmic swelling (ballooning degeneration) and eventually rupture. The remnants of cell walls, however, remain intact so that blister cavity is traversed by strands of cell walls, forming a multilocular blister.

### Pseudoepitheliomatous Hyperplasia

It is a reaction pattern of the skin to widely varying etiologies, characterized by irregular growth pattern of the acanthotic epidermis that has a tendency to invade the dermis. It is usually associated with dysplasia, loss of cell polarity, and some degrees of cellular atypia It is distinguished from squamous cell carcinoma by the conspicuous absence of hyperchromatism and loss of nuclear polarity, a hallmark of squamous cell carcinoma. Also, in pseudoepitheliomatous hyperplasia, the 'invasion' is restricted to dermis, above the level of sweat glands and the epithelial strands are infiltrated by inflammatory cells. Pseudoepitheliomatous hyperplasia is characteristic feature of granular cell myoblastoma, sptiz nevus, long-standing ulcers, long-standing viral, and fungal infections and granulomatous disorders.

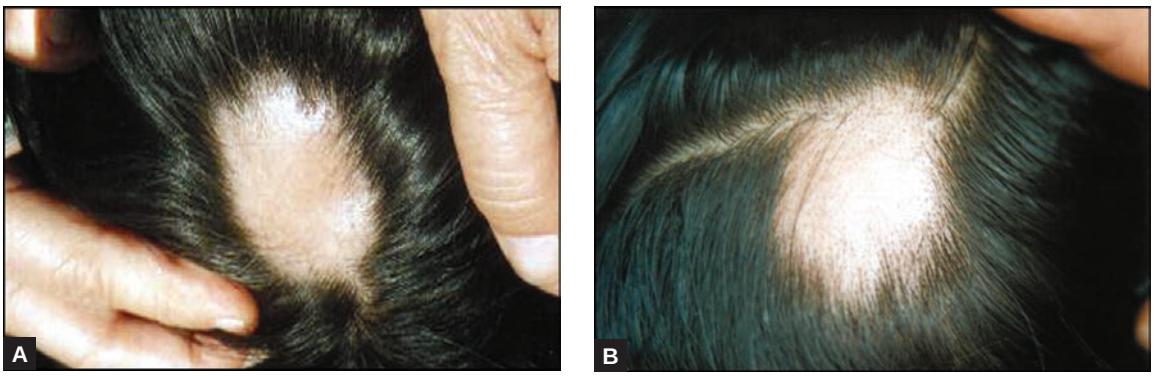
# 52 Chapter

# Alopecia Areata

Alopecia areata (AA) is a well-conceived clinical expression of local hair loss, characterized by well-defined round and/or oval patches. They are confined primarily to an apparently normal scalp/hairy skin. Undoubtedly, environmental factors are essential in initiating the disease. Its course is somewhat unpredictable. Usually, the disease is restricted to a few patches. They may have spontaneous partial/complete hair regrowth over a period of a few months or a year. However, recurrences are well documented, and several episodes of hair loss may be experienced during the lifetime. Alopecia areata may persist as a few chronic stable patches of alopecia. In a few, the disorder manifest spectral phenotypic expression, progressing to alopecia totalis and/or universalis. In these patients, alopecia may be extensive either from the outset/evolve to more severe forms from alopecia areata. Onset in children, atopy, ophiasis and/or onychodystrophy predicts poor prognosis. The treatment is only palliative. The unpredictability of its severity, frequency of recurrences, lack of definitive therapy, may have a negative impact on quality of life. Alopecia areata (AA) is a global phenomenon. Its demographics suggest that 0.05 to 0.1 percent of the population are likely to be affected with the disease at any given time. The active expression of alopecia areata in a population varies from region to region. Lifetime risk of AA is at 1.7 percent. It is an autoimmune disorder. It affects both women and men. The age-at-onset of the disease may be in any decade of life. However, it is generally regarded to develop in younger children.

## CLINICAL FEATURES

Alopecia areata may manifest either as marked hair shedding or with abrupt appearance of bald, circular patch(s), invariably noticed by the hairdresser. Its lesion in its limited form is characterized by well-circumscribed, round/oval patch(s) of alopecia. Its borders are well demarcated between the normal and affected scalp. Neither there are any scales, in-duration of the scalp or loss of follicular markings. On occasions the bald skin may have 'melanin incontinence' resulting in a blue color, a phenomenon usually seen in dark skin in contrast to blonde and red hairs individuals. `Exclamation mark' hair is yet its another noteworthy feature. It develops as lymphocytes accumulate around the hair bulb and the hair shaft which in turn is thinned by the effect of inflammation on hair matrix. The hair becomes aberrant with increasingly irregular shape and constriction of hair fibers. There is deposition of abnormal keratin, cuticle may be missing and there may be longitudinal cracks along the length of hair fiber. The resulting irregular constriction of hair gives it `weak spots'.

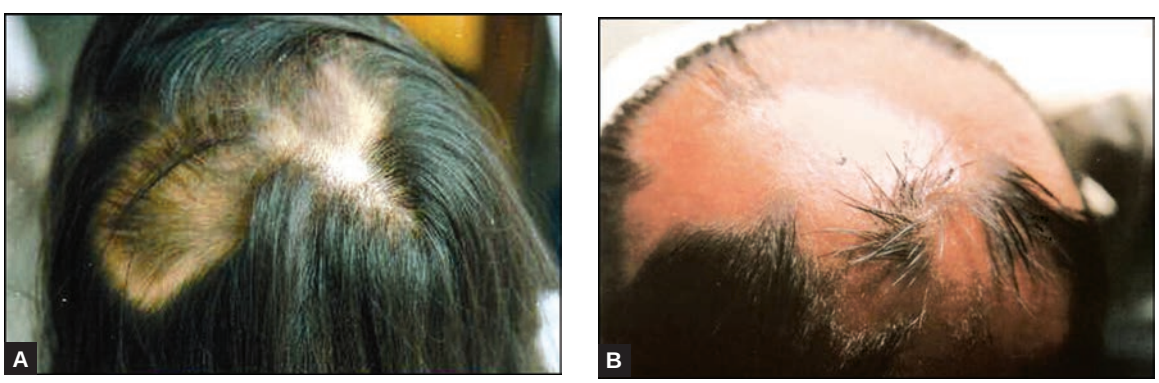



**Figures 52.2A and B:** Classical alopecia areata

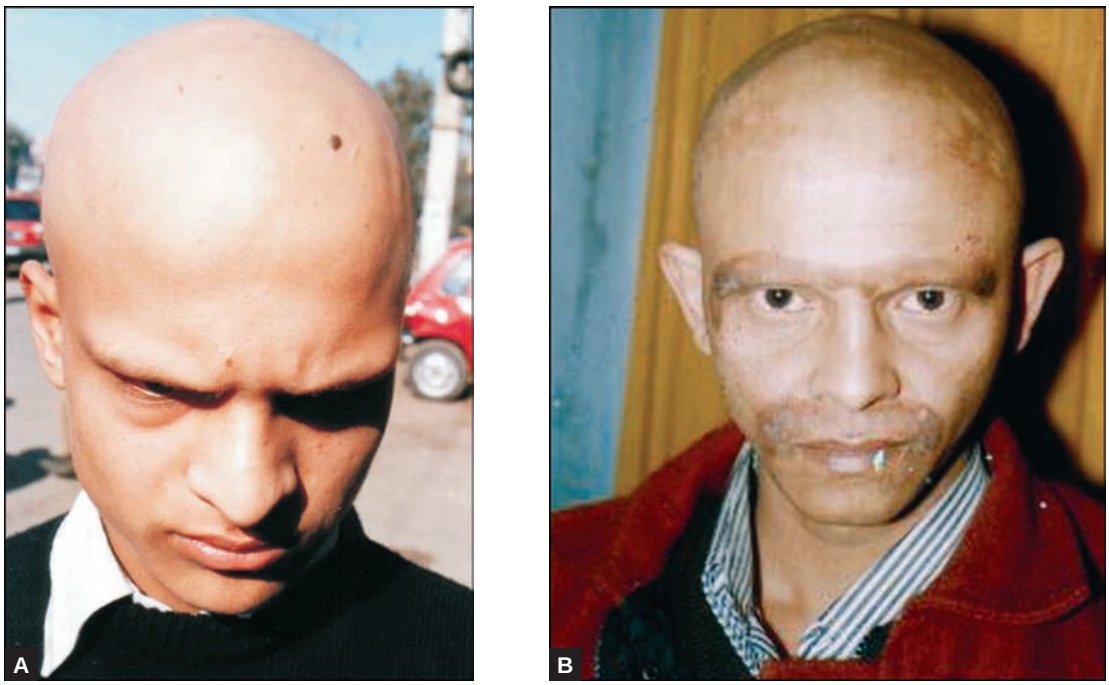
The progressively thinned hair shaft with weak spots emerges and continues to grow beyond the skin surface, before the hair cycle prematurely enters telogen phase. Its unsupported distal end withstands external trauma poorly and fractures, while the hair tapers and loses pigment proximally towards the scalp, giving it the appearance of `exclamation mark'. The 'pull test' may be positive at the margins of the patch, indicating active disease. Although hair loss is asymptomatic in most cases, itching, tingling, burning, or painful sensations may occasionally be experienced. These sensations may begin 1 to 2 weeks prior or during the period of active hair shedding. The patients may predict impending episode of alopecia areata. Pain is severe at times.

The initial lesion of AA is usually identified on the scalp, whereas the other sites are likely to go unnoticed. The occiput and fronto-vertical areas of the scalp are its initial common sites. The eyebrows and eyelashes may also be affected. The loss of hair may either be local or thinning of the eyebrows and eyelashes. Alopecia areata may, therefore, have several clinical variants depending upon the pattern of hair loss.

- Classical alopecia areata (AA), characterized by round and/or oval patches of hair loss (Figs 52.1A and B).
- Reticular alopecia areata (AA), where several patches of hair loss may coalesce to form a reticular pattern (Figs 52.2A and B). Discrete individual patches may coalesce to form either reticulate AA or else complete loss




**Figures 52.2A and B:** Reticular alopecia areata




**Figures 52.3A and B:** Alopecia totalis

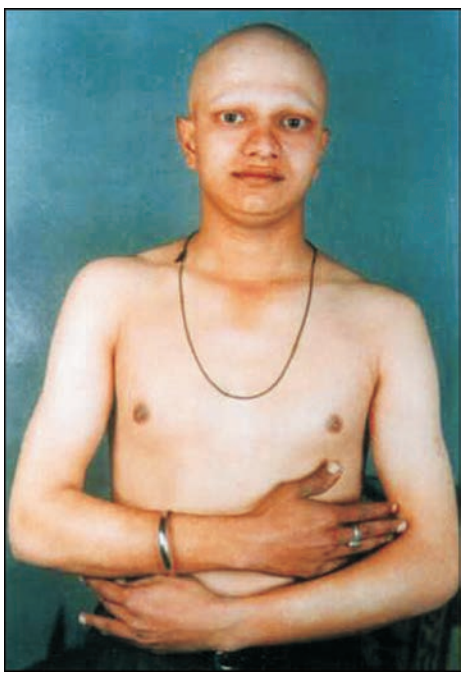


**Figure 52.4:** Alopecia universalis

of intervening hairs to produce alopecia totalis (AT) (Figs 52.3A and B), loss of all hairs on the scalp, or alopecia universalis (AU), where there is total loss of all hair on the body including the scalp (Fig. 52.4). At times alopecia may be extensive from its very outset, rather than progressing to AT or AU from AA. Acute diffuse alopecia areata may be the initial presentation of alopecia totalis, which may develop within 48 hours. As pigmented hairs are affected first, their preferential loss may produce overnight graying. Atopy, an association of autoimmune disease, family history of AA, young age of onset, nail dystrophy, extensive hair loss, and ophiasis are the indicators of poor prognosis.

- Ophiasis band-like AA, here hair loss covering the parieto-temporo-occipital scalp, is conspicuous.

- Ophiasis inversa (Sisapho), a rare-band like pattern of hair loss afflicting in the frontal parieto-temporal scalp in contrast to its preceding variant.
- Diffuse alopecia areata, characterized by a diffuse decrease in the hair density of the entire scalp. Chronic diffuse hair loss is very uncommon and requires either the demonstration of 'exclamation mark' or hair supportive histology to distinguish it from telogen effluvium.
- 'Alopecia areata nevi', a rare form of AA, is characterized by hair loss in the immediate vicinity of the mole/similar anomalous skin growth. The opposite of this has also been described in alopecia universalis where the hair within the hairy nevi remains unaffected. Nail changes may be seen in one, several or all nails. The dystrophy may precede, accompany or follow the resolution of alopecia areata. Pitting with irregular pattern/organized in transverse longitudinal rows, trachyonychia, Beaus' lines, onychorrhexis, onychomadesis, koilonychia, punctata or transverse leukonychia, and red spotted lunula may be its associated features.

## DIAGNOSIS

Forming the diagnosis of alopecia areata envisages a thorough visual examination of the affected hairy region in order to clearly define its conforming morphology *vide supra*. Should it fall into any of its clinical variants, hair pull test should be undertaken. Gently tug on a few stands of hair to see if the fibers pull out easily or they are firmly anchored to the hair follicle(s). At this juncture it is imperative to do hair analysis to find out the texture of the hair comprising, the hair shaft straight and have uniform thickness, are there any cracks, constrictions or bulges along the length of the hair shaft, is the cuticle intact/deformed, is the fiber twisted, knotted or kinked, is the fiber cross section round, oval or grooved, is the hair root healthy or malformed, is the exposed end of the hair cut, frayed, broken, are there any unusual particle on the hair fiber, are there mites, fungal structures. In a situation where fungal structures are identified it is essential to look for mycilia/ hyphae and/or spores on direct microscopy of potassium hydroxide/ sodium hydroxide (10–20%) mount of the scrapings and the hair to exclude tinea capitus. Furthermore, hematoxiline-eosin stained vertical and transverse section(s) prepared from a representative lesion may prove fruitful to ultimately establish its autoimmune status/ hair supportive histology to distinguish it from telogen effluvium/underlying pathology to exclude lichen plano-pilaris and pseudo-pelade.

## TREATMENT

Minoxidil (topical), a potassium channel opener that directly stimulates the hair follicles, forms its mainstay for it increases the duration of anagen and enlarges miniaturized and suboptimal follicles, irrespective of underlying cause. It is thus very effective in alopecia areata. It is intended for external application to the scalp only. A total dose of 1 ml (2–5%) should be applied twice daily to skin and surrounding hair that has been thoroughly shampooed and dried starting at the center of the affected area. The total daily dose should not exceed 2 ml. This twice-daily dosing schedule may be required for 4 months or longer before evidence of hair growth is apparent, and the onset and intensity of hair growth is variable amongst patients. Relapse to the original appearance

following cessation of the treatment has been anecdotal, and may occur within 3 to 4 months. Minoxidil should scrupulously be avoided in children less than 18 years of age. It should never be used in pregnant/lactating/breast-feeding mothers. Safety and efficacy of topical administered minoxidil in patients over 65 years of age have not been established. It is ideal to prepare the affected part of the hairy skin for optimal utilization of minoxidil. This is possible to achieve by thoroughly shampooing the area with ketoconazole (2%) solution and soak in for 3 to 5 minutes before rinsing. Make sure to thoroughly wash the skin itself and not just the hair. Usually a palm full of ketoconazole solution is adequate for one wash. This should be continued as long as the treatment is indicated with minoxidil solution. However, ketoconazole use should be restricted, if the person is oversensitive and responds by itching and/or redness of the skin. The use of preceding procedure and the management of alopecia areata is universal and may be deviated to include finasteride (1 mg) in alopecia universalis/totalis leaving the possibility for a synergistic action in combination exclusively for men.

## RECOMMENDED READING


1. Sehgal VN, Jain S. Alopecia areata: past perceptions. Int. *J Dermatol* 2002;41:189-190.
2. Sehgal VN, Jain S. Alopecia areata: clinical perspective and an insight into pathogenesis. *J Dermatol (Tokyo)* 2003;30:271-289.
3. Gollinick H, Orfenos CE. Alopecia areata pathogenesis and clinical picture. In: Orfonos CE, Happle R (eds). Hair and Hair Diseases. *Berlin, Springer-Verlag* 1990;p.529.
4. Safavi KH, Muller SA, Suman VJ, *et al.* Incidence of alopecia areata in Olmsted County, Minnesotta, 1975 through 1989. *Mayo Clin Proc* 1995;70: 628-633.
5. Price V. Alopecia areata: Clinical aspects. *J Invest Dermatol* 1991;96(Suppl):685.
6. Camacho F. Alopecia areata: Clinical features. Dermatopathology. In: Camacho F, Montagna W, editors. Trichology diseases of the philosebaceous follicle. Madrid: Aula Medical Group 1997;40: p.417.
7. Muralidhar S, Sharma VK, Kaur S. Ophiasis inversus: a rare pattern of alopecia areata [letter]. *Pediatr Dermatol* 1998;15:326-327.

# 53 Chapter Alopecia Androgenetica

Alopecia androgenetica/male pattern baldness/female baldness is an intriguing entity characterized by varying degree of loss of hair. It is largely an androgen dependent inherited disorder. Similar diffuse hair loss may occur in women as well. Its precise prevalence is not known. However, its reporting is fairly common, in particular, amongst ageing individuals. In order to understand the pattern in which the loss of hair from the scalp takes place, an endeavor has been made to classify them into grades in the past. Accordingly, the male pattern baldness has conveniently been delineated into 7 grades, while female baldness into 3 grades. The clinical details of baldness both in men and women are taken cognizance of and formed into precise details defining each one of them. There is likely to be a considerable overlap of the clinical features. Nonetheless, their outlines are imperative to form in an individual case.

## CLINICAL FEATURES

### Male Pattern Baldness

- *Grade 1:* It is marked by no/minimal recession along the anterior border of the hairline in the fronto-temporal region. Virtually, the hair over the scalp is normal/near normal (Fig. 53.1). Usually it is a feature seen before or at puberty.
- *Grade 2:* The loss of hair in this variant is uniform, and is primarily confined to the temporal region. It is usually bilateral and tends to be symmetrical (Fig. 53.2).

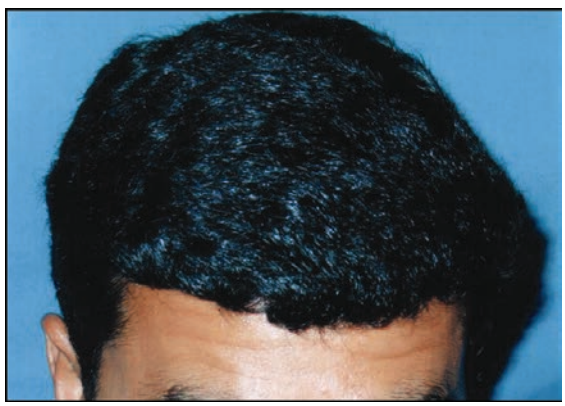


**Figure 53.1:** Male pattern baldness—Grade 1

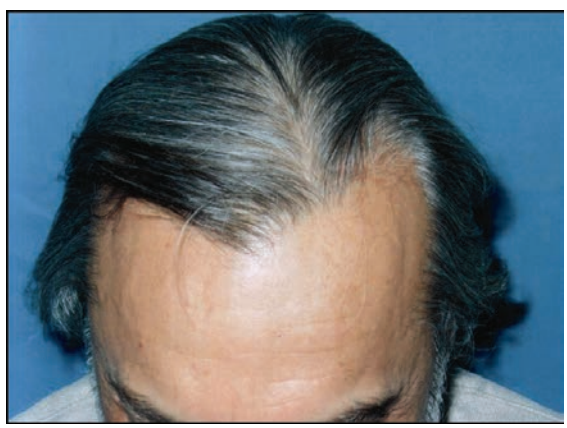
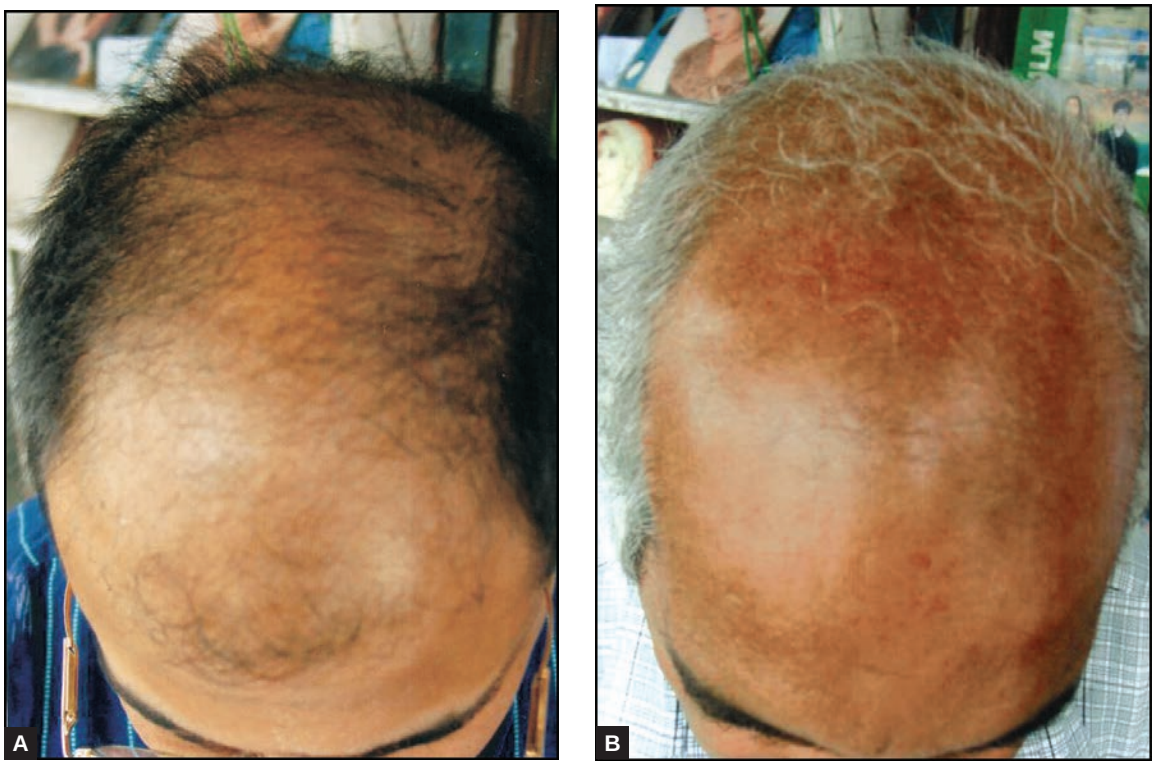


**Figure 53.2:** Male pattern baldness—Grade 2




**Figures 53.3A and B:** Male pattern baldness—Grade 3

It is popularly designated as bi-temporal recession, conforming to a triangle.

- *Grade 3:* This represents the minimal extent of hair loss sufficient to identify baldness. The scalp has either bare/sparse hair at deep fronto-temporal recession and are bilateral and symmetrical. The recession may extend posteriorly to a point, which lies about 2 cm anterior to a coronal line drawn between the external auditory meatus (Fig. 53.3A). Ultimately, the baldness may correspond to a pattern of horseshoe (Fig. 53.3B). Furthermore, there may be loss of hair affecting the vertex in addition. This pattern is commonly encountered as a manifestation of advancing age.
- *Grade 4:* It is an extension of the preceding variant, where frontal and fronto-temporal hair recession continues, and manifests in a pronounced way. The hair are either sparse or absent on the vertex. The areas of baldness are extensive and are separated from each other by a band of moderately dense hair that extends across the vertex. The band joins the fully haired fringe on each side of the head (Fig. 53.4).
- *Grade 5:* The vertex region of alopecia remains separated from the fronto-temporal region of alopecia. The separation is now not as distinct, because the band of hair across the crown has become narrow and sparse. Both the vertex and fronto-temporal areas of

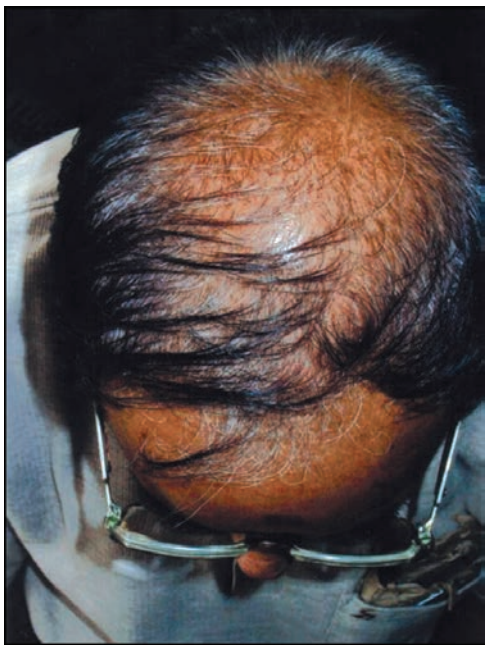


**Figure 53.4:** Male pattern baldness—Grade 4

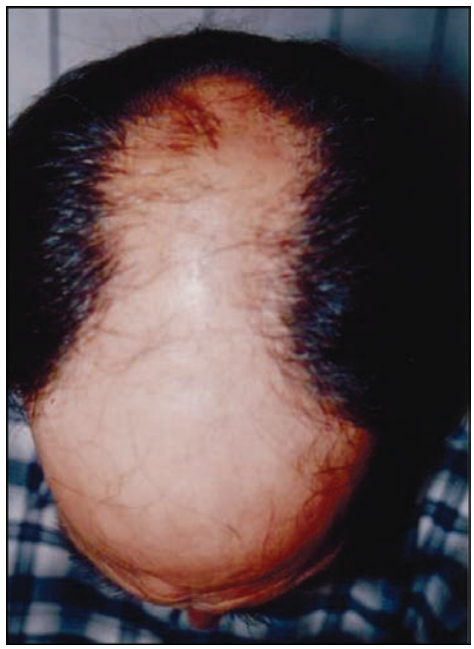


**Figure 53.5:** Male pattern baldness—Grade 5 and 6

alopecia have become larger. Viewed from above, grades 5, 6 and 7 are all characterized by areas of alopecia that are outlined by hair on the sides and back of the scalp, forming the shape of a horseshoe.

- *Grade 6:* The bridge of hair that crossed the crown in the previous type has now been depleted. The fronto-temporal and vertex regions of alopecia have become confluent, and in addition the entire area of alopecia has increased laterally and posteriorly (Fig. 53.5).
- *Grade 7:* It is a very conspicuous variant, and is characterized by a narrow horseshoe-shaped band of sparse hair around the scalp. It begins laterally just anterior to the ear and extend posteriorly to cover the occiput. Virtually, there is a complete loss of hair between fronto-temporal and vertical (vertex) region (Fig. 53.6).

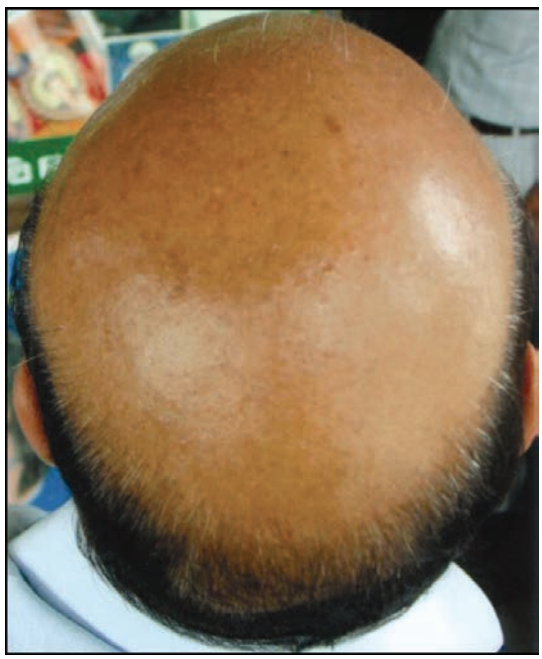


**Figure 53.6:** Male pattern baldness—Grade 7

It is prudent to use grade instead of type. There appears a considerable overlap in grades 5, 6 and 7 shown together in a box. It is worthwhile to consider them together and the line of demarcation amongst them should be erased.

### Female Baldness

- *Grade 1:* There is a perceptible thinning of the hair on the crown, limited in the front by a line situated 1 – 3 cm behind the frontal hairline (Fig. 53.7).
- *Grade 2:* Here there is a pronounced rarefaction of the hair on the crown within the area seen in the preceding variant (Fig. 53.8).

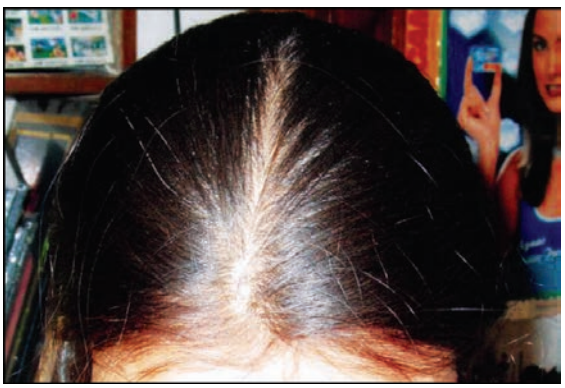


**Figure 53.7:** Female baldness—Grade 1

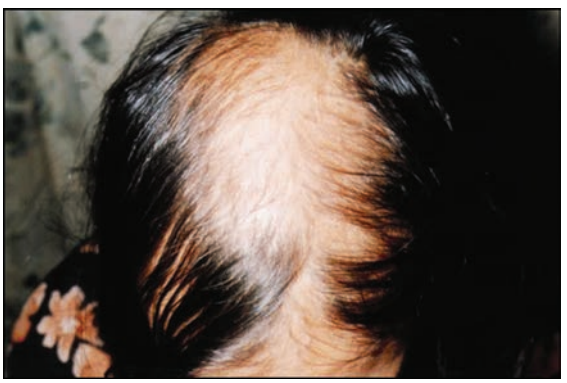


**Figure 53.8:** Female baldness—Grades 2 and 3

- *Grade 3:* It is identified as full baldness (total denudation) within the area seen in Grades 1 and 2 (Fig. 53.8).

## DIAGNOSIS

The diagnosis of male pattern baldness and that of female baldness is required to be formed by clear-cut recording of hair loss from the scalp on the attempted definitions (*vide supra)*. Visual examination of the scalp is paramount to establish the pattern of hair loss. It is worthwhile to inquire about: is it a limited focal/patchy hair loss; is it a diffuse pattern? Is the hair loss all over; is hair loss limited to the scalp, frontal, temporal or fronto-temporal, fronto-parietal or occipital regions of the scalp; is it asymmetrical or symmetrical in disposition. This should be supplemented by the form of hair loss namely: does the hair loss involve inflammation; is there any scar tissue; is there any crusting or scaling of the skin; are there any lumps and bumps in the skin; what does the hair looks like; is it healthy and shiny; is it lackluster, thin?' straight, curly, kinked. Hair pull test may prove useful in certain situation like alopecia areata. Hair analysis may be an adjunct. Besides, the family history of male pattern baldness may be a useful complement. The status of secondary sexual characters should also be carefully recorded. Accordingly, it is essential to undertake hormone bio-assay comprising determination of serum testosteron, follicular stimulating hormone (FSH), leutinizing hormone (LH) and prolactin levels. Wood's light examination may be a useful adjunct. Common hair loss disorders are displayed in the Table 53.1.

## TREATMENT

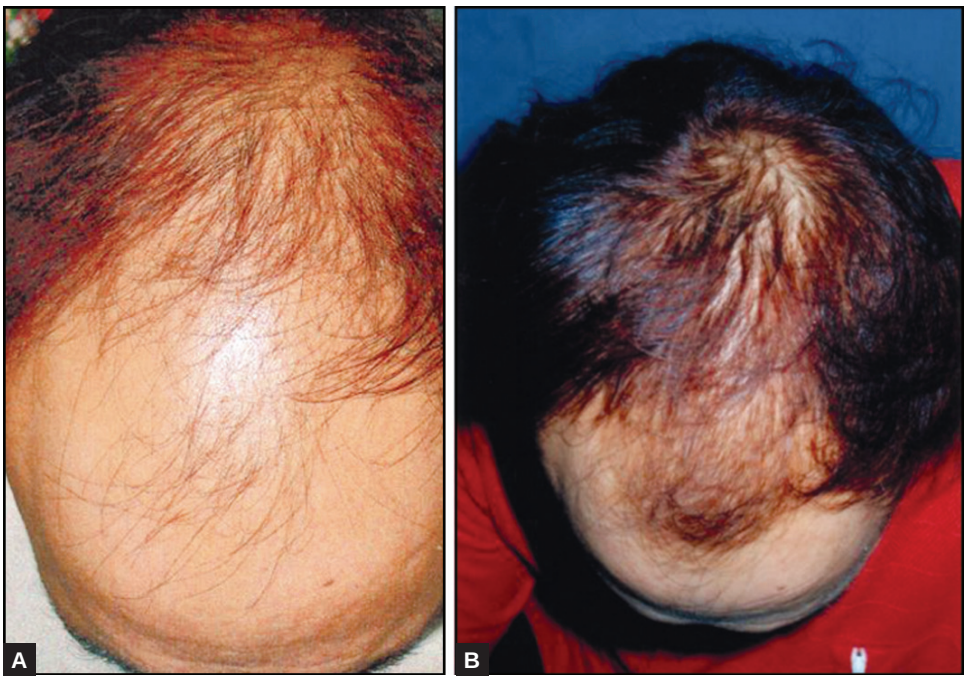
Treatment of male pattern baldness/female baldness is an intrigue and a taxing overture

**Table 53.1: Common hair loss disorders**

| | *Androgenetic alopecia* | *Telogen effluvium* | *Alopecia areata* |
|---|---|---|---|
| Hair loss distribution | Focal balding pattern: Hamilton/Norwood (men) ludwing (women) | Generalized | Usually patchy but can be generalized |
| Course | Gradual onset with progression | Onset abrupt/ Trigger factor | Onset abrupt; often waxes and wanes with relapses |
| Appearances | Thinning with or without bare patches. Bare patches are gradual, not abrupt | Thinning with no bare patches | Thinning with abrupt bare patches |
| Shedding | Minimal | Prominent | Prominent |
| Age-at-onset | Onset at puberty or older | Onset at any age, but usually not childhood | Onset at any age, majority have their first patch before the age of 20 |
| Pull test | Usually negative | Positive; telogen hairs | Positive; dystrophic anagen and telogen hairs |

in itself. It, therefore, envisages degreasing of the hair as well as the affected scalp. This is achieved through the use of detergents. Cetrimide (20% in isopropyl alcohol IP 10%) is the best initial bet. A handful of the solution is thoroughly applied over the wet hair. In a short time it is responsible to produce suds (foam), which should be carefully rinsed. This application is adequate to remove the grease and prepare it for the affective use of ketoconazole (2%)/ketoconazole (2%) with zinc-pyrithione (ZPTO 1%) w/v base quantity sufficient (QS). A handful of any of the latter is applied over the wet scalp for a period of 3–5 minutes, after which an affective rinsing of the scalp is done. The hair is dried with the help of a hair drier. The scalp is now ready to take on the application of Minoxidil (topical). It is a potassium channel opener that directly stimulates the hair follicles and thus forms the mainstay for it increases the duration of anagen and enlarges miniaturized and suboptimal follicles, irrespective of underlying cause (Fig. 53.9). It is thus very effective in male pattern baldness as well as female baldness. It is intended for external application to the scalp only. A total dose of 1 ml (2–5%) should be applied twice daily to the affected skin and surrounding hair that has been thoroughly shampooed and dried starting at the center of the affected area. The total daily dose should not exceed 2 ml. This twice-daily dosing schedule may be required for 4 months or longer before evidence of hair growth is apparent, and the onset and intensity of hair growth is variable amongst patients. Relapse to the original appearance following cessation of the treatment has been anecdotal, and may occur within 3 to 4 months. Minoxidil should scrupulously be avoided in children less than 14 years of age. It should never be used in pregnant/lactating/breastfeeding mothers. Safety and efficacy of topical administered minoxidil in patients over 65 years of age have not been established.

It is ideal to prepare the affected part of the hairy skin for optimal utilization of minoxidil. The afore mentioned step-by-step use of topical preparation should invariably be propped up by the addition of oral finasteride which has been recommended for an exclusive use in male pattern baldness. Finasteride 1mg tablet (UPS)




**Figures 53.9A and B:** Male pattern baldness—Before and after treatment

is administered once daily for a period of 3 to 12 months till a perceptible improvement in the form of re-growth of hair is seen (Figs 53.9A and B). The drug is, however, contraindicated in women, pregnant women and lactating women. It should not be used in children and elderly patients. Occasionally, its prolong use may result in tabulated side-effects.

## SIDE EFFECTS

- Decreased libido
- Decreased volume of ejaculate
- Erectile dysfunction
- Side effects disappeared in all men who discontinued therapy.
- Side effects disappeared in 56% men who continued taking finasteride through the 5th year.
- By the end of the 5th year, the incidence of side effects was ≤ 0.3 percent in men who continued treatment with finasteride *vs.* men on placebo.

Surely, when receding hairline affects the confidence of the patient with male pattern baldness, the initiation and sustenance of the preceding treatment may help in restoring his confidence.

- PUVA-therapy may also be another measure in male pattern and female baldness.

## RECOMMENDED READING

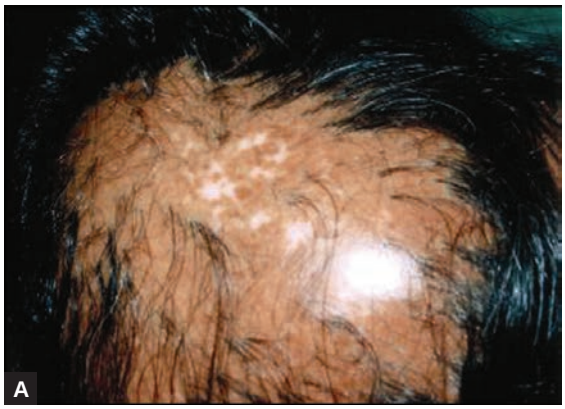
1. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. *Br J Dermatol* 1977;97:247-254.
2. Norwood OT. Male pattern Baldness: classification and incidence. *South Med J* 1975;68:1359-1365.
3. Hamilton JB. Patterned loss of hair in man: types and incidence. *Ann NY Acad Sci* 1991;53:708-728.

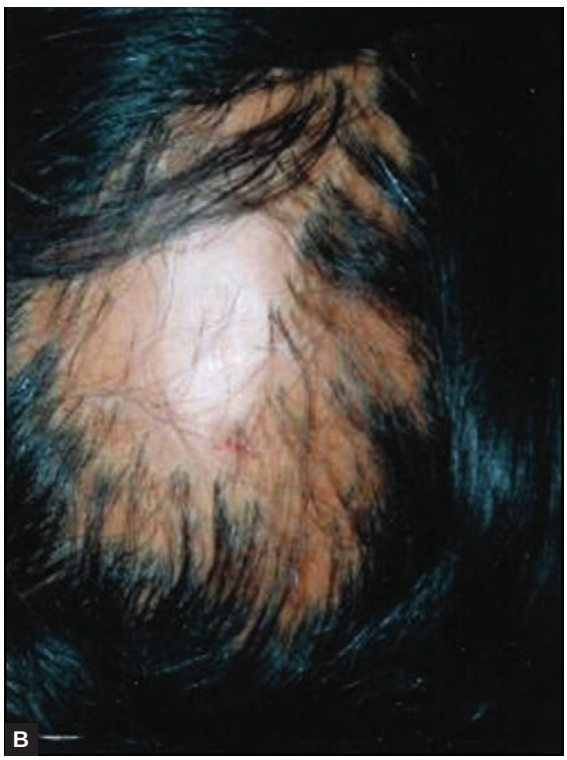
# 54 Chapter Cicatricial Alopecia

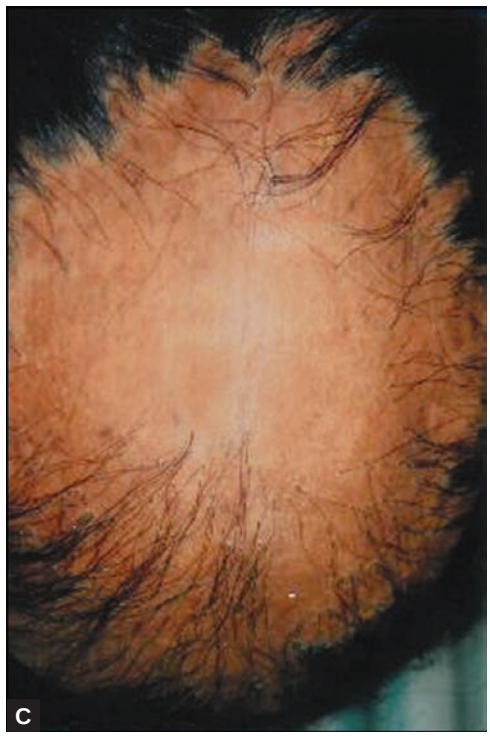
Cicatricial alopecia is a diagnostic dilemma. Most often the patient reports fairly late, because of their wholesome, relentless, and progressive natural course. Ultimately, it may be a reflection of a terminal event of several interrelated clinical conditions, recognized through their overt exhibition of idiopathic/known etiology. Nonetheless, an infamous overlap of several conditions responsible for cicatricial alopecia may prove elusive. The morphological expression of cicatricial alopecia may be grouped according to the natural course of the disease to form a spectrum. Lichen planopilaris, pseudopelade and discoid lupus erythematosis form one group, while folliculitis declavans, folliculitis (acne) keloidalis nuchae, and folliculitis mucinosis embrace the other. Furthermore, it is essential to support the clinical assessment by one time histopathology. There too it is likely to have an overlap. The dilemma may have to be addressed in right perspective by adopting newer techniques namely immunofloursence. The other group may be easier to diagnose because of their histopathological features. Cicatricial alopecias, following the inflammation of the hair follicle and associated pustule(s), include bacterial folliculitis, folliculitis decalvans and dissecting cellulitis of the scalp, acne necrotica miliaris, folliculitis (acne) keloidalis nuchae and tufted folliculitis. While, those following hair follicle inflammation only are pseudopelade of Brocq, follicular lichen planus, discoid lupus erythematosis, follicular mucinosis and alopecia parvimacularis.

## CLINICAL FEATURES

- *Pseudopelade of Brocq:* It is an asymptomatic, flesh colored, bald macules and/or plaques involving parietal scalp of the adults. In due course the lesions coalesce to form irregular, atrophic, bald patches with 'foot prints in the snow' appearance (Figs 54.1A to C). A widened sclerotic fibrous tract characterizes the two histological forms namely inflammatory and non–inflammatory. The irreversible alopecia is because of destruction of hair follicular stem cells located near the insertion of erector pilorum muscle. However, the end stage of morphoea in folliculitis decalvans, lichen planopilaris and discoid lupus erythematous are often similar to that of pseudopelade. Its etiology is still an enigma.
- *Lichen plano-pilaris:* It is an uncommon patchy alopecia, which mostly affects middle-aged women. Of the three clinical variants, the hyperkeratotic follicular papules are the commonest, while papulo-sqamous plaques and pseudopelade-like alopecia are infrequent




**Figures 54.1A to C:** Pseudopelade of Brocq

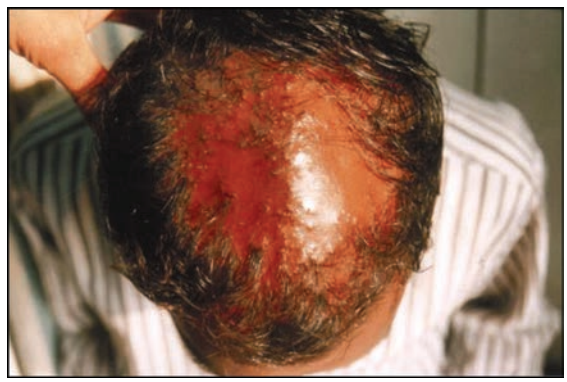
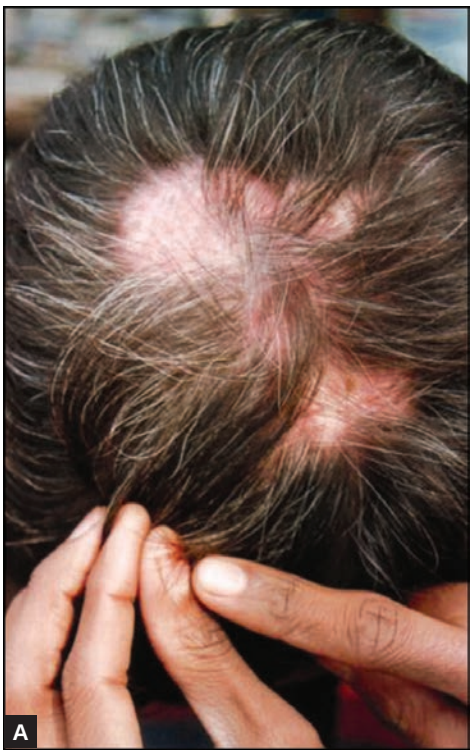
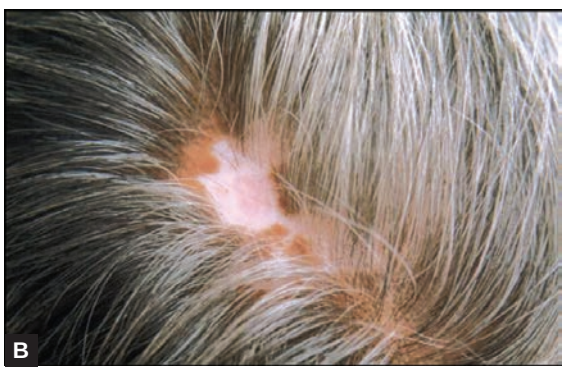


**Figure 54.2:** Lichen plano-pilaris

(Fig. 54.2). Graham–Little syndrome, a variant of Lichen planus, affects middle aged/elderly women. It is accompanied by wide spread keratosis pilaris, a progressive cicatricial alopecia of the scalp, and loss of auxiliary and pubic hair.

- *Discoid lupus erythematosis:* Scarring discoid lesions involve the scalp in 50 percent of chronic cutaneous lupus erythematosis, 10 percent of sub acute cutaneous lupus erythematosis and a few of symptomatic lupus erythematosis patients. In addition to scalp



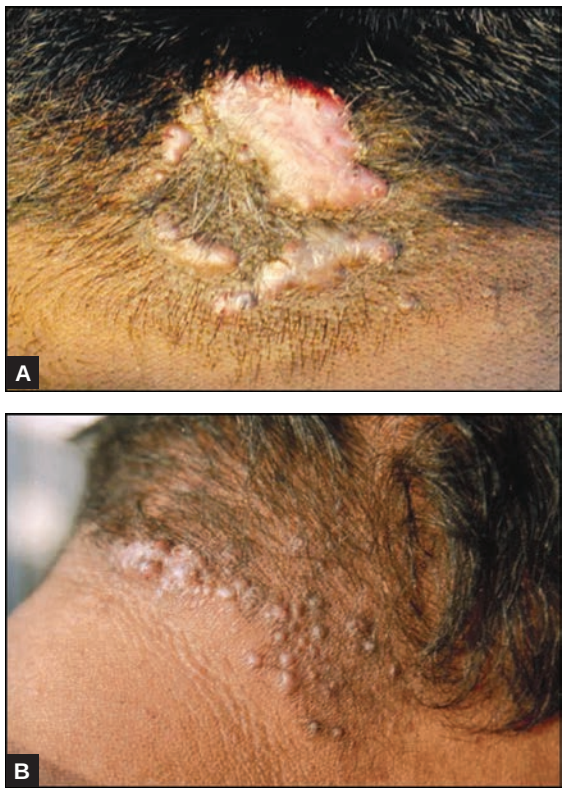

**Figures 54.3A and B:** Discoid lupus erythematosis

involvement the lesions are also present over the other parts of body. Lesion of the scalp often leads to bizarre pattern of cicatricial alopecia, clinically distinct from other disorders (Figs 54.3A and B).

- *Folliculitis decalvans:* Although of obscure primary etiology, yet folliculitis decalvans envisages all group of syndromes in which clinically evident chronic folliculitis lead to progressive scarring. A local failure of leukocytes function/immune response may be the underlying cause in many such disorders. It affects both men and women, the former is affected at a young age as compared to later. The scalp, axillae and pubic region are frequently affected. *Staphylococcus aureus* may be recovered on culture from the pustules. The disease may run a progressive and a relentless course despite antibiotic therapy.
- *Tufted folliculitis:* It is regarded as a variant of folliculitis decalvans. Clinically, a close grouping/tufting of the scalp hair is accompanied by edema and ulceration. It may either be self-limiting or lead to the formation of patches of cicatricial alopecia.
- *Dissecting cellulitis of the scalp (Perifolliculitis capitis abscedens et suffodiens):* It is a rare condition, it may manifest in the form of superficial and deep intercommunicating abscesses and wide spread scarring alopecia. A host of pathogenic organisms have been isolated from the lesions including streptococci, staphylococci and *Pseudomonas*. A protracted course, punctuated by remissions and relapses, warrant the use of systemic corticosteroids and antibiotics.
- *Alopecia parvimacularis:* It is a questionable entity. The term was coined to describe an epidemic of patchy hair loss in children living in clusters having close proximity. Numerous, small, irregular patches of alopecia with atrophic skin, were reversible in most children. However, scarring alopecia may develop in about 10-15 percent. It may represent a childhood variant of pseudopelade or lichen planus. Differential diagnosis

includes mycotic infection, multiple insect bites, and secondary syphilis.

- *Follicular mucinosis:* It may manifest in the form of follicular papules, associated redness and scaling extending to involve perifollicular area. A mucin deposit in long standing lesions is usual, and may be identified in the outer root sheath and sebaceous gland. This may eventually lead to the destruction of the hair follicle(s). One time histopathology is a useful adjunct, especially in mycosis fungoides. Follicular mucinosis /alopecia mucinosa is reversible in early stages.
- *Acne necrotica:* It is characterized by the occurrence of umbilicated follicular papulopustules. Subsequent necrosis may be an associated feature. The frontal scalp involvement is usual, the other body areas in addition may be affected. Adults are its frequent victims. The lesions are multiple and may vary from 5 to over 20. Healing leaves behind characteristic varioliform scar(s). The histopathology shows extensive infundibular necrosis and neutrophilic folliculitis.
- *Folliculitis (acne) keloidalis nuchae:* It is a chronic condition characterized by papular and/or pustular lesions localized to the nape of the neck, and occipital region (Figs 54.4A and B). Lesions often heal with keloidal scarring and alopecia of affected occiput. Previously it was thought to be a disease of Negros, now the condition is also encountered in India, and elsewhere in the world.




**Figures 54.4A and B:** Fulliculitis (acne) keloids nuchae

## DIAGNOSIS

Cicatricial alopecia has always been a diagnostic challenge. Invariably, the expert opinion is sought only when the disease has established itself, resulting in a permanent damage to the hair follicle. The use of indigenous treatment modalities may cause further damage to the hair follicle. It is, therefore, essential to form the precise diagnosis of the condition on the basis of clinical as well as histopathological features, stepwise details of which are depicted in Tables 54.1 and 54.2. Microscopic pathology and immunofluorescent studies, therefore, are paramount to ultimately establish its diagnosis. Often there is an overlap amongst different clinical entities, which need an astute assessment of the laboratory data as well. Perifollicular lamellar fibrosis, and completely fibrosed follicular tracts, a salient histology of fibrosing

**Table 54.1: Salient clinical features of dermatoses causing cicatricial (scarring) alopecia**

| | *Lichen planopilaris* | *Pseudopelade (Brocq)* | *Folliculitis decalvans* | *Follicular mucinosis* | *Discoid lupus erythematosus* | *Folliculitis (acne) keloidalis nuchae* |
|---|---|---|---|---|---|---|
| Age-at-onset | 3rd to 7th decade | 2nd to 4th decade | | Any age | | Young adults |
| Sex | Women | Women | Both young men and women | | 2nd to 6th decade, | Men |
| Symptom | Pruritus, mild to moderate | Asymptomatic | | | Sun light burning, pruritus and pain. | Painful |
| Morphology | Initial peri-follicular erythema, follicular acuminate/spinous papules, dilated hair follicles occupied by keratin plugs. Progressive scalp lesions, patterned alopecia. Presence of grayish blue, flat topped papules and/or plaques elsewhere on the glabrous skin erythematous shinny atrophic plaque(s) studded with occasional acuminate/ spinous papules (Fig. 54.1) | Non-inflammatory progressive patch(s) of partial/ complete alopecia marked by smooth, shinny, skin, isolated, tuft of hair patterned alopecia. occasional Peri-follicular erythema that too at the periphery. Acuminate/spinous papules/ lichen planus papules/ plaques are conspicuously absent. | Well-defined irregular to oval atrophic plaque (s) of alopecia, 'follicular pustules' at advancing margins. The lesions of long duration are devoid of the preceding features and may pseudopelade. Ultimate extensive cicatricial alopecia | Variable, ranges from scaly, erythematous induarted plaques/ nodules to non–inflammatory well-defined round /oval patches of transitory/ permanent alopecia. Lymphoma/ Hodgkin's disease may be associated requiring relevant investigation. | Erythematosis scaly papule/ progressively increasing plaque, form irregular atrophic de-pigmented or hyper-pigmented plaque. The dry scales are adherent and their shape corresponded to dilated hair follicle 'carpet tag'. usual sites scalp and face (Fig. 54.2). | Progressive follicular papules and/or pustules (abscess), followed subsequently by firm nodules confined to the nape of the neck, recalcitrant and may ultimately form patterned cicatricial alopecia. (Fig. 54.3) |

[*Courtesy:* Sehgal VN, Srivastava G, Bajaj P. Cicatricial (scarring) alopecia. *Int J Dermatol 2001;* 40: 241–248 (Blackwell Publishing/Synergy)]

**Table 54.2: Diagnostic parameters of histopathology of dermatoses resulting in cicatricial (scarring) alopecia**

| | *Lichen planopilaris* | *Pseudopelade (Brocq)* | *Folliculitis decalvans* | *Follicular mucinosis* | *Discoid lupus erythematosus* | *Folliculitis (acne) keloidalis nuchae* |
|---|---|---|---|---|---|---|
| Epidermis | • Orthokeratosis<br>• Keratotic follicular plugging | • Epithelial atrophy | • No Change | • Exocytosis of lymphohistiocytic infiltrate [In secondary forms] | • Hyperkeratosis with keratotic follicular plugging<br>• Thinning of stratum malphigii<br>• Hydropic change in basal layer<br>• Squamotization of basal layer (Fig. 54.3B) | No change |
| Dermal connective tissue | • Dense lymphocytic infiltrate hugging the epidermis (Fig. 54.2) | • Perivascular lymphocytic infiltrate in superficial dermis | | | • Lymphocytic infiltrate in the dermo-epidermal junction<br>Civatte bodies [Colloid bodies] may be seen. | |
| Hair follicle early | • Dense lymphocytic (perifollicular) infiltrate at the level of infundibulum and isthmus.<br>• Vacuolar change in the (stem cell) outer root sheath | • Loose lymphocytic infiltrate in peri-infundibular region<br>• Sometimes Inflammation may be totally absent | • Abscess formation around hair follicles<br>• Infiltrate is Predominantly neutrophilic with a few plasma cells and lymphocytes | • Vacuolar change with extensive cavitation of outer root sheath due to collection of acid muco-polysaccharides | • Inflation of lymphocytes and hair follicles and sebaceous glands<br>• Hydropic change in the basal layer of hair follicle | • Change are similar to Folliculitis decalvans (abscess formation) |
| Developed Lesions | • Peri-follicular fibrosis<br>• Infundibular epithelial atrophy<br>• Scarring | | • Chronic granulation tissue with foreign body giant cells around hair follicles | – | – | • Chronic granulation tissue with foreign body giant cell reaction, around naked hair follicle (Figs 54.4A and B) |
| Late Lesions | • Vertically oriented *fibrotic tracts* with dumps of degenerated elastic fiber and hair follicles | • Scar tissue replaces entire pilo-sebaceous unit. | • Fibrosis with collagen formation. | • Atrophy of hair follicles | • Atrophy of hair follicles | • Numerous thick bundles of sclerotic collagen |

[*Courtesy:* Sehgal VN, Srivastava G, Bajaj P. Cicatricial (scarring) alopecia. *Int J Dermatol 2001;* 40: 241–248 (Blackwell Publishing/Synergy)]

androgenitic alopecia in a pattern distribution in advanced stages, is indistinguishable from the end stage lichen plano-pilaris, pseudopelade/follicular degeneration syndrome, point to the existence of a spectrum of cicatricial alopecia. Accordingly, it is possible to explain the clinical and histopathological discrepancies and interchanging features. Advanced techniques of histochemistry, and both vertical and transverse sections of biopsy specimen(s) may enlighten about the predisposing disorder, and departure from one disorder to another at different stages of evolution.

## TREATMENT

It is befitting to recapitulate that cicatricial alopecia forms a definitive spectrum and has several clinical variants with revealing clinical and histopathological features, on its roll. Apparently, there is a considerable overlap. Many a time clear-cut delineation may be a far-reaching objective. Should there be any apparent precipitating factor(s), they should be effectively managed by creating awareness amongst the patients. Otherwise, specific treatment is called for to treat conditions like dissecting cellulitis of the scalp where administration of corticosteroids along with antibiotics may alleviate the condition. Similarly, folliculitis decalvans, folliculitis (acne) keloidalis nuchae may be amenable to antibiotic therapy with a *proviso* that the patient ensures early treatment. Lichen plano-pilaris should be treated as lichen planus. Cicatricial alopecia resulting from discoid/discoid disseminated/systemic lupus erythematosis should be managed by avoidance of direct sun exposure, administration of topical and intralesional glucocorticoids and the use of systemic local agents if significant local disease activity persists or systemic activity is superimposed. Options for systemic therapy in cutaneous LE are outlined below.

| | |
|---|---|
| Ist line | Hydroxychloroquine, chloroquine, quinacrine |
| IInd line | Dapsone, retinoids, etretinate, acitretin, thalidomide |
| IIIrd line | Clofazimine, gold |
| IVth line | Systemic glucocorticoids, oral prednisone intravenous methylprednisolone (Pulse), azathioprine, methotrexate, cyclophosphamide |

The initial adult dose of hydroxychloroquine is 400 mg (< 6.5 mg/kg) once/twice a day for several weeks/months depending upon the clinical response. Once an adequate response has been achieved, the daily dose should be decreased to a maintenance dose of 200–400 mg daily to minimize chances of recurrence.

## RECOMMENDED READING


1. Sehgal VN, Srivastava G, Bajaj P. Cicatricial (scarring) alopecia. *Int J Dermatol* 2001;40:241-248.
2. Nayar M, Schomberg K, Dawber RP et al. A clinicopathological study of scarring alopecia. *Br J Dermatol* 1993;128:533-536.
3. Headington J T. Cicatricial alopecia. *Dermatol Clin* 1992;14:773-782.
4. Olsen EA. *Hair disorders in Fitzpatrick's Dermatology in General Practice,* eds. Freedberg IM, Eisen AZ, Wolff K, et al, 5th Ed., vol. I, New York, McGraw Hill 1999;743-746.
5. Braun –Falco O, Imai S, Schmoeckel C, et al. Pseudopelade of Brocq. *Dermatologica* 1986;172:18-23.
6. Dawber RPR, ed. Cicatricial alopecia. In *Diseases of the Hair and Scalp,* 3rd edn. Oxford: Blackwell Science 1997;588-590.
7. Hermes B, Paus R. Scar forming alopecia. Comments on classification, differential diagnosis and patholbiology. *Hautarzt* 1998;49:462-472.
8. Zinkernagel MS, Trueb, RM. Fibrosing alopecia in a pattern distribution: patterned lichen planopilaris or androgenetic alopecia with a lichenoid tissue reaction pattern? *Arch Dermatol* 2000;136:205-211.

9. Sullivan JR, Kossard S. Acquired Scalp alopecia. Part 1: A review. *Australas J Dermatol* 1998;39: 207-219.
10. Sperleng LC, Mezebish DS. Hair diseases. *Med Clin North Am* 1998;82:1155-1169.
11. Kossard S, Lee S. Lichen planopilaris –keratosis lichenoids chronica revisited. *J Cutan Pathol* 1998; 25:222-227.
12. Sehgal VN, Bajaj P, Srivastava G. Lichen planopilaris [cicatricial (scarring) alopecia] in a child. *Int J Dermatol* 2001;40:461-463.
13. Sehgal VN, Bajaj P. Lichen planopilaris. *Int J Dermatol* 2001;40:516-517.
14. Chieregato C, Zini A, Barba A et al. Lichen planopilaris: report of 30 cases and review of literature. *Int J Dermatol* 2003;42:342-345.

# 55 Chapter

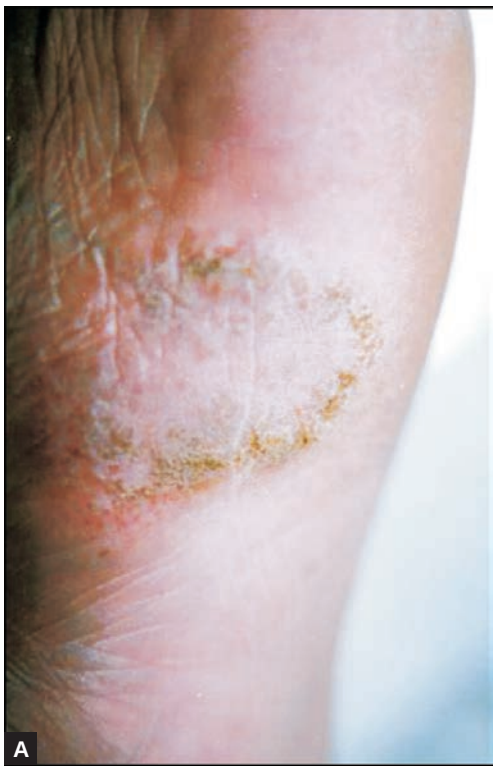
# Leprosy

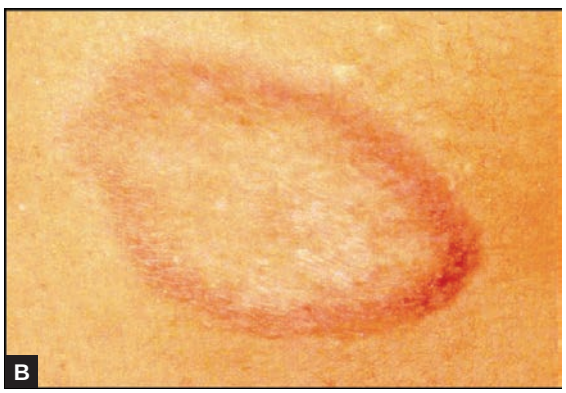
Leprosy, a chronic infective disease, caused by *Mycobacterium leprae*, is recognized to manifest as a spectrum. The spectrum has several peculiar clinical groups of which seven are well recognized. Indeterminate overt or concealed is their prelude. It is only later during the evolving immune responses that well formed clinical groups namely Tuberculoid Tuberculoid (TT), Borderline Tuberculoid (BT), Borderline Borderline (BB), Borderline Lepromatous (BL), Lepromatous Lepromatous (LL) and Neuritic Leprosy (NL) occupy their position on the spectrum. *Mycobacterium leprae* reservoir invariably is a patient who has any one of the preceding diagnoses. Intimate skin-to-skin contact is a strong source of transmission of the disease. However, droplet infection from respiratory and gastrointestinal track, have also been incriminated. In addition needle inoculation may also be responsible to cause the disease.

## CLINICAL FEATURES

In India a large proportion of leprosy continue to be paucibacillary with maximum numbers being from the borderline groups of the modified Ridley and Joplings immunological classification. This was earlier thought to reflect genetic/hereditary resistance. It may also be a reflection of the relative immaturity of the leprosy eradication in the community.

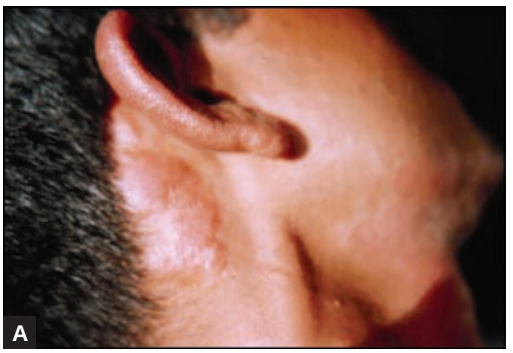
- *Indeterminate:* This expression of the disease is a prelude to the determinate forms of the disease. It is diagnosed when the lesion is a single or a few macules, with well- or ill-defined margins and variably impaired sensations. The surface may be smooth or mildly scaly, and a thickened nerve supplying the lesion(s) may or may not be palpable clinically. Indeterminate leprosy is treated with paucibacillary MDT.
- *Tuberculoid tuberculoid (TT):* Tuberculoid Tuberculoid (TT) leprosy is characterized by a well-defined uniformly circular or oval erythematous/hypopigmented plaque with maximal induration of the margin sloping towards the center and appearing like "a saucer the right way up". The surface is bald, dry and scaly, and completely, anesthesthetic (Figs 55.1A and B). TT lesions usually number from 1 to 3 in a patient and a thickened (sometimes tender) nerve to the lesion is usually palpable. TT leprosy is treated with paucibacillary MDT.
- *Borderline tuberculoid (BT):* Borderline tuberculoid (BT) leprosy is recognized as hypopigmented and/or erythematous macules/plaques with well-defined irregular margins (Figs 55.2A to C). The surface of the lesion(s) are bald, dry and scaly; and sensations are variably lost. The number of lesions may

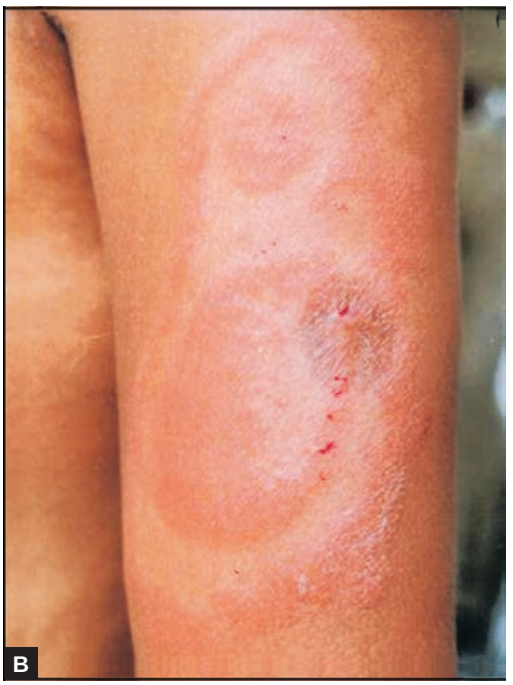


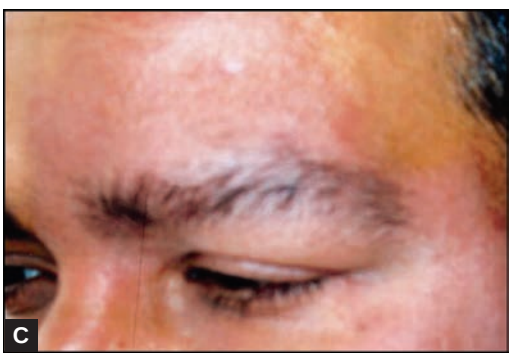




**Figures 55.1A and B:** Tuberculoid tuberculoid leprosy (TT)

vary from 3 to 10, and satellite lesions are a cardinal feature. Nerves to the area of skin lesion may be thickened and/or tender. The lesions tend to be localized to a region or one half of the body. They are treated with




**Figures 55.2A to C:** Borderline tuberculoid (BT)

paucibacllary MDT, if acid-fast bacilli are not demonstrated or total lesions number less than 5.

- *Borderline Borderline (BB):* Borderline borderline (BB) or mid borderline leprosy manifests the clinical morphology of BT as well as borderline lepromatous (BL) disease. The number of BT-type lesions tends to equal the number of lepromatous type lesions. The distribution of skin lesions tend to be bilateral, but asymmetric, and the number varies from a few to numerous and remains countable (Fig. 55.3). Nerves tend to be bilaterally but asymmetrically affected and are thickened and/or tender. There is variable/partial sensory loss over different types of lesions, but the loss tends to be continuous with the clinically apparent skin involvement. They are treated with multibacillary MDT.
- *Borderline lepromatous (BL):* Borderline lepromatous (BL) leprosy shares features of BB; however, lesions resembling BT are outnumbered by lepromatous lepromatous (LL) type of lesions. The lesions have variable sensory loss, tend to vary in number from countable to uncountable, and they are bilaterally distributed with a tendency towards symmetry. Symmetrical involvement of the nerves in the form of thickening and/or tenderness along with sensory loss not limited to clinically apparent skin lesions are features that help in diagnosis. BL leprosy is treated with multibacillary MDT.
- *Lepromatous lepromatous (LL):* Lepromatous lepromatous (LL) is a generalized disease with multisystem involvement, perhaps sparing only the central nervous system. Most strikingly involved are the skin, mucous membranes, nerves and reticuloendothelial systems. Lesions of skin are multiple, bilateral and symmetrical; and then start as hypopigmented (sometimes mildly erythematous), shiny, lesions, the margins of which are ill-defined and merge imperceptibly with the surrounding skin. With progress, there is increasing induration, particularly of the cooler areas of skin. Areas of gross localization of induration results in thick plaques and nodules. Characteristics involvement of the eyebrows, nose and lips, along with flattening of the bridge of the nose results in the classical 'leonine facies'

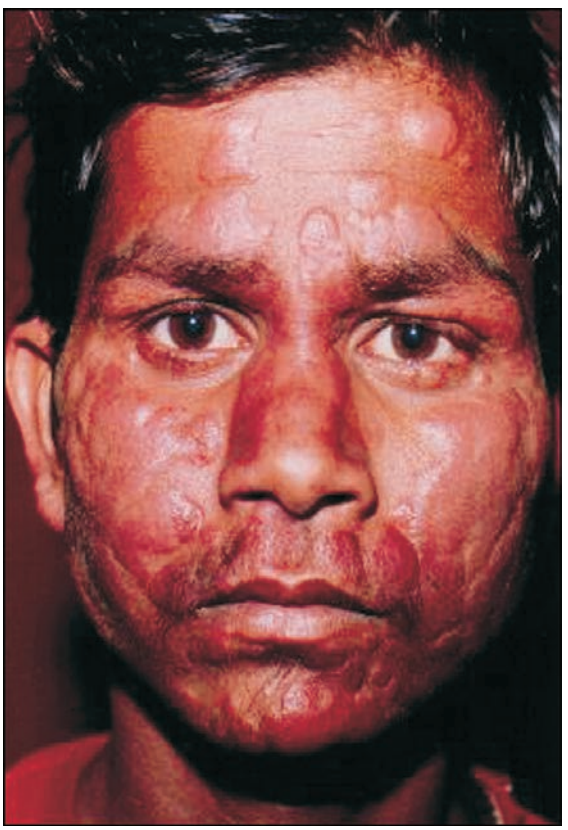
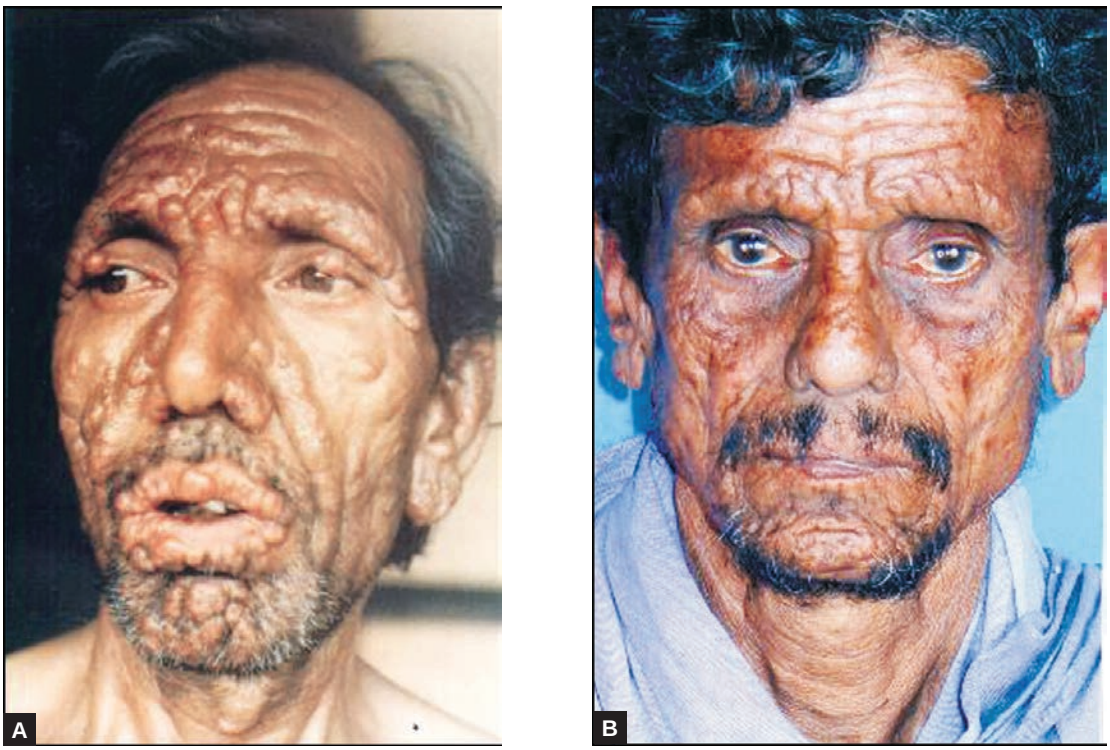


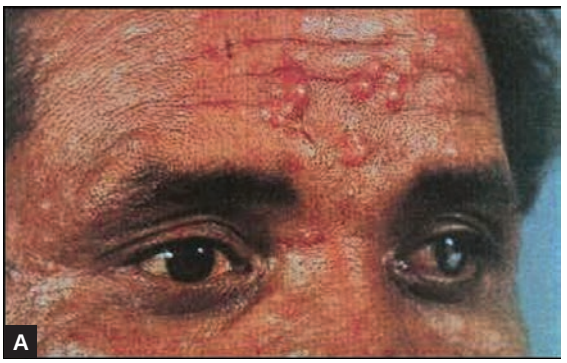
**Figure 55.3:** Borderline borderline (BB)

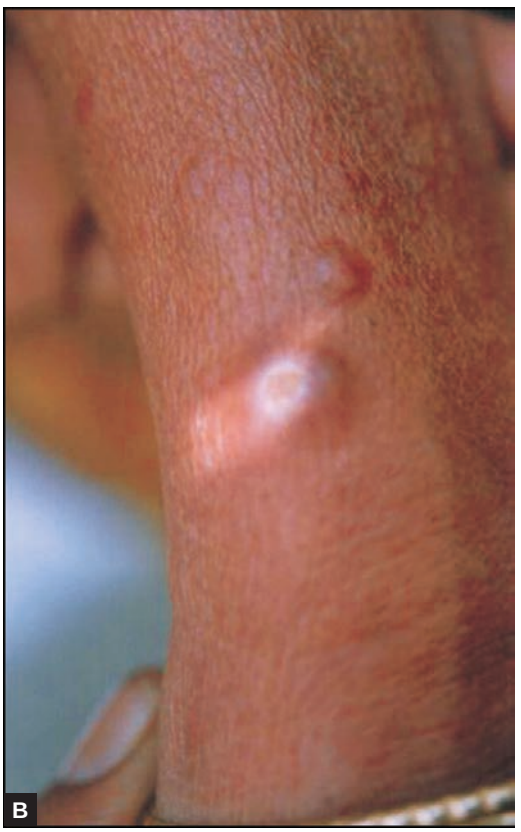



**Figures 55.4A and B:** Lepromatous lepromatous (LL)

(Figs 55.4A and B). There is an accompanying loss of hair, particularly over the lateral part of eyebrows, and loss of secondary sexual characteristics and varying degrees of gynecomastia in males with testicular and/or hepatic involvement. Accompanying lymphadenopathy and hepatosplenomegaly is frequent in the later stages. Nerve involvement results in progressive bilateral symmetrical cutaneous sensory loss that may be near total in late stages and simulate a 'glove-and-stocking' type of anesthesia. The nerves trunks also tend to be bilaterally and symmetrically thickened and/or tender. LL group of disease requires multibacillary MDT.

- *Histoid leprosy:* This is one of the relatively uncommon presentations of multibacillary leprosy that appears to have distinct clinical, bacteriologic, and histopathologic features. Patients with this type of disease may present *de novo* or as a result of secondary drug resistance, with cutaneous and/or subcutaneous nodules and plaques over surrounding apparently normal skin. The lesions vary in color from skin-colored to red, and they appear shiny, with stretched overlying skin. Lesions show prediliction for the lumbar area of back, buttocks, face and bony prominences (Figs 55.5A and B). Induration of earlobes and loss of eyebrows are distinctly uncommon.




**Figures 55.5A and B:** Histoid leprosy

- *Neuritic leprosy:* Neuritic leprosy that manifests with neural signs and/or symptoms without any clinically evident skin involvement. It accounts for a significant proportion of leprosy in the Indian subcontinent. Patients with neuritic leprosy present with symptoms of numbness, tingling, and/or weakness in an affected part. Clinical evaluation may reveal impairment/loss of sensation in areas innervated by the affected nerve, which may be thickened, tender, or both and occasionally may suppurate. In addition, weakness, atrophy, wasting, and/or contracture may be present because of damage to the nerve supply of the muscle(s). The extent and distribution of nerve involvement is variable; and those commonly affected are ulnar, radial, median, lateral popliteal, posterior tibial, facial, and sometimes, trigeminal, nerves. Patients diagnosed as having neuritic leprosy continue to be a challenge in terms of classification and treatment, particularly in the field conditions; and they may require either pauci-or multibacillary MDT, depending upon the number of nerves involved, distribution and demonstrability of acid-fast bacilli, and/or histopathologic classification following nerve biopsy.
- *Leprosy in children:* Leprosy in children appears to have a distinct clinical character as compared to adult leprosy. Both sexes appear equally affected, with perhaps a slight preponderance of girls below 10 years of age, as compared to a significantly higher affliction of men amongst adults. Further, lesions tend to be macular and predominantly over exposed parts that are amenable to trauma and/or accidental inoculation. The paucibacillary leprosy are generally seen; and children with BB, BL, or LL leprosy are distinctly uncommon. The disease tends to be immunologically stable, with reactions occurring infrequently. The importance of focused attention on this group cannot be

overstated. Study of childhood leprosy may hold the key to unraveling the natural history of the disease, particularly the obscure aspects of its incubation and pathogenesis. The incidence of leprosy in children is a sensitive indicator of early success in the leprosy control/eradication measures, because the natural course of leprosy in the community has a fairly distinct course.

## Reactions in Leprosy

The generally indolent course of leprosy is sometimes punctuated by acute exacerbation of the clinical condition of the patients, in terms of worsening of older lesions and appearance of new lesions, or other symptoms, in a short time frame. These episodes can be very distressing for a patient who is on regular treatment for his/her disease and expects only progressive improvement in the condition; and this may, therefore, cause problems with compliance and follow-up. Depending upon the etiopathogenesis, reactions are classified into type 1 (lepra) and type 2 (erythema nodosum leprosum; ENL). They may be precipitated by multi drug therapy (MDT), intercurrent infection, immunization, pregnancy and/or parturition, psychologic and/or physical stress, and so forth. Type 1 (lepra) reactions are due to an abrupt change in the cell-mediated immunity (CMI) of the patient and has been likened to a type 4 hypersensitivity reaction of Gell and Coomb. When the immunity improves, the reaction is said to be of upgrading or reversal type; and when it worsens, the reaction is said to be a downgrading type. The changes occur as a result of modifications of the dynamic neuro-humero-immunologic-regulatory mechanism that result in alteration in the cytokine profile of immunologically active cells in the granuloma of the patient. The acute inflammation that results requires institution of anti-inflammatory therapy in addition to appropriate MDT. Where nerve damage is imminent, corticosteroid therapy is indicated in addition, along with physiotherapy and rehabilitative measures. Type 1 reaction typically occurs in 'immunologically unstable' BT, BB and BL leprosy. Upgrading reactions tend to have involvement of few lesions, severe inflammatory changes, and prominent neuritis (which may precede motor loss, resulting in paralysis of muscles supplied by the affected nerve). Downgrading reactions show diffuse involvement of large numbers of lesions and widespread neuritis that tends to be mild. The lesions become ill-defined/serrated, and fresh lesions appear. Both types may be accompanied by constitutional symptoms such as fever, malaise, anorexia and so forth (Figs 55.2A to C). Type 2 erythema nodosum leprosum (ENL) reaction occurs as a result of immune-complex deposition in the vascular endothelium as well as tissues, and it has been likened to a type 3 (immune-complex mediated) hypersensitivity of Gell and Coomb. ENL tends to occur in patients with high antigen load, namely BL and LL leprosy, as a result of improved/enhanced antibody production. Though this is not protective in terms of limiting the infection and killing *Mycobacterium leprae*, it helps to clear the tissues of accumulated mycobacterial antigen. Clinically, lesions appear in crops as erythematous, tender, evanescent, cutaneous, and/or subcutaneous nodules, which rarely (in severe cases) may ulcerate. Skin lesions are distributed over extensors and forehead.

There may be accompanying nerve, ocular, hepatic, splenic, joint, musculoskeletal, reticuloendothelial, testicular (in men), cardiac, and renal involvement. They are invariably

accompanying constitutional; symptoms such as fever, malaise, anorexia, and arthralgias. Any specific organ involvement leading to failure/malfunction is an indication for intervention with immunosuppressive/immuno-modulating drugs, including corticosteroids, thalidomide, and others, along with appropriate multibacillary MDT.

## DIAGNOSIS

Though the diagnosis of leprosy is essentially clinical, there are several laboratory as well as clinical tests that provide bacteriologic, histopathologic, and immunologic help in order to corroborate and support the clinical diagnosis.

- *Slit-Skin smear:* This was once the cornerstone of successful MDT implementation, however, its recalcitrant unreliability, inter-operator variability, and lack of reproductibility in different hands, along with the high risk of AIDS transmission when performed under difficult field conditions, has eroded its importance, even in the guidelines as issued by WHO. It is prepared by scraping the sides of slits made in skin over lesion(s), earlobes, eyebrows, fingers, and so forth. These scarpings are then stained by Ziehl-Neelsen's technique and examined under high power for acid-fast-bacilli (Fig. 55.6). Failure to observe acid-fast-bacilli is indicative of abacillary/paucibacillary leprosy. Apart from diagnosis, slit-skin smear examinations help in classification and management, as well as in following response to treatment.
- *Histopathology:* Ideally all patients diagnosed to have leprosy should have lesions examined histopathologically. Apart from aiding in correct diagnosis, this also serves as a record against which response to treatment can subsequently be assessed. Histopathologic criteria useful in classifying the disease are given in Table 55.1. However, there are pitfalls in relying on histopathology alone, and it is important to be aware of and avoid them.

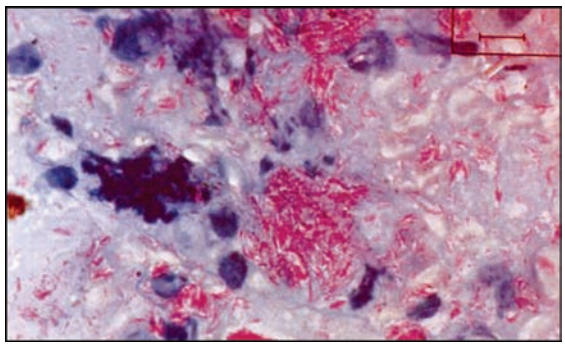


**Figure 55.6:** *Mycobacterium leprae*

- *Lepromin test:* The immunologic status of the patient can be assessed by performing this skin test. It is a measure of hypersensitivity of the individual to *M. leprae* antigens, which may be in the form of integral lepromin, Dharmendra antigen, leprolin, or leprosin. Readings are taken at 24 to 48 hours for the Fernandez responses and at 4 weeks for the Mitsuda response. Lepromin test has no role in diagnosing leprosy, but it helps prognosticate and classify the patient's illness.
- *Immunocytochemical techniques:* These techniques help diagnose leprosy where histopathology is not confirmatory, by demonstrating nerve damage or loss (S100, methenamine silver) and remnants/traces of *M. leprae* (immunofluorescence/immunoperoxidase). Further, negative staining for neuropeptides indirect evidence of damage to dermal nerves. These techniques are available only in tertiary level health care centers, clustered mainly in the urban areas.

| Table 55.1: Criteria for histopathological classification (5 group) of leprosy |
|---|
| **Tuberculoid Tuberculoid (TT)** |
| Compact granuloma of epithelioid cells, giant cells, and a large number of lymphocytes.<br>The granuloma is located just beneath the epidermis extending to mid-dermis; in addition, the infiltrate is also present in the epidermis-epidermal erosin.<br>Infiltration and complete destruction of cutaneous nerves is a constant feature (nerves are unidentifiable). The acid-fast *Mycobacterium leprae* is, however, difficult to demonstrate.<br>AFB 0 – 1<br>Lepromin 2+ to 3+ |
| **Borderline Tuberculoid (BT)** |
| Granuloma formed by epithelioid cells and the plentiful of lymphocytes; giant cells are either absent or occasional. Granuloma adjoins the epidermis.<br>Dermal nerves are swollen with infiltrate, but are recognizable.<br>AFB 0 –2 +<br>Lepromin 1 + to 2 + |
| **Borderline Borderline (BB)** |
| The appearance of granuloma is marked by the presence of epithelioid cells, absence of giant cells, and scanty lymphocytes scattered all over the granuloma.<br>The formation of a relatively free subepidermal zone<br>The texture of the nerves is generally maintained, though they may have infiltration of epithelioid cells. The acid-fast lepra bacilli are easily demonstrable.<br>AFB 3+ to 4+<br>Lepromin –ve to 1+ |
| **Borderline Lepromatous (BL)** |
| The presence of granuloma-comprizing histiocytes, sheets of lymphocytes, and macrophages containing acid-fast bacilli; the granuloma is diffuse and located in the mid-and lower dermis.<br>The presence of eosinophilic-staining zone below the epidermis is conspicuous.<br>The structure of the nerves is maintained and is infiltrate by histiocytes. The classical "Onion-peel" is the landmark in the diagnosis.<br>The acid-fast lepra bacilli are easily identifiable in the sections stained with Ziehl-Neelsen's method.<br>AFB 5+ to 6+<br>Lepromin –ve |
| **Lepromatous Lepromatous (LL)** |
| The formation of scattered granuloma containing numerous foamy macrophages in the lower dermis. The clear zone is well-marked.<br>The nerves are preserved and have an 'Onion-peel' appearance.<br>The acid-fast bacilli are numerous and are found throughout the granuloma.<br>AFB 5+ to 6+<br>Lepromin –ve |

- *Serology:* Antibodies to *M. leprae* specific antigens or, the antigens themselves, such as phenolic glycolipid-1 (PGL-1), can be detected by serologic assay, however, the technique is demanding and cannot be used routinely for every leprosy patient and/or contact, and it is not readily available around the country. PGL-1 antibody titers tend to reflect the bacillary load of the patient, and they can be used to follow-up patients to monitor success of chemotherapy, but such assays have not proved to be an effective tool in the early diagnosis of leprosy in high-risk individuals.

- *Immunofluorenscence:* The fluorescent leprosy antibody absorption test is one of the sensitive tests to determine subclinical infection of patients and contacts and to predict the likely course of the disease in conjunction with lepromin, however, the procedure is technically demanding, and this, combined with its low specificity, has not allowed it to become popular.
- *Cytopathology:* Cytopathology is gaining popularity as a diagnostic tool in leprosy in a few centers (where available) because of its simplicity, low demand on resources, quick results, reproductibility, and reliability that approaches that of histopathology. The cellular assessment in abacillary/ paucibacillary form of leprosy serves as a cross-check, improving diagnostic reliability; however, it requires a technical staff oriented to application of skin cytopuncture and/or needle aspiration for assessment of leprosy and also an appropriate mind-set.
- *Polymerase Chain Reaction:* Polymerase chain reaction performed to detect *M. leprae* specific DNA segments is perhaps the most sensitive as well as specific to confirm the presence of *M. leprae* DNA in any tissue/ fluid sample. However, this is available only in specialized laboratories and requires considerable expense as well as expertise to run. Thus, it has not become widely available and is often impracticable for routine use for difficult cases in the field.

## TREATMENT

Specific chemotherapy with WHO recommended MDT has been the main instrument in an attempt to break the cycle of transmission

**Table 55.2: Recommendation for Multi-drug-therapy (MDT)**

| *Clinical Group* | *Drugs* | *Dose* | *Mode of administration* | *Duration* |
|---|---|---|---|---|
| Paucibacillary I, TT, BT (PB) | Rifampicin | 600 mg | Once a month, supervised | 6 doses in 9 months (maximum gap: 8 weeks) |
| | Dapsone | 100 mg | Daily; self-administrated | 6 months (maximum gap: 4 weeks) |
| | Clofazimine | 50 mg | Daily; self-administrated (in lieu of dapsone) | 6 months (maximum gap: 4 weeks) |
| Multibacillary BT (MB), BB, BL, LL | Rifampicin | 600 mg | Once a month, supervised | 24 doses in 36 months (no single gap > 8 weeks) |
| | Clofazimine | 300 mg | Once a month, supervised | 24 doses in 36 months (no single gap > 8 weeks) |
| | | 50 mg | Daily, self-administrated | 24 monthly cycles in 36 months (no gap > 4 weeks) |
| | Dapsone | 100 mg | Daily, self-administrated | 24 monthly cycles in 36 months (no gap > 4 weeks) |
| Relapse/Rifampicin Resistance/ Toxicity | Clofazimine | 50 mg | Daily, self-administrated plus 2 out of 3 daily (in lieu of Rifampicin and dapsone) | 6 months |
| | Ofloxacin (1) | 400 mg | (Clofazimine plus | 18 months |
| | Minocycline (2) | 100 mg | Ofloxacin or minocycline daily) | Total 24 monthly cycles in 36 months (no gap > 4 weeks) |
| | Clarithromycin (3) | 250 mg | | |
| Single plaque | ROM | | | |
| | Refampicin(R) | 600 mg | Orally Once a month | 6 months, 6 doses |
| | Ofloxacin (O) and | 400 mg | | |
| | Minocycline (M) | 100 mg | | |

of leprosy and result in the decline of its prevalence in the society. This has proved to be the strongest aspect of the eradication program, and whatever success has been achieved has been due to the effectiveness of the regime as well as the robust nature of the design. The current WHO recommendations are outlined in Table 55.2. The need for an effective regimen of shorter duration for better compliance and easier alternative drugs for resistant infections and to eliminate persisters, is warranted.

## RECOMMENDED READING


1. Sehgal VN. *Textbook of Clinical leprosy*. Jaypee Brothers' 4th ed. Delhi 2004.
2. Sehgal VN. Leprosy. *Dermatol Clin* 1994;12: 629-644.
3. Sehgal VN, Jain S, Bhattacharya SN. Persisters, Relapse (Reactivation), Drug Resistance and multi-drug therapy (MDT): Uniform diagnostic guidelines for leprosy are needed. *J Dermatol (Tokyo)* 1996;23:905-907.
4. Sehgal VN, Kumar S, Jain S, et al. Relapse (Reactivation) in borderline tuberculoid (BT) leprosy. *J Dermatol (Tokyo)* 1998;25:63-65.
5. Bhattacharya SN, Sehgal VN. Leprosy in India. *Clin Dermatol* 1999;17:159-170.
6. Bhattacharya SN, Sehgal VN. Leprosy elimination campaign and its impending fallouts. *Int J Dermatol* 2000;39:667-669.
7. Bhattacharya SN, Sehgal VN. reappraisal of drifting scenario of leprosy multi-drug therapy (MDT): New approach proposed for the new millennium. *Int J Dermatol* 2002;41:321-326.

# 56 Chapter Localized Scleroderma/ Morphea

Localized scleroderma/morphea, a relatively benign well-circumscribed scleroderma, is characterized by round and/or oval, irregular/linear plaques. The plaques are initially, dull red/violaceous, smooth and indurated. Ultimately, plaque(s) progress to acquire chalky/ivory white atrophy corresponding to its earlier configuration. The preceding sequence ultimately leads to sclerosis of the dermis (superficial) and /or subcutaneous (deep) tissue, resulting in a spectrum, which encompasses several clinical deviations, the precise details of which are narrated in the following text. Raynauds' phenomenon and systemic organ involvement is conspicuously absent in localized scleroderma. Their etiology is largely up for discussion. However, it is imperative to confirm the diagnosis through microscopic pathology to establish the nature of the tissue changes.

## CLINICAL FEATURES

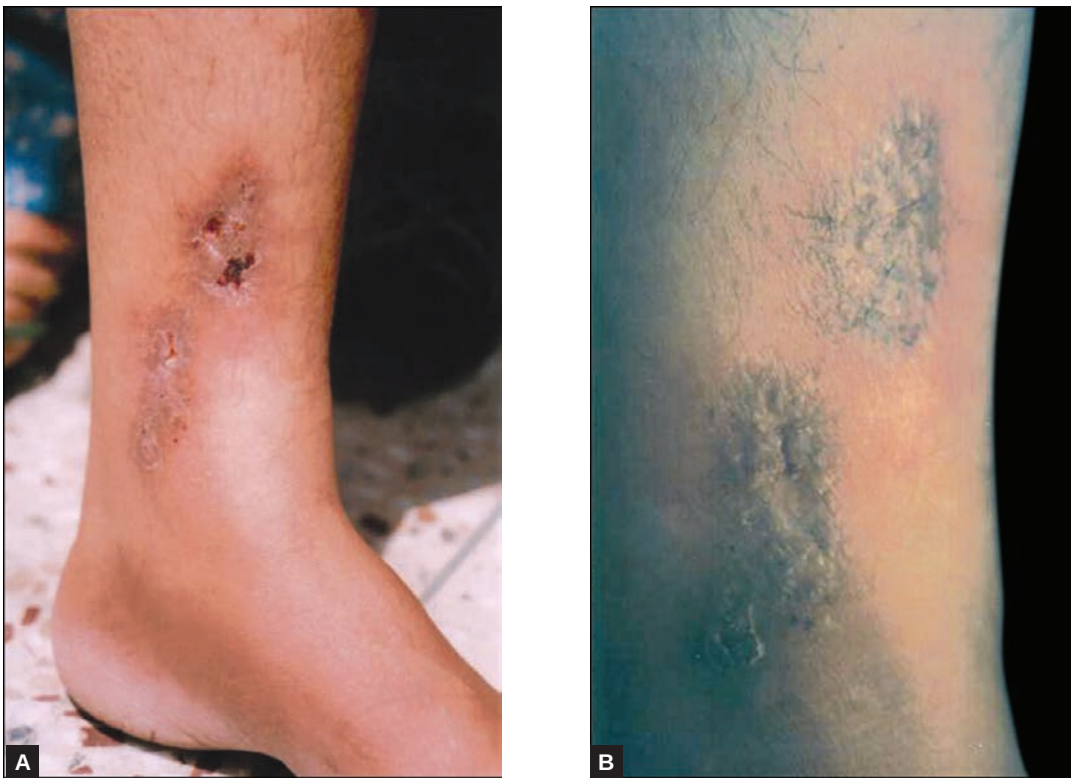
The lesions of localized scleroderma usually follows a mechanical injury, radiotherapy, BCG vaccination, chicken pox or after some medication. The lesions, at times, appear spontaneously without any precipitating factor(s). The lesions usually begin as a red/liliac color, swollen, non-pitting area, with loss of hair and diminished sweat response. As the lesion advance, its center assumes a yellowish white hue and gradual depression with induration. In due course a typical 'ivory white' central area surrounded by a circumscribed sclerotic plaque is identified. The clinical divergence from this basic pattern may result in spectrum, the outlines of which are reflected in Table 56.1.

- *Plaque morphea:* It is a superficial morphea confined to the dermis. It has been delineated into several subtypes, the details of which are formed in the following recount.
  - *Morphea en plaque:* It involves only 1 or 2 areas of the skin. It begins as erythematous halo, progress to sclerosis, and subside leaving behind hypo-or hyper pigmentation (Figs 56.1A and B).
  - *Guttate morphea:* It presents as multiple, oral, small, chalk-white, flat or slightly depressed patches, distributed over the chest, neck, shoulders and upper back (Fig. 56.2). The lesions are mildly firm and less sclerotic and may be mistaken for lichen sclerosis *et* atrophicus.
  - *Atrophoderma of Pasini and Pierini:* It is another variant of plaque morphea and shows asymptomatic, oral hyper-pigmented, atrophic plaque without the evidence of sclerosis. They are recognized by a pathognomonic 'clif-drop' appearance of the border and a depressed center.

**Table 56.1: Scleroderma/morphea; depicting a spectrum**

| *Types* | | *Clinical variation* |
|---|---|---|
| Plaque morphea | – | Lichen sclerosis *et* atrophicus |
| | – | Morphea *en* plaque |
| | – | Guttate morphea |
| | – | Atrophoderma of Pasini, Pierini |
| | – | Keloid/nodular morphea |
| Generalized morphea | | |
| Bullous morphea | | |
| Linear morphea | – | Linear scleroderma *per se* or associated with progressive hemifacial atrophy (*en coup* de sabre) |
| Deep morphea | – | Sub-cutaneous morphea |
| | – | Eosinophilic faciitis |
| | – | Morphea profunda |
| | – | Disabling pansclerotic morphea of children |

*Courtesy:* Sehgal VN, Srivastava G, Aggarwal AK, *et al.:* Localized scleroderma/morphea, *Int J Dermatol* **41:** 467 – 475; 2002. (Modified)




**Figures 56.1A and B:** *Morphea en Plaque*

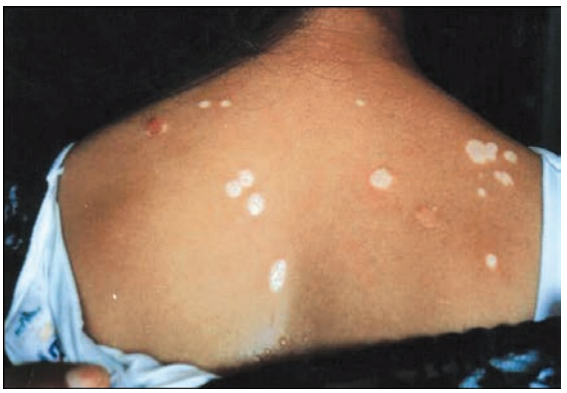
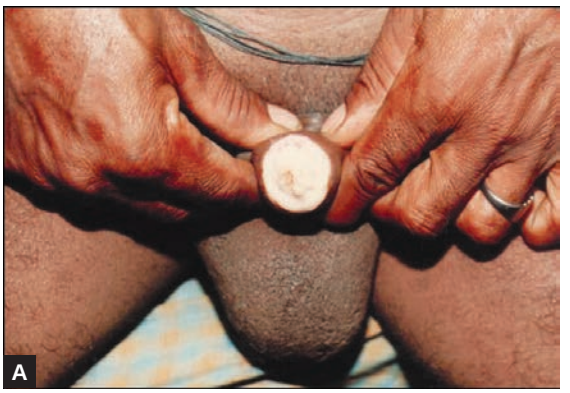
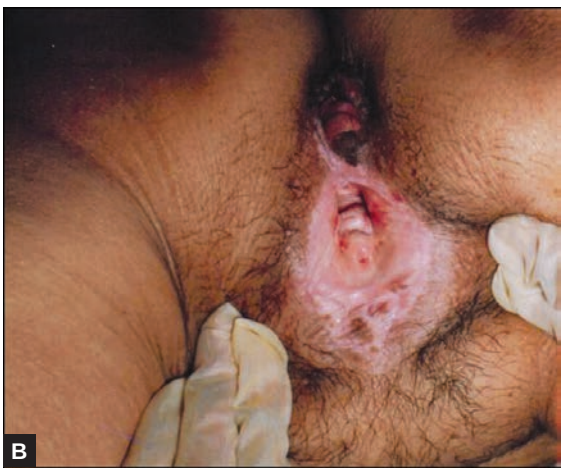


**Figure 56.2:** Gutted morphea

- *Keloid morphea:* It is its rare variant, and is characterized by the presence of nodular lesions in association with typical plaques of morphea.
- *Lichen sclerosis et atrophicus:* It is at times considered a variant of morphea. It is characterized by flat-topped, white papules that may coalesce to form white plaques. Occasional slight induration is associated. Comedo-like plugs are usual. Skin, glans penis (Fig. 56.3A) and the vulva (Fig. 56.3B) are the sites of affliction.

- *Generalized morphea:* It is a severe form of the local disease with wide spread affliction of the skin surface. Initially, it is identical to a localized plaque, but afterwards, plaques of generalized morphea become larger, confluent and multiple. Eventually, multiple indurated plaques with hyper-pigmentation are its classic presentation associated with some degree of muscle atrophy.
- *Bullous morphea:* It presents as co-existing tense subepidermal bullae in conjunction with typical morphea plaques. The histological findings of the vesicular component are characteristic of the lichen sclerosis *et* atrophicus.




**Figures 56.3A and B:** Lichen sclerosis *et* atrophicus

- *Linear scleroderma:* It usually occurs in children as single, linear, unilateral band. It affects the lower limbs (Fig. 56.4), upper limbs, forehead and anterior trunk. Frontal or fronto-parietal linear scleroderma (Fig. 56.5), popularly called *en coup de sabre,* is characterized by atrophy and furrow in the skin. If the furrow is extensive, it may cause facial hemiatrophy (Fig. 56.5). It may also cause limb deformity, joint contractures and limb atrophy. Progressive hemi-facial atrophy/ Parry-Ramberg syndrome may result in a conspicuous hemiatrophy of the face, and

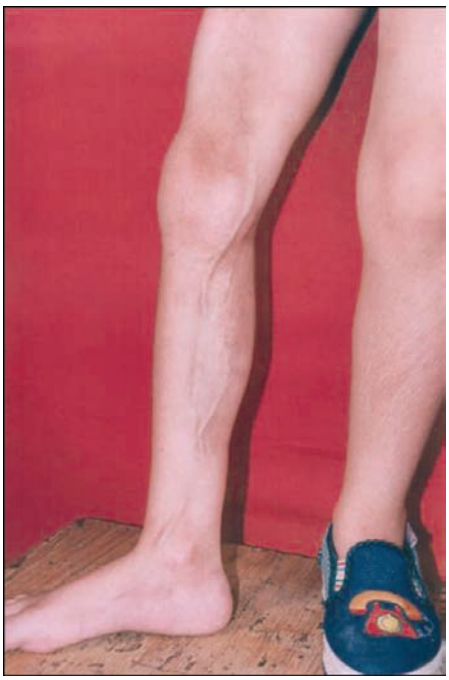


**Figure 56.4:** Linear scleroderma

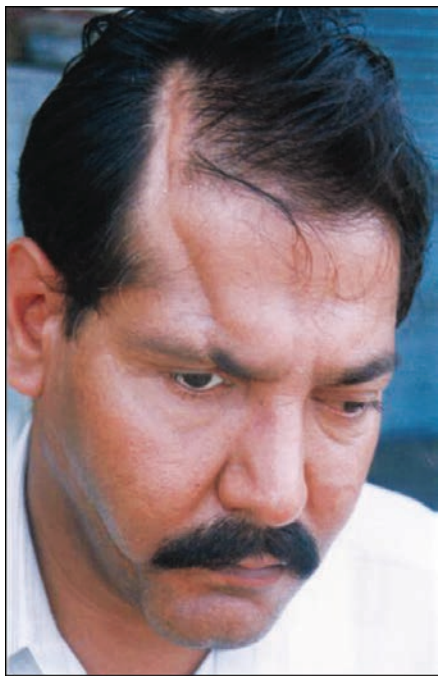


**Figure 56.5:** Fronto-parietal linear scleroderma

the atrophy is usually deeper than *en coup de sabre*.

- *Deep morphea:* It involves the deep dermis subcutaneous tissue, facia or muscles. The lesions are usually diffuse. Morphea profunda, its subtype, the entire skin is thickened. It is characterized by the occurrence of deep, bound down, sclerotic plaques. The typical color changes of the skin of localized morphea are usually absent because the inflammation is deep affecting subcutaneous fat and fascia. Solitary morphea profunda, its another variant, characterized by a solitary fibrous plaque usually localized on the shoulders, back and neck. Fibrosis, hyalinization of collagen fibers with deep dermal and subcutaneous infiltrate, are its salient features. Osteoma cutis may develop in morphea profunda.
- *Disabling pansclerotic morphea of children:* In this condition, there is a generalized full thickness involvement of the trunk, extremities, face and scalp. Its manifestations usually occur before the age of 14, in the form of sclerosis of the dermis, panniculitis, fasciitis, muscle and sometimes bone involvement. It has a relentless, progressive course causing disabling limitation of mobility of joints. Fortunately, it is uncommon.

In general, linear morphea is more common in children and adolescents, while morphea *en* plaque is frequent in adults. The disease activity usually last for 3 to 5 years. Recurrences are common whereas complete clinical resolution is unusual.

## DIAGNOSIS

Indeed, it envisages a thorough workup of the patient including forming of detail history

of predisposing factors. It is important to define the morphological characters of clinical variation according to the stipulated program, which has spectral undertones. It is therefore incumbent on treating physician to imbibe clinical guidelines for making a diagnosis (*vide supra)*. One time skin biopsy of a representative lesion is paramount to ultimately confirm the diagnosis. The details of each condition are correspondingly peculiar to each one of them.

## TREATMENT

Although the disease activity in localized scleroderma gets arrested spontaneously after certain period of activity, yet the disability-both physical and cosmetic, brings the patients for a satisfactory therapy, which unfortunately is not perfect. General measures such as regular massage, warmth, protection from trauma and cold, avoidance of smoking or incriminating drugs and reassurances are very important adjunct. PUVA therapy comprising 8-methoxysoralen (8-MOP) in the dosages of 0.4 mg/kg body weight followed by exposure to UVA 2 hrs later for a period of 1 year in localized scleroderma, and its efficacy in disabling pansclerotic morphea of children is now well acclaimed. It is known to stimulate collagenase activity. Low-dose broadband UVA phototherapy seemed to be an effective and safe modality for treatment of localized scleroderma. Further, topical photodynamic therapy involving application of a gel containing 3 percent 5-aminolevulinic acid followed by irradiation with an incoherent lamp (40 mW/cm$^2$, 10 J/cm$^2$), once/twice a week for 3-6 months period is a useful alternative. It is highly effective for sclerotic plaques, as measured by a quantitative durometer and a clinical skin score. The only side effect was a transient hyperpigmentation of the lesion(s).

Use of systemic steroids along with physiotherapy, external prostheses in early, active cases, and later on surgical correction in localized scleroderma lesions of the hands and upper limbs in children, has been advised. Also use of oral calcitriol as a therapeutic modality in generalized morphea has been invogue along with other effective therapies such as D-penicillamine, low-dose methotrexate, sulfasalazine, topical calcipotriene diphenyl hydantoin and clofidine hydrochloride. The *en coup de sabre,* a variant of linear scleroderma has fascinated the plastic surgeons. Various techniques have been advanced to correct the cosmetic aberration of such patients. Tissue expansion and bone grafting have found good cosmetic acceptance. Progressive facial hemiatrophy requires a microsurgical reconstruction, focussing on the correction of facial asymmetry and restoration of facial contour.

## RECOMMENDED READING

1. Sehgal VN, Srivastava G, Aggarwal AK, et al. Localized scleroderma/morphea. *Int J Dermatol* 2002;41:467-475.
2. Rowell NR, Goodfield MJ. Connective tissue disorders, in *'Textbook of Dermatology'* 6th ed. RH Champion, JL Burton, DA Burns, SM Breathnach, Oxford Blackwell Science 1998;2502-2510.
3. Odom RB, James WD, Berger TG. Scleroderma in diseases of the skin, *'Clinical Dermatology'* 9th ed. Richard B Odom, William D James, Timothy G Berger, Philadelphia, WB Saunders Company 2000;191-200.
4. Peterson LS, Nelson AM, Su WP, et al. The epidemiology of morphea (localized scleroderma) in Olmsted County 1960-1993. *J Rheumatol* 1997;24: 73-80.
5. Peterson LS, Nelson AM, Su WP. Classification of morphea (localized scleroderma). *Mayo Clin Proc* 1995;70:1068-1076.

# 57 Chapter Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is perceived as a systemic neutrophilic/necrotizing vasculitis that involves the medium size muscular arteries of almost all organ systems. Cutaneous polyarteritis nodosa (CPAN) is its well-recognized clinical variant confined mainly to involve the skin, musculoskeletal and nervous system. The former may either affect the adults/children. The clinical manifestation of PAN in adults/children has been well understood through the criteria laid down by American College of Rheumatology (ARA). Weight loss of more than 4 kilograms, livedo reticularis, testicular pain and tenderness, elevated creatinine, positive hepatitis B surface antigen, arteriographic abnormalities, and granulocyte/mixed leukocyte infiltrates in the arterial wall on microscopic pathology, are the criteria in adults. Three of the ten criteria are adequate to form the diagnosis of PAN. Its specificity and sensitivity, therefore, is commendable. Where as in children it is delineated into major and minor criteria. The major criteria includes renal and/or musculoskeletal affliction. The minor criteria, however, has in its fold cutaneous manifestation, gastrointestinal (abdominal pain to gastrointestinal bleeding), peripheral neuropathy, central nervous system disease including electroencephlographic abnormalities, hypertension/cardiovascular (pericarditis/arrthythmias), pulmonary symptoms (infiltrations, pleural effusions), constitutional symptoms, acute phase reactants and presence of hepatitis B surface antigen. One major and 5 minor criteria are rather sufficient to suggest the diagnosis of PAN in this group. Cutaneous polyarteritis nodosa, on the other hand, is conspicuous because of its benign relapsing long-term course and want of explicit systemic components.

## CLINICAL FEATURES

- *Cutaneous polyarteritis nodosa (CPAN):* In adults it expresses itself in the form of painful and/or tender nodule(s) of the size of 0.5 cm to 2 cm. These lesions may heal in due course leaving behind a blue scar. Its recurrence on top of the same site is cardinal. The nodule may be present over the 'starburst' livedo reticularis. Ulceration of the lesions is frequent. The foot, ankle, and lower leg are its usual site. Fever, myalgia, arthralgias, neuralgias, and neuropathy (mononeuritis) are its other accompaniments. An increase in the level of anticardiolipin antibodies, erythrocytic sedimentation rate, blood pressure, creatinine, mild leukocytosis and eosinophilia are salient supportive laboratory findings. Decreased albumin level, normochromic normocytic anemia, thrombocytosis, antihyuronidase and antistreptolysin

antibodies are the other related attributes. Children may have symptoms comprising fever, nonspecific skin lesions, and joint swellings. Purpuric nodule occupying the wrist and ankle may facilitate its diagnosis. Increased erythrocytes sedimentation rate, antistreptolysin and antihyaluronidase antibodies may also be detected in this age group.

- *Polyarteritis nodosa:* It is a systemic vasculitis that involves the medium size muscular arteries affecting most of the organ system. It is seen both in males and females in all age group. It may present with marked constitutional symptoms like fever, malaise, weakness, abdominal pain and myalgia. Nodule(s), ulcerations and livedo reticularis, a pattern of erythema, characterize cutaneous manifestations. The deep-seated nodules are usually painful and tender. The disposition of the lesions over the lower extremities is frequent, however, the trunk and upper extremities may also be affected. The kidneys are the most frequent implicated organ system along with the liver, heart, and gastrointestinal tract. Chronic glomerulonephritis and hypertension are its detrimental outcome. Musculoskeletal and central nervous system are almost always involved. Furthermore, pancreatitis, gastrointestinal bleeding, cholecystitis compounded by urinary protein greater than 1 gm/day and a creatinine greater than 1.58 mg/dl, are responsible for its poor prognosis.

## DIAGNOSIS

At this point of time it is crucial to take cognizance of salient presenting clinical manifestations both of cutaneous polyarteritis nodosa and polyarteritis nodosa. The accountability to ARA criteria should be ensured. Hence, it is worthwhile to establish 3 of the 10 criteria for forming the diagnosis of polyarteritis nodosa (adult) and 1 major and 5 minor criteria in children (*vide supra)*. Of course, definitive supportive evidence should come through by exploitation of well-known laboratory components. Microscopic pathology is the most potent instrument to ultimately arrive at the diagnosis. One time excisional biopsy of the classic nodule is, therefore, mandatory. Neutrophilic/necrotising vasculitis of the blood vessels of the lower dermis and/or subcutaneous tissue is fundamental. The same may be accounted for by kidney biopsy. Furthermore, demonstration of aneurysms of the hepatic, renal/vascular arteries through arteriogram is 'pathognomonic' of polyarteritis nodosa. Nerve conduction studies are also indicated should there be a component of neuritis. Gastrointestinal components should be unfolded by the presence of blood in the stools, if positive, colonoscopy or mesenteric arteriography should be undertaken. Electromyography is advised in myalgias or muscle's weakness. The preceding recount should invariably be in a position to pinpoint the diagnosis of CPAN or PAN. The other related conditions – giant cell arteritis, temporal arteritis, Wegener's granulomatosis, Churg Strauss syndrome, and drug-induced vasculitis, Henoch-Schonlein purpura or cryoglobuminemia – may come for a focus in the differential diagnosis.

## TREATMENT

The treatment of polyarteritis nodosa and cutaneous polyarteritis nodosa revolves around the administration of immunosupressive drugs,

systemic corticosteroids and/or cyclophosphamide. Dexamethazone or betamethazone are the usual steroids given for the purpose. They are administered by slow intravenous infusion in two equal divided dosages of 1mg/ kg body weight per day at 9:00 and 18:00 hrs respectively. They are to be given as long as they are needed. Should the symptoms and signs alleviate, the patients are to be maintained on this therapy. This therapy should be supplemented by the oral administration of cyclophosphamide in the dosage of 50 to 100 mg per day. It is essential to avoid offending drug/infective antigen. It is imperative to treat the underlying disease. Prevention of deposition of immunecomplexes is now possible through plasmaphoresis. Non-steroidal-anti-inflammatory drugs (NSAIDS) may assist in suppression of the inflammatory response. Multidisciplinary approach may be a useful proposition in such cases.

## RECOMMENDED READING


1. Ozen S, Besbas N, Saatci U, et al. Diagnostic Criteria for Polyarteritis Nodosa in Childhood. *J Pediatr* 1992;120:206-209.
2. Daoud MS, Hutton KP, Gibson LE. Cutaneous periarteritis Nodosa: A Clinicopathological Study of 79 Cases. *Br J Dermatol* 1997;136:706-713.
3. Minkowitz G, Smoller BR, McNutt NS. Benign cutaneous polyarteritis nodosa. Relationship to systemic polyarteritis nodosa and to Hepatitis B infection. *Arch Dermatol* 1991;127:1520-1523.
4. Guillevin L., Lhote F, Gayraud M, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996;75:17-28.
5. Ginarte M, Pereiro M, Toribio J. Cutaneous Polyarteritis Nodosa in a child. *Pediatr Dermatol* 1998; 15:103-107.
6. Bauza A, Espana A, Idoate M. Cutaneous polyarteritis nodosa. *Br J Dermatol* 2002;146:694-699.
7. Guillevin L, Lhote F, Cohen P, et al. Corticosteroids plus pulse cyclophosphamide and plasma exchange versus corticosteroids plus cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis. A prospective randomized trial in sixty-two patients. *Arth Rheum* 1995;38:1638-1645.

# 58 Chapter Paraneoplastic Pemphigus/ Paraneoplastic Autoimmune Multiorgan Syndrome

Paraneoplastic pemphigus (PNP) a heterogeneous autoimmune syndrome implicating several systemic organs, pathophysio-mucosal and internal organs are not limited to auto-antibodies targeting the adhesion molecules, encompassing paraneoplastic autoimmune multiorgan syndrome (PAMS) as an alternative self explanatory caption. It may either be a subset of patients with pemphigus and neoplasia, or conceived as a distinct autoimmune vesicular disorder.

## CLINICAL FEATURES

The condition has a wide variety of clinical presentations, and may conform either to pemphigus–like, pemphigoid—like, erythema-multiforme- like, graft-*versus*-host disease – like, or lichen planus–like, the salient clinical features of which are outlined below:

- *Pemphigus-like:* Flaccid blister, (discrete/coalesced), crusts over the raw exuding skin lesions
- *Pemphigoid-like:* Tense blister(s) on brick red erythema
- *Erythema-multiforme-like:* Severe polymorphic skin and/or mucous membrane lesions
- *Graft-versus-host disease-like:* Widespread lichenoid (lichen-planus-like) eruptions with severe mucous membrane involvement
- *Lichen planus-like:* Small red flat-top scaly papules.

The florid mucous membrane lesions of the oral cavity are a constant feature, and may involve the oropharynx, nasopharynx, tongue and vermilion of the lips, conjunctiva of the eye, anogenital region and esophagus. The cutaneous lesions usually follow within a variable period after the onset of the mucosal lesions and depict a characteristic morphology. The blisters often erupt in waves commonly affecting the upper trunk head, neck and proximal extremities. laryngeal and pharyngeal lesions depict a single pemphigus vegetans - like plaque evolved from a flaccid blister. Most of the patients may reveal extensive cutaneous involvement in due course.

It is therefore, imperative to take stock of associated neoplasms/disorders like. They include hematological and non-hematological disorders .

**Hematological disorders such as**

- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukemia
- Castleman's disease
- Thymoma
- Waldenstrom's macroglobulinemia
- Hodgkin's lymphoma
- Monoclonal gammopathy.

**Non-hematological disorders**

1. Epithelial origin – carcinomas
   - Adenocarcinoma of the pancreas , colon , breast and prostate
   - Squamous cell carcinoma of tongue and vagina
   - Basal cell carcinoma of skin
   - Bronchogenic carcinoma
2. Mesenchymal origin – Sarcoma
   - Reticulum cell sarcoma
   - Liposarcomas
   - Leiomyosarcoma
   - Dendritic cell sarcoma and others
3. Malignant melanoma.

## DIAGNOSIS

The diagnosis of the PNP is made on the basis of clinical, histologic, direct immunofluorescence, indirect immunofluorescence and immunoprecipitation tests, the salient briefs of which are depicted below.

1. Major
   - Polymorphic mucocutaneous eruption
   - Concurrent internal neoplasia
   - Serum antibodies with a specific immuno-precipitation pattern.
2. Minor
   - Histologic evidence of acantholysis
   - Direct Immunofluorescence showing intercellular and basement membrane staining.
   - Indirect immunofluorescence staining with rat bladder epithelium.

Three major and minor signs are required for making the diagnosis of PNP. However, the most constant laboratory finding is the characteristic immunoprecipitation pattern. Further more it is worthwhile to subject the patient to contrast coaxial tomography (CAT scan) to pinpoint Non-Hodkins lymphoma. Magnetic Resonant Imaging (MRI) is worthwhile to undertake to exclude the relevant systemic malignancy.

## Treatment Options

The treatment of PNP has largely been disappointing. The skin and mucus membrane lesions are responsible for morbidity, and are paradoxically the frequent cause of death rather than the malignancy itself. The response to the therapy is generally poor. Primarily, the treatment is aimed to restraint the production of auto-antibodies. A better prognosis is expected, if the malignancy is less aggressive.

Initially, high dose corticosteroids form the first line of defense, and are effective to some extent. The addition of steroid-sparing agents such a azathioprine. Cyclosporine A and mycophenolate mofetil may reduce steroid intake, and thus limit the side-effects. However, a high level of caution is the rule in patients of PNP with confirmed malignancy, where immunosuppression is paramount and dictates the mainstay of treatment options. More invasive and toxic therapies are required to be considered, if the initial therapy fails to control the condition and the condition of the patient warrants an aggressive prompt intervention.

Stem cell ablation therapy using high dose cyclophosphamide without skin cell rescue has been considered for use in some cases, but may be hazardous. Rituximab$^{Tm}$ (Mabthera® 500 mg), the monoclonal antibody to $CD_{20}$ has shown promising results when used in PNP patients having B-cell lymphomas. Biobrane$^{Tm}$, a biosynthetic dressing can be used over extensive erosive areas, and is reported to relieve the severe pain experienced by these patients.

## RECOMMENDED READING


1. Anhalt GJ, Kim SC, Stanley JR et al. Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. *N Engl J Med*. 1990;323:1729-1735.
2. Anhalt GJ. Paraneoplastic pemphigus. J Investig *Dermatol Symp Proc* 2004;9:29-33.
3. Anhalt GJ. Paraneoplastic pemphigus: the role of tumours and drugs. *Brit J Dermatol* 2001; 144:1102-1104.
4. Camisa C, Helm TN. Paraneoplastic pemphigus is a distinct neoplasia-induced autoimmune disease. *Arch Dermatol* 1993;129:883-886.
5. Chorzelski T, Hashimoto T, Maciejewska B et al. Paraneoplastic pemphigus associated with Castleman tumor, myasthenia gravis and bronchiolitis obliterans. *J Am Acad Dermatol* 1999;41:393-400.
6. Fried R, Lynfield Y, Vitale P, et al. Paraneoplastic pemphigus appearing as bullous pemphigoid-like eruption after palliative radiation therapy. *J Am Acad Dermatol* 1993;29:815-817.
7. Helm TN, Camisa C, Valenzuela R et al. Paraneoplastic pemphigus. A distinct autoimmune vesiculobullous disorder associated with neoplasia. *Oral Surg Oral Med Oral Pathol* 1993;75:209-213.
8. Heymann WR. Paraneoplastic autoimmune multiorgan syndrome. *J Am Acad Dermatol* 2004; 51: 631-632.
9. Jansen T, Plewig G, Anhalt GJ. Paraneoplastic pemphigus with clinical features of erosive lichen planus associated with Castleman's tumor. *Dermatology* 1995;190:245-250.
10. Mutasim DF, Pelc NJ, Anhalt GJ. Pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus. *Clin Dermatol* 1993;11:113-117.
11. Sehgal VN, Srivastava G. Paraneoplastic pemphigus/paraneoplastic autoimmune multiorgan syndrome. *Int J Dermatol* 2009;48:162-169.

# 59 Chapter

# Pigmented Purpuric Dermatoses

Progressive pigmentary dermatoses (PPD), a chronic, relapsing disorder is characterized by a symmetrical rash of petechial and pigmentary macules on the lower limbs. Extravasations of erythrocytes in the skin and/or marked hemosiderin deposition are their cardinal clinical expressions. They are traditionally divided into:

- Schamberg's purpura,
- Majocchi's purpura,
- Lichen aureus,
- Gougerot-Blum purpura and
- Eczematid-like purpura of Doucas and Kapetanakis.

The other unusual presentations include the itching purpura of Loewenthal, linear, granulomatous, quadrantic, transitory and familial forms.

The etiology is unknown. Venous hypertension, exercise, and gravitational dependency capillary fragility, focal infections and chemical ingestion are important co-factors that appear to influence the disease process. Drugs, acetaminophen, aspirin, adalin, carbromal, chlordiazepoxide, glipizide, glybuzole, hydralazine, meprobamate, persantin, reserpine, thiamine, interferon-alfa, and injection medroxyprogesterone acetate are the most frequently reported provocating factors, especially in Schambergs disease, exercise, contact allergy to dyes, clothing and alcohol ingestion are the other causes.

There are indications that *cell-mediated immunity* might play a role. Immunnohistologically reveals a perivascular infiltrate of CD3+, CD4+, and CD1a + dendritic cells, with close spatial contact between lymphocytes and dendritic cells. The modulation of cellular adhesion molecules in dermal endothelial cells (ICAM-1,ELAM-1) and in lymphocytes (LFA-1), suggest a mechanism for lymphocyte trafficking and their interaction with endothelial cells and dendritic cells. The lesional keratinocytes express surface antigens believed to be characteristic of cytokine-mediated dermatosis. Cytokines like tumor necrosis factor (TNFα) stimulated by ELAM-1, may lead to release of plasminogen activator inhibitor or defective release of endothelial plasminogen activator, which have also been observed in lesion of PPD.

The demonstration of deposits of immunoglobulins and/or complement (C1, $C1_q$) around dermal vessels, suggest a role for immune complexes in the pathogenesis of the disease.

## CLINICAL FEATURES

### Schambergs' disease/Progressive Pigmented Purpuric Dermatosis

The lesions consist of pinhead-sized, reddish puncta resembling grains of cayenne-pepper which may form irregular plaques of orange/brown pigmentation, due to the presence of

hemosiderin. The condition is usually asymptomatic, slight itching may, however, be associated. The eruption is characteristically very chronic and presents with a slow proximal extension. Venous insufficiency might play a role in the localization of these lesions. They are mostly distributed on the lower limbs, but may also occur anywhere on the body.

### Majocchi's Disease/Purpura Annularis Telangiectodes

The early lesions are bluish-red, annular macules, and may have dark red telangiectatic puncta. The central part of the lesion fades, with peripheral extension giving it the annular configuration. Sometimes slight atrophy is noticed in the center. The eruption begins on the lower limb, to extends to involve the upper extremities. The lesions may be a few in number/innumerable. There is an absence of venous stasis, and are persistent in nature. Purpura telangiectatica arciformis is another variant–where the lesions tend to be fewer, larger and irregularly arciform.

### Gougerot –Blum Syndrome/Pigmented Purpuric Lichenoid Dermatosis

This is characterized by minute, lichenoid papules that tend to fuse into plaques of various hues, seen on the legs, and occasionally on the trunk and thighs. The plaques may occasionally simulate Kaposis'/pseudo-Kaposis' sarcoma.

### Lichen Purpuricus/Lichen Aureus

This is a more localized, persistent, intensely purpuric, and rarely painful. The lesions are of golden brown color and /are sufficiently infiltrated clinically as well as histologically to have earned the name lichen. The characteristic of the dermatosis is the appearance of sudden-onset lichenoid papules in association with purpuric lesions, seen commonly on the lower limbs and occasionally on the trunk and the face.

### Itching and Eczematoid Purpura of Doucas and Kapetanakis/Disseminated Pruriginous Angiodermatitis

In itching purpura, the lesions are much more extensive and patients typically also complain of severe pruritus. This is a distinctive clinical entity of unknown etiology. Spontaneous improvement after a few months is usual, but recurrences may occur. An almost identical picture occurs with carbromal sensitivity, and less commonly to other drugs. This might be due to contact allergy to clothing/rubber/and is essentially a variant of Schambergs' disease.

### Linear and Quadrantic Pigmented Purpuric Dermatoses

Linear, unilateral occurrence of PPD is rare, and should be distinguished from linear variants of Schambergs' purpura and lichen aureus. A quadrantic variant may be because of pelvic vascular obstruction.

### Miscellaneous PPD's-gravitational Purpura

It is noticed amongst the males, on the lower limbs, as purpuric macules, plaques and follicular lesions, which usually acquire a brown discoloration due to deposition of hemosiderin. Venous insufficiency is a likely cause, and the dermatosis might progressively increase and could be associated with edema, stasis and varicosities. Transitory PPD includes entities like angioma serpiginosum, apart from other PPD's, though the clinical differences between them are minor. Itching purpura of Lowenthal is considered to be a more symptomatic variant

of Schambergs' disease. Granulomatous variant of PPD may occur in middle-aged women with a PPD-like eruption on the dorsum of the feet. The biopsy reveals a superimposed granulomatous infiltrate. Familial pigmented purpuric eruption, includes familial Schambergs' disease and purpura annularis telangiectoides indicating an autosomal dominant trait.

Diabetes mellitus, rheumatoid athritis, lupus erythematous, thyroid dysfunction, hereditary spherocytosis, hematological disorders, hepatic disease, porphyria malignancies and hyperlipidemia are a few associated conditions.

Laboratory investigations are largely unremarkable in the pigmented purpura. However, a full blood count and peripheral blood smear is necessary to exclude thrombocytopenia. Other occasional findings are target-shaped/teardrop-shaped erythrocytes, anisocytosis and hypochromia. A coagulation screening comprising prothrombin time and partial thromboplastin time help to exclude other possible causes of purpura. Bleeding time (Ivy's method), platelet aggregation function (adenosine-diphosphate, or ristocetin assay tests) and capillary fragility test (Hess test) are imperative. Tests for ANA, RF, anti-HbsAg antibody and anti-HCV antibody should also be performed.

## DIAGNOSIS

Histologically, there is a perivascular infiltrate of lymphocytes and macrophages centered on the superficial small blood vessels of the skin with endothelial cell swelling and narrowing of lumina. However, overt vasculitis is not usually observed. The infiltrate is composed predominantly of CD4+ lymphocytes along with occasional CD1a+ dendritic cells and macrophages. Extravasation of red blood cells with the presence of marked hemosiderin deposition in macrophages is typical. However, the degree of hemosiderin deposition may be variable. Histochemical staining with Perl's stain and Fontana Masson, helps to demonstrate iron (hemosiderin), and the presence of hemosiderin deposition in the superficial dermis, may help to differentiate PPD from stasis dermatitis, where a deeper deposition is seen.

**Table 59.1 Treatment modalities**

| | |
|---|---|
| **Topical** | Topical steroids are recommended either to control, or to improve the existing symptom and signs of PPD for a period of 4 to 6 weeks period · |
| **Systemic** | |
| **1. Psoralen photochemotherapy** | P+UVA has been found to be useful in Schambergs' disease, pigmented purpuric dermatosis of Gougerot and Blum, and lichen aureus. The clearance of the lesions may take 7 to 20 weeks. Immune modulation with alteration in the activity of the T lymphocyte, and the concomitant suppression of interleukin 2 production, may be the mechanism of action. |
| **2. Griseofulvin** | A dose of 500 to 750 mg a day is useful. New lesion stop appearing within a mean of 33 days. It is likely that the immunomodulatory action of the drug plays a significant role in the condition. |
| **3. Pentoxifylline** | It is administered in the dosage of 400 mg three times daily for a period of 2 to 3 weeks. The drug is supposed to act at the level of T-cell adherence to endothelial cells and keratinocytes. |
| **4. Cyclosporine** | It may occasionally be a worthwhile drug, lending credence to the immunological nature of this dermatosis. |
| **5. Bioflavanoids/ Ascorbic acid** | Oral rutoside, 50 mg twice daily, and ascorbic acid, 500 mg daily may yet be another useful modality in these conditions. It may have to be administered for 3 to 4 weeks period. |

Plasma cells and neutrophils may occasionally be present, the latter are seen in lesions of itching purpura. Mild epidermal spongiosis and exocytosis of lymphocytes may be seen in all variants except lichen aureus, which in general tends to show a band-like infiltrate separated from the epidermis by a thin rim of uninvolved collagen. When lymphocytic infiltrate is lichenoid, it is diagnosed as lichenoid dermatosis of Gougerot and Blum. When spongiosis/neutrophils are marked, the diagnosis is itching purpura; and a rare variant .

Essentially, all these conditions have a common histopathology, with minor differences, which correlate with some of the clinical variants.

## TREATMENT

*Pigmented purpuric dermatoses* are a group of chronic conditions where the lesions may either persist, extend or may clear spontaneously, in due course. The recurrences are common. Follow-up consultations are imperative and may warrant to exclusion of mycosis fungoides. Nevertheless, it is worthwhile to take stock of prevalent treatment options (Table 59.1).

## RECOMMENDED READING


1. Kano T, Hirayama K, Orihara M, Shiohara T. Successful treatment of Schamberg's disease with pentoxifylline. *J Am Acad Dermatol* 1997; 36:827-830.
2. Krizsa J, Hunyadi J, Dobozy A. PUVA treatment of pigmented purpuric lichenoid dermatitis (Gougerot-Blum) *J Am Acad Dermatol* 1992;27: 778-780.
3. Ling TC, Goulden V, Goodfield MJ. PUVA therapy in lichen aureus. *J Am Acad Dermatol* 2001; 45:145-146.
4. Newton RC, Raimer SS. Pigmented purpuric eruptions. *Dermatol Clin* 1985;3:165-169.
5. Rheinhold U. Treatment of progressive pigmented purpura with oral bioflavanoids and ascorbic acid: an open pilot study in 3 patients. *J Am Acad Dermatol* 1999;41:207.
6. Rudolph RI. Lichen aureus. *J Am Acad Dermatol* 1983;8:722-724.
7. Sardana K, Sarkar R, Sehgal VN. Pigmented purpuric dermatoses: an overview. *Int J Dermatol* 2004;43:482-488.

# 60 Chapter Psoriasiform Dermatoses

Psoriasiform dermatoses refer to the group of disorders, which clinically and/ or histologically simulate psoriasis. They include several unrelated disorders of the integument, which, begin or in the course of progression/ resolution exhibit lesions resembling psoriasis. Psoriasiform eruptions can commonly be seen in seborrhoeic dermatitis, pityriasis rubra pilaris, psoriasiform syphlids, pityriasis rosea, mycosis fungoides and drug eruptions. However, their inventory is quite exhaustive, especially when the histopathological assessment is also included to conform to the caption of psoriasiform dermatoses. Histopathologically the psoriasiform reaction pattern is defined as the presence of epidermal hyperplasia with elongation of rete ridges in a regular manner. This definition encompasses a heterogeneous group of dermatological conditions. This morphological concept is much broader than the pathogenetic one. The principle features of the psoriasiform tissue reaction is the formation of suprapapillary exudates with parakeratosis, secondary to intermittent release of serum and leukocytes from dilated blood vessels in the papillary dermis (the so called squirting papilla). Psoriasis is a prototype of psoriasiform reaction pattern. This caption means a base line pattern of the clinical/ histologic reaction of several disorders, which can initially be grouped within the umbrella of psoriasiform reaction pattern.

## CLINICAL FEATURES

The clinical presentation of psoriasiform lesions appear as morphological representative of the prototype classical psoriasis. However, depending upon the disorder, the lesions may vary in size, shape, scaling, distribution and configuration. Reiter's syndrome may show classic rupioid/circinate lesions with keratoderma blennorrhagica while pityriasis rubra pilaris reveals hyperkeratotic perifollicular lesions with a halo of erythema. Similarly, pityriasis rosea may reveal oval plaques with collarette of fine scaling while AIDS associated psoriasiform lesions may be more angry looking with a prominent component of seborrhoeic dermatitis. Nummular dermatitis may show only moist coin-shaped lesions. Drug induced psoriasiform lesion and psoriasiform syphilids lesions may retain their classical pathognomonic signs which can delineate the diagnosis. Further, investigation accordingly may clinch the exact pathology. The list of disorders presenting either as clinical or as pathological evidence of psoriasiform eruptions are outlined in Tables 60.1 to 60.4 (*vide supra*). If the clinical examination does not provide a clear cut diagnosis, a histopathology may definitely serve to make a precise assessment of the dermatosis. Accordingly, other relevant tests such as serological test of syphilis, provocations tests for drug eruptions, and so on can be undertaken according to the merits of the disease.

## CLASSIFICATION

Several classifications are *in vogue* to incorporate the entities/groups under the aegis of psoriasiform eruptions. Pinkus grouped such disorders under 2 groups, one with a definite presence of suprapapillary exudates and parakeratosis, while another probable group which often presents a diagnostic dilemma (Table 60.1).

Farmer and Hood based their classification chiefly in the presence of a characteristic pattern of epidermal hyperplasia (Table 60.2).

However, Elder *et al* classified the psoriasiform disorders based on the presence of epidermal hyper-proliferation along with the typical variations of the cell types (Table 60.3).

## ETIOLOGY

As heterogeneous groups of disorders can present like psoriasiform eruptions/ dermatoses, so diverse etiologic agents can be recorded in different instances (Table 60.4). The 'major psoriasiform dermatoses' are psoriasis, pustular psoriasis, AIDS –associated psoriasiform dermatitis, Reiter's syndrome, pityriasis rubra pilaris, parapsoriasis and lichen simplex chronicus. This group of dermatoses is characterized as a rule by regular epidermal hyperplasia, although in the early stage such features are usually absent.

New and new drugs are being added to the list of the psoriasiform drug eruptions. Acquired immunodeficiency syndrome has added another dimension to the entity, by producing the psoriasiform eruption *per se* or through the other infective disorders, such as Leishmaniasis, which gain entry in the AIDS patients (Table 60.4).

## PATHOGENESIS

Although, the exact pathogenesis of psoriasiform dermatoses is speculative, yet it is believed that the events that precipitate the psoriasiform changes are frequently inflammatory. They appear to involve the dys-regulation of cytokines and growth factors which are vital in the maintenance of normal epidermal proliferation. An overexpression of amphiregulin has been shown to induce psoriasiform changes in the skin of the transgenic mice shortly after birth. Transgenic mice with cutaneous over expression of cytokines such as IFN-α, IFN-γ, keratinocytes growth factors have became a valuable tool for studying *in vivo* effects of individual cytokines in the pathogenesis.

The stages of development of the lesions in psoriasiform dermatitis may contribute to the variable morphologic presentation in different

**Table 60.1 Psoriasiform dermatosis: Pinkus view of psoriasiform disorders**

| *Group – I* | *Group –II* |
|---|---|
| **Definite:** Supra-papillary exudate and parakeratosis | **Probable** |
| a. Psoriasis – all presentations | a. Nummular eczema |
| b. Reiter's syndrome | b. Pityriasis rubra pilaris |
| c. Acrodermatitis continua | c. Lichen simplex chronicus |
| d. Impetigo herpetiformis | d. Sub-corneal pustular dermatosis |
| e. Seborrheic dermatitis | e. Folliculitis |
| f. Asteatotic dermatitis | f. Impetigo |
| | g. Pustulosis palmo-plantaris |

| Table 60.2 Psoriasiform dermatosis: Farmer and Hood classification of psoriasiform dermatitis | |
|---|---|
| 1. Group I | Diseases showing psoriasiform epidermal hyperplasia as a characteristic features |
| | A. Psoriasis<br>B. Reiter's disease<br>C. Lichen simplex chronicus<br>D. Pityriasis rubra pilaris<br>E. Pellagra<br>F. Inflammatory liner verrucosa epidermal nevus<br>G. Associated with acquired immunodeficiency syndrome (AIDS)<br>H. Acrodermatitis enteropathica<br>I. Necrolytic migratory erythema |
| 2. Group II | Diseases showing psoriasiform epidermal hyperplasia as a frequent feature |
| | A. Contact dermatitis<br>B. Nummular dermatitis/eczema<br>C. Seborrhoeic dermatitis<br>D. Psoriasiform syphilids<br>E. Mycosis fungoides<br>F. Pityriasis rosea |
| 3. Group III | Diseases showing psoriasis epidermal hyperplasia as an occasional feature |
| | A. Dermatophytoses<br>B. Candidiasis<br>C. Norwegian scabies |

| Table 60.3 Psoriasiform dermatosis: Elder *et al* classification of psoriasiform disorders | |
|---|---|
| *Types* | *Example(s)* |
| A. Lymphocyte predominant | 1. Nummular dermatitis /eczema<br>2. Pityriasis rosea<br>3. Lichen simplex chronicus |
| B. Plasma cell predominant | 1. Psoriasiform syphilids<br>2. Arthropod bite reaction |
| C. Eosinophils predominant | 1. Chronic allergic dermatitis<br>2. Exfoliative dermatitis<br>3. Cutaneous T-cell lymphoma (CTCL) |
| D. Neutrophils predominant | 1. Psoriasis<br>2. Dermatophytoses<br>3. Reiter's disease |

disorders. The temporal evolution of the psoriasiform dermatitis from the initial stage-A to a fully developed stage E has been noticed. The former (stage A) shows a subtle basal cell hyperplasia and focal parakeratosis (stage B), slowly evolving to irregular epidermal hyperplasia, hypergranulosis and occasional neutrophils in parakeratotic area (stage C). Further evolution may lead to a regularly invading epidermal hyperplasia, upward growing edematous dermal papillae with dilated capillary loops (stage D and E).

**Table 60.4 Psoriasiform dermatosis: etiology of psoriasiform eruptions**

| *Etiology* | *Disorders* |
|---|---|
| A. Erythemato scaly disorders | • Psoriasis<br>• Disorders of keratinization<br>• Pityriasis rubra pilaris<br>• Erythrokeratodermia<br>• Papillon-Lefevre syndrome<br>• Lamellar ichthyosis<br>• Reiter's disease<br>• Pityriasis rosea<br>• Erythroderma /exfoliative dermatitis |
| B. Eczematous disorders | • Seborrhoeic dermatitis<br>• Nummular dermatitis<br>• Lichen simplex chronics<br>• Allergic contact dermatitis |
| C. Infective disorders<br>• Viral<br>• Spirochete<br>• Fungal<br>• Parasitic | • AIDS associated psoriasiform dermatitis<br>• Psoriasiform syphilids<br>• Dermatophytes infection<br>• Candidiasis<br>• Leishmaniasis<br>• Norwegian scabies |
| D. Malignant disorders | • Mycosis fungoides<br>• Hodgkin's disease (paraneoplastic)<br>• Bazex syndrome |
| E. Others dermatoses | • Inflammatory linear verrucous epidermal nevus<br>• Pellagra<br>• Necrolytic migratory erythema<br>• Acrodermatitis enteropathica<br>• Parapsoriasis<br>• Kawasaki disease<br>• Chondro-dysplasia<br>• Sarcoidosis<br>• Subacute cutaneous LE<br>• Acral psoriasiform hemispherical papulosis<br>• Psoriasiform acral dermatitis<br>• Psoriasiform and sclerodermoid dermatitis of the fingers<br>• Infantile febrile psoriasiform dermatitis<br>• Sulzberger- Garbe exudative discoid and lichenoid chronic dermatitis |
| F. Drug induced | • Anticonvulsant drugs<br>• Fluorescin sodium<br>• Infliximab<br>• Icodextrin<br>• Metformin<br>• Terbinafine<br>• Recombinant granulocyte – macrophage colony stimulating factor (rG-CSF)<br>• Venlafaxine<br>• Pogylated- liposomal doxorubicin |

*(Contd...)*

*(Contd...)*

| Etiology | Disorders |
|---|---|
| | • Calcium channel blocker<br>• Botulinum A Toxin<br>• Beta blocker<br>• Mitomycin<br>• Captopril<br>• Chlorthalidone<br>• Quinidine<br>• Glibenclamide<br>• Lithium<br>• Digoxin |

## DIAGNOSIS

The clinico-histological correlation of the psoriasiform dermatoses is intriguingly variable. A classical histopathologic pattern of psoriasiform dermatoses display a uniform elongation of the rete ridges, papillomatosis and cellular infiltrate both in epidermis and dermis. Hypergranulosis and parakeratosis may be other accompaniment. The classification on the basis of the spectrum of histopathological changes found in various presentation and combinations are outlined above. However, a certain degree of overlap may often exist. Various cutaneous disorders depicting psoriasiform dermatitis may still retain a few features. They distinguish the histopathology for other disorders such as mycosis fungoides may show a variable degree of epidermotrophism with hyperchromatic and hyperconvoluted nuclei in the lymphocytes. Dermatophytosis show focal parakeratosis, focal spongiosis and uneven epidermal hyperplasia. A sandwich sign-presence of fungal element between viable epidermis below and parakeratotic stratum corneum above can be demonstrated in special stains. Similarly, Norwegian scabies and secondary syphilis can be identified due to presence of the causative mite and spirochete respectively.

## RECOMMENDED READING

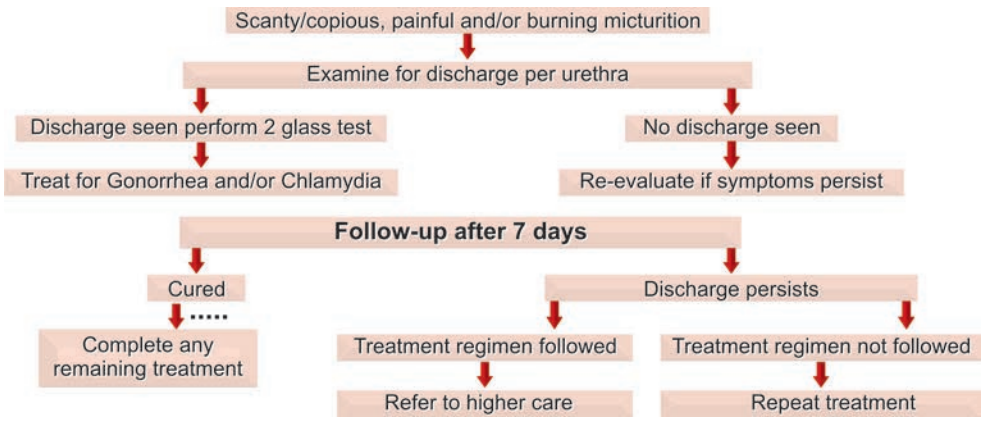

1. Baker H. Psoriasis – a review. *Dermatologica* 1975;180:16-25.
2. David M, Livni E, Stern E, Feuerman EJ, Grinblatt J. Psoriasiform eruption induced by digoxin: confirmed by re-exposure. *J Am Acad Dermatol* 1981;5:702-703
3. Elder D, Rosalie E, Wood ME et al. Algorithmic classification of skin disease for differential diagnosis. In: *Lever's Histopathology of the skin.* Elder D, ed. 8th edn. Philadelphia. Lippincott Williams and Wilkins 1997;93-94.
4. Pinkus H. Psoriasiform tissue reactions. *Australas J Dermatol* 1965;8:31-35.
5. Sehgal VN, Dogra S, Srivastava G, et al. Psoriasiform dermatoses. *Indian J Dermatol Venereol Leprol* 2008;74:94-99.
6. Smotter BR. Psoriasiform Dermatitis. In: *Pathology of the skin.* Farmer ER Hood AF Eds. Ist edn. New York Mc Graw Hill 2000;170-174.

# 61 Chapter Sexually Transmitted Diseases: Syndromic (Symptomatic) Approach

Advent of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) has warranted a major change in eradication and control of sexually transmitted diseases, for sexual intercourse forms one of the major modes of transmission of HIV. Genito-ulcerative disease (GUD), in particular, and non-gonococcal urethritis (NGU), in general, is a risk factor. The precise diagnosis of STD is a dilemma in situation where laboratory component is not readily available for confirming the clinical impression. At that stage, therefore, symptomatic syndromic approach may be ideal for their instant treatment. This option has now been widely approved and acclaimed, and is illustrated through the Flow charts 61.1 to 61.10, encompassing the various manifestations of STD. This approach may facilitate the management of sexually transmitted disease both at under privileged health care center and district and/or teaching institutions. Furthermore, it is imperative to emphasize that these outlines should be supplemented by measures to prevent the spread of sexually transmitted diseases by adopting the following yardsticks namely:

- Treatment
- Instructions for medication and follow up
- Education and counseling comprising:
  - Cure the reservoir of infection.
  - Do not spread STD.
  - Help your sexual partner to get treatment.
  - Come back to make sure that you are cured.
  - Stay cured with condoms.
  - Keep safety but staying with just one sexual partner.
  - Protect yourself against HIV/AIDS.
  - Protect your baby—ask the patient to attend antenatal check-up in the course of pregnancy.
  - Use of condoms.

**Flow Chart 61.1:** Urethral discharge: Syndromic diagnosis, treatment and follow-up




## TREATMENT

*Gonococcal urethritis (gonorrhea):* Institute oral single dose treatment either with

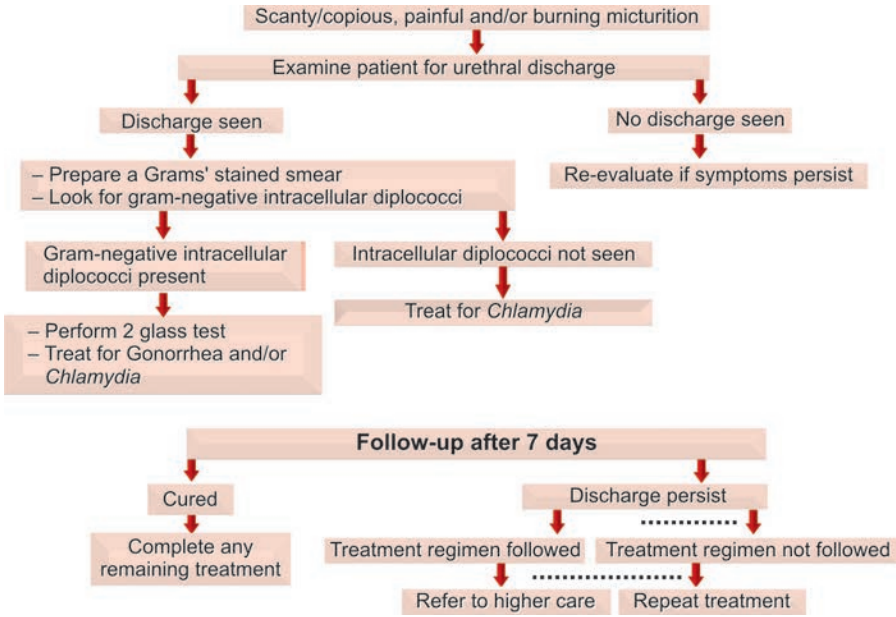
- Ciprofloxacin (biocip, cifran, ciprobid) 500 mg, or
- Cefixime (cefspan, taxim-O, biotax-O) 400 mg, or
- Ceftriaxone (cemax, ceftrax, monocef, comtrax) 250 to 500 mg by slow intravenous infusion/ intramuscular injection or
- Kanamycin (kanamac, kancin) 2 gm by intra-muscular injection.

*Chlamydia*: Institute oral treatment for 7 days' period either with

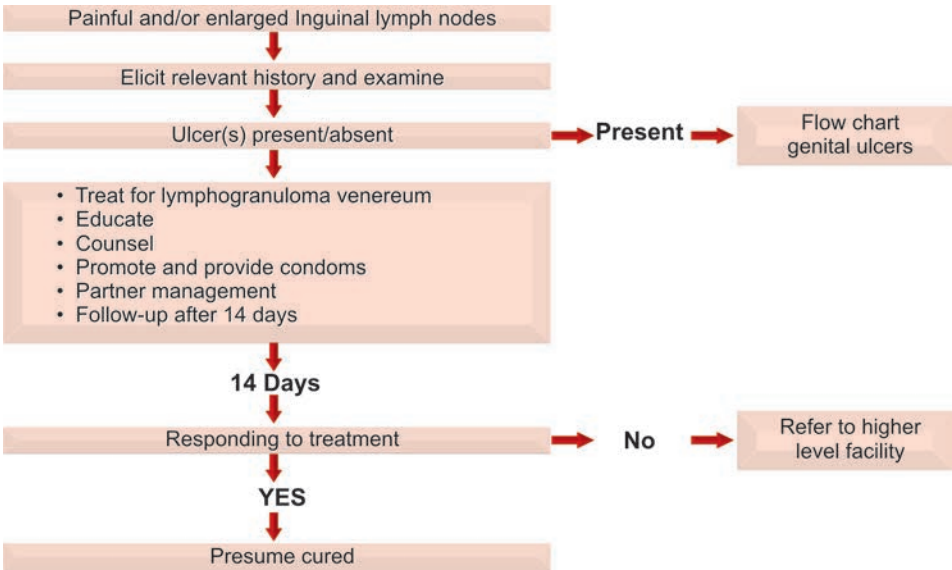
- Doxycycline (biodoxi, doxy-1, doxt, microdox-DS) 200 mg a day or
- Minocycline (cynomycin) 200 mg a day or
- Tetracycline (hostacycline) 2 gm daily in four divided dosage or
- Erythromycin estolate (althrocin, etomin, eromed-333) 2 gm daily in four divided dosage.

**Caution:** Ciprofloxacin, tetracycline, doxycycline and minocycline must not be used during pregnancy and/or lactation.

**Flow Chart 61.2:** Urethral discharge: Syndromic and laboratory diagnosis, treatment and follow-up



**Flow Chart 61.3:** Inguinal Bubo uni-or bilateral

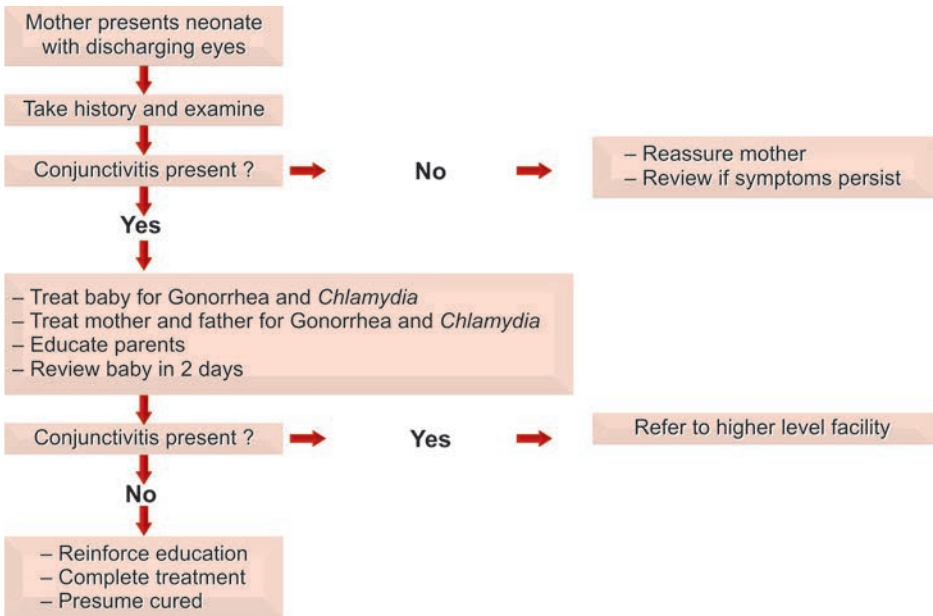



## TREATMENT

*Lymphogranuloma venereum:* Administer either

- Doxycycline (biodoxi, doxy 1, doxt, microdox-DS) a total of 2.8 grams in divided dosage of 100 mg 2 times a day for 14 days or
- Tetracycline (hostacycline) a total of 28 grams in the divided dosage of 2 grams daily for a period for 14 days or
- Erythromycin estolate (althrocin, etomin, eromed-333) a total of 28 grams in the divided dosage of 2 grams daily for 14 days. Aspiration of the fluctuant bubo with wide bore needle may hasten quick recovery.

**Flow Chart 61.4:** Ophthalmia neonatorum (Neonatal conjunctivities)



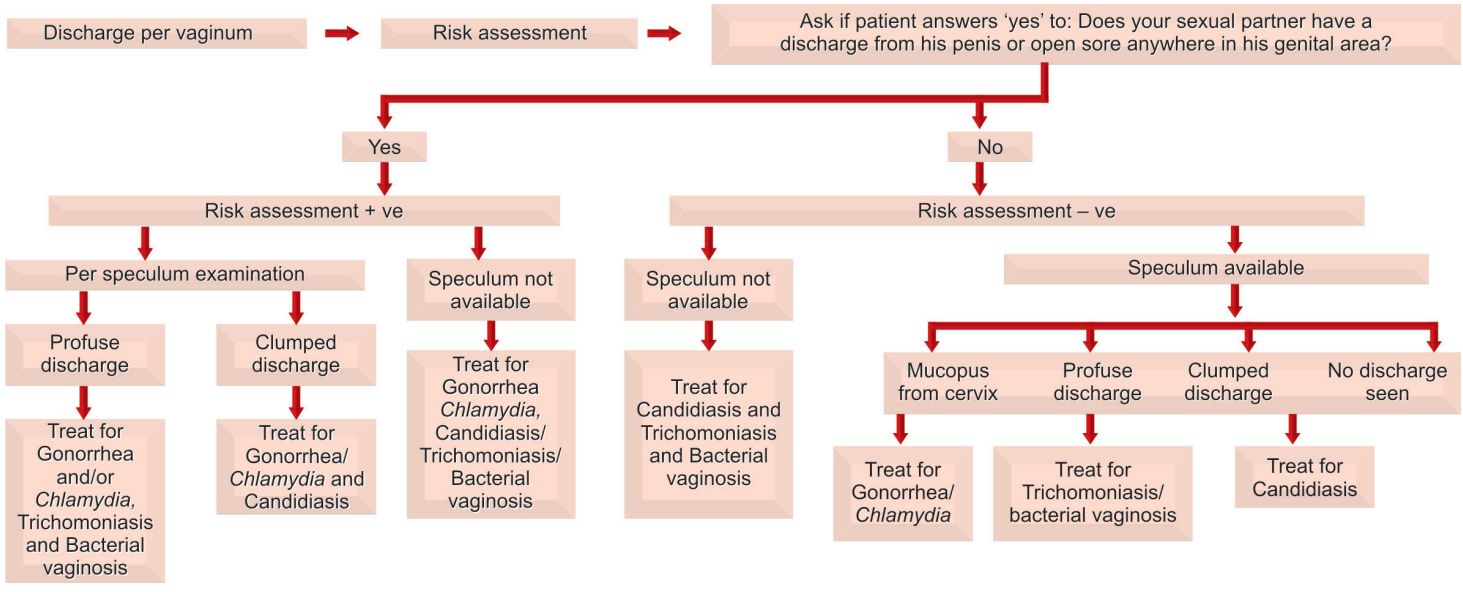

## TREATMENT

- Ceftriaxone (cemax, ceftrax, monocef, comtrax) 50 mg/kg body weight by intramuscular injection as a single dose to a maximum of 125 mg.

*Alternative regimen where ceftriaxone is not available:*

- Kanamycin (kanamac, kancin) 25 mg/kg body weight by intramuscular injection as a single dose to a maximum of 75 mg or
- Spectinomycin (trobicin) 25 mg/kg body weight by intramuscular injection as a single dose to a maximum of 75 mg plus
- Erythromycin syrup (eryc, althrocin) 50 mg/kg body weight per day orally in 4 divided dosage for 14 days.
- Single dose ceftriaxone, kanamycin and spectinomycin are of proven efficacy.
- The addition of tetracycline eye ointment to these regimens is of no documented benefit.

**Flow Chart 61.5:** Vaginal discharge: Syndromic diagnosis, treatment and follow-up



## TREATMENT

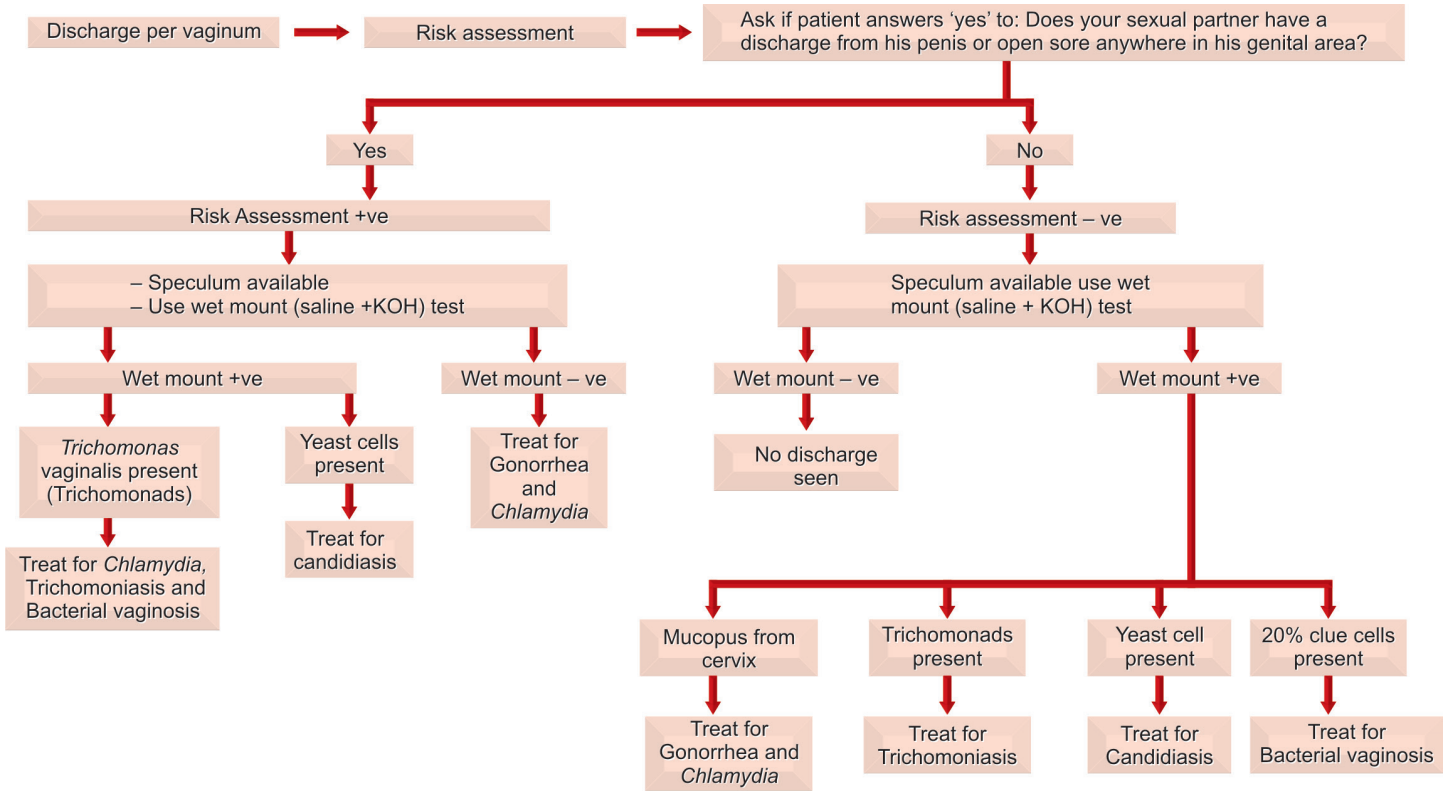
*Vaginal discharge:* Should it be Gonorrhea and/or *Chlamydia* on per speculum examination, institute oral treatment with

- Ciprofloxacin (biocip, cifran, ciprobid) 500 mg in a single dosage supplemented either by
- Doxycycline (biodoxi, doxy 1, doxt, microdox-DS) 100 mg 2 times a day up to 1.4 gm in 7 days or
- Minocycline (cynomycin) 100 mg 2 times a day up to 1.4 gm in 7 days or
- Cerftriaxone (cemax, ceftrax, monocef, comtrax) 250 to 500 mg by slow intravenous

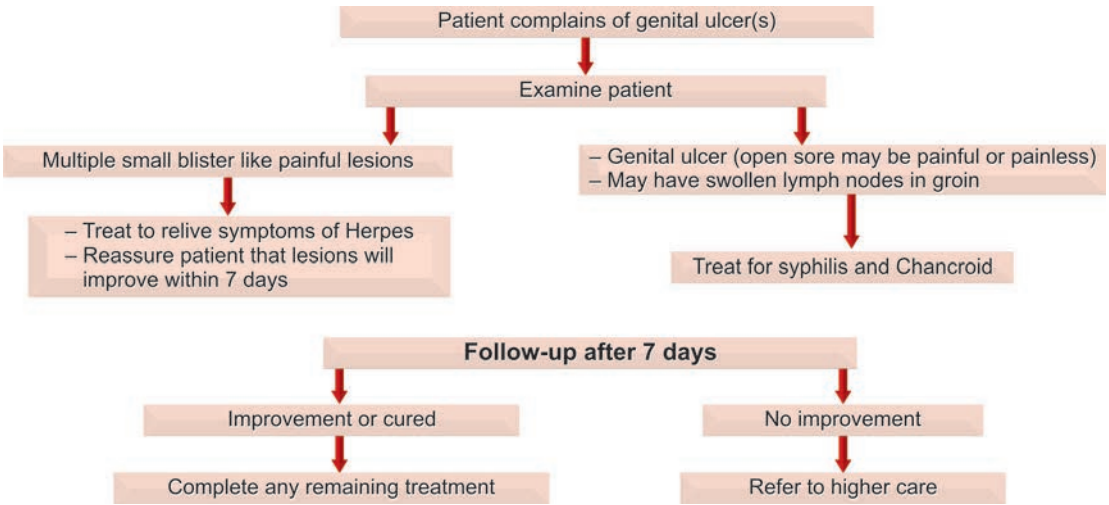
*Preceding drugs are to be avoided in pregnancy and should instead be replaced either by*

- Azithromycin (azithral) 500 mg in a single dose by slow intravenous infusion/intramuscular injection or
- Erythromycin estolate (althrocin, etomin, eromed-333) 500 mg 4 times a day up to 20 to 30 gm for 10 to 15 days
- Metronidazole (aldezol, flagyl, metrogyl) 400 mg 3 times a day or a total of 8.4 gm in equal divided dosage for 7 days period long
- Clotrimazole (canesten, candid) 200 mg once a day for 3 days or
- Clotrimazole (candid, canesten) 500 mg intravaginally only once a day or
- Fluconazole (forcan, fluzon) 150 mg in a single oral dose.

**Flow Chart 61.6:** Vaginal discharge: Syndromic and laboratory diagnosis, treatment and follow-up



**Flow Chart 61.7:** Genital ulcer: Syndromic diagnosis, treatment and follow-up




## TREATMENT

*Syphilis, chancroid and herpes progenitalis* are the major genito-ulcerative diseases.
Treatment guidlines for the preceding diseases are:
*Syphilis:* It is treated either by administering

- Benzathine penicillin (penidure-LA) 2.4 milion units given intramuscular in 2 equal divided dosage of 1.2 million units in each buttock or
- Doxycycline (biodoxi, doxy-1, doxt, microdox-DR) minocyline (cynomycin) 100 mg 2 times a day up to a total dose of 2 to 3 gm in 10-15 days or
- Tetracycline (hostacycline) 500 mg 4 times a day up to 30-40 gm in 10-15 days.
- Erythromycin estolate (althrocin, etomin, eromed-333) 500 mg up to 2-3 gm a day in 10-15 days.

*Chancroid:* Is treated by oral administration of

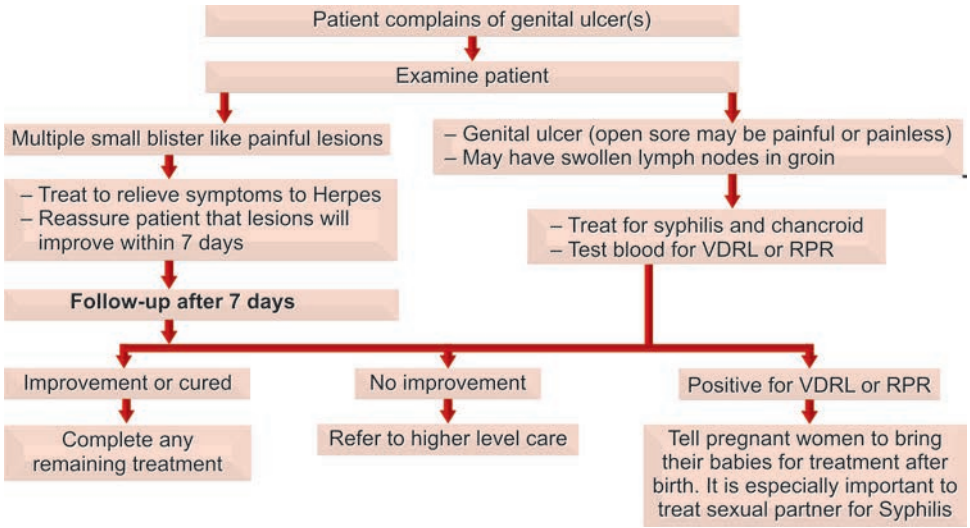
- Ciprofloxacin (cifran, microflox, quintor) 500 mg orally in a single dose or
- Trimethroprim 80 mg/sulphamethoxazole 400 mg/(otrim, septran) 2 tabs 2 times a day for 7 days
  or
- Trimethroprim 160 mg/sulphamethoxazole 800 mg (bactrim, otrim) 1 tab a day for 7 days or
- Ceftriazone (ceftrax, comtrax, cemax) 1 gm intravenous in a single dose.

*Herpes progenitalis:* It is treated by oral administeration of

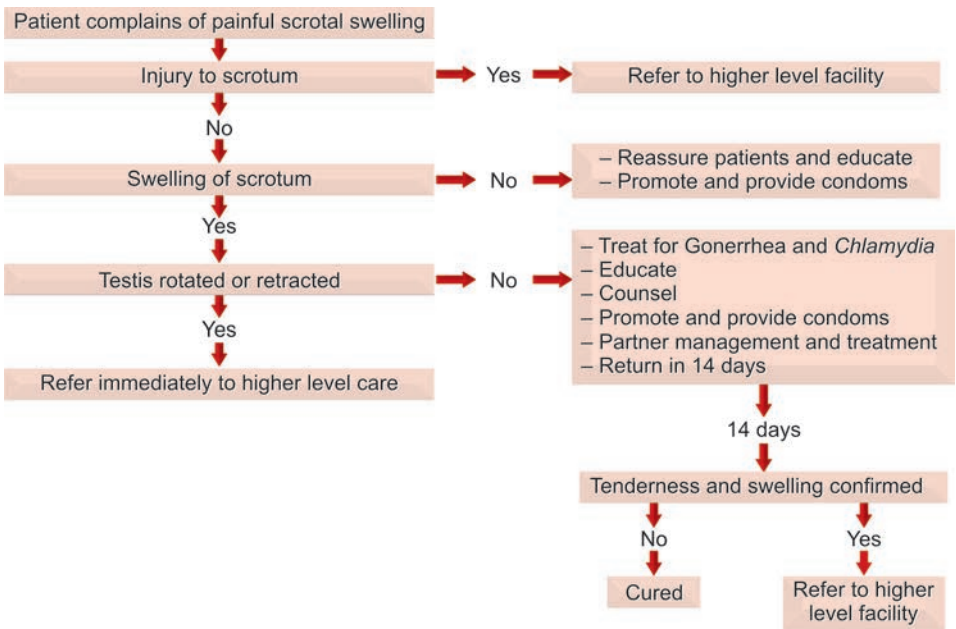
- Acyclovir (zovirax, herpex, herperax) 200 mg 5 times a day for 7 days (first episode)
- Recurrent episode are treated in a similar ways for 5 days.

**Caution:** Ciprofloxacin, tetracycline, doxycycline and minocycline must not be used during pregnancy and lactation.

**Flow Chart 61.8:** Genital ulcer: Syndromic and laboratory diagnosis, treatment and follow-up




**Flow Chart 61.9:** Sexually transmitted diseases scrotal swelling



## TREATMENT

- Ciprofloxacin (cifran, microflox, quintor) 500 mg as a single oral dose (make sure that the patient swallows the tablets under supervision).

### Alternative Regimen

- Ceftriaxone (cemax, ceftrax, monocef, comtrax) 250 mg intramuscular as a single dose or
- Cefixime (cefspan, taxim-O, biotax-O) 400 mg in a single oral dose or
- Kanamycin (kanamac, kancin) 2 g intramuscular as a single dose. Recommended regimen for *Chlamydia.*

### Urethritis

- Doxycycline (biodoxi, doxy 1, doxt, microdox-DS 100 mg orally 2 times a day for 10 days (make sure that the patient receives 20 tablets or capsules with instructions to take one tablet in the morning and one in the evening).

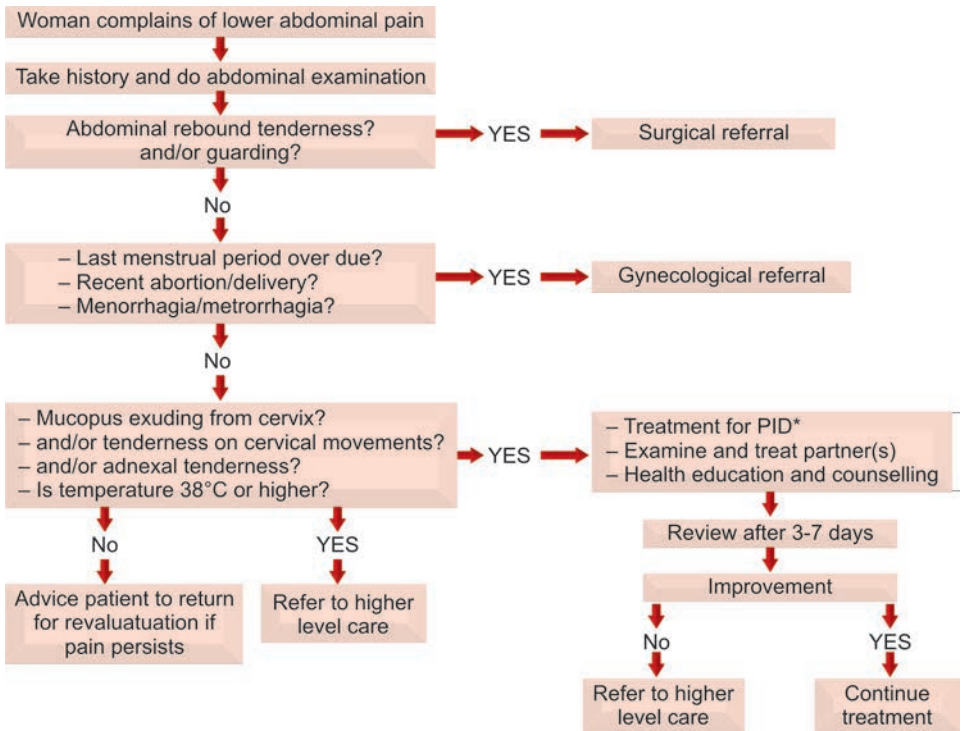
### Alternative Regimen

- Tetracycline (hostacycline) 500 mg orally 4 times a day for 10 days or
- Erythromycin estolate (althrocin, etomin, eromed-333) 500 mg orally 4 times a day for 10 days (equivalent doses of other sulfonamides (triple sulfa) may also be used.)

**This is a painful condition and supportive therapy with:**

- Bed-rest
- Scrotal elevation with a scrotal support and analgesic is essential part of management
- Advise the patient to take all his tablets and inform him about the mode of transmission of STD and the possible complications of infection and, in particular, epididymo-orchitis.

**Flow Chart 61.10:** Lower abdominal pain in women: Syndromic diagnosis, treatment and follow-up




## TREATMENT FOR PELVIC INFLAMMATORY DISEASE (PID)

(*N. gonorrhea* + *C. tricomatis* + anaerobic infection) use this regimen only if patient is well enough to take food and liquid, walk unassisted, take her medication, and return for follow up. Otherwise, refer to higher level care.

### Single dose Treatment for Gonorrhea

- Ciprofloxacin (cifran, ciprobid) 500 mg, orally as a single dose, or
- Ceftriaxone (cemax, ceftrax, monocef, comtrax) 250 mg to 1 gm by slow intravenous infusion/ intramuscular injection as a single dose, or
- Cefixime (cefspan, taxim-O, biotax-O) 400 mg orally as a single dose, or
- Kanamycin (kanamac, kancin) 2 gm by intramuscular injection as a single dose.

### Alternative Treatment, if Single dose Treatment is not Available

- Trimethoprim 80 mg/sulphamethoxazole 400 mg (bactrim, ciplin, cotrimoxazole) 10 tablets stat daily for 3 days, and then two tablets orally, 2 times a day.

### Plus Treatment for Chlamydia Trichomatis

- Doxycycline (biodoxi, doxy 1, doxt, microdox-DS) 100 mg orally 2 times daily for 14 days or
- Tetracycline 500 mg (hostacycline) orally 4 times daily for 14 days.

### Plus Treatment for Anaerobic Infection

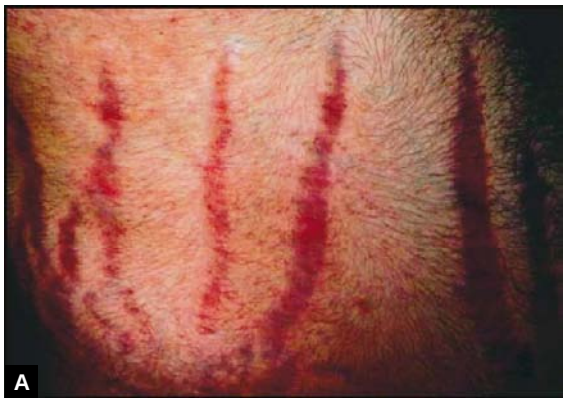
- Metronidazole 400 mg (aldezol, flagyl, metrogyl) 2 times daily for 14 days (avoid in 1st trimester of pregnancy, also avoid alcohol).

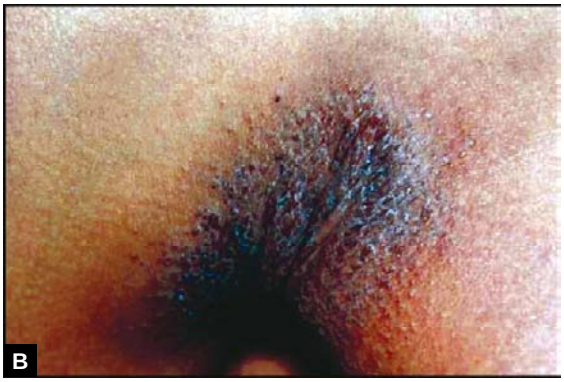
## RECOMMENDED READING

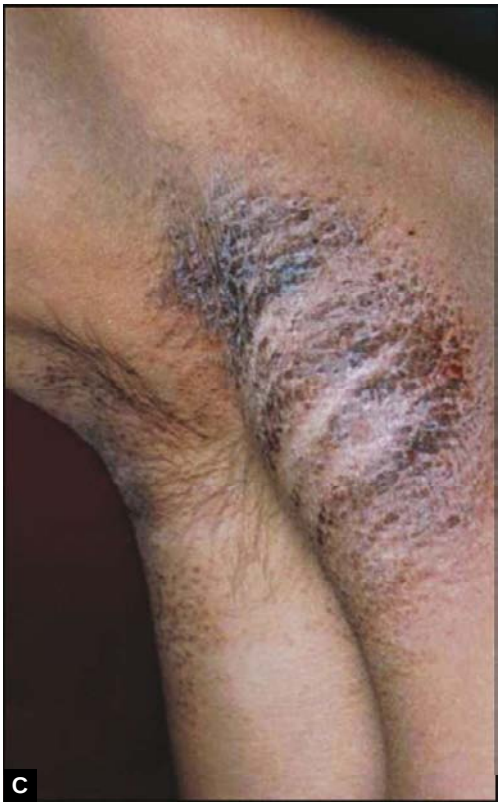
1. Adler MW. Syndromic management of genital ulcer disease. *Genitourin Med* 1995;71:416.
2. Htun Y, Morse SA, Dangor Y et al. Comparison of clinically directed, disease specific, and syndromic protocols for the management of genital ulcer disease in Lesotho. *Sex Transm Infect* 1998; 74:S23-S28.
3. Van Dam CJ, Becker KM, Ndowa F et al. Syndromic approach to STD case management: where do we go from here? *Sex Transm Infect* 1998;74:S175-S178.
4. Pettifor A, Walsh J, Wilkins V et al. How effective is syndromic management of STDs?: A review of current studies. *Sex Transm Dis* 2000;27:371-385.
5. Anonymous. CDC and prevention 1998. Guidelines for the treatment of STD. MMWR 1998;47(RR-1):1-118.

# 62 Chapter Miscellaneous Dermatoses

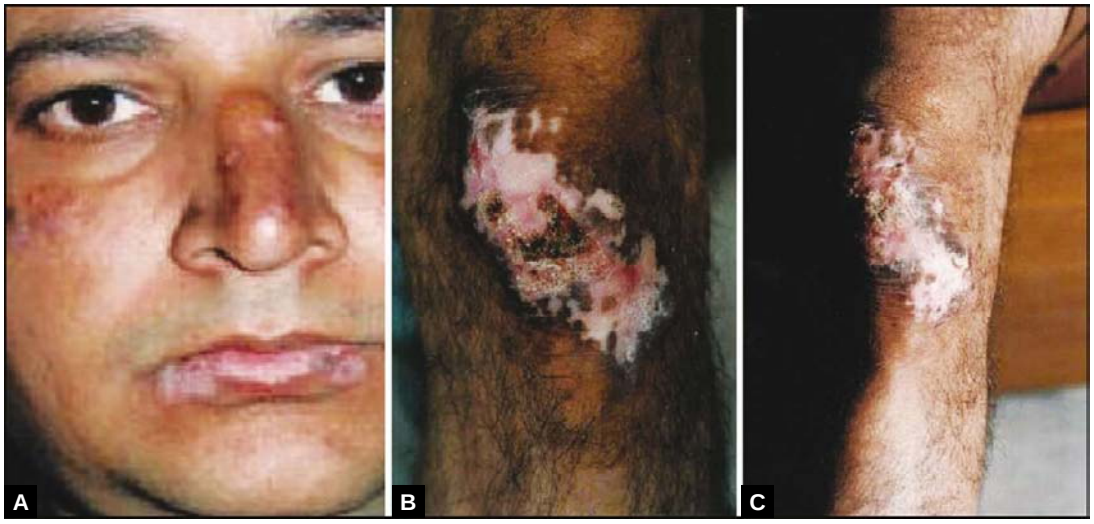
Miscellaneous dermatoses is an essential ingredient of academic contents and/or practice of dermatology. It is therefore, always desirable to cater to this need through descriptive colored illustrations. It is likely to assist every concerned individual practicing the subject. This fits into the bill of changing scenario where time is the major casualty. Hence, quick go over on these illustrations shall be of paramount guide and may help in strengthening the visual orientation and making the instant diagnosis. The precise outlines for diagnosis accompanying the illustrations should adequately decipher and fulfill the aspiration of the astute consumers.



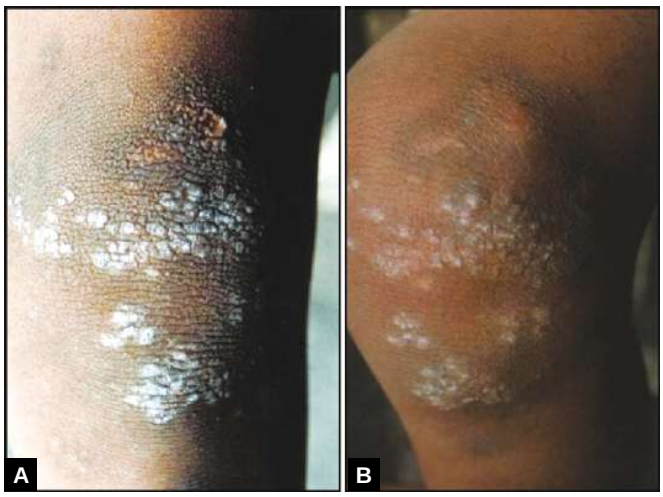




**Figures 62.1A to C:** Striae distensae




**Figures 62.2A to C:** Chronic discoid lupus erythematosis

- Well-defined erythematosquamous plaque(s)
- Keratotic plugging
- Atrophic scarring
- Over the butterfly area of the face
- Diagnostic histopathology




**Figures 62.3A and B:** Phrynoderma

- Follicular hyperkeratosis
- Skin is dry and rough
- With/without night blindness, xerophthalmia, and keratomalacia

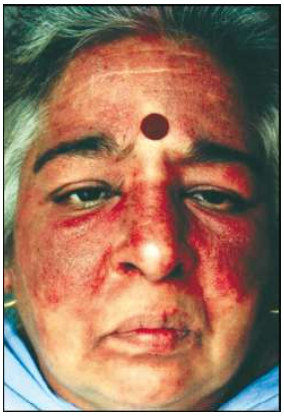


**Figure 62.4:** Dermatomyositis

- Extensive, well demarcated erythema and edema of the face.
- Pain and/or tenderness/weakness of shoulder and pelvic girdle (proximal) muscles.

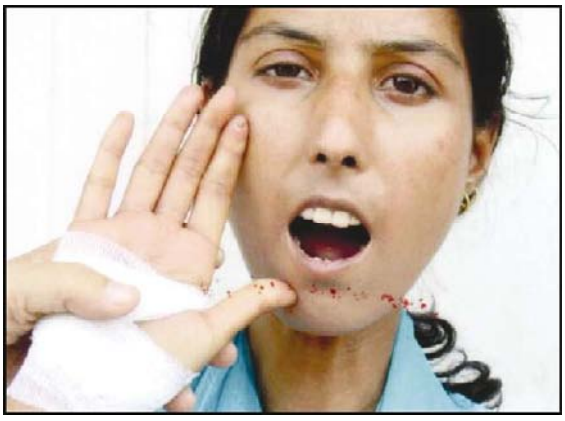
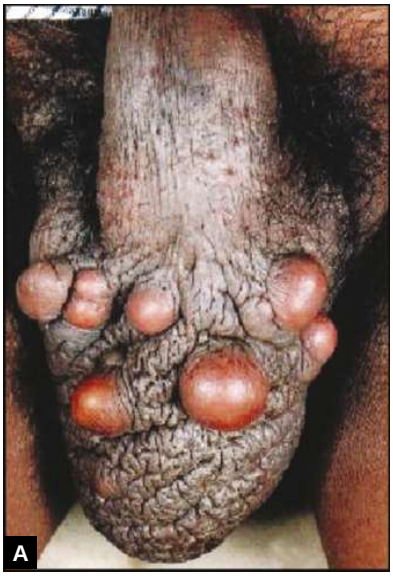
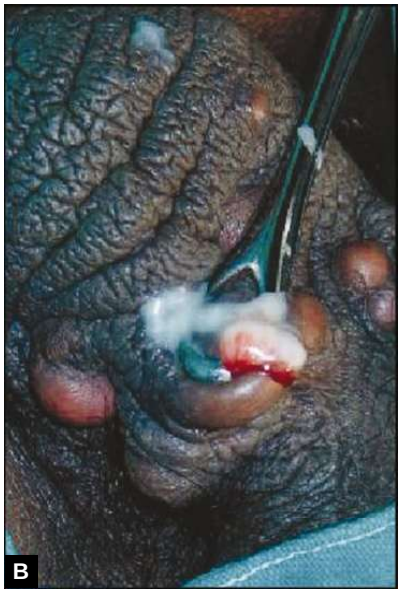


**Figure 62.5:** Systemic sclerosis/scleroderma

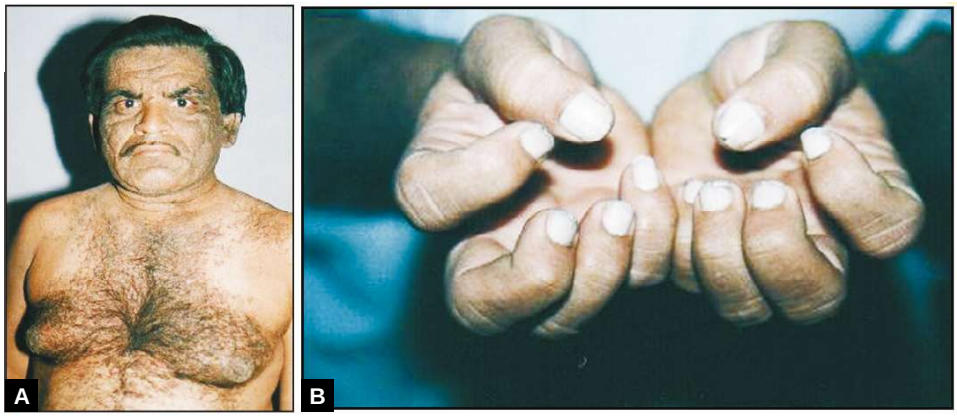
- Peculiar facial appearance, pinched nose, restricted wrinkling of the forehead/opening of the mouth, declining, frowning and deglutition reflex.
- Stretched 'bound down' skin affecting the face and hand. (acrosclerosis).
- Raynards' phenomenon.
- Diagnostic histopathology.
- Organ system affected.



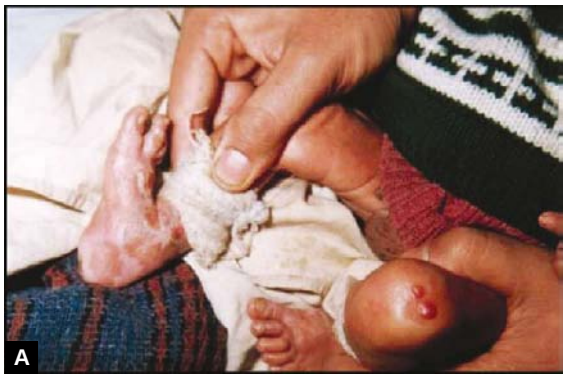

**Figures 62.6A and B:** Sebocystomatosis

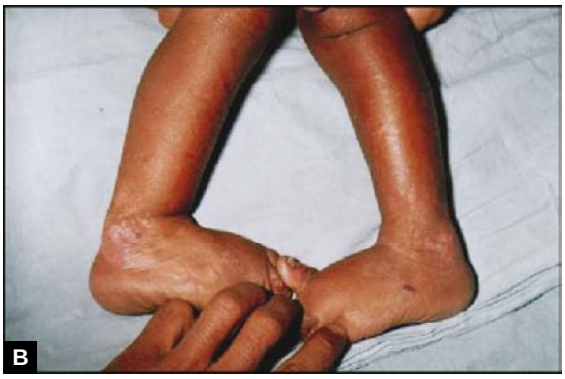
- Slow growing, fluctuating, raised, round, firm intra or subcutaneous swellings, with an occasional puncta on top.
- Curdy white sebum on excision.
- Diagnosis through histopathology.

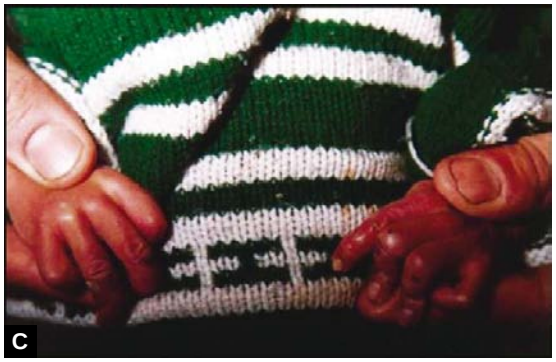



**Figures 62.7A and B:** Darier's disease

- Hereditary.
- Extensive hyperkeratotic/crusted papules/verrucous/plaques.
- Predilection for 'seborrheic' sites.
- Histopathology is pathognomonic.

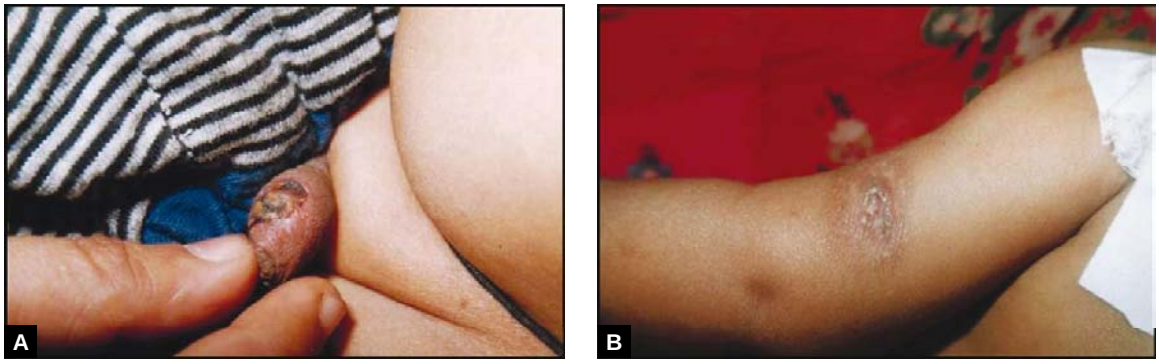


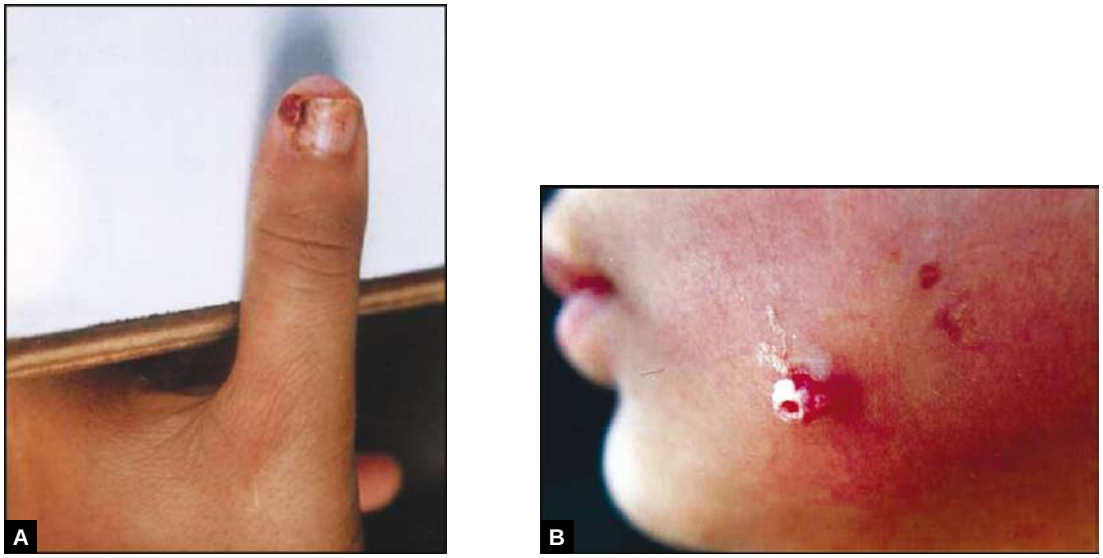

**Figures 62.8A to C:** Epidermolysis bullosa simplex

- An autosomal dominant trait.
- Recurrent bullae at trauma prone areas. Knuckles, elbows, knees, and ankles.
- Spontaneous healing usually without scars.
- Histopathology an essential supplement.




**Figures 62.9A and B:** Mastocytoma

- Solitary nodules/vesicle/bullae.
- Local flushing.
- Darier's sign positive.
- Self-limiting.




**Figures 62.10A and B:** Graniloma pyogenicos

- A single dull red soft/firm raised pedunculated nodule, crusted/smooth/atrophic top.
- Bleeds easily on injury or trauma.
- Histopathology supplementary.

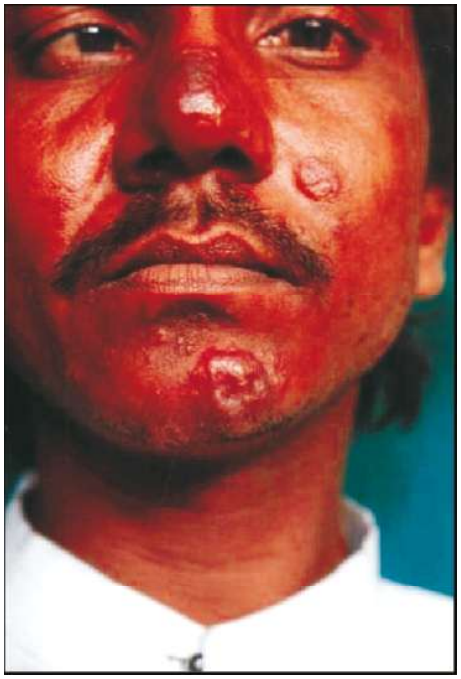
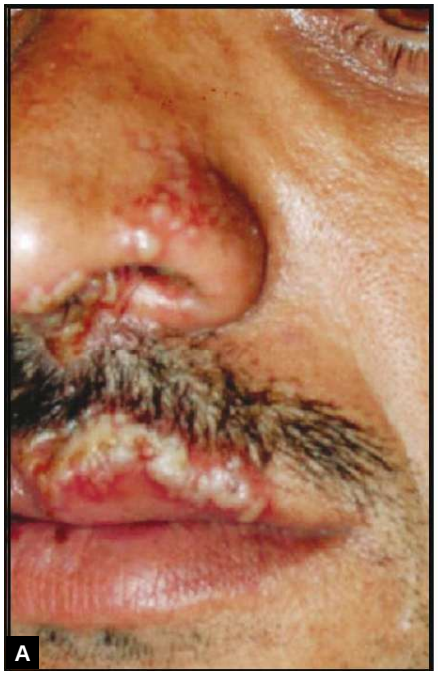
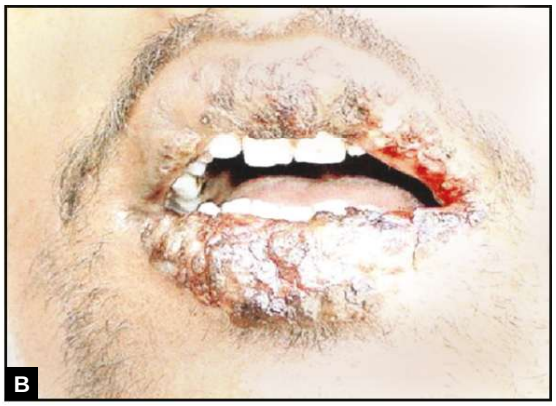


**Figure 62.11:** Post-kala-azar dermal leishmaniasis

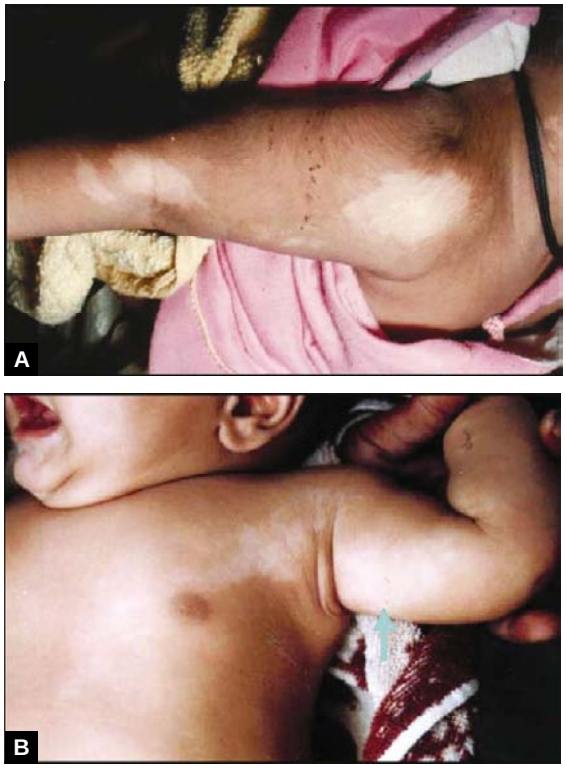
- Soft, nontender, nonulcerative yellowish pink nodules over hypopigmented erythematous maculae.
- Demonstration of leishmania donovani on tissue smear/tissue section is diagnostic.

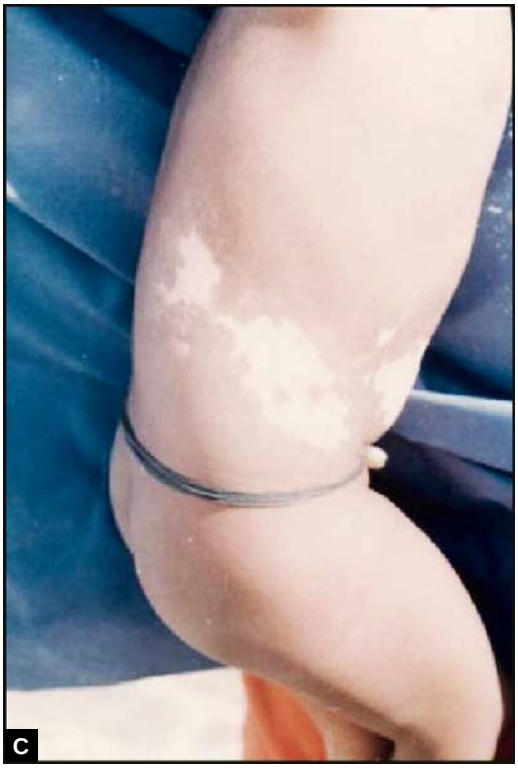



**Figures 62.12A and B:** Herpes labialis

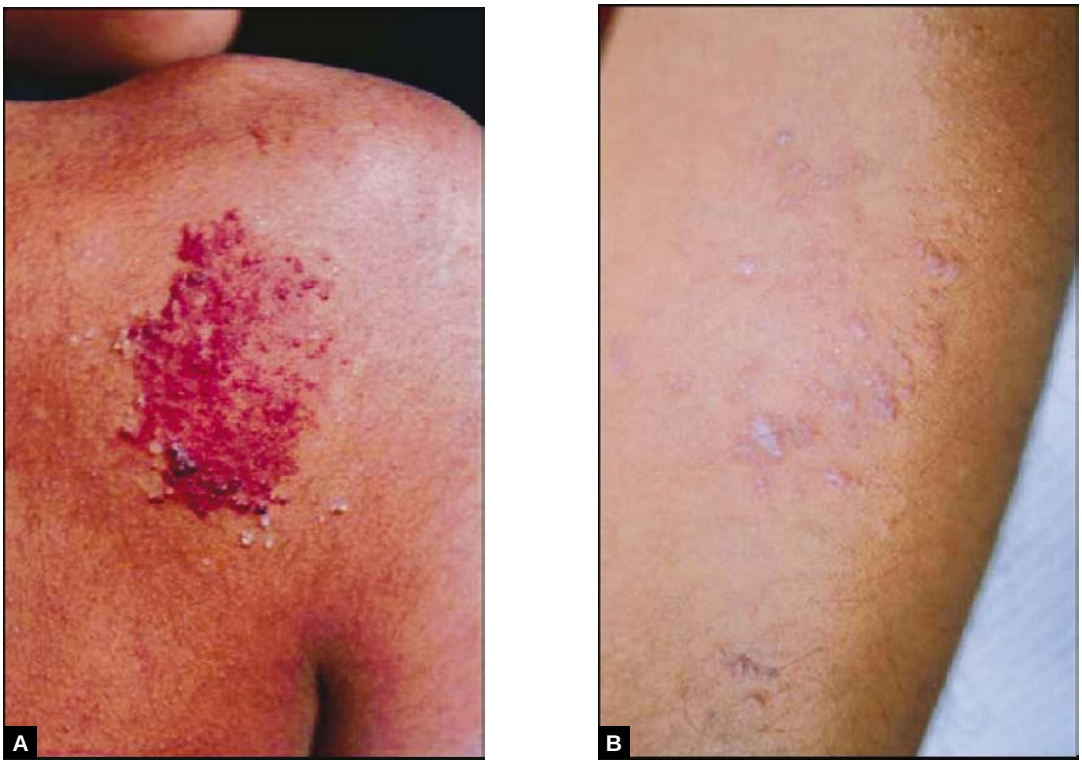
- Multiple, grouped, vesicles over an erythematous background affecting mucocutaneous junction.
- Demonstration of acantholytic cells on smear and in the tissue section depicting intra-epidermal suprabasal cleavage.



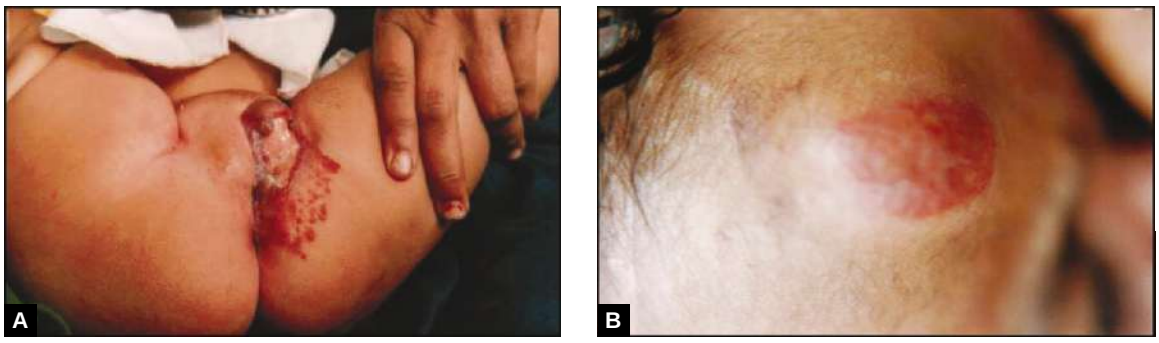

**Figures 62.13A to C:** Naevus anemicus

- An ill defined hypopigmented macules.
- At birth, during childhood or at puberty.
- Absent vascular response.
- D/D indeterminate leprosy.

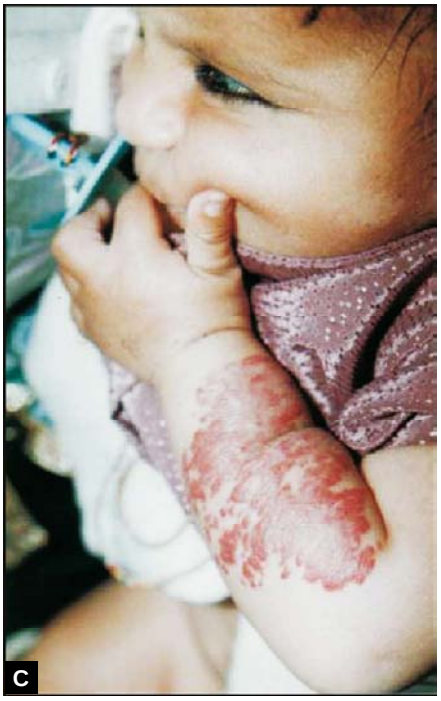


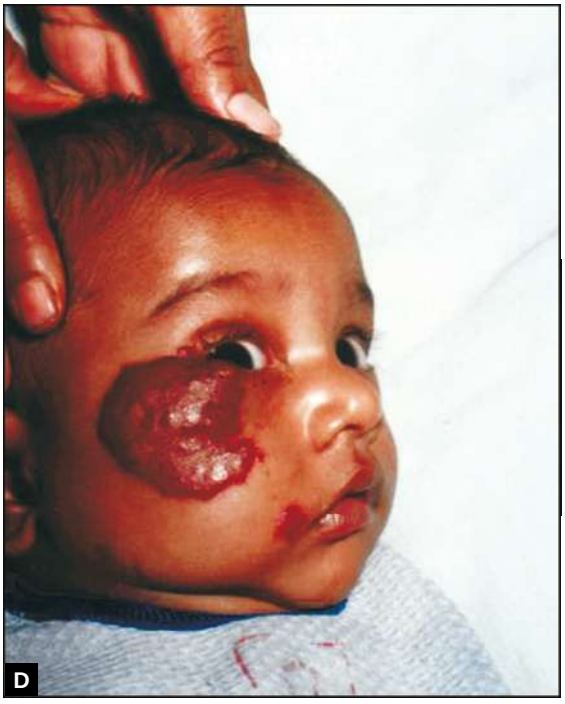

**Figures 62.14A and B:** Lymphangioma circumscriptum

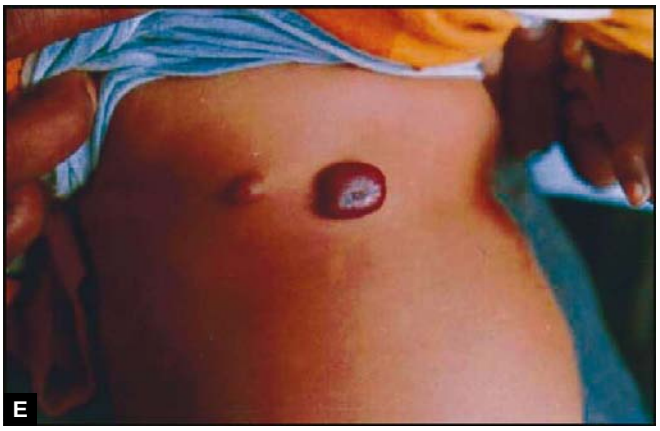
- Presence of well circumscribed superficial groups of small thick wall vesicle, giving an appearance of frog's spawn.




**Figures 62.15A and B**




**Figures 62.15A to E:** Hemangioma of infancy

- Identified at birth/immediately after.
- A raised bright red soft tumor of 'strawberry' contour.
- Spontaneous regression at/after two years of age following an initial growth.
- Diascopy affirmative.

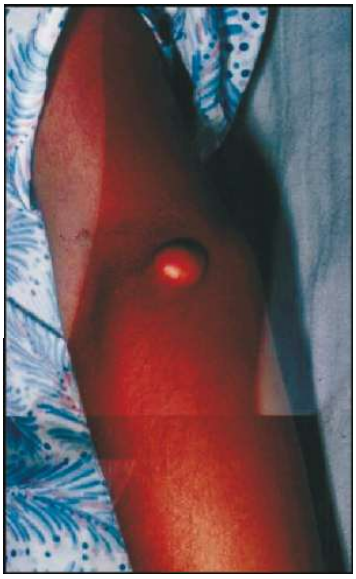


**Figure 62.16:** Xanthoma

- Smooth firm nodule(s) covered by mobile normal appearing skin.
- An indicator for underline disease
- Histopathology is diagnostic

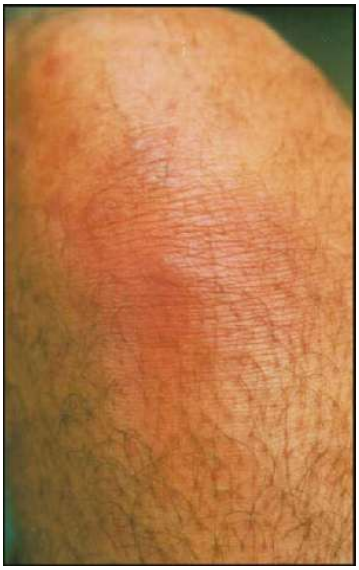
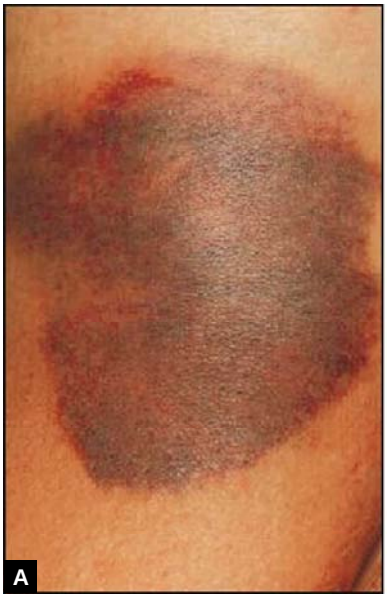
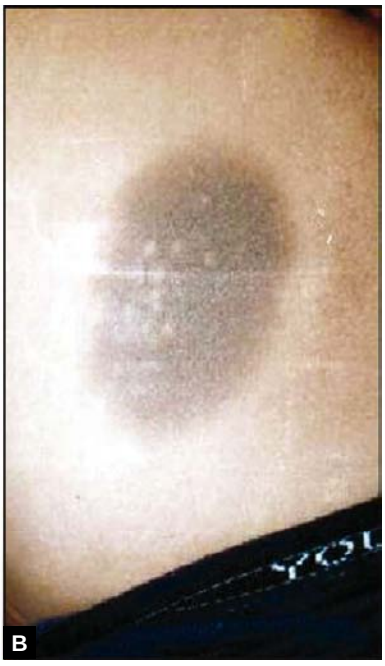


**Figure 62.17:** Pseudoacanthosis nigricans

- Brownish and/or verrucous patches occupying the flexural sites, neck exilian.




**Figures 62.18A and B:** Fixed drug eruption

- Sudden appearance of round and/or oval edematous plaques of varying sizes, of grayish hue affecting any part of the skin and/or mucous membrane.
- Recurrence *in situ* a diagnostic hallmark.

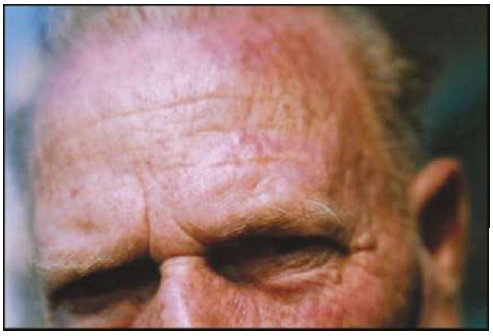
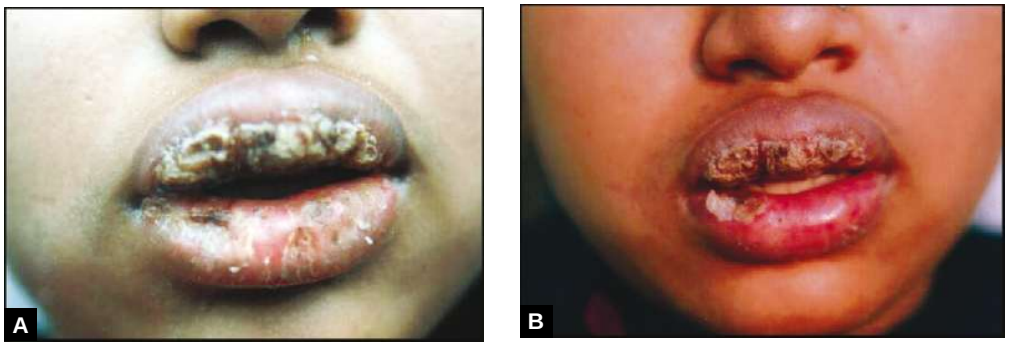


**Figure 62.19:** Actinic keratosis




**Figures 62.20A and B:** Cheilitis

- Erythema, edema, ulceration and crusting.

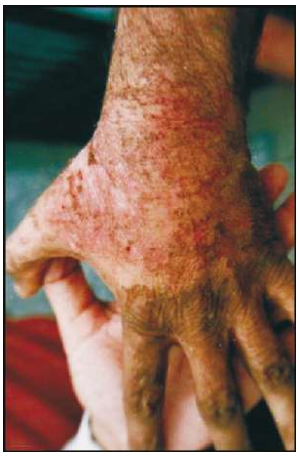


**Figure 62.21:** Pellagrous dermatitis

- Erythema, edema and vesiculation
- An expression of multinutritional deficiency.
- Occasionally encountered in developing countries.

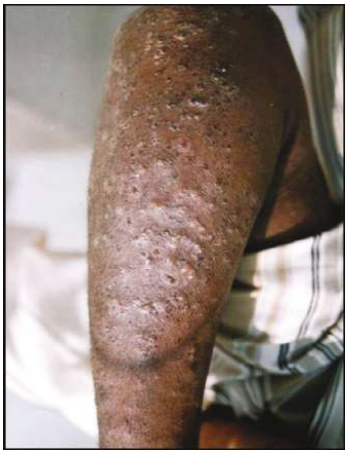


**Figure 62.22:** Bockhart's impetigo

- Multiple follicular pustules affecting the anterior lower leg.

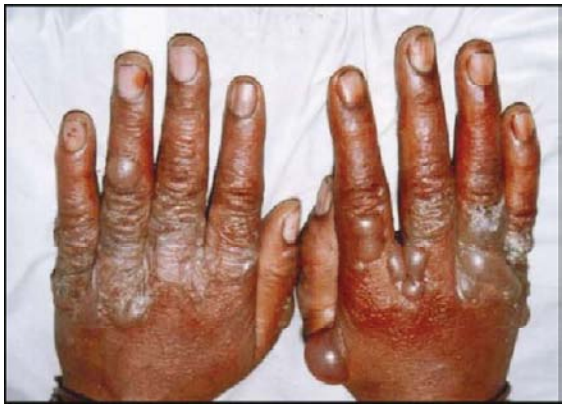


**Figure 62.23:** Contact dermatitis kerosene oil

- Erythema, edema, and bullae over dorsa of the hand.

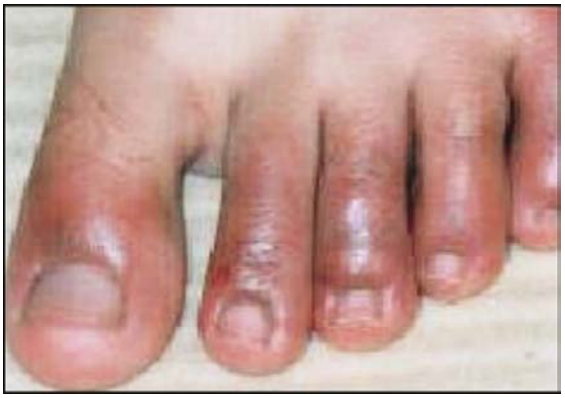


**Figure 62.24:** Chilblains

- Marked edema, erythema and scaling.

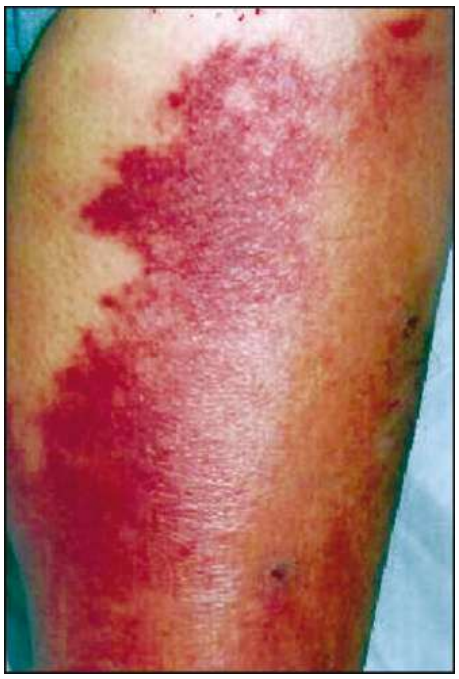


**Figure 62.25:** Erysipelas

- A progressively increasing, sharply demarcated erythematous plaque.
- Attended by constitutional symptoms.
- D/D cellulitis.

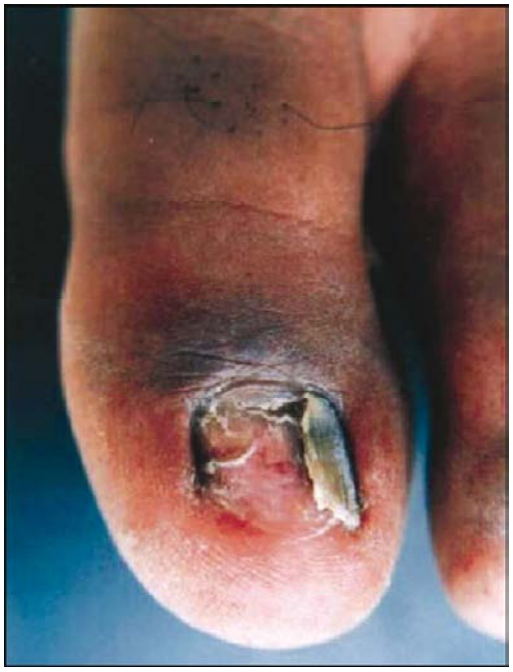


**Figure 62.26:** Onychomycosis

- White, rough and crumble nail plate.

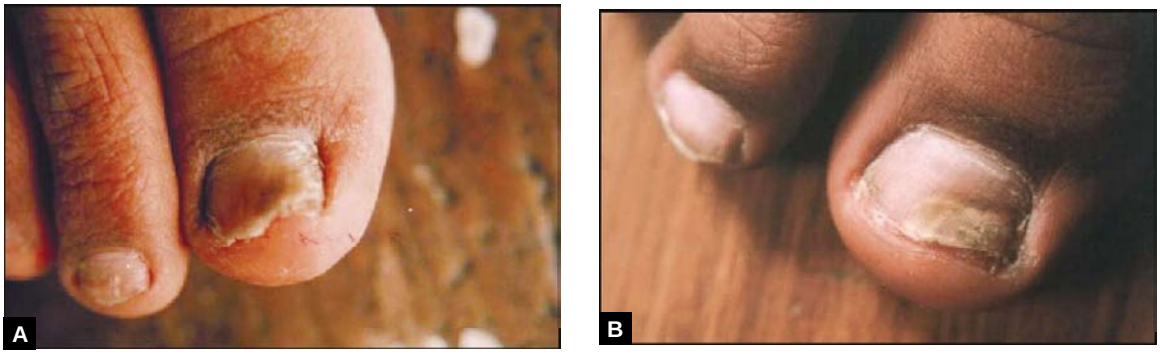



**Figure 62.27A and B:** Onychomycosis: Proximal white subangual

- Whitening of proximal nail plate, extend to involve its distal end.
- Nail plate is smooth and normal, in contrast to the preceding variant.

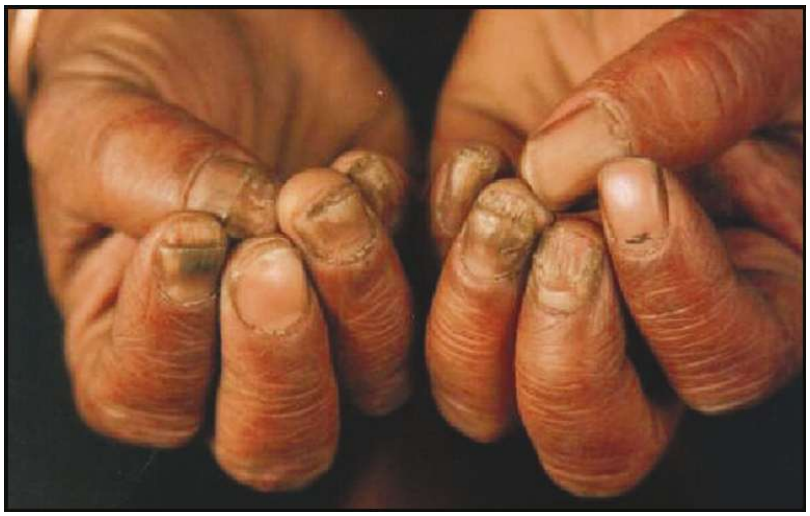
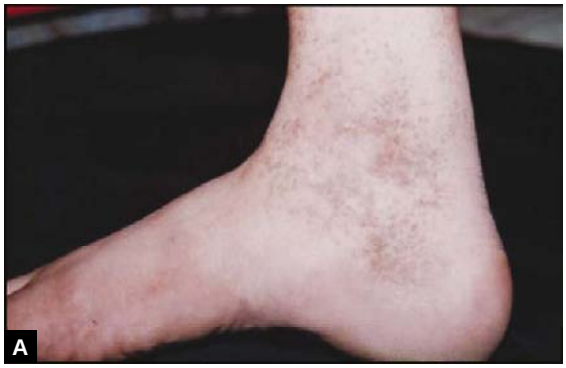
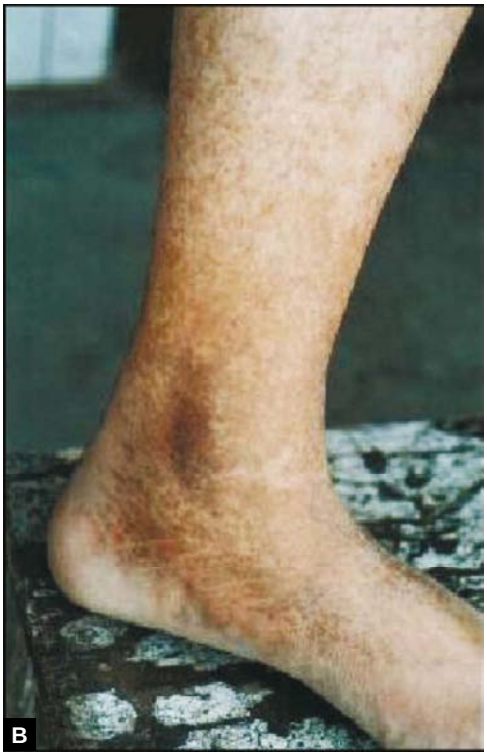


**Figure 62.28:** Onychomycosis: Distal subangual

- Hyperkeratosis of distal and lateral margins, onycholysis, thickening and discoloration of the nail plate.




**Figures 62.29A and B:** Progressive pigmented purpuric dermatosis (Schamberg's disease)

- Pinhead-sized reddish puncta coalese to form irregular plaques of orange/brown pigmentation.
- Asymptomatic.

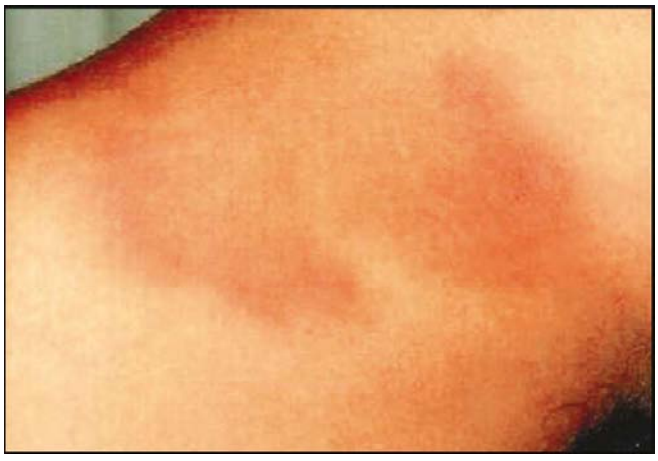
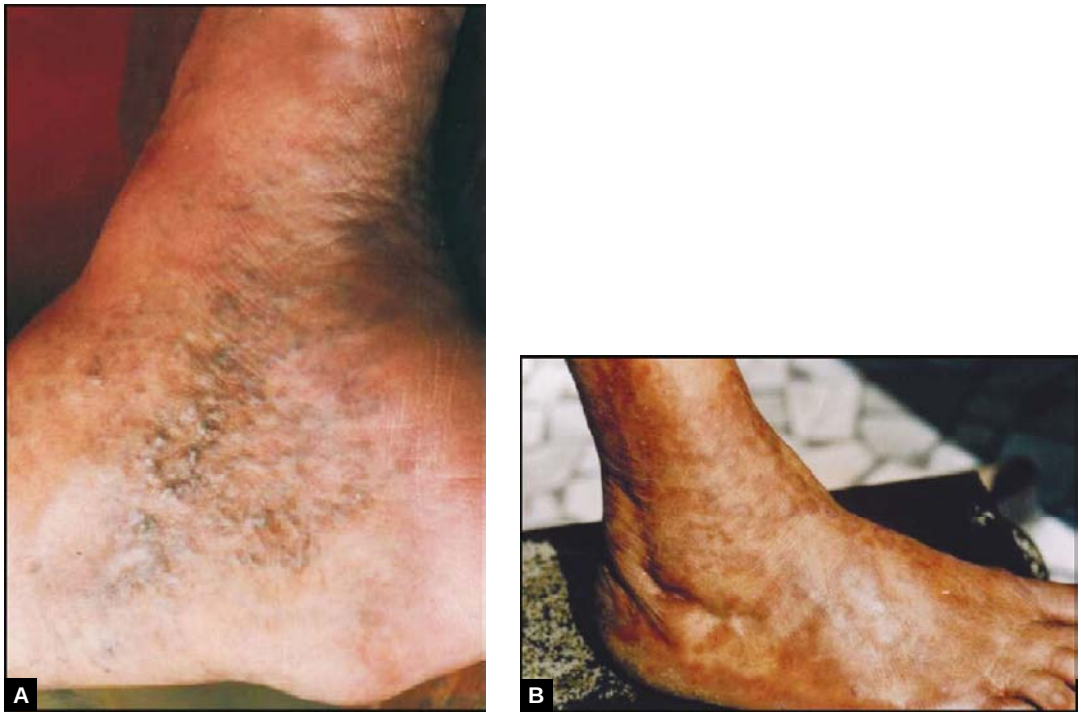


**Figure 62.30:** Lichen purpuricus/Lichen aureus

- Localized, persistent, intensely purpuric lesions of golden-brown color.




**Figures 62.31A and B:** Pigmented purpuric lichenoid dermatosis (Gougerot-Blum syndrome)

- Multiple lichenoid papules and/or plaques of various colors, seen on the legs, and rarely on the trunk and thighs.

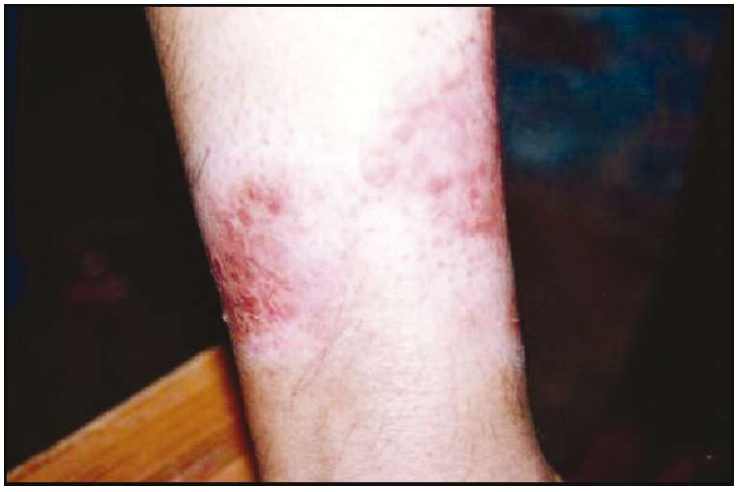
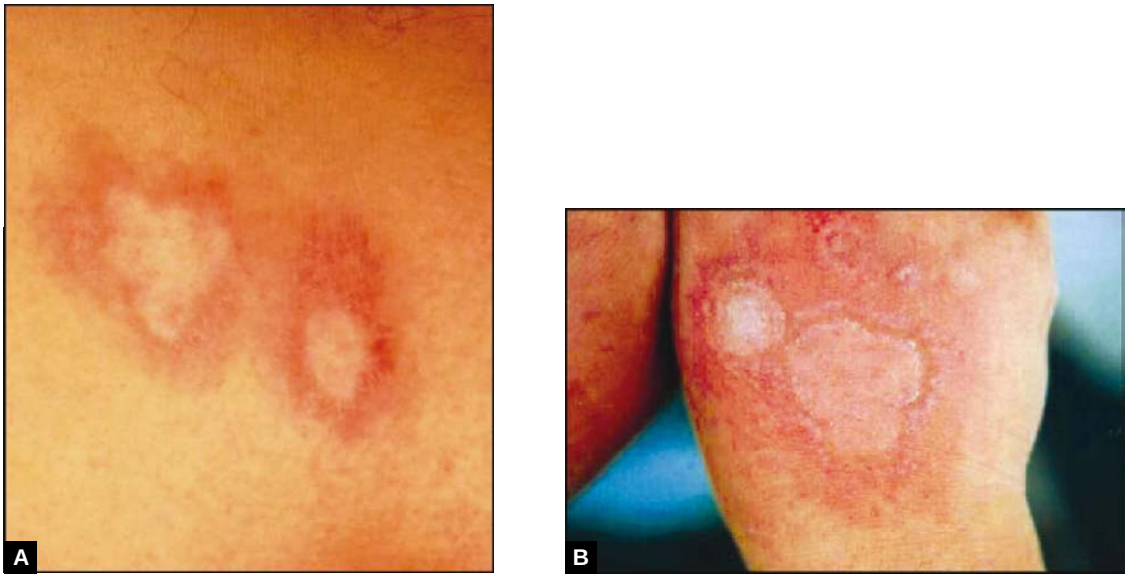


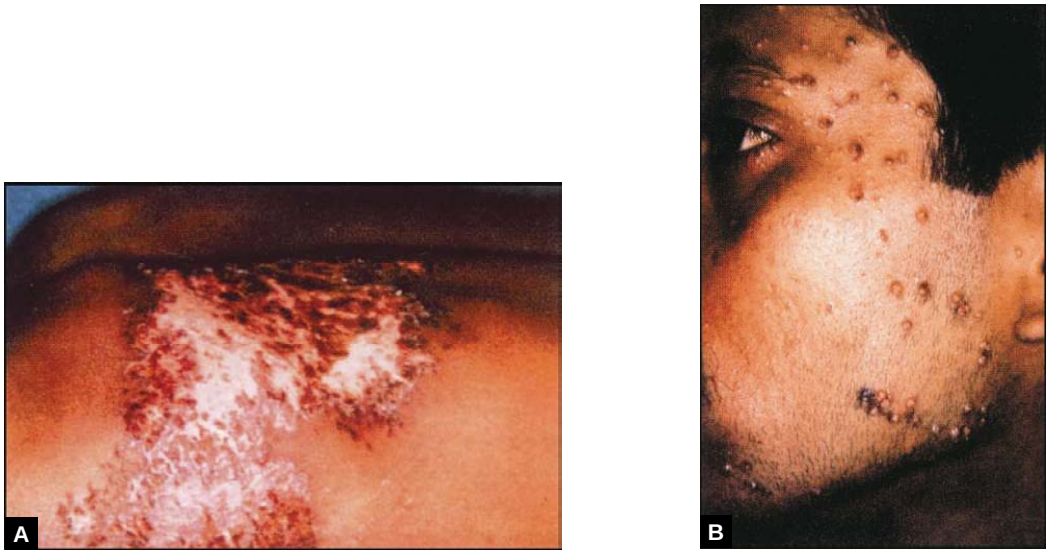
**Figure 62.32:** Purpura annularis telangiectodes (Majocchi's disease)

- Bluish-red annular macules with dark red telangiectatic puncta.

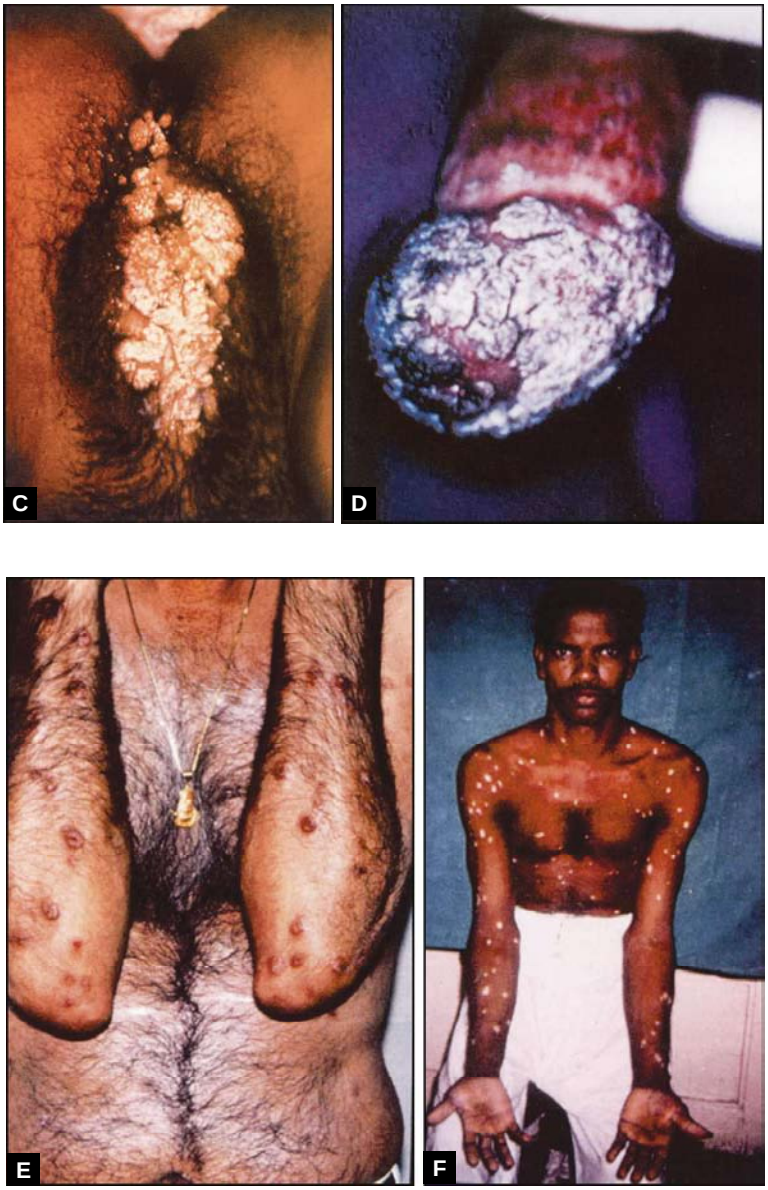



**Figures 62.33A and B:** Erythema annulare centrifugum

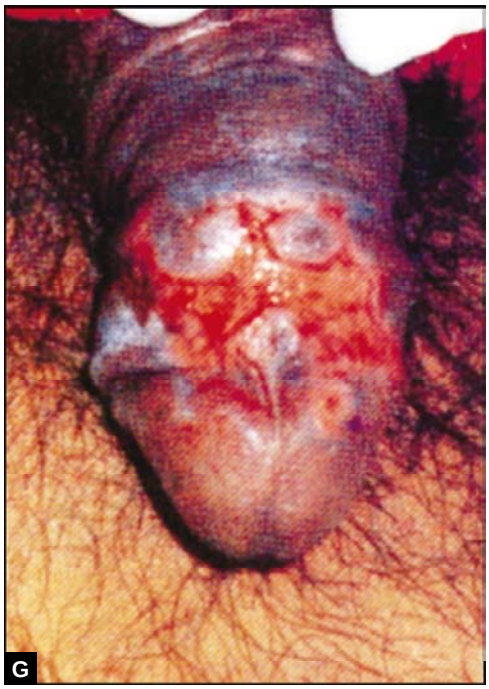
- Asymptomatic.
- Ephemeral, polycyclic, annular, or serpiginous firm lesions, minute scales on the inner margin of the lesion.
- Cutaneous marker for systemic metabolic disease.
- D/D borderline tuberculoid (TT)

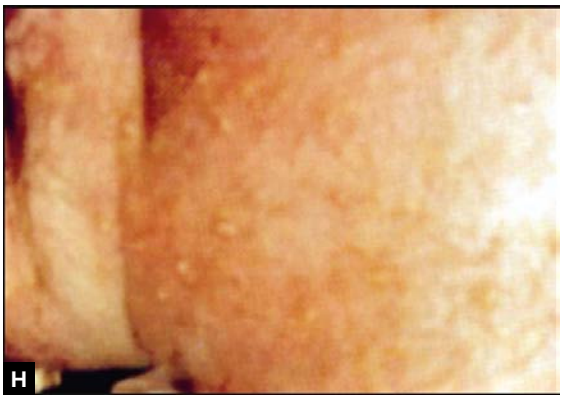



**Figures 62.34A and B:** Herpes zoster, (B) Molluscum contagiosum




**Figures 62.34C to F:** (C) Condylomata accuminata, (D) Giant condylomata accuminata, (E) Syphilis tropical psoriasis, (F) Prurigo nodularis




**Figures 62.34G and H:** Chancroid, (H) Miliaria rubra

**Figures 62.34A to H:** HIV and AIDS (*Courtesy:* Dr. S.S. Samant, Nanavati Hospital, Mumbai)

- Molluscum contagiosum
- Condylomata accuminata
- Giant condylomata accuminata
- Rupioid syphilis
- Prurigo nodularis
- Donovanosis hypertrophic with squamous cell carcinoma.

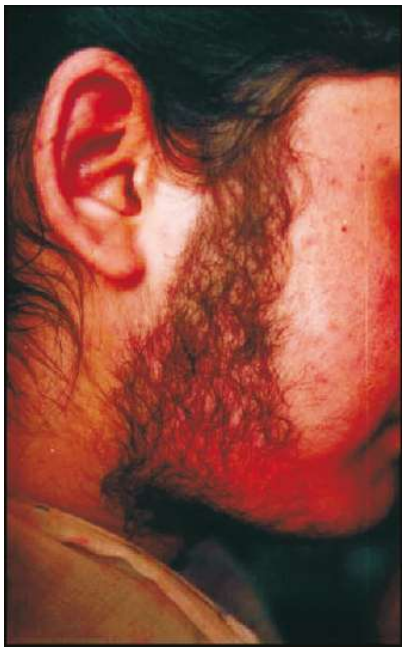


**Figure 62.35:** Hirsutism

- Excessive hair growth on the beard in a young girl.

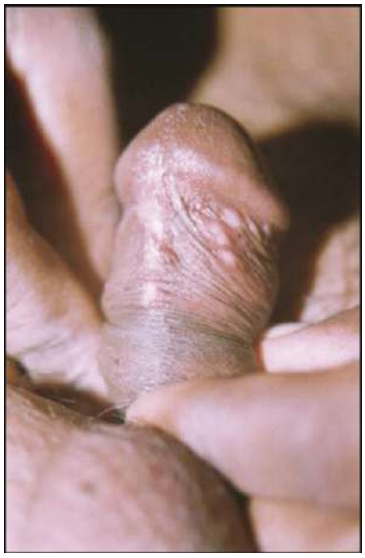


**Figure 62.36:** Herpes genitilis

- Recurrent group vesicles on an erythematous base.
- Tzanck smear affirmative for acantholytic cells.
- Herpes virus – 2 IgM Ab titre.

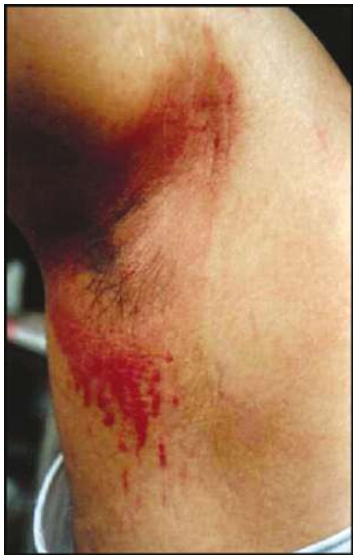


**Figure 62.37:** Erythrasma

- Asymptomatic.
- Red to brown scaling patches.
- Selectively affliction of axillae, groins, submammary regions.

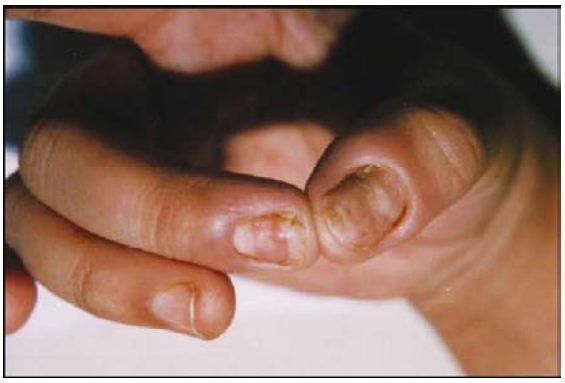
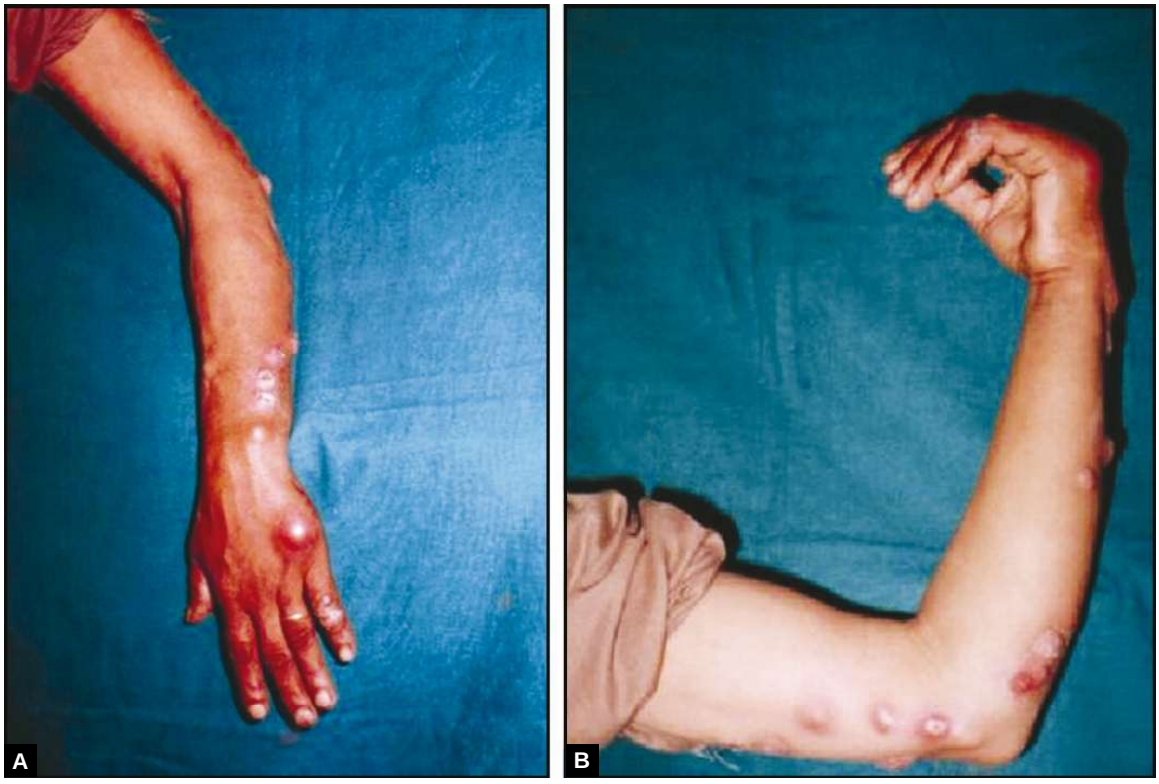


**Figure 62.38:** Paronychia candidiasis

- Asymptomatic.
- Nontender, erythematoscaly swelling of proximal and lateral nail folds.
- Purulent discharge is conspicuous by its absence.
- Common amongst household assistants/food handlers.

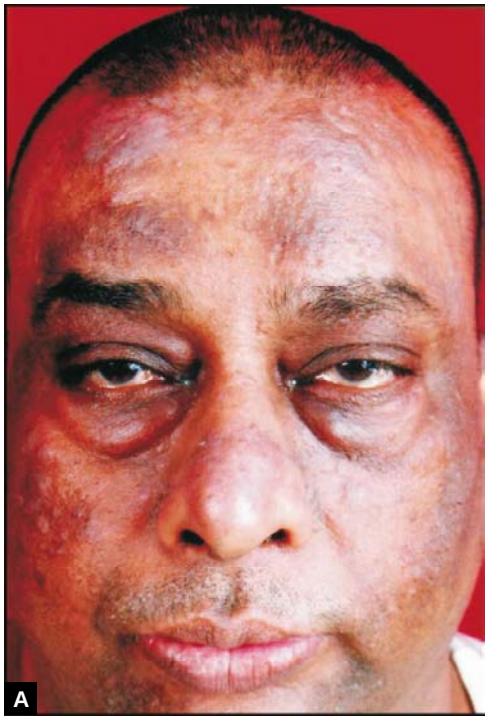
**Figure 62.39:** Tinea barbae

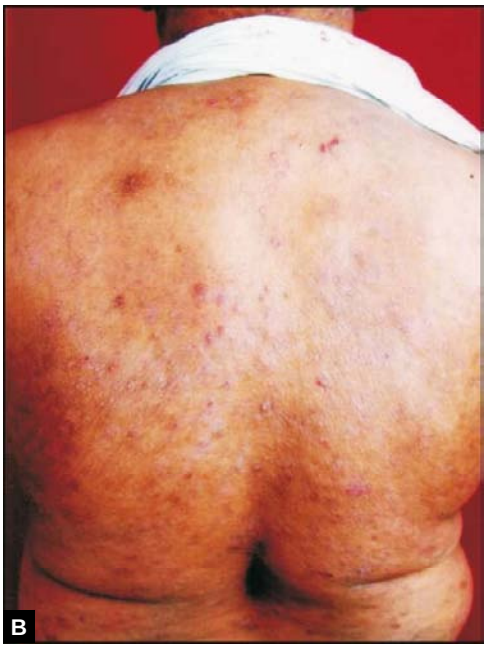
- Intensely itchy.
- Scaly papular eruptions occupying the hair in a circinate configuration, multiple, transparently free area in between.
- Potassium/sodium hydroxide mount of the scraping positive for mycelia/spores.

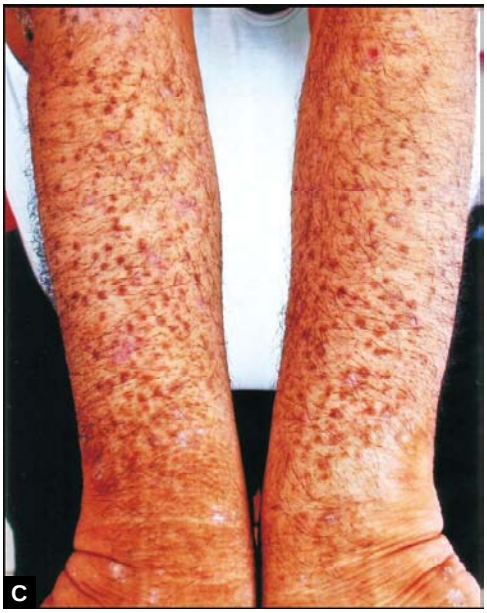


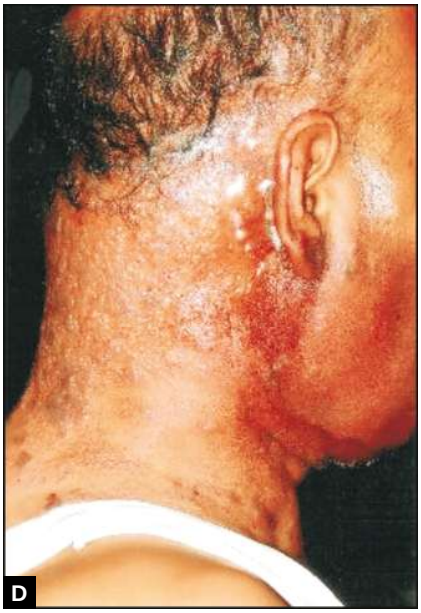

**Figures 62.40A and B:** Sporotrichosis

- Painless indurated nodule/nodulo-ulcerative initial lesion at inoculation sites, followed by appearance of similar nodules along the draining lymphatic and lymphadinopathy.
- Direct immunofluorescent antibodies technique help to identify sporothrix schenckii in the tissue sections.




**Figures 62.41A to D:** Adult onset pityriasis rubra pilaris (a typical) generalized intractable

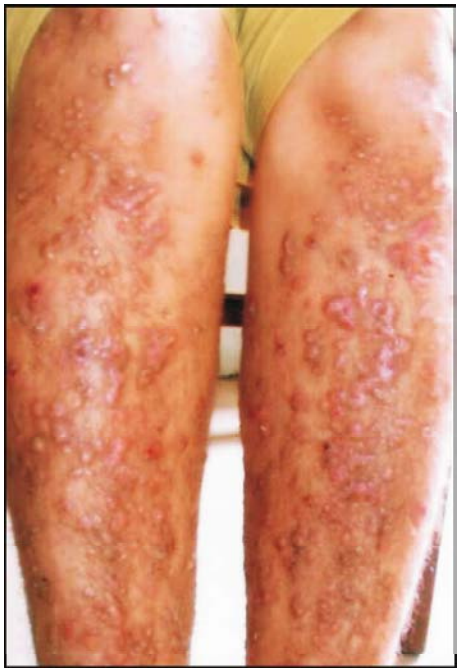


**Figure 62.42:** Lichenoid interdermatosis

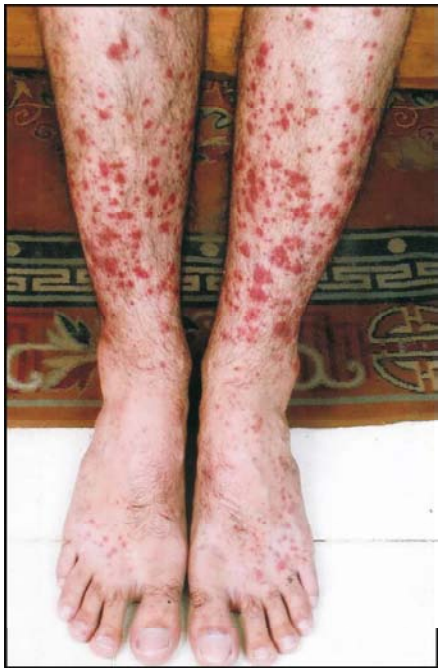
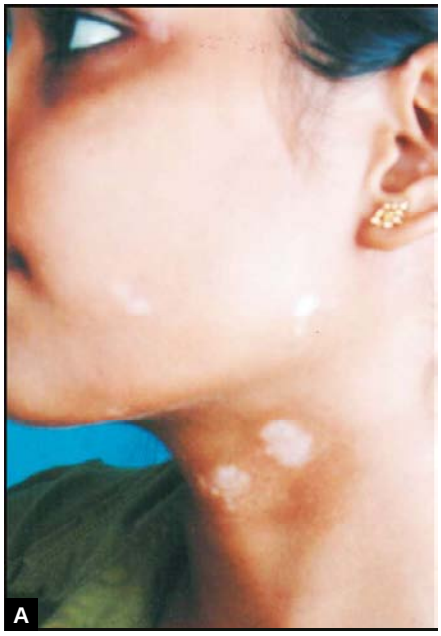
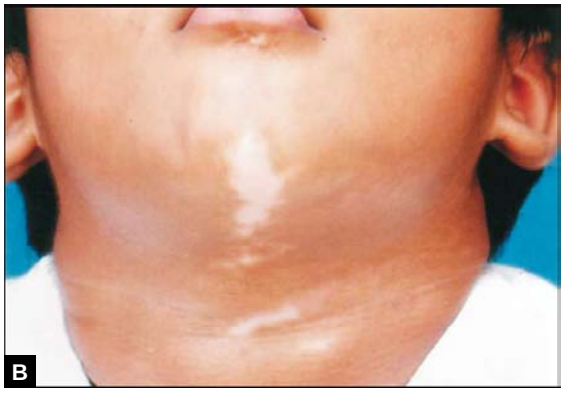


**Figure 62.43:** Pigmented purpuric dermatosis




**Figures 62.44A and B:** Segmental (zostiformis) vitiligo

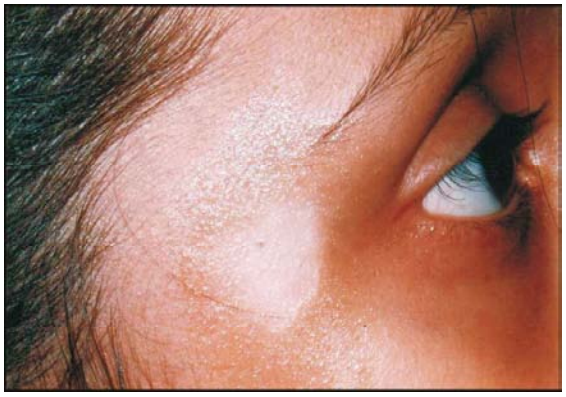


**Figure 62.45:** Non-segmental (areata) vitiligo

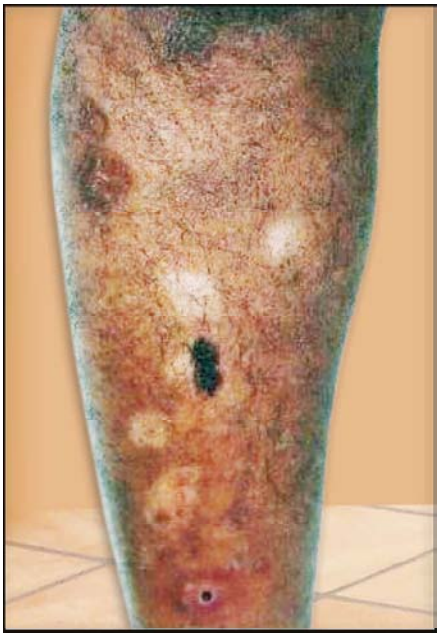


**Figure 62.46:** Halo nevus

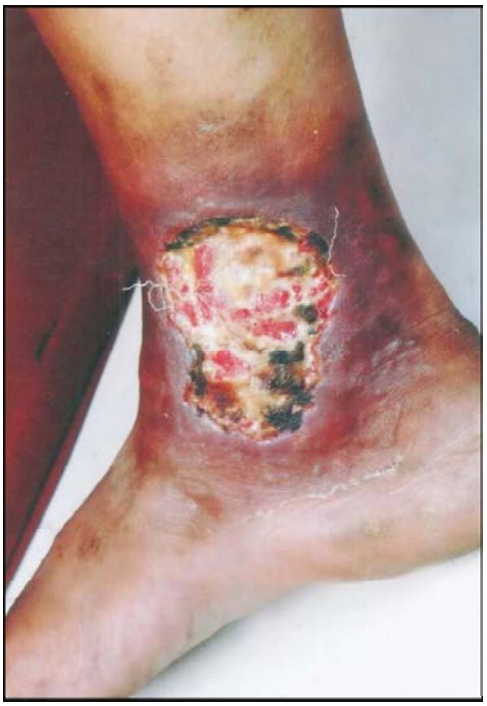


**Figure 62.47:** Stasis dermatitis with an ulcer

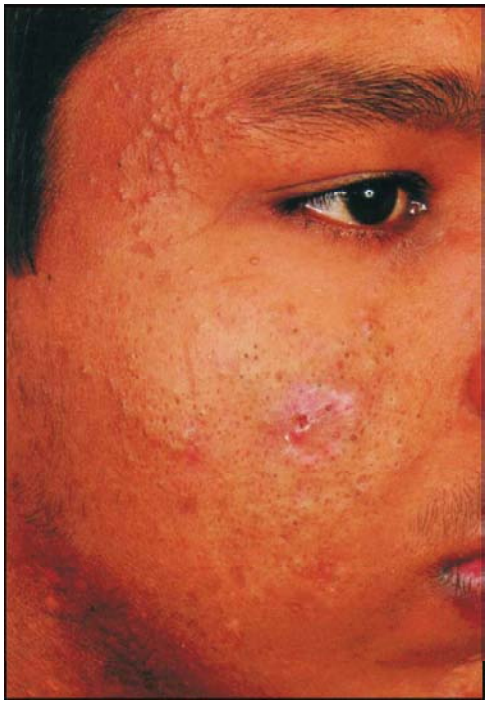
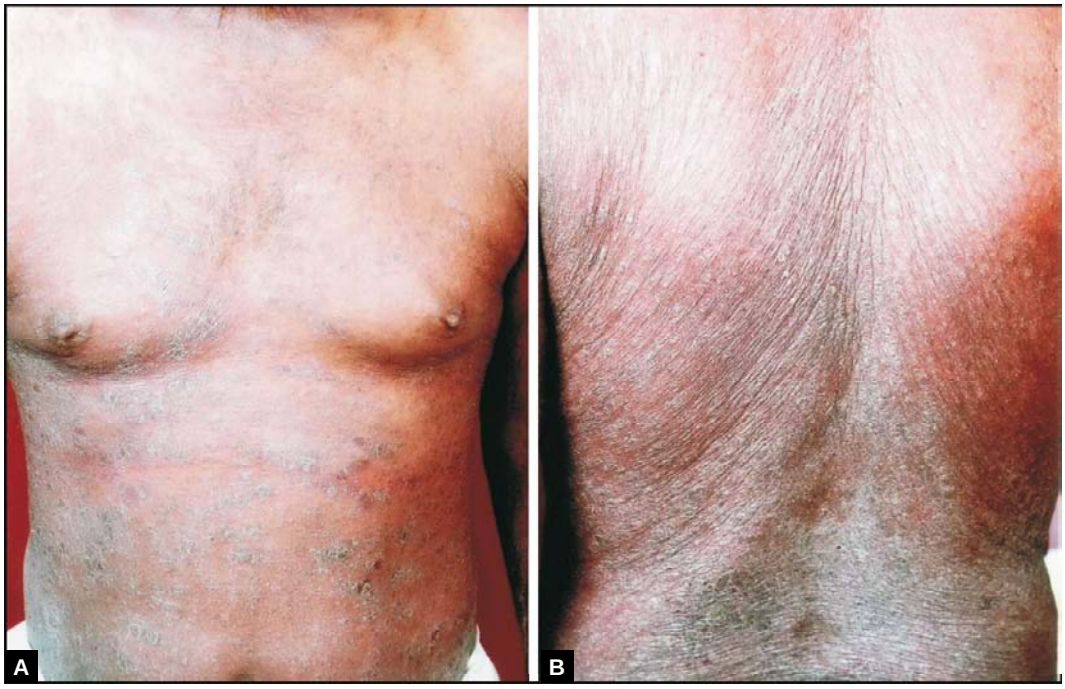
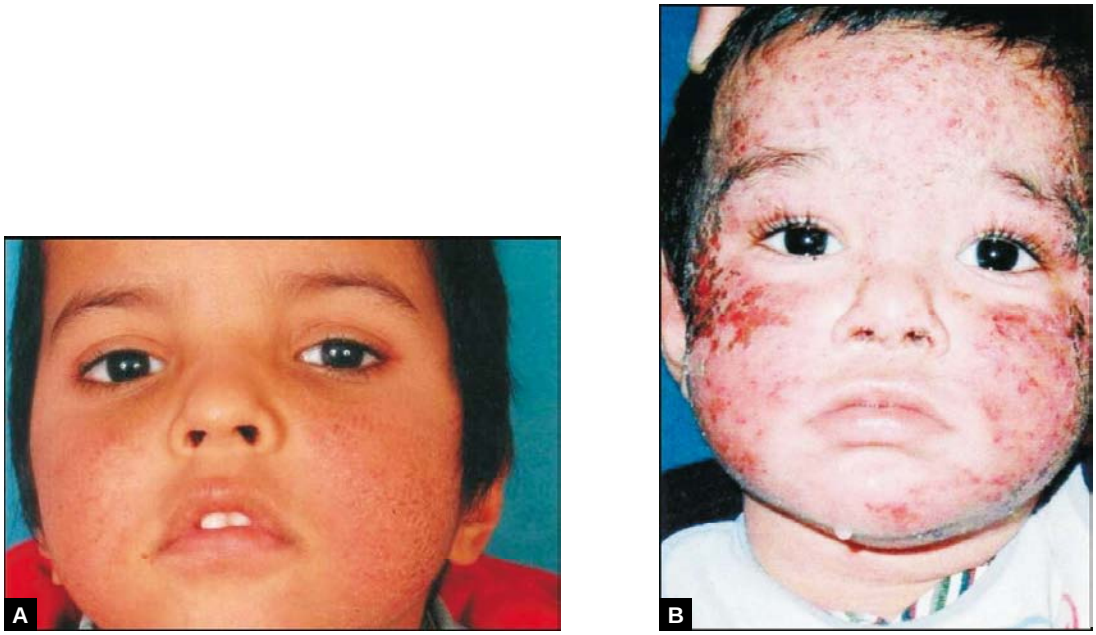


**Figure 62.48:** Acne vulgaris




**Figures 62.49A and B:** Hirsutism




**Figures 62.50A and B:** Atopic dermatitis

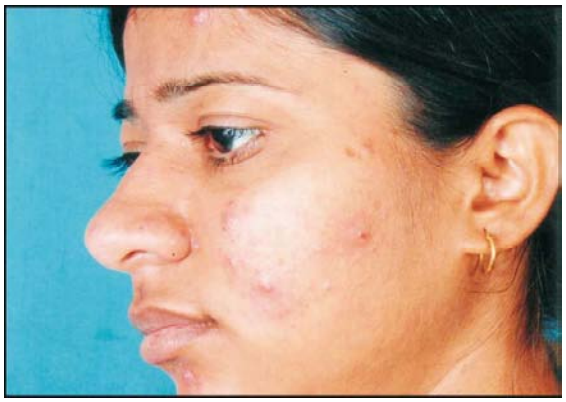


**Figure 62.51:** Acne vulgaris

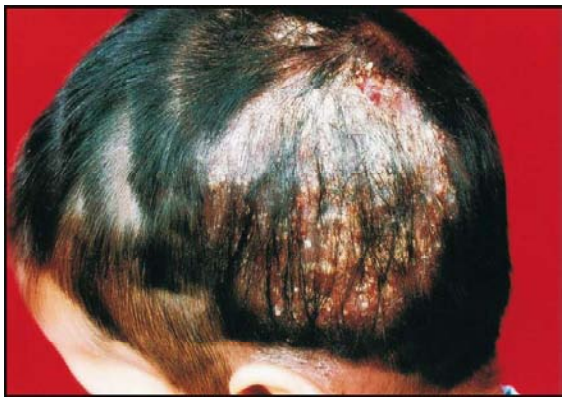
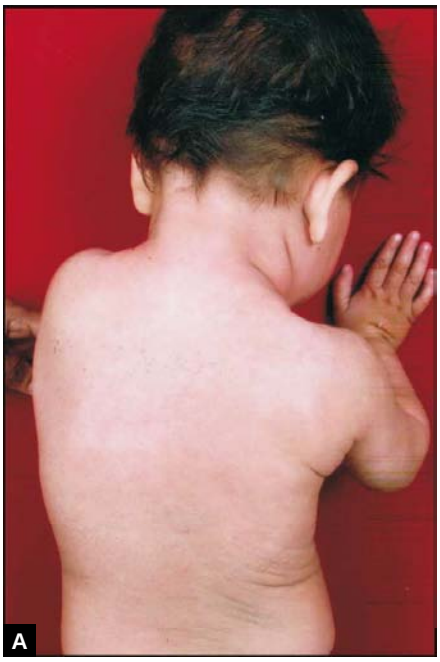
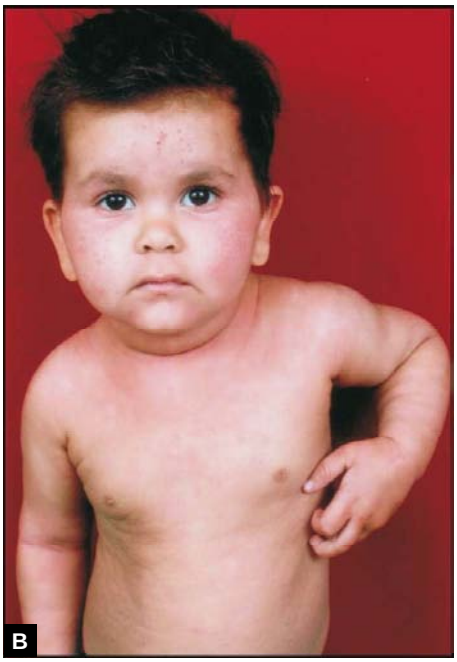


**Figure 62.52:** Tinea capitis




**Figures 62.53A and B:** Juvenile pityriasis rubra pilaris, generalized intractable, depicting erythroderma (A typical)

**Figure 62.54:** Verruca planas

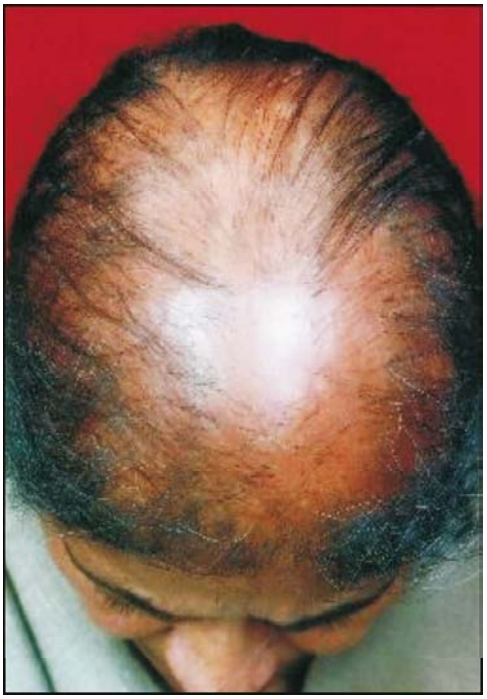
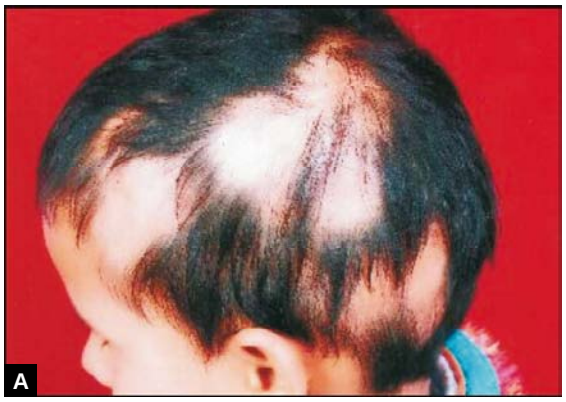
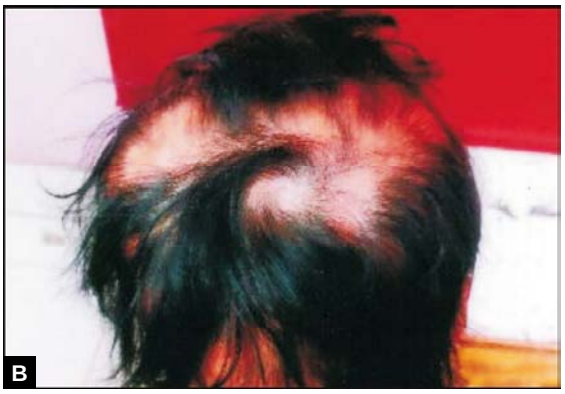


**Figure 62.55:** Female pattern baldness (Ludwig type 3)




**Figures 62.56A and B:** Alopecia areata in two sisters

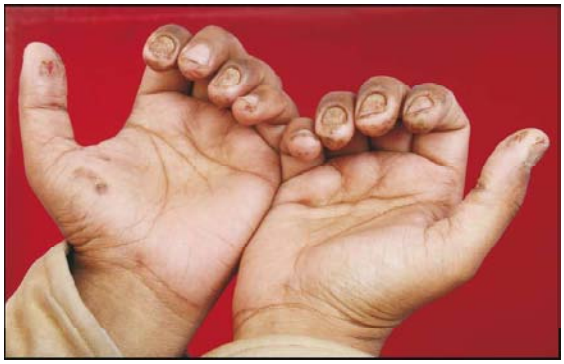


**Figure 62.57:** Paronychia with nail changes

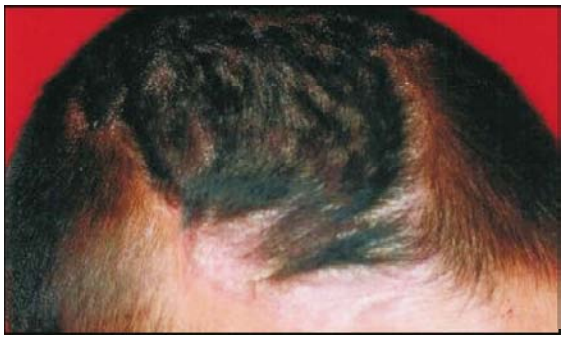


**Figure 62.58:** Scalp psoriasis showing corona psoriatic

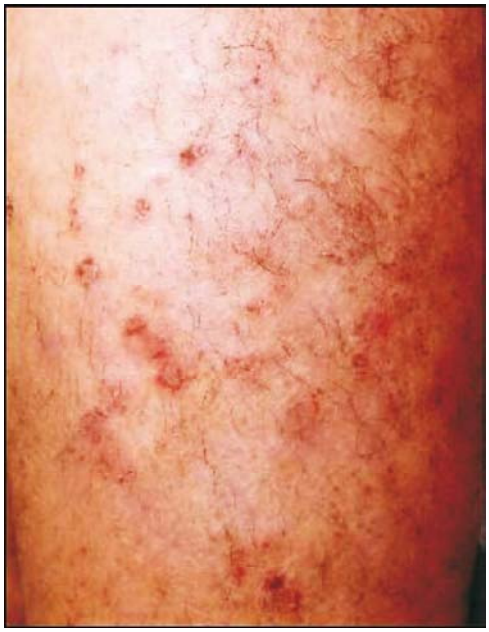
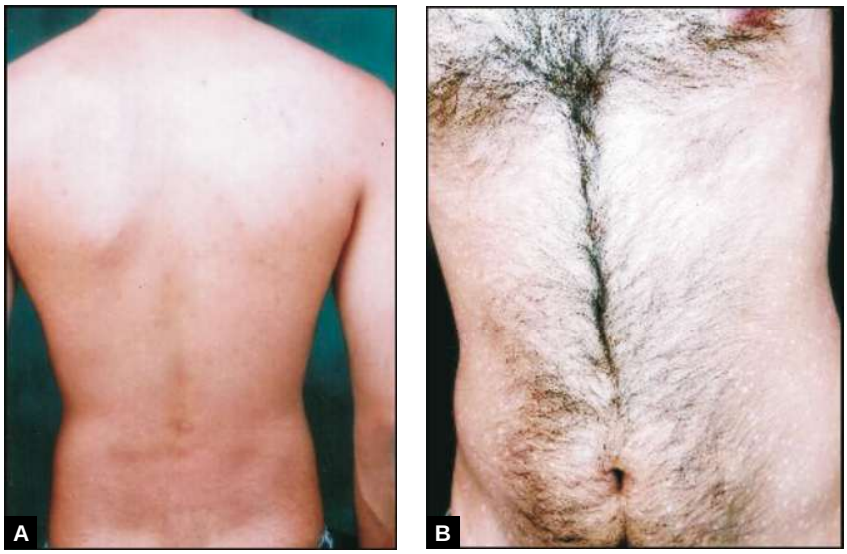
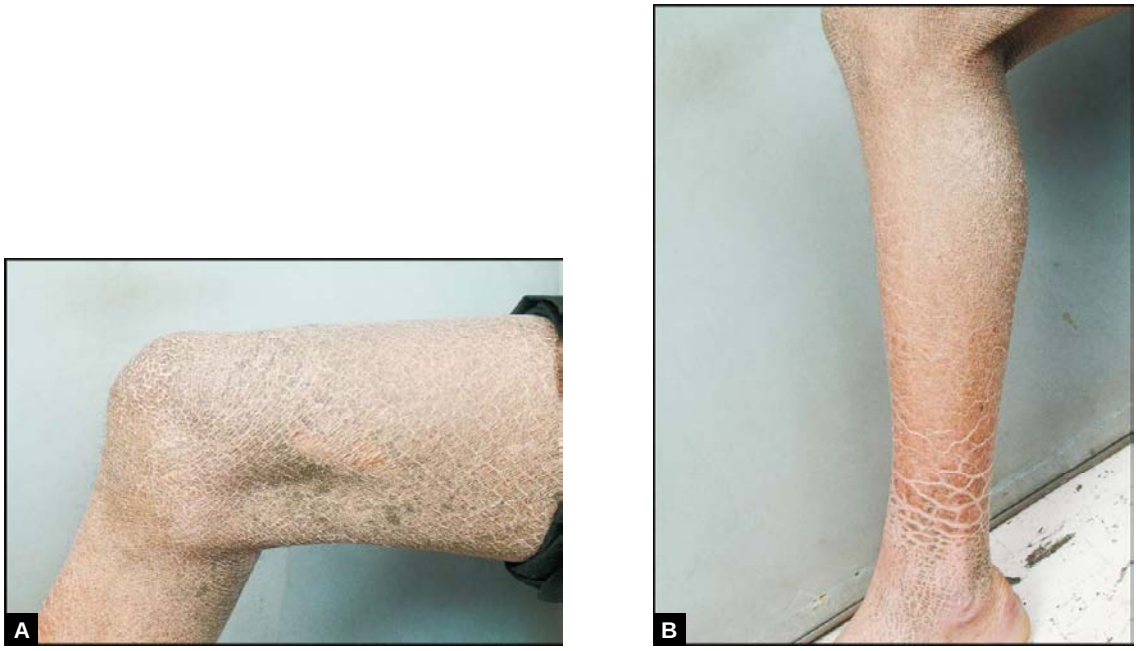


**Figure 62.59:** Pityriasis rosea




**Figures 62.60A and B:** Confetti-like leukoderma depicting chalky/ivory white




**Figures 62.61A and B:** Ichthyosis vulgaris

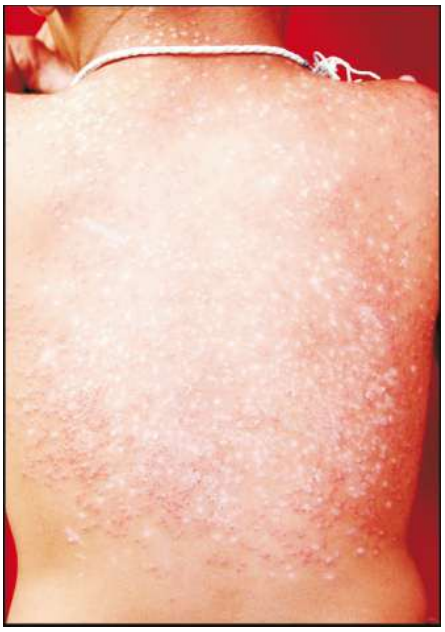


**Figure 62.62:** Guttate psoriasis

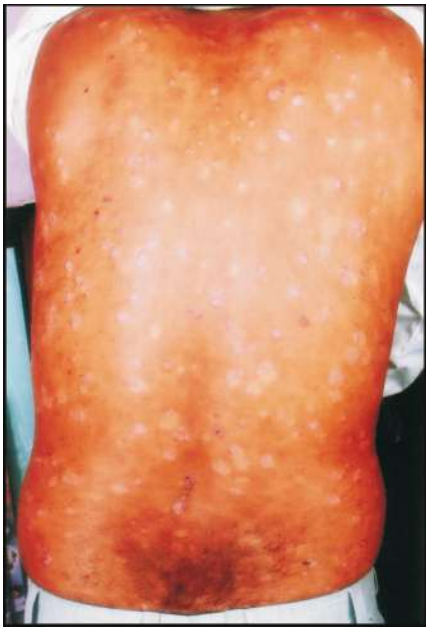


**Figure 62.63:** Psoriasis vulgaris

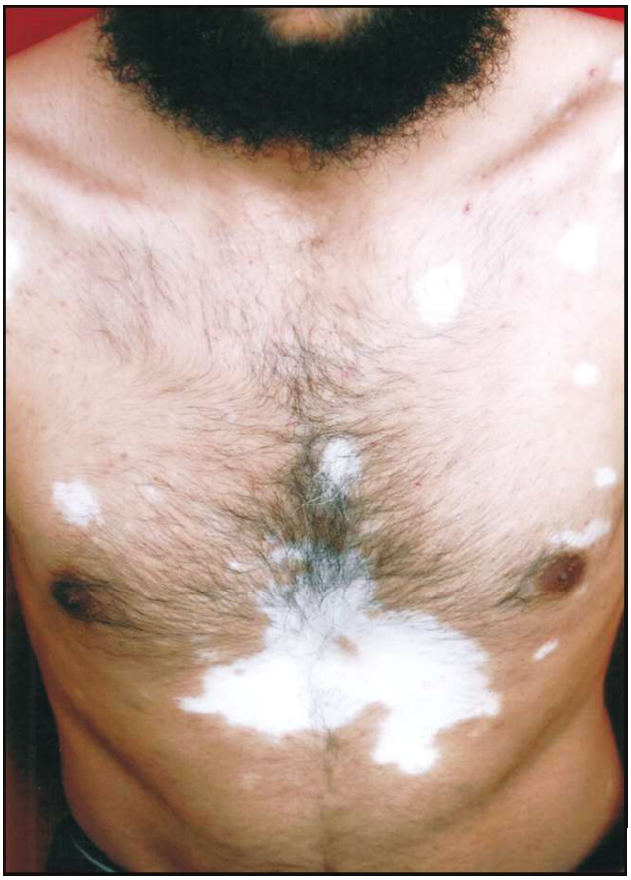


**Figure 62.64:** Non-segmental (Vulgaris) vitiligo

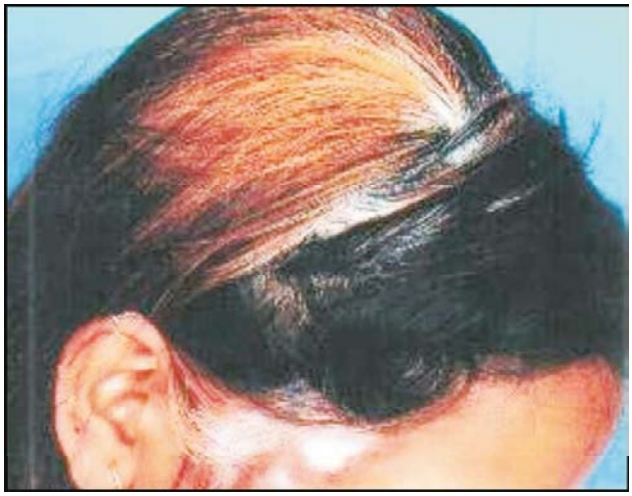


**Figure 62.65:** Segmental vitiligo alopecia areata and Hypothyroidism

# Index

## F



## G

## K



## L



## M

## N



## O

## P

## Q



## R



## S

## T

## X



## Z