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Atlas of Skin Disorders

Challenging Presentations of Common to Rare Conditions

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Foreword

Professor Wen-yuan Zhu is the editor-in-chief emeritus of ***Journal of Clinical Dermatology***, and he is an experienced and well-respected dermatologist as well. After collecting the pictures of difficult, complicated, and unusual cases published in the journal and from his clinical practice, he compiled and edited the atlas.

The atlas consists of 387 cases and 1215 pictures including clinical, histopathological, and other laboratory findings. The pictures are clear, true to life, and sufficiently big. It is really a color atlas of high quality and provides a valuable reference and textbook for dermatologists.

This atlas is illustrated and explained in English, and undoubtedly, this makes it much easier for dermatologists outside China to read and understand the dermatology in China, such as what are the difficult and complicated skin diseases and how do they manifest. I believe this publication will broaden the international academic exchanges, enhance mutual understanding between Chinese dermatologists and their foreign counterparts, and promote the development of dermatology of China.

I warmly congratulate the publication of this atlas edited by Professor Zhu Wen-yuan and other contributors.

Nanjing, China — Wen-Yan Xu

Foreword

I am eagerly awaiting and anticipating the publication of this most important volume on skin diseases in the Chinese population. For Western dermatologists, the world of Chinese skin and skin diseases is still largely a mystery. We know that all of the common diseases must occur in this huge and diverse population, but there must be many unusual variations on the common as well as many unusual and rare disease entities that are still uncommon or unknown outside of China. Therefore, the images in the atlas will tell the long-awaited story of Chinese skin and skin disease to the outside world. The importance of this work is further underscored by the considerable intermingling of our populations that has occurred in recent years due to intense commercial interactions, ever-more common tourism, and visitations among relatives of Chinese in all parts of the world. It will be important for the Western dermatologist, therefore, to have this volume close at hand as a reference work during his/her increasingly frequent interactions with these groups of patients. Finally, increased awareness will not only improve diagnostic capabilities but also open up new treatment options for formerly isolated patients with both common and rare skin diseases. Therefore, I must once again congratulate you on this important effort.

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Preface

China is the third largest country and comprises 9.6 million square kilometers. It has the world's largest population, including 56 nationalities and 1.3 billion individuals, and it is noted for its 5000-year history of ancient civilization. Increasing evidence suggests that there is no ethnic preponderance for skin diseases between the Chinese population and foreigners. Based on these considerations, China undoubtedly comprises the largest patient population of rare to challenging skin disorders. China has a unique geographical environment and diverse climate. Thus, it is likely that the same disease may develop various clinical manifestations and outcomes. We propose that the overwhelming majority of skin diseases recently discovered overseas will soon be identified in China. Moreover, I would like to confidently predict that in the imminent future, an increasingly greater number of novel skin entities will be identified and investigated by Chinese dermatologists if they take advantage of these conditions.

Furthermore, the process of new disease discrimination will be accelerated in terms of the large number of registered dermatologists. According to statistical data in 1995, China had 11,144 registered dermatologists. These individuals serve different hospitals at unequal levels throughout the country. As living standards increase, it becomes increasingly affordable to obtain better medical care in advanced hospitals. Diseases that were once misdiagnosed may now be recognized with the availability of more advanced medications. Therefore, many rare and challenging skin diseases will be consistently identified and will accordingly require publication in journals or books.

The practice of dermatology is based on a visual approach to clinical disease. Visualization also plays a critical role in how new information is integrated into pre-existing frameworks, which serve as the hard drives for the development of modern dermatology. Thus, I have encouraged myself to implement a meaningful publication project that comprises an atlas for rare skin disorders in China. I am an emeritus editor-in-chief for a well-known journal, the ***Clinical Journal of Dermatology***, in China. This journal has been clinically oriented since its debut in 1980. Articles that describe case reports, clinical research, and treatment investigations are preferentially published. Although this journal was initially a quarterly journal, it soon changed to a bimonthly publication. In 2002, as the journal received more valuable submissions that were waiting to be published, it transitioned to a monthly publication with all illustrated pictures printed on coated paper in color. The journal has published many valuable articles regarding rare and challenging skin diseases in Chinese. In my opinion, the articles published in this Chinese journal should not be considered incompetent by peers outside China. I believe that language barriers predominately limit the distribution of these papers outside China.

I realized, one day, that I had a dream to compile a splendid atlas for the wonderful cases described by outstanding Chinese dermatologists for more than four decades. This thought was cultivated with our assiduous perseverance and continued to develop until 2008, when the book ***Atlas of Difficult Skin Disorders*** was published ahead of time at the second requests of domestic readers and peers. In this book, the commitment of visual learning is reflected in the use of 1215 pictures related to 387 rare skin diseases. The majority of the clinical pictures are integrated with pathological images and English legends, which attempt to provide weighted clinical information. This atlas has 274 outstanding authors in China

who contributed at least one case illustration that is of high didactic value to dermatologists. This book has received a steady increase in its popularity and was honorably awarded the ***Three Specialties and One Hundred Each Program for Original Publications*** in 2008, which was issued by the ***China General Administration of Press and Publication***. However, my progress has never slowed down.

The world is currently in an era of globalization, which is characterized by mass migration. For western dermatologists, the world of Chinese skin diseases remains largely a mystery. As stated by Professor Peter M. Elias: "We know that all of the common diseases must occur in this huge and diverse population, but there must be many unusual variations on the common as well as many unusual and rare disease entities that are still uncommon or unknown outside of China." We hope this publication will function as a colleague, albeit a nonverbal one, who is easily approachable and possesses the necessary expertise to sharpen a dermatologist's diagnostic and clinical acumen. This atlas will serve as a bridge for international cultural exchanges in dermatology.

We are incredibly grateful to our outstanding vice editor (Prof. Mai-Hua Hou) for her tremendous effort in the Chinese publication of Color Atlas of Difficult Skin Disorders produced by People's Military Medical Press, to Kevin Zhu and Theodora M. Mauro for their meticulous review of this book, and to outstanding project secretaries (Liu Xia and Yuan-Yuan Li) who have worked indefatigably to help us realize our vision for this book. We are especially indebted to the Springer Editorial Team for their highly professional support of our work and for being so flexible in many small issues intrinsic to publishing a book.

We would also like to give our last farewell to Prof. Rong-Zhi Ni, who is our faithful contributor and dear friend who has now left us.

We consign this book to all those interested in medicine and the art of dermatology, and hope that we contribute to the lofty goal of excellent guide to rare skin disorders.

Nanjing, China — Wen-Yuan Zhu
Nanjing, China — Cheng Tan
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Part I

Infections, Infestations and Bites

Virus Diseases

1

Ren-Gui Chen, Ping Li, Chen Wang, Ming-Yu Xia, Xin-Feng Wu, Cheng Tan, and Ru-Zhi Zhang

Abstract

This chapter consists of neonatal herpes simplex virus infection, bilateral herpes zoster, giant verruca vulgaris with cutaneous horns, papillomatosis of external auditory canal, bowenoid papulosis, and asymmetric periflexural exanthema.

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1.1 Neonatal Herpes Simplex Virus Infection [1]

- Neonatal herpes simplex virus infection (NHSI) is an uncommon but severe, life-threatening condition that is more common in preterm infants and acquired maternal IgG deficiency neonates. If left untreated, neonatal herpes has a high death rate.
- Transmission usually occurs in utero (if the infection occurs in early pregnancy, potentially accompanied by a variety of congenital malformations) or during delivery (the most frequent route) and the postnatal period.
- The lesions are characterized by clusters of blisters on the erythema. If the infection spreads, likely manifestations include seizures, lethargy, respiratory distress, hepatosplenomegaly with hepatitis, and thrombocytopenia.

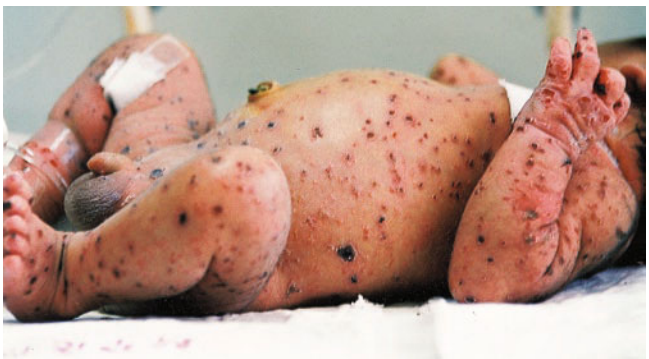

Fig. 1-1-1 Generalized lesions all over the body including erythema, petechiae, umbilicated vesicles, and hemorrhagic bullae on the base of erythema

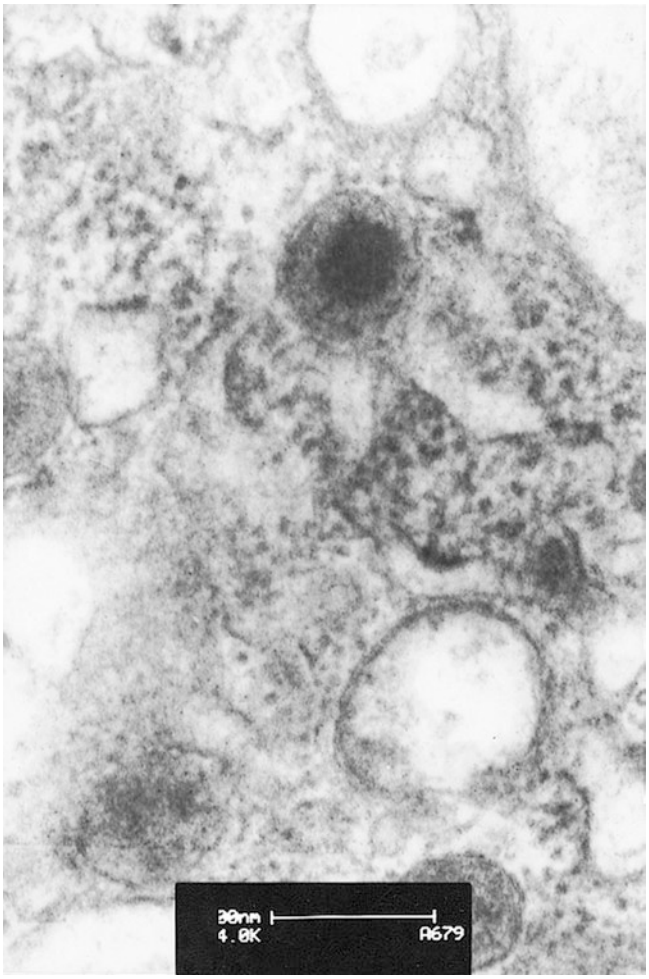

Fig. 1-1-2 Detectable particles of HSV in the biopsied lesion under TEM (×20,000)

1.2 Bilateral Herpes Zoster [2]

- Bilateral asymmetrical distribution of herpes zoster is an uncommon disease, especially in immunocompetent adults.
- Its pathogenesis may be related to body fluids and cellular immune function.
- It is more common in patients undergoing radiotherapy or chemotherapy after surgery, using immunosuppressive agents and high-dose glucocorticoid treatment.

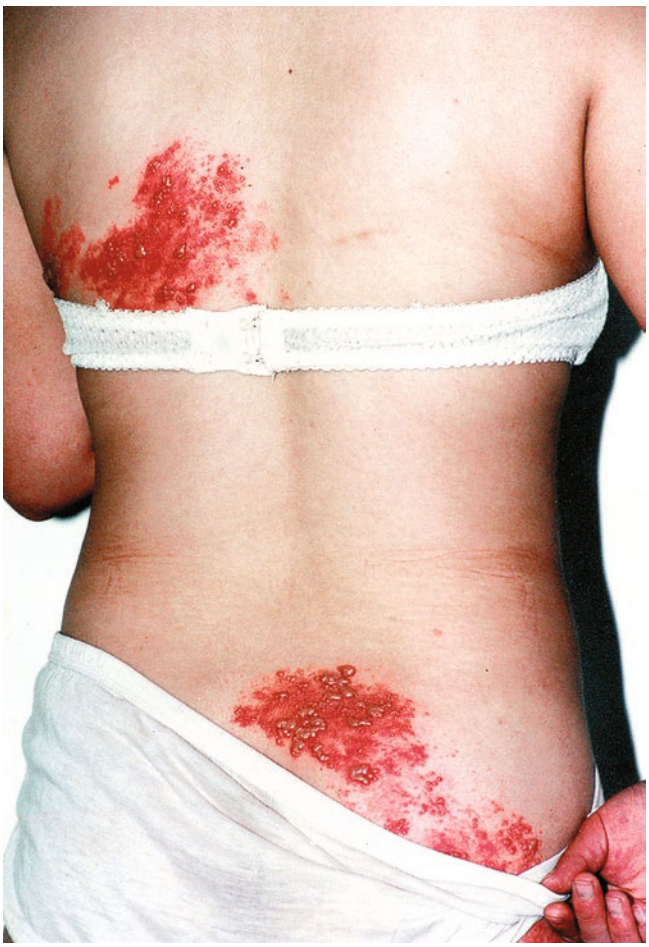

Fig. 1-2-1 Groups of vesicles are situated on an erythema based on the left chest, back, and right buttock

1.3 Giant Verruca Vulgaris with Cutaneous Horns [3]

- Multiple huge verruca vulgaris complicated by huge cutaneous horns is very rare and resistant to conventional therapy.
- This condition is associated with infection by HPV-2a, an HPV subtype, infection which is prone to develop into giant verruca vulgaris complicated by huge cutaneous horns.
- Oral acitretin A, Chinese herbal medicine, and interferon injection combined with radiotherapy are often used to treat patients.

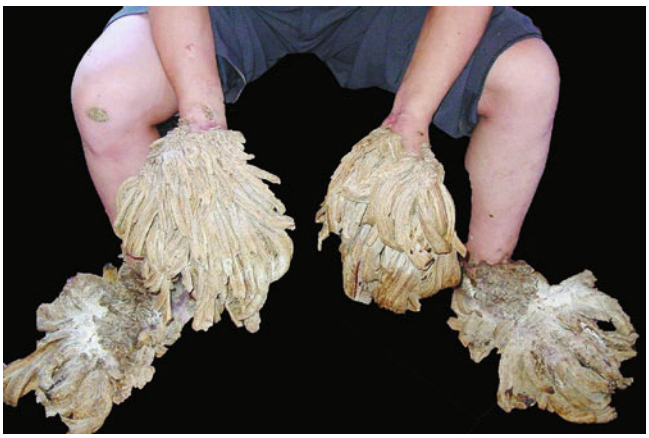

Fig. 1-3-1 Hundreds of giant confluent yellowish-brown, hard cutaneous horns on both hands and feet. The horn size ranged from 0.5 to 5 cm in diameter and from 0.5 to 21 cm in length

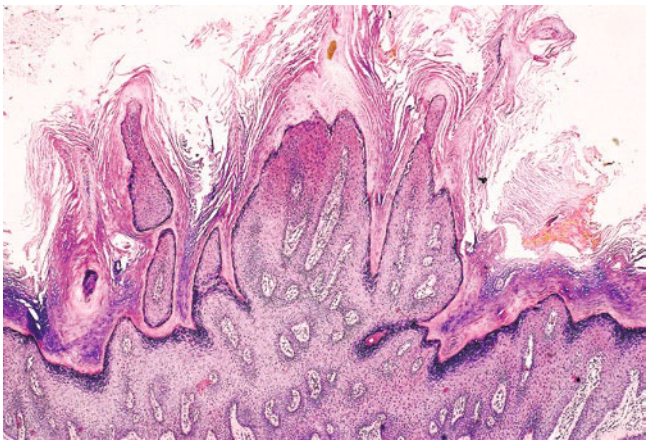

Fig. 1-3-2 Hyperkeratosis, acanthosis, and papillomatosis. Rete ridges elongate and curve inward at both margins (HE stain, ×100)

1.4 Papillomatosis of the External Auditory Canal [4]

- Papillomatosis of the external auditory canal (PEAC) characterized by single or multiple dark-brown verrucous papules (measuring 0.5–1.2 cm in diameter) is the most common benign tumor of the ear and is produced by infection with HPV6.
- PEAC frequently occurs in adult men who have a history of repeated turning of an ear knife in the EAC and then using an ear brush.
- Histopathological examination displays a few vacuolated epithelial cells within the upper stratum Malpighi. Malignant changes in 4 (2%) of 191 cases with PEAC have been reported.

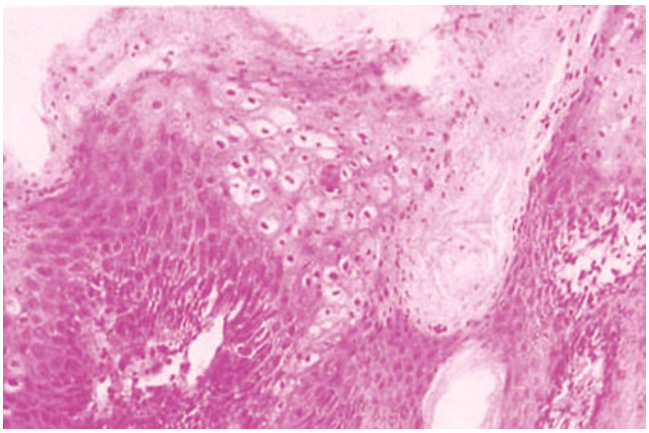

Fig. 1-4-2 Acanthosis and papillomatosis with a few vacuolated cells in the upper stratum Malpighi (HE stain, ×100) (Reproduced with the permission from [7])

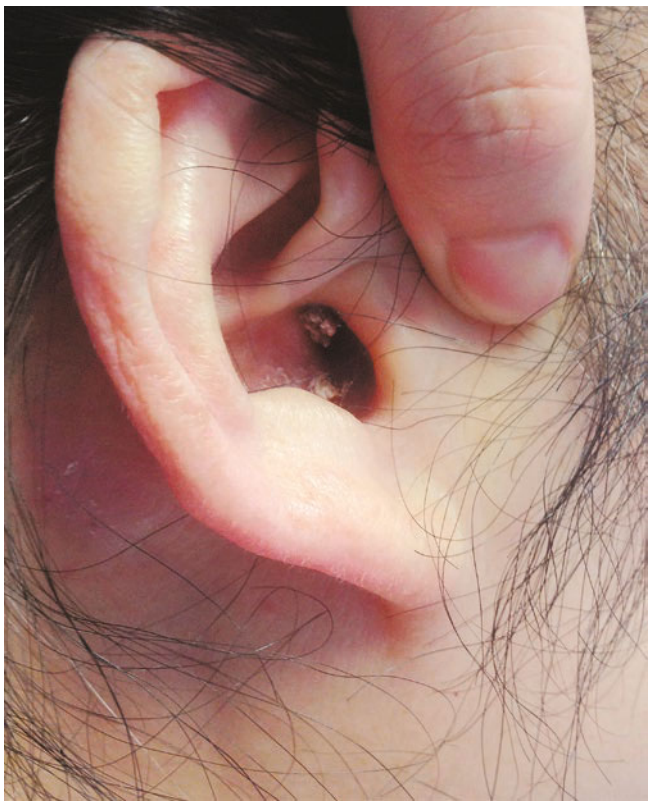

Fig. 1-4-1 Two dark-brown verrucous papules in the right external auditory canal

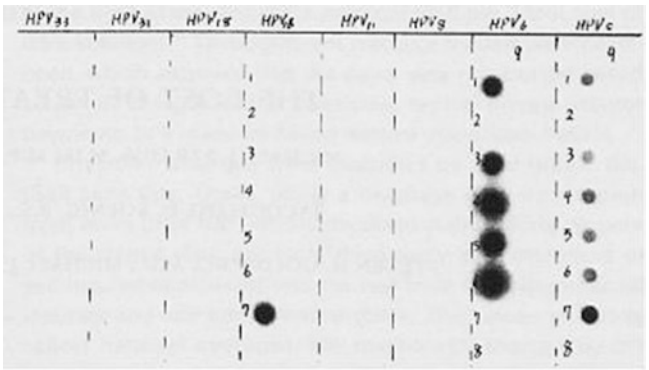

Fig. 1-4-3 HPV DNA Type 6 was detected using polymerase chain reaction (Reproduced with the permission from [7])

1.5 Bowenoid Papulosis [5]

- Bowenoid papulosis (BP) is caused by human papilloma virus (HPV), mostly the HPV-16 subtype, and is characterized by papules on the penis and vulva and occasionally on the oral, periungual, and neck surfaces.
- BP is considered an intermediate phase between squamous carcinoma in situ and genital warts. The histopathology reveals dysplastic changes.
- Treatment can be conservative, including electrofulguration, cryotherapy, excision, CO_2 laser vaporization, photodynamic therapy, and local application of antiviral agents.

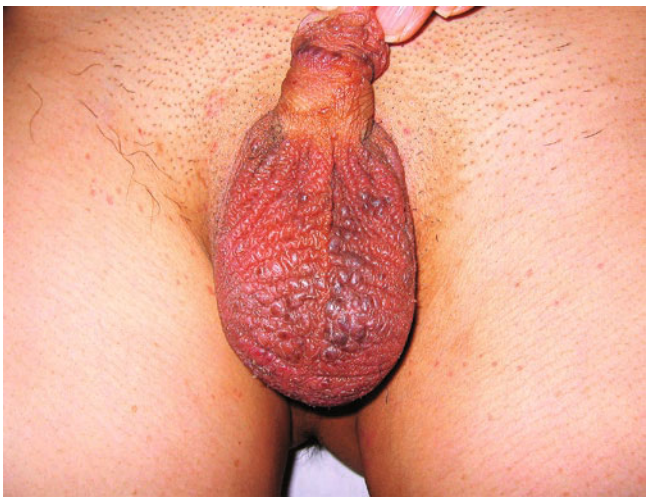

Fig. 1-5-1 Grouped fiat, smooth, violet red papules on the scrotum and penis

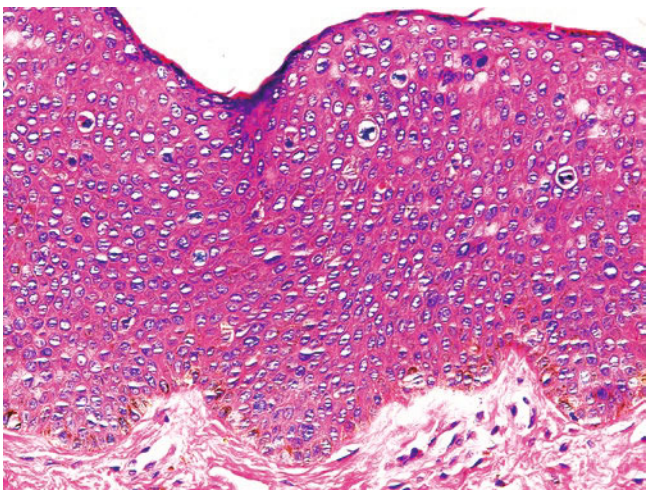

Fig. 1-5-2 Some of epidermal cells are large, hyperchromatic and pleomorphic, and atypical mitoses (HE stain, ×100)

1.6 Asymmetric Periflexural Exanthema [6]

- Asymmetric periflexural exanthem (APE) occurs mostly in children. Digestive or upper respiratory tract prodromes are reported preceding the onset of APE, providing clues of a viral origin.
- Typically, the lesions are multiple, discrete erythematous coalescent maculopapules distributed unilaterally near the axillae, the same side of the trunk and the medial surface of the arm.
- The exanthema usually reaches its greatest intensity in 2–3 weeks and then gradually disappears over 4–6 weeks without residual abnormal changes.

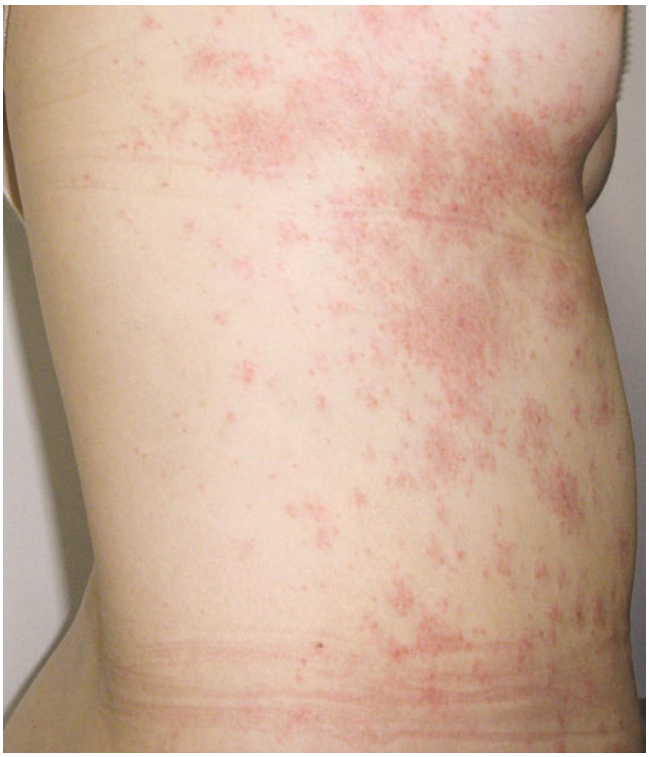

Fig. 1-6-1 Erythemas and papules were densely distributed on the right thorax and abdomen, some of which were tend to be coalesced

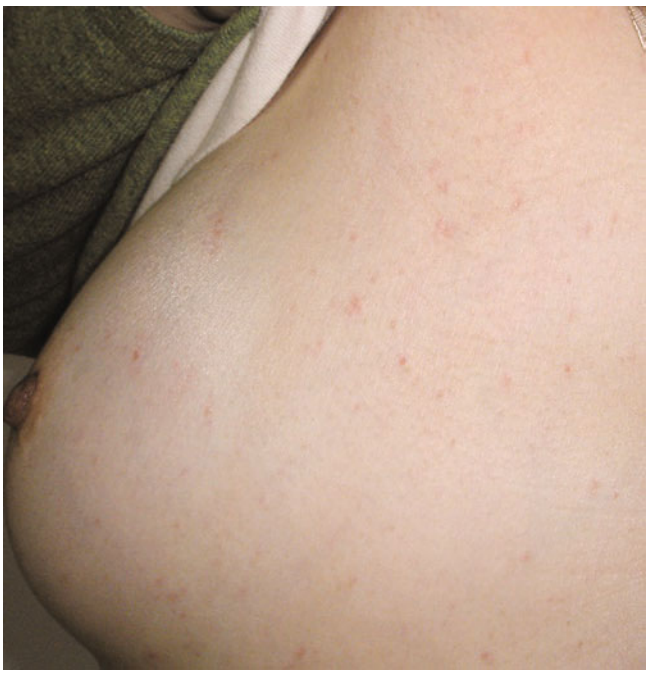

Fig. 1-6-2 Similar lesions were sparsely distributed on the left trunk

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Bacterial Diseases

2

Ying-Bo Wei, Si-Yuan Chen, Ling-Yan Wang, and Ru-Zhi Zhang

Abstract

Several cutaneous conditions associated with bacterial infections are introduced: Fournier's gangrene, superficial granulomatous pyoderma, and Reiter's syndrome.

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2.1 Fournier's Gangrene [1]

- Fournier's gangrene (FG) is an infective necrotizing fasciitis that mostly involves the genitalia and perineum and commonly presents with sudden onset of intense pain, often accompanied by swelling, tenderness, erythema, vesicles, and necrosis.
- Systemic signs can be fever to septic shock and even multiple system organ failure.
- FG, a life-threatening condition with a high mortality, should be treated as soon as possible. The mainstay of therapy comprises hemodynamic stabilization, extensive debridement of all dead tissue, and parenteral administration of broad-spectrum antibiotics.

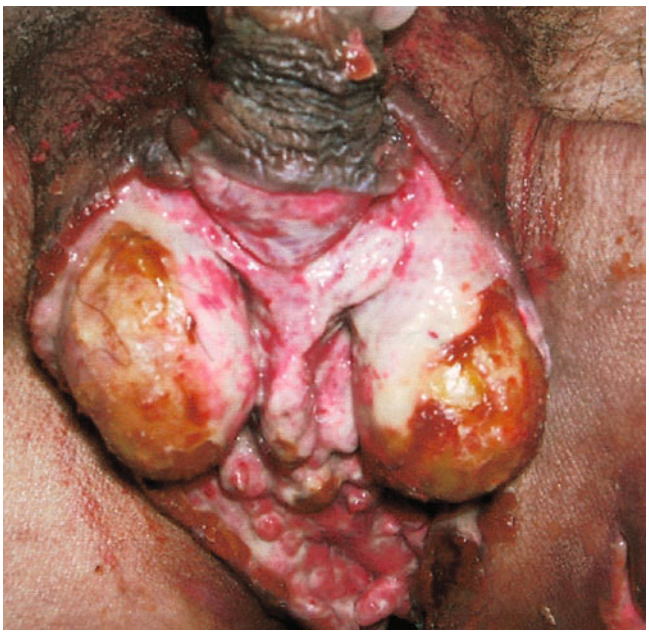


Fig. 2-1-1 Large ulceration on the external genitalia, which involved perianal and scrotal regions

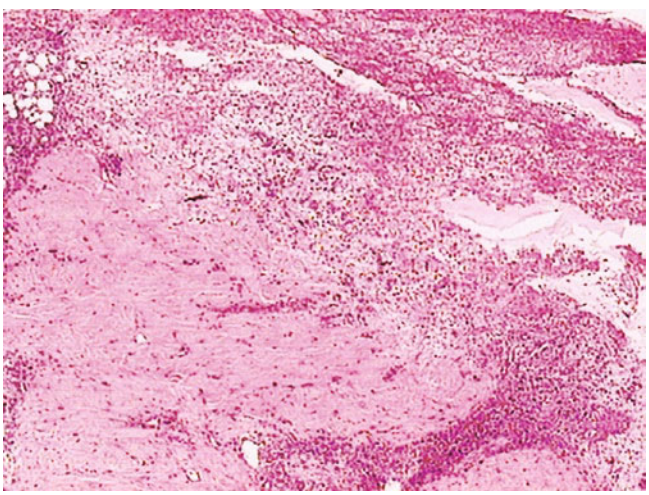


Fig. 2-1-2 Dilated vessels and edema in the superficial dermis and scattered lymphocytes, histiocytes, and neutrophil infiltrate, with focal necrosis in the dermis (HE stain ×20)

2.2 Superficial Granulomatous Pyoderma [2]

- Superficial granulomatous pyoderma (SGP) is an uncommon entity, unlike classic pyoderma gangrenosum (PG) in its chronic and slowly progressive course, lack of underlying disease, and characteristic three-layered granulomas on histology.
- SGP usually presents on the trunk (occasionally on the face or limbs and rarely on the scrotum.) as a slow-growing, painless, and superficial ulcer within alimental borders.
- This condition has a better response to less aggressive treatments with antibacterial or local anti-inflammatory agents.

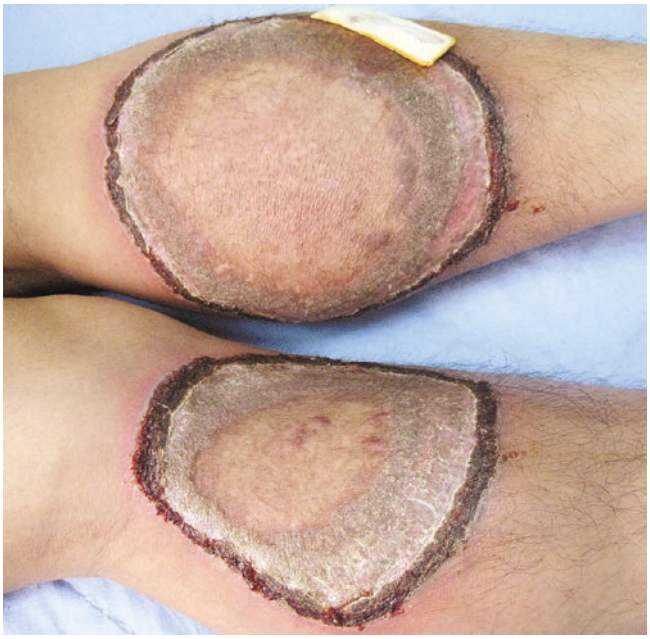
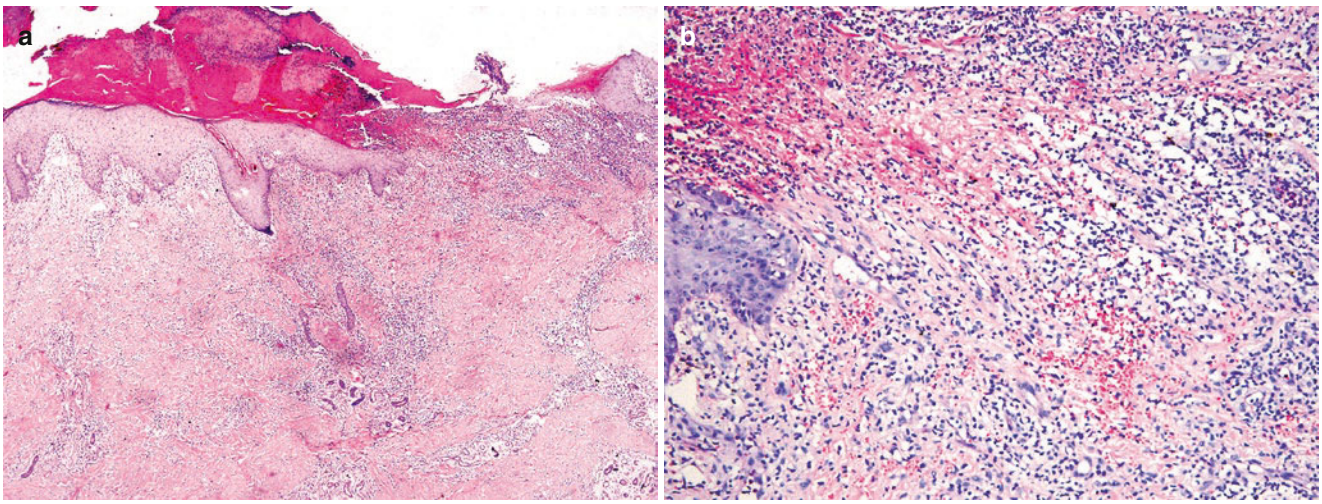


Fig. 2-2-1 Red-brown annular papules and plaques with elevated borders and central scars on the extensors of both calves



Figs. 2-2-2, 2-2-3 (**a**, **b**) Partial epidermal necrosis and defect, some fibrinoid degeneration of vessel walls in the upper dermis, perivascular lymphocyte, histiocyte, neutrophil, and eosinophil infiltration (HE stain, (2) × 40, (3) × 200)

2.3 Reiter's Syndrome [3]

- Reiter's syndrome (RS), also known as reactive arthritis, develops in 1–3% of men after a nonspecific urethritis and in up to 4% of persons after enteric infection caused by *Campylobacter*, *Salmonella,* and *Shigella*.
- The syndrome features the triad of urethritis, ophthalmia, and arthritis. RS commonly tends to occur between 15 and 40 years of age and is related to the human leukocyte antigen B27 (HLA B27) in approximately 75–90% of patients. However, incomplete forms associated with only one or two of the classic triad are more frequent than the complete syndrome.

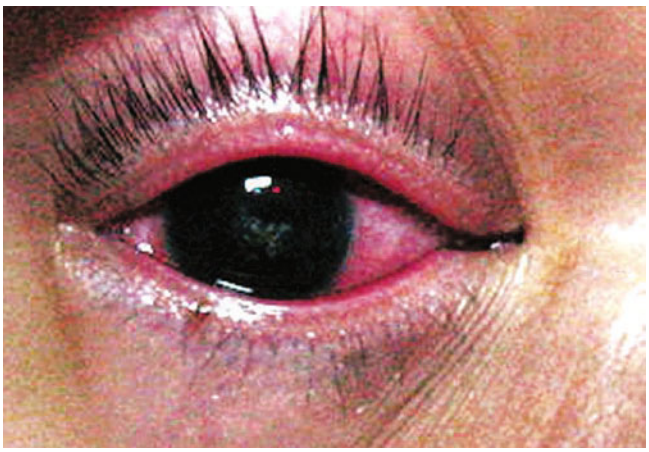


Fig. 2-3-1 Right conjunctivitis

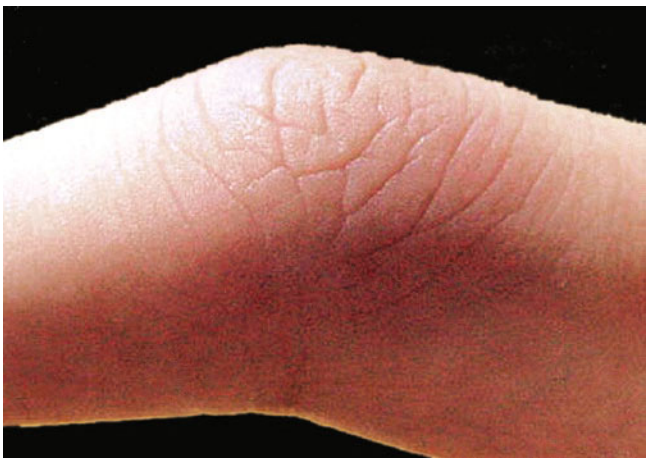


Fig. 2-3-2 Right middle finger joint swelling

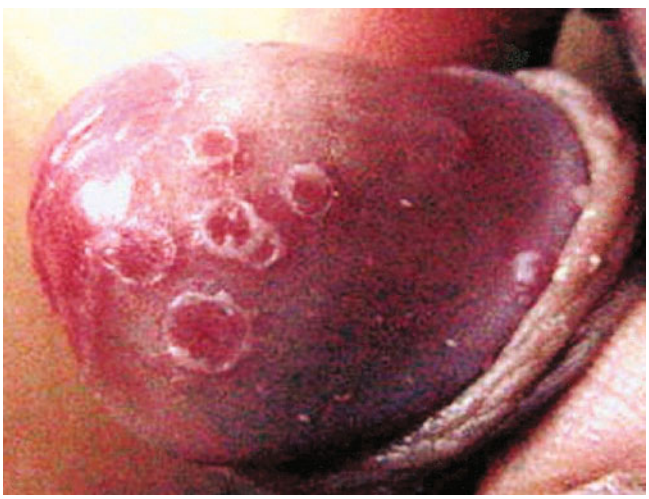


Fig. 2-3-3 Annular superficial ulcers around red and swelling urethra

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Fungal Infections

3

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Abstract

In this chapter, the authors present a variety of skin disorders associated with fungal infections such as adult atypical favus; kerion caused by *Microsporum nanum*; dermatophytosis of the groin, scrotum, and penis; Majocchi's granuloma on the face; disseminated deep dermatophytosis; tinea manuum nigra; blaschkoid tinea versicolor; cutaneous candida granuloma and cervical lymphadenitis; chronic mucocutaneous candidiasis; disseminated cryptococcosis; sporotrichosis presenting with multiple nodules; lymphangitic chromoblastomycosis; cutaneous basidiobolomycosis; primary cutaneous actinomycosis of the hand; human cutaneous protothecosis caused by *Prototheca zopfii*; actinomycetoma caused by *Nocardia brasiliensis*; primary cutaneous mucormycosis caused by *Rhizomucor variabilis*; cutaneous alternariosis; and skin granuloma due to fusarium.

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3.1 Adult Atypical Favus [1]

- Most favus is caused by *Trichophyton schoenleinii*, which preferentially infects the scalp and rarely the glabrous skin and nails. This condition occurs during childhood or adolescence and may persist to adulthood if an effective treatment is lacking.
- Clinically, the classic favus exhibits many yellowish cup-shaped crusts between 0.5 and 1.5 cm in diameter on the scalp. Subsequently, these lesions coalesce into a straw-colored, crisp favic crust. Finally, the involved scalp presents severe alopecia.
- Favus has many clinical variants, including atypical favus, which is similar to seborrheic dermatitis, psoriasis, and tinea amiantacea. Diagnosis is currently based on the mycological examination of the parasitized hair and scutula.
- It is important to diagnose atypical favus at an early stage to prevent the ultimate scarring alopecia.

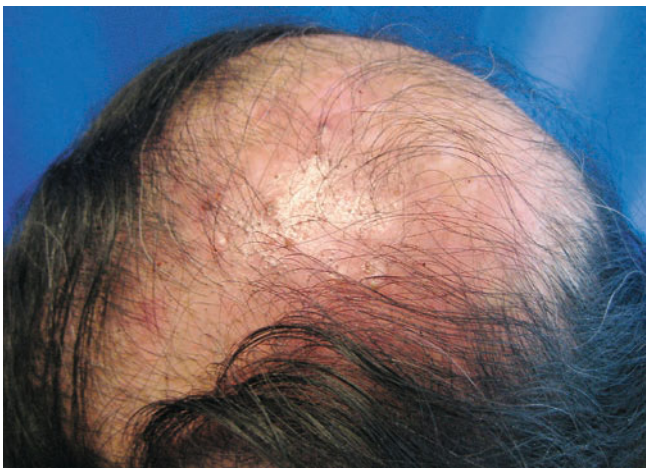


Fig. 3-1-1 A 55-year-old woman suffered from baldness for 50 years. A large, glossy, thin, and paperwhite atrophic lesion presented on the vertex with fine scales

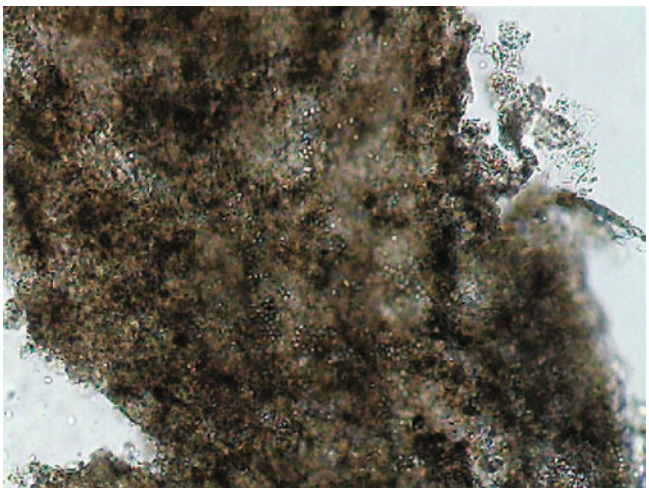


Fig. 3-1-2 Numerous microspores of endothrix were found by microscope

3.2 Kerion Caused by *Microsporum nanum* [2]

- Kerion is an inflammatory type of tinea capitis caused by a T cell-mediated hypersensitive response to the causative dermatophyte and characterized by a tender, erythematous, suppurative swelling with associated alopecia and regional lymphadenopathy.
- *Microsporum nanum* is a dermatophyte that can cause human and animal disorders. It rarely infects human, and it is most frequently relevant to ringworm infection in pigs.
- There are two involvement patterns (endothrix and ectothrix). Ovoid or pear-shaped macroconidia with small projections and collarettes on the shaft can be observed.

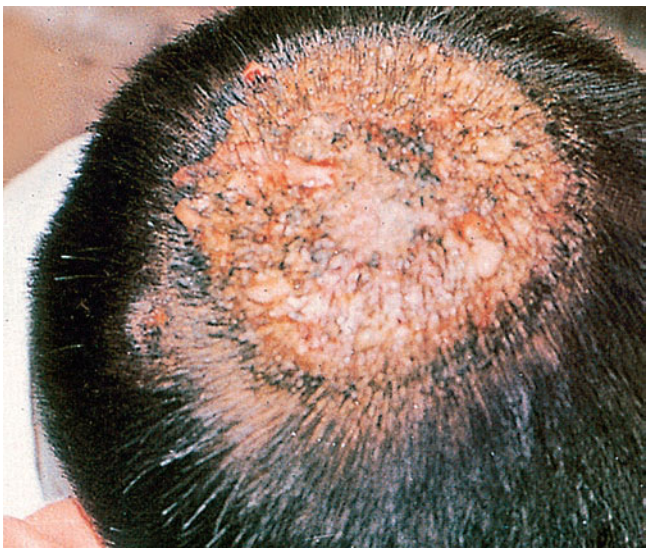


Fig. 3-2-1 There is an inflammatory plaque exuding pus on the vertex

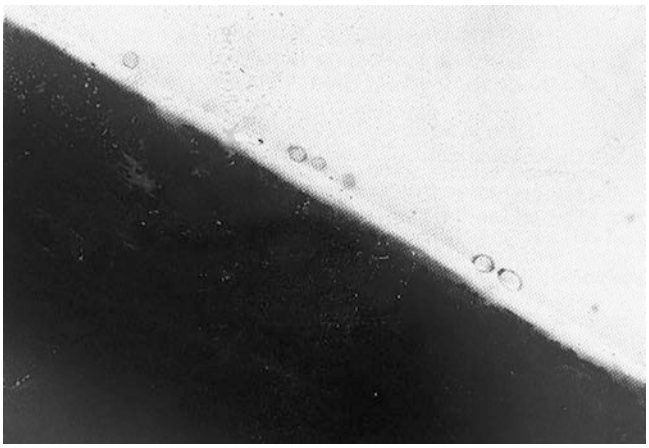


Fig. 3-2-2 Ovoid spores with sparse small projections on the shaft of infected hair (×800) (Reproduced with the permission from [21])

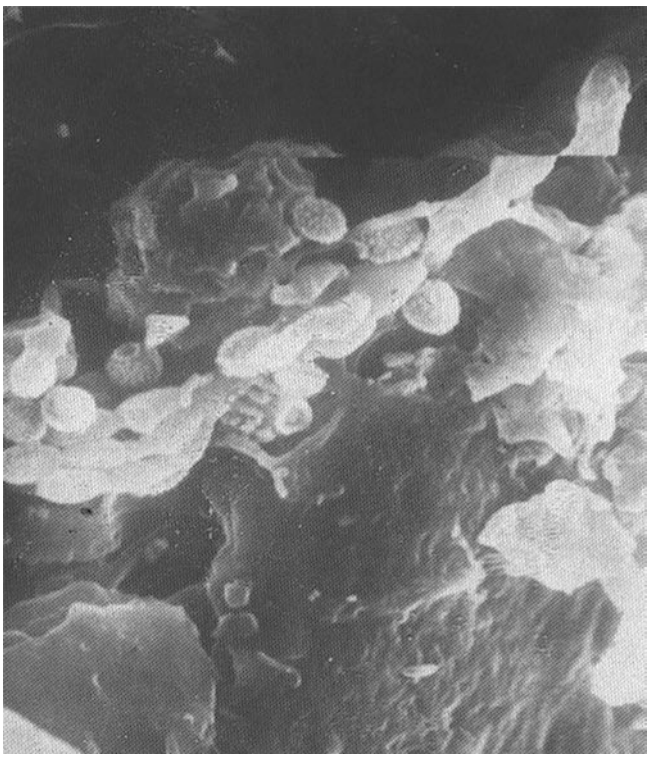


Fig. 3-2-3 Numerous ovoid or pear-shaped macroconidia with sparse small projections and collarettes on the shaft by SEM (Reproduced with the permission from [21])

Fig. 3-2-4 Macroconidia with sparse small projections and collar in culture by SEM (Reproduced with the permission from [21])

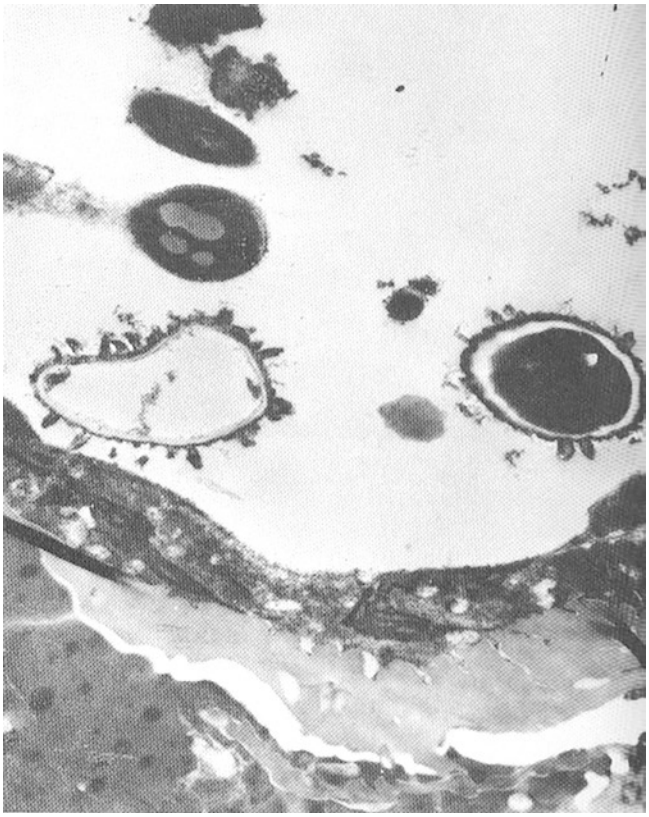
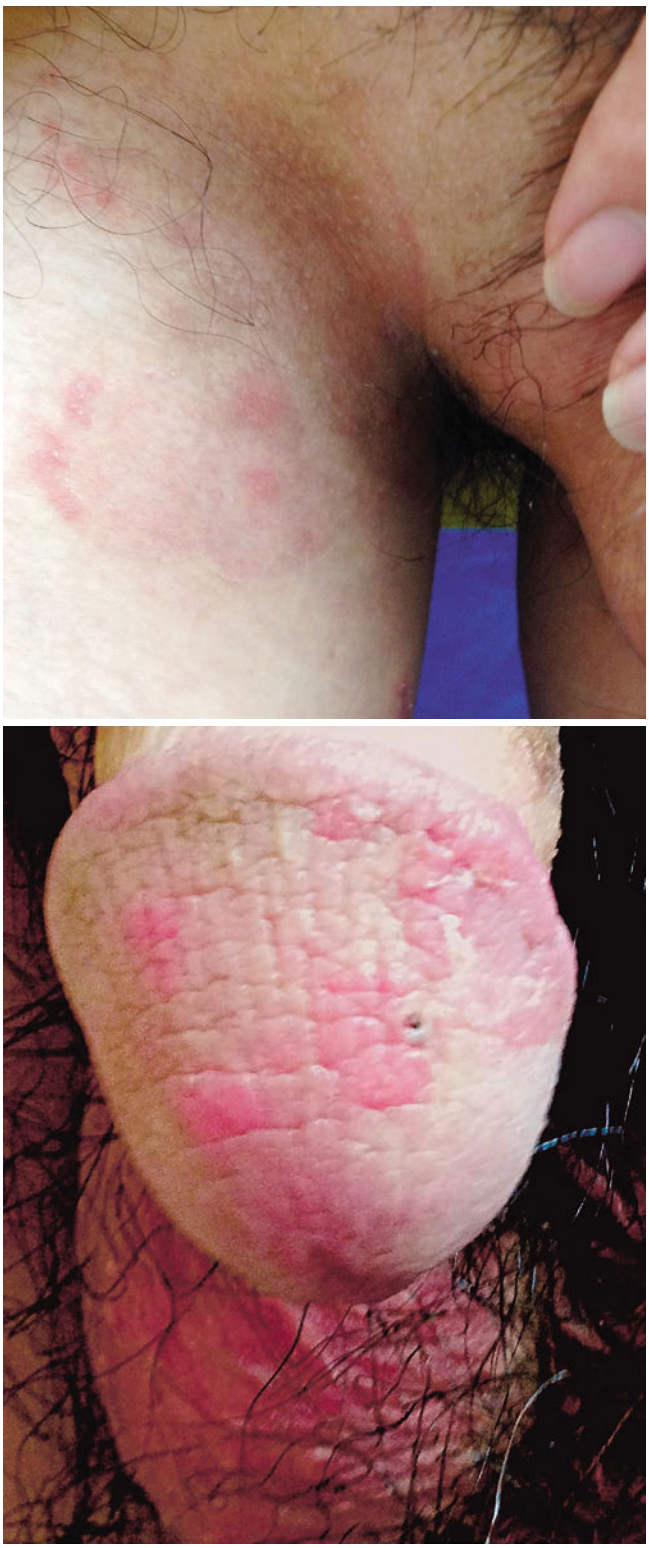


Fig. 3-2-5 Macroconidia has villus-like projections with electron dense areas on the surface of infected hair by TEM (×8000) (Reproduced with the permission from [21])

3.3 Dermatophytosis of the Groin, Scrotum, and Penis [3]

- Tinea cruris is caused by body ringworm and occurs in specific parts of the body, including the groin, perineal region, anus, and buttocks. It is commonly caused by *Trichophyton rubrum*, which is one of the most prominent anthropophilic species of dermatophytes.
- The characteristic lesion exhibits as central intact region surrounded by a scaly, red, advancing, elevated border.
- Tinea cruris rarely appears in the glans penis and scrotum. Genital shaving and concurrent athlete's foot and tinea unguium are predisposing factors.



Figs. 3-3-1, 3-3-2 Scaly erythemas with clear and raised margins of bilateral groin and the glans of the penis

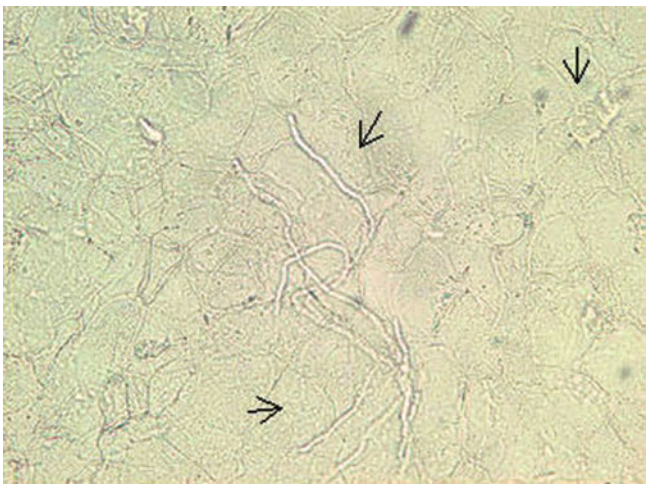


Fig. 3-3-3 Branchingmycelium was found by microscope examination (×40)

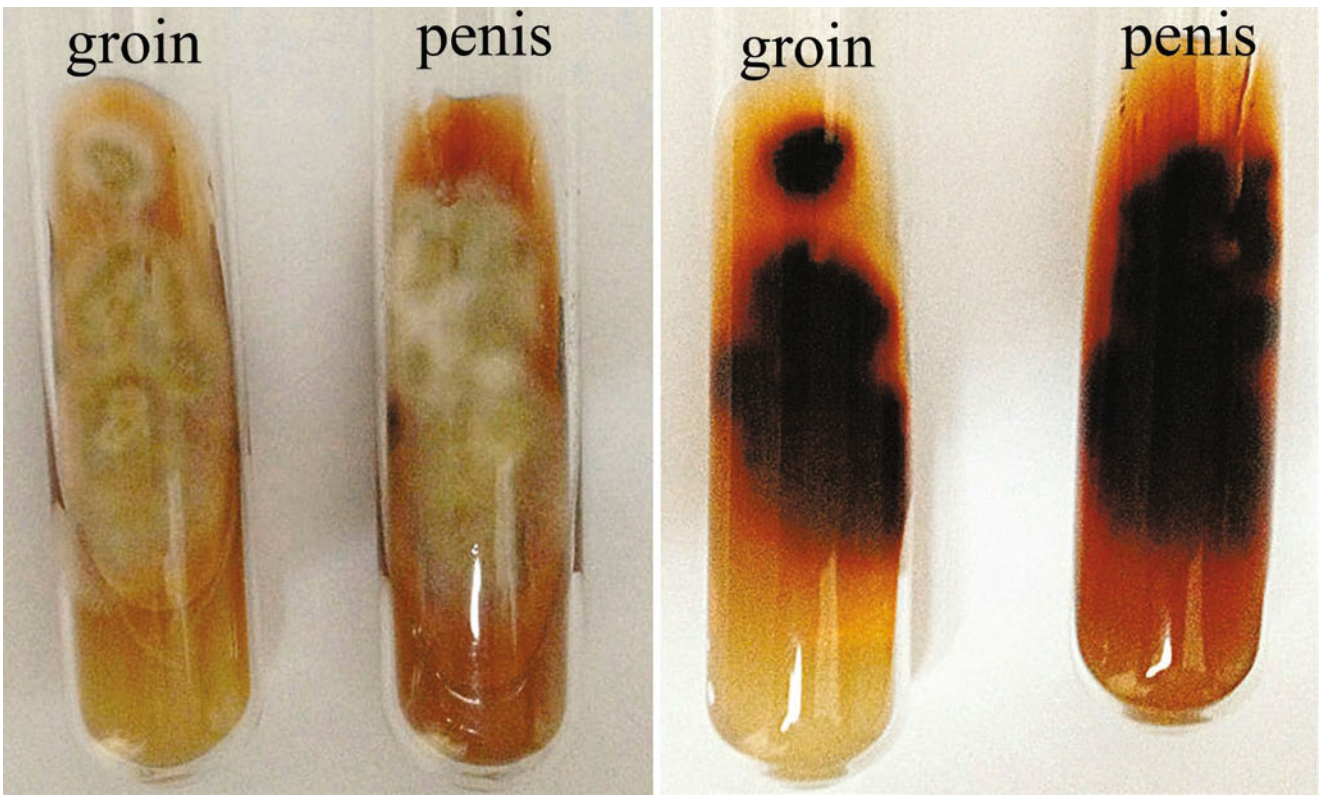


Fig. 3-3-4 The colony was incubated on Sabouraud dextrose agar at 23 °C for days. The color of the medium became port wine (right) from white (left)

3.4 Majocchi's Granuloma on the Face [4]

- Majocchi's granuloma (MG) is a persistent suppurative folliculitis related to a deep granulomatous reaction that is commonly caused by *Trichophyton rubrum* and may develop in any hair-bearing skin, frequently in areas that are prone to trauma. It exhibits nodules, plaques, and papules.
- In healthy individuals and immunocompromised hosts, MG has two clinical presentations: follicular papules and subcutaneous nodular types.
- Diagnosis is confirmed through histopathology, during which granulomas and dermatophytes in the form of filaments or spores are observed in the mid and deep dermis.

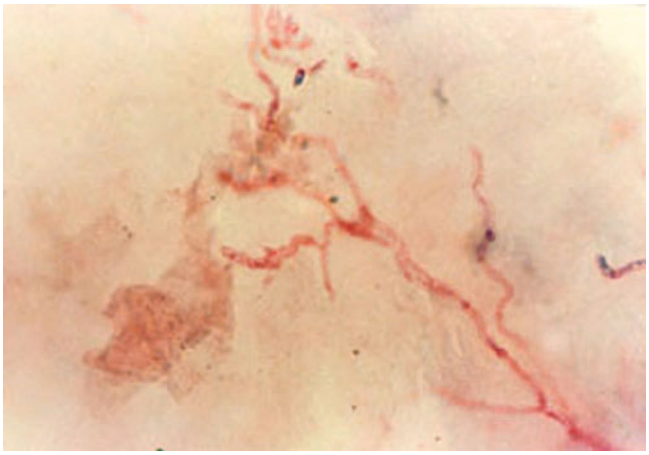


Fig. 3-4-2 Slide showing mycelium

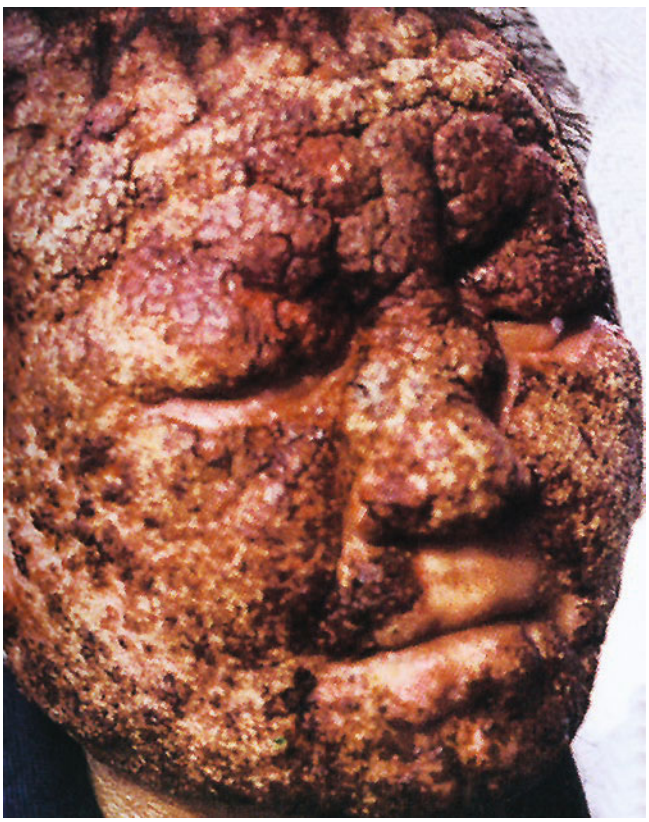


Fig. 3-4-1 Numerous dark red infiltrate plaques and verrucous nodules associated with crusts on the face and scalp

Fig. 3-4-3 Cultures of *Trichophyton rubrum*

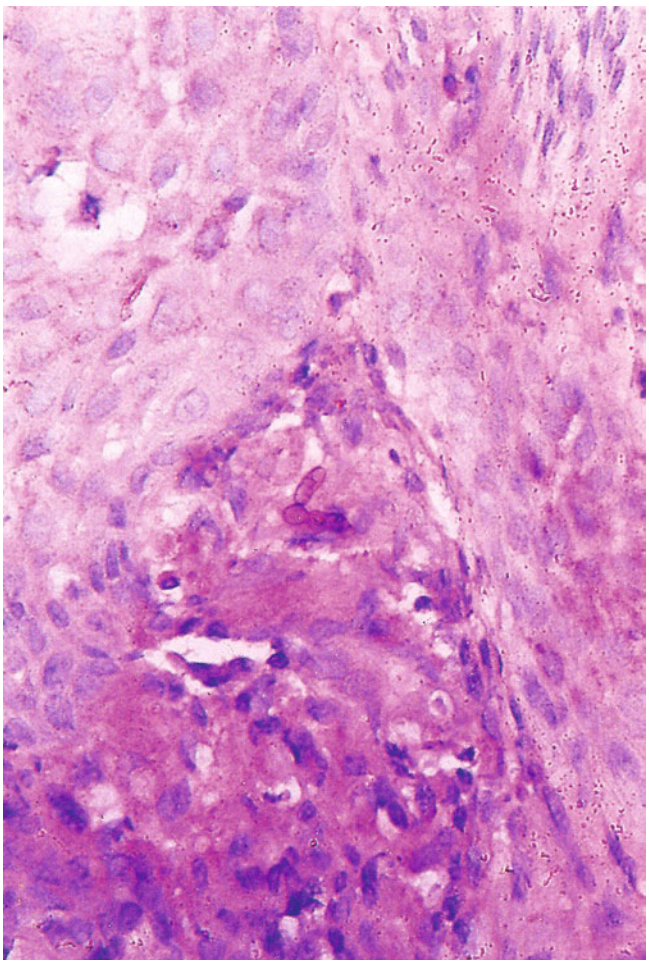


Fig. 3-4-4 Hyperkeratosis and acanthosis; neutrophils, eosinophils, plasma cell, and epithelioid cells infiltrated in the dermis with multinucleated giant cells, fungal spores, and hyphae (PAS stain)

3.5 Disseminated Deep Dermatophytosis [5]

- Disseminated deep dermatophytosis is an uncommon presentation of *Trichophyton rubrum* infection that specifically occurs in immunosuppressed patients.
- Clinically, this condition presents dermal nodules and shiny, skin-colored papules. Pleomorphic, broad hyphae with scattered budding arthrospores can be observed in the dermis. Granulomatous changes are also observed upon histopathological examination.
- For patients who are preparing for immunosuppressive treatment, consideration should be given to appropriately evaluate and treat superficial dermatophytosis.

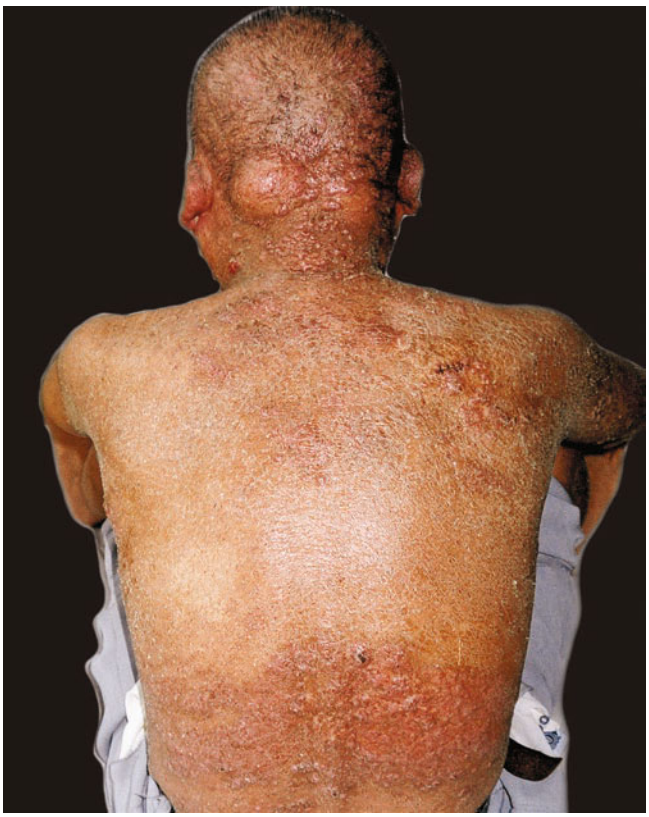


Fig. 3-5-1 Sparse hair, patchy hair loss areas, and dark erythemas with obvious infiltration appeared on the head; two egg-sized masses presented on the occipital area. Variously sized plaques and gray, red, or dark black patches distributed on the trunk and extremities

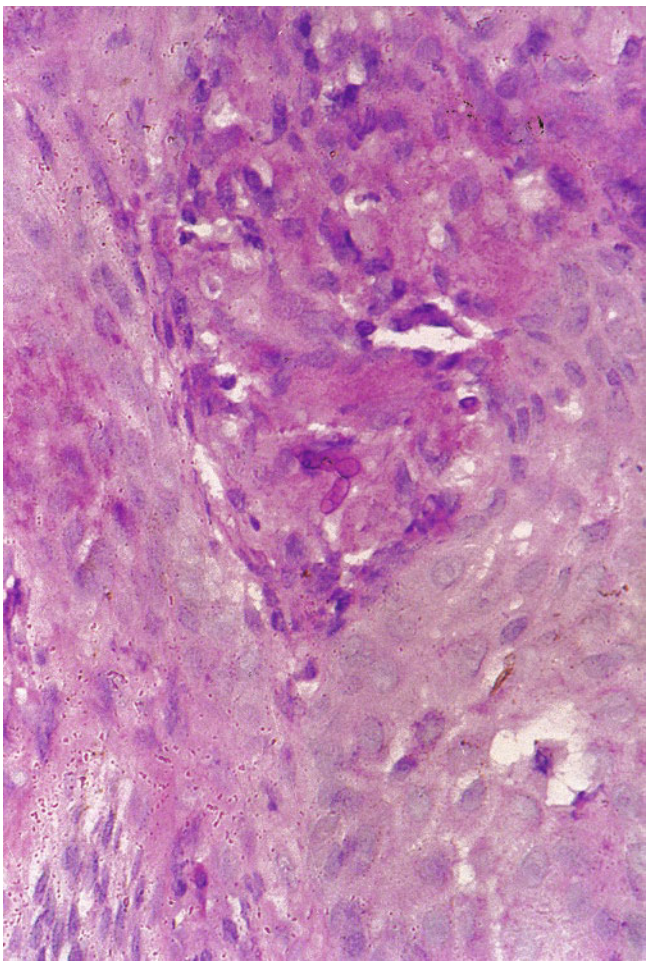


Fig. 3-5-2 The pathological changes of the lesion showed fungal spores and hyphae in the tissue (PAS stain, ×200)

3.6 Tinea Manuum Nigra [6]

- Tinea nigra, an extremely rare mycosis, is commonly caused by *Hortaea werneckii*.
- The most common predisposing factors include hyperhidrosis and living in coastal regions or hypersaline environments.
- The lesions are characterized by pigmented, macular patches on the palms or soles, similar to pigmentary lesions such as melanoma, particularly when they exist as a solitary lesion.
- Once suspected, this condition is easy to diagnose by a simple KOH and dermoscopic examination or culture. Thus, the patient can avoid unnecessary interventions such as biopsy.

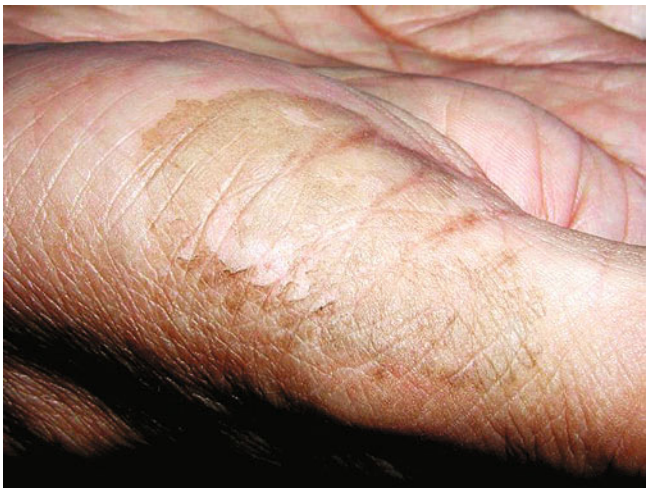


Fig. 3-6-1 A big light/dark macule on the right palm

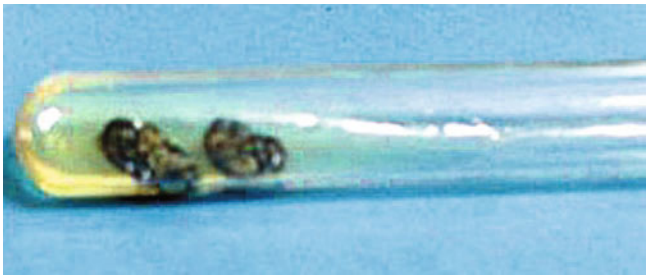


Fig. 3-6-2 A black yeastlike colony on the medium

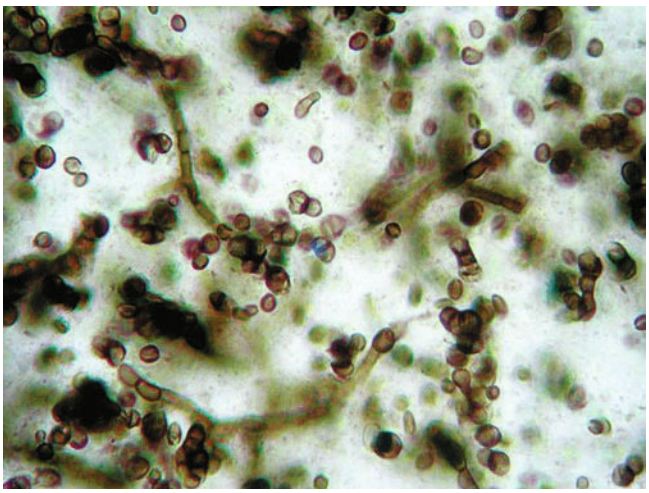


Fig. 3-6-3 Brown septate hyphae and lots of chlamydospores under the microscope (cotton blue stain, ×40)

3.7 Blaschkoid Tinea Versicolor [7]

- Tinea versicolor (TV) is a conventional cutaneous fungal infection with well-delineated macules that are demarcated, round, or oval.
- The color can be pink, tan, brown, purple, black, or hypopigmented. An overlap of the different colored lesions causes a prominent trichromatic change.
- It is most normally encountered in sebum-rich areas such as the chest, shoulders, and upper back. Although uncommon, eruptions confined to the face and scalp, arms and legs, intertriginous sites, genitalia, areolae, and palms and soles have also been noted.
- At least seven clinical variants have been identified, consisting of pigmented, leukodermic, erythematous, atrophic, confetti-like, follicular, and blaschkoid subtypes.

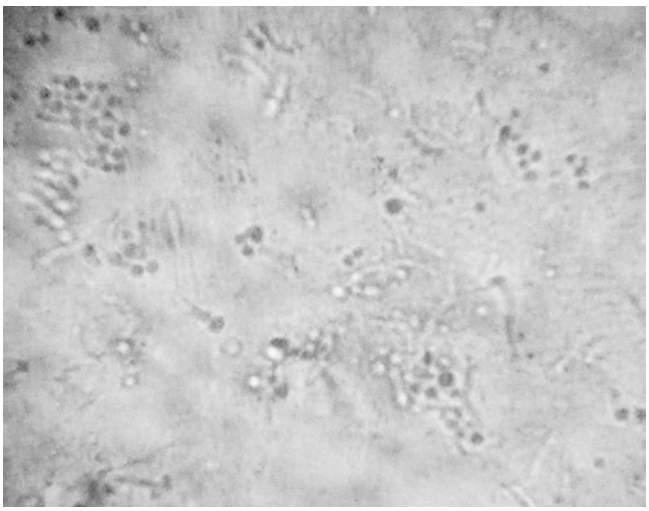


Fig. 3-7-2 Direct mycological examination showed slender septate hyphae and spores with spaghetti and meatball appearance (×40) (Reproduced with the permission from [22])

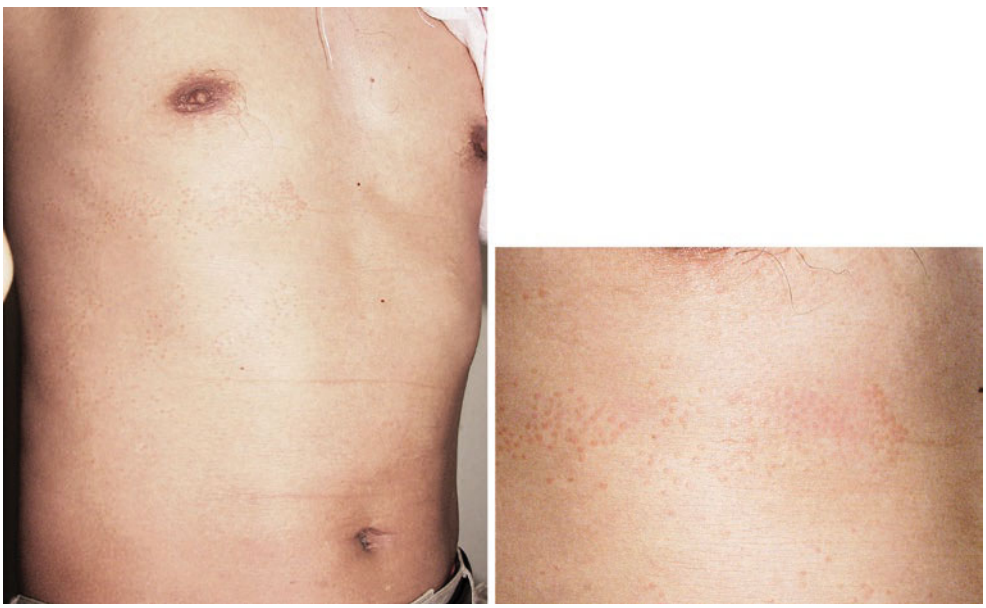


Fig. 3-7-1 On the right chest, there were numerous follicular brownish-red maculopapules, giving several S-shaped band-like appearances (type 1b Blaschko's lines) (Reproduced with the permission from [22])

3.8 Cutaneous Candida Granuloma and Cervical Lymphadenitis [8, 9]

- Granulomatous skin lesions infected by *Candida albicans* are manifestations of a rare form of generalized mucocutaneous candidiasis that has also been described in patients with impaired cell-mediated immunity.
- The mouth, face, fingernails, and scalp are the most familiar areas. Early diagnosis mainly depends on the clinical setting and signs and on proper interpretation of the culture data.
- The involvement of lymph nodes in patients who suffer from disseminated candidiasis has been considered to be a rare occurrence.
- Early and adequate antifungal therapy and improved immunity to remove the pathogenic bacteria and control disease should be emphasized.

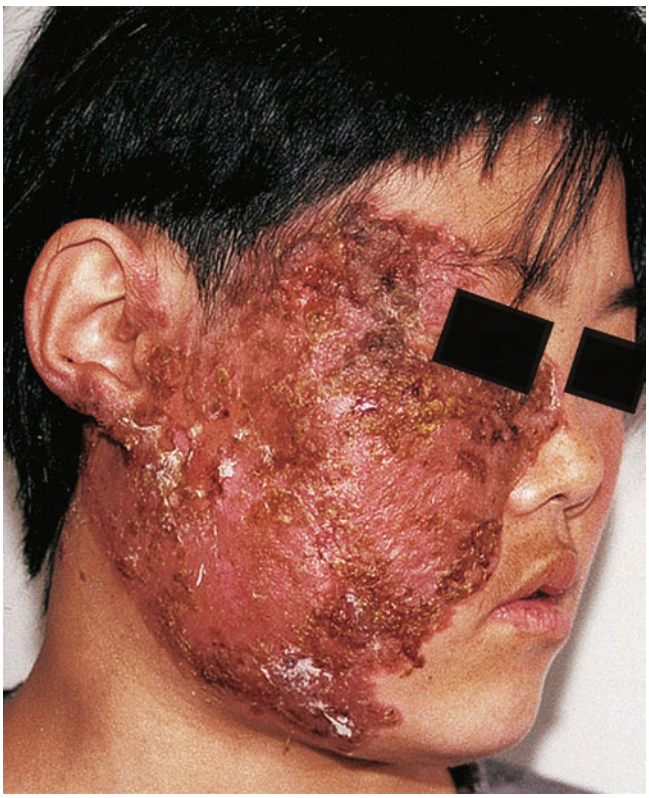


Fig. 3-8-1 Brownish-red neoplasm and granuloma on the face (Reproduced with the permission from [8, 9])

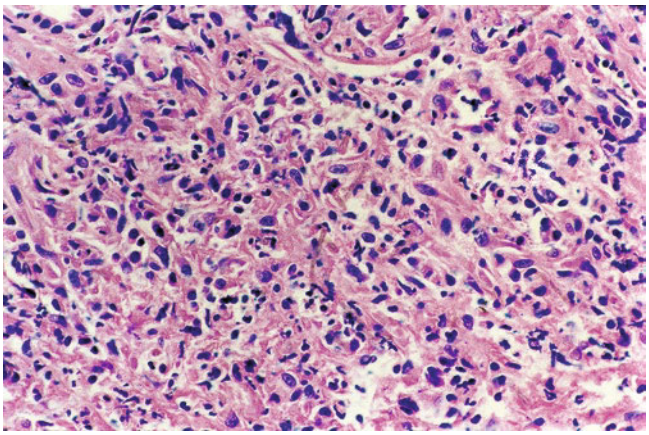


Fig. 3-8-2 Numbers of mycelial filaments in the granuloma tissue (HE stain, ×200)

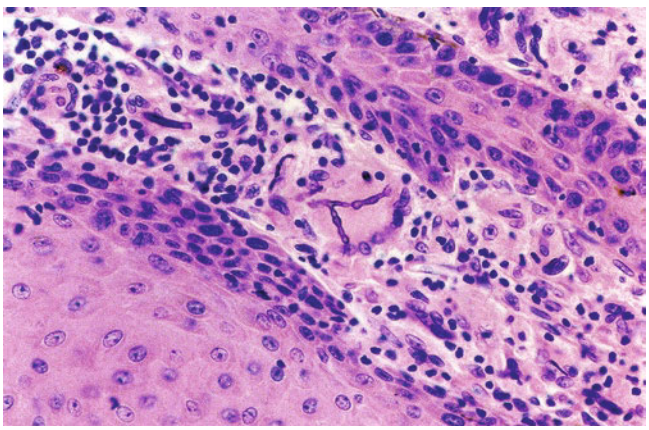
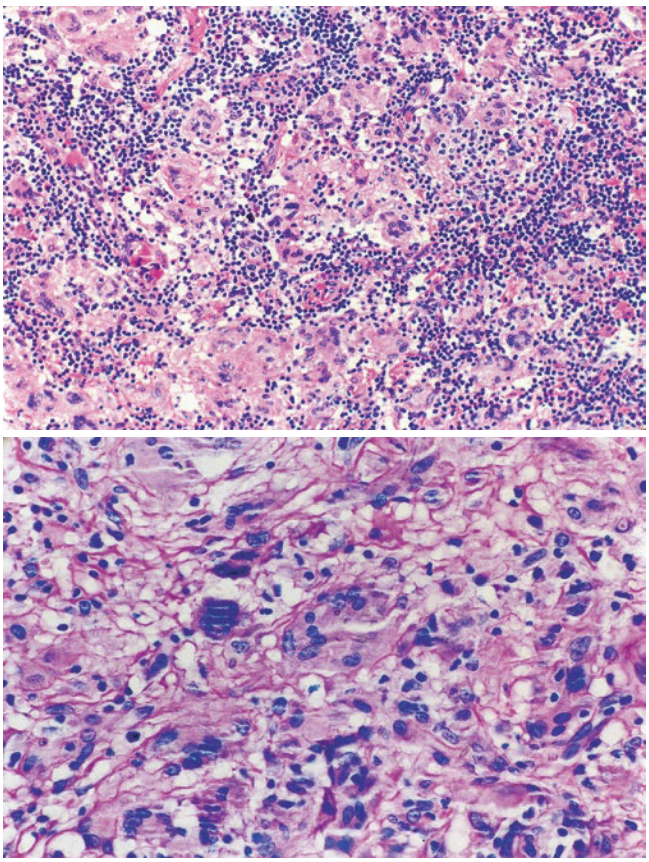


Fig. 3-8-3 Numbers of inflammatory infiltrates and granulomas in the dermis, numbers of mycelial filament in and outside of giant cells (HE stain, ×400)



Figs. 3-8-4, 3-8-5 Numbers of candidal granulomas in the lymph node (HE stain, (4) × 100, (5) × 400)

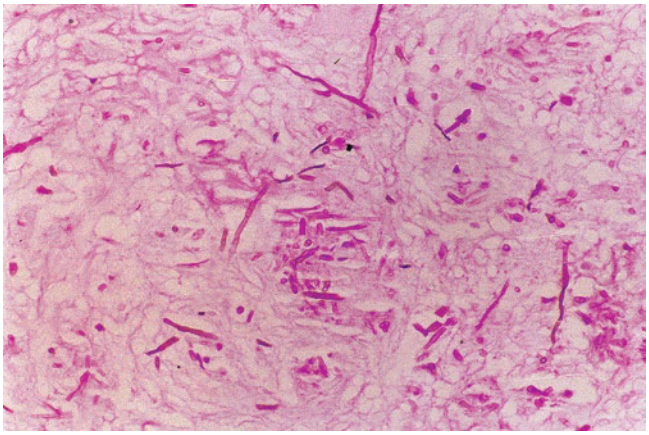


Fig. 3-8-6 Numbers of mycelia filaments in and outside of cells (PAS stain, ×100)

3.9 Chronic Mucocutaneous Candidiasis [10]

- Chronic mucocutaneous candidiasis (CMC) is often caused by *Candida albicans*, featuring recurrent or persistent infections affecting the nails, skin, and oral and genital mucosae.
- CMC is not a specific disorder but a phenotypic presentation of a spectrum of autoimmune, endocrinologic, and immunologic diseases. It is associated with cellular immune and leukocyte dysfunction due to thymic deficiency and usually occurs during infancy or early childhood (60–80% of cases).
- Adult or delayed onset of the disorder is related to bone marrow abnormalities, myasthenia gravis, and thymoma. Typical antifungal treatments are almost noneffective for CMC.

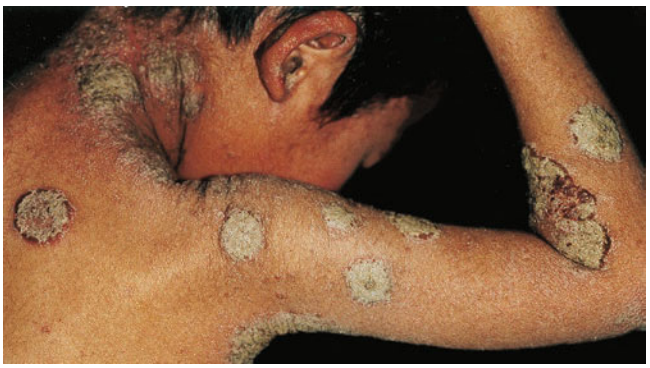


Fig. 3-9-1 Many dark red and brown patches covered with crusts and scales on the right arm

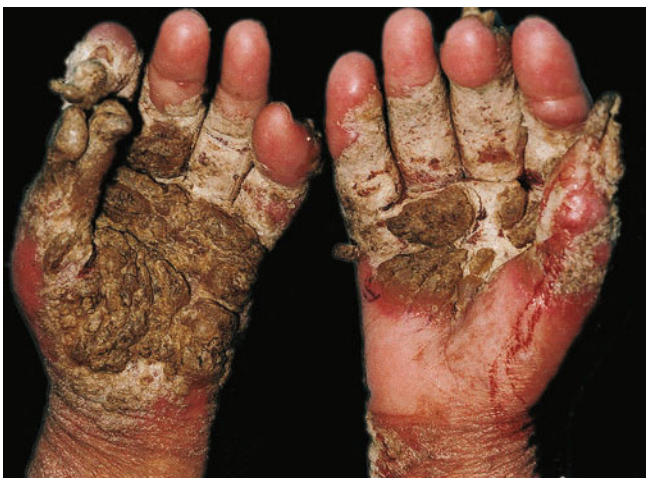


Fig. 3-9-2 Both metacarpophalangeal verrucous vegetation

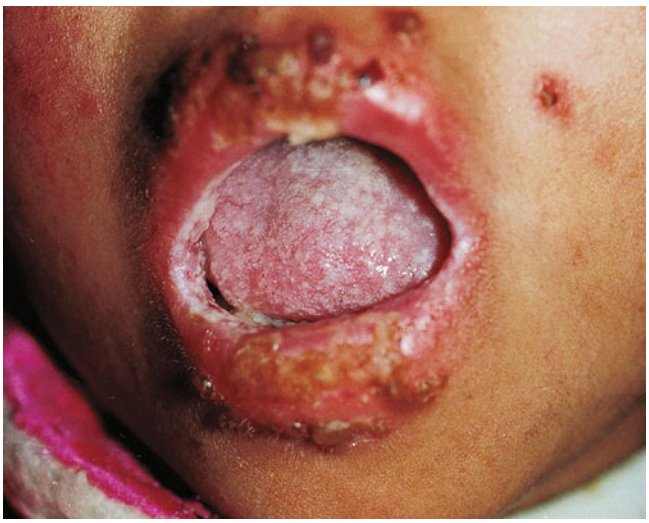


Fig. 3-9-3 Moniliasis of the tongue and lips

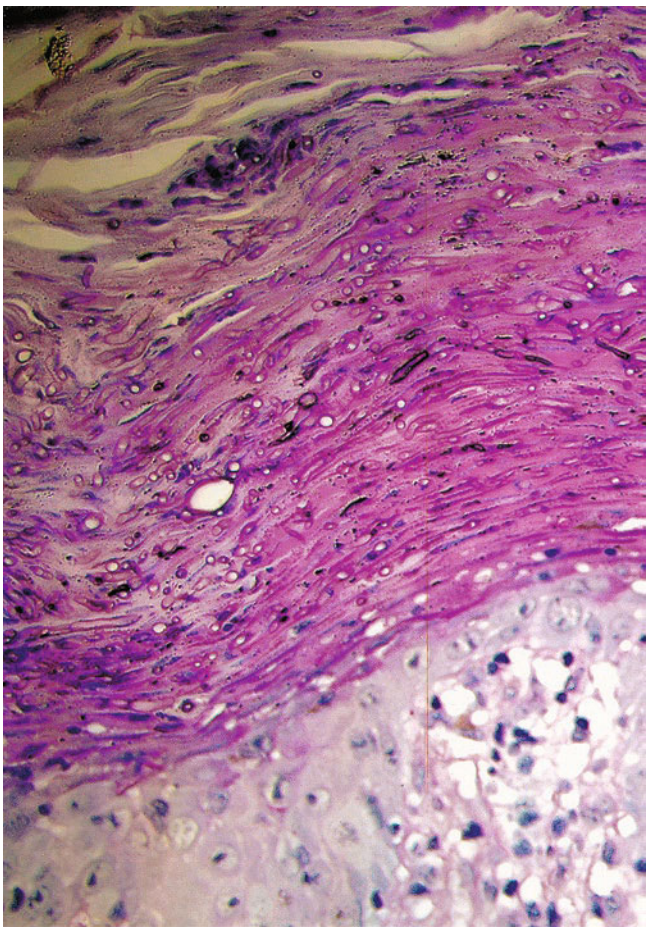


Fig. 3-9-4 Large hyphae and spores in keratotic layer of the epidermis (PAS stain, ×100)

3.10 Disseminated Cryptococcosis [11]

- Cryptococcosis is an opportunistic infection caused by *Cryptococcus neoformans* and tends to affect immunocompromised individuals. The disease is initiated mostly through inhalation of fungi and rarely through inoculation of the fungus via skin injury.
- Primary cutaneous cryptococcosis (PCC) is a rare condition that has been recognized since 2003. This condition results from local inoculation, usually presents as a single infiltrative lesion without systemic involvement, and provides a positive fungal culture.
- Cryptococcosis may spread through the blood, especially affecting the central nervous system (CNS) and skin, and is then called disseminated cryptococcosis (DC). The most familiar recognized area of DC is the central nervous system. Skin findings in DC indicate a poor prognosis.
- The choice of therapy is mainly dependent on the immunocompetence of the host and the extent of the disorder.

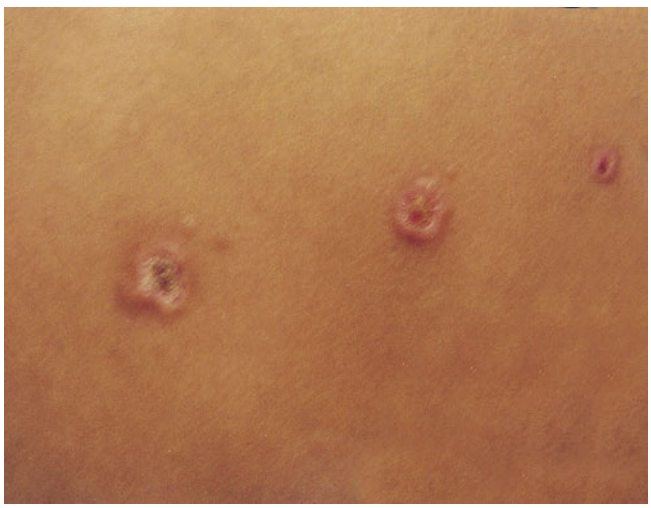


Fig. 3-10a-1 Three elevated papules and nodules with umbilicated centers on the back

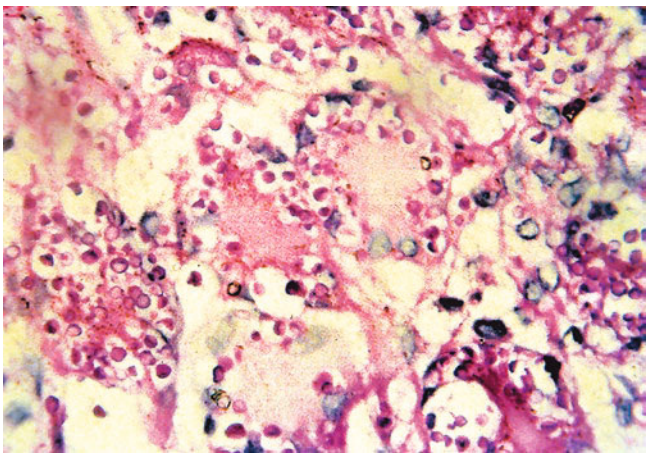


Fig. 3-10a-2 A large mass of spores located in or outside giant cells in the dermis (PAS stain, ×400)

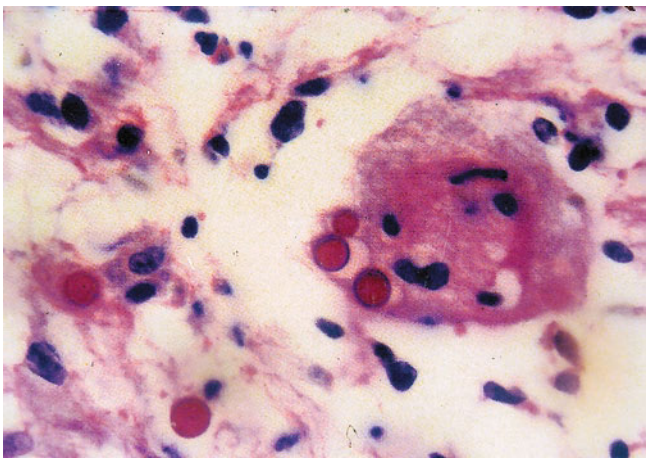


Fig. 3-10a-3 Three typical spores are present in a giant cell in the dermis (PAS stain, ×1300)

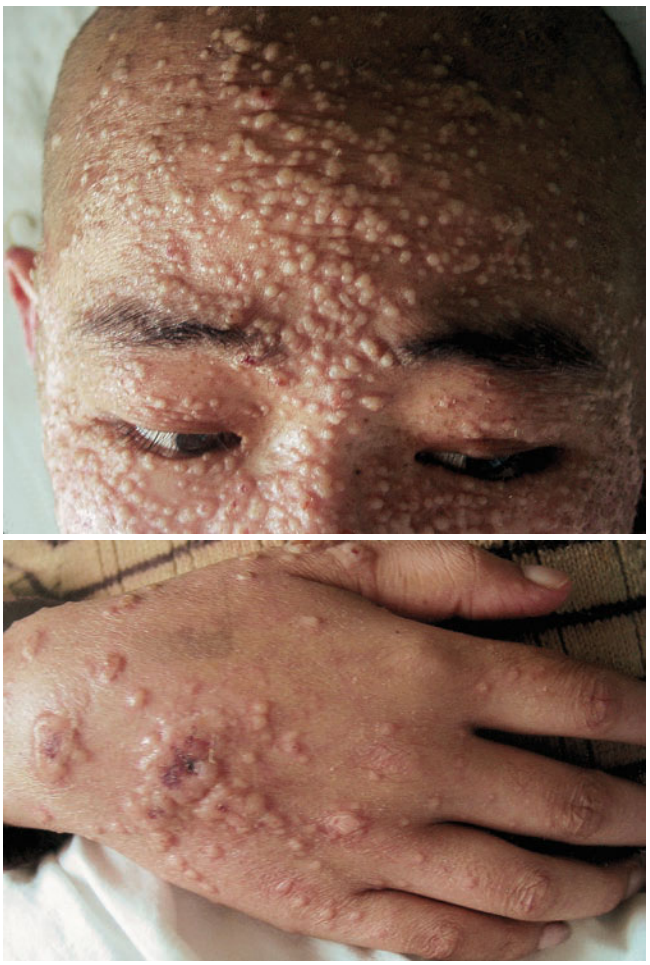


Fig. 3-10b-1, 3-10b-2 Multiple molluscum contagiosum-like skin lesions on the face (1) and forearm (2)

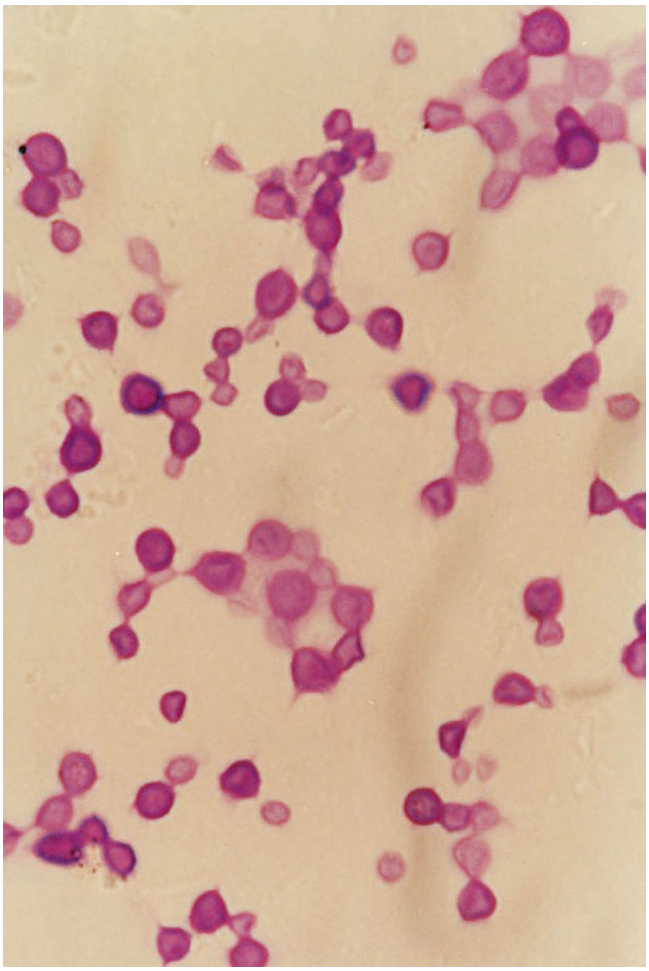


Fig. 3-10b-3 Large violet-red spores in the dermis (PAS stain, ×1000)

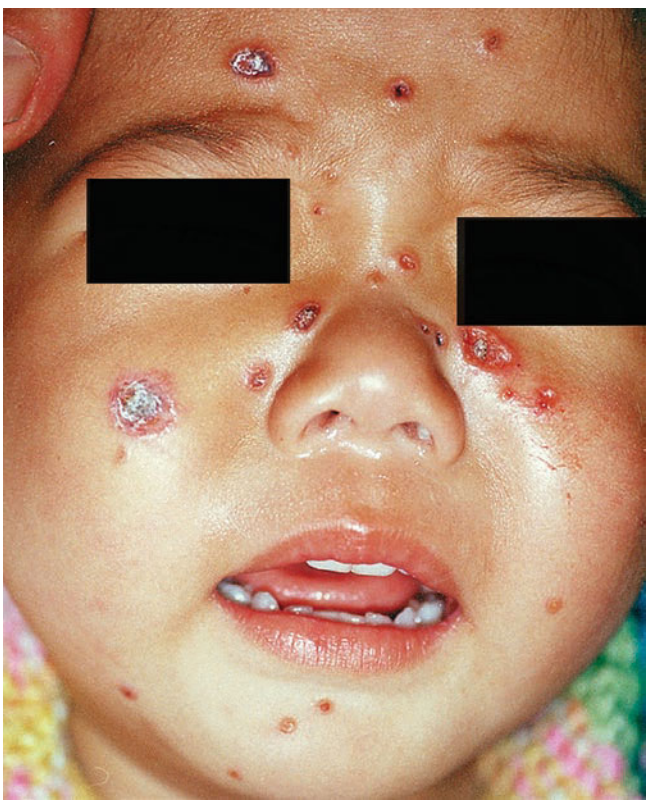


Fig. 3-10c-1 Papules resembling molluscum contagiosum on the face, some of them having necrosis, ulcers, and crust (Reproduced with the permission from [10])

Fig. 3-10c-2 Smears from CSF fluid showed the spore surrounded by a capsule, some of them budding (Indian ink stain, ×40)

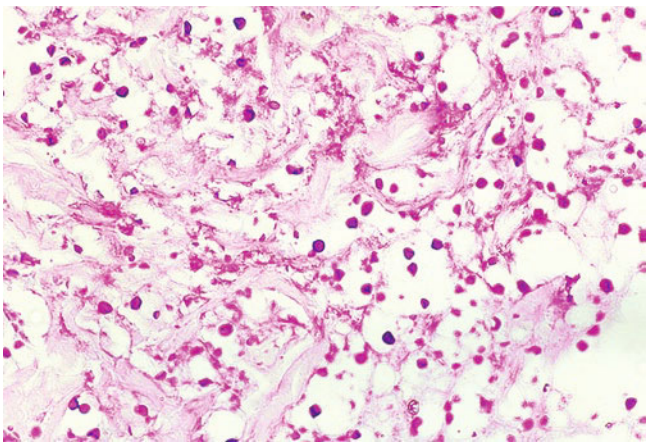


Fig. 3-10c-3 Numerous small round eosinophilic spores in the dermis, some of them budding (PAS stain, ×40)

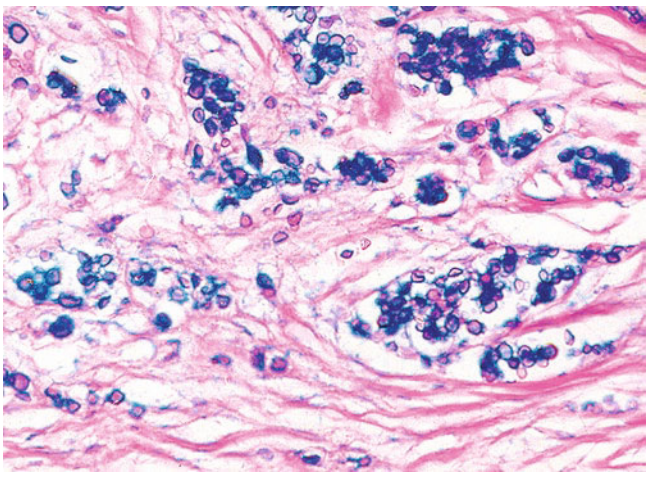


Fig. 3-10c-4 Alcian blue stain and the PAS reaction combined; the red spores surrounding blue capsules (Alcian blue-PAS stain, ×40)

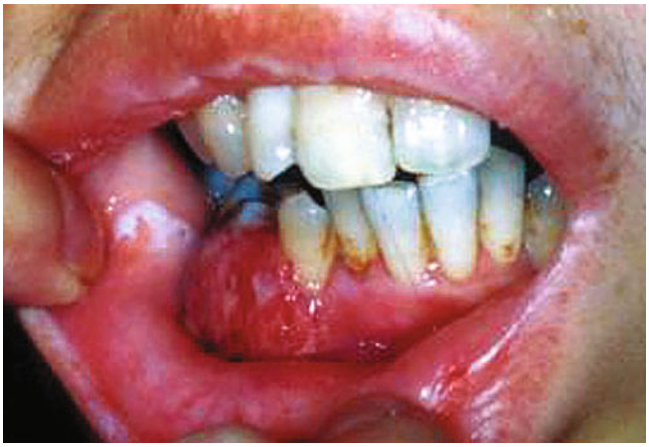


Fig. 3–10d-1 A nodule with ulcer sized 1.3 cm × 2.0 cm on the right lower gum

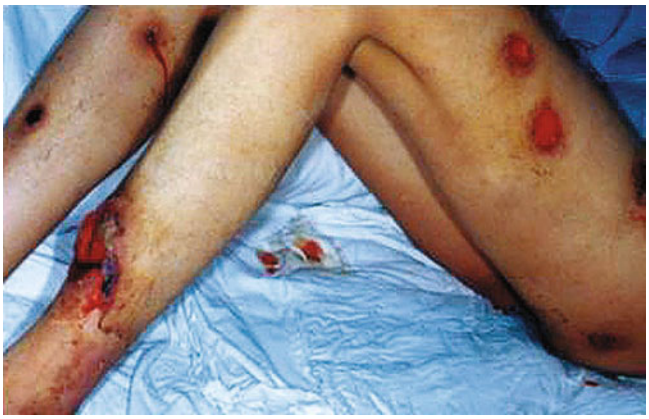


Fig. 3-10d-2 Nodules and ulcers with discharge on the extremities

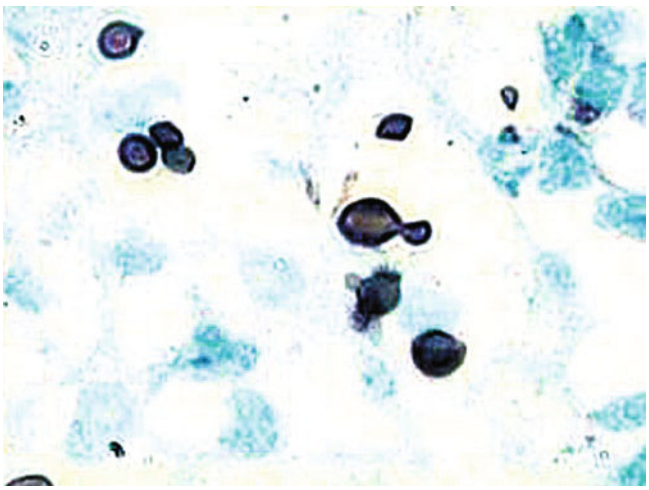


Fig. 3-10d-3 Microscopic examination of the tissue showed numerous budding yeast cells (stained with Gomori's methenamine silver, ×1000)

Fig. 3-10d-4 Transmission electron microscopy showed the section of spores was round or oval with buds (×12,000)

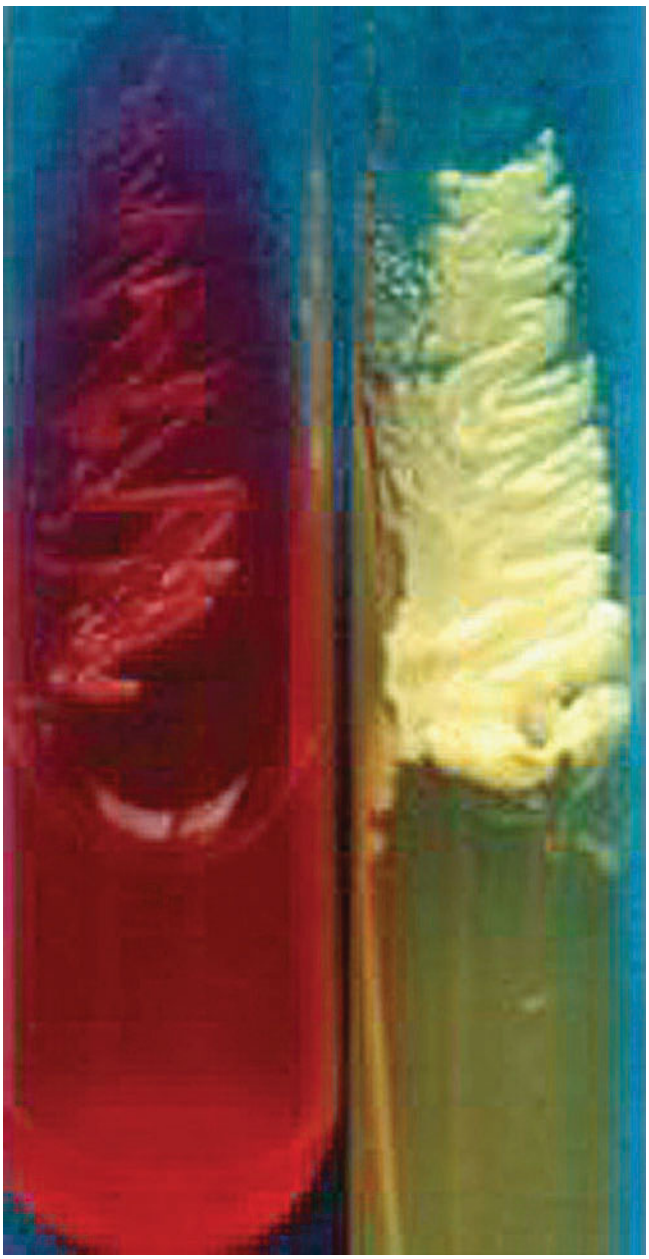


Fig. 3-10d-5 The colony was incubated on Sabouraud dextrose agar containing 20% urea of at 23 °C for 3 years. The color of the medium became port wine from white (left side), while the color of the control did not change (right side)

3.11 Sporotrichosis Presenting with Multiple Nodules [12]

- Sporotrichosis is a chronic granulomatous mycotic infection that results from *Sporothrix schenckii*, which is usually present in hay, decaying wood, soil, and sphagnum moss. Traumatic inoculation is the obvious cause of this disease, which does not discriminate by age, gender, or race but does show a preference for farmers, gardeners, florists, foresters, and nursery workers who often handle plants or plant material.
- This condition comprises four clinical types: lymphocutaneous, fixed cutaneous, multifocal or disseminated cutaneous, and extracutaneous sporotrichosis. The lymphocutaneous type is the most common and accounts for 70–80% of cases. This type is characterized by a noduloulcerative lesion (sporotrichotic chancre) at the inoculation site and a rope of semblable nodules along the proximal lymphatics.
- The primary therapeutic choice for uncomplicated cutaneous sporotrichosis is still a saturated solution of potassium iodide. Itraconazole, terbinafine, or amphotericin B is currently recommended for treating severe or systemic conditions.

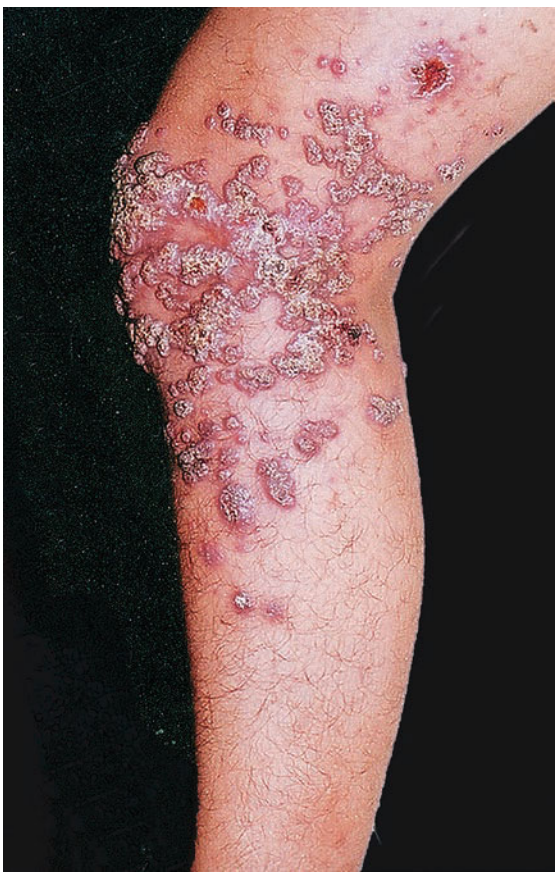


Fig. 3-11-1 Multiple nodules and plaques on the knees

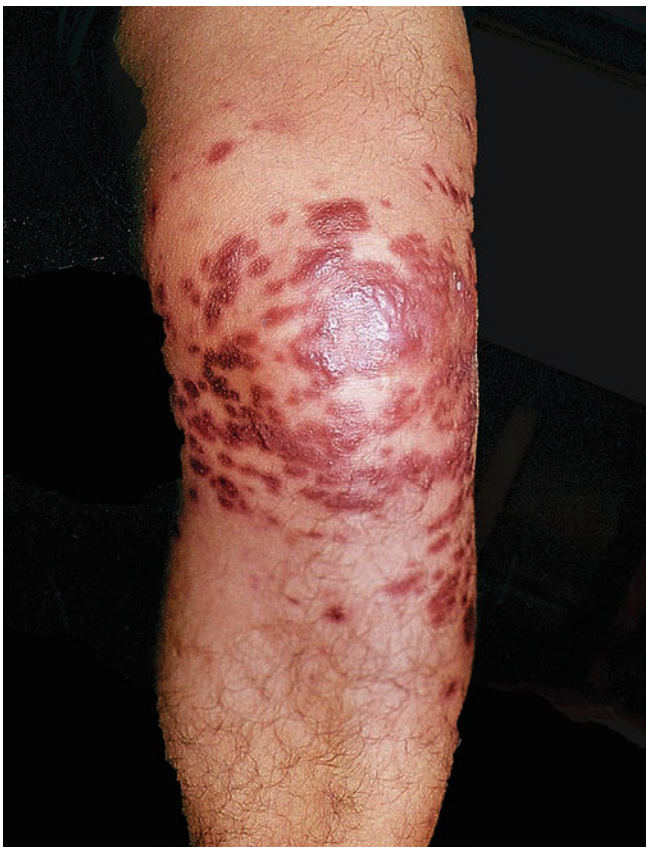


Fig. 3-11-2 Lesions flat with scars after treatment for 3 weeks

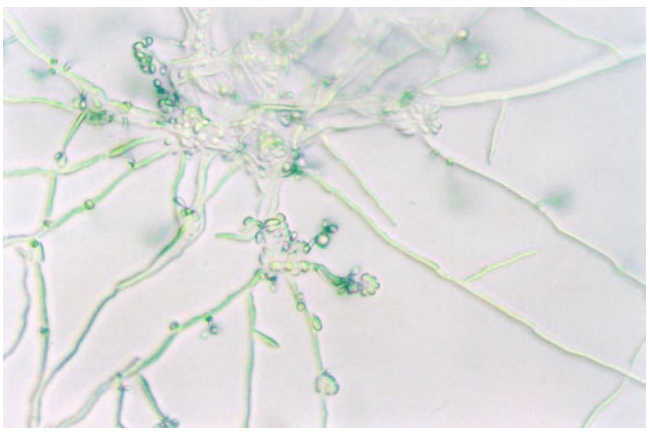


Fig. 3-11-3 Branching pyriform spores in culture (×40)

3.12 Lymphangitic Chromoblastomycosis [13]

- Chromoblastomycosis (CM) is a chronic granulomatous mycotic infection of the subcutaneous tissue and skin caused by pigmented fungi, which usually occurs on the exposed surfaces of the crus after trauma.
- The lesions can invade other sites by hematogenous spread, autoinoculation, or direct diffusion. The lymphatics may also play a role in disseminating the infection. Lesions spread along the lymphatic vessels, and new nodules emerge around the lesions.
- The CM lesion can be verrucous with central scarring or severe scarring with a serpiginous border that is indurated or scaly with fistula formation.
- The diagnosis should be confirmed either by direct microscopy of the scrapings from the lesion in 20% KOH when thick-walled, dark-brown tissue forms of the fungus are seen, by culturing the scrapings, or by histological examination of a biopsy specimen with a granulomatous reaction and spores or biopsy material.

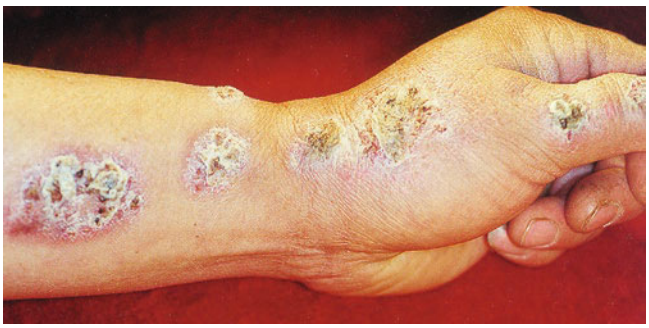


Fig. 3-12-1 Nodules distributed in lines with ulcer and crust from thumb

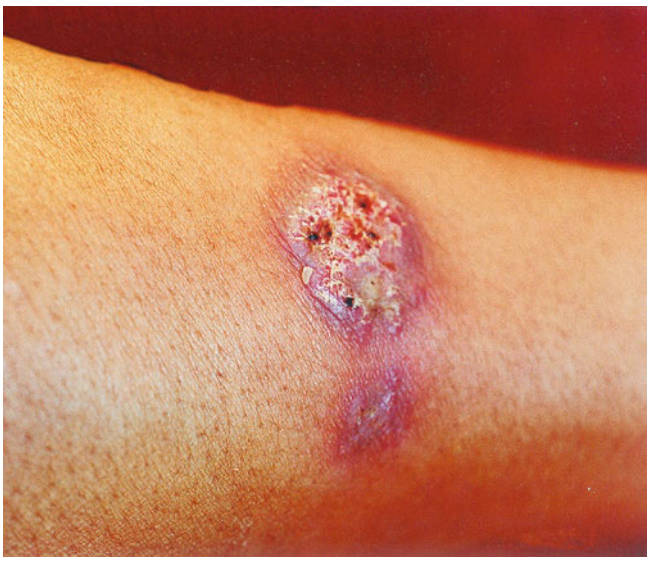


Fig. 3-12-2 Wine-colored plaques covered with yellow-white thickened crust and numerous black speckles

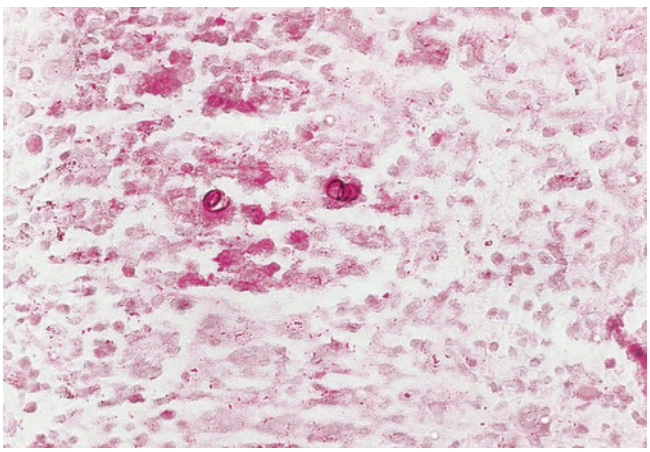
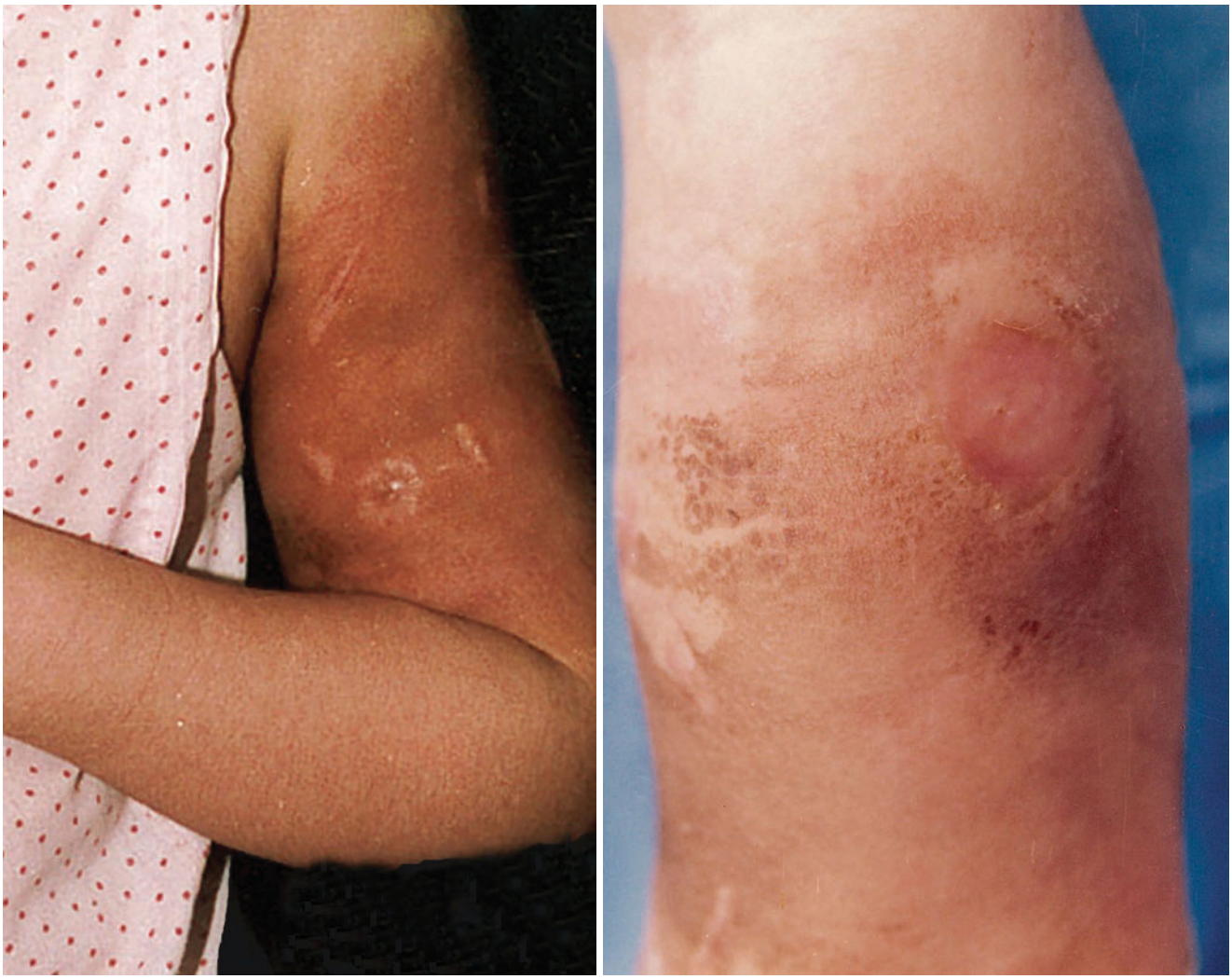


Fig. 3-12-3 Dark-brown thick-walled oval spores with crosswalls in tissue (PAS stain, ×400)

Fig. 3-12-4 *Phialophora verrucosa* in culture (PDA stain, ×200)

3.13 Cutaneous Basidiobolomycosis [14]

- Cutaneous basidiobolomycosis is particularly associated with *Basidiobolus ranarum* and classically presents as a noninflammatory, nonulcerated, nontender woody indurated mass without much contiguous spread, usually in immunocompetent children, less often in adolescents, and rarely in adults. It is mostly located on the trunk, shoulders, and upper part of the limbs, featuring rare small yellow coagula and a yellow line of fungal invasion under the edematous surface.
- Biopsy and fungal culture of the lesion can facilitate diagnosis. Early and precise diagnosis of basidiobolomycosis is vital to avoid dissemination and death.



Figs. 3-13-1, 3-13-2 The brown mass on the left upper arm

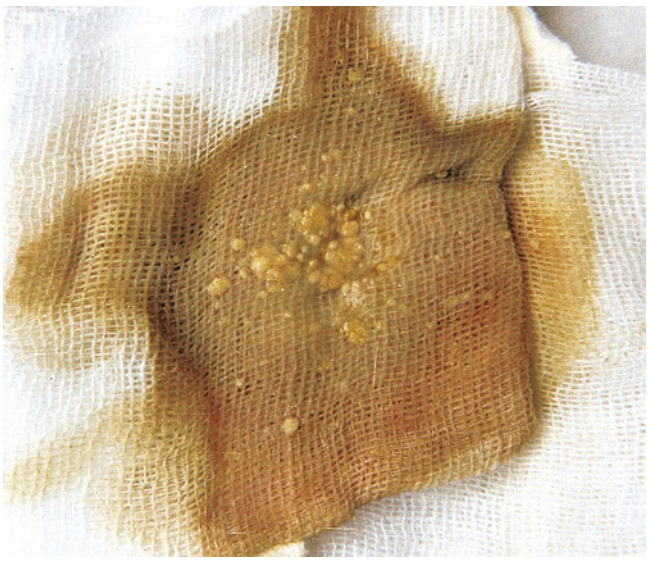


Fig. 3-13-3 The flushing erythemas which were softened and broken in the center, the yellowish granules and pus discharged from broken places

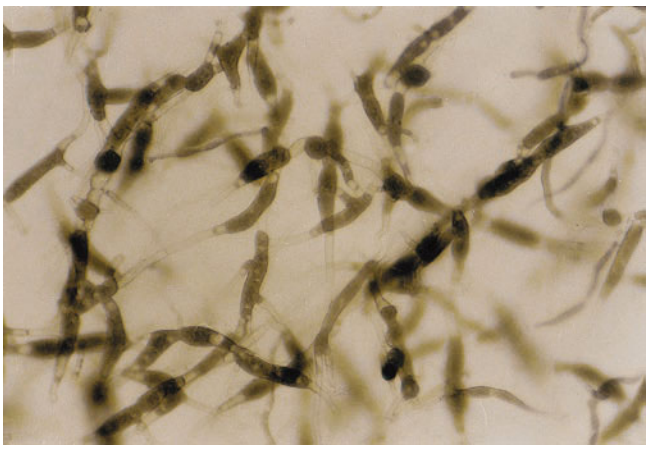


Fig. 3-13-4 The observation of fungal culture; before treatment of itraconazole, septate hyphae grew well, some of which expanded to form sporangia (×11,000)

3.14 Primary Cutaneous Actinomycosis of the Hand [15]

- Primary cutaneous actinomycosis is an uncommon clinical type with variable presentation, usually presenting as a chronic, localized infiltrative process with abscess, fistula formation, and draining sinuses.
- This condition is caused by *Actinomyces* and must be differentiated from tuberculosis, fungal infections, and malignancy, among others.
- The therapeutic regimen comprises surgical excision and an extended period of antimicrobial treatment.

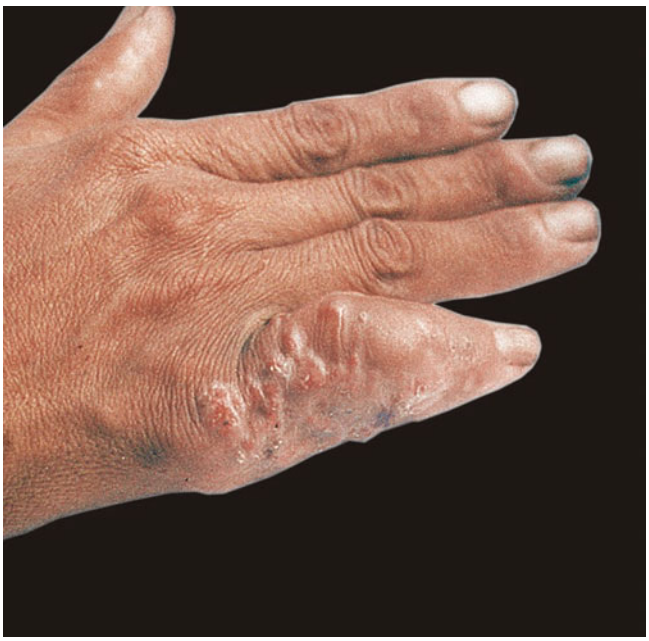


Fig. 3-14-1 Several abscesses in the skin of the swollen finger

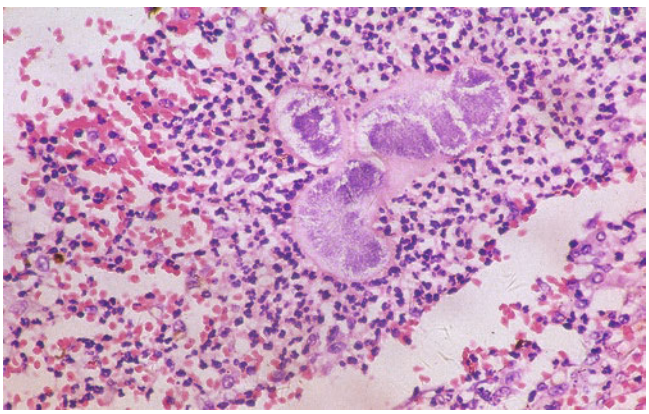


Fig. 3-14-2 *Actinomyces* in small abscesses (HE stain, ×100)

3.15 Human Cutaneous Protothecosis Caused by *Prototheca zopfii* [16]

- Protothecosis is an uncommon infection caused by the genus *Prototheca*, which are omnipresent in nature and in organic material. *Prototheca wickerhamii* and *Prototheca zopfii* are the most frequent organisms reported in humans.
- The disease is divided into three types: cutaneous, bursitis-causing, and disseminated/systemic conditions, affecting both immunocompetent and immunosuppressed patients, with more serious and disseminated infections occurring in immunocompromised individuals.
- Diagnosis is based on observing asexual sporangia (thecas) by histopathological examination. Medical and surgical treatment can be used. Ketoconazole, amphotericin B, fluconazole, posaconazole, voriconazole, and itraconazole are the most commonly administered antifungals.

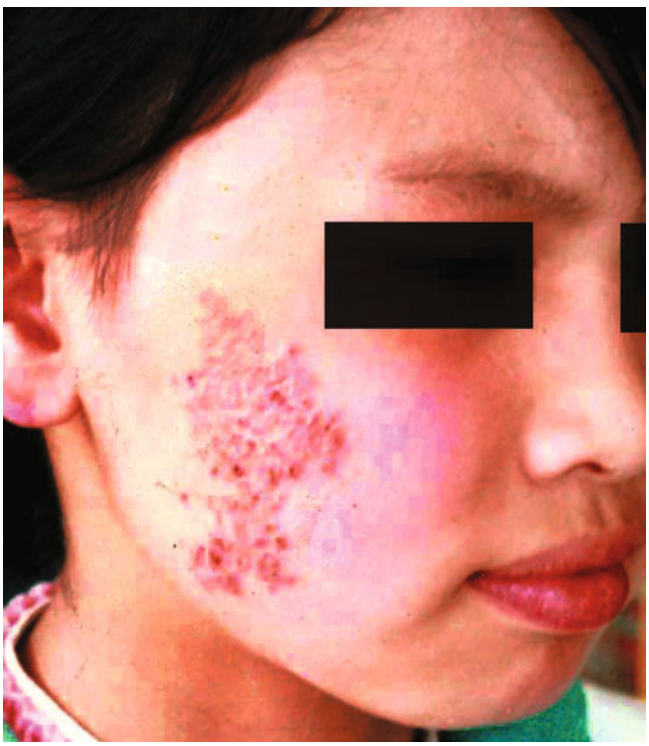


Fig. 3-15-1 The erythemas, papules, and scales occurred on the right side of her face (Reproduced with the permission from [16])

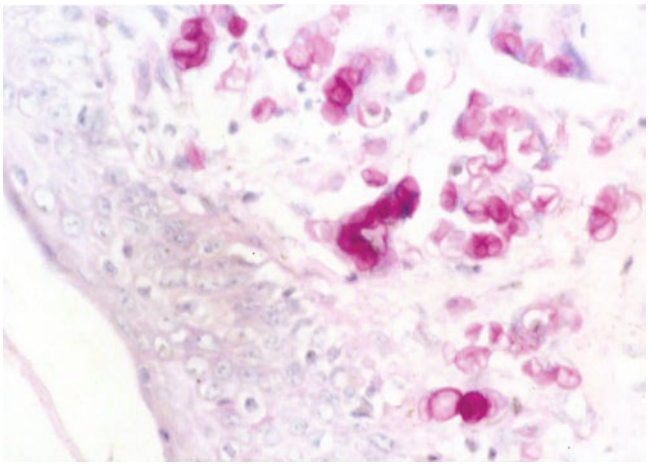


Fig. 3-15-2 A few monocytes infiltrated around the blood vessels and epidermal appendages in the upper dermis (PAS stain, ×100)

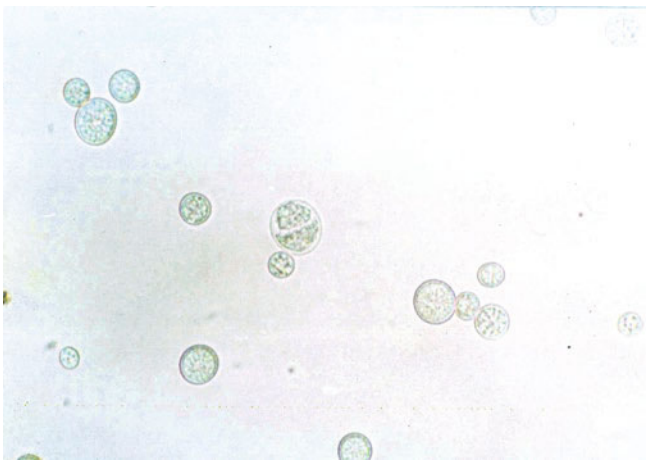


Fig. 3-15-3 A large quantity of chlamydospores (diameter 10–18 μm, some diameter 3–8 μm entosporum inside) were discovered, microscope view (×400)

3.16 Mycetoma Caused by *Nocardia brasiliensis* [17]

- Mycetoma is a chronic subcutaneous infection caused by aerobic branching actinomycetes through minor trauma in susceptible individuals. *Nocardia brasiliensis* is a common infectious agent.
- The clinical characteristics are firm tumefaction of the affected site and the presence of nodules, abscesses, and sinuses that expel a seropurulent exudate, including filamenting granules. The infection generally remains localized, but it may spread to the underlying bone and muscle or to adjacent organs.
- Treatment of *Nocardia* infections should be individualized. Standard treatment for uncomplicated cases is a few months of sulfamethoxazole-trimethoprim. Special locations, disseminated cases, and bone involvement must receive combined therapy with sulfamethoxazole-trimethoprim and amikacin.

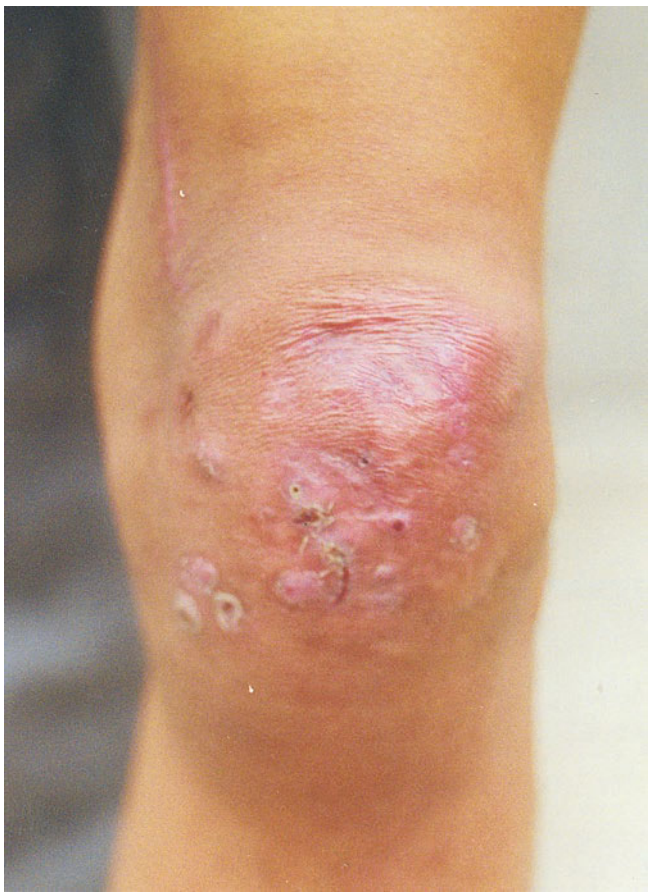


Fig. 3-16-1 Nodules and small sinus on the knee, a surgical cut on the upside of knee

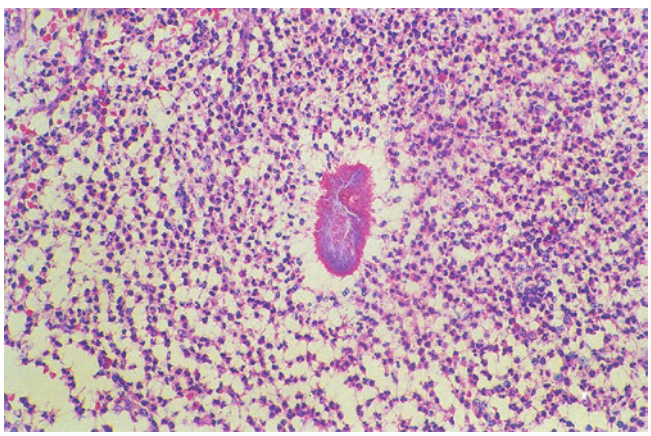


Fig. 3-16-2 Numerous granulomas and inflammatory cells associated with some sulfurate granulas (HE stain, ×200)

3.17 Primary Cutaneous Mucormycosis Caused by *Rhizomucor variabilis* [18]

- Cutaneous mucormycosis usually occurs in individuals with predisposing factors such as diabetes, malignancy, solid organ transplantation, and trauma. Direct inoculation may be the route of transmission.
- *Rhizomucor variabilis*, the main causal agent, is mainly involved in superficial or subcutaneous infections that are more indolent and evolve chronically.
- The clinical features are characterized by erythematous violaceous plaques that show progressive central necrosis, peripheral erythema, and later ulceration, exhibiting the clinical aspect of the so-called bull's eye lesion.
- Early therapy is vital for a good prognosis. The first-line treatment consists of liposomal amphotericin B therapy and surgical resection. Alternatives include posaconazole, hyperbaric oxygen therapy, interferon gamma, and potassium iodide.

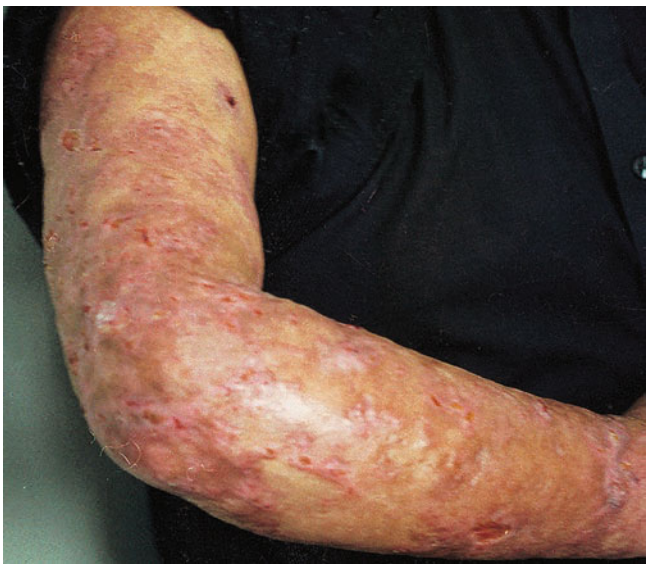


Fig. 3-17-1 Diffused swelling, suppurating plaques, ulcer, and crust on the right arm

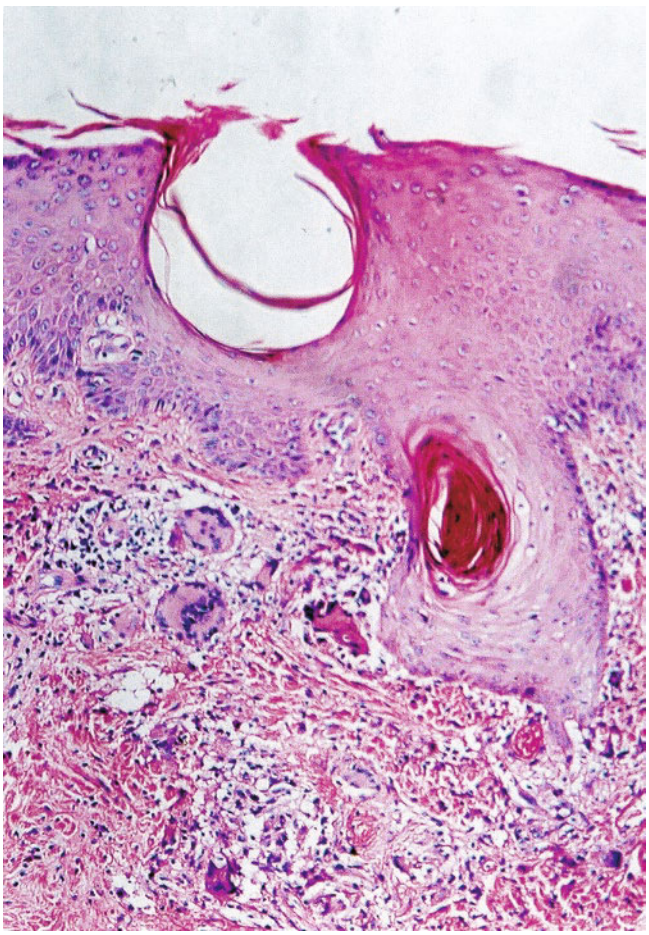


Fig. 3-17-2 Many inflammatory cells and multinucleated giant cells in the dermis (HE stain, ×200)

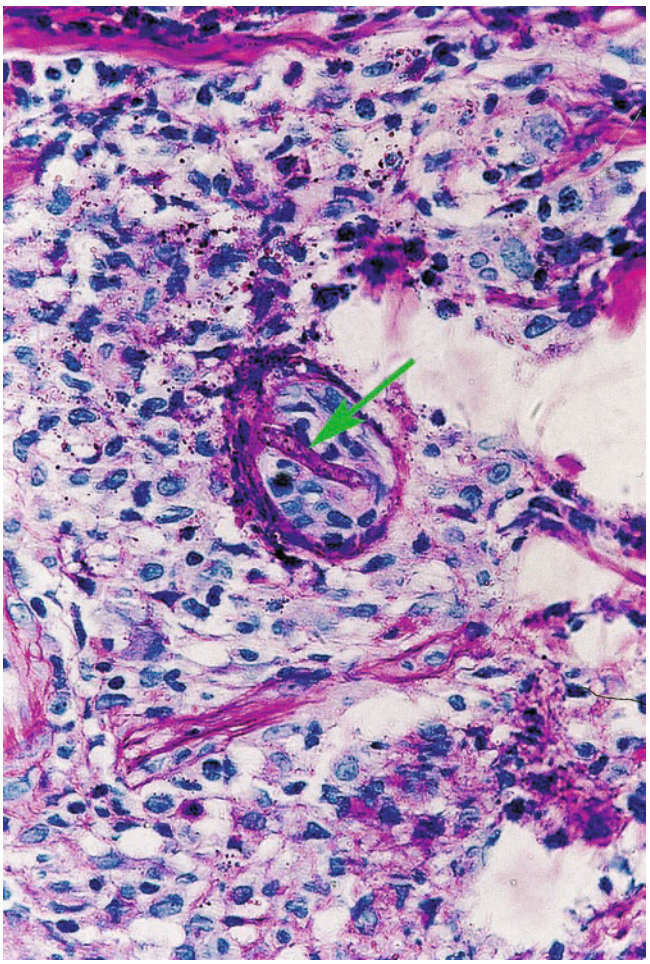
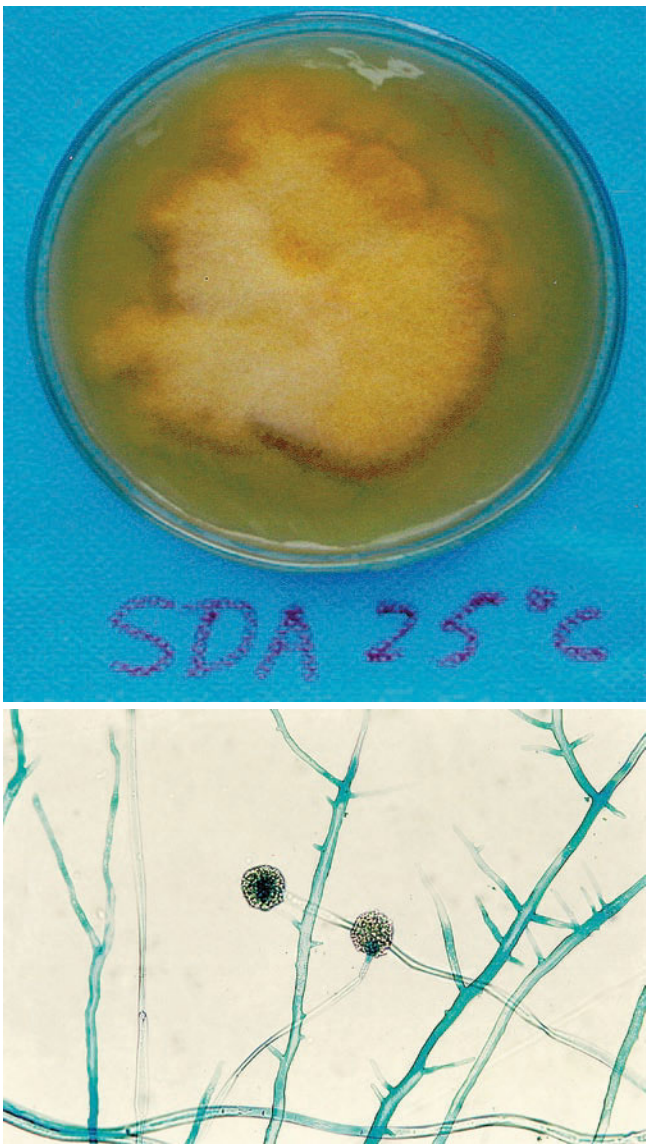


Fig. 3-17-3 A long and wide mycelia (↑), within and around the vessel (PAS stain, ×300)



Figs. 3-17-4, 3-17-5 *Rhizomucor variabilis* colony and macrospore on the medium

3.18 Cutaneous Alternariosis [19]

- Alternariosis is an infection caused by fungi that are generally seen in immunodeficient patients. Cutaneous alternariosis exists in two forms: an epidermal type or a dermal type, depending on the depth of fungal invasion. In both types, the lesion usually appears on exposed sites such as the dorsum of the hands, forearms, knees, and legs. Scaly infiltrated erythematous or ulcerative lesions are observed with the epidermal type. The dermal type has been described as plaques with papules, pustules, and crusts and with a surface that is more or less granular and atrophic.
- There are no clinical trials or guidelines to guide the treatment of this condition; however, itraconazole is the most commonly used antifungal in published cases.

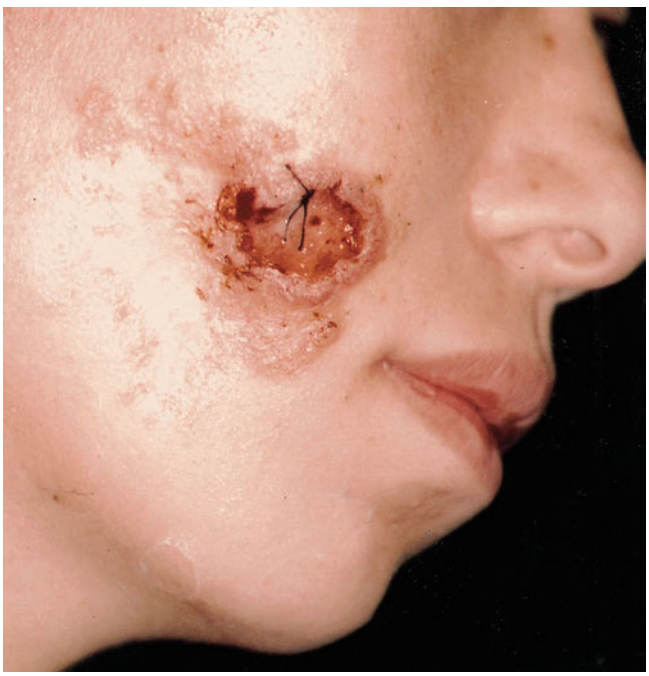


Fig. 3-18-1 Infiltrative plaques on the right cheek with ulceration in the center

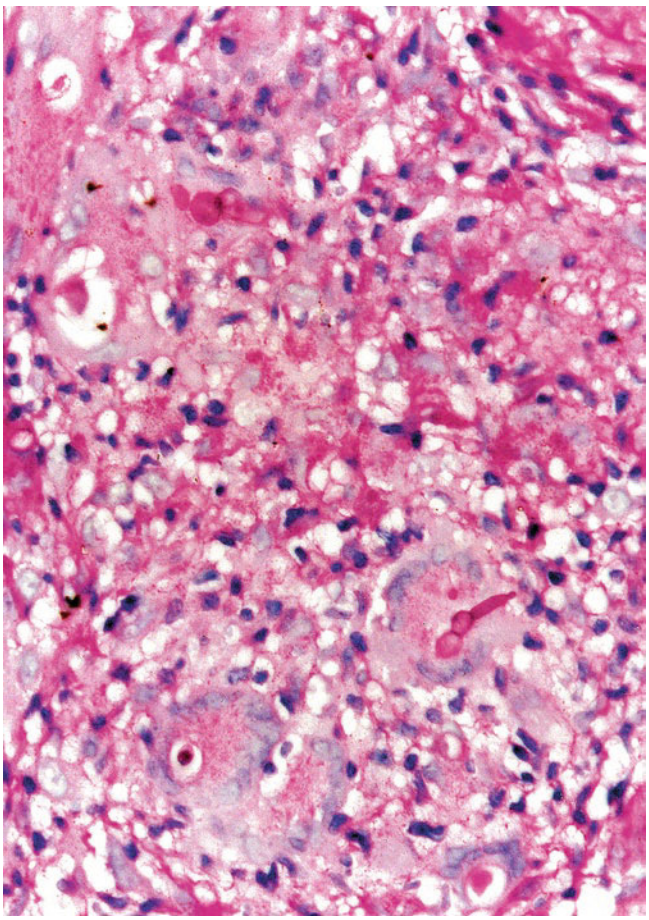


Fig. 3-18-2 Staining revealed irregular septate hyphae and large round spores in the giant cells (PAS stain, ×400)

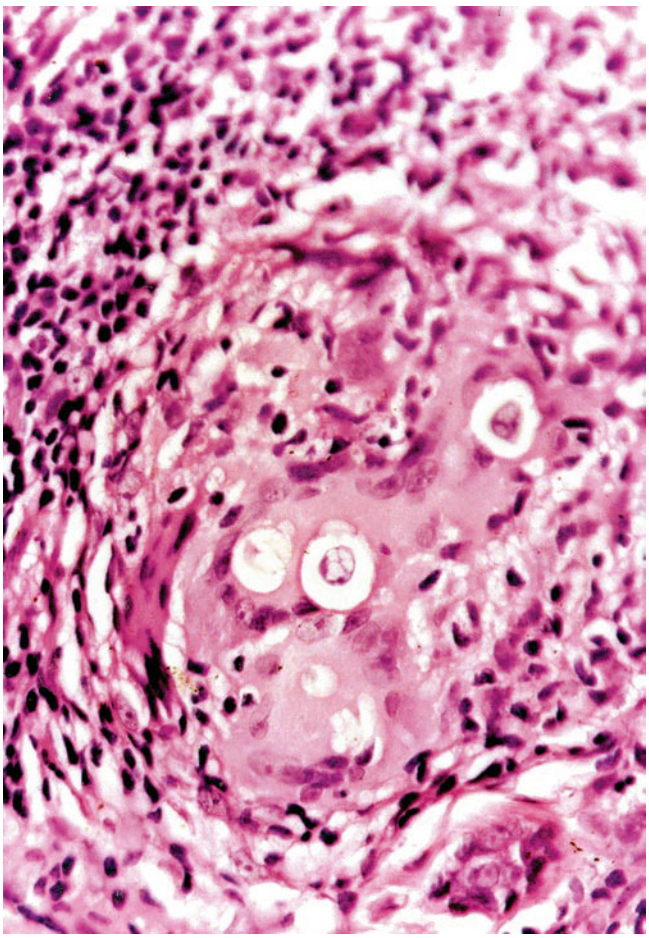


Fig. 3-18-3 Tuberculoid granulomas with numerous giant cells at the margins of ulceration. Vacuole-like structures and brown septate hyphae and brown spores in the giant cells (HE stain, ×400)

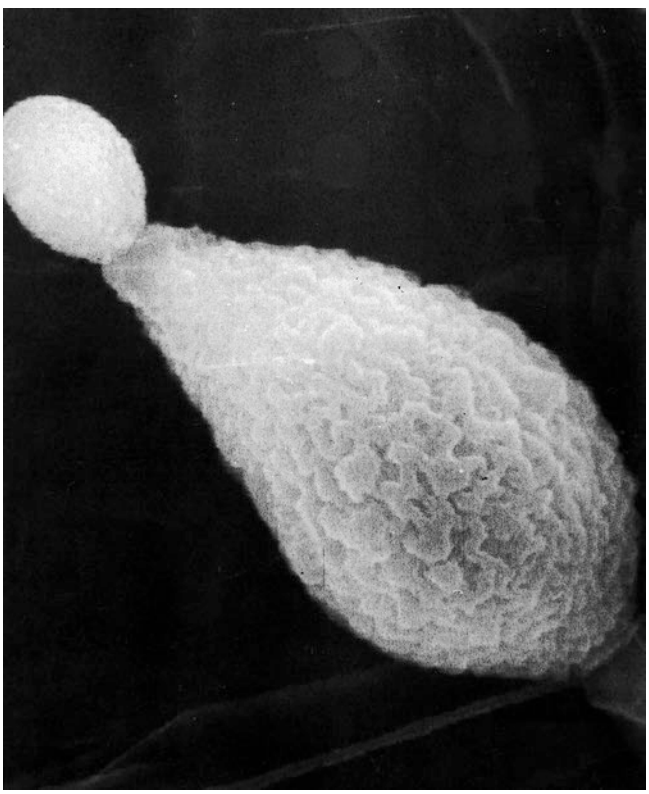


Fig. 3-18-4 Septate hyphae and spores by scanning electron microscopy (×3000)

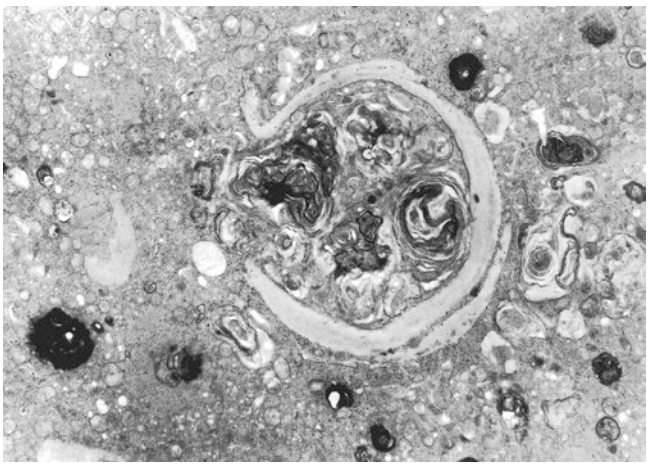


Fig. 3-18-5 Large round spores in the giant cells under transmission electron microscopy (×3000)

3.19 Skin Granuloma Due to Fusarium [20]

- *Fusarium* are opportunistic environmental microorganisms that occasionally result in invasive fusariosis in immunocompromised patients but rarely cause localized infections in immunocompetent individuals.
- The skin lesions can occur at any sites, especially with predominance in the extremities, and they are recognized as nodules, ulcers, mycetoma, and intertrigo.
- Histologically, the lesions consist of necrosis, panniculitis, or granuloma, in which hyaline acute-branching septate hyphae can be seen. The infectious agents invade the dermis and occasionally extend into the blood vessels with thrombosis.

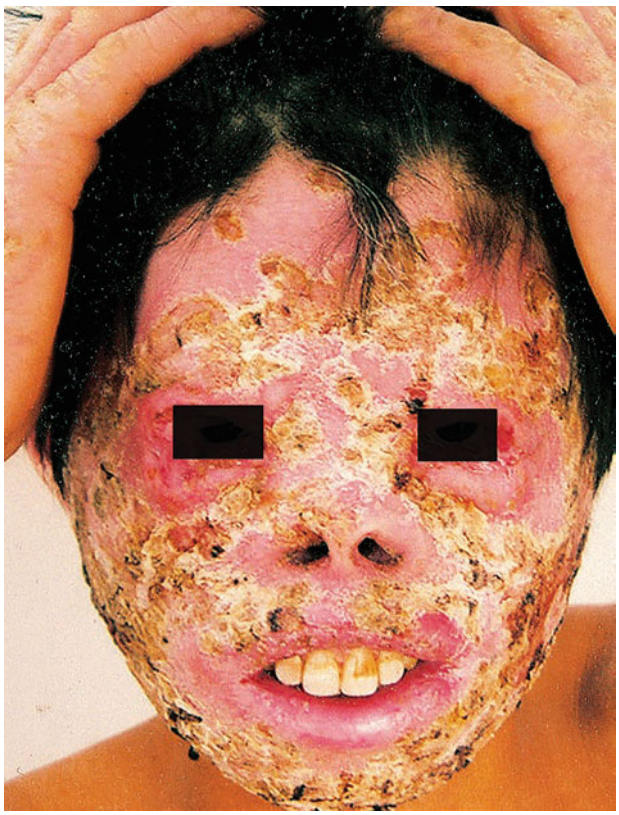
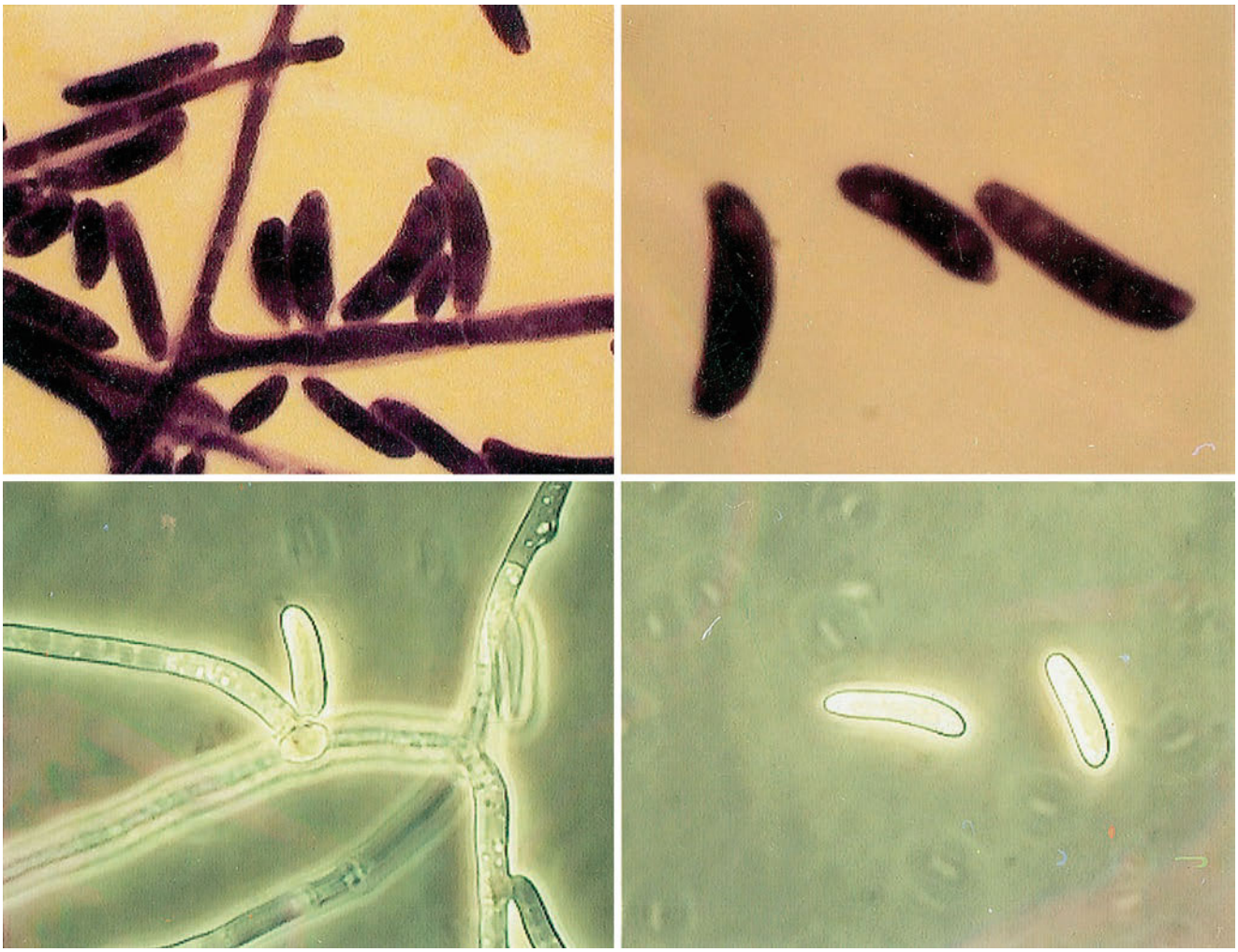


Fig. 3-19-1 A diffuse infiltrated plaque with ulcers, crusts, and scales on the face. Both eyelids, the wing of the nose, and auricle were destroyed or lost, and eyebrows were absent (Reproduced with the permission from [20])



Figs. 3-19-2, 3-19-3 The septate transparent hyphae with branching, oval microspores, and sicklelike macrospores were present (2. Gram stain, ×3680)

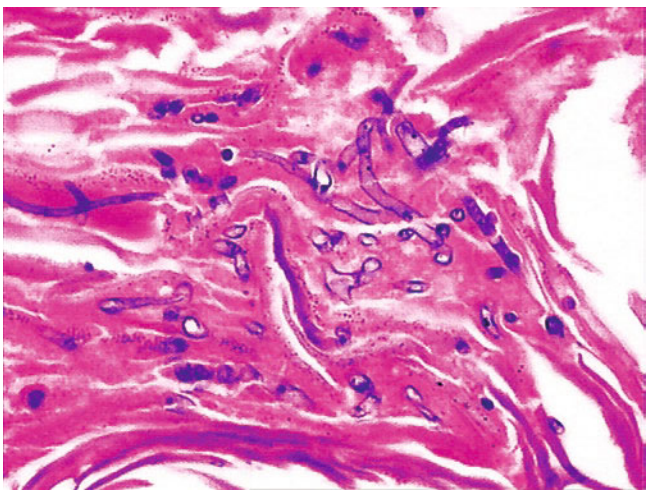


Fig. 3-19-4 Septate hyphae were present in the horny layer (HE stain, ×400)

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Sexually Transmitted Diseases

4

Chun-Li Zhou, Sheng-Yun Liu, Jian Yang, Yan-Fang Tong, Na-Sha Yu, Yan Lu, and Ru-Zhi Zhang

Abstract

The authors present the reader with several venereal diseases: multiple penile chancres, nodular secondary syphilis, syphilitic alopecia, and viral flat condyloma.

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4.1 Multiple Penile Chancres [1]

- Primary syphilis most often manifests as a solitary, painless chancre at the site of *Treponema pallidum* invasion.
- However, multiple lesions in the genital and/or extragenital regions frequently occur. One probable reason is the effect of oral sexual intercourse.
- Early recognition of the atypical manifestations of syphilis is important for the start of treatment, recovery of patients, and prevention of the spread of disease.
- Multiple lesions on the penis indicate the necessity to perform relevant serological tests to rule out the possibility of syphilis.

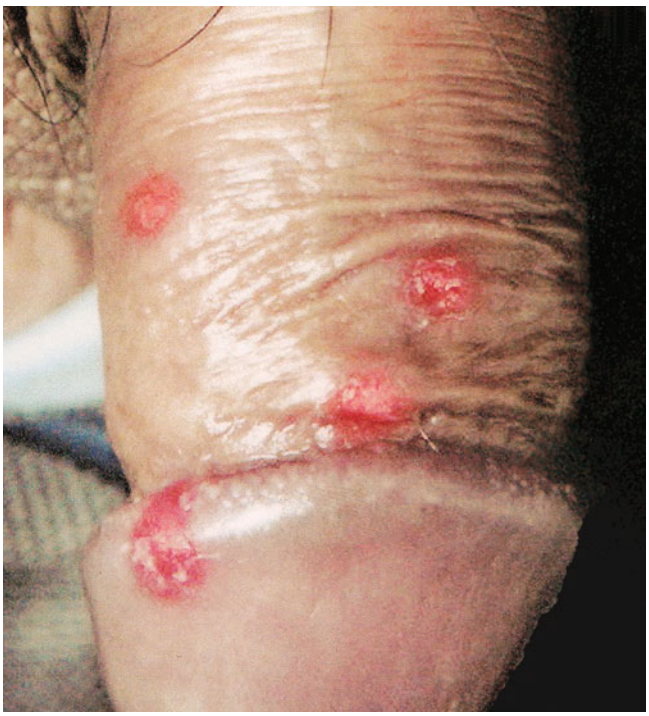

Fig. 4-1-1 Well-circumscribed round ulcers with a few oozing and scaling on the penis and glans

4.2 Nodular Secondary Syphilis [2]

- The clinical features of secondary syphilis are variable, including maculae, papules, maculopapules, and pustules, sometimes accompanied by fever and lymphadenopathy.
- Clinically, annular secondary syphilis presents as multiple violaceous papules and annular plaques with slightly raised scaly borders that may disseminate over the face, penis, legs, and feet. Nodular secondary syphilis is rare, and the lesions display painless red or purple nodule and plaques, occasionally with scales and effusions.
- Histopathological examination shows large numbers of plasma cells and lymphocytes infiltrating around the dermis. Additionally, the rapid plasma reagent test is positive in nodular/annular secondary syphilis.

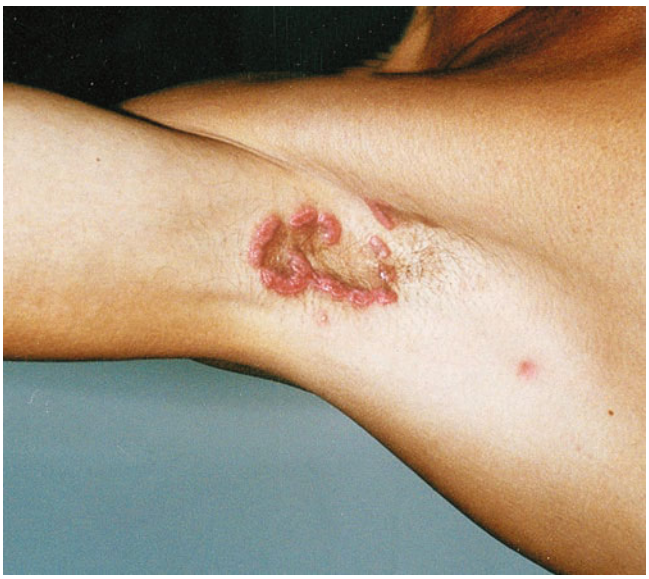

Fig. 4-2a-1 Annular and half-annular wine-colored papules in both axillae, like granuloma annulare

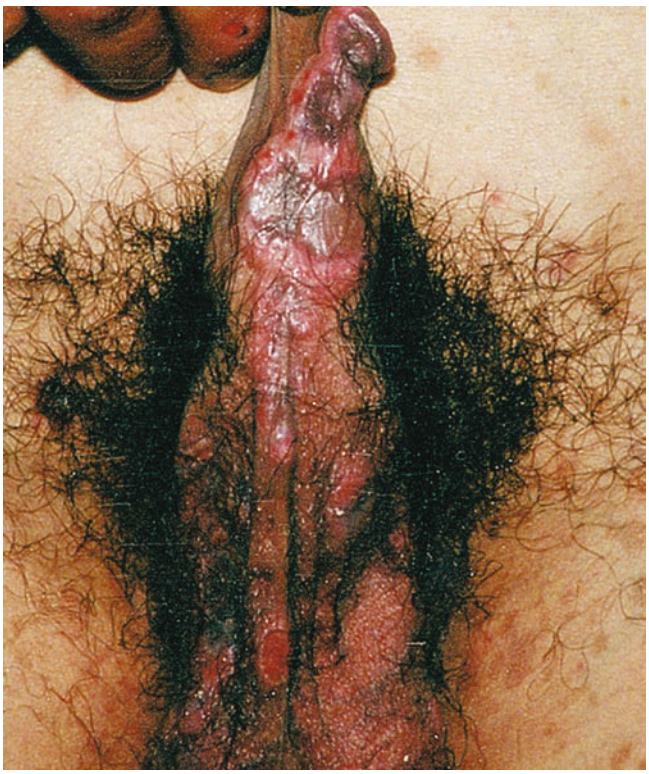

Fig. 4-2a-2 Annular erythematopapulous on the penis and scrotum, with white adhesive scale on the surface, like granuloma annulare

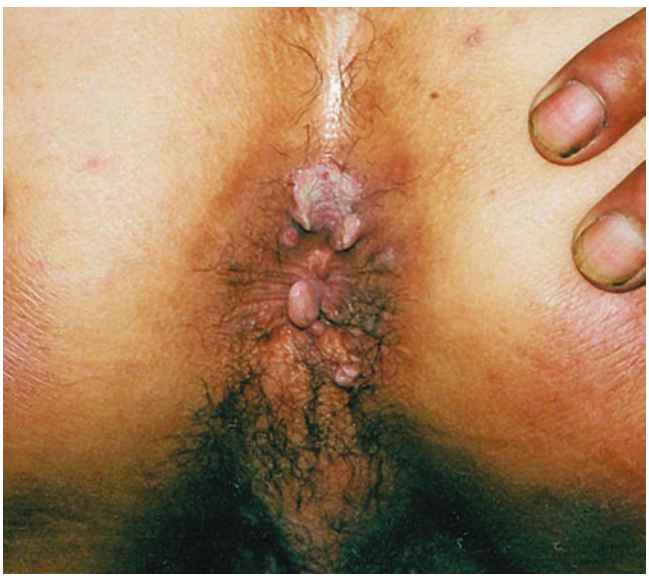

Fig. 4-2a-3 Condyloma latum on the perianal

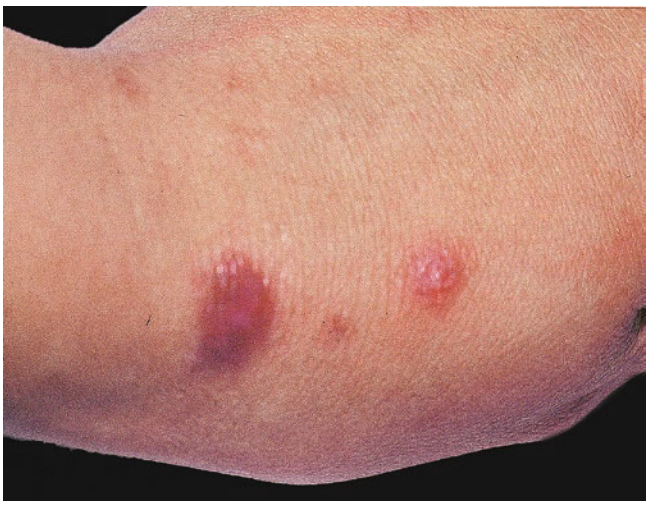

Fig. 4-2b-1 A red nodules 0.8–1.5 cm in diameter on the wrist

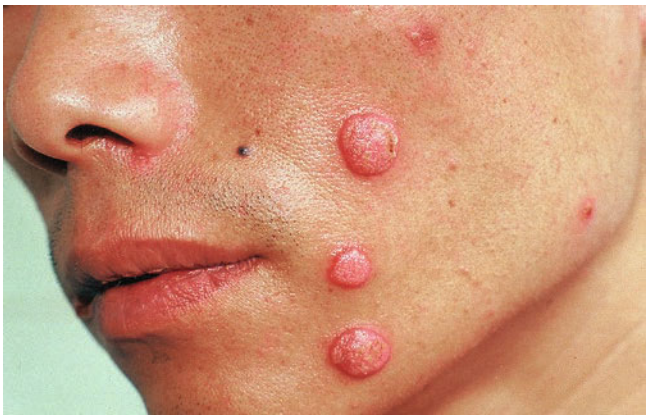

Fig. 4-2b-2 Erythematous nodules and plaques discrete over the face

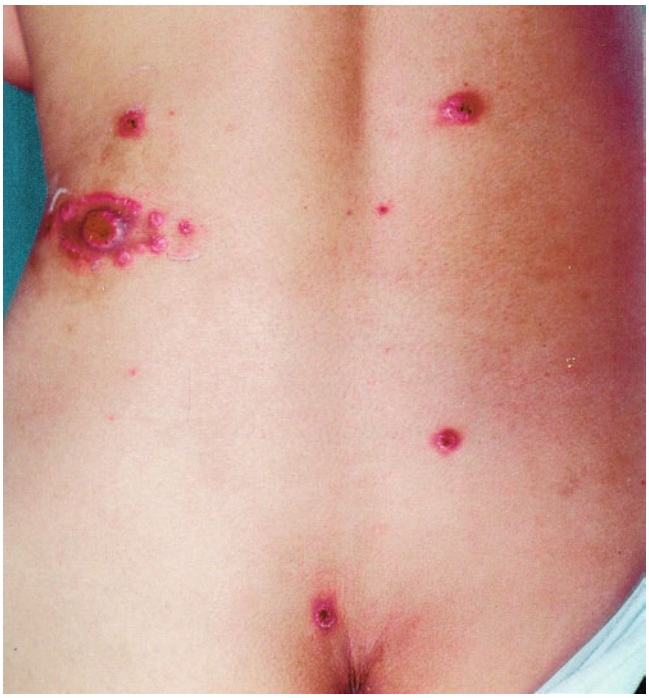

Fig. 4-2b-3 Infiltrative erythematous, plaques, and plaques discrete over the trunk

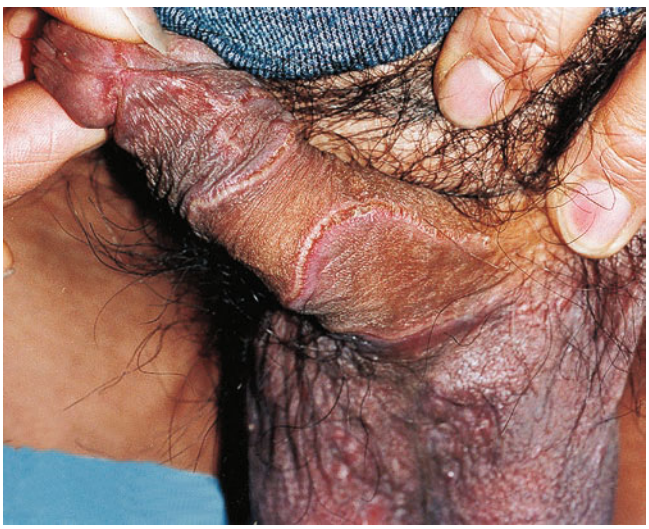

Fig. 4-2c-1 Multiple round, semicircular, and irregular annular erythema with few scales on the penis

4.3 Syphilitic Alopecia [3]

- Syphilitic alopecia (SA) occurs in 2.9–11.2% of patients with syphilis. The most common site of infection is the scalp, but other regions that are covered with hairs can also be affected.
- SA was divided into two types, symptomatic and essential SA, and formed three different clinical patterns: "moth-eaten," "diffuse," and mixed-pattern alopecia. Moth-eaten pattern alopecia considered the main and characteristic form.
- It is important for physicians to consider syphilis and perform the appropriate serological tests in patients who are at risk based on their sexual history and present with unexplained rapid hair loss.

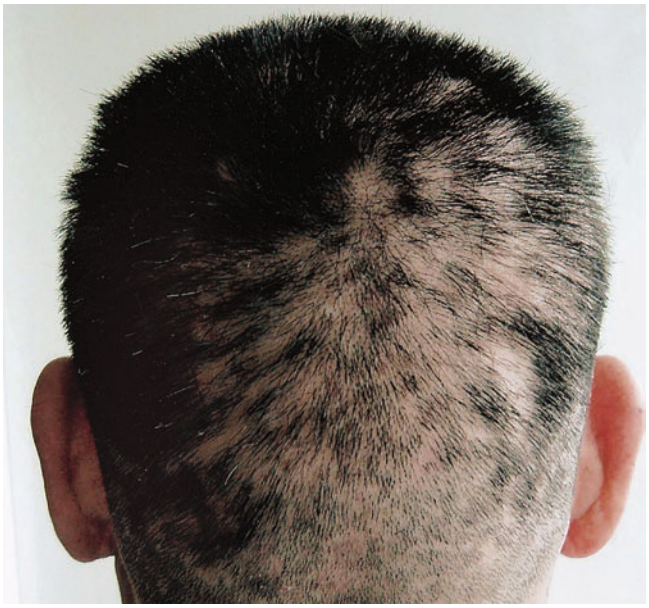

Fig. 4-3-1 Worm-biting-like or diffused small patches, with hyperemia and redness surrounding the follicular orifice in the lesions

4.4 Viral Flat Condyloma [4]

- The most common clinical signs of HPV genital tract infections are a characteristic "cauliflower" appearance and papular warts, but flat condylomata acuminatum (CA) is also a frequent manifestation, and a prevalence is observed in the cervix and most areas that exhibit exophytic warts.
- The flat warts are not visible to the naked eye, but 3% acetic acid will highlight them in contrast to the surrounding normal skin or mucosa.
- Flat CA frequently clusters in multiple lesions, which are often confluent. The distinction between flat warts and latent HPV infection is somewhat semantic.
- Flat CA should be distinguished from Bowenoid papulosis, lichen planus, verruca plana, seborrheic keratosis, and condylomata lata of secondary syphilis.

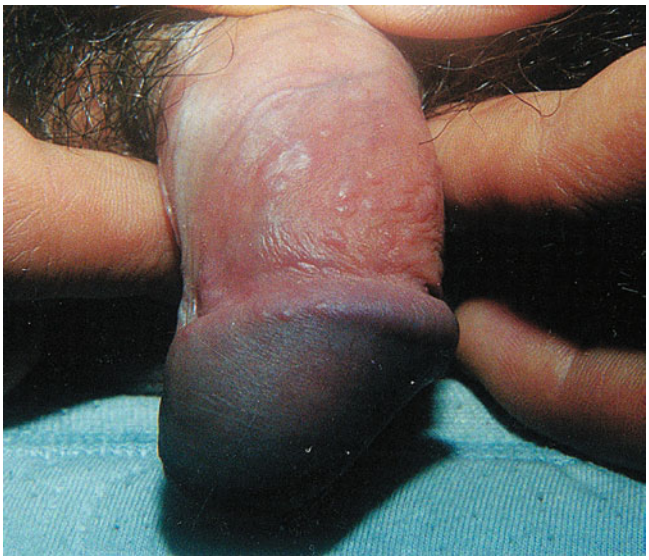

Fig. 4-4-1 Flesh-colored flat maculopapules on the inferior of his prepuce

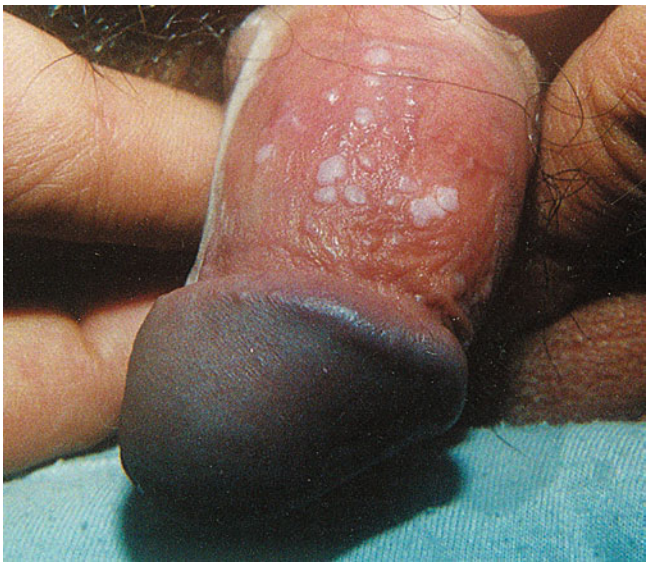

Fig. 4-4-2 Positive aceto-white staining

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Mycobacterial Infections

5

Wei Jiang, Xiao-Ping Tao, Li-Hua Qi, Jian-Zhong Zhang, Fa-Long Cao, Wen-Yuan Zhu, Ming-Yu Xia, and Ru-Zhi Zhang

Abstract

Skin mycobacterial infection is still a big issue for the clinicians even today. This chapter comprises borderline tuberculoid leprosy, hypertrophic lupus vulgaris, tuberculosis verrucosa cutis, swimming pool granuloma, cutaneous anthrax, pitted keratolysis, and trichomycosis axillaris.

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5.1 Borderline Tuberculoid Leprosy [1]

- Leprosy is a chronic disease that is mainly caused by *Mycobacterium leprae*, which affects the peripheral nervous system, skin, and other tissues.
- Borderline tuberculoid leprosy (BTL) is unstable. This form may continue, return to tuberculoid leprosy (TL), or advance to other forms. Lesions in BT leprosy are similar to tuberculoid leprosy but smaller and more numerous and present less nerve enlargement.
- Histologically, this condition can be distinguished from the tuberculoid and borderline forms due to the presence of a free subepidermal grenz zone and granulomas formed by Langhans multinucleated giant cells and foci of epithelioid cells beset by lymphocytic halos.
- Strongly infiltrated but discernible nerve fibers can be observed, with no or scarce bacilli, usually ranging from + to ++.

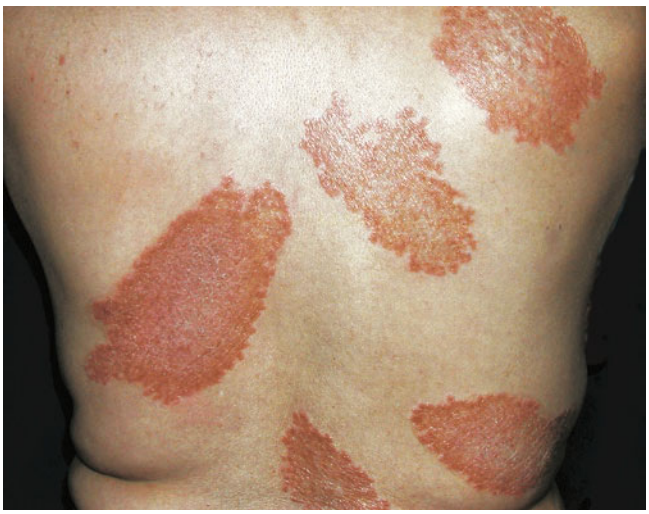

Fig. 5-1-1 Well-circumscribed, scaly, slight brown plaques with central atrophy on the back

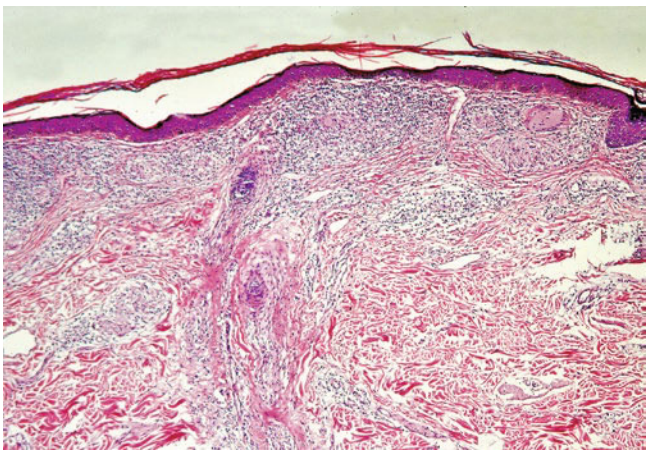

Fig. 5-1-2 Atrophied epidermis, flat rete ridges, and tuberculoid granuloma in the upper and middle dermis (HE stain, ×100)

5.2 Hypertrophic Lupus Vulgaris [2]

- Lupus vulgaris (LV) is a paucibacillary and advanced form of cutaneous tuberculosis (TB).
- Depending on previous contact and the patient's immune status, LV takes different clinical forms, including a plaque form, ulcerative and mutilating forms, vegetating forms, hypertrophic (tumor-like) forms, and papular and nodular forms.
- The hypertrophic variant presents either as soft tumorous growths exhibiting a nodular knobby surface or showing epithelial hyperplasia with the production of hyperkeratotic masses. This condition makes diagnosis difficult and is often refractory to antituberculous therapy.
- The histopathology is characterized by the formation of tuberculoid granulomas composed of epithelioid cells and giant cells, usually the Langhans type, with absent or slight caseation necrosis.

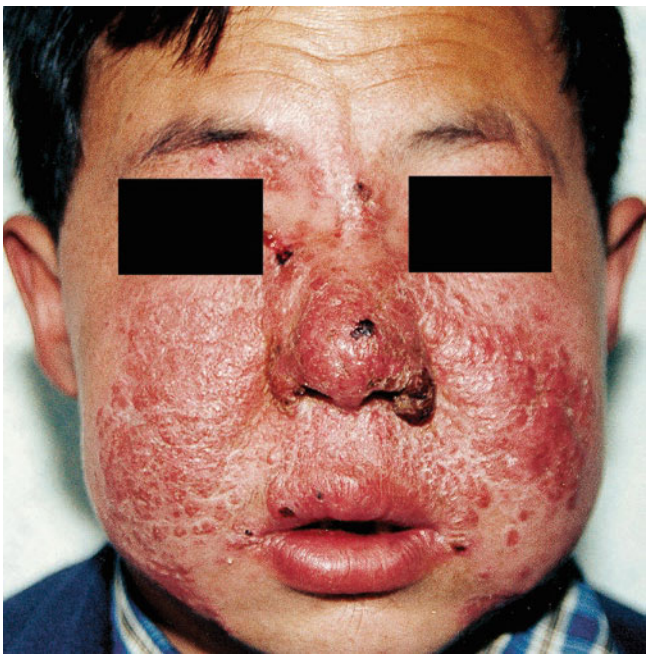

Fig. 5-2-1 Brown reddish plaques and nodules on the face and nose (Reproduced with the permission from [2])

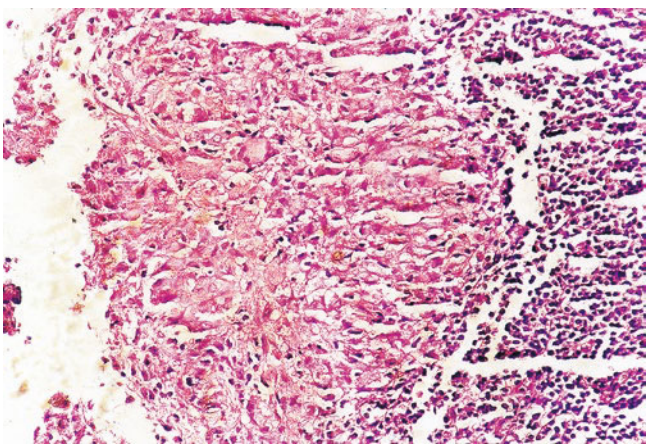

Fig. 5-2-2 Tuberculoid structures consisting of epithelioid cells, giant cells, and lymphocytes in the reticular dermis (HE stain, ×200)

5.3 Tuberculosis Verrucosa Cutis [3]

- Tuberculosis verrucosa cutis (TVC) is caused by direct inoculation of the bacilli into the skin of previously infected patients with intact immunity. It sometimes occurs on the hands and lower extremities.
- The lesions are typically asymptomatic and start as a small papule or papulopustule that progresses to warty or hyperkeratotic plaques, the center of which may involute to leave behind a white atrophic scar.
- The histopathological features are a dense inflammatory cell infiltrate containing neutrophils, lymphocytes, and giant cells and marked pseudoepitheliomatous hyperplasia of the epidermis with hyperkeratosis.
- The diagnosis mainly depends on clinical appearance and tuberculin tests, as well as microscopic and histopathological features.

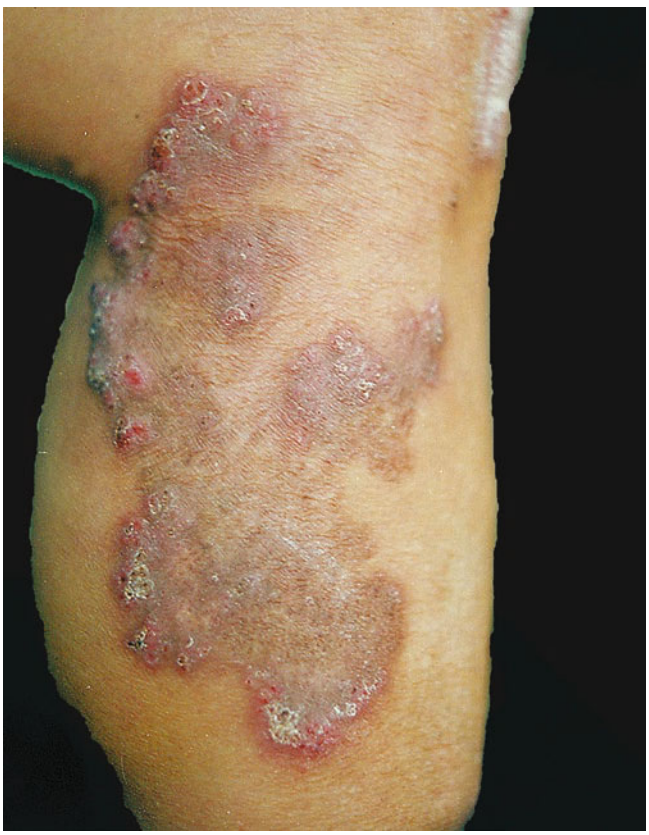

Fig. 5-3-1 A large verrucous plaque with an inflammatory border and atrophy at the center on the left leg

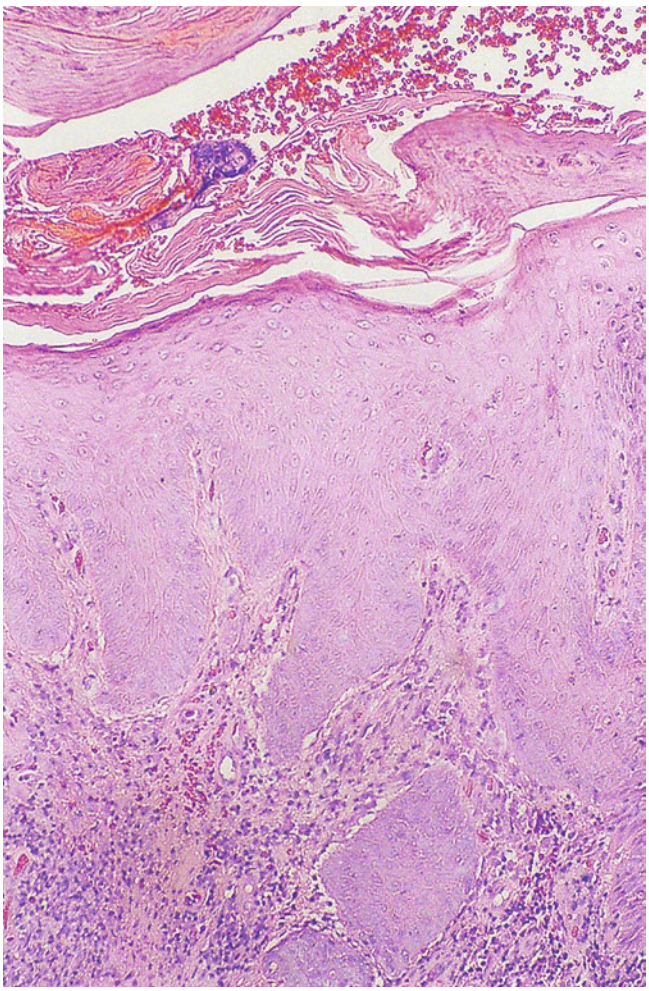

Fig. 5-3-2 Tuberculoid granulomas in the dermis (HE stain, ×40)

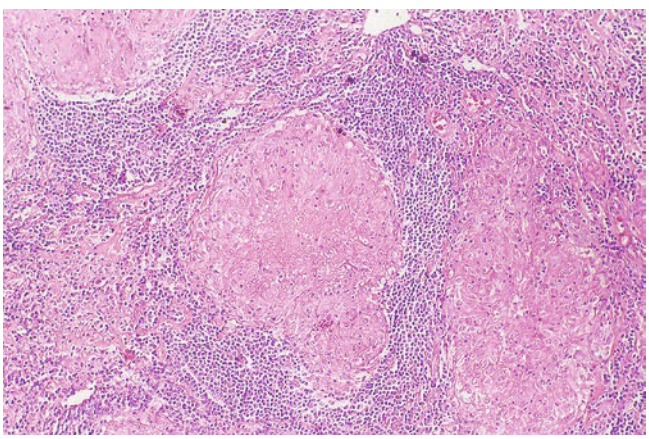

Fig. 5-3-3 Hyperkeratosis and acanthosis associated with tuberculoid granuloma beneath the epidermis (HE stain, × 100)

5.4 Swimming Pool Granuloma [4]

- Swimming pool granuloma or fish tank granuloma results from *Mycobacterium marinum*, which is usually limited to the skin, but occasionally disseminates to submucosal tissue, bone, bursa, or joint in people with immunodeficiency.
- The lesions usually begin with nodules or plaques in areas of minor injuries, with subjective symptoms varying from asymptomatic to painful. After 2–3 weeks, these lesions can evolve into an ulcer with a purulent discharge. Sometimes, the lesions exhibit a sporotrichoid distribution along the lymphatic pathway.
- The treatment includes antibiotics such as minocycline, trimethoprim sulfamethoxazole, rifampicin, and clarithromycin.

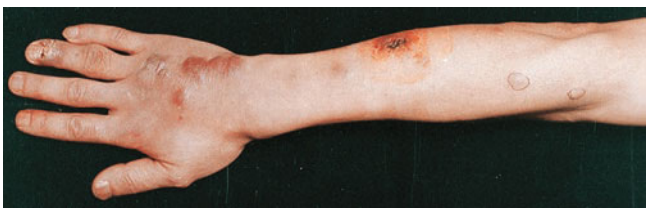

Fig. 5-4-1 The soybean-sized and horsebean dusky red plagues and nodules on the right fingers, back of the hands, the wrist, the forearm, and the upper arm, in linear arrangement

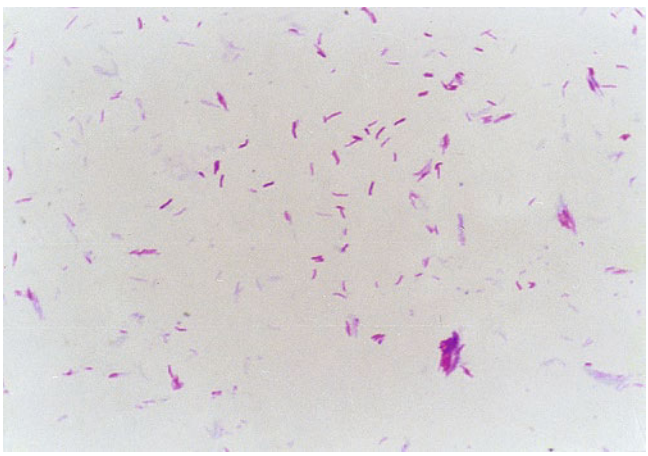

Fig. 5-4-2 Identification of *Mycobacterium marinum* in tissue culture (Ziehl-Neelsen stain, ×1000)

Fig. 5-4-3 *Mycobacterium marinum* colony produces yellow color under sunlight, before sunlight (left), and after sunlight (right)

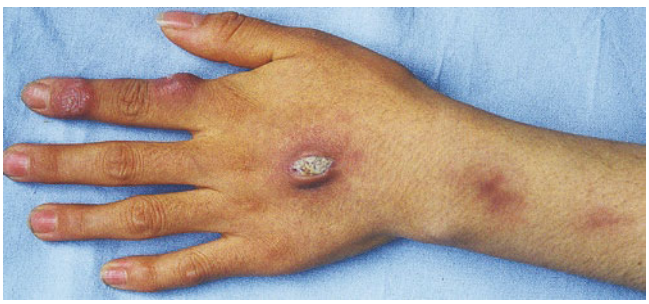

Fig. 5-4-4 Three reddish nodules on the forefinger and back of the hands, two reddish infiltrative plaques on the back of the wrist

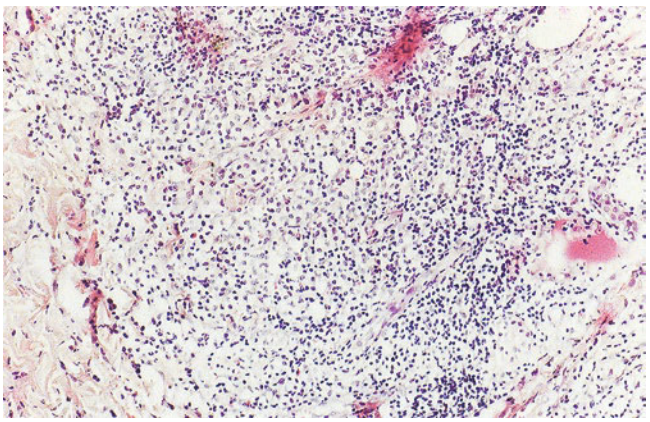

Fig. 5-4-5 Multiple histiocytes and lymphocytes infiltrated in the dermis with sporadic eosinophil and granuloma information (HE stain, ×200)

5.5 Cutaneous Anthrax [5]

- Cutaneous anthrax (CA) is caused by spores of *Bacillus anthracis*, which enter the skin, usually through skin lacerations, abrasions, or biting flies during the slaughtering or processing of animal products.
- The symptoms usually present as a pruritic painless papule, which subsequently broadens and becomes an ulcerated lesion encircled by vesicles and covered by a typical black eschar.
- The diagnosis of CV is mainly based on a detailed history, dermatologic findings, microbiological procedures including Gram staining, and culture of materials acquired from the lesions. CV is sensitive to intravenous penicillin G treatment for 7–14 days.

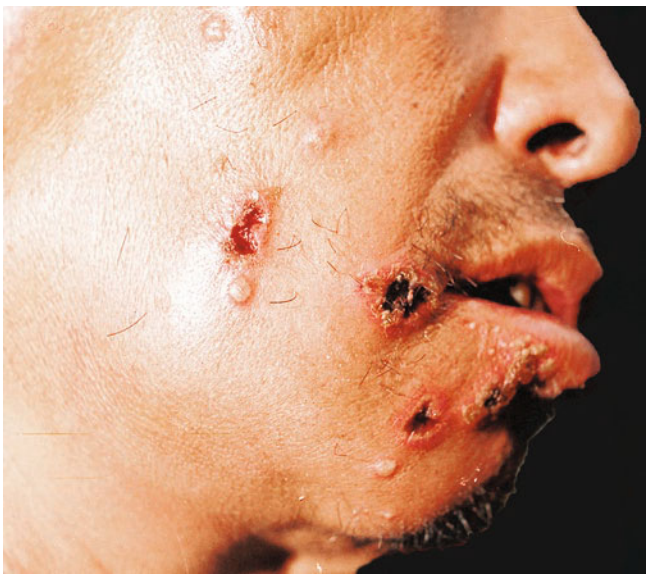

Fig. 5-5-1 Four ulcers covered with dark crusts surrounded by vesicles and pustules on the right cheek

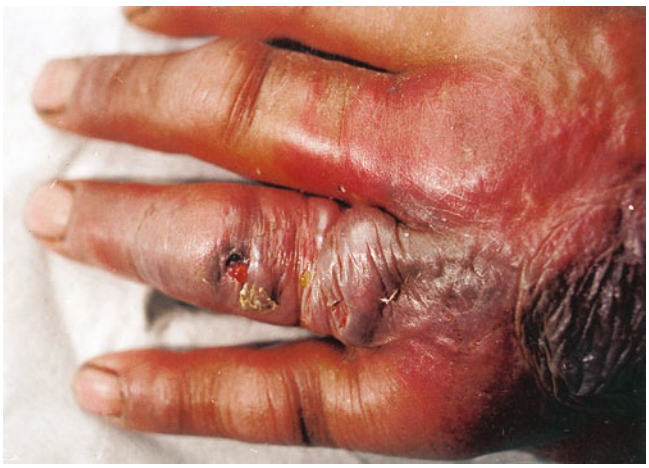

Fig. 5-5-2 Intense diffuse swelling and violet red patches on the dorsum of left hand, and there are ulcers in the center of patches

Fig. 5-5-3 *Bacillus anthracis* are large rod-shaped, gram-positive organisms (Gram stain, ×400)

5.6 Pitted Keratolysis [6]

- Pitted keratolysis (PK), also called keratolysis plantare sulcatum, features asymptomatic discrete pits that are round and 1–3 mm in diameter on the plantar pressure regions of the foot, but seldom on the palm. Some of pits become syncretic.
- *Kytococcus sedentarius* has been considered as the pathogen, which produces two proteases that destroy keratin detachment. Hyperhidrosis may be a predisposing factor. Topical application of erythromycin or clindamycin ointment is a satisfactory therapy.

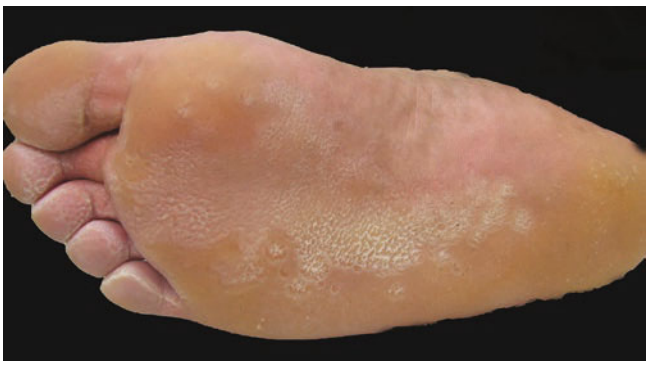

Fig. 5-6-1 Many discrete round pits in the size of 1–4 mm in diameter were on the planter

5.7 Trichomycosis Axillaris [7]

- Trichomycosis axillaris (TA) is caused by *Corynebacterium tenuis*, characterized by nodular concretions along the hair shafts, commonly affecting the axillae and sometimes the pubic region. Common predisposing factors include a moist or warm environment, excessive sweating, and poor local hygiene.
- Wood's light examination presents flavescent fluorescence. Physical measures to clear the infection and topical application of erythromycin or clindamycin are generally helpful to control the infection.

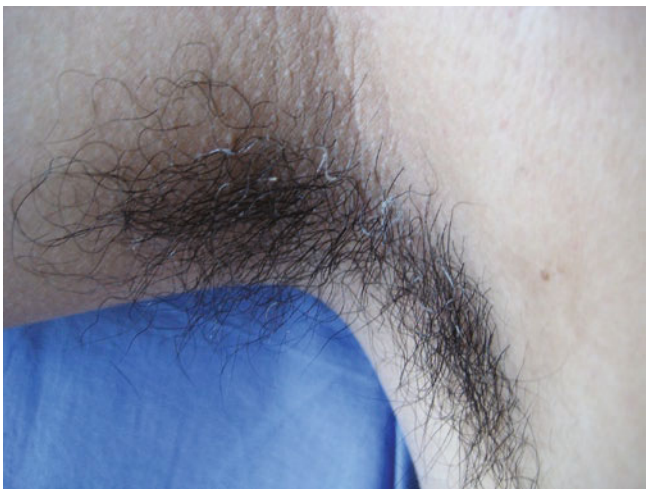

Fig. 5-7-1 The affected axillary's hair is surrounded by many nodular or tubular concretions in various sizes and irregular shape

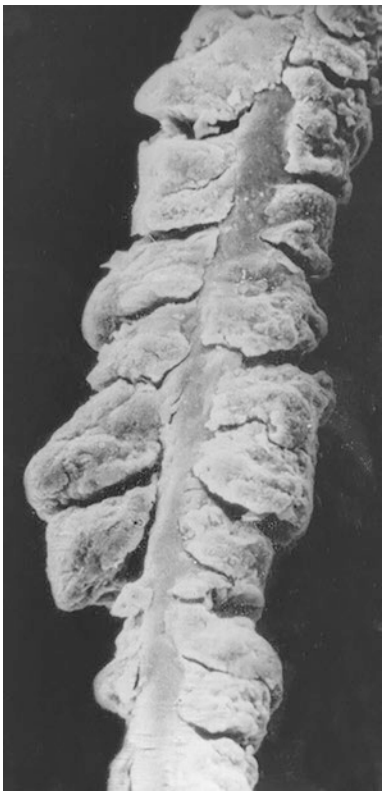

Fig. 5-7-2 The affected axillary's hair is surrounded by many nodular or tubular concretions in various sizes and irregular shape under SEM

Fig. 5-7-3 On the surface of the concretions in their pits, there are lots of *Corynebacterium tenuis* under SEM

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Parasitic Infestations, Stings, and Bites

6

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Abstract

This chapter deals with a heterogeneous group of skin disorders caused by parasitic infection, sting, and bites and consists of cutaneous leishmaniasis, cutaneous paragonimiasis, cutaneous larva migrans, cerebral and subcutaneous cysticercosis, cutaneous myiasis caused by larvae of *Hypoderma bovis*, phthiriasis palpebrarum, tick bite, Norwegian scabies, infant *Pyemotes dermatitis*, and jellyfish dermatitis.

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6.1 Cutaneous Leishmaniasis [1]

- Cutaneous leishmaniasis (CL) is a tropical disease caused by *Leishmania*, spread by the bite of infected female sandflies, and characterized by an ulcerated lesion.
- Depending on the condition of the host's immunity and the species of parasite, CL presents very different clinical manifestations. The first sign of CL is a small erythema, which then changes into a papule and nodule, subsequently developing an ulceration in 2 weeks to 6 months, after which the lesions heal spontaneously.
- The diagnosis of CL is usually based on specific clinical features and parasitological investigations.
- The standard treatment of cutaneous leishmaniasis is based on pentavalent antimonials, mainly sodium stibogluconate and meglumine antimoniate.

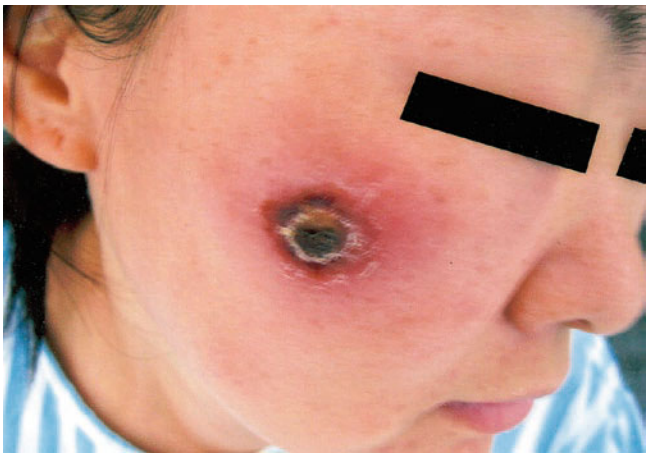


Fig. 6-1-1 A round ulcer with crust around rufous skin on the left cheek

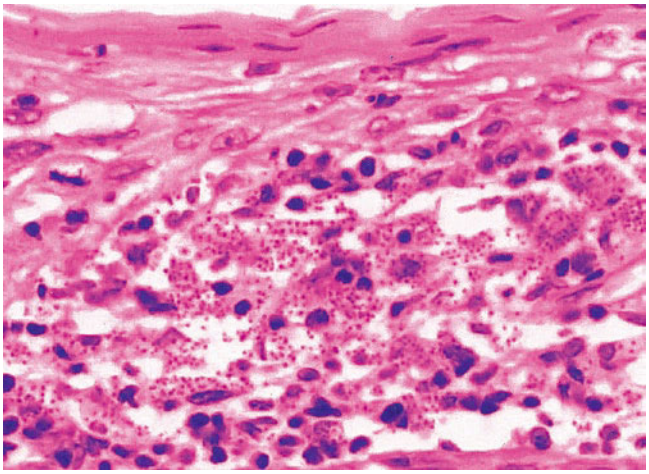


Fig. 6-1-2 Granule-like bodies in the dermis papillaries (HE stain, ×400)

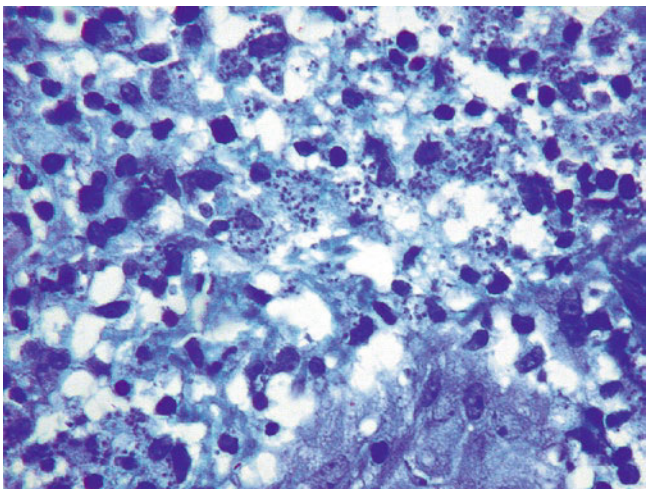


Fig. 6-1-3 A red round nucleus and a smaller rod-like paranucleus in the parasites (Giemsa stain, ×400)

6.2 Cutaneous Paragonimiasis [2]

- Clinically, paragonimiasis caused by *Paragonimus* is broadly classified into pulmonary, pleuropulmonary, and extrapulmonary forms.
- Cutaneous paragonimiasis (CP) is considered one of the representative types of ectopic infection, especially in its earlier stage, and it usually presents as a slowly migrating and painless subcutaneous nodular induration that is often located on the abdominal wall, with deep larva migrans hypodermatitis or subcutaneous swelling.
- The diagnosis is based on a history of consumption of crabs, a positive specific serological test, and blood eosinophilia.
- Cures have been accomplished by the administration of praziquantel. An alternative drug is triclabendazole, which is as effective as praziquantel and better tolerated.

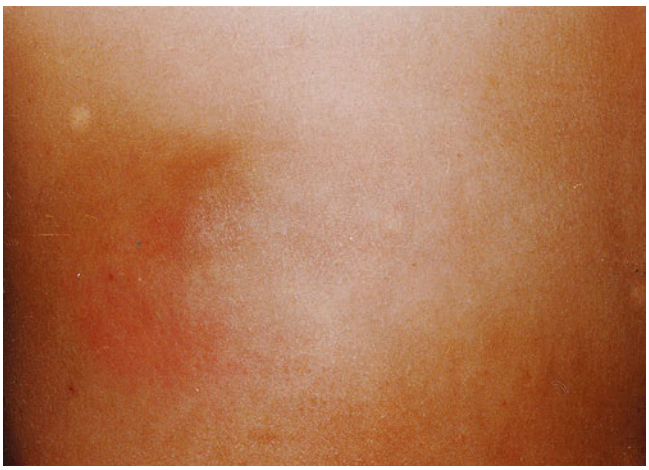
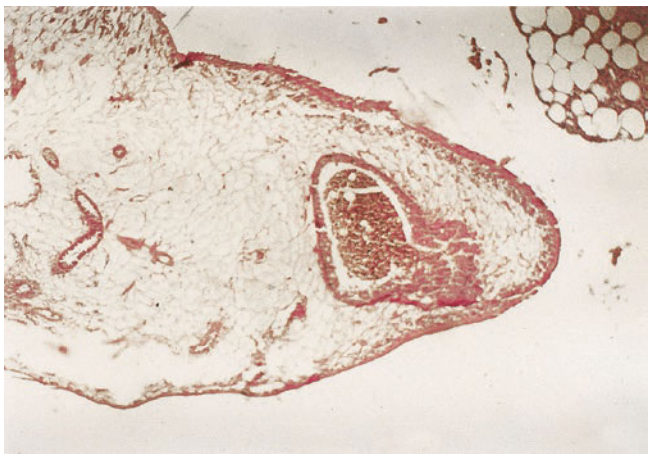
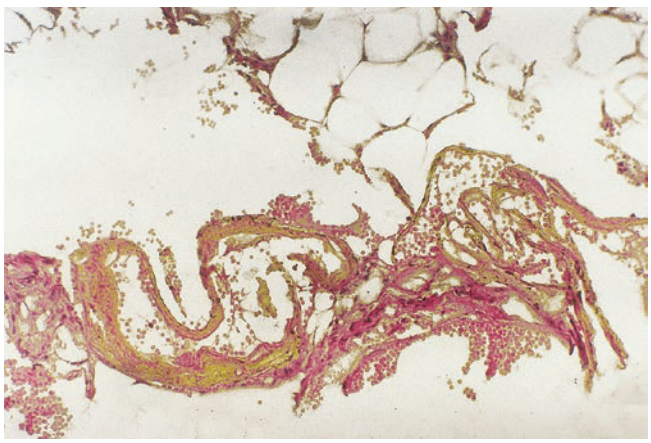


Fig. 6-2-1 A subcutaneous mass in size of 3 cm × 6 cm in diameter on the abdomen





Figs. 6-2-2, 6-2-3 Digestine tuke (2) and tail (3) of distoma in subcutis (HE stain, (2) × 40 (3) × 40)

6.3 Cutaneous Larva Migrans [3]

- Cutaneous larva migrans (CLM) is a serpiginous, erythematous infection that is usually caused by percutaneous penetration of the larvae into the skin and is often seen in the lower extremities, especially in the dorsal and plantar surface of the foot through contact with feces of infected animals.
- The lesion is characterized by a skin-colored tortuous, linear thread-like, papular or vesicular advancing and slightly raised track, which moves at a rate of approximately 2 mm–3 cm/day with variable pruritus intensity and symptom duration.
- The natural history of CLM is spontaneous resolution without treatment within a few weeks. Treatment is often necessary due to potential complications such as a superimposed bacterial infection and intense pruritus. Albendazole 400 mg/day or ivermectin 200 mg/kg single for 3 days is recommended.

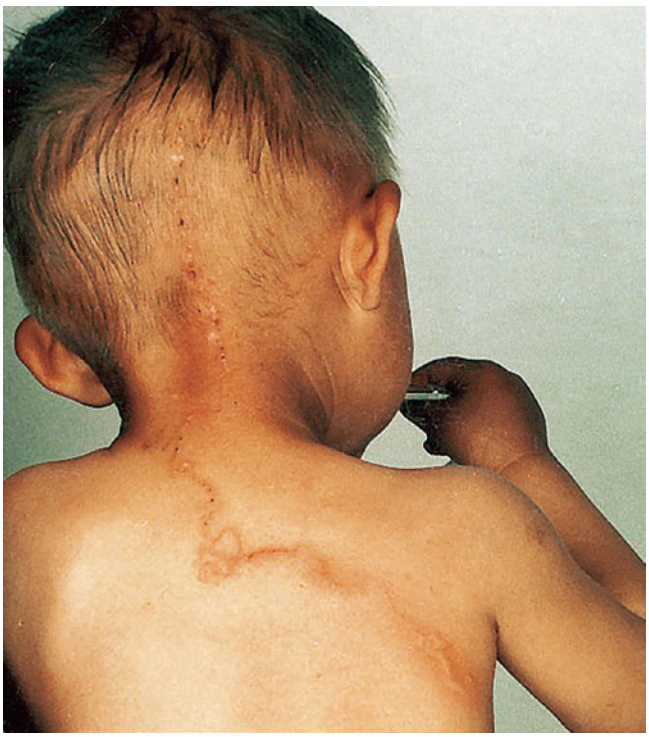


Fig. 6-3-1 Curve lesions on the occiput, neck, and back

6.4 Cerebral and Subcutaneous Cysticercosis [4]

- Cysticercosis is an infection caused by the larvae of *Taenia solium,* which infect humans via accidental ingestion of the parasite's eggs.
- Cysticercosis is one of the most usual parasitosis in the central nervous system, subcutaneous, and muscle tissue. Subcutaneous nodules are usually seen in approximately 54% of patients.
- Histopathology reveals a thick, fibrous capsule covered by some layers of epithelioid cells mixed with several Langhans giant cells but without caseous necrosis and encircling a cystic cavity containing clear fluid and a patchy, white membranous structure shaped like a cysticercus larva.
- Albendazole and praziquantel are both effective. Albendazole is more effective and less expensive than other drugs for the treatment of neurocysticercosis.

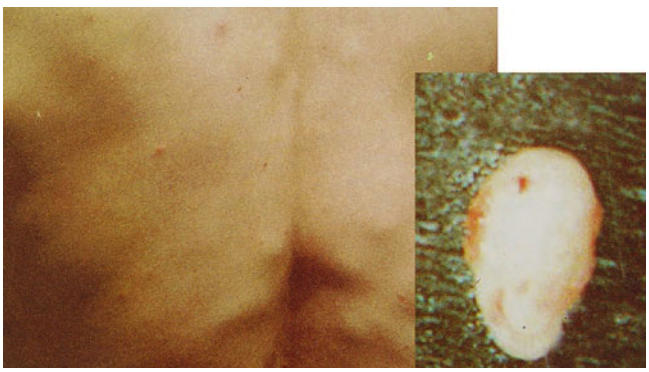


Fig. 6-4-1 Numerous subcutaneous nodules on the back

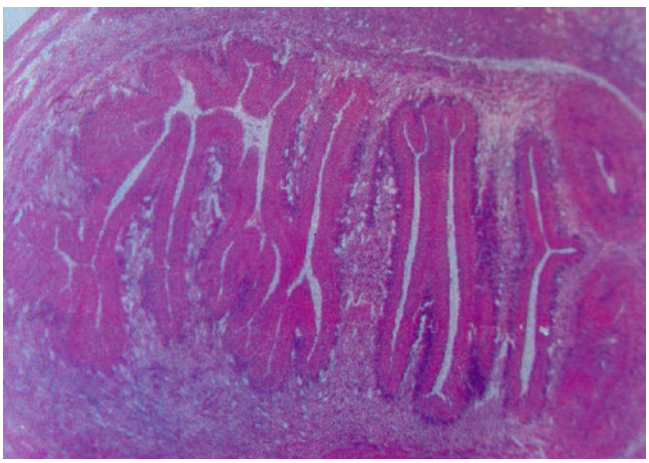


Fig. 6-4-2 A parasite in the cystic wall under the subcutaneous (HE stain, ×40)

Fig. 6-4-3 Computed tomography of the brain showed an enhancing lesion in the cerebral, dilated lateral ventricle of cerebrum

6.5 Cutaneous Myiasis Caused by the Larvae of *Hypoderma bovis* [5]

- Cutaneous involvement is the most usual type of myiasis caused by dipterous fly larvae. Depending on the type of infesting larvae, cutaneous presentations involve furuncular, wound myiasis, and migratory forms.
- The larva of *Hypoderma bovis* forms a less distinct, erythematous, linear lesion when it burrows subcutaneously, but it pierces a hole through the skin surface when terminating its migration for pupation in the soil. Therefore, myiasis caused by *Hypoderma* is also considered a furuncular myiasis.
- Treatment is based on full extraction of the larva by covering the opening of the lesion with an oily ointment and suffocating it, facilitating extraction.

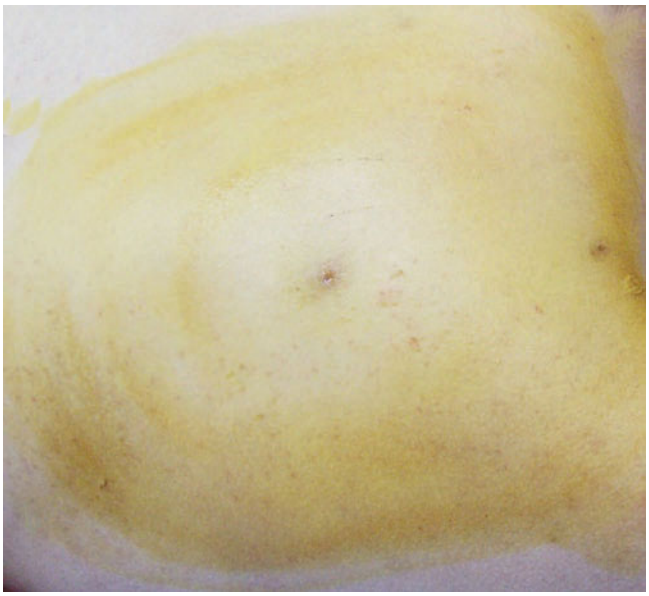


Fig. 6-5-1 Three furuncle-like lesions and pigmentation on the shoulder and back (site C is the most recent lesion with no larva)

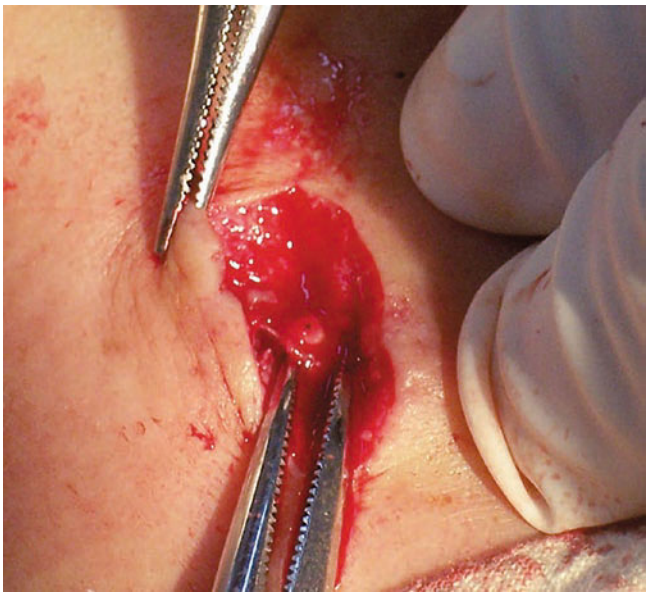


Fig. 6-5-2 A larva surrounded by tissue (held by vessel forceps with black spot on the top could been seen)

Fig. 6-5-3 A cylindrical and milky body with pointed front-end and blunt back end. The size of larvae ranges from 12 mm × 5 mm to 7 mm × 2 mm

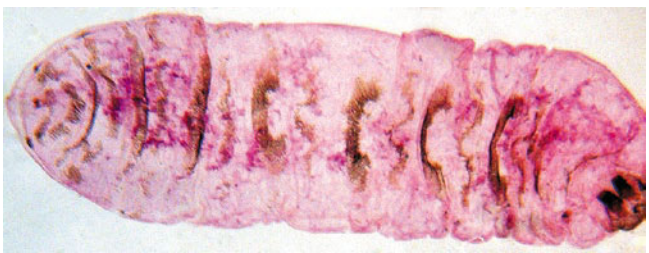


Fig. 6-5-4 Third instar larvae under microscope: the segmented cylindrical body (the left side is scolex and the right side is abdomen) (×10)

6.6 Phthiriasis Palpebrarum [6]

- Phthiriasis palpebrarum is an infection of the eyelashes by the crab (pubic) louse, *Pthirus pubis*, and its ova. Direct contact is required for transmission.
- The eyelashes are the usual site of crab louse infestation in children because of specific temperature and moisture requirements, as well as the lack of terminal hairs on most body regions before puberty.
- This infestation can lead to pruritic lid margins or itchy eye, gritty sensation, blepharitis, follicular conjunctivitis, and marginal keratitis.
- The most effective physical method is the manual removal of adults and nits with forceps.

Fig. 6-6-1 Alive public lice and gray white scabs at the roots of the eyelash on the left upper eyelid, mimicking the appearance of the scales in blepharitis

Fig. 6-6-2 The egg is attached to the side of the hair (× 50)

6.7 Tick Bite [7]

- Ticks are small, bloodsucking arachnids. After biting, the tick can remain attached to the skin for up to 10 days.
- Tick bites are usually harmless but occasionally can cause allergic reactions. Ticks may transmit disease to humans and lead to a variety of symptoms, which generally develop within several days to a few weeks after a tick bite.
- It is most important to remove the tick with a tick removal device or with a set of tweezers and not leave any of the tick's head or mouth parts in the bite.
- The best way to avoid a tick-borne disorder is to prevent tick bites.

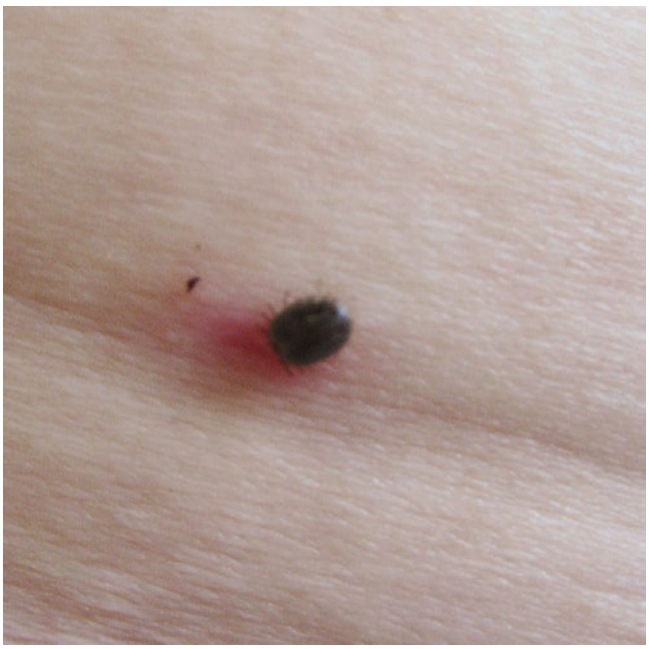


Fig. 6-7-1 An attached tick occurred on the abdomen

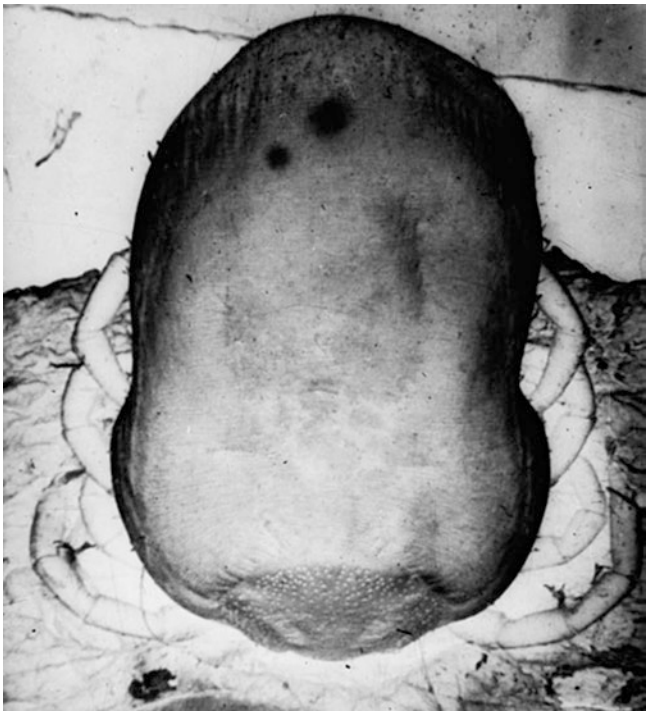


Fig. 6-7-2 The attached ticks had four pairs of segmented legs and a scutum with many punctations that were observed by SME

6.8 Norwegian Scabies [8]

- Crusted (Norwegian) scabies is an uncommon and extremely debilitating type of *Sarcoptes scabiei* var. *hominis* infestation that generally occurs in patients with sensory anesthesia, mental impairment, physical incapacity, and immunosuppression.
- The patients present with scaly, hyperkeratotic, gray to erythematous plaques in and on which are observed a large number of mites. Therefore, it is highly infectious.
- The importance of lesion scraping is highlighted to obtain a correct and early diagnosis.
- The therapy for mild cases is the same as for simplex scabies infections. However, oral or intravenous ivermectin should be given for some cases.

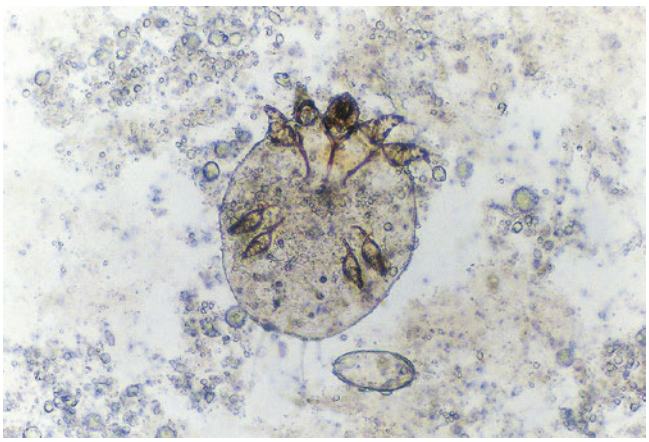
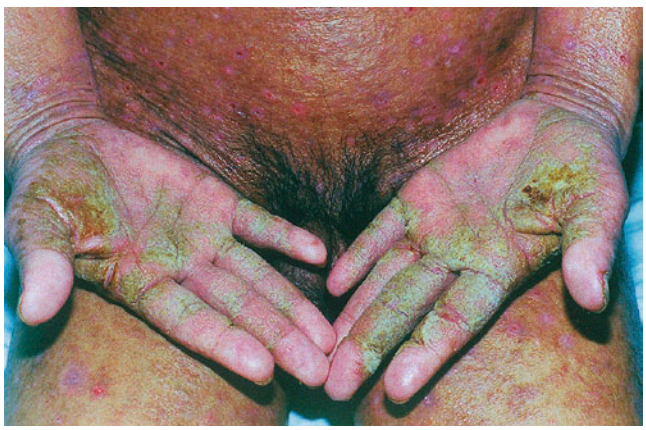
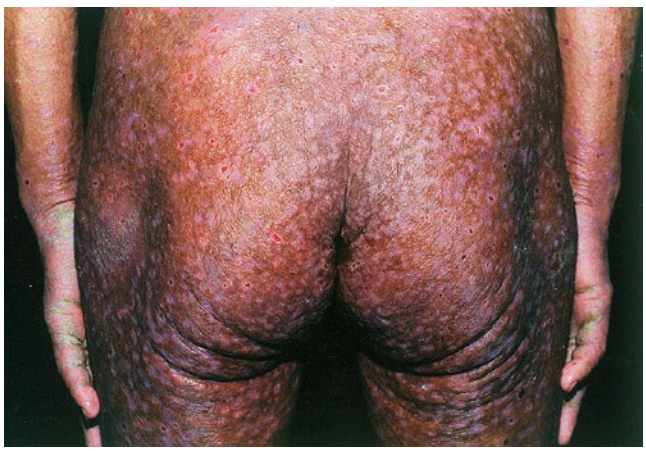


Fig. 6-8-3 Large numbers of *Sarcoptes scabiei* mites in skin scrapings examined by microscope





Figs. 6-8-1, 6-8-2 Numerous wine papules, papulovesicles, and pustules on the trunk and four limbs, diffuse generalized hyperkeratotic and scale lesions of both palms

6.9 Infant Pyemotes Dermatitis [9]

- *Pyemotes* mites have been responsible for attacks of dermatitis in those shoveling grain or coming into contact with infested straw and husk rice.
- The dermatitis has been referred to by a number of terms, including "grain itch," "straw itch," "barley itch," "prairie itch," and "hay itch," among others.
- The lesions are urticated papules encircled by vesicles and occasionally can be bullous. There are usually many lesions, with a distribution based on the mode of exposure.
- In grain handlers, the lesions are usually on the forearms and neck, but they may be profuse around the waist and in the groin.

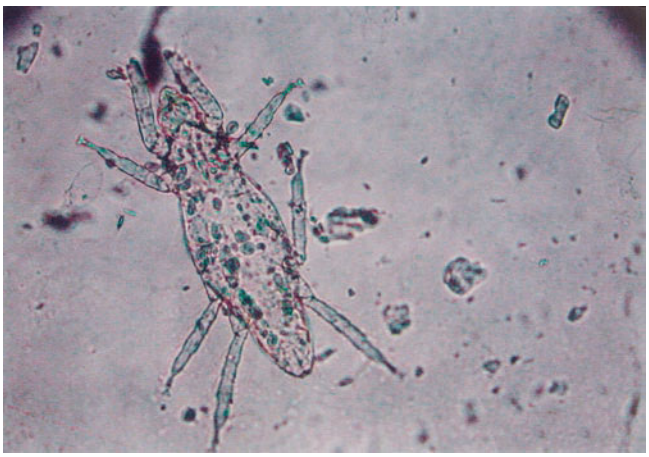


Fig. 6-9-2 Spindly worm with 8 ft and two-scoop receptivity organ on the front of the back (×100)

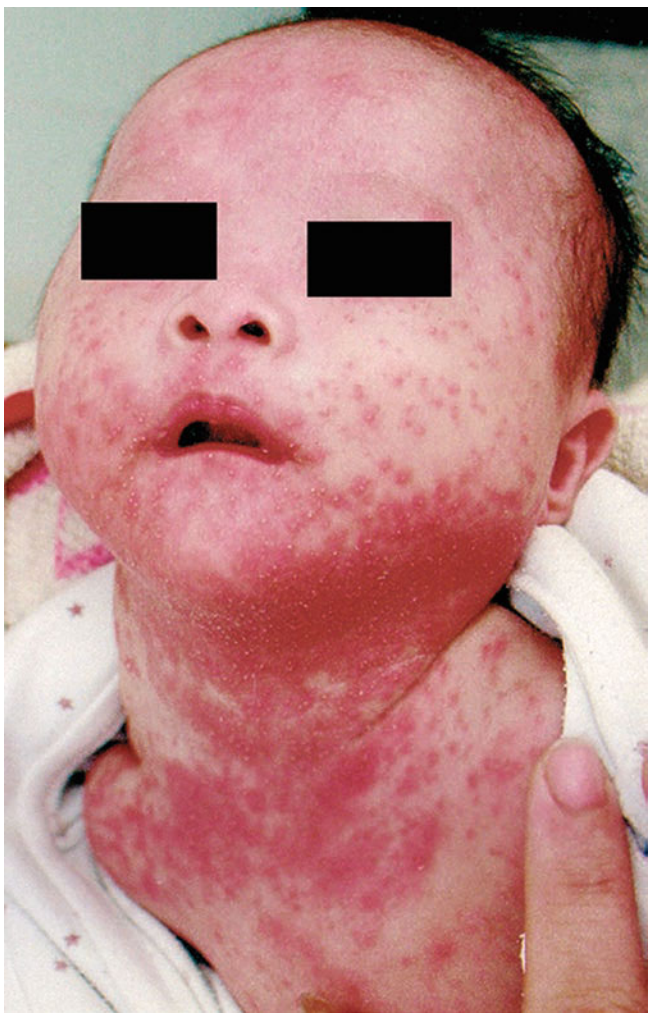


Fig. 6-9-1 Dense, pinpoint to millet-sized papules or papulovesicles on the head, neck, and chest

6.10 Jellyfish Dermatitis [10]

- Jellyfish have a bell-shaped body with tentacles covered with numerous cnidocytes containing a complex toxic mixture of heat-labile proteins.
- Jellyfish stings induce bitter, papular-urticarial eruptions with an itchy or burning sensation within a few minutes because of the immediate allergic, acute toxic, and continuous inflammatory responses.
- It is valuable to rinse the affected area carefully with seawater or vinegar to inactivate the toxins. Less commonly, jellyfish stings can cause delayed or recurrent cutaneous lesions, displaying groups of painless and itchy erythematous monomorphic papular rashes.
- This recurrent dermatitis can be decreased by applying pimecrolimus, tacrolimus, and corticosteroids.

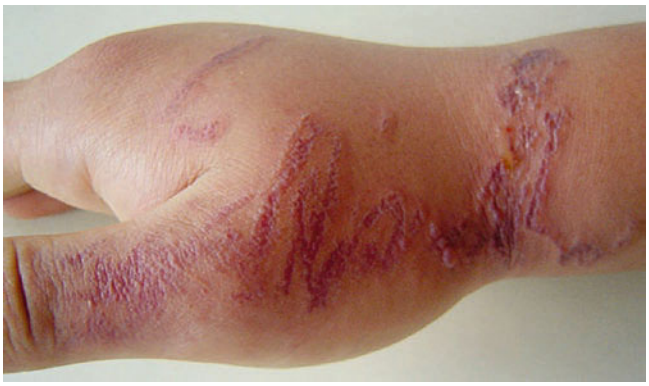


Fig. 6-10-1 Erythema and vesicles could be seen on the dorsa of the hand and upper limb

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Part II

Papulosquamous and Eczematous Dermatoses

Allergic Disorders

7

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Abstract

This chapter describes selected allergic diseases with distinctive cutaneous findings: irritant contact dermatitis with rare morphology; mango dermatitis; contact dermatitis caused by Bengal water dropwort herb; Blaschko dermatitis; posttraumatic eczema; halo dermatitis; recall urticarial, bullous urticarial, pruritic urticarial papules, and plaques of pregnancy; annular fixed drug eruption; and dapsone hypersensitivity syndrome.

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7.1 Irritant Contact Dermatitis with a Rare Morphology [1]

- Irritant contact dermatitis (ICD) is an inflammatory, nonimmunologic cutaneous reaction that occurs as a result of direct damage to the stratum corneum by physical and chemical factors.
- Although the irritation of soap is slight, it can still result in ICD with long-term contact. Contactants are conducive to the formation of the lesion morphology of ICD.
- It is extremely rare to observe multiple white scales arranged in a whorl-like and annular pattern on the patient's hands after prolonged exposure to soapy water, without erythema, swelling, papules, or pustules.

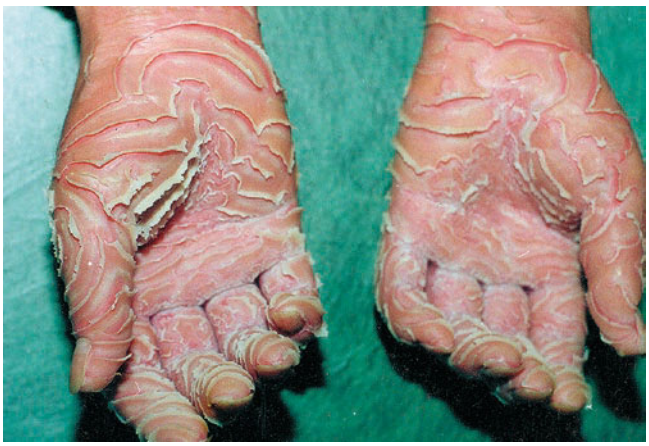


Fig. 7-1-1 Multiple white scales circling the palms from the wrist to fingertip, arranged in a clear whorl in the center

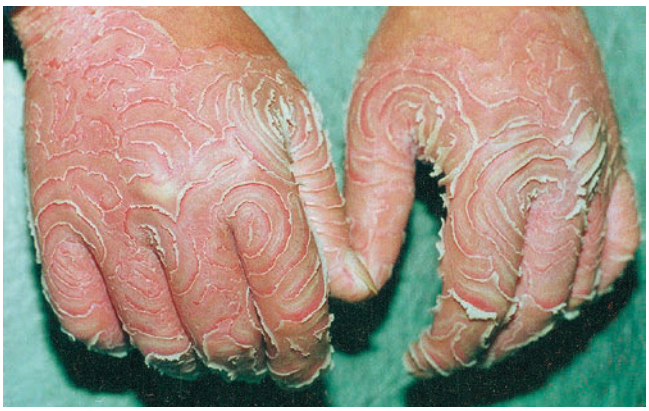


Fig. 7-1-2 Lesions on the back of the hand

7.2 Mango Dermatitis [2]

- Mango dermatitis is a kind of allergic contact dermatitis, which is caused by the sap, leaves, or pulp of mango. Urushiol (pentadecyl catechol) and heptadecenyl resorcinol may be responsible for this condition.
- Clinical presentations include linear papulovesicles and, most commonly, a combination of urticarial and eczematous.
- Treatment requires gentle, immediate soap and water irrigation after exposure and local glucocorticoid.

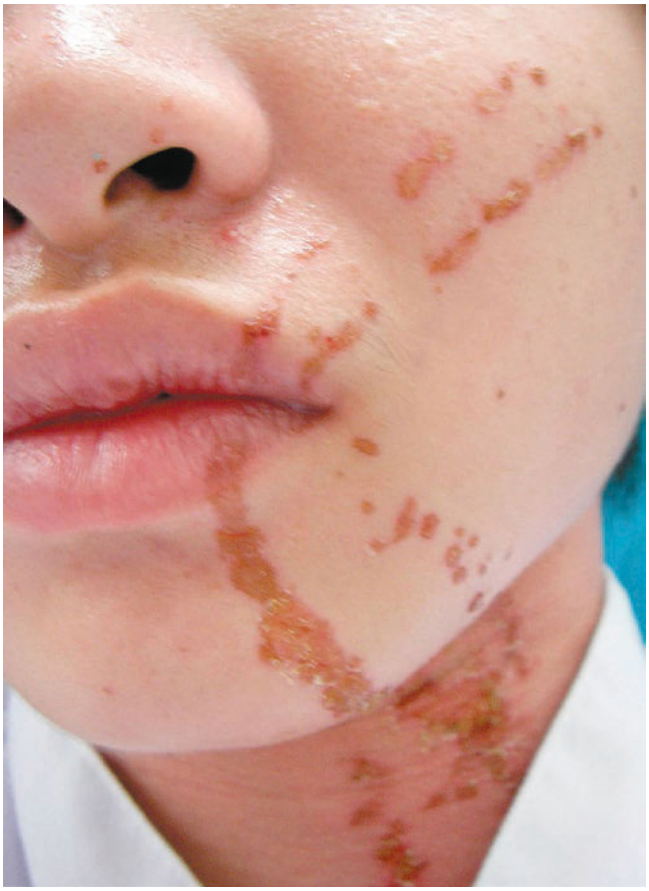


Fig. 7-2-1 Erythemas and vesicles arranged in lines on the left face; formation of erosion and crusts resulting from the breaches of vesicles

7.3 Contact Dermatitis Caused by Bengal Water Dropwort Herb [3]

- Severe irritant contact dermatitis (ICD) caused by the Bengal water dropwort herb is uncommon, and the lesions especially occur in indirect contact areas.
- The fresh leaves of water dropwort contain a strong stimulating ingredient, namely, protoanemonin. A proper diagnosis rests upon the contact history and manifestation of the condition.
- The patient presents several irregular patches of erythema, blisters, and escharosis with pain and itching on her forearms and abdomen. The main therapy includes antiallergic treatment and prevention of secondary infection.

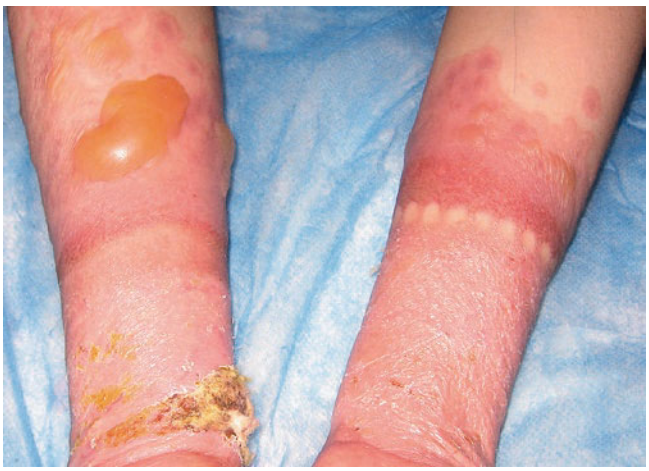


Fig. 7-3-2 Primary irritant: well-circumscribed erythema with a number of thin-walled vesicles, ulcers, and crusts on the forearms

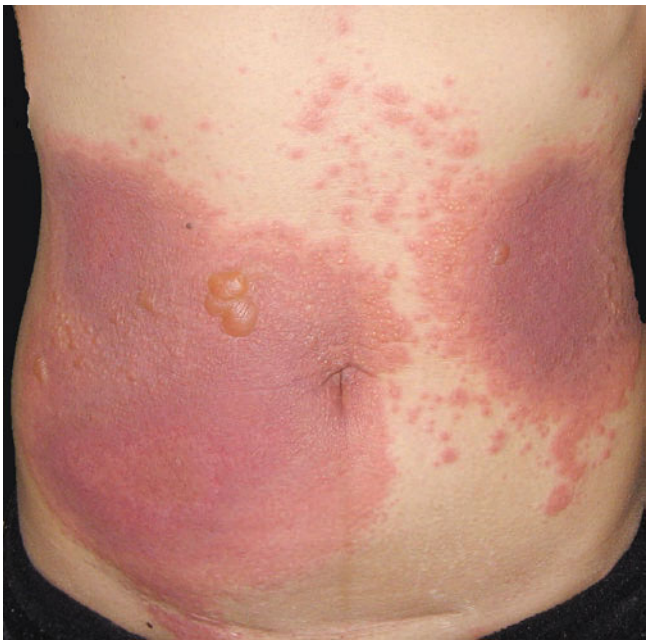


Fig. 7-3-1 Well-circumscribed edematous erythema with a few thin-walled vesicles on the lower belly

Fig. 7-3-3 Bengal water dropwort herb

7.4 Blaschko Dermatitis [4]

- Blaschkitis exhibits whorled, erythematous papules and vesicles along Blaschko's lines. It is hypothesized that a somatic mutation in a keratinocyte may result in a subsequent immune response.
- The lines of Blaschko may be linear and S-shaped over the limbs and torso, respectively. Histological examination of Blaschko dermatitis suggests spongiotic dermatitis.
- Blaschkolinear lesions can be discerned in a large spectrum of inflammatory dermatoses and can be categorized according to the pathological changes. Spongiotic changes are observed in blaschkitis and atopic dermatitis. Lichenoid alterations suggest the occurrence of lichen planus and GVHD. Psoriasiform proliferation suggests a specific form of psoriasis. In contrast, in lichen striatus, spongiotic changes, lichenoid infiltration, and psoriasiform proliferation may all be present in an individual.
- The broader streaks of the lesion, susceptibility (predisposing) of the adult, and rapid healing fulfill the criteria for blaschkitis and help to differentiate it from lichen striatus.

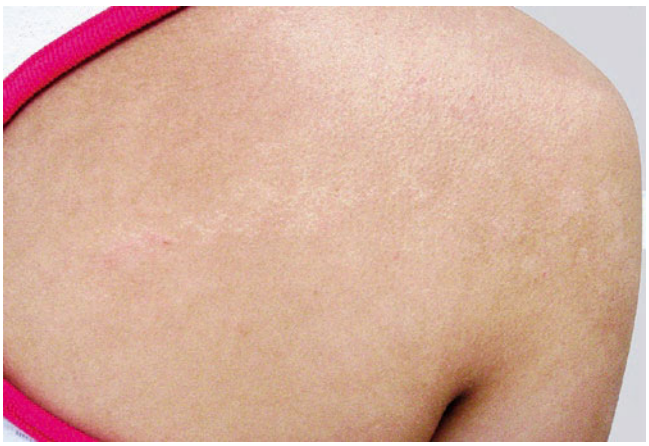


Fig. 7-4-1 The scapular region presented with band-like hypopigmented macules with superimposed inflammatory papules and scales

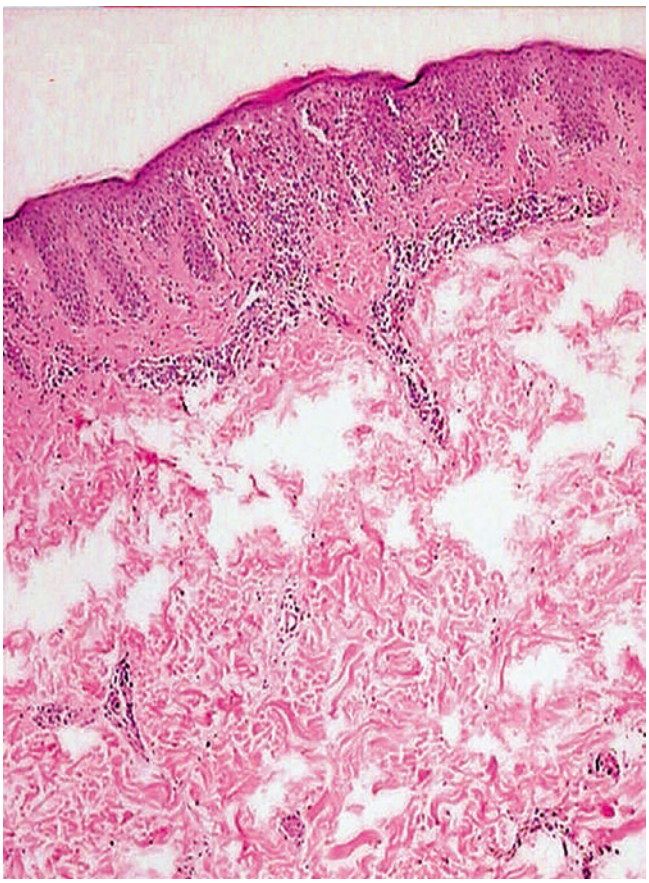


Fig. 7-4-2 Focal hyperkeratosis, dyskeratosis, and spongiosis. Lymphocytic infiltration can be found in the superficial dermis (HE stain, ×40)

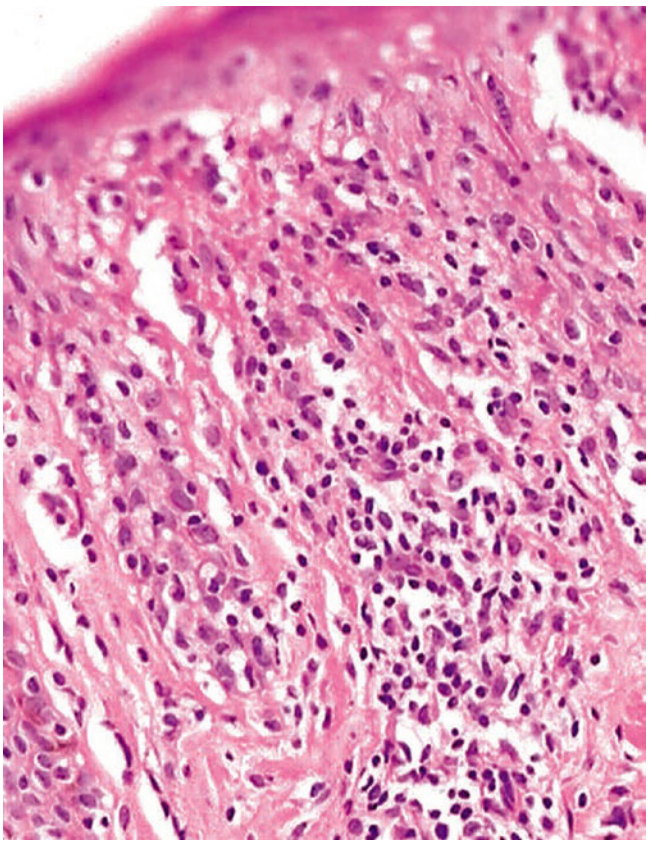


Fig. 7-4-3 Intracellular edema and spongiosis were notable pathological findings, with lymphocytes infiltrated at the junctions between the dermis and epidermis (HE stain, ×100)

7.5 Posttraumatic Eczema [5]

- Although posttraumatic eczema (PTE) was first reported by Mathias in 1988, it is likely underdiagnosed. Eczematous lesions occur at sites with a positive history of previous invasive traumas.
- It is crucial to discern different traumatic factors. The most common are surgical performance, venipuncture, and irradiation, among others.

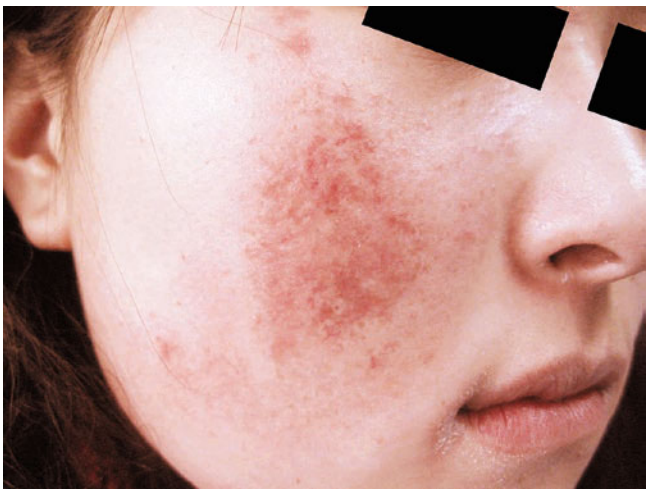


Fig. 7-5-1 Thirteen years after the radionuclides application, eczematoid changes with erythema, papules, and mild oozing presented on the previous sites of hemangioma on her right cheek. Without involvement of the normal skin (Reproduced with the permission from [5])

7.6 Halo Dermatitis [6, 7]

- Halo dermatitis clears rapidly to topical corticosteroid. Some may persist for years before spontaneous resolution without malignant transformation.
- The disorder might occur secondary to other dermatoses, including seborrheic keratosis, basal cell carcinomas, keloid scars, smooth muscle hamartoma, dermatofibroma, and the application of interferon α-2b or ribavirin.
- While Sutton's nevus is characterized by a predominant infiltration of CD8 + T-cells, the halo dermatitis shows a prevalence of CD4+ T-cell infiltration.
- Halo dermatitis is characterized by the development of eczematous changes that usually surround a preexisting melanocytic nevus.

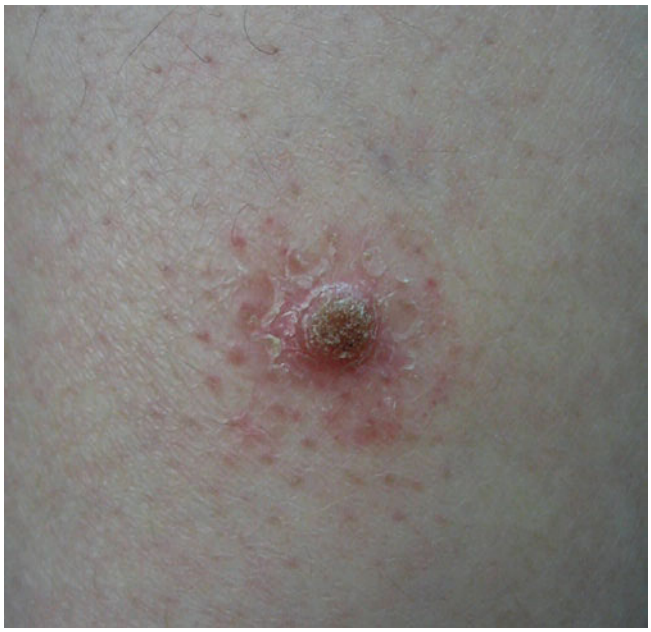


Fig. 7-6-1 An 8-mm-sized papule on the left pretibial skin, with neighboring eczematoid changes like erythema, papules, and scales

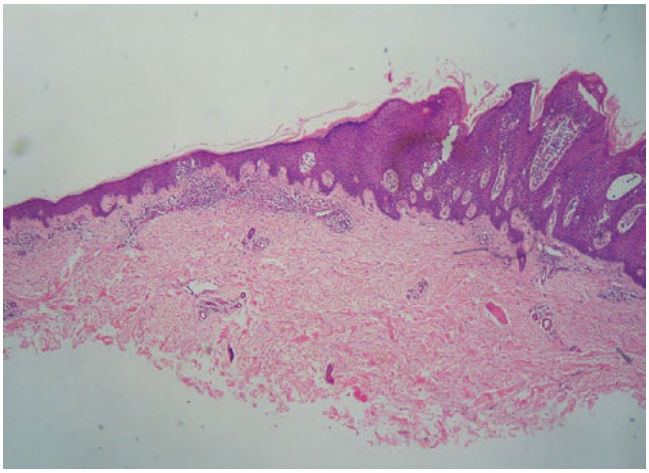


Fig. 7-6-2 Hyperkeratosis, acanthosis, keratotic plug, and a flat bottom are present. Infiltrating lymphocytes can be seen in the superficial dermis (HE stain, ×40)

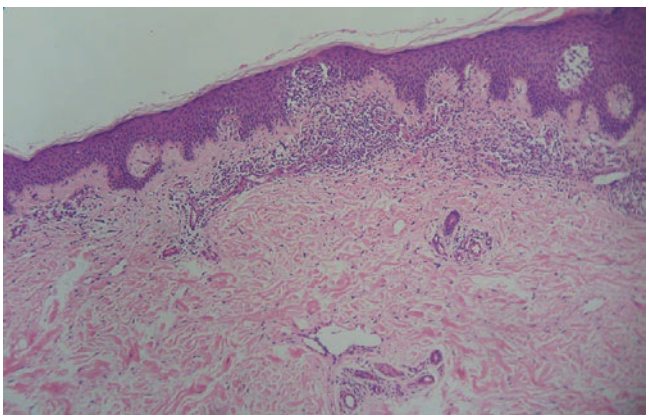


Fig. 7-6-3 Pathological changes of the skin neighboring seborrheic keratosis show focal parakeratosis, spongiosis, and lymphocyte infiltration around vessels in the dermis (HE stain, ×100)

7.7 Recall Urticaria [8, 9]

- Most patients with recall urticaria (RU) result from intravenous and oral exposure to certain immunological therapies or polypeptides.
- Levofloxacin, norfloxacin, and other low-molecular-weight drugs can induce RU.
- RU is provoked once the same drug or antigen is administered orally, intravenously, or through other methods.
- Fixed drug eruptions, fixed solar urticaria, recall injection-site reactions, ultraviolet recall, and radiation recall are other recall reactions besides RU.

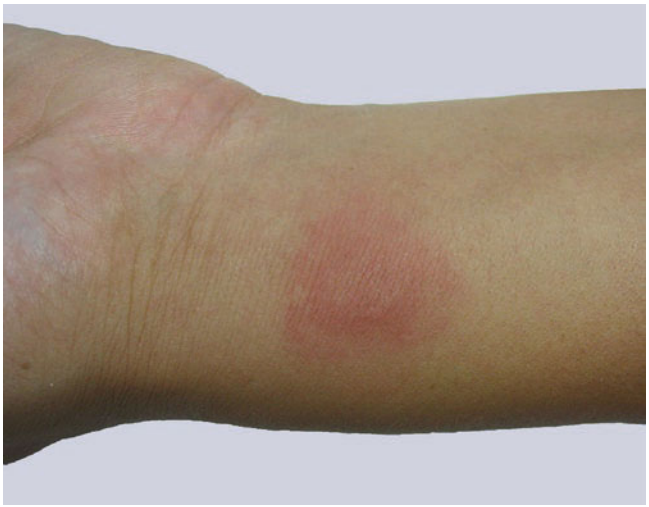


Fig. 7-7-1 A solitary oval wheal is noted on the right wrist. Localized hyperpigmentation was not obvious. (Reproduced with the permission from [14]

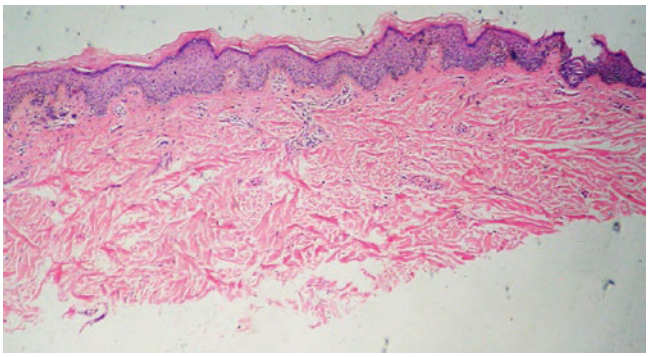


Fig. 7-7-2 Histology of the lesions revealed interstitial dermal edema, dilated venules, and a paucity of lymphocyte infiltration (HE stain, ×100). (Reproduced with the permission from [15]

7.8 Bullous Urticaria [10]

- Bullous urticaria (BU) is a rare entity that should be differentiated from contact dermatitis, bullous mastocytosis, bullous pemphigoid, and insect bite reactions.
- The etiology of BU is considered to be associated with an IgE-mediated eosinophilic disorder. Bullous lesions can occur as a complication of spontaneous urticaria or delayed pressure urticaria.
- Standard chronic urticaria therapies with antihistamines can lead to a modest improvement in some cases.

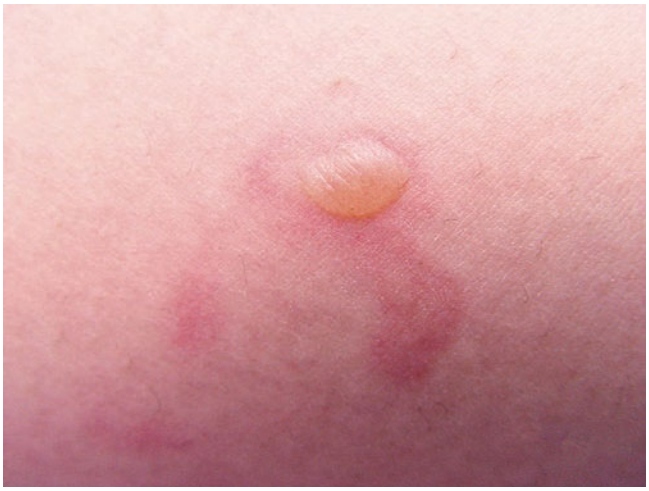


Fig. 7-8-2 Large tense bullae arising on wheals

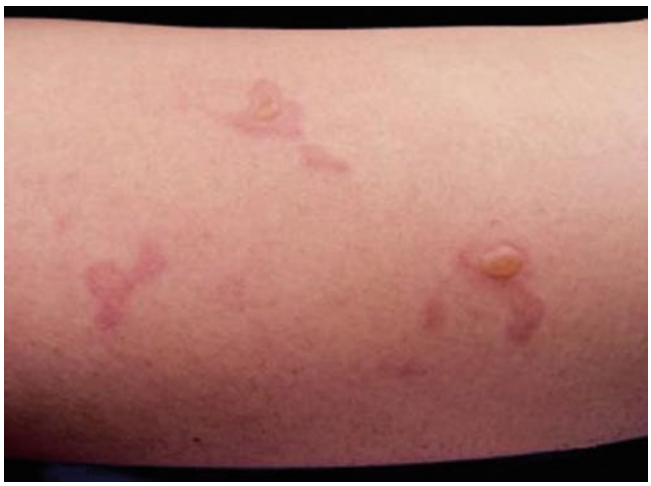


Fig. 7-8-1 A few large wheals covered with a transparent bullae occurred on the inside of the right thigh

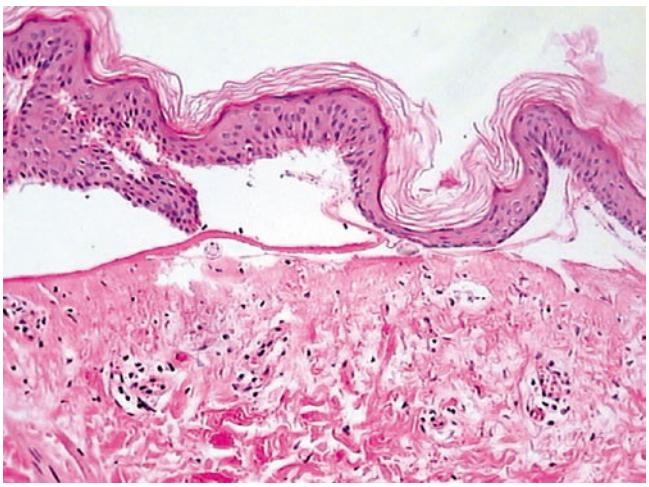


Fig. 7-8-3 A subepidermal bulla and papillary dermal edema (HE stain, ×200)

7.9 Pruritic Urticarial Papules and Plaques of Pregnancy [11]

- Pruritic urticarial papules and plaques of pregnancy (PUPPP) is a benign and frequent disorder that presents with severe pruritus.
- The classical presentation of PUPPP starts with erythematous papules within the abdominal striae, excluding the navel, which then progresses urticarial plaques and spreads to the proximal extremities, often developing in the third trimester of primigravida.
- Commonly, bland emollients, antipruritic emollient formulations, and low- to mid-potency topical steroids are suggested as initial therapy. Oral antihistamines and systemic glucocorticoids might be valid and effective.

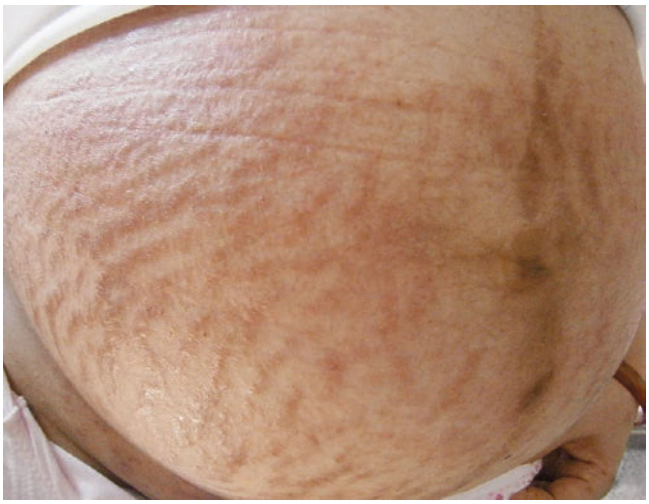
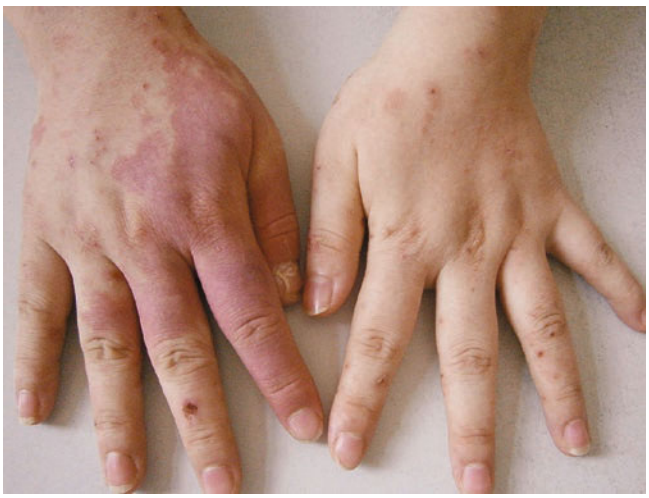
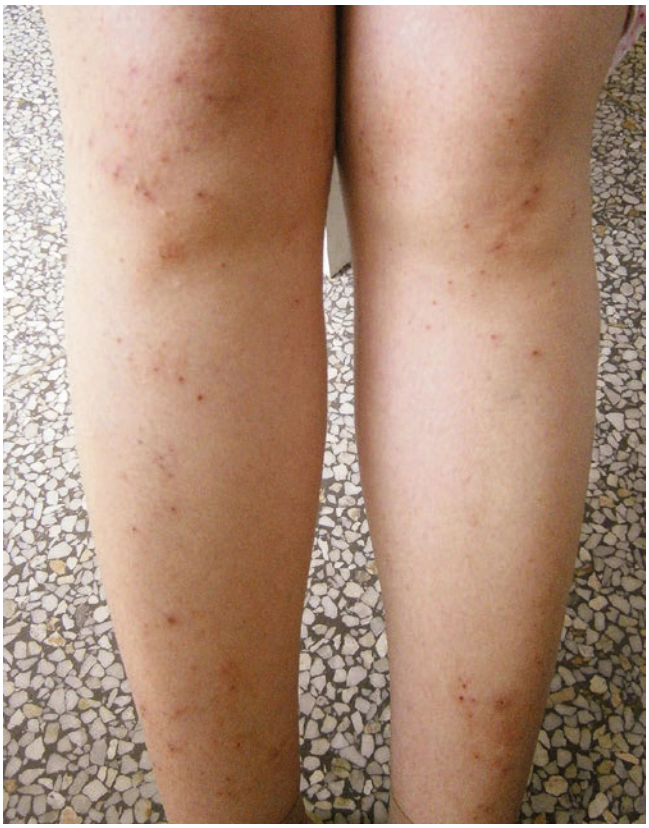


Fig. 7-9-1 Urticarial papules and plaques on the striae distensae of abdomen





Figs. 7-9-2, 7-9-3 Erythema papulovesicles on the dorsal hands and the lower limbs

7.10 Annular Fixed Drug Eruption [12]

- Fixed drug eruption (FDE) is a kind of skin eruption that mostly recurs in the same parts of the skin once the same incriminating drug or food (fixed food eruption is used instead in this condition) is consumed.
- Its pathognomonic lesion is demarcated by an erythematous patch, which evolves to exhibit pigmentation with repeated onsets.
- The classical pathologic findings consist of interface dermatitis and predominant perivascular infiltration of lymphocytes.
- Lesions of FDE can be considerably diverse, including giant, papular, bullous, purpuric, linear, reticular, zosteriform, nonpigmented, butterfly-like, and annular FDE. Pruritus vulva has also been observed.
- It is particularly significant to discriminate FDE from erythema multiforme, vulval/perianal hypermelanosis, paronychia, cheilitis, housewife's eczema, and psoriasis.
- FDE may result from cheese-flavored crisps, strawberries, licorice, tartrazine, lentils, peanut, cashew, tonic water, asparagus, lactose, and Japanese sand lance.
- Sexually transmitted FDE refers to the case in which no significant drug history is determined, but the condition is provoked by sexual intercourse with a partner who might take the offending medicine.

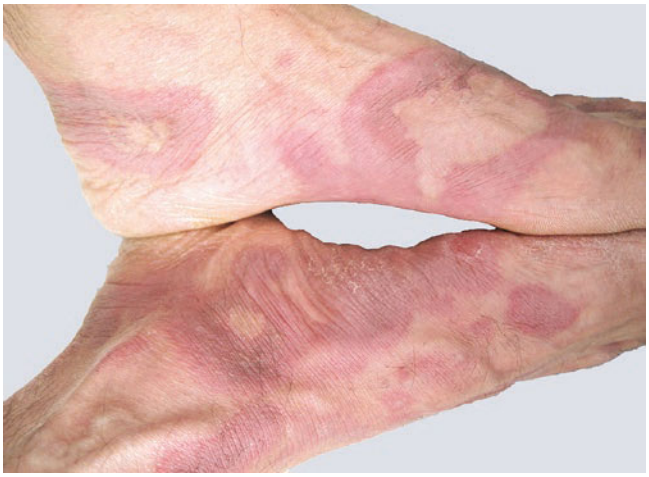


Fig. 7-10-1 Several well-circumscribed annular erythematous and violaceous patches over the dorsal aspects of both feet. In addition, a few smaller targetoid lesions were admixed. (Reproduced with the permission from [12]

7.11 Dapsone Hypersensitivity Syndrome [13]

- Dapsone hypersensitivity syndrome (DHS) is also known as "5-week dermatitis" because it occurs suddenly, 5–6 weeks after the administration of dapsone.
- The hydroxylated metabolites, genetic susceptibility, and environmental factors are regarded as crucial in the disease etiology.
- The presentations of DHS include popular or exfoliative rash, fever, malaise, occasionally jaundice, and lymphadenopathy.
- The death rate of DHS is approximately 9.9%, which can be prevented by HLA testing for HLA-B*13:01 (withholding dapsone in patients who test positive), early withdrawal of dapsone, and appropriate treatment.

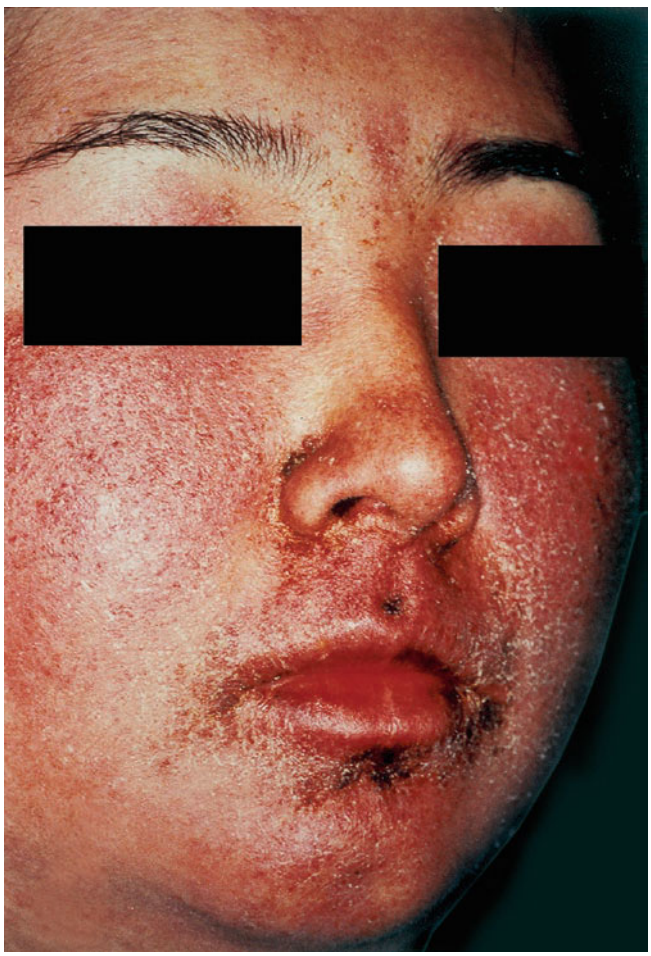


Fig. 7-11-1 Highly edematous, with erythematous and purple papules on the face (Reproduced with the permission from [13])

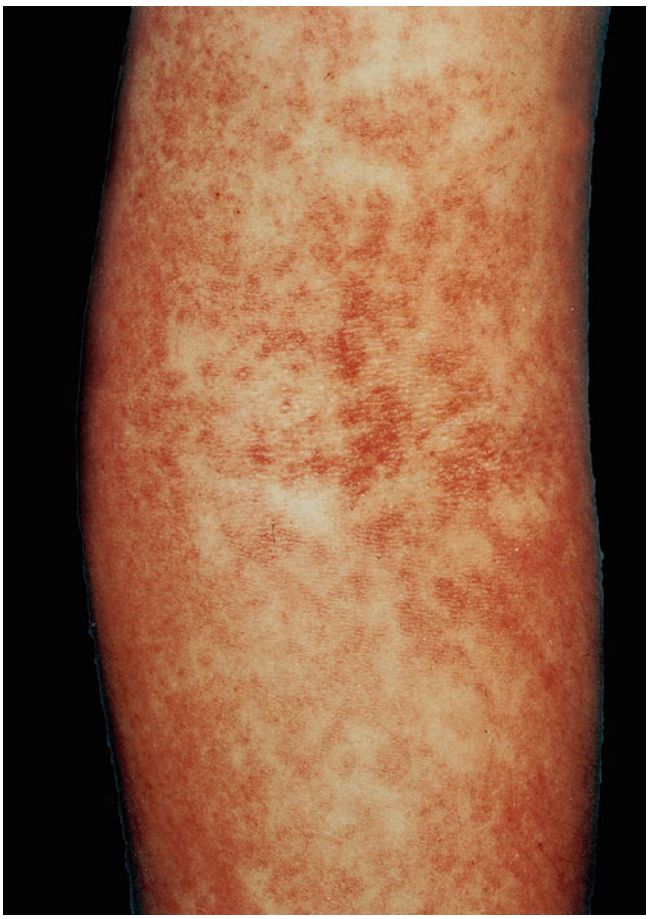


Fig. 7-11-2 Erythematous and purple papules on the arm

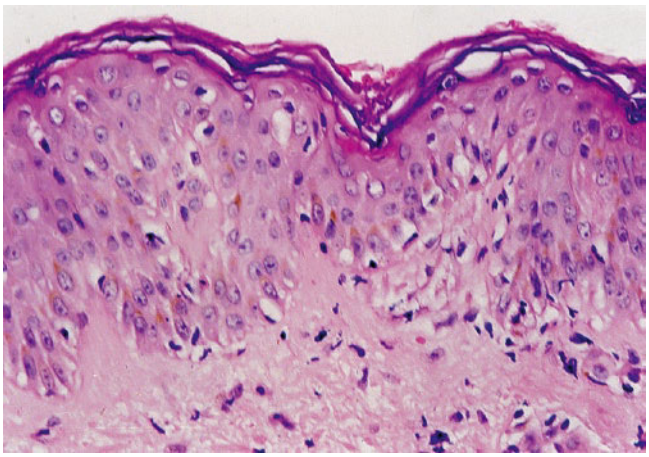


Fig. 7-11-3 Mild hyperkeratosis and liquefaction of the basal cell layer (HE stain, ×200)

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Disorders Resulting from Physical Factors

8

Dong-Lai Ma, Bo Li, Cheng Li, Feng Li, Ru-Zhi Zhang, Wen-Yuan Zhu, Min Yang, and Jian Chen

Abstract

The skin is especially vulnerable to many physical triggering factors, causing many distinctive clinical features as shown in this chapter: erythema ab igne, actinic lichen planus, phytophotodermatitis, colloid milium, and dermatitis artefacta.

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8.1 Erythema Ab Igne [1, 2]

- Erythema ab igne (EAI) is a relatively rare disorder that features a persistent and chronic course. EAI is usually caused by long-range exposure to infrared irradiation.
- EAI initially presents as transient blanchable erythema and then progresses to a lacunosus pattern of excessive pigmentation, often accompanied by atrophy of the epidermis and telangiectasias.
- Rarely, premalignant cutaneous dysplasia and cutaneous carcinoma may be associated with long-standing EAI. Biopsy should be carried out to eliminate malignancy.
- The outcome of EAI is good, with elimination of the thermal source leading to complete remission. Tretinoin and hydroquinone can prevent persistent hypermelanosis. Supernumerary therapies might be essential for chronic lesions and a malignant tendency.

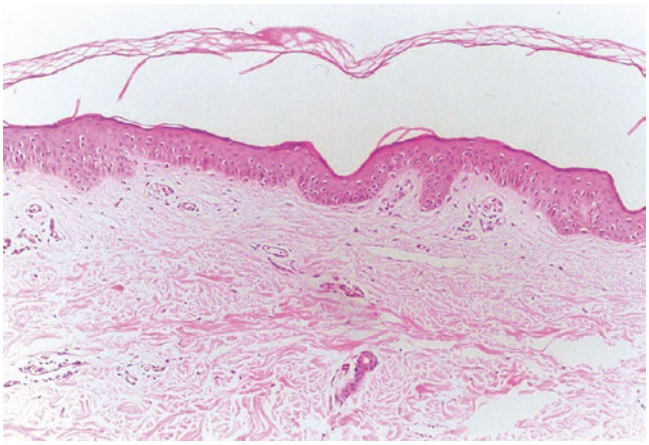
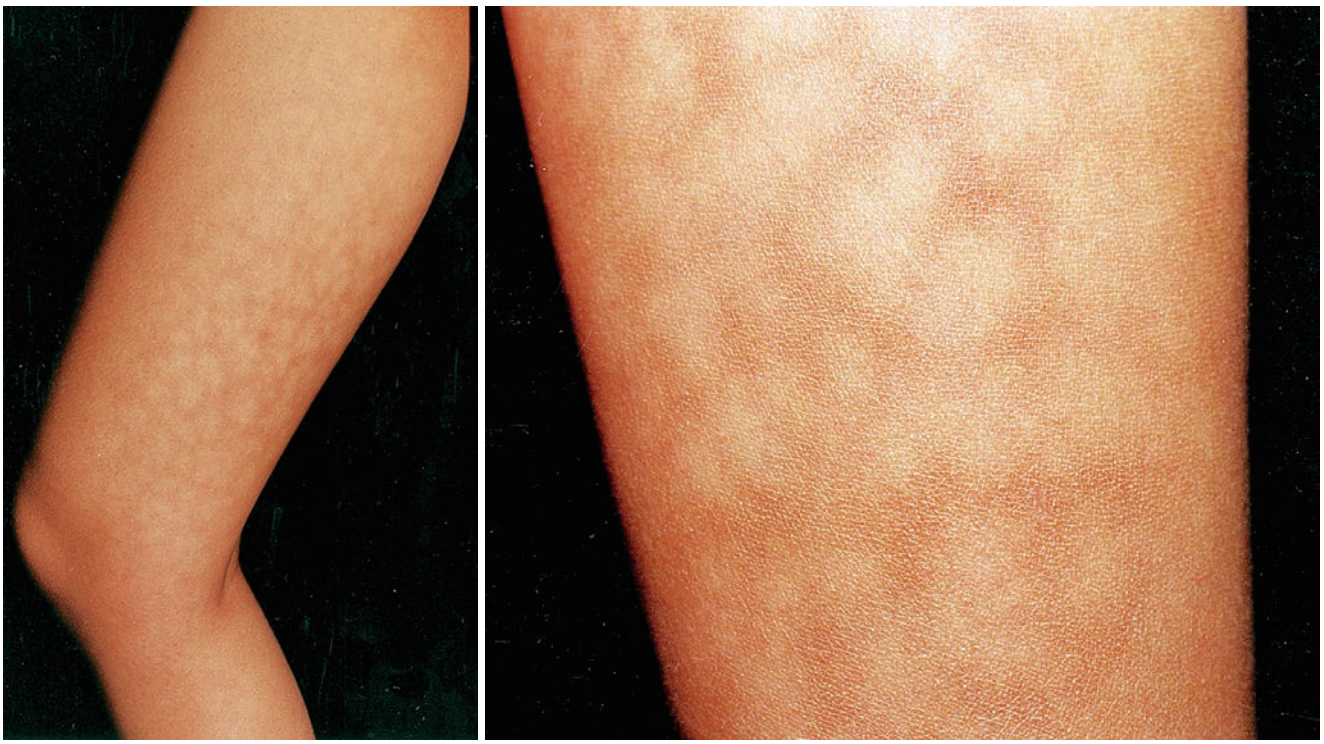


Fig. 8-1-3 Hyperkeratosis, flattened epidermis, and hyperpigmentation in the basal cells, telangiectasis in papillary dermis, and surrounding inflammatory cells infiltrated (HE stain, ×40)



Figs. 8-1-1, 8-1-2 Reticular erythema with pigmentation on the inner of both thighs without definite borderlines

8.2 Actinic Lichen Planus [3]

- Actinic lichen planus (ALP), also referred to as lichen planus tropicus, is a rare variant of LP. It typically affects children or young adults who live in tropical or subtropical regions.
- The etiology of ALP remains ambiguous. Potential relevant factors include sunlight and hormonal, toxic, infectious, or genetic factors, among others.
- ALP can be divided into three subtypes: annular, pigmented, and dyschromic. The three forms display erythematous brownish plaques with an annular configuration, hypermelanotic patches with a melasma-like appearance, and whitish pinhead and coalescent papules, respectively.
- The eruption usually appears during spring and summer and improves or fades away during winter. In the summer of the subsequent year, relapse is likely to occur.
- Treatment with antimalarial agents or intralesional corticosteroids combined with sunscreens has shown good results with prolonged remission.

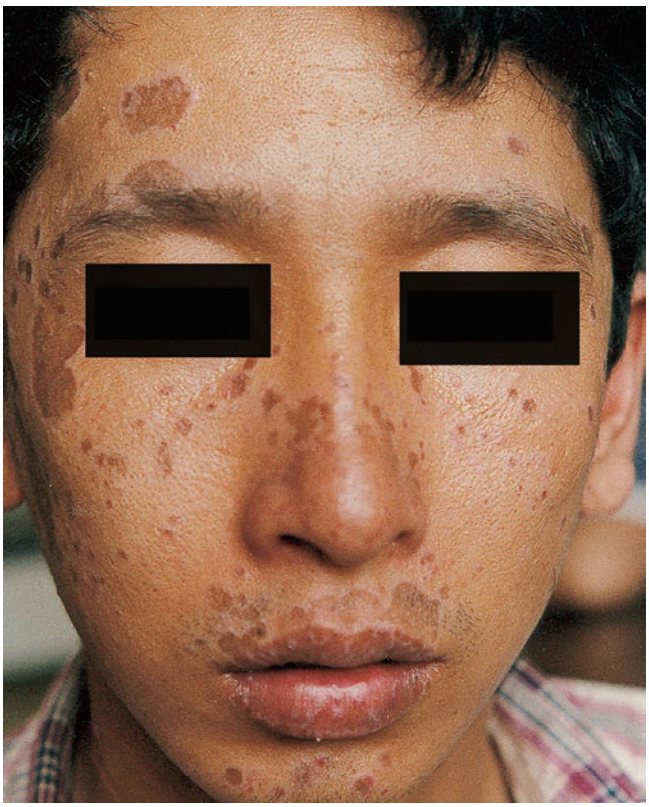


Fig. 8-2-1 Numerous light and dark brown patches with slightly raised edges on the face (Reproduced with the permission from [3])

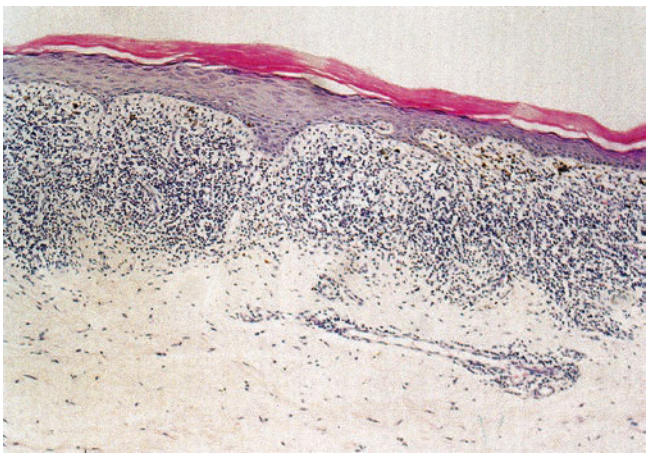
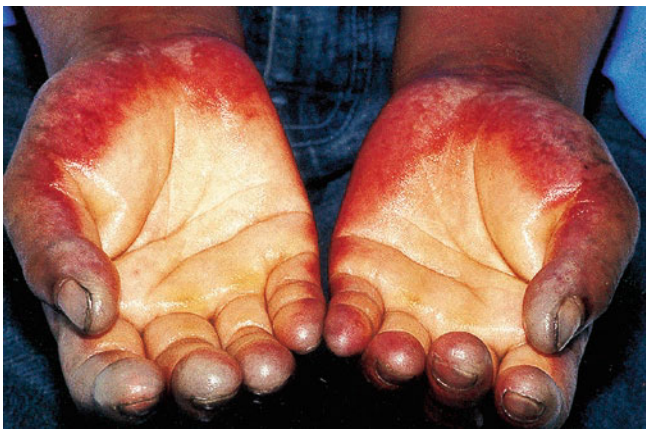


Fig. 8-2-2 It shows light hyperkeratosis and increases in thickness of the stratum granulosum. There are destruction of the basal layer and band-like infiltrate (HE stain, ×40)

8.3 Phytophotodermatitis [4, 5]

- Phytophotodermatitis is a reaction to activation by long-wavelength ultraviolet radiation of botanical substances. It generally leads to sharply circumscribed cutaneous lesions, often with bizarre shapes.
- These lesions might simply turn into vesicles, erythematous, or bullae or appear as hyperpigmented patches without a preceding erythematous phase, and the hyperpigmentation may appear between 24 and 48 h but persists as long as 6 months.
- Photopatch testing in such patients is contraindicated because a positive response might be severe; it would also be expected to occur in the general population, and thus it would not discriminate in making the diagnosis.
- Wild carrot leaves are rich in furocoumarins, which can lead to allergic contact dermatitis from leaves, especially when wet.



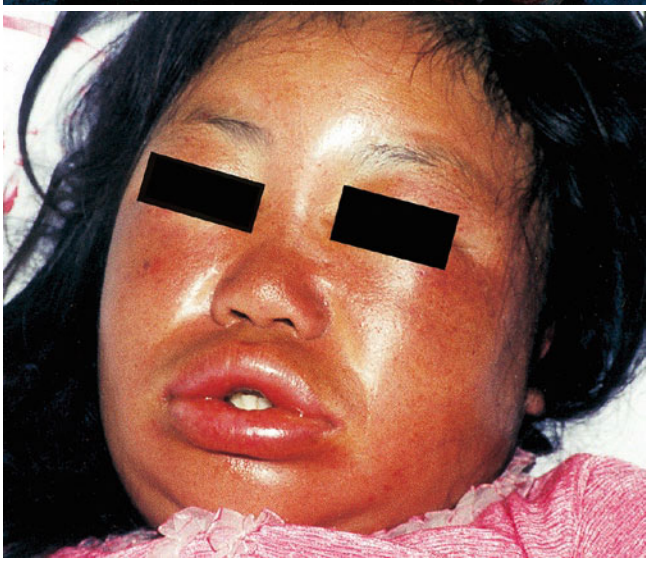
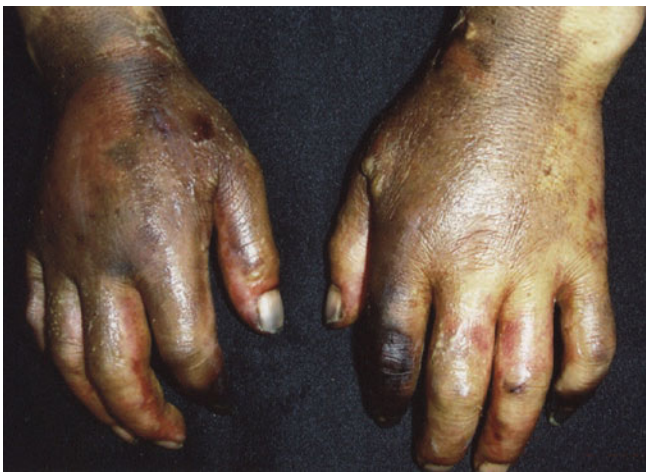


Fig. 8-3a-1, 8-3a-2 Marked swell, well-circumscribed, violaceous petechiae with increased intensity (1) and shine (2), swollen eyelids with opening restricted, and eversion of the lips with difficulty opening the mouth (Reproduced with the permission from [4, 5])



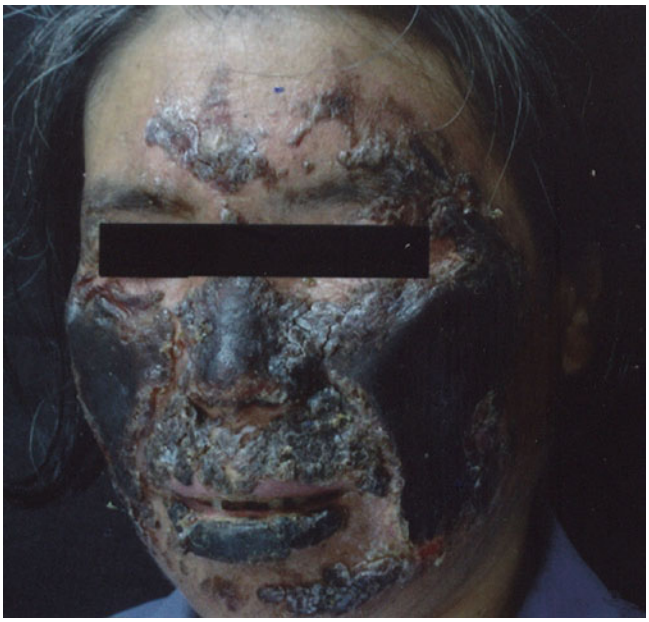


Fig. 8-3b-1, 8-3b-2 The patient had some edible wild herbs before 2 h of sun exposure: (1) dark brown ecchymosis and non-edematous swelling on the both dorsal of the hands, gangrene on the fingers; (2) a large dark brown patch with crusts on the face (Reproduced with the permission from [4, 5])

Fig. 8-3b-3, 8-3b-4 *Sonchus brachyotus* dc (3) and *Taraxacum lugubre* Hand-Mazz (4)

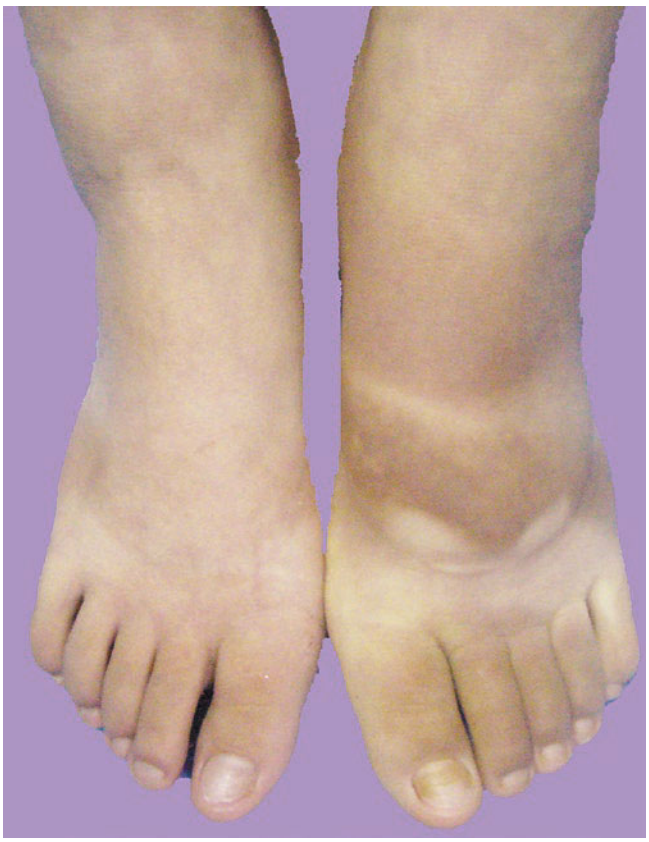


Fig. 8-3c-1 Well-demarcated dark brown patches on the dorsum of the left foot and anterior aspect of the left ankle. The skin of her right foot remained normal

Fig. 8-3c-2, 8-3c-3 An image comparing the wild carrot (2) and ordinary carrot (3)

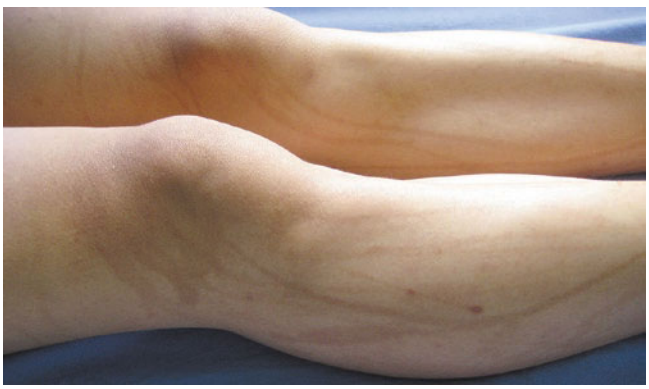


Fig. 8-3d-1 Sharply demarcated hyperpigmented lines and curves on the extensor aspects of thighs and legs

8.4 Colloid Milium [6, 7]

- The main risk factors of colloid milium (CM) may incorporate hydroquinone bleaching creams, prolonged exposure to UV light, and genetic susceptibility.
- There are four types of CM: adult forms, juvenile onset, pigmented types, and nodular forms. The clinical manifestation of CM mainly presents as translucent nodules or cysts with a diameter of 1–2 mm. The lesions are gray-white or yellowish. Lesions of CM preferentially appear on the face, the back of the hands, and the neck.
- Histologically, largely fissured eosinophilic colloid in dermal papillae is suggested. The primary therapy for CM covers dermabrasion, local retinoid application, and YAG laser.

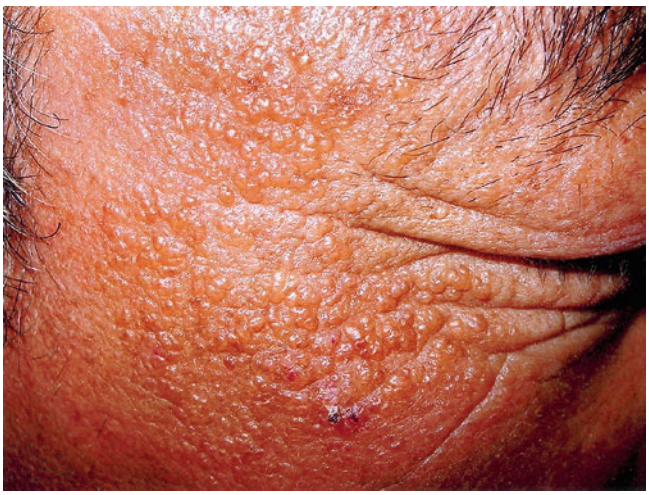


Fig. 8-4-1 Translucent, slightly yellow papules on the outer of right eye

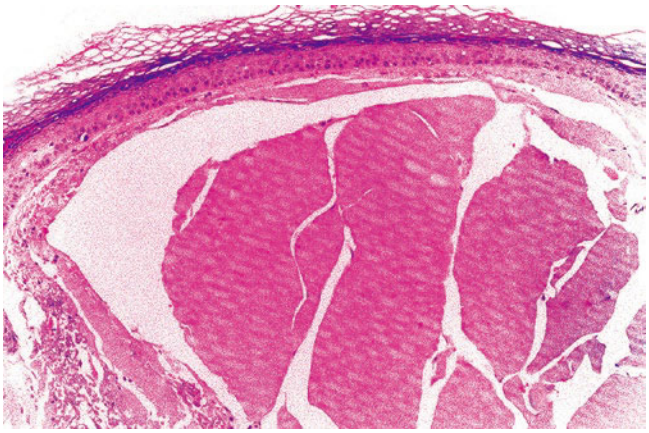


Fig. 8-4-2 Homogenous, fissured masses deposited in the dermal papillae (HE stain, ×100)

8.5 Dermatitis Artefacta [8]

- Dermatitis artefacta (DA), also called factitious dermatitis, refers to self-inflicted dermatosis by a fully aware patient for secondary psychological gain.
- The clinical manifestations reveal a use of creative methods involving diverse but easily available household items, including excoriations, ulcers, blisters, burns, and hematomas, among others.
- The diagnosis of DA may be difficult if the clinician is unaware of its existence. It is often based on bizarre shapes of lesions with irregular outlines, exhibiting a definite boundary with the normal skin.
- The treatment of DA should be mild, nonantagonistic, and elastic and based on bilateral mutual trust. Critical patients also require advisable psychotherapy.

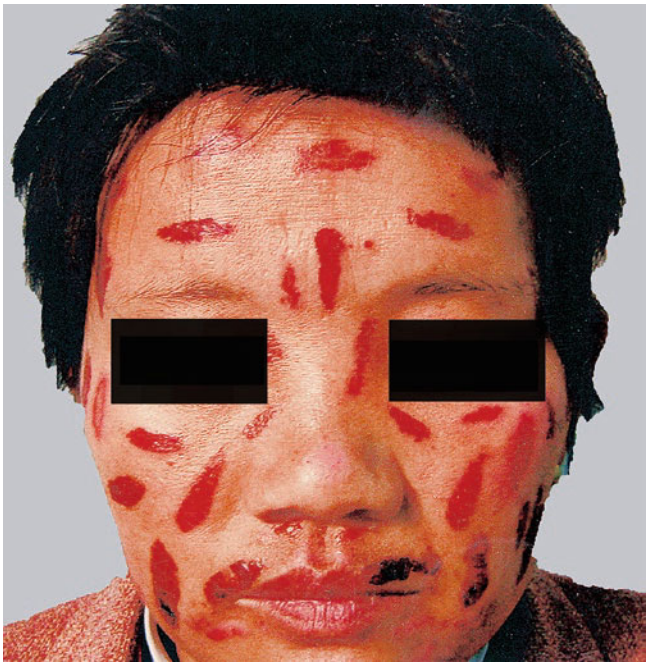


Fig. 8-5-1 Multiple stripe, regular erythema with epidermis peeling, and partly covered with blood crasts or extravasate (Reproduced with the permission from [8])

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Papulosquamous Diseases

9

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Cheng-Rang Li, and Jie Yan

Abstract

Papulosquamous diseases that will be shown in this chapter are palmoplantar psoriasis, inverse psoriasis, pityriasis lichenoides et varioliformis acuta, purpuric pityriasis rosea, generalized papular pityriasis rosea, pigmentary pityriasis rosea, keratosis follicularis squamosa (Dohi), hypertrophic lichen planus, lichen planopilaris, lichen planus pigmentosus-inversus, linear lichen planus pigmentosus, nail lichen planus, coincidence of lichen planus and vitiligo, acute generalized lichen planus, dermatosis papulosa nigra, lichen sclerosus, erythromelanosis follicularis faciei et colli, lichen aureus, generalized lichen nitidus, and pityriasis rotunda.

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9.1 Palmoplantar Psoriasis [1]

- Palmoplantar psoriasis (PP) refers to a localized psoriasis variant and accounts for 3–4% of all psoriasis cases.
- The classical lesions display some thick scaly, hyperkeratotic plaques, which cause a significant psychological impact on the sufferer and hampers his/her daily movements.
- Diagnosis is not always straightforward considering the frequent clinical overlap with chronic eczema. It is worth noting that syphilis can be observed in the palmoplantar area mimicking psoriasis, and therefore simple screening and verification tests should be performed in suspected patients.
- Palmoplantar psoriasis is a treatment challenge. Topical treatment is always preferred as the first-line therapy, including emollients, keratolytics, tazarotene, calcipotriol, PUVA, and UVB. Systemic therapy is needed when the topical treatments fail or when the disease becomes more severe.

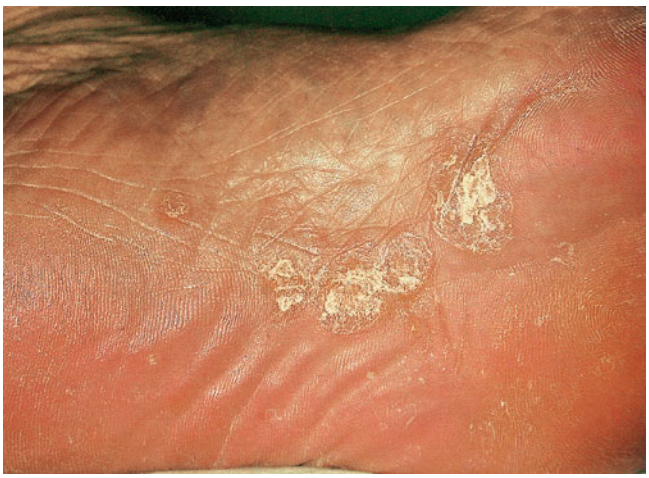


Fig. 9-1-1 Demarcated, hyperkeratotic plaques covered with scales on the left sole

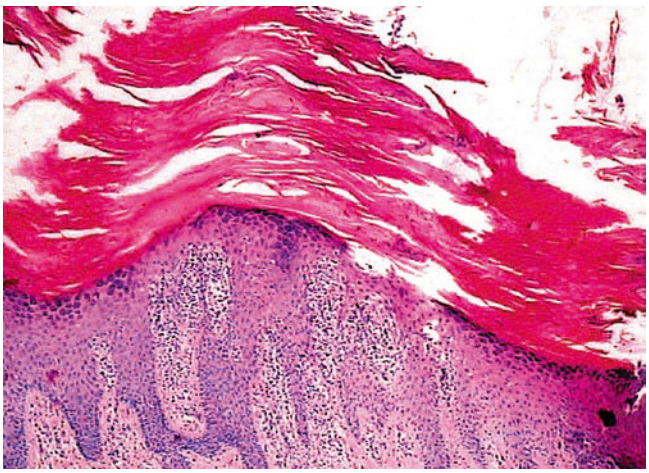


Fig. 9-1-2 Parakeratosis, the rete ridges show regular elongation with thickening in the lower portion, the papillae are elongated and the capillaries dilated, and lymphocytes infiltrated around the vessels in the upper dermis (HE stain, ×40)

9.2 Inverse Psoriasis [2]

- Inverse psoriasis (IP), also referred to as intertriginous psoriasis, is not considered a separate entity but rather a special site of involvement of plaque psoriasis, making up approximately 3–7% of patients with psoriasis.
- This condition is characterized by the development of erythematous, shiny, non-scaly plaques at intertriginous areas such as the buttocks, gluteal cleft, and axillae. Although the lesions lack the typical scaling of plaque psoriasis, minimal scaling can be seen in the more keratinized regions.
- Inverse psoriasis is treatment resistant. The preferred therapies of IP are local glucocorticosteroids and vitamin D analogues. It also requires a modified therapeutic method because it is usually less responsive to standard therapeutic regimens.

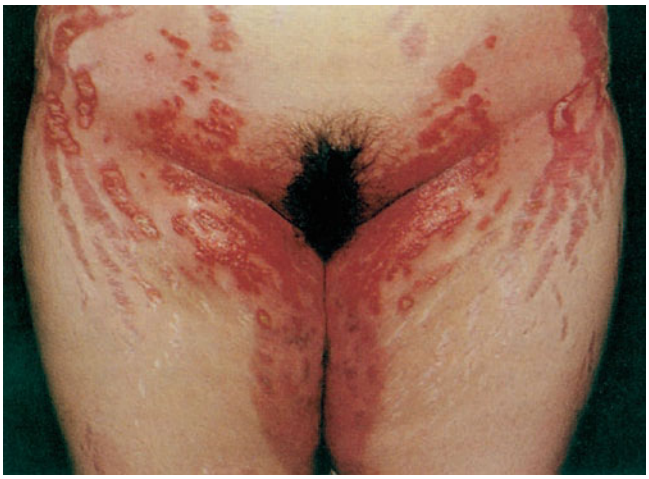


Fig. 9-2-1 Circumscribed large erythematous patches in inguinal region

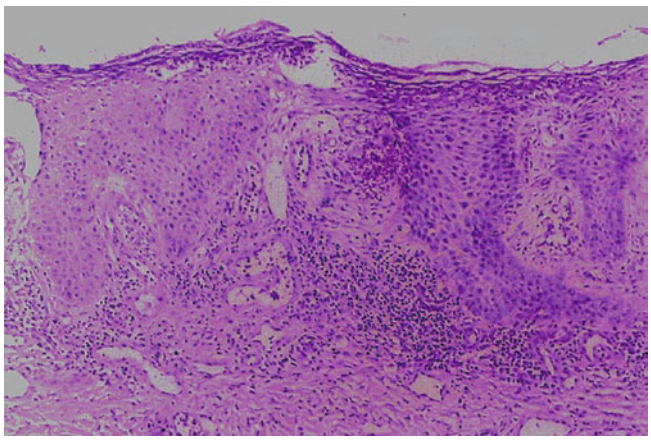


Fig. 9-2-2 Hyperkeratosis, parakeratosis, acanthosis, and elongated rete ridges; a Munro microabscess present in the stratum corneum (HE stain, ×100)

9.3 Pityriasis Lichenoides Et Varioliformis Acuta [3]

- Pityriasis lichenoides et varioliformis acuta (PLEVA) is primarily associated with lymphoproliferative reactions and may be triggered by extrinsic agents, including microbial pathogens, certain drugs, and vaccinations.
- PLEVA frequently appears on the limbs, torso, and flexural regions, which might emerge as diffuse patterns or generalized patterns. The eruption is polymorphous because lesions exist in all phases of development, which can last from a few weeks to months or years with burning and pruritus.
- PLEVA features erythematous macules that quickly evolve into papules with a fine micaceous scale. The papule usually has a central punctum that becomes vesiculopustular, goes through hemorrhagic necrosis, and then becomes ulcerated, covered with reddish brown crusts.
- PLEVA tends to be self-limited in its course, except the febrile ulcerative variant, which can be fatal. Therapy is targeted mainly at relieving itching.

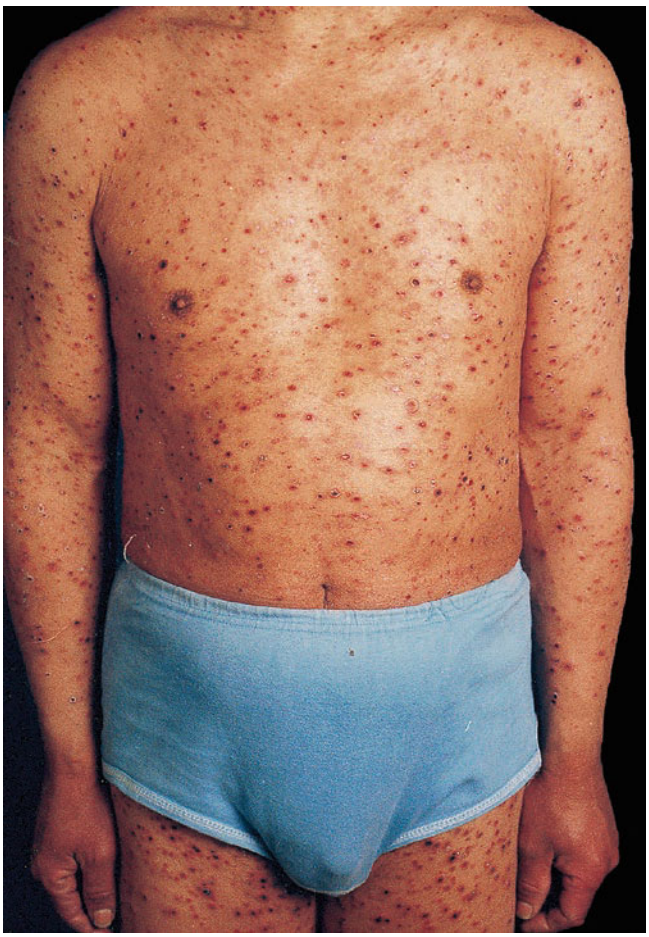


Fig. 9-3-1 A large number of papules and vesicles covered with scales and dark crests on the trunk and extremities

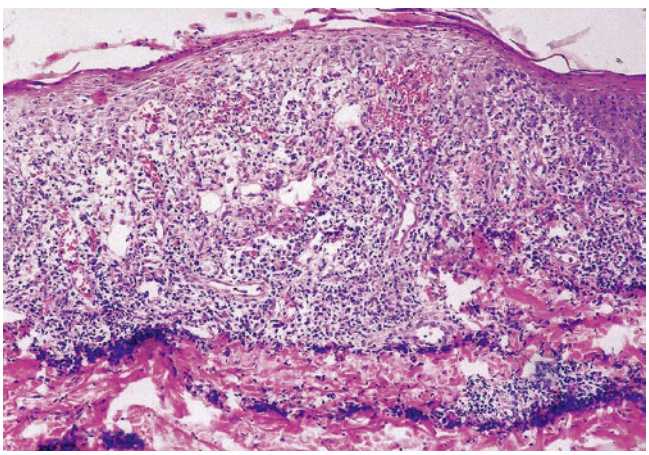


Fig. 9-3-2 Predominantly lymphocytic infiltrate invades the epidermis. The necrotic keratinocytes and liquefaction degeneration of basal cells appear in the epidermis (HE stain, ×100)

9.4 Purpuric Pityriasis Rosea [4]

- Purpuric pityriasis rosea (PPR), an uncommon type of pityriasis rosea (PR), is characterized by round to oval purpuric macules and papules over the body and proximal limbs. A herald patch might be observed. The lesions are usually oriented along skin fragmentation lines ("Christmas tree" pattern).
- The histological examination of PPR reveals patchy parakeratosis, spongiosis, dermal edema, and extravasation of erythrocytes without evidence of capillaritis or vasculitis.
- The course and prognosis of PPR are similar to classical PR, which is self-limiting. The treatment only requires emollients and oral antihistamines. To control pruritus and hasten the resolution of lesions, low-potency topical steroids may be added.

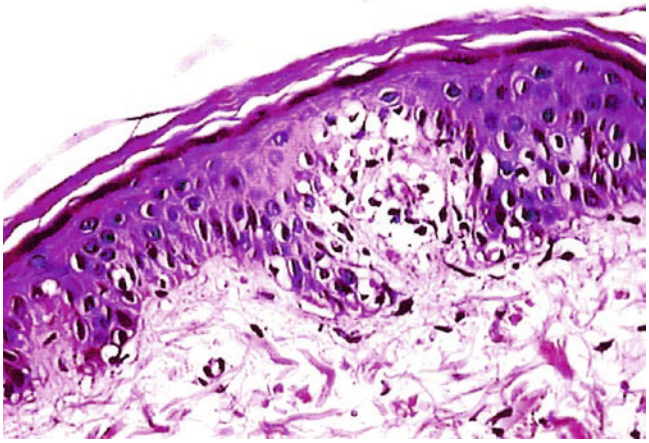
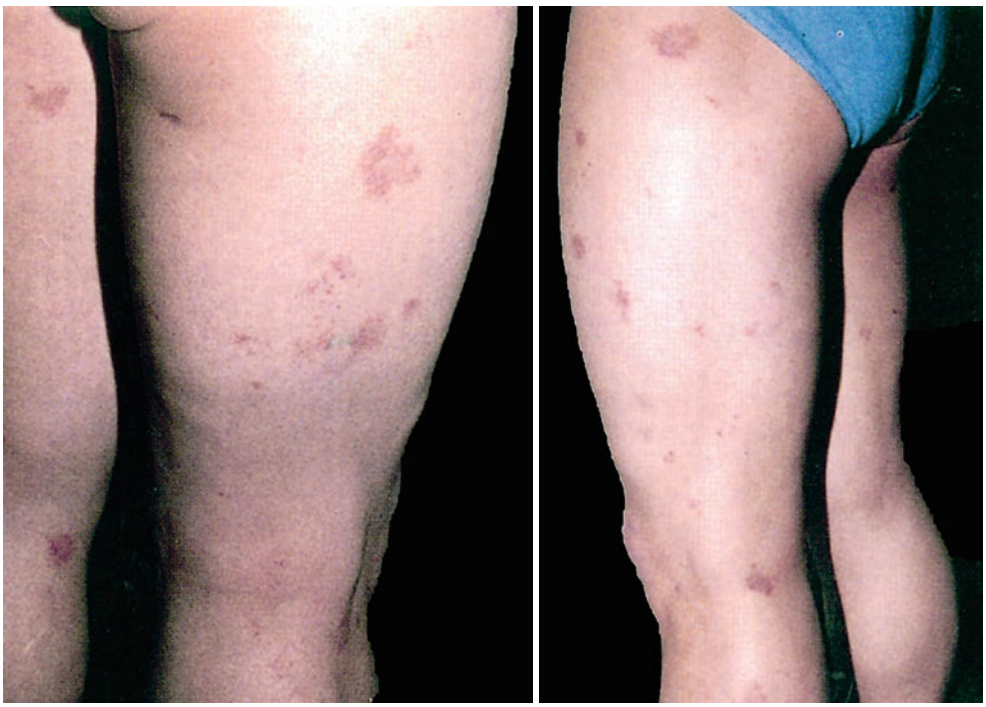


Fig. 9-4-3 Intracellular and intercellular edema, hydropic degeneration of basal cells in the epidermis, edema, and dilated vessels with extravasation of erythrocytes in the papillary dermis (HE stain, ×400)



Figs. 9-4-1, 9-4-2 Petechiae and ecchymoses covered with finely crinkled scaling on the lower limbs

9.5 Generalized Papular Pityriasis Rosea [5]

- Atypical forms of pityriasis rosea (PR) are not uncommon, accounting for up to 20% of all cases and comprising five types: relapsing, persistent, pediatric, pregnancy, and PR-like eruption.
- In terms of morphology, papular, vesicular, and purpuric forms are more common variants of PR.
- The papular form occurs in a minority of patients but is common in children and pregnant women, emerging as various papules (1–2 mm). The lesions may be observed together with classic PR lesions.
- The popular PR is easily confused with a wide variety of similarly appearing cutaneous disorders, posing a challenge for an accurate and timely diagnosis.

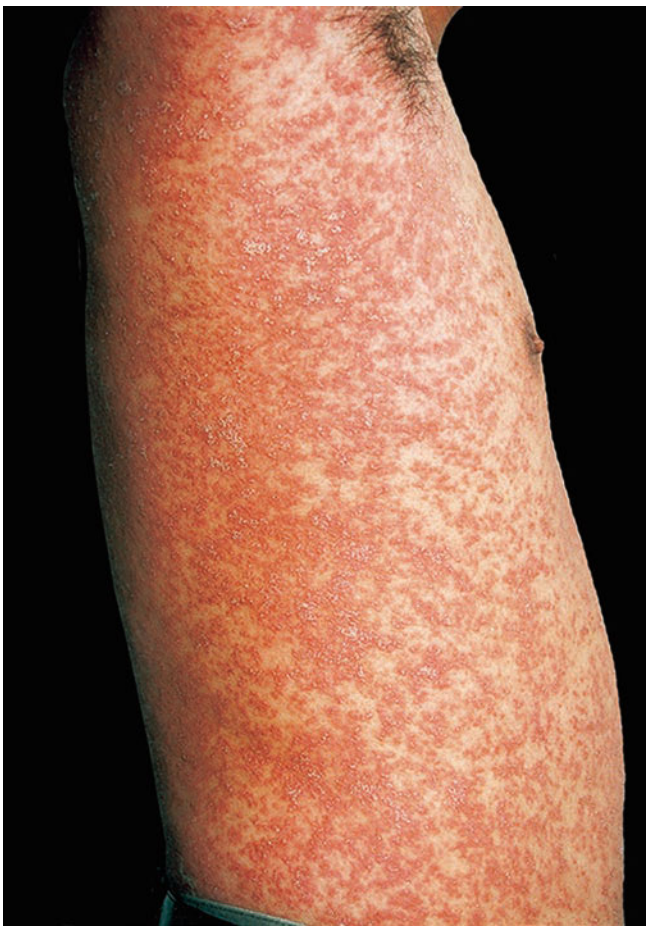


Fig. 9-5-1 Dense red scaly papules on the right flank and waist, part of them confluent with macules

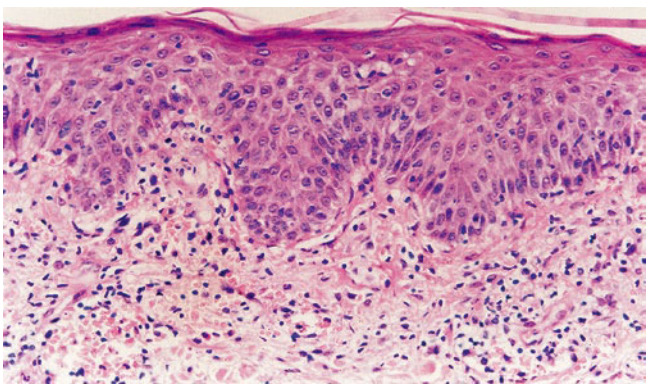


Fig. 9-5-2 Parakeratosis and slight acanthosis, spongiosis, intracellular edema, dilated capillaries, erythrocyte extravasation, and perivascular lymphocyte infiltrate were present (HE stain, ×200)

9.6 Pigmented Pityriasis Rosea [6]

- The incidence rate of atypical pityriasis rosea is 10–15%. According to their morphology, atypical pityriasis rosea can be grouped under the following varieties: purpuric, vesicular, urticaria, generalized popular, lichenoid, erythrodermic, and EM-like forms.
- Many light or dark brown ovular macules without scales occur on the trunk and minimally sun-exposed surfaces. These are arranged along the long axis and run parallel to the lines of cleavage. Skin lesions may be asymptomatic and continue for a long time.

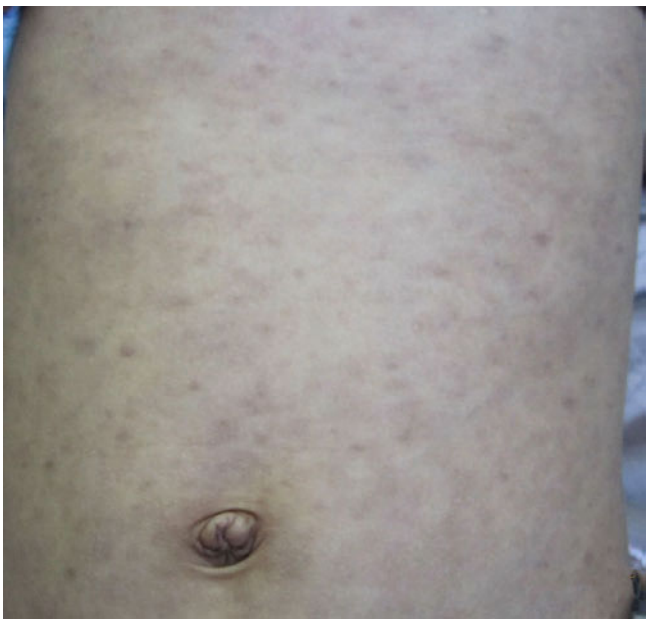


Fig. 9-6-1 Many oval or circinate pigmented patches were arranged along the long axis of the ribs

9.7 Keratosis Follicularis Squamosa (Dohi) [7, 8]

- Keratosis follicularis squamosa (KFS) is characterized by 3–10-mm-diameter asymptomatic scaly patches with follicular plugs on the trunk.
- Bacterial infection, hormonal disorders, and heredity have been considered as methods of pathogenesis of KFS.
- Five cases of KFS have been reported. The skin lesions of KFS were caused by a tight brassiere, belt, and swimsuit, respectively.

Fig. 9-7a-1 The brownish scales with black follicular horny plugs in the center were limited to the area beneath the cloth brassiere

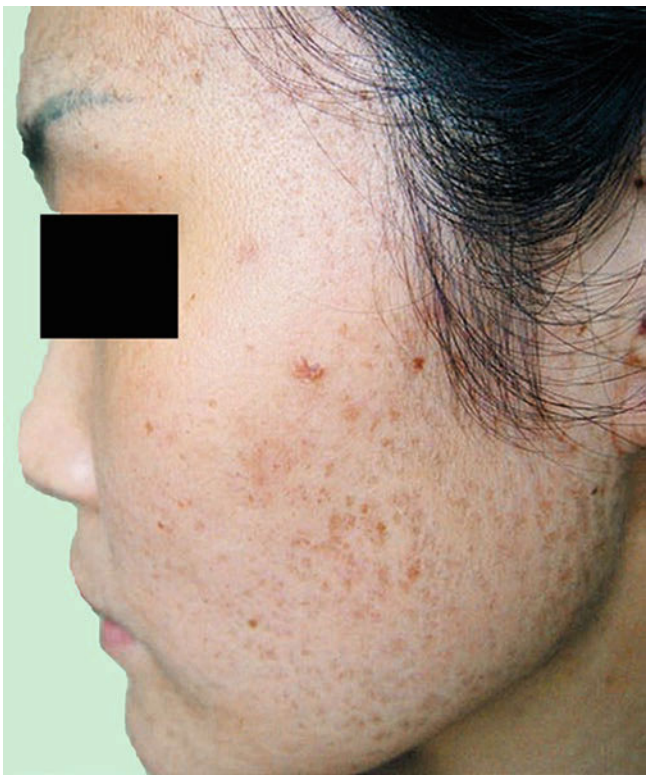


Fig. 9-7b-1 Atrophic acne scars like lesions, with a tiny brownish follicular plug in the center

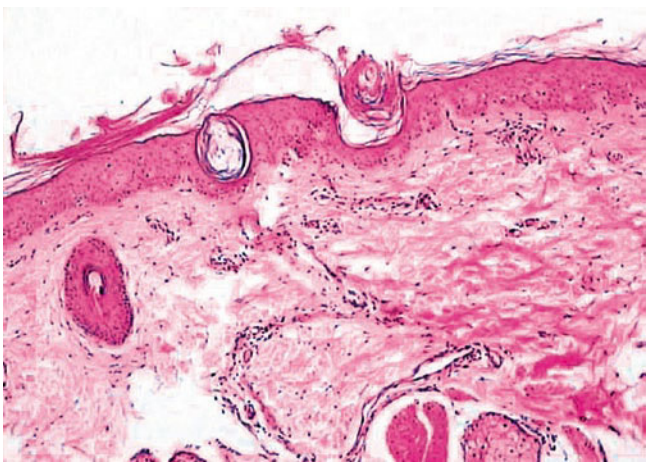


Fig. 9-7b-2 Dilated follicles with keratotic plugs and orthohyperkeratosis of the epidermis. Lateral margins of the scales were slightly detached from the granular layer (HE stain, ×40)

9.8 Hypertrophic Lichen Planus [9, 10]

- Hypertrophic lichen planus (HLP) is a distinct variant of cutaneous LP that features prominent proliferation in the epidermis and severe itching. It prevails on the lower limbs, particularly the tibia and ankle joints.
- Histological examination of HLP suggests excessive hyperplasia of the epidermis, acanthosis, a thickening stratum granulosum, and compact or lamellated hyperkeratosis, with pseudoepitheliomatous observations and liquefaction of the basal cells and a band infiltration of inflammatory cells in the higher dermis.
- The favored treatment for cutaneous LP is high-potency topical corticosteroids. Local triamcinolone acetonide is a satisfactory treatment for HLA. Acitretin (Soriatane) is used for more severe cases that do not respond to topical treatment.

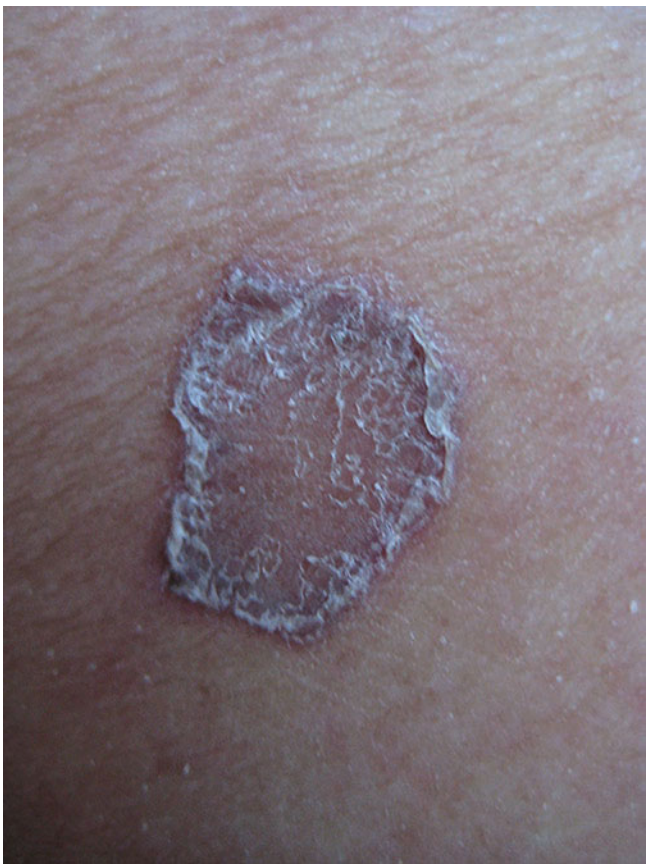


Fig. 9-8-1 A large verrucous plaque with a few scales had an elevated border and center pigmentation

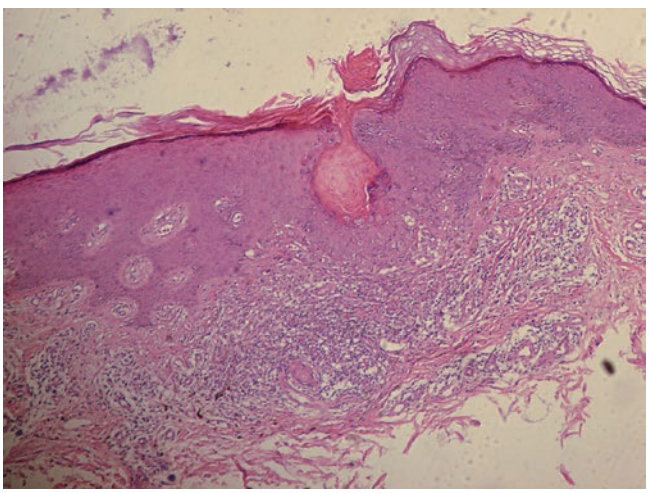


Fig. 9-8-2 Hyperkeratosis and epidermal hyperplasia, liquefaction of the basal cells, and a band-like infiltration of inflammatory cells in the upper dermis

9.9 Lichen Planopilaris [11]

- Lichen planopilaris (LPP), also known as follicular lichen or follicular lichen planus, is a common form of primary cicatricial alopecia that is seen in 80% of middle-aged women.
- The clinical presentation of LPP varies, with early forms presenting slight hair loss. Dermatoscopy and scalp biopsy are helpful for a diagnosis of LP.
- Its treatment is controversial and often unusual. The main goal of therapy is to prevent the progression of cicatricial alopecia.

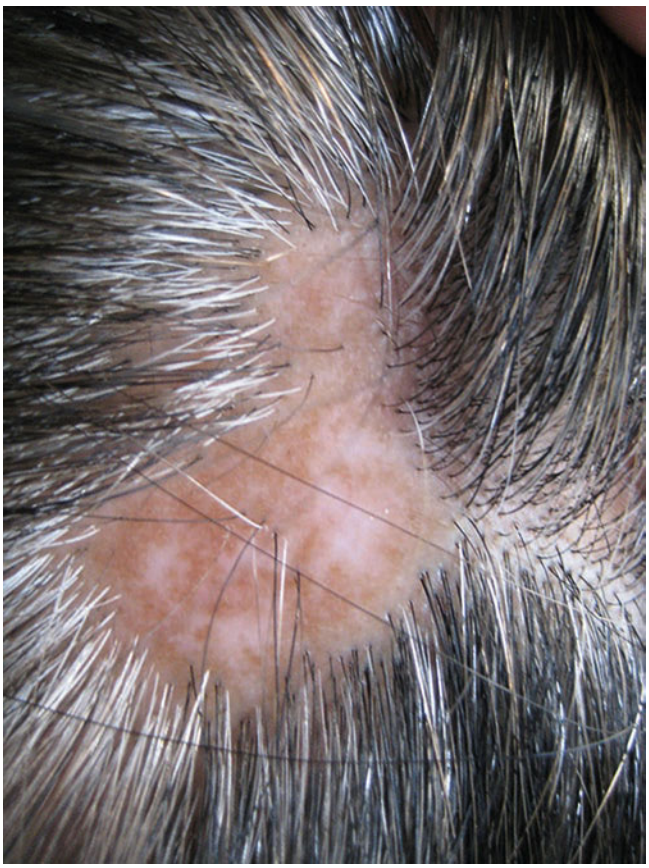


Fig. 9-9-1 The ivory white irregular patches of pseudopelade on the vertex

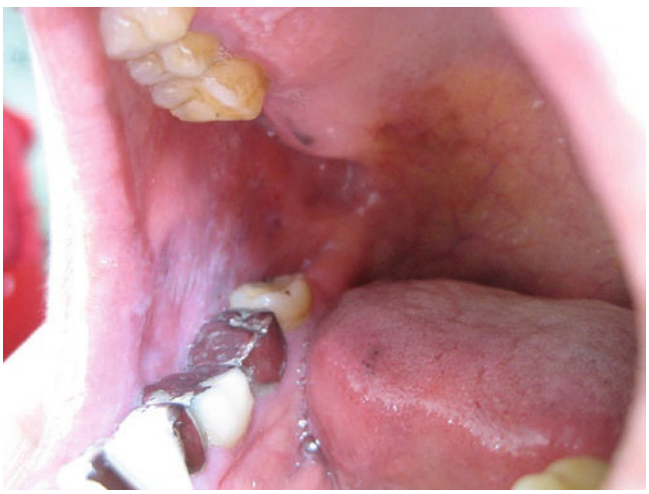


Fig. 9-9-2 The lacy white lesions were on the buccal mucosa

9.10 Lichen Planus Pigmentosus-Inversus [12]

- Lichen planus pigmentosus-inversus (LPPI) features hyperpigmented macules, predominantly over the intertriginous and flexural skin folds.
- Rarely, the lesions in LPPI coincide with Langer's lines of cleavage. External mechanical stimulus to intertriginous areas is a reasonable explanation for its occurrence.

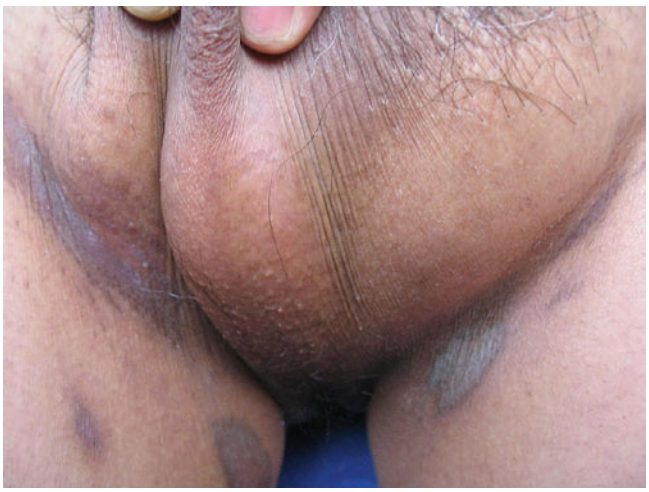


Fig. 9-10-1 Brownish to grayish macules distributed along Langer's lines in the bilateral gluteal areas

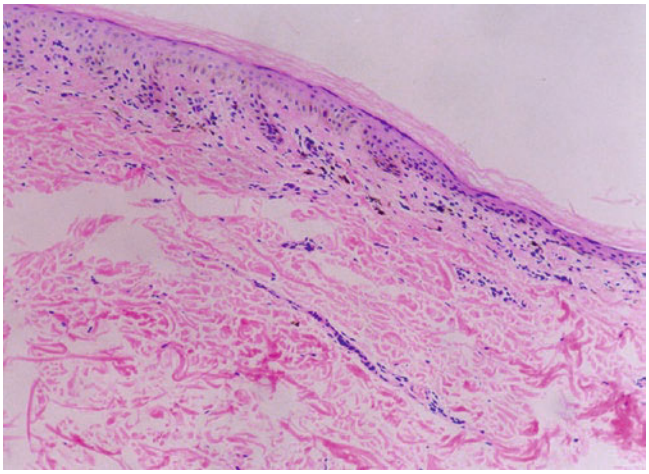


Fig. 9-10-2 Hyperkeratosis, epidermal atrophy, and lymphocytic infiltration in the dermis (HE stain, ×100)

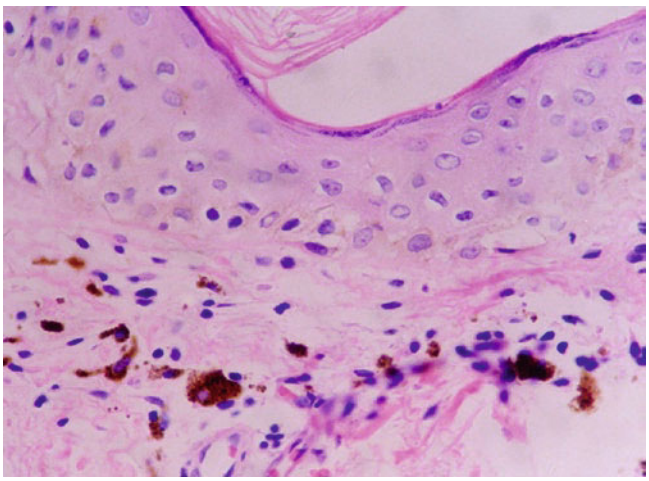


Fig. 9-10-3 Liquefaction degeneration of basal layer cells; melanophages can be noted in the dermis (HE stain, ×400)

9.11 Linear Lichen Planus Pigmentosus [13]

- Lichen planus pigmentosus (LPP), a subtype of lichen planus, is a relatively infrequent cutaneous disorder that runs along Blaschko's lines.
- The representative presentations of LPP are spotted or retiform hyperpigmented, with nigger-brown macules or papules. Lesions of LPP preferentially emerge in regions that are usually exposed to the sun and in flexural folds.
- The differential diagnosis of LPP involves linear dermatosis such as lichen striatus, postinflammatory hyperpigmentation, linear and ashy dermatosis, and whorled nevoid hypermelanosis. At present, hydroquinone may be a pivotal kind of topical agent.

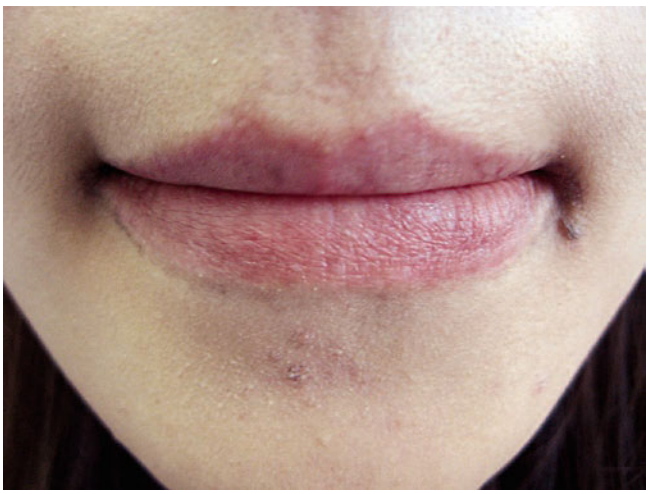


Fig. 9-11-1 There was a well-defined dark brown streak paralleling near the lower lip line

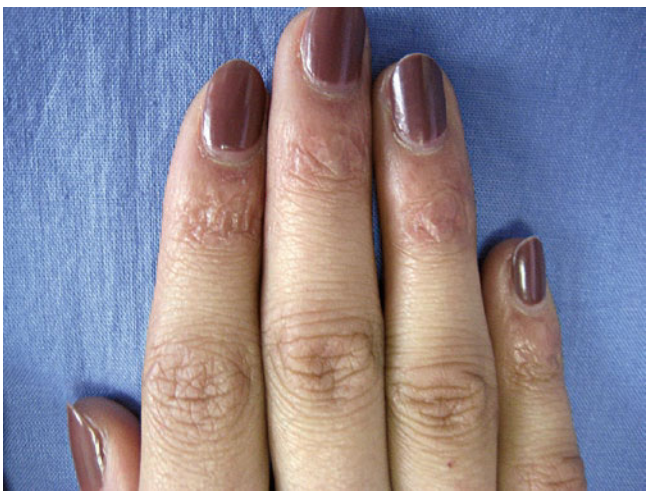


Fig. 9-11-2 A few dark porphyreous speckles clustered on the skin near to the nail fold of right fingers except the thumb

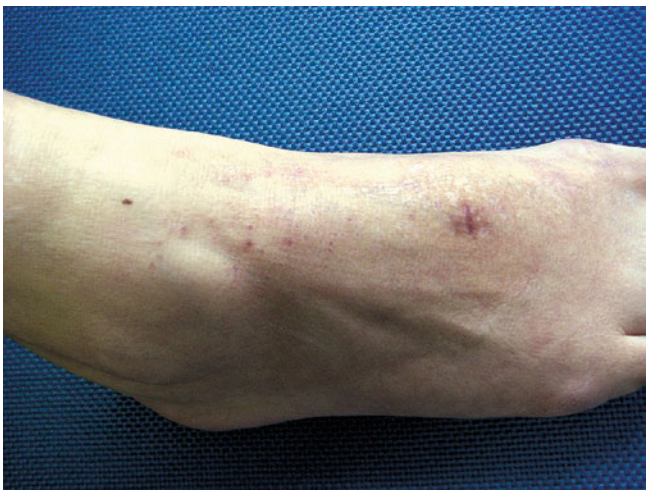


Fig. 9-11-3 On the dorsum of the right foot, many flat-topped, shiny, purple, and polygonal papules are presented, showing a distribution of zosteriform pattern

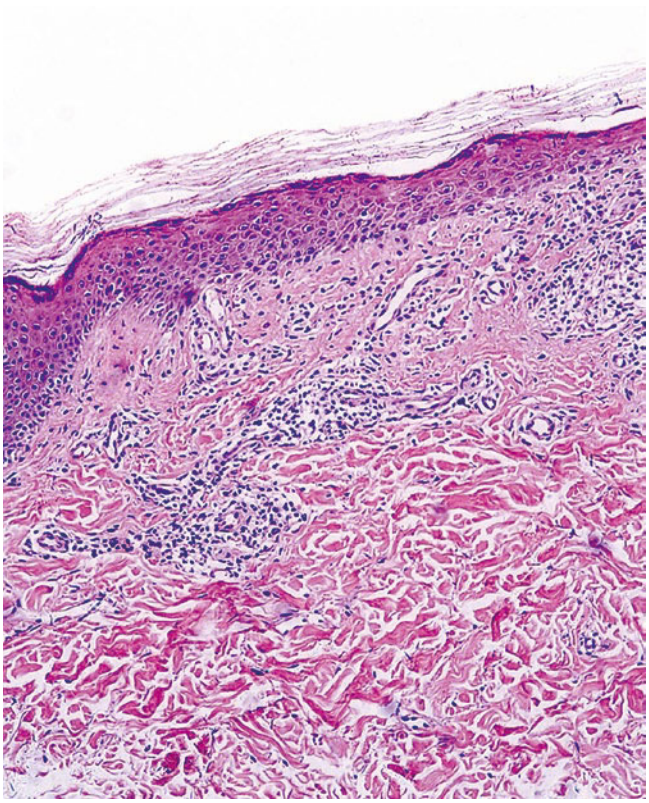


Fig. 9-11-4 Hyperkeratosis, parakeratosis, and atrophy of the epidermis with liquescent degeneration of the basal cells. A perivascular lymphohistiocytic infiltration and pigmentary incontinence in the dermis were also noted (HE stain, ×200)

9.12 Nail Lichen Planus [14]

- The incidence rate of nail lichen planus (NLP) is approximately 10% in patients with lichen planus (LP). NLP features destruction of the nail plate, particularly the fingernails.
- NLP is usually located in the matrix, presenting with nail plate thinning, longitudinal ridging, and fissuring, with occasional onycholysis with or without subungual hyperkeratosis.
- Early diagnosis is vital because of its aggressive behavior. Histopathology should be carried out in suspected cases, while dermatoscopy has proven to be useful for its diagnosis.
- It is hard to treat this disorder, which has a high rate of recurrence. Alitretinoin is a satisfactory treatment option.

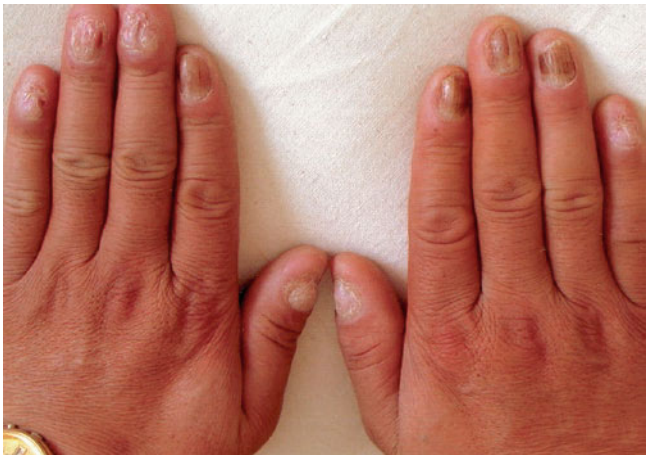


Fig. 9-12-1 Irregular longitudinal grooving and ridging of the nail plate, thinning of the nail plate, pterygium formation, and shedding of the nail plate with atrophy of the nail bed

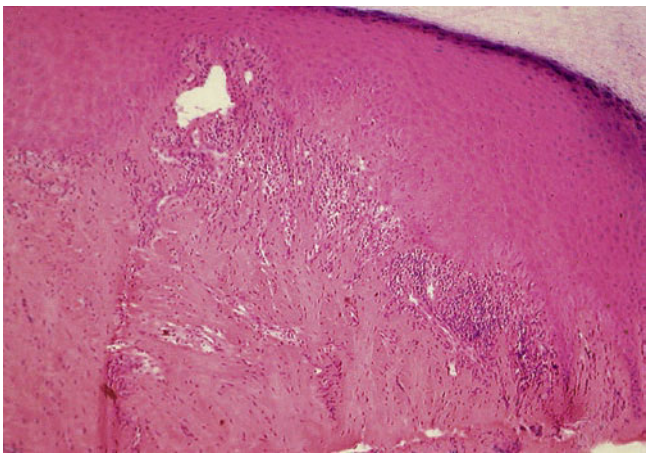


Fig. 9-12-2 Acanthosis, liquefaction degeneration of basal layer cells, and lymphocyte band-like infiltrate in the upper dermis (HE stain, ×100)

9.13 Coincidence of Lichen Planus and Vitiligo [15]

- Lichen planus and vitiligo are relatively frequent cutaneous diseases. Given a relevant prevalence of 0.5~1% of vitiligo and lichen planus, the coexistence of these disorders in one patient is predictable.
- However, the appearance of both conditions in one patient is not just an occasional phenomenon based on the probability of an autoimmune background or usual pathogenesis.
- Immunity has a direct effect on the etiology of lichen planus and vitiligo. The coincidence of these two skin disorders has been reported solely or concomitant with other autoimmune disorders.

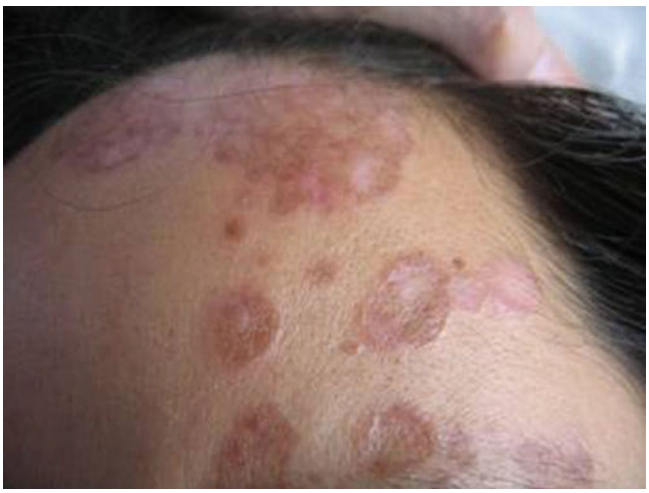


Fig. 9-13-1 Madder red or brown, round or polygonal, 0.3~3.0 cm in diameter maculae or patches, with an elevated borderline on the left side of the frontal region

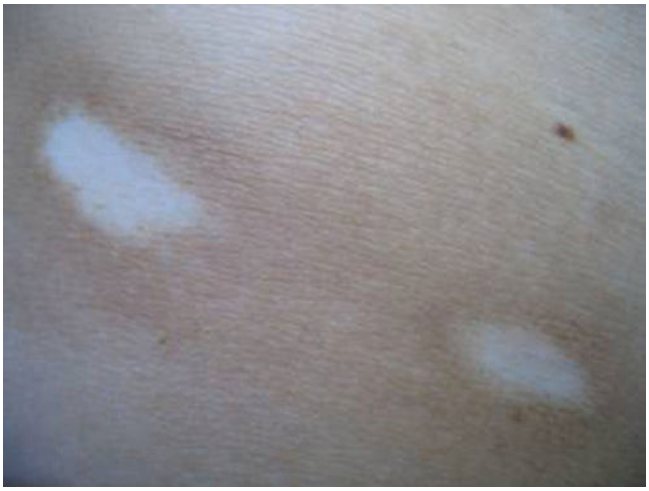


Fig. 9-13-2 Irregular depigmented patches on the right side of the waist (2 cm × 2 cm ~ 2 cm × 5 cm)

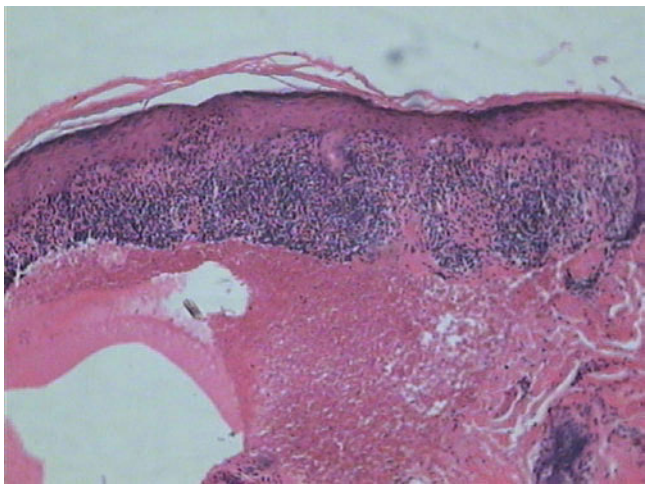


Fig. 9-13-3 Hyperkeratosis, focal hypergranulosis, and irregular acanthosis in the epidermis (HE stain, ×40)

9.14 Acute Generalized Lichen Planus [16]

- Acute generalized lichen planus presents as generalized, erythematous papules and hyperpigmented macules with a flat to. The shape of the lesions is round, polygonal, or umbilicated. Patients mostly present severe pruritus.
- This condition may pose a therapeutic challenge for dermatologists if the condition persists or flares after topical or systemic corticosteroid therapy. Another choice of therapy for this disease might be acitretin.

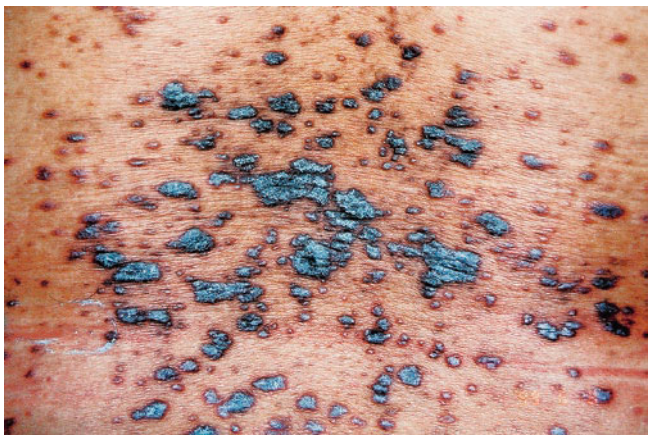


Fig. 9-14-1 Thick, polygonal, violaceous, hyperkeratotic papules on the waist

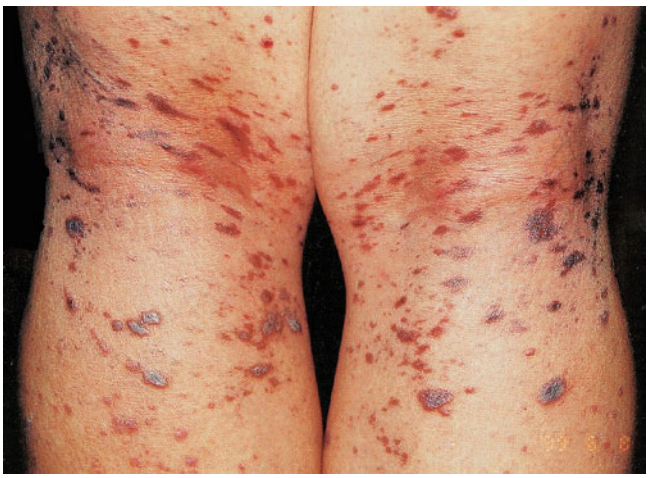


Fig. 9-14-2 Dense violaceous papules on the flexor surfaces of both lower limbs

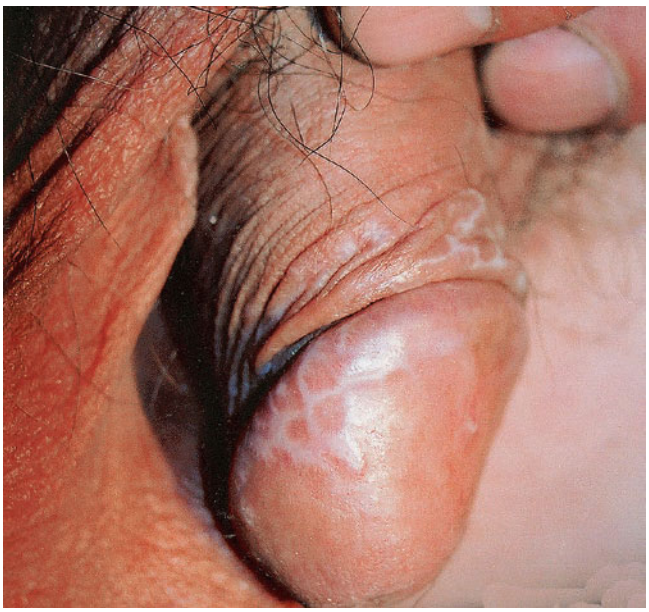


Fig. 9-14-3 Dendritic whitish maculae on the glans penis and foreskin

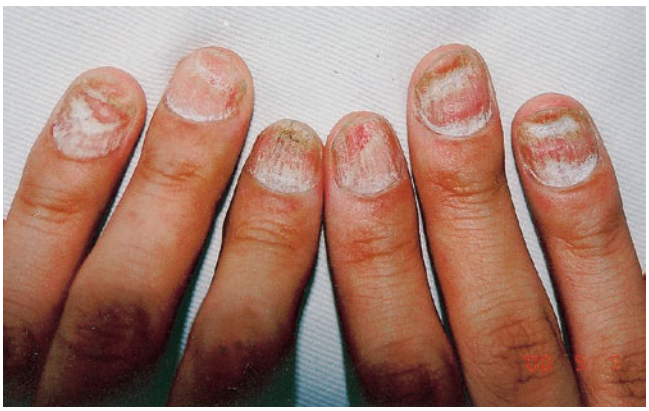


Fig. 9-14-4 Roughened nails with white scales on the fingers

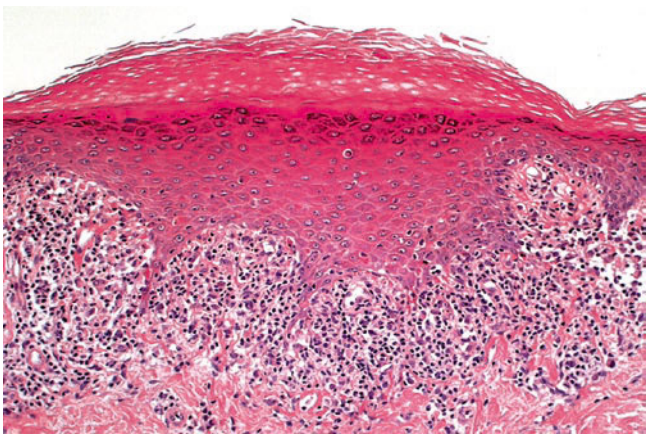


Fig. 9-14-5 Hyperkeratosis, hypergranulosis, acanthosis, basal cell liquefaction degeneration, and a band-like lymphocyte infiltrate in the upper dermis (HE stain, ×100)

9.15 Dermatosis Papulosa Nigra [17]

- Dermatosis papulosa nigra (DPN) is considered to be a benign cutaneous disorder. The manifestation of DPN presents as multiple, small (1–5 mm), excessive pigmentation macules and papules. Lesions frequently occur in the malar regions of the face, neck, forehead, and trunk.
- It usually begins in adolescence and is far more common in females than males, with a ratio of two to one. The histological findings of DPN are the same as those of seborrheic keratosis (acanthotic type). Horn pseudocysts may sometimes occur.
- The mainstay treatments for DPN cover curettage, surgical excision, cryotherapy, laser procedure, and electrodesiccation.

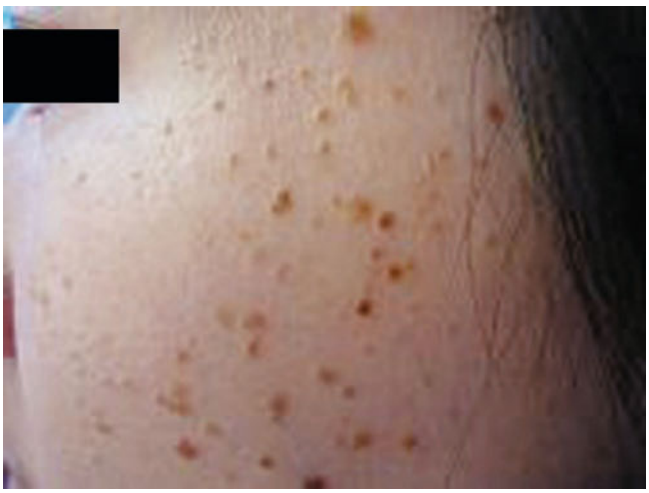


Fig. 9-15-1 Diffuse symmetric distribution of flat, round papules with papillomatous tops in sizes of 1–5 mm in diameter

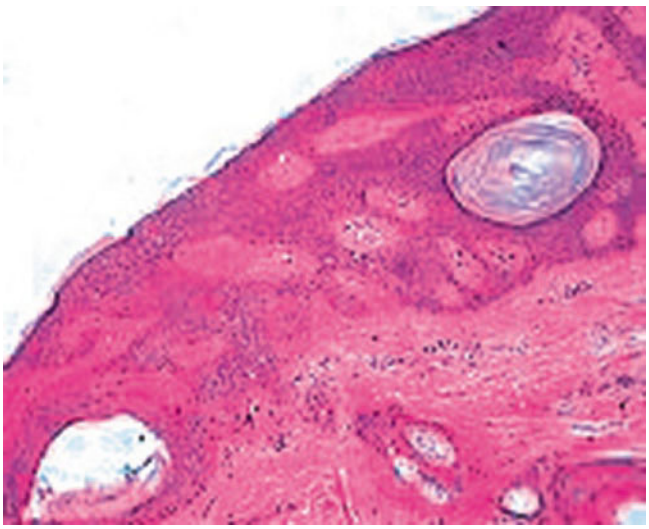


Fig. 9-15-2 Hyperkeratosis, mild acanthosis, and normal granular layer; elongation of rete ridge forming net-like structure; two keratin cysts in the spinous layer and increased melanin granules in the basal layer; a few of lymphocytes around the small vessels in the super dermis (HE stain, ×40)

9.16 Lichen Sclerosus [18]

- The terms lichen sclerosus et atrophicus, kraurosis vulvae, and balanitis xerotica obliterans are replaced by the single term lichen sclerosus, which can present from childhood to old age and occurs most commonly in females.
- In females, white, polygonal, flat-topped papules, plaques, or atrophic patches with severe itching may be seen in the vulvar and perianal areas. In males, the white atrophic macules may present on the glans penis, penile shaft, perianal area, and scrotum.
- Phimosis and paraphimosis are common complications of lichen sclerosus. Extragenital lesions preferentially occur on the upper back, chest, and breasts. Between 44% and 55% of cases of penile SCC are associated with lichen sclerosis.
- The histopathology shows atrophy of the epidermal layer with hydropic degeneration of basal cells and edema, accompanied by homogenization of the collagen in the dermis.

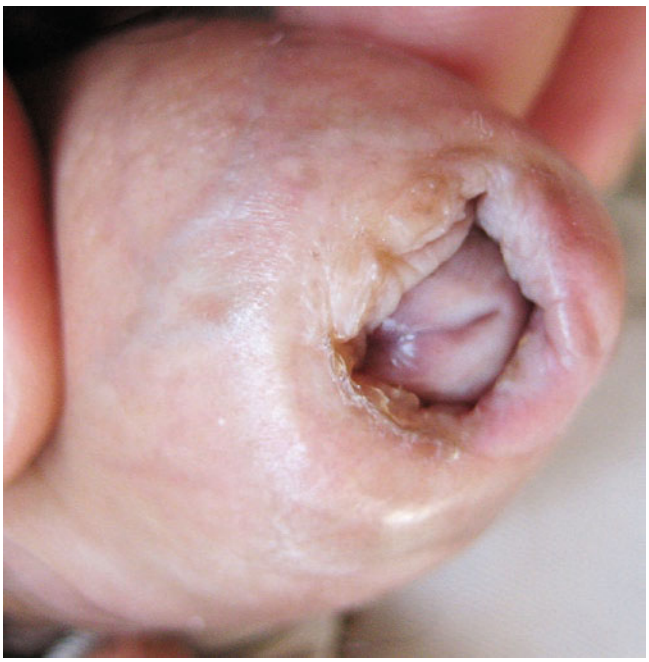


Fig. 9-16a-1 White and sclerosus plaques involved the penile shaft and the glans penis

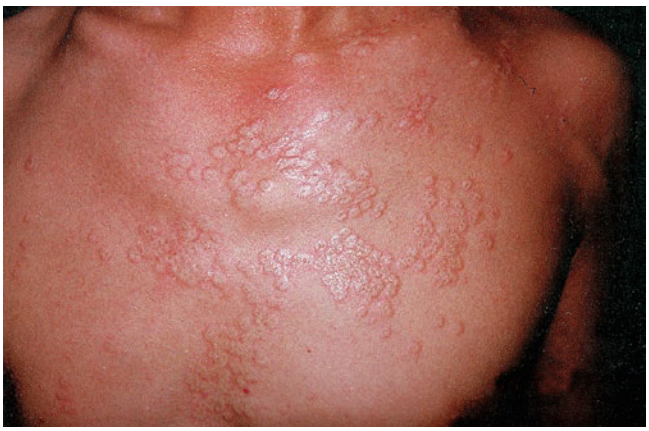


Fig. 9-16b-1 White flat-topped, discoid papules or plaques covered with horny plugs and surrounded by an erythematous halo on the chest

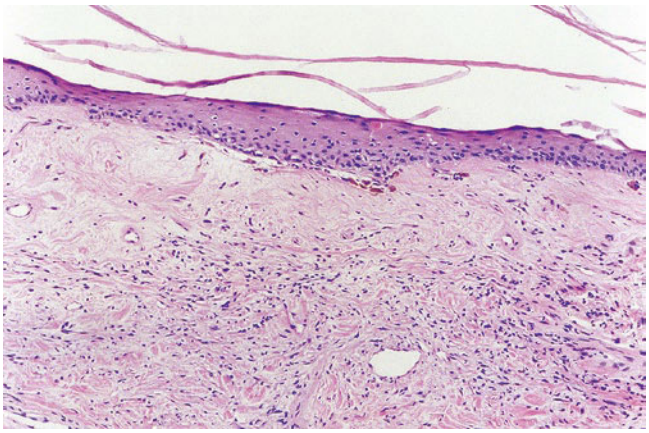


Fig. 9-16b-2 Hyperkeratosis with follicular plugging, atrophy of the stratum malpighii with hydropic degeneration of basal cells, pronounced edema and homogenization of the collagen in the upper dermis, and an inflammatory infiltrate in the middermis (HE stain, ×20)

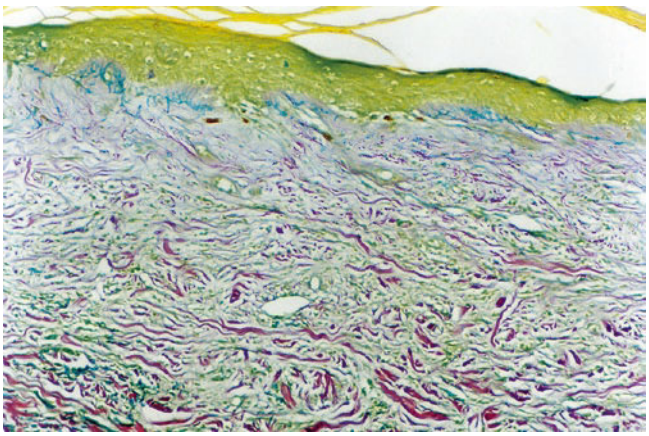


Fig. 9-16b-3 The diminution of elastic fibers sparse in the upper dermis (Verhoeff stain, ×20)

9.17 Erythromelanosis Follicularis Faciei Et Colli [19]

- Erythromelanosis follicularis faciei et colli (EFFC) is considered to be a relatively infrequent cutaneous disorder. Clinically, erythema, follicular papules, and light brown pigmentation are easily observed. The lesions preferentially present on the preauricular and maxillary region.
- EFFC occurs mostly in men during adolescence and occasionally in women. Keratosis pilaris occurring on the arms and shoulders is frequently found.
- No treatment has proven satisfactory for EFFC. Various options have been attempted, but the lesions recur after discontinuing treatment.

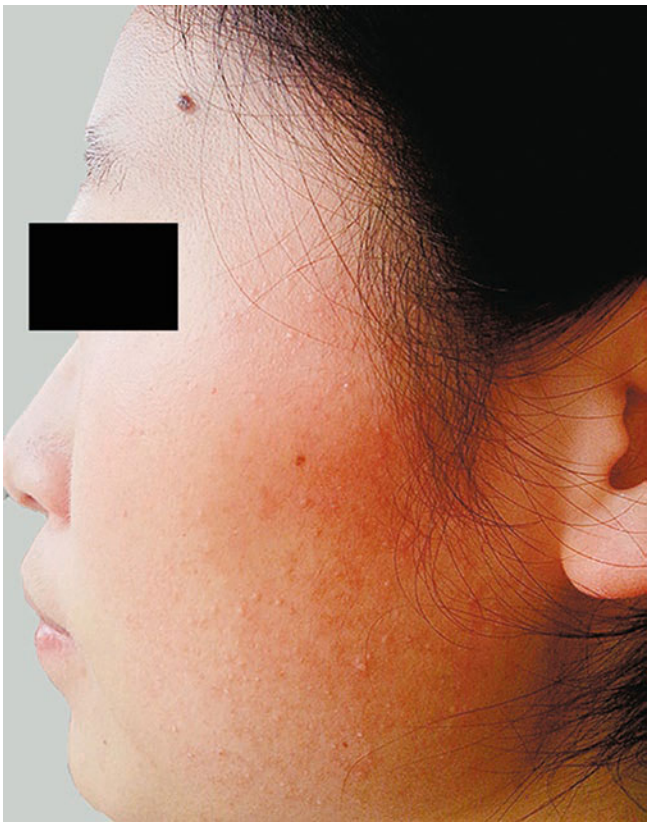


Fig. 9-17-1 Follicular papules and reddish-brown spots or patches on the cheeks and temples

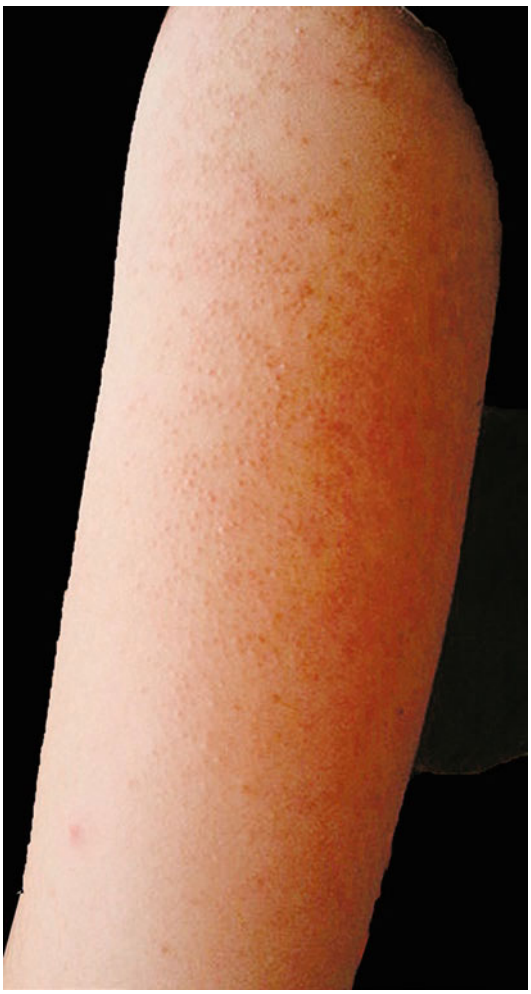


Fig. 9-17-2 Follicular keratosis papules on the extensor aspect of the arms. Her mother had similar condition

9.18 Lichen Aureus [20, 21]

- Lichen aureus (also called "lichen purpuricus") is an uncommon subtype of pigmented purpuric dermatosis with a chronic and benign course.
- Clinically, lichen aureus usually shows asymptomatic, unilateral, and solitary plaques, which are more frequently located on the lower extremities. Skin lesions vary in color, ranging from dark brown to copper and a golden hue.
- The histopathological examination of lichen aureus suggests infiltration of lymphocytes and histiocytes and extravasation of erythrocytes and hemosiderin, with little or no epidermal alteration.
- Treatment is difficult. The therapeutic arsenal includes topical corticosteroids, calcineurin inhibitors, and PUVA.

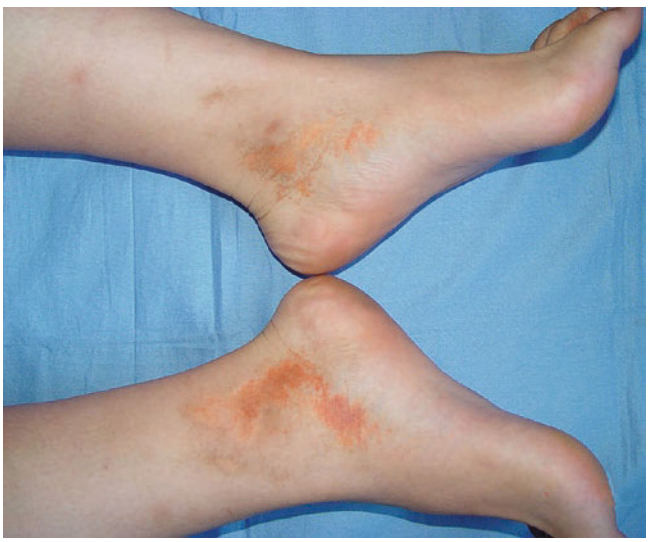


Fig. 9-18-1 Golden pigmented maculae presented as "cayenne pepper" on the dorsum of both feet. The skin lesions are confluent on the inner malleolus

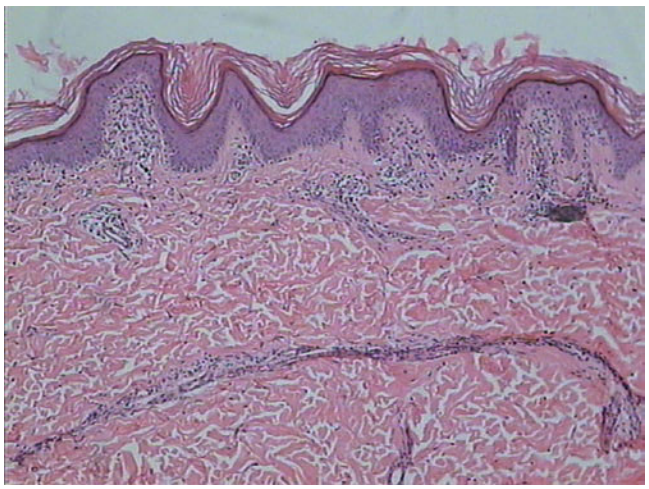


Fig. 9-18-2 A band-like infiltration of mononuclear and histiocytic cells in the upper dermis (HE stain, ×100)

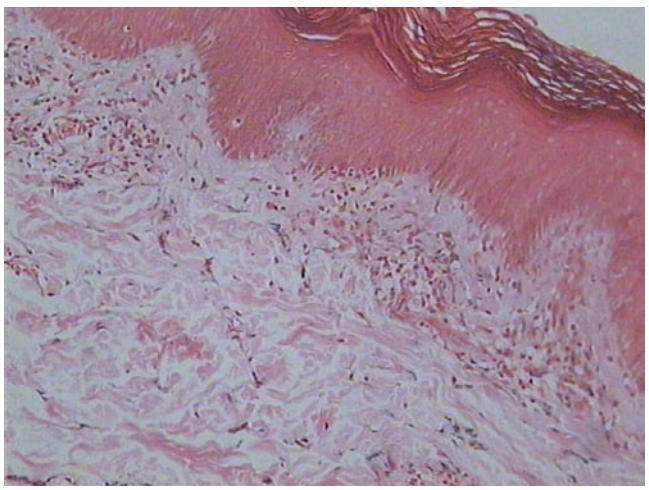


Fig. 9-18-3 Perls staining showed the presence of massive hemosiderin in the upper dermis (HE stain, ×200)

9.19 Generalized Lichen Nitidus [22, 23]

- Lichen nitidus (LN) is a rare chronic inflammatory dermatosis. Small (1–2 mm) and skin-colored or erythematous papules may be observed in many cases. Children and young adult are among the most vulnerable. Commonly, it occurs on the penis, abdomen, genital region, and extremities.
- LN can be segmented into seven types, including vesicular, hemorrhagic, follicular, linear, actinic, and generalized variants. Generalized LN is extremely unusual and can be associated with Down syndrome and multiple endocrine neoplasia (MEN).
- Local steroids, antagonists, antituberculous agents, narrowband UVB phototherapy, acitretin, and low-dose cyclosporine may also play a role.

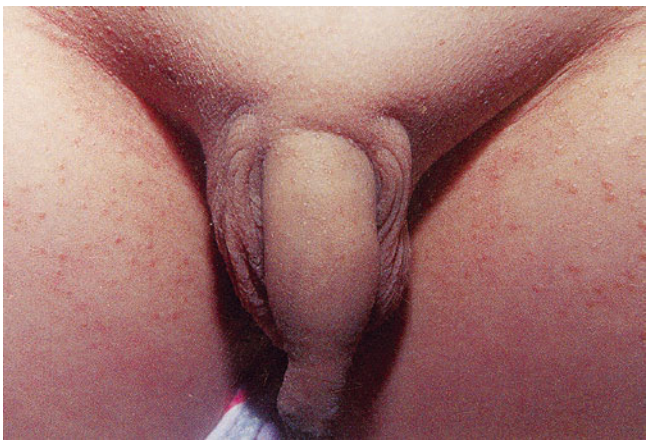


Fig. 9-19-1 Numerous flat-topped, skin-colored, round or polygonal papules without coalescence on the penis and foreskin

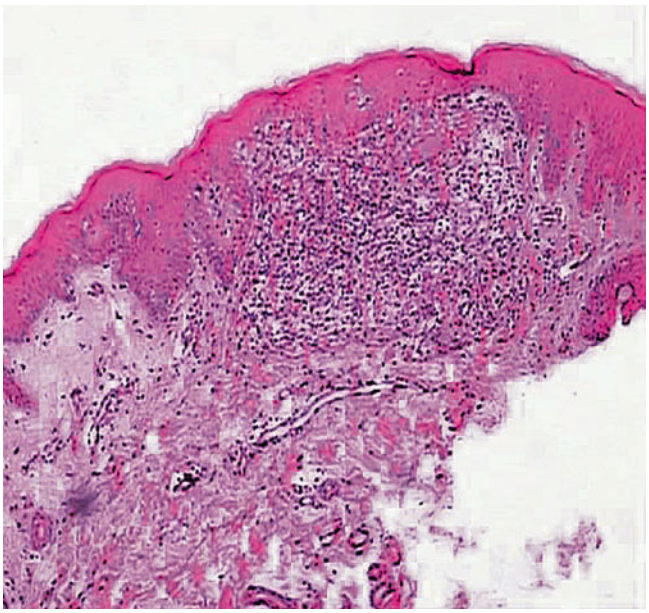


Fig. 9-19-2 Circumscribed nest of cells in the dermis papillary; the infiltrate consisted of lymphocytes, epithelioid cells, histiocytes, and a few multinucleated giant cells (HE stain, ×100)

9.20 Pityriasis Rotunda [24]

- Pityriasis rotunda (PR), also called "pityriasis circinata" and "tinea circinata," is a relatively rare disorder. Typical features are scaly, circular, well-demarcated, hypo- or hyperpigmented fine plaques over the trunk and extremities.
- PR may be idiopathic or related to infections or malignancy. The number may range from 1 to rarely greater than 100, with a typical diameter of 2–3 cm that may, in some cases, exceed 20 cm.
- Histopathological examination of PR shows hyperkeratosis, an absent granular layer, a pigmented basal layer, pigmentary incontinence, and a perivascular lymphocytic infiltrate.
- Conventional topical therapies have shown no benefit. Lactic acid lotion and oral vitamins may improve the lesions. In some cases, successful treatment of the underlying disease leads to clearance of the lesions.

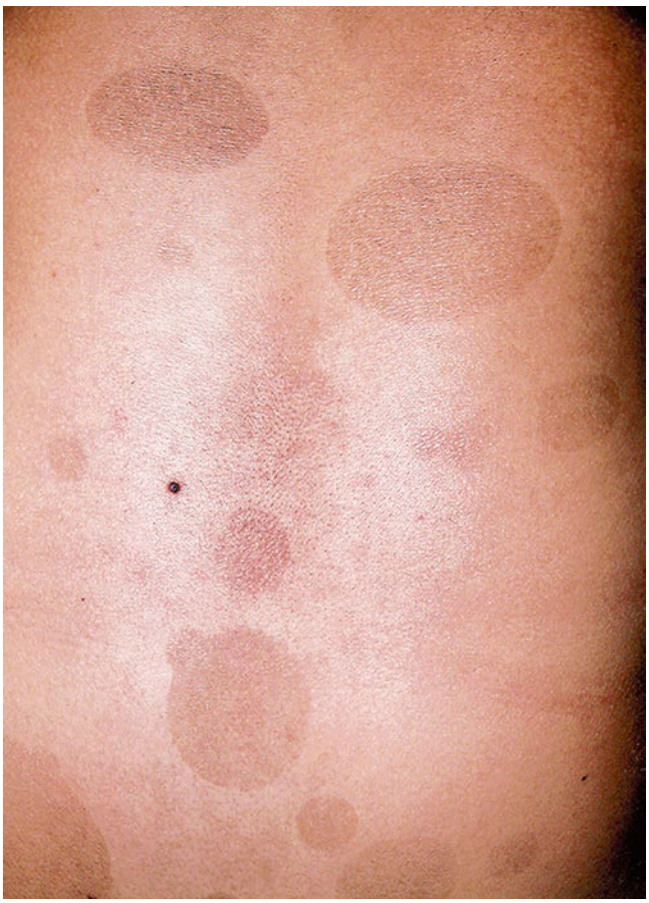


Fig. 9-20-1 Multiple, strikingly circular, or oval scaly patches on the trunk

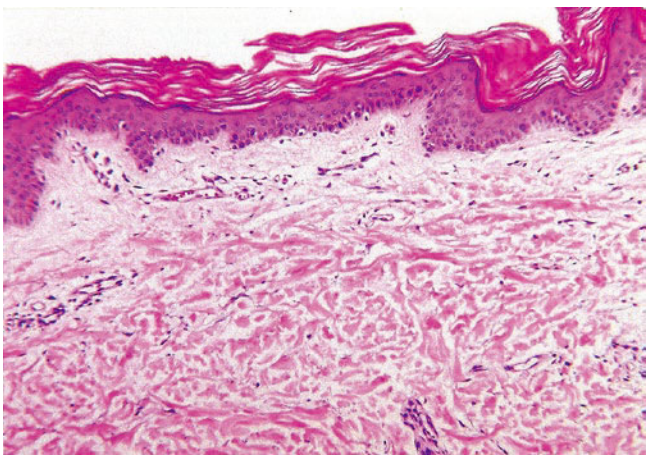


Fig. 9-20-2 Hyperkeratosis and infiltrate of a few lymphocytes and histiocytes around blood vessels in the dermis (HE stain, ×100)

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Part III

Reumatologic and Vesiculobullous Diseases

Rheumatologic Diseases

10

Xiang-Yang Su, You-Shou Gu, Dong-Lai Ma, Shu-Xian Yan, Tao Qu, Ru-Zhi Zhang, Ding-Hua Kang, Li-Wen Ma, Cheng Tan, and Wen-Yuan Zhu

Abstract

Rheumatologic diseases have a diversity of cutaneous and systemic manifestations. This chapter presents with annular erythematous type of subacute cutaneous lupus erythematosus, bullous systemic lupus erythematosus, lupus erythematosus tumidus, neonatal lupus erythematosus, antiphospholipid syndrome, nodular scleroderma, atrophoderma of Pasini and Pierini, acrodermatitis chronica atrophicans, linear atrophoderma of Moulin, rheumatoid neutrophilic dermatitis, and graft-versus-host disease.

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10.1 Annular Erythematous Type of Subacute Cutaneous Lupus Erythematosus [1]

- Subacute cutaneous lupus erythematosus (SCLE) comprises approximately 10% of LE and exhibits either non-scarring papulosquamous (two-thirds) or annular polycyclic (one-third) lesions, with positive circulating SSA/anti-Ro antibodies.
- Certain genetic backgrounds favor development, with ultraviolet light and drugs, as potentially the most important triggers. Histopathological examination reveals interface dermatitis with vacuolar degeneration of basal keratinocytes and dermal mucinosis.
- The treatments are variable, including topical sunscreens, tacrolimus, pimecrolimus, moderate potency steroids, oral antimalarials, and glucocorticoids.

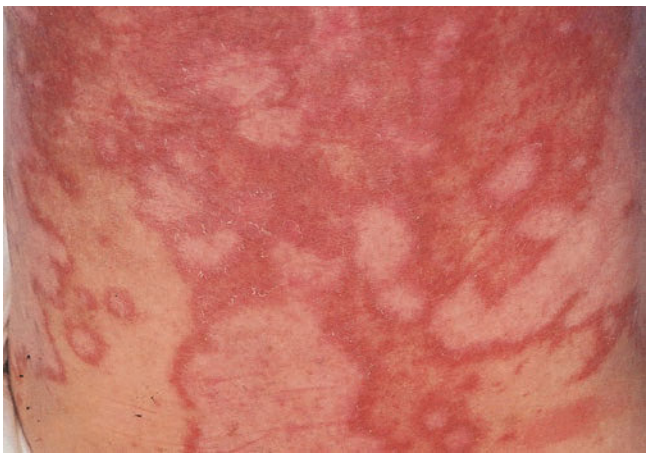


Fig. 10-1-1 Annular and polycyclic erythema with thin scales and elevated edges on the back

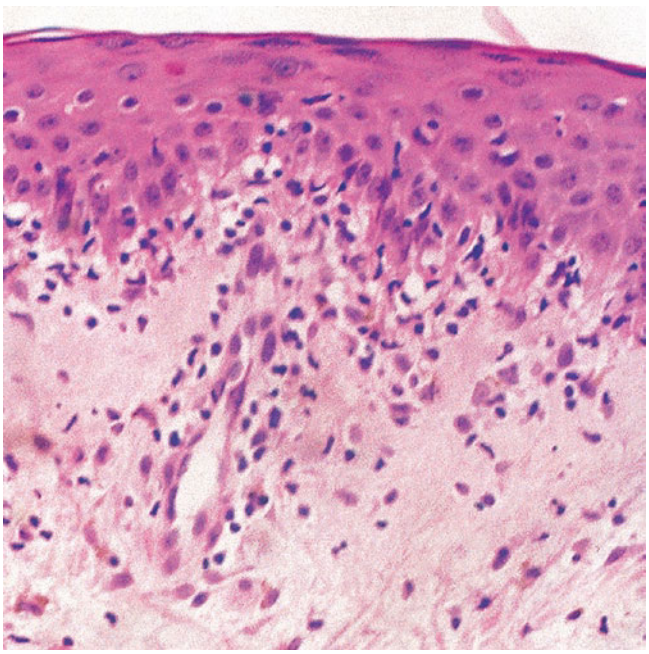


Fig. 10-1-2 The epidermis is atrophic. There is liquefaction degeneration of the basal cells and lymphocytic and eosinophilic perivascular infiltrations in the upper dermis (HE stain, ×400)

10.2 Bullous Systemic Lupus Erythematosus [2]

- Bullous systemic lupus erythematosus (BSLE) is an acquired autoimmune dermatosis that has a preference for patients with SLE. It typically presents with multiple, tense, and clear fluid-filled vesicles and bullae overlying erythematous plaques.
- Although the relationship between bullous eruptions and symptom flares in SLE has not been determined, BSLE may lead to a risk for developing lupus nephritis and may be related to a worse prognosis and refractory disease.
- The autoimmune characteristics of bullous lupus erythematosus are manifested as the presence of circulating anti-VII collagen antibodies. Histopathological examination reveals subepidermal blisters with a neutrophil-predominant infiltrate in the upper dermis.
- According to the findings during treatment, corticosteroids are ineffective, while dapsone generally improves the condition of the skin.

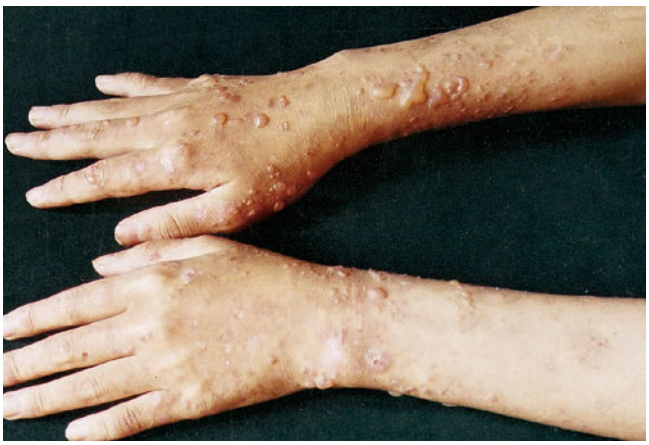


Fig. 10-2-1 Numerous blisters on the forearms and dorsum of both hands

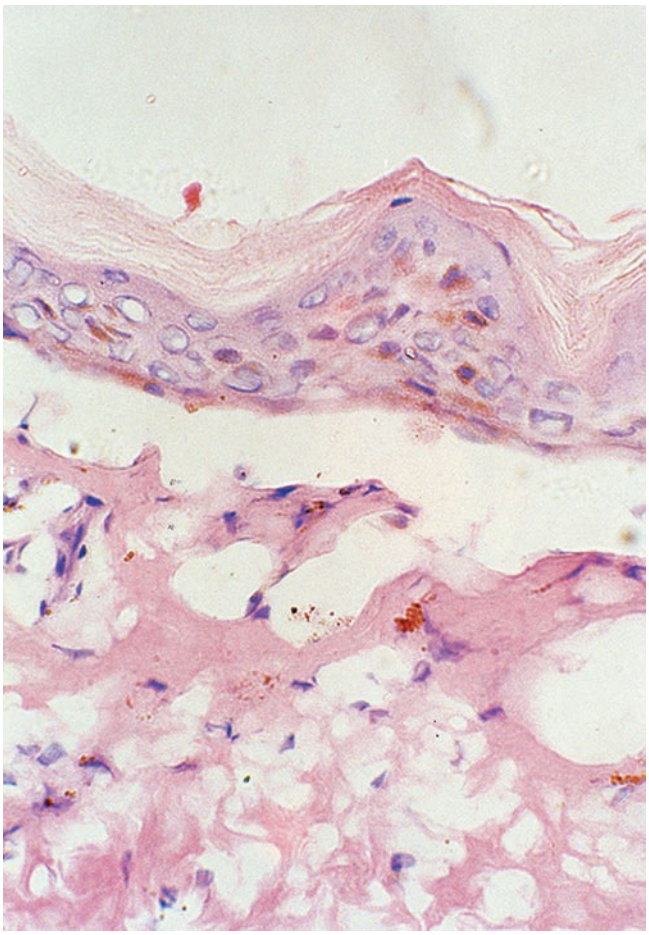


Fig. 10-2-2 A subepidermal bulla and liquefaction degeneration of basal cells (HE stain, ×400)

10.3 Lupus Erythematosus Tumidus [3, 4]

- Lupus erythematosus tumidus (LET) is an uncommon photosensitive dermatosis. However, there are no changes on the epidermal surface and scarring on resolution in most cases. The succulent, edematous, and non-scarring plaques preferentially occur on sun-exposed regions.
- Histologically, perivascular and periadnexal infiltration of lymphocytes and interstitial deposition of mucin are observed.
- Usually, LET is a benign disease. Photo-protective measures and antimalarials are often effective. In addition, corticosteroids, tacrolimus ointment, and methotrexate may play a role.

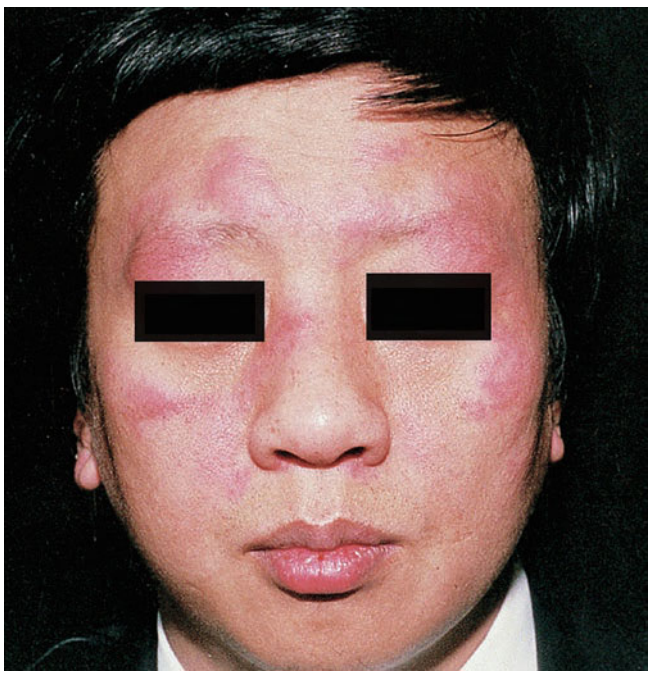


Fig. 10-3-1 Edematous erythema on the face (Reproduced with the permission from [3, 4])

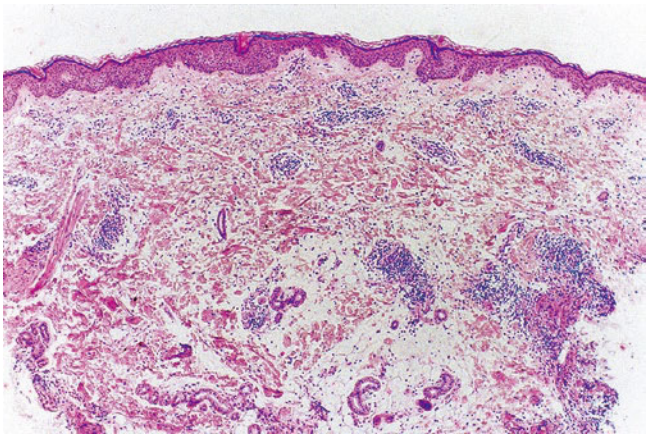


Fig. 10-3-2 Lymphohistiocytic infiltration in superficial and deep perivasculatures and around the appendages of the skin (HE stain, ×40)

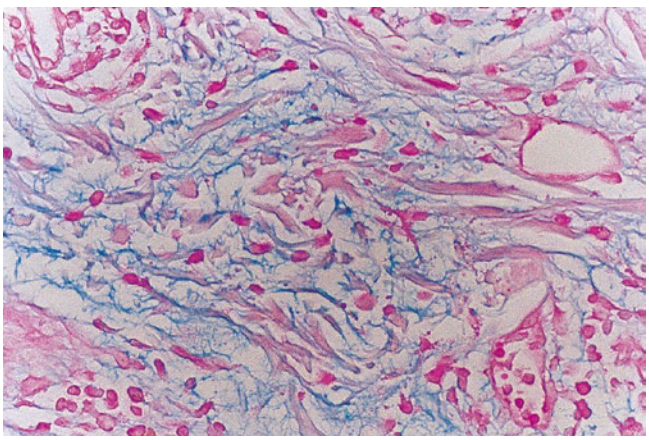


Fig. 10-3-3 Alcian blue stain showed abundant mucin deposition in collagen bundles of dermis (Alcian blue stain, ×100)

10.4 Neonatal Lupus Erythematosus [5]

- Neonatal lupus erythematosus (NLE) is a relatively uncommon autoimmune disease. The typical clinical features are cutaneous lesions, hematological or hepatic abnormalities, and congenital heart block.
- Generally, NLE is related to the transplacental passage of maternal IgG against Ro/SSA, La/SSB, and U1-RNP after 3 months of pregnancy.
- Typical lesions comprise erythematous, centrally atrophic plaques that are annular or polycyclic and preferentially affect the face and scalp. They usually begin in the first weeks of life and improve within 4–6 months.
- The diagnosis depends on the typical clinical features and the occurrence of autoantibodies in maternal or infant serum.

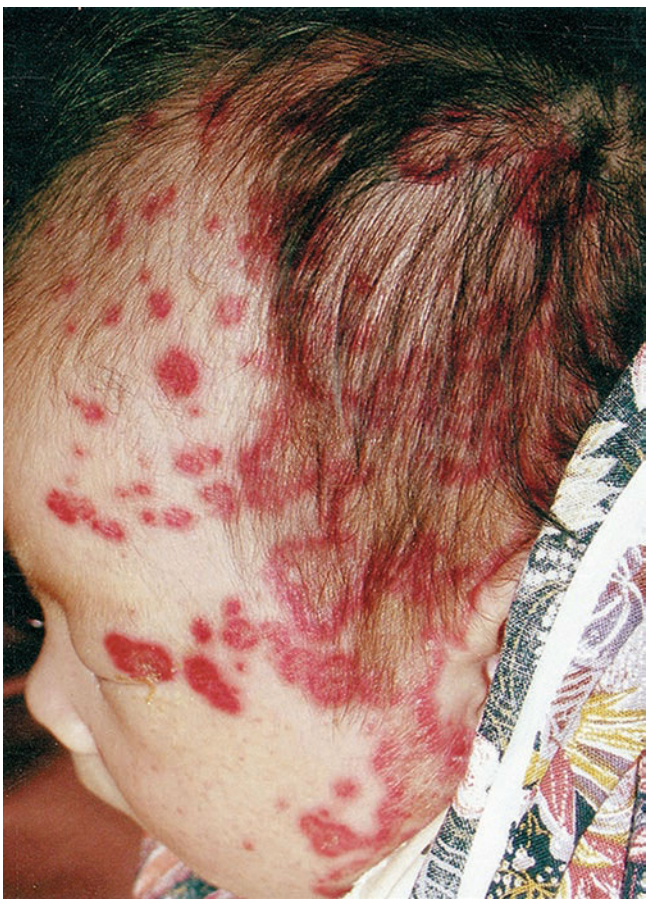


Fig. 10-4-1 Annular violaceous macules on the head and face

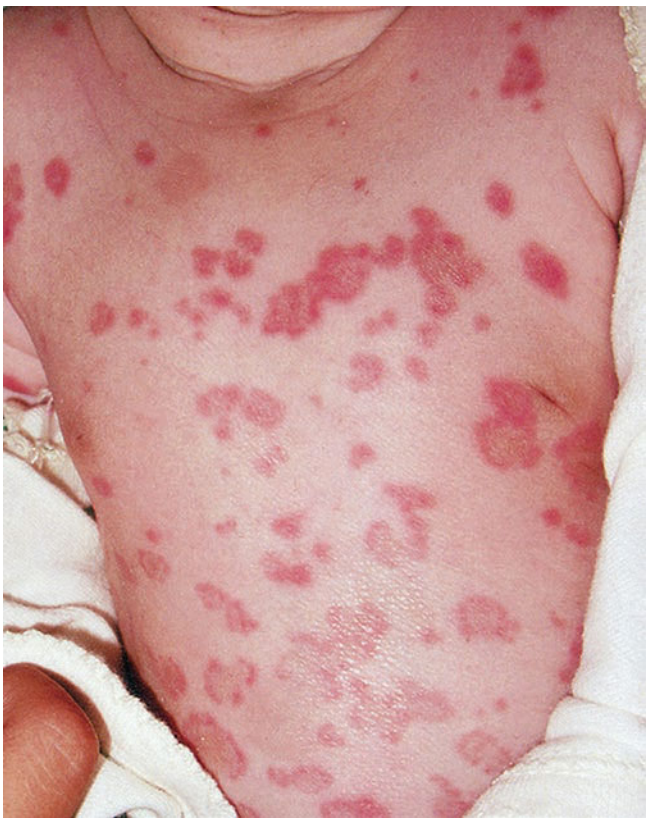


Fig. 10-4-2 Annular slight red macules on the chest and abdomen

10.5 Antiphospholipid Syndrome [6]

- Antiphospholipid syndrome, also called antiphospholipid antibody syndrome (APS or APLS), is an autoimmune disease presenting with characteristic antiphospholipid antibodies. The blood of the patient often shows a hypercoagulable state.
- APS may result in the formation of blood clots (thrombosis) in arteries and veins as well as pregnancy-related complications, for instance, miscarriage, stillbirth, preterm delivery, and severe preeclampsia.
- To make an accurate diagnosis, typical clinical manifestations and the lupus anticoagulant or anti-β_2-glycoprotein-I are essential.
- Anticoagulant may decrease the risk of further episodes of thrombosis and improve the prognosis of pregnancy of patients with APS.

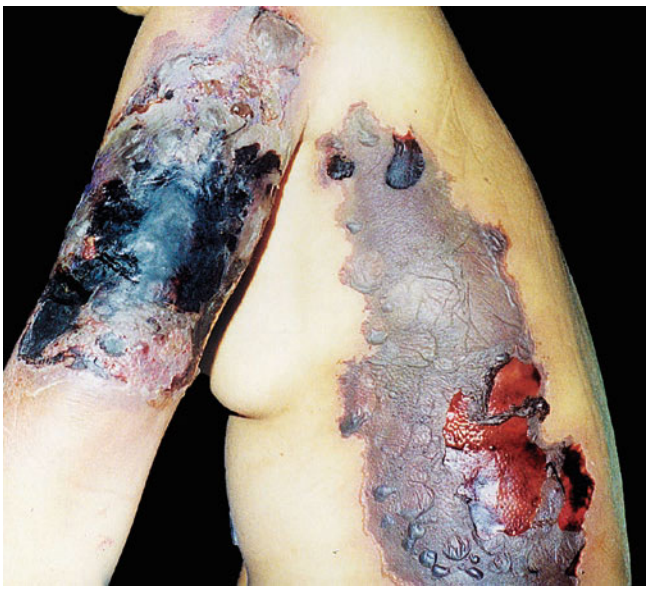


Fig. 10-5-1 Infiltrate erythema, dark crusts, and erosions on the extensor of the left upper arm and flank

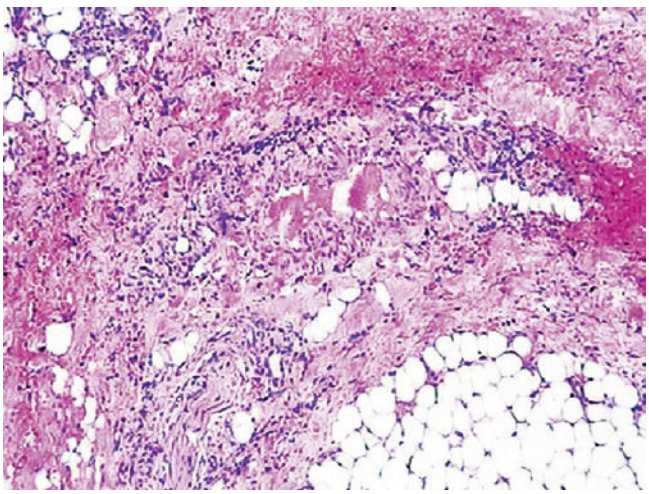


Fig. 10-5-2 Inflammatory infiltrate around small perivascular in subcutaneous and embolism in the small vascular (HE stain, ×100)

10.6 Nodular Scleroderma [7]

- Nodular scleroderma (NS) is a very unusual variant of scleroderma and preferentially occurs in middle-aged females.
- Typical manifestations comprise firm nodules or plaques resembling keloid, distributed predominantly on the proximal extremities.
- Steroids, topical calcipotriene, cyclosporine, D-penicillamine, methotrexate, photochemotherapy, and excision may improve symptoms of patients with NS.

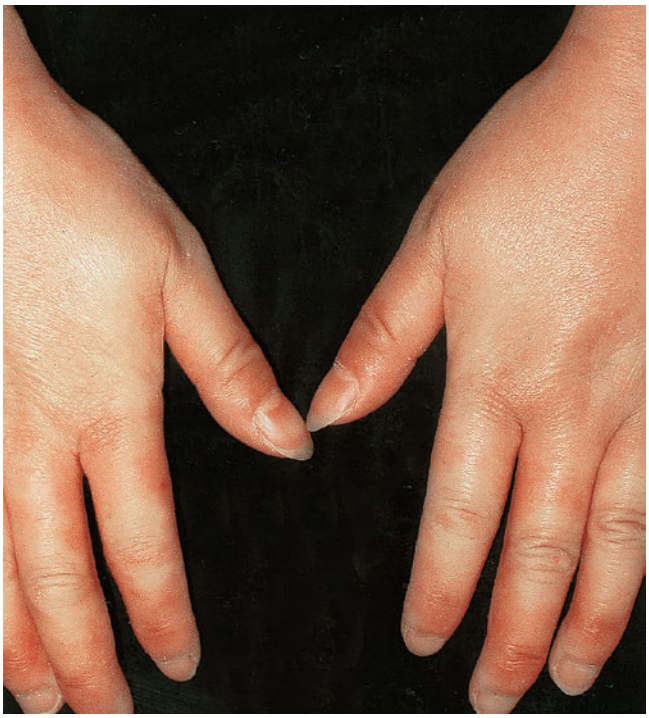


Fig. 10-6-1 Slight-red maculae on the fingers and dorsum of both hands

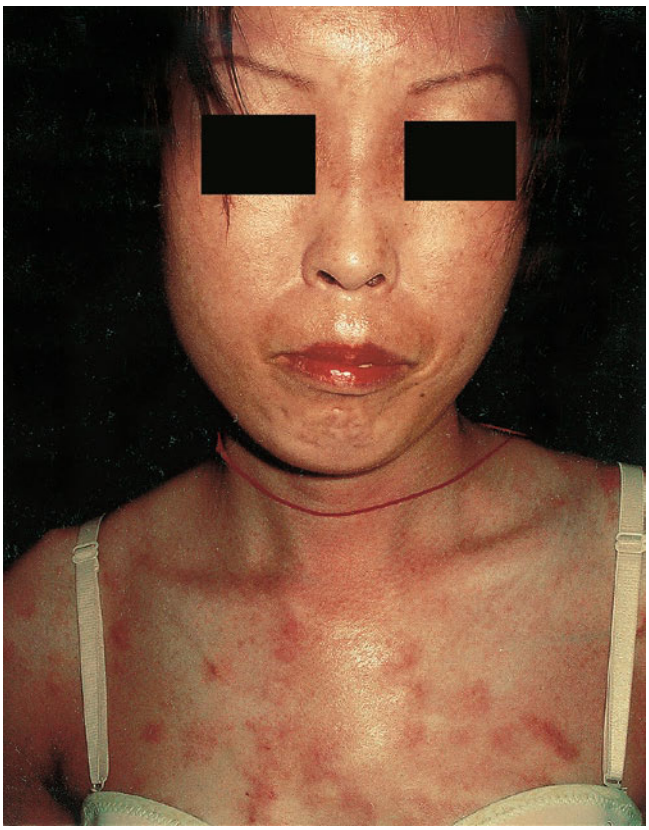


Fig. 10-6-2 Skin texture decreased on the forehead and plaques on the chest (Reproduced with the permission from [7])

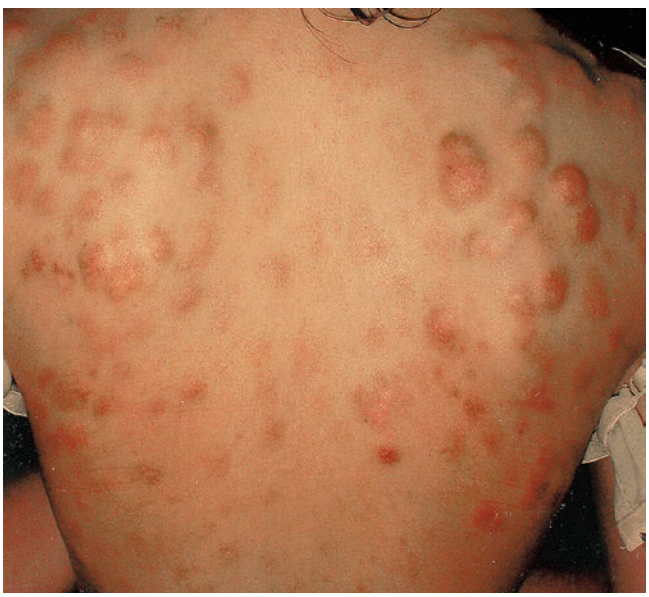


Fig. 10-6-3 Several slight red nodules on the shoulder and back

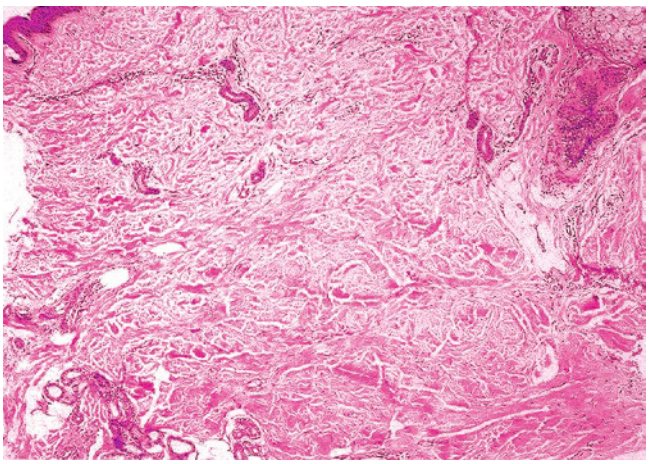


Fig. 10-6-4 Collagen fibers increased and packed in the dermis, a few blood vessels decreased and hair follicle atrophy (HE stain, ×40)

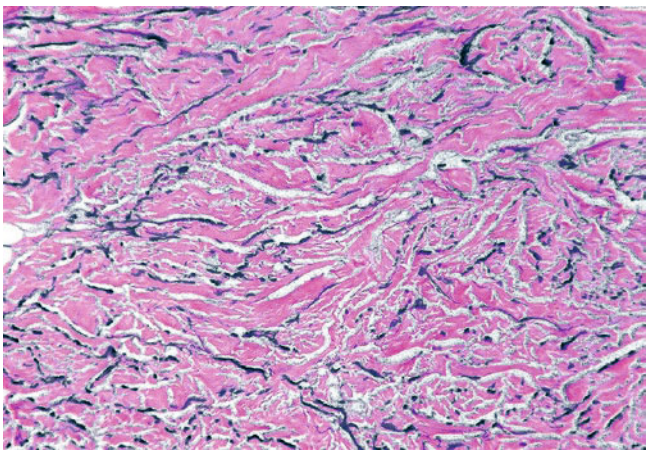


Fig. 10-6-5 Elastic fibers increased in the lower dermis (combined stain, ×100)

10.7 Atrophoderma of Pasini and Pierini [8, 9]

- Atrophoderma of Pasini and Pierini (APP) is an infrequent dermatologic condition. Its main feature is an asymptomatic, violaceous brownish discolored patch, generally showing one or more sharply demarcated depressed lesions. Clinically, the lesions most commonly occur in the lumbosacral region.
- Genetic factors, neurogenic causes, immunological factors and abnormal metabolism of dermatan sulfate may play roles in the pathogenesis of AP.
- Most patients with APP show a bilateral symmetric distribution. Occasionally, a segmental zosteriform distribution may be observed in a small subset of patients. APP could be associated with crossed total hemiatrophy, which implies facial atrophy and contralateral atrophy of the trunk and extremities.
- Considering the possibility of an underlying borrelial infection, it has been suggested that early cases of APP be treated with a course of appropriate oral antibiotics. Because the condition is asymptomatic and limited to the skin, most patients do not have to accept any treatment.

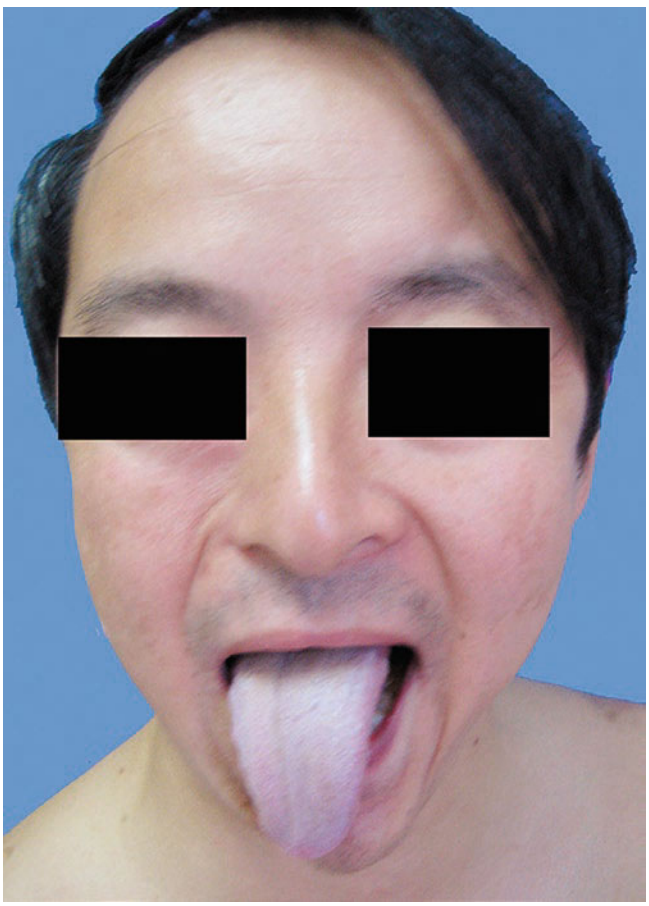


Fig. 10-7-1 Significant atrophy in right side of the tongue (Reproduced with the permission from [8, 9])

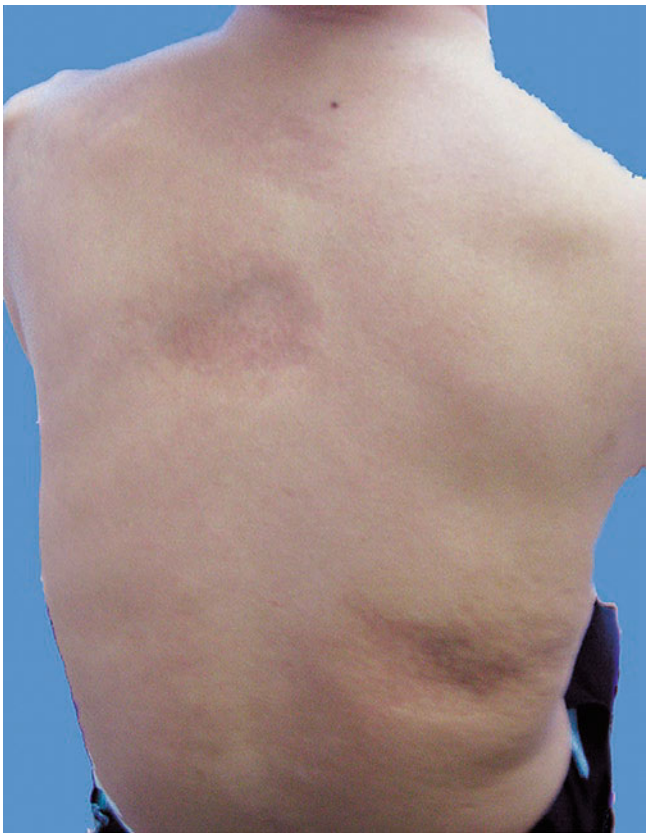


Fig. 10-7-2 A few brownish patches appeared on his back and lumbar part

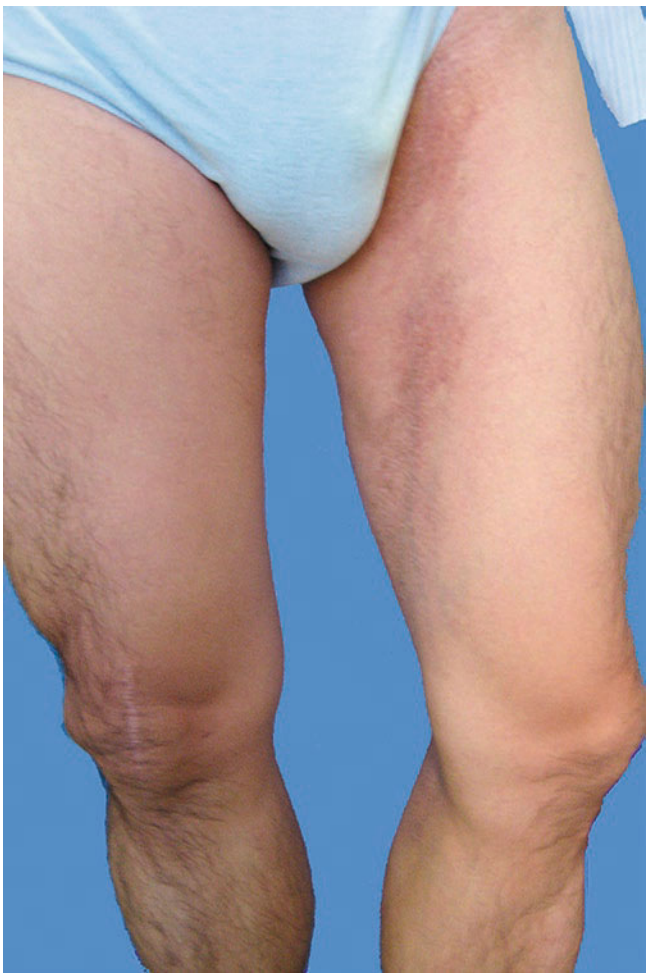


Fig. 10-7-3 A few brownish patches appeared on medial region of the left thigh. In the centers of these patches, variciform superficial veins could be seen clearly without of redness or induration

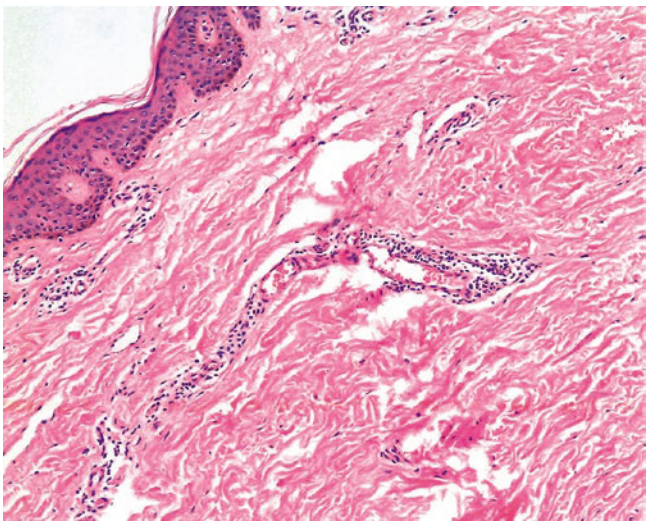
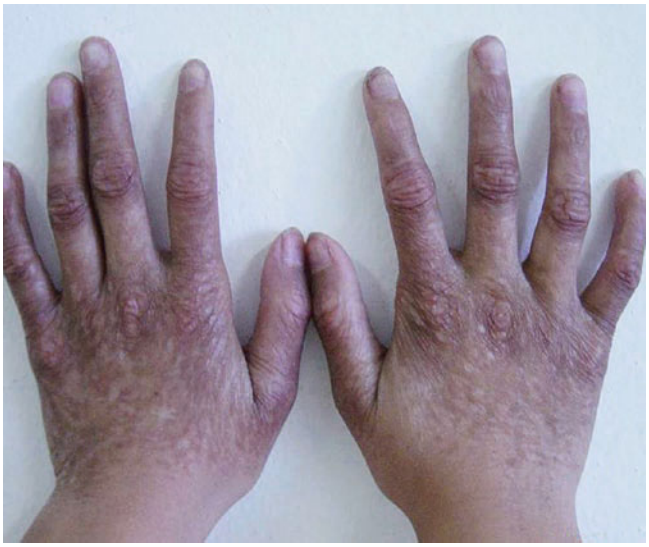
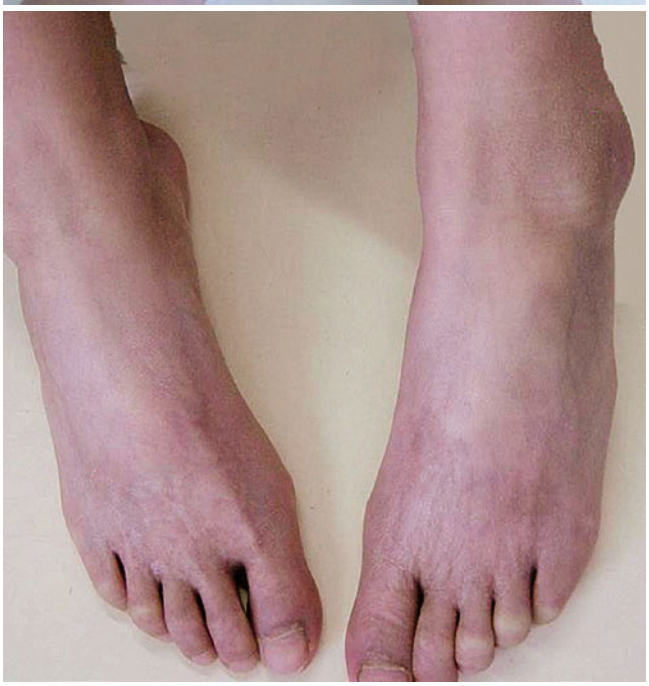


Fig. 10-7-4 Normal epidermis with increased pigment granules in the basal layer, perivascular mononuclear infiltration of the atrophic dermis, and subcutaneous adipose tissue moving up (HE stain, ×100)

10.8 Acrodermatitis Chronica Atrophicans [10]

- Acrodermatitis chronica atrophicans (ACA) is an uncommon late manifestation of tick-borne *Borrelia burgdorferi* infection, with inflammatory and atrophic lesions on acral skin.
- A correct diagnosis may depend on the characteristic clinical manifestations, histologic findings, and serum IgG antibody against borrelial antigens.
- The course of disease includes two stages: the inflammatory stage with bluish red discoloration and cutaneous swelling, and the atrophic phase.
- Doxycycline and penicillin may be effective for the acute case.





Figs. 10-8-1, 10-8-2 Brown plaques with keratotic and slightly atrophic appearance distributed on the back of the hands (1), fingers, and feet (2), especially on the joints

10.9 Linear Atrophoderma of Moulin [11]

- Linear atrophoderma of Moulin (LAM) is an acquired cutaneous disorder. Children and adolescents are mainly involved.
- Clinically, it is characterized by atrophic pigmentation spots along the unilateral Blaschko line of the body without special uncomfortable symptoms, without a preceding inflammation, and with subsequent induration or scleroderma.
- Histopathology, hyperpigmentation of the basal epidermis and a normal dermis with unaltered connective tissue and elastic fibers can be observed.
- There is no normative treatment for LAM, the progress of which is slow and can be self-cured.

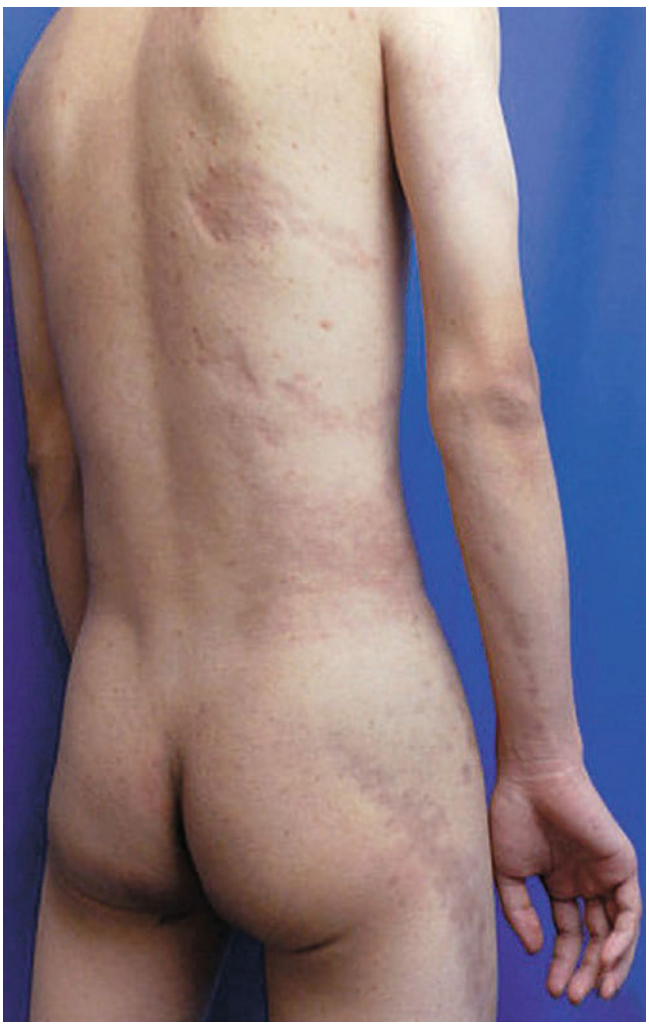


Fig. 10-9-1 Dark-brown atrophic patches along Blaschko's lines on the right backside, right forearm, and buttock

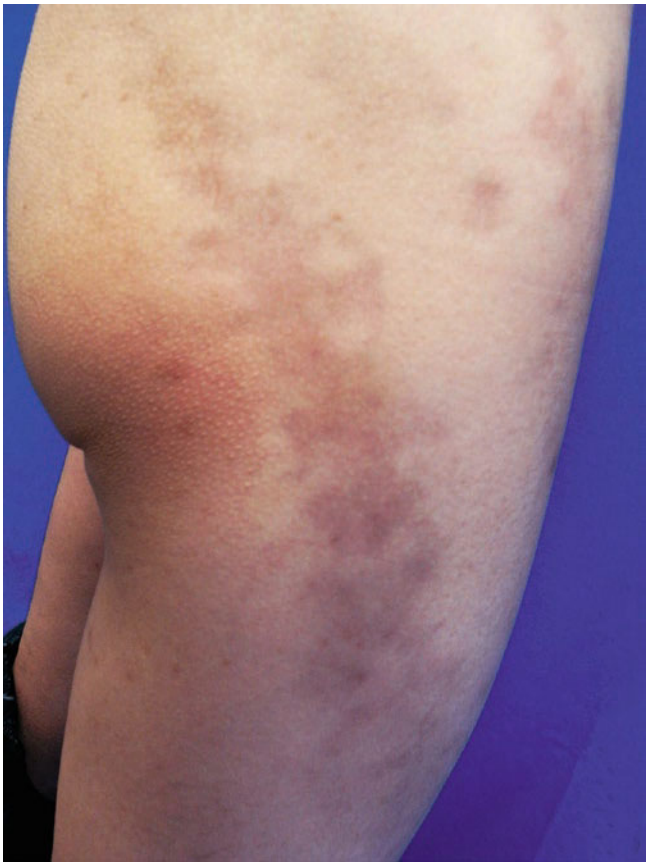


Fig. 10-9-2 Hyperpigmented atrophic patches without angiotelectasis on the right buttock

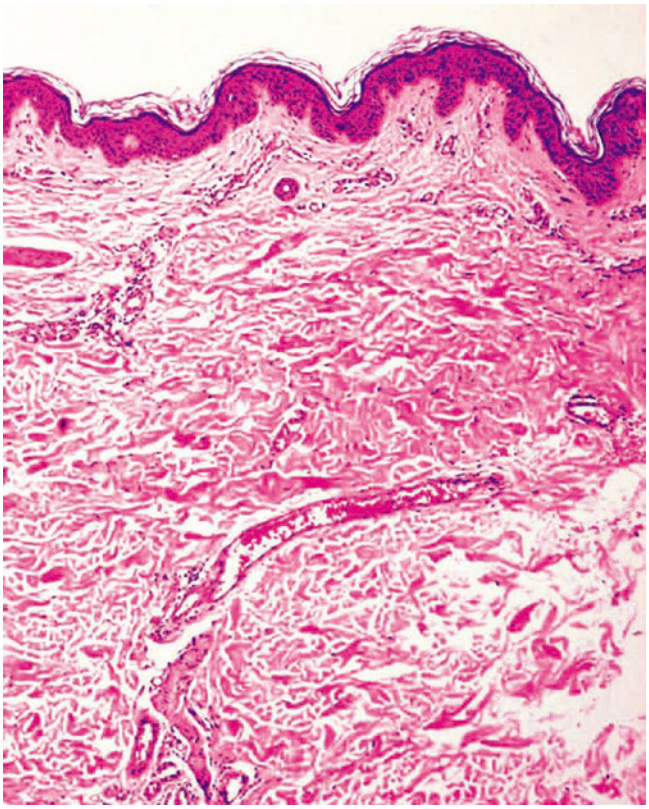


Fig. 10-9-3 Normal epidermis with increased melanin in the basal layer; telangiectasia and perivascular mononuclear cell infiltration in the upper dermis (HE stain, ×40)

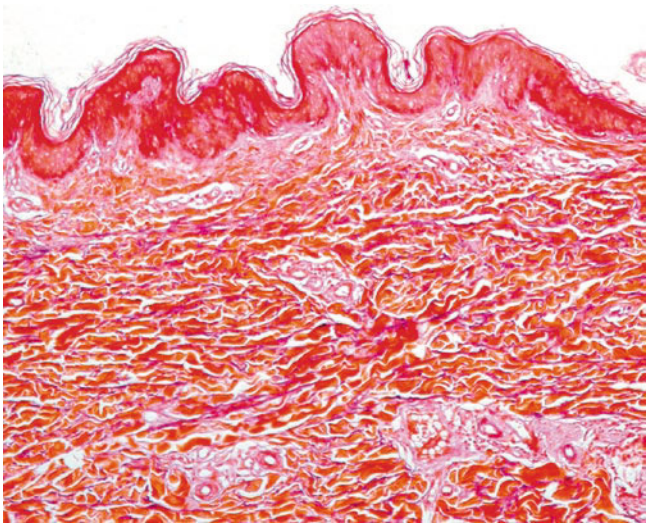


Fig. 10-9-4 Reduced elastic fibers without fragmentation in the upper dermis (Elastic fiber stain, ×100)

10.10 Rheumatoid Neutrophilic Dermatitis [12, 13]

- Rheumatoid neutrophilic dermatitis (RND) is a unique skin complication of severe seropositive RA.
- Clinically, it shows symmetrically distributed nodular erythema or plaque, mainly occurring on the joints and exterior surfaces of the extremities.
- Pathological changes in RND comprise heavy dermal infiltration of neutrophils without vasculitis. Microabscesses are infrequently observed in the dermal papillae.
- Although RND generally heals without scarring, residual atrophic scars have been documented.
- Other skin manifestations of RA include rheumatoid nodules, interstitial granulomatous dermatitis, vasculitis, pyoderma gangrenosum, urticarial, vitiligo, and neutrophilic lobular panniculitis.

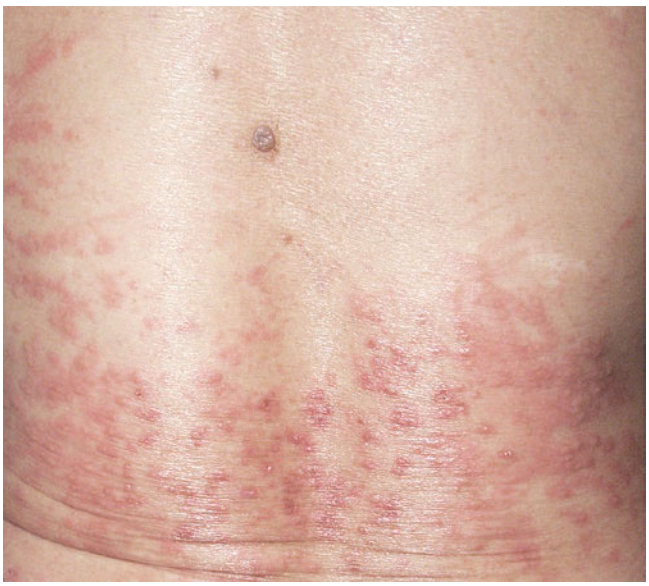


Fig. 10-10-1 On the waist and abdomen, there were densely distributed red- or skin-colored papules and nodules, ranging from 2 to 4 mm in diameter. Erosions, crusts, and ulceration were not discovered

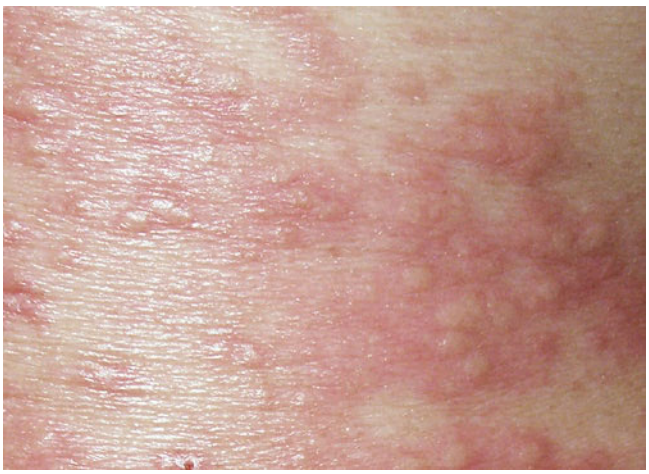


Fig. 10-10-2 Urticarial erythema or pseudo-vesicles upon amplification of the lesions

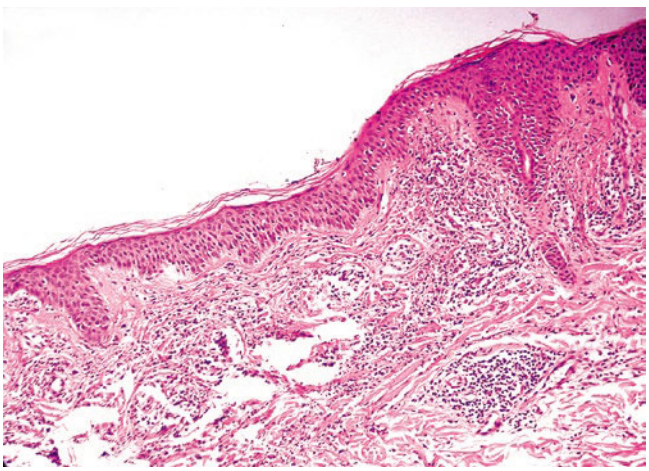


Fig. 10-10-3 Edema in the dermis, with neutrophilic cell infiltration in a band-like pattern (HE stain, ×100)

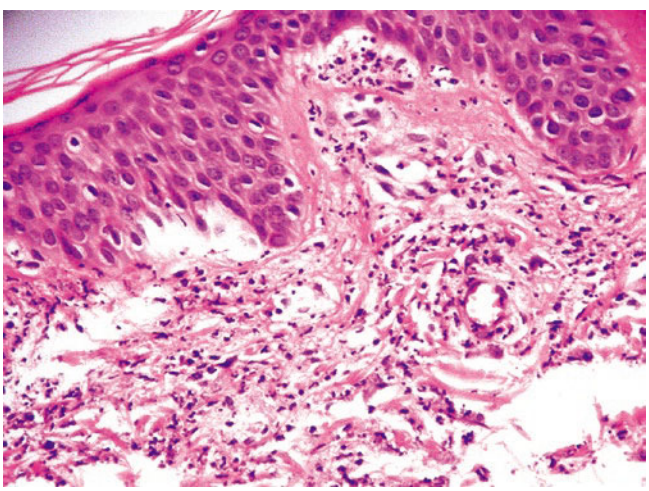
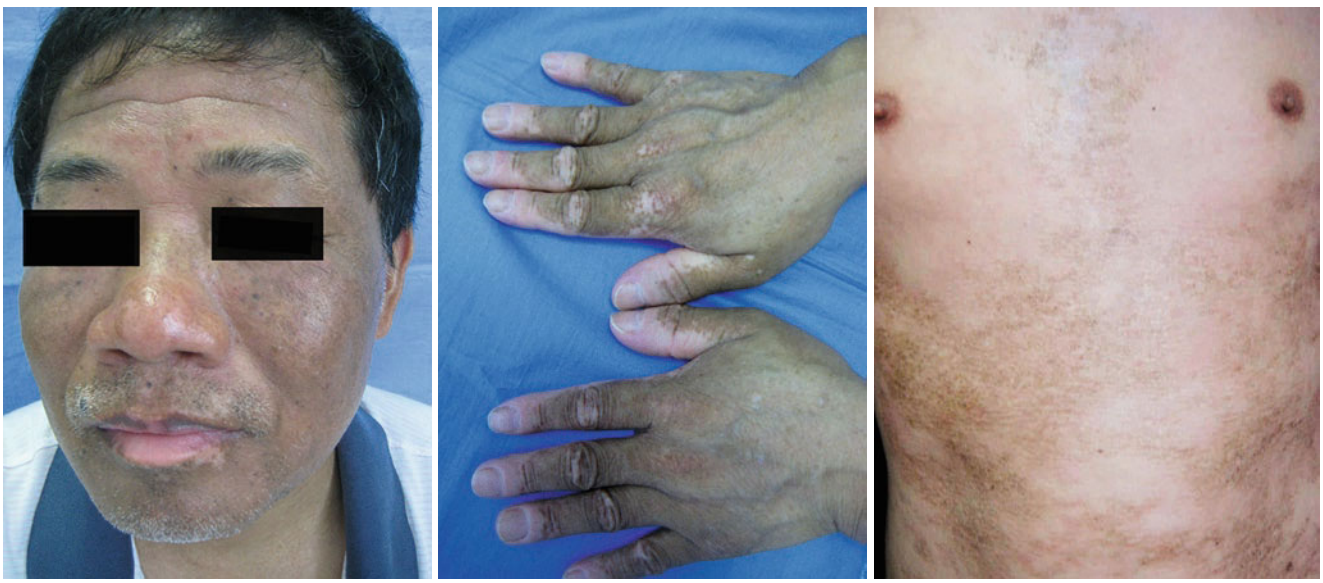


Fig. 10-10-4 Skin biopsy revealed leukocytoclasis without fibrinoid necrosis, thrombosis, or extravasation of erythrocytes There is collagen degeneration in foci, as well as neutrophilic microabscess (HE stain, ×400)

10.11 Graft-Versus-Host Disease [14]

- The cutaneous eruptions of graft-versus-host disease (GVHD) occur between the fourth and the fifth weeks after transplantation.
- GVHD may be divided into acute and chronic. Morbilli-like lesions, erythroderma, and conditions mimicking toxic epidermal necrolysis are mainly observed in acute patients. In chronic cases, lichen planus-like lesions, multiple sclerosis, hypo- or hyperpigmentation, atrophy, and alopecia are observed.
- In 30–40% of patients, chronic GVHD develops 3–5 months after grafting. The vast majority of GVHD patients present cutaneous involvement.



Figs. 10-11-1, 10-11-2, 10-11-3 Chronic GVHD with diffuse dyschromia and hyperpigmentation on the face (1), hands (2), and trunk (3) (Reproduced with the permission from [14])

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Vesiculobullous Diseases

11

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Abstract

This chapter encompasses a unique group of blistering conditions, including pemphigus neonatorum, keratosis follicularis pemphigus, paraneoplastic pemphigus with Castleman's disease, paraneoplastic pemphigus, pemphigoid nodularis, linear IgA bullous dermatosis, relapsing linear acantholytic dermatosis, epidermolysis bullosa acquisita, impetigo herpetiformis associated with intrahepatic cholestasis of pregnancy, pustulosis palmoplantaris accompanied with anterior chest wall syndromes, eosinophilic pustular folliculitis, infantile acropustulosis, and generalized acrodermatitis continua.

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11.1 Pemphigus Neonatorum [1]

- Neonatal pemphigus, which shows blisters from the time of birth, is caused by transplacental transmission of autoantibodies when a pemphigus vulgaris (PV) or pemphigus foliaceus (PF) patient is pregnant.
- Neonatal pemphigus is rare because PV commonly affects adults between the fourth and sixth decades of life.
- Histopathological features display intraepithelial vesicles accompanied by acantholytic cells.
- Neonatal pemphigus has a good prognosis, with complete healing of lesions usually within 3 weeks.

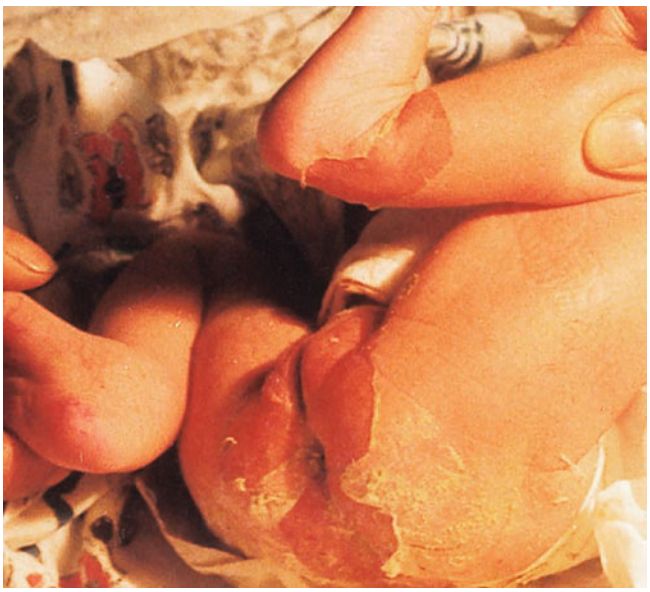


Fig. 11-1-1 Varying sized erosions on the buttocks and the left lower limb

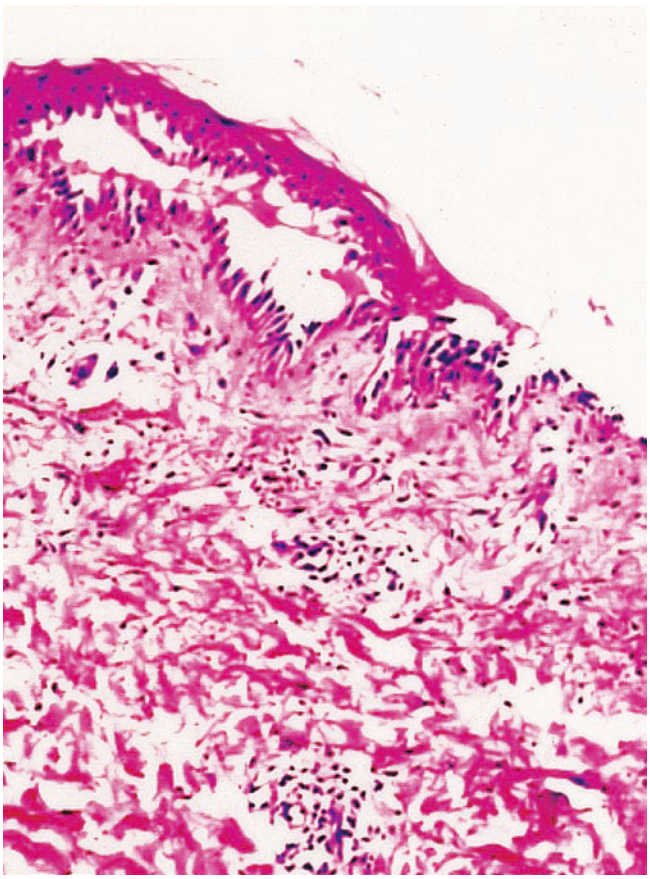


Fig. 11-1-2 Acantholysis in the upper of basal layer, part of the epidermis is absent, a few inflammatory infiltrates in the dermis (HE stain, ×100)

11.2 Keratosis Follicularis Pemphigus [2, 3]

- Darier's disease (keratosis follicularis, DD) is caused by mutations in the ATP2A2 gene, which leads to the development of keratotic papular lesions and plaques in seborrheic areas. Dyskeratosis and acantholysis are the main histological characteristics.
- Pemphigus vulgaris (PV) is an autoimmune disease related to the binding of autoantibodies to the desmosomal cadherins and desmoglein 3. The histological examination shows acantholysis.
- DD and PV have the same histological features as epidermal suprabasilar acantholysis. The former is owing to the loss of adhesion between keratinocytes, but the latter is related to autoantibodies.
- The histological overlap clearly may occasionally catch the pathologist's eyes, although the nuances of this overlap may be unrelated to the clinical diagnosis or treatment.

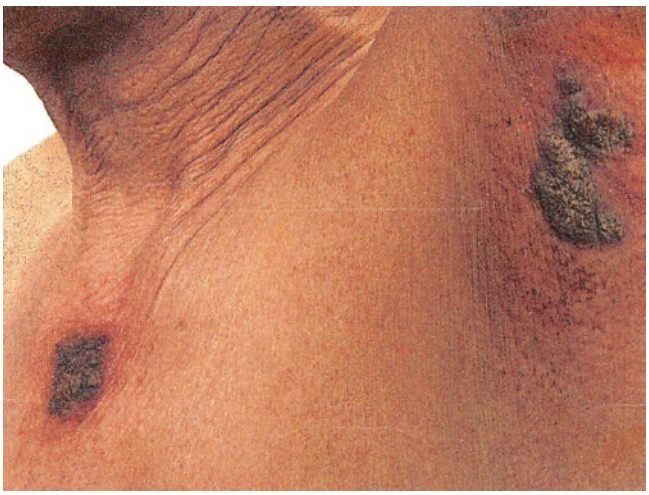


Fig. 11-2-1 Red papules, vesicles, brown-red eczematous plaques on the chest and axillae

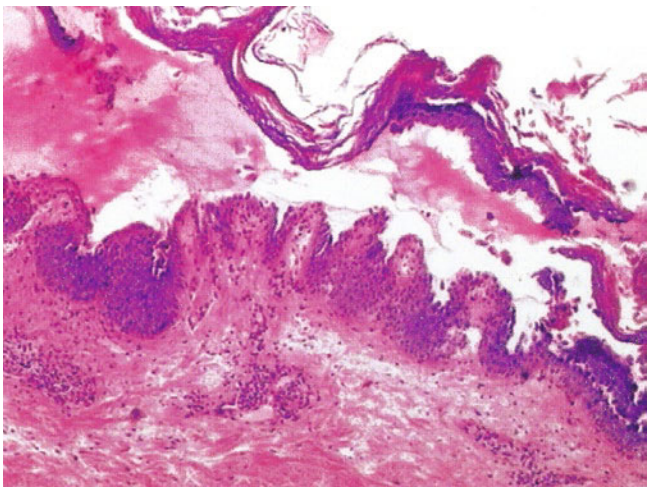


Fig. 11-2-2 Acantholysis in the upper basal layer with acantholytic cells, grain, and villi (HE stain, ×20)

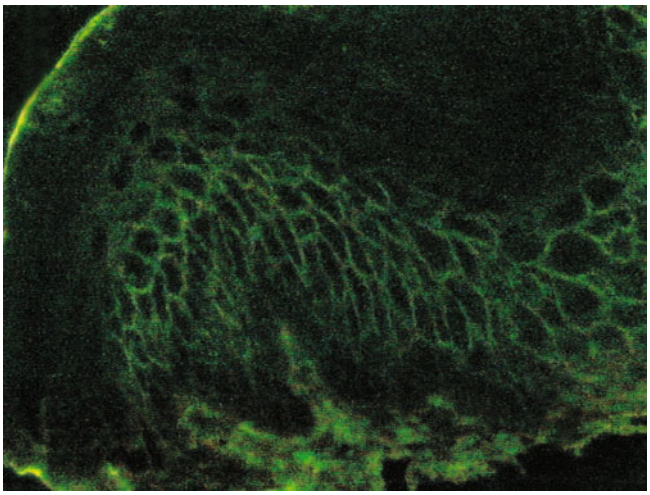


Fig. 11-2-3 Direct immunofluorescence examination showed a positive deposition of IgG and C3 among the keratinocytes (DIF, ×200)

11.3 Paraneoplastic Pemphigus with Castleman's Disease [4, 5]

- Castleman's disease (CD) is an uncommon lymphoproliferative disorder that involves hyperactivation of the immune system with multiple organ system dysfunction. Clinically, it may present as an isolated lymph node (unicentric) or systemic occurrence (multicentric).
- Paraneoplastic pemphigus (PNP) is a distinctive autoimmune mucocutaneous blistering disease related to neoplasms or Castleman's disease (CD), for example.
- Some authors have proposed many hypotheses, such as the secretion of autoantibodies from the tumor and cross-reaction of tumor antigens with epidermal antigens.
- Complete resection of a localized Castleman's tumor can treat the disease and improve mucocutaneous lesions in most patients. However, the immune reaction may persist for as long as 2–4 years after surgery. Thus, maintaining effective immunosuppression for a prolonged postoperative period is required.

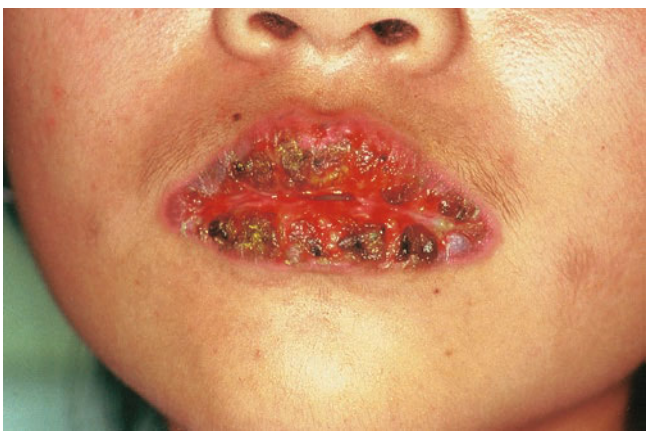


Fig. 11-3-1 Erosions and crusting of the lips

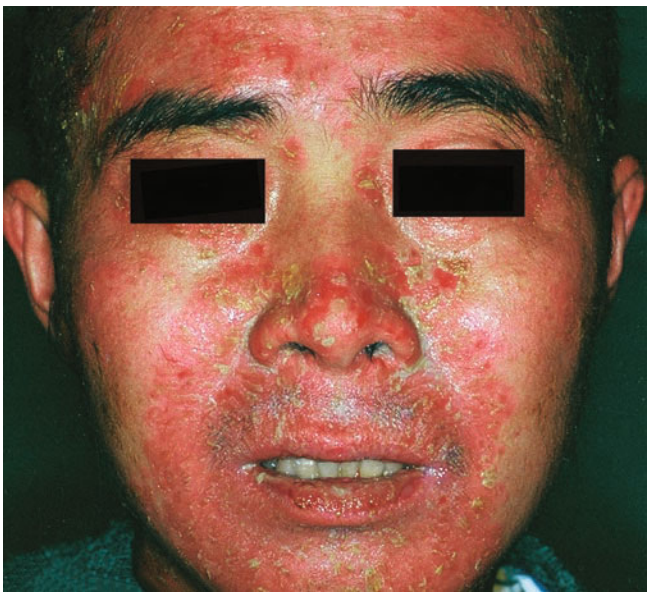


Fig. 11-3-2 Erythematous macules and crusting on the face, erosions of the lips and eyes (Reproduced with the permission from [4, 5])

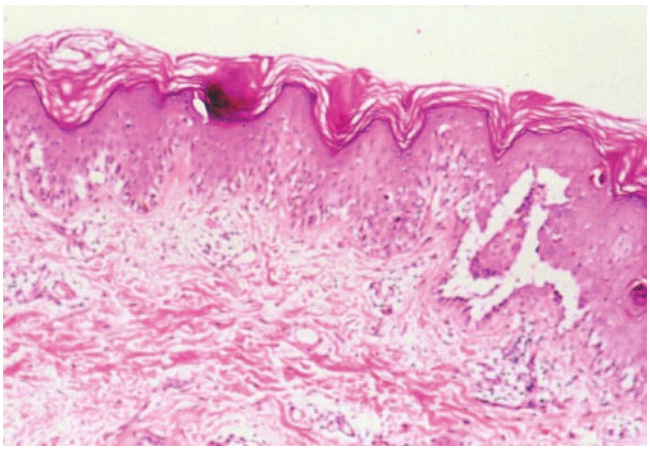


Fig. 11-3-3 Necrobiosis of keratinocytes in the epidermis

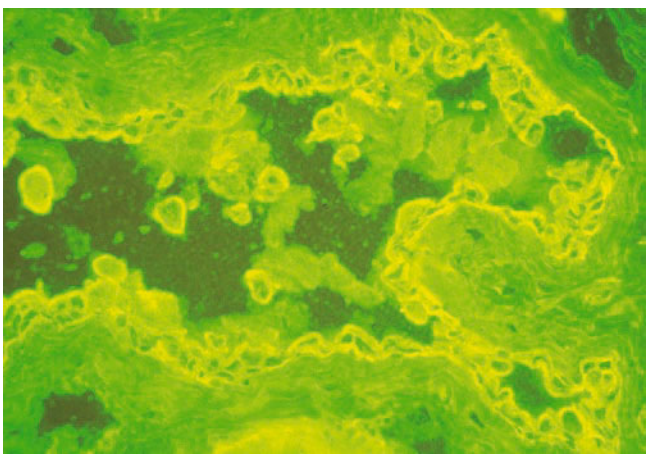


Fig. 11-3-4 IgG and C3 deposition in the intercellular spaces of the epithelium (DIF)

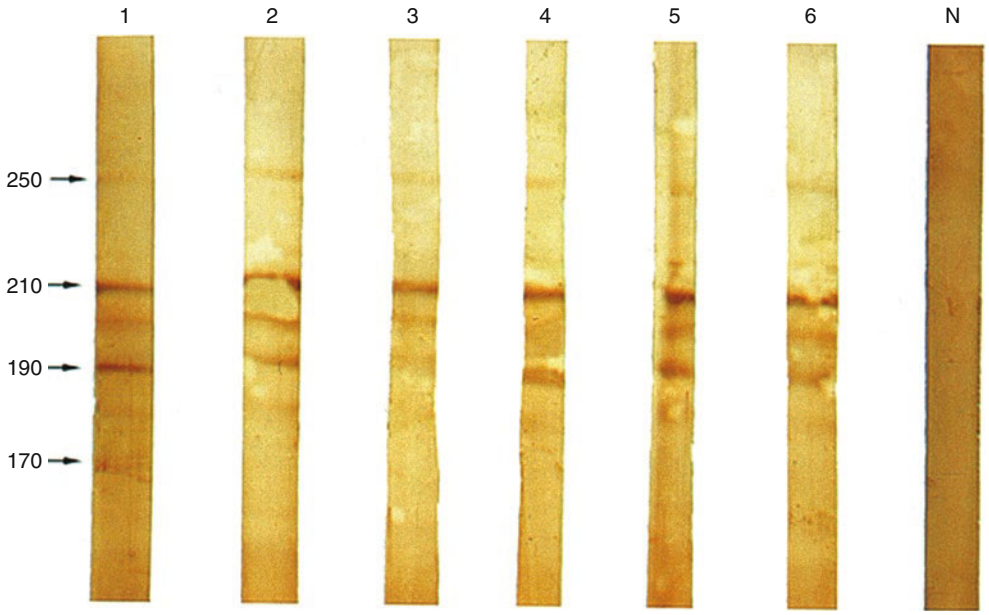


Fig. 11-3-5 Desmoplakin 1 (250KD), envoplakin (210KD), and periplakin (190KD) were positive by Western blotting

11.4 Paraneoplastic Pemphigus [6, 7]

- Paraneoplastic pemphigus (PNP) is an autoimmune bullous skin disease initiated by an underlying malignant or benign neoplasm. The antigens mainly belong to the plakin family.
- The clinical hallmark of paraneoplastic pemphigus is painful and persistent stomatitis, which is extremely resistant to therapy. The cutaneous presentation is various, including flaccid or tense blisters, lichenoid lesions, erythema multiforme-like lesions, or confluent-erosive lesions, among others.
- Histopathologically, PNP demonstrates dyskeratosis, acantholysis, and interface dermatitis. Direct immunofluorescence examination suggests the deposition of IgG and C3 in the intercellular spaces of the epithelium.
- It is vital to define and treat the associated benign and malignant tumors in PN. The first-line treatment for mucocutaneous lesions is high-dose corticosteroids with the addition of steroid-sparing agents.

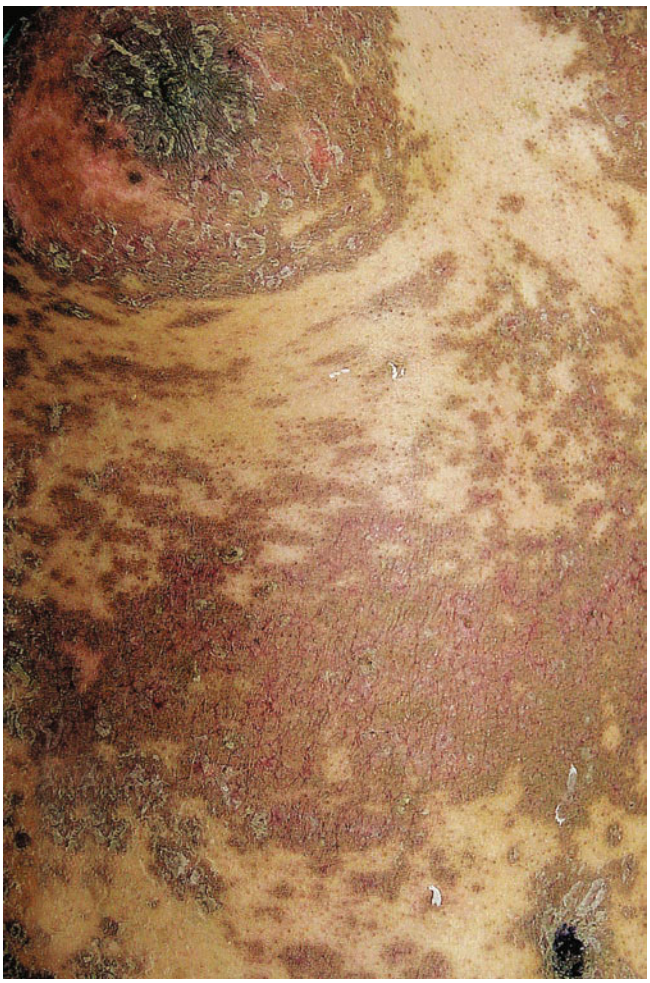


Fig. 11-4-1 Dark red or brown macules with erosion, effusion, and crust on the trunk

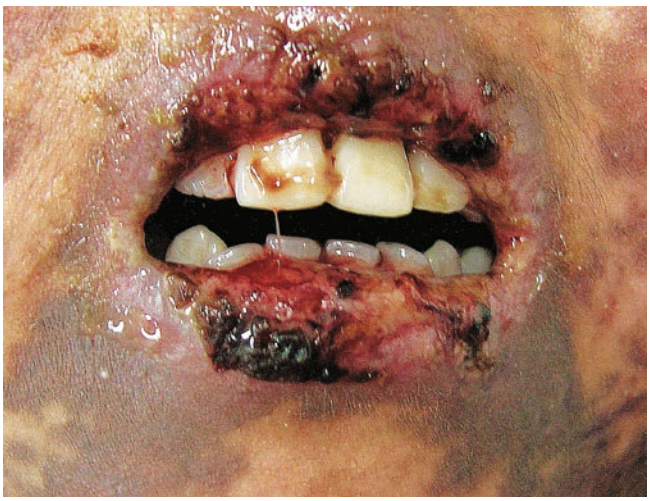


Fig. 11-4-2 Extensive erosion with blood crust on the bilabial

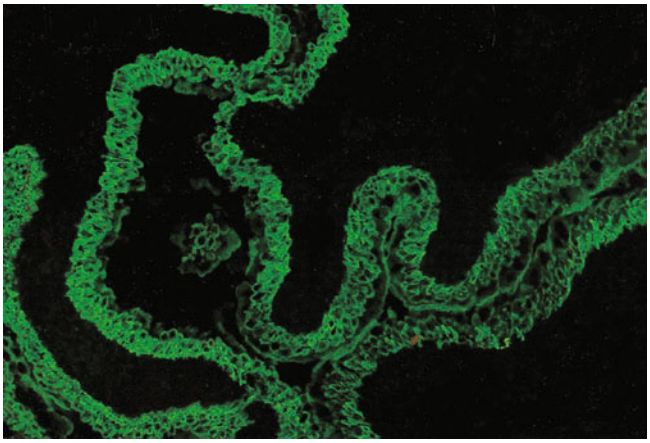


Fig. 11-4-3 Squamous intercellular substance deposition of IgG (indirect immunofluorescence testing)

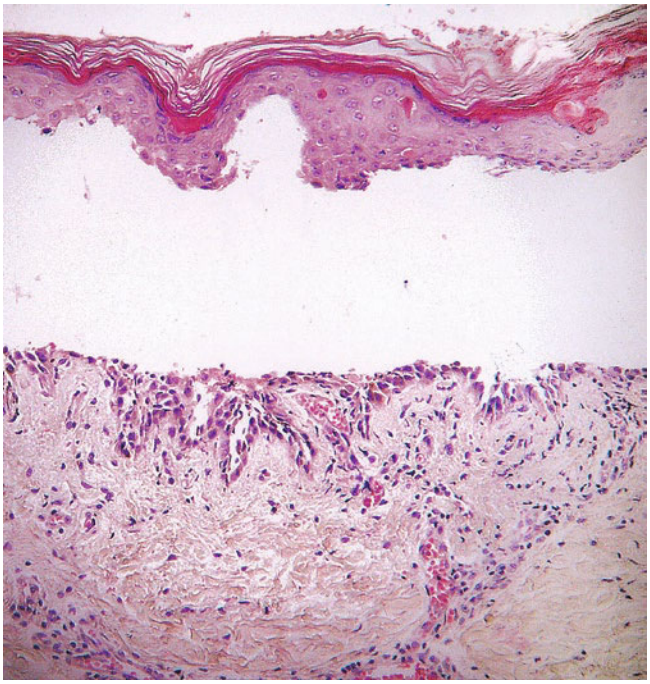
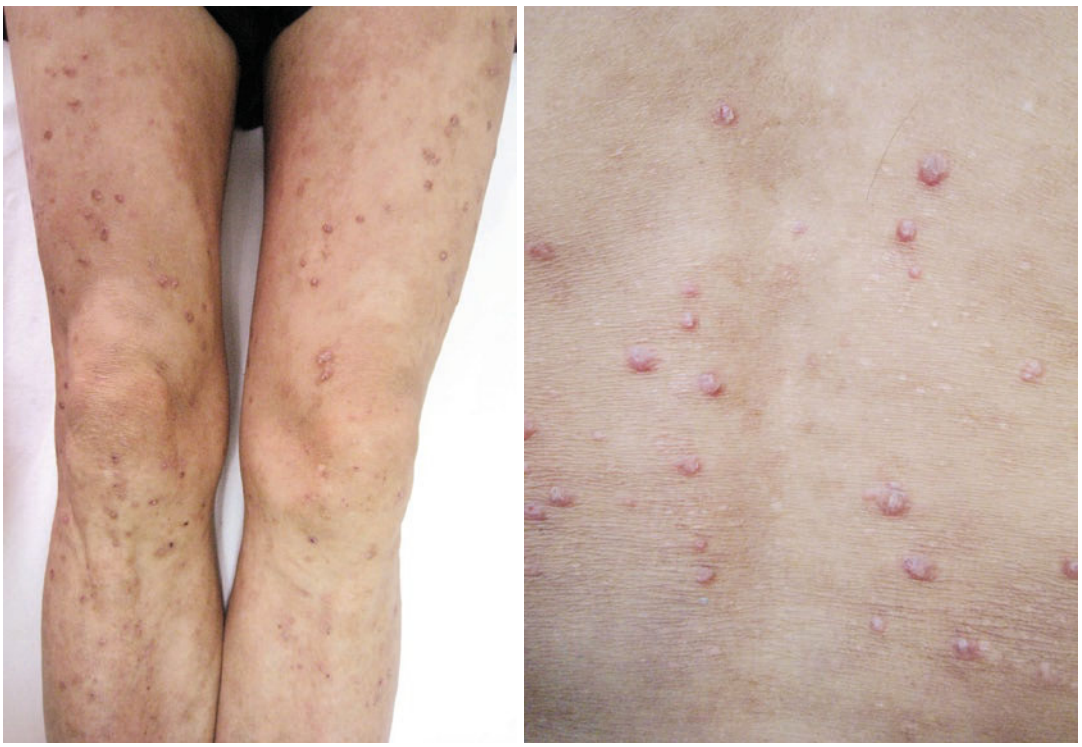


Fig. 11-4-4 Bulla above the basal layer, necrosis of keratocytes in the stratum Malpighi, liquefaction degeneration of basal cells, perivascular lymphocyte infiltrate perivascular in the superficial dermis (HE stain, ×100)

11.5 Pemphigoid Nodularis [8, 9]

- Pemphigoid nodularis (PN) is a relatively unusual clinical variant of bullous pemphigoid (BP). Prurigo nodularis lesions and pemphigoid-like blisters are vital clinical features.
- Clinically, elderly female patients are more common. It often presents as pruritic nodules, papules, or plaques. Occasionally, bullae may occur on the nodular lesions or healthy skin.
- The immunopathological expression of PN is similar to B. The diagnosis depends on positive direct and indirect immunofluorescence, demonstrating anti-basement membrane zone (BMZ) antibodies.



Figs. 11-5-1, 11-5-2 Multiple scattered papules and nodules in the size of bean on the extremities and trunk

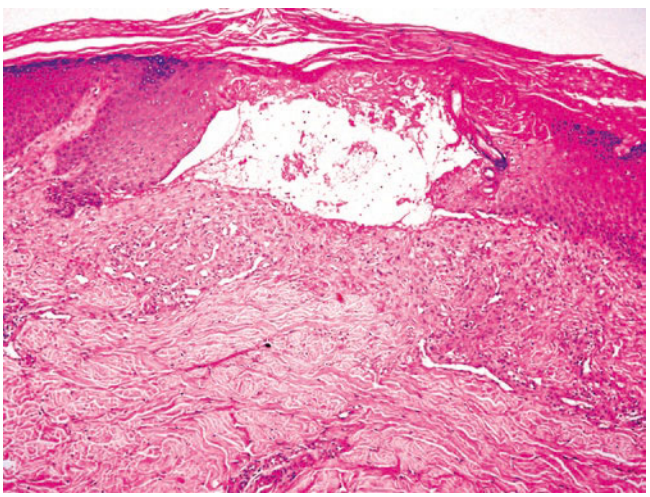


Fig. 11-5-3 Hyperkeratosis, parakeratosis, acanthosis, and a subepidermal blister; lymphocytes, eosinophils, and neutrophils in the blisters and around the blood vessels in the upper dermis (HE stain, ×200)

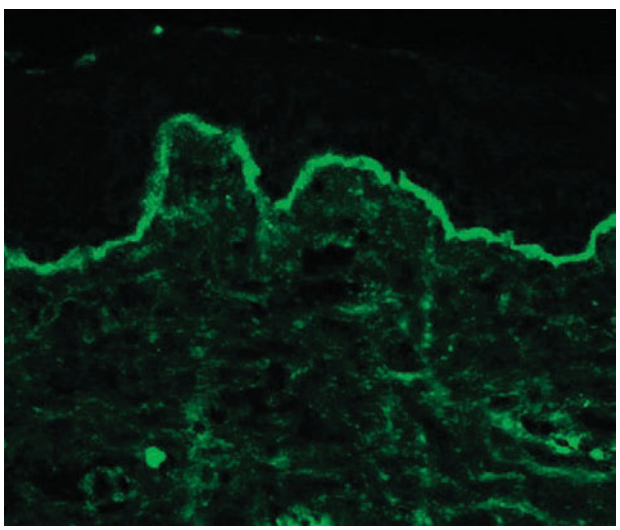


Fig. 11-5-4 A linear deposition of IgG and C3 at the basement membrane zone (DIF, ×200)

11.6 Linear IgA Bullous Dermatosis [10]

- Linear IgA bullous dermatosis (LABD) is a relatively uncommon, pruritic, vesiculobullous, autoimmune disease.
- LABD may occur at all ages but has a preference for children of 1–5 years old and adults older than 60 years. According to the age of onset, childhood and adult LABD are distinct.
- Clinically, childhood LABD presents as tense vesicles and bullae, exhibiting a "cluster of jewels" appearance. However, the clinical manifestations of adult LABD are variable and are easily confused with bullous pemphigoid, dermatitis herpetiformis, and epidermolysis bullosa.
- The diagnosis of LABD depends on direct immunofluorescence findings, revealing linear and homogeneous deposition of IgA in the basement membrane zone.
- Dapsone is the first-line drug for the treatment of this disease

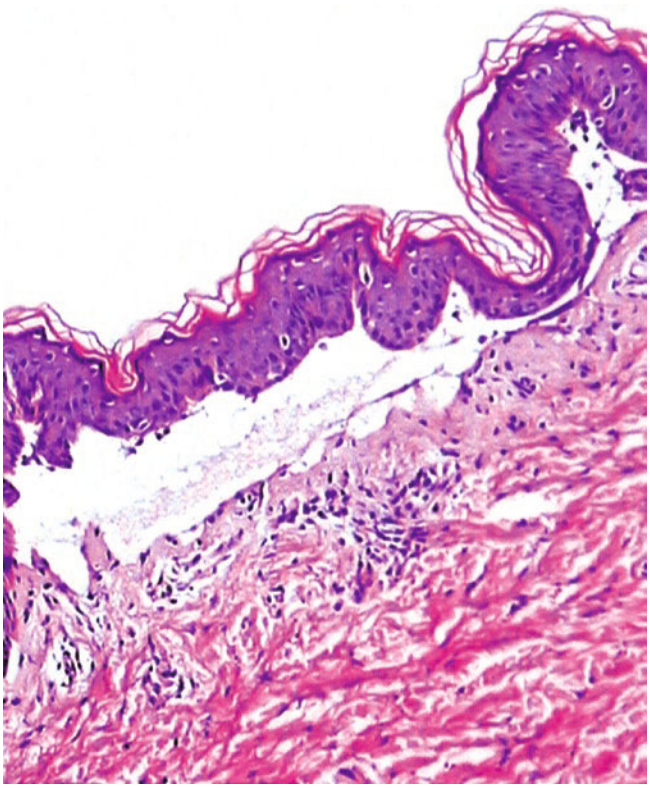


Fig. 11-6a-2 Subepidermal blister with mild neutrophil infiltration in the dermis (HE stain, ×100)

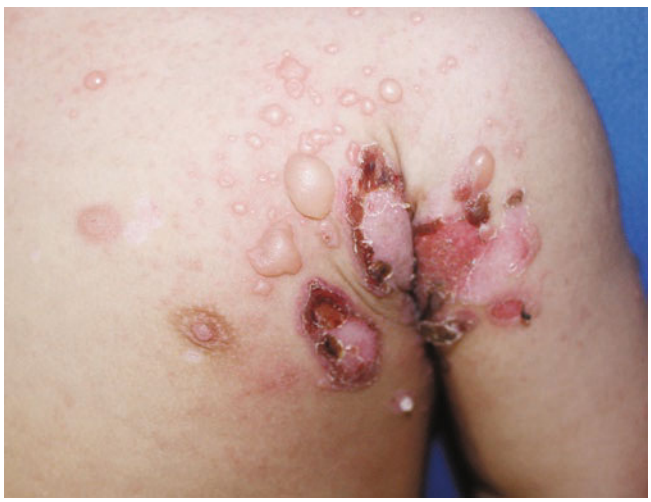


Fig. 11-6a-1 Tensional blisters and erosion with crust around the axilla

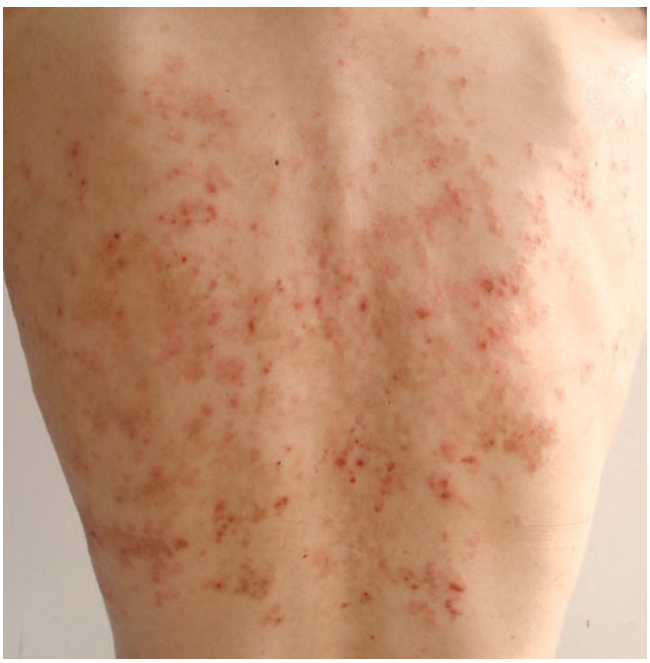


Fig. 11-6b-1 Generalized erythemas, distributed in an annular form on the back

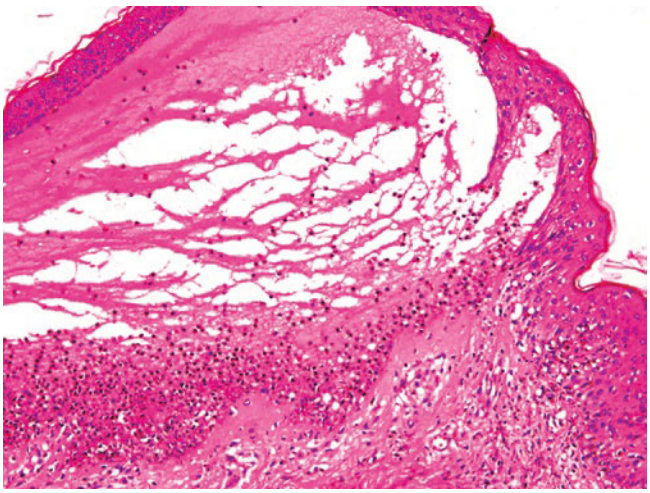


Fig. 11-6b-2 Subepidermal blister contained with dermal eosinophils and a few neutrophils infiltration (HE stain, ×100)

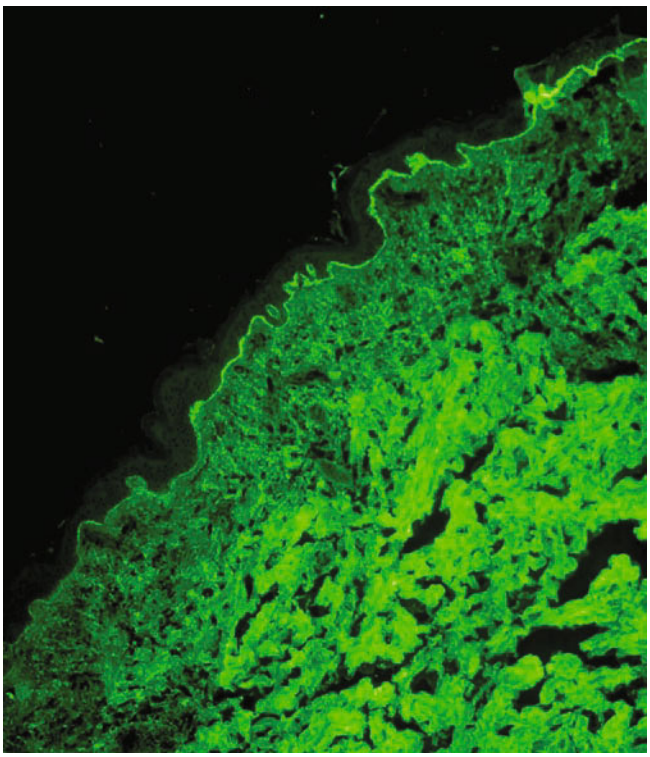


Fig. 11-6b-3 Direct immunofluorescence showed continuous linear deposits of IgA along the basement membrane zone (DIF, ×100)

11.7 Relapsing Linear Acantholytic Dermatosis [11, 12]

- Relapsing linear acantholytic dermatosis (RLAD) is a disorder within the spectrum of linear skin diseases. Its histopathological and ultrastructural features are similar to those of Hailey-Hailey disease.
- The etiology of LAD is still undefined. Genetic mosaicism may play a role. The lesions of LAD are zosteriform or follow the lines of Blaschko, presenting as recurrent vesiculation or erosions.
- Sun exposure and local infections may exacerbate further disease. Consequently, protection from sunlight is essential

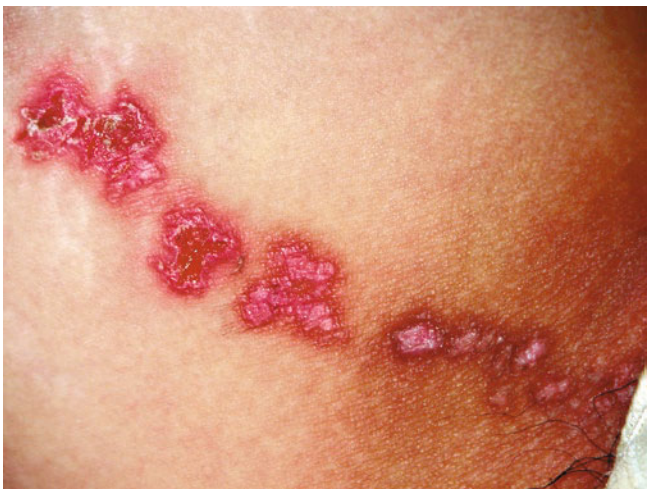


Fig. 11-7-2 New erythema and vesicula on the upper of line eruption of right thigh, part broken vesicula forming erosion and scab

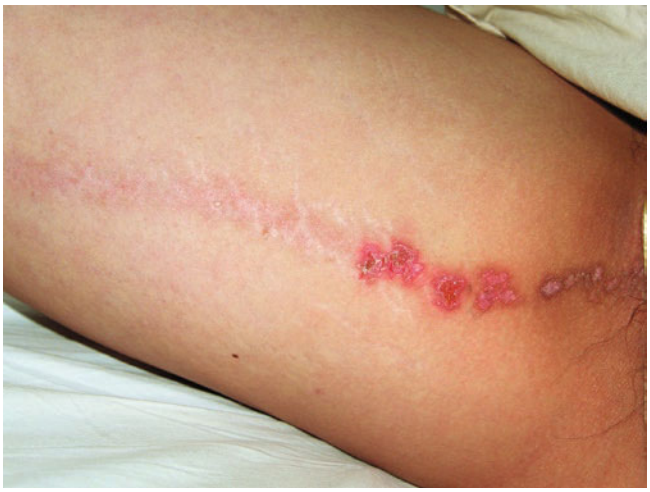
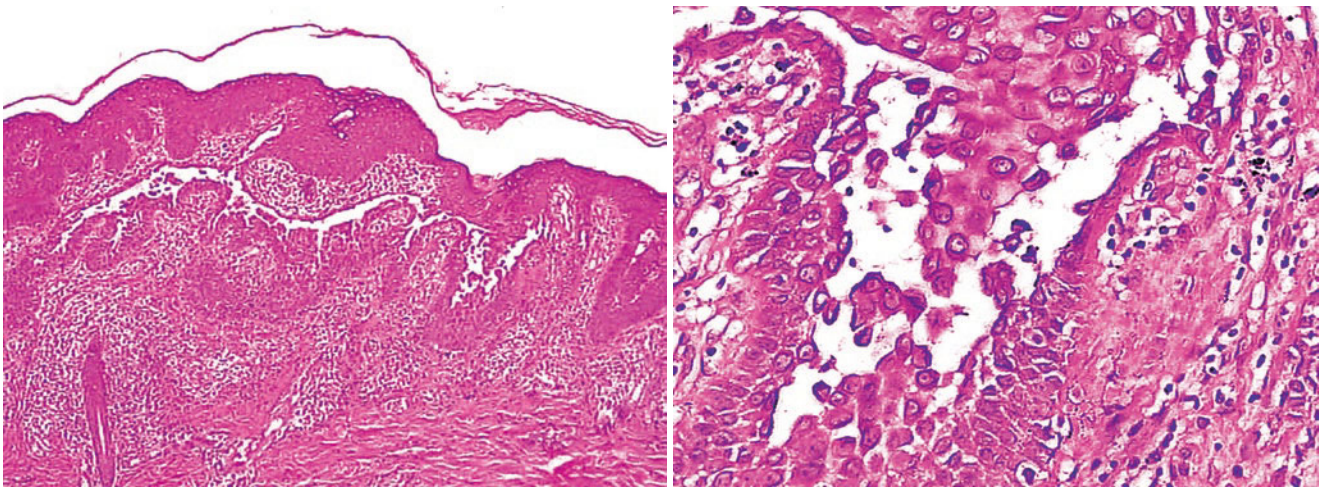


Fig. 11-7-1 Erythema and vesicular eruption on the interior of right thigh and distributed along Blaschko's line



Figs. 11-7-3, 11-7-4 Epidermal acantholysis with multiple acantholytic keratinocytes and the appearance of a "dilapidated brick wall" in suprabasal cell layer (HE stain, (1) × 100; (2) ×200)

11.8 Epidermolysis Bullosa Acquisita [13, 14]

- Epidermolysis bullosa acquisita (EBA) is a prototypic organ-specific autoimmune disease induced by autoantibodies to type VII collagen.
- The two main phenotypes consist of the classic mechanobullous type characterized by noninflammatory blisters on trauma-prone areas, often healing with scarring and milia formation, and the inflammatory vesiculobullous type manifested as widespread blisters on an erythematous base.
- Direct immunofluorescence suggests that IgG and/or C3 are linearly deposited along the basement membrane zone (BMZ). The indirect immunofluorescence findings show circulating autoantibodies distributed in the dermis.
- Steroids, cyclosporine, minocycline, dapsone, mycophenolic acid, methotrexate, plasmapheresis, intravenous immunoglobulins, and rituximab have been reported.

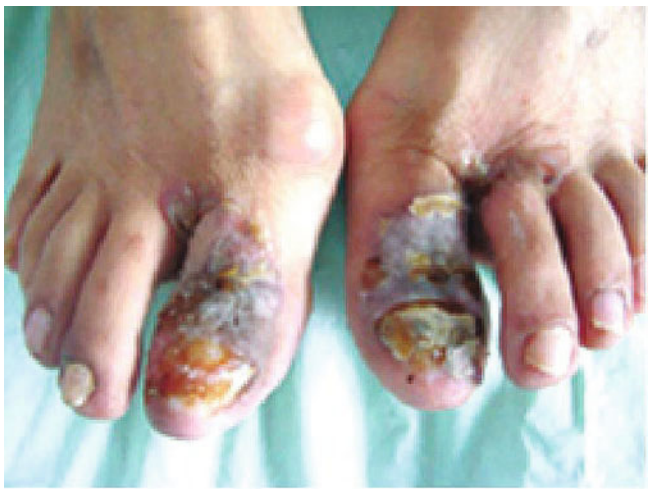


Fig. 11-8-1 The blister and scarring on the extensor surface of thumb and between toes

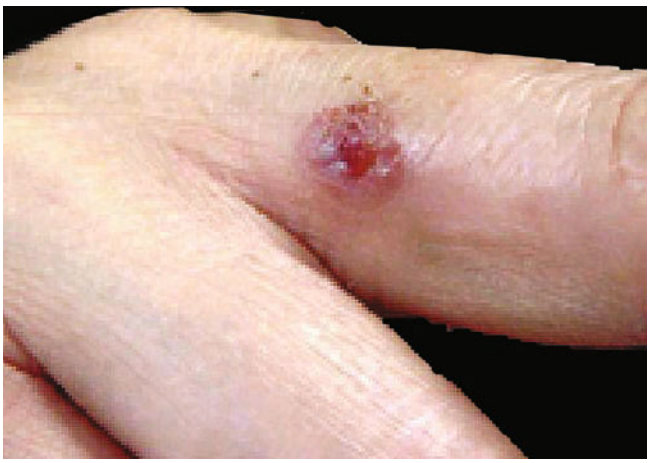


Fig. 11-8-2 The blister and scarring between the fingers

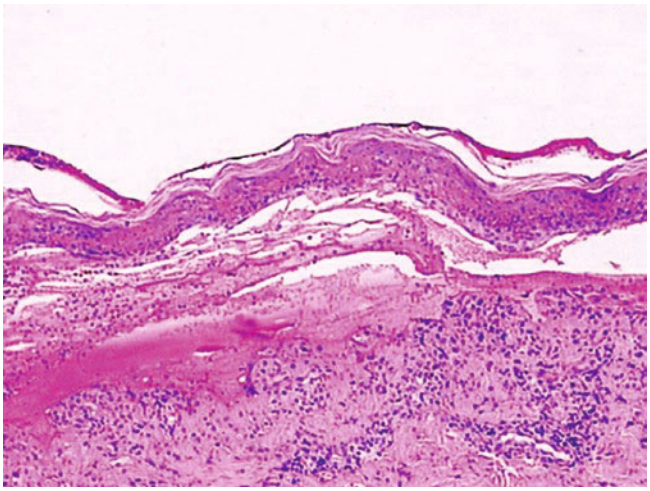


Fig. 11-8-3 Bullae in the subepidermis, numerous neutrophils in the bullae, neutrophils and monocytes infiltrate in the superficial dermis (HE stain, ×40)

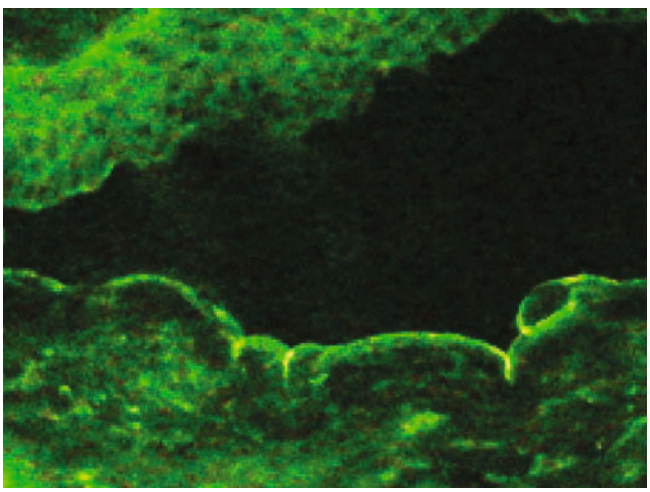


Fig. 11-8-4 Deposition of IgG and C3 in the dermis papillary (DIF, ×40)

11.9 Impetigo Herpetiformis Associated with Intrahepatic Cholestasis of Pregnancy [15]

- Impetigo herpetiformis (IH) is a potentially life-threatening pregnancy dermatosis. It usually involves pregnant women in the third trimester and can recur in subsequent pregnancies, characterized by sterile grouped pustules on the periphery of polycyclic erythematous plaques on the trunk and extremities, which are often associated with systemic symptoms, including fever, nausea, and malaise.
- Intrahepatic cholestasis of pregnancy (ICP) is mainly present in pregnant women. It is usually diagnosed in the third trimester of gestation and typically resolves without treatment after delivery.
- ICP can result in preterm delivery, respiratory distress syndrome of newborns, fetal distress, and sudden intrauterine fetal death, leading to a clear increase in fetal morbidity and mortality.

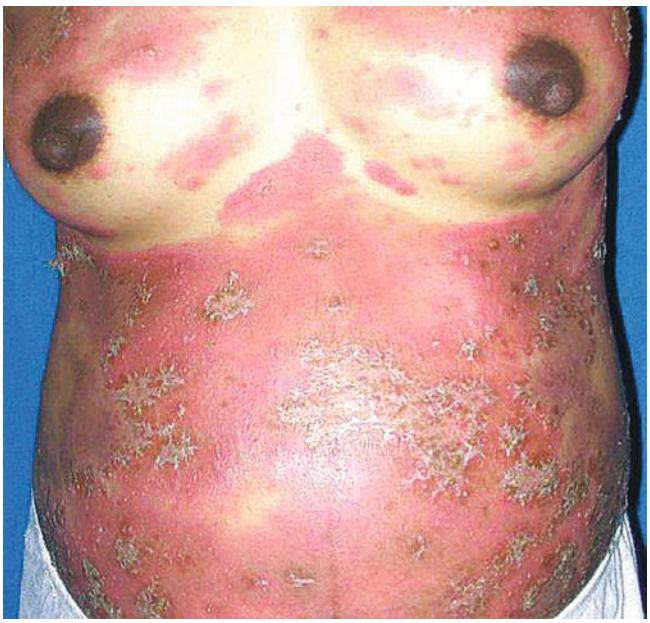


Fig. 11-9-1 Erythema and pustules on the trunk

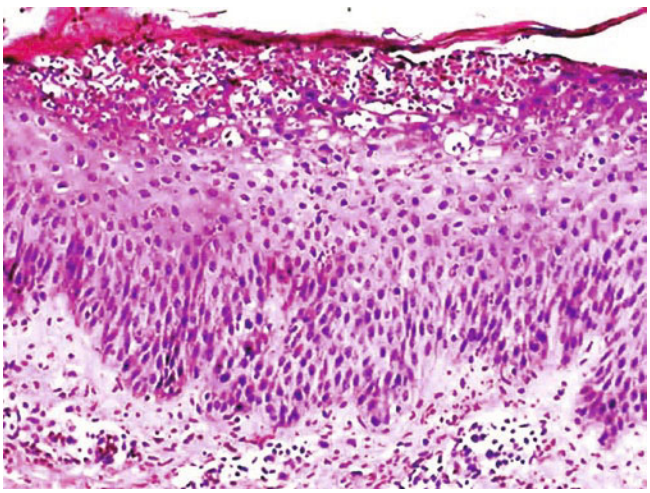


Fig. 11-9-2 The spongiform pustule of Kogoj in the epidermis (HE stain, ×400)

11.10 Pustulosis Palmoplantaris Accompanied by Anterior Chest Wall Syndromes [16, 17]

- Pustulosis palmoplantaris (PPP) is most frequently seen in adults and is more common in female patients. Patients may present with pustules, erythema, and scaling of the hands and/or feet. Psoriasis-like eruptions are also occasionally found on the forearms and legs.
- Histopathologically, the pustules are present on the upper part of the epidermis and are commonly filled with eosinophils and neutrophils.
- PPP is speculated to be related to chronic recurrent multifocal osteomyelitis (CRMO). Approximately 20% CRMO cases are associated with PP

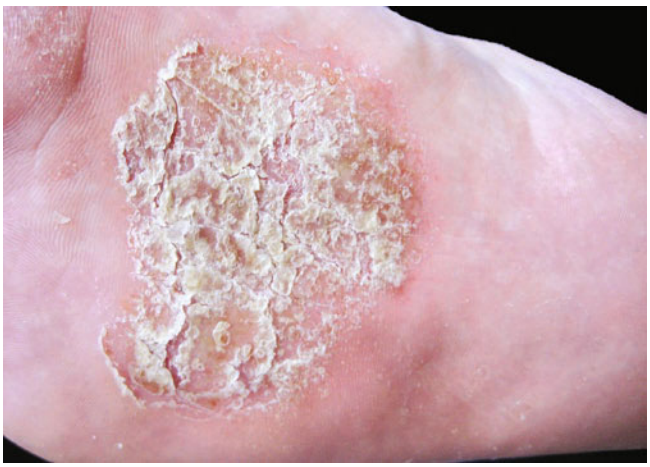


Fig. 11-10-1 Multiple pustules on both sole and palmar

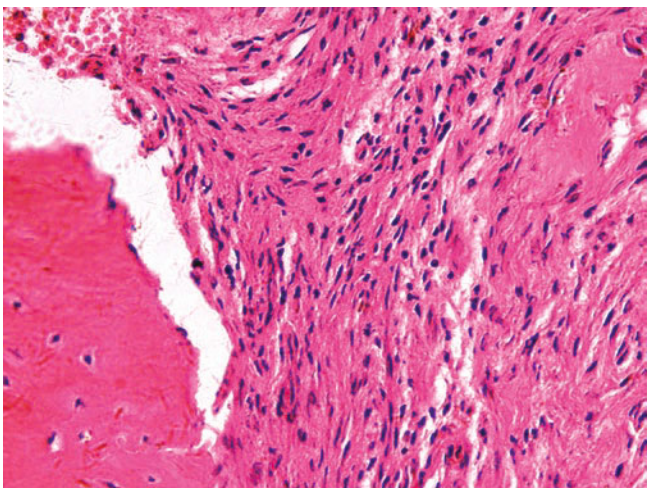


Fig. 11-10-2 There are monocycle and fibroblast infiltrate among the articular cartilage of the first left sternocostal joint (HE stain, ×200)

11.11 Eosinophilic Pustular Folliculitis [18, 19]

- Eosinophilic pustular folliculitis (EPF), also called Ofuji's disease, is a chronic sterile inflammatory dermatosis. Clinically, it can be classified into three subtypes: classic EPF, infancy-associated EPF, and immunosuppression-associated EPF.
- Clinically, EPF shows a gradual increase and fused papular pustules, resulting in erythematous plaque formation. Lesions typically take 7–10 days to heal and recur every 3–4 weeks.
- Histologically, EPF manifests an eosinophil-dominated infiltrate within and around the pilosebaceous units, often accompanied by the formation of an eosinophilic microabscess.
- Given that EPF is a chronic and recurring disease, treatment is relatively difficult. The treatment options are variable, including topical corticosteroids, topical calcineurin inhibitors, systemic isotretinoin, minocycline, phototherapy, trimethoprim, doxycycline, erythromycin, dapsone, colchicine, and clofazimine.

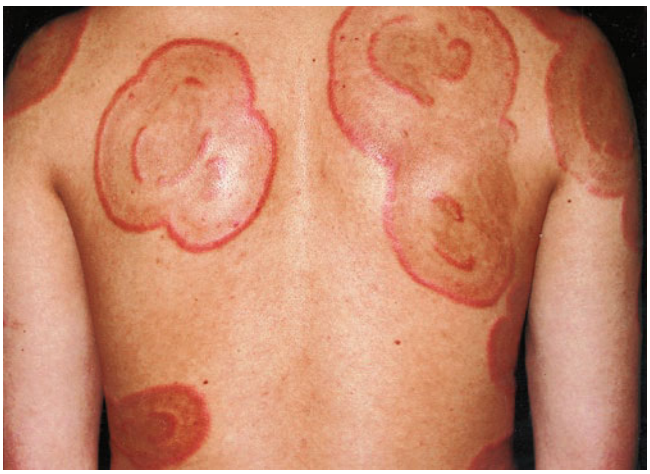
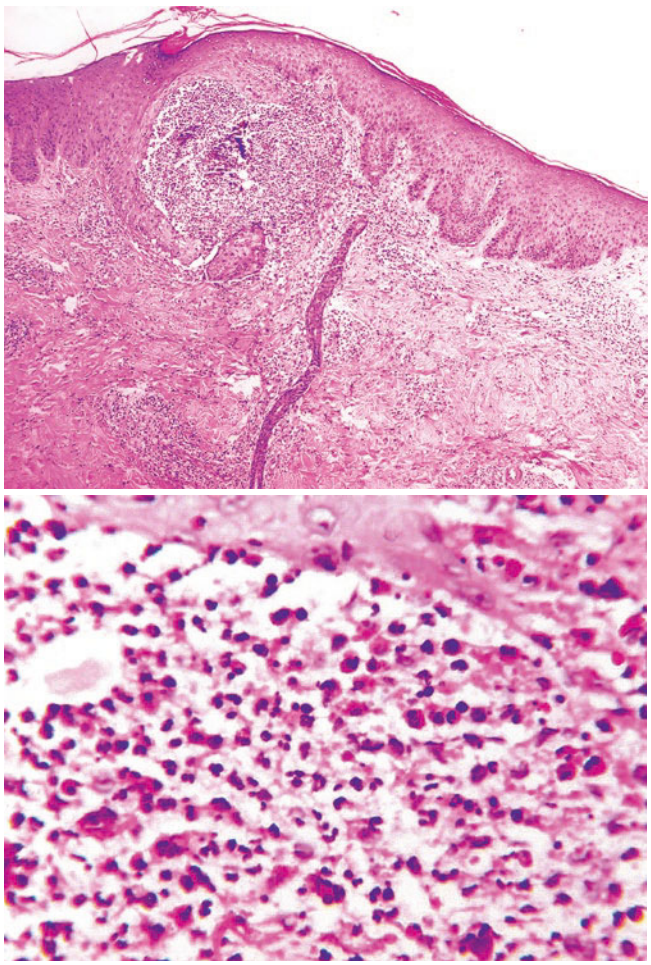


Fig. 11-11-1 Numerous and various sizes of circle erythema, some of them have pustules at peripheral on the back



Figs. 11-11-2, 11-11-3 Microabscess formation contained numerous eosinophils and neutrophils in the hair follicle (HE stain, (2) ×100; (3) ×400)

11.12 Infantile Acropustulosis [20, 21]

- Infantile acropustulosis (IA) is an inflammatory, neutrophilic dermatosis that is most common in infants aged from 2 to 12 months. The lesions preferentially occur on palms and soles. Initially, small, red papules occur on the involved skin. The lesions then gradually evolve into vesicles and pustules, with eruptions that last between 7 and 14 days, interspersed with periods of a few weeks of remission.
- Typical clinical manifestation plays a vital role in the diagnosis of IA. The most important is to distinguish them from scabies.
- Mid- to high-potency topical corticosteroids are routinely used in the past decades. Occasionally, dapsone may play a role within 24–72 h.

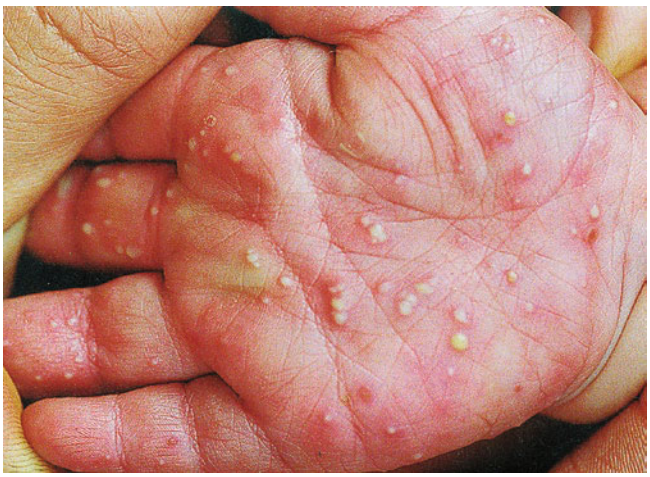


Fig. 11-12-1 The pustules with intense wall and pale yellow fluid in size from 1 to 2 mm on the palms and flexor surface of the finger, intense wall and pale yellow fluid in the pustules

11.13 Generalized Acrodermatitis Continua [22, 23]

- Acrodermatitis continua of Hallopeau (ACH) is a chronic, recurrent, sterile pustular disorder. Commonly, lesions erupt at the tips of the fingers or toes and then gradually extend proximally. The disease may even extend to the nail bed and matrix.
- Topical treatments, photochemotherapy, cyclosporin, methotrexate, retinoids, dapsone, and tetracyclines may play a role.
- Most cases with ACH tend to remain localized to the digits for months or years, rarely evolving into the generalized form, especially in the elderly.
- Although some people think that ACH is an independent disease, most consider it to be a kind of pustular psoriasis, particularly regarding patients with generalized pustular psoriasis.

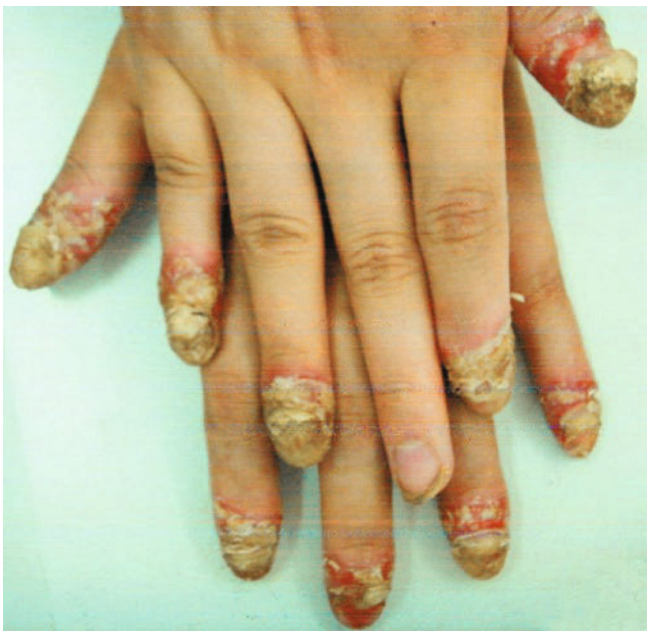


Fig. 11-13-2 Nails deformed, some of them thin or missing, others thickened and pustules under them

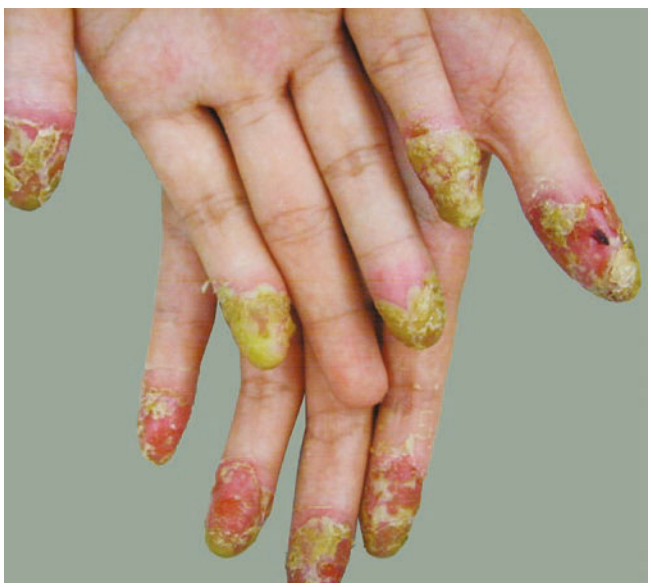


Fig. 11-13-1 Different degrees of erythema on ten fingers, which the size of sesame seeds scattered pustules on erythema, the pustules integration or dry scab

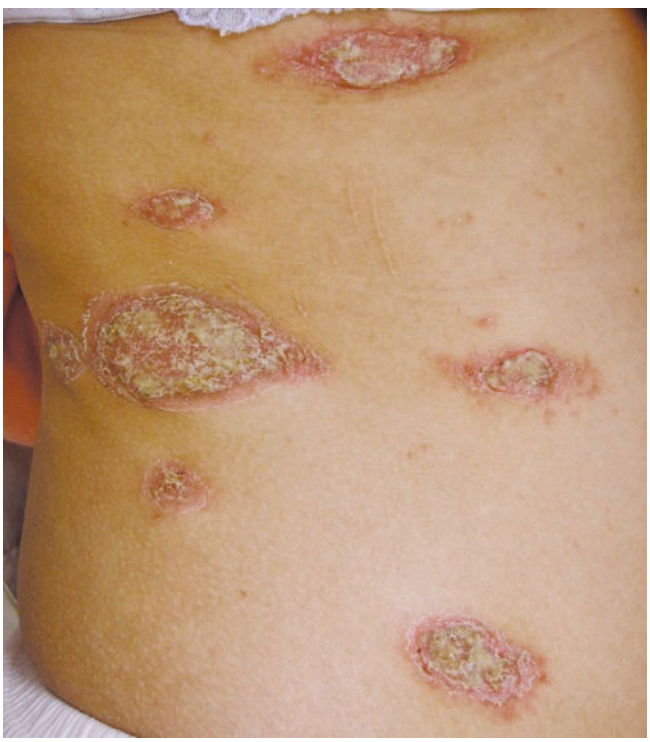


Fig. 11-13-3 Some pustules on erythema of chest and abdomen integrate into lake, others dry or crusted

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Part IV

Erythemas and Vascular Related Diseases

Erythematous Diseases

12

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Abstract

In this chapter, the authors deal with the erythematous diseases including erythema gyratum repens, palpable migratory arciform erythema, left atrial myxoma presenting with painful erythematous macules on the palms and soles, recurrent painful erythema, erythema papulosa semicircularis recidivans, and the red scrotum syndrome.

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12.1 Erythema Gyratum Repens [1, 2]

- Erythema gyratum repens (EGR) is a very uncommon paraneoplastic syndrome, manifesting as serpiginous, erythematous rings that develop trailing scales at the leading edges. Lesions can occur before, after, or concurrently with the neoplasm.
- More than 80% of patients also harbor internal malignancies. Among these, bronchial cancer is the most common.
- The therapy for most patients involves treating the underlying malignancy with the proper radiotherapy, chemotherapy, or surgery. Patients without underlying malignancy or other diseases need to be followed up closely.

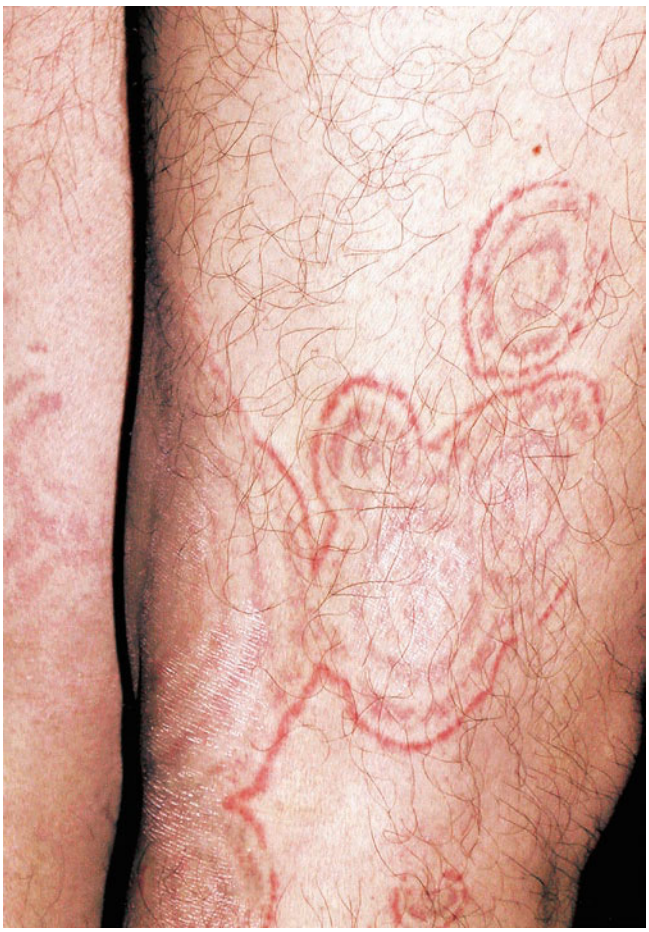


Fig. 12-1-1 Concentric bands of flat-to-raised erythema on the lower limbs

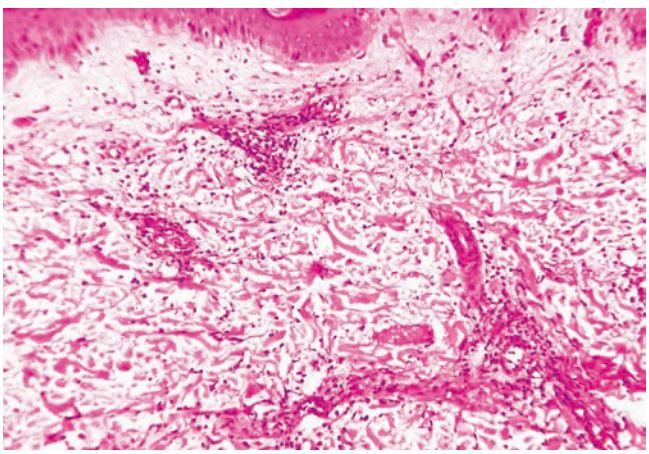


Fig. 12-1-2 Hyperkeratosis, mild atrophy of the epidermis, and superficial perivascular lymphocyte and neutrophil infiltrate in the dermis (HE stain, ×200)

12.2 Palpable Migratory Arciform Erythema [3]

- Palpable migratory arciform erythema (PMAE) is an infrequent chronic T-cell pseudolymphoma.
- The lesion is characterized by sharply circumscribed, infiltrated erythematous patches that lean toward migration unregularly, leading to arciform morphologic features. This condition commonly appears in adult males. The lesions mainly occur on the trunk area.
- The histological examination shows a moderate to severe perivascular and periadnexal T-lymphocytic infiltrate throughout the dermis, mostly of the CD4+ phenotype.
- Many treatments have been tried, including antimicrobials such as penicillin, topical corticosteroids, and UVA-1 phototherapy.

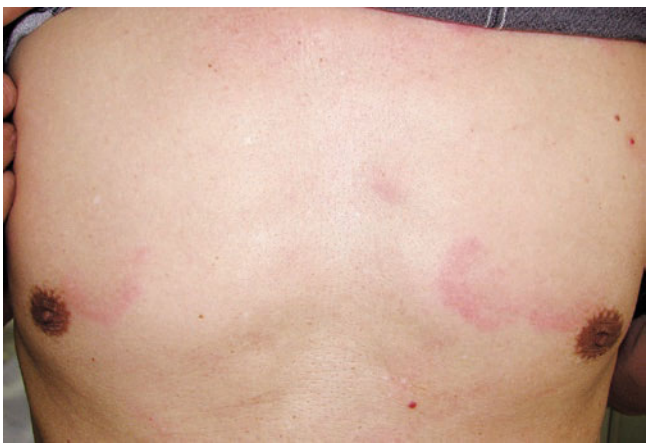


Fig. 12-2-1 There were two arciform erythemas on the chest which were approximately 10 cm in length and 1 cm in width, normal texture with slight elevation

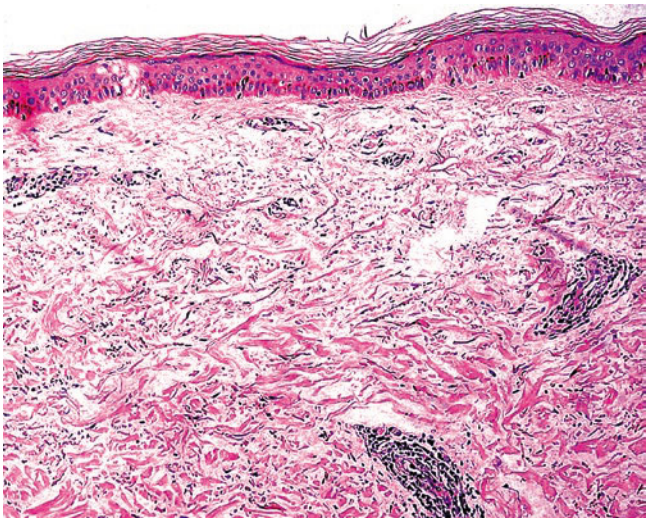


Fig. 12-2-2 Epidermis was slight atrophy without liquefaction degeneration of basal cells

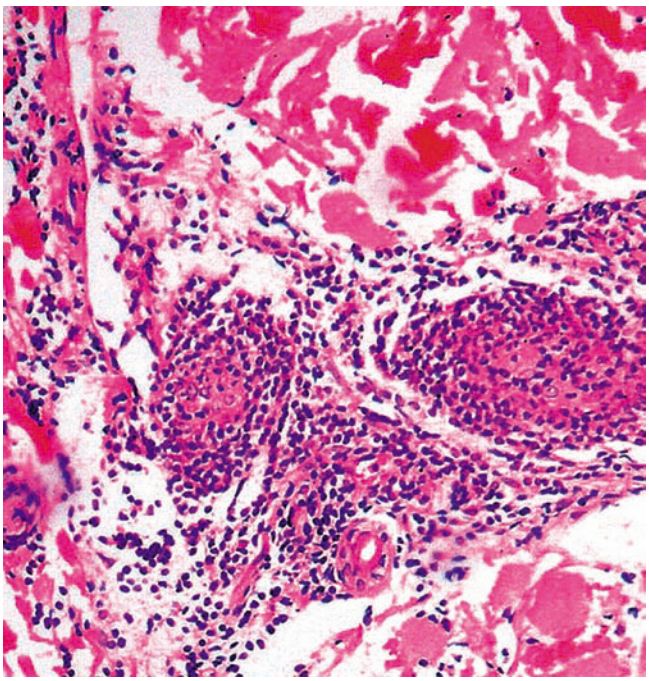


Fig. 12-2-3 Mononuclear cells infiltrated densely around the blood vessels in the reticular layer of the dermis

12.3 Left Atrial Myxoma Presenting with Painful Erythematous Macules on the Palms and Soles [4]

- Atrial myxoma is the most common primary cardiac tumor and is generally accompanied by prominent cardiac and embolic manifestations. It is a rare benign tumor that can be completely cured by surgical excision.
- Cutaneous manifestations are usually non-specific and can be classified into three subtypes: embolic cutaneous signs, signs associated with autoimmune symptoms, and cutaneous signs of a complex syndrome.
- Cutaneous signs may be the sole symptoms and/or first sign, warranting the dermatologist's attention. In most cases, cutaneous signs are transient and non-specific therefore easily overlooked. The diagnosis depends on the histological finding of the myxomatous emboli. An echocardiogram examination must be performed immediately.

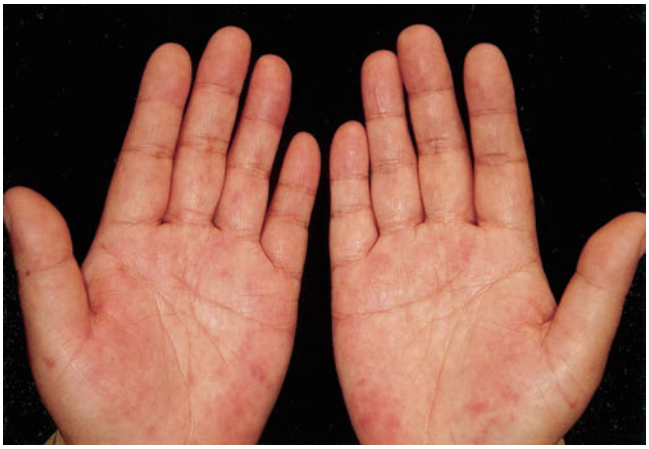


Fig. 12-3-1 Painful erythematous macules on the palms

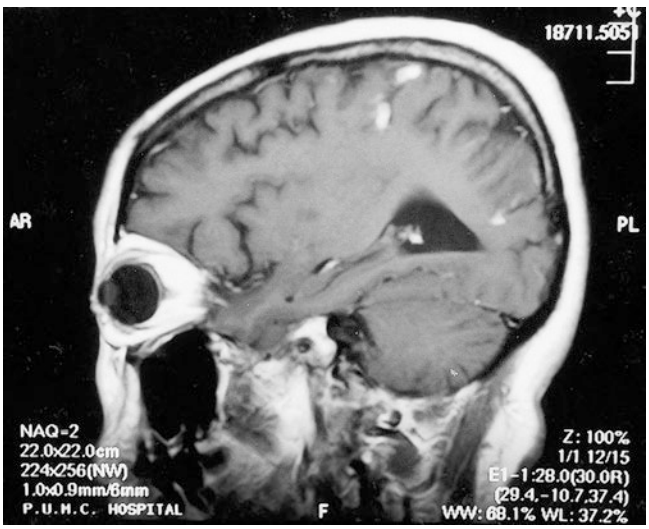


Fig. 12-3-2 The MRI of the skull showed multiple cerebral infarctions

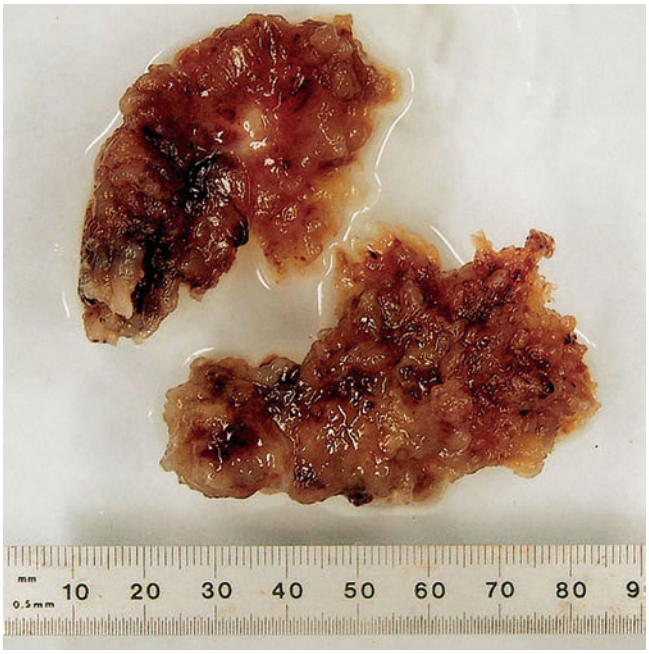


Fig. 12-3-3 The appearance of excised tumor

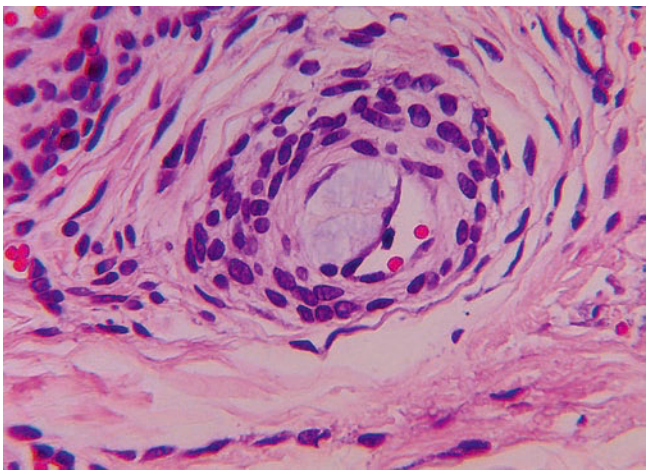


Fig. 12-3-4 An embolus within a vessel in the reticular dermis (HE stain, ×400)

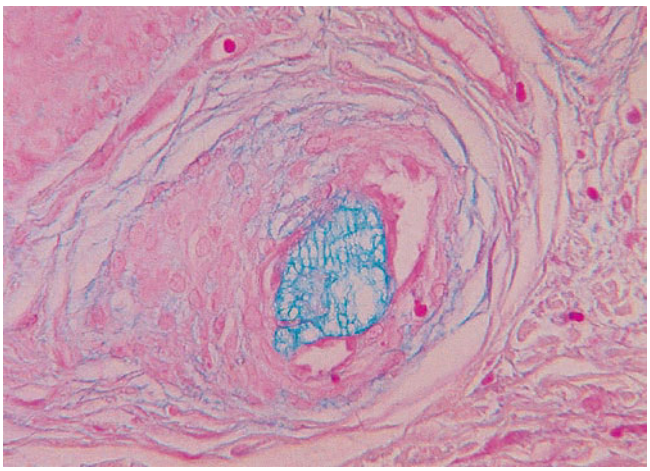


Fig. 12-3-5 Alcian Blue staining positive embolus in blood vessel in the dermis (Alcian Blue stain, ×400)

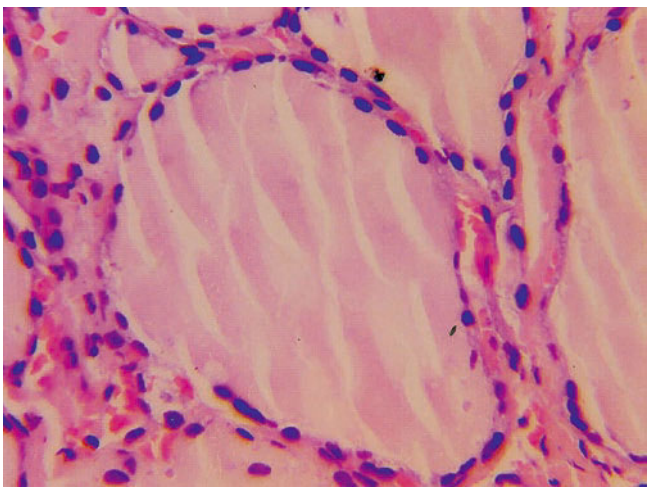


Fig. 12-3-6 Scattered spindle cells with scant pink cytoplasm in a loose myxoid stroma (HE stain, ×400)

12.4 Recurrent Painful Erythema [5]

- The extensor surfaces of extremities are the predilection sites, while lesions on the trunk or flexor surfaces of the extremities are apparently rare.
- The manifestations present as transient erythema but without annular configuration. Almost all patients experience severe spontaneous pain that disturbs their sleep. Physical motion and bruising may trigger the frequent appearance of erythema. The occurrence of erythema is not progressive, but it can continue for at least 5 years.
- The differential diagnoses include skin leiomyoma, dermatalgia, and erythema nodosum. Glucocorticoids may relieve symptoms in some patients.

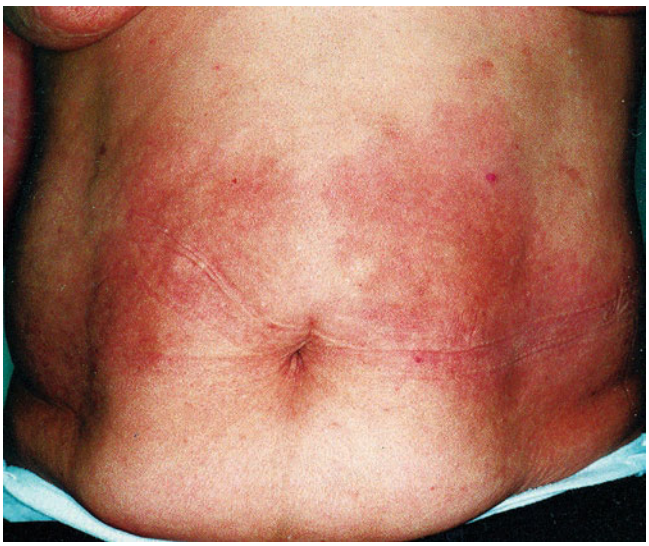


Fig. 12-4-1 Erythema on the abdomen and confluent around the umbilicus

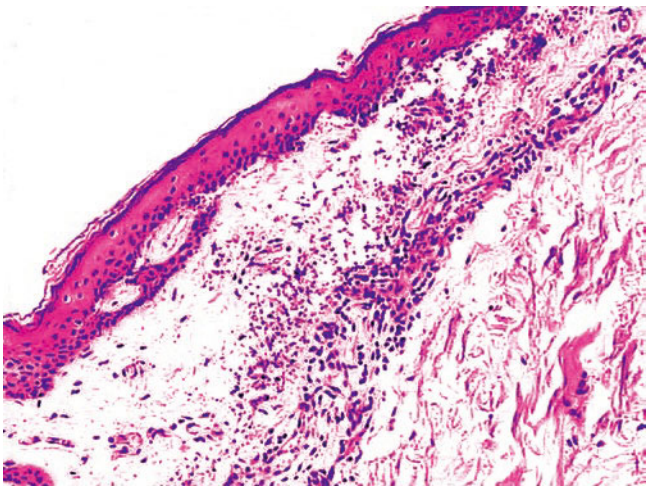


Fig. 12-4-2 Hyperkeratosis, edema in the upper dermis, dilated capillaries, and a few lymphocytes infiltrated around the vessels (HE stain, ×100)

12.5 Erythema Papulosa Semicircularis Recidivans [6]

- Erythema papulosa semicircularis recidivans (EPSR) is a clinically new and rare cutaneous condition, which preferentially appears in males.
- Commonly, the lesions are characterized by erythematous papules with a semicircular edge that occurs in early summer, regressing spontaneously in the late fall. However, they relapse at almost same seasonal time in the subsequent year.
- The possible differential diagnoses are erythema annulare centrifugum, erythema migrans, and papular pityriasis rosea. Of note, some patients may simultaneously suffer from an underlying malignancy.

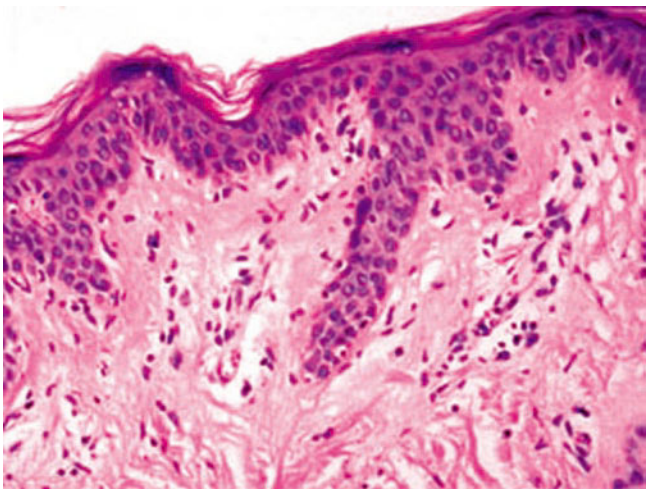
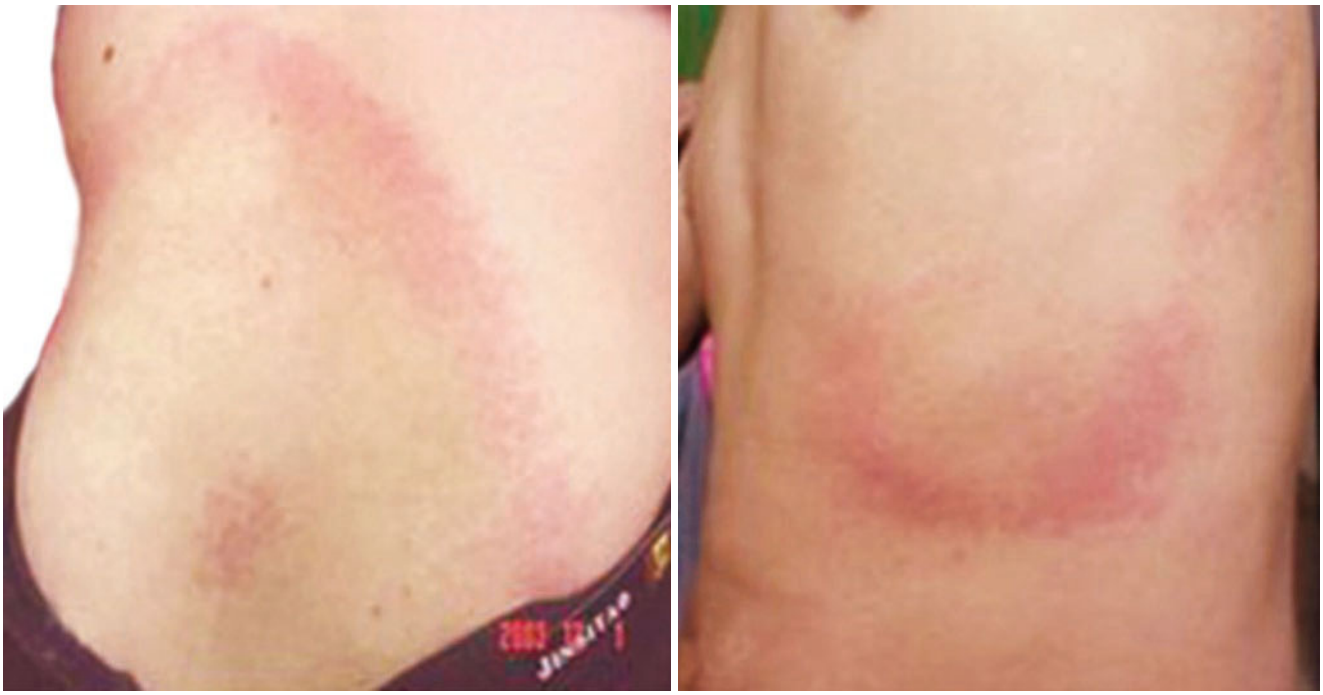


Fig. 12-5-3 Mild hyperkeratosis, slight papillary dermal edema, and sparse superficial perivascular lymphocytic infiltrate (HE stain, ×100) (Reproduced with the permission from [6])



Figs. 12-5-1, 12-5-2 Papuloerythematous lesions arranged in semicircles on the trunks (Reproduced with the permission from [6])

12.6 Red Scrotum Syndrome [7]

- Red scrotum syndrome (RSS) is a poorly understood, chronic unwieldy genital erythema. Commonly, the anterior scrotum is involved, with a burning sensation and hyperalgesia, which preferentially occurs in men over 50 years of age.
- RSS usually occurs after prolonged topical corticosteroid in the scrotal region.
- Generally, RSS responds poorly to drug treatments. Topical calcineurin inhibitors may relieve clinical symptoms of some cases, but they are unable to ease the burning and pain sensations. Occasionally, oral doxycycline and oral gabapentin may play a role.

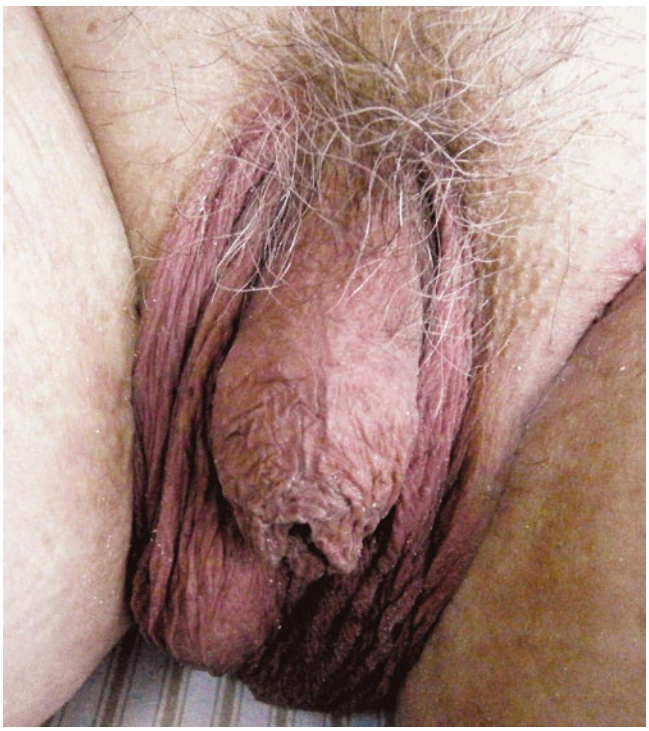


Fig. 12-6-1 Demarcated erythematous lesion on the scrotum

Fig. 12-6-2 The skin at the root of the penis

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Vasculitis

13

Chun-Lei Han, Ying Wang, Chun-Xiang Zhang, Ren-Gui Chen, Guo-Jun Sun, Jun-Hong Ao, Jian-Min Chang, Xia Xiong, Bin Xu, and Ru-Zhi Zhang

Abstract

Vasculitis represents a wide spectrum of disorders encompassing erythema elevatum diutinum, Sweet's syndrome and its subcutaneous variant, granulomatosis with polyangiitis, pyoderma gangrenosum, malignant atrophic papulosis accompanying intestinal perforation, livedoid vasculitis, thrombocythemia purpura, and disseminated pruriginous angiodermatitis, as shown in this chapter.

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13.1 Erythema Elevatum Diutinum [1, 2]

- Erythematous violaceous papules and nodules are the most common clinical manifestations, and the distribution is symmetrical. Generally, isolated or fused lesions with a hardened consistency occur over extensor surfaces of the extremities, particularly on the skin overlying the joints.
- Erythema elevatum diutinum (EED) is an unusual cutaneous vasculitis. Its etiology and exact pathogenesis are poorly understood but are thought to be related to the deposition of circulating immune complexes in perivascular spaces. Generally, EED is considered to be induced by infections or hematologic or autoimmune disease.
- In most patients with EED, the skin lesions are asymptomatic. Systemic symptoms such as fever and arthralgias often attract the attention of patients.
- Histologic characteristics consist of leukocytoclastic vasculitis of the mid and papillary dermal vessels with fibrinoid necrosis and a dense infiltration of neutrophils in the deeper dermis.

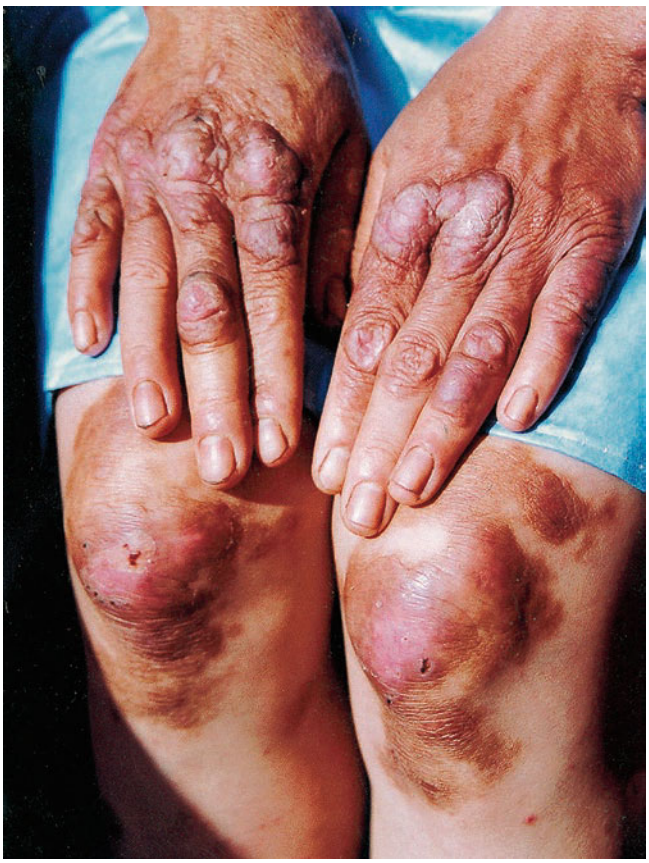


Fig. 13-1-1 Brownish-red to purple nodules and plaques on the extensor surfaces of the knees and hands

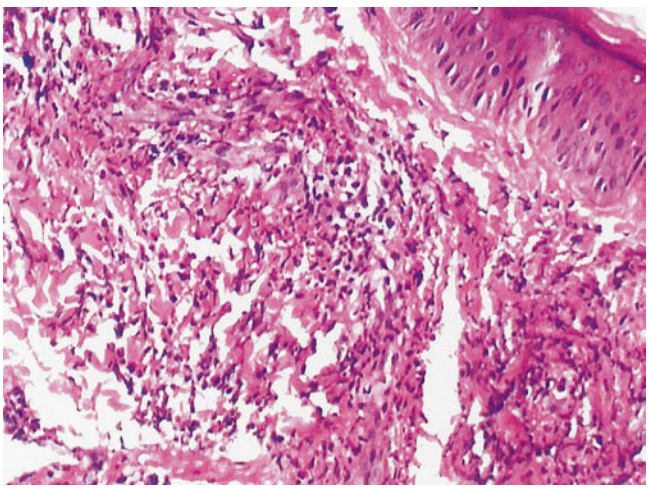


Fig. 13-1-2 Dense neutrophils intermingled with varying numbers of lymphocyte and histiocyte infiltrate in the superficial dermis and perivascular area (HE stain, ×100)

13.2 Sweet's Syndrome and Its Subcutaneous Variant [3]

- Sweet's syndrome (SS), also called acute febrile neutrophilic dermatosis, is an apparently rare dermatosis. Its greatest features are sudden onset and recurrent symptoms. The most common recurrent symptoms are fever, neutrophilia, and tender erythematous papules or nodules on the head, neck, and upper and lower limbs.
- SS may be a hypersensitivity or immunological phenomenon, which may be induced by many drugs, paraneoplastic, infections, and neoplasms.
- Subcutaneous Sweet's syndrome (SSS), or Sweet's panniculitis, is a rare variant of the classic syndrome, in which neutrophilic infiltrate is exclusively or predominantly located in the subcutaneous tissue, causing lobular or septal panniculitis. Clinically, the majority of SSS have been related to extremity involvement.
- The most commonly used systemic drugs are colchicine, potassium iodide, and corticosteroids, followed by indomethacin, clofazimine, dapsone, and cyclosporine. The biological treatments may be promising therapy.

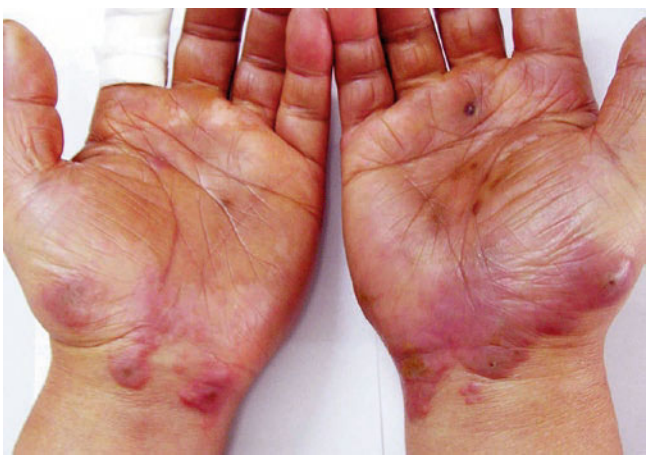


Fig. 13-2a-1 Well-circumscribed annular-like violaceous plaques on both palms

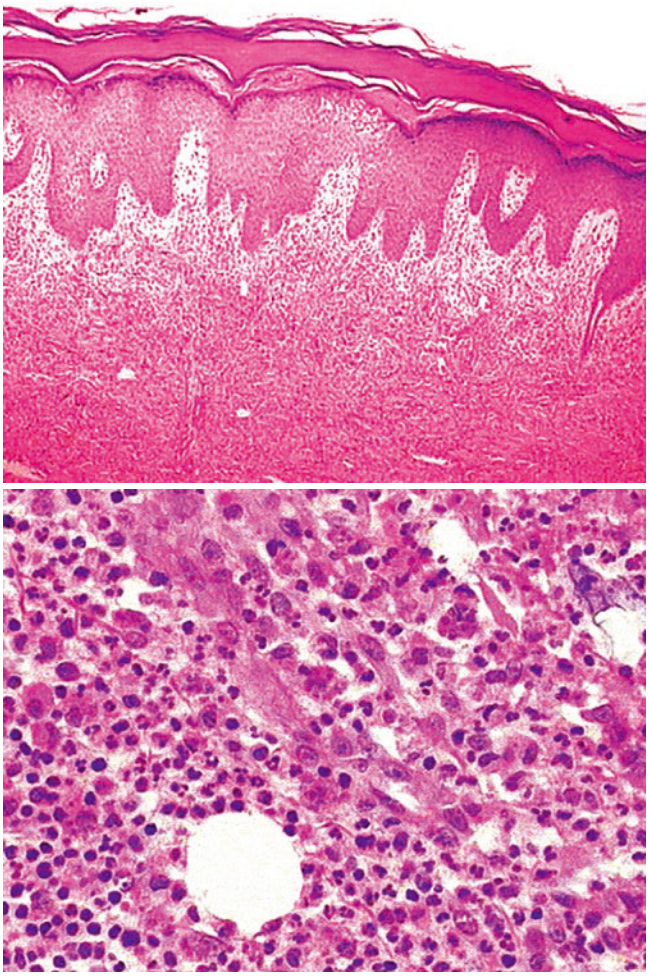
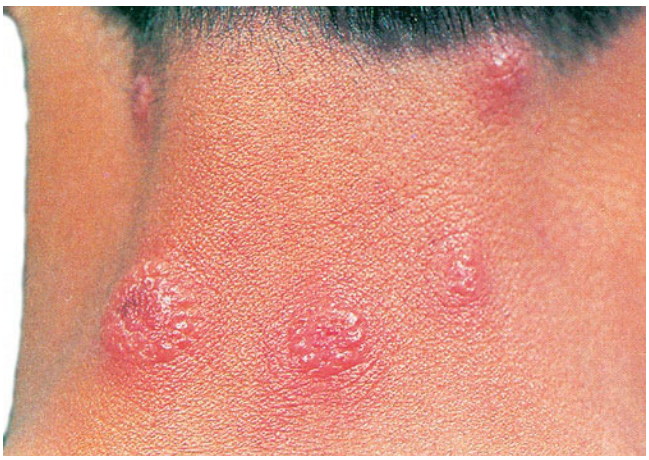


Fig. 13-2a-2, 13-2a-3 Focal spongiosis in the epidermis and diffuse perivascular neutrophil, histiocyte, and lymphocyte infiltrate in the dermis (HE stain, (2) × 40, (3) × 200)



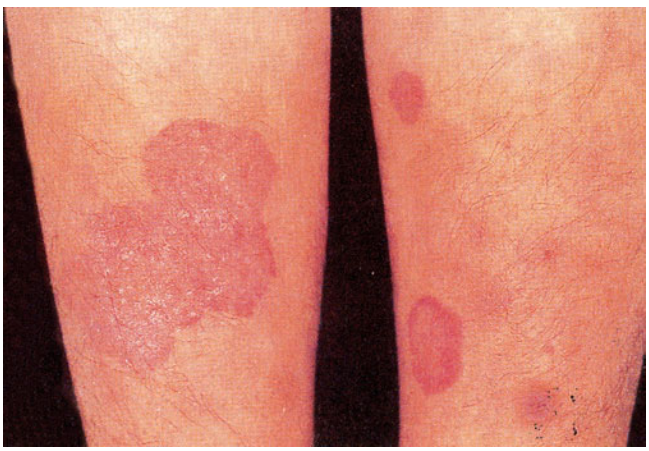


Fig. 13-2b-1, 13-2b-2 Erythematous plaques and nodules on the nape (1) and the leg (2)

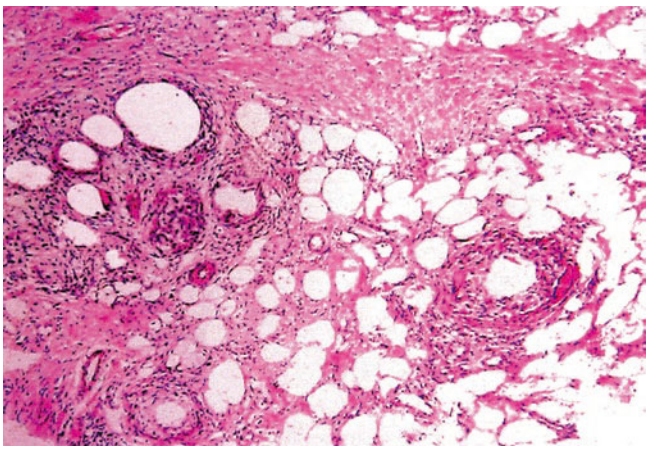


Fig. 13-2b-3 Prominent infiltrate composed of neutrophils around the vasculature in the dermis (HE stain, ×100)

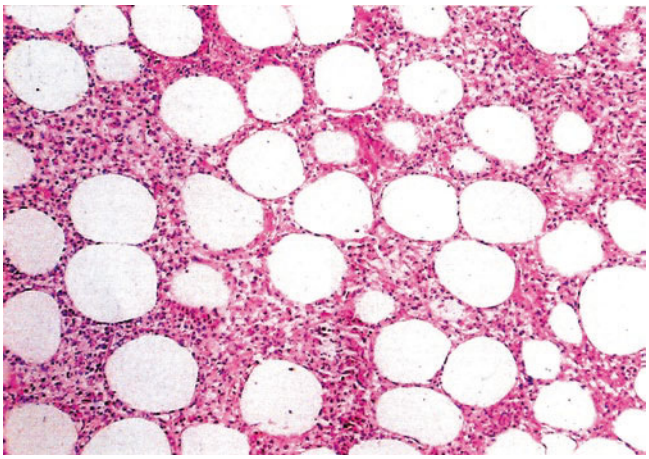


Fig. 13-2b-4 There is a dense infiltrate composed of neutrophils associated with nuclear fragmentation in subcutaneous tissue (HE stain, ×160)

13.3 Granulomatosis with Polyangiitis [4, 5]

- Granulomatosis with polyangiitis (GPA), also known as Wegener's granulomatosis, is a small and medium vessel vasculitis. Necrotizing granuloma of the respiratory tract, necrotizing cutaneous vasculitis, and necrotizing glomerulonephritis are the distinctive clinical manifestations.
- The synergistic effects of environmental and infectious factors induce the onset of disease in genetically susceptible individuals. The antineutrophil cytoplasmic antibody profile plays a vital role in the diagnosis of G.
- Half of patients present with cutaneous lesions, comprising papules, nodules, palpable purpura, ulcers, or necrotizing lesions. Among these, papulonecrotic lesions mainly in the lower limbs are the most common.
- Untreated GPA is uniformly fatal, and mortality may reach 90% at 2 years. Early treatment of remission induction plays a vital role in reversing the renal damage. Cyclophosphamide and other immunosuppressive agents play a vital role in treatment. Biological agents may be a promising therapy.

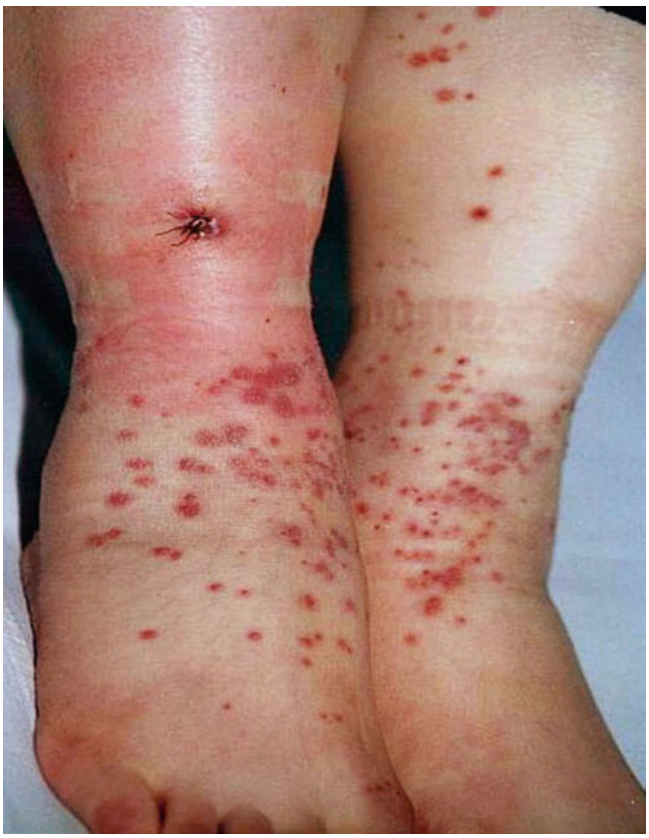


Fig. 13-3-2 Millet-sized red papules with central vesicles, pustule, and necrosis crust on the back of the feet and calves

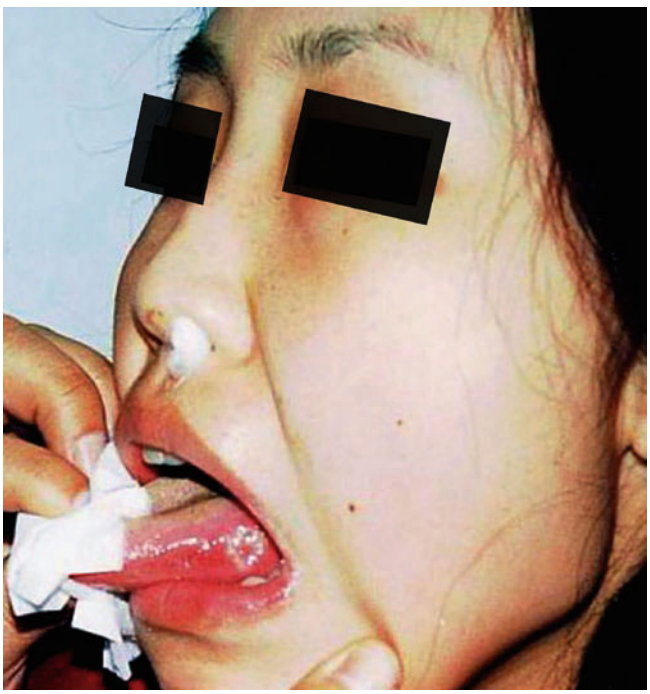


Fig. 13-3-1 A soybean-sized ulcer on the left aspect of tongue (Reproduced with the permission from [4, 5])

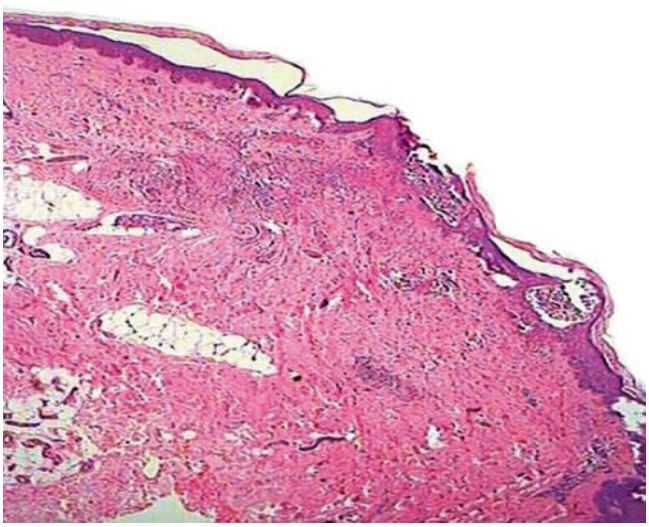


Fig. 13-3-3 Leukocytoclastic vasculitis with granulomatous inflammation and majority histiocytes (HE stain, ×10)

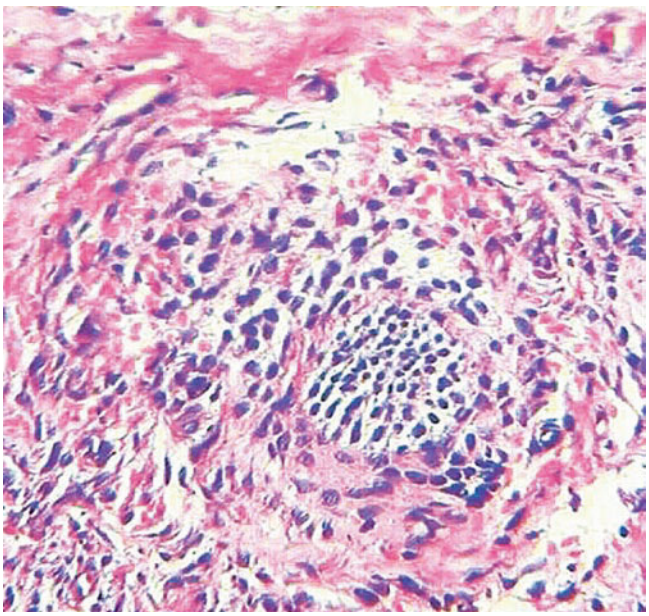


Fig. 13-3-4 Granulomatous vasculitis (HE stain, ×40)

13.4 Pyoderma Gangrenosum [6, 7]

- Pyoderma gangrenosum (PG) is an apparently infrequent, inflammatory neutrophilic dermatosis, which may had been classified as an autoinflammatory disease and usually leads to a devastating consequence. The exact etiology remains unclarified, and it may be accompanied by systemic disorders, which could precede, coexist with, or follow PG.
- Clinically, PG is divided into four subtypes: ulcerative (or classic), pustular, vegetative, and bullous (or atypical). The ulcerative form is the most frequent kind, with a preference for the trunk and lower extremities. Occasionally, the face and neck may be involved.
- Initially, the lesions present as blisters, pustules, papules, or hemorrhagic papules and promptly evolve to an ulcer, which might regress with mutilating scars. A biopsy is contributed to exclude infections and neoplastic and vasculitic diseases.
- Currently, systemic corticosteroids or cyclosporine are recommended for routine use in the treatment of PG. Biologic agents are used to control severe or intractable PG.

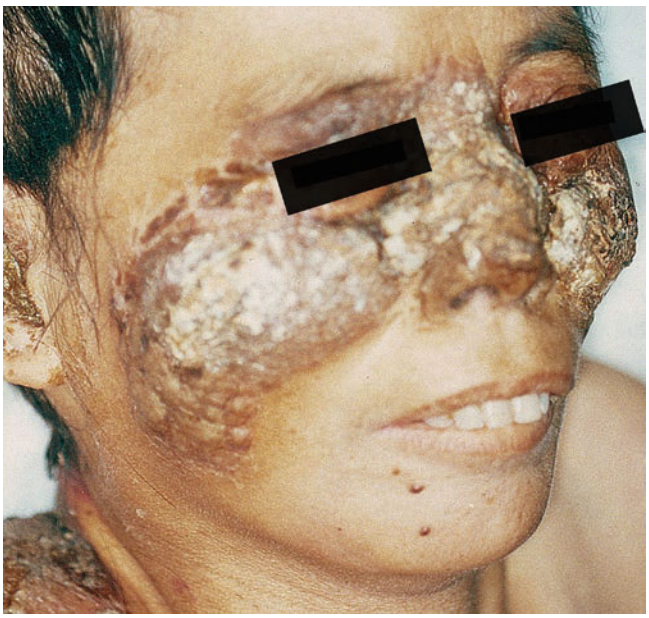


Fig. 13-4-1 Butterfly ulcerative plaques on the face (Reproduced with the permission from [6, 7])

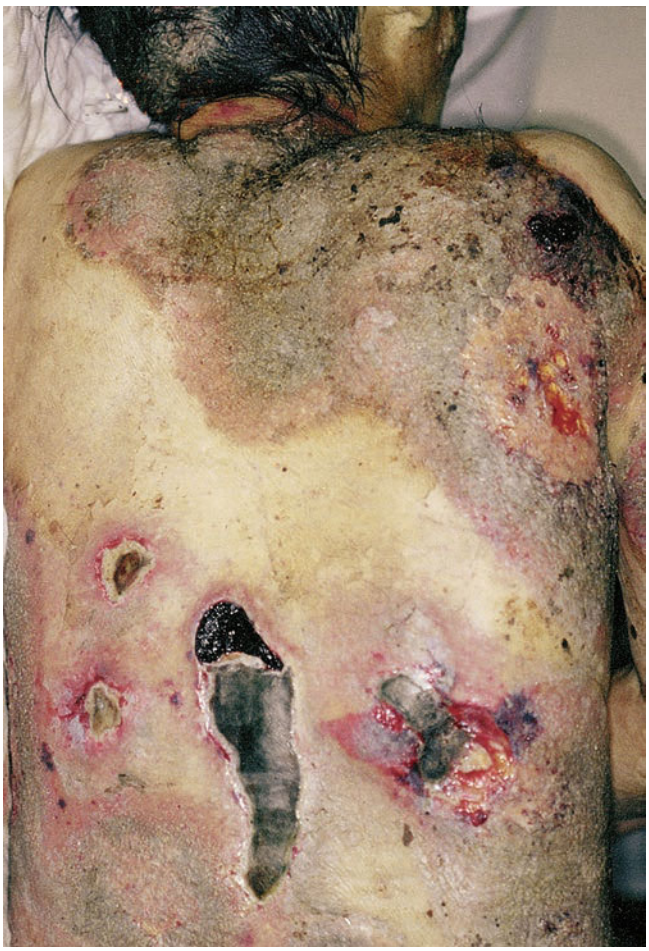


Fig. 13-4-2 Varying sizes of ulcers and scars on the shoulder and back

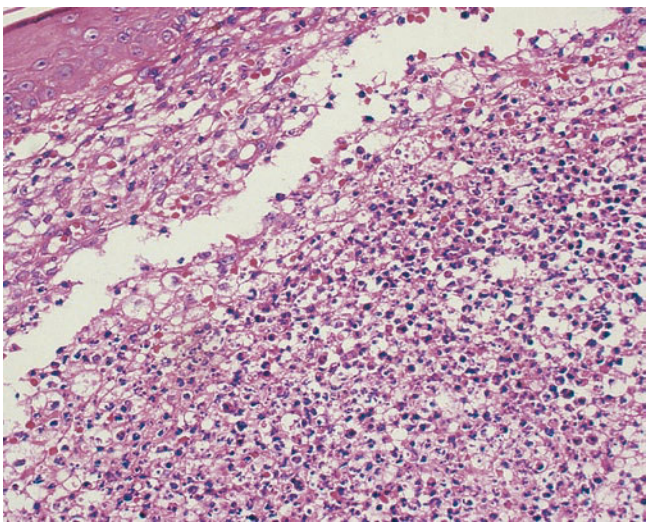


Fig. 13-4-3 A dense infiltrate of neutrophils and eosinophils in the dermis (HE stain, ×400)

13.5 Malignant Atrophic Papulosis Accompanying Intestinal Perforation [8]

- Malignant atrophic papulosis (MAP), also known as Degos disease, is a very rare condition characterized by atrophic papules and various systemic involvements, usually with an onset between the age of 20 and 50 years.
- The skin, gastrointestinal tract, and central nervous system are often involved. Ischemia and infarction of the involved organs are the common complications, owing to the narrowing and occlusion of the vascular lumen.
- Cutaneous manifestation of MAP presents as disseminated papules with central porcelain-white atrophy and a telangiectatic border.
- The treatment for MAPs is still a challenge for dermatologists. MAPs may be potentially life-threatening with regard to systemic involvement. The highest mortality is found among patients aged 2–3 years with systemic involvement. Small bowel perforation is the most common cause of death. Fasting and parenteral nutrition might be helpful measures in relieving the gastrointestinal symptoms.

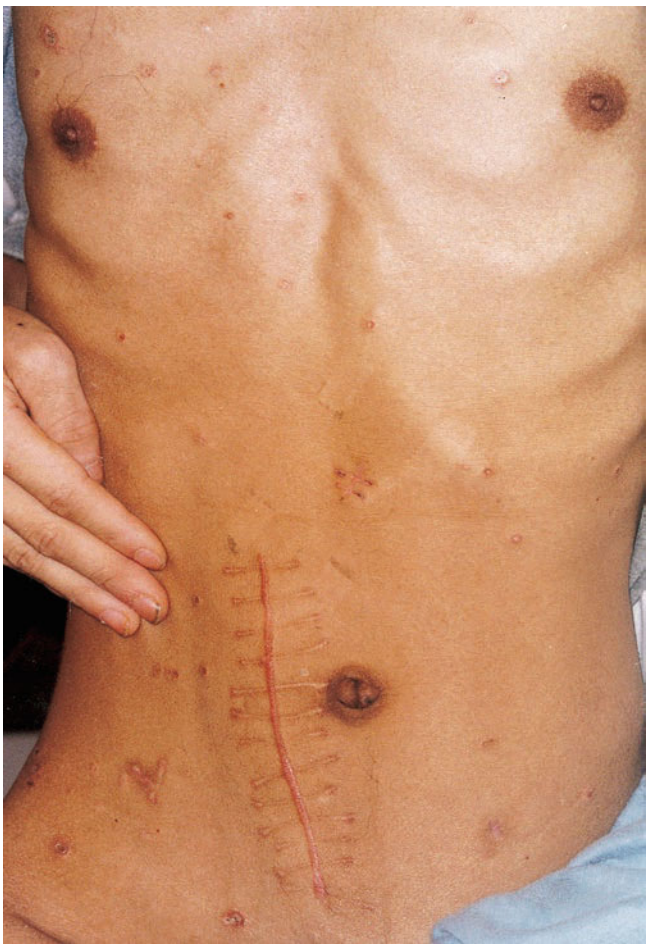


Fig. 13-5-1 Millet to soybean-sized pale-red or yellowish-red papules with atrophic porcelain-white center, partly with fine scales on the surface

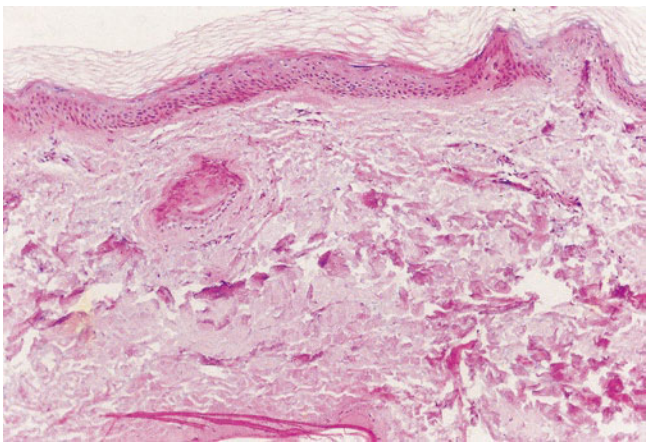


Fig. 13-5-2 Marked atrophy of the stratum Malpighi associated with slight hyperkeratosis and rete ridge vanishing (HE stain, ×100)

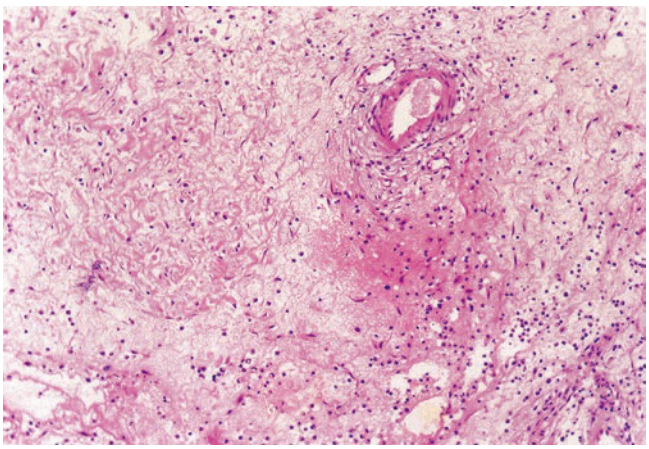


Fig. 13-5-3 Focal necrobiosis in the dermis, appendages decrease, collagen fibrous tissue hyperplasia, and focal lymphocyte infiltrate in the perivascular area (HE stain, ×100)

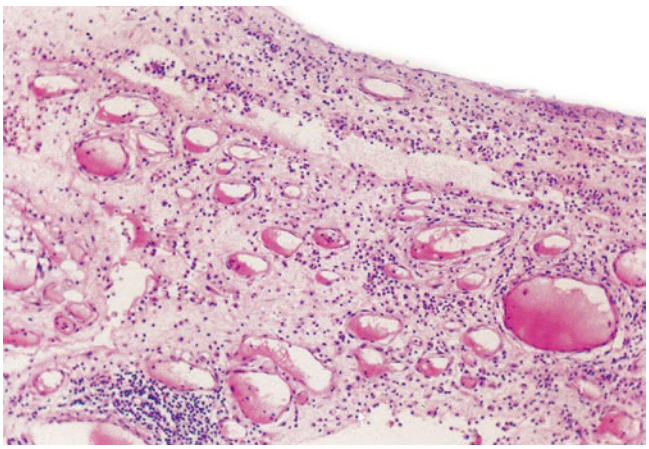


Fig. 13-5-4 Scattered neutrophils infiltrate in the intestine, with subserosal arterioles endothelial cell hyperplasia occluded by thrombosis (HE stain, ×100)

13.6 Livedoid Vasculitis [9]

- Livedoid vasculitis, also known as atrophie blanche or segmental hyalinizing vasculitis, is a rare chronic, seasonal dermatosis, which generally involves the lower legs, ankles, and dorsum of the feet.
- Lesions start with purpuric macules and papules. However, the typical lesions are recurrent, bizarrely shaped ulcers, leaving hyperpigmentation and stellate white scars or atrophie blanche.
- Histologically, this condition demonstrates fibrin deposition within both the wall and lumen of affected vessels. The epidermal atrophy with thickened hyalinized vessels and deposition of hemosiderin are observed in the late stage of disease.
- Treatment remains intractable, and the existing methods include bed rest with leg elevation, saline soaking, vasodilators, systemic steroids, antiplatelet agents, intravenous immunoglobulin (IVIg), and PUVA using 8-methoxypsoralen (8-MOP).

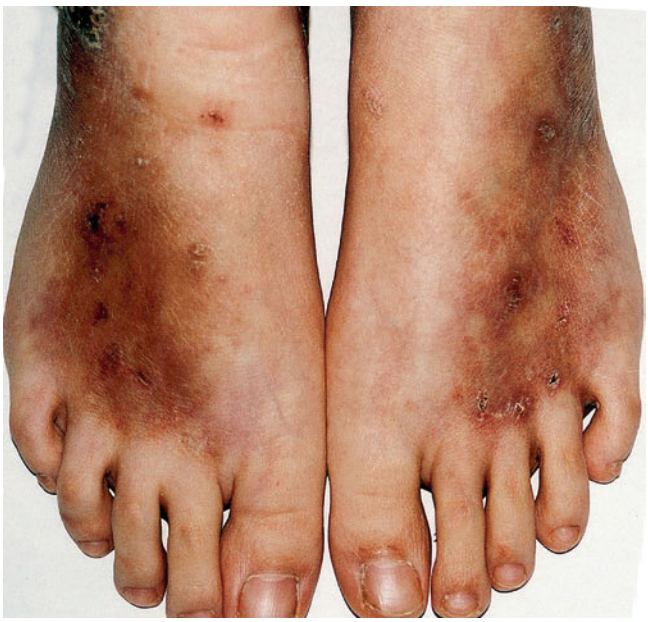


Fig. 13-6-1 Ulcer and hyperpigmentation on the dorsal of the feet

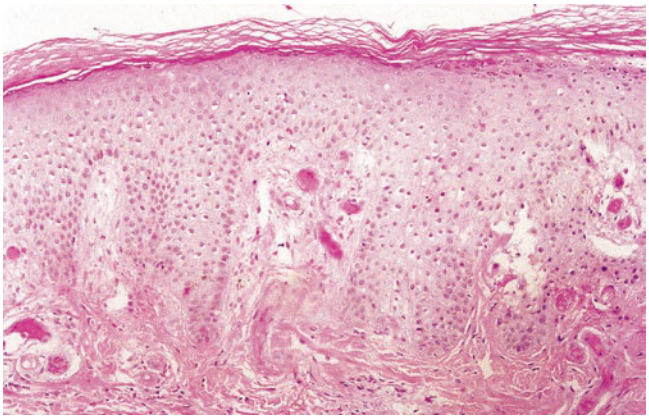


Fig. 13-6-2 Edema and multiple small vessels thrombogenesis in the upper dermis (HE stain, ×100)

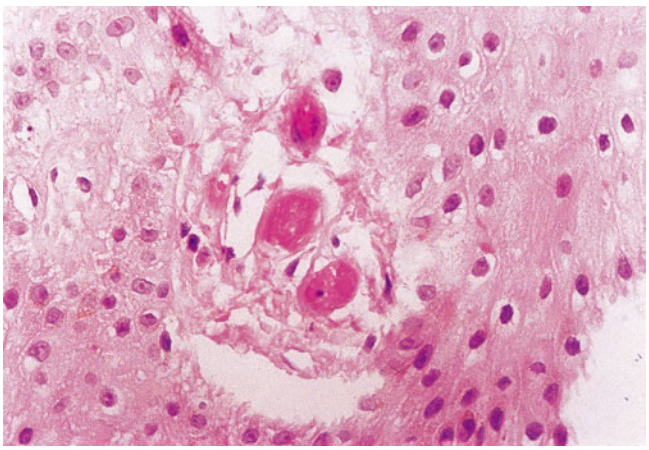


Fig. 13-6-3 Multiple thrombogenesis in small vessels in the dermis papilla (HE stain, ×200)

13.7 Thrombocythemia Purpura [10]

- Essential thrombocythemia (ET) is a rare chronic myeloproliferative disorder that usually occurs in people aged 60 years and older. The pathogenesis of ET is thought to involve hyperplasia of platelets without normal function.
- The typical clinical manifestation of ET is vascular occlusive events and hemorrhages. Various cutaneous presentations of ET usually appear after microvascular thrombosis. In terms of cutaneous symptoms, purpura is most common, followed by erythromelalgia, dermal ulcer, and livedo reticularis.
- ET may be confused with reactive thrombocythemia, such as iron deficiency anemia and splenectomy. Clinically, low-dose aspirin alone and combination with hydroxyurea are routinely used.

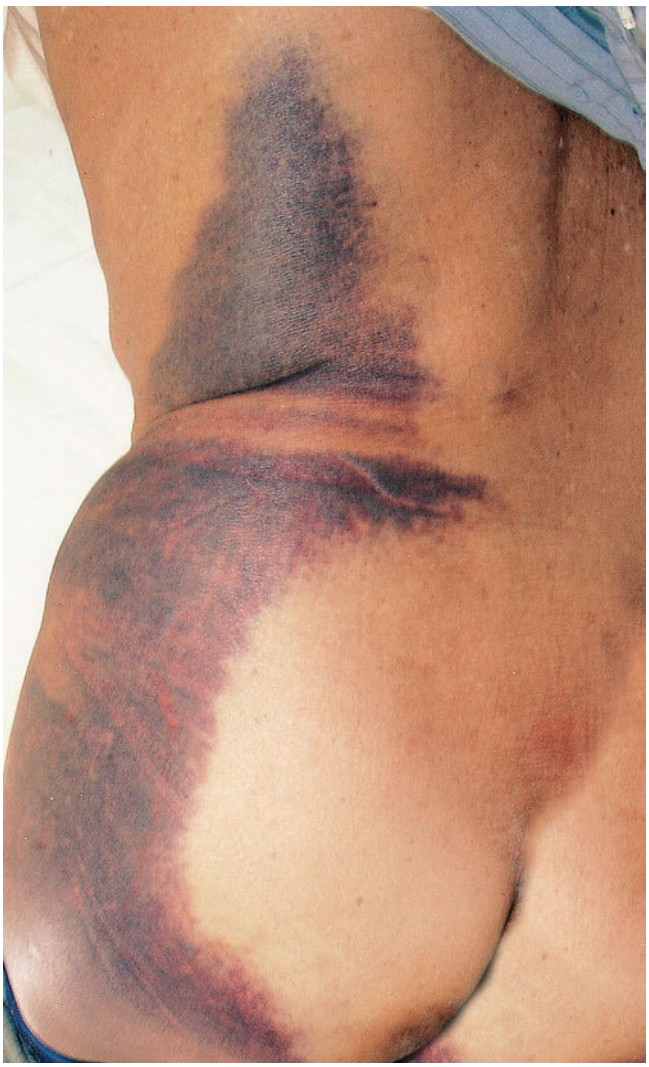
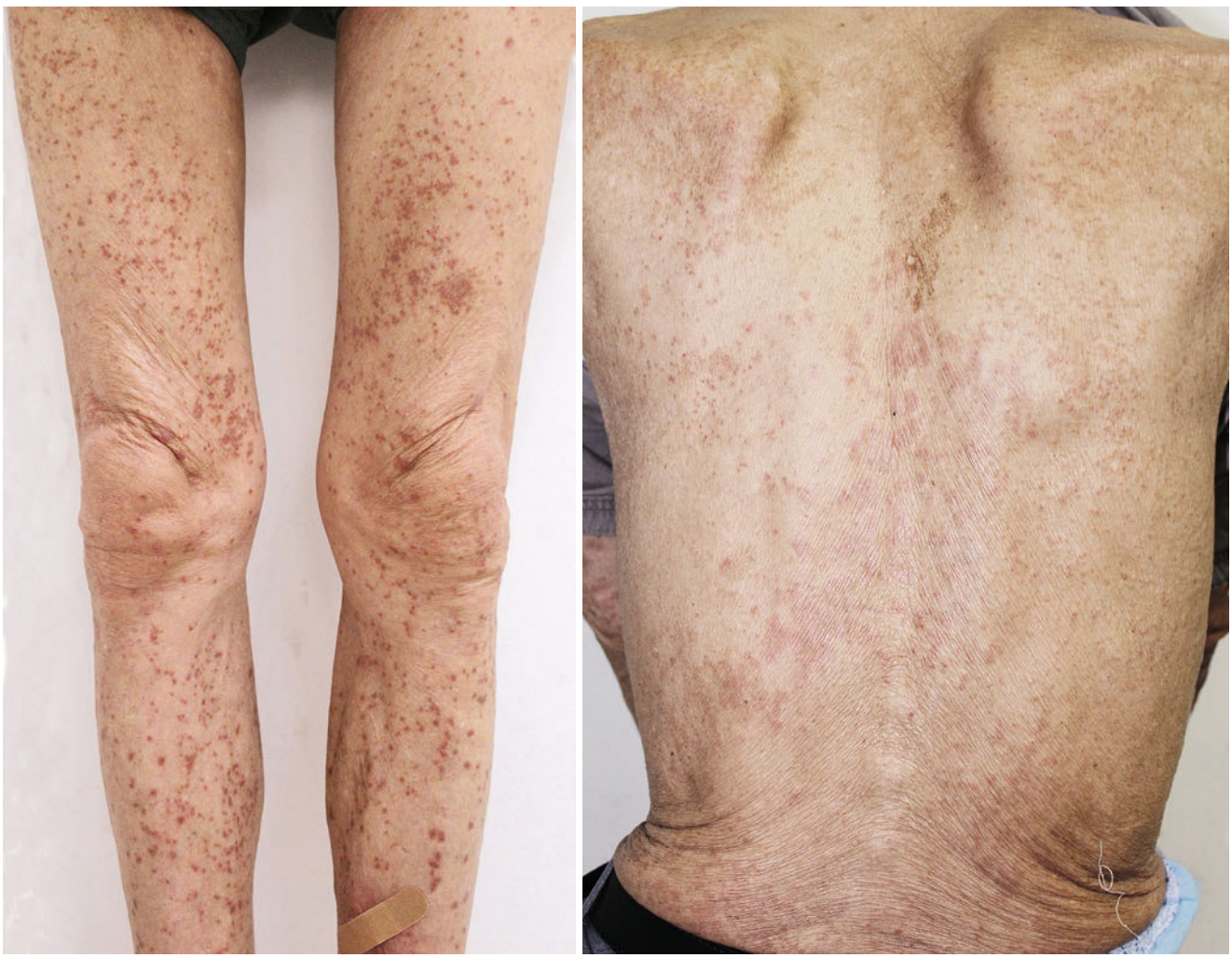


Fig. 13-7-1 Uncircumscribed violaceous maculae on the left waist, buttocks, and extensor surface of the thigh

13.8 Disseminated Pruriginous Angiodermatitis [11]

- Disseminated pruriginous angiodermatitis, also known as itching purpura or eczematid-like purpura, is an uncommon dermatosis characterized by persistent and severe itching, with a preference for adult obese males.
- Clinically, punctiform purpuric spots initially occur on the ankles and dorsum of the feet, later spreading onto the legs and gluteal regions and even extending to the trunk, upper limbs, and skinfolds. Over 2 weeks, the purpuric maculae may become confluent, which is more significant in clothing friction areas.
- Photodynamic therapy, adrenochrome monosemicarbazone, rutin, vitamins C and K, and antihistaminics have been described in the literature.



Figs. 13-8-1, 13-8-2 Irregular pink papules, plaques, petechiae, and ecchymosis distributed on the lower limbs (1) and back (2) of the patient, some lesions were covered with a few scales

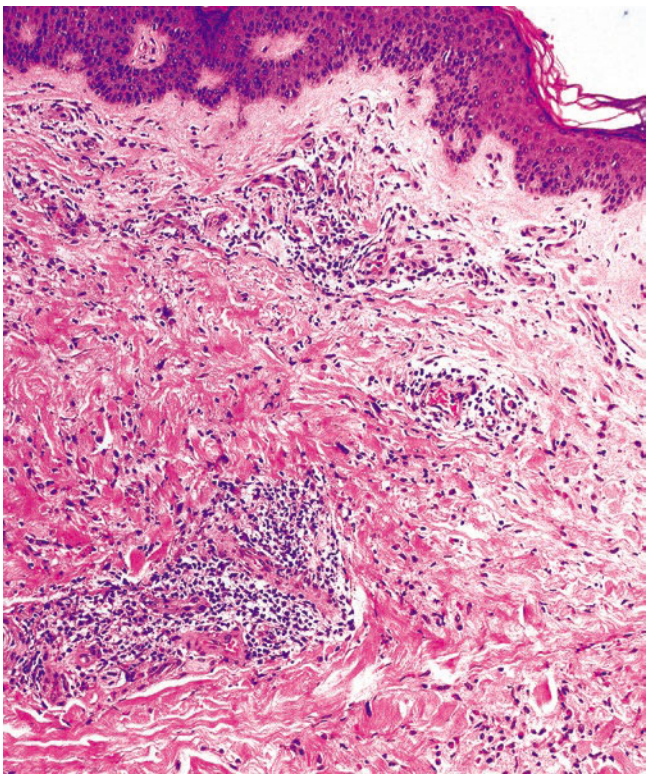


Fig. 13-8-3 The dermal microvascular endothelial cells swelling, mainly lymphocyte and mononuclear cells around blood vessels, meanwhile a few erythrocytes leakage (HE stain, ×200)

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Cutaneous Vascular Diseases

14

Cheng Tan, Hong-Mei Jing, Li-Tao Zhang, Dong-Lai Ma, and Ru-Zhi Zhang

Abstract

Various cutaneous vascular diseases are presented in this chapter: eruptive recurrent pigmented telangiectasia, telangiectasia macularis eruptiva perstans, unilateral nevoid telangiectasia superimposed on the Bier spots, Mondor's disease, arteriosclerosis obliterans, and eruptive pseudoangiomatosis.

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14.1 Eruptive Recurrent Pigmented Telangiectasia [1]

- Eruptive recurrent pigmented telangiectasia (ERPT) is a newly described skin disorder that appeared initially as red, dome-shaped papules.
- Pathological feature consists of conspicuous dilation of the superficial blood vessels without blood vessel proliferation.
- Clinically, ERPT occurs annually and shows cyclical morphological changes from red papules to pigmented macules and finally clears spontaneously.

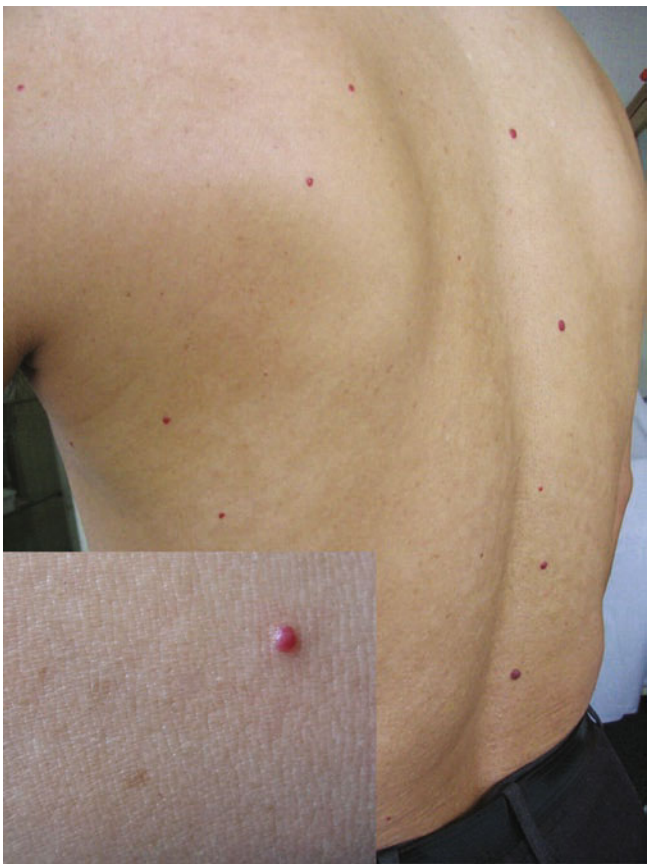

Fig. 14-1-1 Bright red, dome-shaped papules measuring 1–4 mm on the trunk. Similar-sized oval or guttate pigmented macules distributed around the red papules (left low) (Reproduced with the permission from [1])

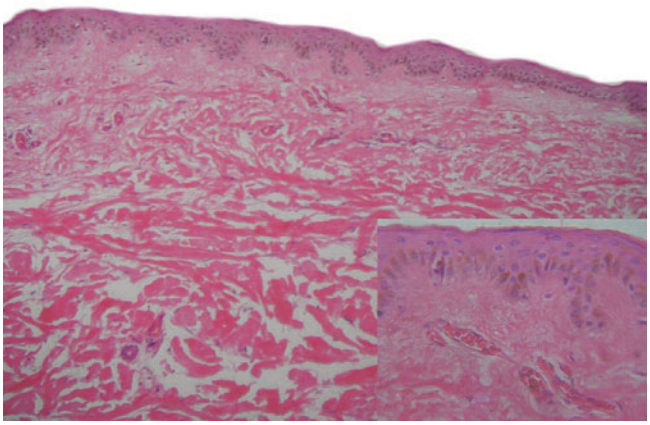

Fig. 14-1-2 14-1-3 Superficial plexus are prominently dilated. There is no vessel proliferation, and perivascular lymphocytic infiltration is unremarkable ((1), HE stain, ×100). Dilated superficial blood vessels laden with red blood cells. The basement layer is slightly hyperpigmented ((2), HE stain, ×400) (Reproduced with the permission from [1])

14.2 Telangiectasia Macularis Eruptiva Perstans [2]

- Telangiectasia macularis eruptiva perstans (TMEP) is an extremely unusual form of cutaneous mastocytosis, preferentially occurring on the torso and proximal extremities, with occasional systemic involvement.
- The representative manifestations of TMEP are small, irregular reddish-brown telangiectatic macules covered by a tan to brown setting without pruritic phenomena. The diameter of the isolated lesion is approximately 2–4 mm.
- Adults are easily affected. Cold stimulation, shellfish, and aspirin may induce relapse. Skin biopsy is crucial for the diagnosis, revealing a slight increase in mast cells with infiltration of the epidermis.
- Treatment usually involves a focus on the relief of symptoms, phototherapy (PUVA and UVB), histamine receptor antagonists, and injectable epinephrine, for example.

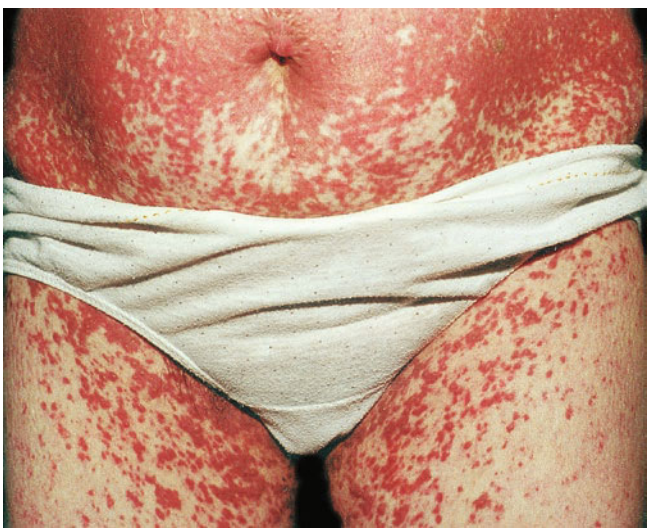

Fig. 14-2-1 Numerous red-tan macules and papules 0.3–0.5 cm in diameter are scatted on the abdomen and lower limbs

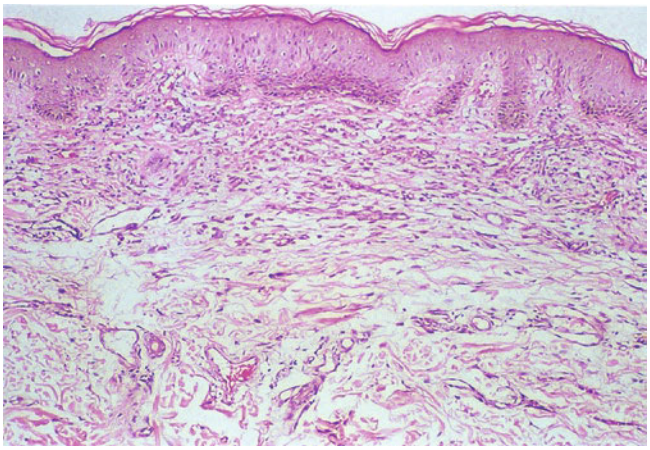

Fig. 14-2-2 Hyperkeratosis and hyperpigmentation of the epidermal basal layer and an increased number of mast cells in the papillary dermis (HE stain, ×100)

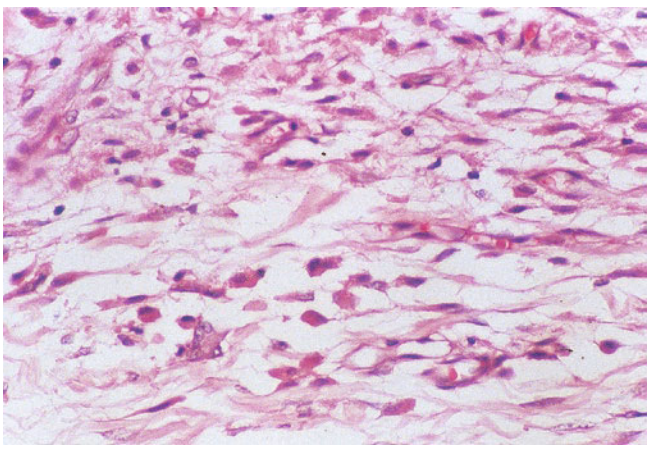

Fig. 14-2-3 Numerous mast cells infiltrated in the dermis (HE stain, ×400)

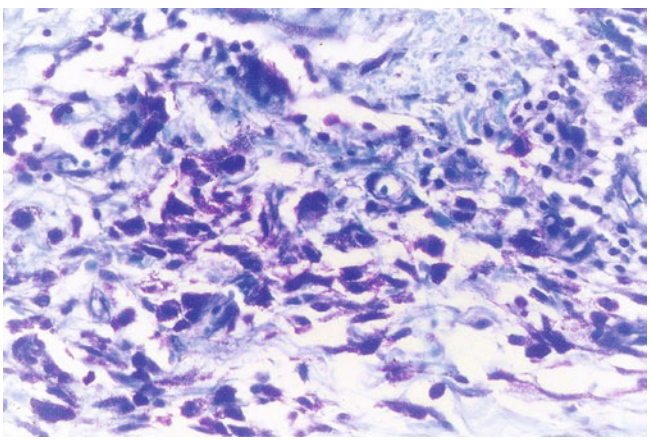

Fig. 14-2-4 Metachromatic granules are found in mast cells (Giemsa stain, ×400)

14.3 Unilateral Nevoid Telangiectasia Superimposed on Bier Spots [3]

- Twin spotting represents two different visible neighboring spots originating from two mutant cell clones on a genetically normal background.
- Twin spotting can be categorized as allelic and nonallelic. The allelic category comprises vascular twin nevi, cutis tricolor, segmental lentiginosis with ipsilateral nevus depigmentosus, partial lipomatosis and partial lipohypoplasia, paired hairless and hairy nevus, and paired melanotic and achromic macules. Phakomatosis pigmentovascularis (types I–V), phakomatosis pigmentokeratotica, unilateral nevoid telangiectasia and Becker's nevus, nevus depigmentosus with intralesional lentiginosis and Becker's nevus, didymosis melorheosebacea, nevoid hypertrichosis and melanosis, and didymosis aplasticosebacea are examples of nonallelic forms.
- Vascular twin spotting defines two adjacent vascular birthmarks with different biological functions. Nevus anemicus and nevus flammeus are examples. Several cases of unilateral nevoid telangiectasia superimposed on Bier's spots reinforce the notion that it is a type of vascular twin spot.
- Examination of unilateral nevoid telangiectasia (UNT) reveals a unilateral distribution of numerous telangiectasias on the trunk, shoulders, and arms along with curtain dermatomes. UNT syndrome is applied with concurrent cirrhosis, malignancies, hepatitis B or C infections, and hyperthyroidism.
- Negative Darier's sign helps to differentiate the condition from cutaneous mastocytosis.
- UNT may have an increased number of estrogen receptors compared with the normal skin, although serum estrogen and progesterone are normal in most cases.

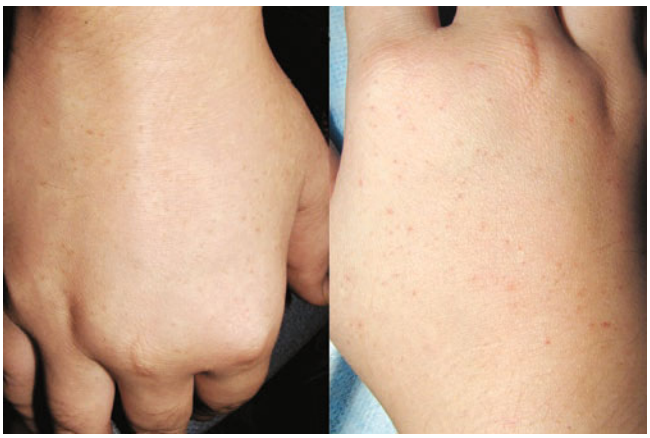

Fig. 14-3-1 Multiple pin-sized wiry and spiderlike telangiectasia with peripheral pale macule unilaterally distributed on her right hand (Reproduced with the permission from [4])

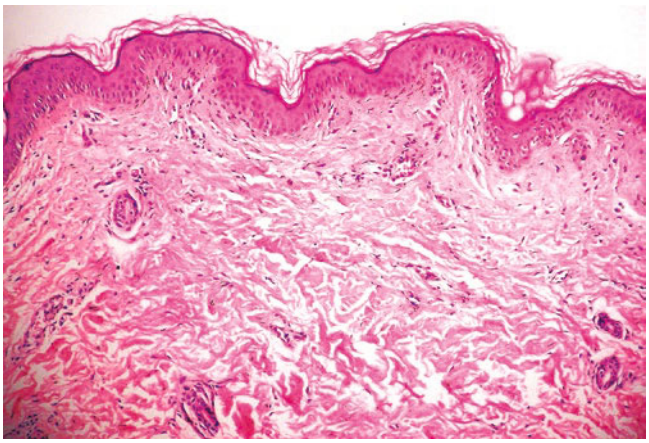

Fig. 14-3-2 Skin biopsy revealed vascular dilation with mild perivascular infiltration of mononuclear cells in the papillary dermis (HE stain, ×100) (Reproduced with the permission from [4])

14.4 Mondor's Disease [5]

- Mondor's disease is characterized by a hypodermal, solid, painful cord companied by depression of the overlying skin. The aggravated pain factors include pressure on the lesion, breathing, or movement of the homolateral arm. There is no redness, increased temperature, or edema around the lesion.
- The pain and tenderness will be spontaneously relieved within a few days to several weeks. Treatment is focused on symptomatic relief.
- Mondor's disease, which mostly occurs in women aged 30–60 years, is an uncommon, innocuous, and self-limited disorder, also known as superficial thrombophlebitis of the chest. It affects the lateral thoracic vein.

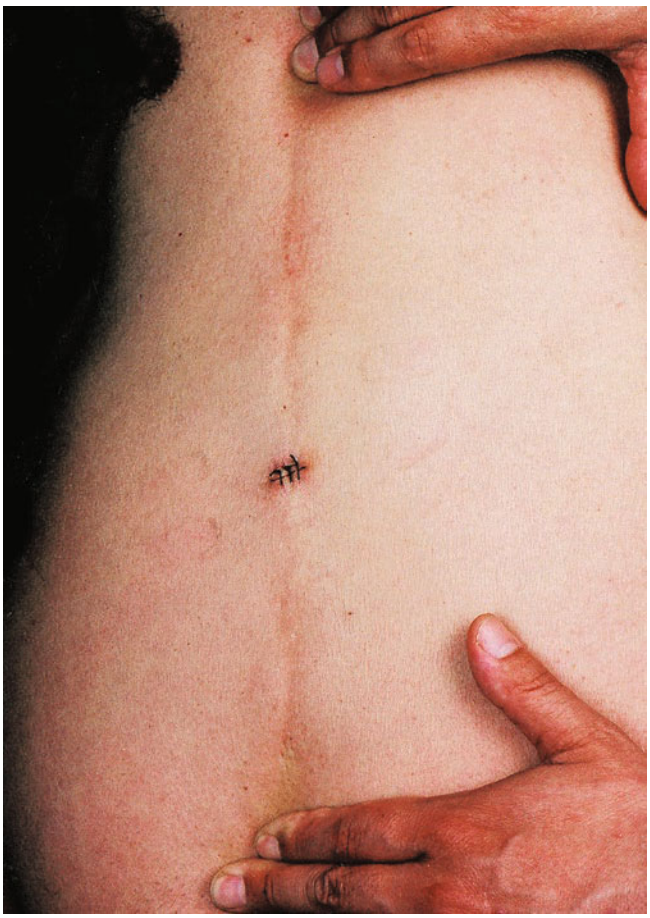

Fig. 14-4-1 Strip hollow on the left breast

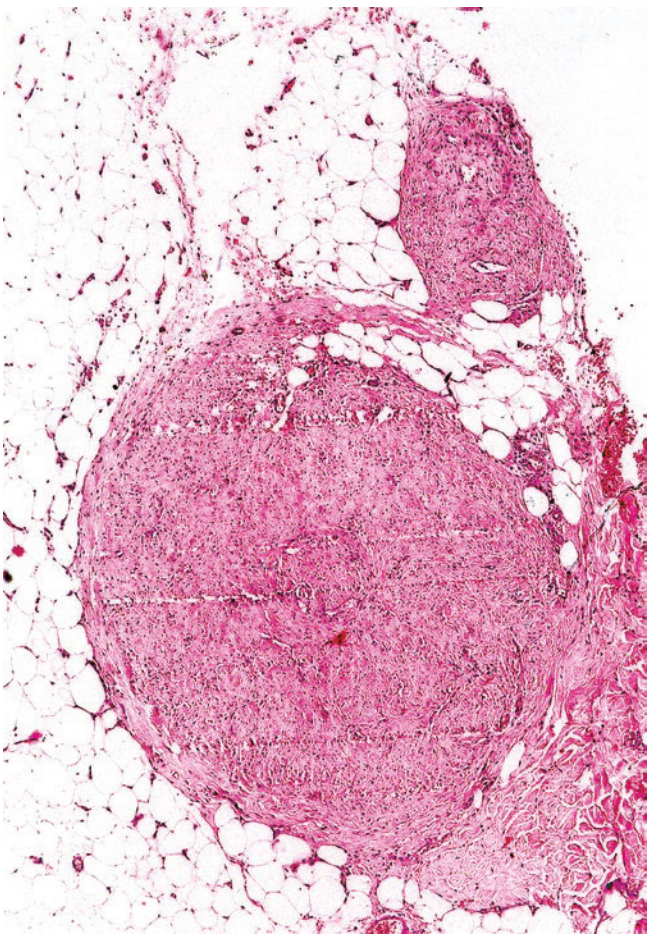

Fig. 14-4-2 Tube structures with thrombosis in the dermis and vein wall thickening and fibrosis (HE stain, ×100)

14.5 Arteriosclerosis Obliterans [6]

- Arteriosclerosis obliterans (ASO) is one of the most frequent peripheral vascular diseases, characterized by claudication and rest pain. It usually affects the arteries of the lower extremities, as well as those of the heart, brain, kidney, and viscera.
- Skin ulcers due to ischemia appear along the peripheral arteries in ASO, usually leading to amputation. The pulsation of impaired arteries is attenuated and sometimes cannot even be felt. The temperature of the skin in the relevant area is usually reduced.
- Risk factors of ASO include age, male gender, smoking, hyperlipidemia, hypertension, diabetes mellitus, chronic renal failure, and hyperhomocysteinemia.

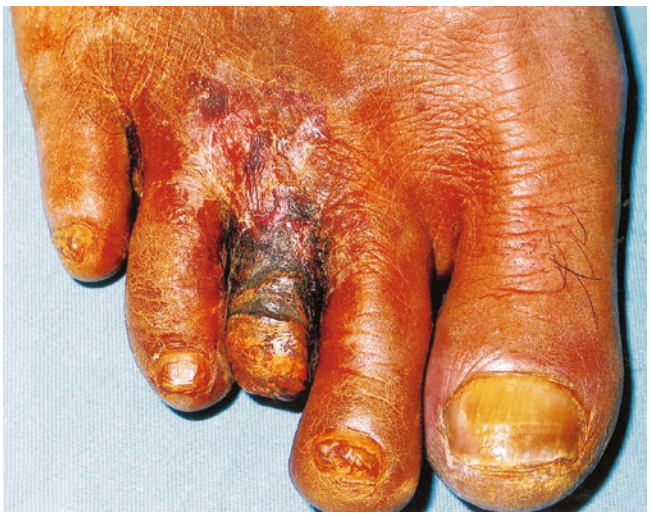

Fig. 14-5-1 The toe of the right foot is purple, and the third toe is necrotic and shortened

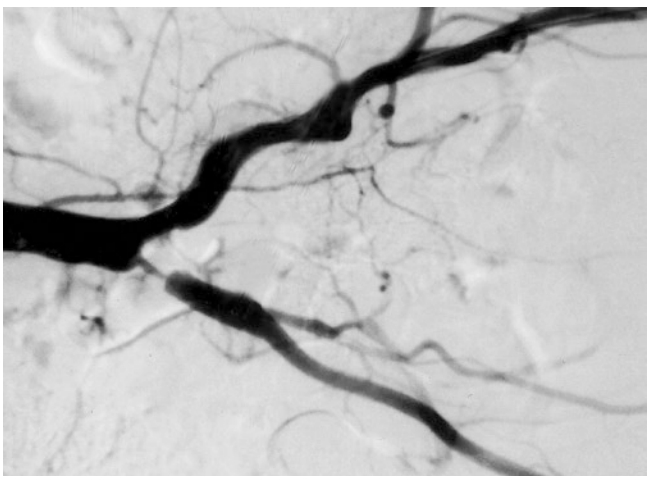

Fig. 14-5-2 The narrowing of the hypogastric artery from the arteria femoralis

14.6 Eruptive Pseudoangiomatosis [7]

- Eruptive pseudoangiomatosis (EP) is characterized by degenerative erythematous papules with a faded halo.
- Pathological findings are hobnail-shaped endothelial cells in the dilated blood vessels. The blood vessels are not proliferative.
- EP can be misdiagnosed as erythema punctatum Higuchi following mosquito bites. Although dilation of dermal blood vessels is similarly present, the absence of hobnail endothelial cells distinguishes the condition from E.
- Most EP patients persist from 1 week to 5 months. It is advisable to use 1% pimecrolimus cream if necessary.

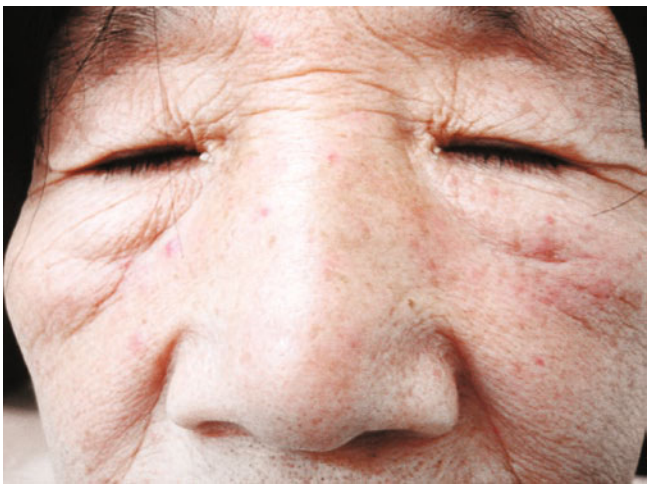

Fig. 14-6-1 Disseminated, smooth, and angioma-like papules with diameters up to 2–5 mm mainly located on the face (Reproduced with the permission from [8])

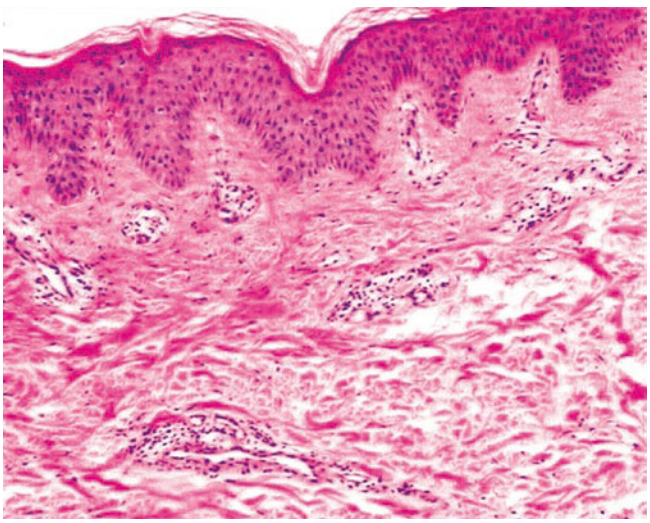

Fig. 14-6-2 The epidermis was normal. The blood vessels in the superficial dermis were dilated and surrounded mainly by a lymphocyte infiltration (HE stain, ×100) (Reproduced with the permission from [8])

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Part V

Atrophies and Disorders of Dermal Connective Tissues

Atrophy Diseases

15

Wen-Yuan Zhu, Sheng-Hong Guo, Da-Guang Wang, and Ru-Zhi Zhang

Abstract

Striae distensae and localized atrophy, macular atrophy, and pseudoainhum of the penis are concisely selected in this chapter.

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15.1 Striae Distensae and Localized Atrophy [1, 2]

- Striae distensae are permanent dermal lesions characterized by deep purple or white depressed lines or bands.
- These lesions commonly occur on the abdomen and the breasts after pregnancy. They may occur after application of topical corticosteroid cream, especially under occlusion in folds.
- Striae distensae are esthetically troublesome and therapeutically challenging, without a completely effective treatment.

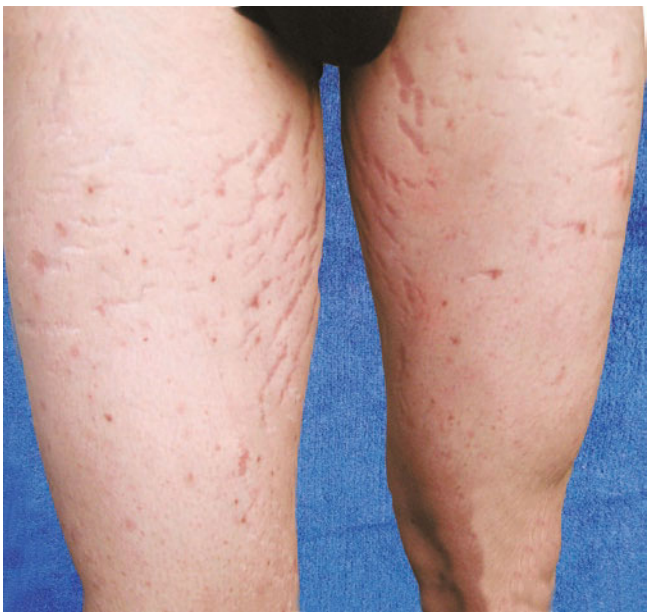

Fig. 15-1-1 The striae distensae widely distributed over both thighs after applications of 0.1% triamcinolone cream for 3 months

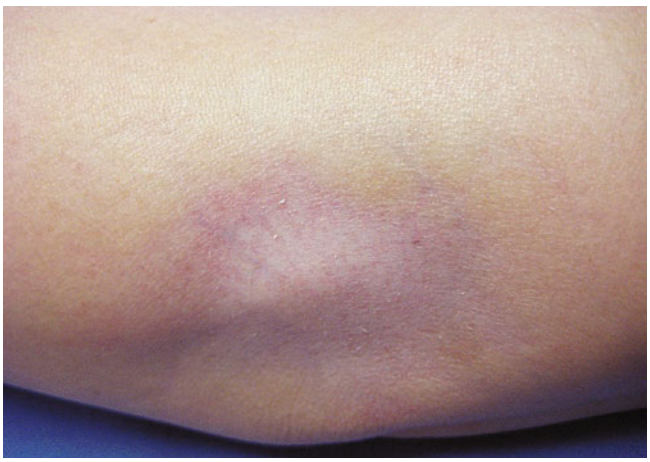

Fig. 15-1-2 Subcutaneous atrophy at the site injection of 5 mg triamcinolone for two times

15.2 Macular Atrophy [3]

- Macular atrophy of the skin, also known atrophoderma, is a relatively uncommon and inconspicuous dermatosis characterized by laxity of the regional skin. It is usually separated into two hypotypes: primary idiopathic or acquired forms. Its exact etiology and pathogenesis remain unclarified.
- The lesion typically appears as single or multiple, gray or brown, round to oval, circumscribed circinate asymptomatic patches, which are depressed and shrunken. The average diameter of the individual lesion is 5–25 mm, and it usually appears on the upper torso and proximal extremities.
- Histological examination shows reduction and fracturing of elastic tissue fibers in the dermis with a variable pattern.
- Commonly, there is no need to administer a specific treatment, but close follow-up is necessary.

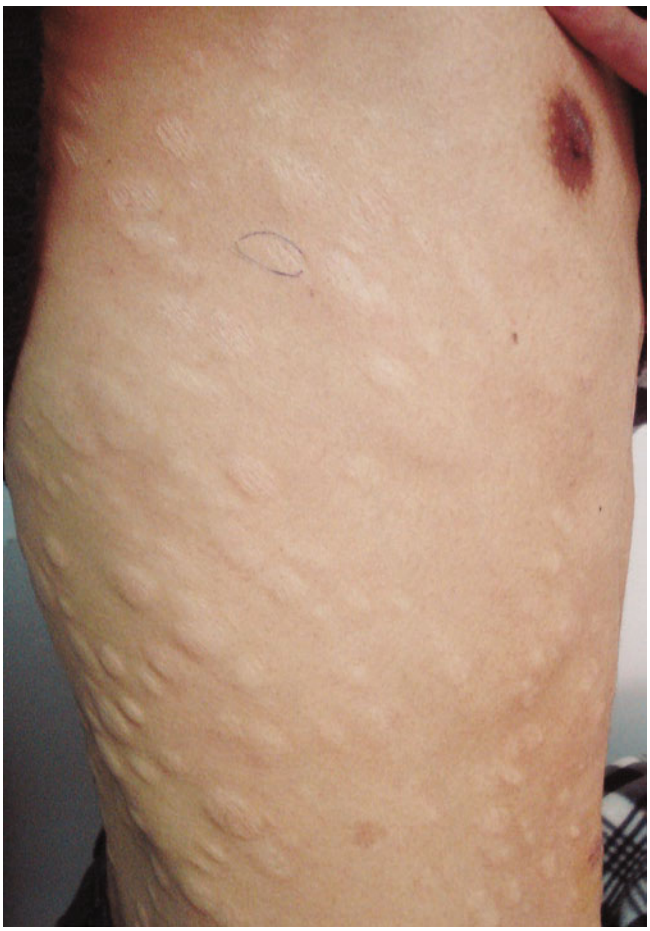

Fig. 15-2-1 General lined isolated rounded and atrophic cuticolor patches with mild frustration feeling by touch distributed on the trunk

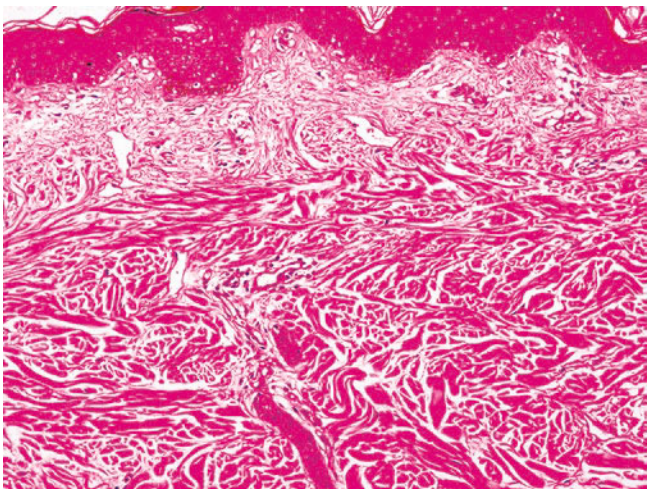

Fig. 15-2-2 Epidermis was normal, some lymphocytes infiltrated around the vessels and skin appendages in the dermis. The collagenous fibers proliferated at papillary layer (HE satin, ×100)

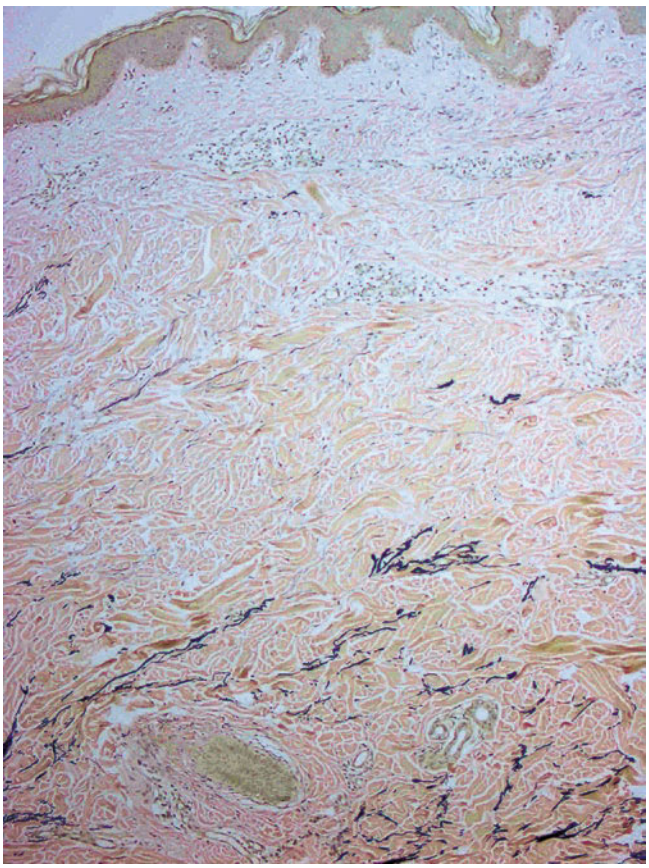

Fig. 15-2-3 Elastin fibers fractured, decreased, and even disappeared in the dermis (Elastic tissue stain, ×100)

15.3 Pseudoainhum of the Penis [4]

- Pseudoainhum is an uncommon disorder characterized by progressively constricting bands around one or many fingers or toes, occasionally around the penis or nipple. It may result in secondary amputation unless treated properly.
- The exact pathogenesis is not yet clear. The disease is usually classified as one of three clinical subtypes. Primary pseudoainhum commonly presents at birth. Secondary pseudoainhum occurs later in life and results from an identifiable disease process. The third type is related to trauma and mechanical injury, such as burns and frostbite.
- It traditionally begins as a circumferential groove, crease, or constricting band. This primarily appears superficially or as a deep groove that may reach the bone.
- Surgery is the main therapy to release the constricting bands.

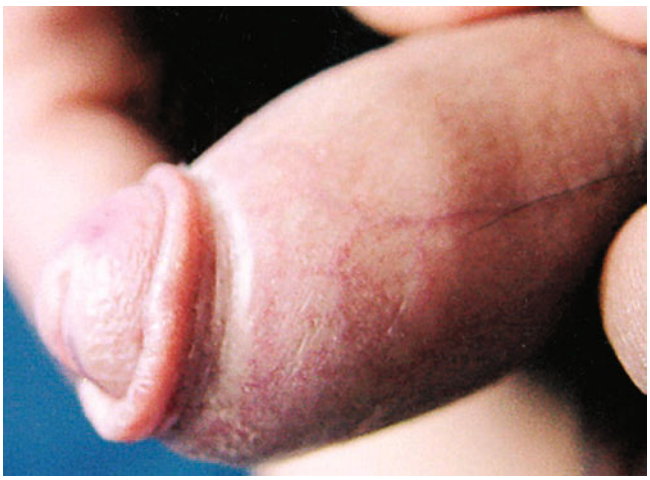

Fig. 15-3-1 Intact constricting band around the penis

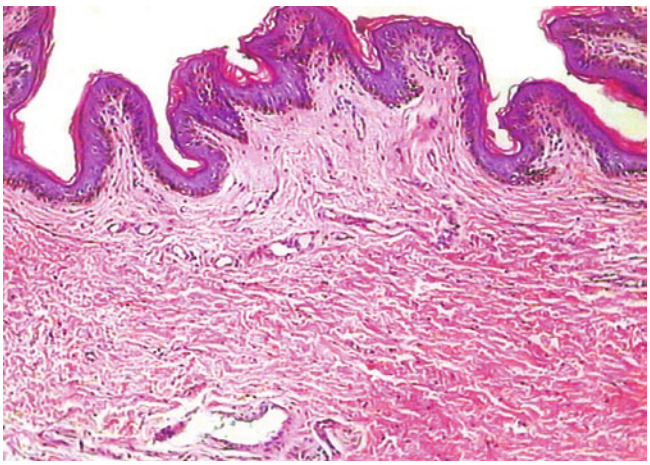

Fig. 15-3-2 There is slight increase of collagen fibers in the dermis without epidermal charge (HE satin, ×100)

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Dermal Elastic Tissue Diseases

16

Jie Yan, Cheng Tan, Qing Miao, Wei Liu, Dong-Lai Ma, Gang Wang, Yi-Ming Fan, Xiao-Wen Pang, Hui Li, Qiang Ju, Da-Guang Wang, Wen-Yuan Zhu, and Ru-Zhi Zhang

Abstract

Defects of dermal elastic fibers are relatively uncommon. This chapter touches upon disseminated elastosis perforans serpiginosa, papular elastorrhexis, congenital cutis laxa, cutis laxa, blepharochalasis, pseudoxanthoma elasticum, cutis hyperelastica complicated by the abnormity in immunoassay, giant connective tissue nevus, eruptive collagenoma, white fibrous papulosis of the neck, and pseudoainhum.

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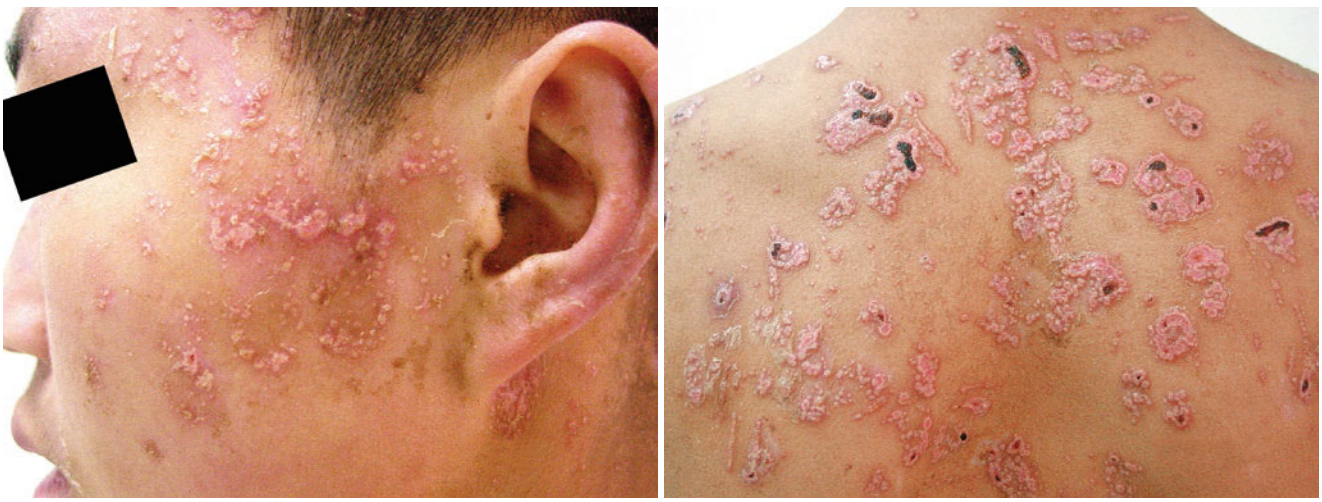
16.1 Disseminated Elastosis Perforans Serpiginosa [1, 2]

- Disseminated elastosis perforans serpiginosa (DEPS) is also called Lutz disease or Lutz-Miescher disease. Clinically, it can be classified into three groups: (1) idiopathic type, (2) reactive type, and (3) drug-induced type.
- DEPS is a chronic disease with an onset in infancy, characterized by gradual dispersion and progression interspersed with remission, as well as systemic involvement.
- The lesions exhibit multiple reddish keratotic papules with sizes of millet grains to rice grains, and they are arranged in rings, serpiginously, in maps, and in various random shapes. Central atrophy in normal color appears in the lesion, with a hilar depression at the center. Escharosis can be observed on top of some of the papules, with pigmentation at sites of remission. There are usually no systemic symptoms.
- The pathology features an elongated and broadened cuticular process, as well as canalization of partial epidermis-forming tracts, which contain basophilic fragments and are infiltrated with mixed inflammatory cells.



Figs. 16-1-1, 16-1-2 These papules are arranged in arcuate or serpiginous groups on the face (1) and on the back (2) (Reproduced with the permission from [1, 2])

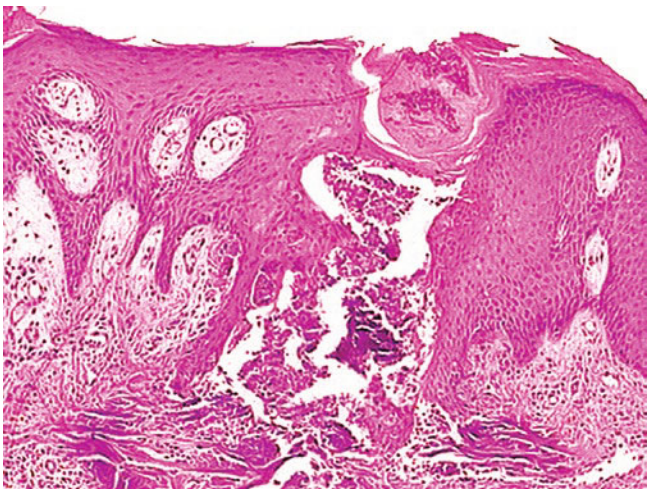


Fig. 16-1-3 A narrow, curved channel which contained basophilic necrotic material and inflammatory cells through an acanthotic epidermis is shown (HE stain, ×200)

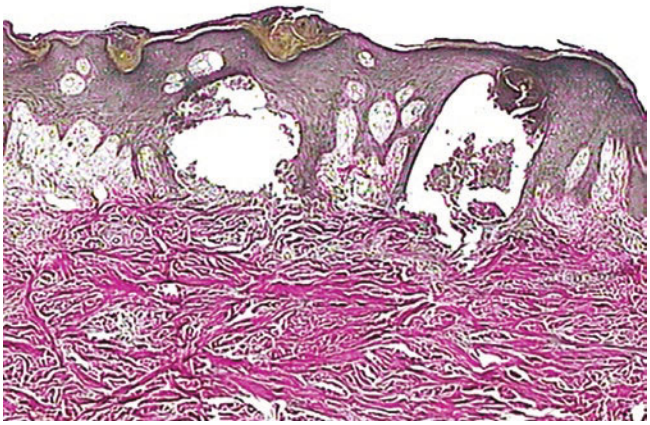


Fig. 16-1-4 There are increased and thickened degenerated elastic fibers (Verhoeff stain, ×100)

16.2 Papular Elastorrhexis [3, 4]

- Papular elastorrhexis (PE) is an uncommon elastic tissue disorder that occurs in girls during or after adolescence. Lesions in PE are tiny, non-follicular, white papules or macules, the morphology of which varies from oval to round and is sometimes stellated. The trunk and extremities are preferentially affected. Occipito-cervical and mandibular areas can be similarly involved.
- The essential histological feature is the decline and fragmentation of elastic fibers. Collagen may be homogenized, condensed, or normal in the dermis.
- There is still controversy about whether PE is a distinctive entity. PE should be differed from juvenile elastoma, pseudoxanthoma elasticum-like papillary dermal elastolysis, papular acne scars, and mid-dermal elastolysis. White fibrous papulosis of the neck, morphea guttate, and dermatofibrosis lenticularis disseminata are also present in this differential category.

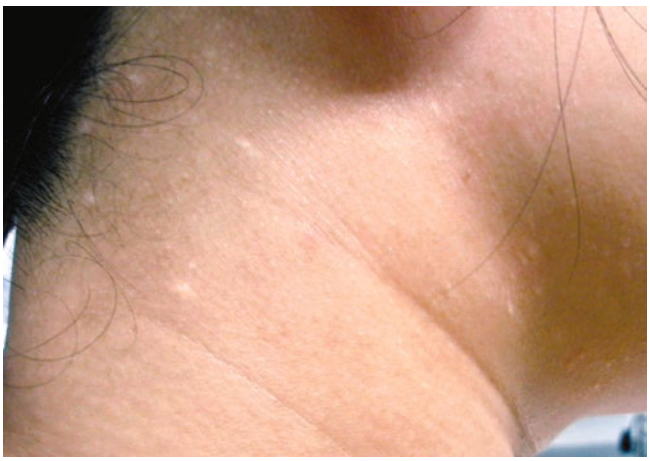


Fig. 16-2-1 White indurated macules and papules on the neck and mandibular region. Some are polygonal in shape (Reproduced with the permission from [5])

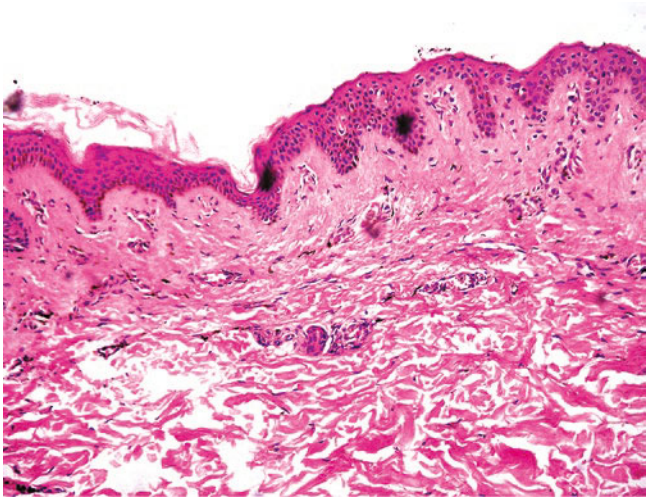


Fig. 16-2-2 Pathologically, mild acanthosis and a perivascular lymphocytic infiltration in the dermis. Collagen fibers increased slightly in the papillary dermis (HE stain, ×100) (Reproduced with the permission from [5])

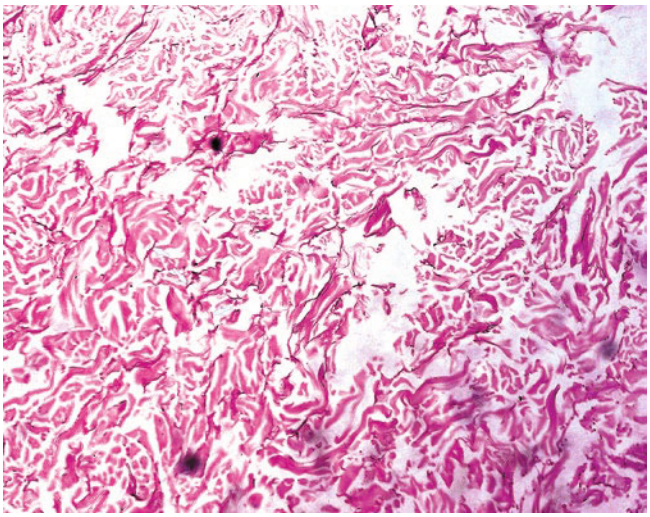
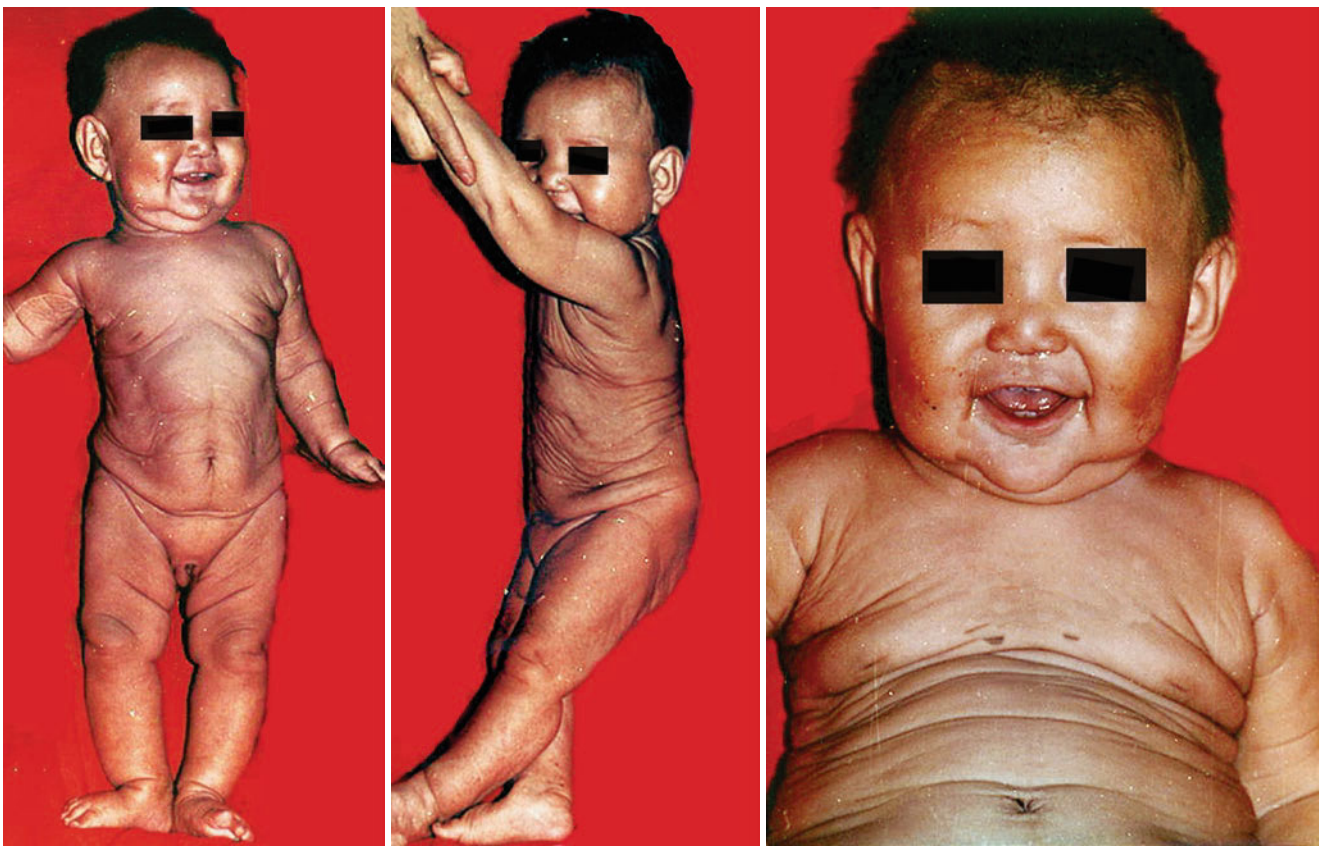


Fig. 16-2-3 Fragmentation and reduction of elastic fiber in the dermis (Acid orcein stain, ×200) (Reproduced with the permission from [5])

16.3 Congenital Cutis Laxa [6, 7]

- Congenital cutis laxa is commonly first observed in infancy and seldom in teenagers, manifesting as a prolonged duration without an obvious cause in most cases and in rare cases showing an onset following a stimulus such as injury, fracture, or inflammation.
- Lesions are characterized as sagging and relaxing of the skin and progressing gradually and systemically, exhibiting an elderly appearance, sometimes complicated with emphysema, multiple hernias, and diverticula. Additional symptoms include scarce body hair and tooth loss.
- Pathology features a decrease or even an absence of elastic fibers. There is no vital method available for this disease.



Figs. 16-3-1, 16-3-2, 16-3-3 Loose, redundant skin, hanging in folds around the face, jaw, neck, chest, waist, and breasts (Reproduced with the permission from [6, 7])

16.4 Cutis Laxa [8]

- Cutis laxa (CL), also called dermatochalasis or generalized elastolysis, is a rare group of elastic tissue disorders. It is classified into acquired and congenital types. The acquired form is more unusual than the inherited form.
- The exact pathogenesis of this disease is not well understood. Clinically, it features loose, pendulous, and lax skin associated with elastic tissue loss and leads to an appearance of premature aging.
- Histopathologically, it is characterized by a reduction in the number of elastic fibers and associated degenerative changes.
- There is no satisfactory treatment available for CL, but psychological and emotional support can be provided.

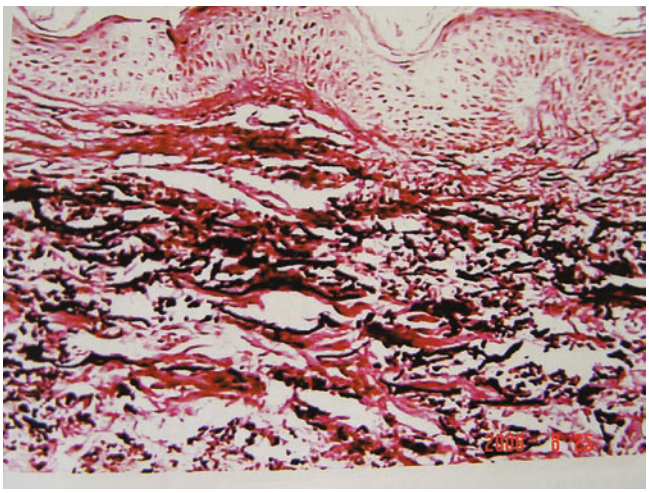


Fig. 16-4a-2 Fragmentation, granular appearance, and diminution of elastic fibers in the dermis (Verhoeff stain, ×100)

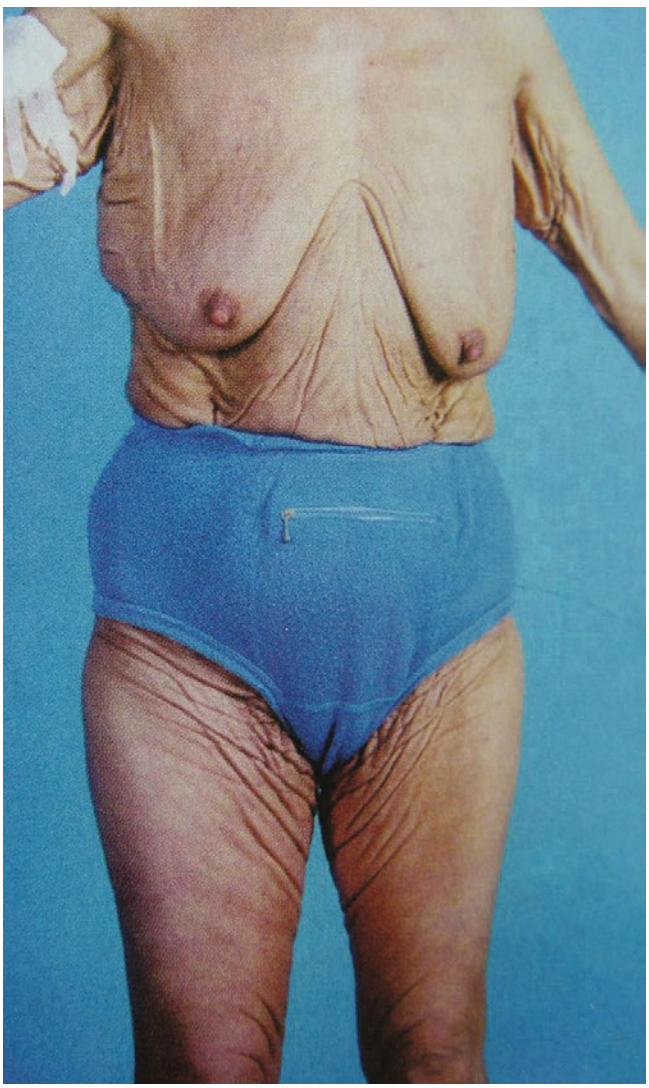


Fig. 16-4a-1 A woman with loose and pendulous skin

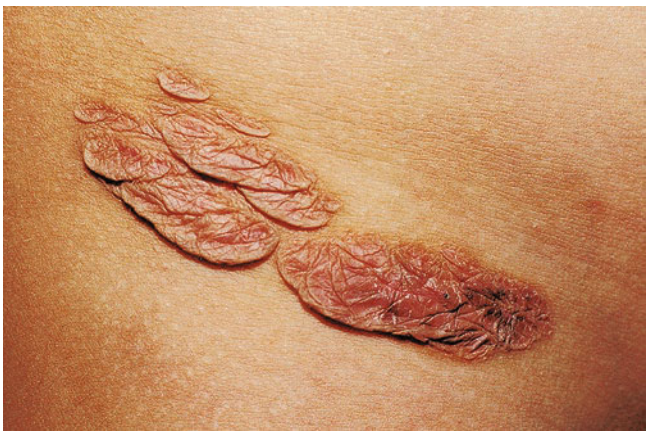


Fig. 16-4b-1 Three oval, circumscribed loose maculae on the inguinal

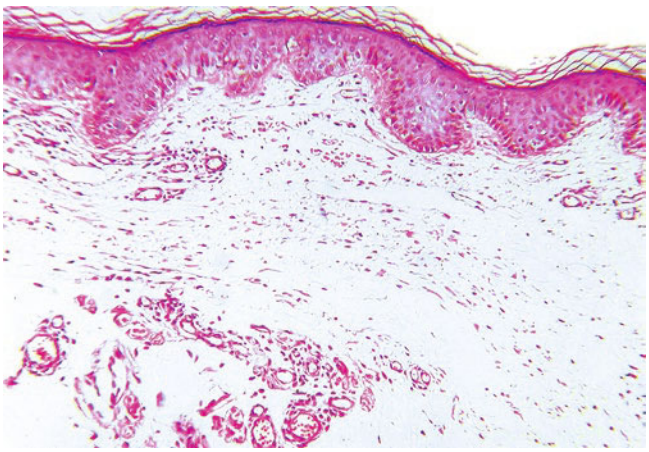


Fig. 16-4b-2 Hyperpigmentation in the basal layer and connective tissue lined loosely; a few chronic inflammatory cells infiltrated around blood vessels (HE stain, ×100)

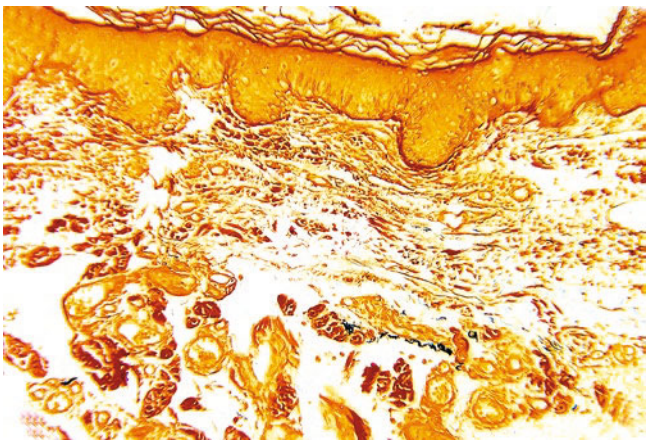


Fig. 16-4b-3 Diminished elastic fibers in the dermis and the shape of elastic fibers are abnormal (Combind stain, ×100)

16.5 Blepharochalasis [9]

- Blepharochalasis is normally limited to the upper lid and is characterized by progressive skin sagging and relaxing with multiple folds, complicated by local angiotelectasis.
- The congenital type has the common onset at a young age, with amelioration after adolescence. The onset of the senile type usually occurs in people older than 50 years as a consequence of biological degeneration. The acquired type occurs more frequently than the inherited type in adults.
- The exact pathogenesis and etiology of this disease remain unknown, and an effective treatment is lacking.

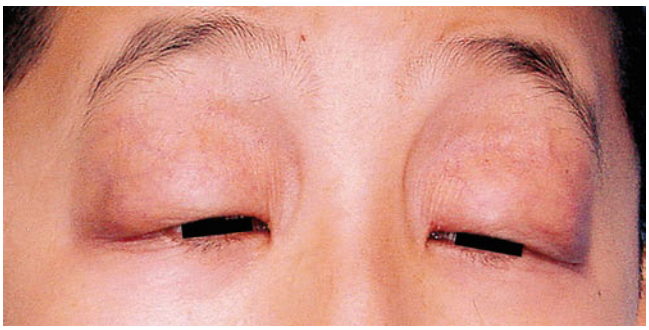


Fig. 16-5-1 Swelling of the upper lids leading to thinning of the skin and excessive upper lid skin clear vein being seen

16.6 Pseudoxanthoma Elasticum [10, 11]

- Pseudoxanthoma elasticum (PE) is a congenital hereditary disease of elastic fibers, and it has been shown to occur in close correlation with the ABCC6 mutation.
- Its onset is usually in infancy and, for a small number of cases, after birth or during youth.
- It is characterized by yellow spots with a cobblestone appearance distributed on the neck and axilla or as diamond yellow spots distributed along the long axial region of the dermatogly. Sagging skin usually occurs in the later phase. Some of the patients are complicated by lesions in the fundus oculi, cardiovascular system, and gastrointestinal tract.
- Pathological features include degeneration, swelling, and an increase in elastic fibers in the dermis, accompanied by calcification.

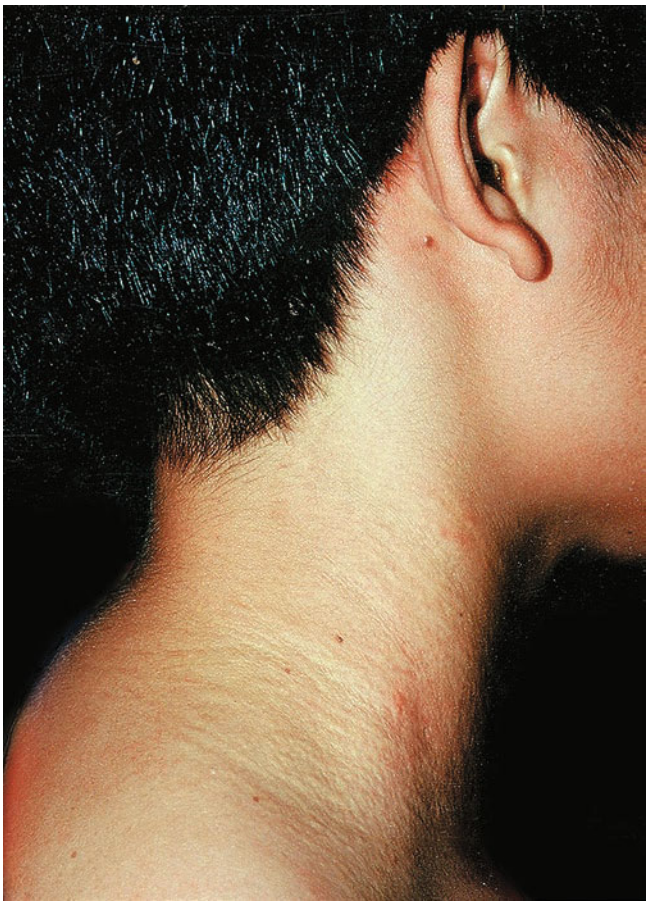


Fig. 16-6-1 The soft yellowish flat papules in linear arrangement on the neck to appear loose and wrinkled

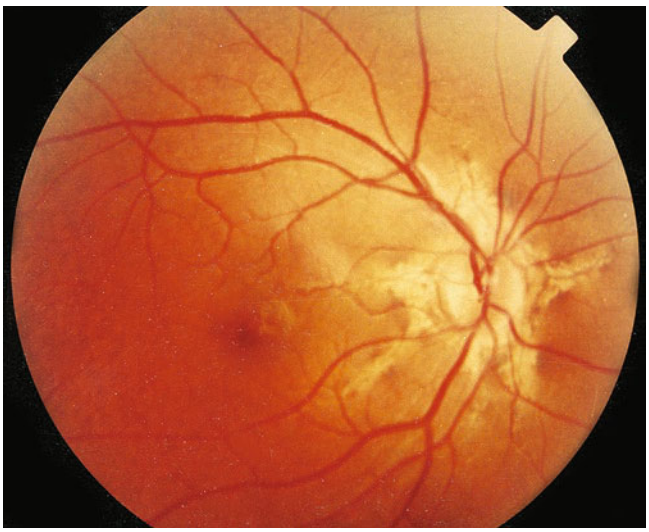


Fig. 16-6-2 Six angioid streaks in the fundi in the right eye

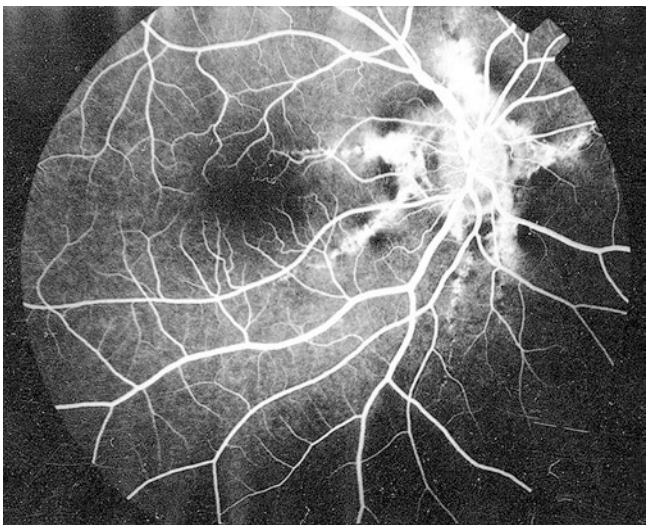


Fig. 16-6-3 The fluorescence of angioid streaks by fundus angiography

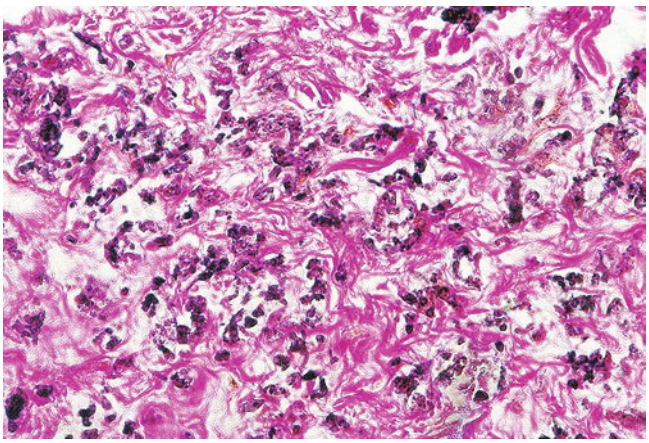


Fig. 16-6-4 The dark black elastic fibers are increased in number and showed fragmentation and clamping in the dermis (Verhoeff stain, ×400)

16.7 Cutis Hyperelastica Complicated by Abnormal Immunity [12]

- Cutis hyperelastica is a genetic susceptibility disease, characterized as dermal hyperelasticity and joint hyperextension.
- Its onset is usually in infancy, with slow progression, often involving the visceral system and, in severe cases, complicated by abnormalities in immunity, usually including defects in cellular immunity and an increase in immunoglobulin.The main clinical manifestations are long and recurrent infections and anemia.
- There is no effective treatment for this disorder. Symptomatic treatments are centered on including anti-infection, iron supplementation, and improved immunity, in the case of immune abnormalities.

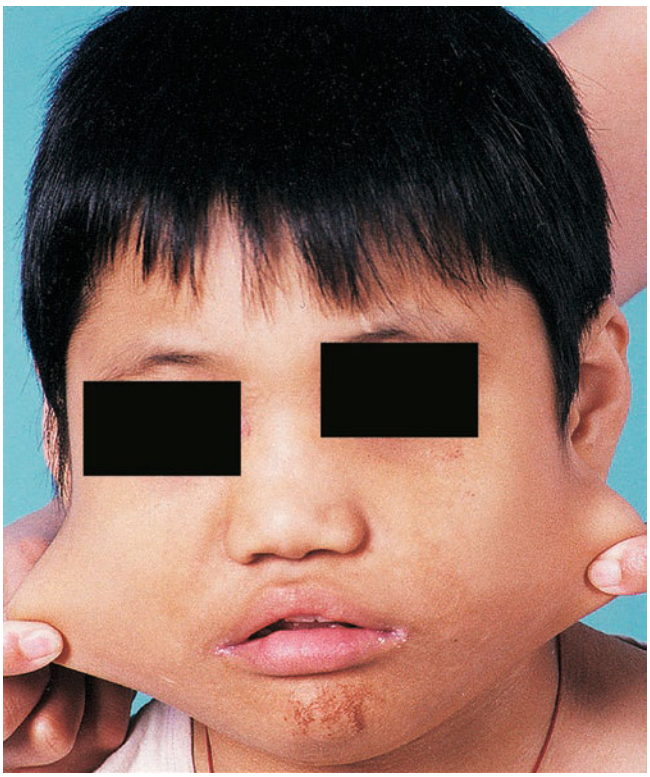


Fig. 16-7-1 Cutis hyperelastica, stretched skin at face (Reproduced with the permission from [12])

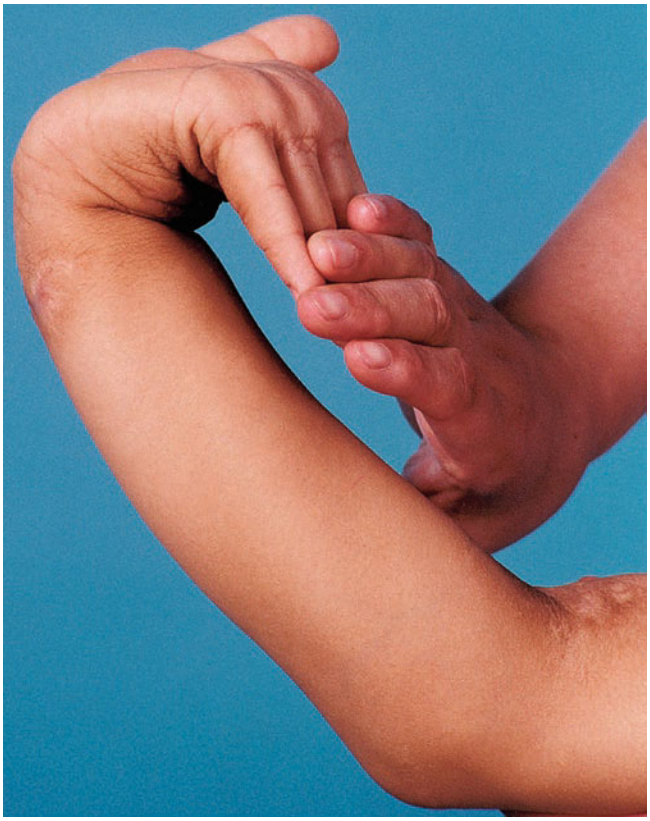


Fig. 16-7-2 Hyperextensibility of the wrist

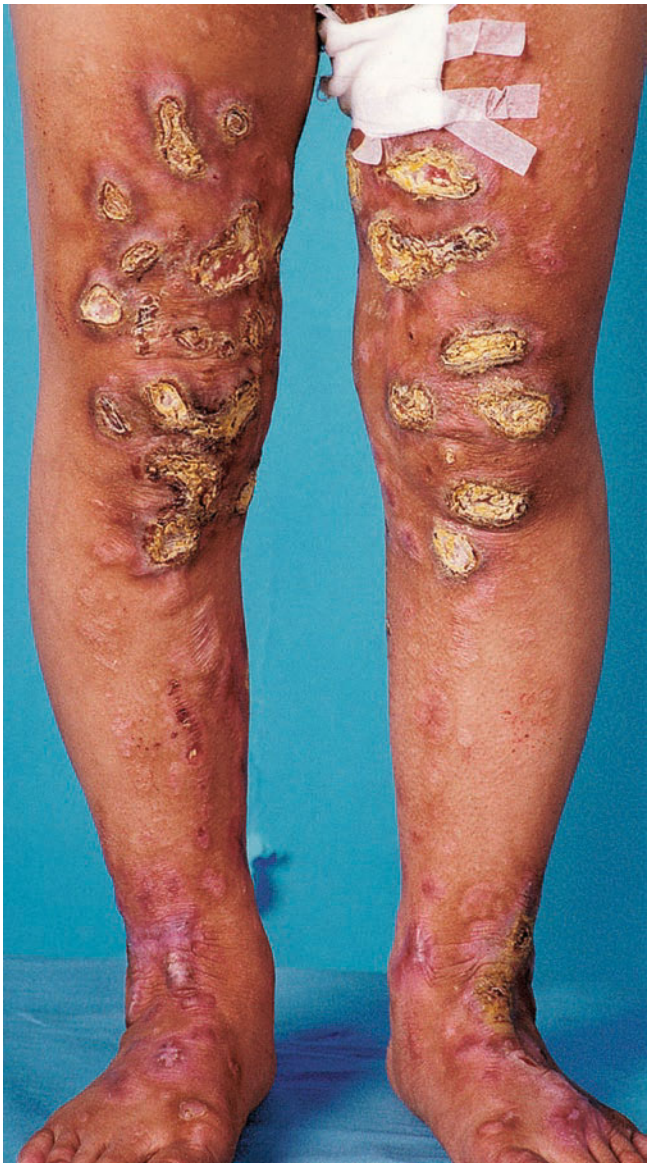


Fig. 16-7-3 Numerous varying-size ulcers with pus secretion, hyperplastic scar, hyperpigmentation, and hypopigmented macules in the scar

16.8 Giant Connective Tissue Nevus [13]

- Connective tissue nevus usually occurs in infancy without subjective symptoms and gradually grows and expands. Some patients are complicated with diseases such as tuberous sclerosis and disseminated condensing osteopathy.
- Its main features include elevated yellow, brown, white, or tan solid plaques with a clear border, involving mainly the trunk and sometimes the extremities.
- The pathology is characterized as increasing and thickening collagen fibers with a horizontal and homogenized arrangement in the lower or middle dermis.

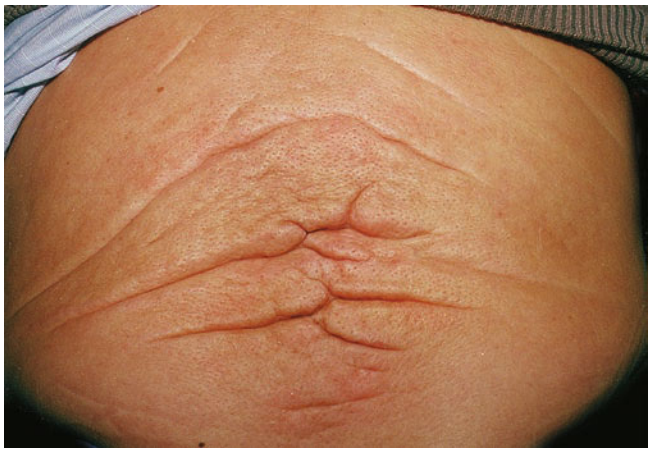


Fig. 16-8-1 Slightly elevated and indurated plaques 19 cm × 22 cm in size on the waist

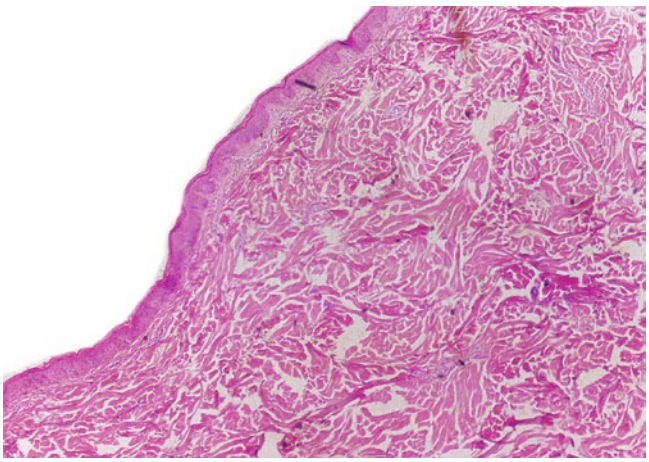


Fig. 16-8-2 The collagen bundles are thickened and homogenized in the dermis (HE stain, ×100)

16.9 Eruptive Collagenoma [14, 15]

- Eruptive collagenoma is an unusual disease of unclear etiology that occurs in young adults as symptomless discrete, firm, skin-colored, and slightly elevated cutaneous nodules, papules, or plaques on the extremities and body for several years.
- Histologically, it is characterized by an overaccumulation of dense, rough collagen fibers in the dermis.
- Normally, it is not complicated by systemic diseases, and no specific treatment is available.

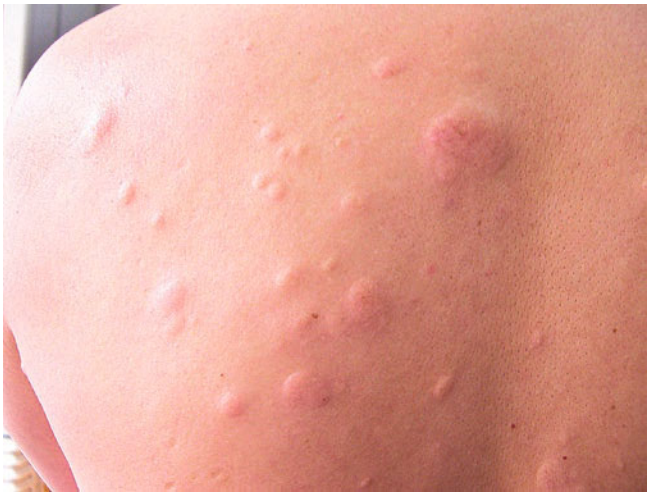


Fig. 16-9-1 Multiple skin-colored flat papules, nodules, and plaques on the shoulders and back

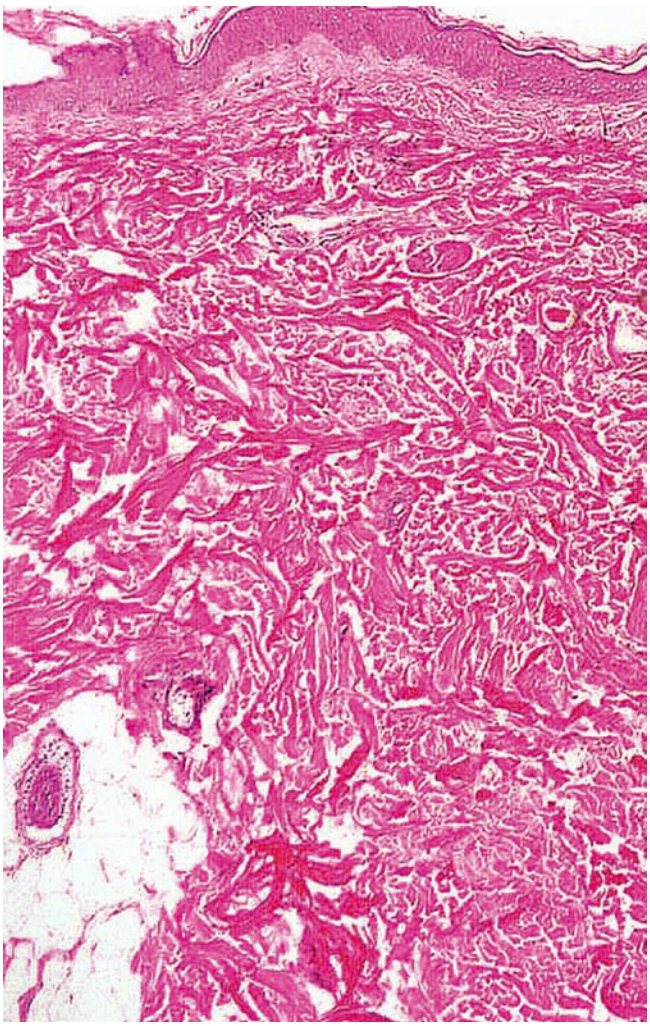


Fig. 16-9-2 Collagen fibers are coarse and increased in the dermis (HE stain, ×200)

16.10 White Fibrous Papulosis of the Neck [16, 17]

- White fibrous papulosis of the neck (WFPN) frequently occurs on the posterior aspect of the neck in elderly individuals, typically presenting with numerous 2–3-mm-sized, dispersive, symptomless, pale to skin-colored, non-follicular, firm papules.
- Histologically, it is characterized by a slight, focal increase and thickening of the collagen fibers in the papillary dermis, accompanied by normal to decreased elastic fibers.

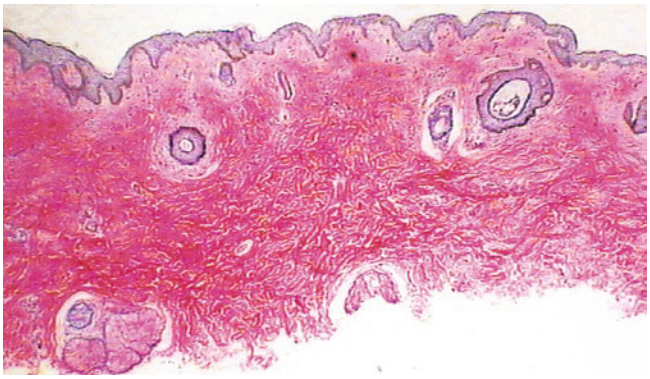


Fig. 16-10-2 Circumscribed thickening collagen bundles in the dermis (HE stain, ×40)

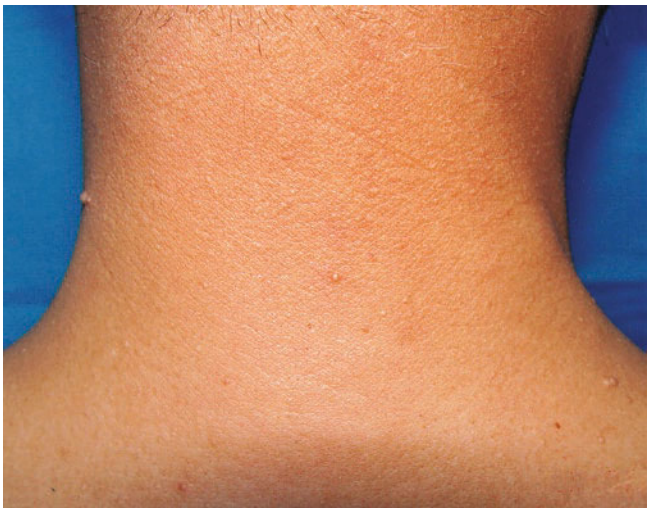


Fig. 16-10-1 Multiple round-to-oval, whitish, firm papules on the nape

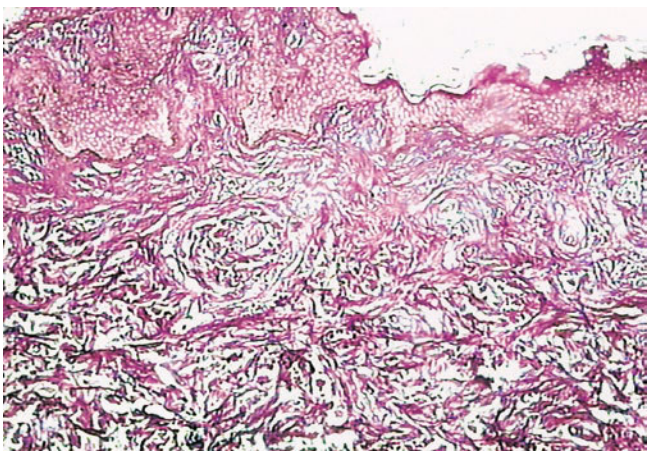


Fig. 16-10-3 No abnormality of elastic fibers could be found in the dermis (Verhoeff stain, ×100)

16.11 Pseudoainhum [18]

- Pseudoainhum syndrome (PAS) presents with a constriction band that varies in depth from a shallow depression in the skin to the deep tissue of the bone.
- PAS often arises as a circumferential groove, crease, or constricting band that gradually deepens. PAS has an unpredictable course and prognosis. At times, it may progress to auto-amputation of the digits or limbs.
- The concepts of ainhum and PAS have caused long-standing confusion and misclassification. Ainhum refers to the auto-amputation of a digit, resulting from a constricting band, and is common among black people. However, in PAS, there is a unanimous process of an identifiable or associated disease without racial predilection.Neumann proposed that amniotic band lesions are not part of PAS.
- There is no consistently validated modality in PAS due to the limited number of reported cases.

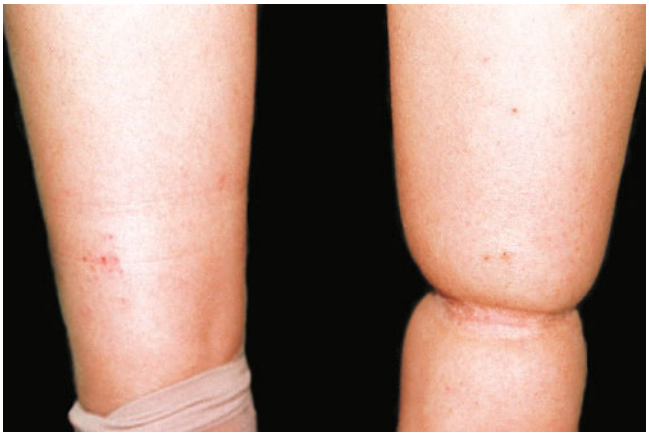


Fig. 16-11-1 Linear constrictions on the left calf

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Disorders of Subcutaneous Fat

17

Heng Yan, Da-Guang Wang, Ling Yang, Ren-Gui Chen, Ying-Ying Gao, and Ru-Zhi Zhang

Abstract

Atrophic subcutaneous fat is the chief complaint in cytophagic histiocytic panniculitis, sclerosing panniculitis, eosinophilic panniculitis, generalized lipodystrophy, and lipodystrophia centrifugalis abdominalis infantilis, as illustrated in this chapter.

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17.1 Cytophagic Histiocytic Panniculitis [1]

- Cytophagic histiocytic panniculitis (CHP) is characterized by lobular panniculitis with histiocytes containing blood cell fragments, mostly caused by viral infections and/or lymphoproliferative diseases, and frequently associated with marked systemic features such as pyrexia, pancytopenia, liver and spleen swelling, abnormal liver function, and coagulopathy.
- Dermal lesions in CHP include chronic, recurrent, and painful subcutaneous nodules, which are mainly distributed at the ends of extremities and occasionally in the cheek, cervical region, and trunk.
- Histologically, panniculitis lesions show adipose tissue lymphocytic and histiocytic infiltration along with hemophagocytosis, which may also appear in the bone marrow, spleen, lymph nodes, and liver.
- Options for treatment on CHP correlate closely with its prognosis. Chemotherapy in combination is recommended, with strict follow-up and constant vigilance to avoid its progression into a malignancy.

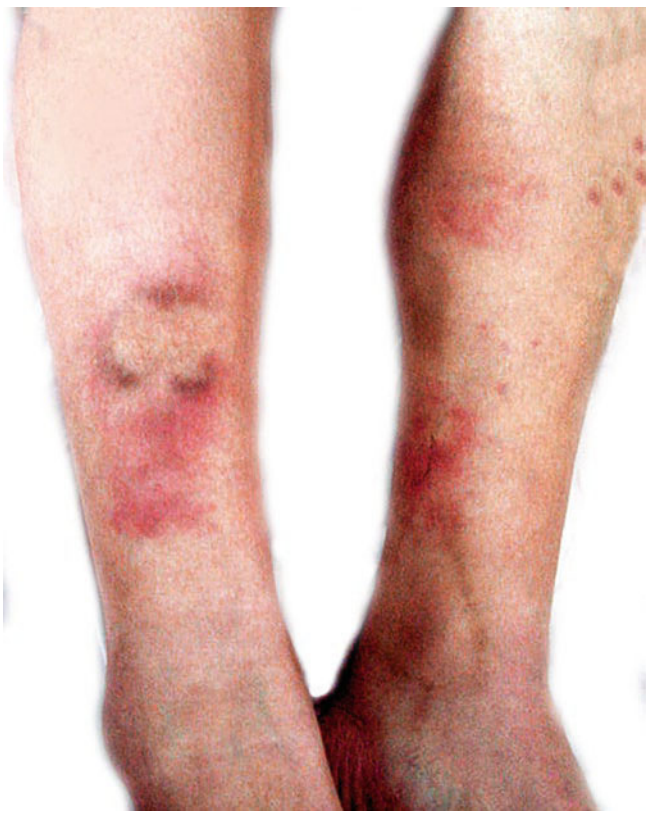


Fig. 17-1-1 Several violaceous plaques and petechia on both pretibial areas

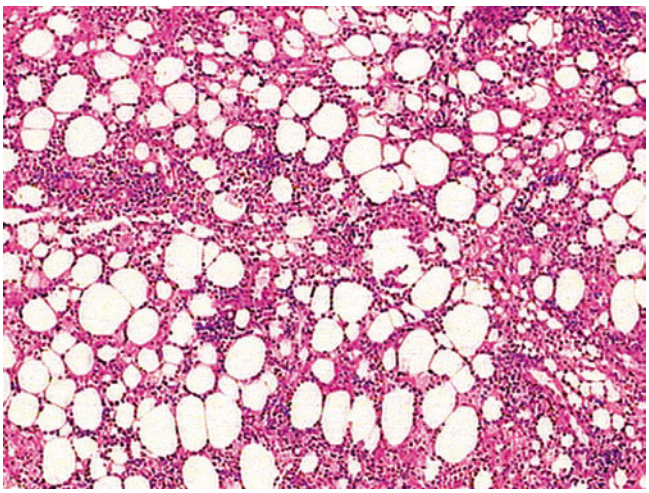


Fig. 17-1-2 Subcutaneous fat lobe necrosis and a massive infiltration of lymphocytes and histiocytes phagocytosing nuclear debris in the subcutaneous layer (GE stain, ×40)

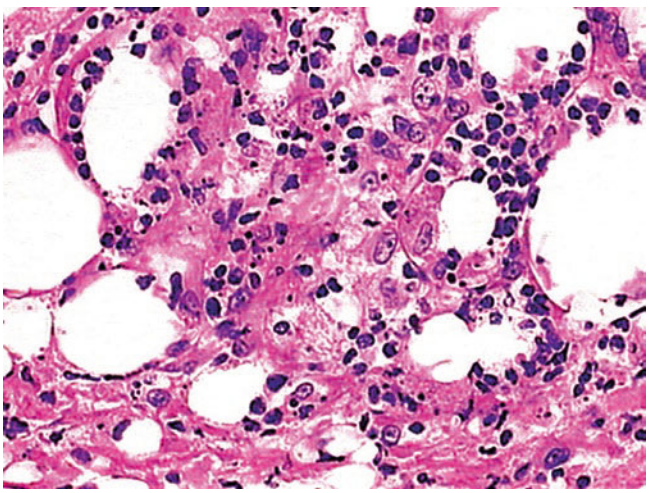


Fig. 17-1-3 Histiocytes phagocytosing leukocytes and nuclear debris, forming "bean bag cells" (HE stain, ×200)

17.2 Sclerosing Panniculitis [2]

- Sclerosing panniculitis frequently occurs in patients with venous insufficiency, and it is a chronic panniculitis.
- Clinically, it is characterized by skin induration and hyperpigmentation of one or both legs. The indurated plaques are often painful and frequently accompanied by a characteristic "inverted wine bottle" appearance of the involved legs.
- Histopathologically, there is mostly lobular panniculitis with steatonecrosis and without angiitis. In the late stage of disease, diaphragmatic sclerosis and membranocystic changes can be observed.
- Its treatment is centered at amelioration of local circulation including compression therapy with graded stockings and anabolic steroids.

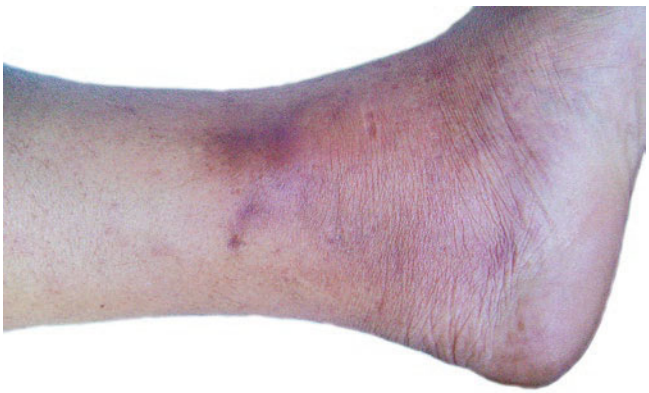


Fig. 17-2-1 A well-circumscribed, indurated, erythematous plaque and hyperpigmentation on the lateral malleolus of the right leg

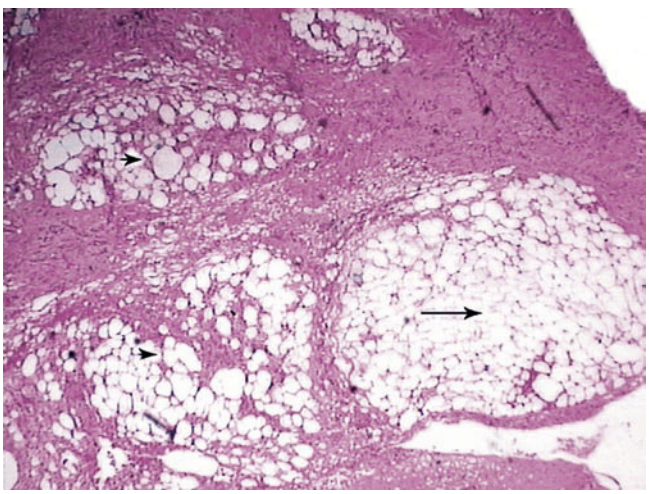


Fig. 17-2-2 Centrilobular ischemic necrosis (arrows), fat microcysts (arrowheads), and septal fibrosis (HE stain, ×40)

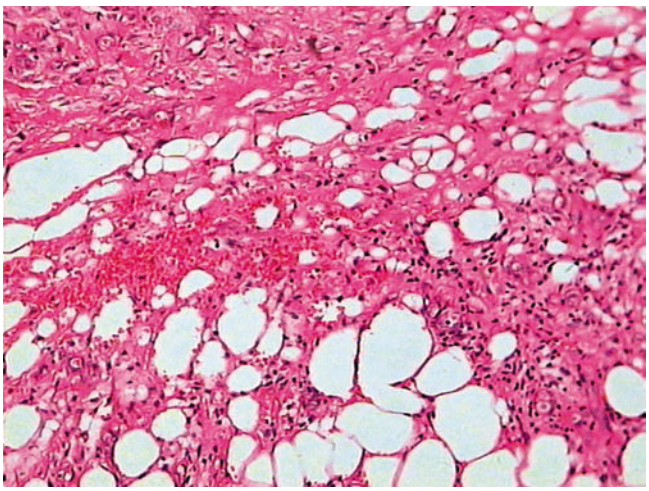


Fig. 17-2-3 Pale centrilobular ischemic necrosis with inflammatory infiltration (arrows) (HE stain, ×100)

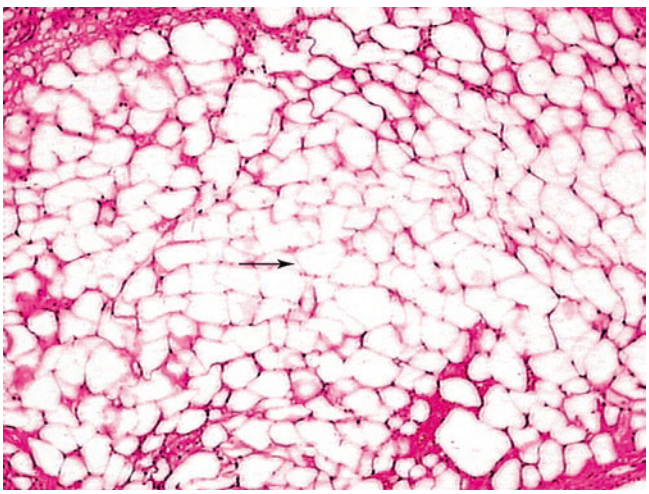


Fig. 17-2-4 Centrilobular membranous fat necrosis (arrows) and feather-like appearance of necrotic tissue (HE stain, ×400)

17.3 Eosinophilic Panniculitis [3, 4]

Extensive adipogenesis (GL) is a rare genetic or acquired disease characterized by extensive loss of visceral and subcutaneous fat, resulting in leptin deficiency, ectopic fat storage, and serious metabolic disorders.

- Eosinophilic panniculitis (EP) may be identified as a course of reaction that may occur in a variety of circumstances. It is believed that immunodeficiency, a trigger, or viral infection induces excess production of IL-4 and IL-5, causing an altered immune response.
- EP is seen more frequently in females than males and tends to occur in the third and sixth decades.
- Lesions present with nodules, plaques, papules, or pustules, single or multiple, mainly affecting the legs, arms, trunk, and face in decreasing order.
- Histopathologically, eosinophils associated with other inflammatory cells infiltrate the lobules and septa.

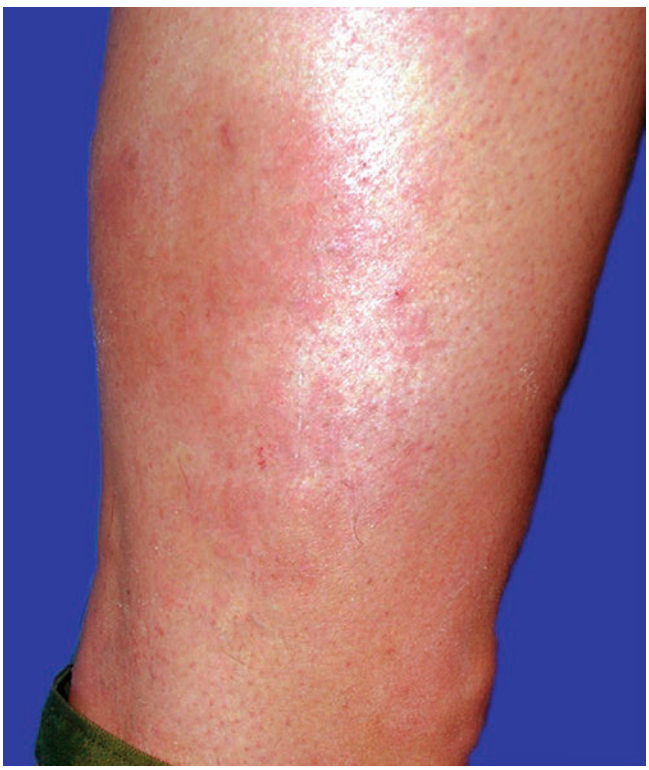


Fig. 17-3-1 A red indurated plague on the right leg

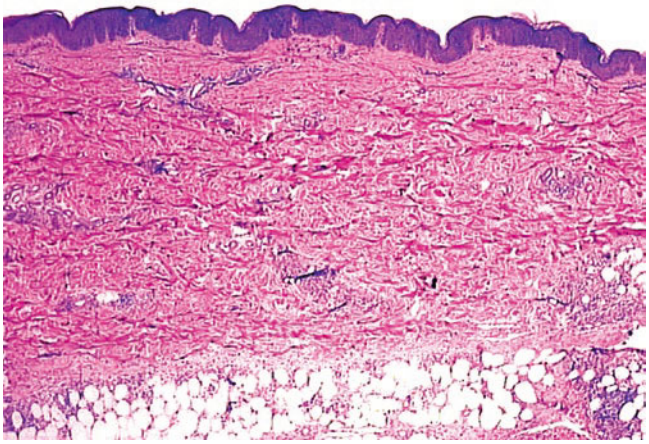
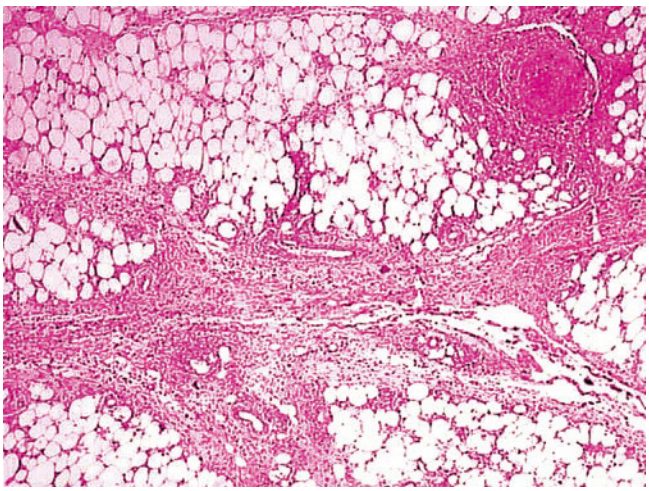
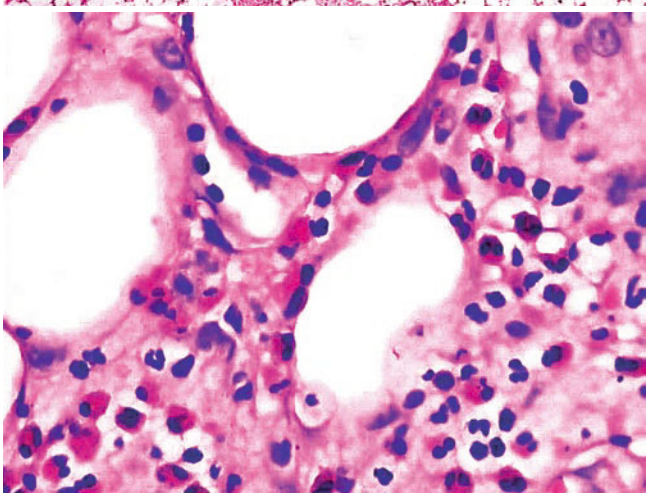


Fig. 17-3-2 The epidermis and dermis are normal (HE stain, ×20)





Figs. 17-3-3, 17-3-4 Eosinophils and mononuclear cells are very abundant in both septa and lobules (HE stain, (3) ×20; (4) × 400)

17.4 Generalized Lipodystrophy [5]

- The congenital type has its onset in infancy and even at birth and is often complicated by systemic diseases, especially diabetes. In contrast, the acquired type begins in adults with other diseases, especially autoimmune diseases and connective tissue diseases.
- The clinical features include defects in subcutaneous fat, proliferation of muscular tissues, lusterless complexion, long scull, large hand and foot joints, and extensive pigmentation.

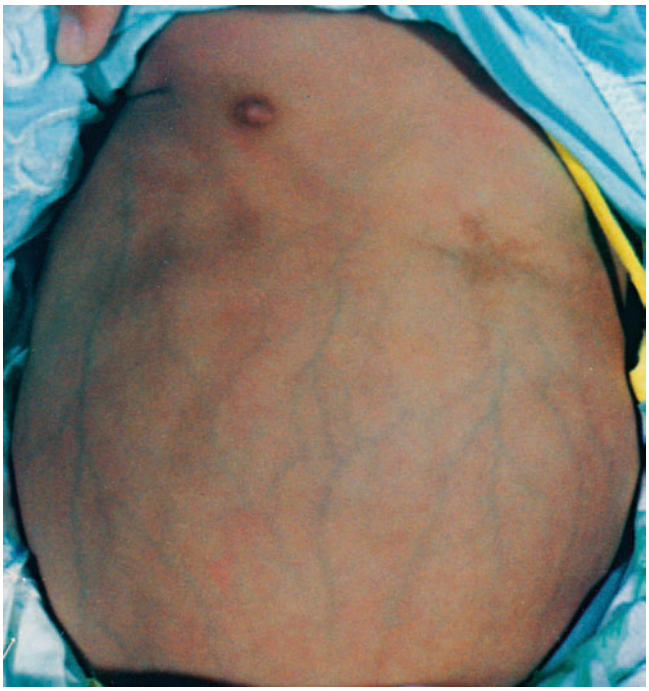


Fig. 17-4-1 A large depressed area on the abdomen and associated clear veins

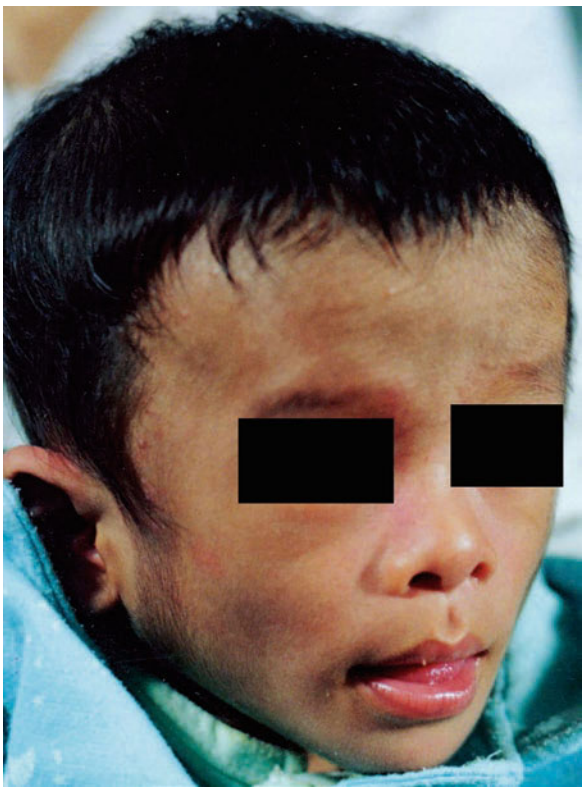


Fig. 17-4-2 The loss of large areas of subcutaneous fat on the face and four lesions of xanthoma on the forehead (Reproduced with the permission from [5])

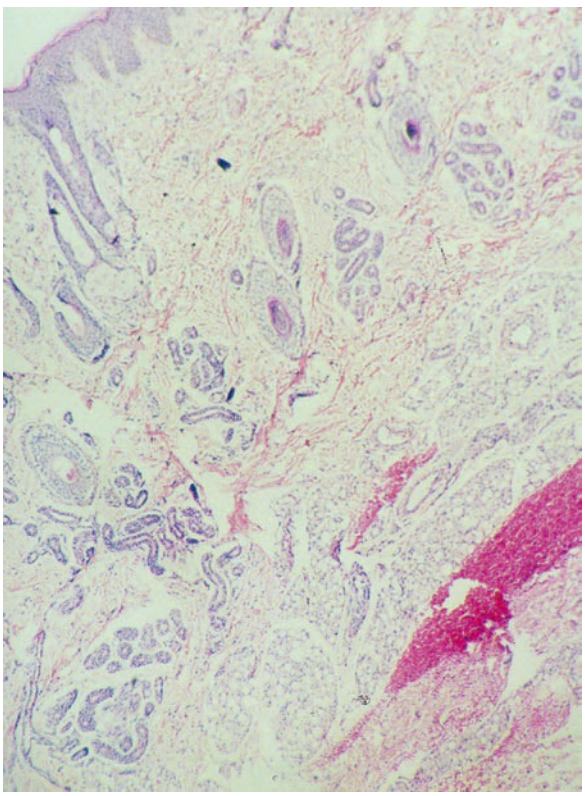


Fig. 17-4-3 Total loss of the subcutaneous fat-producing dermis adjacent to fascia (HE stain, ×40)

17.5 Lipodystrophia Centrifugalis Abdominalis Infantilis [6]

- Lipodystrophia centrifugalis abdominalis infantilis (LCAI), which can result in regional adipose metabolism obstacles, is a rare disease affecting young children (average age of onset of 4 years) mostly in Asian countries.
- This disease usually begins as an erythematous macule; it subsequently expands centrifugally and leaves a central depression. The depression starts either from the groin or axillae regions to involve the larger part of the abdominal and/or chest wall, with slight erythema and scaling borders. Regional lymph nodes are usually swollen.
- The disease is self-limiting. No drugs can effectually prevent the enlargement of depressed lesions, but more than 60% of patients exhibit idiopathic improvement after halting the enlargement.

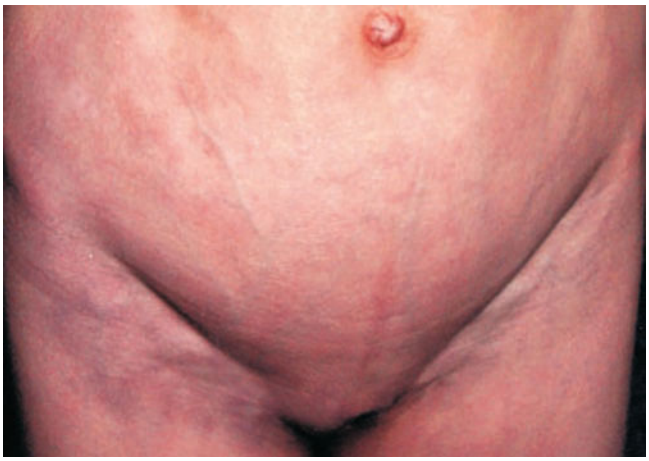


Fig. 17-5-1 Large depressed spadiceous patches with reddish edge on the lower abdomen and bilateral groin, from which subcutaneous veins could be seen

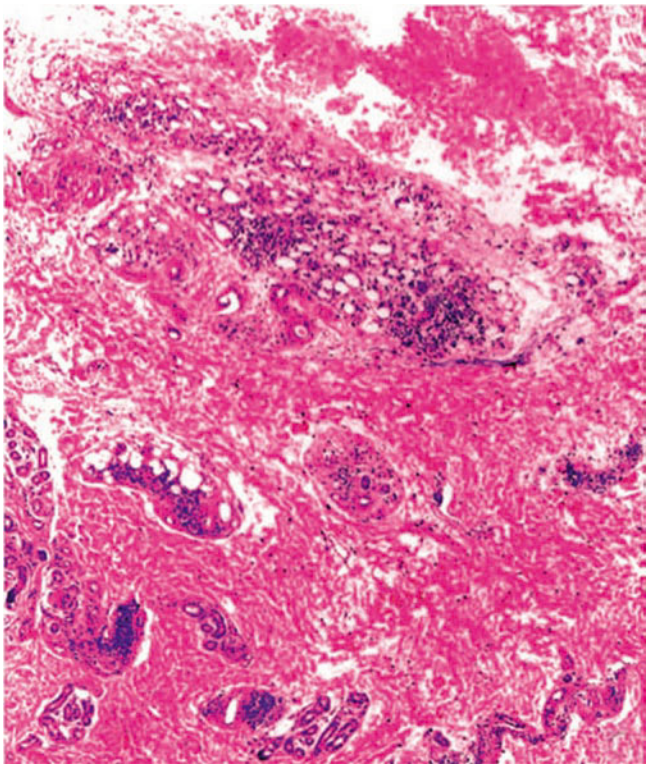


Fig. 17-5-2 Histopathologic changes showed a decrease or absence of subcutaneous fat and a mild inflammatory infiltrate of lymphocytes and histiocytes in the lower dermis and subcutis (HE stain, ×40)

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Noninfectious Granuloma

18

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Abstract

In this chapter, granuloma annulare, granuloma multiforme, annular elastolytic giant cell granuloma, cutaneous silica granuloma, and reactive nodular hyperplasia are all in the broad spectrum of noninfectious granuloma of the skin.

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18.1 Granuloma Annulare [1]

- Granuloma annulare (GA) is characterized by red to pink papules that enlarge to exhibit an annular configuration.
- Skin biopsy shows palisading granulomatous inflammation and mucin in GA.
- A dermoscopic observation shows red dots or red lines on a background color of red, white, or its combination, which is highly suggestive of GA. Crystalline leaf venation is a dermoscopic pattern characterized by whitish, parallel, secondary striated branching from a central vein.
- Although initially revealed in lichen planus, crystalline leaf venation may also be identified in GA.

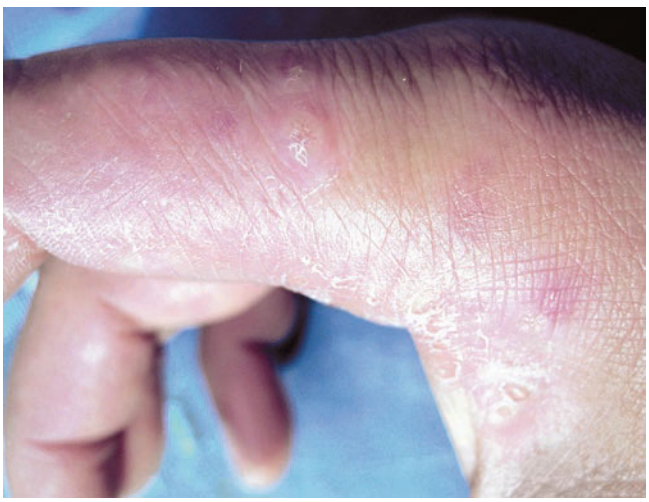


Fig. 18-1a-1 A small papule presented on the lateral surface of the index finger, with a flat and smooth top (Reproduced with the permission from [2])

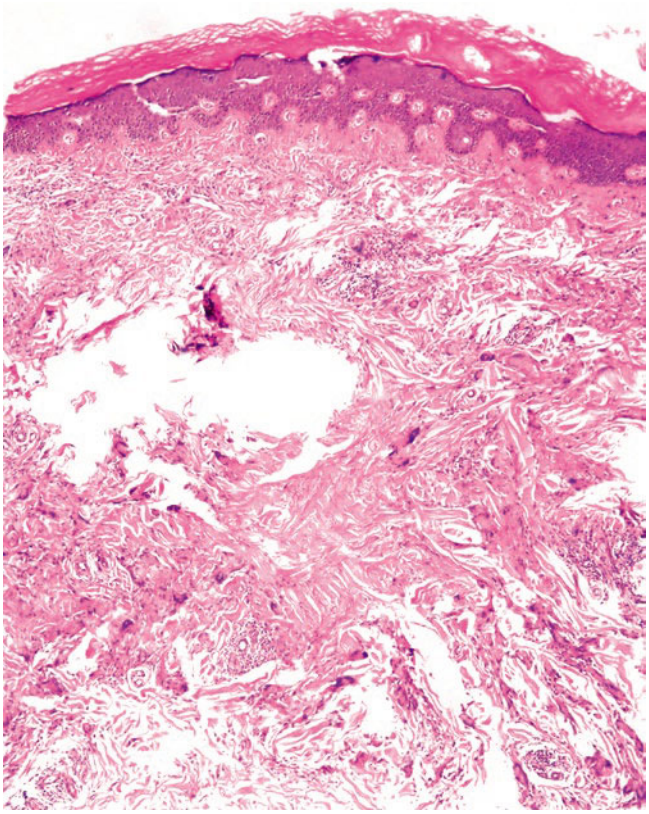


Fig. 18-1a-2 Skin biopsy showed areas of fibrinoid necrosis which were surrounded by histiocytes and lymphocytes which showed palisading arrangement in the superficial and mid-dermis (HE stain, ×40) (Reproduced with the permission from [2])

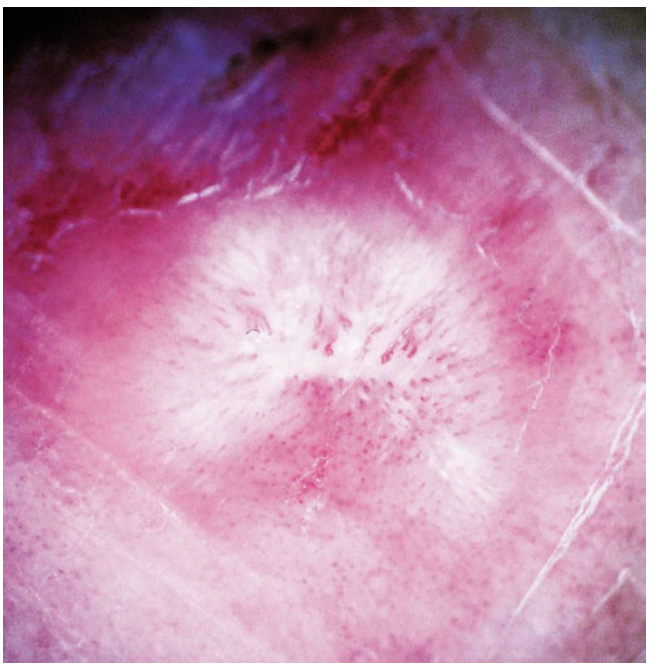


Fig. 18-1a-3 Dermatoscopically, there were numerous, paralleled crystal-white striae interspersed with fine red dots at their roots, which were characterized by the pattern of transverse parallel venation (Reproduced with the permission from [2])

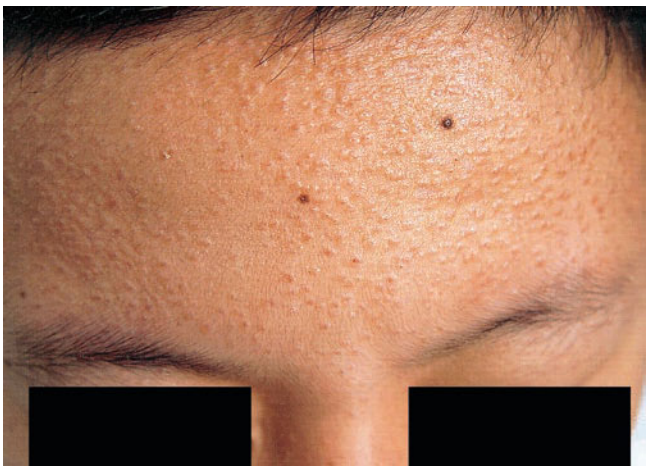


Fig. 18-1b-1 White-yellow or pale-red firm papules with smooth surface on the forehead

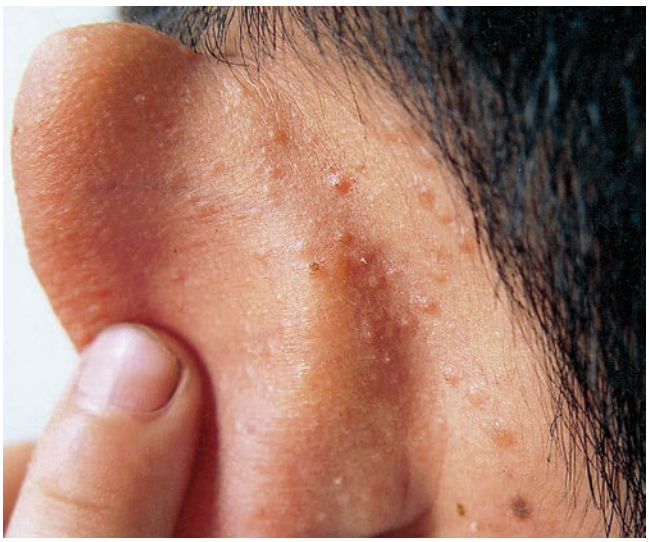


Fig. 18-1b-2 Pale-red firm papules on the back of the ear

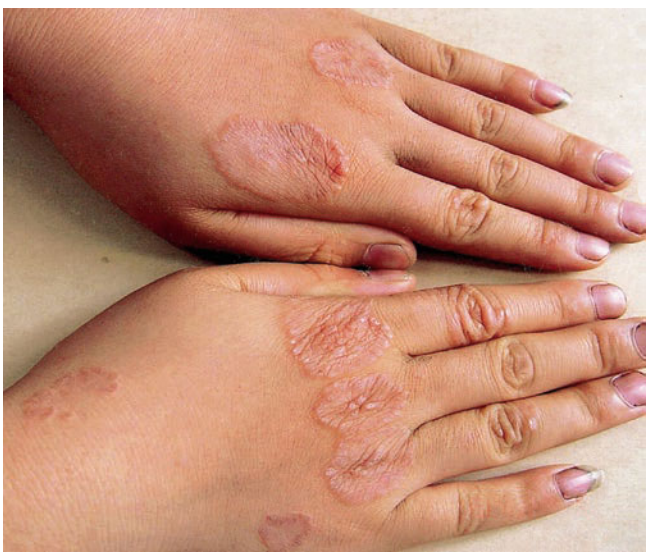


Fig. 18-1b-3 Pale-purple circinate macular on the dorsal of both hands with elevated edge

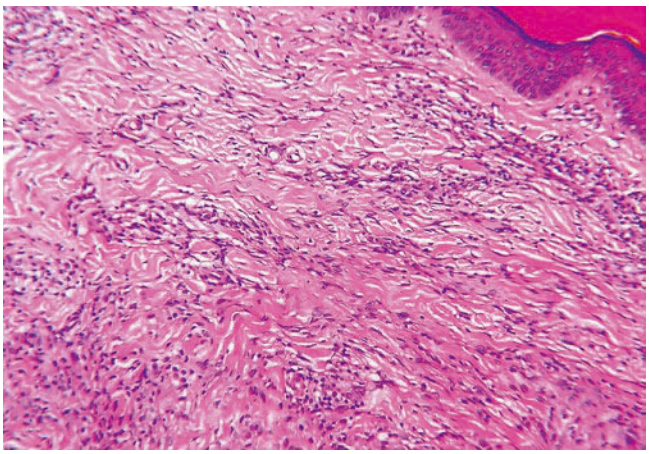


Fig. 18-1b-4 Hyperkeratosis, degeneration of collagen in the upper dermis, epithelioid cells in a palisading arrangement (HE stain, ×100)

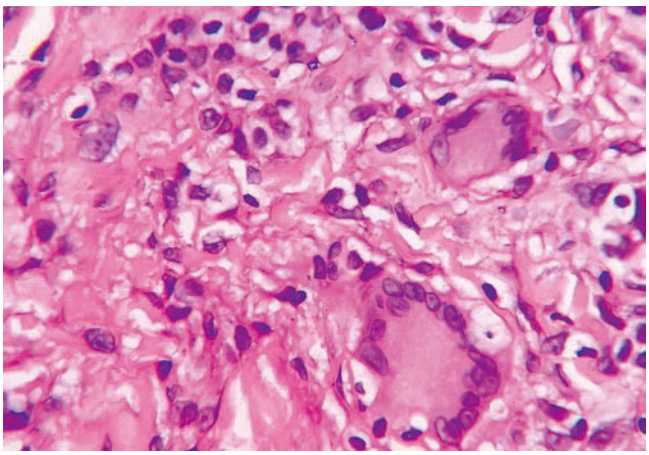


Fig. 18-1b-5 Multinuclear giant cells in the dermis (HE stain, ×100)

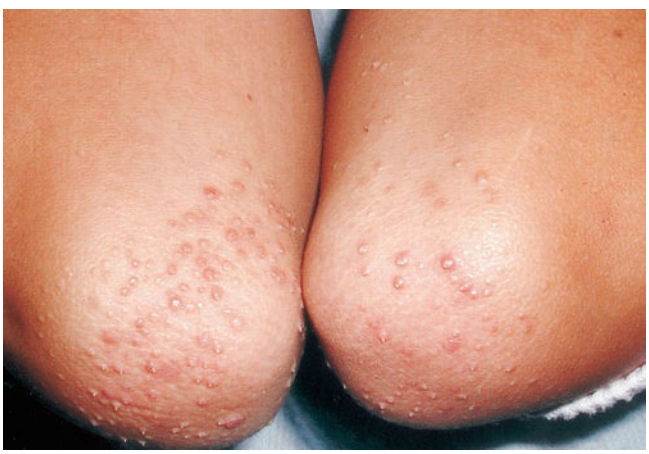


Fig. 18-1c-1 The flesh-colored or pale-red papules are grouped on both elbows

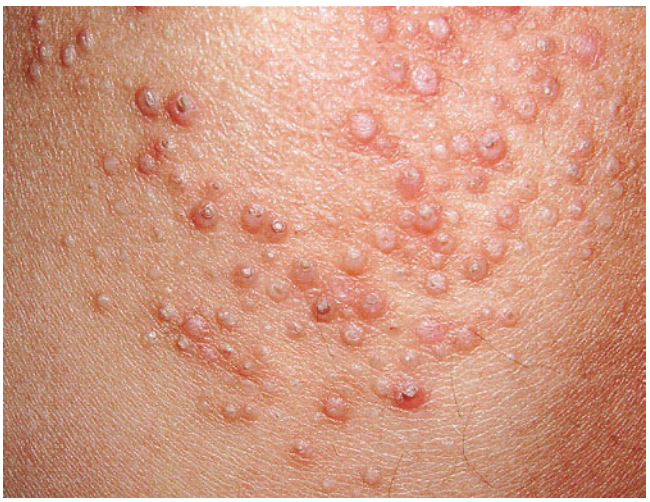


Fig. 18-1c-2 Most of papules have a keratic plug at center

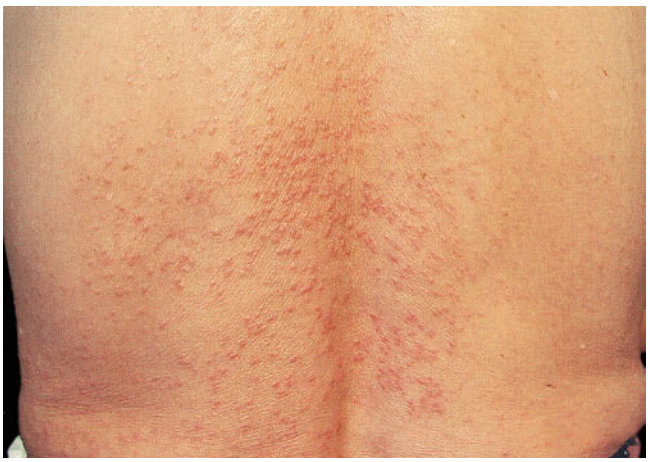


Fig. 18-1d-1 Skin-colored, firm papules with smooth surfaces grouped on the back

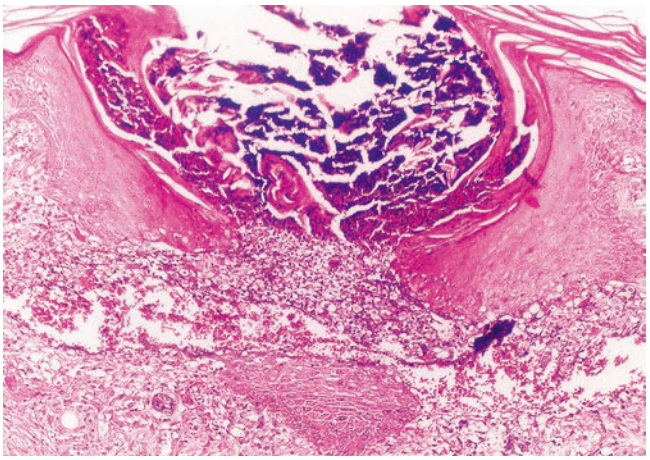


Fig. 18-1c-3 A narrow channel contained necrosis tissues and degenerated collagen fibers through the epidermis (HE stain, ×100)

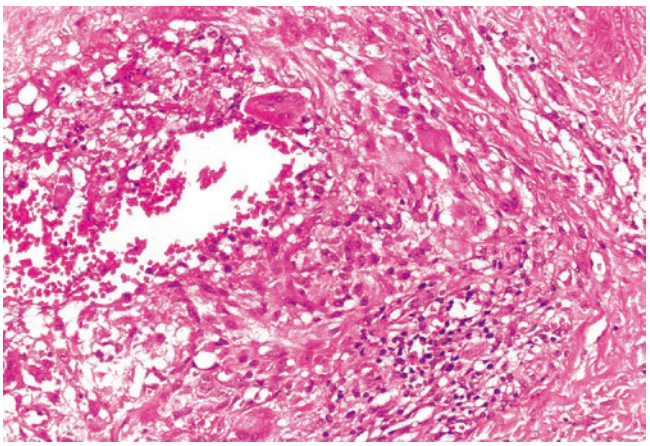


Fig. 18-1c-4 A palisade of histiocytes around the necrobiosis area in the upper dermis (HE stain, ×200)

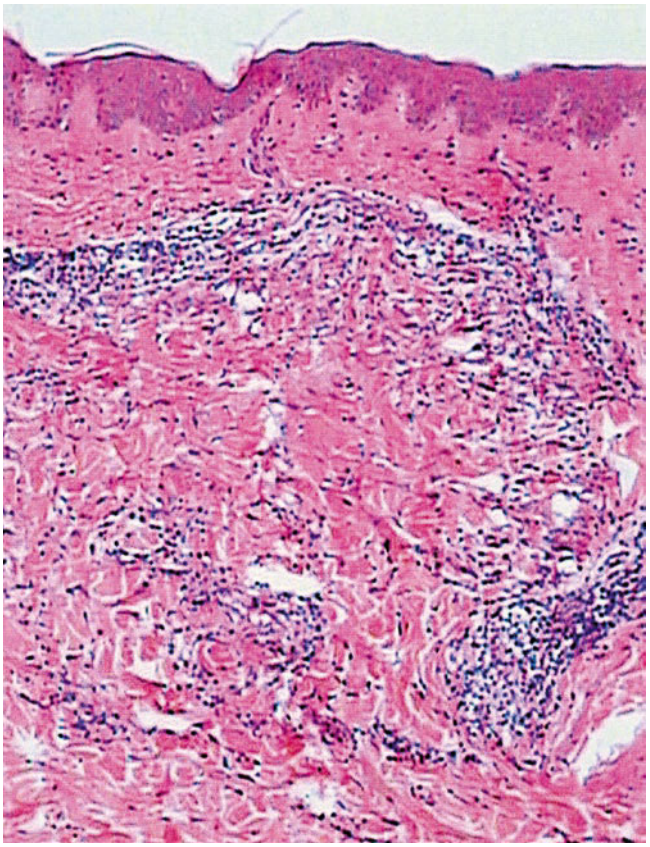


Fig. 18-1d-2 Considerable epithelioid cells and lymphocytes in a palisading arrangement between degeneration of collagen bundles in the middle of dermis (HE stain, ×200)

18.2 Granuloma Multiforme [3, 4]

- We should bear in mind that granuloma multiforme (GM) can be misdiagnosed and mistakenly receive treatment for tuberculoid leprosy. Most individuals with GM are over 40 years old.The sun-exposed position on the chest, cervical region, and arms is most likely to be affected.
- The lesions associated with GM are multiple papules, which aggregate to form annular and polycyclic popular edges.
- GM differs from granuloma annulare in the dense perivascular infiltration, the absence of mucin and elastic fibers, and the relatively sparse infiltration of larger multinucleate giant cells observed in GM.
- Tuberculoid leprosy features nerve trunk thickening and sensory injury but an absence of degenerated collagen.

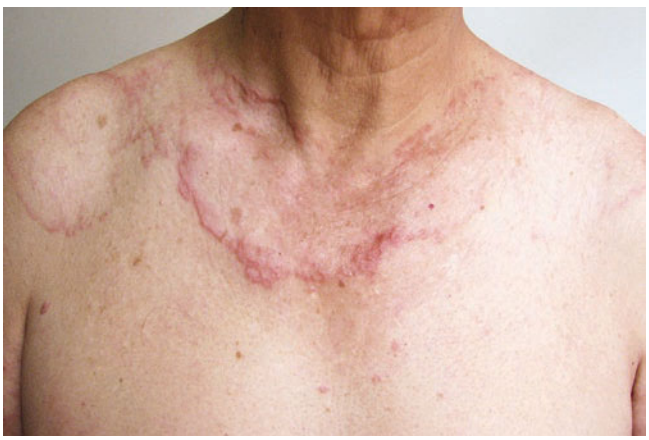


Fig. 18-2-1 Papules on the neck and upper quarter of the trunk coalesce to be reticular or irregular in shape with a smooth surface. There were no ulcerations, scars, or abnormal pigmentary changes

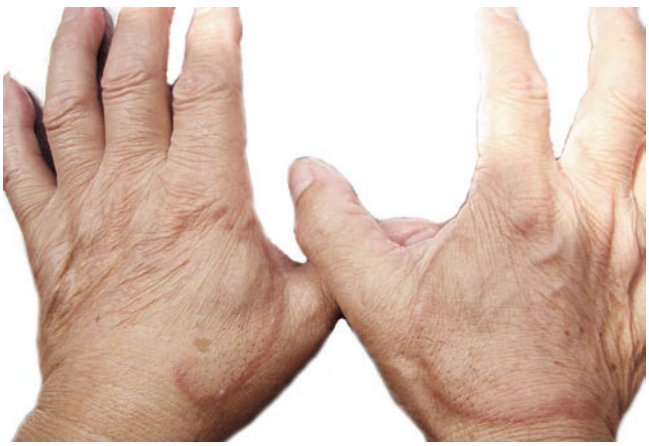


Fig. 18-2-2 On the dorsal hands, there were lesions with an elevated serpiginous border

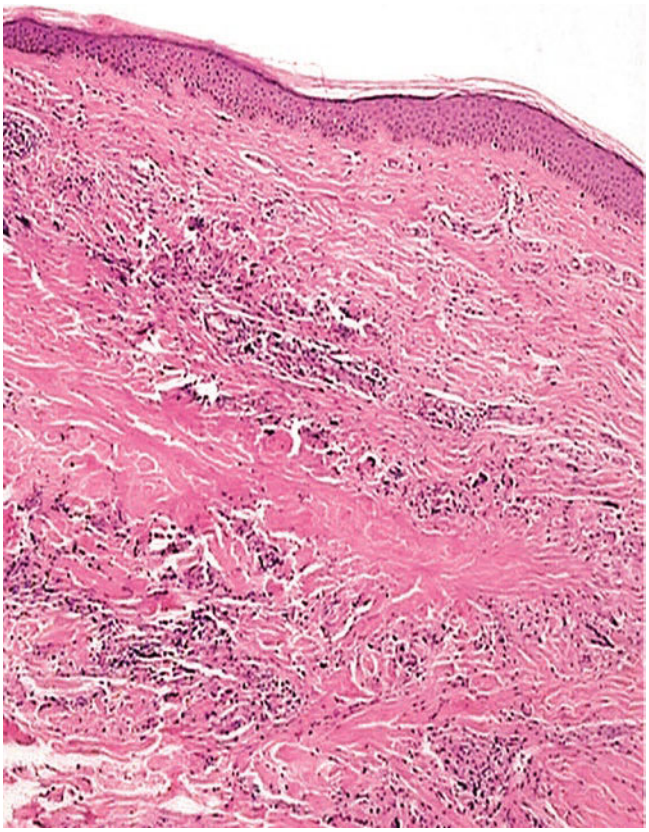


Fig. 18-2-3 Areas of necrobiosis surrounded by palisaded rim of histiocytes in the mid- and upper dermis (HE stain, ×40)

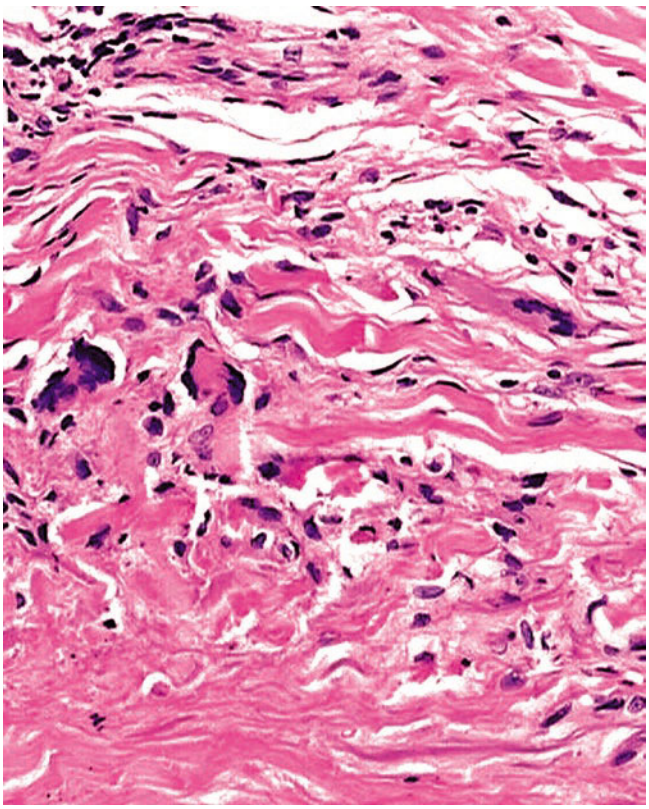
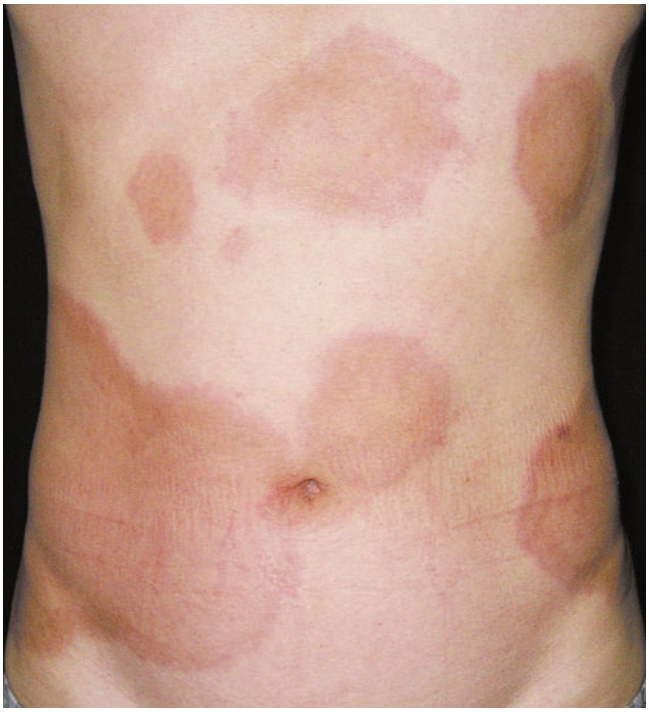
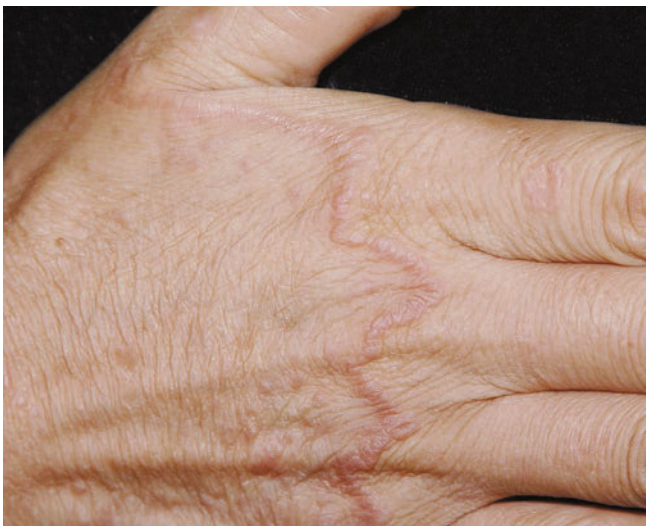


Fig. 18-2-4 Palisading granuloma was shown typically with multinucleated giant cells and occasional asteroid bodies (HE stain, ×200)

18.3 Annular Elastolytic Giant Cell Granuloma [5, 6]

- Annular elastolytic giant cell granuloma (AEGCG), also known as giant cell elastolytic granuloma, was described by O'Brien in 1975.
- It presents initially as one or more papules that enlarge into annular/polycyclic plaques with elevated borders and atrophic centers. The sun-exposed trunk and cervical region are the predominant sites.
- A feature of AEGCG is the phagocytosis of elastotic material by histiocytes, usually in the presence of giant cells.
- Treatment options include topical and intralesional steroids, dapsone, topical tacrolimus and pimecrolimus, cyclosporine, hydroxychloroquine, isotretinoin, and PUVA with alterable responses.





Figs. 18-3-1, 18-3-2 Multiple annular, demarcated erythemas with elevated borders and a less erythematous, atrophic center on the trunk (1) and the dorsal of hands (2)

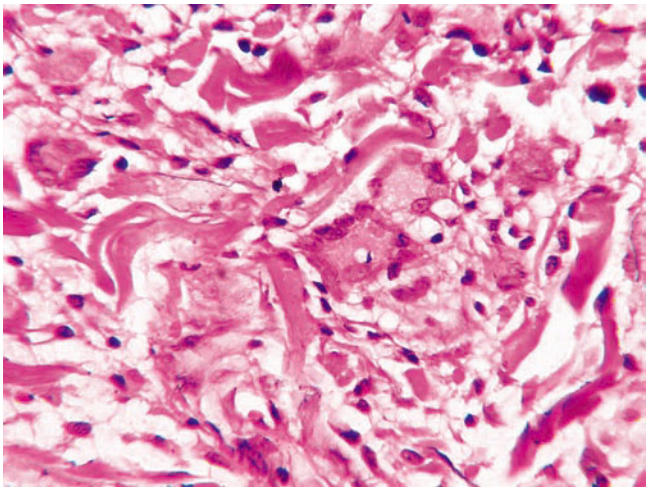
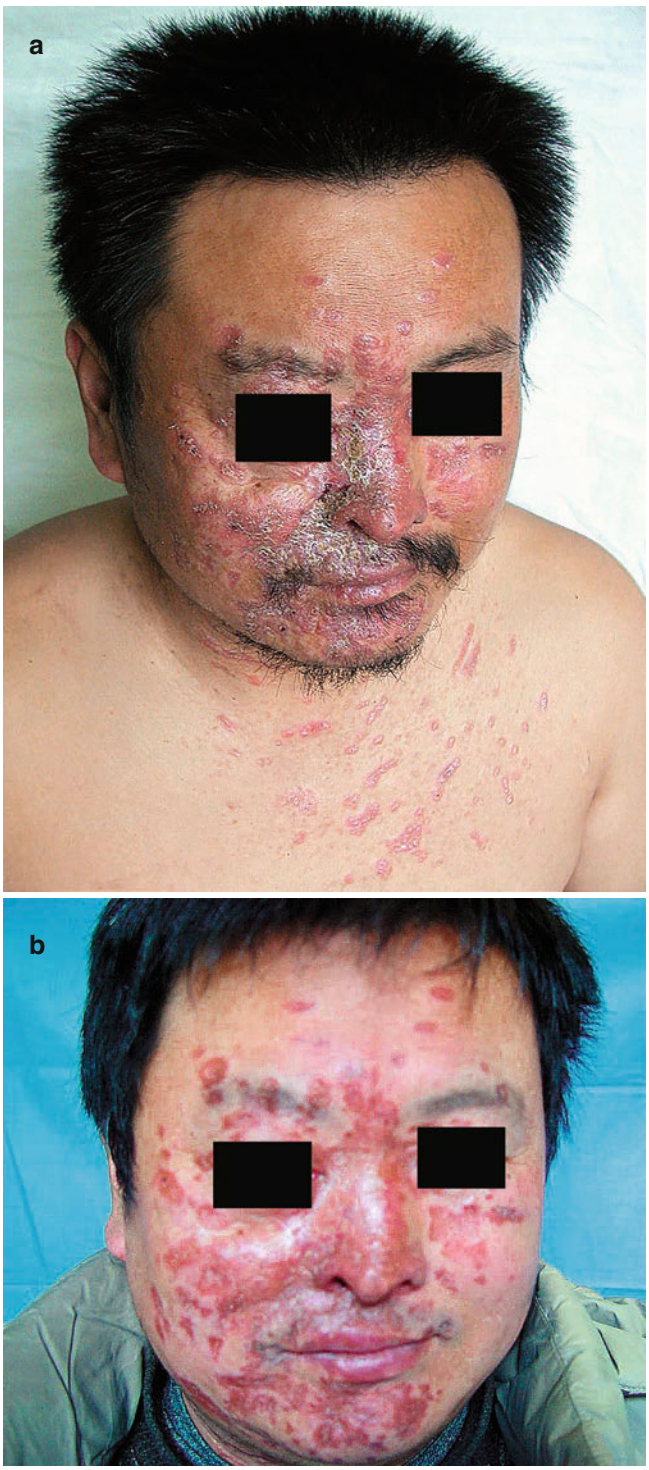


Fig. 18-3-3 Dermal infiltrate of macrophages and multinucleated giant cells and absence of necrobiosis in the center of the lesion (HE stain, ×100)

18.4 Cutaneous Silica Granuloma [7, 8]

- Cutaneous silica granuloma (CSG) is a poorly understood, uncommon condition that is occasionally encountered after trauma.
- CSG is often underdiagnosed and misdiagnosed because of a characteristic latency period between the time of silica exposure and the time of clinical granuloma appearance. The period ranges from less than 1 year to more than 50 years, with a mean interval of approximately 10 years.
- Lesions usually present as erythematous, firm, nontender, dermal, or subcutaneous nodules.
- A biopsy specimen shows a foreign body granuloma with abundant giant cells surrounding numerous crystalline structures, which can be visualized under a polarized light microscope and further confirmed by energy-dispersive X-ray analysis.
- Surgical resection seems to be the most effective treatment. Other treatments include intralesional steroid injections, systemic steroids, irradiation, and antibiotics.



Figs. 18-4-1, 18-4-2 Erythematous nodules on his face, around the lips, left eye, submaxillary mentoniane furrow, chin, and prothorax (a. before treatment; b. after treatment) (Reproduced with the permission from [7, 8])

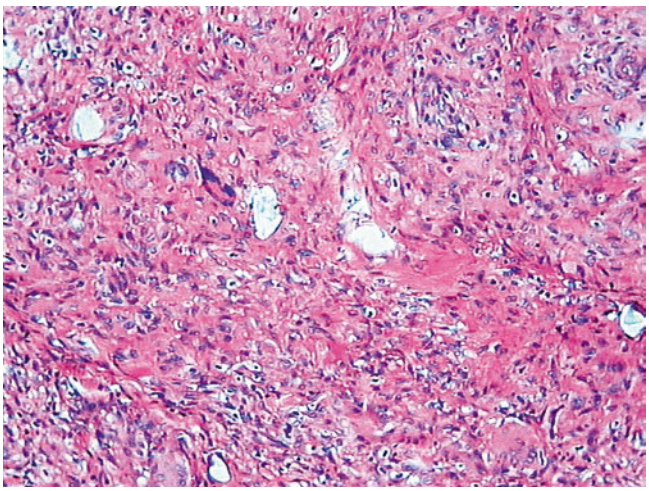


Fig. 18-4-3 Circumscribed granulomas of epithelioid cell tubercles showing no necrosis in dermis and giant cell with a foreign body in the cytoplasm (HE stain, ×200)

Fig. 18-4-4 Birefringent foreign body under polarized light in the cytoplasm of a giant cell (×200)

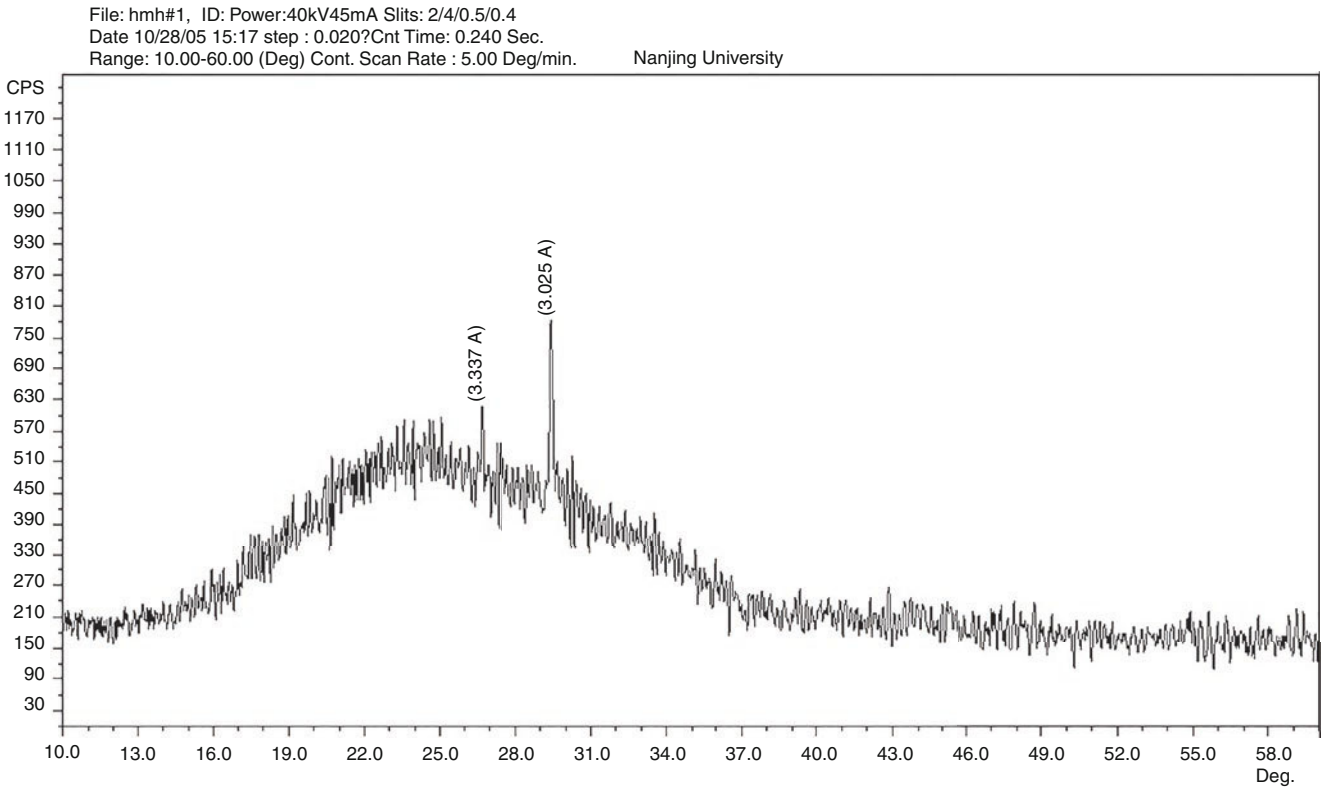


Fig. 18-4-5 X-ray spectrum of one of the crystalline shoused major constituents of silica, oxygen, and aluminum

18.5 Reactive Nodular Hyperplasia [9]

- Reactive nodular hyperplasia is a clinically infrequent disorder. Elucidation of its pathogenesis and etiology requires further study.
- It tends to occur on the distal extremities, particularly on the palms and fingers. Occasionally, it appears on mucosal sites such as the prolabium and buccal mucosa.
- The clinical manifestations usually present as solitary, hard, well-defined, and dome-shaped nodule. It is usually asymptomatic.
- The histological examination is characterized by hyperkeratosis and hyperplasia of the epidermis and fibrotic nodules without an envelope in the upper part of the dermis and without an increase in melanin in the basal layer of the epidermis.
- Surgical excision is the primary treatment.

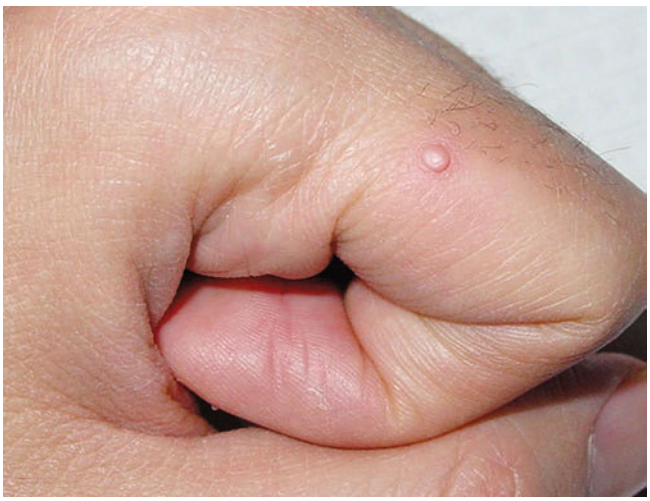


Fig. 18-5-1 A solitary green bean-sized hyperkeratotic nodule with narrow base on the extensor of the left index finger

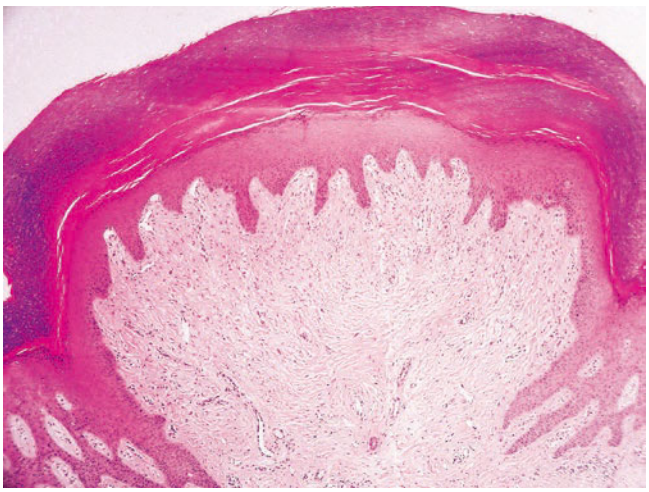


Fig. 18-5-2 Epidermal hyperkeratosis and the collar-like hyperplasia; dermal fibroblast and collagen fiber hyperplasia were present (HE stain, ×40)

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Part VI

Pigmentary Disorders

Pigmentary Disorder

19

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Abstract

Pigmentary disturbance is a very common presentation among Chinese populations. This chapter covers a variety of skin disease characterized with hypopigmentation, hyperpigmentation, and other pigmentary manifestations, including pigmentary demarcation lines, melisma, LEOPARD syndrome, PUVA lentigo, giant congenital melanocytic nevus, nevus of Ota, Ota nevus associated with nevus flammeus, partial depigmentation arising in the nevus of Ito, acquired bilateral nevus of Ota-like macules, acne confined to the Becker's nevus, neurocutaneous melanosis, progressive acromelanosis, periorbital melanosis, reticulate acropigmentation of Kitamura, Kindler syndrome, Dowling-Degos disease, macromelanosomes in dyschromatosis universalis hereditaria, familial progressive hyperpigmentation, familial progressive hypo- and hyperpigmentation, linear and whorled nevoid hypermelanosis, pointillist melanotic macules, acquired dermal melanocytosis, accidental tattoos, rippling lesions of confluent and reticulated papillomatosis, trichrome vitiligo, pentachrome vitiligo in a segmental pattern, inflammatory vitiligo, coexistence of piebaldism and neurofibromatosis type I, nevus depigmentosus, and stellate spontaneous pseudoscars.

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19.1 Pigmentary Demarcation Lines [1]

- Pigmentary demarcation lines (PDLs) are considered as normal variation of skin pigmentation with a linear configuration. These lines are formed as a result of abrupt pigmentation change from the heavily pigmented external surfaces to the lighter internal ones. PDLs specify a dualism in the populations of melanocytes. It may underlie an influence from the neurological system synergistic with ultraviolet stimulation, which, at least phylogenetically, is obvious over the extensor surfaces with prolonged sun exposure.
- Updated data show the existence of eight demonstrations of PDLs, defined from A to H, among which types A, C, and E have multiple subtypes of their own. PDLs mostly keep unchanged for a long time except type B line which only persists for a certain period of time and regresses spontaneously after childbirth.
- The medio-sternal subtype of PDL C lines appears where a transmedian overlap of nerves is frequently suggested clinically. It is formed due to the sharp termination of melanocytic migration from the neural crest during the process of embryo development.
- Type E lines are representative of a dermatome pattern.
- PDLs need no treatment, and the Q-switched alexandrite laser can be tried for patients for aesthetic purpose.

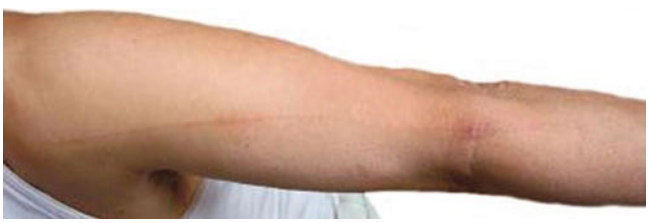


Fig. 19-1-1 A pigmentary band, approximately 0.5 cm × 20 cm, distributed over the left upper limb (type A)

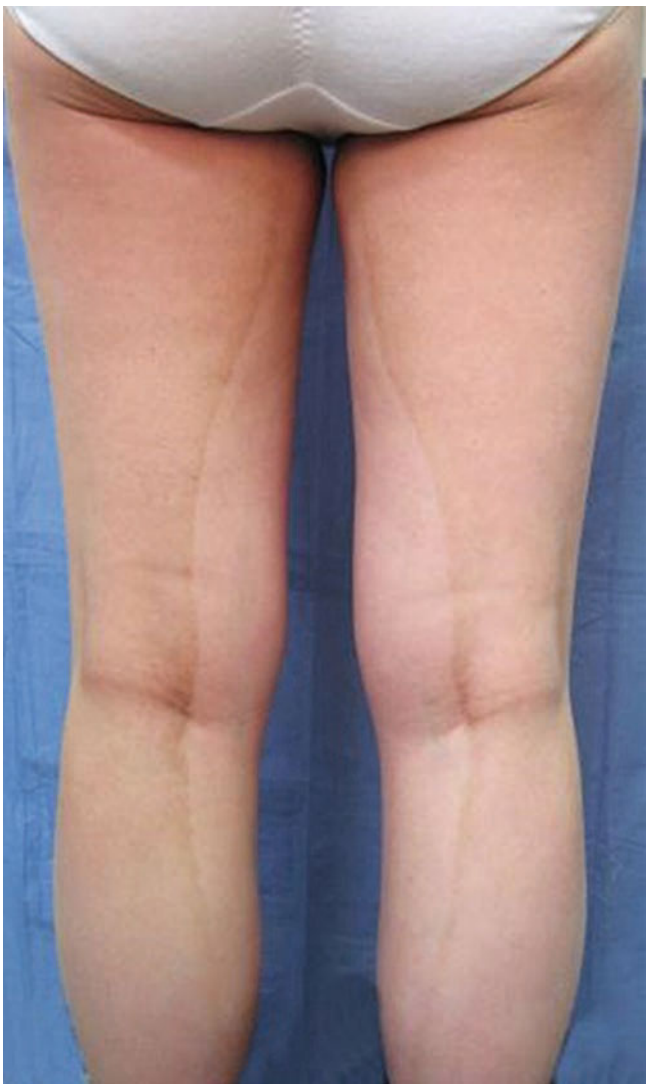


Fig. 19-1-2 Type B pigmentary demarcation lines: 58 cm × 15 (to 20) cm. The pigmentary band runs on the flexor area of the feet. The lesion was well demarcated in the medial part of the line and was almost imperceptible on the other parts

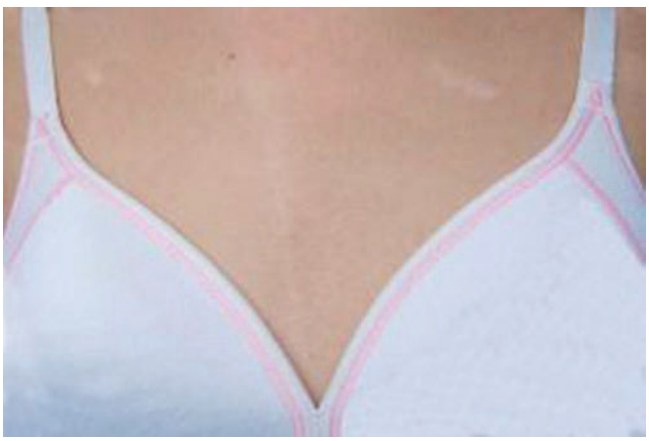


Fig. 19-1-3 The type C demarcation line was hypopigmented in the midline of the chest. The type E displayed as two aslant-oriented, hypopigmented macules occurred on both sides of the chest (Reproduced with the permission from [2])

19.2 Melasma [3]

- Melasma is most frequently seen in middle-aged women, although it may occur in men.
- The brown patches are usually on the malar and forehead. Occasionally they may be found on the forearms.
- There are three clinical patters: (1) Centrofacial form is observed in about two-thirds of affected individuals. In these patients, lesions occur on the forehead, nose, chin, and aspects of the cheeks. (2) The malar patter appears in about 20% of patients. In these patients, lesions are limited to the cheeks and nose. (3) Mandibular.
- Bleaching cream with hydroquinone, azelaic acid, kojic acid, arbutin, and licorice extract is an effective treatment.

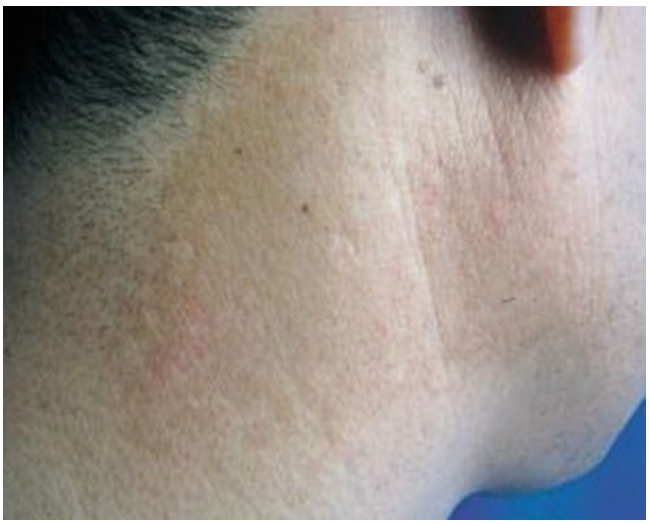


Fig. 19-2-1 Brownish macules on the neck with irregular border

19.3 LEOPARD Syndrome [4]

- LEOPARD syndrome consists of the following abnormalities: lentigines, EKG abnormality, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness.
- Lentigines are distributed over the entire body at or shortly after birth. These macules are round to oval in shape with the size ranging from 2 to 5 mm in diameter. The color is dark brown to deep black. Individual lesion may be larger, even up to 1–1.5 cm. Uncommon presentations include café au lait spots and Crowe's sign.
- Microscopically, the rete ridges are elongated and club shaped. The basal layer of projecting rete ridges shows considerable hyperpigmentation and a significant increase in the number of melanocytes.
- NF1 gene (PTPN 11) is the culprit gene both for LEOPARD syndrome and Noonan syndrome and is mapped 12q24.
- Generalized lentiginosis is a rather rare pigmented disorder which has generalized lentigines without associated systemic abnormalities.

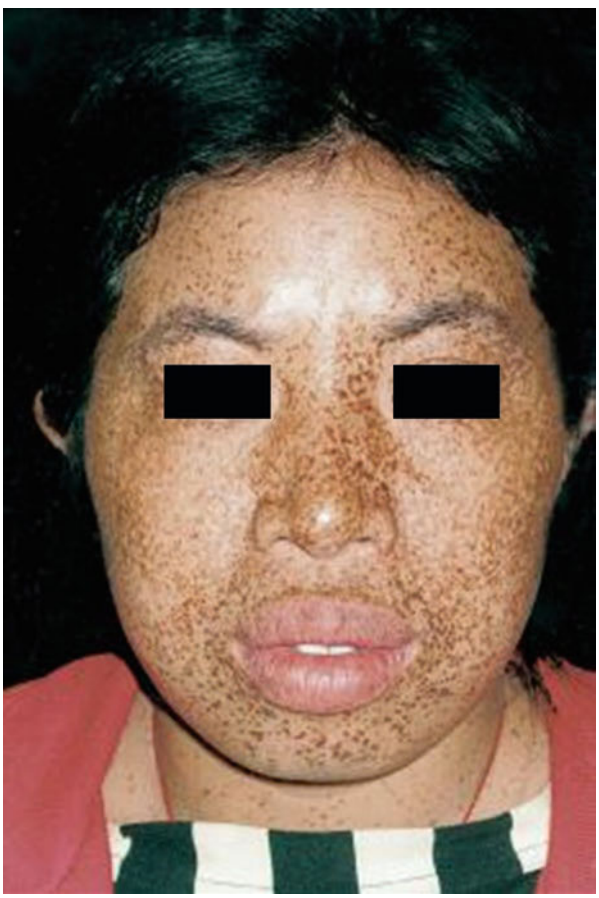


Fig. 19-3-1 Without mosaic numerous tiny dark-brown macules on the face

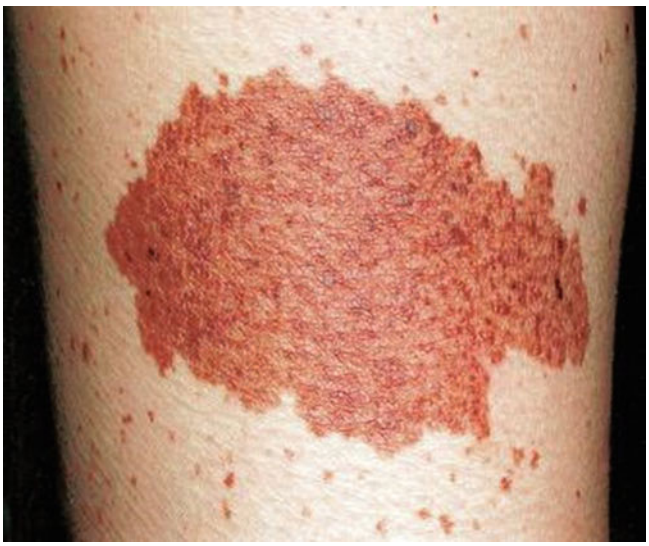


Fig. 19-3-2 A large brown plaque on the left limb with scattered dark papules on it

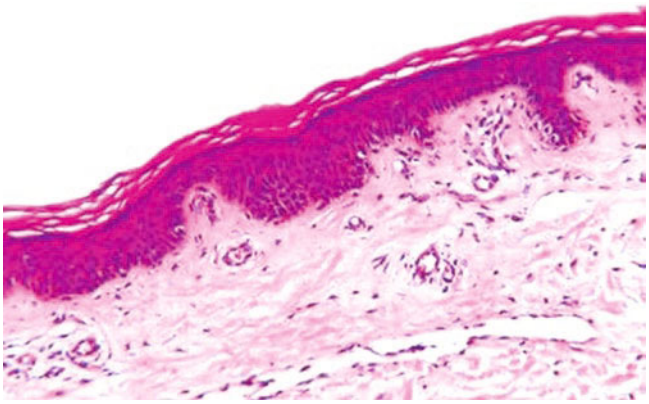


Fig. 19-3-3 Light hyperkeratosis, acanthosis, and hyperpigmentation in basilar layer of the epidermis. Melanophages were found in the dermis (HE stain, ×400)

19.4 PUVA Lentigo [5]

- Lentigines are a familiar pigmentary disease in adults, among whom they are common in patients receiving ultraviolet A (PUVA) radiation and psoralen treatment. They are a famous secondary effect of PUVA.
- Their frequency and severity are firsthand correlated with the treatments in total. UVA-induced lentigines often exhibit darker pigmentation and a more stellate appearance than NB-UVB-induced lentigines.
- The histopathological findings of lentigines include hyperpigmentation of the basal layer with a slight proliferation of the melanocytes. PUVA-induced lentigines are often characterized by elongated rete ridges, studded with melanocytes with proliferation potentials.

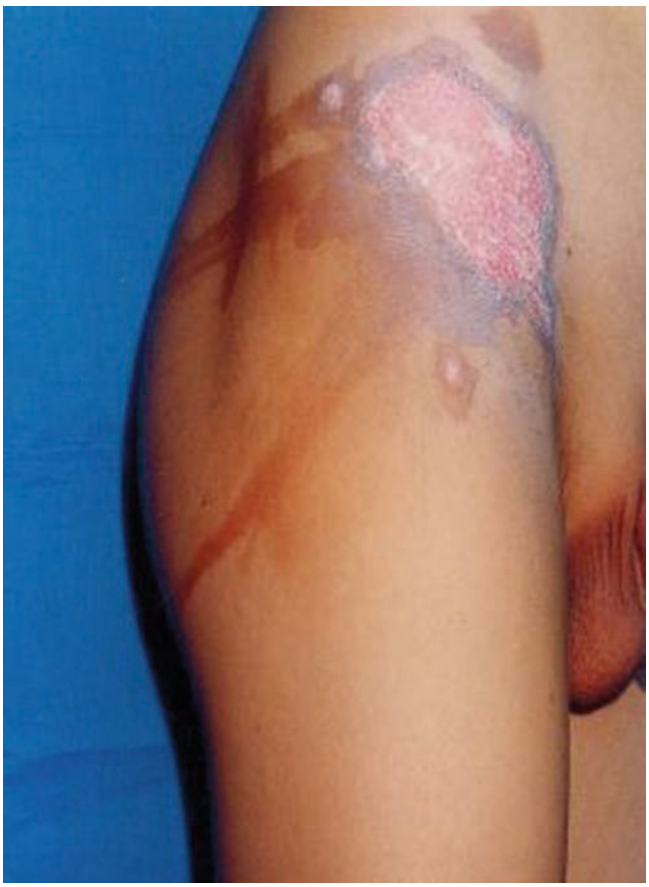


Fig. 19-4-1 Hyperpigmentation alteration around edematous erythema

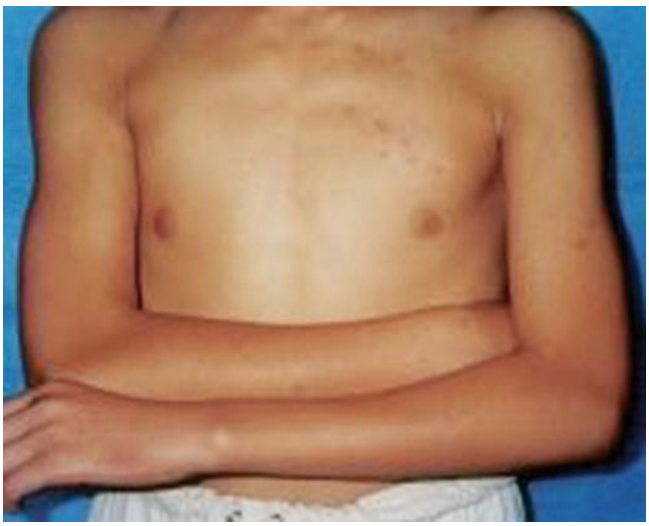


Fig. 19-4-2 Generalized brown to black speckles

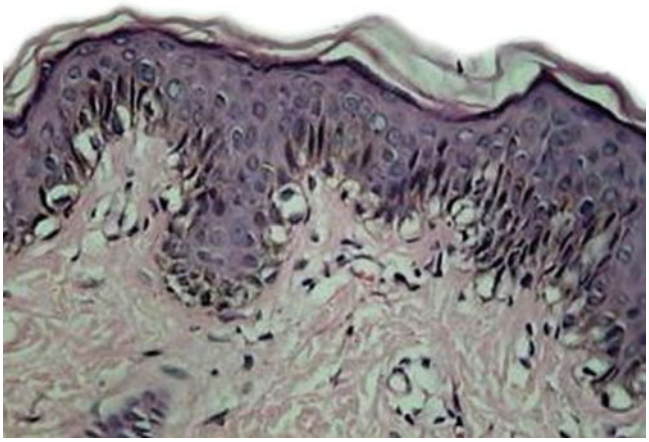


Fig. 19-4-3 In the epidermis, clear cells were markedly increased in the basal layer, some of which are binuclear (HE stain ×400)

19.5 Giant Congenital Melanocytic Nevus [6]

- Giant congenital melanocytic nevus (GCMN) is often at birth and grows proportionally with age.
- GCMN predominantly affects the trunk. In some cases, the lesions are thickened, verrucous, or coated with darkly pigmented hairs.
- It is estimated that about 2% and 15% individuals develop melanomas in certain stage of the disease. Axial or paravertebral location is a risk factor for melanoma transformation.
- Nevus cells in GCMN extend into the deep dermis, subcutis, and fascia. No atypia, mitosis, and necrosis are found in these cells.
- Besides GCMN, vitiligo colocalizes with lichen planus, mycosis fungoides, psoriasis, alopecia areata, and scleroderma.

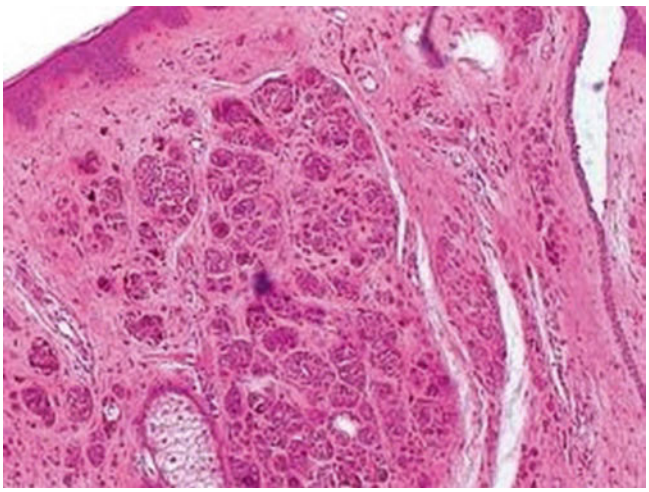


Fig. 19-5-2 Variously sized nevus cell nests in the dermis (HE stain, ×40)

Fig. 19-5-1 Large pigmented cerebriform masses on the scalp covered with a few black short hairs

19.6 Nevus of Ota [7]

The nevus of Ota may be divided into four types (2): types 1–3 are unilateral. The brown-, slate-, or blue-spotted pigmentations are confined to the upper and lower eyelids (type 1A). The zygomatic area and base of the nose can be similarly affected (type 1B). Type 2 comprises type 1A and type 1B. Type 3 includes type 2 and the pigmentation on the forehead, external ear, and scalp. Type 4 (bilateral) involves both sides of the face.

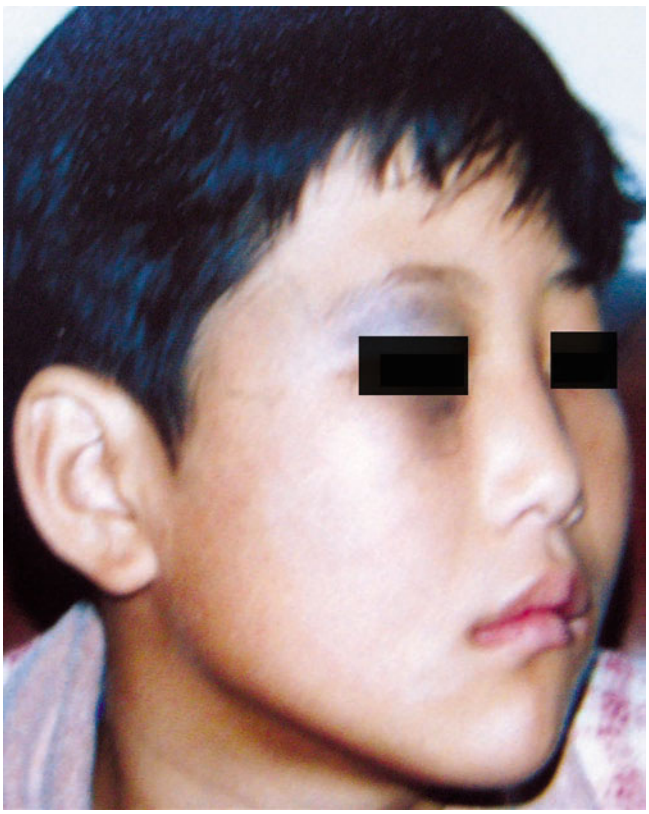


Fig. 19-6a-1 Pigmentary spots limited to the upper and lower eyelids (Reproduced with the permission from [7])

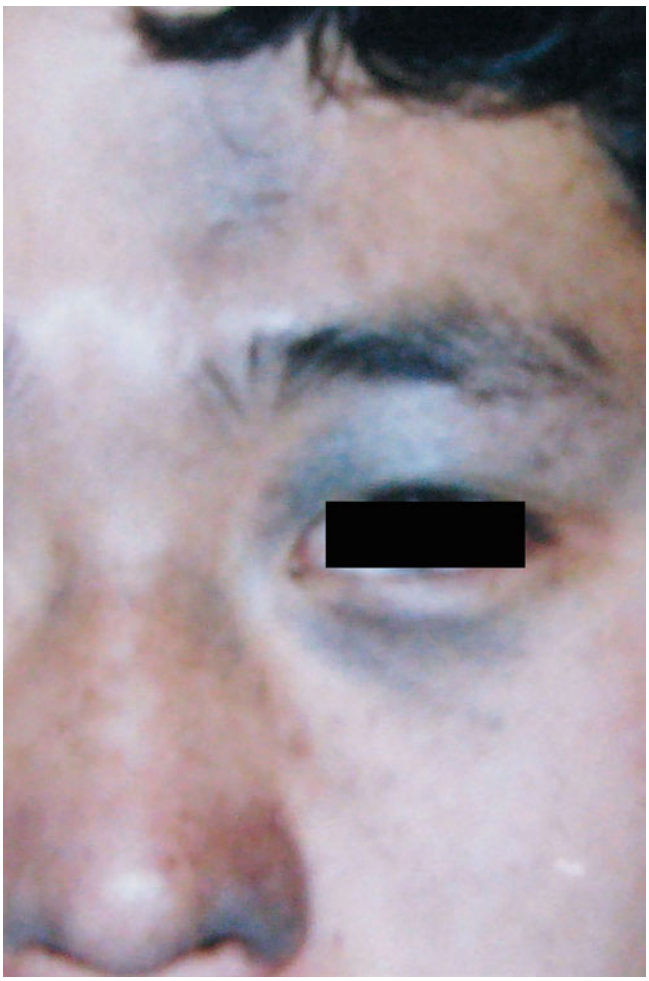


Fig. 19-6a-2 Spotted pigmentation limited to the zygomatic region (Reproduced with the permission from [7])

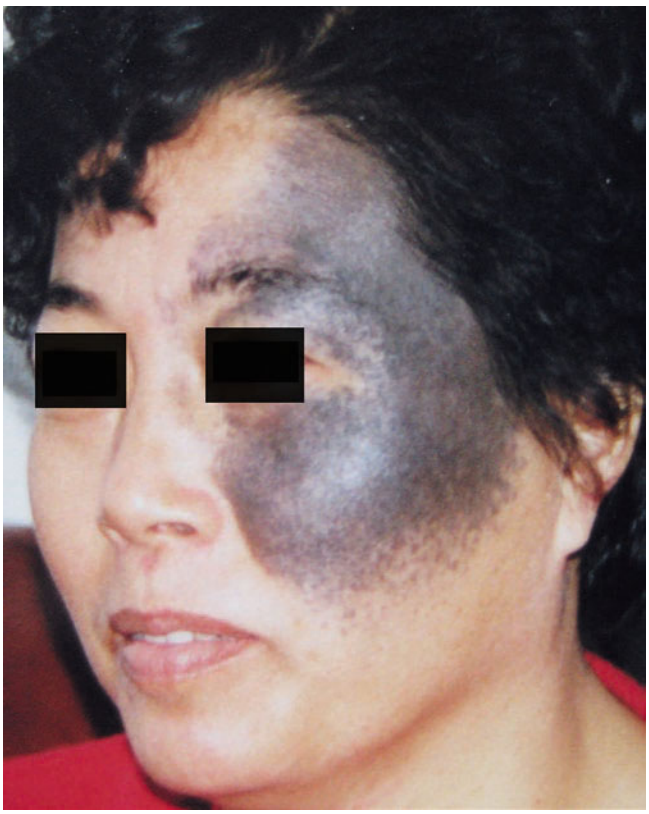


Fig. 19-6b-1 Pigmentary spots limited to the eyelids and zygomatic and nose region (Reproduced with the permission from [7])

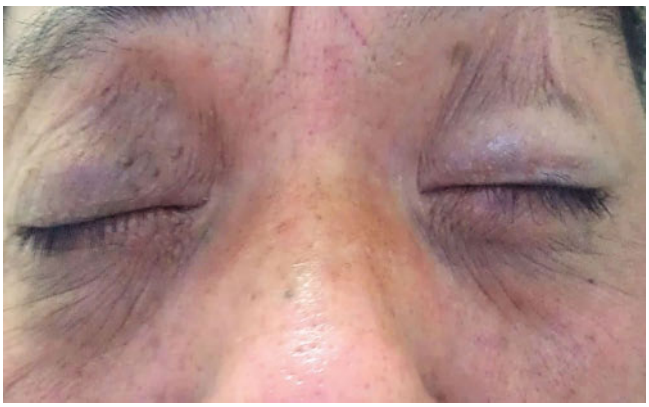


Fig. 19-6c-1 Pigmentary spots on the eyelids, zygomatic and nose region, and forehead

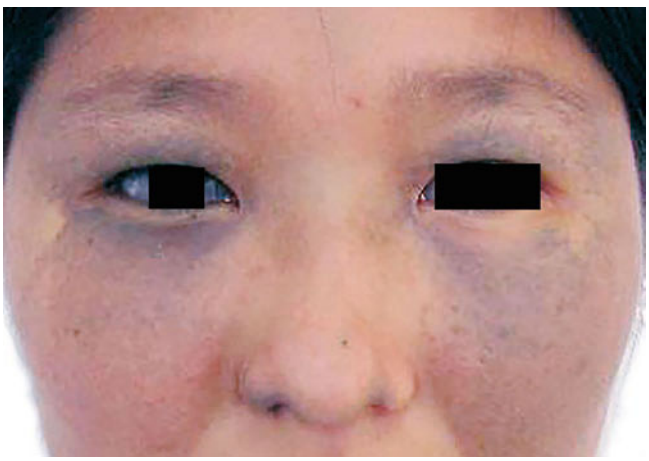


Fig. 19-6d-1 Bilateral pigmentation affected both sides of the face (Reproduced with the permission from [7])

19.7 Ota Nevus Associated with Nevus Flammeus [8]

- Nevus flammeus, which is common around the peripheral nerve, is a pink or deep royal purple macular vascular malformation.
- The nevus of Ota is a distinctive, congenital, benign, pigmented lesion, which usually occurs unilaterally, particularly affecting the skin of the periorbital region.
- During embryonic development, neural crest cells may be disturbed by an overlying vascular malformation, such as nevus flammeus, affecting the migration of chromocytes (both ocular and non-ocular). This process would explain why Ota nevus and nevus flammeus appear in one patient.
- This concomitant situation is extremely unusual, and it should alert the physician to the possibility of the existence of a severe outflow obstruction and glaucoma.

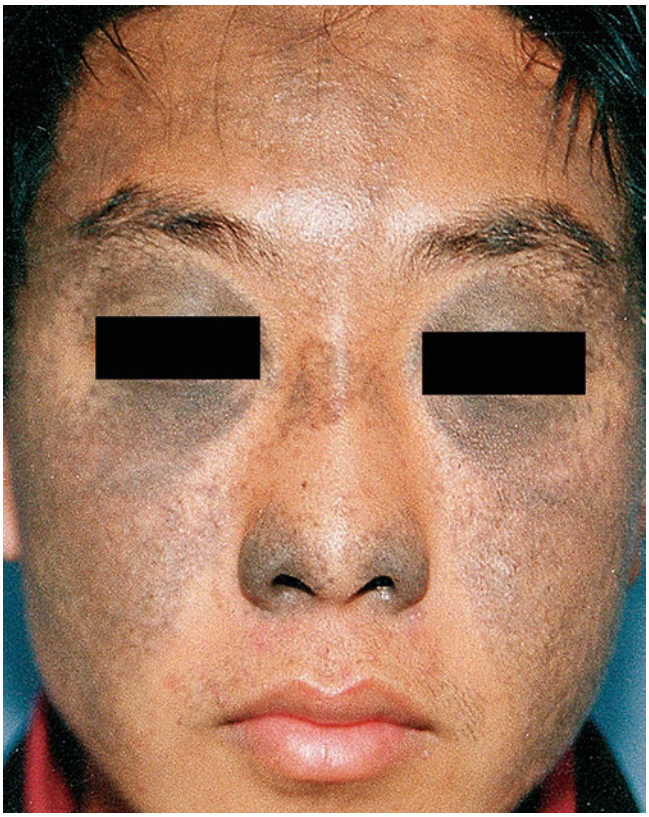


Fig. 19-7-1 Symmetrical bluish and brownish macules on the face (Reproduced with the permission from [8])

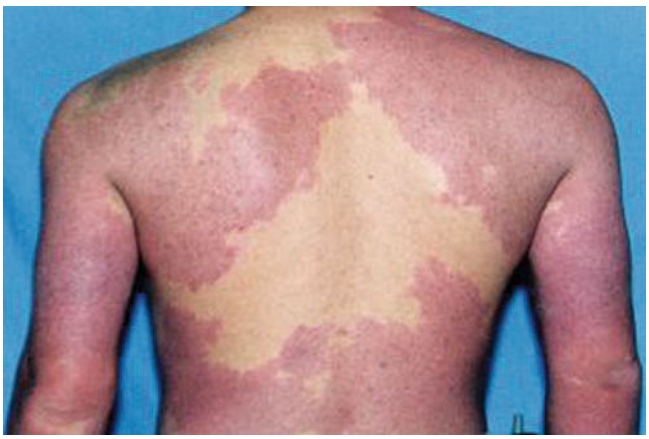


Fig. 19-7-2 Erythematous patches on the upper limbs, hands, chest, shoulder blade, waist, and sacrum

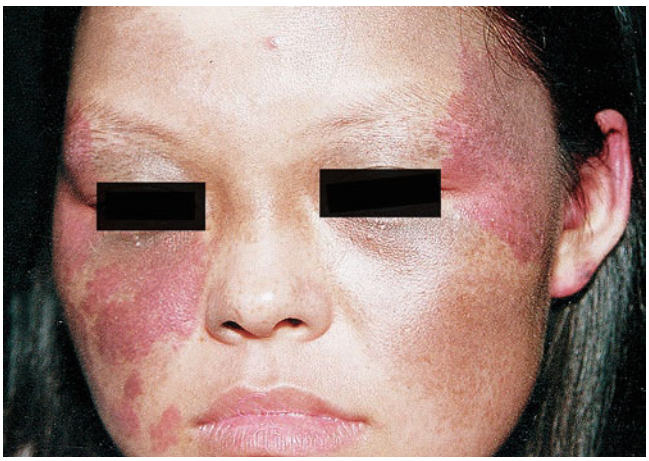


Fig. 19-7-3 Symmetrical brownish macules on the forehead and periorbital area (Reproduced with the permission from [8])

19.8 Partial Depigmentation Arising from the Nevus of Ito [9]

- Nevus of Ito, a rare demonstration of dermal melanocytosis, is a bluish-gray pigmentation distributed over the supraclavicular, scapular, and deltoid region.
- Progressive depigmentation which arises in the nevus of Ito is perhaps a kind of "halo phenomenon," which is commonly described as a sharp zone of hypopigmentation around the pigmented nevi.
- Malignant transformation rarely occurs in the nevus of Ito.

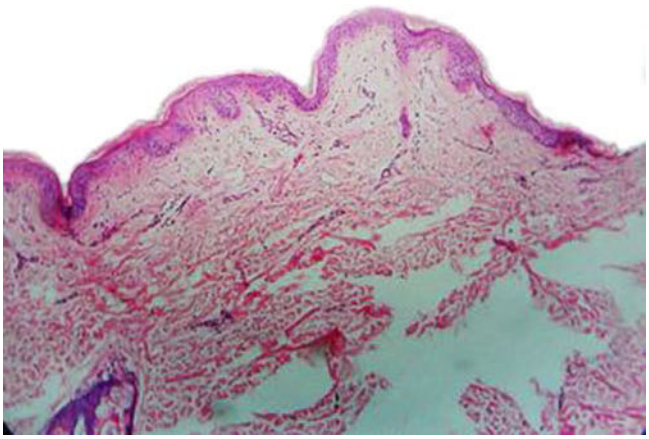


Fig. 19-8-2 Skin biopsy of the lesion showed few lymphocytes were scattered around capillaries in the superficial dermis (HE stain, ×40)

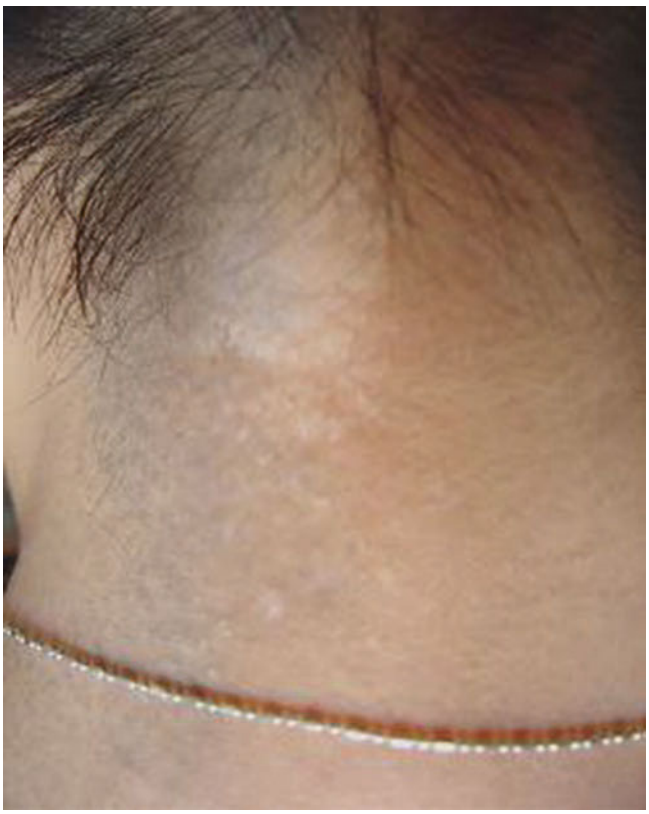


Fig. 19-8-1 Triphasic pigmentations varied from porcelain white, sapphire, to brownish blue in the lateral side. It runs from the mid-neck to its left side. The lower part of the lesion consisted of many confetti-like hypopigmented macules ranging from 2 to 5 mm. These lesions were sparsely distributed, some of which were coalesced to be polygonal (Reproduced with the permission from [10])

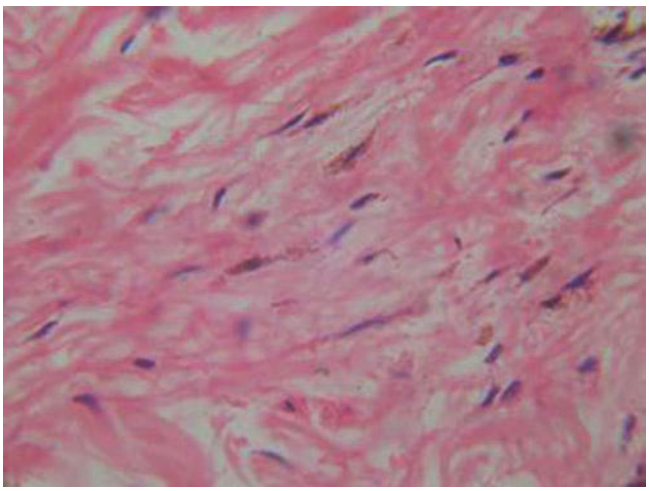


Fig. 19-8-3 In the mid-dermis, residual spindle-shaped melanocytes are distributed paralleling the long axis of the collagen (HE stain, ×400)

19.9 Acquired Bilateral Nevus of Ota-Like Macules [11]

- Acquired bilateral nevus of Ota-like macules (ABNOM), the other name is Hori's nevus, is categorized as an acquired dermal melanocytosis (ADM), which often appears in the third or fourth decade of life and appears as a conspicuous preponderance in Asian woman.
- ABNOM is featured by multiple macules with brown-blue and/or slate-gray color. It occurs bilaterally on the malar regions or less commonly on the forehead, palpebra superior, nose, and both sides of the face.
- The origin of the dermal melanocytes and the pathogenesis of ABNOM remain little understood. It has been presumed that dermal melanocytes appear at the time that melanocytes migrating from the neural crest during embryological development are unable to reach their target place in the stratum basal epidermidis.
- QS lasers, such as the QS alexandrite laser and QS ruby laser, all have been used for the treatment of ABNOM.

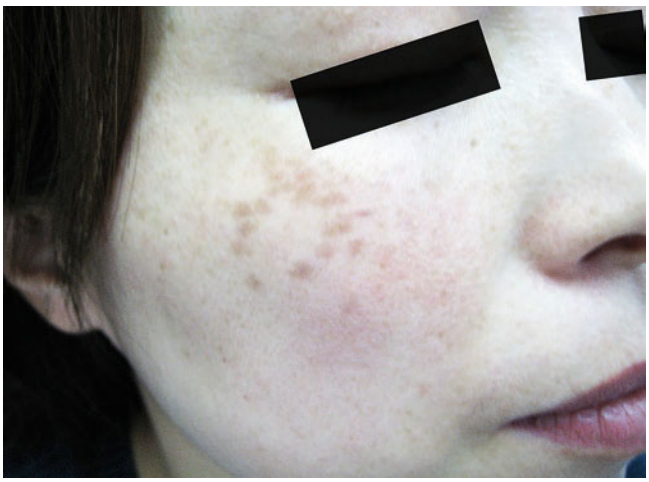


Fig. 19-9-1 A triangular deep-gray patch in the zygomatic arch area; the color was ununiform. The skin over her nasal dorsum was ecru; on the contrary, the skin on the medial angle of her eyes appeared dim or blue-brown. The pigmented borders were jagged (Reproduced with the permission from [11])

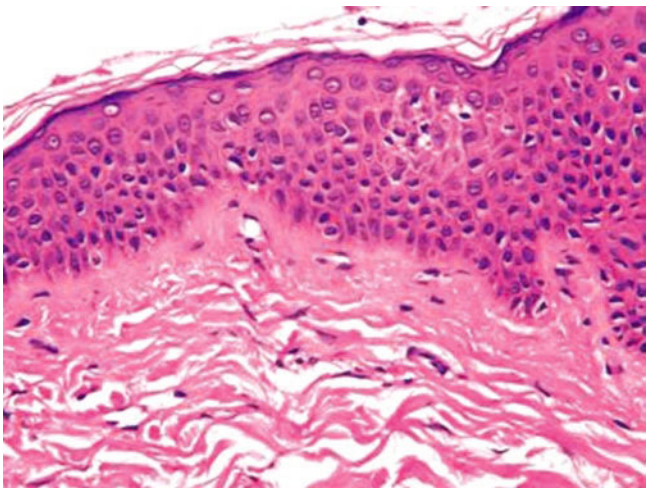


Fig. 19-9-2 Histologic and immunohistochemical examination showed proliferated melanocytes and increased melanin in the keratinocytes but no elongation of the rete ridges (HE stain, ×200)

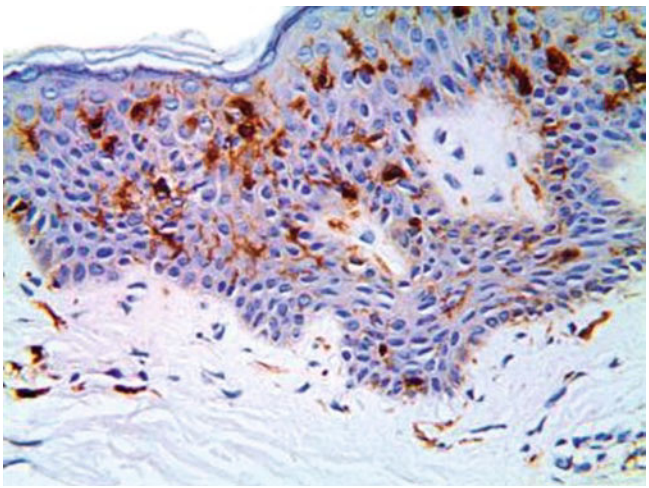
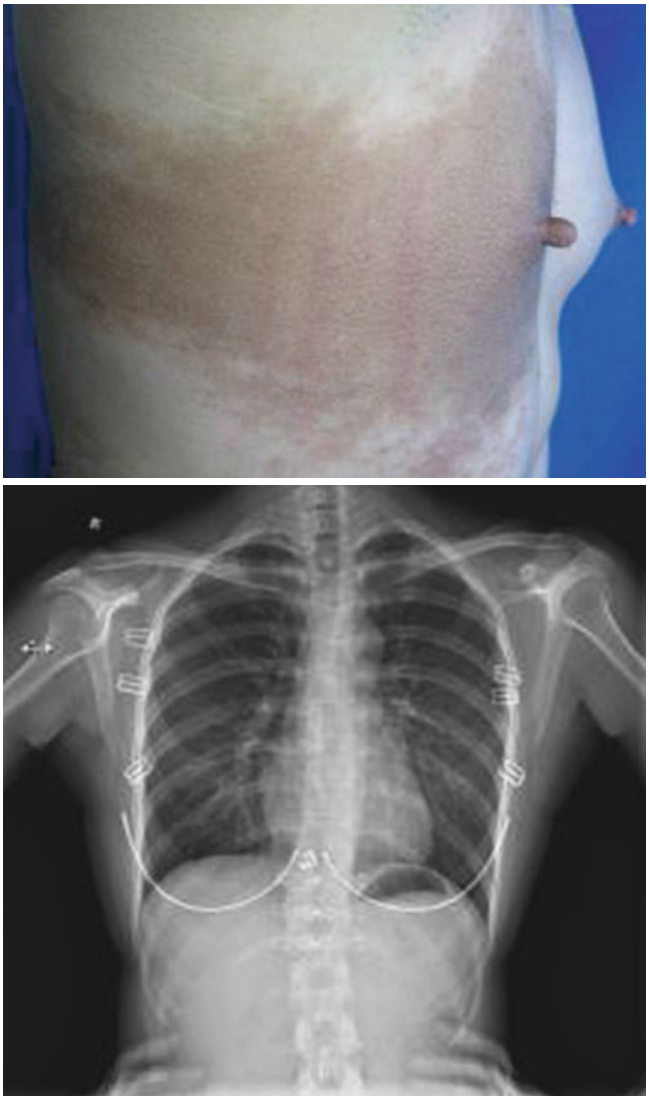


Fig. 19-9-3 Melanocytes were bipolar or dendritic and were sparsely distributed in the reticular dermis and were noticeably pigmented (S100 staining ×200)

19.10 Becker's Nevus Syndrome [12]

- Becker's nevus commonly develops or extends at puberty.Sharply demarcated hyperpigmented macule or patch with coarse dark hair is seen on the anterior chest, shoulder, scapula, or upper arm.
- In patients with Becker's syndrome, many isolated defects such as breast hypoplasia, skeletal abnormalities (scoliosis, hemivertebra, spina bifida occulta, and cervical ribs), cystic lymphangioma, and ipsilateral foot enlargement have been described.
- Microscopically, there is a pronounced hyperpigmentation in the epidermal without melanocytic proliferation.



Figs. 19-10-1, 19-10-2 A large, sharply demarcated, hyperpigmented macula was seen on the right chest and back with a few vellus hairs. They were 1–2 cm long with concomitant breast dysplasia (1) and scoliosis (2)

19.11 Acne Confined to Becker's Nevus [13]

- Becker's nevus is a long-lasting, demarcated skin melanosis. It usually appears around puberty with commitment hypertrichosis over the pigmented patch.
- High 5α-reductase activity or androgen hypersensitivity may be attributed to this kind of coincidence.
- On the upper arm, shoulder, scapula, or anterior chest, there were well-demarcated hyperpigmented macules or patches with coarse dark hair.
- Lichen planus, lymphangioma, granuloma annulare, pityriasis versicolor, hypohidrosis, vitiligo, and basal cell carcinoma have been anecdotally reported with Becker's nevus.
- Histopathologically, the melanocyte count is normal without nevus cells. However, the melanin is increased in the epidermis.

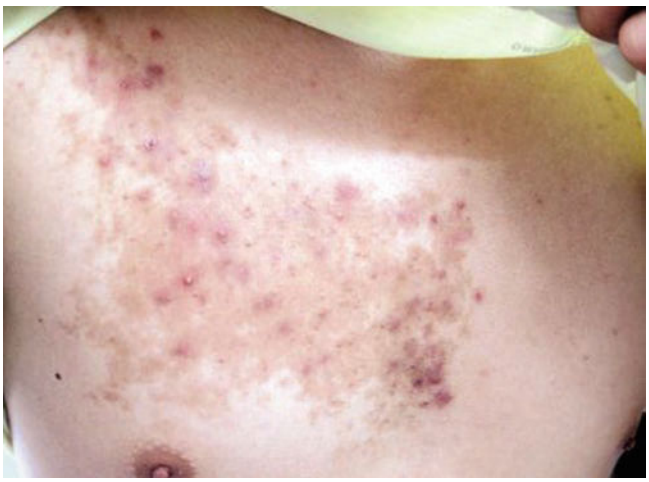


Fig. 19-11-1 Brownish macules presented on the right chest. The hair in the macules was slightly thicker than normal. Comedones, inflammatory follicular papules, and cysts were strictly confined within the pigmented macules

19.12 Neurocutaneous Melanosis [14]

- Neurocutaneousmelanosis (NCM) was first described in 1861 by Rokitansky and named by Van Bongaert in 1948. This condition presents melanocyte tumors in the pia mater of the central nervous system and congenital melanocyte nevi on the skin.
- The pathogenesis of NCM may be associated with NRAS transgeneration and the unusual postzygotic development of melanoblasts.
- A small number have symptoms, including papilledema, cranial palsies, headache, vomiting, and seizures, usually present before the age of 2 years.
- The diagnosis is typically validated through biopsy of the cutaneous lesions and imaging of the central nervous system. It is vital to ensure that the skin lesions are innocuous.
- Most patients are asymptomatic and have a good prognosis. Patients with symptoms have a poor prognosis.

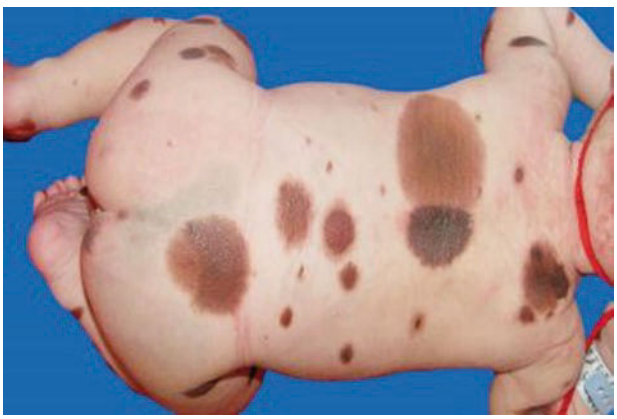


Fig. 19-12-1 Multiple giant congenital melanotic nevi on the back and extremities

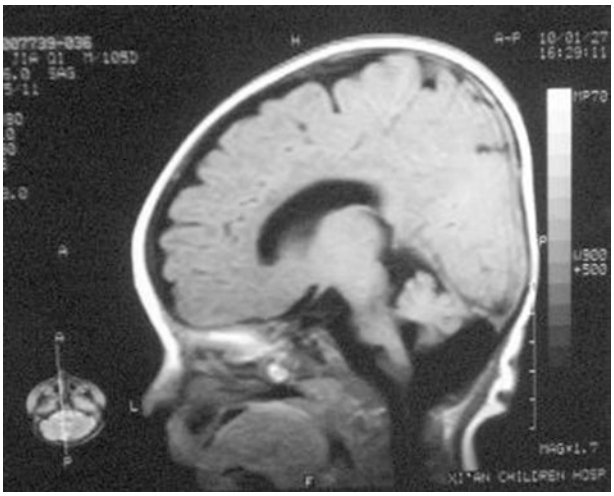


Fig. 19-12-2 Magnetic resonance imaging showed enlarged lateral ventricles, cerebellomedullary cistern, epicele, and hydrocephalus, which were in compatible with features in Dandy-Walker syndrome

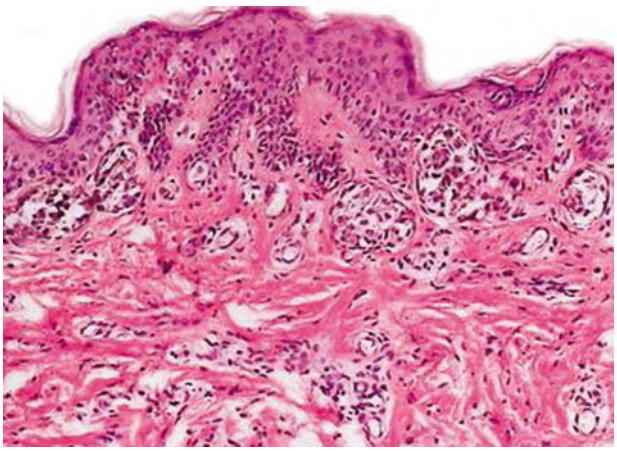


Fig. 19-12-3 Nested nevocytes were mainly distributed in the basilar layer and the superficial dermis, extending to deep dermis. The appendages were infiltrated with these tumor cells; some nevocytes were mature without karyokinesis; mild mononuclear cell infiltration and melanophage were noted in the dermis

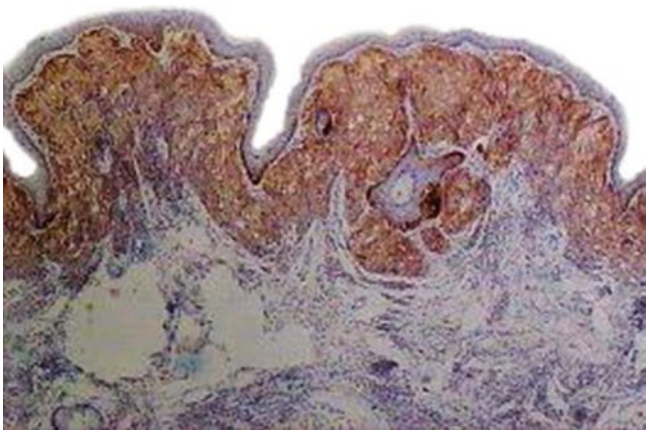
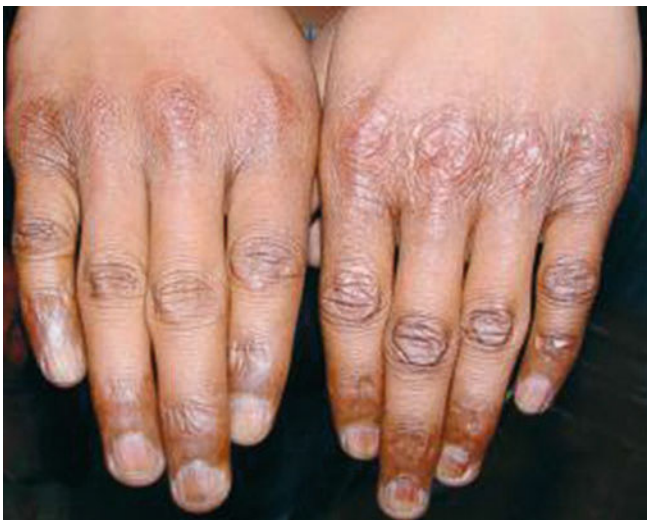
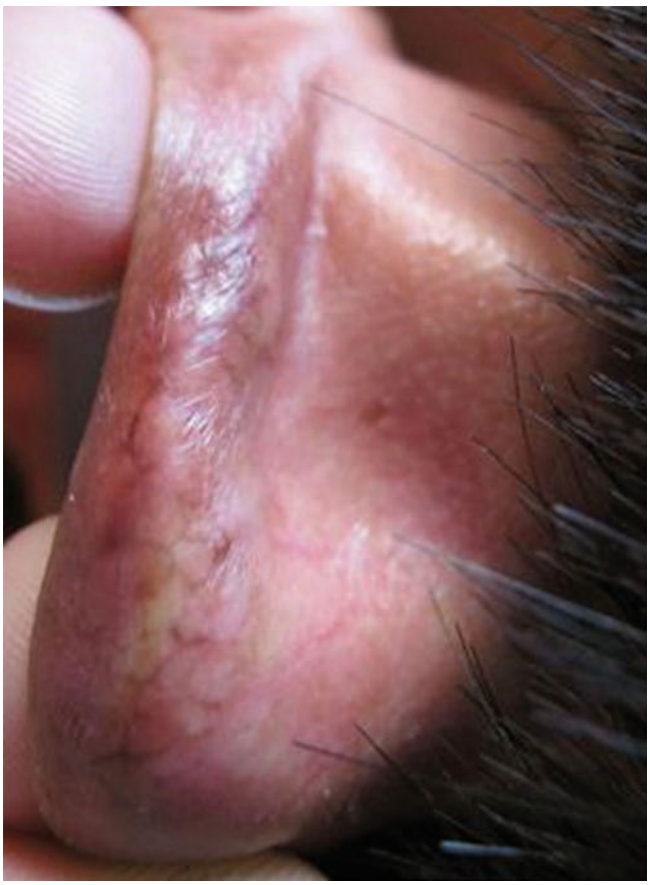


Fig. 19-12-4 Nevocytes were positively stained by HMB45

19.13 Progressive Acromelanosis [15]

- Progressive acropigmentation reported by Furuya and Mishimais in 1962 is a pigmentary condition in infancy. The hyperpigmentation is restricted to the fingers and toes. However, the cervical region, cheeks, and limbs may eventually become involved.
- Histologically, melanocyte proliferation in a palisade arrangement at the epidermal-dermal junction is observed, in association with hyperkeratosis and papillomatosis.
- Differential diagnosis includes a wide variety of systemic and dermatologic conditions, especially dermatoses with macular hyperpigmentation in an acral distribution.





Figs. 19-13-1, 19-13-2 Diffuse dark-brown patches on the acromelic areas of the fingers and both auricles; brown striated pigmentation on the nails and flexor aspect of interphalangeal joints; spider weblike brown maculae on both auricles

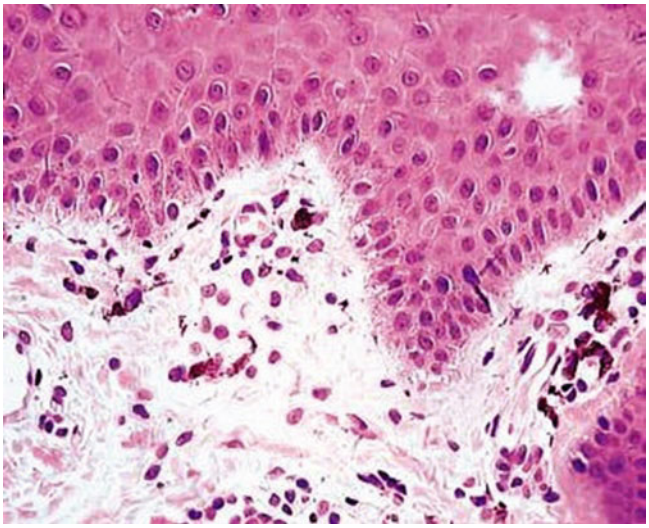


Fig. 19-13-3 Melanocytes were increased in clusters in basal layer without vacuolar changes of the basal cells; in addition, mild lymphocytic infiltration and numerous melanophages were presented in the dermis (HE stain, ×400)

19.14 Periorbital Melanosis [16]

- "Dark circles" is an alternative term to designate the darkened infraorbital skin by nonmedical professions.
- Dermal melanocytosis and post-inflammatory hyperpigmentation are two possible causes for the hyperpigmentation of the infraorbital skin.
- Topical depigmenting chemicals, laser therapy, and chemical peeling serve as the mainstay of treatment.

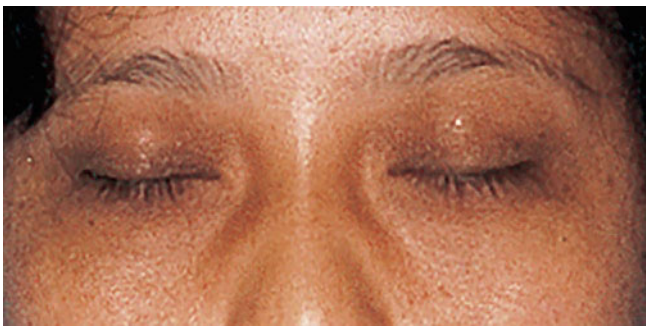


Fig. 19-14-1 Mild periorbital hyperpigmentation (elder sister)

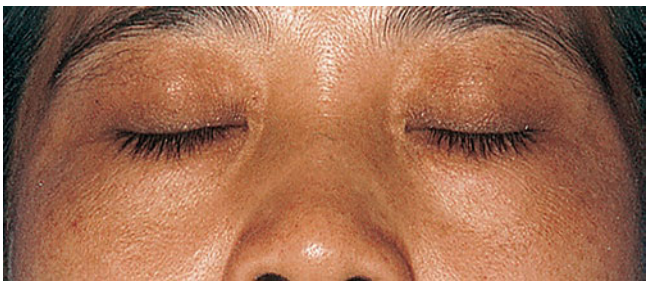
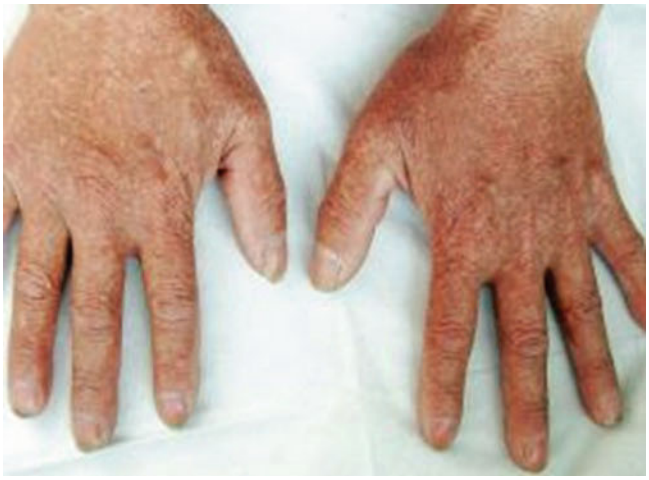
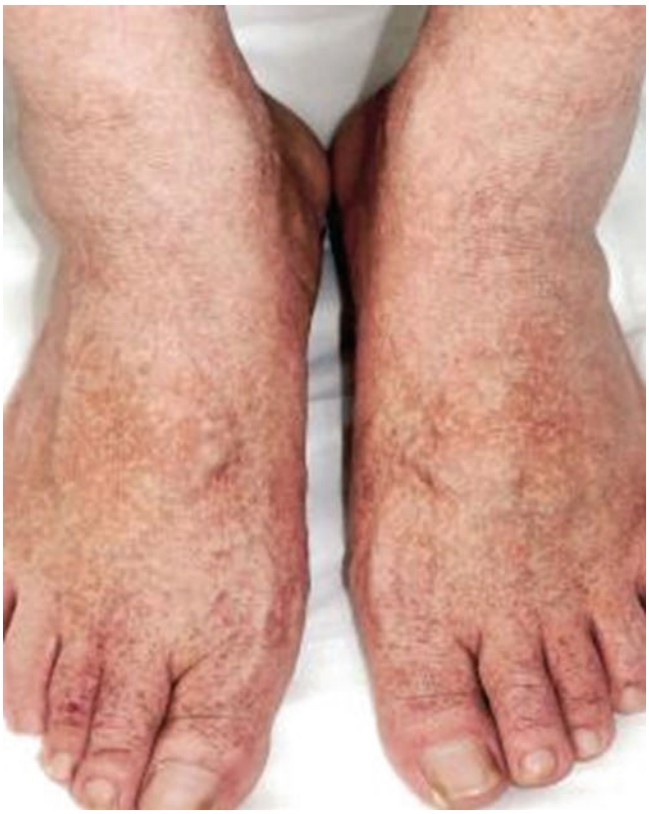


Fig. 19-14-2 Mild periorbital hyperpigmentation (younger sister)

19.15 Reticulate Acropigmentation of Kitamura [17]

- Reticulate acropigmentation of Kitamura (RAPK) is an autosomal dominant disease with a slight preponderance in females.
- The typical hyperpigmented, atrophic, angulated macules generally start before 10 years or 20 years of age over the dorsum of the hands and increasingly extend onto the extremities.
- Skin biopsy presents with epidermal atrophy, elongation of the rete ridges, as well as abundant melanin deposit in the basal layer.
- Treatment is generally not very effective, but 20% azelaic acid, topical hydroquinone, systemic retinoids, topical corticosteroids, and phototherapy provide minimal improvement.





Figs. 19-15-1, 19-15-2 Slightly depressed hyperpigmented macules were reticulated on both dorsal hands and feet

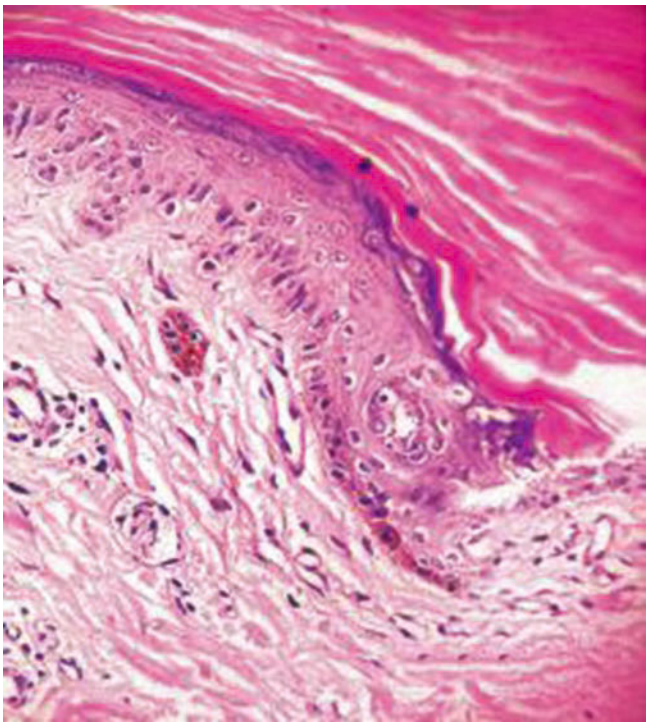


Fig. 19-15-3 Hyperkeratosis and hyperpigmentation of the basal layer (HE stain ×200)

19.16 Kindler Syndrome [18]

- Kindler syndrome is a genodermatosis with an autosomal recessive mode of inheritance, resulting from homozygous mutations in both alleles of the KIND-1 gene encoding the protein kindlin-1.
- The disease is characterized by progressive poikiloderma with widespread adermotrophia, early baby skin blistering, and slight photosensitivity, and those symptoms gradually diminish with age.
- Ultrastructural examination shows alterable levels of cleavage and remarkable basement membrane reduplication at the dermal-epidermal junction.
- Diagnosis is based on clinical evidence. Differential diagnosis includes congenital epidermolysis bullosa, Weary's syndrome, and other bullous hereditary poikilodermas.

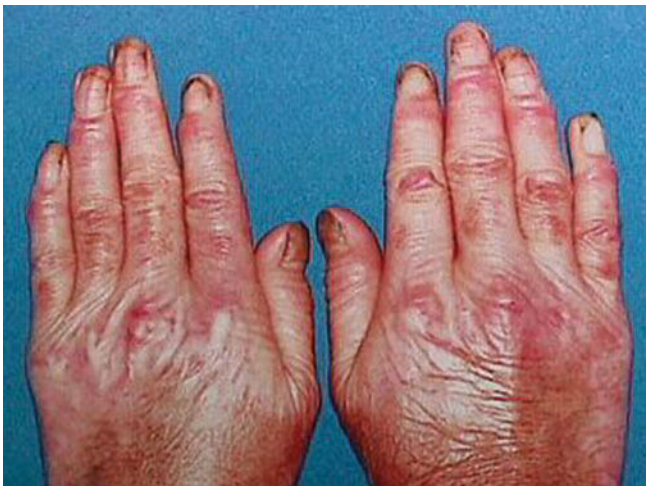


Fig. 19-16-1 Skin atrophy on the dorsa of both hands with dystrophic nails

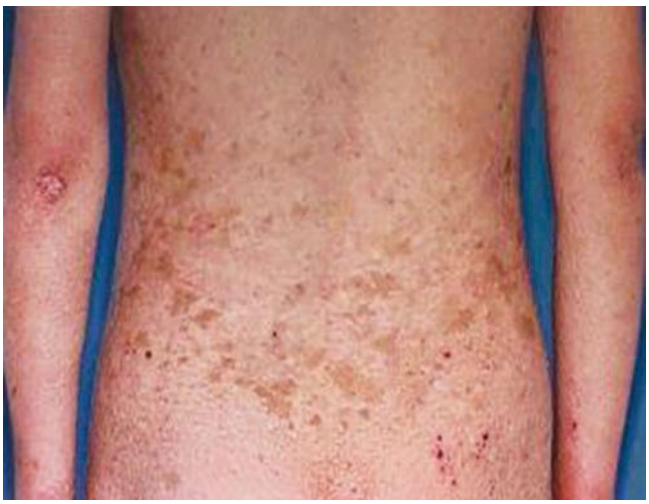


Fig. 19-16-2 Poikilodermatous changes on the waist and back

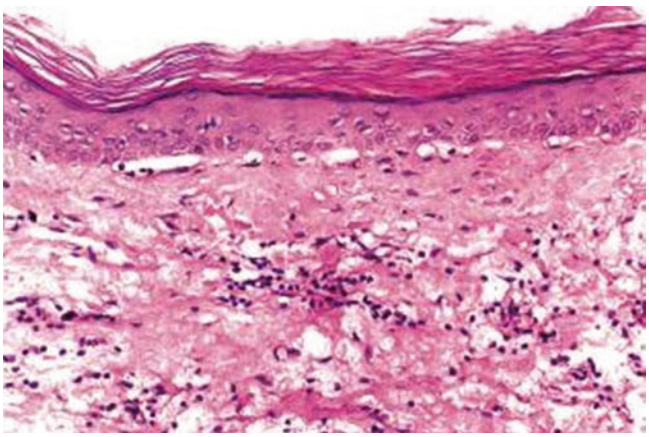


Fig. 19-16-3 Epidermal atrophy, hydropic degeneration of basal cells, and inflammatory infiltration around the capillaries (HE stain, ×100)

19.17 Dowling-Degos Disease [19]

- Dowling-Degos disease (DDD) is an inherited disorder with another name of reticulate pigmented anomaly of flexures. The proposed pathogenesis is a mutation on chromosome 12, leading to melanosome uptake deficiencies and structural defects in hair follicles and sebaceous glands.
- Clinical features are many small, asymptomatic, round, pigmented macules in the armpits and inguinal region, cheeks, trunk, arms, and cervical region, associated with pitted acneiform scars and scattered comedo-like lesions.
- The histologic features consist of filiform elongation of rete ridges with an antler-like configuration. There are many III–IV and few I–II stage melanosomes in melanocytes from DDD lesions.There has been no effective treatment to date. A combination of fractional (CO2) lasers and Q-switched Nd:YAG may be a modality with prosperous outcomes.

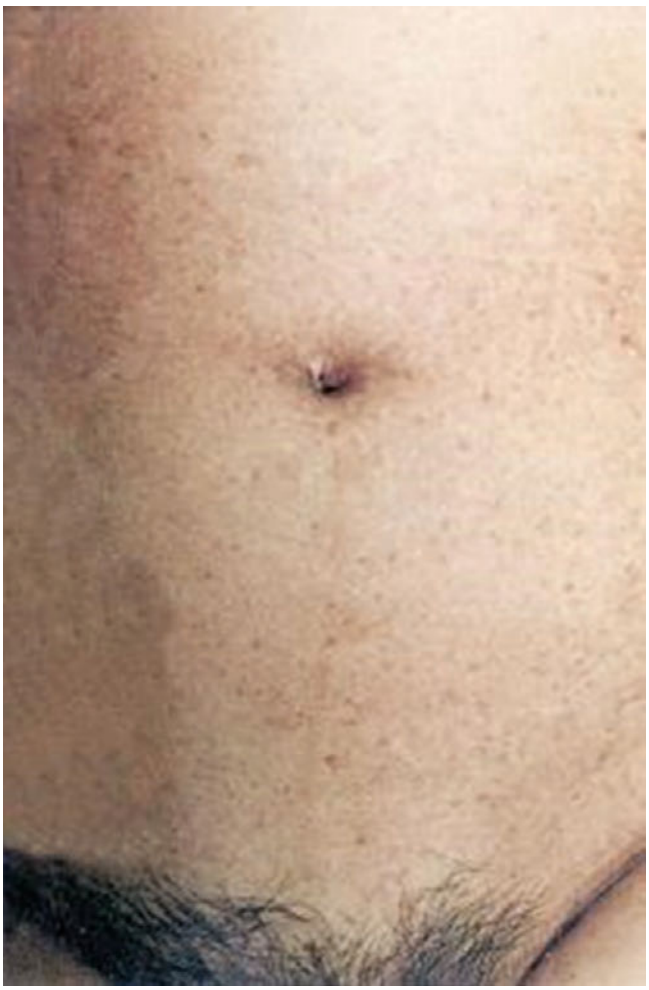


Fig. 19-17-1 Dark-brown spots on the abdomen

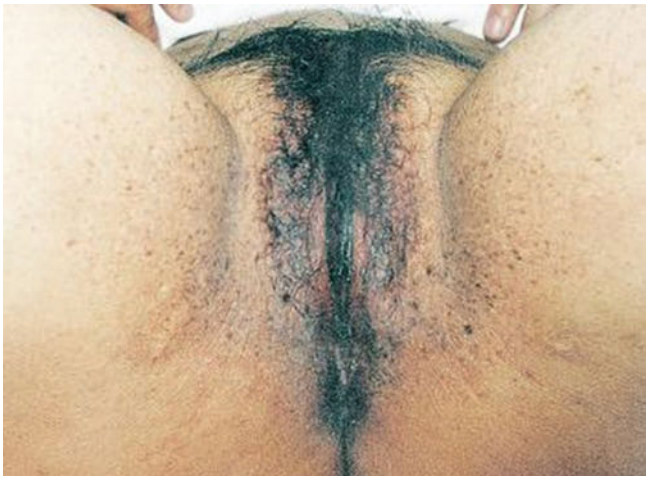


Fig. 19-17-2 Reticular pigmented macules on the vulva and both inner sides of the thighs

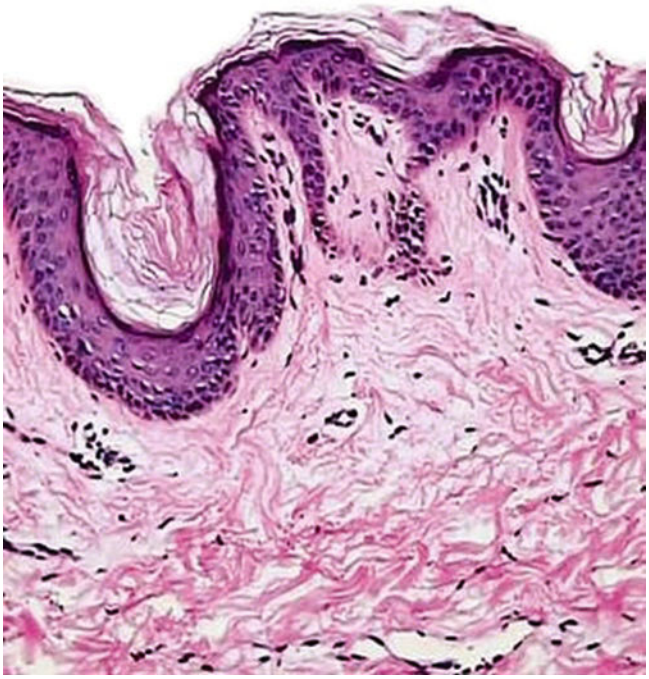


Fig. 19-17-3 Pronounced follicular plugging, rete ridge elongation, and hyperpigmentation of the basal layer. Perivascular lymphohistiocytic infiltration and melanophages in the papillary dermis (HE stain, ×100)

19.18 Macromelanosomes in Dyschromatosis Universalis Hereditaria [20]

- Dyschromatosis universalis hereditaria (DUH) is an unusual inherited skin disease. It typically presents with numerous, reticulated, hypo- and hyperpigmented spots spread in the entire extremities and the trunk.
- Mutation of the ABCB6 gene results in a defection of maturation and transfer of the melanosome. Macromelanosomes are 1- to 7-ìm-sized spherical structures with dark-brown or golden particles.
- Macromelanosomes are commonly observed as Hermansky-Pudlak syndrome, LEOPARD syndrome, B-K mole syndrome, nevus spilus, X-linked ocular albinism, Chediak-Higashi syndrome, xeroderma pigmentosum, malignant melanoma, melanocytic compound nevus, dysplastic melanocytic nevus, and café au lait spots.
- Macromelanosomes are rarely been observed in DUH.

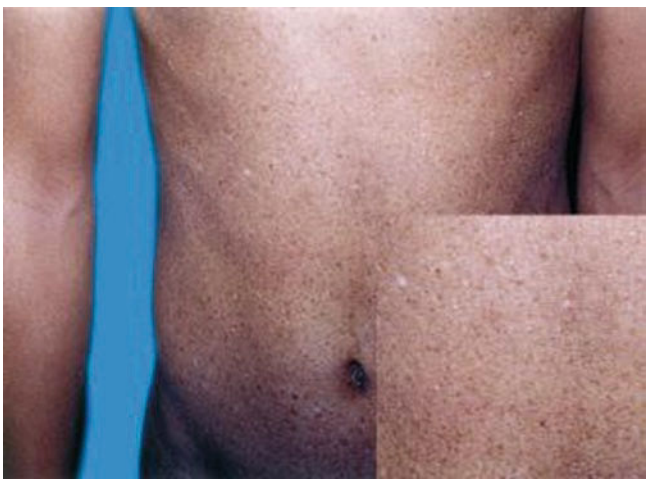


Fig. 19-18-1 Generalized hyperchromic macules mingled with achromic macules on the abdomen (Reproduced with the permission from [21])

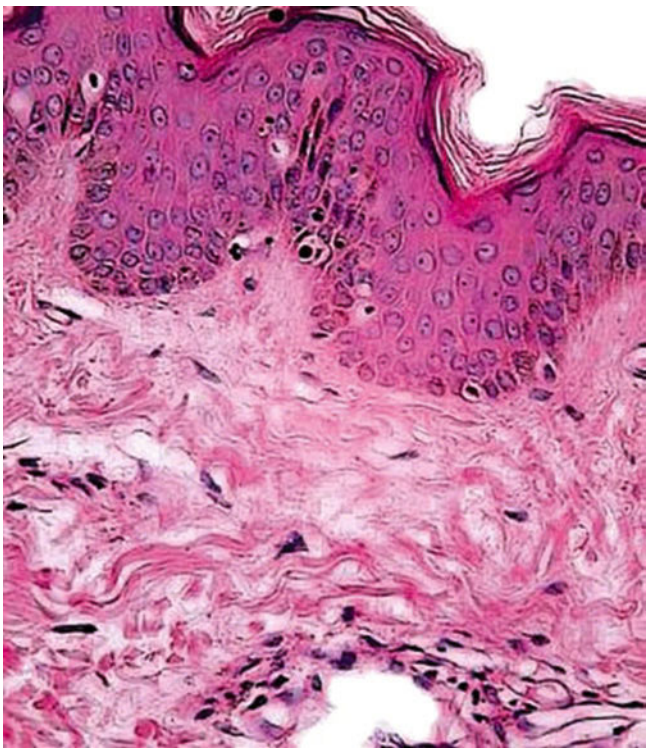


Fig. 19-18-2 Histopathology of the hyperchromic macule shows heavily stained melanin in the basilar layer of the epidermis (HE stain, ×400) (Reproduced with the permission from [21])

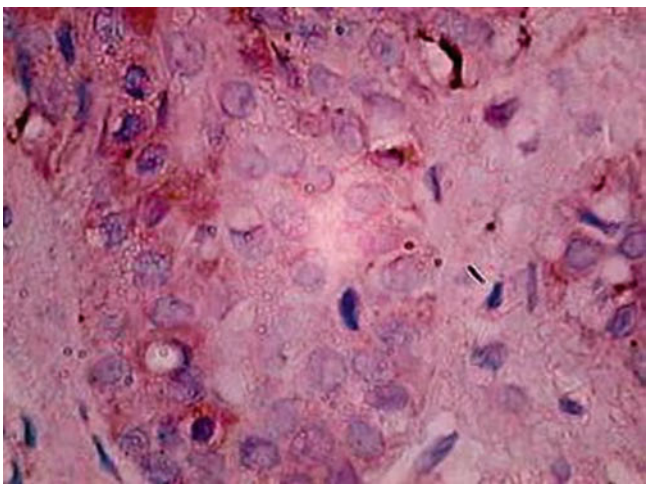
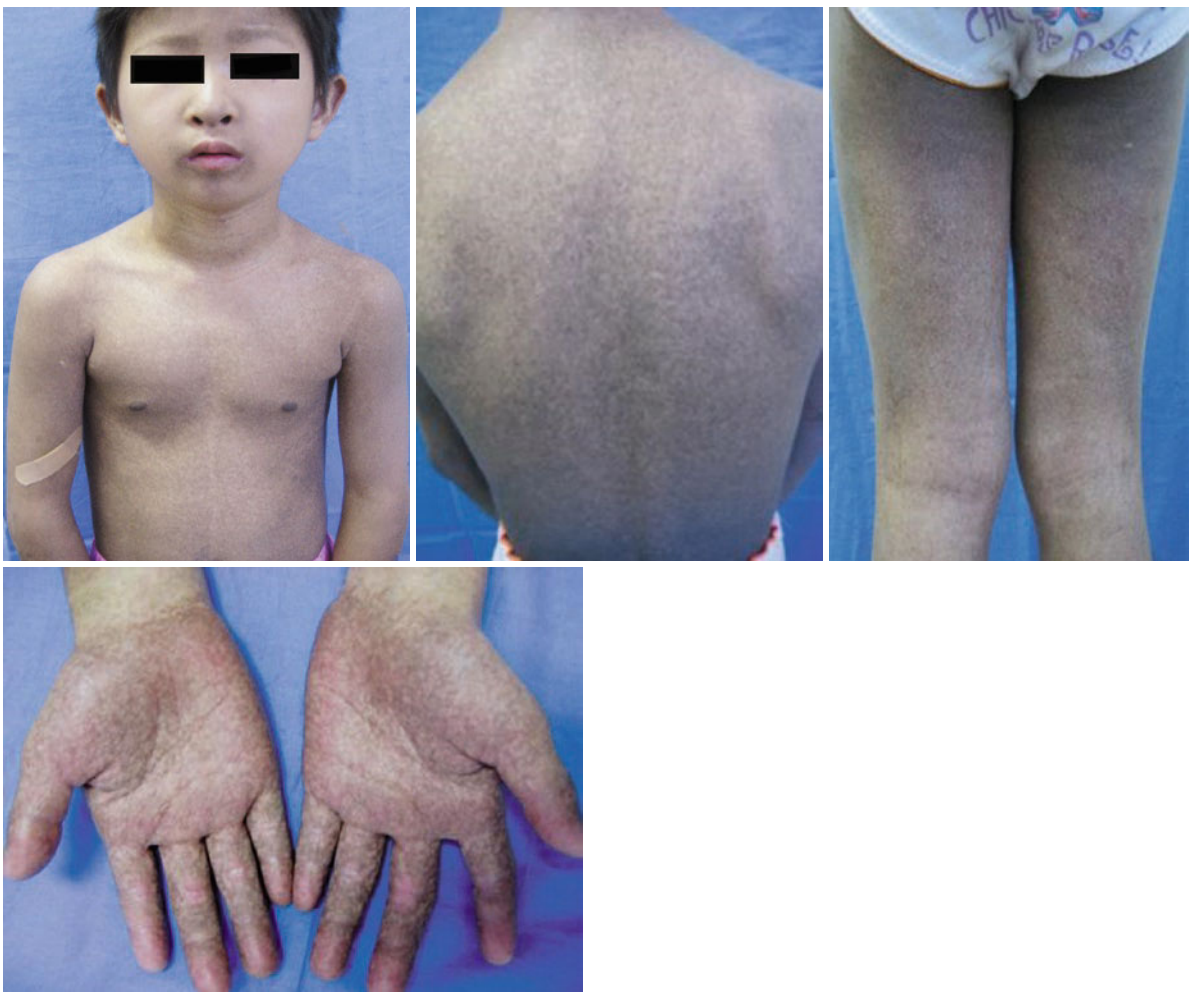


Fig. 19-18-3 Reduced or absence of the melanin with normal amounts of melanocytes in the achromic area (HE stain, ×400)

19.19 Familial Progressive Hyperpigmentation [22]

- Familial progressive hyperpigmentation (FPH) is an autosomal dominant inherited or recessive inherited disease featuring a gradual, progressive, diffuse, generalized skin hyperpigmentation that starts around birth and increases in size and number with age, with no systemic or developmental defects.
- It features intense pigmentation such as bronze, dark brown, and pitch black. The face or groin is initially involved. The oral mucus membranes, including the lips, tongue, buccal mucosa, and hard palate, exhibit a mottled appearance.
- Histologically, the lesion shows a remarkable increase in melanin throughout the epithelium, becoming more obvious in the basal layer, in which the melanocytes are normal in size and quantity.



Figs. 19-19-1, 19-19-2, 19-19-3, and 19-19-4 Hyperpigmented spots generalized the whole body. Other sites of involvement are the perioral area, neck, corpus linguae, thoracic region, and abdominal part (1); shoulder, back, and lumbar parts (2); lower limbs (3); and the palms (4) (Reproduced with the permission from [22])

19.20 Familial Progressive Hypo- and Hyperpigmentation [23]

- Familial progressive hypo- and hyperpigmentation (FPHH) is a skin disorder inherited in autosomal dominant pattern.
- Clinical symptoms include widening, partly scabbed hyperpigmented lesions, and multiple café au lait spots with scattered hypopigmented-appearing lentigines and maculae.
- FPHH differs from familial progressive hyperpigmentation, which exhibits no hypopigmented macules. It shares similarities with dyschromatosis universalis hereditaria phenotypically and histologically.

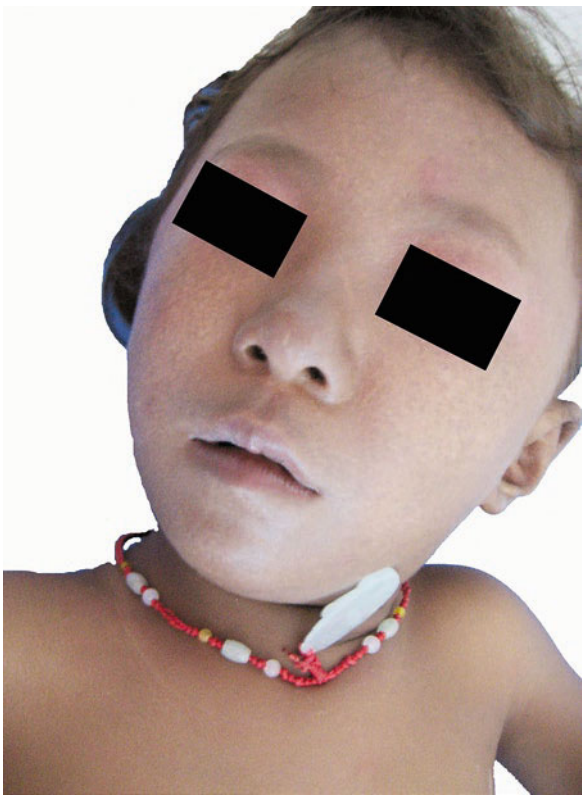
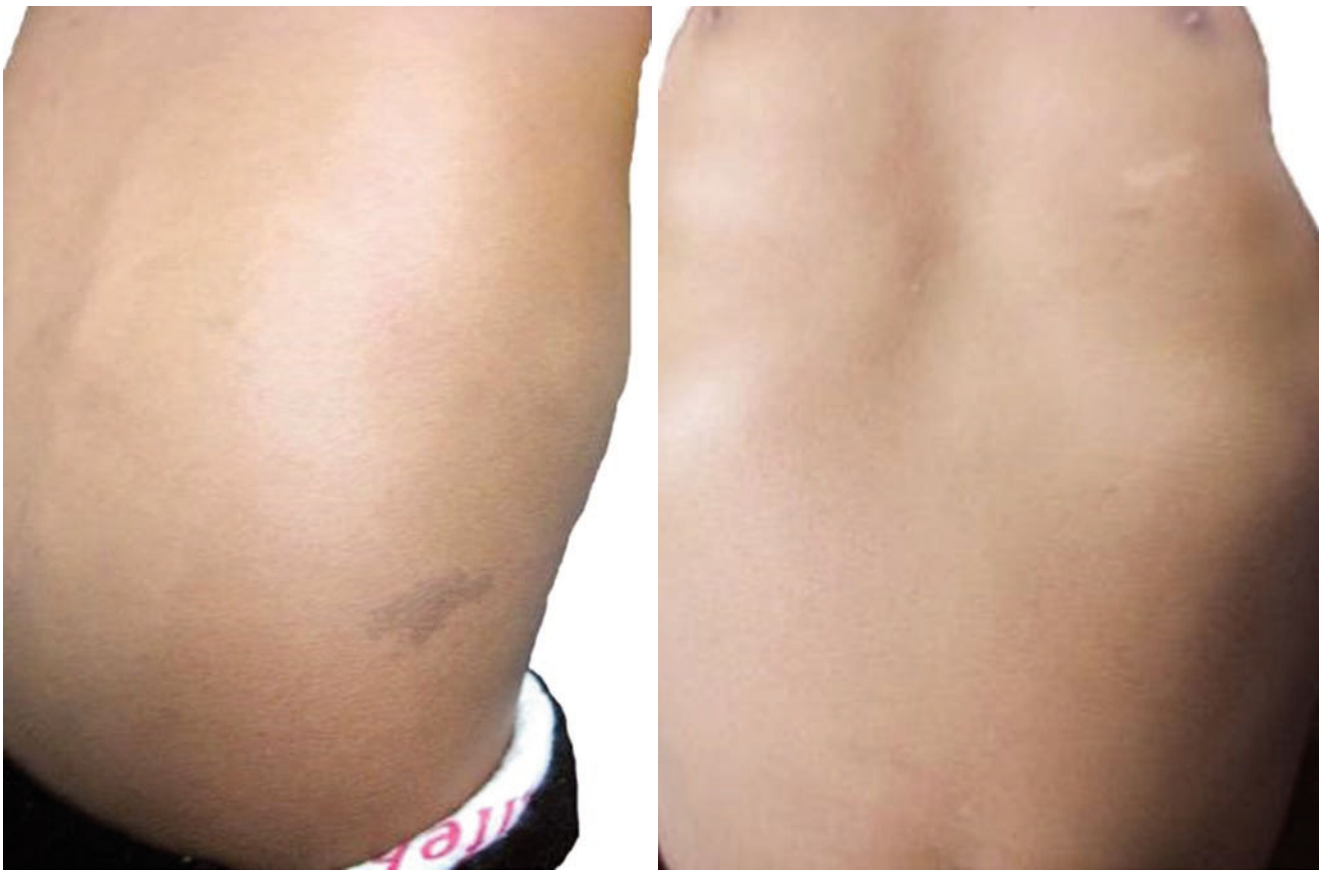


Fig. 19-20-1 Reticulated hyperpigmentation over the face (Reproduced with the permission from [23])



Figs. 19-20-2, 19-20-3 Irregularly shaped café au lait spots, together with the ash-leaf-like white macules, superimposed the uniform deep bronze-brown skin. Lesions on the back; lesions on the chest

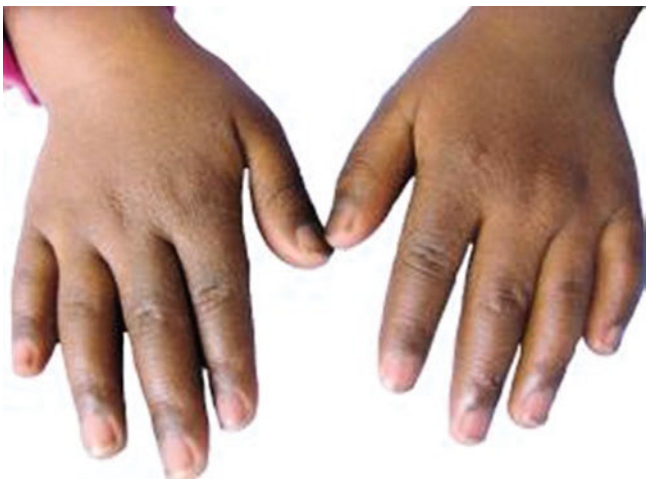


Fig. 19-20-4 Markedly hyperpigmented skin over the knuckles

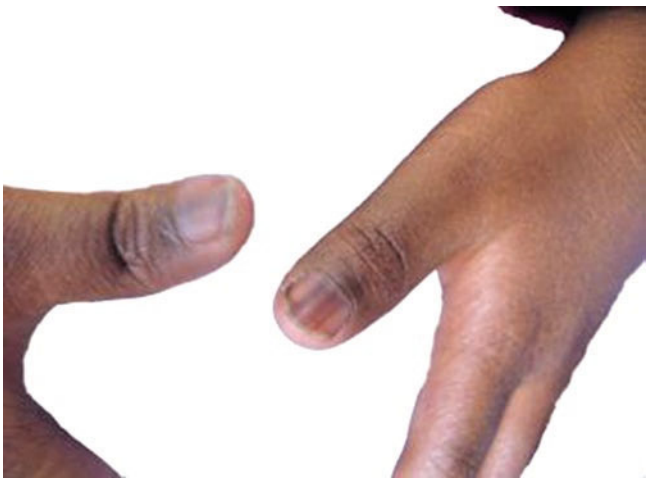
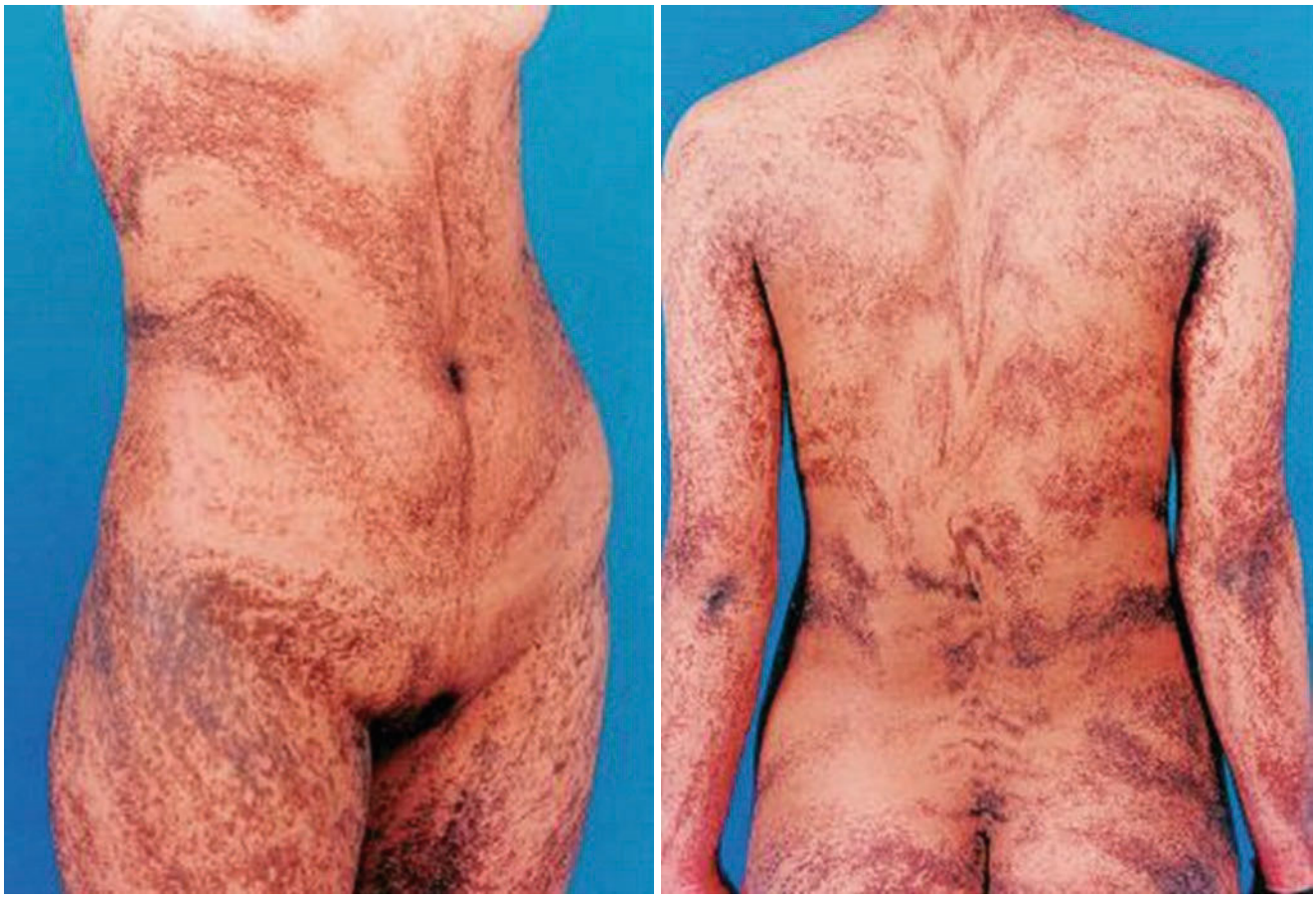


Fig. 19-20-5 Longitudinal melanonychia (multiple bands) on both thumbnails

19.21 Linear and Whorled Nevoid Hypermelanosis [24]

- Linear and whorled nevoid hypermelanosis (LWNH) is resulted from mosaicisms of 7, 14, 18, 20, and X chromosomes.
- Pigmentary macules in LWNH are linear on the extremities, V shaped over the central back, and S shaped or whorled over other parts of the trunk. The genitalia, the soles, the palms, and the mucosae are all spared.
- LWNH begins within the first few weeks after birth and progresses for one to several years before it becomes stabilized. Extracutaneous characteristics include bone, ocular, and nerve function abnormalities.



Figs. 19-21-1, 19-21-2 Linear and whorled hyperpigmentation distributed along the Blaschko's lines on the skin

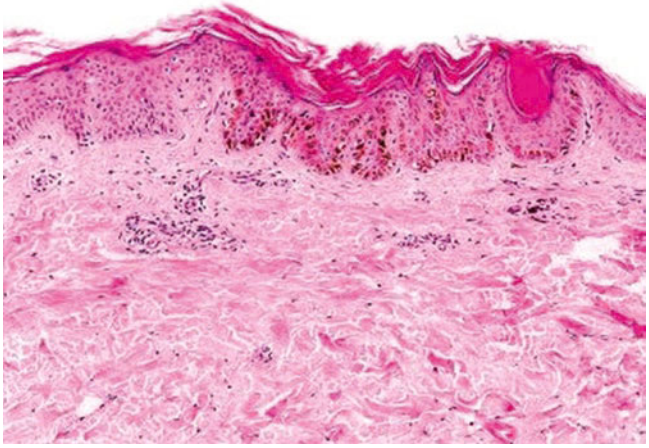


Fig. 19-21-3 Epidermal hyperkeratosis, increased pigmentation, and melanocytes in the basilar layer of the epidermis. A few melanophages were found in the superficial dermis (HE stain, ×100)

19.22 Pointillist Melanotic Macules [25]

- Pointillist melanotic macules (PMMs) are characterized by numerous pigmentary spots and macules involving most part of the skin. Some of the lesions are stellate or to be claw-like.
- Skin biopsy reveals increased basilar hyperpigmentation without melanocyte proliferation.
- Systemic involvement and other dermatological manifestation should be excluded before the establishment of this diagnosis.

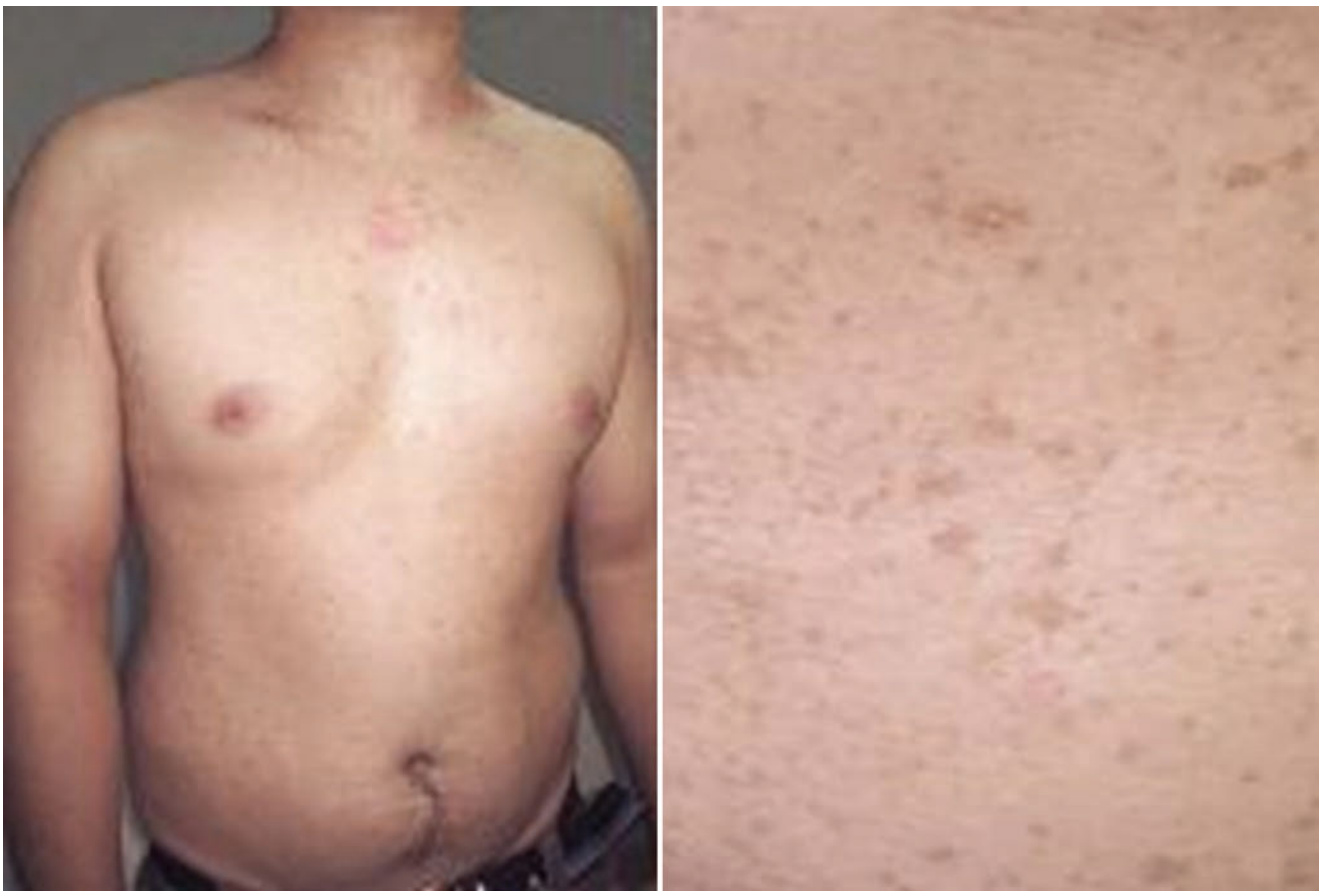


Fig. 19-22-1 The lesions were evenly pigmented in a remarkable stellate configuration. Most of the lesions were pin sized and round to oval. The bizarre spots varied in size, ranging from 0.1 to several centimeters in diameters

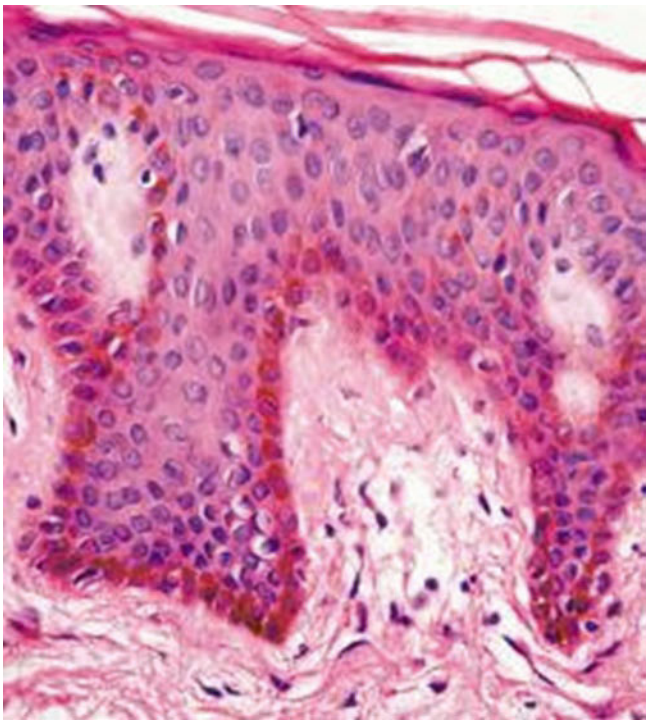
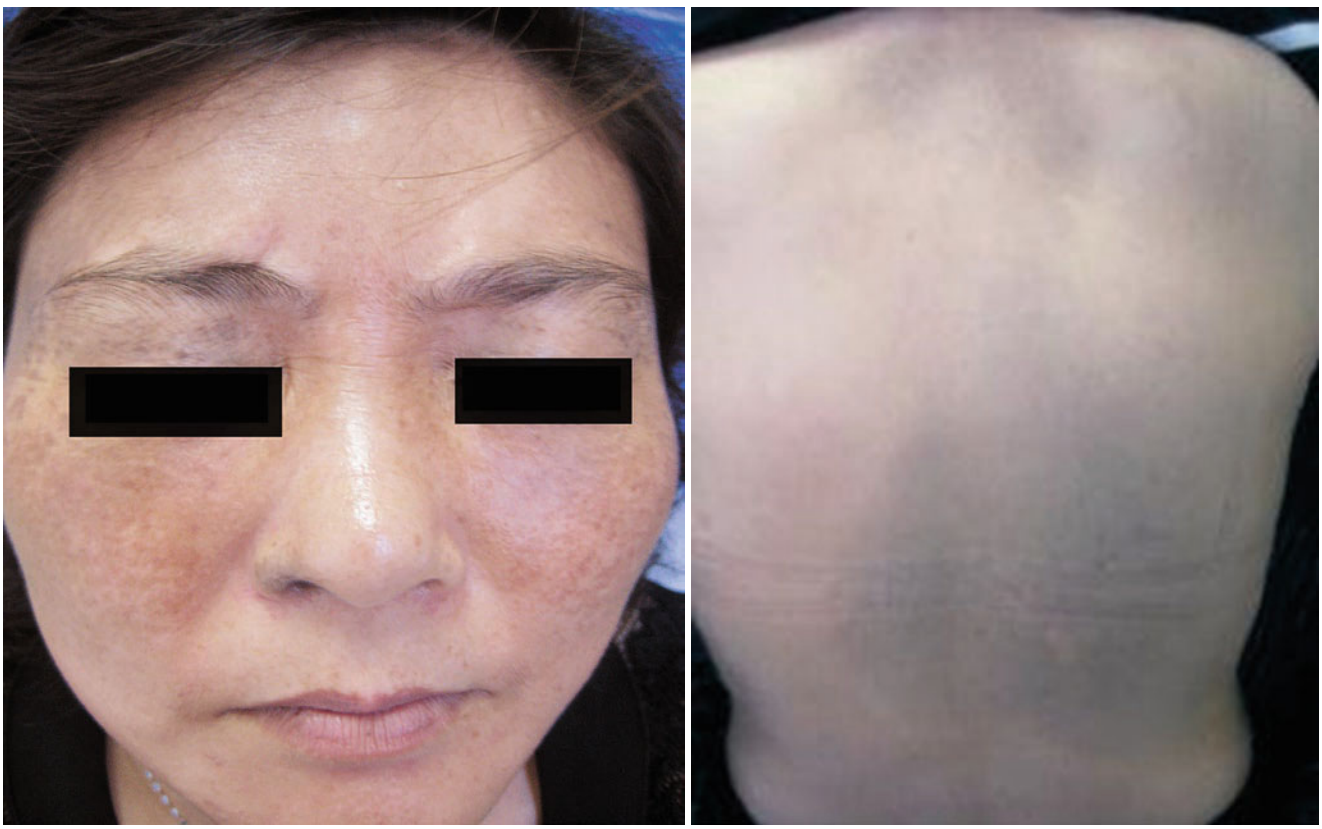


Fig. 19-22-2 The accounts of the melanocytes were normal with pronounced basilar hyperpigmentation (pigmented eye linear sign). Melanophages were seen in the papillary dermis (HE stain, ×400)

19.23 Acquired Dermal Melanocytosis [26]

- Acquired dermal melanocytosis (ADM) generally affects adults. Women are preferentially affected.
- The pigment macules are noted on both palpebral conjunctivae and gingiva. ADM could be divided into localized, linear, and generalized types. It is characterized by multiple sapphire macules on the face, the back, the shoulders, and the upper extremities. The pigmentation macules in several cases of ADM only involve the back and extremities.
- Histopathology: dendritic melanocytes can be observed in the papillary dermis.
- The dormant dermal melanocytes can be reactivated by dermal inflammation and sexual hormones in patients with ADM.



Figs. 19-23-1, 19-23-2 Generalized multiple sapphire maculae on the face (**a**) and back (**b**) (Reproduced with the permission from [26])

19.24 Accidental Tattoo [27]

- Accidental tattoos (AT) are induced by blast injury. AT usually influences the cheeks, head, hands, and neck.
- It is important to clear away all foreign matter and particles using brushes or dermabrasion. Deeply embedded pigmented particles, which become traumatic tattoos, are not easy to clear away by dermabrasion.
- Q-switched ruby laser therapy for traumatic tattoos is very effective.

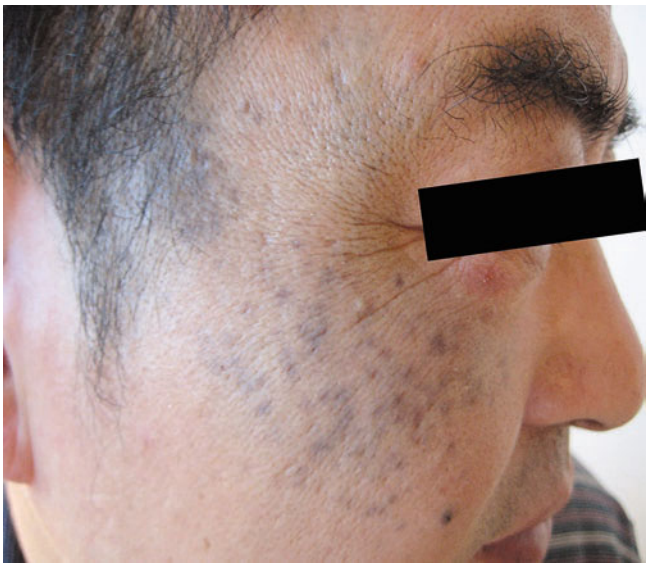


Fig. 19-24-1 Light-blue and dark maculae on the right cheek and temple (Reproduced with the permission from [27])

19.25 Rippling Lesions of Confluent and Reticulated Papillomatosis [28]

- Confluent and reticulated papillomatosis (CRP) develops as persistent brown papules and plaques. Occasionally, there is a central confluence and peripheral reticulated appearance.
- This condition has a propensity to involve the neck, abdomen, axillae, and interscapular areas of young adults. The knee, elbow, hand, and antecubital and popliteal fossae may be similarly affected.
- Several cases of CRP with rippled reticulated erythema have been reported. Atrophic macules that are shiny or resemble cigarette paper are another rare manifestation.

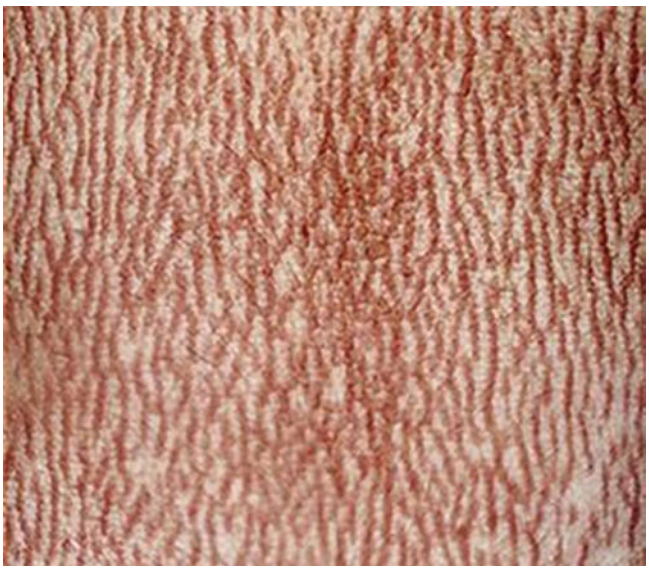


Fig. 19-25-2 A closer inspection of the lesions reveals successive, multiple, and keratotic papules, which were vertically rippled

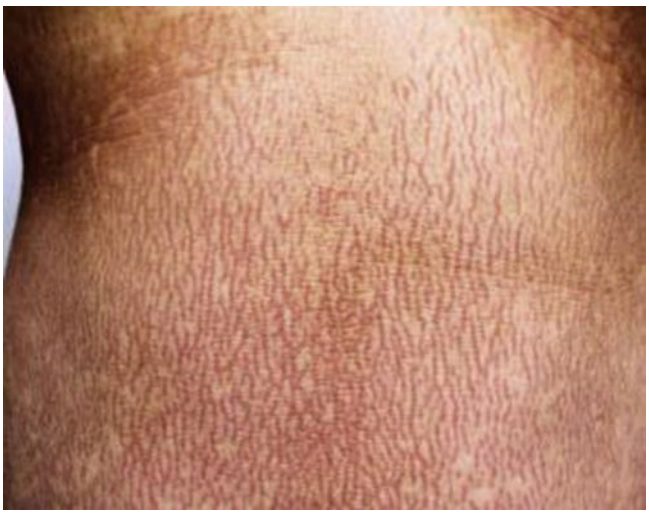


Fig. 19-25-1 The lesions mainly involved the waist and the abdomen

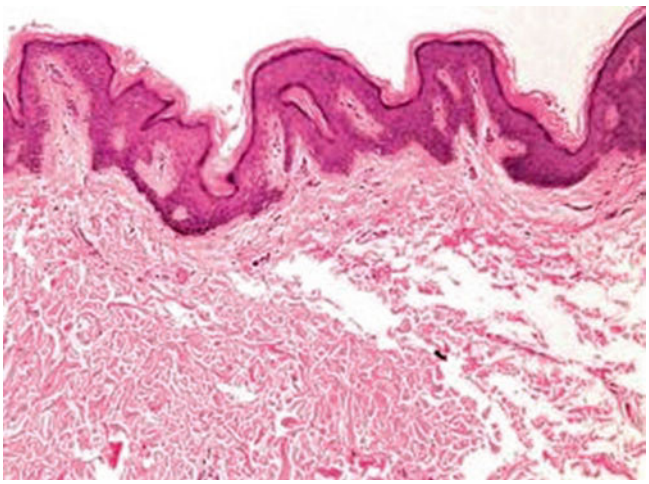


Fig. 19-25-3 In the epidermis, there were notable basket-weaved hyperkeratosis and mild papillomatosis. Mononuclear cells infiltrated superficial small vessels in the dermis

19.26 Trichrome Vitiligo [29]

- Vitiligo is a type of skin hypopigmentation or depigmentation. It can be localized and generalized and can be categorized into the blue, the inflammatory, the trichrome, the quadrichrome, and the pentachrome subtypes according to the different skin colors and tones.
- Trichrome vitiligo has a sepia zone of alterable width between normally colored and depigmented skin, which appears as an intermedium hue. Trichrome vitiligo can be cockade-like.
- The variation of melanocytes, Langerhans cells, and keratinocytes could be a part of the pathogenesis of depigmentation in trichrome vitiligo, although its pathogenesis and histopathologic characteristics remain unknown.
- Trichrome vitiligo occurs most commonly on the trunk in active vitiligo vulgaris, occasionally in the segmental type, and it seems to be resistant to medical treatment.

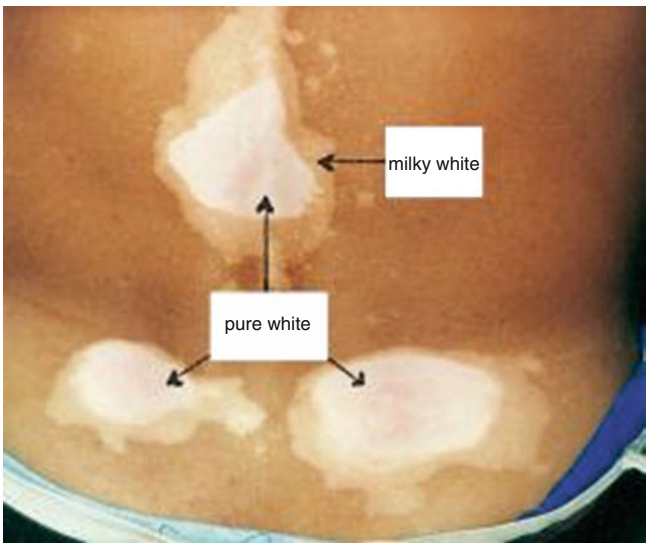


Fig. 19-26-1 White macule or patch in the center, surrounded by intermediate milky white zone and peripheral normal skin

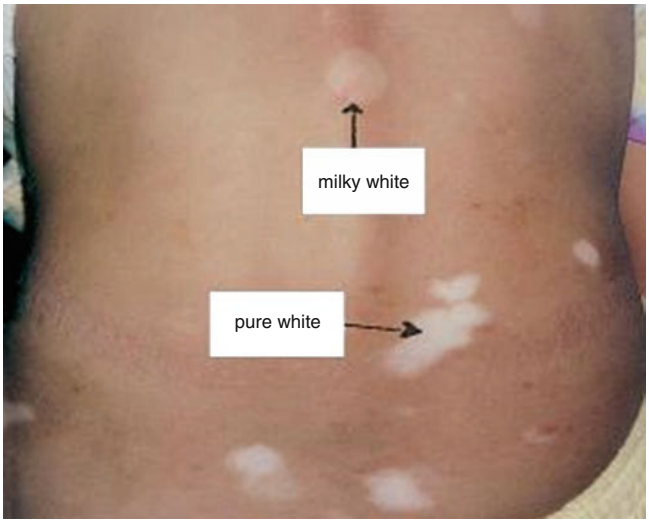


Fig. 19-26-2 The achromic skin was partially milky white with normal skin-colored background

19.27 Pentachrome Vitiligo in a Segmental Pattern [30]

- Fargnoli first described the term "pentachrome vitiligo" in 1995. It is a rare variant that displays, in the following order, white, sepia, brownish, and glaucous gray hyperpigmentation and normal skin color.
- Pentachrome vitiligo may be a metastable or in vicissitudinous pigmentary state during the slow recovery process.
- Early-stage or progressive lesions may be partly depigmented, resulting in a spotted presentation or a multi-shaded hue.

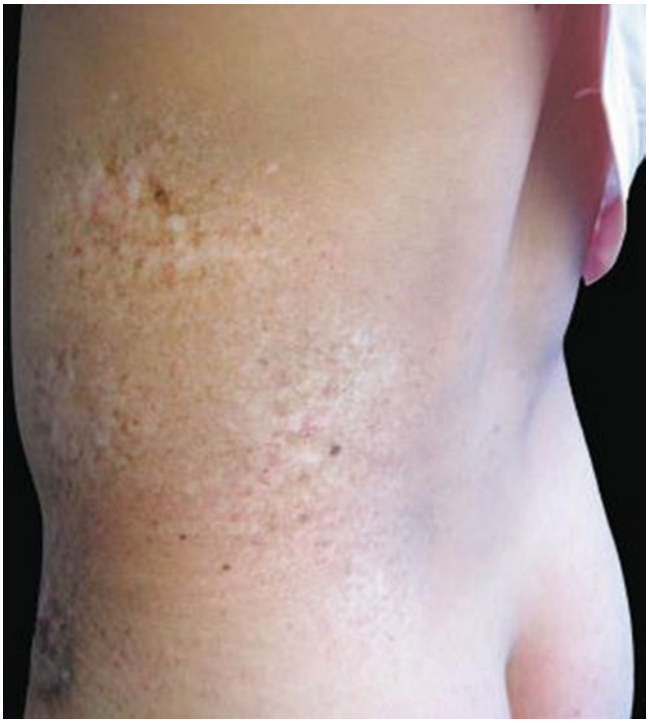


Fig. 19-27-1 Multiple depigmented and hyperpigmented macules on the left part of the abdomen and the lump (Reproduced with the permission from [30])

19.28 Inflammatory Vitiligo [31]

- Inflammatory vitiligo (IV) is a particular form of vitiligo with erythematous, micro-papular or fine scaling edge with or without pruritus.
- IV is generally regarded as a progressive type of vitiligo.
- IV has been sometimes associated with HIV, hepatitis C infection, atopic dermatitis, and Vogt-Koyanagi-Harada disease.

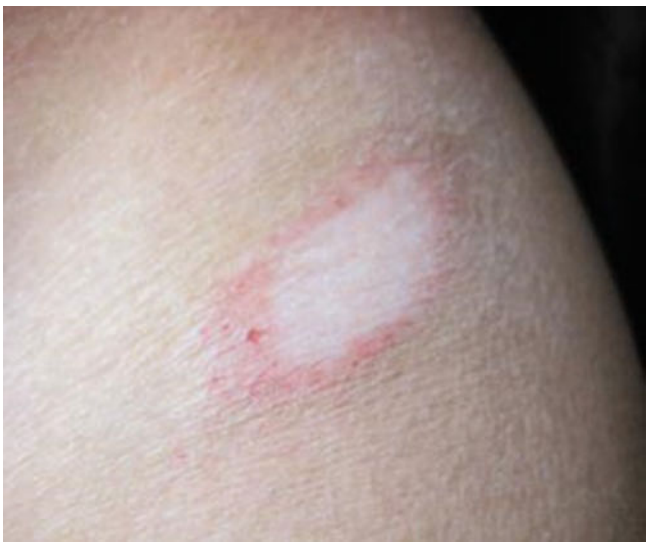


Fig. 19-28-1 Depigmented macule with a raised erythematous border

19.29 Nevus Depigmentosus [32]

- Nevus depigmentosus (ND) or nevus achromicus is an uncommon pigmentary disease that may be related to postzygotic mutation.
- ND preferentially occurs on the trunk, limbs, neck, and face, may be noted at birth, or may change more apparent early in life. It commonly presents as a solitary, limited, hypo- or amelanotic macule that remains stable throughout life.
- NP has three clinical forms: the solitary is the most common. The segmental and the systematized are much less common.
- The lesion can exhibit various shapes, including a checkerboard, phylloid, or leafy pattern.
- The skin lesions may disappear in a few patients with NP.

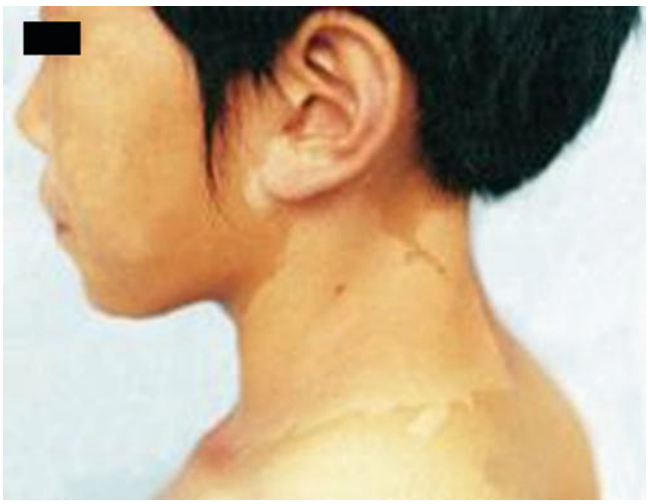


Fig. 19-29-1 Serrated border shown in isolated pattern of nevus depigmentosus was shown

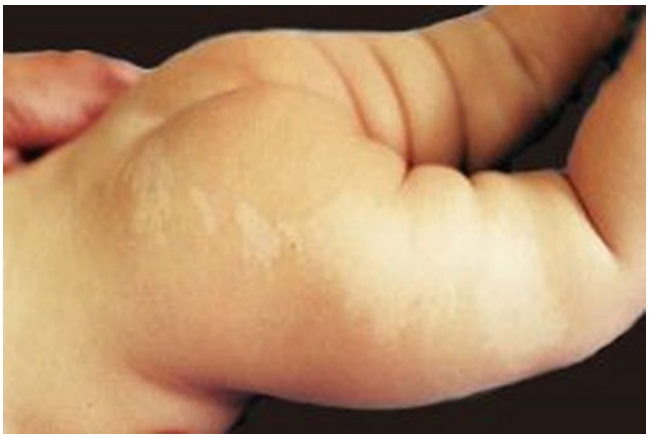


Fig. 19-29-2 Serrated border in segmental pattern of nevus depigmentosus was shown

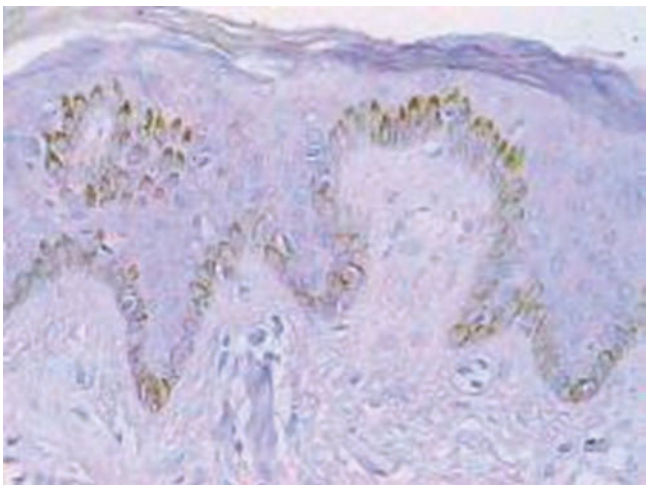


Fig. 19-29-3 Melanocyte number was normal in the basal layer (HMB45 antibody stain, ×200)

19.30 Stellate Spontaneous Pseudoscars [33]

- Stellate spontaneous pseudoscars (SSPs) presents as multiple, whitish, slightly depressed, scar-like, stellate lesions on the backs of the hands and the radial and extensor aspects of the forearms.
- Clinically, it is classified into two types: senile and presenile forms. The senile form commonly involves individuals over 60 years of age. About 20% French senile citizens have SSP. The presenile form appears at an unusually early age (before 60 years of age and even before 50 years of age), and it involves the legs and face more often than the senile type.
- Histological changes comprise a small mass of fibrous connective tissue below with disappearance of elastic fibers.
- Although the etiology remains ambiguous, prolonged corticosteroid therapy might be involved in the progression. There is no special treatment for SS.

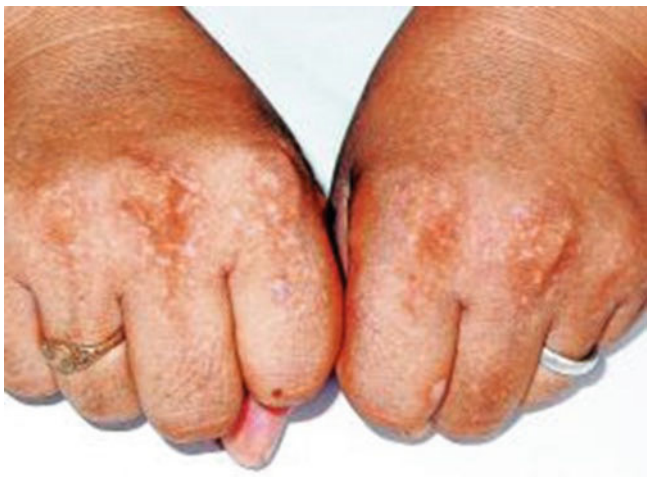


Fig. 19-30-1 The white, stellate, and linear lesions on both dorsal hands

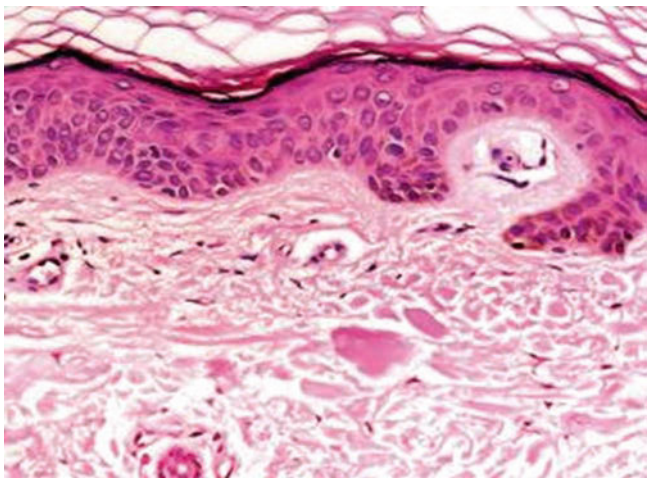


Fig. 19-30-2 Epidermal hyperkeratosis, hyperpigmentation in the basal layer, inflammatory cell infiltration, and degenerated elastic fibers in the upper dermis (HE stain, ×150)

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Part VII

Disorders of Appendages and Mucous Membranes

Disorders of the Skin Appendages

20

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Abstract

This chapter presents with granulosis rubra nasi, Fox-Fordyce disease, ophiasis and sisaipho hair regrowth pattern, pseudopelade of Brocq, alopecia areata sparing white hairs within lesion, coexistence of acquired hypertrichosis and scalp alopecia, woolly hair, monilethrix, pili annulati, trichonodosis, hair cast, trichostasis spinulosa, cutaneous pili migrans, red hair, permanent poliosis after plucking, congenital leukonychia totalis, hyperpigmentation of the nail from lead deposition, longitudinal erythronychia, chromonychias, subungual splinter hemorrhage, sebaceous gland hyperplasia, as well as sebaceous hyperplasia within epidermis after scald.

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20.1 Granulosis Rubra Nasi [1]

- Granulosis rubra nasi (GRN), also defined as "Acne papulo-rosacea of the nose," is a rare disorder of the eccrine glands and is inherited as an autosomal dominant trait.
- Clinical features are hyperhidrosis of the midface, which is most serious at the tip of the nose, followed by the appearance of diffuse erythema on the nose, upper lip, chin, and cheeks.
- Histological examination reveals dilation of the dermal blood and lymphatic vessels with perivascular lymphocytic infiltration and dilation of the sweat ducts.
- GRN is commonly seen in childhood between 6 months and 15 years of age, but it can also occur in adults. The disease is basically asymptomatic, with occasional itching or tingling feelings.
- For most patients, GRN has a favorable prognosis with self-resolution at puberty. Therapies, including local anti-inflammatory substances, cryotherapy, tetracycline, and oral steroids, provide temporary benefit.

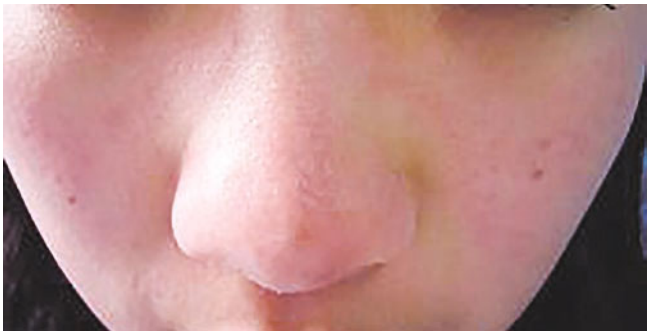


Fig. 20-1-1 Erythema on the nose and cheeks. Sweat beads on the nasal tip

20.2 Fox-Fordyce Disease [2]

- Fox-Fordyce disease (FFD), also known as apocrine miliaria, is an uncommon, chronic, pruritic, inflammatory disease of apocrine glands characterized by multiple skin-colored, equidistant, perifollicular papules distributed in axillae, anogenital, and periareolar regions.
- FFD primarily affects young females between 15 and 35 years of age. Hormonal factors, genetics, and stress contribute to the pathogenesis of this disease, which is related to blockage of apocrine sweat ducts.
- Sympathetic stimulation, such as stress, exercise, excitement, and hot weather, may exacerbate the pruritus.
- FFD undergoes a chronic course with intermittent flares, and there is no definitive treatment. Topical clindamycin, adapalene and tretinoin, pimecrolimus, benzoyl peroxide, corticosteroids, oral contraceptive pills, and isotretinoin may be tried.

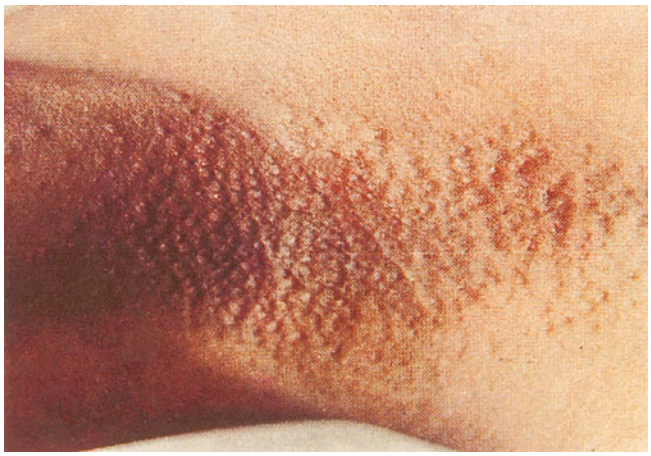


Fig. 20-2-1 Dense, round, smooth, millet-sized, firm, follicular, skin-colored, or dust-colored papules on the axillae

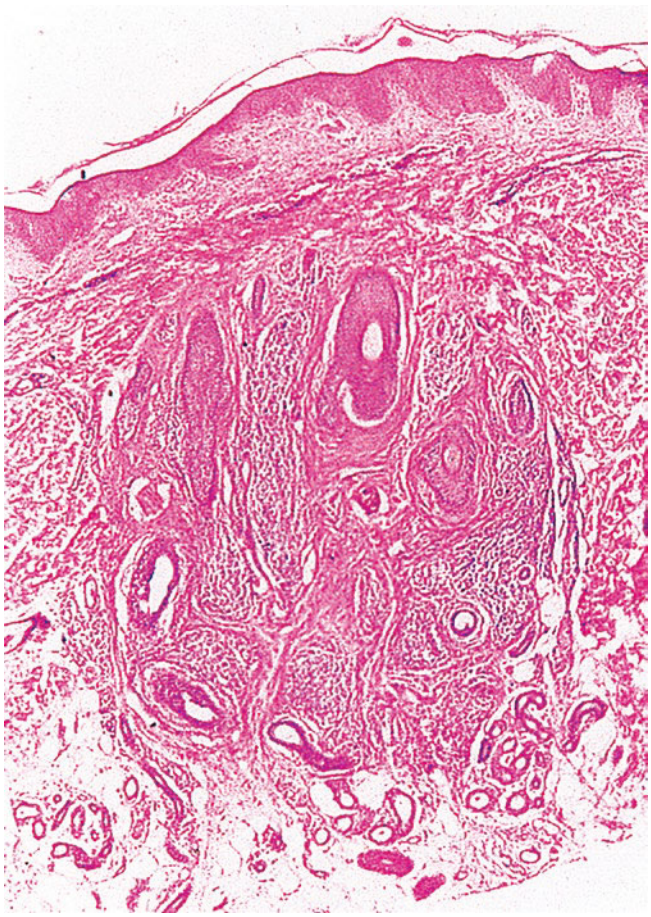


Fig. 20-2-2 Dilated apocrine duct and chronic inflammatory cells infiltration in the dermis (HE stain, ×20)

20.3 Ophiasis and Sisaipho Hair Regrowth Pattern [3]

- Mosaic hair regrowth pattern in alopecia areata (AA) may assume the combination pattern of ophiasis and androgenic dependent alopecia.
- Alopecia areata in red-haired individuals may heal with the regrowth of black hair. We have also observed a black-haired Chinese patient recover with focal red hair.
- Curly hair in alopecia areata patients sometimes resolves with regrowth of straight hair.
- A targetoid pattern of hair regrowth has also been seen in AA patients, and the "earthquake wave theory" has been proposed for the associated pathogenesis.

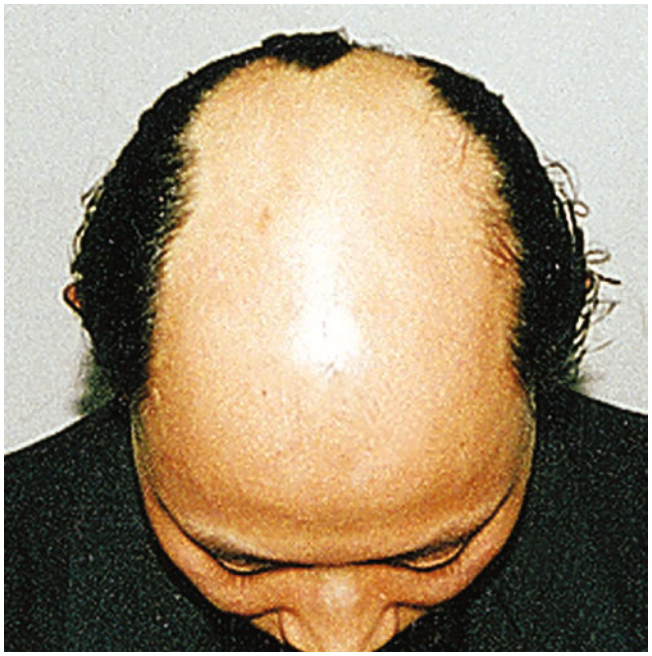


Fig. 20-3-1 A circumscribed U-shaped display of hair loss over the center of the scalp, with persistence of hair only at the hair margin, mimicking grade VI male-pattern baldness on Hamilton's scale, another affected hair margin of the right temple, with an area ranging 3 cm in diameter

20.4 Pseudopelade of Brocq [4]

- Pseudopelade of Brocq (PPB) is an uncommon, self-restricted, chronic, progressive cicatricial alopecia, which is mainly related to the vertex and parietal scalp.
- Acquired immunity, senescence of the follicular stem cell reservoir, and *Borrelia* infection have an uncertain effect on the pathogenesis of PPB.
- Classically, PPB presents as asymptomatic porcelain white hypopigmented and slightly depressed atrophic plaques with a smooth surface without hair follicles.
- No satisfactory treatment protocol is available for PPB. Local corticosteroids and intralesional triamcinolone acetonide may be options. Mycophenolate, cyclosporine mofetil, and systemic corticosteroids are needed during the acute phase of this disease.

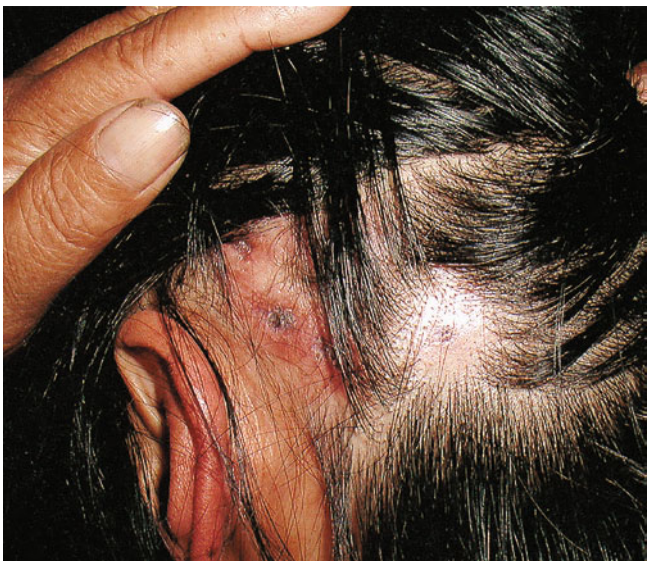


Fig. 20-4-1 Pale red macules with central atrophy and brown crusts on the scalp

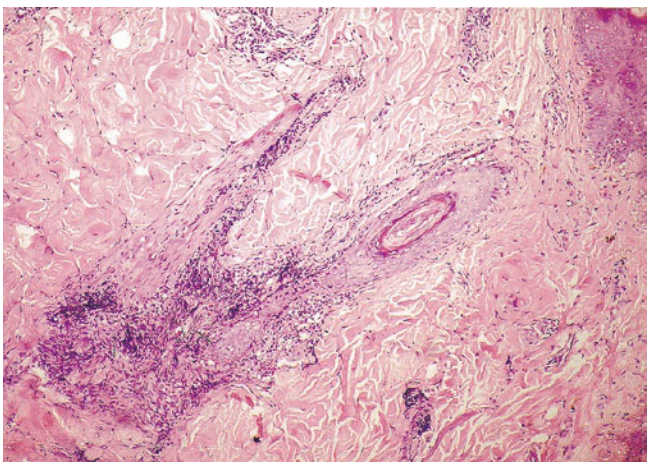


Fig. 20-4-2 Many hair follicles were destroyed in the dermis (HE stain, ×100)

20.5 Alopecia Areata Sparing White Hairs Within Lesions [5]

- Alopecia areata (AA) is a sudden loss of the hair over any haired area. The lesion is often hairless.
- Clinically, AA can be categorized as patchy AA, reticular AA, ophiasis band-like AA, ophiasis inversus, diffuse AA, AA totalis, and AA universalis.
- Patchy AA sparing lesional graying hairs is a new subtype of AA.
- AA around central, pigmented nevi is called perinevoid alopecia, and the inverse counterpart of AA sparing the nevi is defined as Renbok phenomenon.
- Nevus flammeus is another disorder that might spare AA.

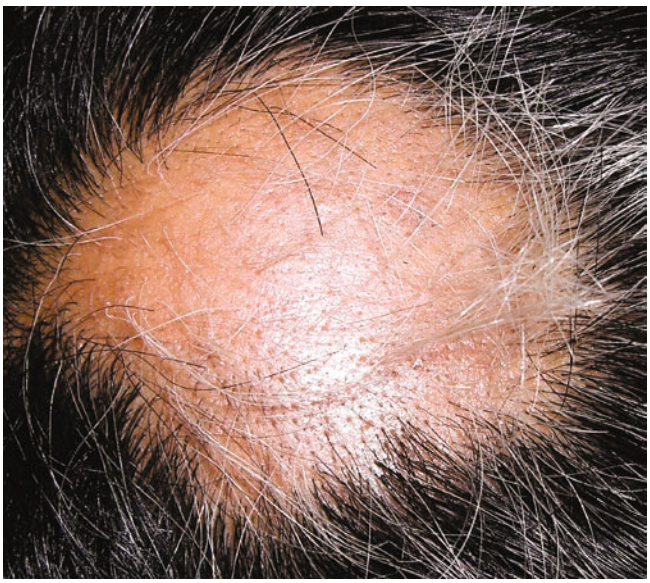


Fig. 20-5-1 A round, well-defined alopecic patch was presented on the vertex of the scalp with a diameter of about 5 cm. Some graying hairs were randomly distributed among the balding patch, which were similar with neighboring unshedding pigmented hairs in diameter and length (Reproduced with the permission from [6])

20.6 Coexistence of Acquired Hypertrichosis and Scalp Alopecia [7]

- Generalized hypertrichosis in the patient is caused by an as yet uncertain tumor-derived humoral factor, which can result in an extension of the anagen stage of vellus hair follicles, resulting in hypertrichosis.
- The excess hair presents vellus-type hypertrichosis, implying the conversion of vellus to terminal hairs rather than lanugo-type acquired hypertrichosis, which frequently appears in patients with malignant tumors.
- Scalp hair loss is a usual side effect in patients receiving chemotherapy for malignant tumors.
- Although hypertrichosis and scalp hair loss are familiar signs, the coexistence of both in a patient with infiltrating breast ductal carcinoma is infrequent.

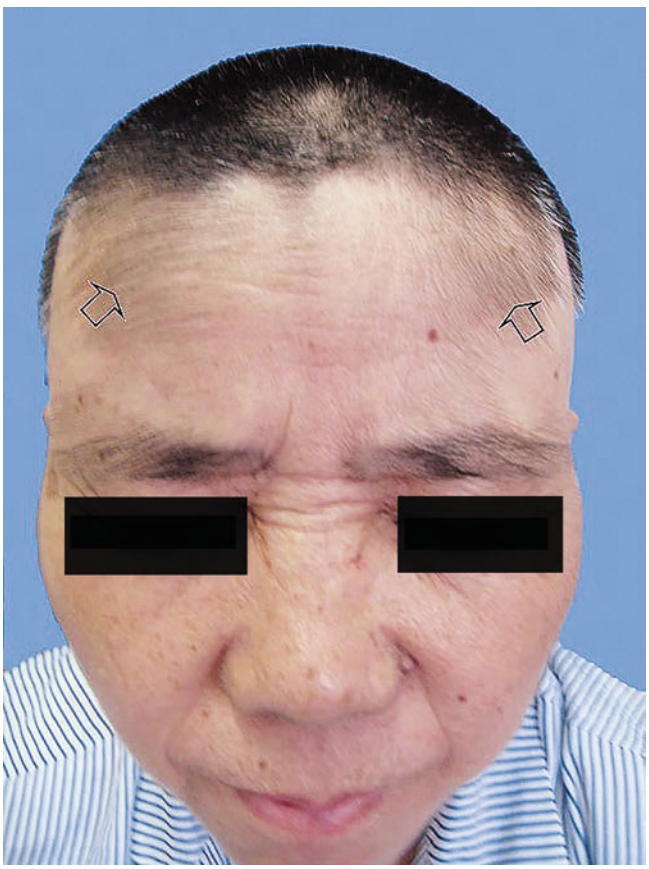


Fig. 20-6-1 Facial hypertrichosis (hollowed arrows), bushy eyebrows, and trichomegaly (Reproduced with the permission from [7])

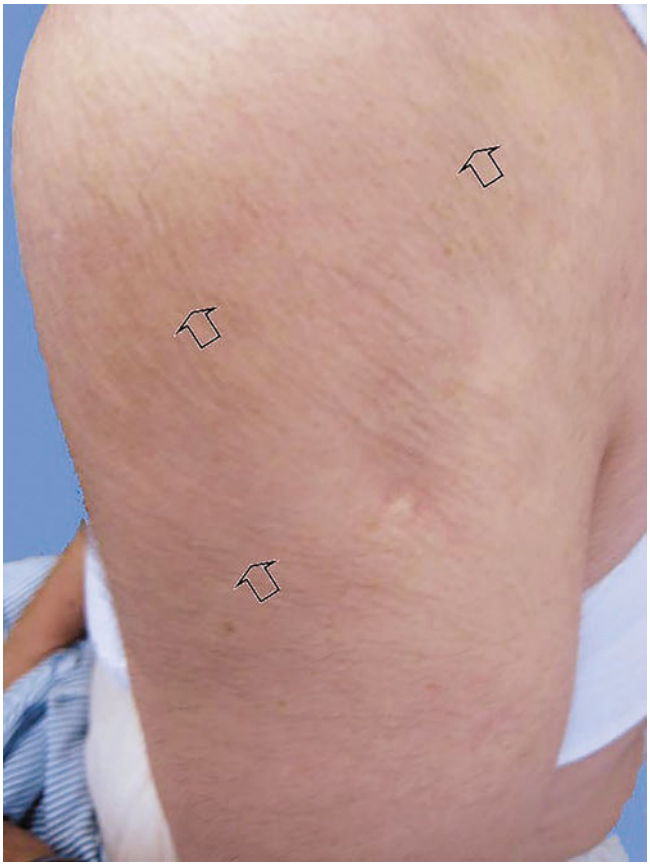


Fig. 20-6-2 Hypertrichosis over the arms (hollowed arrows)

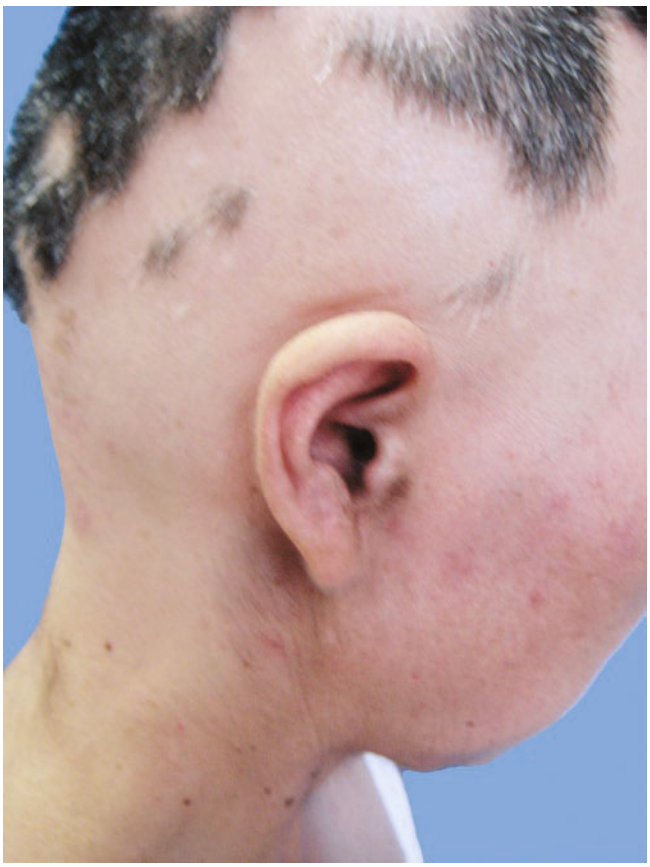


Fig. 20-6-3 Scalp alopecia with smooth, noninflammatory scalp and intact follicular openings

20.7 Woolly Hair [8]

- Woolly hair (WH) is an uncommon congenital anomaly of the structure of the scalp hair, which features tightly curled and tiny hair involving part or the whole scalp.
- The hair looks tiny, curled, and depigmented. It has three features: a decreased diameter, oval form, and tight coiling in the lateral section.
- WH is divided into three variants: a localized variant (woolly hair nevus) and two generalized variants (autosomal dominant/hereditary woolly hair and autosomal recessive/familial woolly hair).
- There is no satisfactory therapy for this disease. It is important to advise and counsel the patients or their parents about the benign nature of this disease.

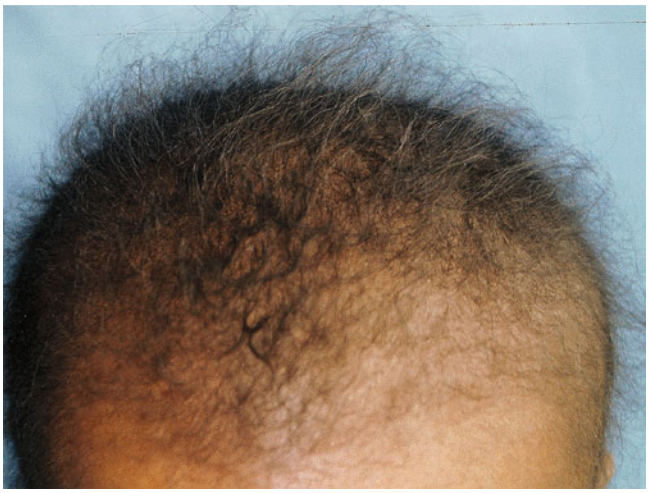


Fig. 20-7-1 The sparse, curled, light gray hair without sheen

20.8 Monilethrix [9]

- Monilethrix is a rare, hereditary, and autosomal dominant condition caused by mutations of the genes encoding three types of keratin: hHb1, hHb3, and bHb6 type II keratin.
- Monilethrix is characterized by weakness of the hair, keratosis suprafollicularis, especially in the occipital region, as well as specific beading of the hair shaft. Hair fragility may result in hair breakage and the appearance of generalized alopecia.
- Trichoscopy reveals regular changes in the diameter of the hair shaft with constrictions (internodes) and elliptical dilations (nodes). There is generally no hair marrow (medulla) between the fusiform nodes, which are microscopically observed every 0.7–1 mm along its long axis.
- There is no satisfactory treatment for monilethrix. Patients could be treated with oral retinoid and topical 2% minoxidil solution.

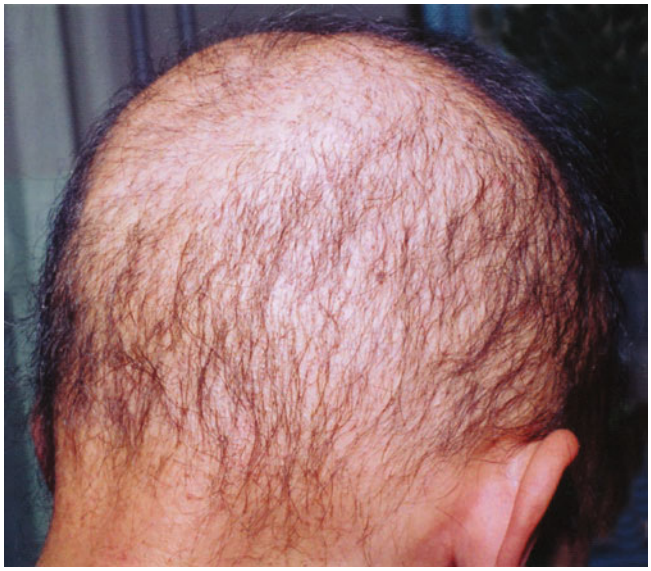


Fig. 20-8-1 Spare beaded hairs on the scalp

20.9 Pili Annulati [10]

- Pili annulati (PA) is an uncommon, sporadic, autosomal dominant, or benign hair shaft disease that features a pattern of alternating dark and bright bands of hair that give them a lustrous appearance. This phenomenon is created by the periodic occurrence of air-filled cavities along the hair cortex. The susceptibility gene locus is in the telomeric region of chromosome 12q.
- PA can present at birth, during infancy, or after 2 years of age, and it becomes more noticeable with age. The scalp is mainly influenced, and the pubic, beard, and armpit hair can also be involved.
- Vigorous combing, brushing of the hair, or cosmetic measures can result in excessive weathering and structural damage of the hairs in PA. Therefore, avoiding these precipitating factors is recommended in patients with PA.

Fig. 20-9-1 Alternating segments of light and dark color made hairs annulated

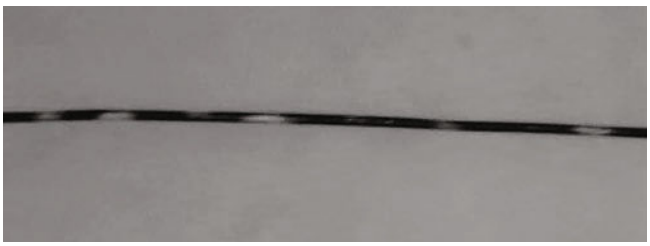


Fig. 20-9-2 Alternation of light and dark bands at various intervals along the hair shaft (×40)

20.10 Trichonodosis [11]

- The clinical features of this condition are a knot at the hair shaft. Trichonodosis can be classified into spontaneous and acquired types.
- Spontaneous trichonodosis is a rare disease and occurs frequently in children. This type of trichonodosis may be associated with abnormal androgenic hair. SEM examination reveals twisted and longitudinal fissuring of the hair shaft.
- Acquired trichonodosis is frequently observed a knot at the far end of the hair shaft in long-haired women due to mechanical factors such as scratching or combing.

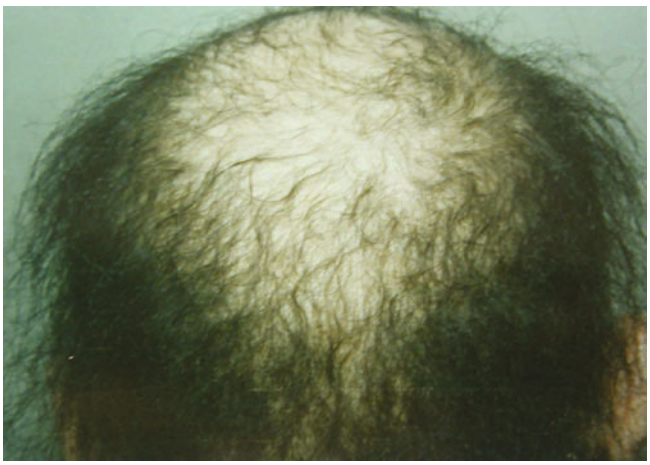
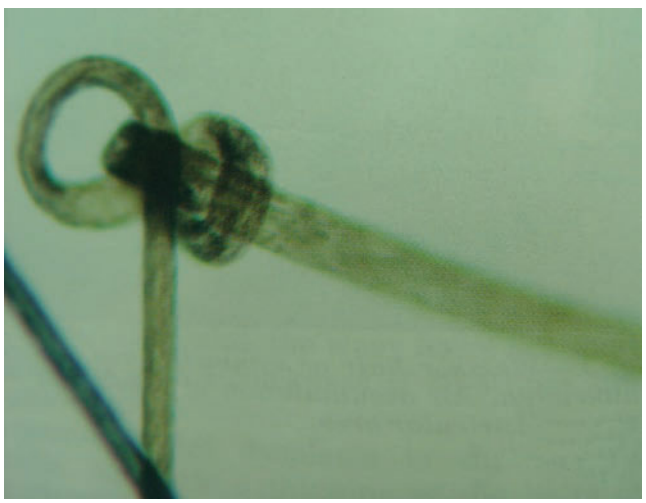


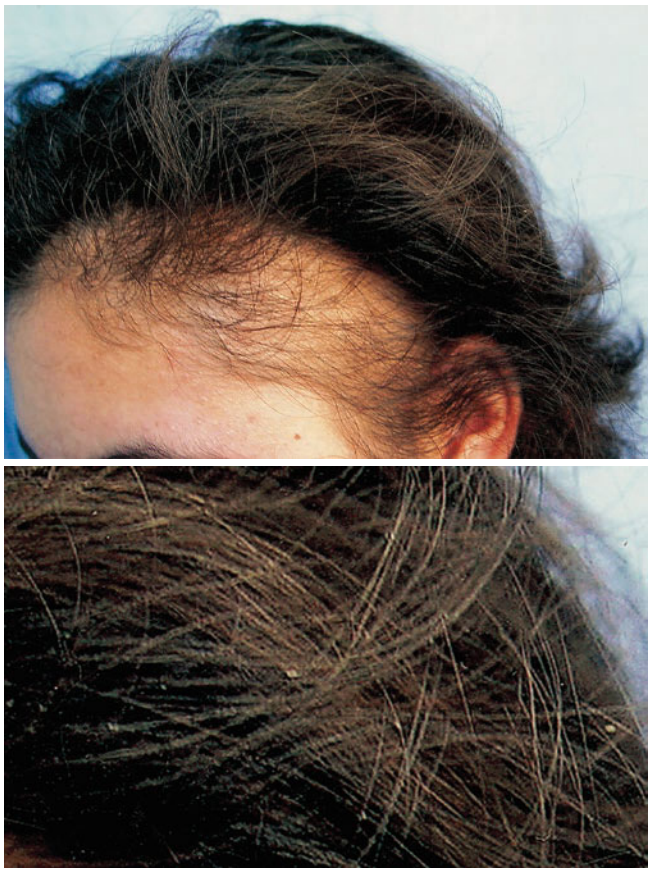
Fig. 20-10-1 Diffused alopecia of the frontal region and the vertex with hyperhidrosis (Reproduced with the permission from [12])



Figs. 20-10-2, 20-10-3 Double knots in hair shaft (Reproduced with the permission from [12])

20.11 Hair Cast [13]

- Pseudonits or hair casts are peripheral concretions that cover the hair shaft and can be effortlessly removed.
- Traction alopecia is clinically characterized by loss and thinning of hair in the affected area.
- Prolonged hair traction may cause cicatricial alopecia, which is more commonly localized at hair margins behind the frontal hairline or along the temporoparietal margin (marginal alopecia) but may involve any scalp area depending on the cause of traction.



Figs. 20-11-1, 20-11-2 Sparse hairs on frontal and temporal areas of the scalp (1), with white nodules on hair shafts (2)

Fig. 20-11-3 Microscopic observation of hair cast (×100)

20.12 Trichostasis Spinulosa [14]

- Blackhead comedo-like lesions occur on the nose, forehead, and trunk and are also accompanied by pruritus.
- Dilated hair follicles with numerous pigmented vellus hairs (up to 50 hairs) are present.
- Dermoscopic findings include tufts of multiple pigmented vellus hairs with projections of varying diameters.
- Absent hair cuticles or many fragments of keratinocytes on the surface of lanugo may be observed in some vellus hairs by SEM.

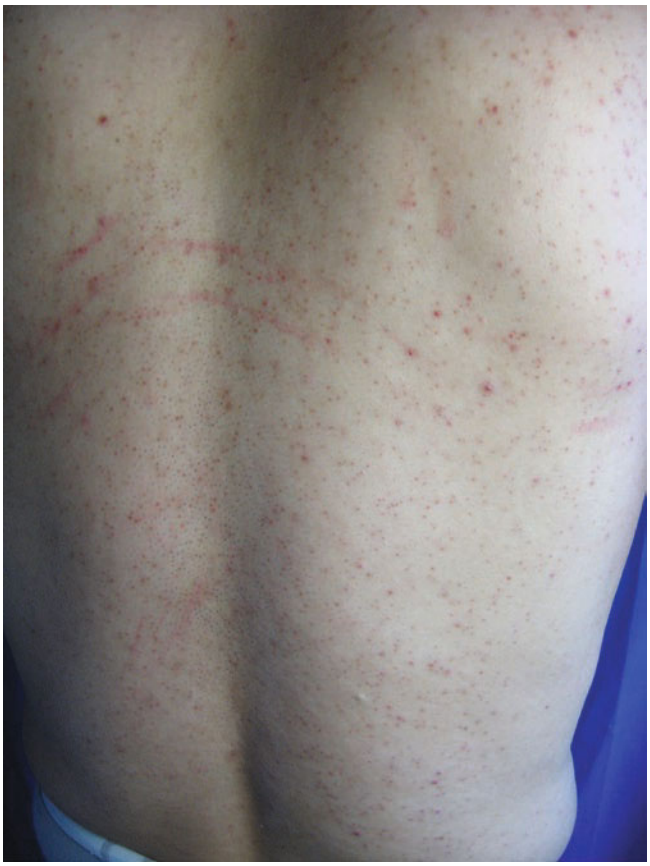


Fig. 20-12-1 Many blackheads were on the trunk and filled with horny plugs

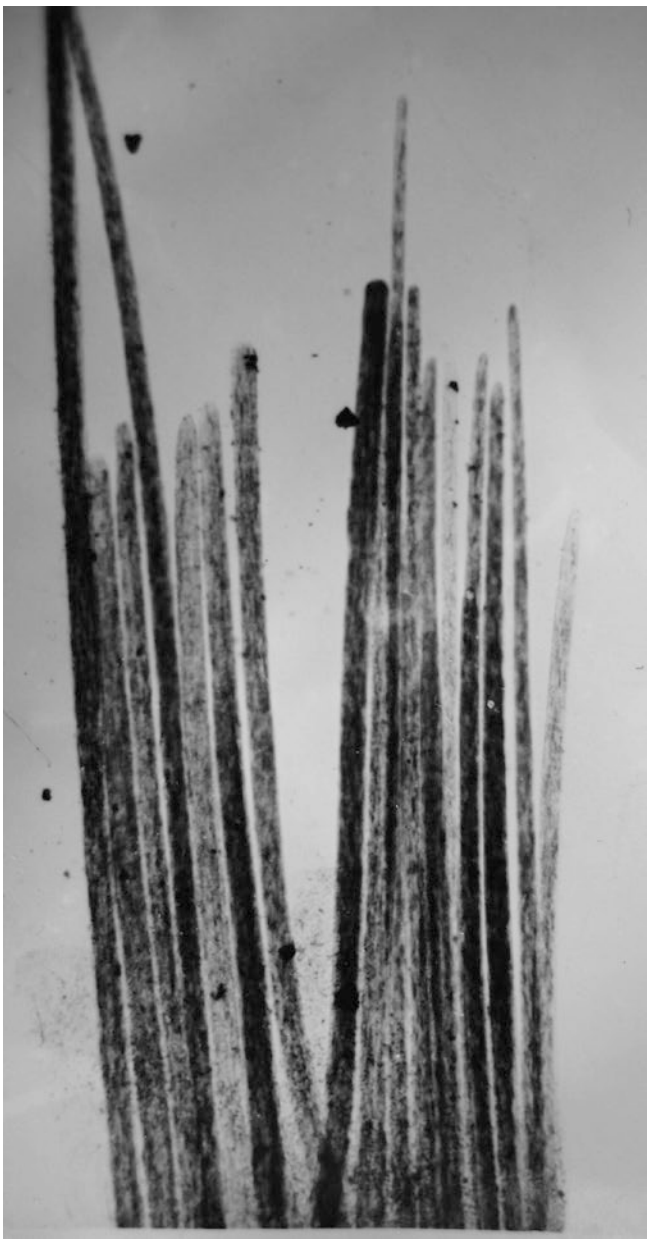
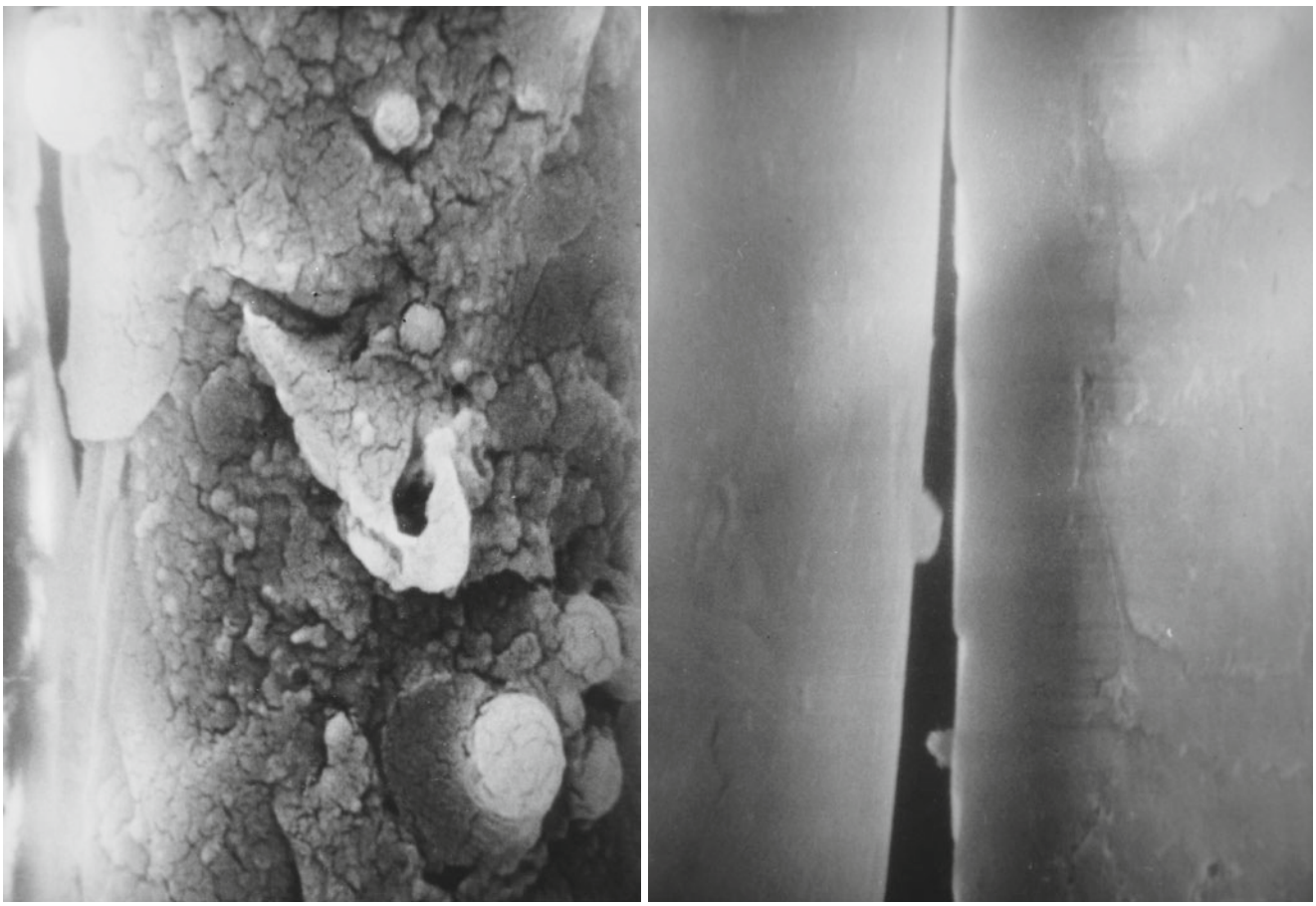


Fig. 20-12-2 A single blackhead contained a bundle of 16 vellus hairs



Figs. 20-12-3, 20-12-4 Cuticle disappeared or many fragments of keratinocytes on the surface of lanugo by SEM

20.13 Cutaneous Pili Migrans [15]

- Cutaneous pili migrans (CPM) is a rare condition resulting from a hair shaft or fragment embedded in the surface skin and sometimes in the middle dermis following an injury or occasionally for no known reason.
- It is characterized by serpigo with a black line-like hair at the ongoing end. After removing the black hair shaft, the lesion will be completely healed.
- To our knowledge, the locations involved include the ankle, sole, toe, breast, cheek or neck, jaw, and abdomen.
- The manifestation of CPM closely resembles that of cutaneous larva migrans; therefore, a close-up examination is needed.

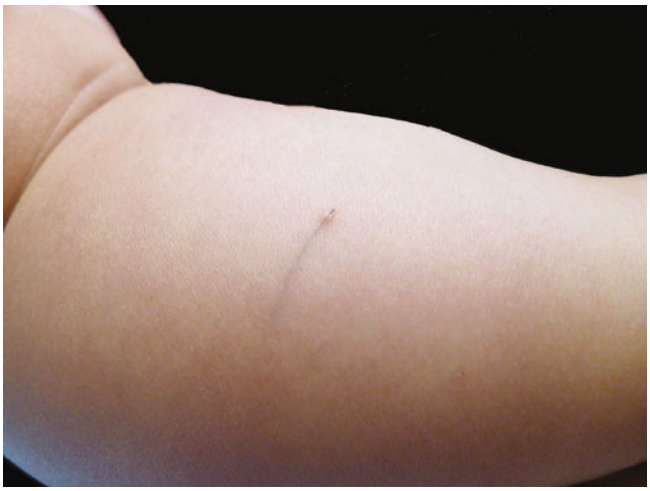


Fig. 20-13-1 A fine, black hair was seen to pierce through the skin, without any signs of inflammation on the surrounding skin

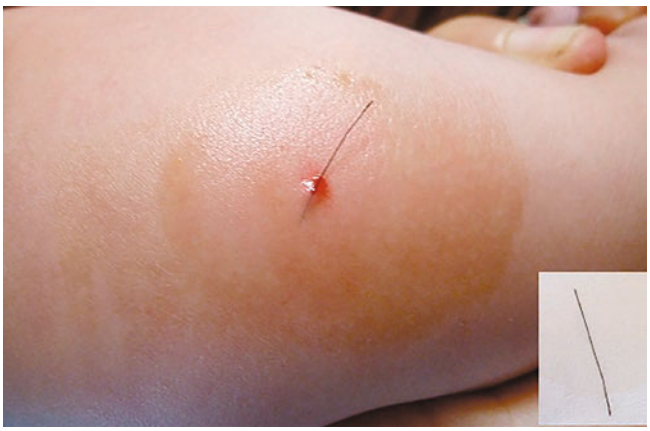


Fig. 20-13-2 A dark hair was extracted from the skin with little bleeding

20.14 Red Hair [16]

- Red hair can be divided into two subtypes: focal and universal.
- The focal pattern of red hair is present on a portion of the scalp. The diffuse universal type affects the entire surface of the scalp.
- Many possible mechanisms have been proposed to explain how red hair is induced: reduced levels of eumelanin and induction by selenium and dihydroxyacetone.

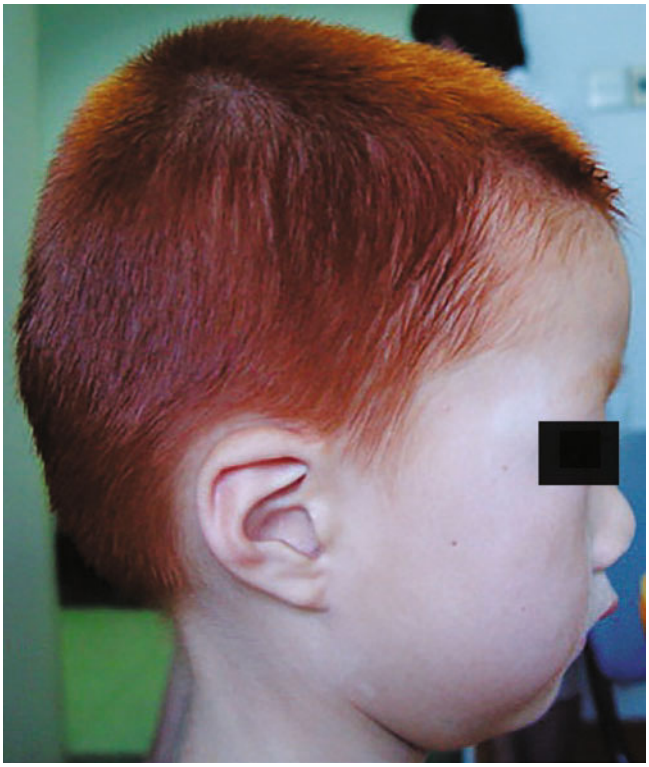


Fig. 20-14-1 Total red hair of the scalp (Reproduced with the permission from [16])

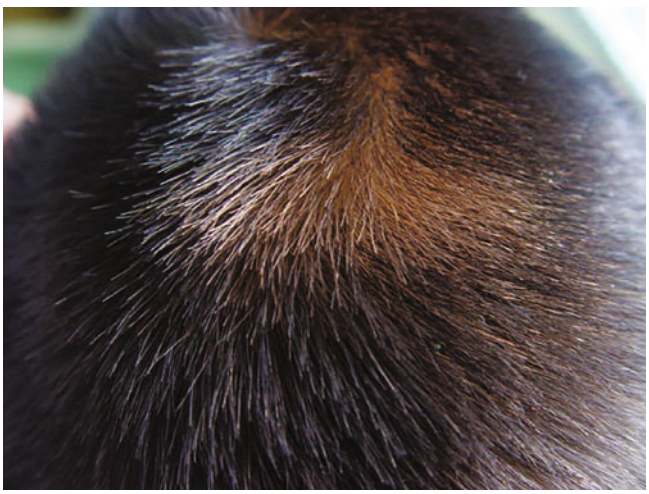


Fig. 20-14-2 Localized red hairs on the top of scalp

20.15 Permanent Poliosis After Plucking [17]

- Poliosis circumscripta features a regional patch of white hair. Poliosis may influence the beard area, eyebrows, eyelashes, and scalp.
- Poliosis is classically known to occur outside the setting of several genetic syndromes, such as tuberous sclerosis, Rubinstein-Taybi syndrome, Tietze syndrome, Waardenburg syndrome, Marfan syndrome, prolidase deficiency, piebaldism, and neurofibromatosis type 1.
- It has also been described in association with various acquired inflammatory conditions, malignant neoplastic entities, medications, and other conditions.

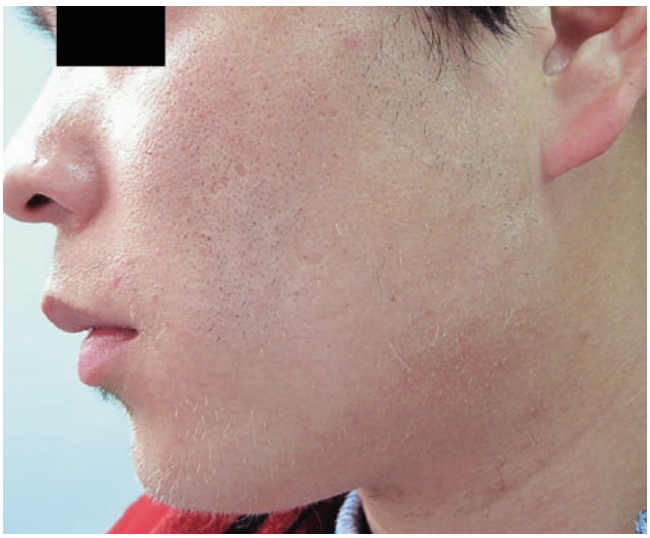


Fig. 20-15-1 Permanent poliosis affecting the submaxilla area after repetitive plucking. The pigment of several peripheral rows of beard hairs was unchanged. Perioral beard hairs were untouched. The color of the submaxilla skin was normal (Reproduced with the permission from [17])

20.16 Congenital Leukonychia Totalis [18]

- Congenital leukonychia totalis is a very rare hereditary condition in which all nails are milky white; inheritance is typically autosomal dominant, but it can be autosomal recessive in few cases. Mutations in the PLCD1 gene on chromosome 3p21.3-p22 cause hereditary leukonychia.
- Clinically, all 20 nails of each influenced patient are white and chalky in appearance, with no other cutaneous, appendageal, or systemic findings.
- Histologically, disorganization and parakeratosis of keratin bundles exist in the white part of the nail.
- Congenital leukonychia totalis is persistent and resistant to treatment.

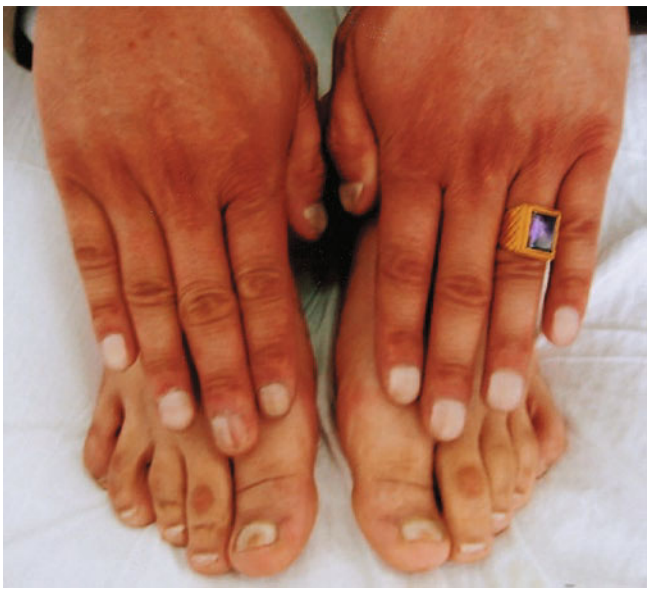
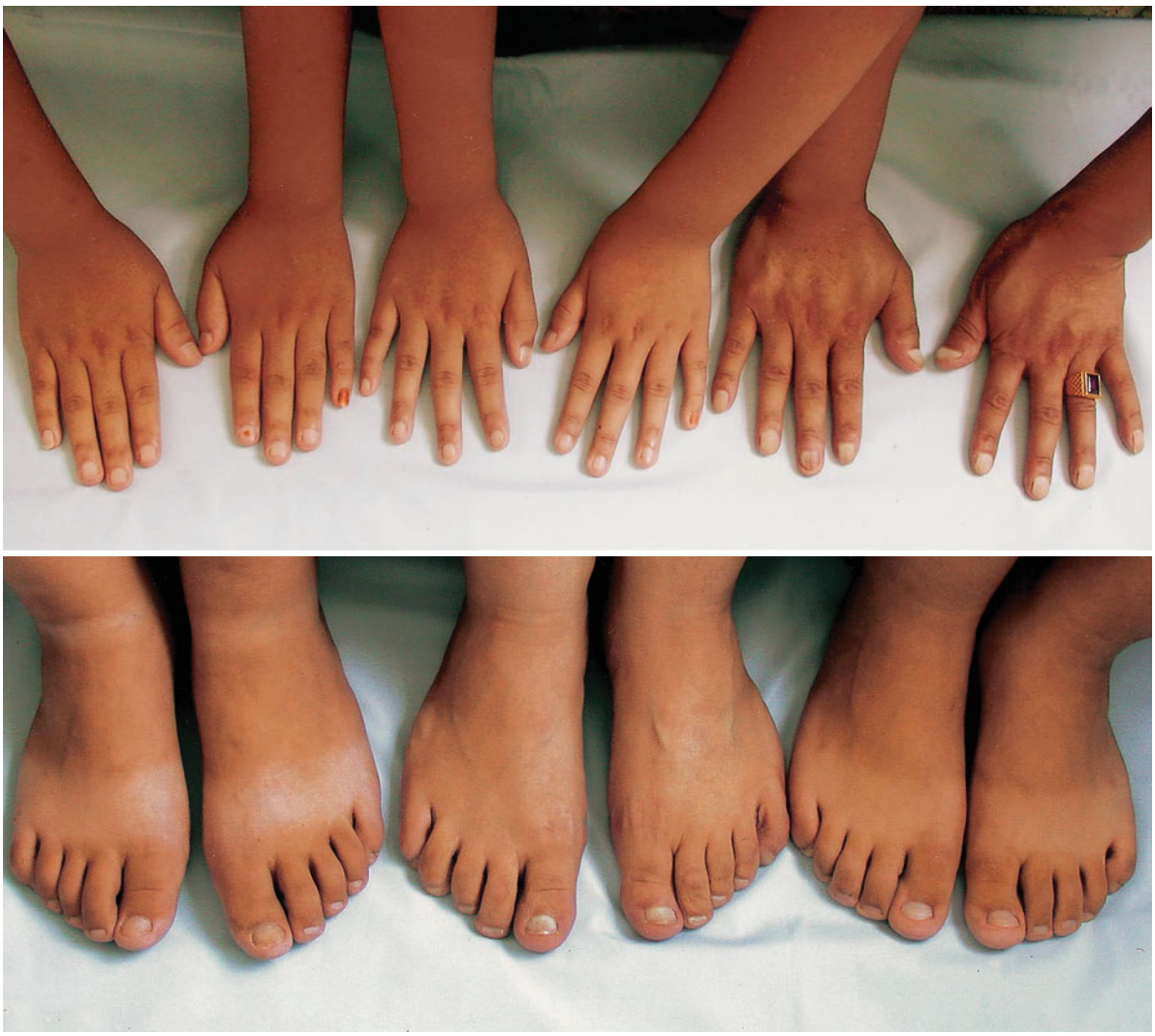


Fig. 20-16-1 Twenty nails with milk-white coloring on both hands and feet



Figs. 20-16-2, 20-16-3 Leukonychia totalis on the hands and feet of the affected family members

20.17 Hyperpigmentation of the Nail from Lead Deposition [19]

- The symptoms of plumbism include peripheral neuritis, lethargy, encephalopathy, and gastrointestinal distress.
- Skin pigmentation in saturnism has not been reported. We reported hyperpigmentation of the nails in an infant treated daily with Tao Dan powder on the skin of the whole body. The blood lead level rose in this infant. Energy-dispersive X-ray microanalysis confirmed the presence of lead within the nail plate.
- Approximately 80% of patients with chronic lead intoxication present with a characteristic blue-gray color.

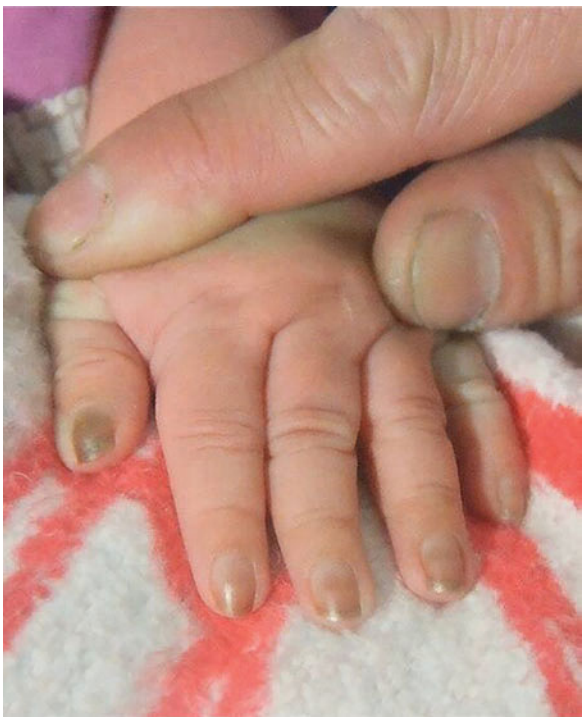


Fig. 20-17-1 Diffuse pigmentation of the fingernails of the left hand (Reproduced with the permission from [19])

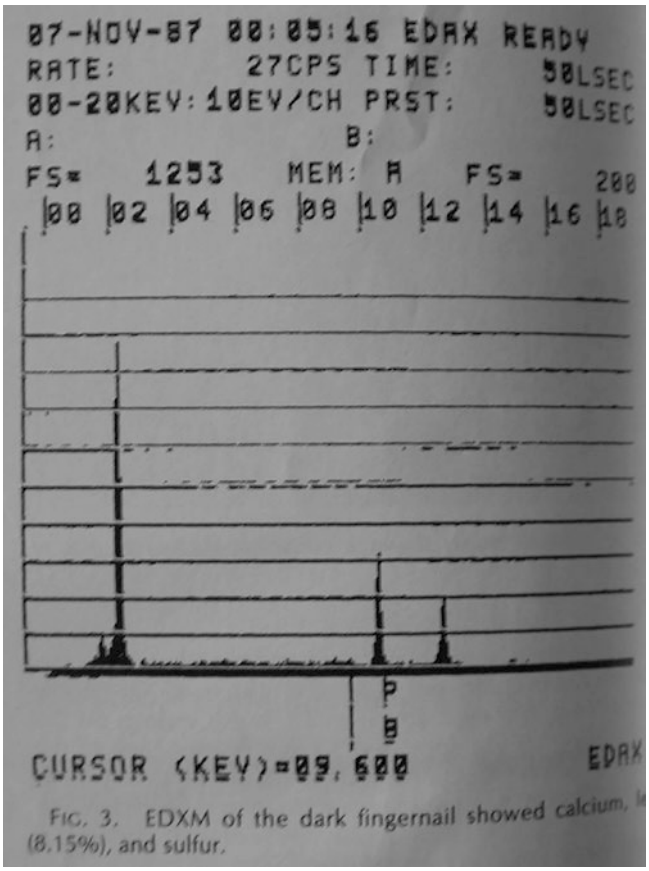


Fig. 20-17-2 EDXM of the dark fingernail showed the deposition of calcium, lead (8.15%), and sulfur (Reproduced with the permission from [19])

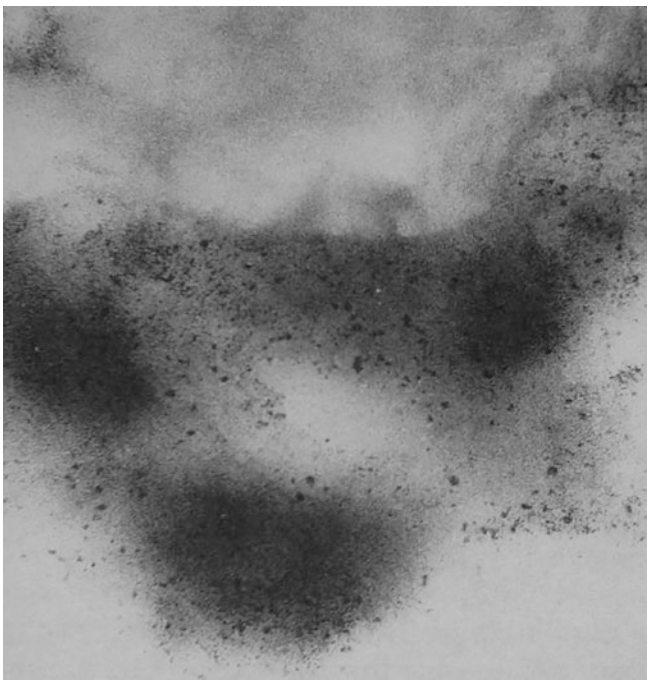


Fig. 20-17-3 Electron-dense small granules distributed along the membrane of keratinocyte (×14,000) (Reproduced with the permission from [19])

20.18 Longitudinal Erythronychia [20]

- Longitudinal erythronychia (LE) is a linear red nail plate dyschromia.
- The line begins in the proximal nail folds, traverses the lunula, and finally ends at the free edge of the nail. Four subtypes have been identified: type Ia (monodactylous, single band), type IIa (polydactylous, single band), type Ib (monodactylous, bifid bands), and type IIb (polydactylous, multiple bands).
- Fragility, onycholysis, splinter hemorrhage, splitting, subungual keratosis, thinning, and V-shaped nick are additional findings at its tip.
- Warty dyskeratoma, glomus tumor, and onychopapilloma may be benign local causes. Longitudinal erythronychia may originate from squamous cell carcinoma, melanoma, and other malignancies.
- Longitudinal erythronychia occasionally underlies hemiplegia, Darier disease, acantholytic dyskeratotic epidermal nevus, postsurgical scarring, and graft-versus-host disease.
- This condition is not commonly associated with acantholytic epidermolysis bullosa, pseudobulbar syndrome, amyloidosis, lichen planus, and acrokeratosis verruciformis of Hopf. Discriminating underlying condition is of exceeding importance for the management of these patients.

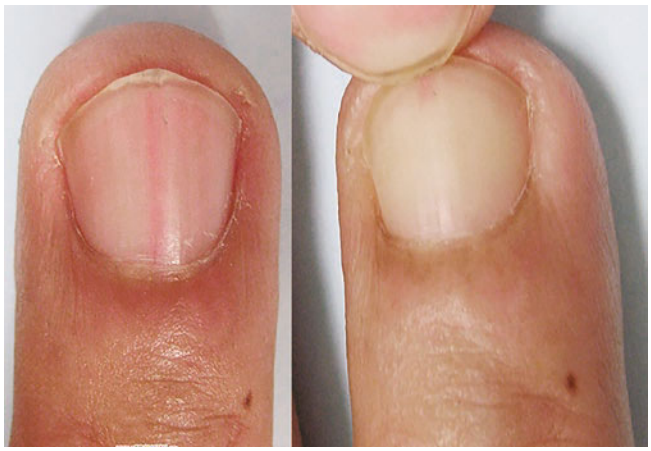


Fig. 20-18-1 The nail was overall normal. A longitudinal red band presented in the middle nail, with a width of 1.5 mm. It began right from the matrix of the nail, extending longitudinally to its proximal end, and it vanished upon slight pressing of the nail

20.19 Chromonychia [21]

- Chromonychia is the discoloring of the subungual soft tissue or nail plate due to miscellaneous causes. Sometimes, chromonychia seems to be a window that provides information about what is occurring in the body.
- The causes of chromonychia are various, including exogenous causes and infection and congenital diseases. Generally, systemic disorders affect many or all the nails simultaneously, whereas infection or localized tumor causes changes in a single or limited number of nails. Sometimes, KOH examination is helpful to identify the exact cause.
- The discoloration follows the shape of the proximal nail fold if the causes are external agents. In contrast, if the cause is internal, the discoloring corresponds to the shape of the lunula.
- Chromonychia involves melanonychia, leukonychia, erythronychia, and yellow and blue chromonychia. Yellow-, green-, or umber-colored chromonychia on the lateral and proximal nail plate are usually caused by fungal and bacterial infection.

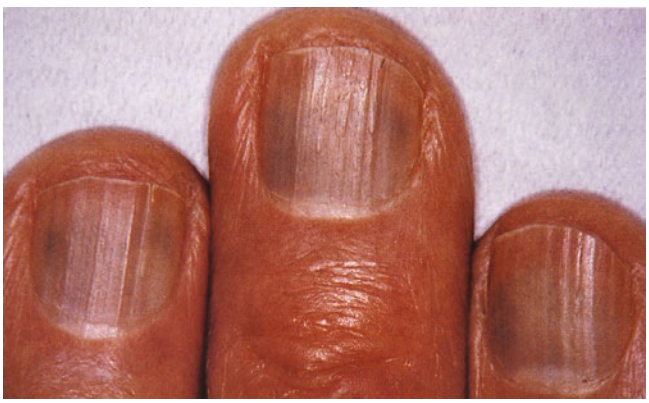


Fig. 20-19a-1 Argyria of the nails

Fig. 20-19a-2 Leukonychia striata

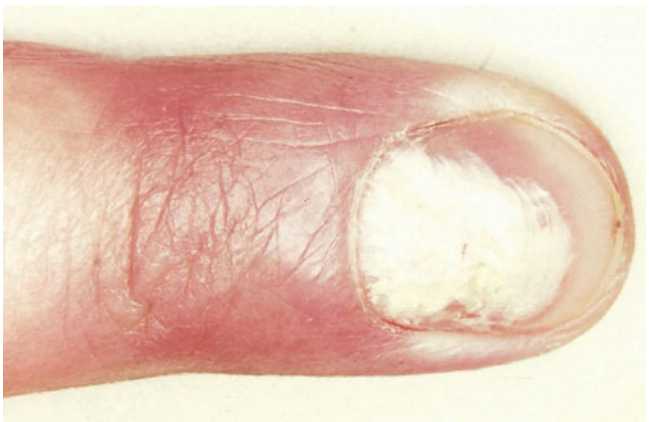


Fig. 20-19a-3 Pseudoleukonychia

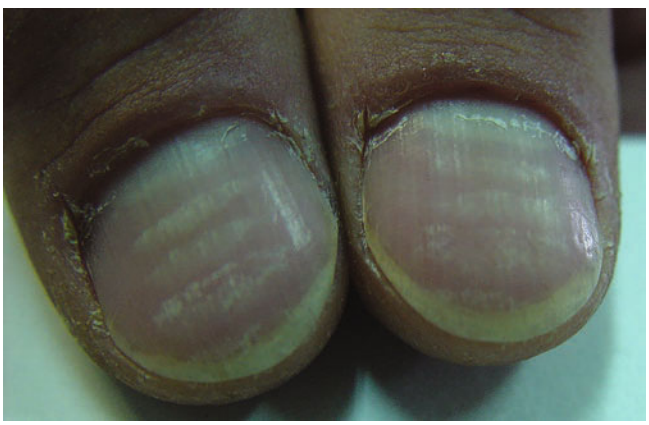


Fig. 20-19a-4 Mees' lines

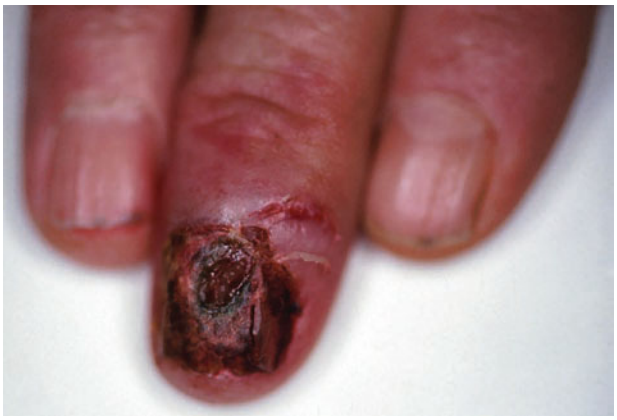


Fig. 20-19b-1 Diffuse black color of the nail plate due to malignant melanoma (MM)

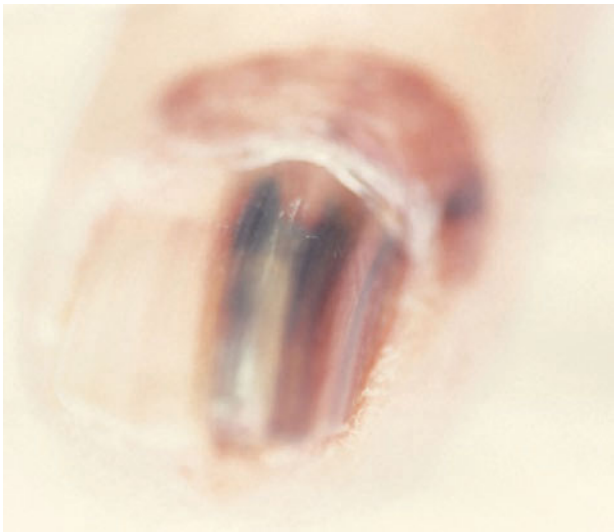


Fig. 20-19b-2 Longitudinal melanonychia (LM) due to malignant melanoma (MM). Hutchinson's sign was positive

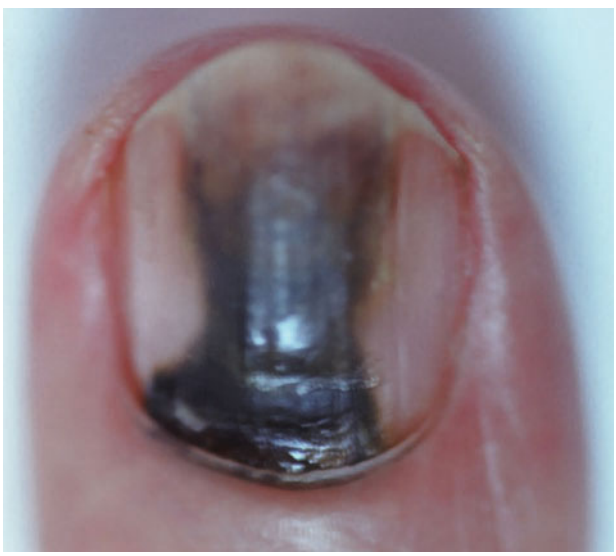


Fig. 20-19b-3 Longitudinal melanonychia (LM) due to malignant melanoma (MM). Hutchinson's sign was negative

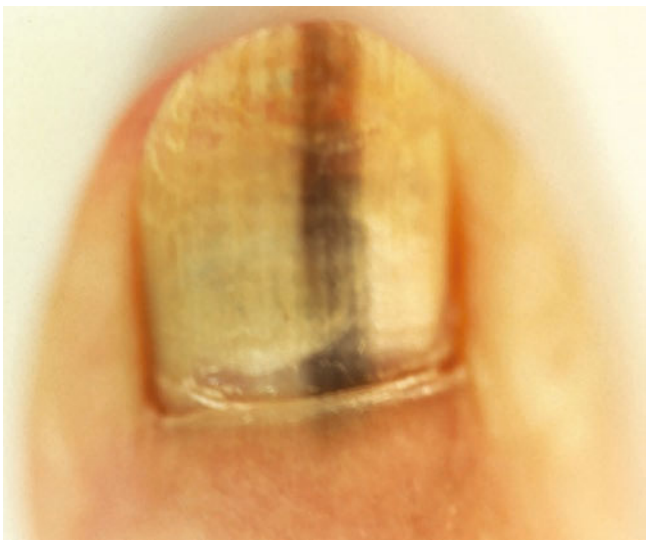


Fig. 20-19b-4 Longitudinal melanonychia (LM) due to congenital melanocytic nevus of the nail

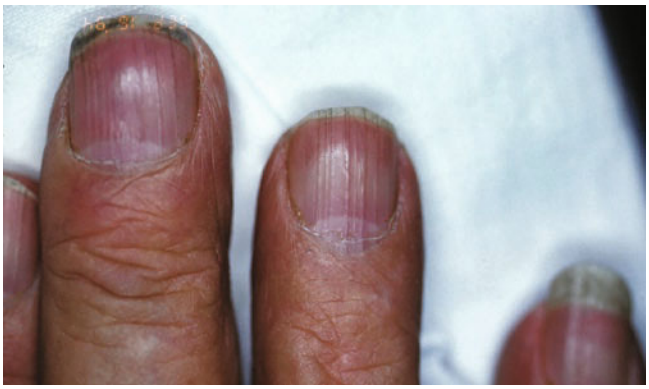


Fig. 20-19c-1 Blue nails due to hypoxia

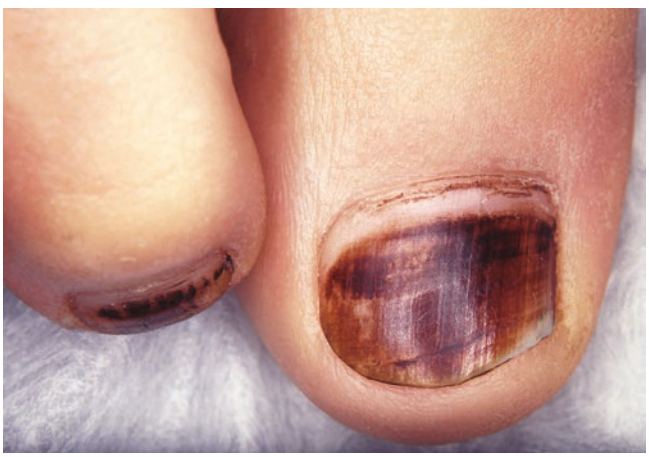


Fig. 20-19c-2 Diffuse brown color of the nail plate due to Betadine solution

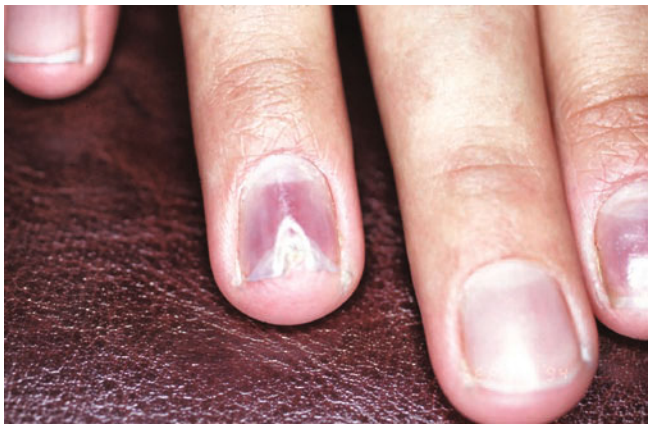


Fig. 20-19c-3 Diffuse brown-purple color of the nail plate due to abuse of amorolfine lacquer

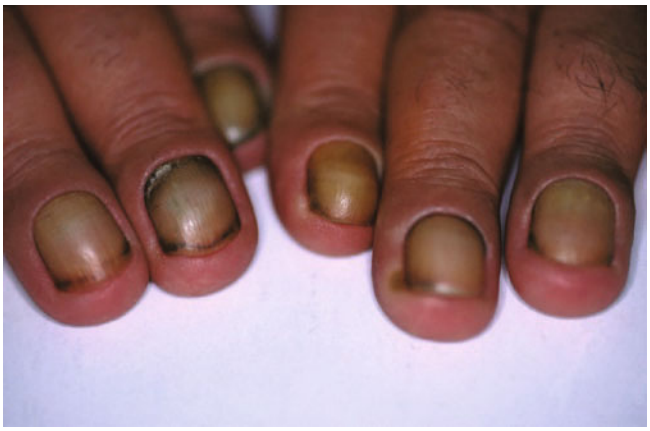


Fig. 20-19d-2 Yellow nail syndrome

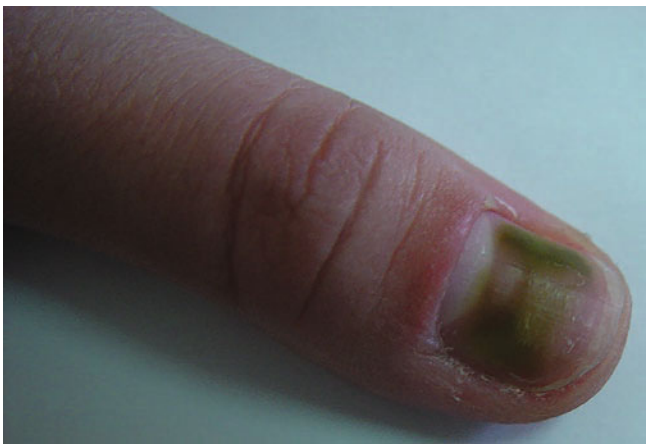


Fig. 20-19c-4 Green nail associated with Pseudomonas infection

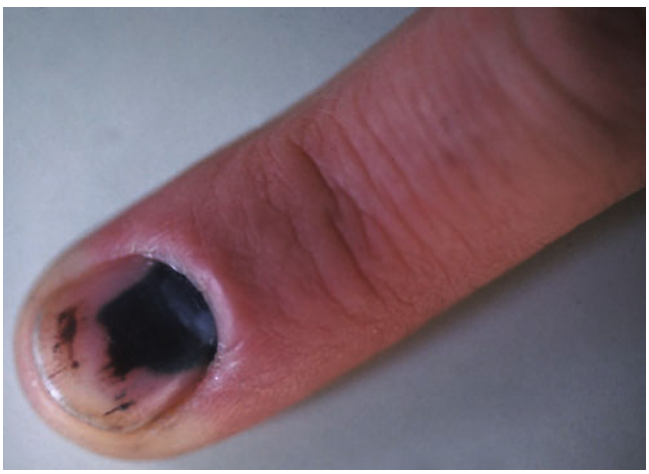


Fig. 20-19d-3 Black nail related to hemorrhage

Fig. 20-19d-1 Orange nails

20.20 Subungual Splinter Hemorrhage [22]

- Subungual splinter hemorrhages (SSH) are characterized by fragility of the underlying capillaries resulting in bleeding under the nail. The bleeding resembles a brown streak or splinter that does not grow out with the nail.
- SSH can be caused by a variety of factors, including trauma, vitamin C deficiency, some drugs, hemodialysis, psoriasis, nail lichen planus, subacute endocarditis, and primary antiphospholipid syndrome. Idiopathic atraumatic SSH has been reported in healthy individuals.
- The new lesions are associated with intense pain and tenderness that persists for several days. Bleeding is commonly located in the distal one-third of nails but is also seen in the middle and proximal thirds.
- The treatment consists of controlling underlying pathologies such as infections, connective tissue diseases, and vasculitis. Drug-induced SSHs generally regress after drug discontinuation.

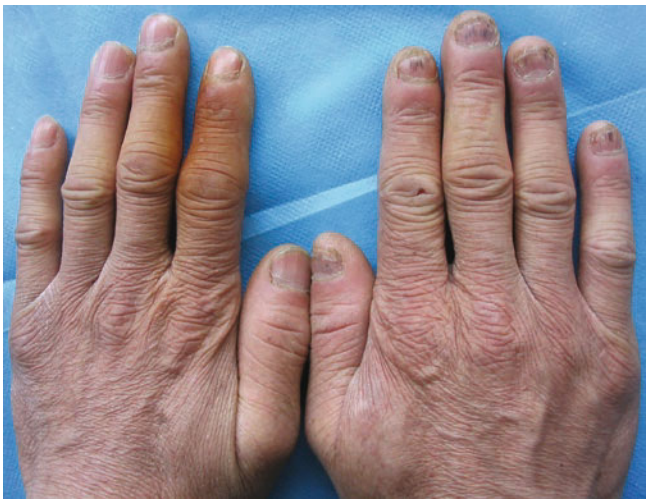


Fig. 20-20-1 Non-blanchable, reddish-brown, linear hemorrhages involved the distal half of the right five nails. All the left fingernails were normal

20.21 Sebaceous Gland Hyperplasia [23]

- Sebaceous gland hyperplasia (SGH) is multiple papules or occasionally solitary nodule occurring mainly on the forehead, infraorbital regions, and temples. Unusual sites may be observed such as the areolas, nipples, scrotum, and chest.
- The lesions are small flaxen umbilicated papules that are 2–6 mm in diameter. There are two types of SGH: circumscribed (senile) and diffuse (presenile). Circumscribed SGH may occur in elderly persons. Single or multiple flaxen papules with central umbilication are present on the forehead.
- Diffuse SGH occurs mainly in young adults. The neck, upper chest, and back may be involved in a marked region of seborrhea.
- Unique appearances of SGH have been reported: for example, giant nodular (a nodule of 5 cm in diameter), cystic, diffuse presenile, and multiple polypoid.
- Histopathology: The sebaceous glands are hypertrophied and grouped around a dilated sebaceous duct just beneath the epidermis.

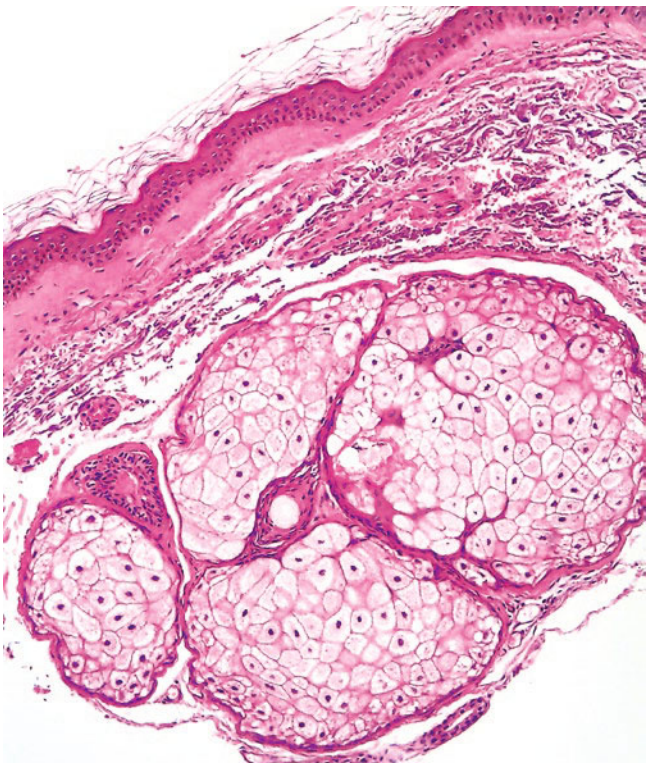


Fig. 20-21a-2 A large sebaceous gland in the upper dermis

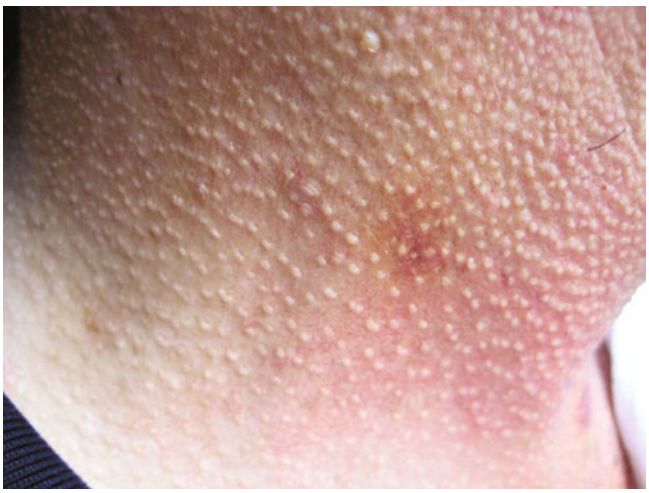


Fig. 20-21a-1 Numerous small yellowish papules ranging from 2 to 6 mm in diameter on the neck

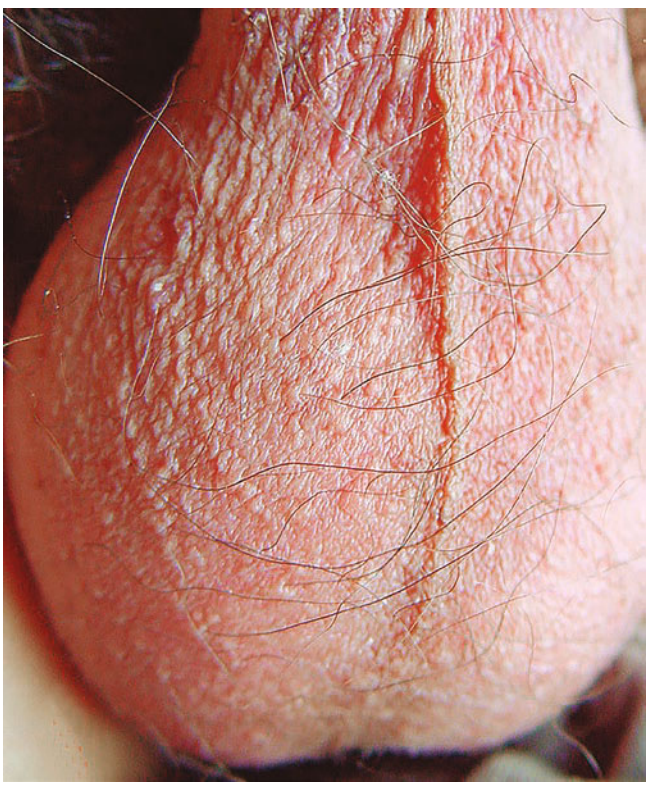


Fig. 20-21b-1 Fresh-colored or yellowish papules on the scrotum

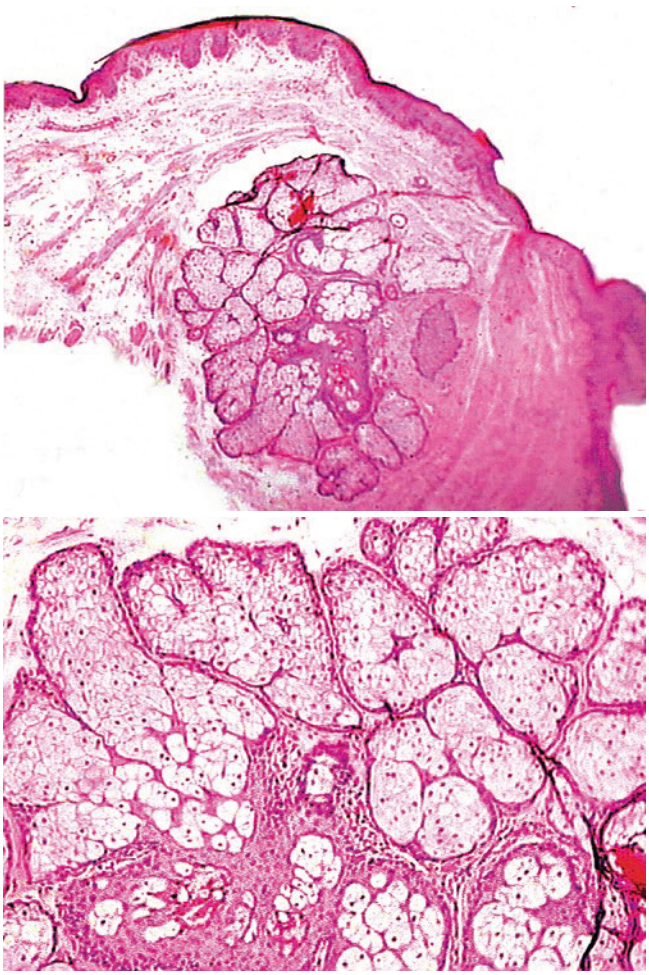


Fig. 20-21b-2, 20-21b-3 Hyperplasia of well-differentiated sebaceous gland in lobules, with dilated gland duct (HE stain ((2) ×40, (3) ×200)

20.22 Sebaceous Hyperplasia within Epidermis After Scald [24]

- Sebaceous hyperplasia appearing within epidermis after scald is unique.
- The clinical manifestation is highlighted by numerous, small rufous, 2–5 mm papules appearing in a large, irregular depigmented patch after a severe scald. Some papules have a semicircular configuration.
- Microscopic examination revealed numerous mature sebaceous glands in the middle and bottom of the epidermis with slight acanthosis.
- The pathogenesis of this phenomenon may be related to high androgen levels in the healing of the skin after a scald because the girl had a history of polycystic ovarian syndrome.

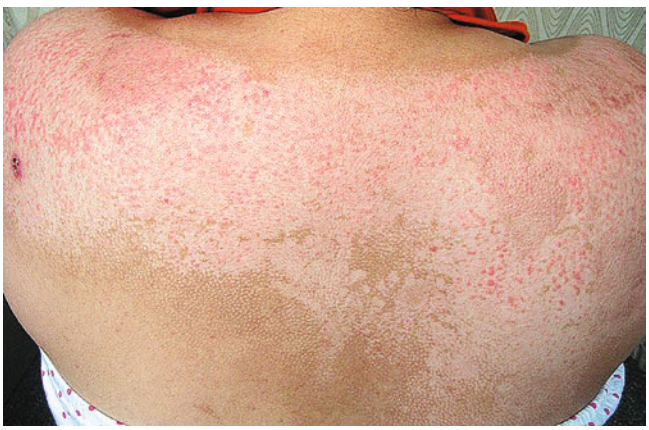


Fig. 20-22-1 On the upper back, there was a large depigmented area dotted with brown papules with the diameter ranging from 2 to 3 mm (Reproduced with the permission from [25])

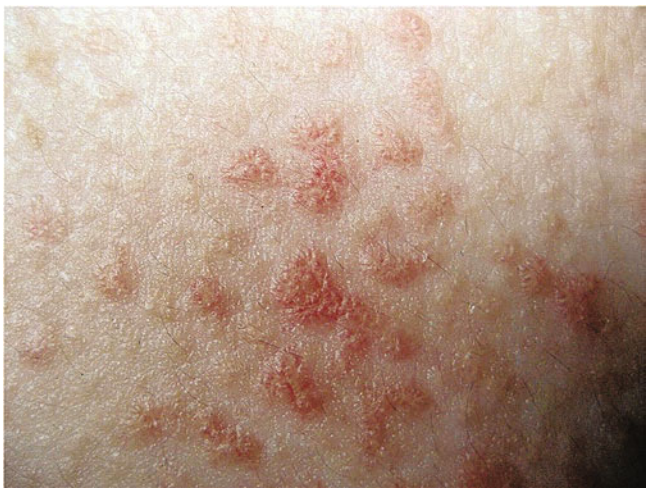


Fig. 20-22-2 Semicircular papules on the back (Reproduced with the permission from [25])

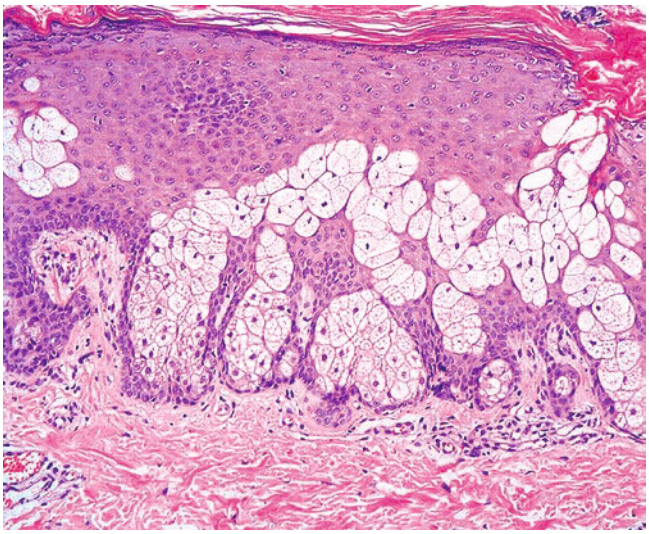


Fig. 20-22-3 Many mature sebaceous glands were aberrantly distributed in the middle and lower part of the epidermis. There was slight acanthosis (HE stain, ×100) (Reproduced with the permission from [25])

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Disorders of the Mucous Membranes

21

Xue-Song Jia, Qing Sun, Hong-Wei Wang, and Ru-Zhi Zhang

Abstract

Melkersson-Rosenthal syndrome, plasma cell cheilitis, and nonvenereal sclerosing lymphangitis of the penis are elaborately chosen in this chapter.

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21.1 Melkersson-Rosenthal Syndrome [1, 2]

- Melkersson-Rosenthal syndrome (MRS) has an autosomal dominant pattern of inheritance with incomplete penetrance and usually occurs in childhood and adolescence. The responsible gene is on chromosome 9p11.
- The etiology is unknown. Several risk factors, including infection, allergy, hereditary predisposition, autoimmune disorder, and foreign-body irritation, have been reported.
- The MRS comprises the triad of symptoms: recurrent lip and/or face swelling, fissured tongue, and intermittent facial palsy. The most familiar symptom is nonpitting swelling in the orofacial areas, most frequently involving the upper lip.
- The characteristic histopathological finding is noncaseating granuloma, which is distributed mainly in the superficial and middle layers of the dermis.
- Systemic or intralesional corticosteroid and immunosuppressive regimens are often temporarily beneficial. Surgery is more effective for serious cases.

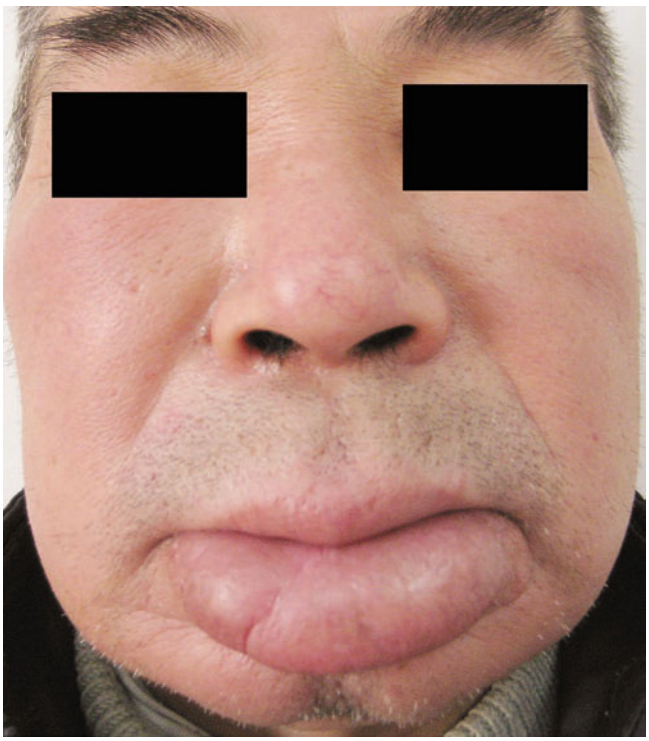

Fig. 21-1-1 Left nasolabial shallow fold, slightly rightward commissure (Reproduced with the permission from [1, 2])

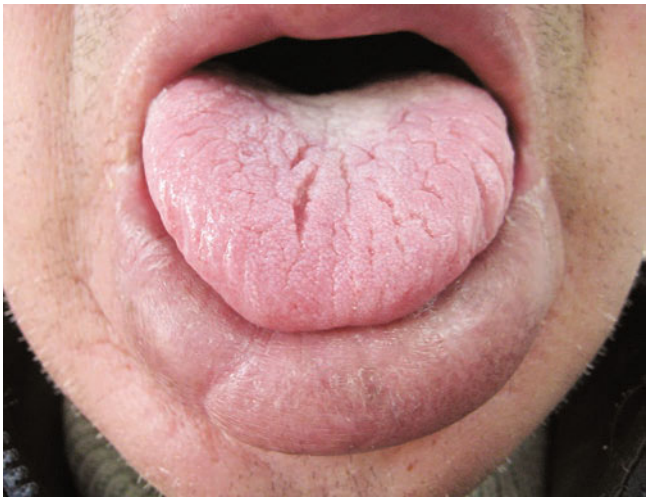

Fig. 21-1-2 Diffuse swelling of the lower lip, tongue slightly skewed to the right, enlarged fissured tongue

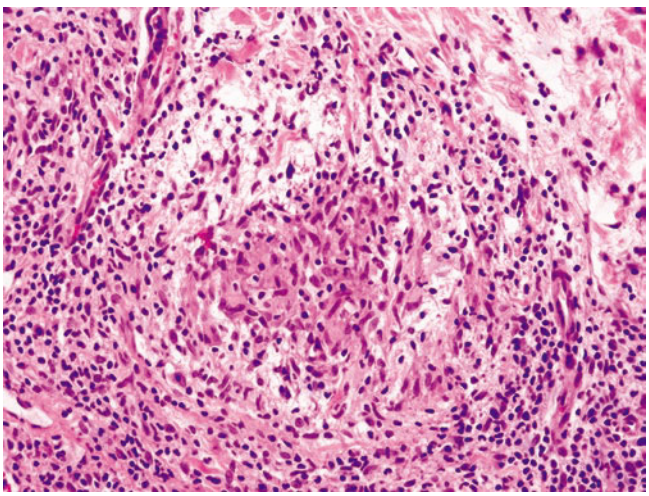

Fig. 21-1-3 Epithelioid granulomas surrounded by lymphocytic infiltrate in the deep dermis (HE stain, ×200)

21.2 Plasma Cell Cheilitis [3, 4]

- Plasma cell cheilitis (PCC), known as plasma cell orificial mucositis, is an idiopathic, uncommon, and benign inflammatory mucosal condition. There may be a nonspecific inflammatory response to unknown exogenous agents, such as subclinical infection, poor hygiene, trauma, friction, moisture, or candidiasis.
- PCC is characterized by sharply demarcated, infiltrated, reddish plaque, erosions, ulcers, and occasional nodules within the mucosa, usually on the lower lip of elderly individuals. The histological characteristics include dense polyclonal plasma cell infiltrates within the dermis.
- Several treatments for PCC have been reported, including topical steroids, intralesional injections of corticosteroids, topical antibiotics, tacrolimus, pimecrolimus, or other calcineurin inhibitors.

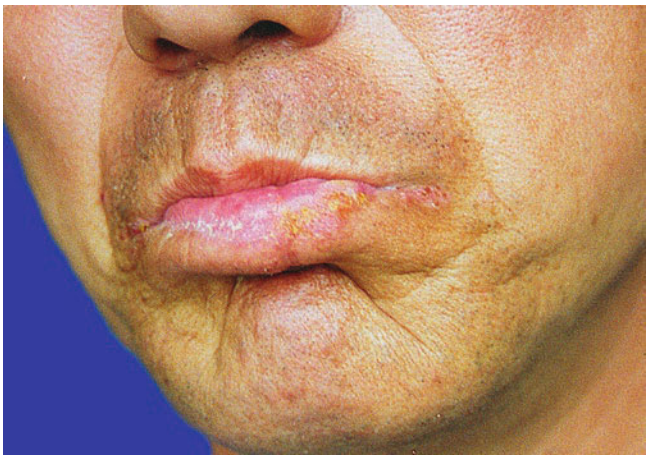

Fig. 21-2-1 A dark red plaque covered with scales and crusts on the lower lip

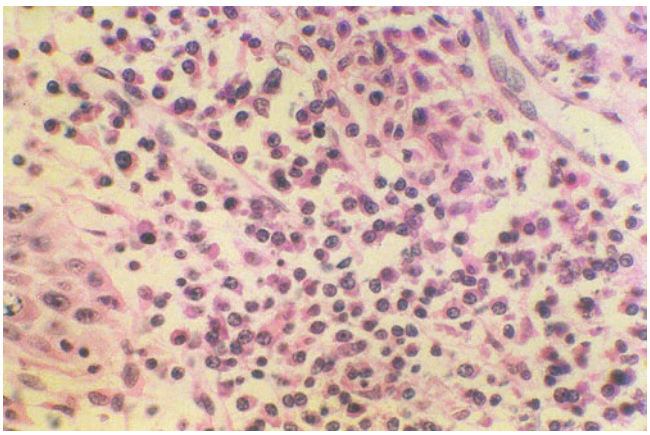

Fig. 21-2-2 Diffuse infiltration of plasma cells and a few lymphocytes in the dermis (HE stain, ×500)

21.3 Nonvenereal Sclerosing Lymphangitis of the Penis [5]

- Sclerosing lymphangitis of the penis is an infrequent benign self-resolving process of unknown etiology, which affects the distal lymphatics of this organ. It has been related to microtraumas in the area after intense sexual activity.
- The lesion displays a minimally tender, translucent, and indurated cord involving the coronal sulcus and occasionally adjacent distal penile skin, most often within 7 days after vigorous sexual intercourse or masturbation.
- The condition can cause anxiety and embarrassment owing to its genital location and alarming appearance. Since it is self-limited, resolution occurs spontaneously within 4–6 weeks. Initial treatment should be conservative, with only reassurance along with abstinence from sexual activity required.

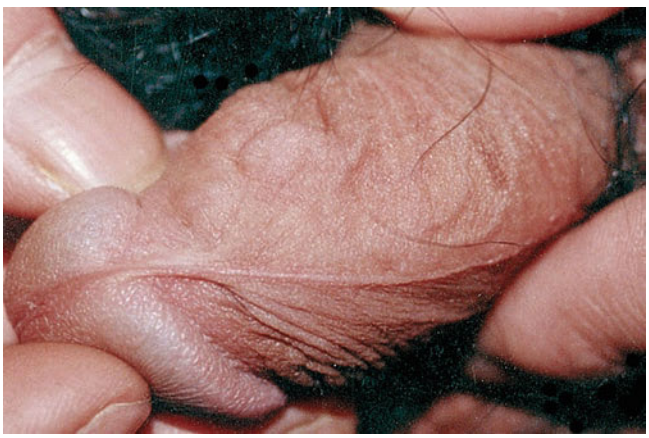

Fig. 21-3-1 A cordlike structure encircling the coronal sulcus of the penis

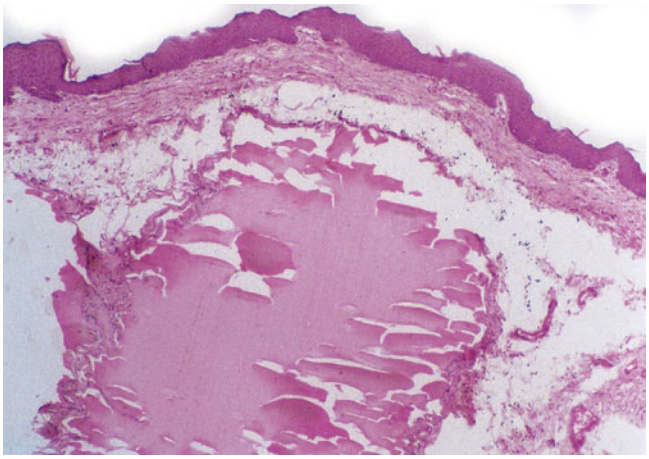

Fig. 21-3-2 A dilated lymph vessel containing homogeneous lymph liquid in the dermis (HE stain, ×40)

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Part VIII

Metabolic and Systemic Diseases

Metabolic and Nutritional Skin Diseases

22

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Abstract

Metabolic and nutritional skin diseases presented in this chapter comprise tuberous xanthoma associated with aortic stenosis, xanthoma disseminatum, lipoid proteinosis, necrobiosis lipoidica, juvenile xanthoma, necrobiotic xanthogranuloma, adult xanthogranuloma, congenital erythropoietic porphyria, poikiloderma-like cutaneous amyloidosis, nodular amyloidosis, lichen myxedematosus, scleromyxedema, follicular mucinosis, reticular erythematous mucinosis, cutaneous focal mucinosis, acral persistent papular mucinosis, pellagra, carotenemia, glycogen storage disease type I, and alkaptonuric ochronosis.

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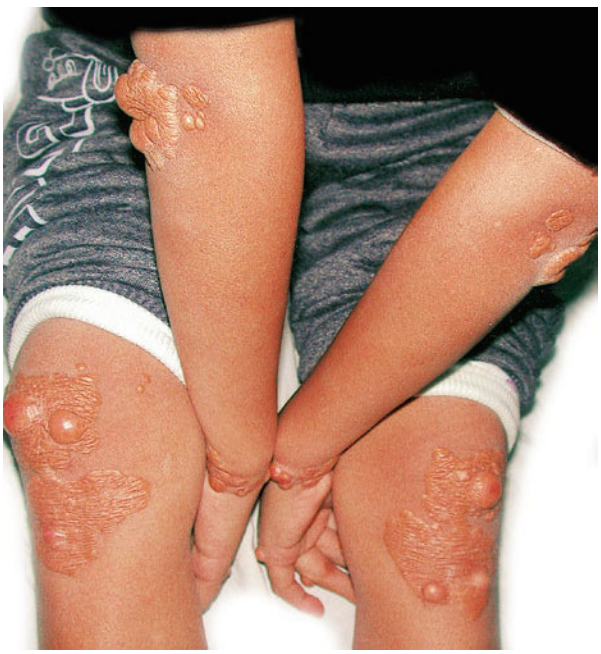
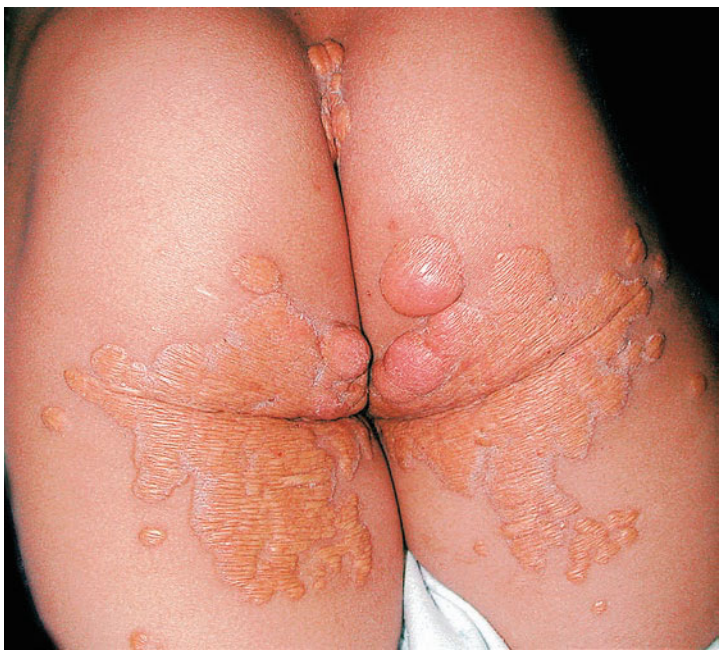
22.1 Tuberous Xanthoma Associated with Aortic Stenosis [1]

- Tuberous xanthoma is an important clinical marker of disordered lipid metabolism. It predominantly occurs in patients with familial hypercholesterolemia (FH) and usually manifests as asymptomatic yellowish or reddish nodules within the dermis and subcutaneous tissue, such as the extensor surface of the buttocks and limbs.
- Histopathologic examination shows foam cells, some of which form nodular proliferation in the dermis and others within collagen bundles.
- Aortic stenosis is stenosis of the exit of the left ventricle of the heart in which the aorta begins, mostly in association with FH. Early diagnosis of FH is vital for assuring long-term survival of the patients.





Figs. 22-1-1, 22-1-2 Symmetric yellow nodules partly confluent on the extensors of the finger, wrist, elbow, knee joint (1), and stern (2)

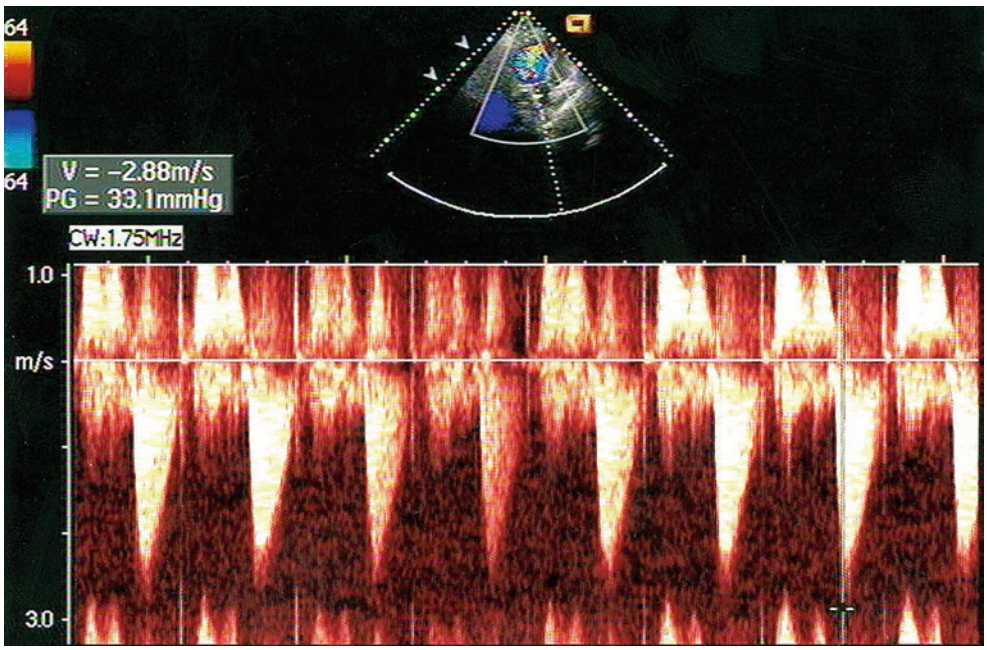


Fig. 22-1-3 Flow velocity was 2.88 m/s through the aortic valve, and the pressure gradient of aortic valve was 4.4 kPa, in the aortic stenosis by color Doppler ultrasound

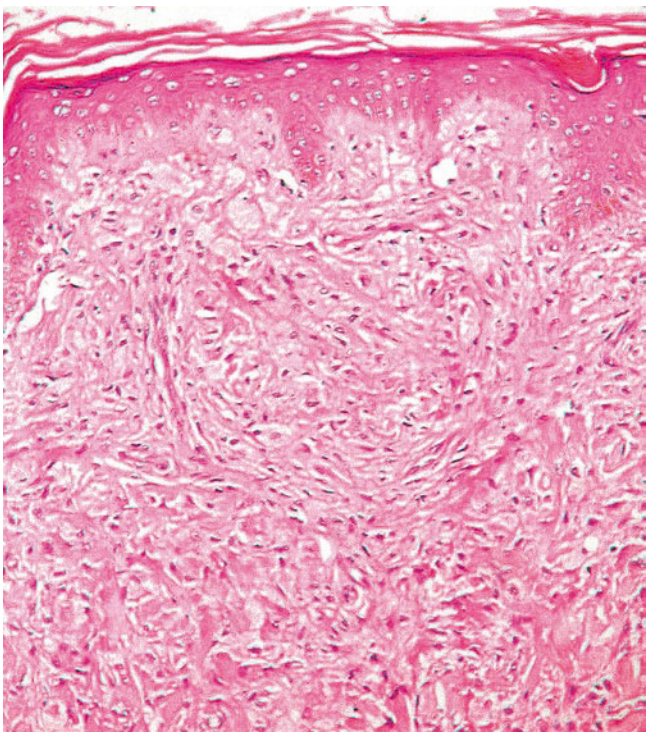
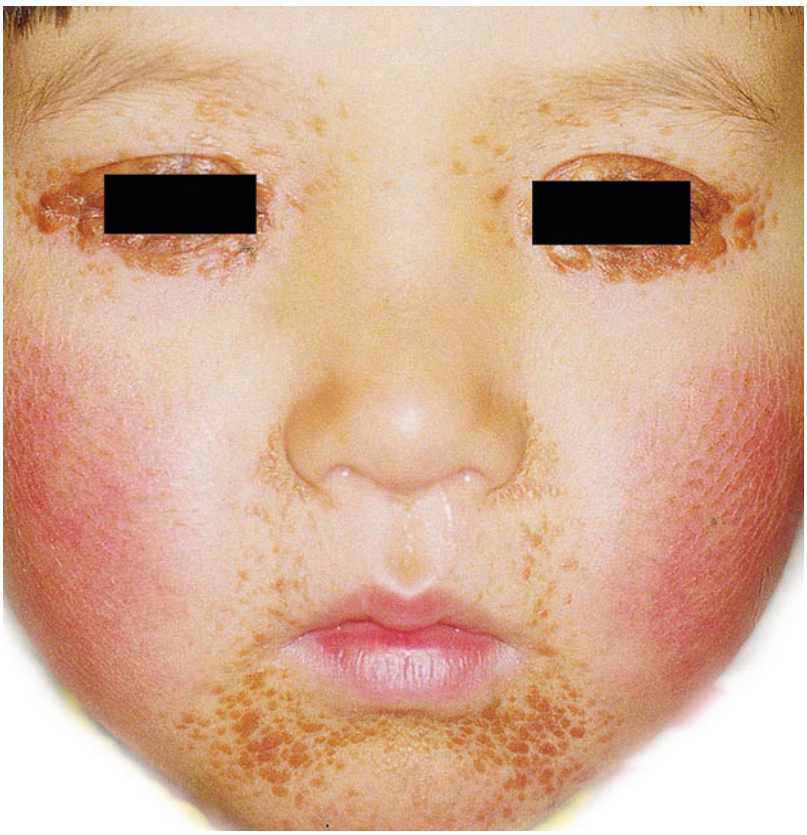
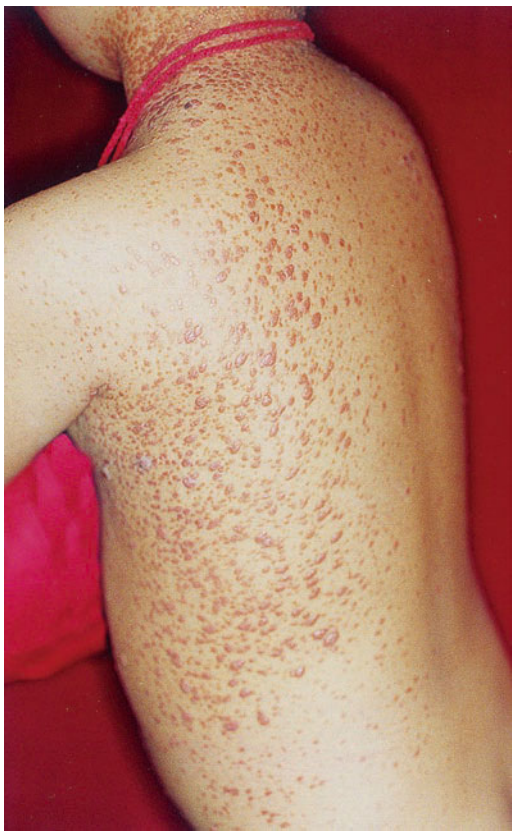


Fig. 22-1-4 Considerable foam cells in the dermis (HE stain, ×200)

22.2 Xanthoma Disseminatum [2, 3]

- Xanthoma disseminatum (XD), also named Montgomery syndrome, is a benign histiocytic proliferative disorder of non-Langerhans cell origin. The patient usually lacks a lipid metabolism disorder and hyperlipidemia.
- The lesions of XD typically present as hundreds of discrete brownish-yellow xanthoma-like papules and nodules, chiefly involving the face and trunk and also occurring in flexures and folds. They may damage the mucous membranes of the cornea, pharynx, throat, conjunctiva, and oral cavity.
- The exact diagnosis of XD relies on pathological examination, which demonstrates the infiltration of tissue cells and Touton giant cells.
- Because of the asymptomatic and self-healing characteristics, most patients do not require early and intensive treatments.





Figs. 22-2-1, 22-2-2 Numerous disseminated orange and yellow brown papules with smooth appearance over the face, neck, trunk, and limbs (Reproduced with the permission from [2, 3])

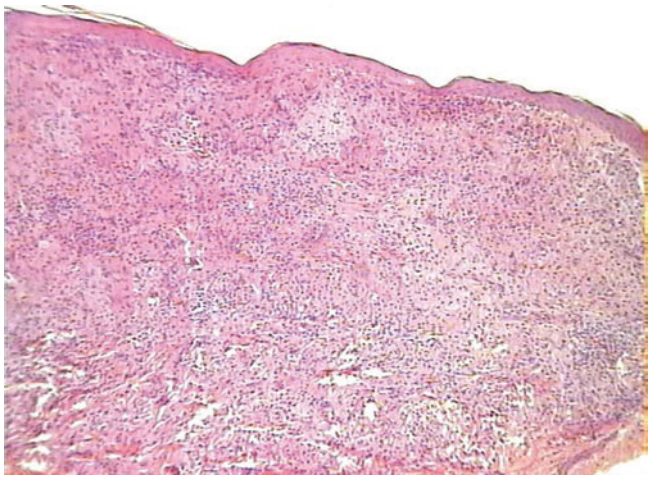


Fig. 22-2-3 Numerous histiocytes and foam cells infiltrate in the dermis (HE stain, ×40)

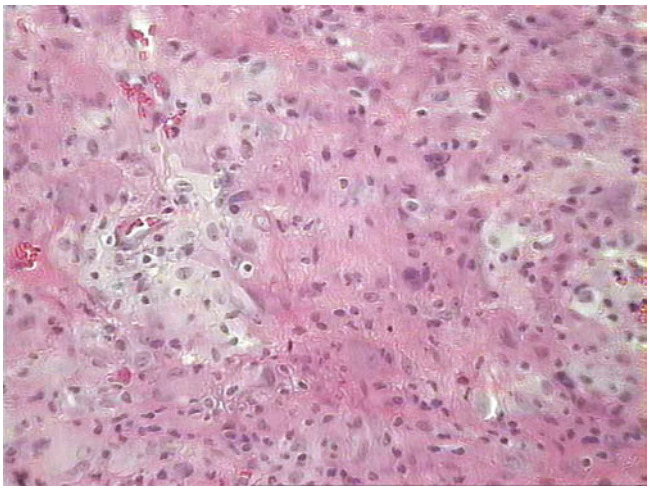


Fig. 22-2-4 A few multinucleated giant cells and lymphocytes without Touton giant cell in the dermis (HE stain, ×100)

22.3 Lipoid Proteinosis [4, 5]

- Lipoid proteinosis (LP) or Urbach–Wiethe syndrome is a rare, autosomal recessive, inherited disorder characterized by the deposition of hyaline materials in the mucosal membrane and skin.
- The clinical presentation is variable, including poor nail growth, alopecia areata, hypohidrosis, dental anomalies, hoarseness, air duct obstruction, epileptic seizures, and behavioral changes.
- The classic and most easily recognizable sign is beaded eyelid papules along the upper and lower eyelid margins and brownish verrucous plaques over the extensor surfaces.
- Histology is characterized by the periodic deposition of characteristic amorphous PAS-positive material in the extracellular and perivascular regions.

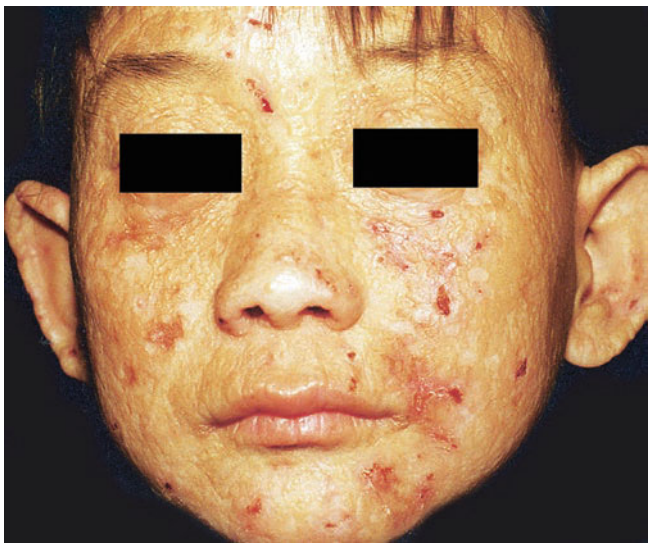


Fig. 22-3-1 Numerous, skin-colored, waxy papules on the face, with acneiform scarring (Reproduced with the permission from [4, 5])

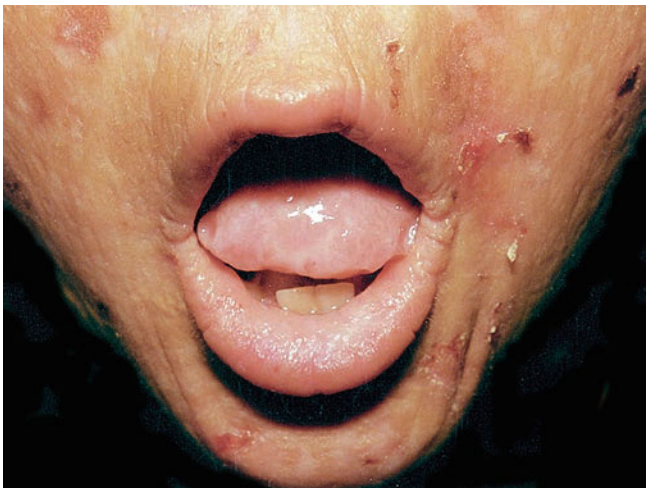


Fig. 22-3-2 Yellow white macroglossia with infiltration, and the tongue is big and hard, and the patient was unable to protrude it beyond the margins of the lips

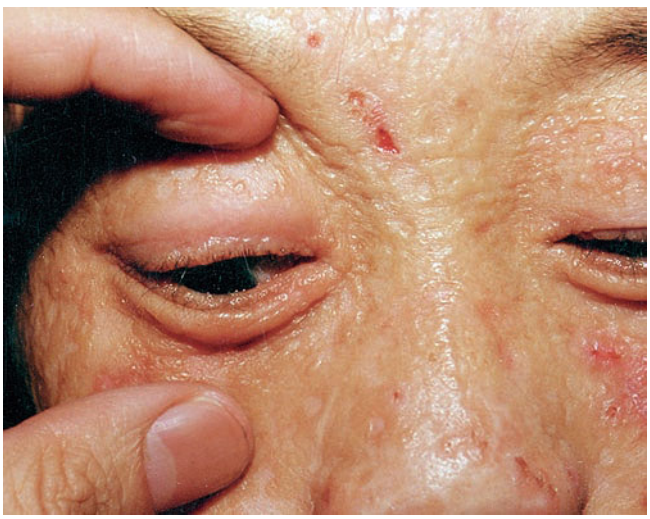


Fig. 22-3-3 Papules arranged like beads on a string on the upper and lower eyelid margins

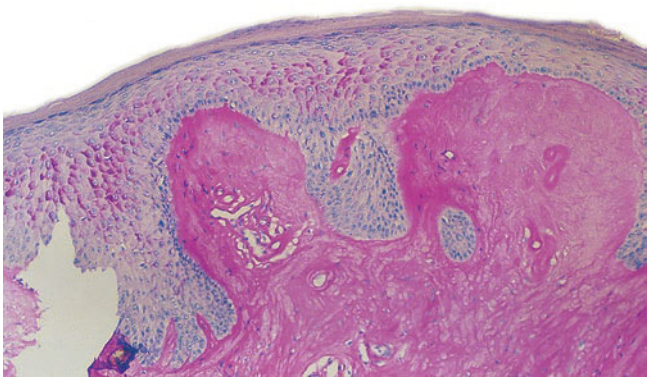


Fig. 22-3-4 An amorphous hyaline material in the papillary dermis (×100)

22.4 Necrobiosis Lipoidica [6]

- Necrobiosis lipoidica (NL) is an uncommon chronic inflammatory granulomatous dermatosis of unknown etiology that may be related to diabetes mellitus. It is usual during the third to fourth decade of life with a small female predominance.
- Skin lesions are primarily located in the pretibial region and are characterized by well-circumscribed, firm, sunken, waxy, brownish atrophic plaques. Other areas of the body can also be influenced. The histological characteristics are necrosis of dermal collagen surrounded by palisading histiocytes.
- There are a multitude of possible treatment options for NL, including topical and intralesional glucocorticoids, topical calcineurin inhibitors, pentoxifylline, and adalimumab, among others. Ulcerative NL has been a therapeutic challenge to date.

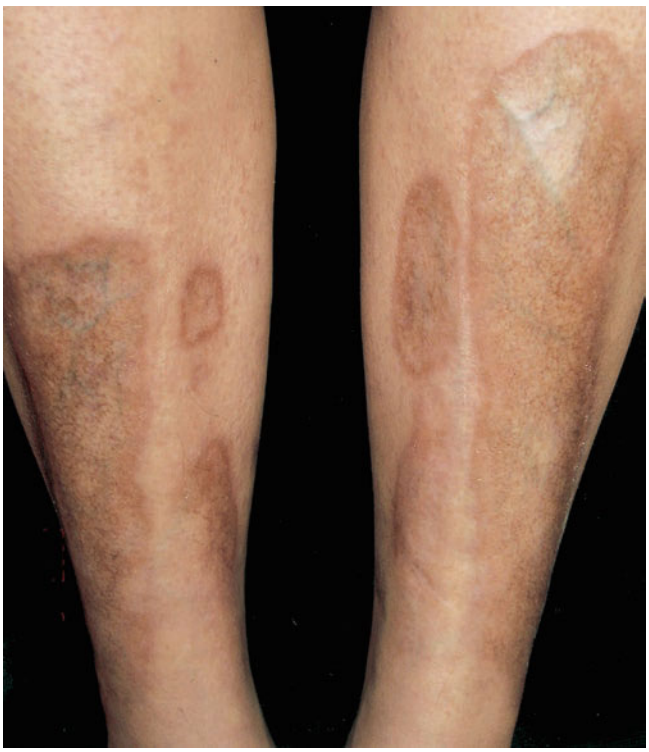


Fig. 22-4-1 Variously sized, oval violaceous plaques with slight atrophy and telangiectases in the center of both pretibial

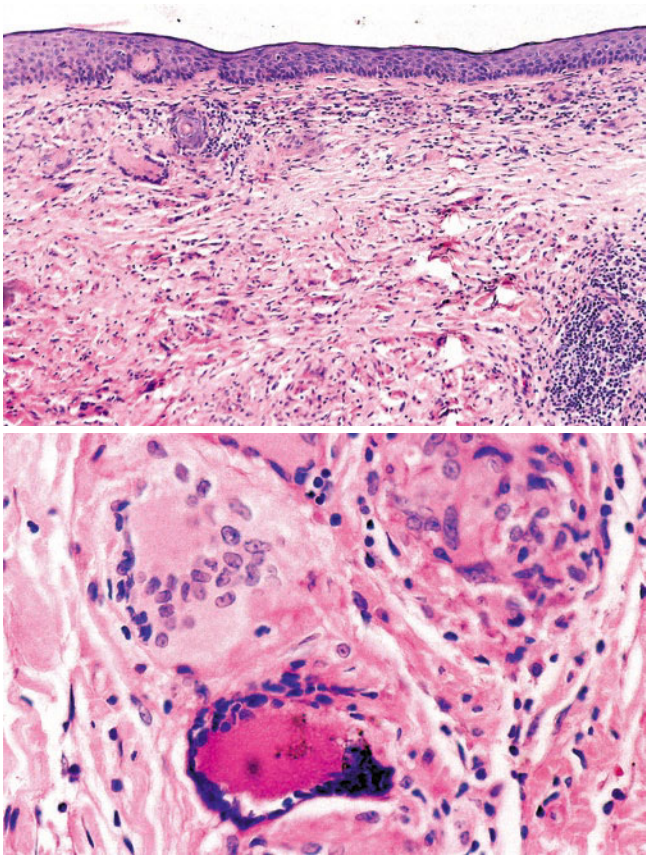


Fig. 22-4-2, 22-4-3 Epidermal atrophy, collagen degeneration, multinucleated giant cells, epithelioid cells, lymphocytes and plasma cells infiltrated in the dermis, and multiple multinucleated giant cells located between the dermis and the subcutaneous tissue (HE stain (2) ×100, (3) ×400)

22.5 Juvenile Xanthoma [7, 8]

- Juvenile xanthogranuloma (JXG) is a rare non-Langerhans cell histiocytosis that is mainly limited to the skin but sometimes presents in extracutaneous locations and as a solitary or multiple papulonodular lesions mostly involving the head and neck area. It generally occurs in children's skin.
- Clinically, it is characterized by the presence of papules or firm nodules of a pinkish or yellow-brownish nature, which mainly compromise the skin and, unconventionally, other organs.
- Histological and immunohistochemical examinations reveal proliferation of non-Langerhans cell histiocytes and foamy cells. JXG includes three typical histologic types: early JXG (EJXG), transitional JXG (TJXG), and classic JXG (CJXG).

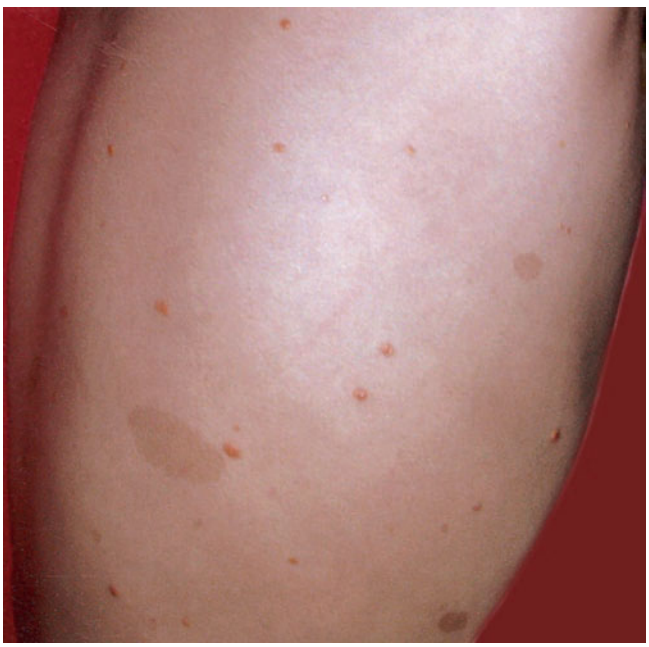


Fig. 22-5a-1 Multiple buff flat papules and several café macules

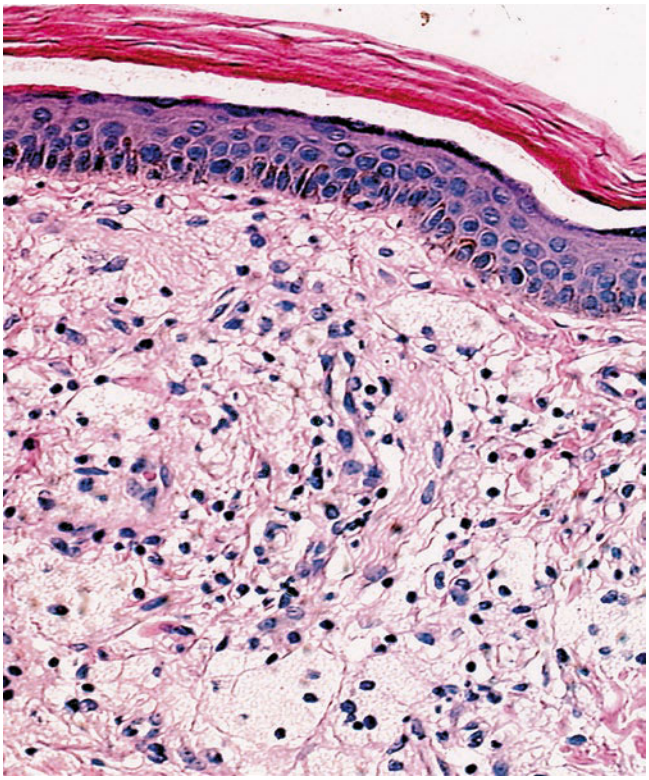


Fig. 22-5a-2 Numerous histiocytes and foam cells and a few lymphoid cells infiltrated in the upper and middle dermis (HE stain, ×400)

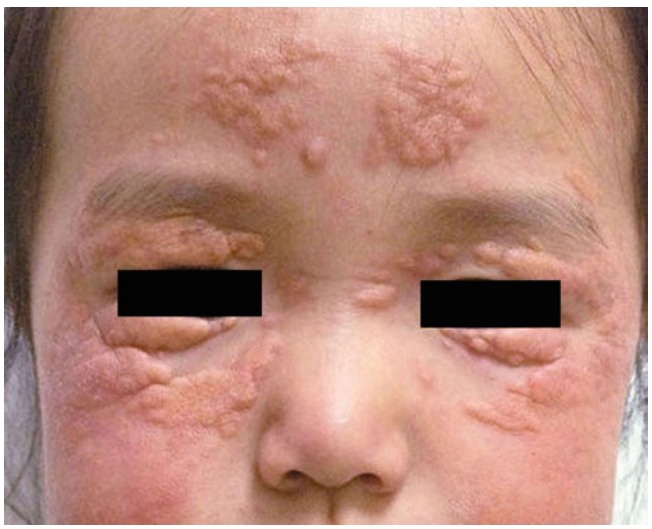


Fig. 22-5b-1 Diffused red-brown papules with infiltration, as well as some solitary yellow nodules among the papules over the face (Reproduced with the permission from [7, 8])

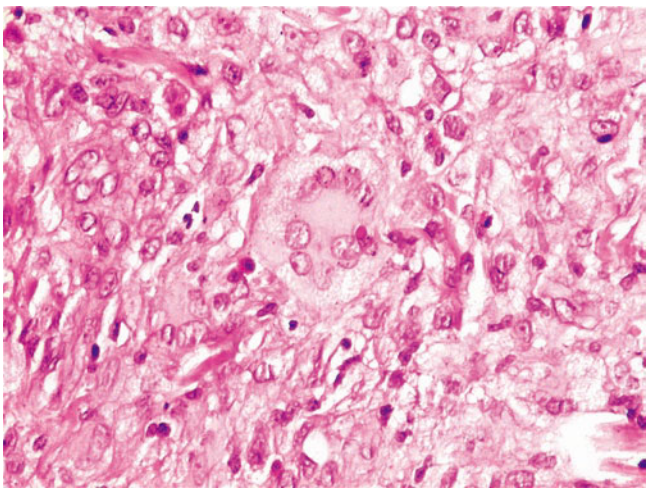


Fig. 22-5b-2 Typical Touton giant cells (HE stain, ×400)

22.6 Necrobiotic Xanthogranuloma [9, 10]

- Necrobiotic xanthogranuloma (NXG) is an indolent dermatological disease with unknown etiology and pathogenesis. Eighty percent of patients with NXG have paraproteinemia, and 10% have multiple myeloma.
- Clinically, it presents multiple yellowish tumor-like plaques and plaques, which predominantly involve the trunk, extremities, and face (periorbital regions). The regions of necrobiosis often exhibit a foamy appearance.
- Histology is characterized by the formation of a granuloma within the subcutaneous and dermal layers, with focal areas of necrobiosis.

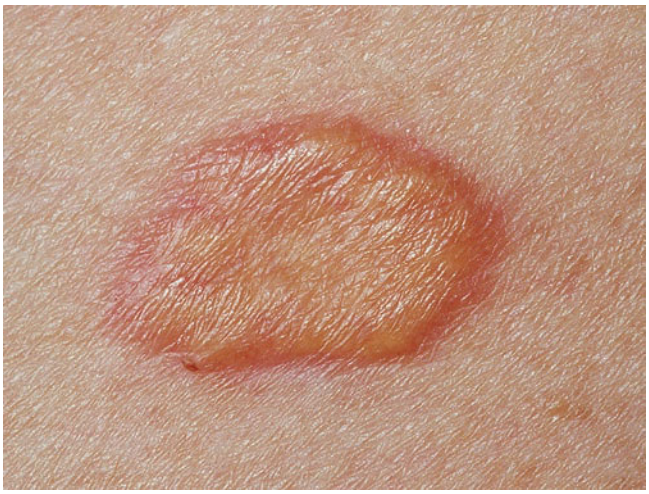


Fig. 22-6-1 Round xanthomatous plaques with central atrophy and elevated edge

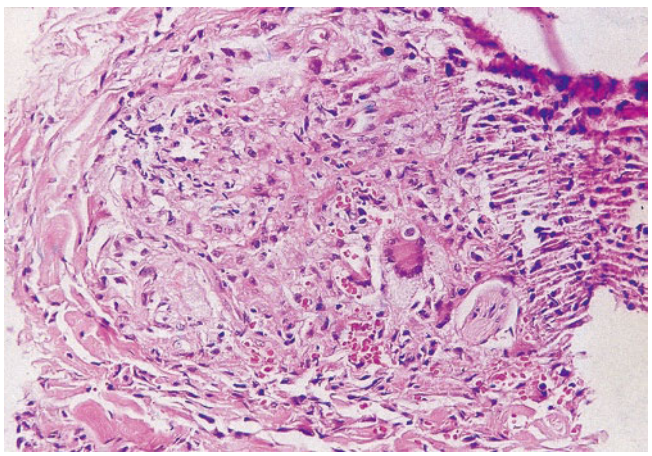


Fig. 22-6-2 Xanthogranulomatous pictures accompanied with necrobiosis in the dermis (HE stain, ×200)

22.7 Adult Xanthogranuloma [11, 12]

- Juvenile xanthogranuloma (JXG) is a disease that mostly influences infants and children. Approximately 10% of JXGs manifest in adulthood, which is termed "late-onset JXG," also known as adult xanthogranuloma (AXG).
- The etiopathogenesis of AXG is poorly understood. Physical trauma, infection, and malignancy may be induced factors.
- Clinically, AXG presents as solitary or multiple yellowish, orange-red, or tan-hued papules without systemic manifestations.
- Histopathology reveals dendritic-like mixed cell infiltration in the dermis and/or subcutaneous tissue.
- AXG does not commonly resolve spontaneously. Surgery and carbon dioxide laser have been shown to be effective for a solitary lesion. Systemic retinoids can be administered for the treatment of multiple lesions.

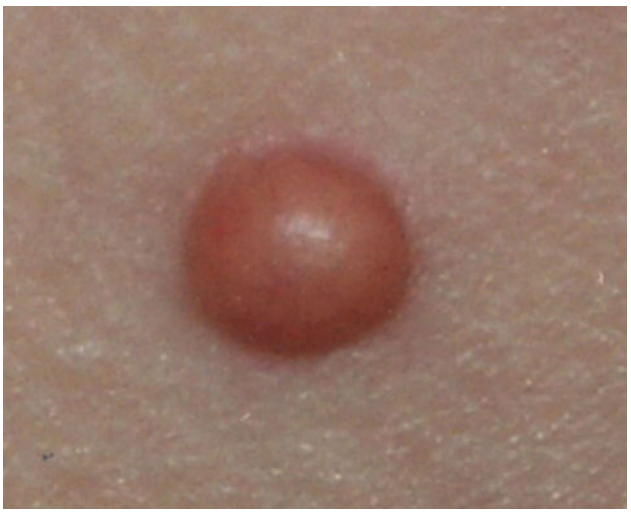


Fig. 22-7-1 A light yellow nodule on the neck

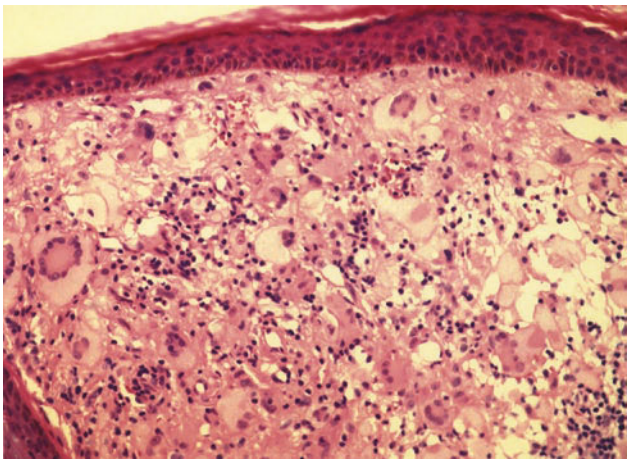


Fig. 22-7-2 Epidermal atrophy and numerous foam cells and lymphocytes associated with Touton giant cell in the dermis (HE stain, ×100)

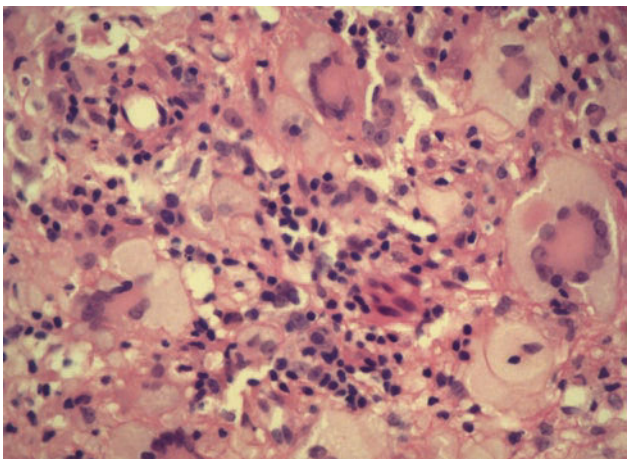
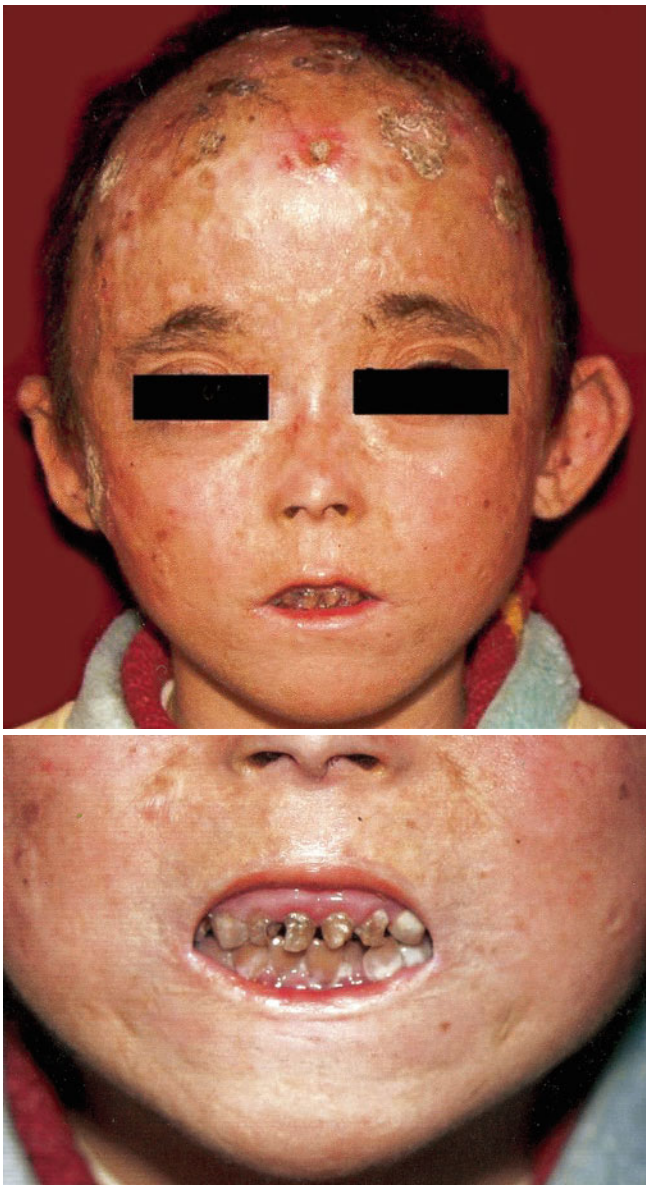


Fig. 22-7-3 The Touton giant cell has nuclei forming a ring surrounded by foamy cytoplasm (HE stain, ×150)

22.8 Congenital Erythropoietic Porphyria [13]

- Congenital erythropoietic porphyria (CEP), also called Gunther's disease, is an extremely uncommon recessive disease caused by a decline in uroporphyrinogen III synthase enzymatic activity.
- Clinically, patients with CEP present with childhood onset of photosensitivity, recurrent blistering, erosions, scarring and fluorescent teeth, and urine under Wood's lamp. Additionally, different degrees of hemolytic anemia and splenomegaly are common symptoms.
- Sun avoidance, prevention of minor trauma, broad spectrum sunscreens, and prompt treatment of secondary infections are the most common therapeutic modalities.



Figs. 22-8-1, 22-8-2 Old facial appearance, hypertrichosis hyperpigmentation, mutilating scar, partial loss of auricle, nose diminishment, lip attenuation, actinomorphic lines around the mouth, and multiple erythrodontia (Reproduced with the permission from [13])

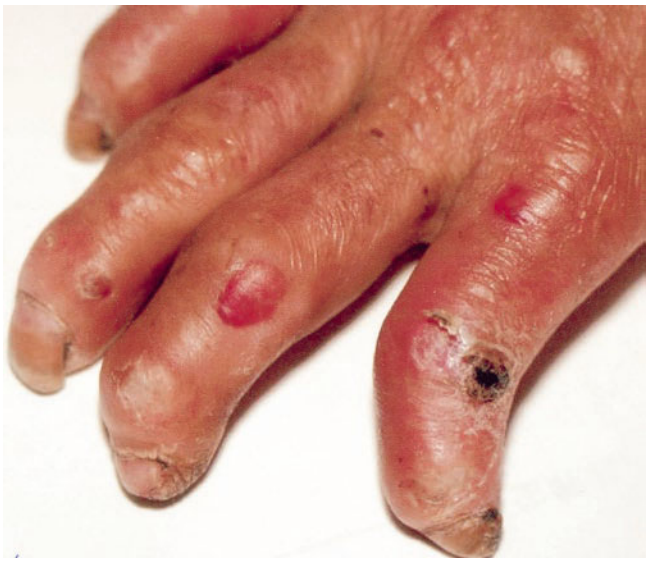


Fig. 22-8-3 Deformities of extremity ends and several soybean-sized blood blisters on the fingers

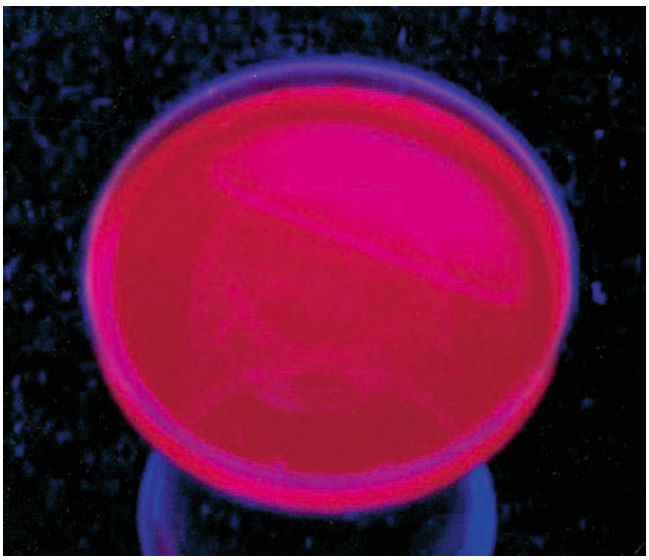


Fig. 22-8-5 Urine's pink fluorescence when exposed to a Wood's light

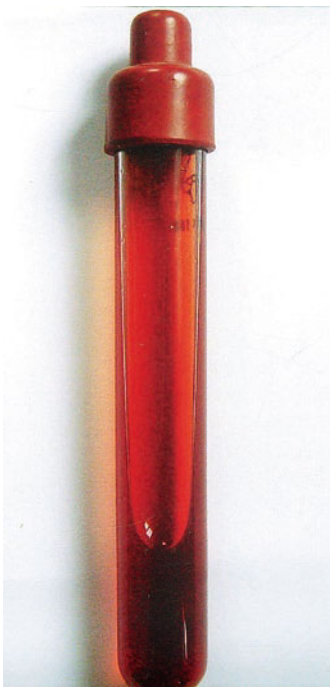
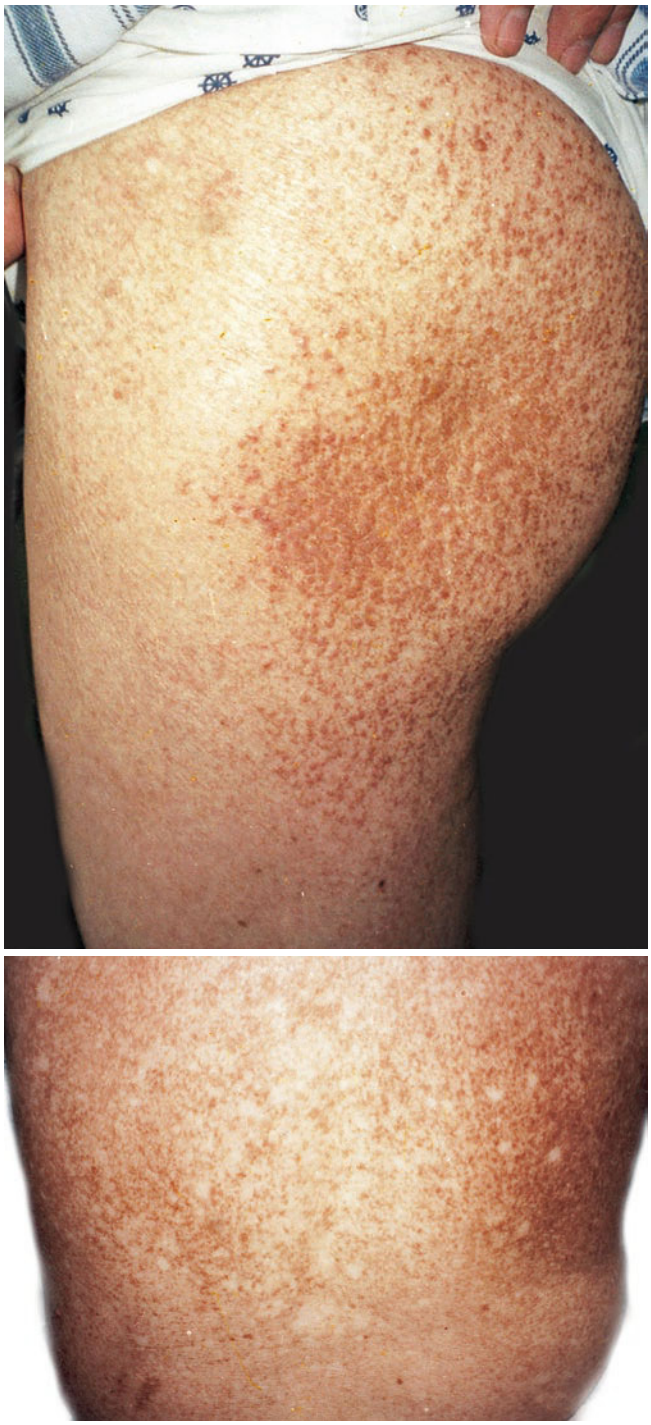


Fig. 22-8-4 Wine-colored urine under normal light

22.9 Poikiloderma-Like Cutaneous Amyloidosis [14, 15]

- Poikiloderma-like cutaneous amyloidosis (PCA) is an uncommon genetic dyschromic skin disorder consisting of two clinical forms: ordinary type and PCA syndrome.
- The clinical features of PCA include poikilodermic lesions, lichenoid papules, and blisters especially located on the limbs. Pruritus is the most frequent symptom.
- Histological examination reveals the deposition of amorphous eosinophilic material in the papillary dermis.
- There is currently no satisfactory therapeutic method for PCA. Topical and intralesional steroids and antihistamines may be effective.



Figs. 22-9-1, 22-9-2 Poikilodermatous skin and lichenoid papules on the left back

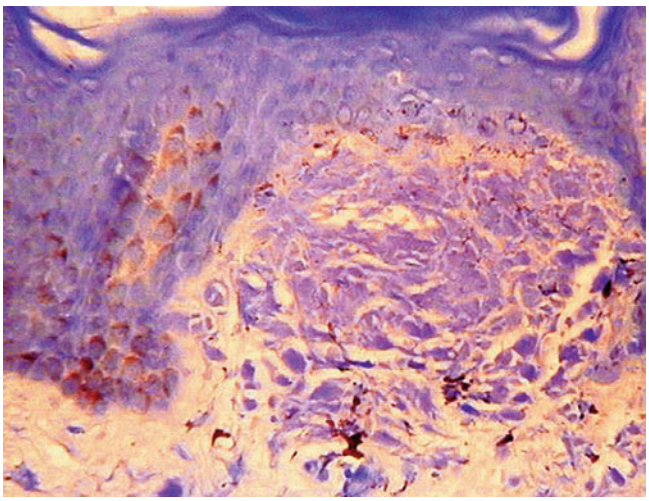


Fig. 22-9-3 Deposits of amyloid in the uppermost dermis (methyl violet stain, ×100)

22.10 Nodular Amyloidosis [16, 17]

- Primary localized cutaneous amyloidosis (PLCA) includes three variants: macular, papular (lichenoid), and nodular forms (primary cutaneous nodular amyloidosis, PCNA). PCNA is the rarest form, which has a preference for male patients.
- Clinically, it displays single or multiple nodules and plaques that may coalesce. There is a predilection for acral areas, but they are also found on the legs, head, trunk, arms, and genital areas.
- Histopathologically, hematoxylin and eosin staining shows large deposits of amorphous, sometimes fissured, pale, eosinophilic, material in the reticular dermis and papillary dermis.

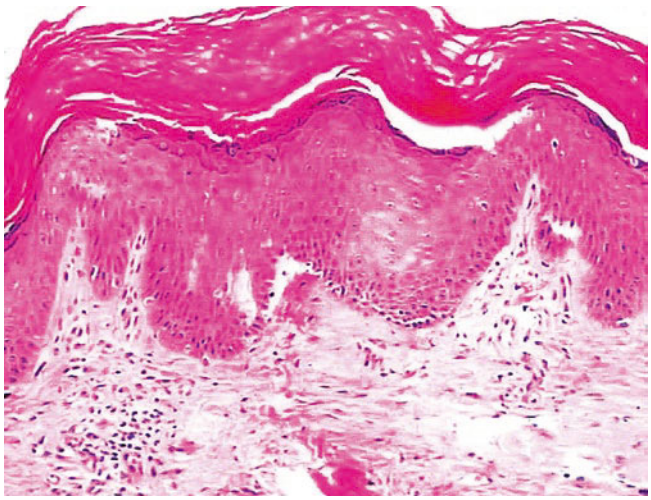


Fig. 22-10-2 There is hyperkeratosis and epidermal hyperplasia. Dermal papillae are rounded eosinophilic amorphous amyloids (HE stain, ×200)

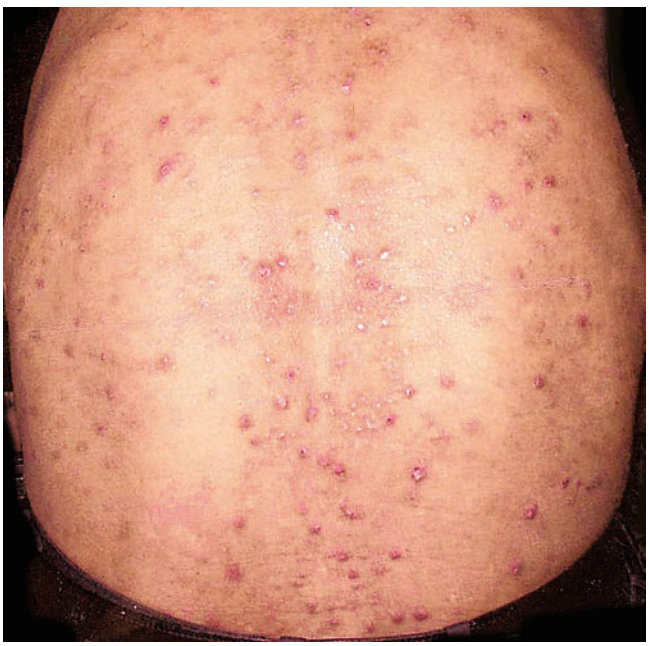


Fig. 22-10-1 Several brown nodules on the back

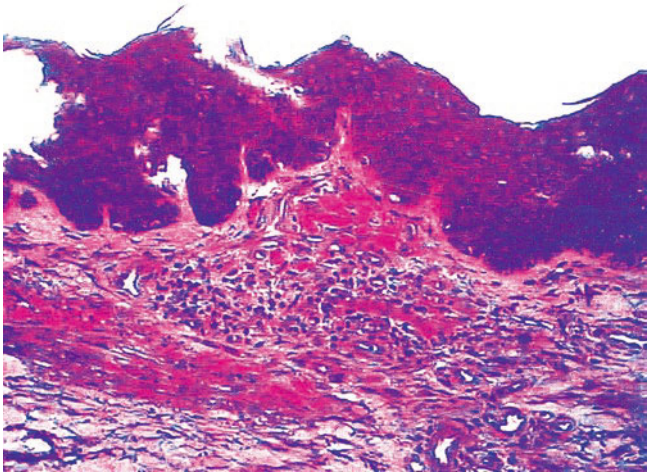


Fig. 22-10-3 Red masses of amyloids are present in the upper dermis (violet stain, ×200)

22.11 Lichen Myxedematosus [18, 19]

- Lichen myxedematosus (LM), also known as papular mucinosis, is a rare, idiopathic chronic disorder, which preferably involves 30–50-year-old individuals.
- The lesions of LM often present as waxy, stiff, and grouped normochromic or erythematous papules with a diameter of 2–4 mm, occurring symmetrically on the back of the hands and fingers, armpits, forearms, and the extensor surface of the legs. The lesion may coalesce into a widespread induration of the skin.
- Histological examination reveals a horizontal band of mucinous material between the round and star-shaped and patchily distributed fusiform fibroblasts and collagen fibers and dermal fibrosis.
- Treatment of LM is a challenge. The alkylating agent melphalan is frequently used as the first-line treatment. However, its potentially severe adverse effects limit its use. Other treatments, such as cyclophosphamide, CO_2 laser, and retinoids, have been reported.

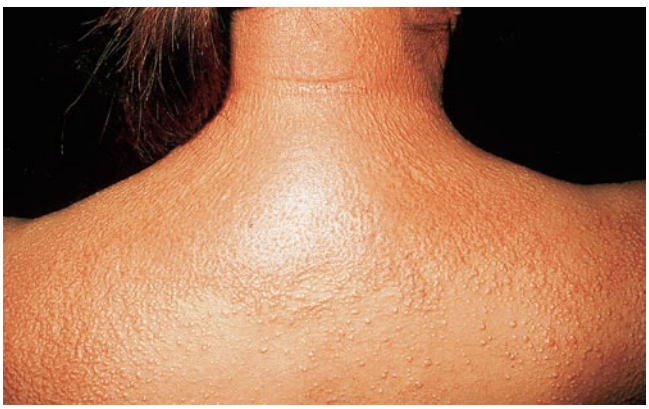


Fig. 22-11-1 Pale-red or yellowish papules on the nape

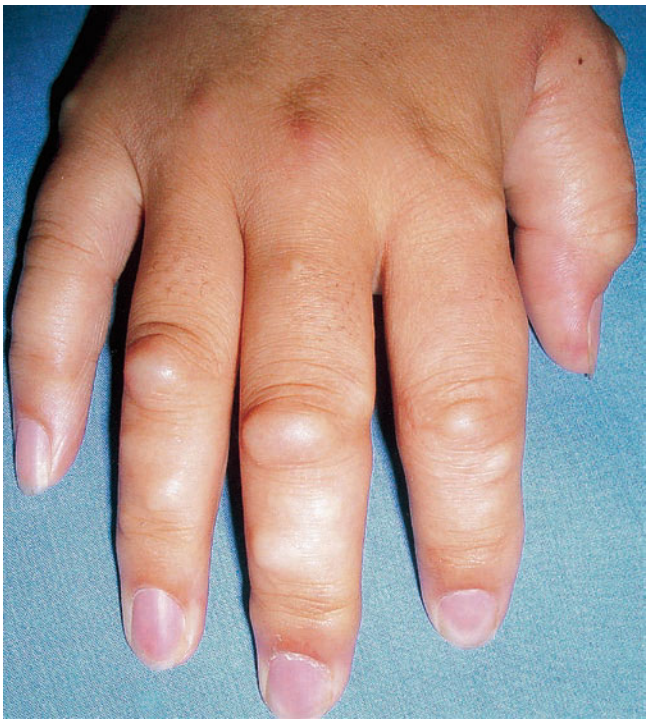


Fig. 22-11-2 Flesh-colored nodules on the fingers

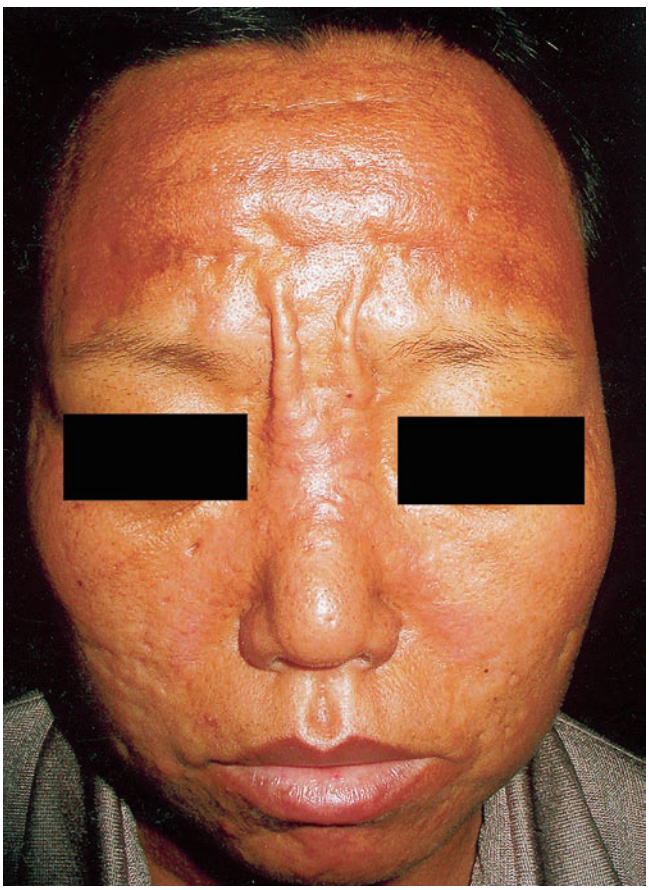


Fig. 22-11-3 Infiltrate plaques on the face (Reproduced with the permission from [18, 19])

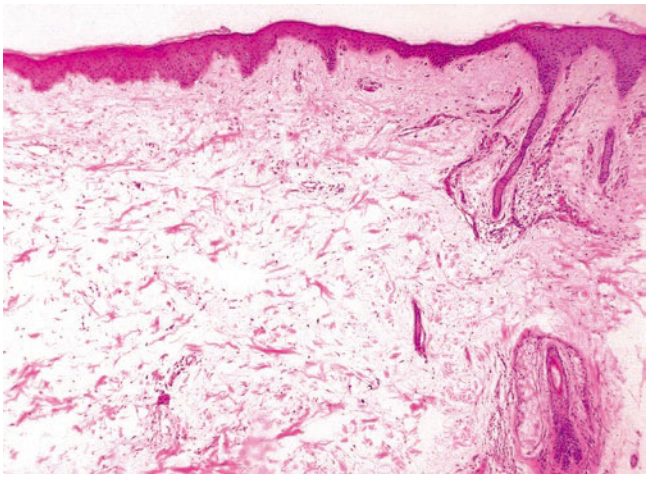


Fig. 22-11-4 There are unstained spaces of various sizes in the dermis (HE stain, ×40)

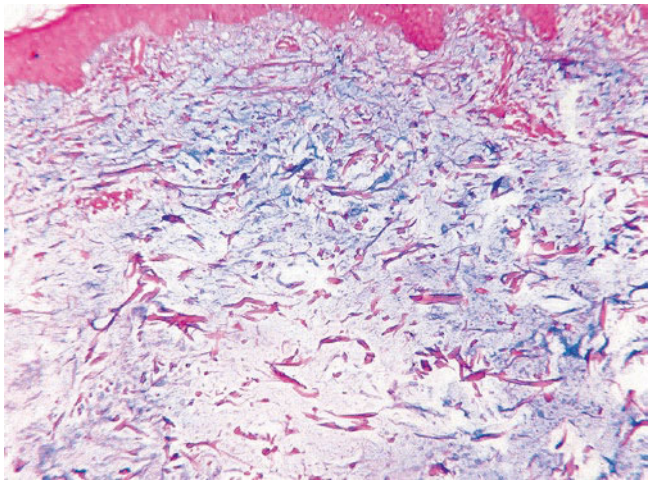


Fig. 22-11-5 Diffuse infiltration with mucin among the collagen bundles (Alcian blue, ×400)

22.12 Scleromyxedema [20, 21]

- Scleromyxedema is the sclerodermoid and generalized papular form of lichen myxedematosus, characterized by dermal fibroblast proliferation and mucinous deposits and associated with monoclonal M-proteinemia or paraproteinemia. It mostly affects middle-aged adults.
- Clinically, scleromyxedema has been further divided into three types: localized, generalized, and atypical forms. The lesions commonly present as waxy papules with a predilection for sun-exposed areas. Alcian blue staining reveals the deposition of mucin in the collagen.
- Scleromyxedema is a progressive and chronic disorder with a high mortality. There is no effective treatment. Plasmapheresis, systemic steroids, and melphalan are worth evaluating.

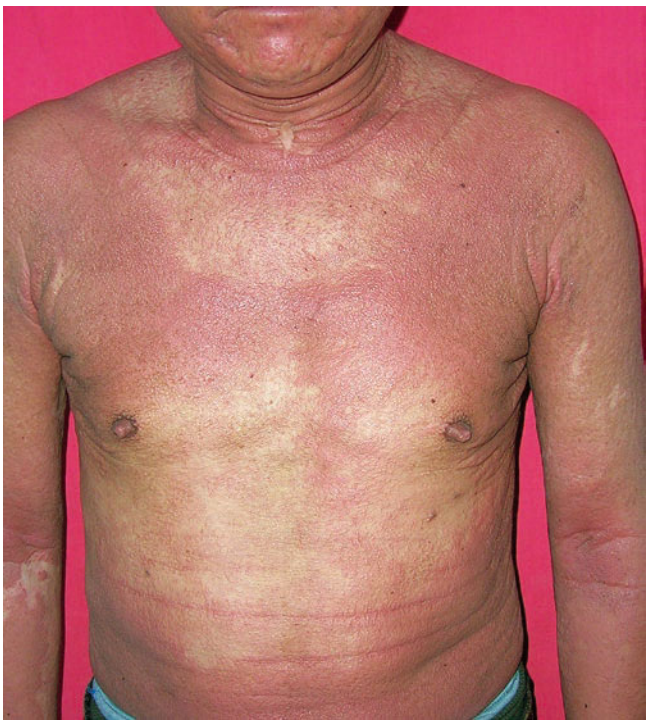


Fig. 22-12-1 Thickened skin and infiltrated plaques over the trunk and the upper arm

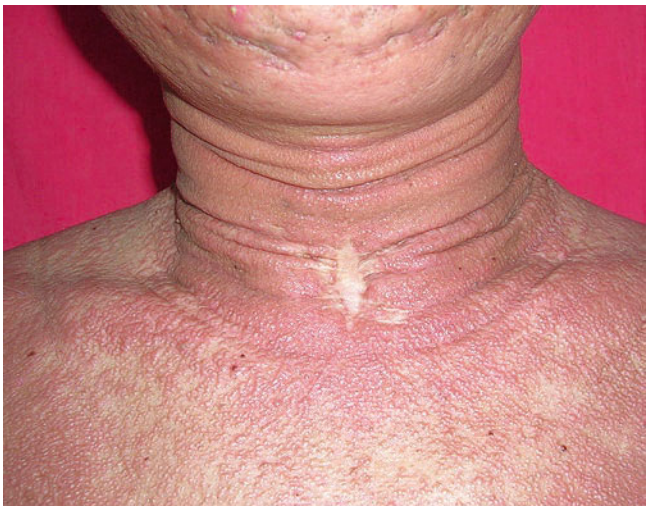


Fig. 22-12-2 Multiple lichenoid papules on the neck and chest

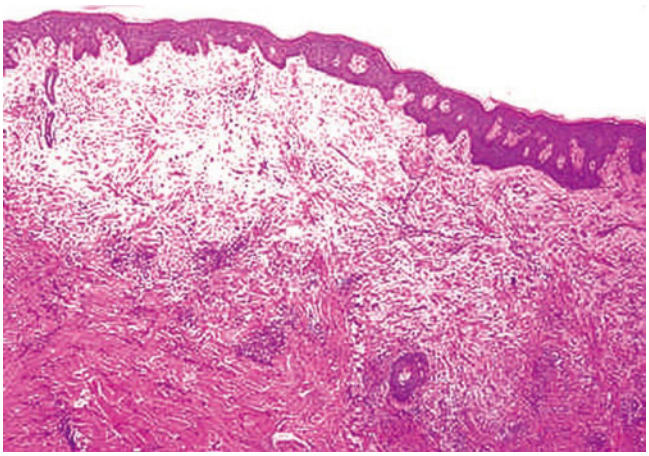


Fig. 22-12-3 Sparseness and edema of collagen in the upper dermis (HE stain, ×100)

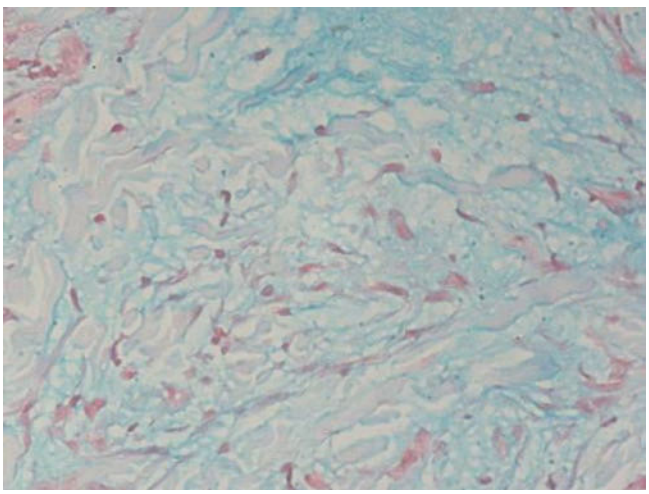


Fig. 22-12-4 Mucin deposition between the collagen bundles (Alcian blue stain, ×100)

22.13 Follicular Mucinosis [22, 23]

- Follicular mucinosis, namely, alopecia mucinosa, is a cutaneous mucinosis. It is classified as a primary idiopathic disease and secondary lymphoma-associated dermatosis. The primary form is further divided into two subtypes: primary of short evolution and primary of prolonged course.
- Clinically, it features the presence of an erythematous, infiltrated, boggy plaque with prominent follicular orifices and overlying alopecia. The scalp, neck, and face are the most commonly influenced sites.
- Histologically, it is characterized by accumulation in hair follicles and sebaceous glands, with an inflammatory infiltrate of lymphocytes and eosinophils.
- Photodynamic therapy, isotretinoin, indomethacin, dapsone, interferon, minocycline, PUVA, cyclophosphamide, and methotrexate have been with alterable success reported for the main form.

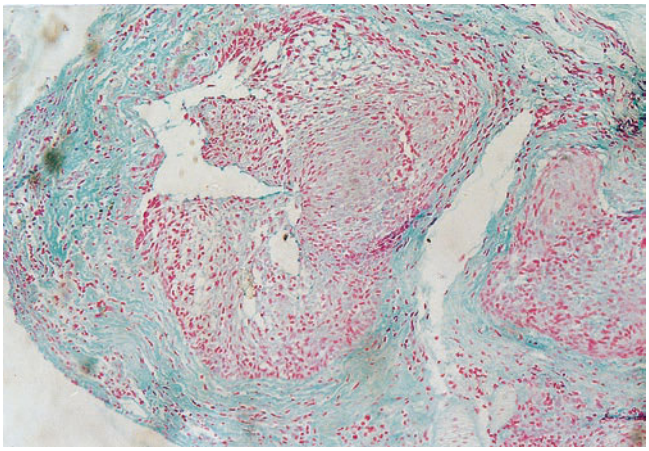


Fig. 22-13-2 Deposition of much in the outer root sheath (Alcian blue stain, ×100)

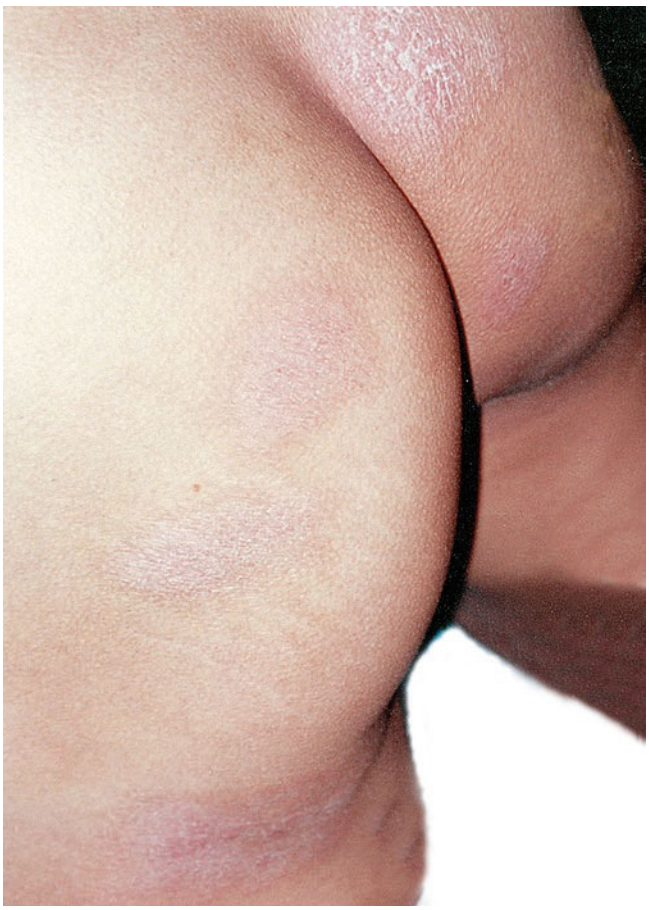


Fig. 22-13-1 Several infiltrate erythema on the buttocks and sacrum

22.14 Reticular Erythematous Mucinosis [24, 25]

- Reticular erythematous mucinosis (REM syndrome) is an uncommon dermatosis that shows erythematous macules and papules that coalesce into reticulated patterns on the midline of the chest or back area of middle-aged women.
- The cause of REM syndrome is largely unclear, but several factors such as UV light, immunologic disturbances, and viral infections may contribute to its development. Its clinical and histopathologic characteristics suggest a close relationship with cutaneous lupus erythematosus (CLE).
- Histopathology reveals superficial and mid-dermal perivascular lymphocytic infiltrates as well as dermal mucin deposition, which is positive for Alcian blue staining.
- Antimalarial drugs are considered an efficient therapy. Other treatments, including topical and systemic corticosteroids, topical tacrolimus, oral antihistamines, tetracycline, cyclosporine, UVB, or UVA irradiation, have been used with variable results.

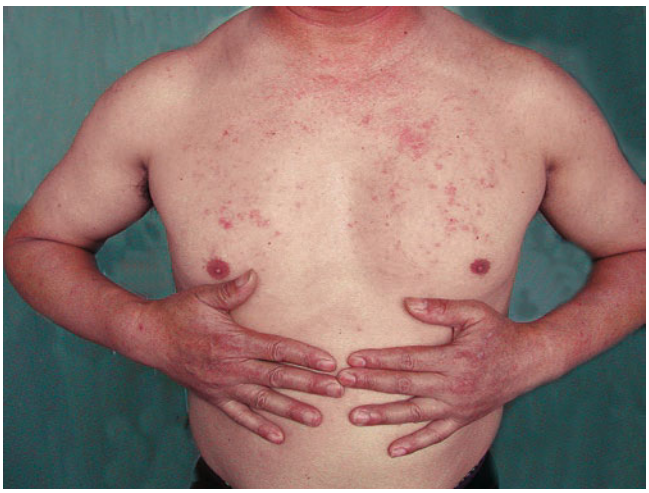


Fig. 22-14-1 Reticular erythematous maculopapular lesion on the upper chest

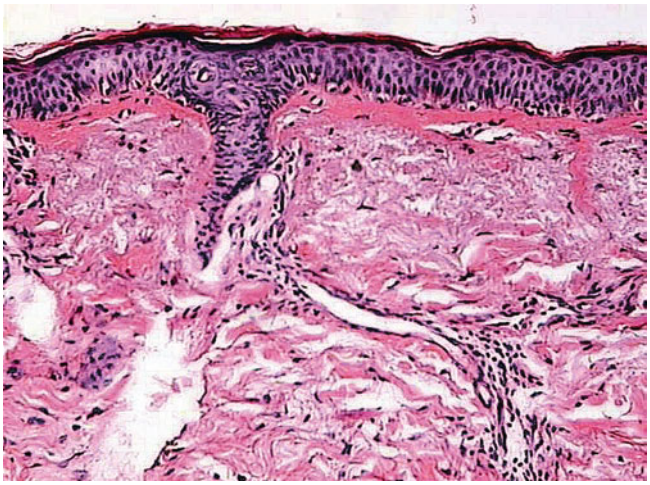


Fig. 22-14-2 Perivascular and perifollicular lymphocytic infiltration in the upper reticular dermis (HE stain, ×200)

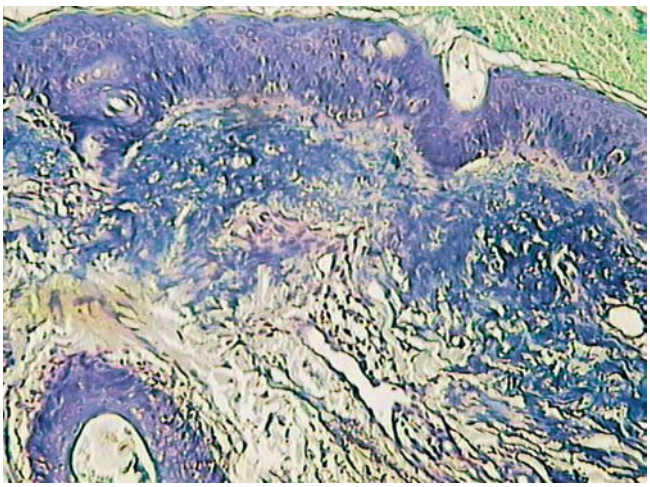


Fig. 22-14-3 Mucin deposition between collagen bundles (Alcian blue stain, ×200)

22.15 Cutaneous Focal Mucinosis [23, 26]

- Cutaneous focal mucinosis (CFM) is a heterogeneous disorder that is listed under primary dermal mucinosis, characterized by the deposition of mucin in the dermis.
- The lesions of CFM usually present an asymptomatic solitary papule or nodule with a preference for the face, trunk, or extremities in middle-aged adults.
- Histopathological examination shows focal and diffuse mucin deposition within the dermis. Simultaneously, thinned collagen fibers within mucinous stroma and fractures are observed.
- Excision is the therapy of choice for CFM, with a lower recurrence rate.

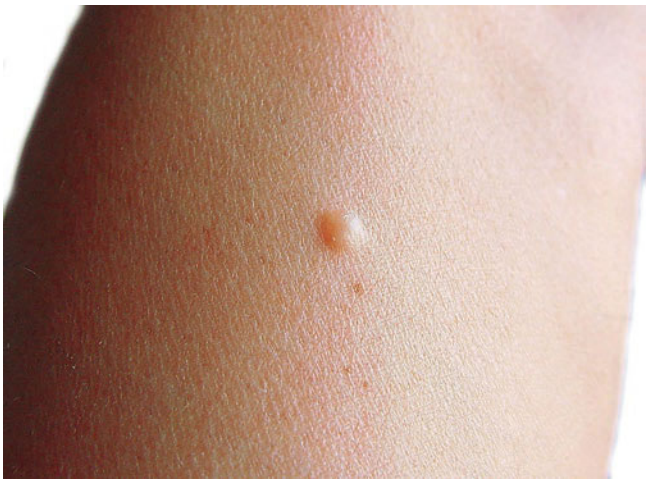


Fig. 22-15-1 A well-circumscribed translucent skin-colored nodule 4 mm in diameter with smooth surface on the extensor surface of left arm

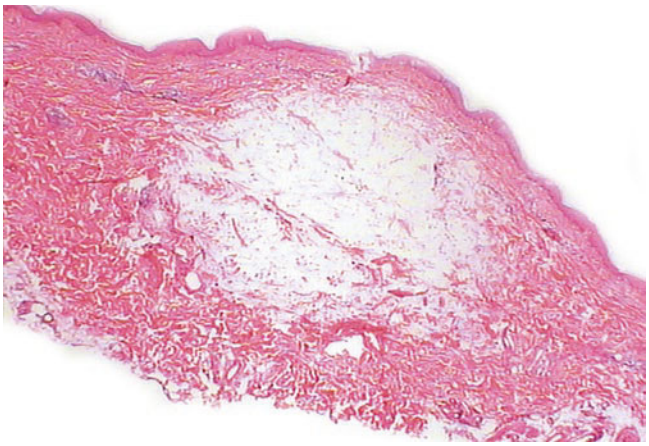


Fig. 22-15-2 Loose formless substance, uncircumscribed in the middle dermis, and increased fibroblast and collagen hyperplasia (HE stain, ×40)

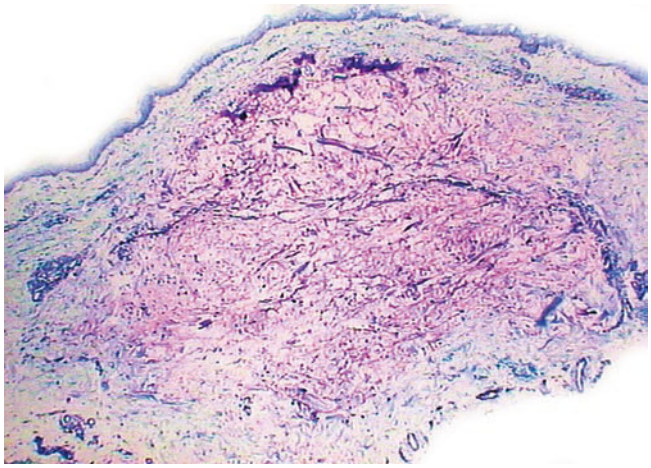


Fig. 22-15-3 Pronounced purple metachromatic area in the middle dermis (Alcian blue stain, ×100)

22.16 Acral Persistent Papular Mucinosis [27]

- Acral persistent papular mucinosis (APPM) is a type of localized lichen myxedematosus featuring chronic, asymptomatic, symmetric, and ivory to flesh-colored. 2–5-mm-sized papules localized exclusively on the backs of the hands, wrists, and extensor aspects of the distal forearms. The lesions tend to continue and may gradually increase in number.
- Microscopic examination reveals well-circumscribed nodular hyaluronic acid deposits between the collagen bundles, particularly in the superficial dermis but also in the mid-reticular dermis.
- APPM is only a cosmetic problem without any systemic involvement. Treatment is not required. Destructive therapies such as liquid nitrogen, carbon dioxide laser, or electrodesiccation can leave scars. Topical corticosteroids, pimecrolimus, and tacrolimus have been used with some achievements.

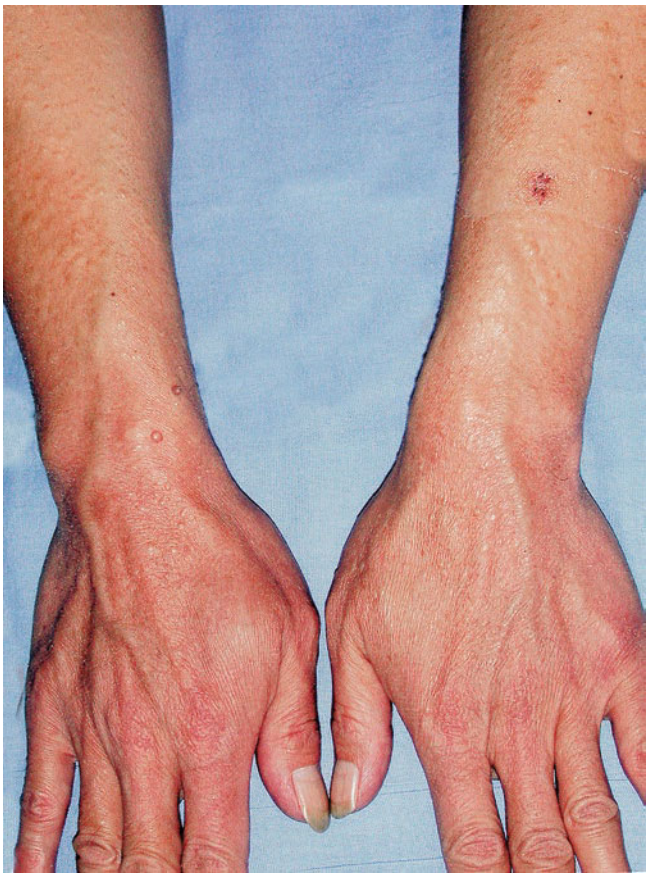


Fig. 22-16-1 Numerous waxy papules are asymmetrically distributed on both arms and dorsa of both hands

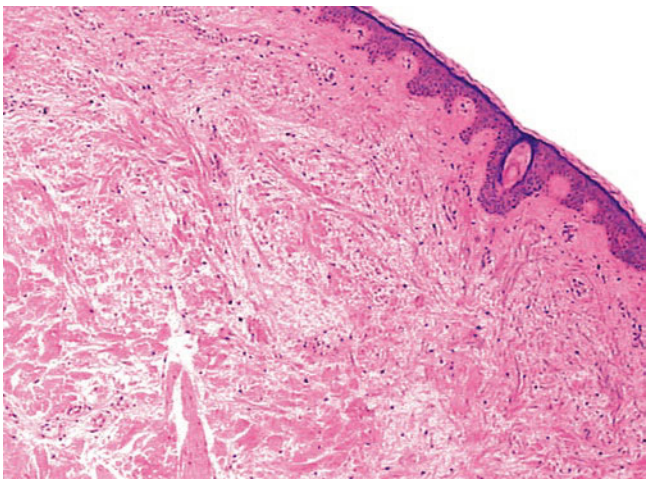


Fig. 22-16-2 The collagen fibers in the reticular dermis are widely separated by deposits of mucin (HE stain, ×40)

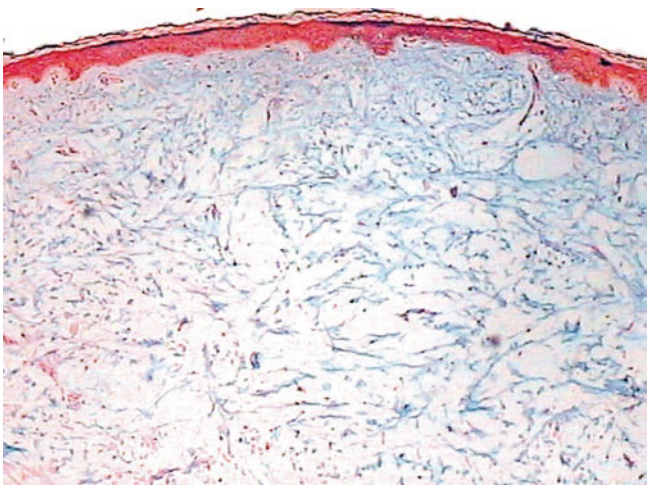


Fig. 22-16-3 The deposit of mucin in the upper and middle dermis (Alcian blue stain, ×40)

22.17 Pellagra [28, 29]

- Pellagra is a chronic wasting disorder characterized by dermatitis, dementia, and diarrhea, which results from niacin deficiency, most commonly from the following conditions: malnutrition, malabsorption, chronic alcoholism, hemodialysis or peritoneal dialysis, and drug intake.
- Patients with pellagra have a brown discoloration of the skin, especially in sun-exposed areas. The increased pigmentation generally results in thin varnish-like eruptive scales in late stages. The characteristic lesion has a typical photosensitive distribution with well-defined borders.
- Patients with pellagra have delirium, stomatitis and memory loss, pellagrous encephalopathy presenting with apathy, glossitis, disorientation, depression, or intractable diarrhea.
- Diagnostic delay and no diagnosis will cause death. The primary management is replacement of nicotinamide. Supplementation of other B vitamins, zinc, and magnesium is helpful.

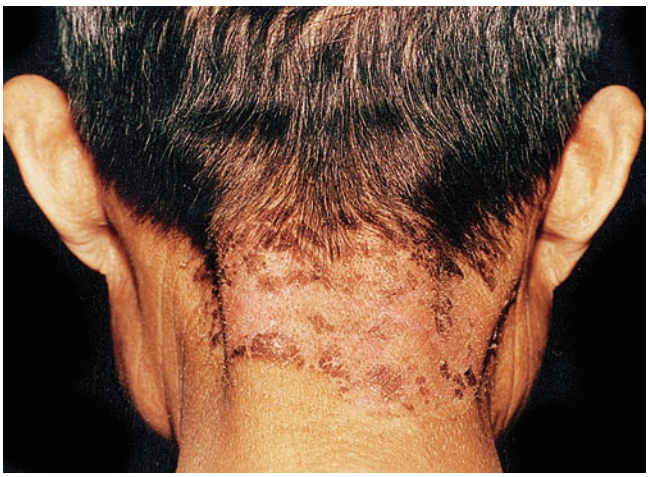


Fig. 22-17-1 Erythema with scaling greasily, sharply defined amaranth macules and thick skin on the neck

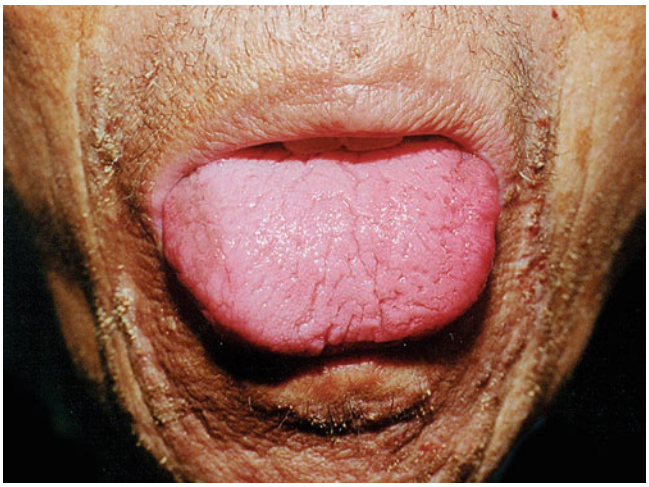


Fig. 22-17-2 Oral mucosa erosion and small ulcer in the mouth

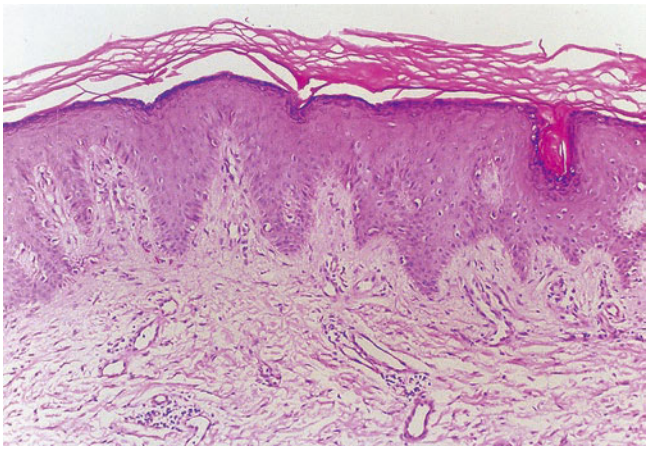


Fig. 22-17-3 Hyperkeratosis, thickened granular layer and acanthosis, elongation of the rete ridges, and a few lymphocytes and histiocytes infiltrated perivascular area of the upper dermis (HE stain, ×40)

22.18 Carotenemia [30, 31]

- β-Carotene can accumulate in the stratum corneum and impart a yellow color to the skin when the circulating levels are high. This coloration is termed carotenemia, which may arise by three mechanisms: excessive dietary intake, defective conversion of carotene to vitamin A, and in relation to hyperlipidemia.
- Carotenemia is usually seen in infants and young children who have diets rich in green and orange vegetable purees, featured by an increase in the beta-carotene level in the blood and yellow pigmentation of the skin.
- Carotene deposits are most notable in areas with a thick stratum corneum, such as nasolabial folds, palms, and soles.
- The treatment requires restriction of dietary habits.

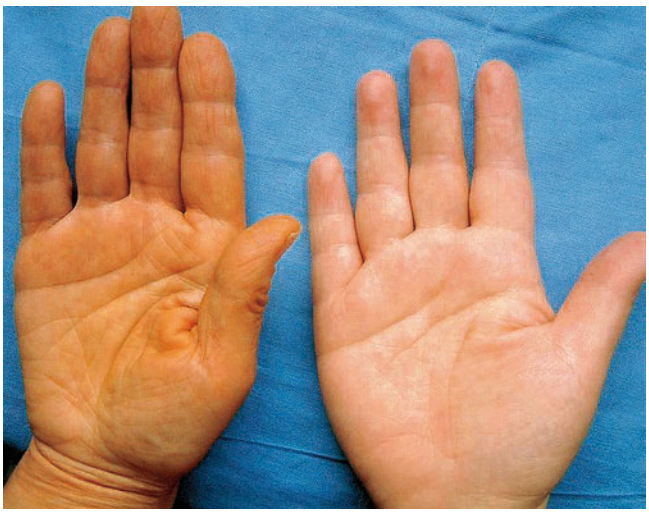


Fig. 22-18-1 Yellowish orange pigmentation of the skin on right palm (left side)

22.19 Glycogen Storage Disease Type I [32, 33]

- Glycogen storage disease type I (GSD I, or von Gierke's disease) is an autosomal recessive metabolic disorder characterized by severe fasting hypoglycemia caused by a deficiency of glucose-6-phosphatase activity. It primarily affects the liver and kidney and has variable clinical severity.
- GSD I consists of two major subtypes: GSD type Ia, resulting from a mutation affecting the catalytic sub-unit of G6Pase-alpha, and GSD type Ib, caused by a defect in G6P translocase.
- Patients with GSD1b present with hepatomegaly, a characteristic "doll-like" face, chronic fatigue, and short stature.
- These patients are prone to recurrent bacterial infections, usually involving the perirectal area, skin, urinary tract, and ears. The occurrence of staphylococcal ecthyma and pyoderma gangrenosum is associated with polynuclear neutrophil abnormalities.

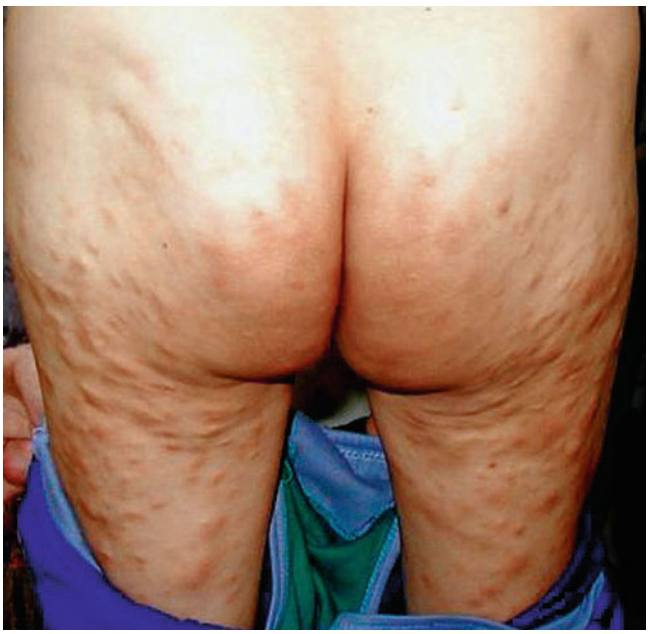


Fig. 22-19-1 Numerous nodules on the buttocks and thighs

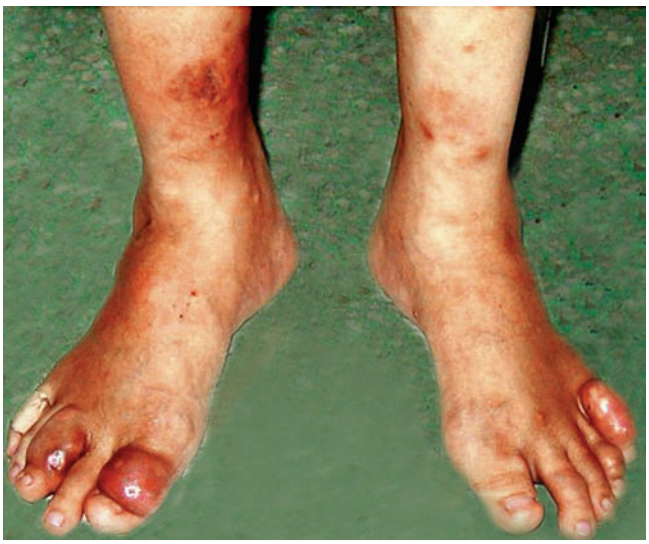


Fig. 22-19-2 Wine-colored nodules on the feet

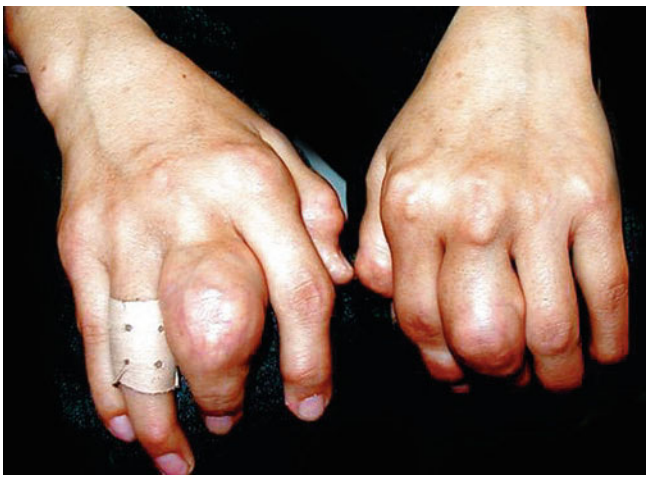


Fig. 22-19-3 Many nodules on the knuckles

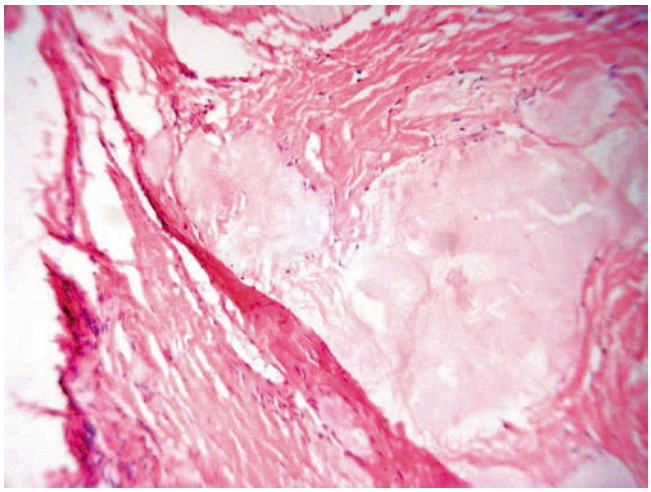


Fig. 22-19-4 Homogeneous red masses in the dermis (HE stain, ×100)

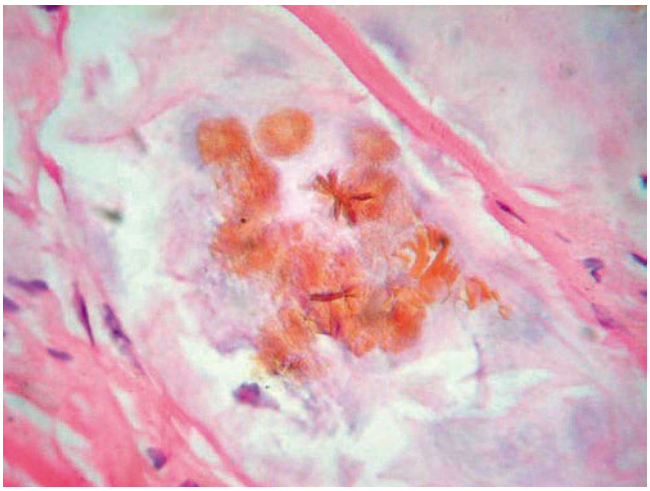


Fig. 22-19-5 Brown uric acid crystal with actinomorphic shape in the dermis (HE stain, ×400)

22.20 Alkaptonuric Ochronosis [34, 35]

- Ochronosis is a disease in which ochre pigment is deposited in the tissues. It is divided into two subtypes: exogenous and endogenous.
- Endogenous ochronosis, or alkaptonuric ochronosis, is an autosomal recessive inheritance. It is due to a congenital deficiency of the enzyme homogentisic acid oxidase (HGAO), which leads to accumulation of homogentisic acid (HGA) in the connective tissues. Excretion of excessive HGA in urine causes deep-colored urine on exposure to air.
- The cutaneous manifestation shows apparent hyperpigmentation, particularly in the cartilage of the ears and the sclerae. Histopathology showed long, banana-shaped deposits of an acellular material of a pale gold color, with a mild lymphohistiocytic interstitial inflammatory infiltrate.
- There is no satisfactory therapy for alkaptonuria. However, nitisinone, a drug that inhibits the enzyme that produces HGA, has been proposed as a potential therapy.

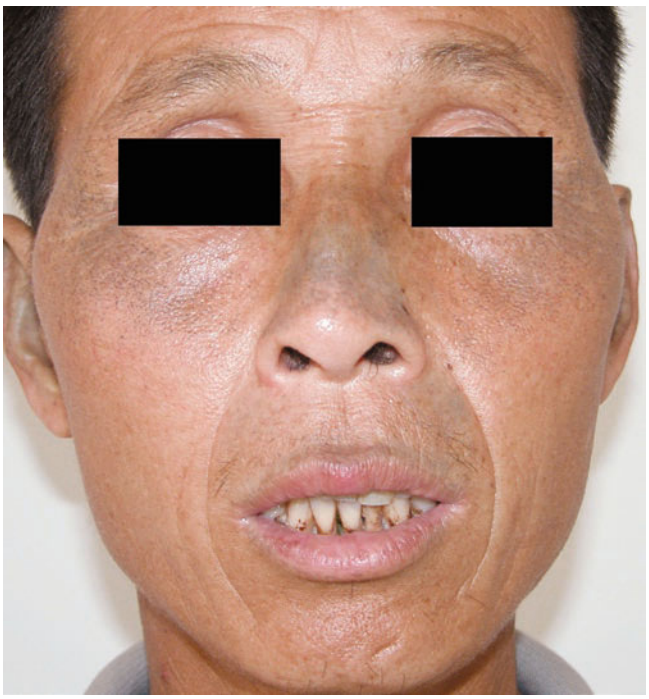


Fig. 22-20-2 Greenish and brown maculae with obscure boundary on the cheekbones, nasal bridge and, the upper lip (Reproduced with the permission from [34, 35])

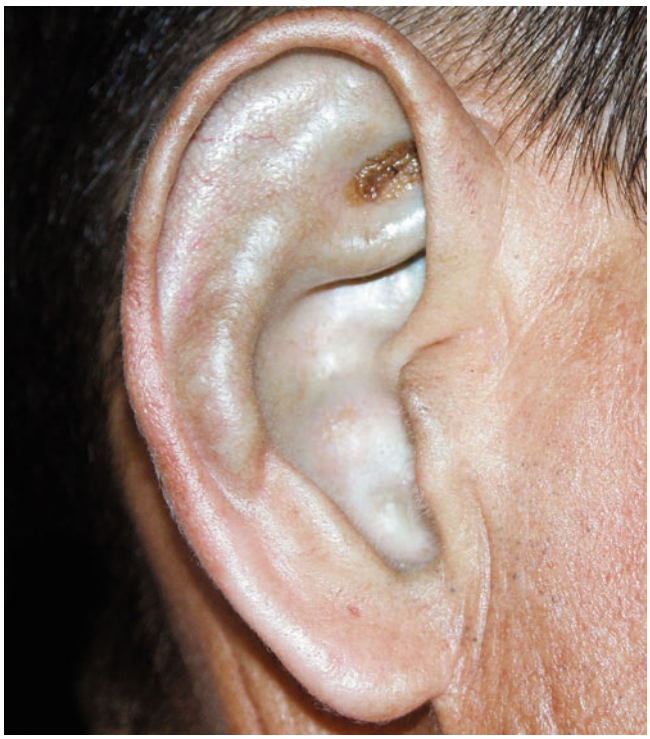


Fig. 22-20-1 Horsebean-sized brown plaques on the inner auricle

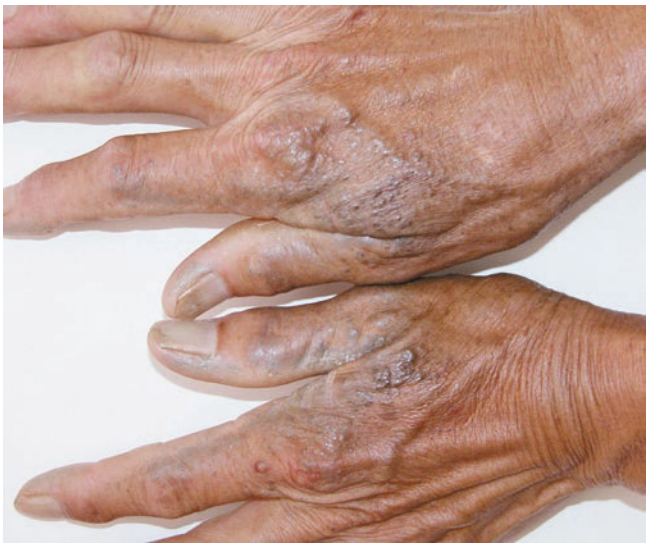


Fig. 22-20-3 Firm black brown papules on the dorsa of both hands

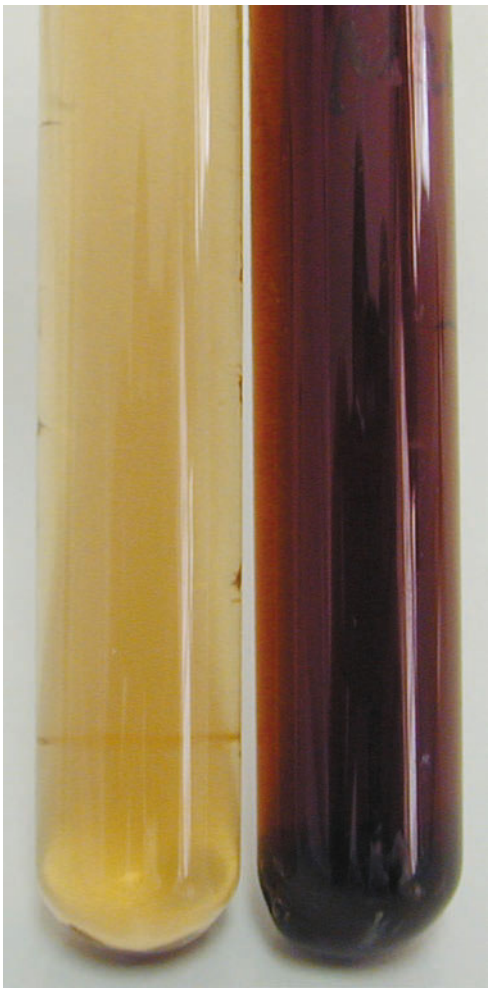


Fig. 22-20-4 The color of fresh urine rapidly became black after addition of 10% NaOH solution

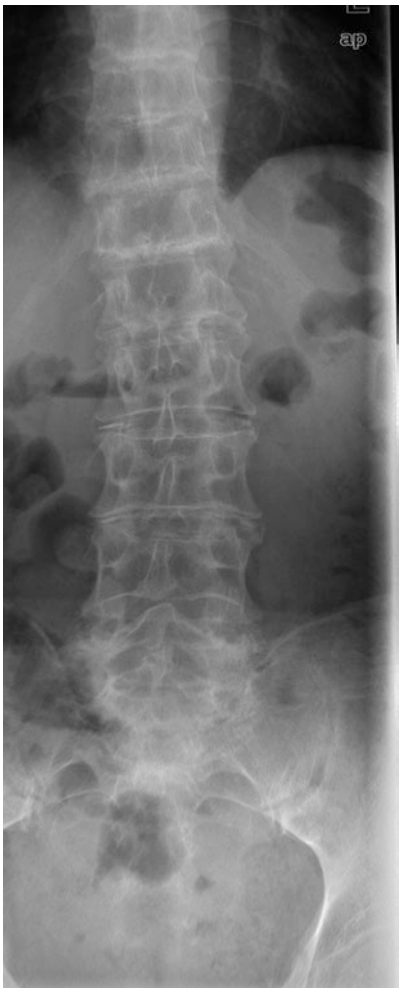


Fig. 22-20-5 Spine X-ray: showed osteoporosis of lumbar vertebrae

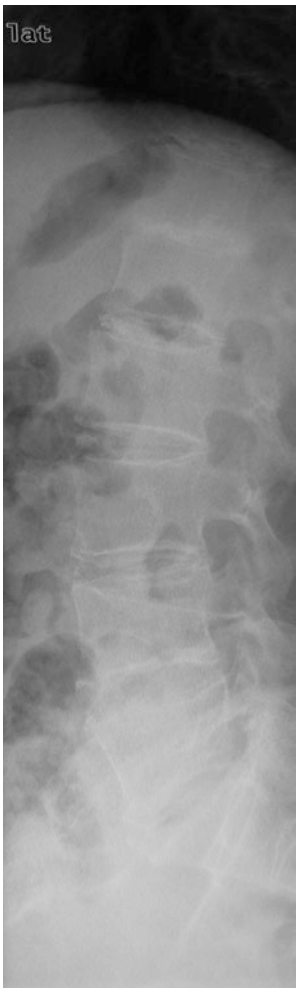


Fig. 22-20-6 Calcification and protrusion of intervertebral disc

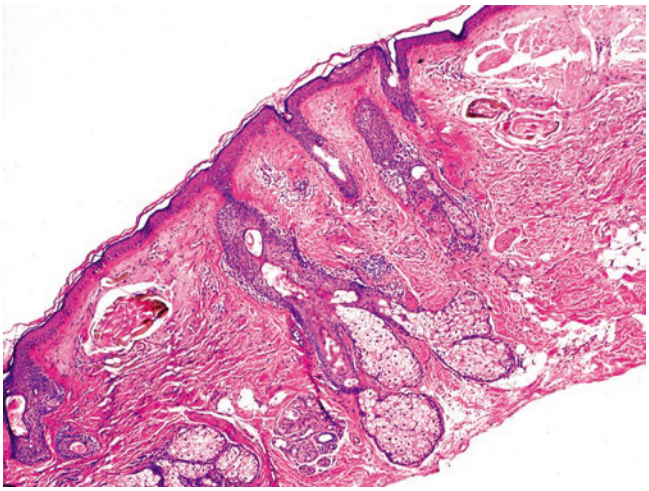


Fig. 22-20-7 Slight epidermal atrophy and thinning, degeneration of collagen fibers, collagen bundle swelling, deposition of yellow-brown boluses between collagens

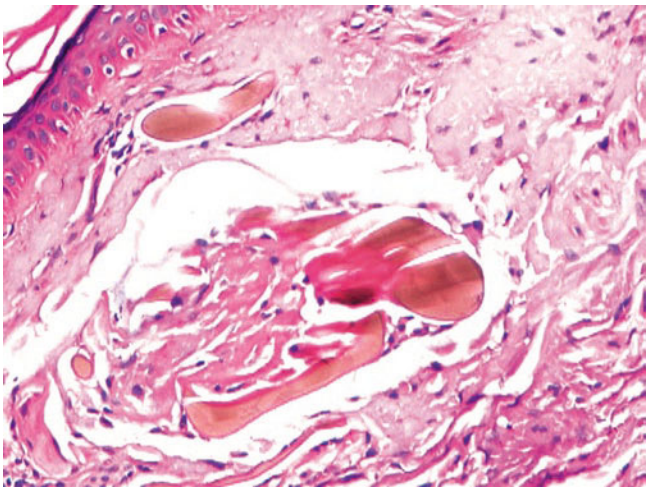


Fig. 22-20-8 Toluene blue staining showed that the mass material was black

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Endocrine Skin Diseases

23

Li Li, Hong He, Jia-Hong Zhu, Jin-Yao Liu, Ru-Zhi Zhang, Yu-Feng Liu, and Rui-Yao Yu

Abstract

This chapter consists of pretibial myxedema, calcinosis cutis, idiopathic scrotal calcinosis, unilateral nevoid acanthosis nigricans, malignant acanthosis nigricans complicated by gastric adenocarcinoma, hyperandrogenism, insulin resistance and acanthosis nigricans syndrome, and necrolytic migratory erythema.

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23.1 Pretibial Myxedema [1, 2]

- Pretibial myxedema (PTM) or thyroid dermopathy is a cutaneous mucinosis, commonly occurs in <5% of patients with Graves' disease, occasionally occurs in cases with Hashimoto's thyroiditis, and is classified as non-pitting edema, plaque form, nodular form, or elephantiasic form.
- Lesions generally are asymptomatic and symmetrical in the pretibial area and feet, and they are rarely accompanied by pain and pruritus, finally becoming indurated.
- Histological examination reveals that a certain amount of mucinous substance is present in reticular dermis, fragmentation, and fraying of collagen fibers.
- Treatments include topical corticosteroid, compressive therapy, systemic immunomodulation, and surgery.

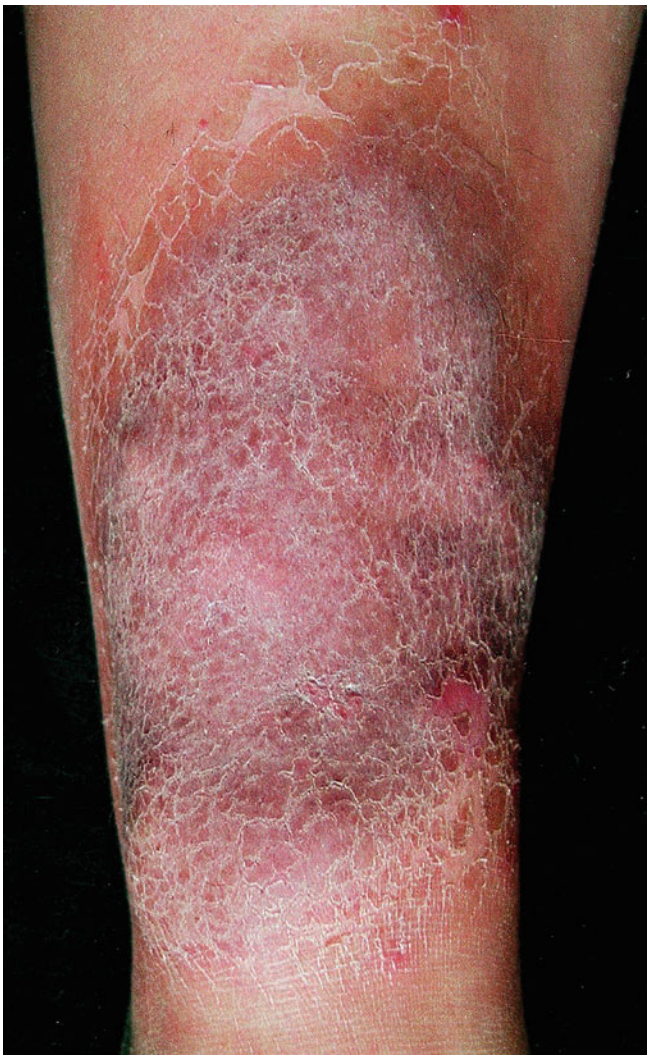

Fig. 23-1-1 A large brown infiltrate plaques with hyperkeratosis and a nodular 3 cm in diameter in the pretibial region

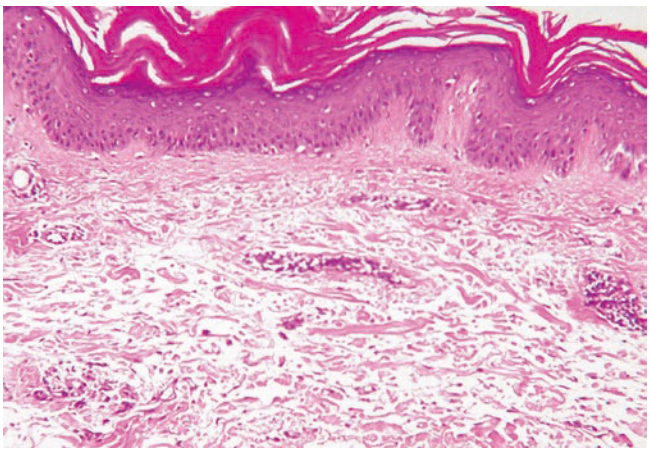

Fig. 23-1-2 Hyperkeratosis and parakeratosis, thickened granular layer, and deposition of mucinosis in the dermis between collagen fibers (HE stain, ×40)

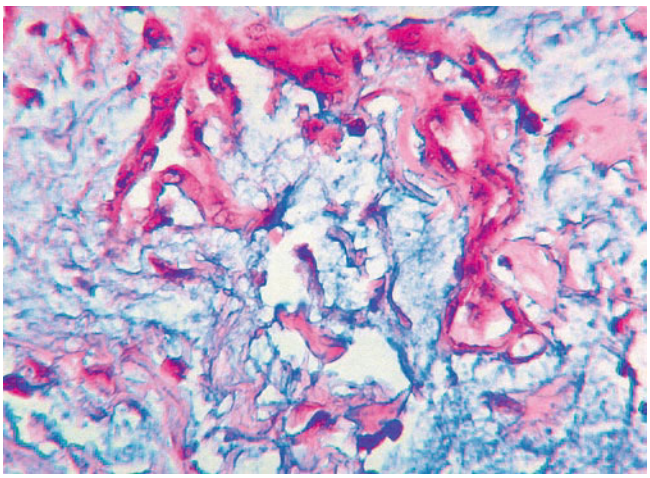

Fig. 23-1-3 Positive stain with Alcian blue (Alcian blue stain, ×100)

23.2 Calcinosis Cutis [3, 4]

- Calcinosis cutis is an uncommon disease characterized by calcium deposition in the skin and subcutaneous tissues, which is usually related to autoimmune connective tissue diseases, and could be classified into four clinical subtypes: dystrophic, metastatic, idiopathic, and iatrogenic.
- Many regions including the face, extremities, penis, and scrotum can be involved. The lesions may ulcerate and extrude a chalky milk-like substance consisted of calcium salts, which form insoluble hydroxyapatite crystals in the tissues, most commonly following chronic tissue damage or electrolyte abnormality.
- Complications of calcinosis cutis include cosmetic damage, pain, ulcers, and mechanical compromise.
- No therapy has been widely considered a standard treatment to date. Determining the precise type of calcinosis cutis is vital for selecting accurate management.

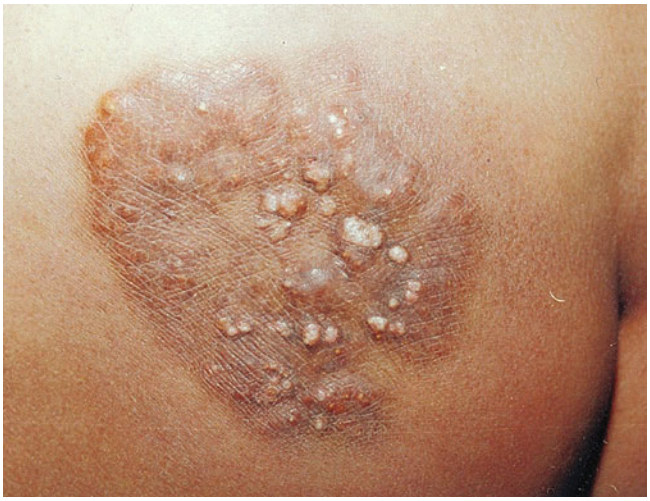

Fig. 23-2-1 A brown plaque 15 cm in diameter on the outside of the left buttock, associated with white yellow nodules on it

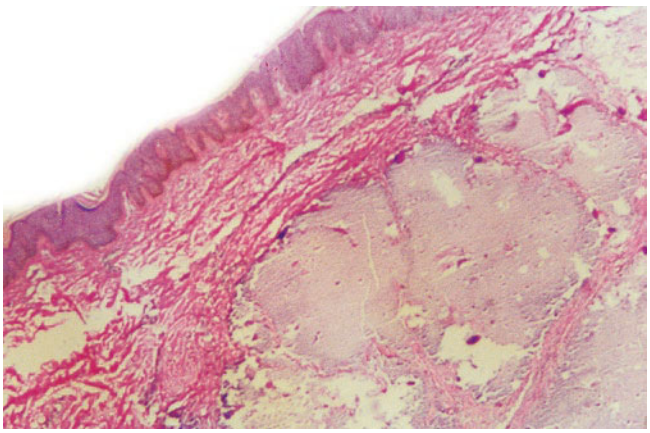

Fig. 23-2-2 Slight atrophy of the epidermis, variously sized calcific masses in the deep dermis (HE stain, ×40)

23.3 Idiopathic Scrotal Calcinosis [5, 6]

- Idiopathic scrotal calcinosis (ISC) is an uncommon and benign condition that generally appears in childhood or early adult life and is characterized by calcified nodules in the scrotal skin.
- The major subtypes are idiopathic calcinosis, metastatic, and dystrophic. Most patients are painless and symptomless. White and chalky material may be extruded in severe patients.
- Histological examination reveals amorphous calcific deposits of various sizes which occur in the dermis and usually encircled by foreign body granulomatous inflammation.
- Epidermal inclusion cyst, wen, steatoma, and sebaceous cyst must be identified with the disease. Surgical removal is an effective method.

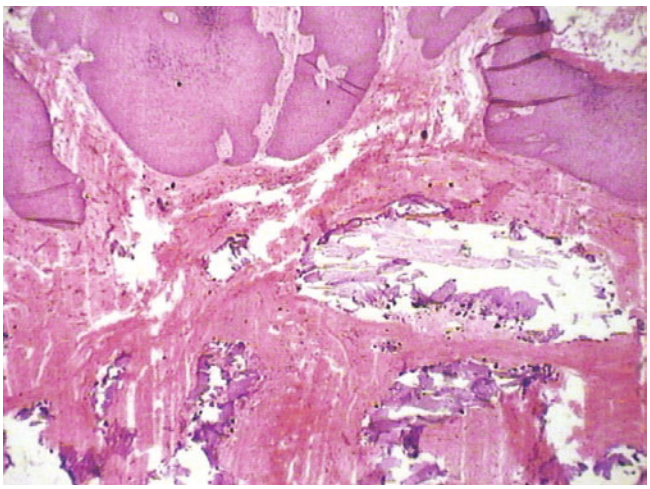

Fig. 23-3-2 Many globular bluish nodules containing amorphous and homogenous deposits of calcium with epidermal papillomatous hyperplasia in the dermis (HE stain, ×100)

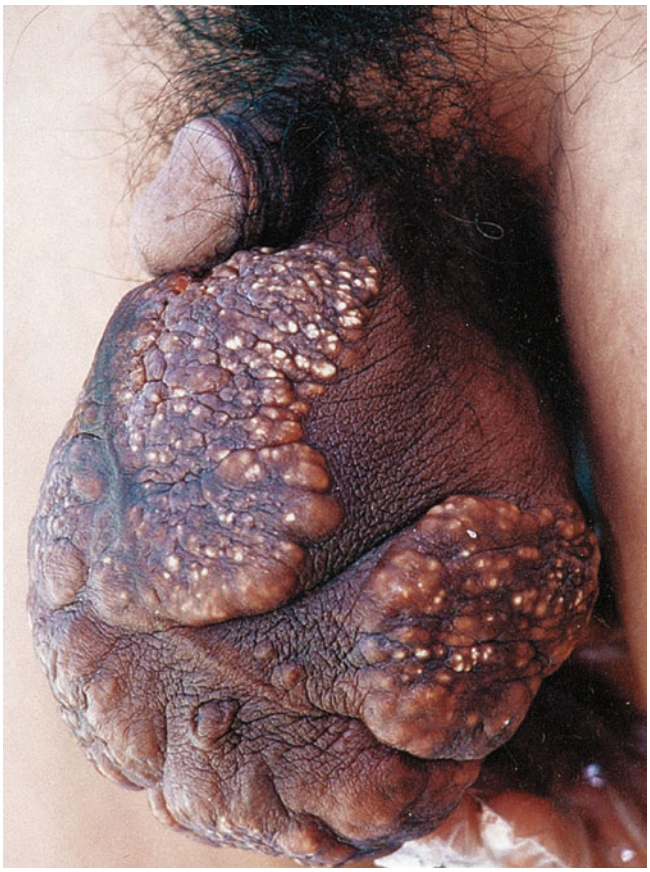

Fig. 23-3-1 Numerous firm yellowish subcutaneous nodules beneath the scrotal skin

23.4 Unilateral Nevoid Acanthosis Nigricans [7, 8]

- Unilateral nevoid acanthosis nigricans (UNAN) is an infrequent, benign, irregular autosomal dominant form of acanthosis nigricans (AN) due to somatic mosaicism of postzygotic gene mutation.
- It commonly occurs at birth or during childhood or puberty, displays hyperpigmented papillomatous thickening with a velvety texture, and usually appears in a solitary or multiple lesions along the line of Blaschko.
- The histological examination shows moderate acanthosis, papillomatosis, and hyperkeratosis.
- The first choice of therapy is topical tretinoin. Other treatments include excision (if the lesion is small), ammonium lactate cream, cryotherapy, calcipotriol, dermabrasion, and long-pulse alexandrite laser.

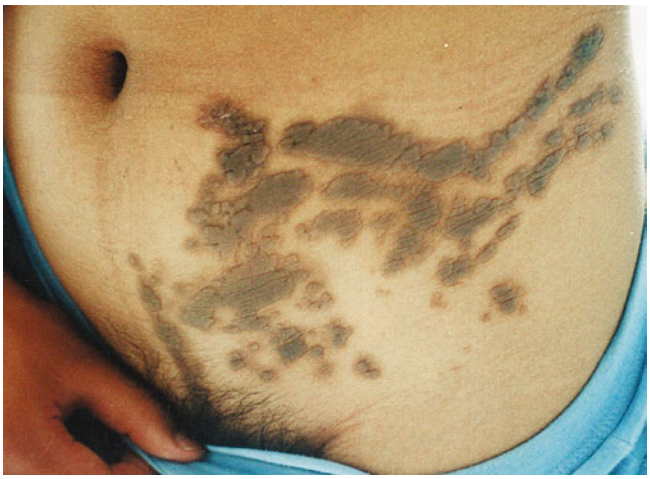

Fig. 23-4-1 Dark-brown warty lesion, velvet-like appearance on the left abdomen

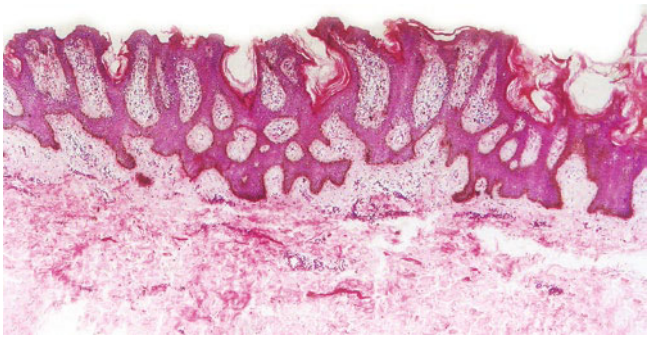

Fig. 23-4-2 Hyperkeratosis and papillomatosis, the dermal papillae project upward as fingerlike projections, and the valleys between the papillae are due to mild to moderate acanthosis; the thick of stratum malpighii at the tips of the papillae and on the sides of the protruding papillae are thinned (HE stain, ×100)

23.5 Malignant Acanthosis Nigricans Complicated by Gastric Adenocarcinoma [9, 10]

- Malignant acanthosis nigricans (MAN) is a paraneoplastic skin syndrome that is mainly related to gastric adenocarcinoma and characterized by pruritic, hyperkeratotic, and hyperpigmented plaques, which subsequently form velvety papillomas in the flexures, skin folds, neck, nipples, and anogenital area. It presents an abrupt onset, rapid progression, and more extensive skin and mucosa involvement.
- Florid cutaneous papillomatosis (FCP) and tripe palms (TP) are considered abortive clinical variants of AN. The combination of MAN, FCP, and TP is extremely rare.
- Neoplastic upregulation of transforming growth factor α is considered to play a principal role in paraneoplastic skin syndrome. The mainstream therapy should be a focus on the underlying neoplasm.

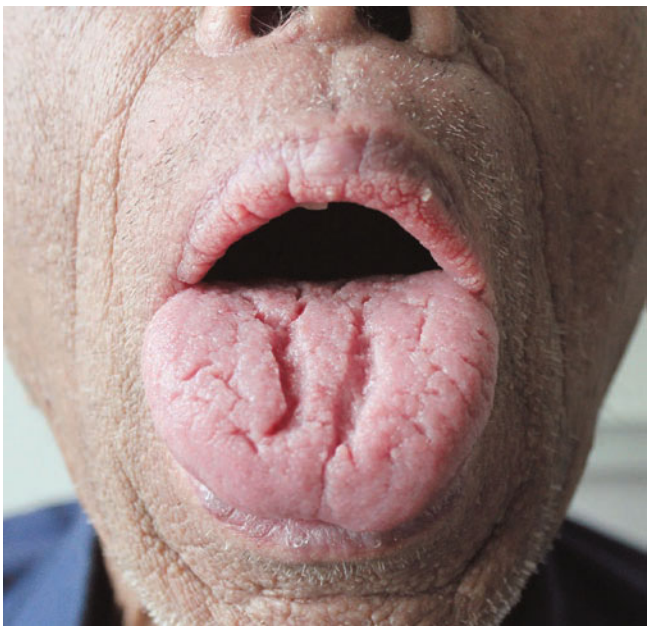

Fig. 23-5-2 Thickened and furrowed tongue

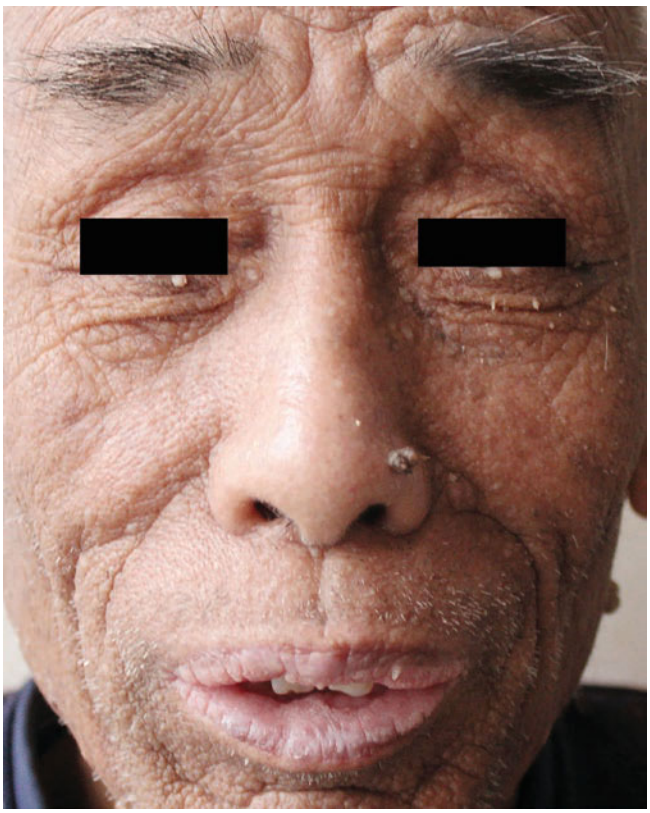

Fig. 23-5-1 Dirty-looking appearance with diffuse hyperpigmentation and velvety thickening on his face (Reproduced with the permission from [9, 10])

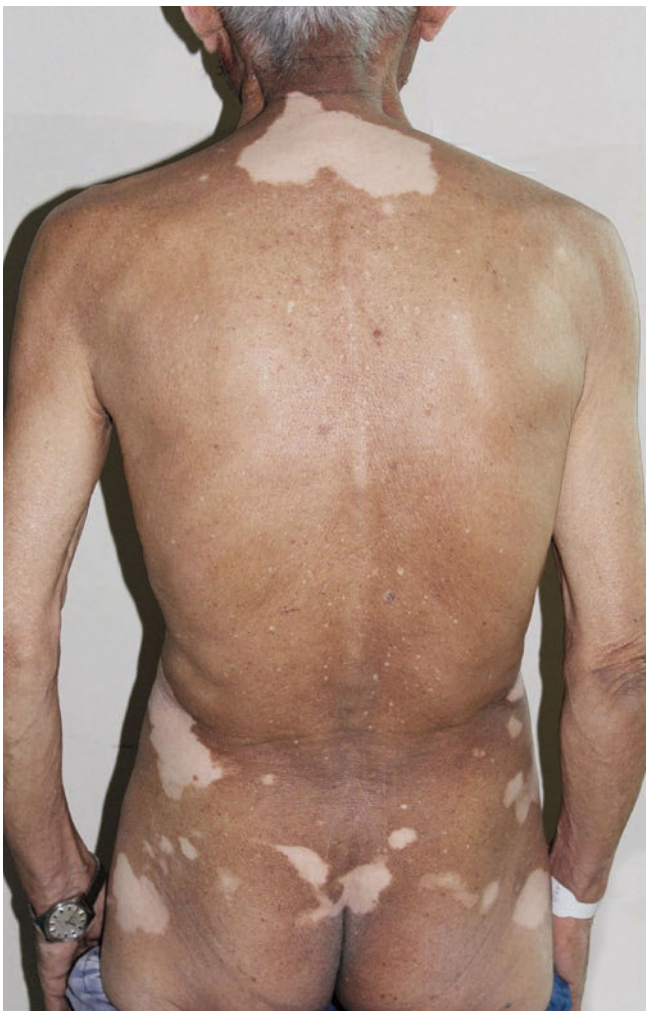

Fig. 23-5-3 Many irregular depigmented patches on the head and trunk

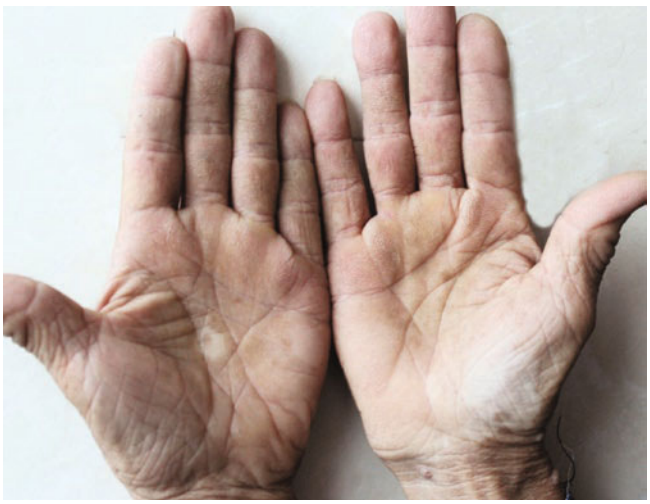

Fig. 23-5-4 Diffuse velvety thickening and prominent ridges of the palms

23.6 Hyperandrogenism, Insulin Resistance, and Acanthosis Nigricans Syndrome [11]

- Hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIR-AN) syndrome is an uncommon multisystem disease. Its etiology is associated with genetic and environmental factors.
- The lesions usually occur during adolescence, presenting as hyperpigmentation, dryness, and roughness of the skin in the early and gradually becoming into gray-brown or black, palpably thickened, and covered with small, papillomatous elevations.
- Multiple laboratory tests are needful for diagnosis. Histological results usually reveal epidermal papillomatosis and acanthosis with orthohyperkeratosis.
- Taking metformin is a satisfactory therapeutic regimen.

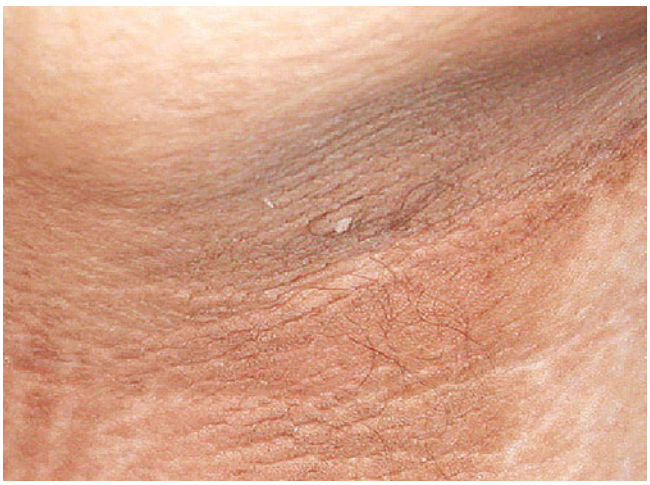

Fig. 23-6-1 Hyperpigmentation, dryness, and coarseness of the skin, like the papillary hypertrophy on the axillae

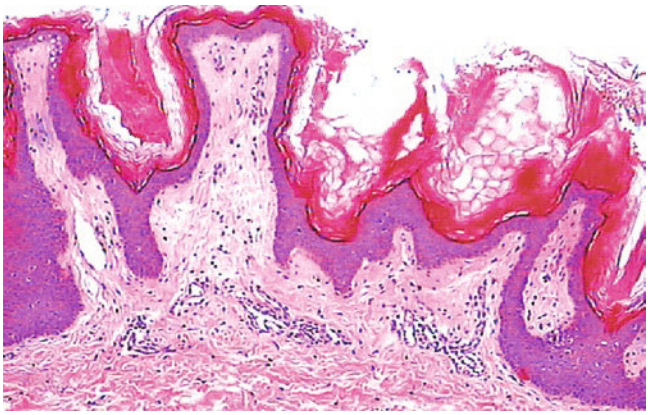

Fig. 23-6-2 The dermal papillae project upward as fingerlike projections, the valleys between the papillae mild acanthosis and filed with keratotic material, and the stratum malpighii at the tips of the papillae and on the sides of the protruding papillae are thinned (HE stain, ×40)

23.7 Necrolytic Migratory Erythema [12, 13]

- Necrolytic migratory erythema (NME) is a characteristically cutaneous presentation of glucagonoma syndrome that preferentially appears in the perioral region, distal extremities, buttocks, thighs, and perineum.
- Although NME is suggestive of glucagonoma, it is not specific. The eruption is characterized by spontaneous remissions and exacerbations without identifiable precipitating factors.
- At early stages, the lesions are commonly erythematous macules and papules that develop into well-demarcated, confluent, circinate plaques with a variable scale. The erythematous margins typically spread centrifugally with progression from erythema to vesiculation, to crusting, and then to resolution.
- Histologically, this condition shows epidermal pallor, necrolytic keratinocytes, and parakeratosis.
- Treatment of the skin eruption before surgery may be challenging. The lesions may regress after removal.

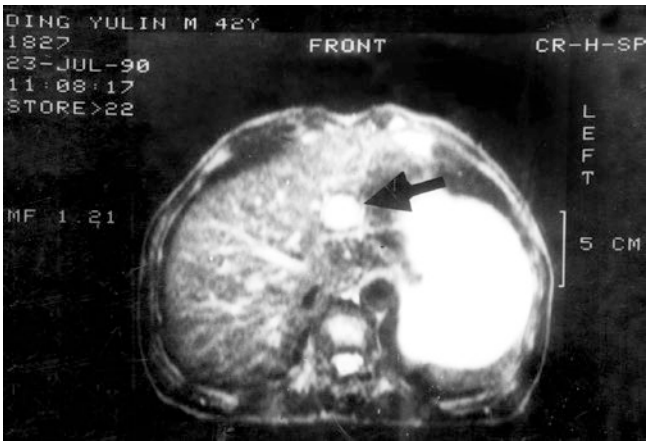

Fig. 23-7-1 Tumor in the pancreas

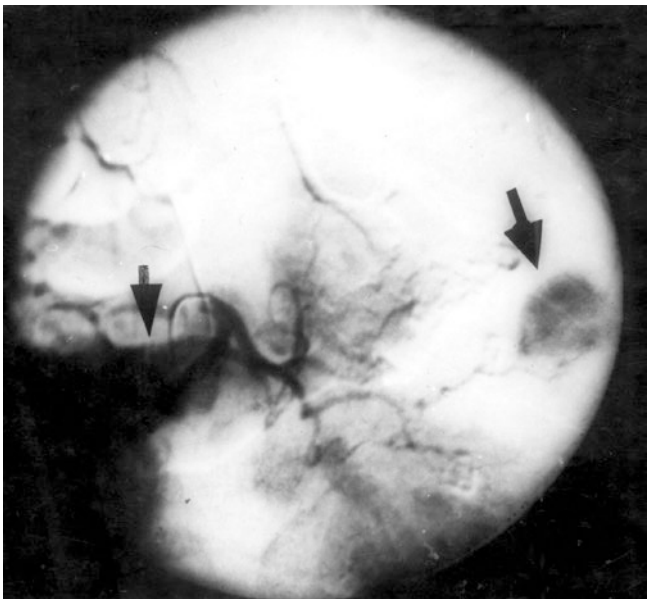

Fig. 23-7-2 Tumor in the liver

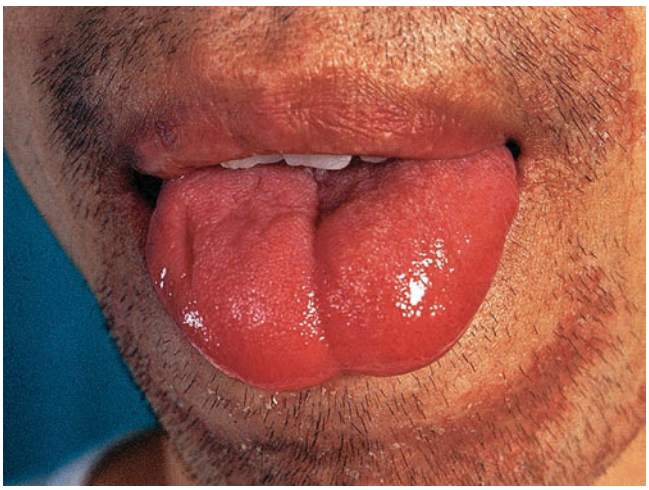

Fig. 23-7-3 Oral mucosa engorgement and vermeil tongue with erosions and edema

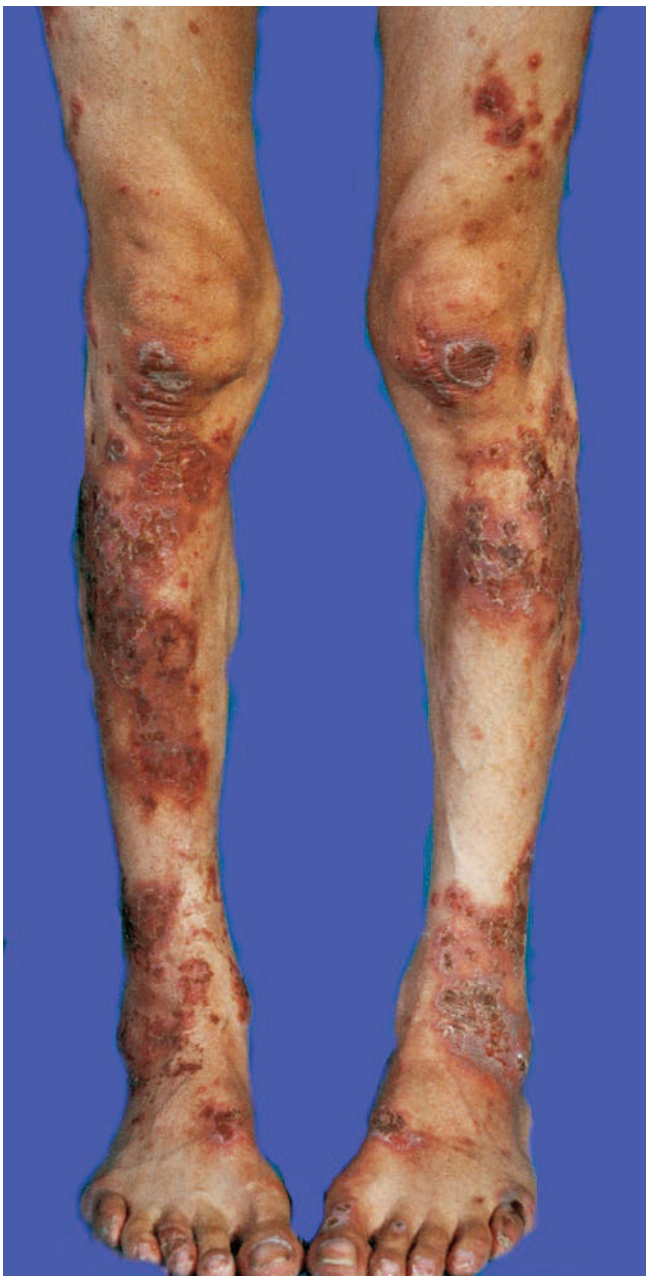

Fig. 23-7-4 Symmetric erythema, erosions, effusion, and crust with shininess on the lower limbs

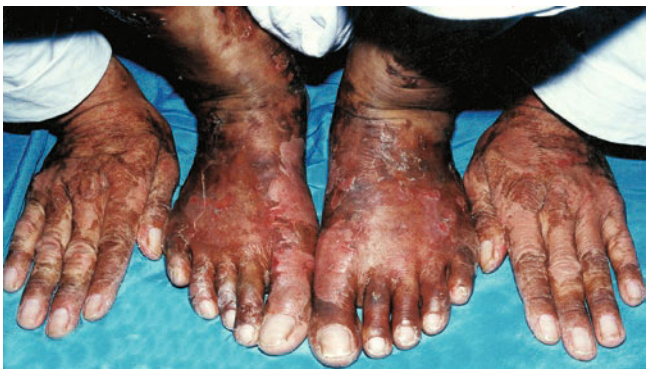

Fig. 23-7-5 Erythema, coarseness, desquamation, and hyperpigmentation on the dorsa of both the hands and feet

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Non-inherited Cutaneous Syndromes

24

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Abstract

Non-inherited syndromes of dermatological interest are classified together in this chapter: Ascher syndrome, Baboon syndrome, blue rubber bleb nevus syndrome, Cronkhite-Canada syndrome, Favre-Racouchot syndrome associated with eyelid papilloma, Gorham syndrome, vulvovaginal-gingival lichen planus, Laugier-Hunziker syndrome, Parry-Romberg syndrome with subclinical cerebral involvement, and Marshall-white syndrome.

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24.1 Ascher Syndrome [1, 2]

- Ascher syndrome occurs with a triad of ptosis, enlarged lip, and euthyroid goiter.
- Facial malformation in Ascher syndrome is the greatest concern for the patient, although it has no functional outcomes.
- Both Ascher syndrome and Saethre-Chotzen syndrome present blepharochalasis, while the latter has the involvement of multiple other systems.
- Histologic observation of the enlarged lip reveals abundant minor salivary glands and infiltration of mixed inflammatory cells.

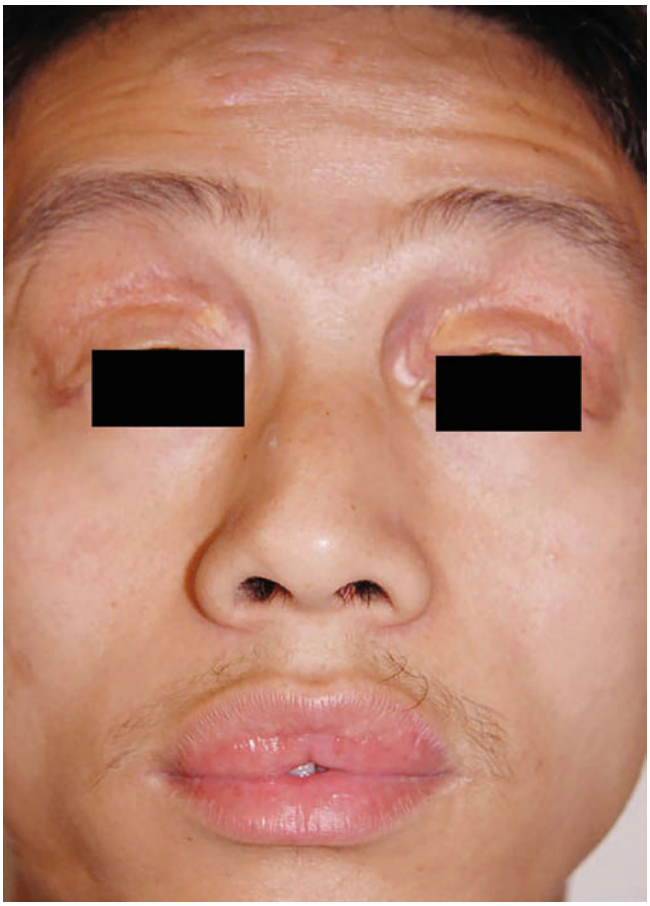


Fig. 24-1-1 Relaxation and ptosis of the both upper eyelids with atrophy and slight edema. Swollen upper lip and double upper lip (Reproduced with the permission from [1, 2])

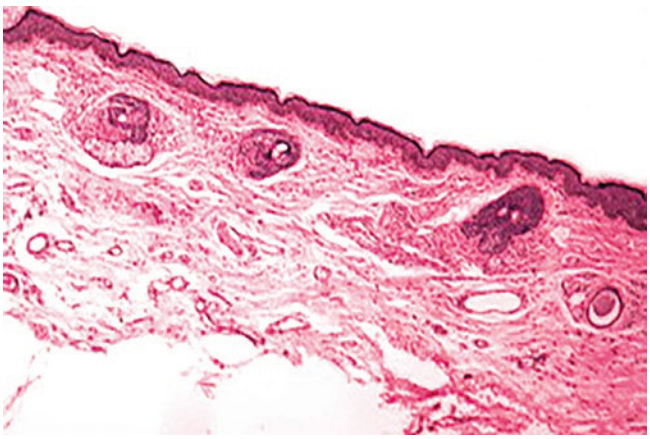


Fig. 24-1-2 Apparent dermal atrophy, telangiectasia, and capillary proliferation (HE stain ×40)

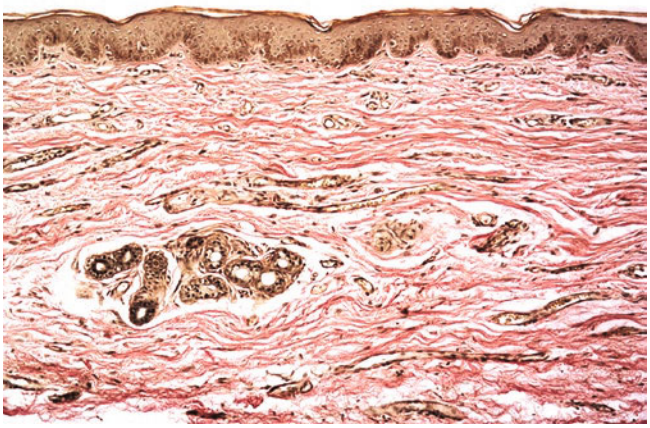
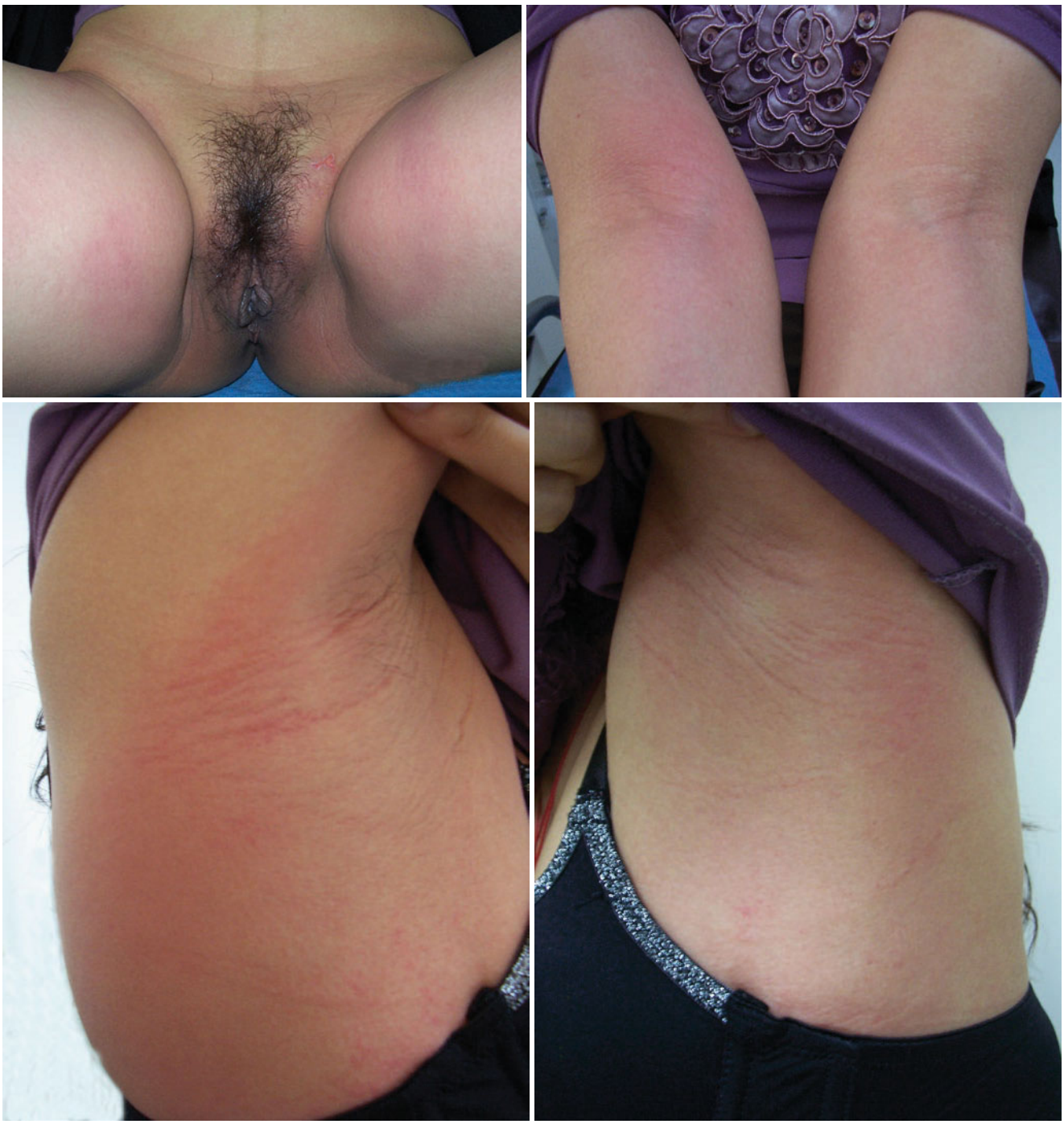


Fig. 24-1-3 Reduced elastic fibers in the dermis (Verhoeff stain, ×100)

24.2 Baboon Syndrome [3]

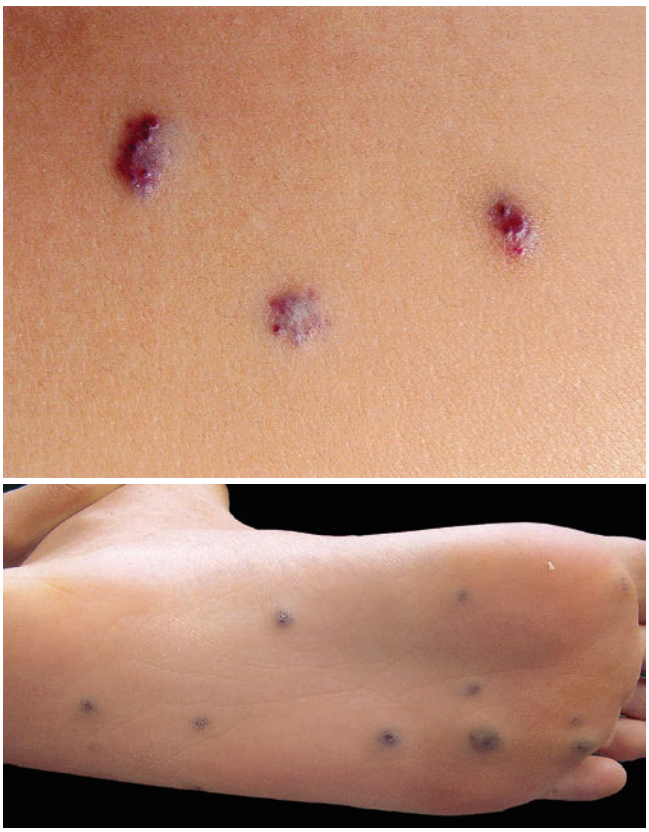
- Baboon syndrome (BS) (symmetric drug-related intertriginous and flexural exanthema) is regarded as a systemic contact dermatitis.
- Clinically, it presents with a symmetric intertriginous erythema involving the gluteal area or a V-shaped erythema of the inguinal area, resembling the rump of a baboon.
- The peculiar reaction of BS was initially observed after inhaling mercury vapor. It is also associated with exposure to nickel, intake of aminopenicillins, β-lactam antibacterials, or certain chemotherapeutic agents.
- Although both BS and acute generalized exanthematous pustulosis affect the intertriginous folds, the latter tends to have a high fever, elevated white blood cell count and numerous pinhead-sized pustules that are lacking in BS.



Figs. 24-2-1, 24-2-2, 24-2-3, 24-2-4 Circumscribed erythema symmetrically distributed on the—inguinal—vulva, bilateral armpit, chelidon, and other major intertriginous areas

24.3 Blue Rubber Bleb Nevus Syndrome [4–6]

- Blue rubber nevus syndrome (BRBNS) clinically shows a constellation of cutaneous and gastrointestinal hemangiomas.
- BRBNS was named for the distinctive blue tint of the lesions.
- Skin lesions in BRBNS include a few to hundreds of blue or purple tumors on the limbs and trunk.
- The extent of visceral organ involvement is the main determination factor for the morbidity and mortality of BRBNS. The gastrointestinal tract is the predominantly affected organ. Gastrointestinal complications, such as bleeding, thrombotic complications, and secondary coagulopathies, are sometimes lethal.
- Skin biopsy of the lesion exhibits ecstatic blood vessels with a singular layer of endothelial cells and a thin matrix.
- Propranolol and bevacizumab suppress vascular proliferation and lead to a halt or partial remission of the disease.
- A panel of antibodies, such as GLUT-1, LYVE-1, and D2-40, can be used to confirm the diagnosis of BRBNS, if needed.



Figs. 24-3-1, 24-3-2 Multiple blue macules, papules, and nodules were in different sizes and were distributed on the trunk (1) and feet (2)

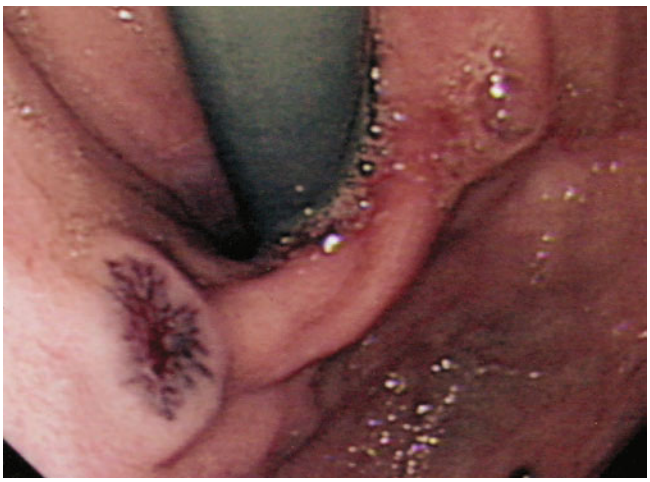


Fig. 24-3-3 A number of angioma-like neoplasms were found on the stomach, with a diameter ranging from 0.5 to 1 cm

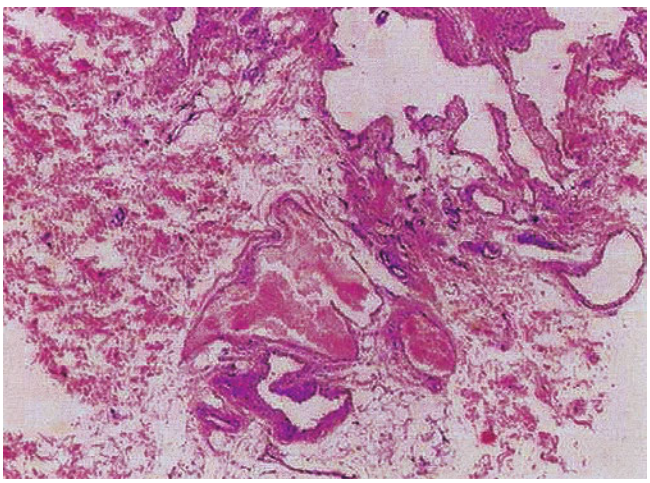


Fig. 24-3-4 In the lower dermis, there were large irregular spaces filled with red blood cells and was lined by a single layer of endothelial cells (HE stain)

24.4 Cronkhite-Canada Syndrome [7–9]

- Cronkhite-Canada syndrome (CCS) consists of diffuse gastrointestinal polyposis and ectodermal abnormalities, including onychodystrophy, abnormal pigmentation, and alopecia.
- The typical manifestation of the nails in CCS is a thin, proximal triangular nail surrounded by a thick nail plate. Onycholysis, thin nail, onychoschizia, and onychomadesis are additional changes of CCS.
- It has been speculated that thrombosis in gastrointestinal blood vessels, malnutrition, infection, and glomerulonephritis all contribute to considerable morbidity in CCS. Immune abnormality, mental stress, and fatigue are precipitating factors for CCS.

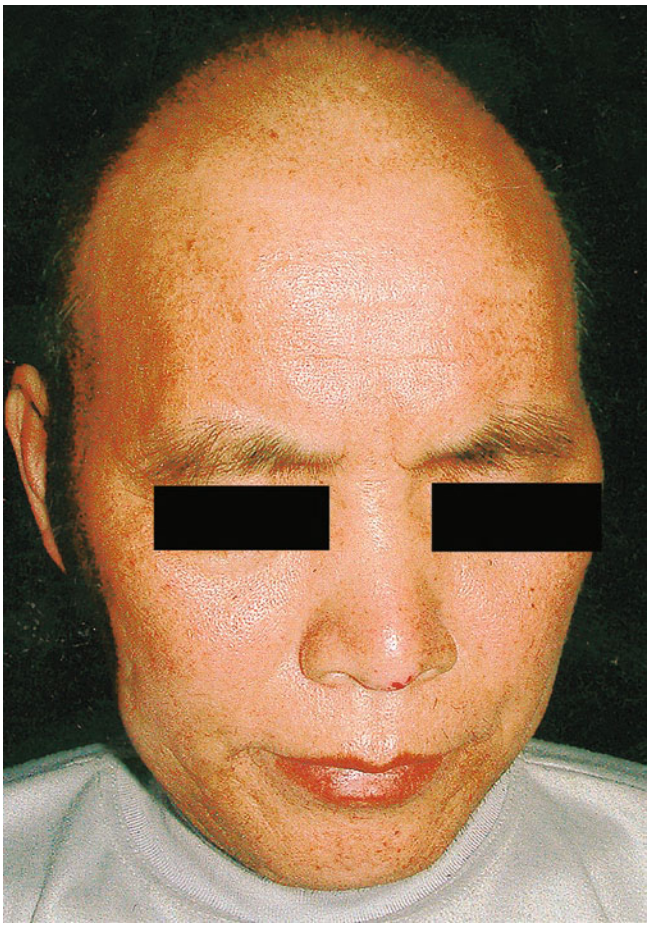


Fig. 24-4-1 Sparse and thin hairs on the scalp (Reproduced with the permission from [7, 8, 9])

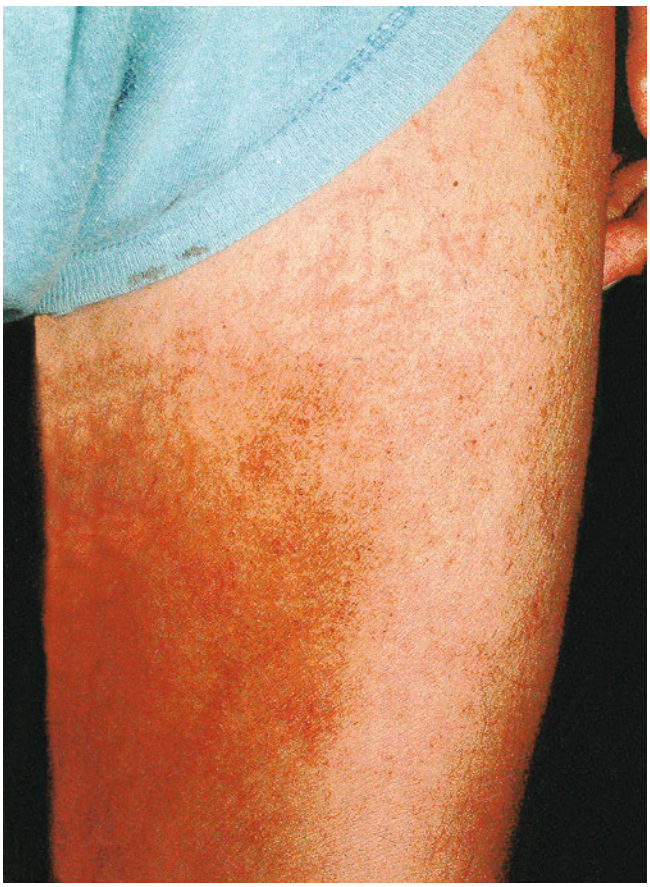


Fig. 24-4-2 Diffuse and spotty hyperpigmentation on the right thigh

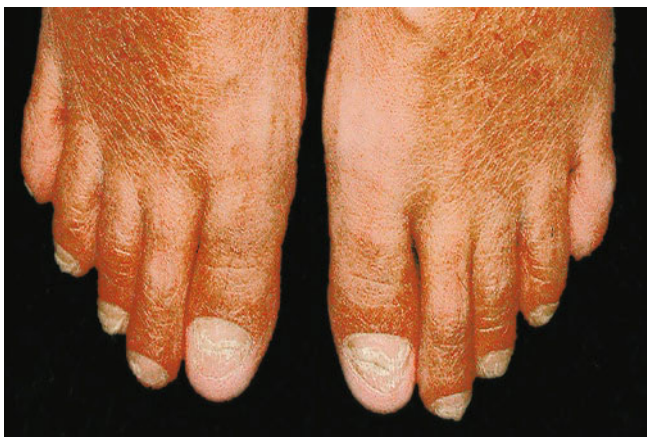


Fig. 24-4-3 Triangular nail plate in a dystrophic nail

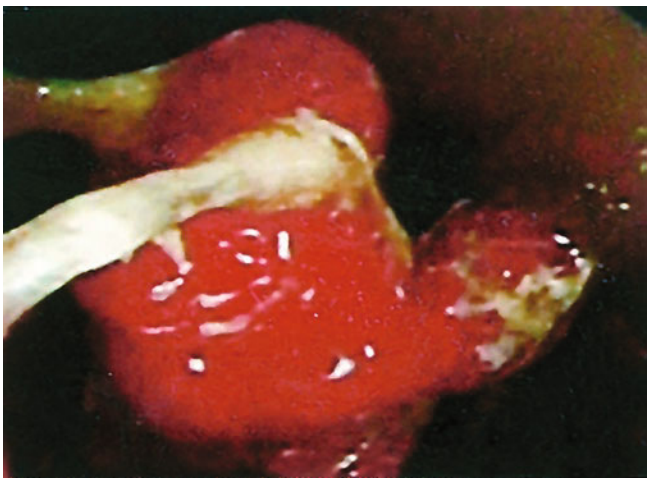


Fig. 24-4-4 Multiple polyposis with different sizes was noticed in the splenic flexure of the colon

24.5 Favre-Racouchot Syndrome Associated with Eyelid Papilloma [10, 11]

- Favre-Racouchot syndrome is not an uncommon condition, its incidence increases with age, and it occurs in up to 6% of people older than 50 years of age.
- Examination reveals actinically damaged skin with atrophy, yellowish discoloration, wrinkles and furrows, cystic nodules, and punctate, waxy, non-inflamed, soft, open or closed comedones.
- Topical retinoids, such as tretinoin, adapalene, or tazarotene, are the most effective pharmacologic treatments. Surgical techniques include excision, dermabrasion, curettage, comedone extraction, and laser resurfacing.

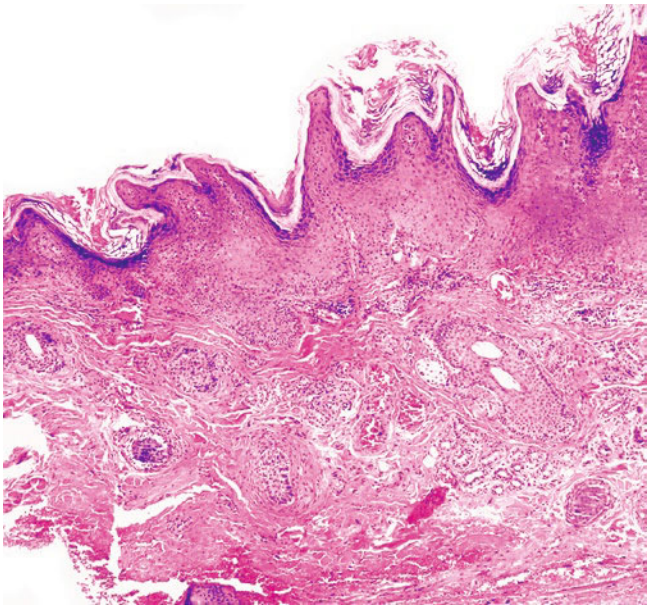


Fig. 24-5-2 Histology of the papilloma showed hyperkeratosis, hypergranulosis, and acanthosis with multiple follicular keratinous plugs (HE stain, ×100)

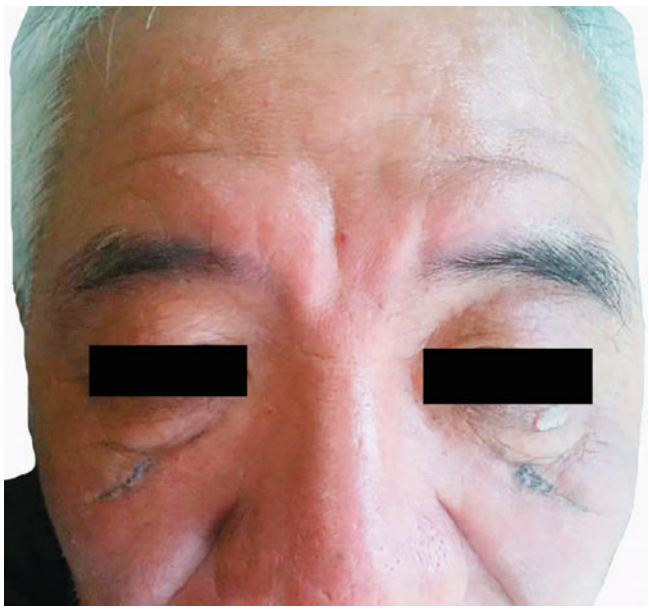


Fig. 24-5-1 Several open comedones were located at two obliquely linear furrows in both infraorbital regions. These lesions were bilaterally distributed. A flesh-colored nipple-like growth, approximately groundnut kernel sized, on the patient's left lower eyelid (Reproduced with the permission from [10, 11])

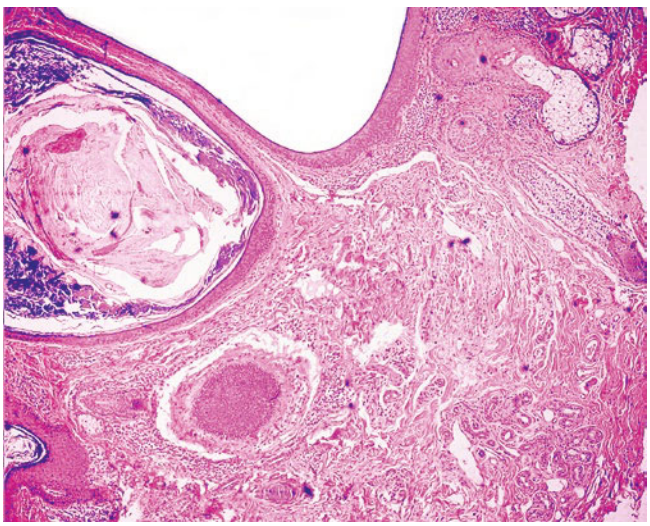


Fig. 24-5-3 The open comedones typically showed dilated elongated infundibula which were filled with keratotic and parakeratotic materials. The upper part of the comedones contained nests, yeast-like organisms (pityrosporum), and bacterium (HE stain, ×100)

24.6 Gorham Syndrome [12, 13]

- Gorham syndrome (GS) is a process of progressive massive osteolysis associated with proliferated vascular tissues invading the bones and surrounding tissues.
- GS commonly occurs in the long bones, shoulder, and pelvis.
- Cutaneous vascular lesions may herald underlying osteolysis, and concomitant chylothorax or pericardial effusions are fatal to GS individuals.
- Generally, GS arrests its progression without any medical intervention.
- Cutaneous lesions appear in approximately 6% of GS cases. They consist of skin-colored papules and vesicles and are described as either hemangioma or lymphangioma.

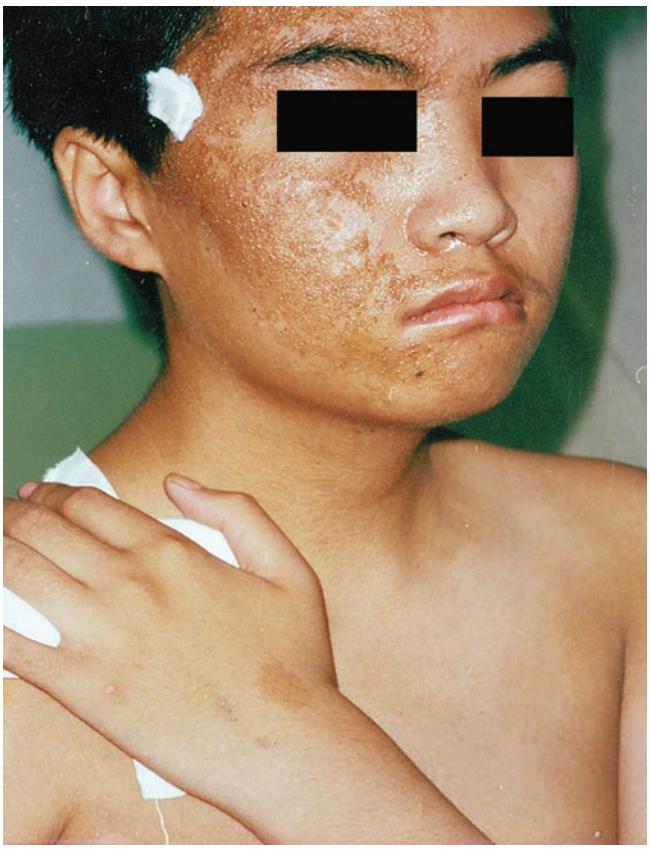


Fig. 24-6-1 White, millet-like vesicles with greasy appearance on the right side of the face (Reproduced with the permission from [12, 13])

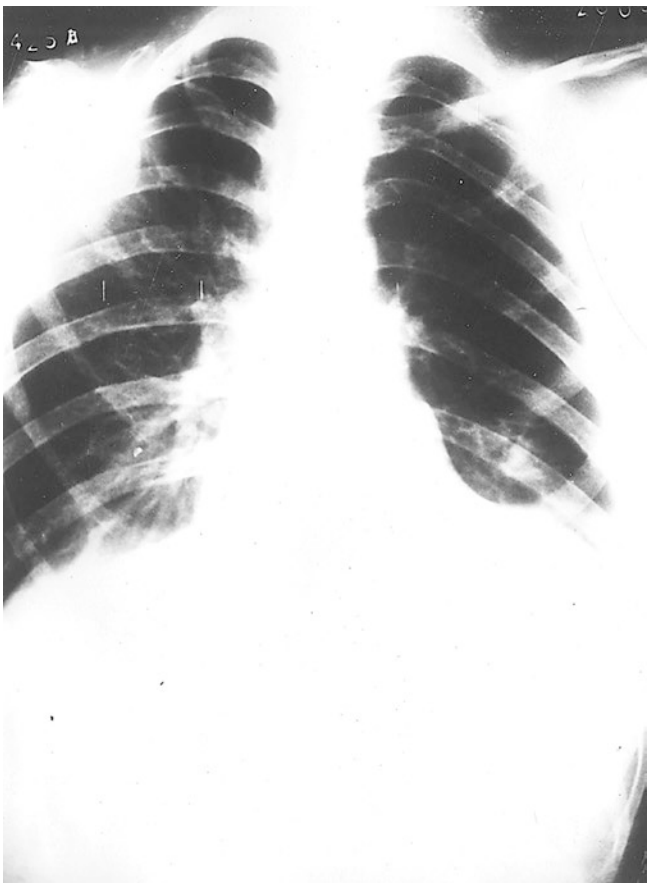


Fig. 24-6-2 Bilateral pleuroclysis effusions, right clavicle deformity

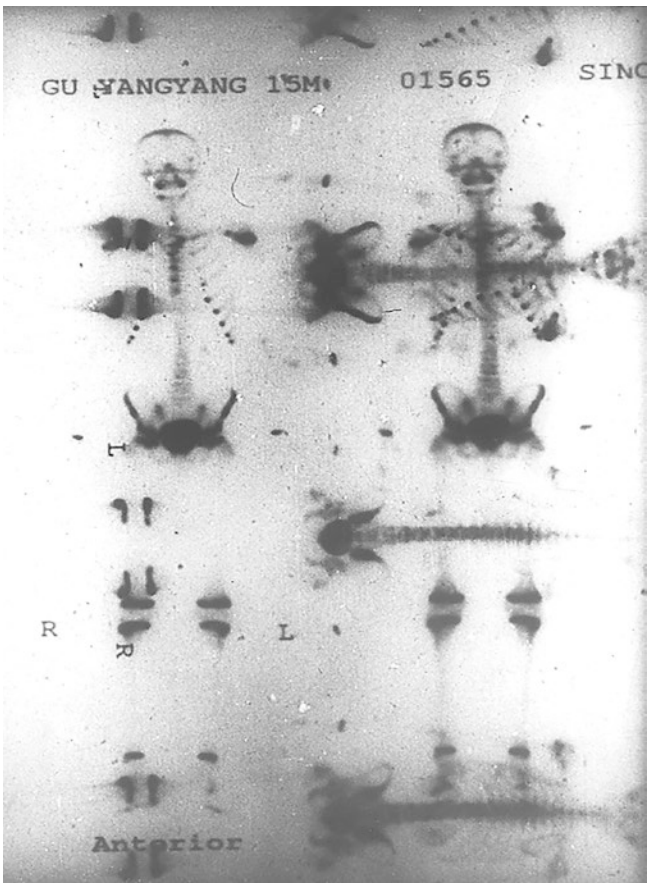


Fig. 24-6-3 Increased signal intensity in the proximal aspect of left humerus by SPECT

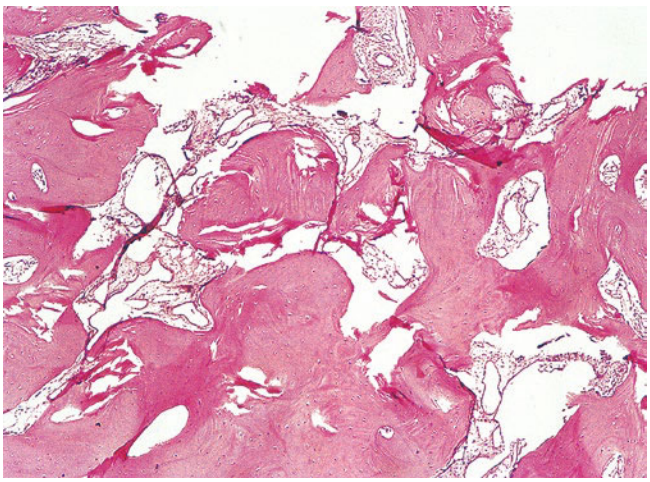


Fig. 24-6-4 Fibrosis and lymphangial hyperplasia in right clavicle biopsy (HE stain, ×40)

24.7 Vulvovaginal-Gingival Lichen Planus [14, 15]

- Vulvovaginal-gingival lichen planus (VVGLP) is a distinctive erosive type of lichen planus in females. The male counterpart is named peno-gingival lichen planus.
- VVGLP presents with lichen planus with a triad of vulval, vaginal, and gingival regions. Scar or stenosis develops on the mucosal site with previous onset of VVGLP. Malignancies occur in long-standing mucosal lesions.
- Patients with VVGLP mainly complain of localized burning, pain, pruritus, dyspareunia, and seropurulent discharge.
- Immunobullous diseases should be excluded with direct or indirect immunofluorescence stains before the diagnosis of VVGLP is established.

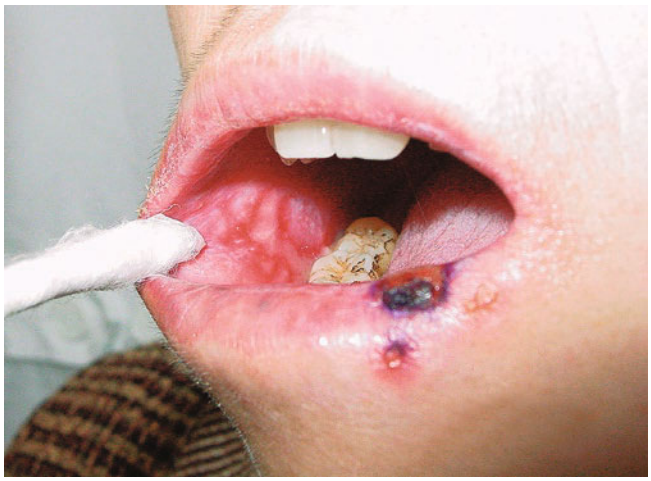


Fig. 24-7-1 Erosions were presented in right buccal mucosa and on the upper and lower gingival regions

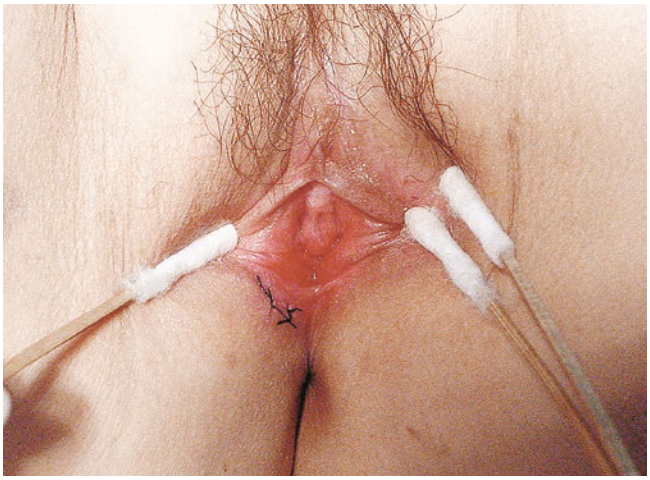


Fig. 24-7-2 Erosions were presented on the aditus vaginae and the lower part of labium minus

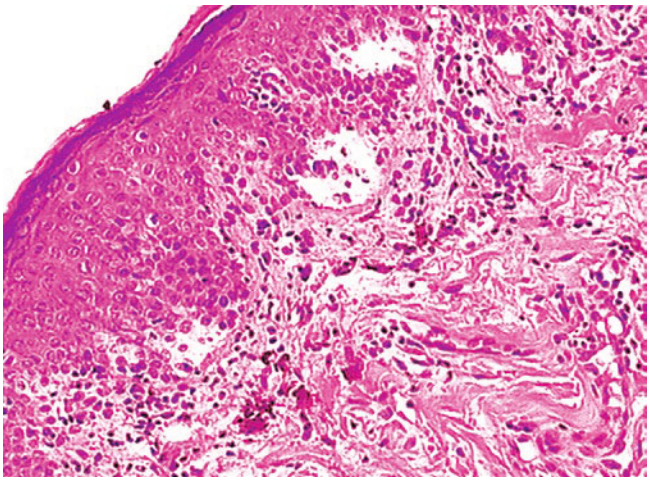


Fig. 24-7-3 There was hydropic degeneration of basal cells and a band-like lymphohistiocytic infiltration beneath the epidermis (HE stain, ×200)

24.8 Laugier-Hunziker Syndrome [16, 17]

- Laugier-Hunziker syndrome (LHS) is an uncommon pigmentary disease that affects the mucosa and skin. Concomitant systemic complications underlying malignancies are extremely rare in LHS.
- LHS has hyperpigmented macules on the lips and oral mucosa. Longitudinal melanonychia is another sign.
- Although LHS and Peutz-Jeghers syndrome share some similarities, the absence of intestinal polyposis in LHS helps with their differentiation.
- Skin biopsy shows basilar hyperpigmentation without proliferation of melanocytes. Pigmentary incontinence is noticeable in the papillary dermis.
- Pigmented macules in LHS are solitary or confluent. Their color ranges from slate gray to dark brown with ill-defined or clear margins.

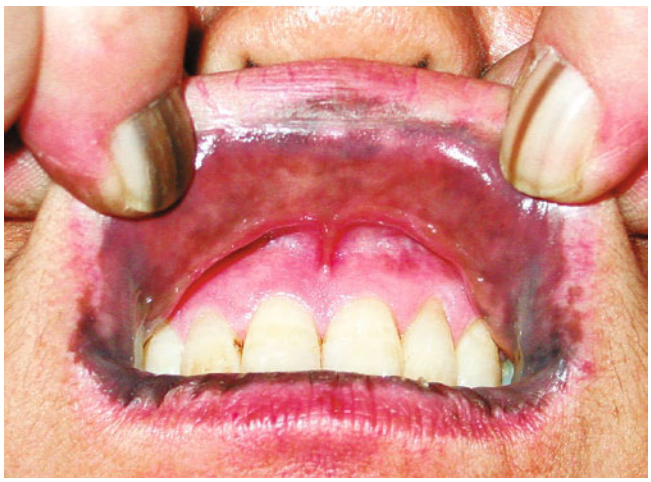


Fig. 24-8-1 Lentiginous pigmentation of the upper and lower lips

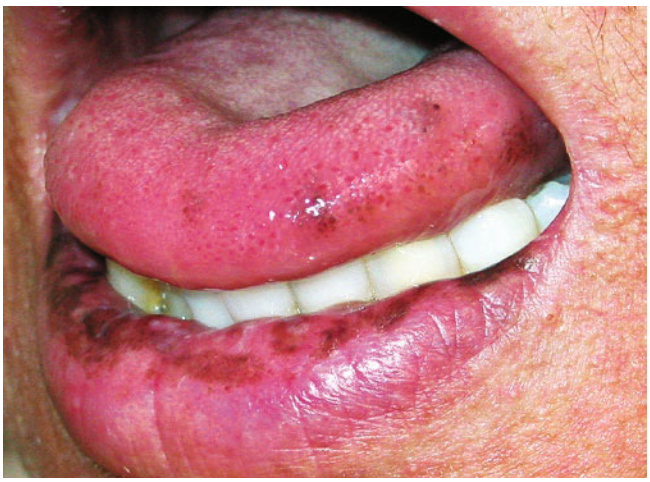


Fig. 24-8-2 Lentiginous pigmentation of the lower lip and tongue

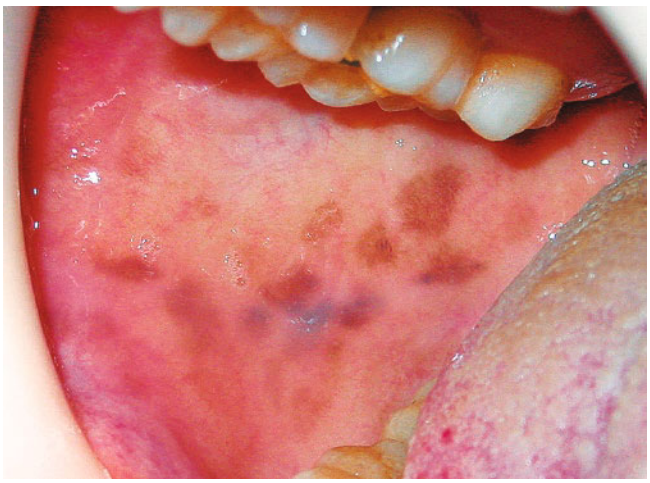


Fig. 24-8-3 Lentiginous pigmentation of the right buccal mucosa

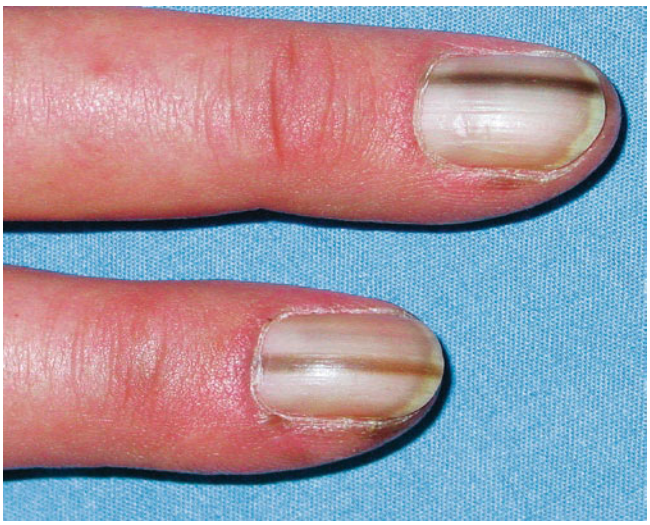


Fig. 24-8-4 Lentiginous pigmentation on the finger joint of the right hand; dark brow stripes on the fingernail

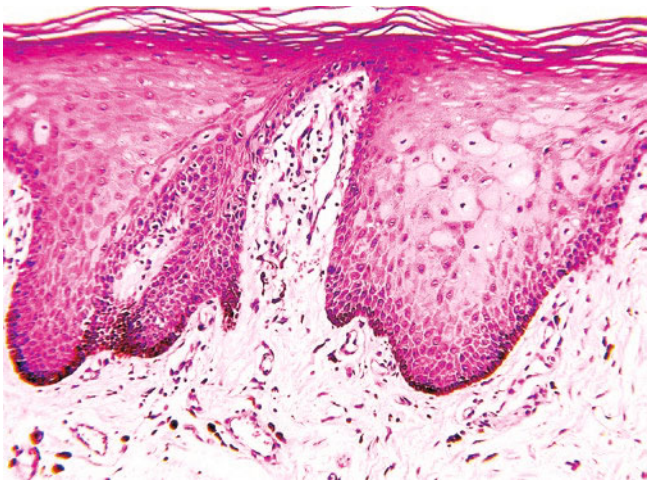


Fig. 24-8-5 Hyperpigmentation in the basal cell layer (HE stain, ×100)

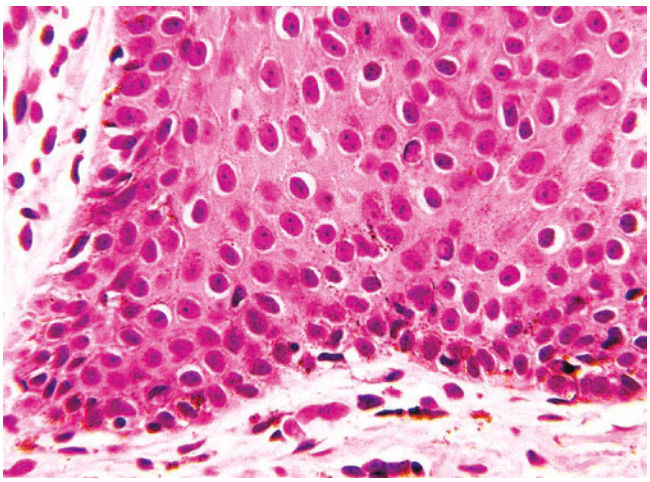


Fig. 24-8-6 Numerous melanin in basal cells (HE stain, ×400)

24.9 Parry-Romberg Syndrome [18, 19]

- Parry-Romberg syndrome (PRS) belongs to the spectrum of neurocutaneous disorders.
- It is characterized by the progression of hemifacial atrophy that affects the skin, subcutaneous tissue, muscle, cartilage, and underlying bone tissue. Abnormalities in ocular, neurological, hair, and dental tissue have also been documented.
- PRS tends to have an insidious onset of facial atrophy, and it stabilizes after several years of rapid development.
- The neurological complications are comprised of trigeminal neuralgia, epilepsy, facial paraesthesia, and headaches.
- Concomitant linear scleroderma "en coup de sabre" is fairly common in PRS.
- PRS affects the face, mainly in the maxillary region, and it may affect one to several dermatomal branches of the trigeminal nerve.

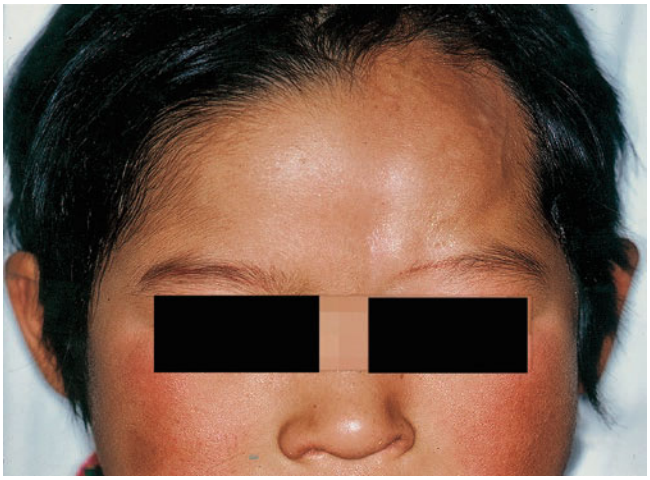


Fig. 24-9-1 Parasagittally on the left forehead, about 10 cm in length, sunken on the left forehead (Reproduced with the permission from [18, 19])

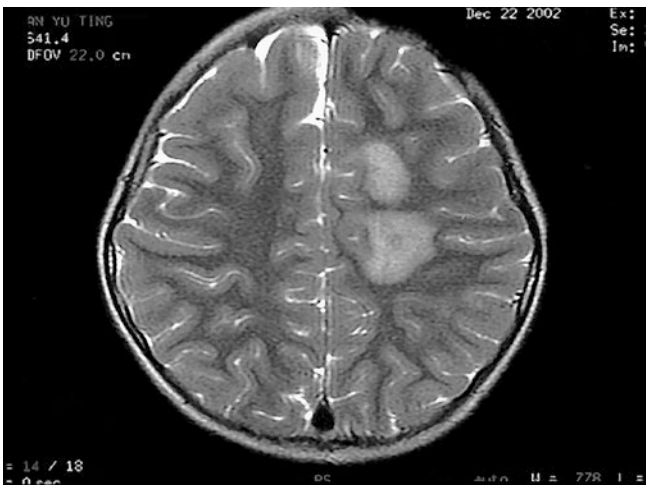


Fig. 24-9-2 Foci in white matter in foci on the left occipital lobe, temporal lobe under cortical, fat scarcity, and skull attenuation in the left forehead

24.10 Marshall-White Syndrome [20, 21]

- Bier's spot (BS) is a distinctive vascular mottling of the skin due to an underlying functional abnormality of the blood vessels.
- Clinically, it features asymptomatic pale macules against an erythematocyanotic background. These macules measure approximately 10 mm and commonly distribute along the extensor extremities.
- BS accentuates when the limb is in a dependent position and disappears when the limb is raised.
- BS is reported in miscellaneous disorders, including palmar hyperhidrosis, insomnia, tachycardia, pregnancy, cryoglobulinemia, scleroderma, aortic hypoplasia, varicosity, lichen planus, alopecia, and Peutz-Jeghers syndrome.

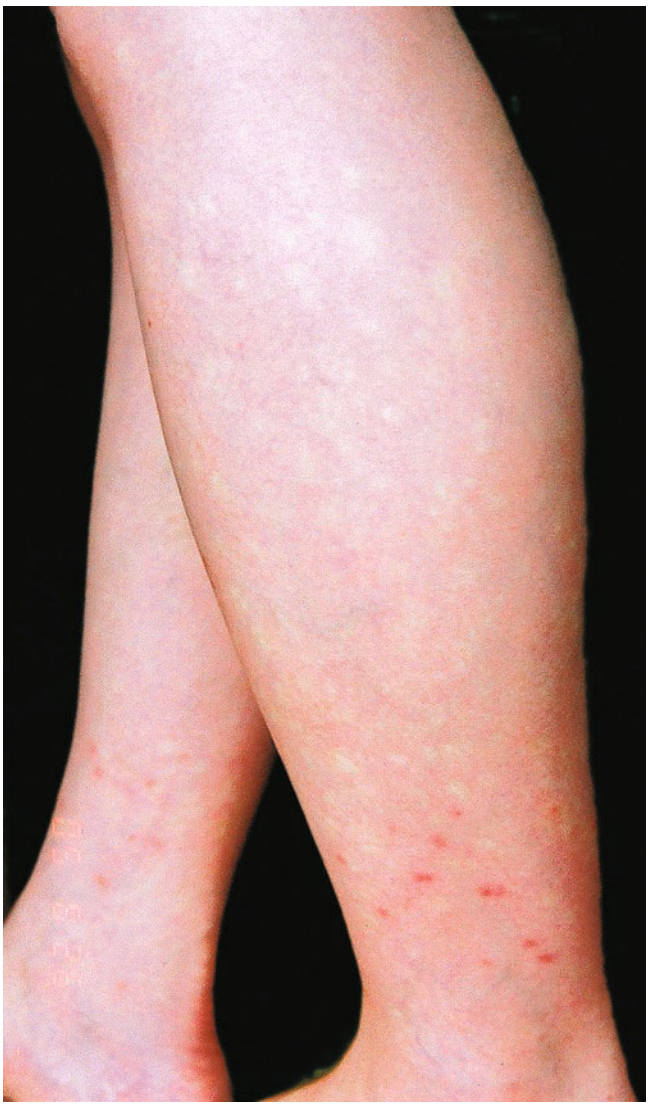


Fig. 24-10-1 Numerous small pale macules, 0.2–2.0 cm in diameter, were scattered in pink or red on both legs

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Part IX

Genodermatoses

Keratoderma

25

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Abstract

In this chapter, genodermatoses with characteristic keratoderma are distinctively presented, including porokeratosis, rare manifestations of porokeratosis, striate palmoplantar keratoderma, spiny keratoderma, epidermolytic palmoplantar keratoderma, acrokeratosis verruciformis, warty dyskeratoma, progressive symmetric erythrokeratodermia, arsenic keratosis, hyperkeratosis of the nipple and areola, waxy keratosis, acrokeratoelastoidosis, lichen planus-like keratosis, and aquagenic acrokeratoderma.

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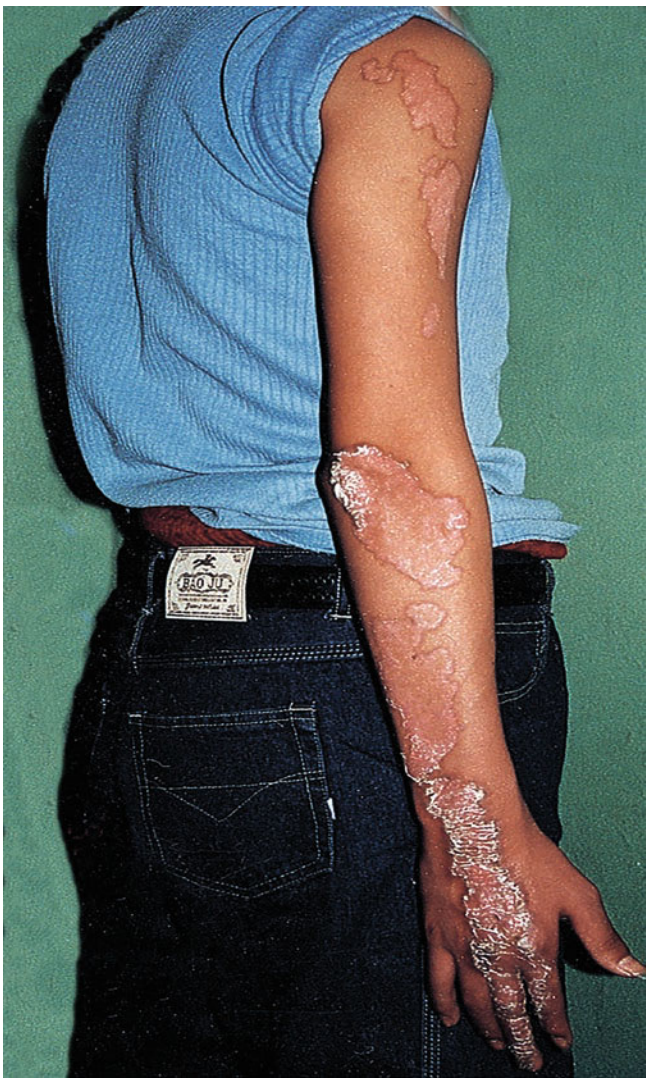
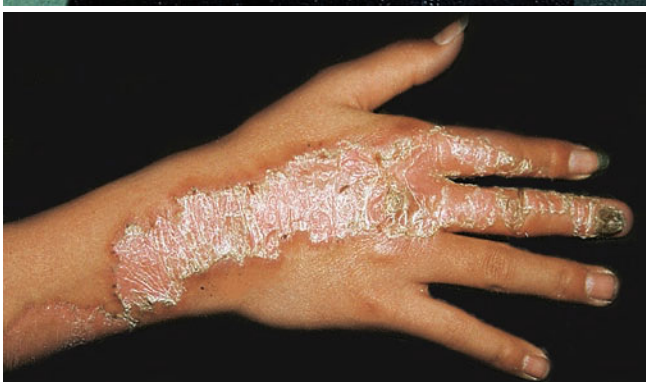
25.1 Porokeratosis [1–3]

- Porokeratosis (PK) has a clinically heterogeneous set of genodermatosis featuring clonal keratinization defects.
- It is characterized by circumferential papules or plaques of variable size. These lesions enlarge centrifugally and develop a distinctive peripheral keratotic rim and central nonspecific findings (atrophy, hyperkeratosis).
- Histology of porokeratosis typically shows cornoid lamella, corresponding to its pathognomonic elevated border. Therefore, it should be kept in mind that the edge of the peripheral border should be included in skin biopsy.
- Cornoid lamella is described as a tiered column of parakeratosis with diminution of the granular layer or dyskeratotic cells in the superficial epidermis. Linear and reticulate forms often show multiple cornoid lamellae, and palmoplantar porokeratoses have broad cornoid lamella. In porokeratosis of Mibelli, cornoid lamella arises with adjacent mild papillomatosis.
- Although most commonly found in porokeratosis, cornoid lamella can be found in many cutaneous inflammatory, hyperplastic, and neoplastic conditions.





Figs. 25-1-1, 25-1-2 Numerous keratotic plaques were distributed in a segment of the extensor surface of the right arm

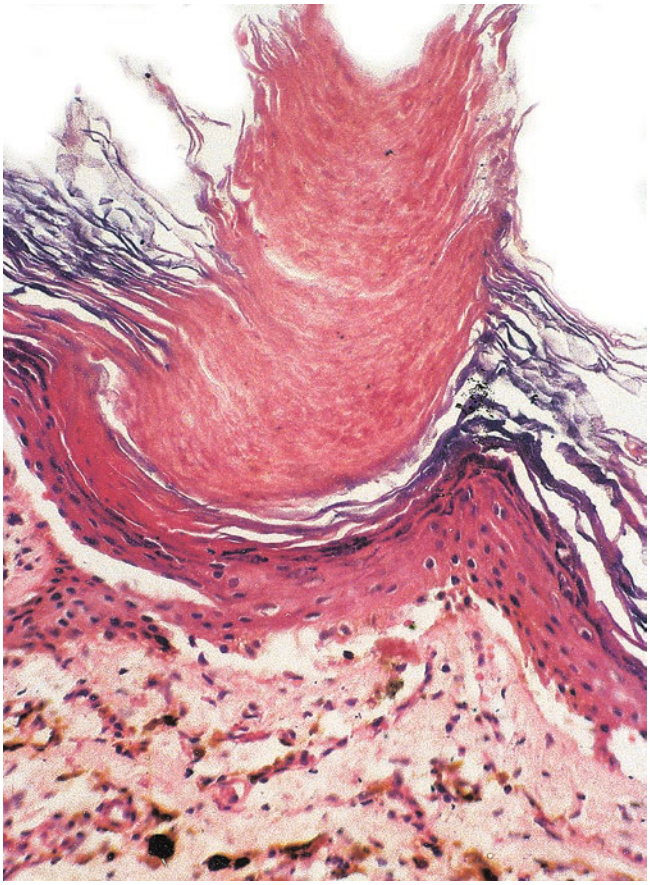


Fig. 25-1-3 Stacked parakeratosis invaginating the epidermis. The underlying granular cell layer was diminished (HE stain)

25.2 Rare Manifestations of Porokeratosis [3–7]

- A variety of clinical and pathological types are recognized that mainly include porokeratosis of Mibelli (PM), disseminated superficial actinic porokeratosis (DSAP), disseminated superficial porokeratosis (DSP), linear porokeratosis, hyperkeratotic porokeratosis, follicular porokeratosis, inflammatory porokeratosis, eruptive pruritic porokeratosis, palmoplantar porokeratoses, porokeratotic eccrine ostial and dermal duct nevus, porokeratotic eccrine duct and hair follicle nevus, porokeratoma, and CAP syndrome (craniosynostosis, anal anomalies).
- Other morphological types have also been reported, which are giant porokeratosis, facial porokeratosis, punched-out porokeratosis, reticulate porokeratosis, porokeratosis ptychotropica, or hypertrophic porokeratosis.
- PM is the classic form of porokeratosis that begins in infancy to early childhood. It begins as variable-sized plaques that expand for years, reaching as large as 20 cm in diameter.
- DSAP usually comes out in the third or fourth decade of age. Its lesions are distributed on sun-exposed regions of the skin and are much smaller than those in PM. Clinically, DSP is a counterpart of DSAP, whose lesions are not confined to only the sun-exposed area.
- Punctate porokeratosis appears on the palms and soles during adulthood. Seed-like punctate keratoses are its characteristic manifestation.
- Hyperkeratotic porokeratosis may be found in porokeratosis of Mibelli, linear porokeratosis, and disseminated superficial actinic porokeratosis. The individual lesion in hyperkeratotic DSAP mainly distributes in sun-exposed areas and is much smaller than hyperkeratotic porokeratosis of Mibelli.
- Linear porokeratosis presents in a linear, blaschkoid, or segmental distribution. Although only 7% of porokeratosis develops malignancy, linear porokeratosis is the most likely to develop a malignancy. Other extrinsic precipitating factors include ultraviolet exposure, linear form, long duration, and large lesion.
- Porokeratosis involving the digits is a potential triggering factor for pseudoainhum.
- Several reports showed that porokeratosis may colocalize with other disorders, such as vitiligo, lichen planus, psoriasis, or in the region of hemodialysis or scarring.
- Sporadic individuals are associated with organ transplantation and drug administration (prednisolone, thiazide diuretics, or azathioprine).
- There is no standard treatment in porokeratosis. Porokeratosis of Mibelli responds well to topical imiquimod cream. In linear porokeratosis, retinoids can be applied topically or systemically. Vitamin D derivatives are considered the first-line option in the disseminated type.

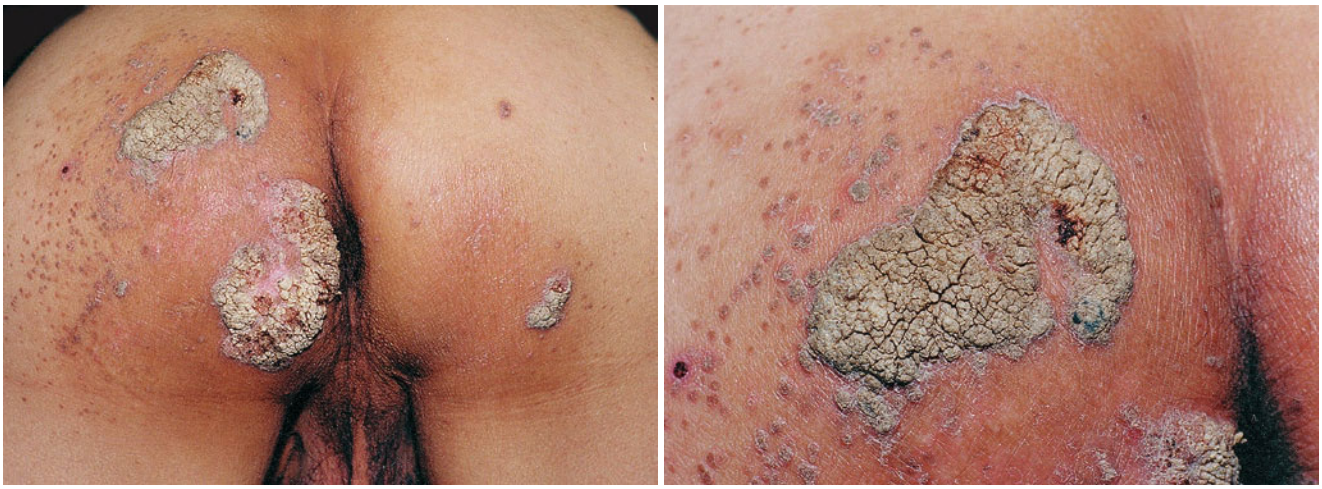


Fig. 25-2a-1, 25-2a-2 Three thick hyperpigmented and hyperkeratotic plaques with verrucous surfaces on both buttocks

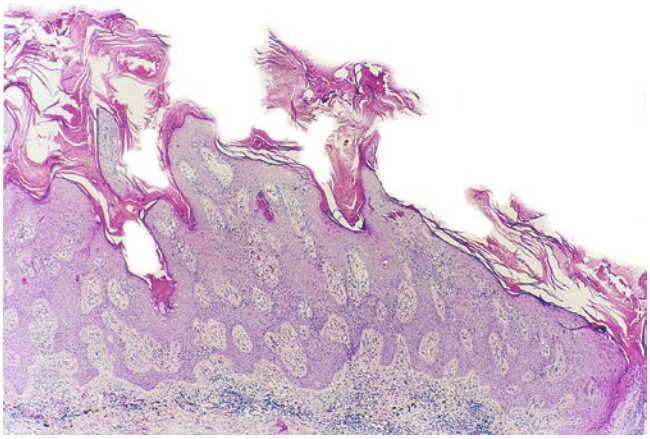


Fig. 25-2a-3 Marked hyperkeratosis with multiple parakeratotic columns and sparse, chronic inflammatory infiltration in the superficial dermis (HE stain, ×40)

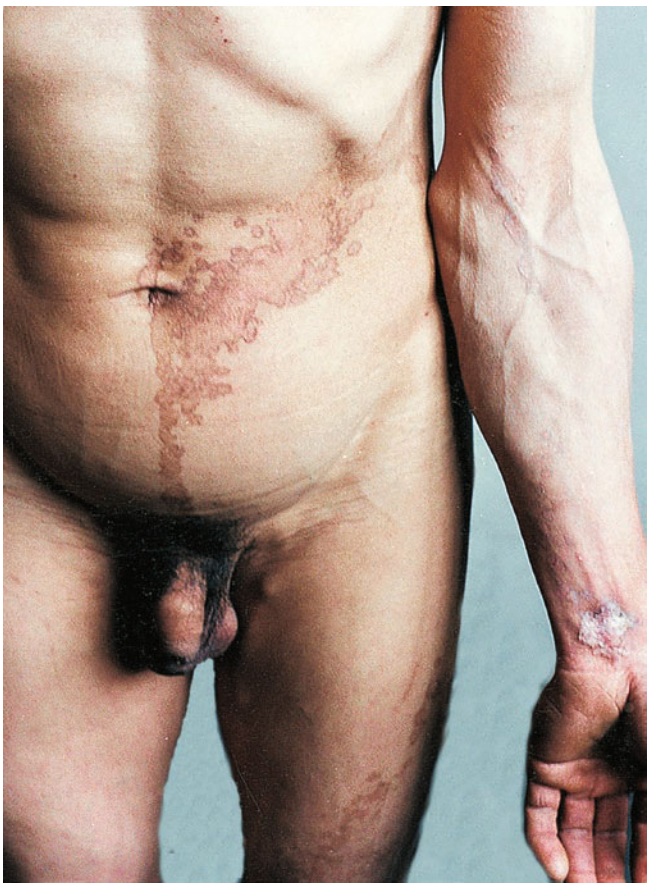


Fig. 25-2b-1 Multiple brown annular macules on the trunk and upper left arm

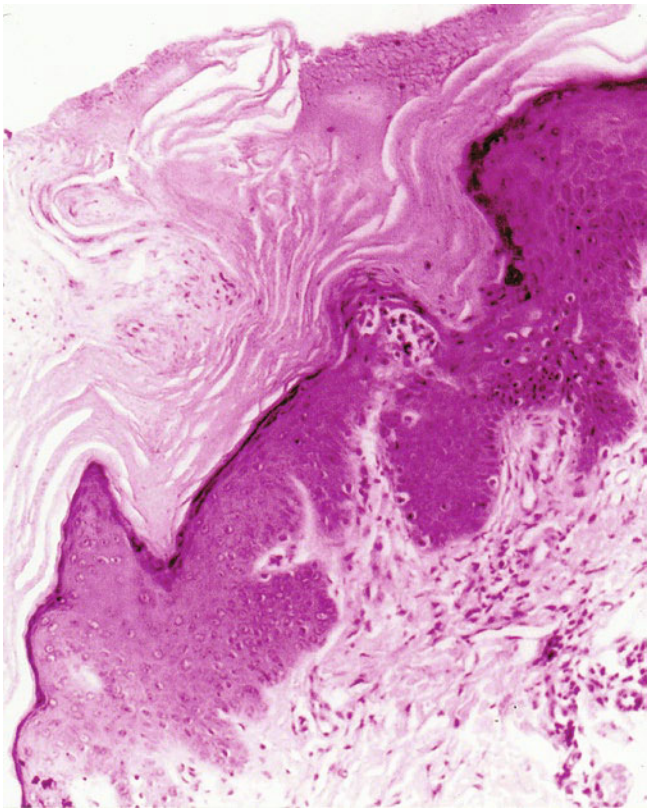


Fig. 25-2b-2 Hyperkeratosis, parakeratotic column in the superficial epidermis, and perivascular lymphocytic infiltration (HE stain, ×200)

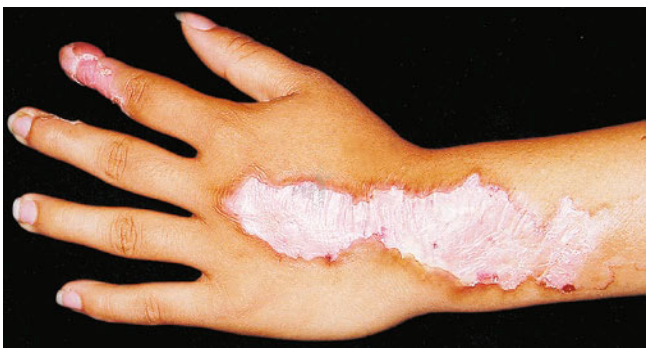


Fig. 25-2c-1 Well-circumscribed annular erythema with elevated margin and central atrophy on the left dorsal hand and extensor surface of the left index finger

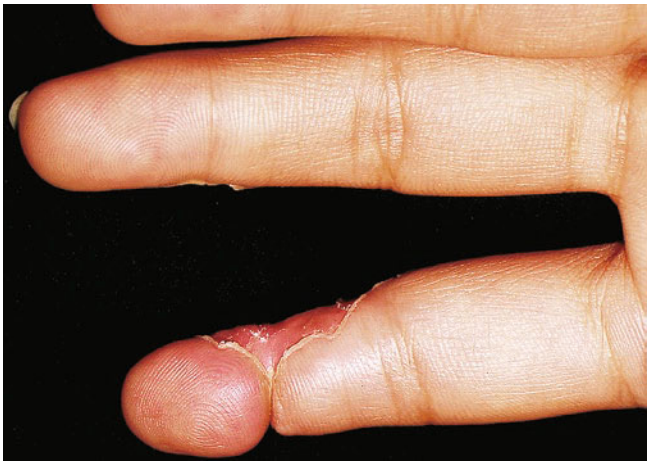


Fig. 25-2c-2 Transverse groove of first interphalangeal joint constricted the middle finger of the left hand

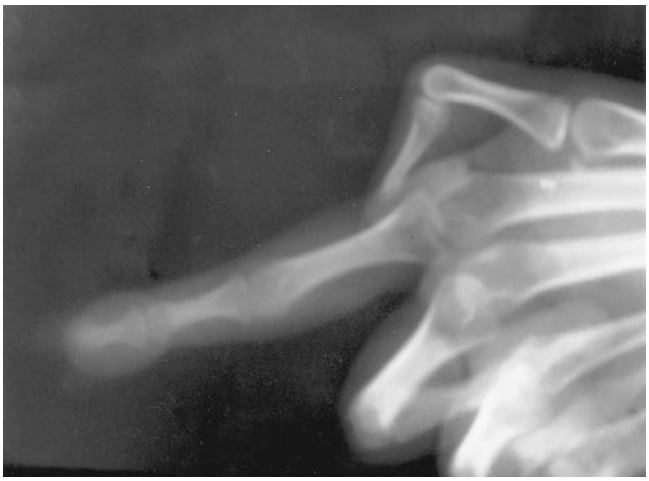


Fig. 25-2c-3 X-ray: parenchyma atrophy and shrinking on the terminal joint of the left index finger

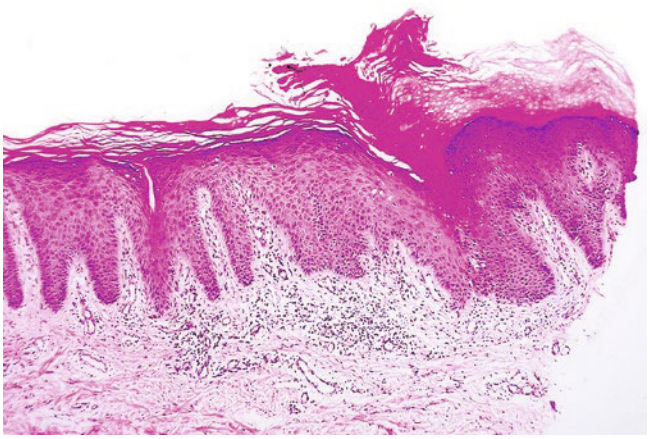


Fig. 25-2c-4 Hyperkeratosis, parakeratotic column, and mild inflammation in the superficial dermis (HE stain, ×100)

25.3 Striate Palmoplantar Keratoderma [8, 9]

- Palmoplantar keratoderma (PPK) can be classified into diffuse, punctate, and localized types.
- Striated palmoplantar keratoderma (SPK) is a rare genetic dermatosis inherited in an autosomal dominant pattern.
- SPK is characterized by a linear hyperkeratosis of the palms and volar aspects of the fingers. It manifests as an islet on the soles of the feet. Rarely, it extends to the elbows and knees.
- Type 1 SPK is associated with a mutated desmoglein 1 gene, while Type 2 results from the mutation of the desmoplakin gene.
- Nail changes, dysplasia of dental enamel, and receptor insensitivity may be found in patients with SPK.

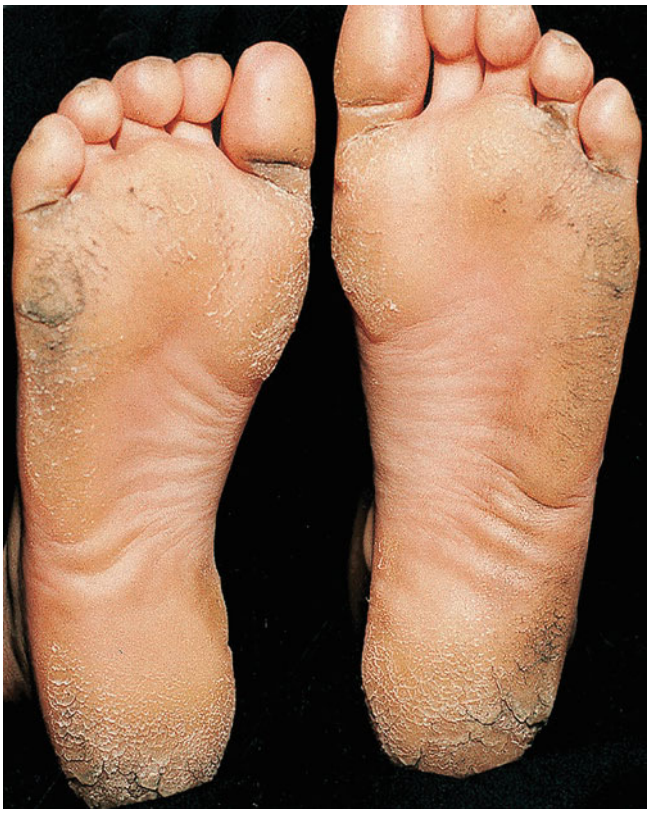


Fig. 25-3-1 Marked hyperkeratosis, thickening, and chaps on the pressed soles

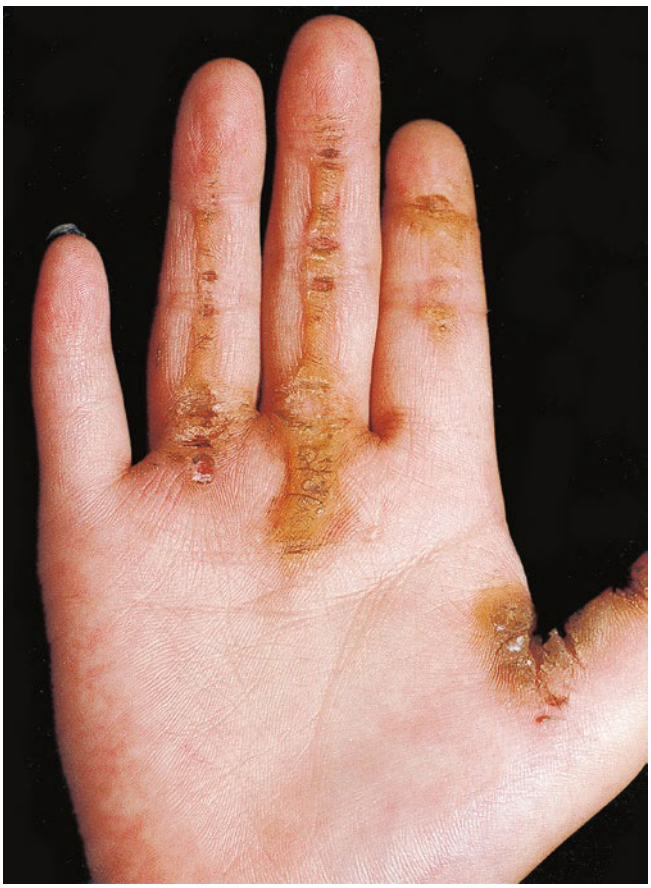


Fig. 25-3-2 Striated hyperkeratosis and thickening on the right index finger, the middle finger, and the ring fingers

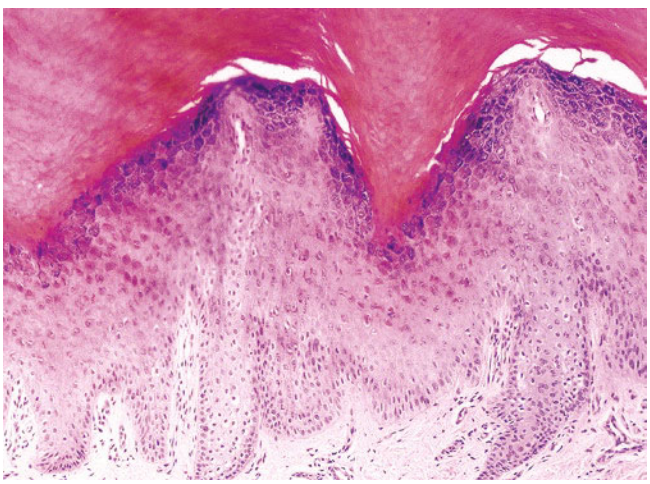


Fig. 25-3-3 Marked hyperkeratosis, thickened granular layer, slight papillomatosis, and perivascular inflammatory infiltration in the superficial dermis (HE stain, ×100)

25.4 Spiny Keratoderma [10, 11]

- Spiny keratoderma (SK) is a disorder of defective keratinization.
- SK is confusingly grouped under minute digitate hyperkeratosis, filiform hyperkeratosis, spiny keratoderma of the palms and soles, punctate keratoderma, and punctate porokeratotic keratoderma.
- SK occurs as numerous discrete keratotic spicules on the palms and soles.
- There is consensus that SK, multiple filiform verrucae, and arsenical keratosis are three digitate keratoses distributed on the palmoplantar skin.
- Hereditary SK begins at the age of 12–50 years old without visceral malignancy, whereas in acquired SK, patients are often older than 50 years with a predisposition for aggressive neoplasms.
- Differentiation from porokeratosis is of great importance, and the presence of an underlying granular layer points to a diagnosis of SK rather than porokeratosis.
- SK occasionally presents with Darier's disease, kidney disorders, hyperlipidemia, liver cysts, and malignancies.

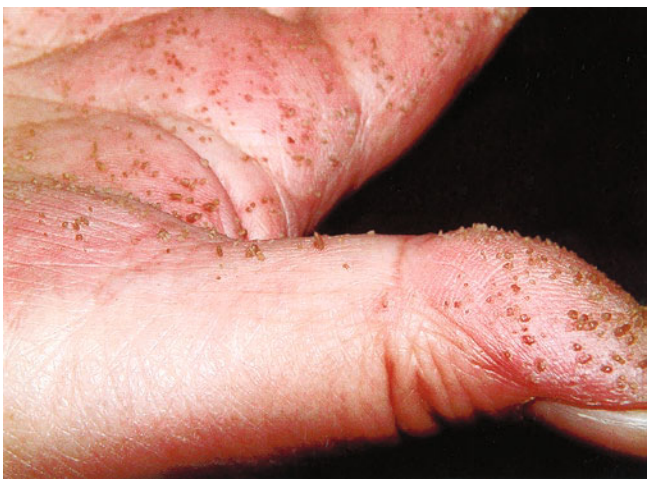


Fig. 25-4-1 Tiny spiked keratotic projection located on the palm

Fig. 25-4-2 There were hyperkeratosis, columnar parakeratosis, and acanthosis in the epidermis. The epidermis underlying parakeratotic column was invaginated and the granular layer was decreased (HE stain, ×40)

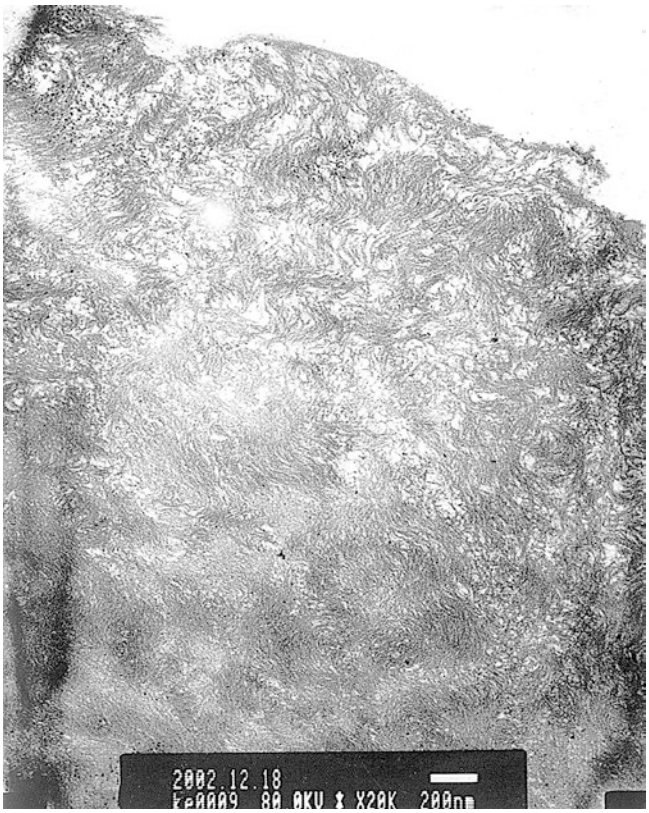
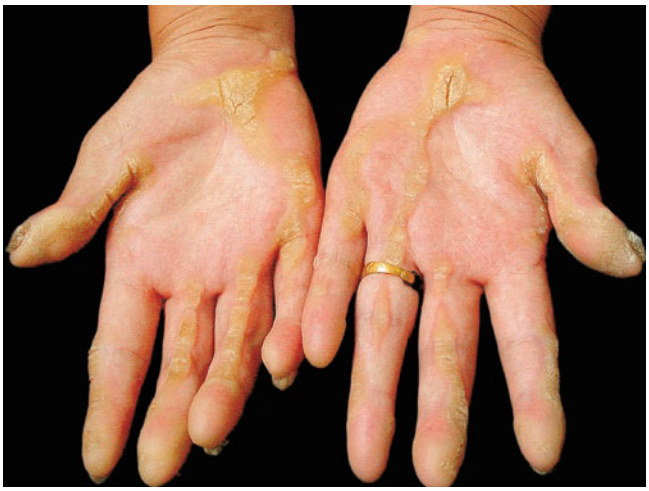
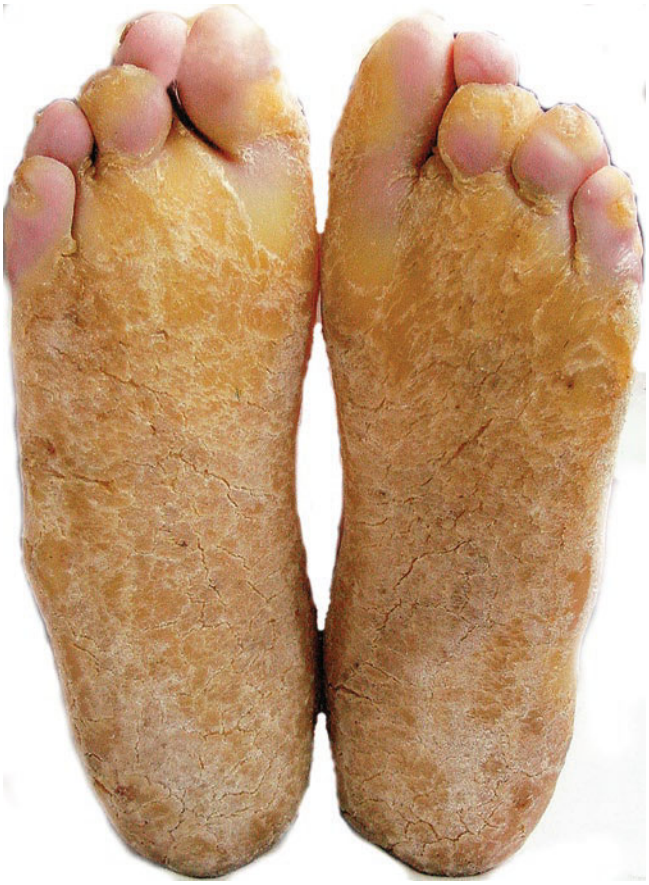


Fig. 25-4-3 Keratin filaments arranged rather loosely under transmission electron microscopy (×20,000)

25.5 Epidermolytic Palmoplantar Keratoderma [12, 13]

- Epidermolytic palmoplantar keratoderma (EPK) is an autosomal dominant disorder caused mostly by keratin 9 gene (KRT9) mutation.
- EPK begins as an erythema of the palms and soles within months after birth, and it progresses to become diffuse yellow hyperkeratosis with well-demarcated erythematous borders.
- Blisters, scaling, and erosions may be induced by trauma.
- Microscopic features of EPK are patchy distribution of epidermolytic hyperkeratosis, large keratohyalin granules, and vacuolated spinous and granular keratinocytes. If these changes are localized, a diagnosis of Unna-Thost would be more appropriate.





Figs. 25-5-1, 25-5-2 Marked epidermal hyperkeratosis was developed in a linear pattern on both palms and diffused pattern on both soles

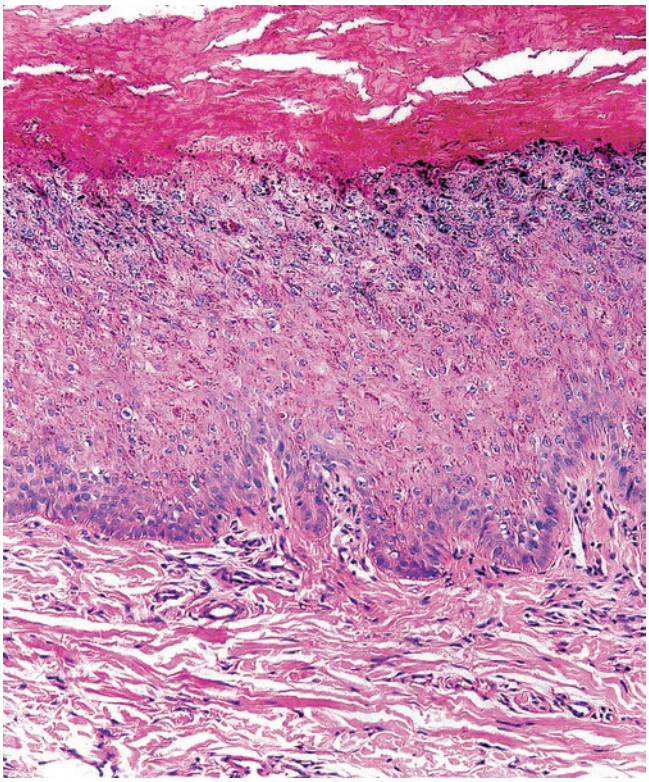


Fig. 25-5-3 Pronounced hyperkeratosis, moderate acanthosis, and thick granular layer (HE stain, ×100)

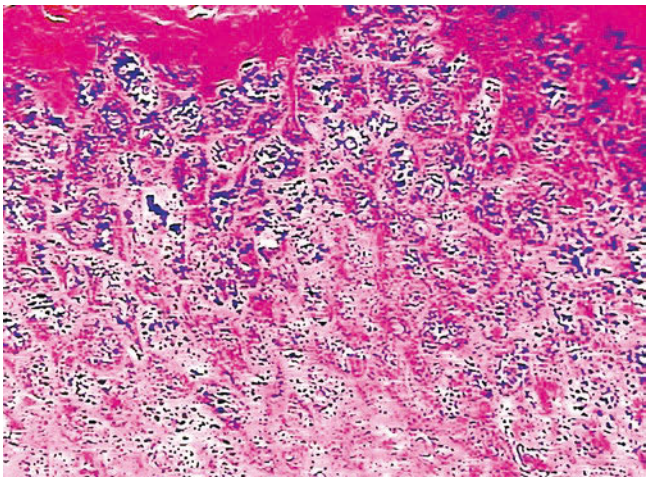


Fig. 25-5-4 The granules in the swollen granular cells with clumped appearance (HE stain, ×200)

25.6 Acrokeratosis Verruciformis [14, 15]

- Acrokeratosis verruciformis (AV) is an inherited disorder of keratinization that occurs at birth or during childhood.
- Clinically, it manifests many flat, flesh-colored keratotic papules on the dorsal hands and feet. Punctate keratosis presents on the palms and soles.
- Skin pathology of the lesion shows distinctive hyperkeratosis, hypergranulosis, and circumscribed epidermal elevation resembling a "church spire." Clefts and acantholysis are rarely seen.

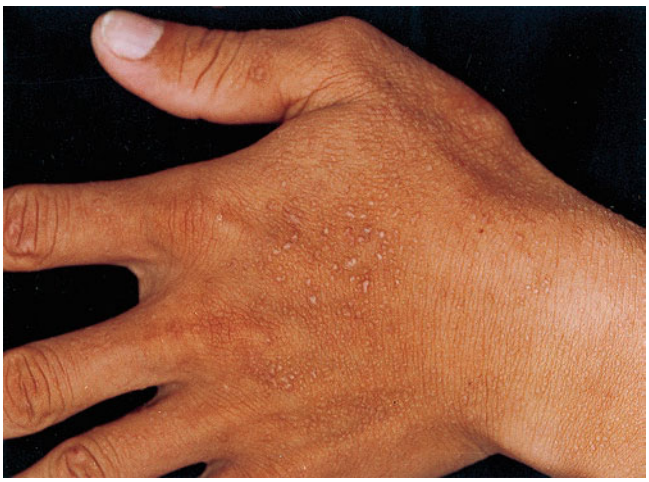


Fig. 25-6-1 Skin-colored or graying flat papules on the left dorsum hand and the white thumb nail

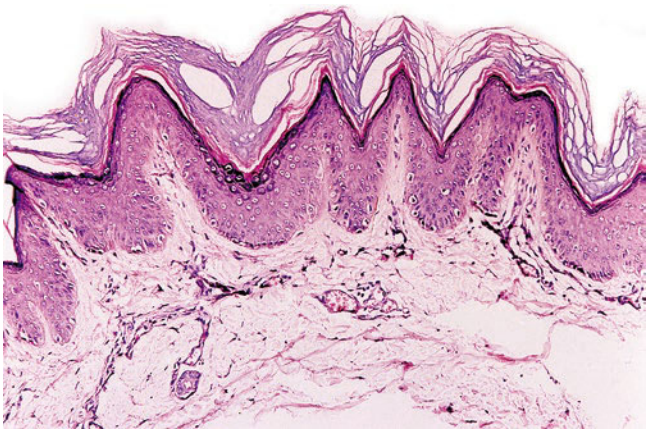


Fig. 25-6-2 Considerable hyperkeratosis, thickness of the granular layer and acanthosis, papillomatosis, and slightly elongated rete ridges (HE stain, ×100)

25.7 Warty Dyskeratoma [16, 17]

- Warty dyskeratoma (WD) is an uncommon disorder of keratinization that is mainly seen in adults.
- WD most commonly presents a circumscribed papule and nodule or papule on the head, face, or neck.
- Histopathologically, it usually shows a cup-shaped epidermal invagination with prominent dyskeratosis, acantholysis, and a dense infiltration of lymphocytes underneath.
- Focal acantholytic dyskeratosis is not an exclusive pathological hallmark of WD, as it also presents in Grover's diseases, Darier's disease, and an acantholytic variant of squamous cell carcinoma.

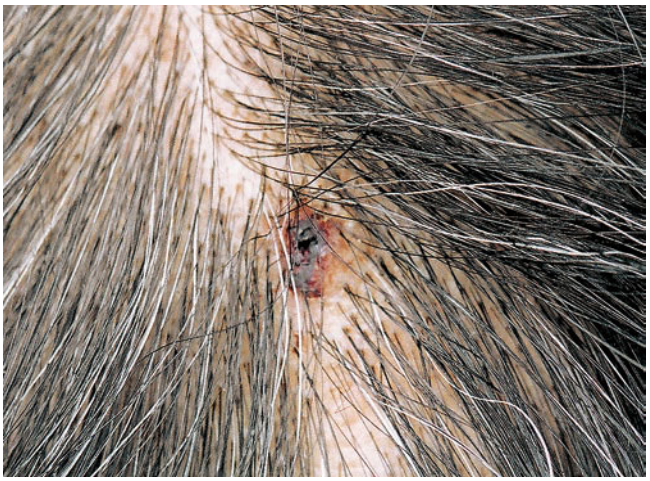


Fig. 25-7-1 A dome-shaped tumor with umbilicated center on the scalp

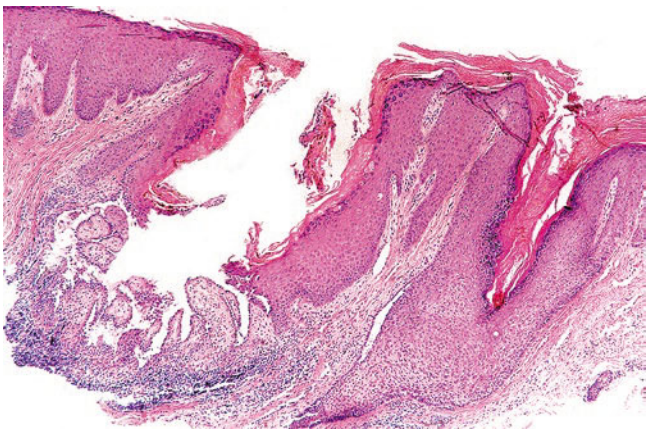


Fig. 25-7-2 Epidermal invagination with keratinous material (HE stain, ×40)

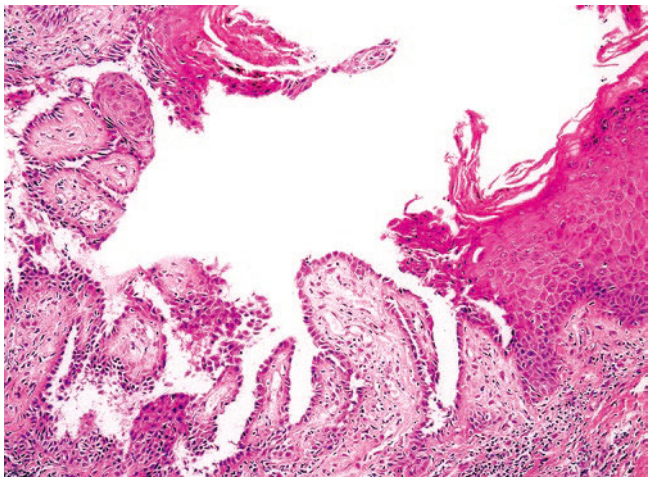


Fig. 25-7-3 The epidermal invagination congested with numerous villi. Acantholytic and dyskeratotic keratinocytes were seen in its basal layer (HE stain, ×100)

25.8 Progressive Symmetric Erythrokeratodermia [18]

- Erythrokeratodermia has two subtypes: the migratory type of erythrokeratodermia variabilis and the stable form of progressive symmetric erythrokeratodermia (PSEK).
- PSEK is characterized by erythematous hyperkeratotic patches that develop symmetrically shortly after birth. Palmoplantar keratoderma also appears in individuals with PSEK.
- It distributes mainly on the face, buttocks, and extremities.

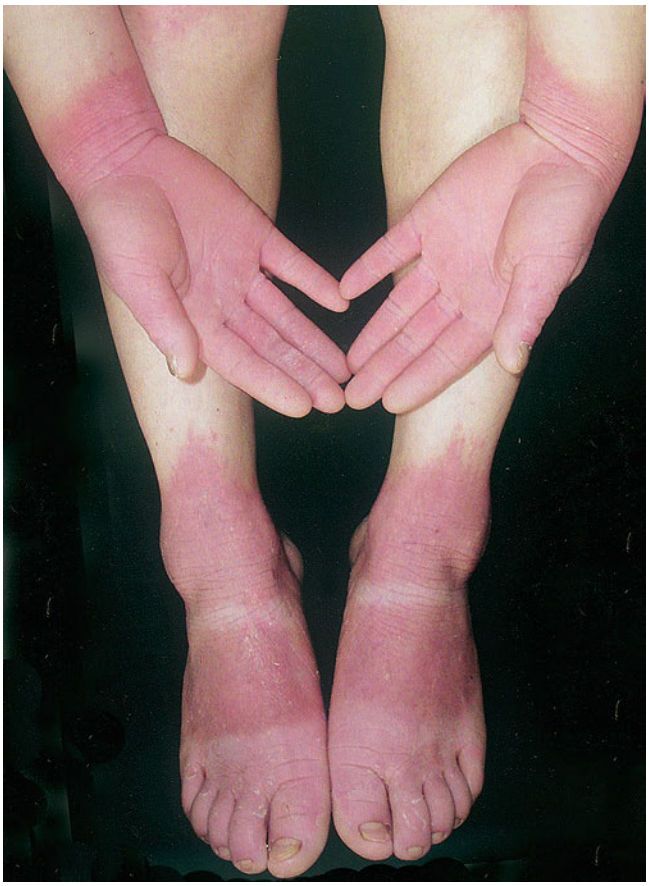


Fig. 25-8-1 Demarcated erythemas were distributed symmetrically on the palms and dorsal feet

25.9 Arsenic Keratosis [19, 20]

- Dermatological signs are usually the earliest presentation in chronic arsenicism, and therefore awareness of hallmark lesions is of great significance.
- Most arsenic enriches at the keratin-rich tissues, and thus it can be detected at about 2 weeks of exposure.
- Pigmentary changes, palmoplantar keratosis, and "Mees' lines" of the nails are the most common presentations for cutaneous arsenic toxicity.
- Pigmentary disturbances in chronic arsenicism show diffuse or localized hyperpigmentation, superimposed by multiple guttate hypopigmented macules. This distinctive presentation of "raindrops on a dusty road" preferentially affects the skin folds.
- Arsenic keratosis is characterized by palmoplantar keratotic papules or plaques that are larger and verrucous with friction or localized trauma. The color of the lesion is mostly yellow, although brown or dark black is also reported.
- Arsenic-related cutaneous malignancies are comprised of Bowen's disease, squamous cell carcinoma, and basal cell carcinoma. In addition to the dose and frequency of arsenic exposure, this process of malignant transformation can be precipitated by other factors, such as human papillomavirus infection and a poor nutritional condition.
- Whenever palmoplantar keratosis presents in any patients, arsenicism should be part of the differentiation.

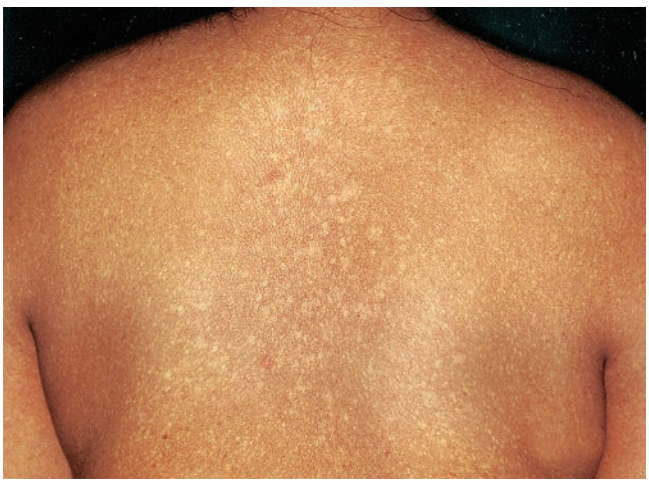


Fig. 25-9-1 Numerous grayish and raindrop-like depigmented macules on the back

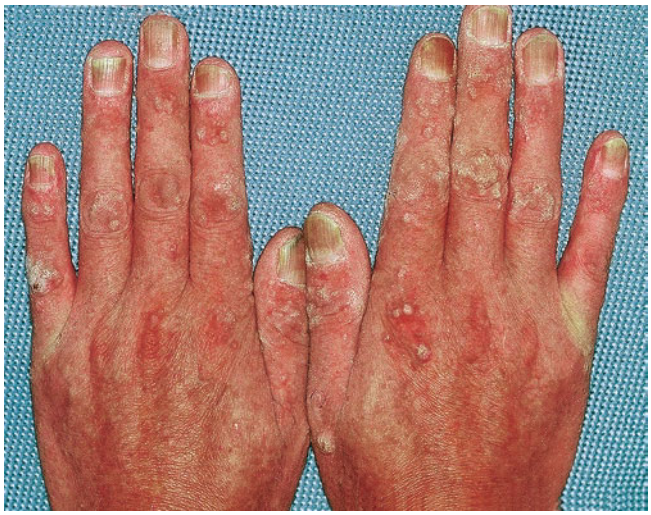


Fig. 25-9-2 Many punctate keratotic papules on the dorsal hands

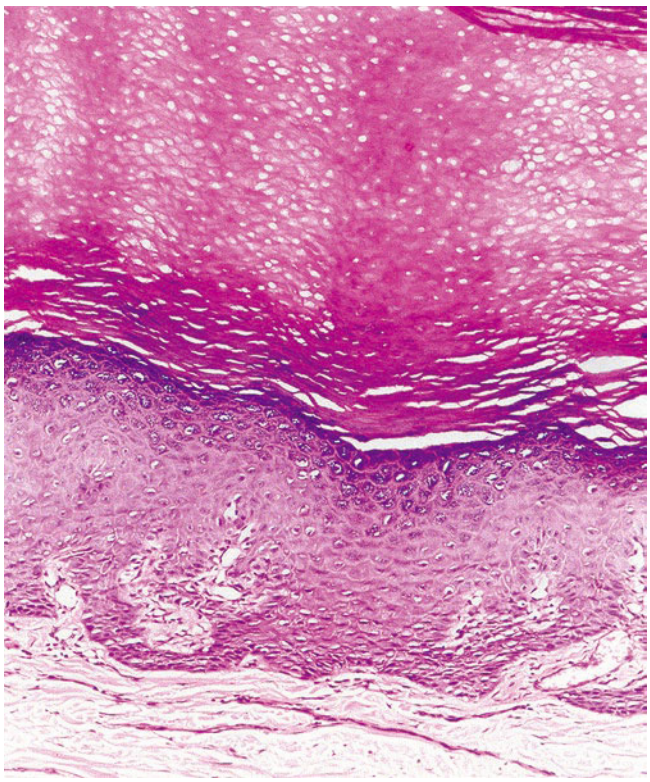
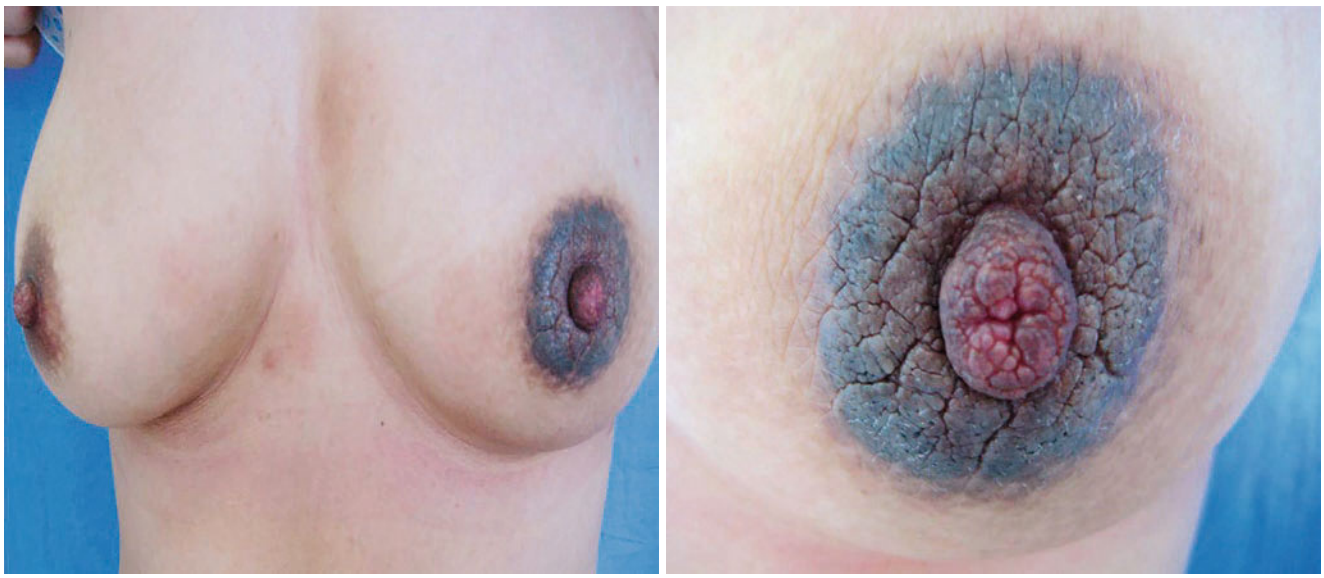


Fig. 25-9-3 Hyperkeratosis and epidermal hyperplasia (HE stain, ×20)

25.10 Hyperkeratosis of the Nipple and Areola [21, 22]

- Hyperkeratosis of the nipple and areola affects both men and women; approximately 80% cases occur in middle-aged women.
- The skin of the nipple and/or areola is verrucous, thickened, and brownish discolored.
- Most cases are bilateral and unilateral cases rarely occur. They may involve the nipple, areola, or both.
- Histopathology: there are acanthosis, hyperkeratosis, and papillomatosis.



Figs. 25-10-1, 25-10-2 Verrucous thickening and brownish discoloration of the skin on the left nipple and areola

25.11 Waxy Keratosis [23]

- Waxy keratosis (WK) is also named waxy keratosis of childhood or kerinokeratosis papulosa.
- It predominantly has an onset in childhood, although adult cases have been reported.
- Modified diagnostic criteria have been introduced for waxy keratosis: (1) it shows uniform, non-follicular, shiny skin-colored to reddish papules; (2) it shows asymptomatic, easily detached papules; (3) itching may be accompanied; (4) the diameter of the papules usually exceeds their height; (5) histological exhibition of lamellar and compact orthokeratosis, acanthosis, and pronounced papillomatosis; (6) Spongiosis, koilocytosis, or inflammatory changes are absent; (7) dermatoscopy showed a cribriform pattern.
- Rarely, the lesion takes a segmental distribution pattern.

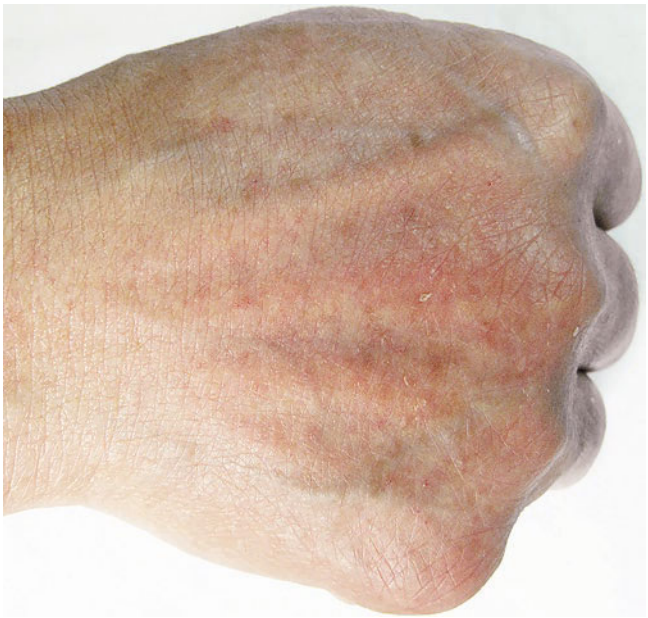


Fig. 25-11-1 Multiple skin-colored or red papules distributed on the dorsa of the hands. The lesions became flake-like and detached by a slight scratch (Reproduced with the permission from [23])

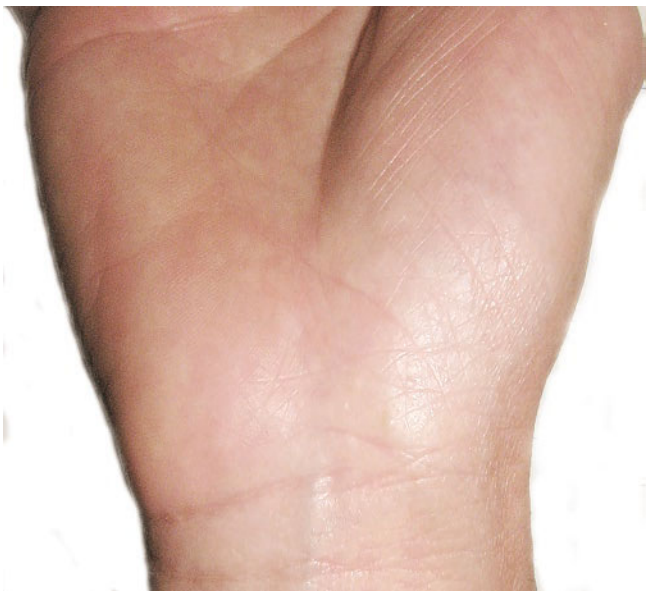


Fig. 25-11-2 Primary shiny, "waxy" papules measuring 2–3 mm in diameter on the wrist (Reproduced with the permission from [23])

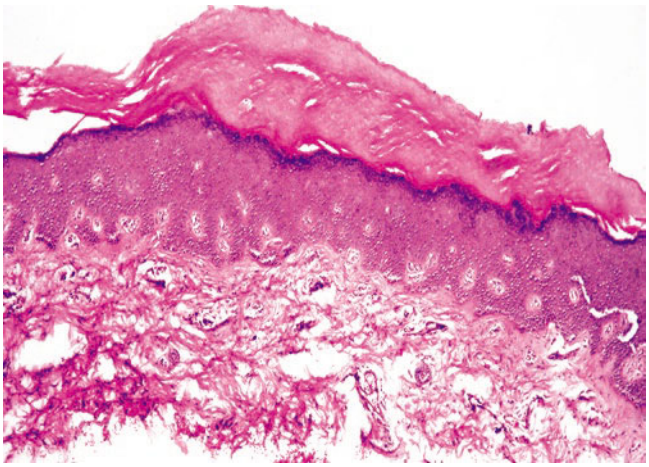


Fig. 25-11-3 Skin biopsy of the primary shiny papules showed coalesced orthohyperkeratosis, papillomatosis, and mild acanthosis without granular degeneration. No spongiosis or obvious inflammatory changes were apparent (HE stain, ×100) (Reproduced with the permission from [23])

25.12 Acrokeratoelastoidosis [24, 25]

- Acrokeratoelastoidosis (AKE) is characterized by the presence of small, skin-colored to yellow, discrete, wart-like papules on the palmoplantar radial and ulnar margins.
- The finger, anterior surface of the wrist, and lower extremities may also be affected in AKE.
- Fragmentation of elastic fibers and circumscribed orthohyperkeratosis are histologic hallmarks of AKE. In addition, broadening of the granular layer is also shown.
- Keratoelastoidosis marginalis, focal acral hyperkeratosis, and hereditary papulotranslucent acrokeratoderma share some similarities with AKE and should be differentiated.

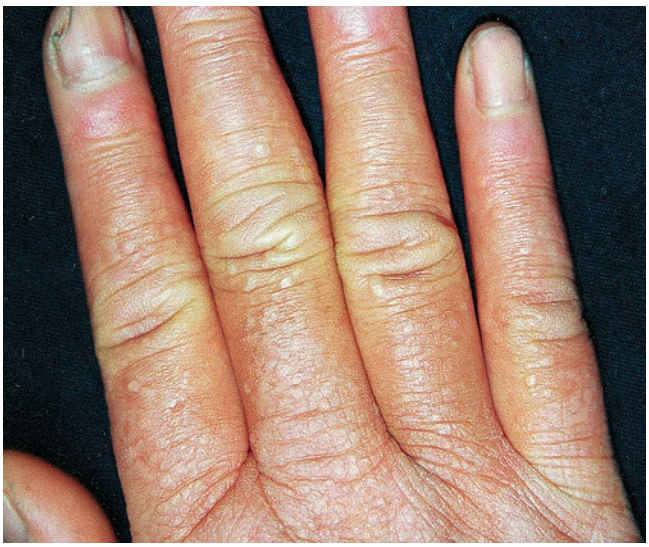


Fig. 25-12-1 Numerous white firm papules on the dorsa of the hands and hypothenar

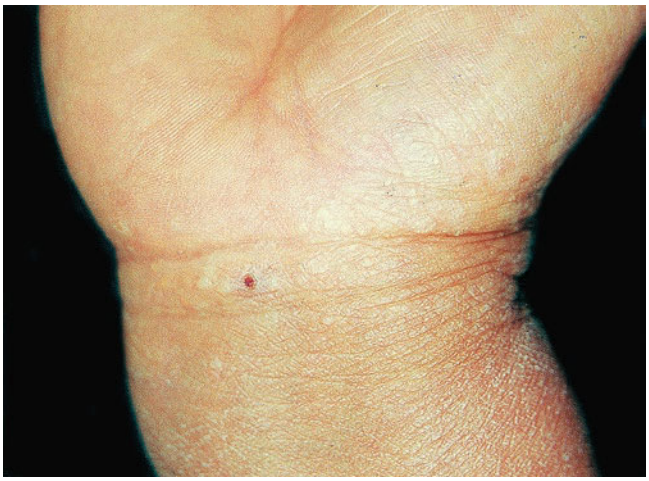


Fig. 25-12-2 Smooth translucent papules were on the inside of both wrists with their sizes similar to the millets or mung beans

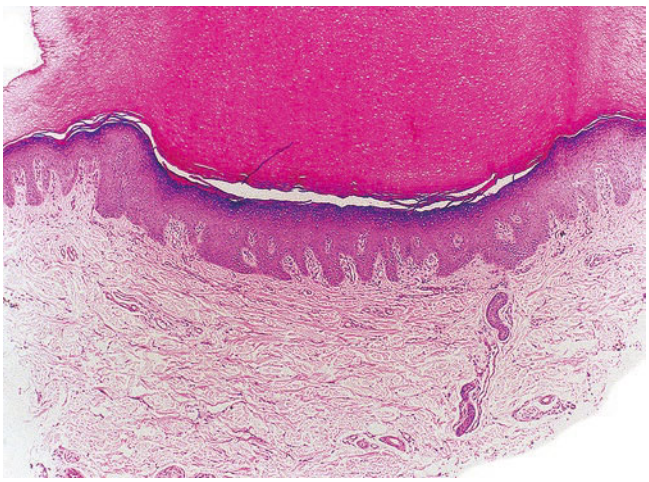


Fig. 25-12-3 Striking hyperkeratosis, thickened granular layer, acanthosis, and mild perivascular infiltrations of inflammatory cell in the upper dermis (HE stain, ×40)

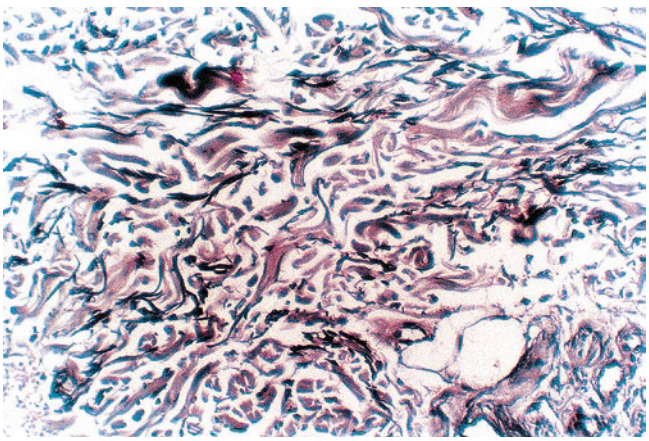


Fig. 25-12-4 Fragmentation and diminution of coarse elastic fibers in the reticular dermis (Verhoeff-van Gieson stain, ×100)

25.13 Lichen Planus-Like Keratosis [26–28]

- Lichen planus-like keratosis (LPLK) presents as a solitary, pink to crimson, rusty brown papule to small plaque.
- The erythematous, papulokeratotic, and plaque types are three morphologic forms of LPLK, which are reminiscent of actinic keratosis, seborrheic keratosis, and Bowen's disease, respectively.
- Microscopic observation of LPLK reveals parakeratosis, a florid lichenoid infiltration in the epidermal-dermal junction, vacuolar changes in the basilar layer, and pigment incontinence.
- The presence of focal parakeratosis in LPLK makes lichen planus unlikely.
- LPLK generally resolves spontaneously between 3 to 18 months.

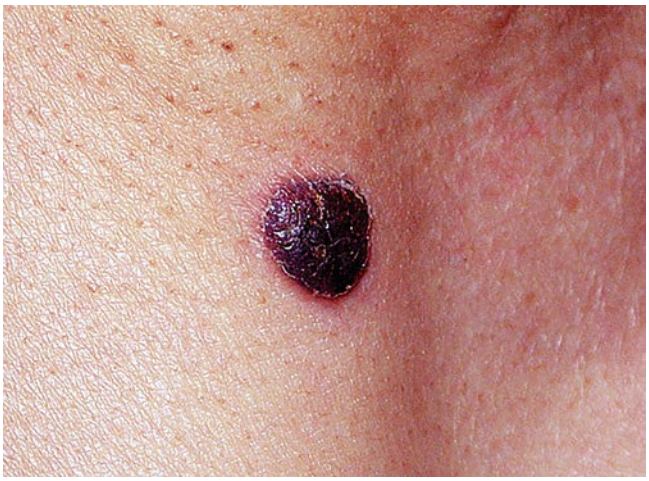


Fig. 25-13-1 A solitary circumscribed, keratotic papular lesion arise on the right shoulder. It is brownish in color and sized as a horsebean

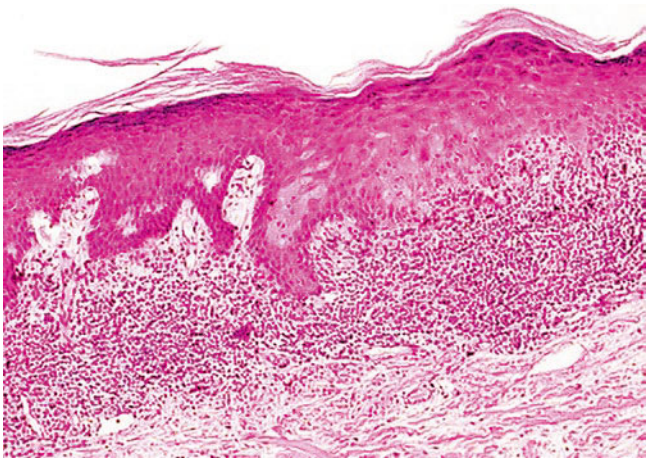


Fig. 25-13-2 Histology of the epidermis showed hyperkeratosis, thickening of the granular layer, and vacuolar degeneration of the basal layer with the presence of colloid body. In addition, infiltration of lymphohistiocytes was in a band-like pattern with a few melanophages scattered in the superficial dermis (HE stain ×40)

25.14 Aquagenic Acrokeratoderma [29, 30]

- Aquagenic acrokeratoderma (AA) presents with translucent, whitish papules or plaques on the palms and soles shortly after immersion in water. This change dramatically vanishes several minutes to hours after drying.
- Histopathologic examination reveals nonspecific changes, such as orthohyperkeratosis, hypergranulosis, and dilated eccrine ducts. Sometimes, there are no abnormal pathological findings.
- Although spontaneous amelioration occurs in AA, topical aluminum hydroxide is mostly recommended as treatment with variable results.
- It is implicated that AA is possibly related to the impairment of the eccrine glands, hyperkeratosis, and barrier dysfunction of the stratum corneum.

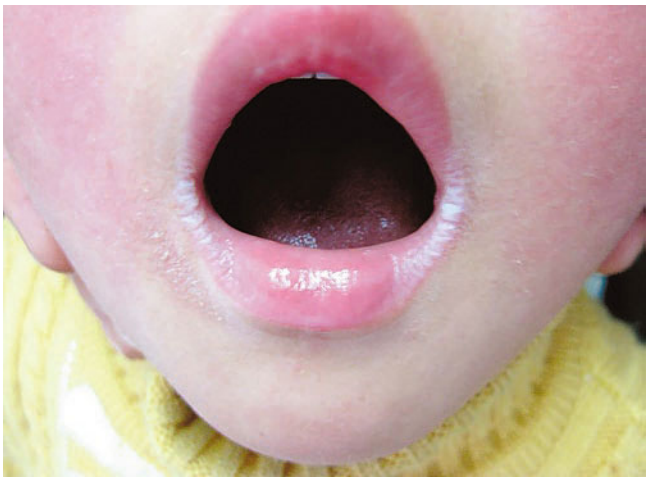
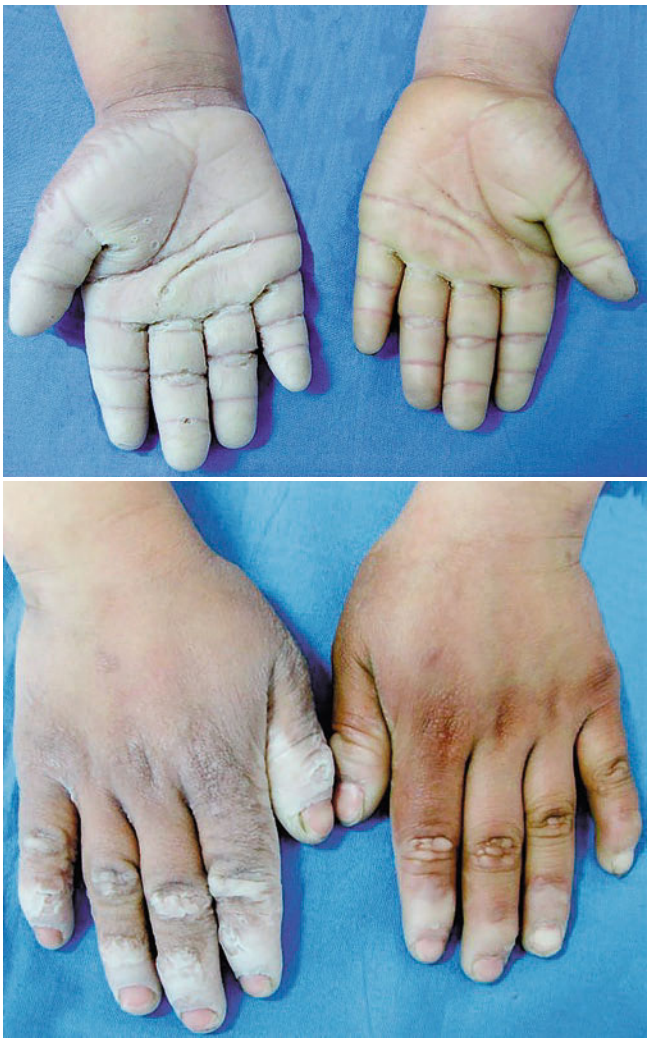


Fig. 25-14-1 Whitening of corners of the mouth due to saliva dipping



Figs. 25-14-2, 25-14-3 Whitish discoloration of the palms and fingers with thickening of the palmar surface after immersion of the right hand in water; the left hand remains unaffected

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Other Genodermatoses

26

Ru-Zhi Zhang, Qiang Ju, Ying Sun, Li-Xin Zhai, Jian-Fang Sun, Shu-Qiong Huang, Xiu-Kun Sun, Jian-Kai Pan, Yuan Lu, Zhi-Yuan Yao, Ai-Qin Wang, Shu-Xiao Zhao, Wen-Yuan Zhu, Dong-Lai Ma, Wen-Jun Liao, Jun Li, Liang Zhao, Cheng Tan, Jin Hu, Bin Xu, Song Li, Ji-Hong Gan, Tao Wang, Xiao-Hai Yuan, Hong-wei Wang, Liu-Qing Chen, Liang Gao, Mei Wu, Zhi-Fang Zhai, and Yin Xiao

Abstract

Besides genodermatoses with presentation of keratoderma, other hereditary cutaneous diseases and syndromes considered in this chapter are incontinentia pigmenti, epidermolysis bullosa simplex, recessive dystrophic epidermolysis bullosa (generalized, severe), dystrophic epidermolysis bullosa pruriginosa, pretibial epidermolysis bullosa, Hailey-Hailey disease, ichthyosis bullosa of Siemens, bullous congenital ichthyosiform erythroderma, collodion baby, Rothmund-Thomson syndrome, Rapp-Hodgkin syndrome, focal dermal hypoplasia, aplasia cutis congenital, dyskeratosis congenita, rudimentary polydactyly, keratosis follicularis spinulosa decalvans, pachydermoperiostosis, xeroderma pigmentosum, cutis tricolor parvimaculata, congenital thymic dysplasia, pachyonychia congenita, Papillon-Lefèvre syndrome, Olmsted syndrome, nail-patella syndrome, Keratitis-ichthyosis-deafness syndrome, Netherton syndrome, Bloom's syndrome, tricho-rhino-phalangeal syndrome, proteus syndrome, stiff skin syndrome, Rombo syndrome, prune-belly syndrome, infantile digital fibromatosis, and juvenile hyaline fibromatosis.

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26.1 Incontinentia Pigmenti [1–4]

- Incontinentiapigmenti (IP) is a rare multisystem X-linked dominant genetic disorder caused by mutations in IKBKG.
- IP classically begins with blisters on an erythematous background along the Blaschko's lines at birth or in early infancy.
- The second phase of IP presents with elevated, warty, hyperkeratotic lesions after the resolution of the blisters.
- The third phase is characterized by whorled pigmented macules or streaks, which fade away and are replaced by hypopigmented, atrophic, hairless, or even sweatless skin.
- There are many structural malformations, such as cleft lip, breast hypoplasia, short stature, and club foot.
- Other defects include mental retardation, seizures, ocular abnormalities, and so on.

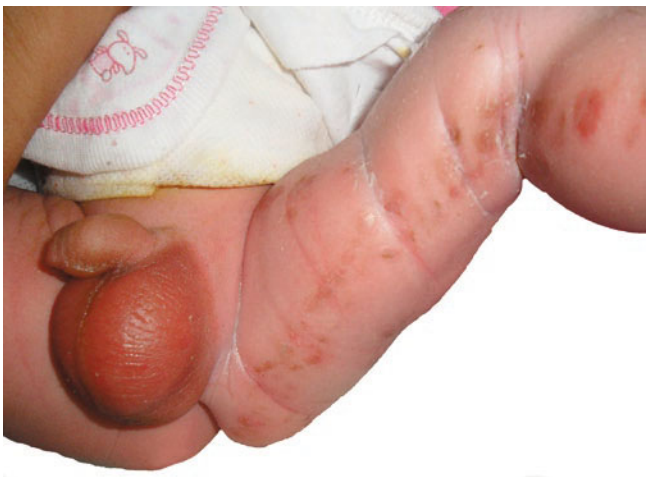


Fig. 26-1-1 Erythemas and small vesicles were arranged in a linear pattern on the left mid-posterior leg and run from the inner aspect of the ankle to the infragluteal region

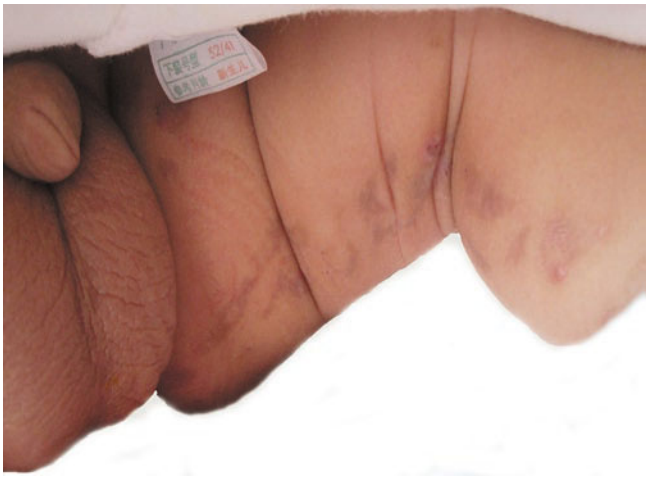


Fig. 26-1-2 On the 45th day after birth, the lesions transformed to be linear, slightly pigmented spots and streaks

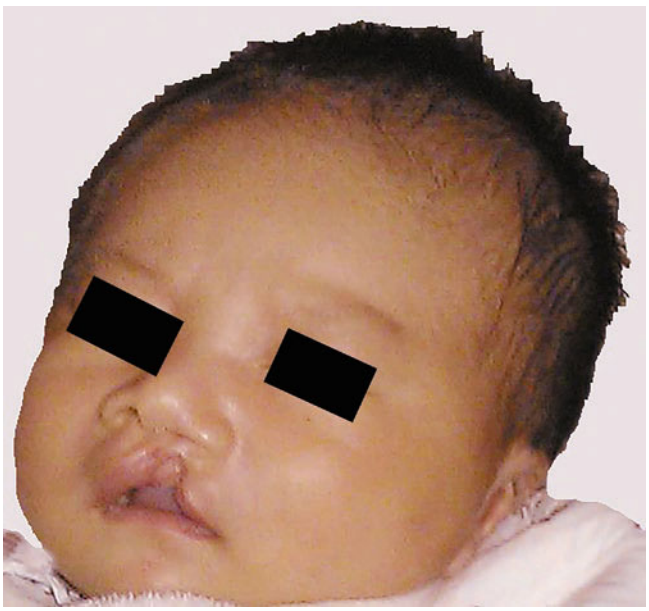


Fig. 26-1-3 Complete cleft formation of the upper lip

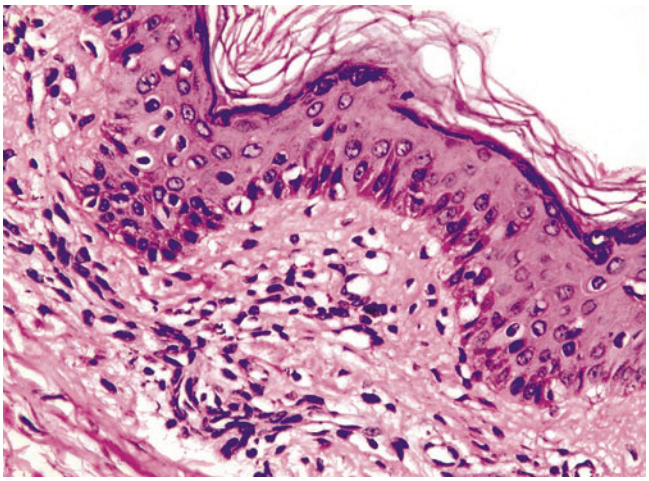


Fig. 26-1-4 Pathology of the pigmented lesion was characterized with dyskeratotic cells, hyperpigmentation in the basilar layer, and numerous macrophages in the dermis. The basement membrane was normal (HE satin, ×200)

26.2 Epidermolysis Bullosa Simplex [5, 6]

- Epidermis bullosa (EB) is mechanobullous dermatoses of the skin or mucosa.
- EB is categorized into 4 main subtypes (simplex, junctional, dystrophic, and Kindler syndrome) and 33 minor subtypes with at least 18 mutated genes.
- Skin separation occurs in the layers of the epidermis (EBS), the lamina lucida (JEB), the sub-lamina densa (DEB), and a mixed type of multiple cleavage strata in Kindler syndrome.
- The major culprit genes involved in EB are also identified in the gastrointestinal tract, urinary tract, lung, or mesenchymal tissues, and this reasonably explains the extracutaneous comorbidities in such organs.
- Epithelial fragility of the skin leads to formation of blistering, erosion, ulceration, crust, and scar. Severe subtype with scarring manifestation may present with stricture, stenosis, and pseudosyndactyly. Uncommon features include nail complications, milia, pigmentary changes, and infections, and alopecia may also be found in certain EB subtypes.
- Most forms of EB have regular life spans due to its autosomal dominant entity. In contrast, a recessive form is associated with a much worse outcome.
- The most common and mildest form in EB is EB simplex, which accounts for nearly 70% of the patients. Blisters in this type develop in the outer layer of the epidermis without scarring.

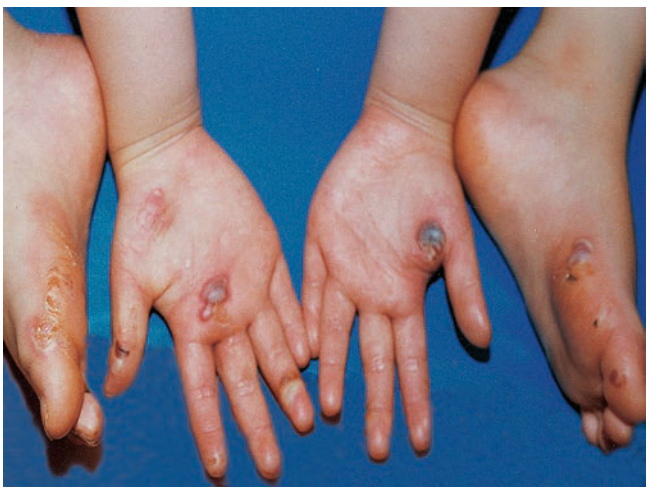


Fig. 26-2-1 Thick-walled blisters were soybean-sized with and affected on the palms and soles

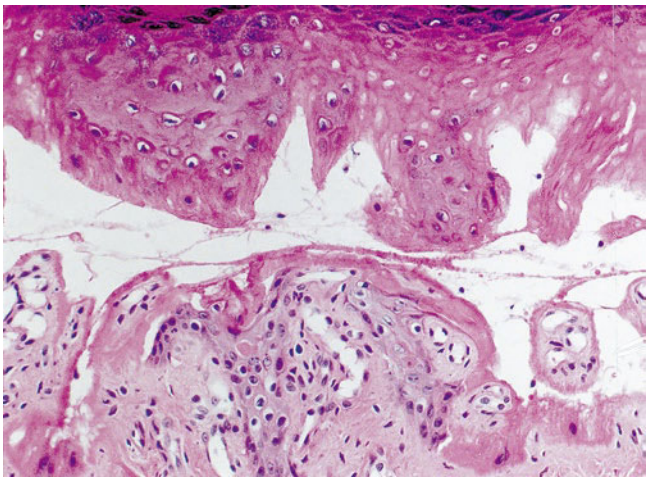


Fig. 26-2-2 The presence of suprabasal blisters with edematous keratinocytes (HE stain, ×200)

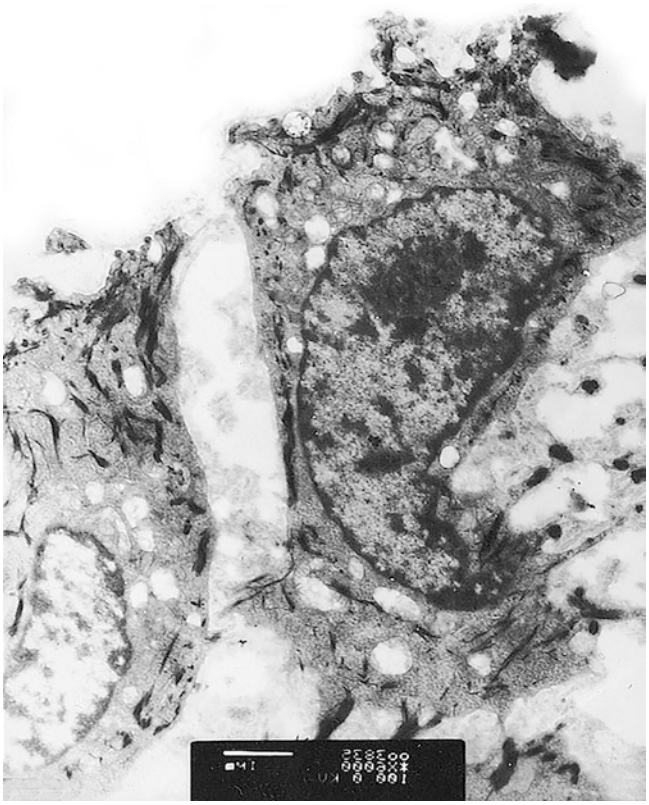


Fig. 26-2-3 Vacuolar degeneration in the plasma of the basal cells (TEM, ×6000)

26.3 Recessive Dystrophic Epidermolysis Bullosa (Generalized, Severe) [7]

- Generalized severe form of recessive dystrophic epidermolysis bullosa (GSRDEB), or Hallopeau-Siemens EB, is considered to be the severe type of dystrophic EB.
- GSRDEB is caused by mutations in the COL7A1 gene, which encodes type VII collagen.
- GSRDEB has a wide spectrum of clinical presentations, including generalized blisters, extensive scarring, pseudosyndactyly, scarring alopecia, and pigmentary disturbances. The oral mucosa, esophagus, and anus may also be involved. Scarring of these tissues contributes to restrictions of their functions and malnourishment of the patients.
- Children with GSRDEB have a high likelihood to develop glomerulonephritis, IgA nephropathy, and cardiomyopathy, and they always die before adults, mainly due to these lethal complications.

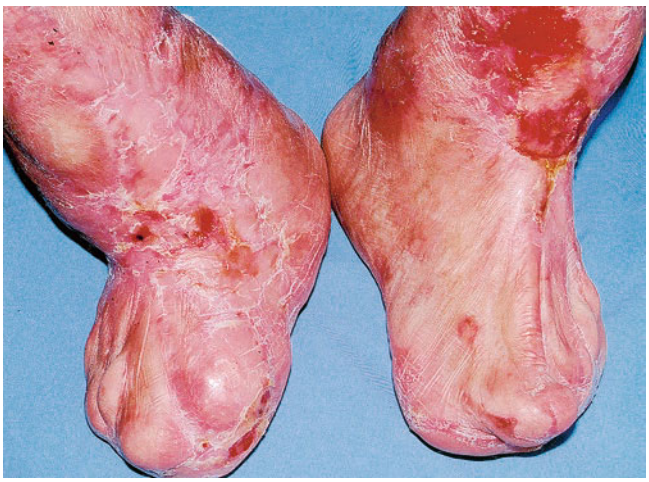


Fig. 26-3-1 Mitten-like deformities of the ten toes with shedding of the nails and secondary scarring

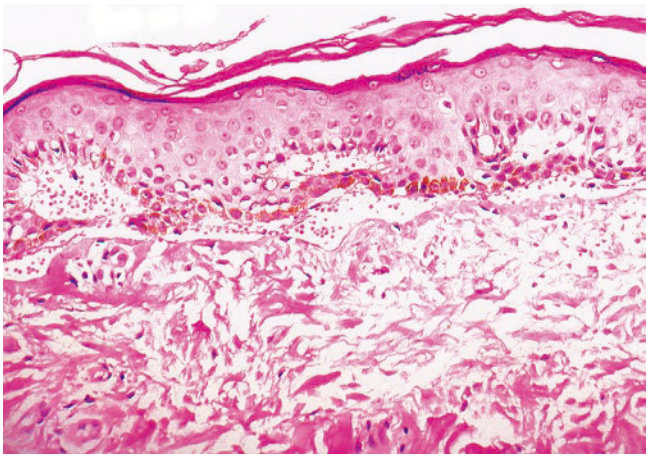


Fig. 26-3-2 A subepidermal blister (HE stain,×200)

26.4 Dystrophic Epidermolysis Bullosa Pruriginosa [8, 9]

- Among all types of dystrophic epidermolysis bullosa, dystrophic epidermolysis bullosa pruriginosa (DEBP) can be inherited in both a dominant and a recessive pattern.
- Clinical manifestations of DEBP are blisters, severe itching, erosions, pruriginous or lichenified plaques after repetitive scratching, and marked scarring. Its onset is relatively late compared to other EB types, and almost all patients present toenail dystrophy.

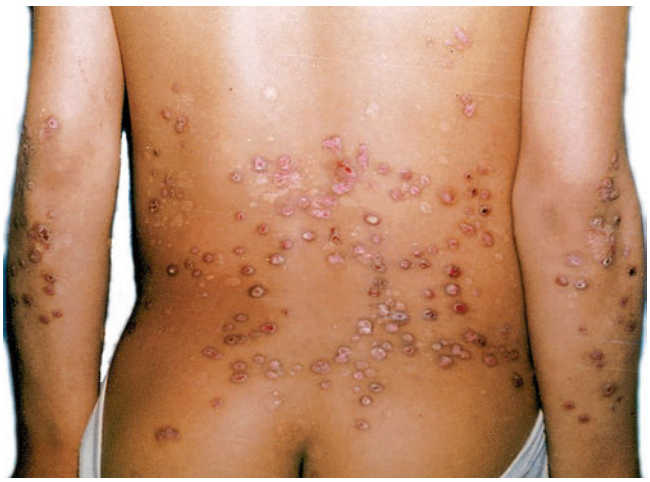


Fig. 26-4-1 Round or oval, brownish-red nodules and plaques on the waist and back

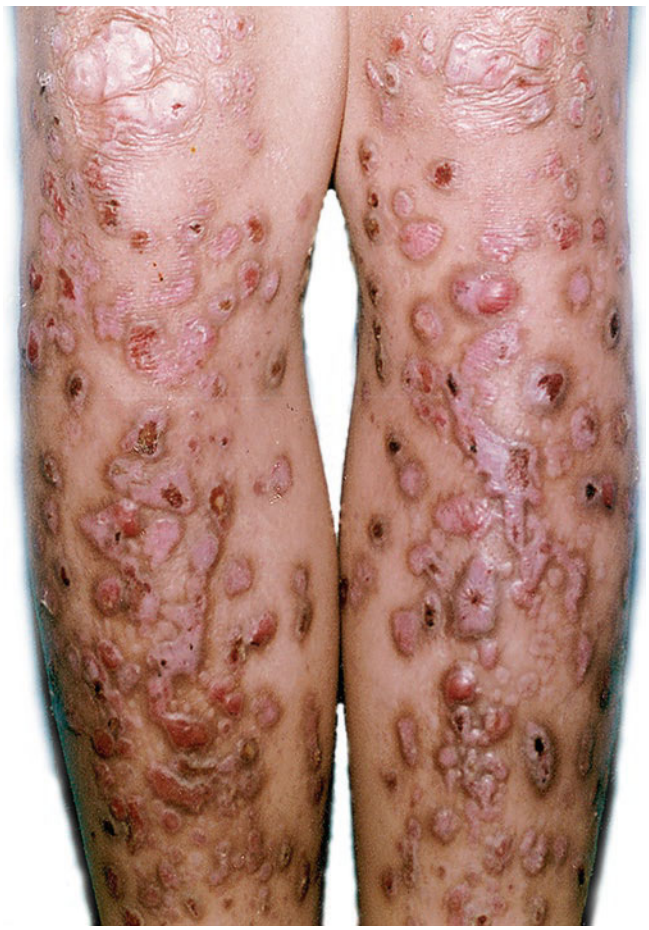


Fig. 26-4-2 Funicular scars and thick plaques on knees

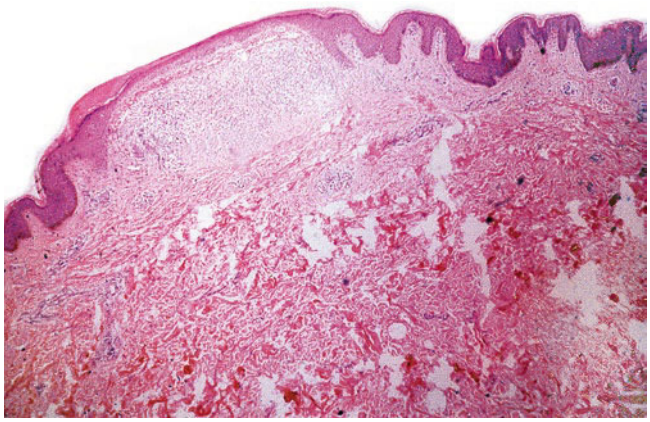


Fig. 26-4-3 Epidermal atrophy, liquefaction degeneration of the basal layer with typical milia structure (HE stain, ×40)

26.5 Pretibial Epidermolysis Bullosa [10–12]

- Pretibial epidermolysis bullosa (PEB) is an unusual presentation of localized epidermolysis bullosa dystrophica showing autosomal dominant inheritance.
- Compared to other forms of EB, skin lesions almost only present on the shin and occur in late life.
- Lichenoid papules and plaques can also be seen in PEB.
- The clinical features of PEB partially overlap with dystrophic epidermolysis bullosa pruriginosa, and their differentiation poses a big challenge.

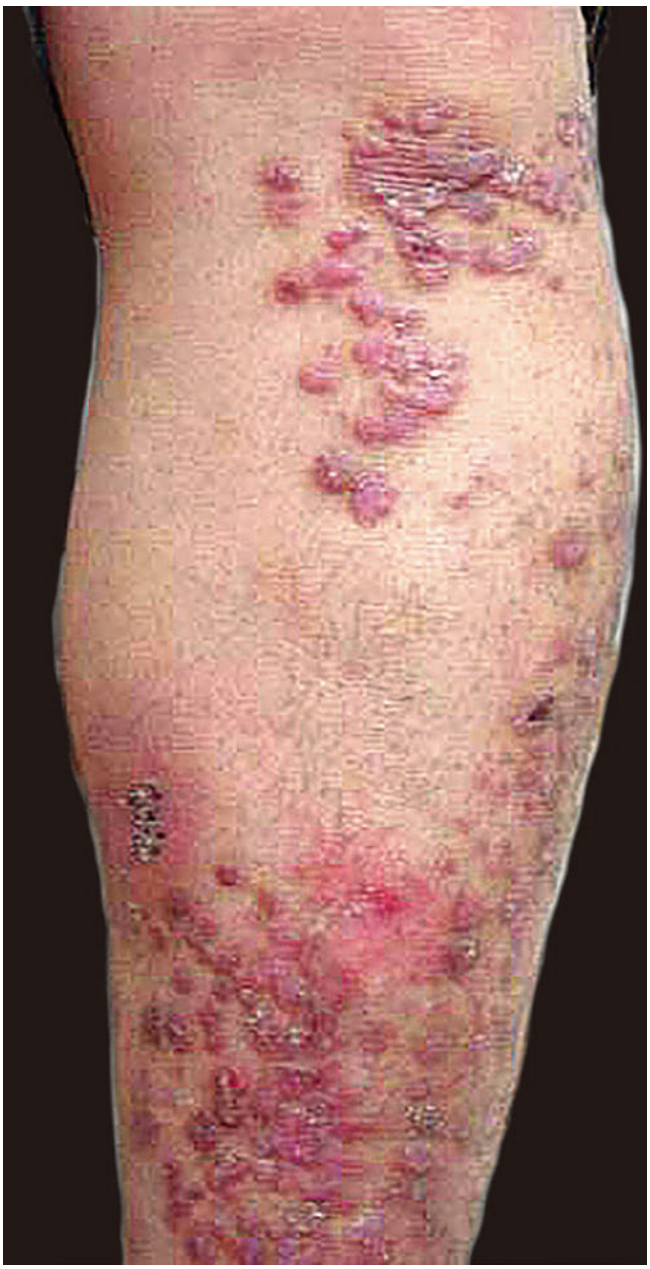


Fig. 26-5-1 Multiple violaceous nodules and plaques, some mung bean-sized blisters on the pretibial area

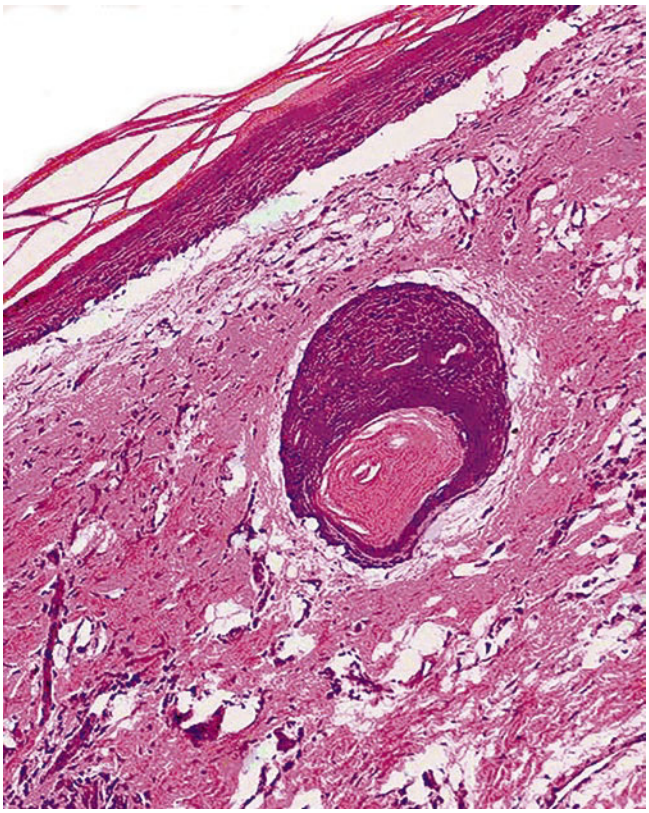


Fig. 26-5-2 Hyperkeratosis associated with the cavity forming between the epidermis and dermis, dilated capillaries and slight hyperplasia of connective tissue in superficial dermis, perivascular infiltration of a few lymphocytes, and several cystoid structures, which walls consisting of squamous epithelium (HE stain, ×100)

26.6 Hailey-Hailey Disease [13, 14]

- Hailey-Hailey disease (HHD), also known as familial benign chronic pemphigus, is an autosomal dominant blistering dermatosis with a predilection for the intertriginous regions.
- The clinical features include malodorous erythematous plaques or erosions at sites of friction and flexures. There is itching, pain, or spontaneous remission and recurrences.
- Segmental unilateral, verrucous, and seborrheic dermatitis-like HHD are uncommon variants of HHD.
- The symptoms are often triggered and aggravated by heat, excessive sweating, friction, infection, and exposure to ultraviolet rays.
- Skin biopsy of HHD reveals the sign of "dilapidated brick wall," which refers to incomplete suprabasilar acantholysis in the epidermis. The nucleus is surrounded by a red dyskeratotic rim, which helps to distinguish HHD from other acantholytic conditions.
- Skin hygiene, clothing, and lifestyle alterations are beneficial in the remission of the disease.
- For widespread recalcitrant patients, laser surgery, photodynamic therapy, electron beam radiotherapy, and botulinum toxin type A may provide long-term relief.
- Mutation in the ATP2C1 gene has been implicated in the development of HHD.

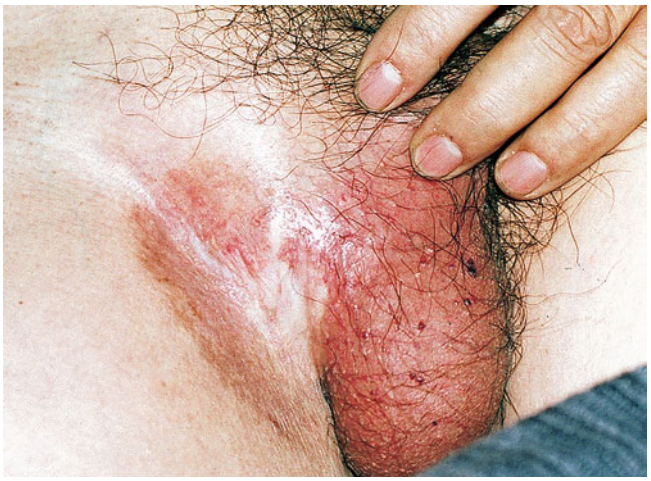


Fig. 26-6-1 Erythemas, macerates, and erosions on the right groin

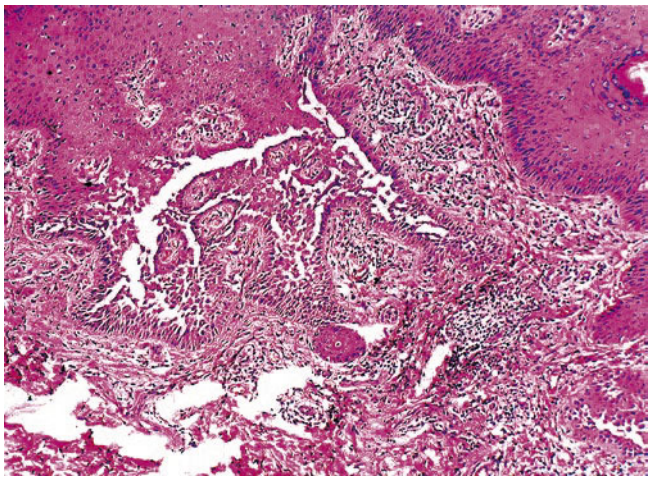


Fig. 26-6-2 Suprabasal lacunae with elongated papillae protrude upward in the bulla forming villi and acantholysis cell in the bulla cavity, inflammatory infiltrate in the upper dermis (HE stain, ×100)

26.7 Ichthyosis Bullosa of Siemens [15–17]

- Ichthyosis bullosa of Siemens (IBS) is characterized by dark-gray hyperkeratosis over the flexural region with focal denudation or erosion after trauma.
- IBS is regarded as a milder form of bullous congenital ichthyosiform erythroderma. The milder clinical presentation, nonexistence of erythroderma, and erosion over hyperkeratotic skin in IBS facilitate this differentiation.
- IBS usually spares both the palms and the soles.
- Mutated keratin 2e is responsible for epidermolytic hyperkeratosis, which only involves the granular layer and the upper layer of stratum spinosum in IBS. Mutation detection now serves as a diagnostic tool in IBS.

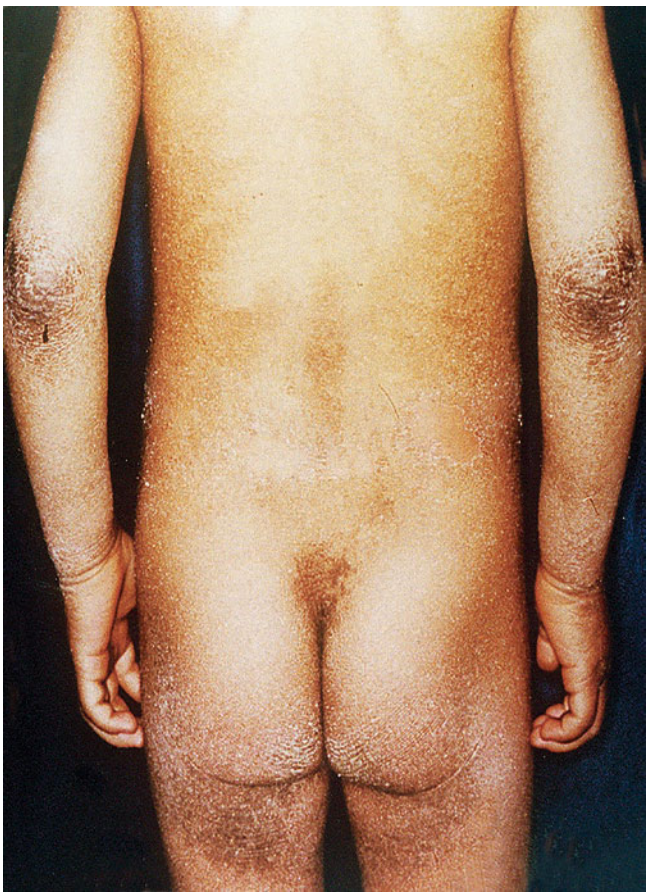


Fig. 26-7-1 Marked hyperkeratosis on the whole skin, mauserung peeling of the skin on the right waist

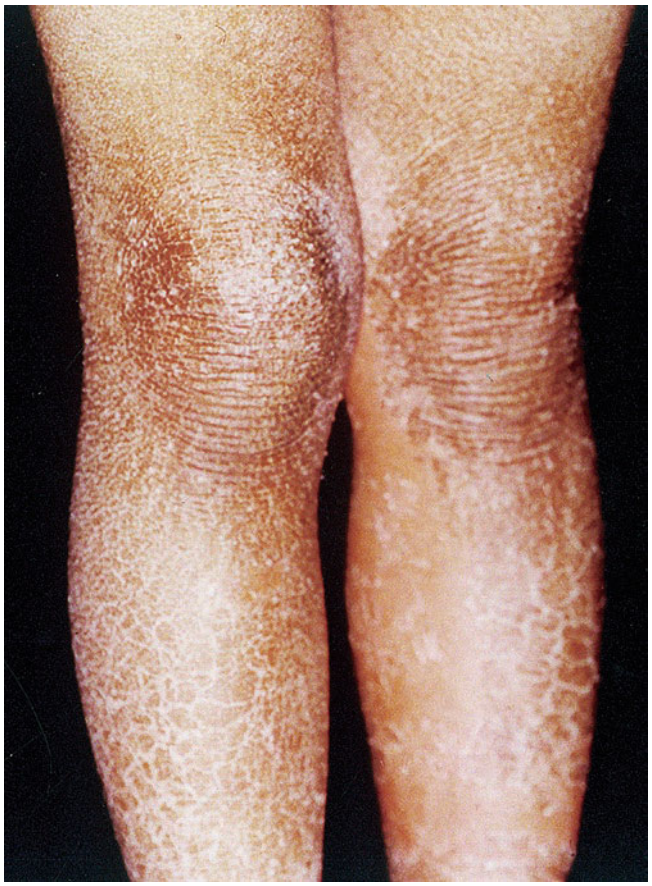


Fig. 26-7-2 Marked hyperkeratosis on the both lower limbs, mauserung peeling of the skin on the flexures of the left knee

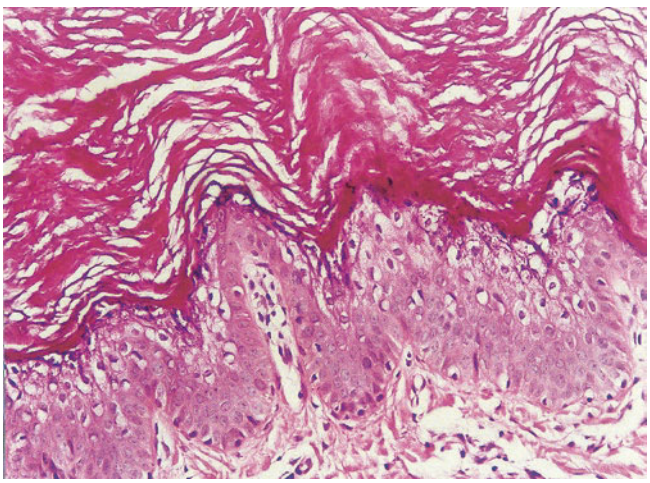


Fig. 26-7-3 Hyperkeratosis and swollen granular cells (HE stain, ×200)

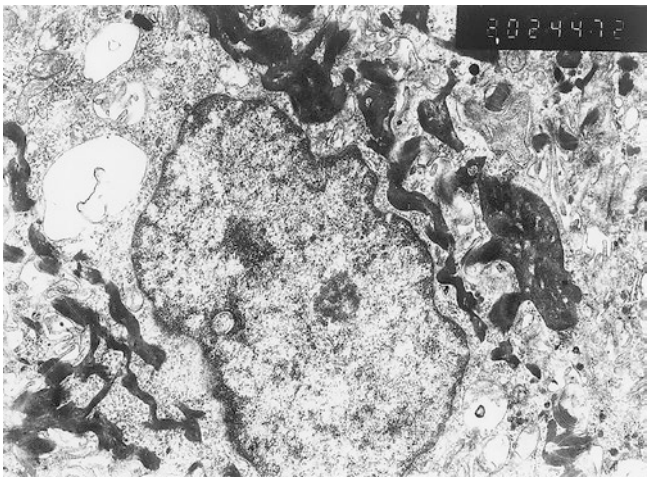


Fig. 26-7-4 High electron density conglomeration in the granular layer (TEM, ×5000)

26.8 Bullous Congenital Ichthyosiform Erythroderma [18, 19]

- Ichthyosis encompasses a variety of presentations, ranging from the mild ichthyosis vulgaris form to the most severe form of lamellar ichthyosis.
- All forms of ichthyosis have dry, thickened, generalized scaly skin.
- Bullous congenital ichthyosiform erythroderma (BCIE) presents as extensive erythema and blistering, with secondary denuded skin, scaling, fissuring, or thickening of the lesions.
- The flexural area is predominantly involved, while the hair, nails, and mucosal surfaces are spared.
- Although BCIE is congenital or develops shortly after birth, symptoms improve with age.
- Skin specimens of BCIE show the vacuolated cytoplasm of the keratinocytes with big keratohyaline granules in the granular layer.
- Mutations in keratin 1 and keratin 10 cause epidermolysis in the epidermis in BCIE.
- Symptomatic ichthyosis may present with dwarfism in Conradi-Hunermann syndrome, Tay syndrome, Rud syndrome, Passwell syndrome, and BCIE.

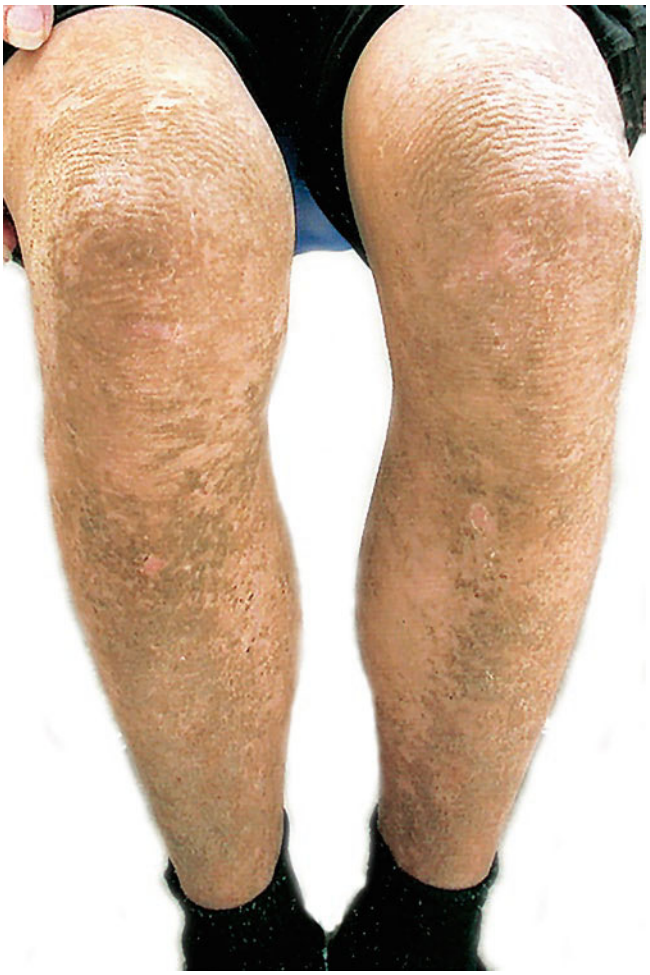


Fig. 26-8-1 Gray or brown, dry plaques with thickened scales, partially verrucous scaling on the lower limbs, furrowed hyperkeratosis on the extensor of knees

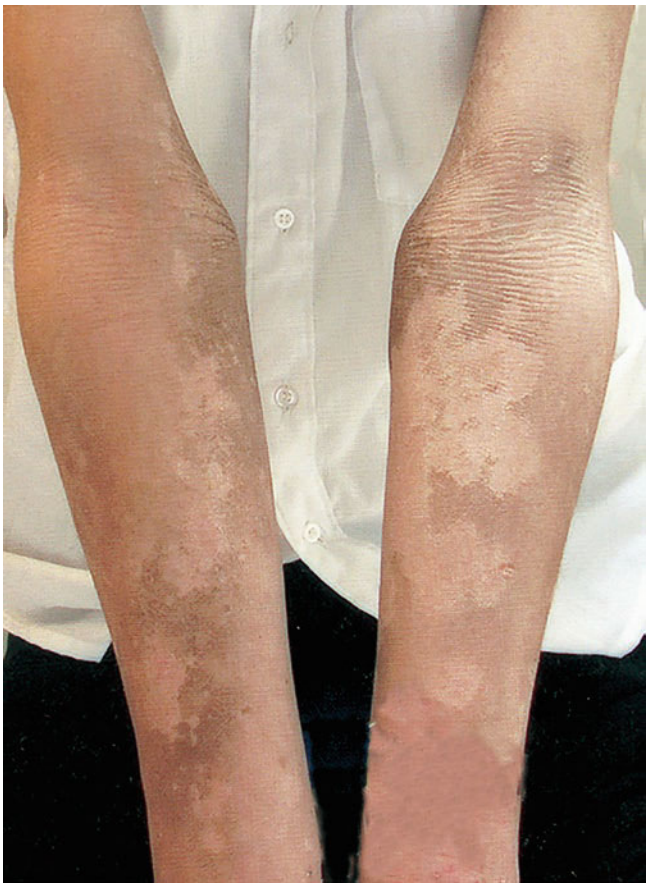


Fig. 26-8-2 Grayish-brown macules with dry scales on the upper limbs, furrowed hyperkeratosis on the elbow joints

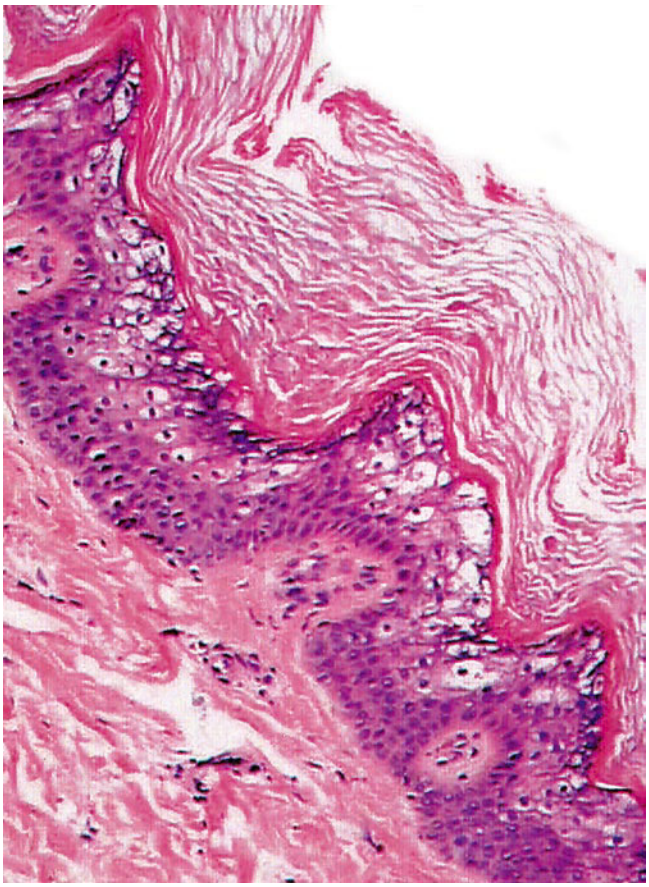


Fig. 26-8-3 Horny layer arrangement in lamellar, thickened granular layer containing irregularly shaped keratohyaline granules and perinuclear haloes, epidermal cells detached in the granular cell layer (HE stain, ×100)

26.9 Collodion Baby [20–22]

- Collodion baby (CB) refers to an infant covered with glistening, parchment-like membrane that eventually cracks and sheds within 3–4 weeks after birth.
- Transepidermal water loss (TEWL) in CB is six times greater than that of normal skin due to disruption of the skin barrier. Therefore, the patient should be promptly put into the incubator with the humidity at 40–60% for 4 weeks until the membrane detaches.
- CB may develop certain types of ichthyosis after spontaneous healing.
- "Crumpled" ears, "fish mouth" lip, and ectropion are important features displayed in CB.
- Harlequin ichthyosis (HI) is a fatal form of ichthyosis and should not be misdiagnosed as CB.

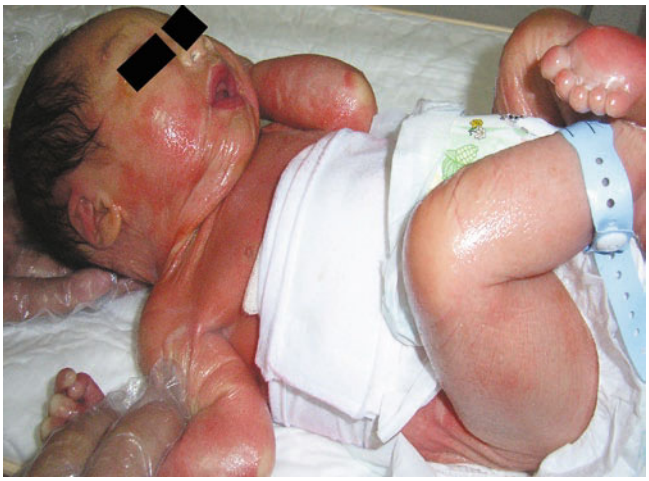


Fig. 26-9-1 Infant born enclosed in a constricting parchment-like membrane that limits motion

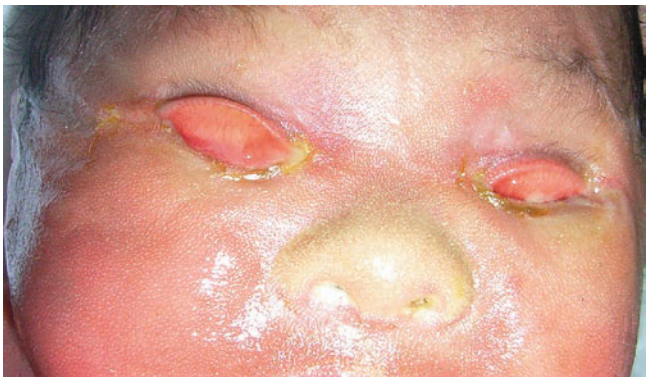


Fig. 26-9-2 Ectropion of the eyelids

26.10 Rothmund-Thomson Syndrome [23–25]

- Rothmund-Thomson syndrome (RTS) is a photosensitive genodermatosis with an autosomal recessive mode of inheritance.
- RTS arises as erythema, blisters, and swelling on the cheeks at age 3–6 months. These lesions then extend to the extremities and eventually become poikilodermatous.
- A large percentage of patients have other heterogeneous abnormalities, such as growth retardation, hypogonadism, alopecia, juvenile cataracts, gastrointestinal problems, skeletal deformities, radial ray abnormalities, and proneness for malignancies.

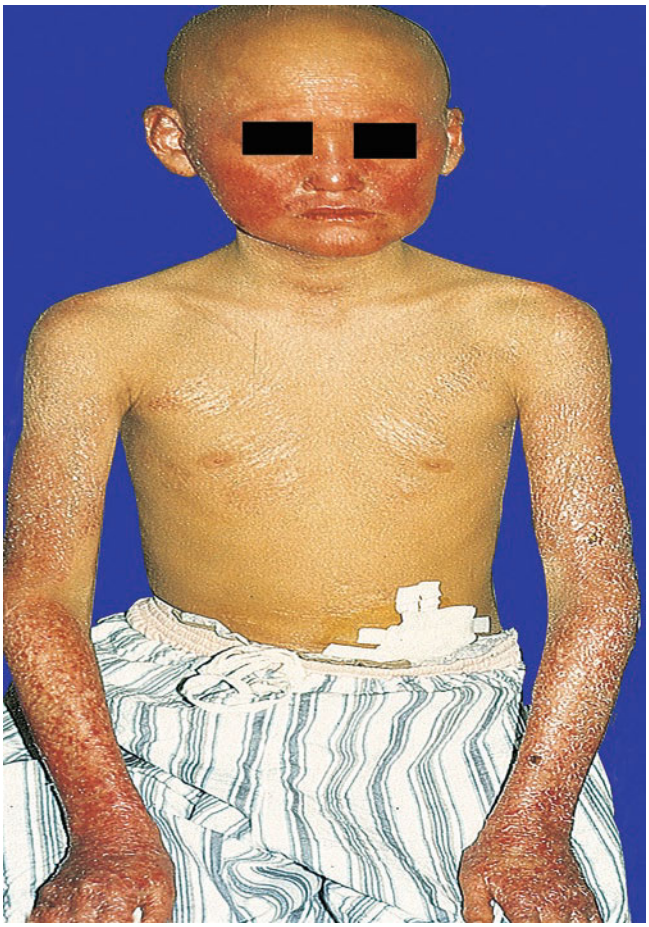


Fig. 26-10-1 Generalized poikiloderma: reticulated erythema, telangiectasias, hyperpigmentation, and hypopigmentation on face, buttocks, and extremities

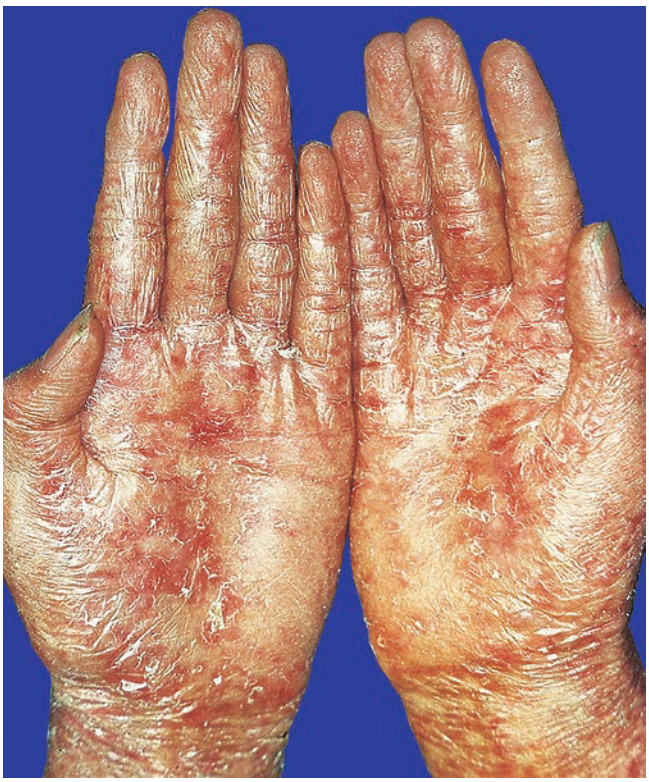


Fig. 26-10-2 Erythema and hyperkeratosis of both palms

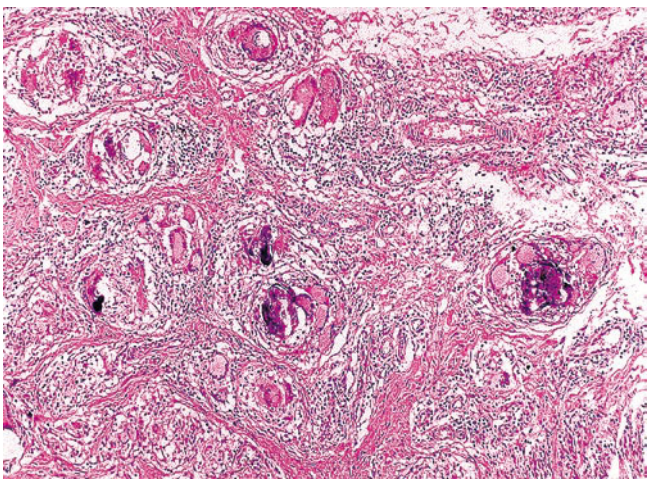


Fig. 26-10-3 The deposition of calcium and lipoids associated with foamy cells, multinucleated macrophages, and granulomatous structure in the dermis (HE stain, ×25)

26.11 Rapp-Hodgkin Syndrome [26–28]

- Over 170 phenotypes of ectodermal dysplasia or associated syndromes have been identified to date, although many of them exhibit certain overlapping characteristics.
- Mutations in the p63 gene were shown to cause a large spectrum of ectodermal dysplasia syndromes, including split-hand split-foot malformation syndrome, ADULT syndrome, Hay-Wells syndrome, limb-mammary syndrome, ectrodactyly-ectodermal dysplasia syndrome, and Rapp-Hodgkin syndrome (RHS).
- RHS is mainly characterized by ectodermal dysplasia, oral clefting, and a unique face (narrow nose with small mouth). Additionally, alopecia and scalp dermatitis may also present.

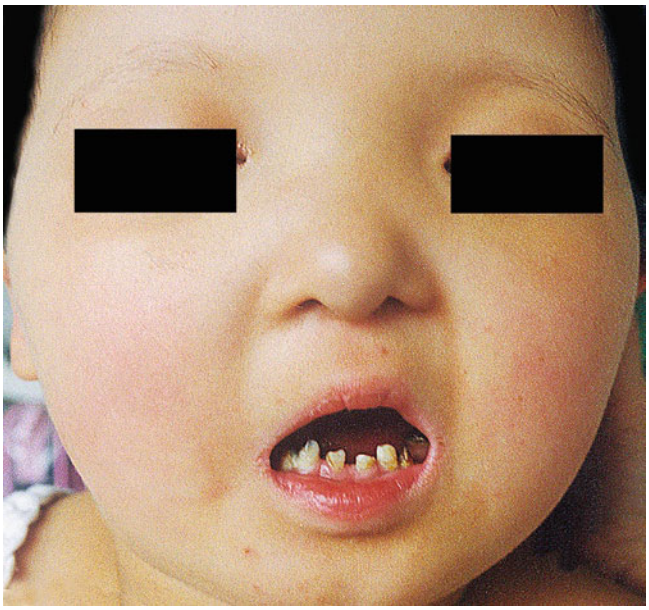


Fig. 26-11-1 Sparse teeth, irregular, and cone-shaped incisor teeth

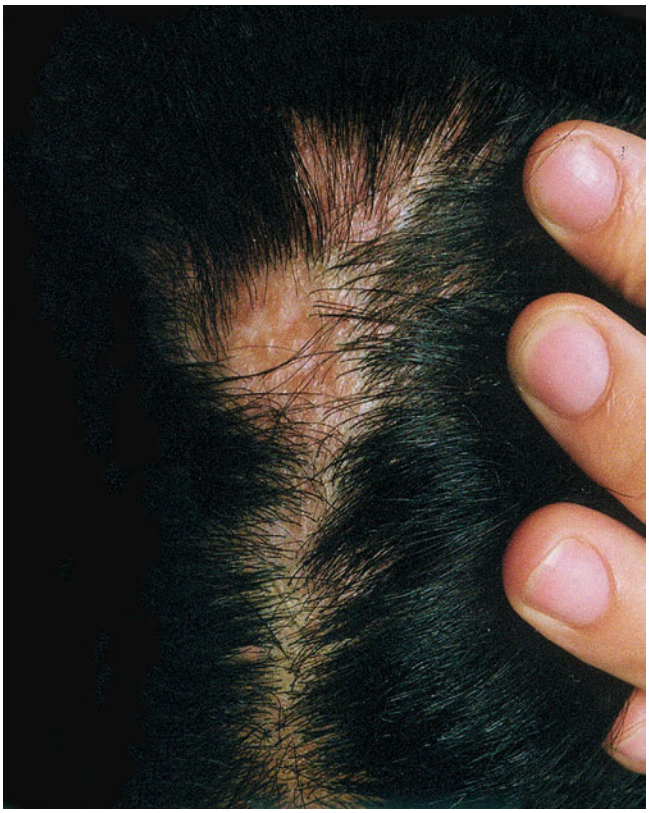


Fig. 26-11-2 Sheet-shaped alopecia on the scalp

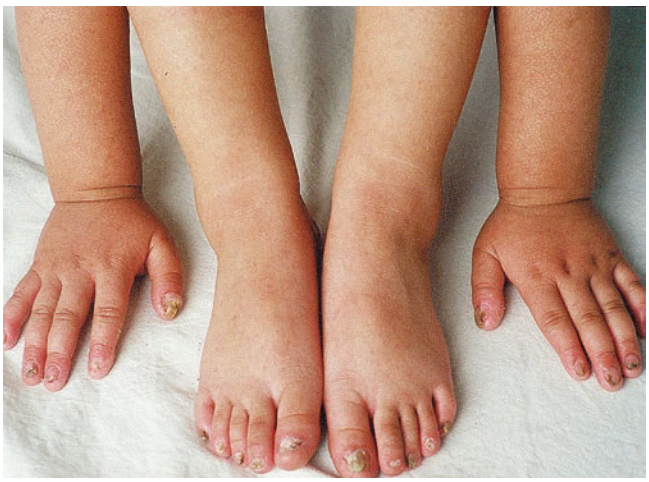


Fig. 26-11-3 Cone-shaped thickened nails and toenails

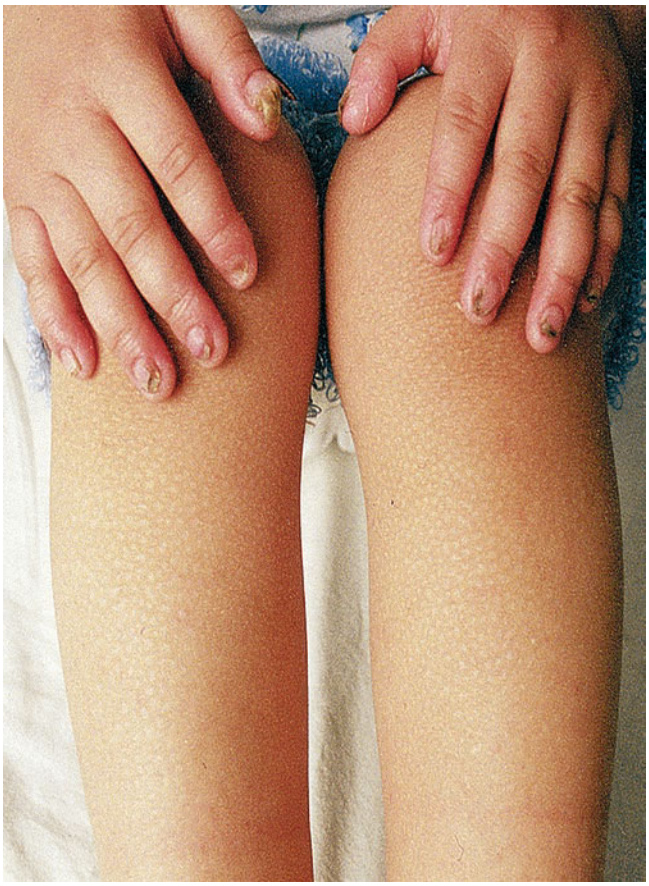


Fig. 26-11-4 Dryness and coarse skin with perifollicular keratosis on the calf

26.12 Focal Dermal Hypoplasia [29–32]

- Focal dermal hypoplasia (FDH) is an X-linked, dominant genodermatosis with meso-ectodermal abnormalities.
- The distinctive findings of the skin in FDH consist of linear, streaky, punctate cribriform hypoplasia of the skin with telangiectasias and pigmentary changes. These linear, pinpoint, and "grid-like" depressions are regarded as a hallmark of the disorder.
- A number of patients may have red-yellow outpouchings of the skin caused by herniation of fat into the atrophic dermis.
- Raspberry-like papilloma, nail abnormalities, osteopathia striata, and miscarriage are its additional pathognomonic signs.
- Only mosaic male patients can survive because hemizygosity of the PORCN mutants in males is lethal.

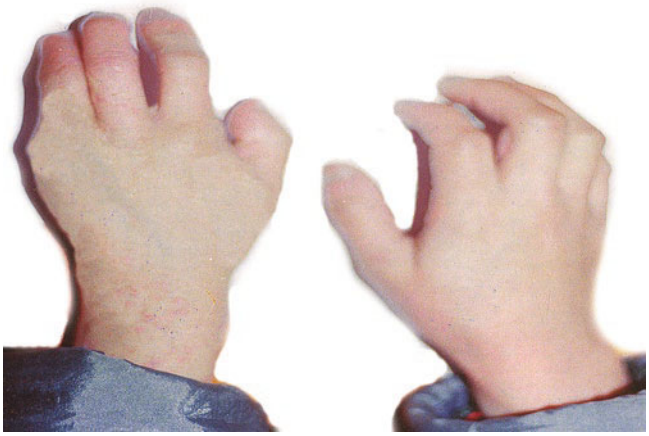


Fig. 26-12-1 The right hand was normal, the left third and fourth finger were splitted with syndactyly, and the fifth finger was amputated

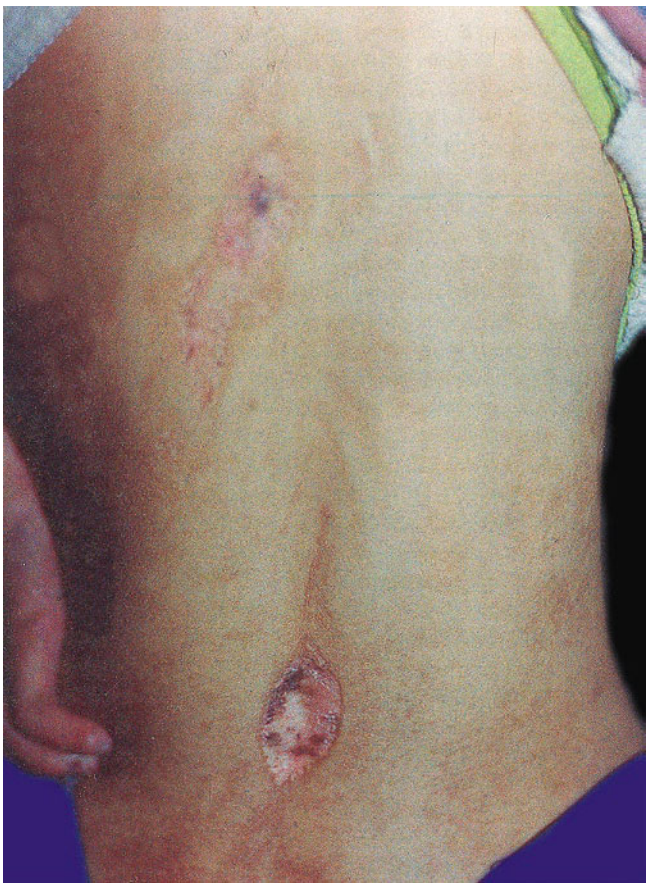


Fig. 26-12-2 Two cicatricial atrophied areas on the back, reticular pigmentation, telangiectasis, longitudinally cupped on the spinal column

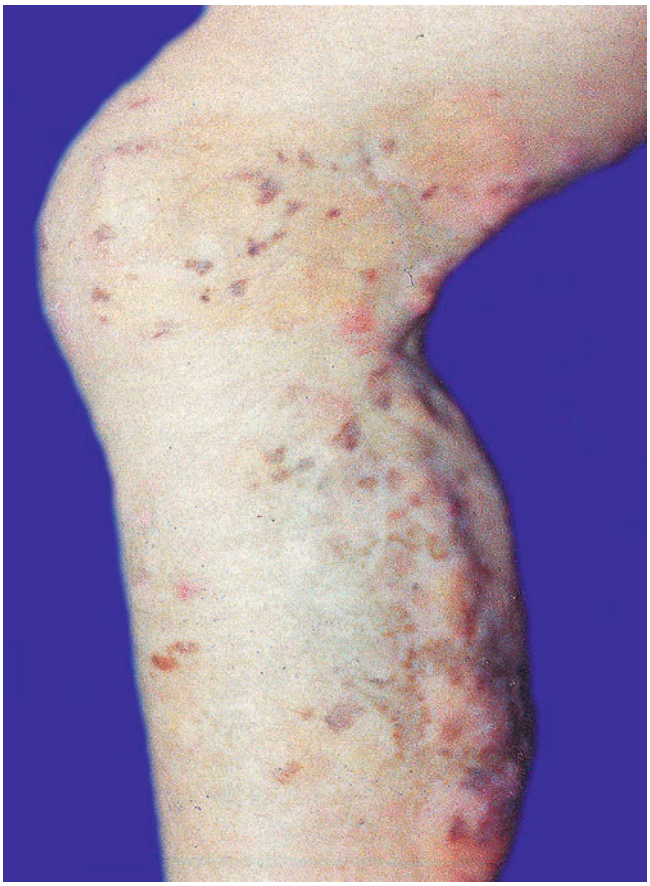


Fig. 26-12-3 Cicatricial atrophy, fatty herniation, hypo- and hyperpigmented patches on the right lower limb

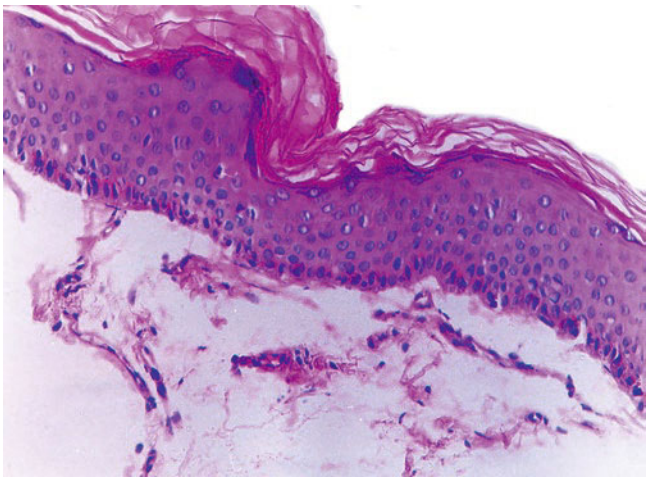


Fig. 26-12-4 Marked dermal atrophy with thin collagen fibers, consistent hypoplasia, and fat hyperplasia (HE stain, ×200)

26.13 Aplasia Cutis Congenita [33–35]

- Aplasia cutis congenita (ACC) has an inherited and non-inherited subtype.
- The lesions of the inherited subtype usually located on the head with a positive family history of onset. However, the non-inherited ACC often affects the region outside the scalp, including the trunk and extremities.
- ACC may associate with various forms of epidermolysis bullosa (EB). Kanler et al. recommended the term "Bart's syndrome."
- Pyloric atresia (PA) is a rare disease which has been associated with EB and ACC (2).

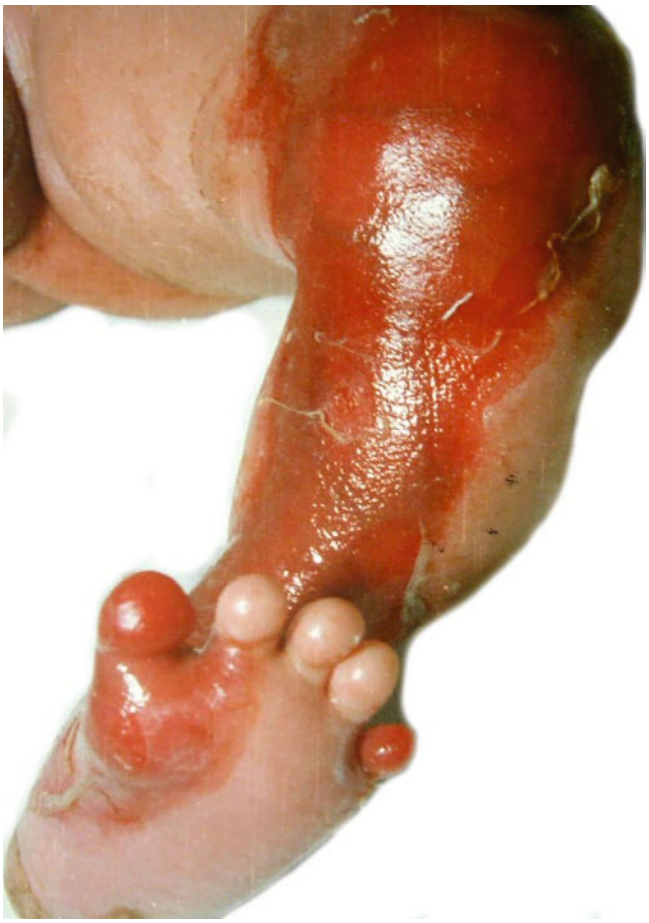


Fig. 26-13-1 Large eroded areas on both lower legs and dorsa of feet at birth (Reproduced with the permission from [36])

26.14 Dyskeratosis Congenita [37–39]

- Dyskeratosis congenita (DC) is an X-linked genetic disorder that causes bone marrow failure (BMF). Both autosomal dominant and autosomal recessive (AR) patterns present in DC.
- The classical features in DC consist of BMF and the mucocutaneous triad of nail dystrophy, skin discoloration, and mucosal leukoplakia.
- DC also has a predisposition for non-cutaneous abnormalities, including pancytopenia, pulmonary fibrosis, hepatic cirrhosis, cancers, and other relevant systemic complications.
- Skin pigmentation and nail changes initially occur in childhood, followed by oral leukoplakia, BMF, and pulmonary fibrosis in adulthood.
- Aplastic anemia is a fatal cause for children with BMF, while pulmonary fibrosis and cancers (squamous cell carcinoma and hematolymphoid malignancies are most common) are considered the main causes of death in adult cases.
- Revesz syndrome, Coats plus disease, and Hoyeraal-Hreidarsson syndrome all are variants of DC.
- Pathogenesis of DC is mainly due to the shortening of telomere, leading to genomic instability and the development of malignancies.
- Nearly 40–50% of the patients with DC may undergo certain forms of malignant transformation by age 50 years. Squamous cell carcinoma, lymphoma, gastrointestinal adenocarcinoma, and lung cancers are the most common malignancies.

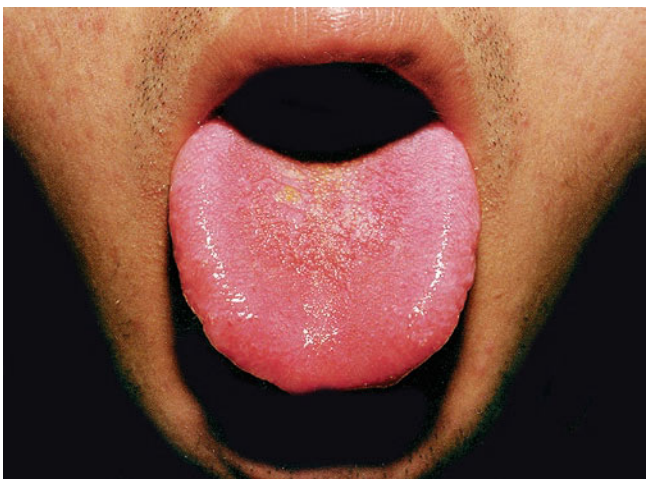


Fig. 26-14-1 Shed leukoplakia on the central of the tongue

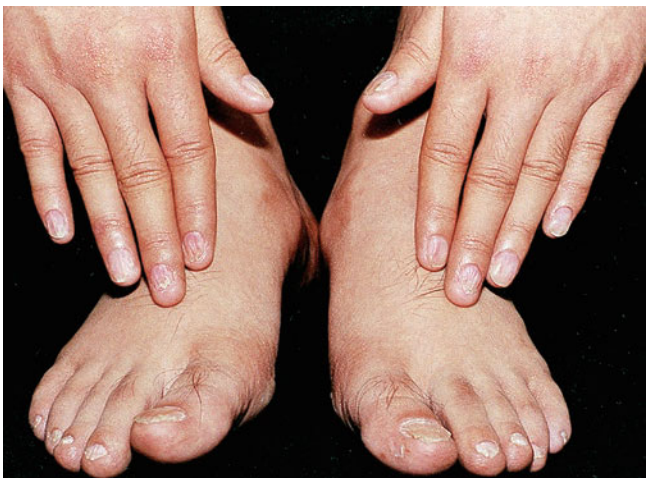


Fig. 26-14-2 Finger nail and toenail atrophied with vertical splitting stria

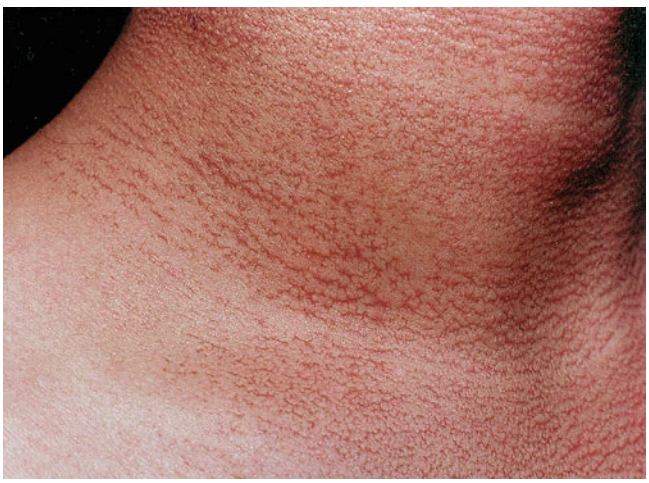


Fig. 26-14-3 Widespread reticulated and hyperpigmented brown patches on the neck

26.15 Rudimentary Polydactyly [40, 41]

- Two types of polydactyly have been described: type A, which has a completely formed accessory digit, and type B, which is characterized with a rudimentary digit.
- RP (rudimentary polydactyly) is inherited as an autosomal dominant trait.
- Rudimentary digit in RP shows a small warty papule or a pedunculated configuration.
- It is attached on the ulnar side of the little digit or the thumb. Cartilage or vestigial nail apparatus can also be found.
- Excision is recommended when RP poses cosmetic stigmatization.
- Histologically, RP exhibits obvious neural proliferation in the dermis. Meanwhile, many Wagner- Meissner bodies are distributed in the papilla of the lesion.

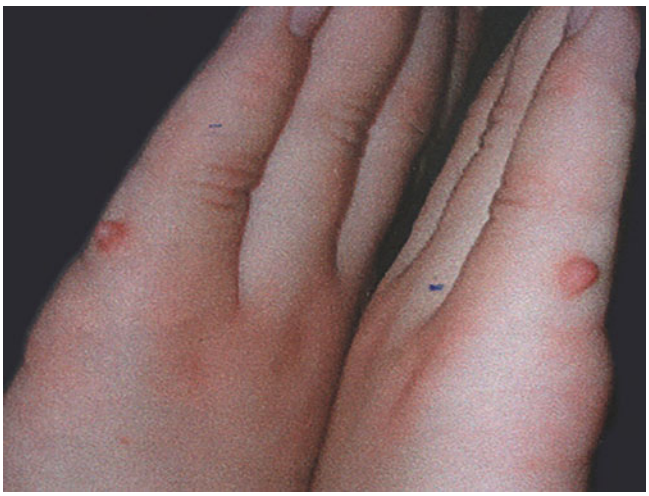


Fig. 26-15-1 Reddish nodules on the ulnar side of the fifth fingers on both hands

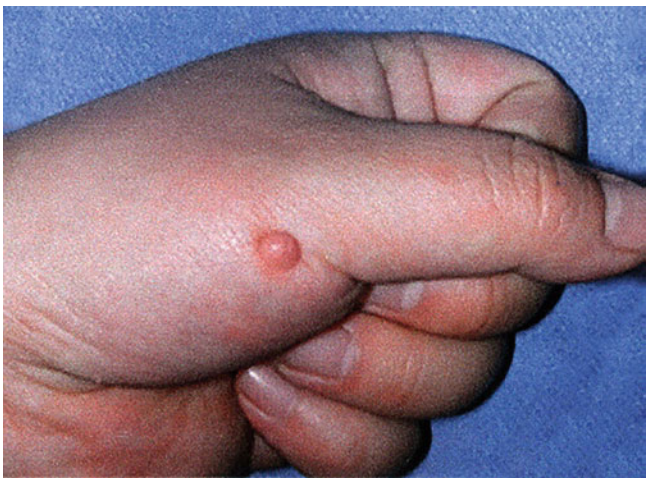


Fig. 26-15-2 A reddish hemispherical nodule on the radial aspect of the left thumb

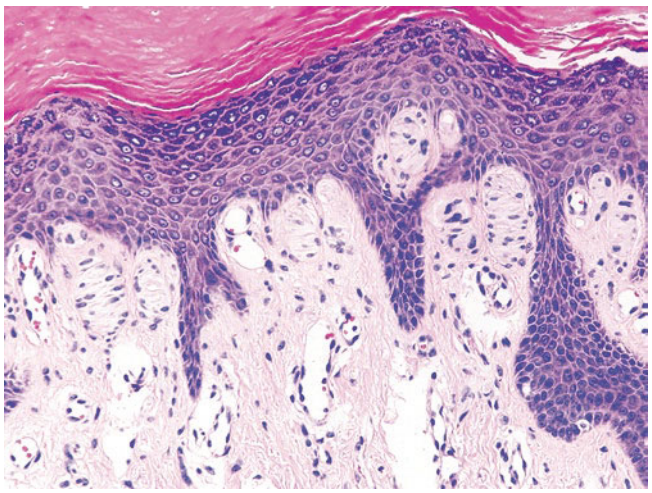


Fig. 26-15-3 Many Meissner corpuscles and telangiectasias in the dermal papillae

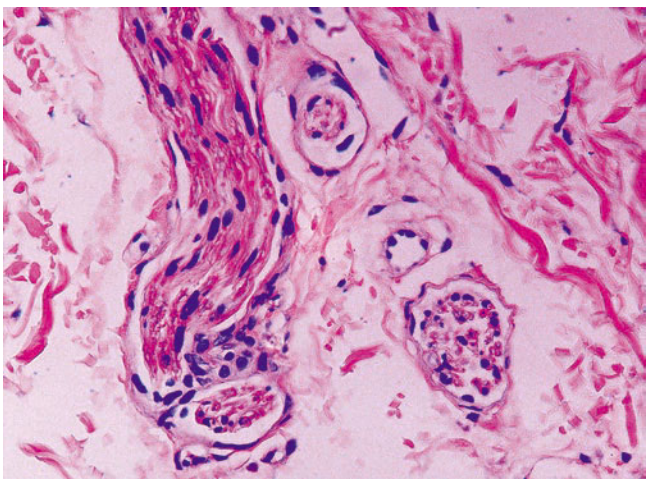
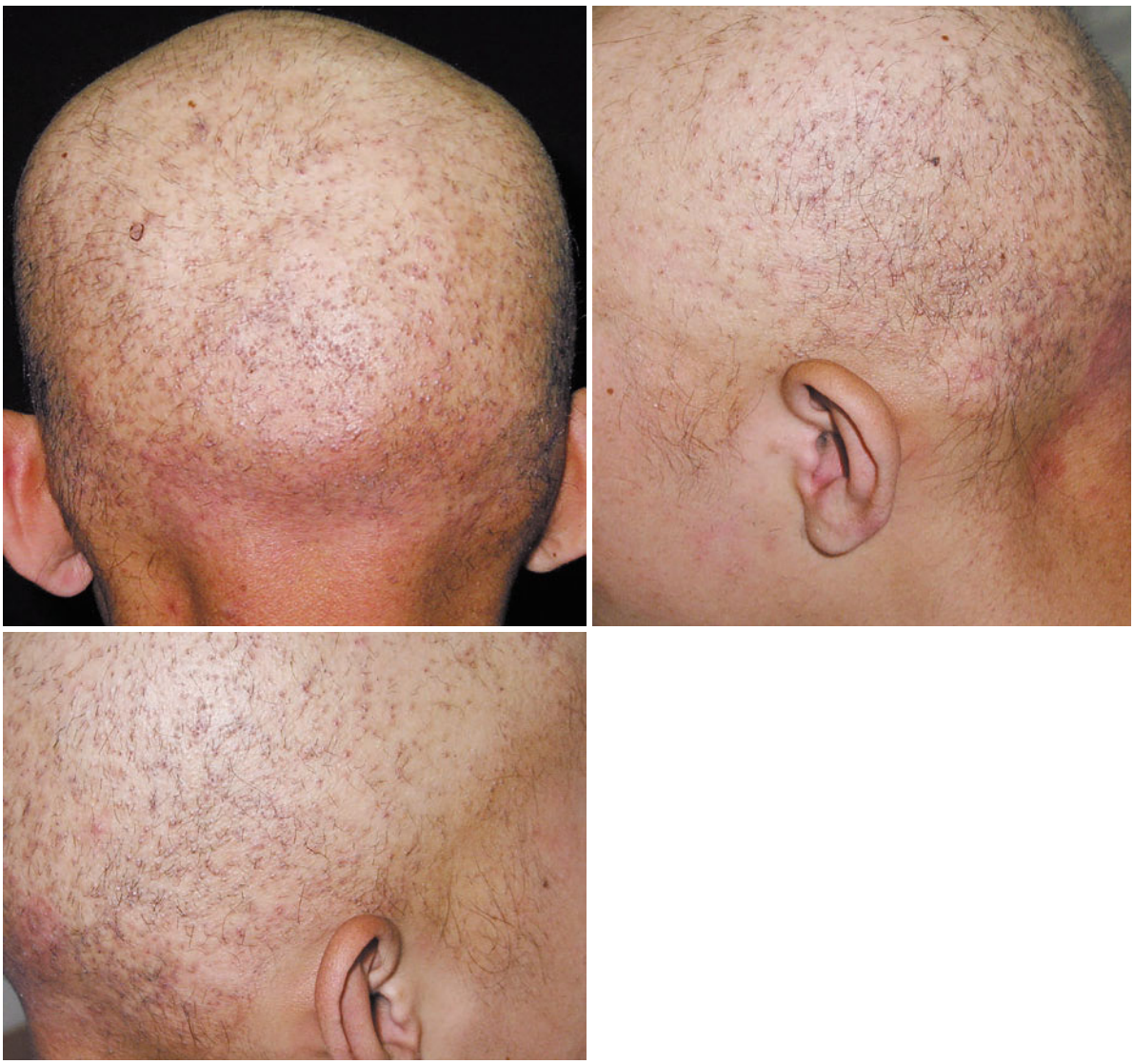


Fig. 26-15-4 Many nerve fibers, proliferating endothelial cells, and capillaries in the upper dermis, increased number of nerve fascicles with intact membrane in the reticular dermis

26.16 Keratosis Follicularis Spinulosa Decalvans [42, 43]

- Keratosis follicularis spinulosa decalvans (KFSD) is a rare inherited X-linked condition of keratinization. It arises as diffused follicular hyperkeratosis, scarring hair loss, corneal dystrophy, and photophobia.
- KFSD describes a group of disorders comprised of keratosis pilaris atrophicans faciei, atrophoderma vermiculatum, and itself.
- KFSD appears as extensive follicular hyperkeratosis and photophobia in early childhood, followed by progressive hair loss of scalp, eyelashes, and eyebrows. Rarer features include ocular symptoms and palmoplantar keratoderma.
- The characteristic pathological features are follicular keratotic plug, scarring, and lymphocytic infiltration around the follicles and blood vessels.
- KFSD should be distinguished from other dermatoses with cutaneous follicular hyperkeratosis, such as ichthyosis follicularis and ichthyosis follicularis-alopecia-photophobia syndrome.



Figs. 26-16-1, 26-16-2, 26-16-3 Extensive cicatricial alopecia involved the entire scalp with follicular hyperkeratotic papules

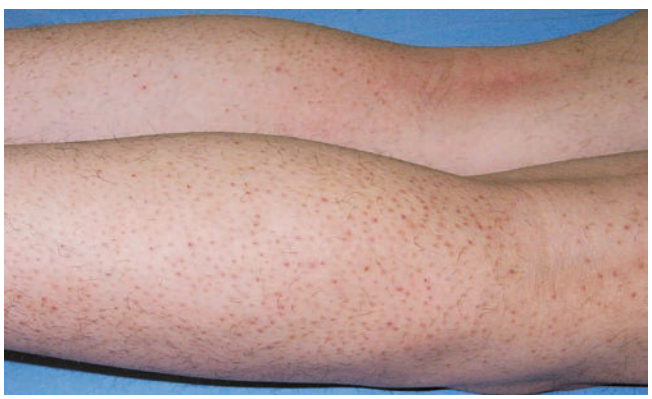


Fig. 26-16-4 Keratosis pilaris on the flexor surfaces of the lower extremities

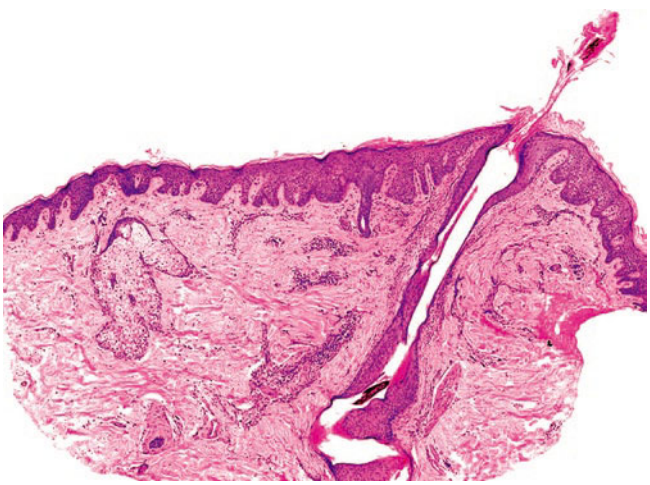


Fig. 26-16-5 Follicular hyperkeratosis, mild perifollicular fibrosis with moderately dense chronic inflammatory cell infiltrate (HE stain, ×40)

26.17 Pachydermoperiostosis [44–46]

- Pachydermoperiostosis (PDP), an autosomal dominant illness, mainly affects the skin and skeletal system.
- Digital clubbing, periostosis, and pachydermia (including cutis verticis gyrata) are the distinctive features of PDP. Seborrheic hyperplasia, hyperhidrosis, and arthropathy are its additional alterations.
- Conspicuous furrowing of the face, cutis verticis gyrata, finger clubbing, and periostosis are prerequisite findings for the complete form. Incomplete form designates individuals without pachydermia (including cutis verticis gyrata). The frustrated form is applicable when at least one typical skin change presents with minimal or no bone involvement.
- Compared with primary PDP, the cutaneous findings in the secondary form are less severe, while osteoarthropathy is more severe and painful.
- Acromegaly, thyroid acropachy, syphilitic periostitis, and lepromatous leprosy share similarities with PDP and should be carefully differentiated.
- PDP may be triggered by elevated prostaglandin E2 levels as a result of mutations of the 2A1 gene (15-hydroxyprostaglandin dehydrogenase gene), which belongs to the organic anion transporter family.

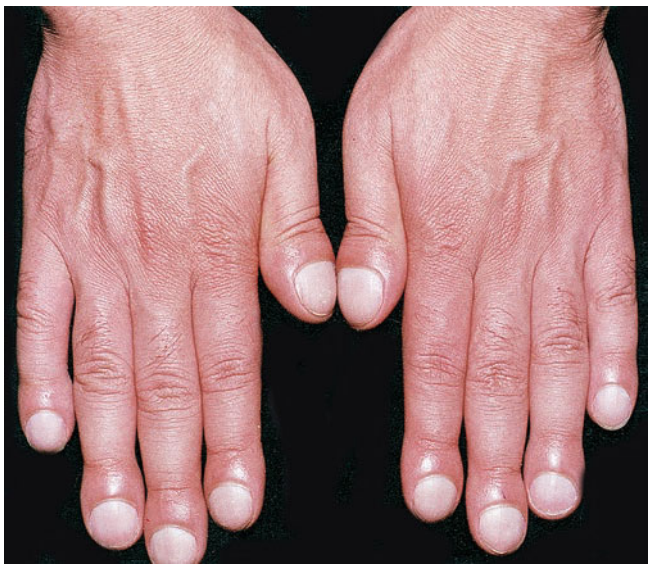


Fig. 26-17-1 Clubbing of the digits

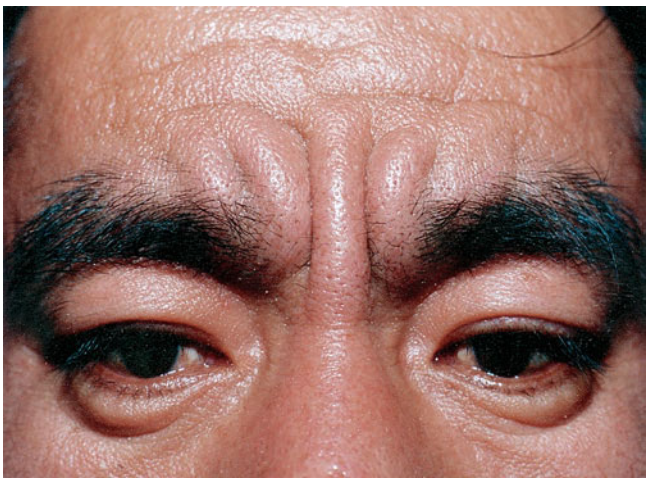


Fig. 26-17-2 Thickening and furrowing of the skin of the face and scalp

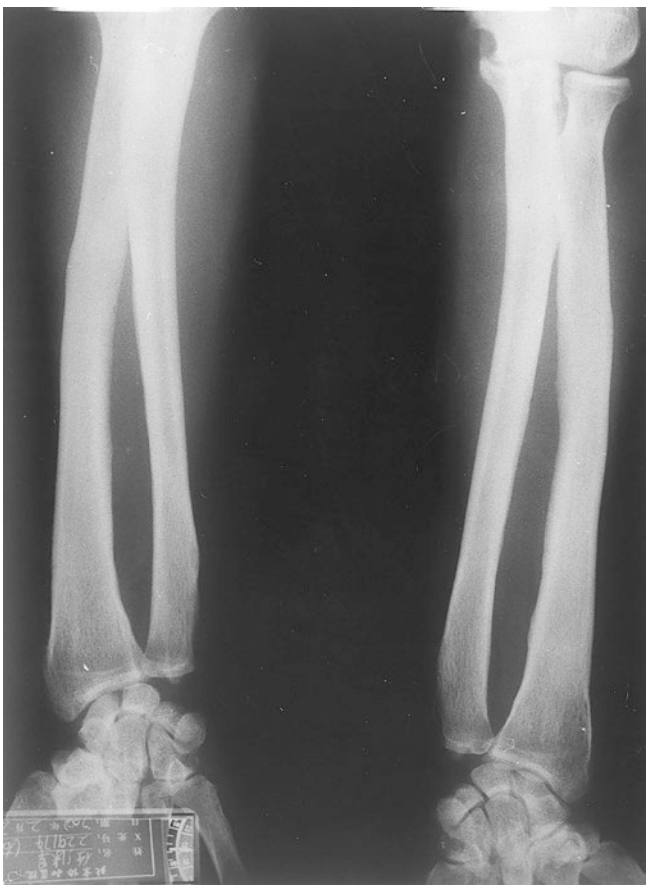


Fig. 26-17-3 The periosteal proliferation of the bones of both ulnas, radius, tibias, and fibulae

26.18 Xeroderma Pigmentosum [47–49]

- Xeroderma pigmentosum (XP) refers to a genodermatosis inherited in an autosomal recessive pattern.
- Patients with XP exhibit defective nucleotide excision repair due to a genetic defect in the nucleotide excision repair pathway.
- XP can be classified into six distinct types according to the mutated gene profile: classical XP, XP with neurologic symptoms, trichothiodystrophy, XP with trichothiodystrophy symptoms, cerebro-oculo-facio-skeletal syndrome, and XP with Cockayne syndrome.
- Cutaneous manifestations of XP include increased sunlight sensitivity and pigmentary disturbances in UV exposed areas, increased lentiginosis, freckling, actinic keratosis, premature aging in early childhood, and occurrence of basal cell carcinoma, squamous cell carcinoma, and melanoma afterward.
- There is a solid association between the neurodegenerative disorders and various ophthalmologic complications.

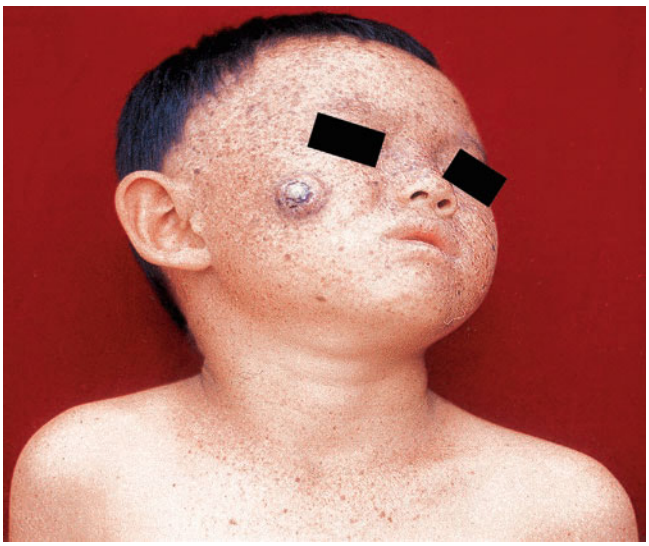


Fig. 26-18-1 Mottled pigmentation on the face, a tumor with shallow ulcer on the right face

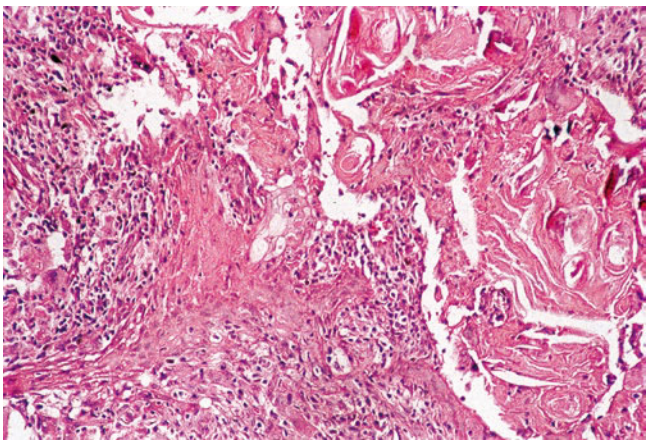


Fig. 26-18-2 Invasive carcinoma of the epidermis, uncircumscribed tumor consisting of atypical squamous cells and horn pearls in the dermis (HE stain, ×100)

26.19 Cutis Tricolor Parvimaculata [50]

- Cutis tricolor parvimaculata is characterized by a combination of small, congenital, paired hyper- and hypopigmented macules on a background of normal-colored skin.
- It designates a type of allelic didymosis.

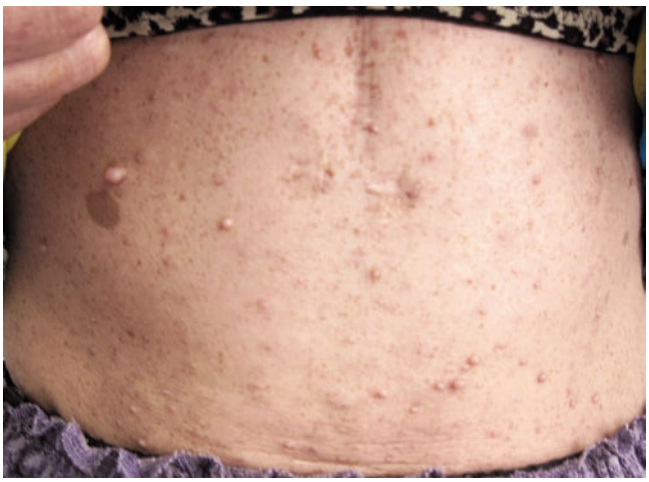


Fig. 26-19-2 Abdominal lesions of neurofibromatosis presented in the patient's mother. Multiple cafe au lait spots and soft neurofibromas were shown on the abdomen

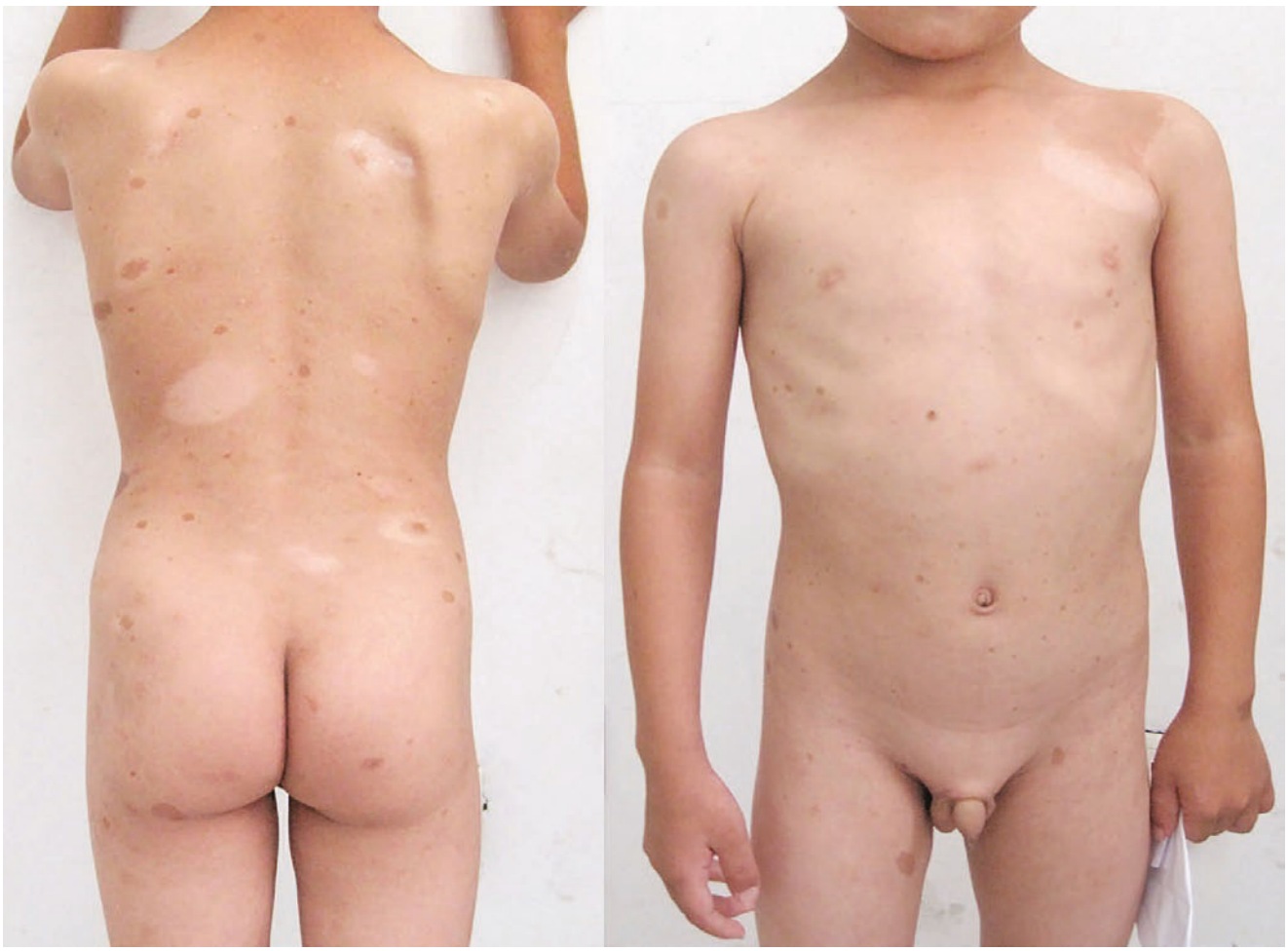


Fig. 26-19-1 Numerous hyperpigmented macules disseminated on his skin at birth, with closely-neighbored hypopigmented macules. Small patches of hyperpigmentation, hypopigmentation, and normally pigmented skin indicated the diagnosis of cutis tricolor parvimaculata

26.20 Congenital Thymic Dysplasia [51]

- Congenital thymic dysplasia (CHD), or DiGeorge syndrome, has variable clinical phenotypes caused by a de novo microdeletion of band 22q11.2.
- CHD is an embryologic defect in the third and fourth pharyngeal pouch, together with the surrounding arch. It will subsequently result in thymus dysfunction, cardiac malformations, and dysfunctions of the thymus and parathyroid glands.
- A subset of individuals with CHD show eczematous dermatitis as its cutaneous manifestation. The histological findings of satellite cell necrosis and dyskeratotic cells in CHD distinguish it from eczema.

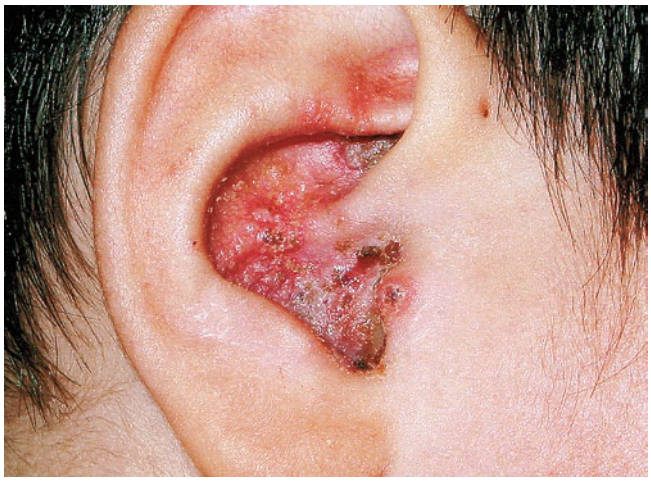


Fig. 26-20-2 Numerous papules and vesicles with crusts on the auricle

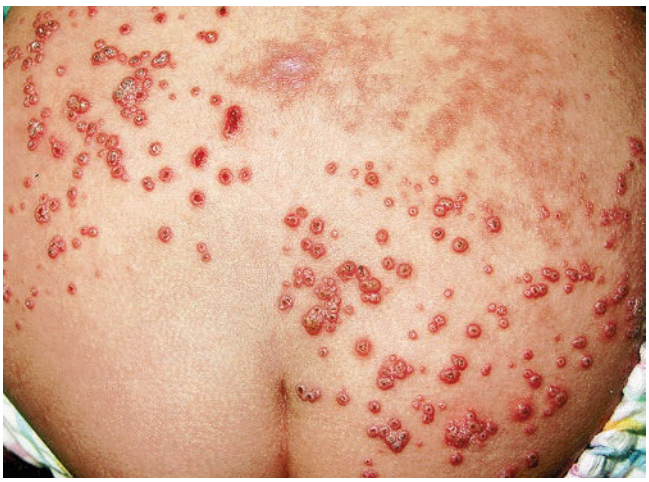


Fig. 26-20-1 Numerous millet to mung bean-sized, brownish-red papules, and vesicles on the buttocks, partly with crust

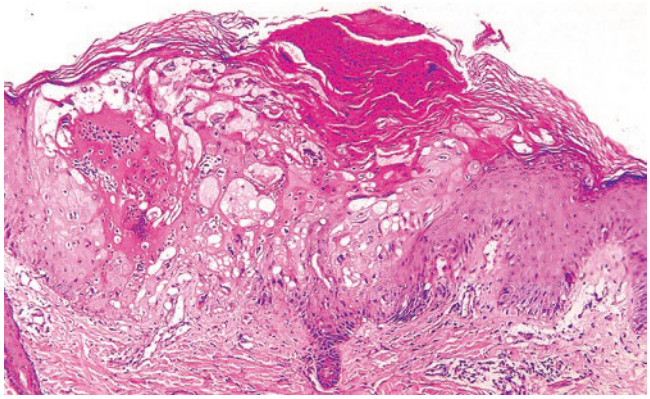


Fig. 26-20-3 Ballooning degeneration of epidermis forming vesicles (HE stain, ×100)

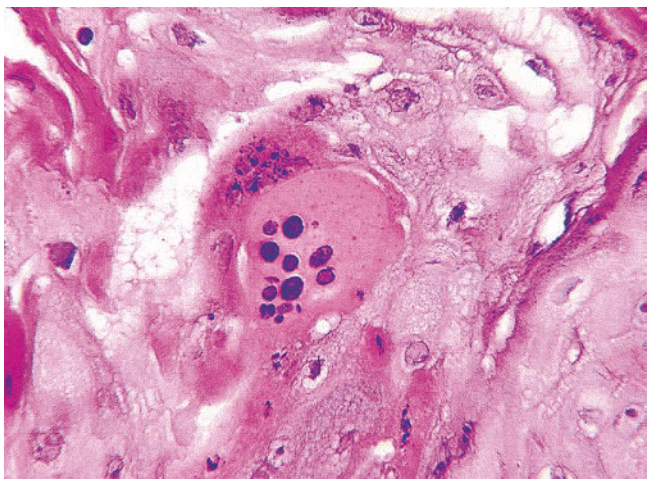


Fig. 26-20-4 Strange multinucleated giant cells in the vesicles (HE stain, ×400)

26.21 Pachyonychia Congenita [52–54]

- Pachyonychia congenita (PC) is a rare dermatosis of ectodermal dysplasias that is inherited in an autosomal dominant pattern.
- The chief features of PC include nail abnormalities, palmoplantar keratoderma, follicular keratosis, leukokeratosis of the mucous membranes, hoarse voice, and natal teeth.
- Nail abnormalities are diagnostic hallmarks in PC, which arise at birth or shortly afterward. Their changes may vary from transverse convex curvature or subungual hyperkeratosis to thickening of the nail plate.
- In PC, mutations have been detected in the four keratin genes (KRT6A, KRT6B, KRT6C, KRT16), and these mutations cause epidermolysis and compensatory hyperkeratosis.
- PC is classically divided into two groups: type I often shows associated oral leukokeratoses. PC type 2 has multiple cysts and intermittently natal teeth.
- Recently, PC was classified into PC-K6a, PC-K6b, PC-K6c, PC-K16, and PC-K17 subtypes based on the genotypes of KRT6A that encode keratins.

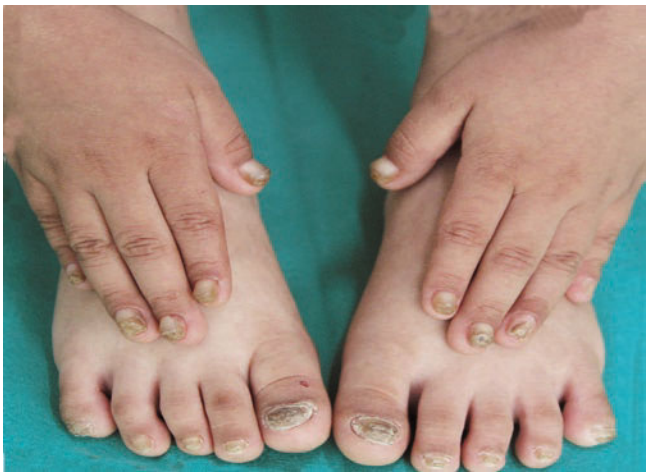
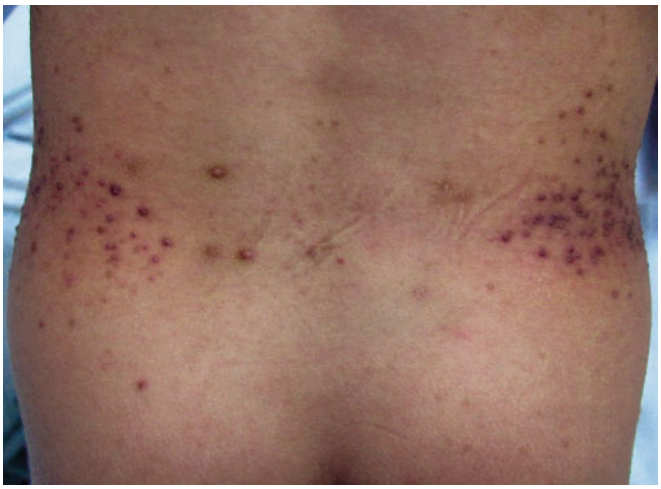
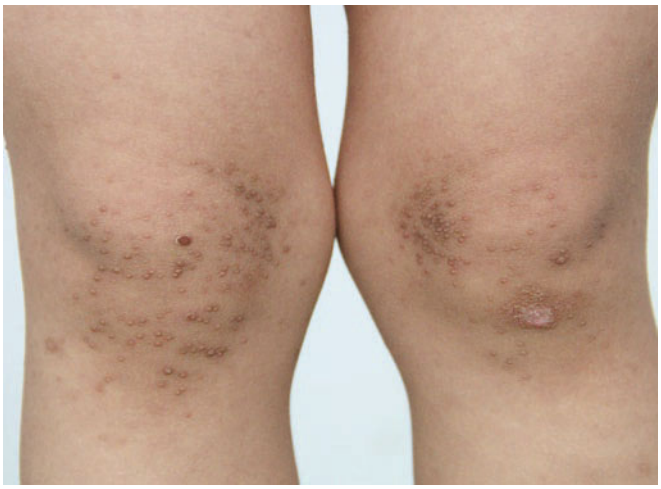


Fig. 26-21-1 Thick yellow keratoses were wedge-like thickening of distal finger and toenails





Figs. 26-21-2, 26-21-3 Many brown papules on the waist and knees

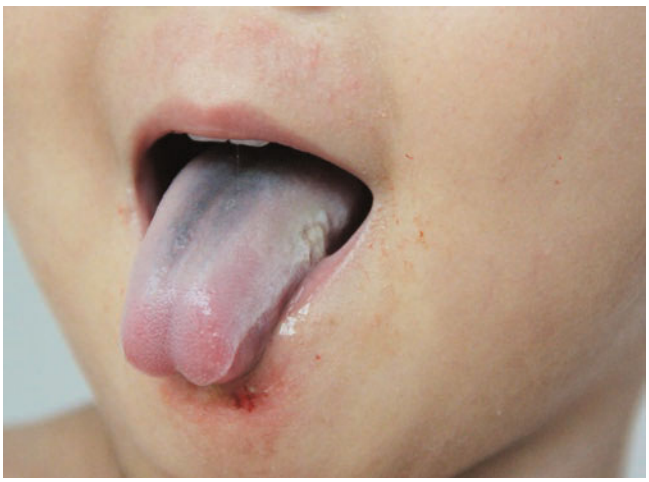


Fig. 26-21-4 The thickened tongue coating was yellow and black

26.22 Papillon-Lefèvre Syndrome [55, 56]

- Clinical presentations of Papillon-Lefèvre syndrome (PLS) are the combination of early-onset severe periodontitis and palmoplantar hyperkeratosis.
- Keratoderma may also affect the elbows and knees.
- Gingival inflammation and destructive periodontitis occur as early as 3–4 years, which, in return, lead to the loss of both permanent and primary teeth by the age of 15 years.
- The cathepsin C gene is mapped to chromosome 11q14, and it encodes a lysosomal protease. Mutation of this gene in PLS impairs chemotaxis, phagocytosis, and immunological functions, causing a variety of infections of the gum.
- Compelling evidence shows that mechanical debridement and administration of antibiotics are beneficial in preventing or delaying tooth loss.

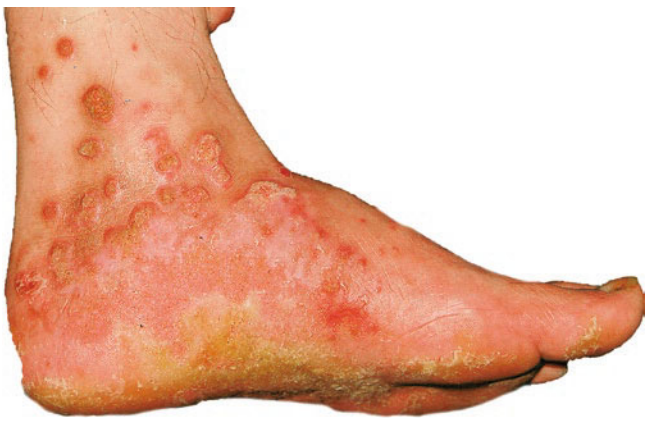


Fig. 26-22-1 Many papules were partly confluent on the inboard of left ankle, yellowish, scaly, keratotic plaques over the soles

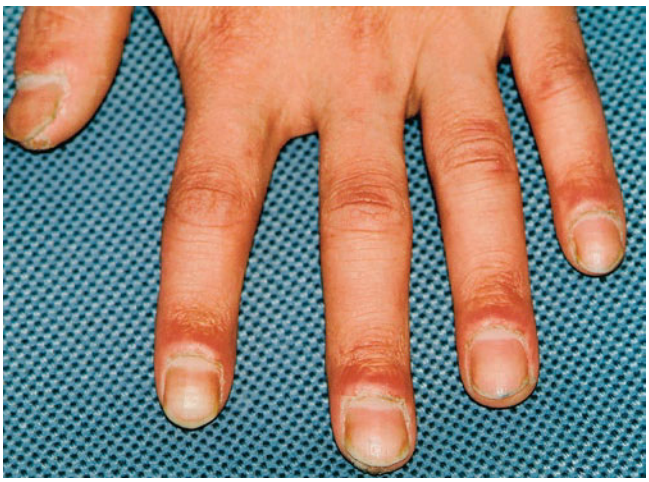


Fig. 26-22-2 Thickened skin around crimp eponychium and the extensor surface of distal interphalangeal joint

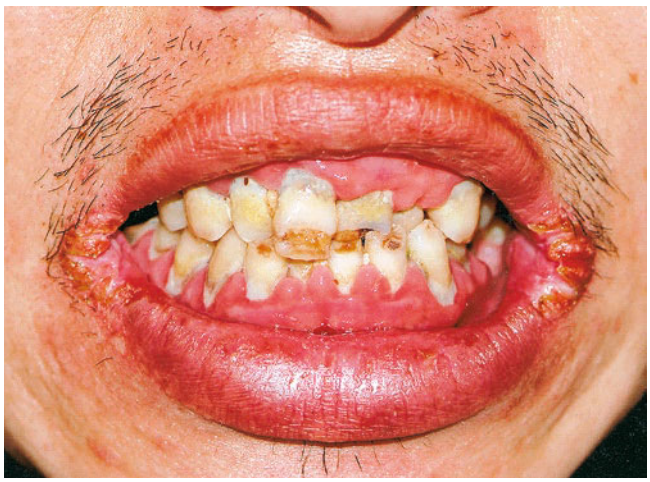


Fig. 26-22-3 Erosions around the mouth, gingival inflammation, and periodontal pocket

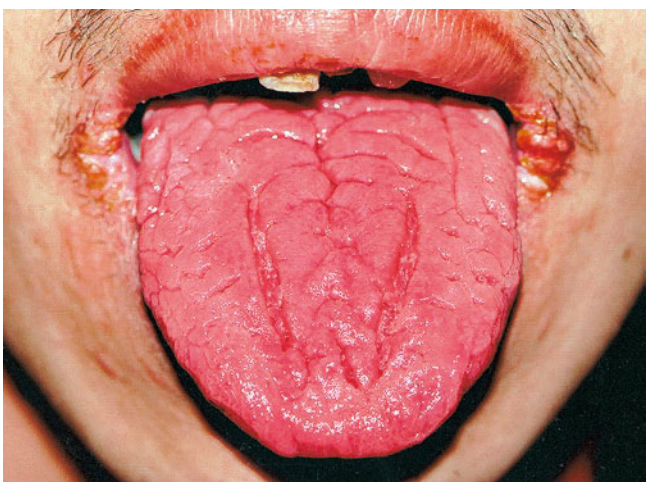


Fig. 26-22-4 Numerous deep grooves or furrows on the dorsal surface of the tongue

26.23 Olmsted Syndrome [57–59]

- Olmsted syndrome (OS) is an unusual genodermatosis of keratinization. Keratotic plaque around the orifice and palmoplantar keratoderma are two major abnormalities in OS.
- The vast majority of OS patients develop disabling palmoplantar keratoderma and periorificial keratotic lesions. Pseudoainhum feature, hair and nail changes, eye lesions, and intermittent infections all belong to the varieties of its presentations.
- Keratoderma may begin focally and become confluent. Nonperiorificial keratotic lesions are also reported in OS. Painful keratoderma, together with deformed skeletons and joints, impedes the mobility of patients.
- Mutations in both TRPV3 and MBTPS2 genes are identified as the main cause of OS.

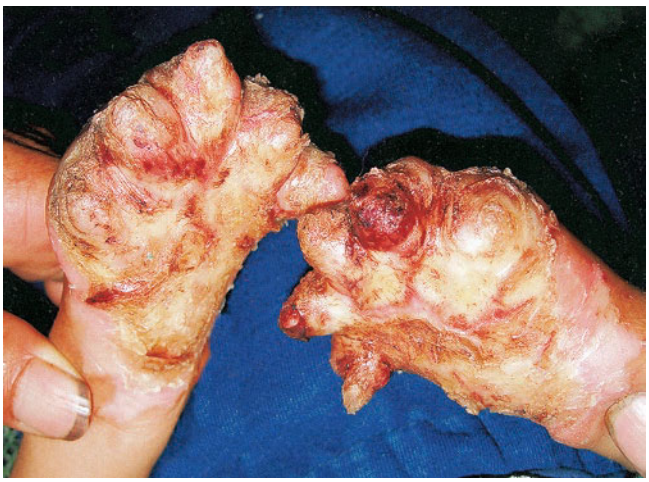


Fig. 26-23-1 Both hands with severe palmar keratoderma and digital spontaneous amputation

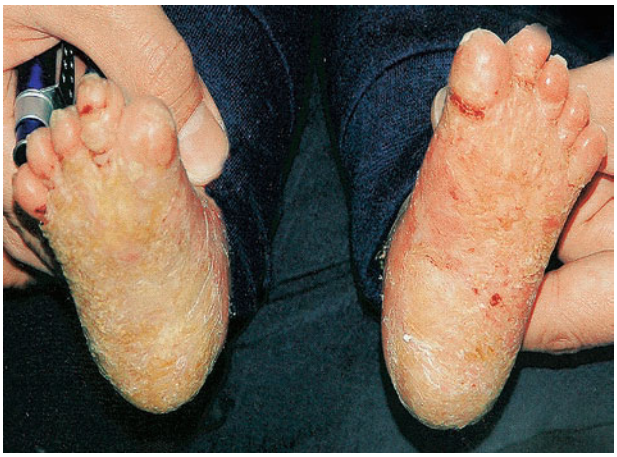


Fig. 26-23-2 Both feet with severe plantar keratoderma with fissures and bloodiness

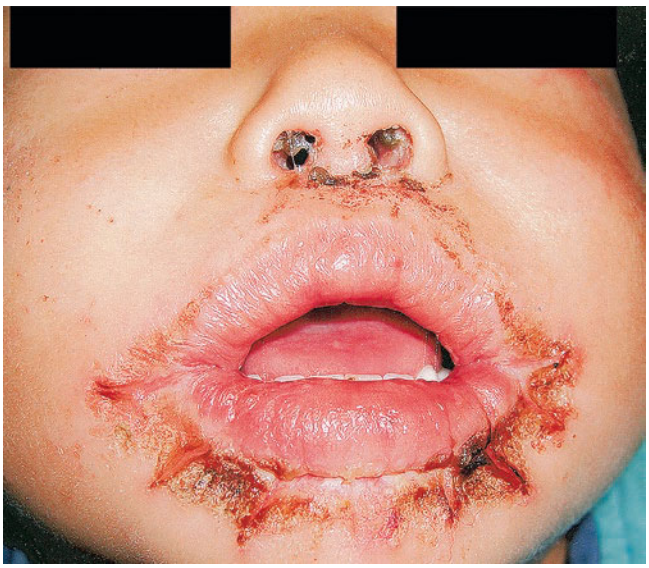


Fig. 26-23-3 Hyperkeratotic erythematous plaques around the mouth with radial fissures

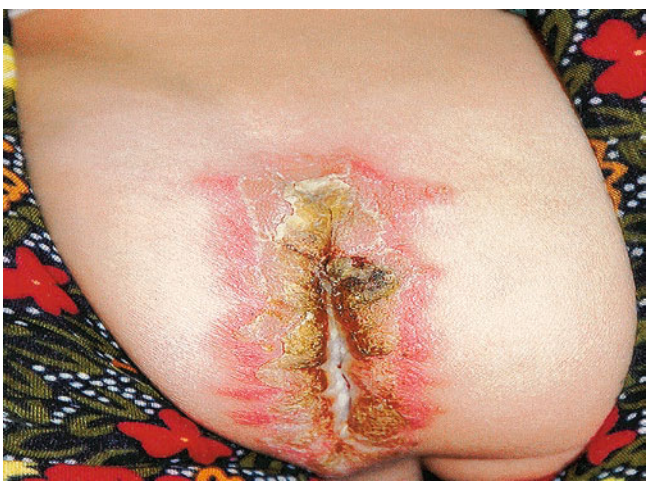


Fig. 26-23-4 Hyperkeratotic plaques with crusts around the sacrococcyx and anus

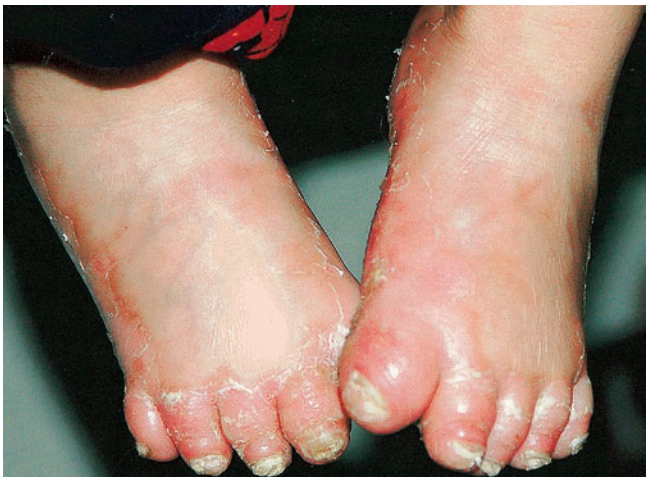


Fig. 26-23-5 Thick toenails of the feet with lateral groove

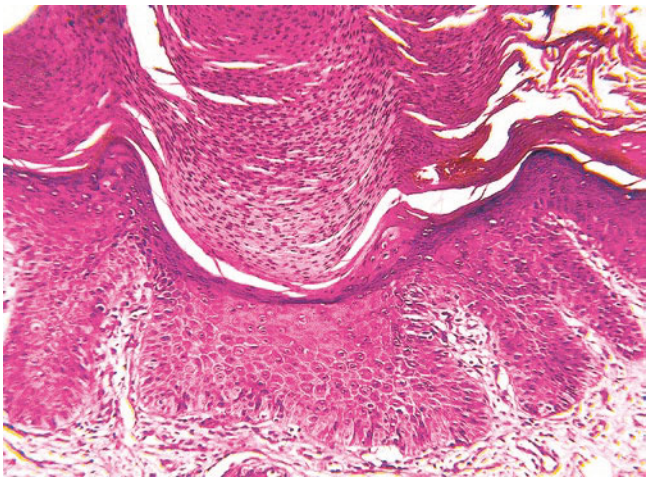


Fig. 26-23-6 Epidermal hyperkeratosis with parakeratosis and acanthosis was associated with a few lymphocytes infiltrated in the upper dermis (HE stain, ×100)

26.24 Nail-Patella Syndrome [60, 61]

- Nail-patella syndrome (NPS) is an autosomal dominant, pleiotropic disorder due to a mutated LMX1B gene (located on chromosome 9q34).
- NPS classically shows a characteristic tetrad of dysplasia of the nails, hypoplastic or absent patellae, iliac horns, and hypoplastic radial heads. Nephropathy, ocular disorders, hearing loss, and neuropathies are less likely to be present.
- Triangular lunulae of the nails, loss of skin crease on the distal interphalangeal joint, and iliac horns are considered to be pathognomonic findings of NPS.
- Nails may be absent, hypoplastic, discolored, fragile, spoon-shaped, or separated by a cleft. The abnormalities are the most severe on the ulnar side of the thumbs.
- Patellae abnormalities are responsible for the complaint of recurrent patellar subluxation, pain, and instability.

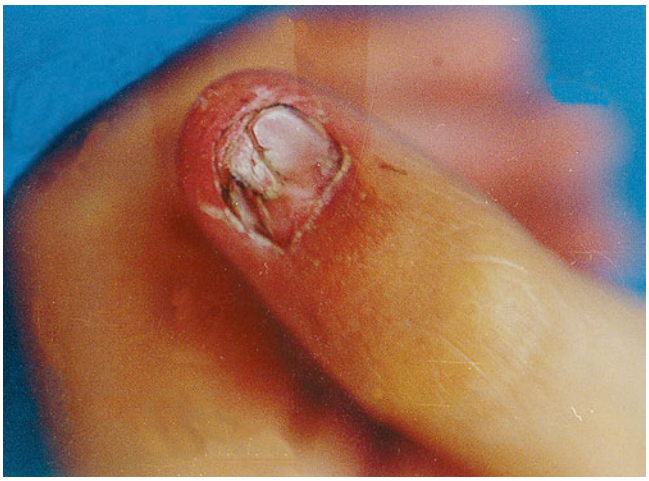


Fig. 26-24-1 Severe dysplasia on the ulnar border of the thumbnail, ridged longitudinally or horizontally, separated into two halves by a longitudinal cleft or ridge of the skin, triangular lunula

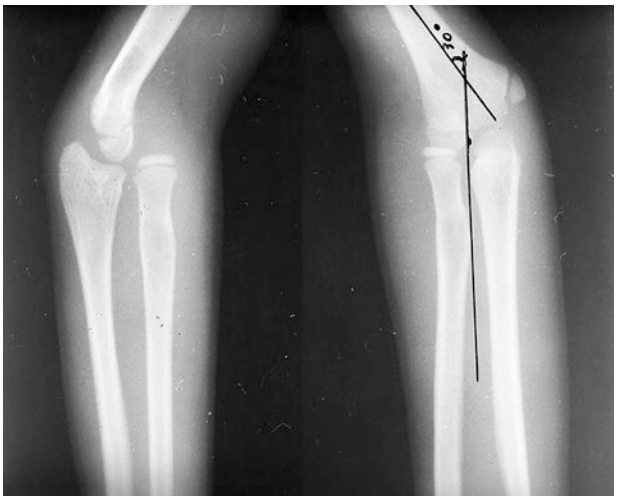


Fig. 26-24-2 X-ray of the elbow showed a dysplastic, dislocated radial head and hypoplasia of the left capitellum

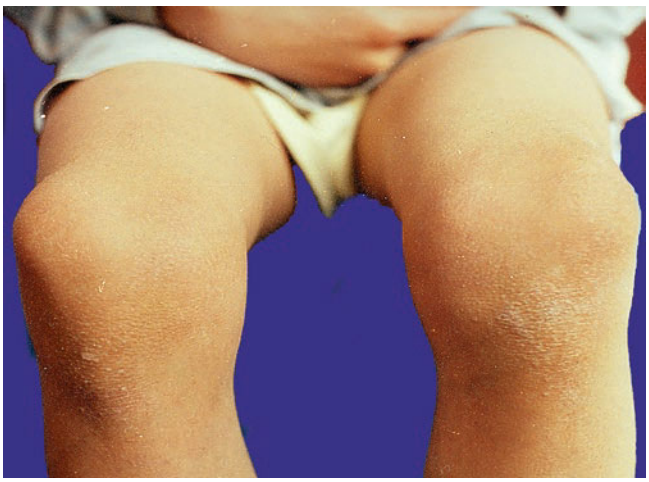


Fig. 26-24-3 Small patellae and subluxed patellae on knee flexion, flattened profile

26.25 Keratitis-Ichthyosis-Deafness Syndrome [62–64]

- Keratitis-ichthyosis-deafness syndrome (KIDS) is a congenital ectodermal syndrome due to germ line mutations in the GJB2 connexin gene.
- KIDS develops within the first 3 months of life and is characterized by a triad of ichthyosis, vascularizing keratitis, and hearing loss.
- Cutaneous alteration is not typical ichthyosis but rather erythrokeratoderma-like. It usually appears as an erythematous, verrucous plaque mainly distributed on the face, elbows, knees, and scalp.
- Early discrimination of this syndrome allows for prompt intervention for auditory and ocular complications.

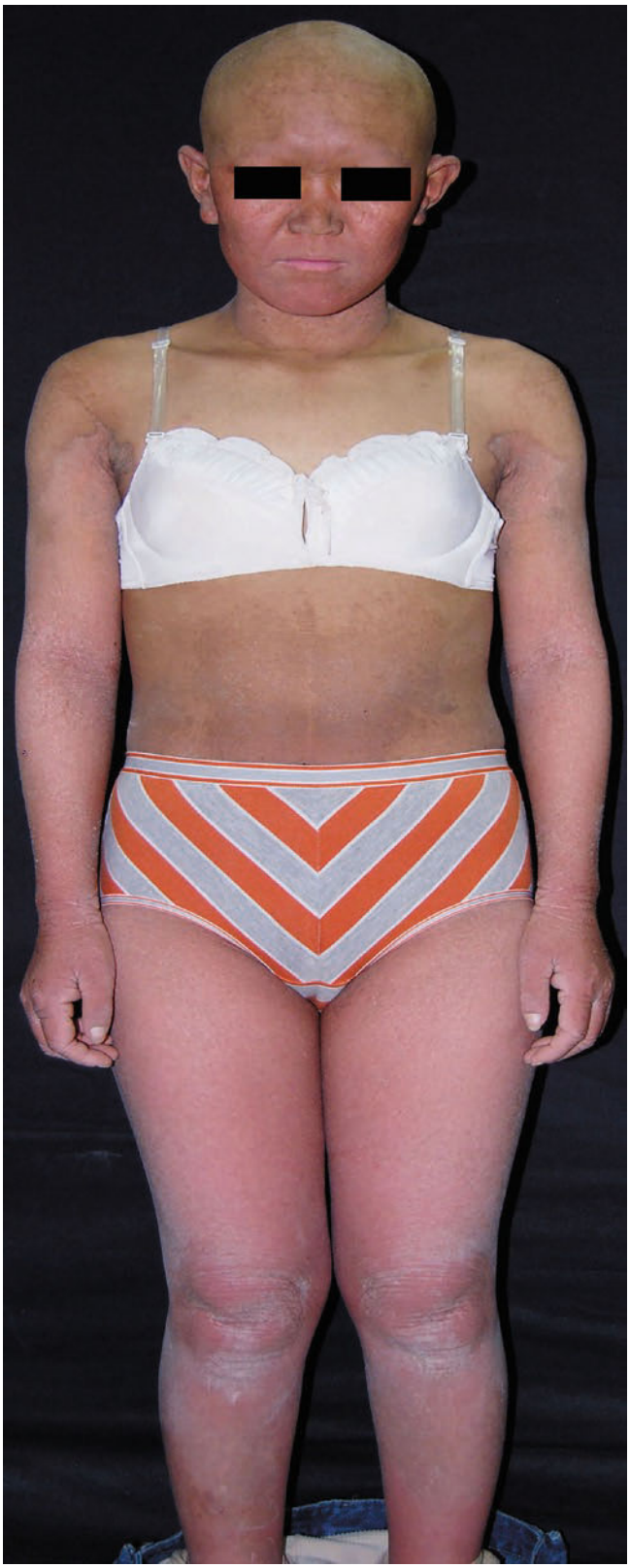
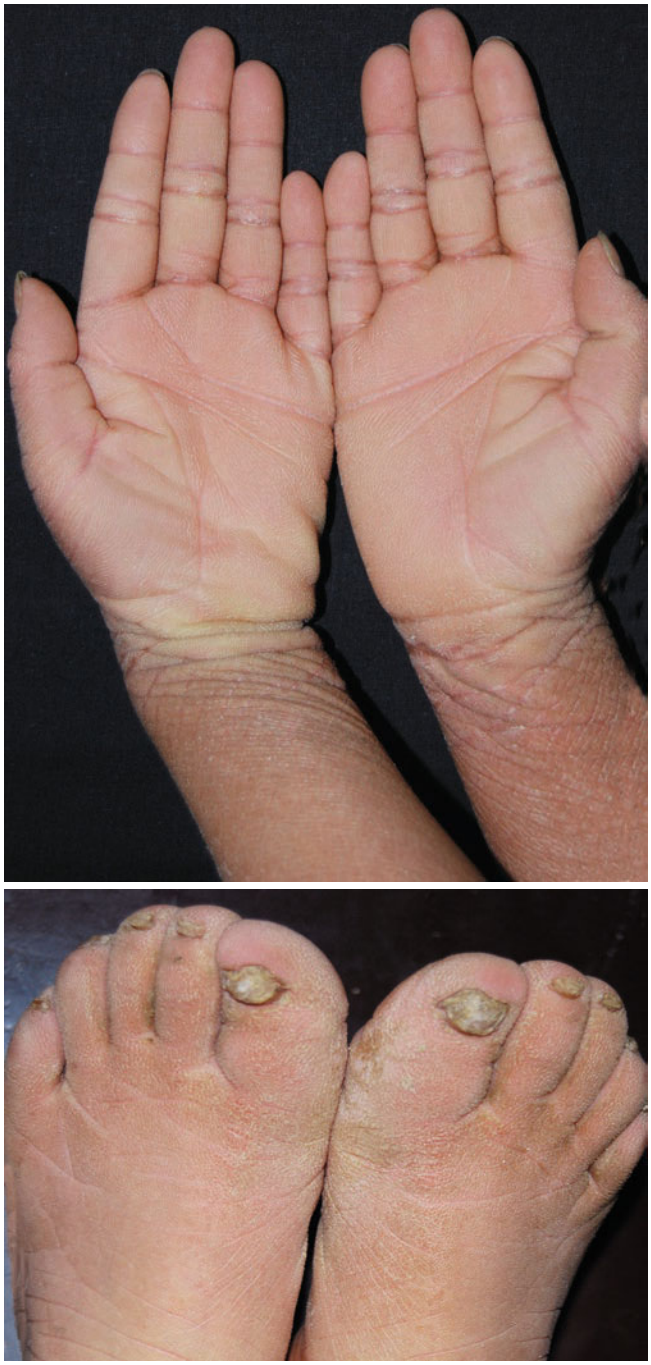


Fig. 26-25-1 Generalized dry skin; atrichia and anhydrosis; rough erythemas on the face, ears, and neck; hyperkeratosis and desquamation on armpits, inguinal grooves, and popliteal fossa



Figs. 26-25-2, 26-25-3 Grain or leather-like hyperkeratosis with acanthoid neoplasms on the fingers and toes; pachyonychia and whitening

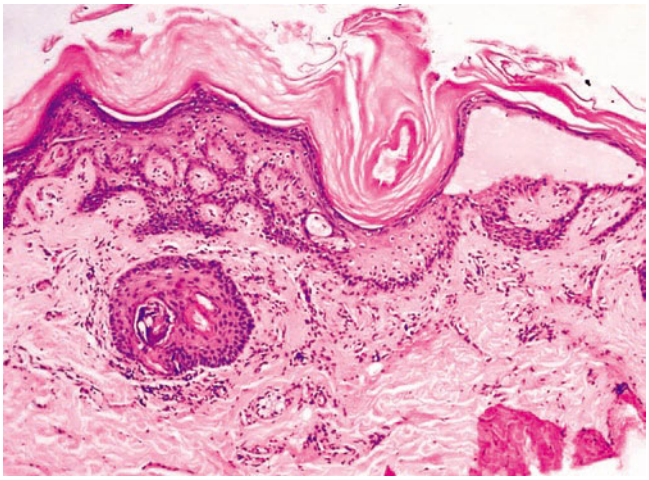


Fig. 26-25-4 Hyperkeratosis with parakeratosis and acanthosis; slight papillomatous hyperplasia and keratotic follicular plugs, mild lymphocyte, and histiocytic infiltration around the vessels in the upper dermis (HE stain, ×100)

26.26 Netherton Syndrome [65, 66]

- Netherton syndrome (NS) is a rare syndrome inherited in an autosomal recessive pattern. It mainly consists of ichthyosis linearis circumflexa, trichorrhexis invaginata, and atopic diathesis.
- Ichthyosis linearis circumflexa in NS is described as migratory, annular, and polycyclic erythema bordered by double-edged scales.
- Genetic studies found that the SPINK5 gene encodes the serine protease inhibitor LEKTI (lymphoepithelial Kazal-type-related inhibitor) and that mutated SPINK5 results in severe epidermal barrier impairment.

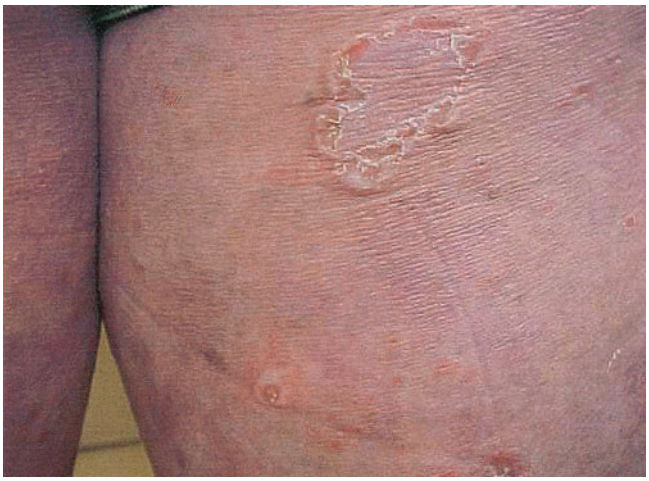


Fig. 26-26-1 Annular lesions on the left thing's inner side and small gray "double border" scaling around it

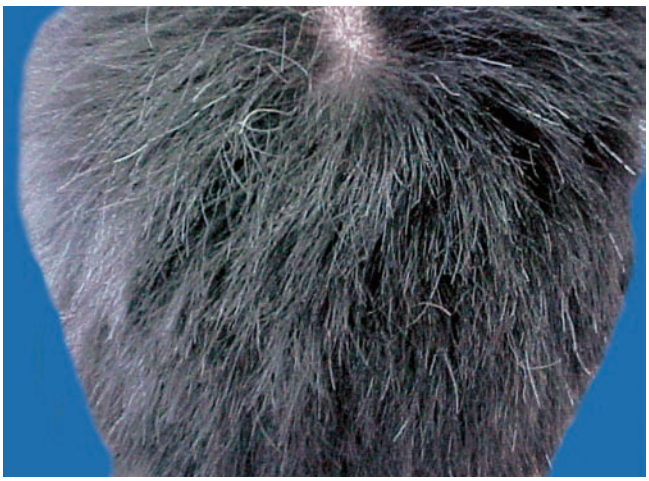


Fig. 26-26-2 Hairs were coarse, dry, and lusterless

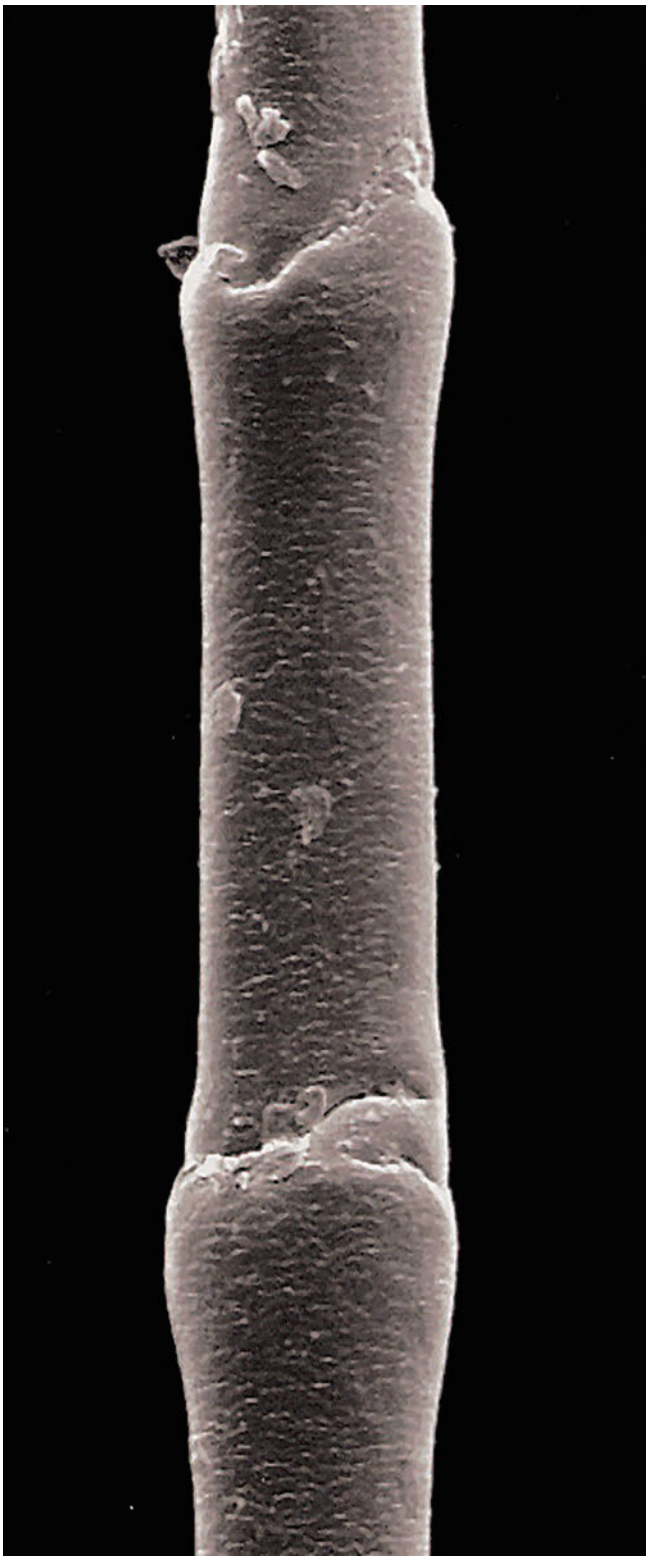


Fig. 26-26-3 Sick hair looked like "bamboo nodes," observed by scanning electron microscopy

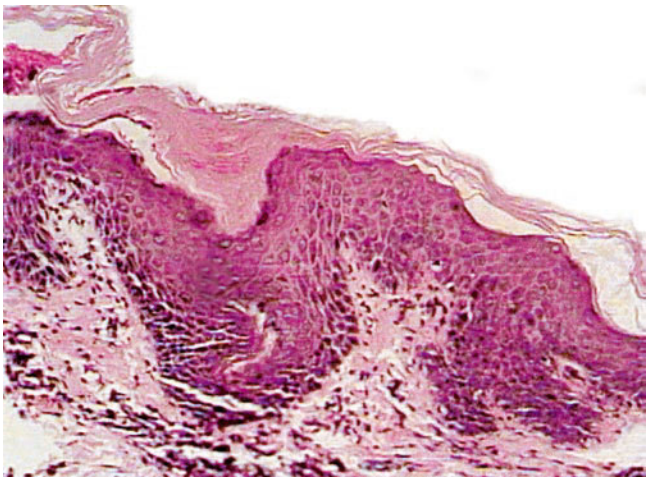


Fig. 26-26-4 Hyperkeratosis and local parakeratosis, intercellular edema (HE stain, ×160)

26.27 Bloom's Syndrome [67, 68]

- Genetically, Bloom's syndrome (BS) is inherited in an autosomal recessive mode. Patients with BS tend to have a higher risk for colorectal and cutaneous neoplasms than normal individuals.
- Clinical manifestations in BS primarily consist of growth retardation, dolichocephaly, malar hypoplasia, photosensitive malar telangiectasis, and immunodeficiency. Other associated abnormalities include diabetes mellitus, recurrent infections, syndactyly, congenital heart disease, and various ocular symptoms.
- BLM gene encodes a DNA repair enzyme homology to the RecQ helicases, and mutations of this gene give rise to an inordinate frequency of chromosomal disruption and rearrangement.
- Genomic instability in BS involves almost all gene loci, cells, and tissues, which reasonably explain the variable clinical features of multiple systems.
- Prenatal screening for BS is now available to many parents. Siblings of heterozygous carriers are at 25% risk for the phenotype of BS, whereas the risk goes up to 50% for a carrier.
- In addition to RTS, poikiloderma is a major change in Bloom's syndrome, Clericuzio-type poikiloderma with neutropenia, and xeroderma pigmentosum.
- The differential syndromes with photosensitivity include Kindler syndrome, dyskeratosis congenita, and xeroderma pigmentosum.
- Osteosarcoma accounts for nearly 30% of malignancies in RTS.

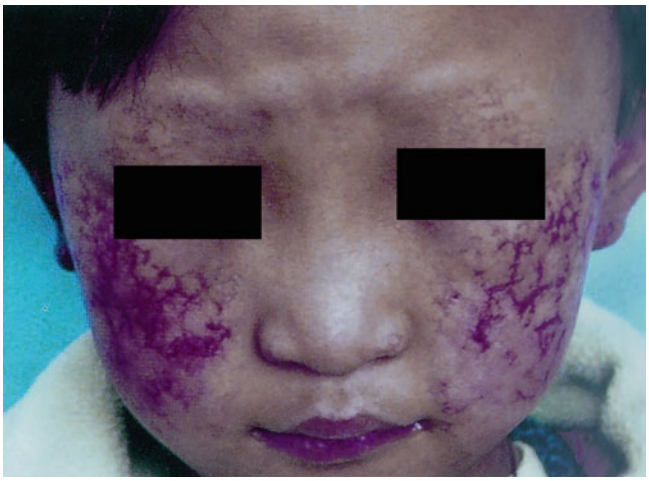


Fig. 26-27-1 Telangiectatic erythema in the butterfly area of the face

26.28 Tricho-rhino-phalangeal Syndrome [69–71]

- Tricho-rhino-phalangeal syndrome (TRPS) is an unusual genodermatosis with sparse hair, craniofacial malformations, and skeletal disorders.
- TRPS is a result of mutations in the TRPS1 gene, which maps to 8q24.12 and encodes a putative zinc finger transcription factor.
- TRPS can be classified into three groups, clinically and genetically.
- TRPS type I is characterized by slow-growing scalp hair, laterally sparse eyebrows, thin upper vermilion border, and elongated philtrum. Uncommon complications include craniofacial skeletal deformities, multiple cartilaginous exostoses, pear-shaped nose, brachydactyly, and protruding ears.
- In addition to classical features of type I TRPS, type II usually has mental retardation and remarkably short stature. Defects in the TRPS1 gene and the adjacent exostosin 1 gene are its main triggering factors.
- TRPS type III mainly differs from the other types in its feature of striking cone-shaped epiphysis and severe skeletal abnormalities that trouble in everyday life.

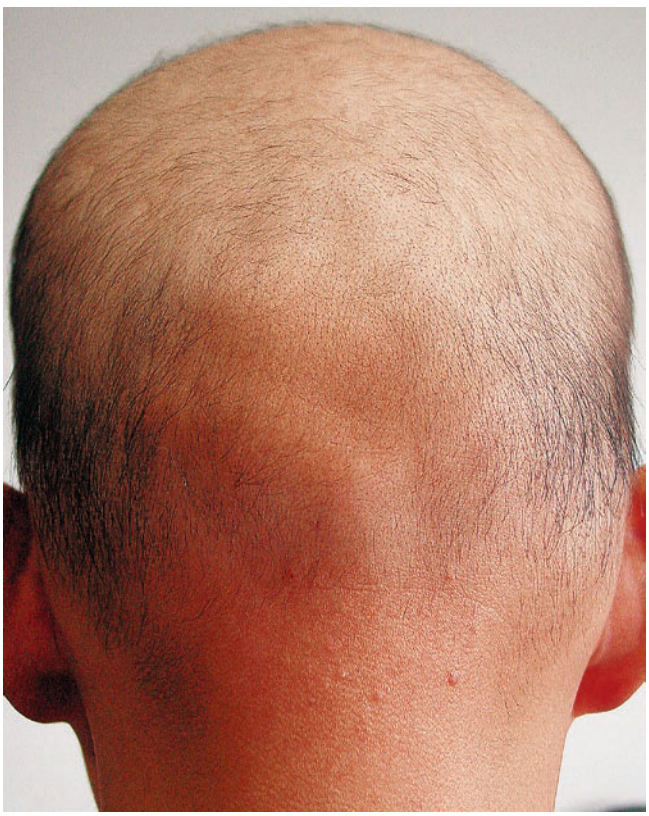


Fig. 26-28-1 Sparse and brittle hairs on the scalp, prominent feature on the temple

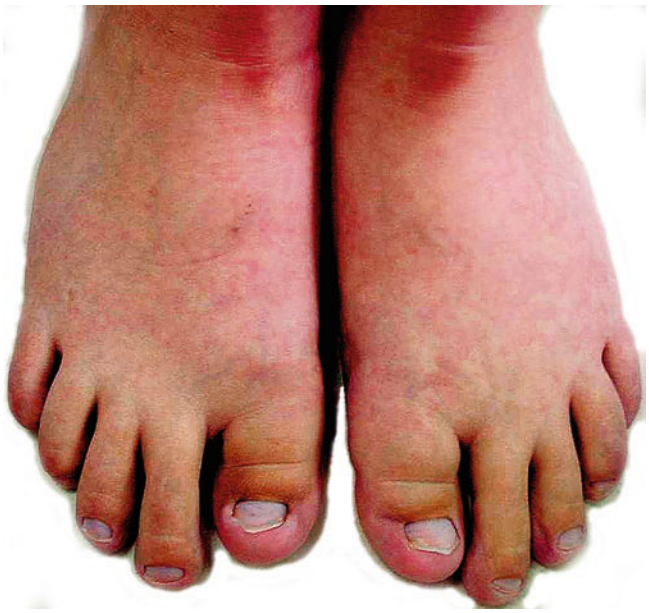


Fig. 26-28-2 Short thumb and thin toenails

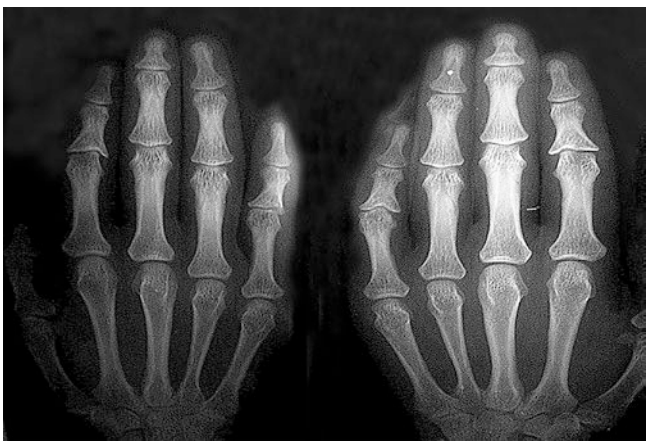


Fig. 26-28-3 Radiological features showed cone-shaped epiphyses

26.29 Proteus Syndrome [72, 73]

- Proteus syndrome (PS) is a rather complicated disease due to disproportionate and progressive overgrowth of various tissues.
- PS commonly affects the skin, skeleton system, adipose tissue, and brain.
- Epidermal nevus, malformations of the vessels, lipomas, and connective tissue nevus are four major cutaneous presentations in PS.
- According to Biesecker's proposition, a diagnosis of PS requires all three general criteria plus one criterion from category A, two criteria from category B, or three criteria from category C (explained in Table 26.1).
- The occurrence of PS is associated with somatic mosaicisms in the AKT1 gene.

Table 26.1 Diagnostic criteria for proteus syndrome

Major	*Sporadic occurrence *Mosaic distribution of lesions *Progressive course	
Minor	Category A	Cerebriform connective tissue nevus
	Category B	Epidermal nevus *Asymmetric disproportionate overgrowth (one or more) *Tumors (parotid monomorphic adenomas or bilateral ovarian cystadenomas)
	Category C	Dysregulated adipose tissue *Vascular malformations *Lung bullae *Facial phenotype (dolichocephaly, long face, downward slanting palpebral fissures and/or minor ptosis, depressed nasal bridge, wide or anteverted nares, open mouth at rest)

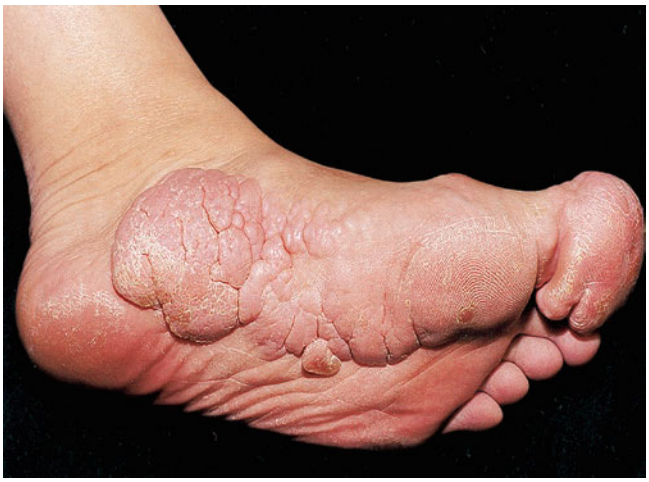


Fig. 26-29-1 Cerebriform hyperplastic mass and nodules on the left sole

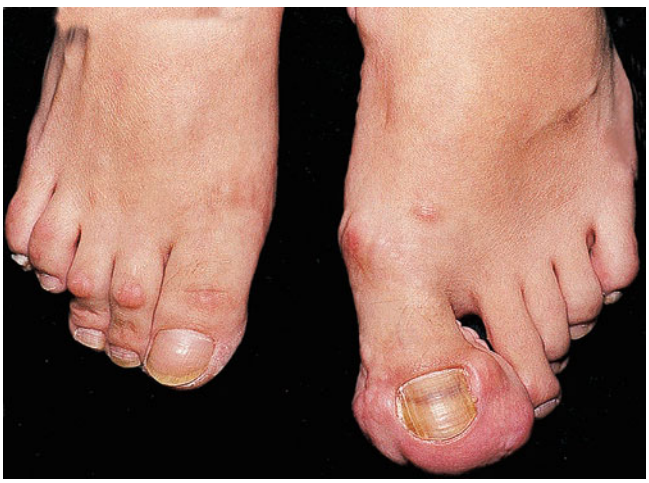


Fig. 26-29-2 Macrodactyly of the left thumb

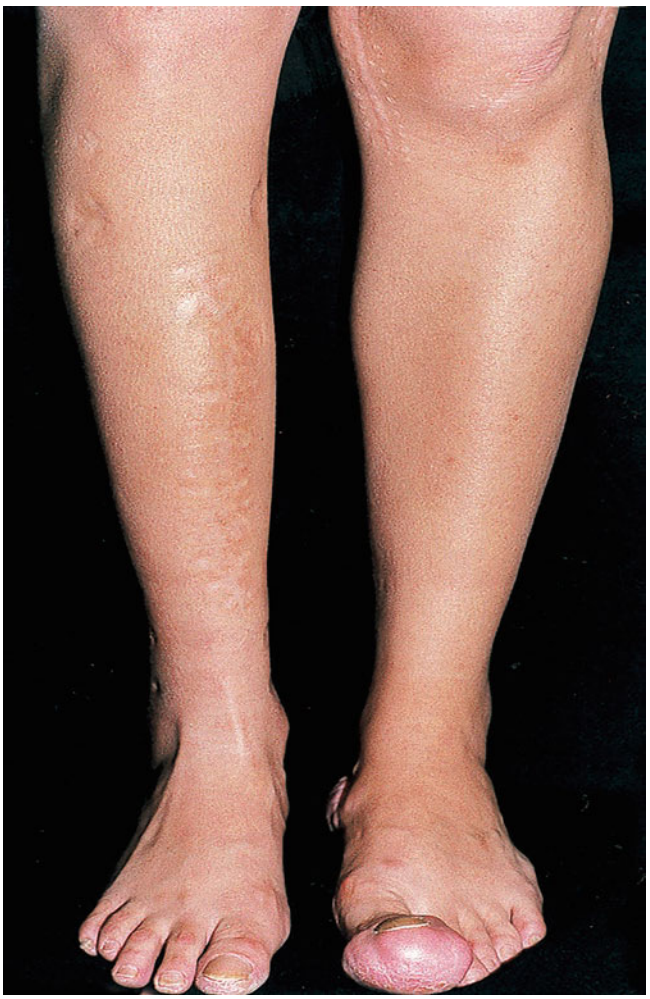


Fig. 26-29-3 Hemihypertrophy of the left lower extremity

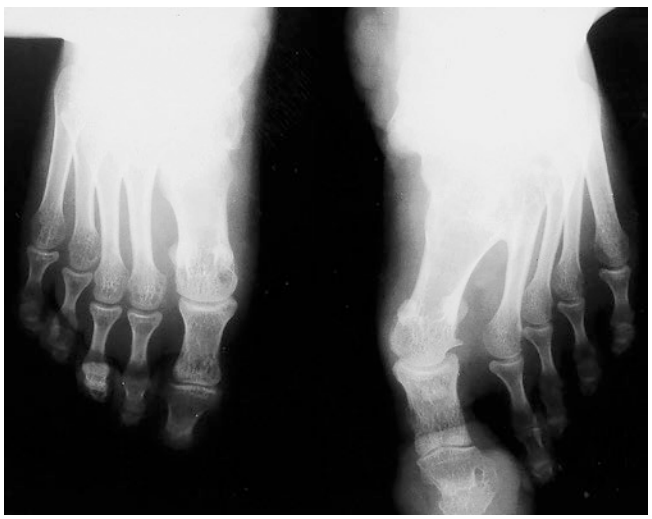


Fig. 26-29-4 Roentgenogram demonstrated exostosis on the lateral side of the left first metatarsal bone

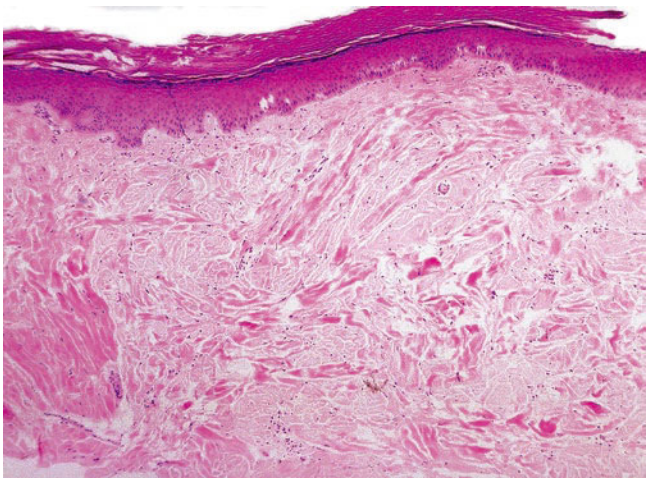
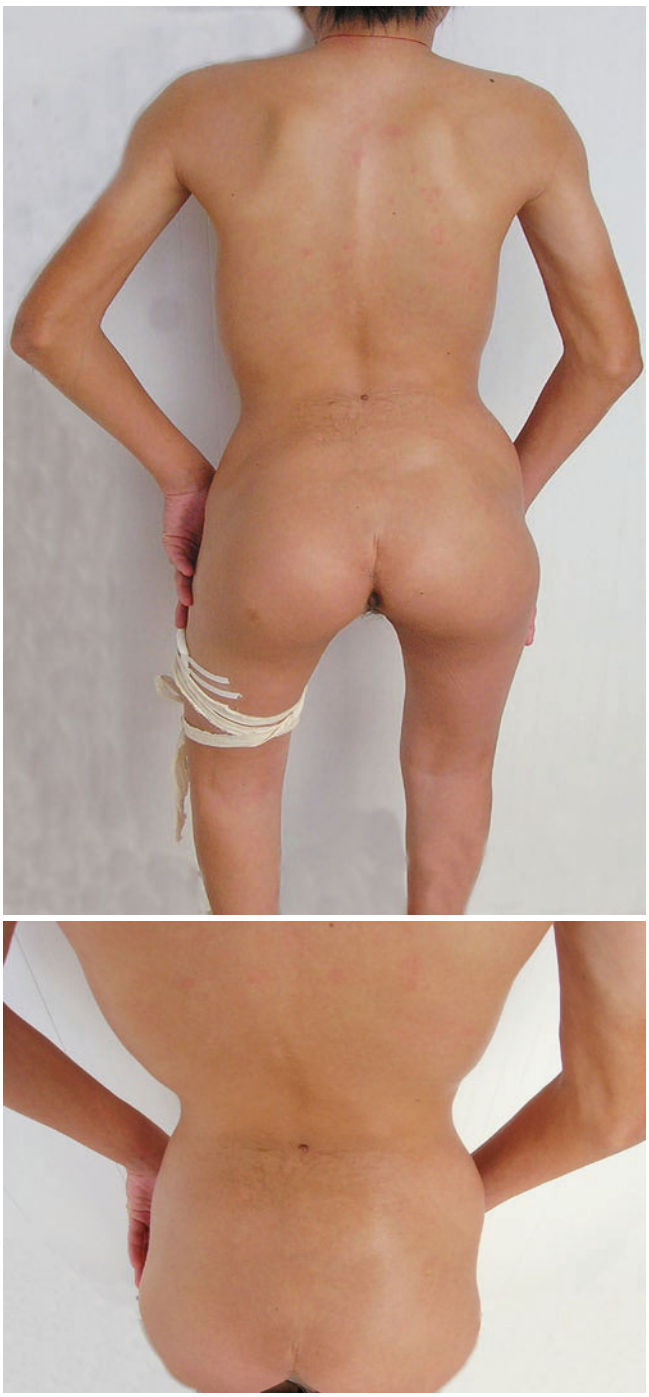


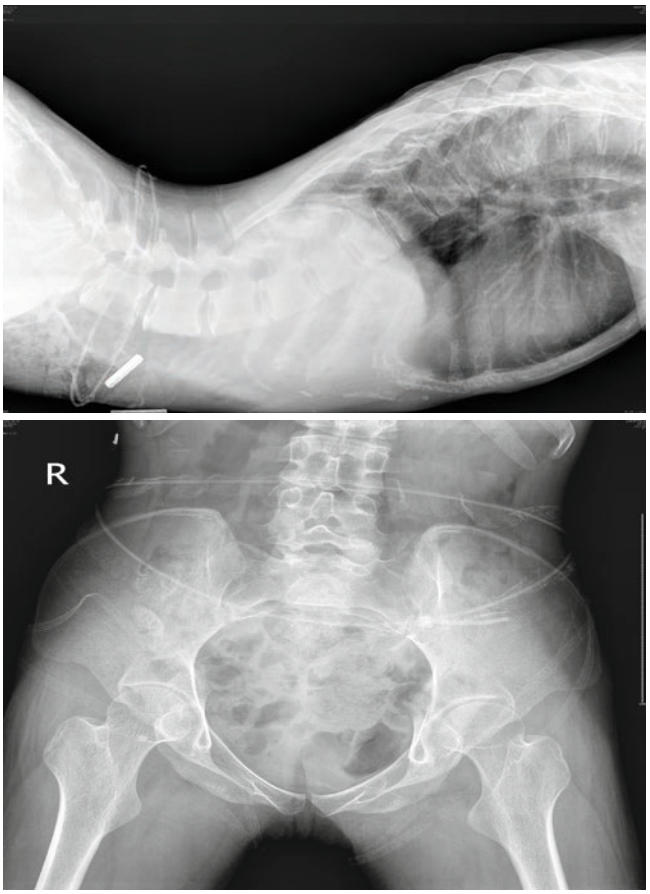
Fig. 26-29-5 Hyperkeratosis of the epidermis and dense and thick collagen fibers in the dermis (HE stain, ×40)

26.30 Stiff Skin Syndrome [74, 75]

- Stiff skin syndrome (SSS) is a generalized, noninflammatory fascial disorder without involvement of the viscera, muscle, vessels, or immunologic system.
- SSS is slowly progressive and nonfatal with a clinical triad of woody cutaneous induration of the skin, mild hypertrichosis, and limitations in joint mobility during infancy or early childhood.
- Light microscopy of the lesions shows thickened, horizontally oriented collagen bundles, fibroblast proliferation, absence of inflammation, increased fibroblast cellularity, and fascial thickening.
- Limitations in both joint mobility and respiratory capacity occur as a consequence of skin restriction, which is quite different from scleroderma.
- Contractures, a tiptoe gait, restrictive pulmonary changes, and growth retardation constitute the main extracutaneous features of SSS.



Figs. 26-30-1, 26-30-2 Limitation of large joints (shoulder, elbow, hip, and knee), mobility, and genu varum; stony hard skin on the neck, trunk, upper limbs, thighs, and buttocks. Hirsutism on the lumbar area



Figs. 26-30-3, 26-30-4 X-ray image: Abnormal physiological curvature of the thoracic and lumbar spine, ape-like pelvis

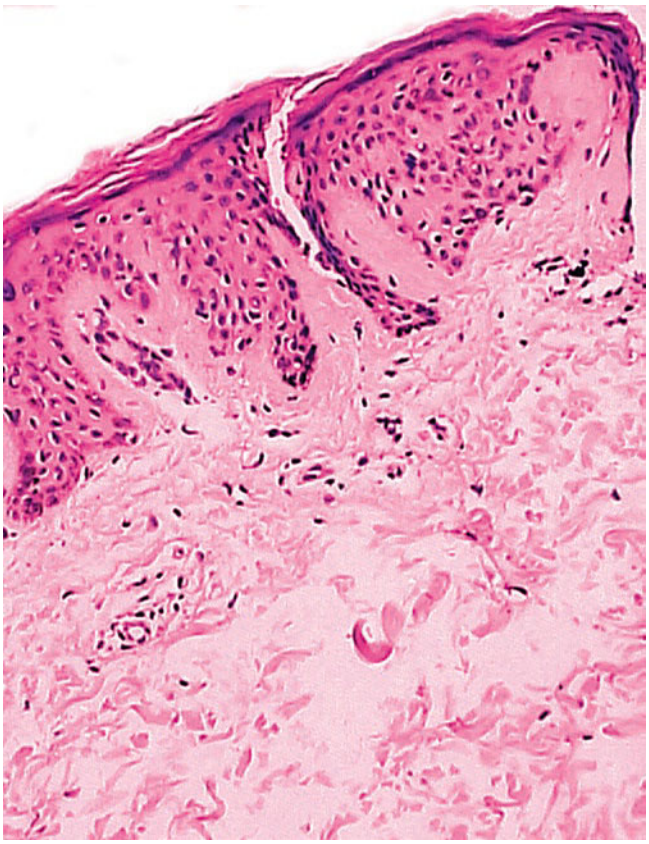


Fig. 26-30-5 Normal epidermal and thickened dermis with increased number of fibroblasts and well-preserved appendages

26.31 Rombo Syndrome [76, 77]

- Clinical manifestations of Rombo syndrome (RS) are comprised of vermiculate atrophoderma, milia, hypotrichosis, trichoepithelioma, basal cell carcinoma (BCC), and a peculiar cyanotic redness of the extremities.
- RS has a grainy lesion, and vermiculate atrophoderma is predominantly seen on the elbows and cheeks.
- Pathological features of RS consist of thickened elastic fibers, which aggregate or clump throughout the dermis.

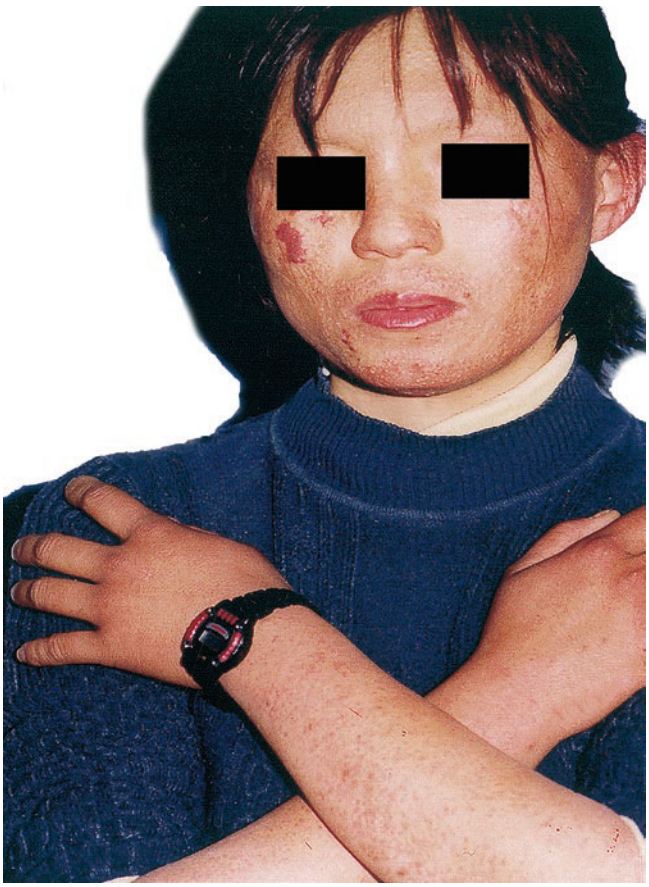


Fig. 26-31-1 Multiple whitish macules, numerous milia, atrophoderma vermiculatum, loss of lashes of the upper and lower lids; only several eyebrow hairs very thinly implanted on the interior sides and ectropion of both upper and lower eyelids, especially the lower ones; erythema and telangiectasias on the face and hands

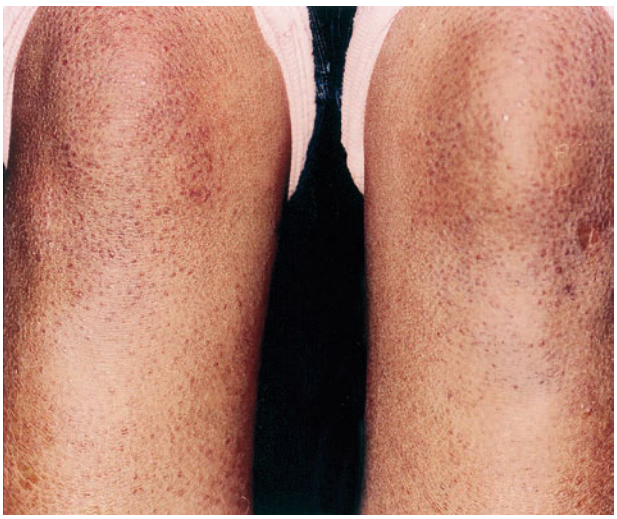


Fig. 26-31-2 Red follicular papules on the knees and fine scales on the calves

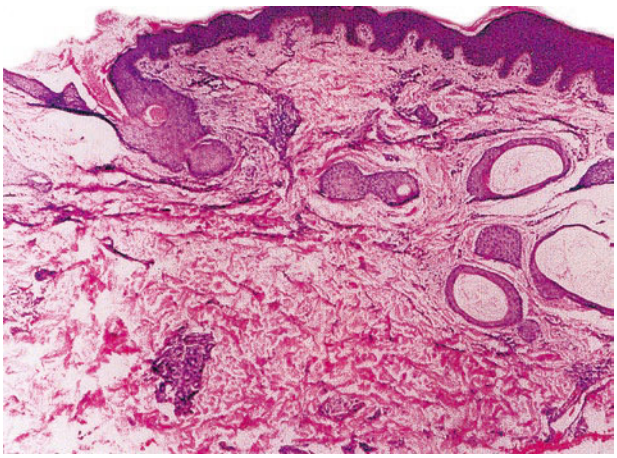


Fig. 26-31-3 Three cystic structures located in the upper and middle dermis, covered on the inside with normal-appearing squamous epithelium. Inside the cysts, multiple vellus hairs and horny material were seen. Some proliferation and dilation of small vessels was noted, accompanied by a lymphocytic infiltration (HE stain, ×40)

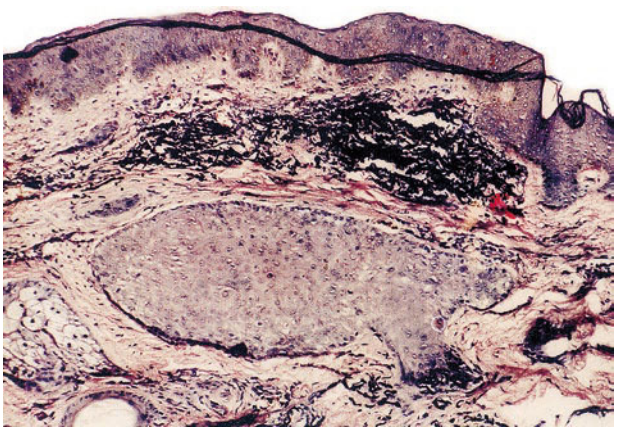


Fig. 26-31-4 Highly irregular distribution of elastin, with clumping in some areas, whereas other skin areas appeared to have no elastin (Verhoeff stain, ×40)

26.32 Prune-Belly Syndrome [78]

- Abdominal muscular hypoplasia, ectasia of the urinary tract, and cryptorchidism are accepted as the clinical manifestations of prune-belly syndrome (PBS).
- A pathognomonic cutaneous feature of PBS is the slack, wrinkled skin of the abdomen of the newborn, which shows a "potbelly" appearance during adulthood.
- Abdominal musculature hypoplasia is mainly responsible for delayed sitting and walking, pulmonary infections, and chronic constipation in PBS.
- Megacystis, dilated ureters, and hydronephrosis constitute the urinary tract abnormalities associated with PBS.

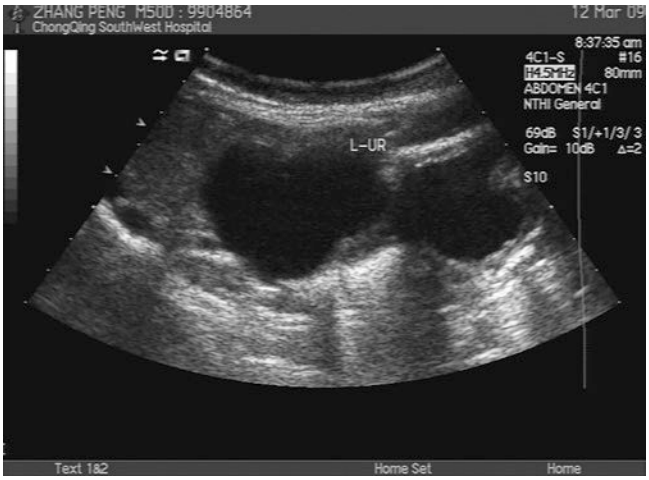


Fig. 26-32-2 Abdominal ultrasound: hydronephrosis in both kidneys, large left ureter, right renal sinus, and bladder separation; thickened bladder wall with calcification

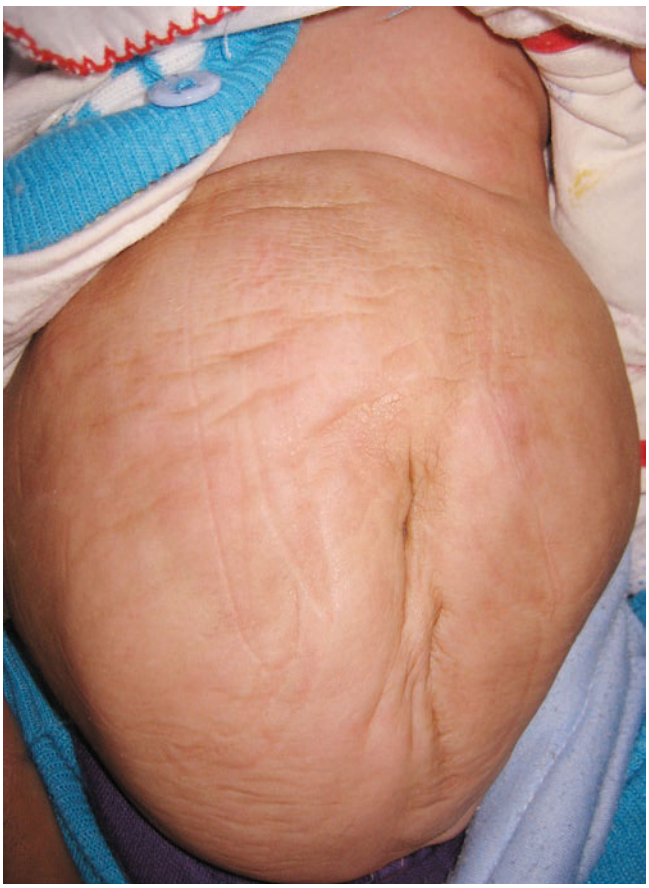


Fig. 26-32-1 Wrinkly folds of skin covering the abdomen

26.33 Infantile Digital Fibromatosis [79, 80]

- Infantile digital fibromatosis (IDF) is a rare neoplasm that most occurs in infancy.
- The lesions are characterized by single or multiple, firms, red, and smooth nodules. Ulceration may occur. Spontaneous regression has been noted.
- Most of the lesions are distributed on the dorsum or lateral area of the distal phalanges. Histopathology: Proliferating myofibroblasts and collagen bundles are present in the dermis. Eosinophilic inclusions exist in many fibroblasts.

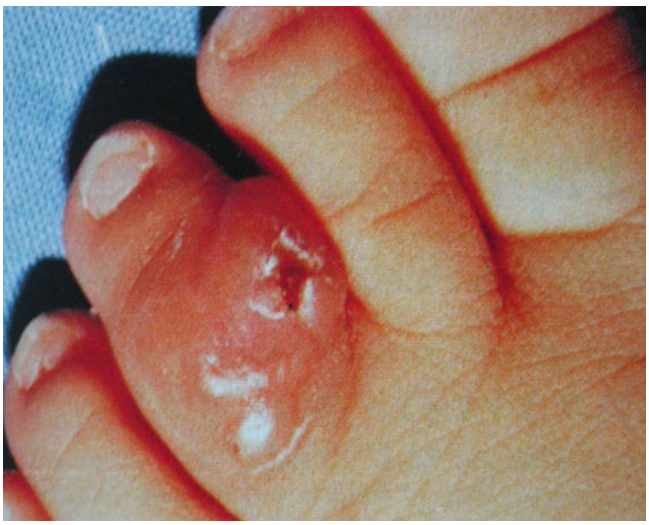


Fig. 26-33-1 A smooth, hard, pink, non-tender nodule on the left third toe (Reproduced with the permission from [81])

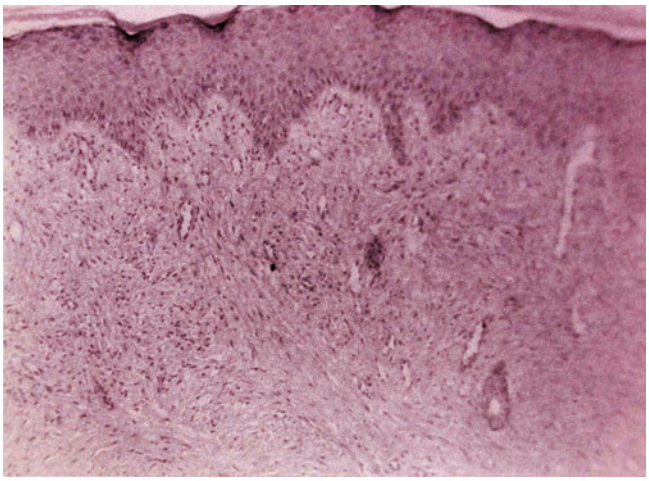


Fig. 26-33-2 A large proliferation of spindle-shaped fibroblasts in the upper dermis (HE stain, ×60) (Reproduced with the permission from [81])

26.34 Juvenile Hyaline Fibromatosis [82, 83]

- Juvenile hyaline fibromatosis (JHF) appears as an autosomal recessive disease whose culprit gene maps to chromosome 4 at 4q21.
- Typical diagnostic criteria of JHF are hyaline subcutaneous fibroma, joint contractures, hypertrophy of gingiva, osteolysis, and osteoporosis.
- Histological examination of JHF's lesion revealed an abundant amorphous hyaline matrix and many fibroblast-like cells showing granular cytoplasm. Production of collagen type I is increased, and production of collagen type III is reduced.
- The mutated CMG2 gene in JFH results in the leakage of hyaline from the basilar layer and aberrant accumulation in the dermis.
- Infantile systemic hyalinosis (ISH) shares some similarities with JHF, including skin lesions, gingival hypertrophy, and joint contractures. ISH, however, develops obstinate diarrhea and invariably leads to death due to an accumulation of hyaline material throughout the gastrointestinal system, lung, and other tissues.

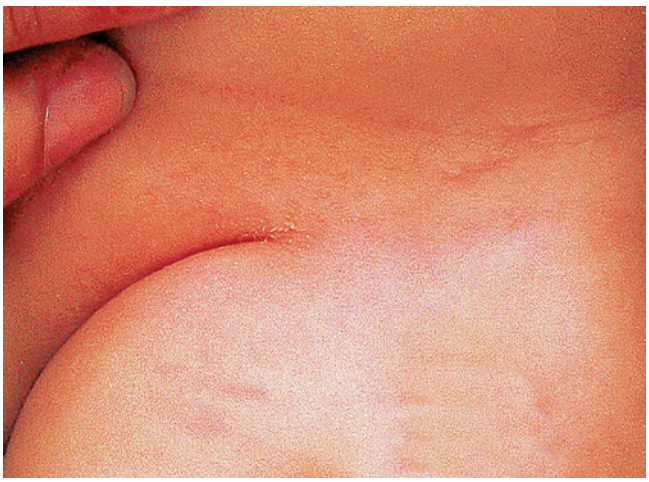


Fig. 26-34-1 Fusiform subcutaneous nodules on the right groin

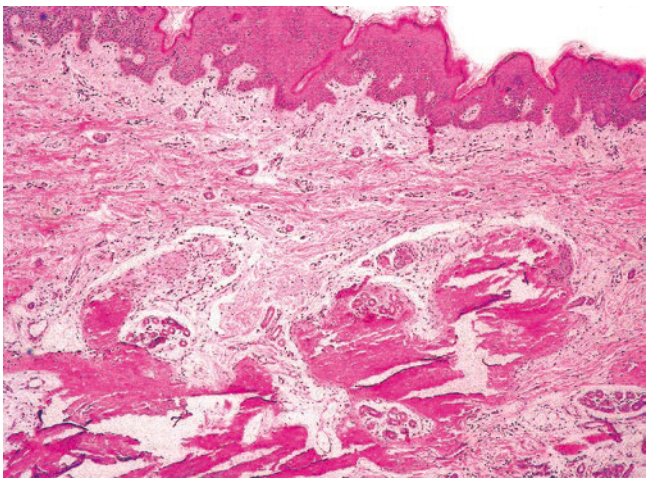


Fig. 26-34-2 Tumor cells embedded in the eosinophilic hyaline ground substance with chondroid appearance in the dermis

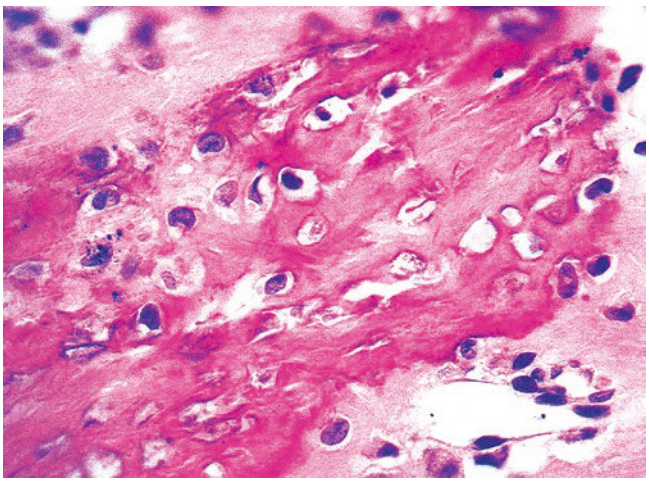


Fig. 26-34-3 PAS positive in tumor stroma (PAS stain, ×100)

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Part X

Neoplasms of the Skin

Tumors of the Skin

27

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Abstract

Skin tumor is the most intriguing topic for the clinicians. This chapter covers a wide range of issues and provides with informative clues and tips associated with clinical features and pathological presentations and keeps pace with the latest development in molecular biology and immunohistochemistry to assist the readers in the establishment of accurate diagnosis. These following disorders are elaborately selected and arranged from a histopathological perspective.

(1) Tumors of the epidermis include epidermal nevus, unilateral epidermal nevus, epidermal nevus syndrome, seborrheic keratosis, seborrheic keratosis and pityrosporum ovale, large cell acanthoma, giant cutaneous horn, multiple Bowen's disease, extramammary Paget's disease, eruptive keratoacanthoma, superficial basal cell carcinoma, fibroepithelioma of Pinkus, Marjolin's ulcer of squamous cell carcinoma secondary to radiation, cutaneous clear cell squamous cell carcinoma, and milia en plaque.

(2) The list of cutaneous appendage proliferations and tumors present cases with eruptive vellus hair cysts, nevus comedonicus, dilated pore, inverted follicular keratosis, infundibulocystic basal cell carcinoma, trichofolliculoma, trichoepithelioma, bullous pilomatricoma, areolar sebaceous hyperplasia, nevus sebaceous with apocrine cystadenoma, linear nevus sebaceous syndrome, apocrine hidrocystoma, eccrine angiomatous hamartoma, syringocystadenoma papilliferum, eruptive milium-like syringoma, segmental multiple eccrine spiradenomas, clear cell hidradenoma, malignant eccrine poroma, or microcystic adnexal carcinoma.

(3) The category of cutaneous soft tissue proliferations and neoplasms introduces acquired digital fibrokeratoma, epithelioid cell histiocytoma, multiple eruptive dermatofibromas, intradermal nodular fasciitis, dermatofibrosarcoma protuberan, epithelioid sarcoma, superficial angiomyxoma, multicentric reticulohistiocytosis, Letterer-Siwe disease, cutaneous Rosai-Dorfman disease, phakomatosis pigmentovascularis, angiokeratoma corporis diffusum, angiokeratoma of Fordyce, angioma serpiginosum, reactive angioendotheliomatosis, epithelioid hemangioma, tufted angioma, verrucous hemangioma, targetoid hemosiderotic hemangioma, microvenular hemangioma, glomus tumor, spindle cell hemangioma, Kaposiform hemangioendothelioma, classic Kaposi's sarcoma, cutaneous angiosarcoma, acquired progressive lymphangioma, lymphangioma, nevus lipomatosus superficialis, encephalocraniocutaneous lipomatosis, madelung disease, multiple leiomyoma, cutaneous leiomyosarcoma, subungual exostosis, and cutaneous endometriosis.

(4) Palisaded encapsulated neuroma, schwannoma, and cutaneous Merkel cell carcinoma belong to neural tumors.

(5) Melanocytic nevi and neoplasms include agminated Spitz nevus, subungual melanoma, fatal leptomeningeal melanoma in neurocutaneous melanosis, as well as rare forms of cutaneous melanoma.

(6) Cutaneous lymphoid proliferations and leukemic infiltration consist of cutaneous pseudolymphoma, Jessner's lymphocytic infiltration of the skin Jessner, Ketron-Goodman disease, mycosis fungoides, erythrodermic cutaneous T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, hydroa vacciniforme-like lymphoma, extranodal NK-/T-cell lymphoma, primary cutaneous B-cell lymphoma, maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis, mastocytoma, cutaneous plasmacytoma, polycythemia vera, leukemia cutis, and so on.

(7) Cutaneous metastases include cutaneous metastasis for lung cancer, cutaneous metastasis of gastrointestinal malignancy, Sister Mary Joseph's nodule, and carcinoma en cuirasse.

27.1 Epidermal Nevus [1–3]

- The clinical features of epidermal nevus (DE) are quite variable from forms of the localized, the generalized, and the inflammatory.
- Hyperkeratosis, hypergranulosis, and papillomatosis with elongation of the rete ridges are common pathological traits found in DE. Uncommonly it may display epidermal changes such as acrokeratosis-like, seborrheic keratosis-like, psoriasiform, verrucoid, porokeratosis-like, acantholytic dyskeratotic type (Darier-like), acanthosis nigricans-like, and nevus comedonicus.
- Acantholytic dyskeratotic epidermal nevus (ADEN) used to describe a rare variant of the DE presenting as a linear keratotic lesion with additional acantholytic and dyskeratotic signs.
- ADEN should be differentiated from other dermatoses with similar acantholytic and dyskeratotic changes including Darier's disease, warty dyskeratoma, transient acantholytic dermatosis, and Hailey-Hailey disease.
- Both ADEN and linear Darier's disease similarly have a linear configuration and acantholytic dyskeratotic changes under the microscope; however, the former lacks of ATP2A2 gene mutation.

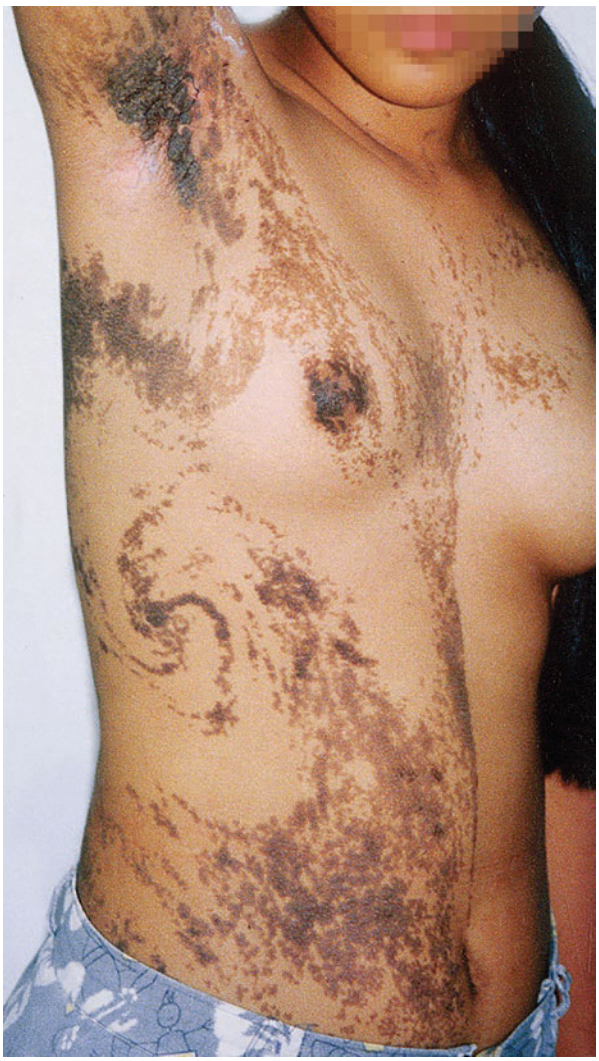


Fig. 27-1-1 Brown papillomatous papules arrangement in sheets and helixes on the axilla and trunk

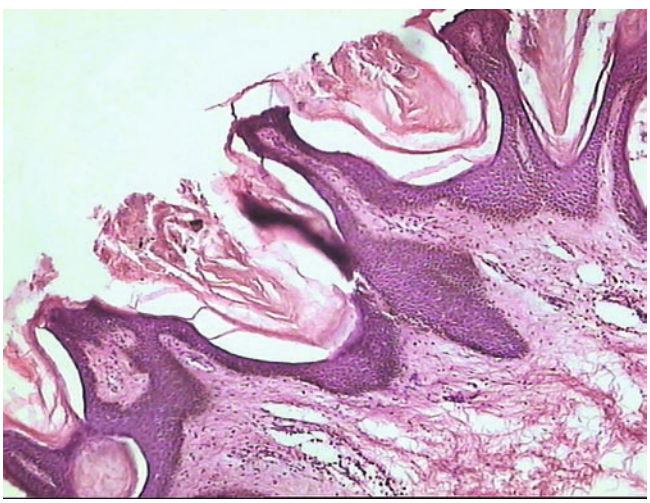


Fig. 27-1-2 Hyperkeratosis, papillomatosis, and acanthosis with elongation of the rete ridges (HE stain, ×400)

27.2 Unilateral Epidermal Nevus [4, 5]

- Epidermal nevus (EN) is thought to represent a form of cutaneous mosaicism and is called verrucous epidermal nevus, inflammatory linear verrucous epidermal nevus, or linear epidermal nevus.
- EN arises as brown, warty papules or plaques that are typically distributed in a linear or whorled fashion.
- EN may aggregate to be localized, unilateral, or generalized to spread across the whole skin.
- EN is a congenital, benign form of mosaicism of keratinocytes, hair follicles, sebaceous glands, smooth muscle cells, apocrine glands, and eccrine glands.

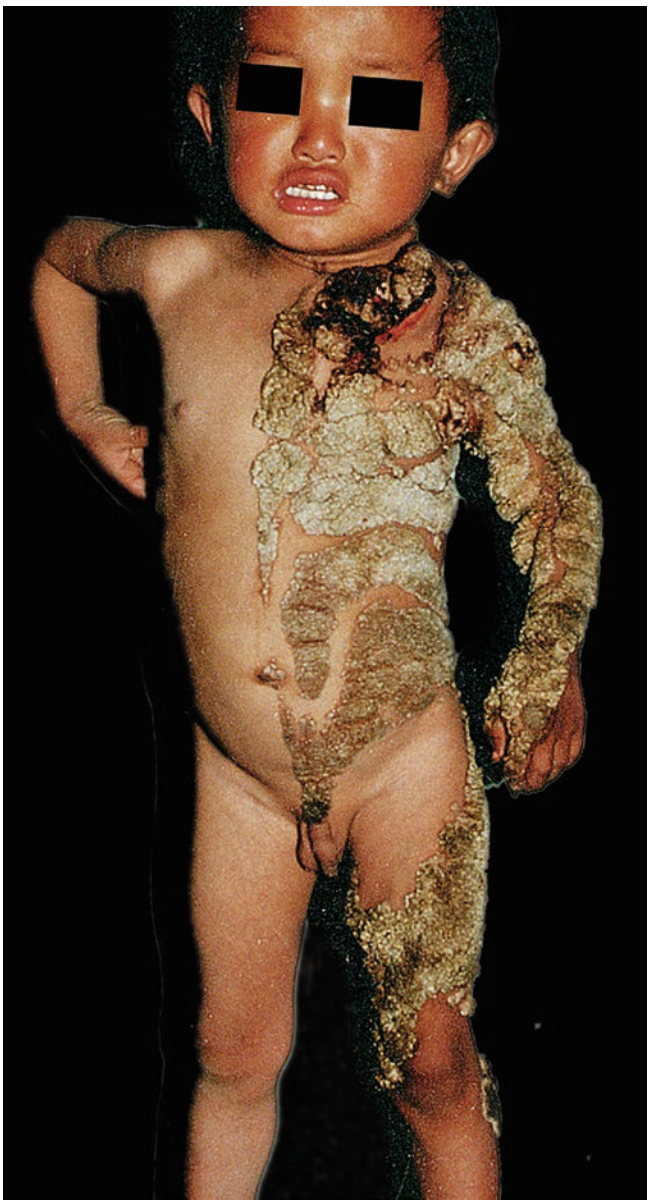


Fig. 27-2-1 Verrucous and hyperkeratotic plaques arranged linearly on the left neck, shoulder, trunk, and upper limb

27.3 Epidermal Nevus Syndrome [6–8]

- Epidermal nevus syndrome (ENS) presents with epidermal nevus with concomitant skeletal defects and ocular anomalies, including lipodermoid of the conjunctiva or coloboma and neurologic defects, such as hemimegalencephaly with contralateral motor disease.
- ENS is delineated into nine different syndromes. These are Proteus syndrome, CHILD syndrome, Schimmelpenning syndrome, angora hair nevus syndrome, phakomatosis pigmentokeratotica, FGFR3 epidermal nevus syndrome, Becker's nevus, type 2 segmental Cowden disease, and nevus comedonicus syndromes.
- In addition to epidermal nevus, cerebriform connective tissue nevi on the soles are pathognomonic for Proteus syndrome. Additional anomalies include asymmetrical macrodactyly, facial dysmorphism, disproportionate skull, cystic pulmonary lesions, lipomas, mental deficiency, brain malformations, lymphangiomas, telangiectasis, and ovarian cystadenoma.
- Epidermal nevus in Proteus syndrome tends to be soft, velvety, and rather flat compared to the classical type.
- ENS is also associated with other disorders, including SCALP syndrome, Bafverstedt syndrome, nevus trichilemmocysticus syndrome, Gobello syndrome, NEVADA syndrome, didymosis aplasticosebacea, and CLOVE syndrome.

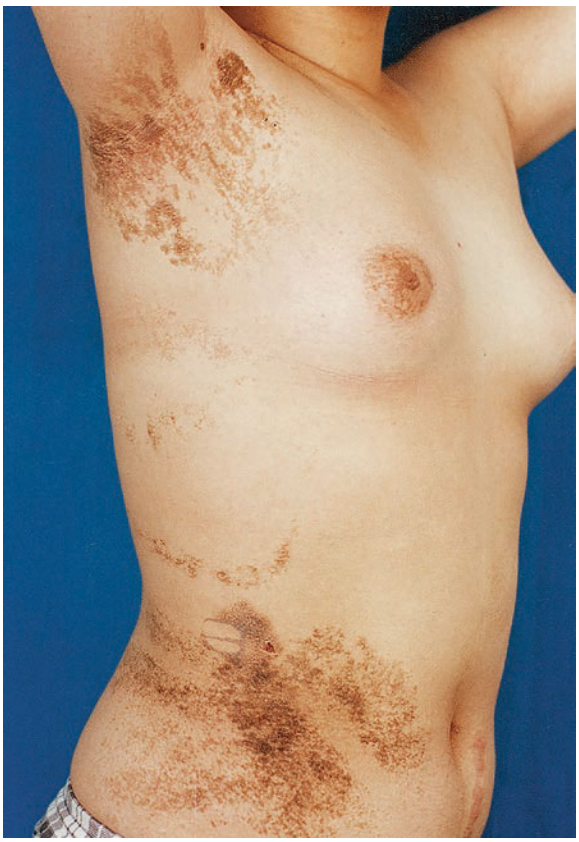


Fig. 27-3-1 Verrucous plaques on the right axilla, chest, periareola, and abdomen

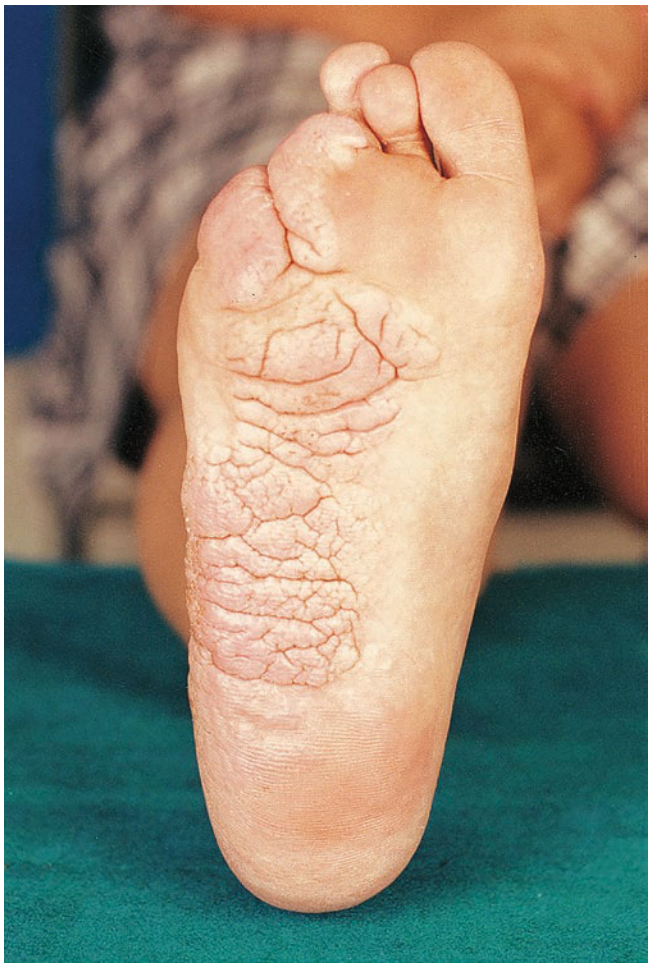


Fig. 27-3-2 Toe skin was thickened, with the third toe macrodactyly and the fourth and fifth toes shortened

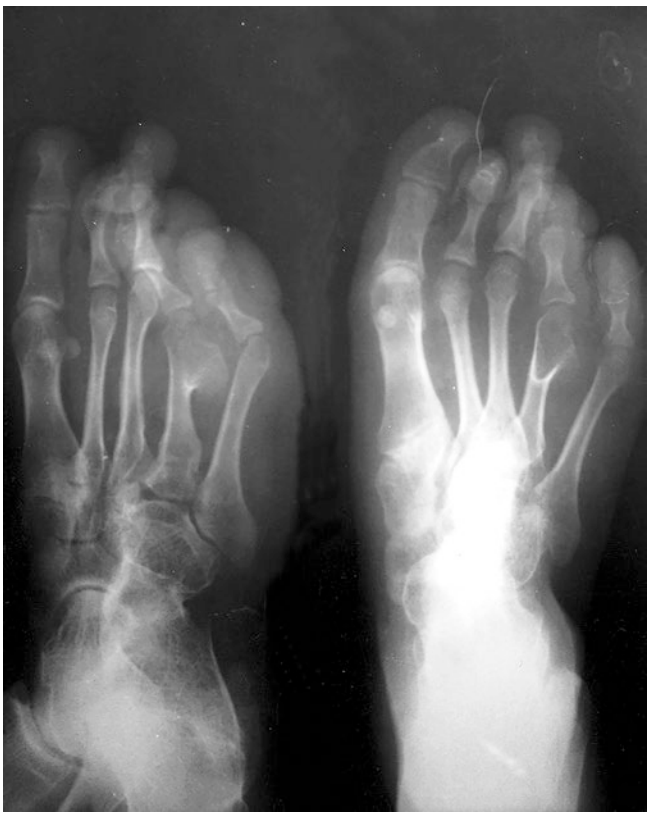


Fig. 27-3-3 Multiple osteochondroma on the right feet, with the third toe macrodactyly

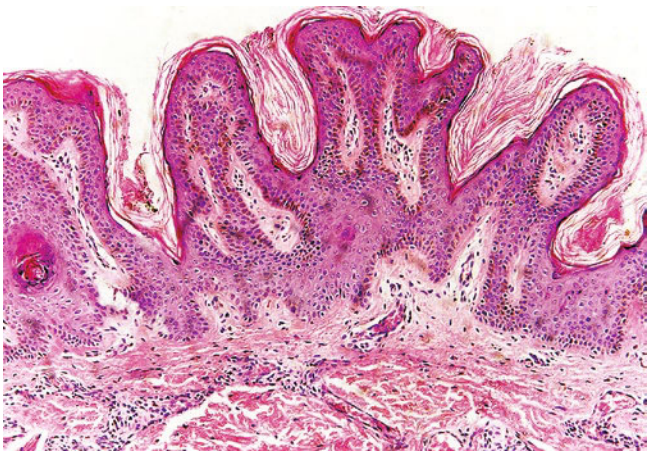


Fig. 27-3-4 Hyperkeratosis, acanthosis, hyperpigmentation of the basal layer, and infiltration by perivascular lymphocytes in the upper dermis (HE stain, ×100)

27.4 Seborrheic Keratosis [9–11]

- The clinical manifestations of seborrheic keratosis (SK) are quite variable.
- Although SK is mainly distributed over sun-exposed regions, small, popular SK has a predilection for the trunk, presenting with numerous small lesions.
- SK is configured as linear, dermatomal, or Blaschkoid.
- The lesions in SK may also run along the Langer's lines or may cross these lines (defined as raindrop SK).
- All these mentioned variants are believed to have no relation to internal malignancy.

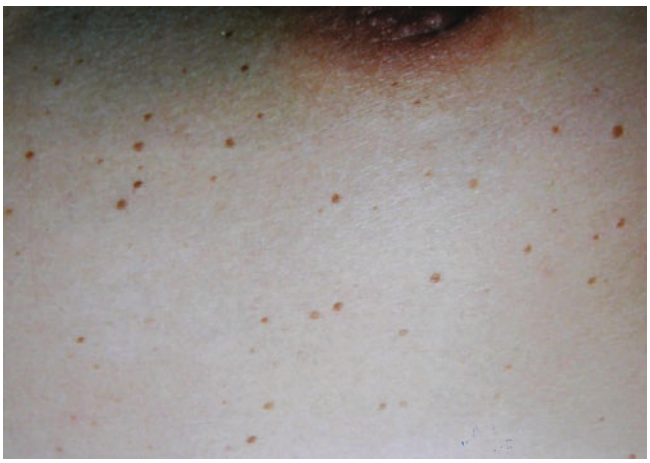


Fig. 27-4b-1 Brownish, spindle, and slightly raised papules tended to follow skin cleavage lines on lower back

Fig. 27-4a-1 Numerous small brown papules on the chest and abdomen

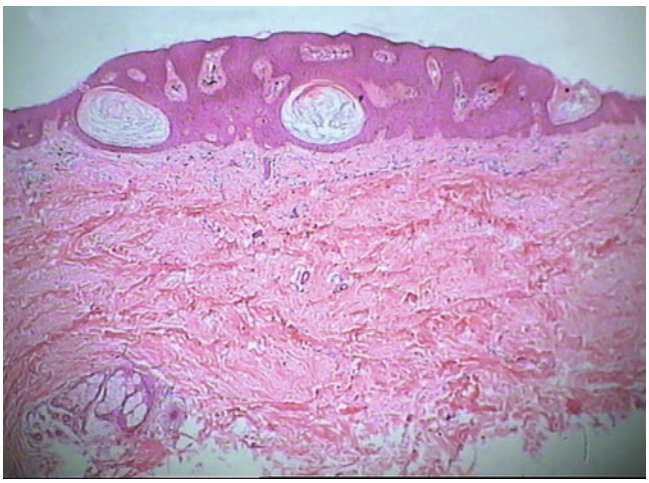


Fig. 27-4b-2 Hyperkeratosis, acanthosis, horn cysts, and proliferation of basal cells in the epidermis (HE stain, ×100)

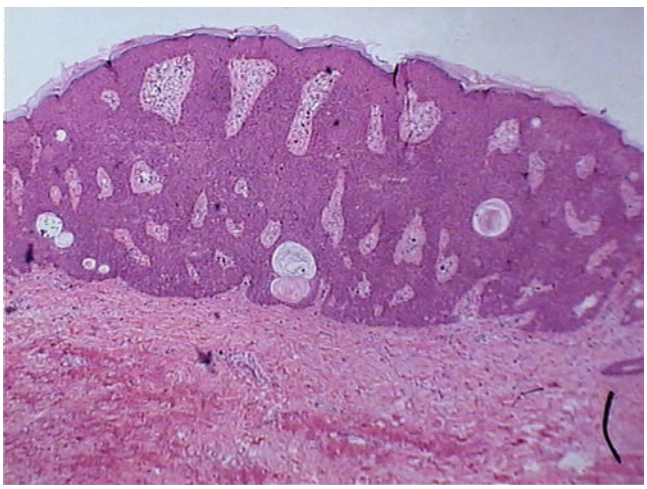


Fig. 27-4a-2 Moderate acanthosis and horn cysts in the epidermis (HE stain, ×l00)

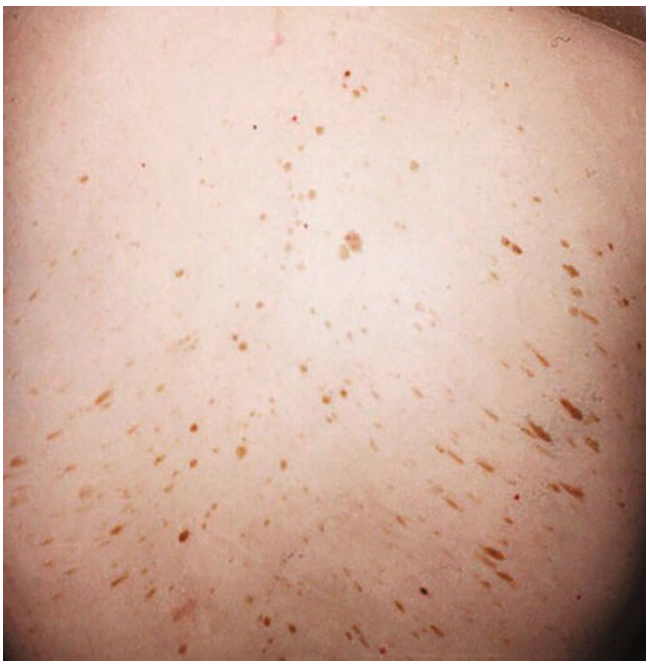


Fig. 27-4c-1 Multiple linear, spindle- or leaf-shaped eruptions distributed linearly or radially along the direction of skin cleavage lines

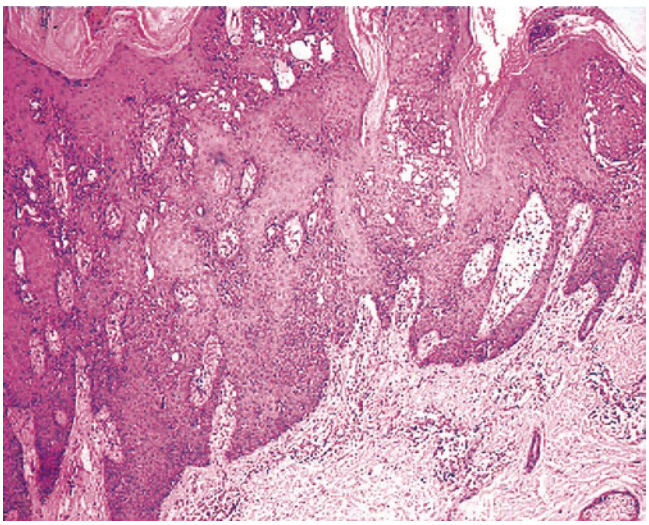


Fig. 27-4c-2 Hyperkeratosis, acanthosis, and horn cysts in the epidermis and chronic inflammatory reaction in the dermis. The stratum malpighii showed moderate acanthosis caused by proliferation of squamous and basal cells (HE stain, ×100)

27.5 Seborrheic Keratosis and Pityrosporum Ovale [12]

- Our study showed that a large number of variously sized spores without fungal hyphae are present in the skin scrapings of 20 (95%) cases with large seborrheic keratosis (SK).
- A cohort of 21 cases consists of 15 men and 6 women were investigated. Results showed that the average age at the time of diagnosis is 65 years old, and the mean duration was 5 years (0.5–11 years). The most involved site was the head and face (11 cases), followed by the trunk (9 cases) and extremities (1 case).
- There were multiple PAS-positive organisms in the stratum corneum in 18 (85%) cases. Scanning electron microscopic (SCM) observation of warty lesions found that numerous pityrosporum ovale were present on the keratinized cells. They were round to ovoid in shape and ranged from 3 to 5 μm in diameter. The surfaces of the spores were smooth without hyphae.
- Pityrosporum ovale is oval and Pityrosporum orbiculare is round in morphology, and both are distributed on the trunk and scalp, since Pityrosporum orbiculare is known to produce hyphae, which were absent in the skin lesions of SK. The results suggested the presence of pityrosporum ovale.
- Borenstein et al. reported that the Pityrosporum organisms in the stratum corneum were present in 61% of SK on routine histopathologic sections.

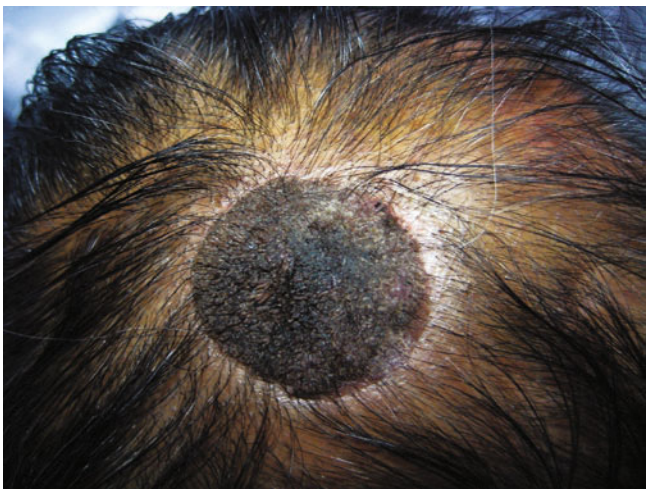


Fig. 27-5-1 A large black keratotic plaque on the head

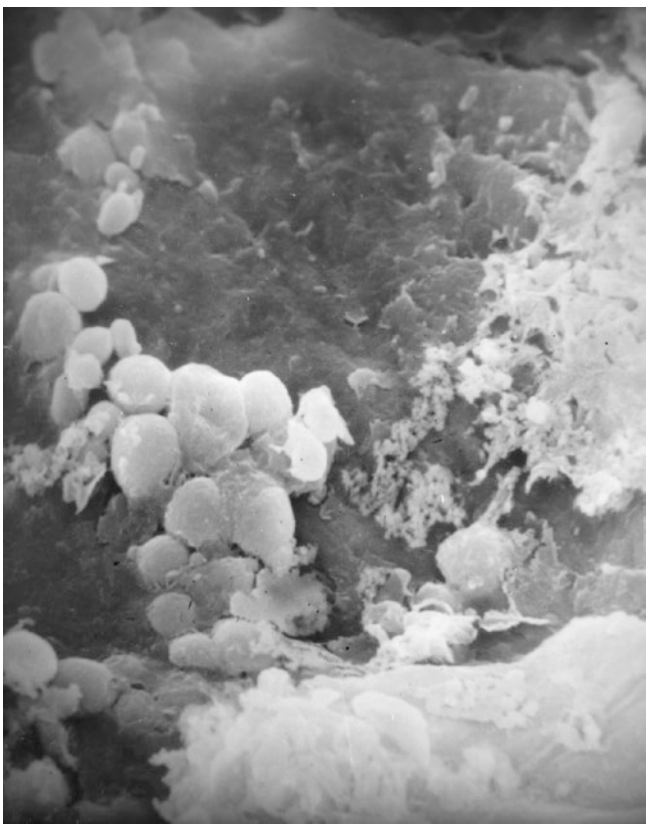


Fig. 27-5-2 Scanning electronic microscopy showed that lots of round and oval spores on the upper horny layer

27.6 Large Cell Acanthoma [13, 14]

- Large cell acanthoma (LCA) has a predilection for sun-exposed areas.
- LCA is clinically indistinguishable from solar lentigo or actinic keratosis.
- Skin biopsy shows a circumscribed proliferation of keratinocytes whose sizes are no less than twice the normal size.
- Pinkus suggests that LCA is instead a sign of cutaneous mosaicism, while most investigators consider it to be a histopathologic form of solar lentigo.

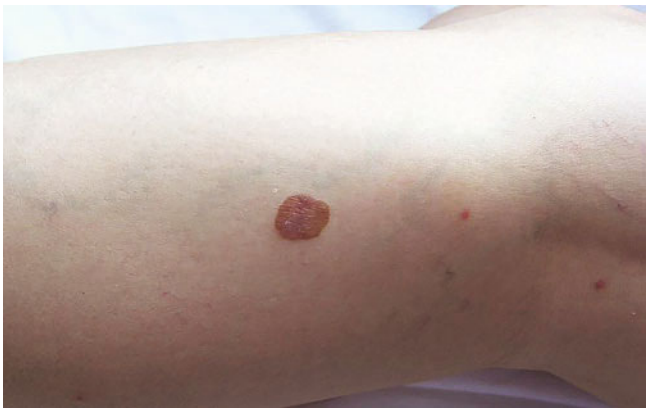


Fig. 27-6-1 Brown and slightly raised plaque on the outer side of the calf

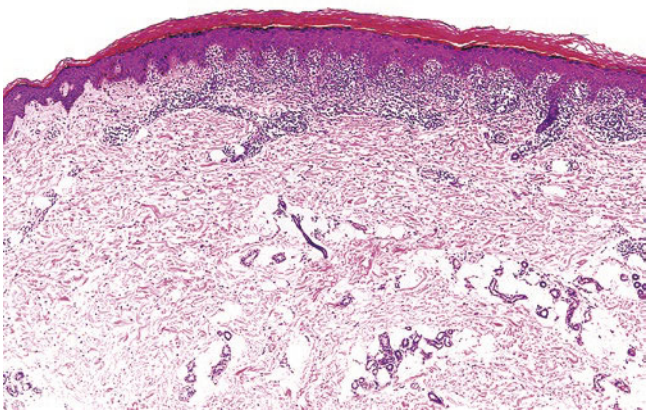


Fig. 27-6-2 Epidermal hyperplasia, acanthosis, and inflammatory cell infiltration (HE stain, ×100)

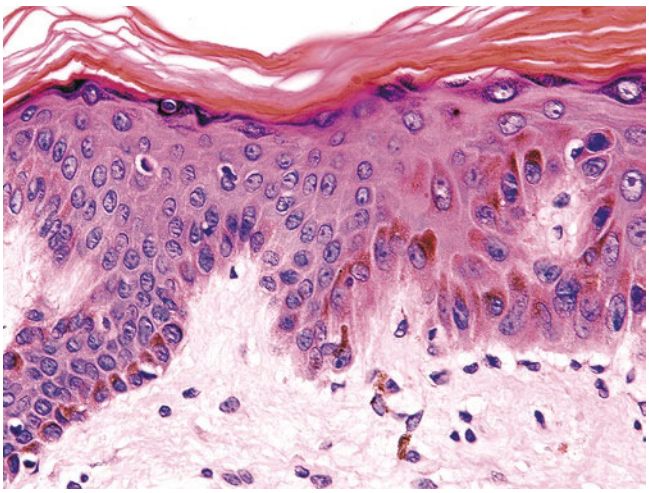


Fig. 27-6-3 Enlarged keratinocytes and acanthosis (HE stain, ×400)

27.7 Giant Cutaneous Horn [15, 16]

- Cutaneous horn (CH) is a kind of keratotic projection reminiscent of animal horns. CH is a clinical description rather than a pathologic diagnosis.
- The lesion can be straight, curved, conical, cylindrical, or spiral, with its length ranging from several millimeters to 38 cm.
- CH often has underlying benign or malignant skin disease, and therefore, ruling out this malignancy is of the utmost importance.
- It can be categorized into five groups: I CH originated from an epidermoid cyst, II CH developed from the mucosa, III verrucous CH arising from warts, IV papillomatous CH from keratotic epithelial cells, and V filiform variant resulting from normal or hyperkeratotic skin.
- Squamous cell carcinoma, seborrheic keratosis, Bowen's disease, actinic keratosis, basal cell carcinoma, melanoma, trichilemma, pilomatricoma, verrucous dyskeratoma, and juvenile xanthogranuloma are classified as the tumorous causes of CH. Other possible causes include molluscum contagiosum, verruca vulgaris, cutaneous leishmaniasis, pyogenic granuloma, epidermal nevus, and tuberculosis.

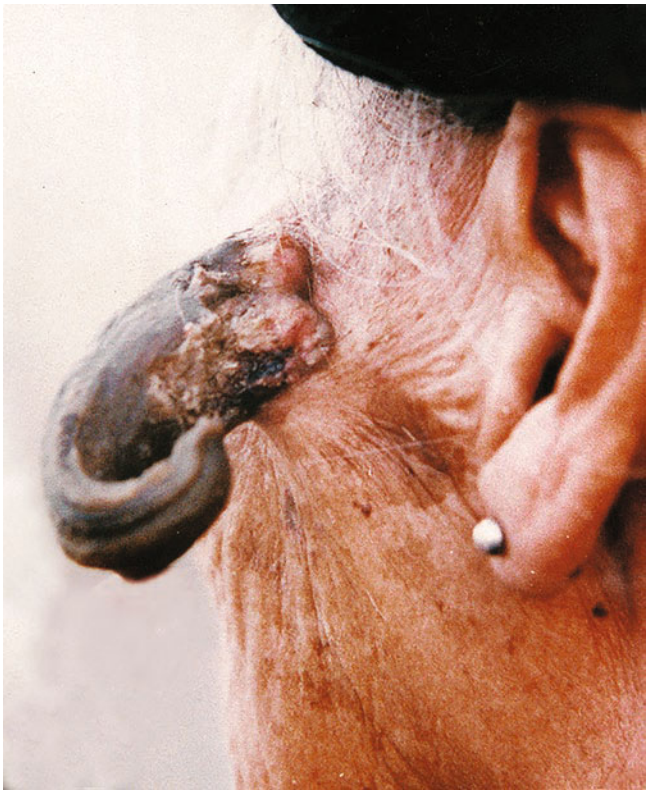


Fig. 27-7-1 Ox hornlike dark-purple lesion with coarse surface

27.8 Multiple Bowen's Disease [17, 18]

- Bowen's disease (BD) is considered to be a noninvasive, early stage of squamous cell carcinoma.
- BD presents as well-defined reddish plaques that crust and enlarge gradually. Pathologically, it presents with full-thickness epidermal atypia with adnexal involvement.
- Only 10–20% of BD has multiple lesions, and this form is defined as multiple BD. Other forms consist of pigmented BD, palmar BD, subungual/periungual BD, and verrucous BD.
- Vulval intraepithelial neoplasia (VIN), erythroplasia of Queyrat, and Bowenoid papulosis are associated with BD in the genital region, and they have a strong association with human papillomavirus infection.
- The disease shows a favorable response to currently available treatments, and 3–5% of BD risk the development of an invasive carcinoma.
- Photodynamic therapy, topical imiquimod, and topical diclofenac are newer options for BD treatment.

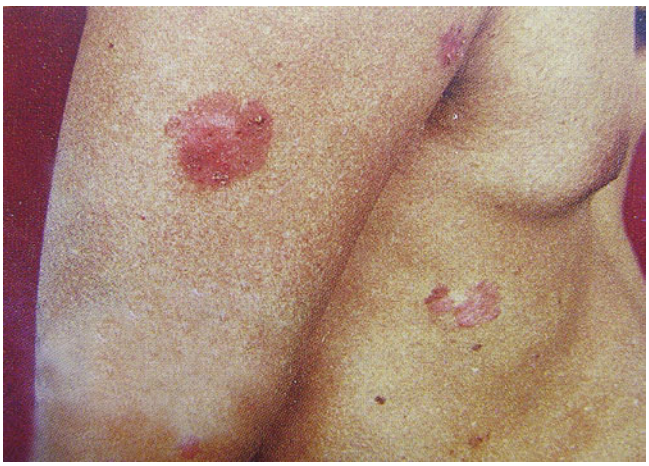


Fig. 27-8-1 Brownish papules and plaques with superficial erosions and crusts on the upper arm, chest, and abdomen

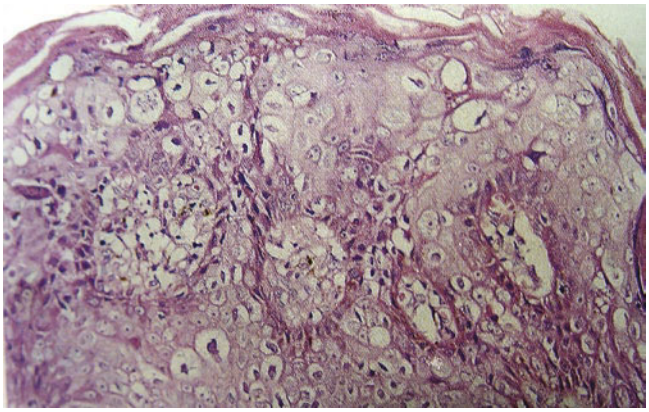


Fig. 27-8-2 The cells of the stratum malpighii in different sizes were arranged in chaos, which showed some physaliferous cells and atypia mitoses (HE stain, ×400)

27.9 Extramammary Paget's Disease (EMPD) [19, 20]

- Paget's disease (PD) is an intraepidermal adenocarcinoma with neoplastic mucin-producing Paget's cells.
- Primary EMPD only involves the epidermis and cutaneous adnexa.
- PD shows a predilection for apocrine gland-rich regions, comprising the mammary area and extramammary region.
- Secondary EMPD is associated with an underlying visceral malignancy.
- EMPD manifests as a red macule or plaque with characteristic "cake-icing scaling," and the diagnosis is always complicated by its ulcerated, crusted, or papillomatous surface.
- It is likely for EMPD patients to have a second primary cancer, particularly the first year after diagnosis.
- The diagnosis is established with the presentation of Paget's cells in the epidermis. Paget's cells are characterized by large nuclei and vacuolated cytoplasm. These cells are highlighted by PAS stain, and they express CK7, CEA, and EMA. However, EMPD with an elevated expression of fatty acid synthase and p53 is likely to have a higher invasive potential.
- Type I EMPD (keratin 7+, keratin 20+, and GCDFP-15−) is related to distant tumors, and Paget's cells in type II (keratin 7+, keratin 20−, and GCDFP15 +) are of primary cutaneous origin.

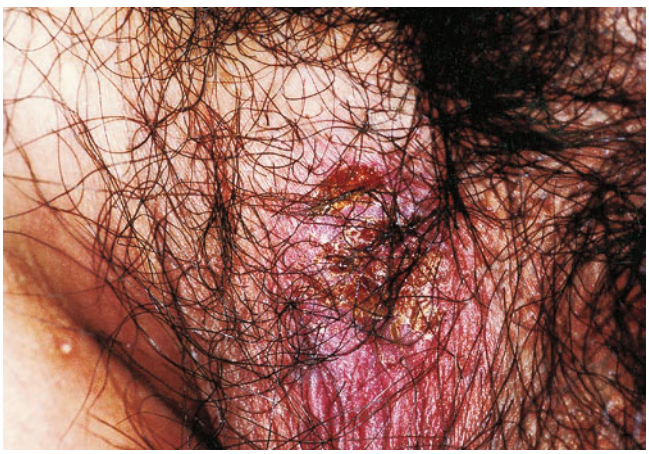


Fig. 27-9-1 Infiltrated well-circumscribed erythemas and plaques with central erosion and superficial ulcers on the scrotum, penis, and perineum

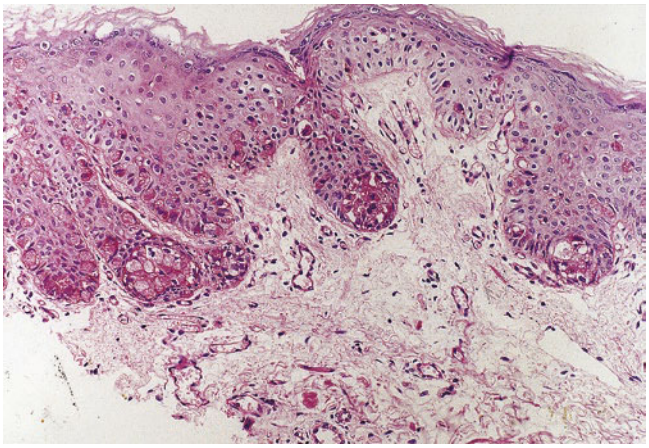


Fig. 27-9-2 Scattered PAS-positive Paget's cells in the epidermis (PAS stain, ×200)

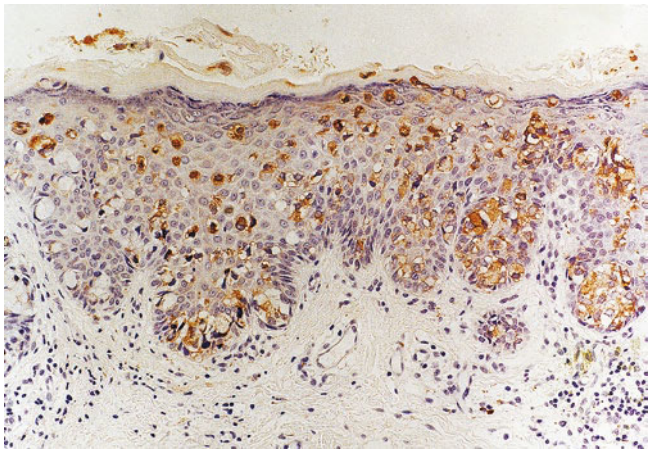


Fig. 27-9-3 Epithelial membrane antigen (EMA)-positive cells were scattered or grouped in the epidermis (APC stain, ×200)

27.10 Eruptive Keratoacanthoma [21–23]

- Keratoacanthoma (KA) typically shows a solitary, rapidly enlarging, and well-differentiated squamous cell epithelium in the epidermis with a central, keratin-filled crater.
- After 6 months' induration period, the neoplasm decreases until it completely resolves.
- In comparison with the classical solitary type, multiple KA tends to arise abruptly, develop quickly, regress slowly, and recur periodically.
- The number of eruptive KA ranges from a few to several hundred, and they mostly resolve with residual scarring.
- Although multiple KAs mostly appear in Muir-Torre syndrome, Ferguson-Smith syndrome, xeroderma pigmentosum, and other syndromes, it can be induced by medication with leflunomide, BRAF kinase inhibitors (vemurafenib or sorafenib), or photodynamic therapy. Topical application of 5% imiquimod can be effective in the treatment of multiple KAs.

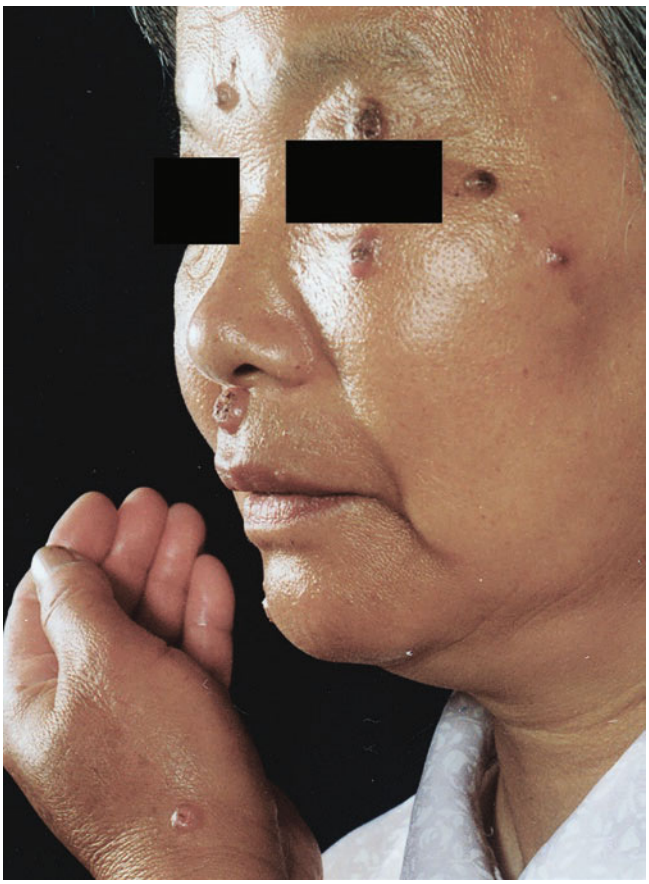


Fig. 27-10-1 Thirteen firm, dome-shaped nodules of 0.5–1.0 cm in diameter with crateriform centers on the face and wrist

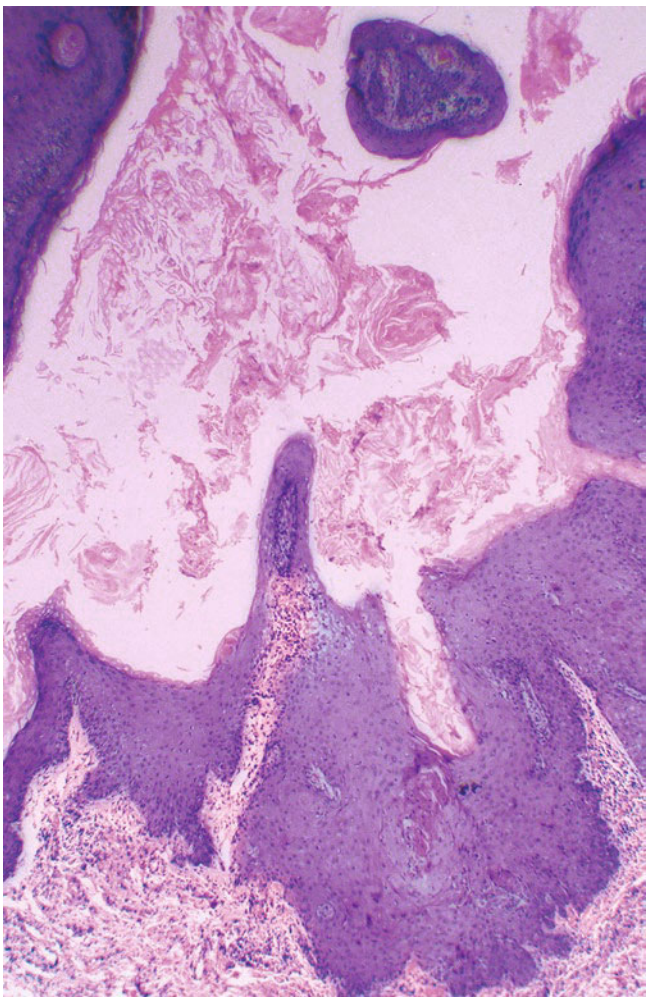


Fig. 27-10-2 A large, irregularly shaped crater was filled with keratin (HE stain, ×40)

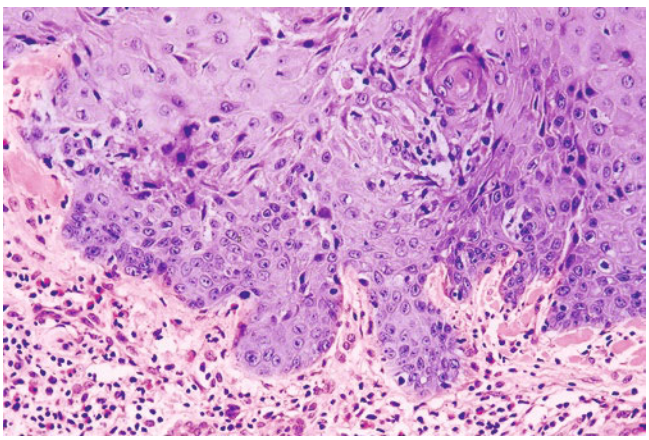


Fig. 27-10-3 The proliferative epidermal cells at the base of crater showed nuclear atypia and atypical mitoses (HE stain, ×100)

27.11 Superficial Basal Cell Carcinoma [24, 25]

- We can classify basal cell carcinoma (BCC) into nodular, infiltrative, superficial, and mixed subtypes based on their morphological descriptions.
- Superficial BCC, or multicentric BCC, shows a scaly, pink to red-brown demarcated macule. It predominantly affects the trunk, in contrast to nodular BCC on UV-exposed areas.
- It can easily be mistaken as psoriasis, lichen planus-like keratosis, or Bowen's disease.
- Dermoscopic findings of maple leaflike areas, spoke wheel areas, blue-gray globules and ovoid nest, and arborizing telangiectasis can be helpful in its early diagnosis.
- Imiquimod 5% is recommended as a treatment in superficial BCC, in addition to its wide application in the management of genital warts and solar keratoses. However, vitiligo-like depigmentation is likely to be a rare complication following its application.

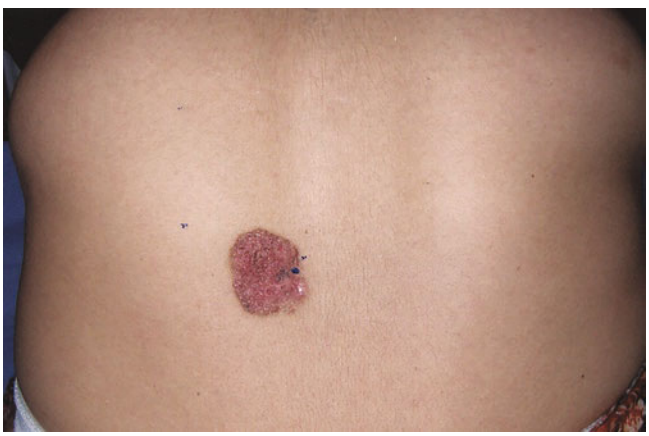


Fig. 27-11-1 A purplish red patch surrounded by dark-brown papules on the back

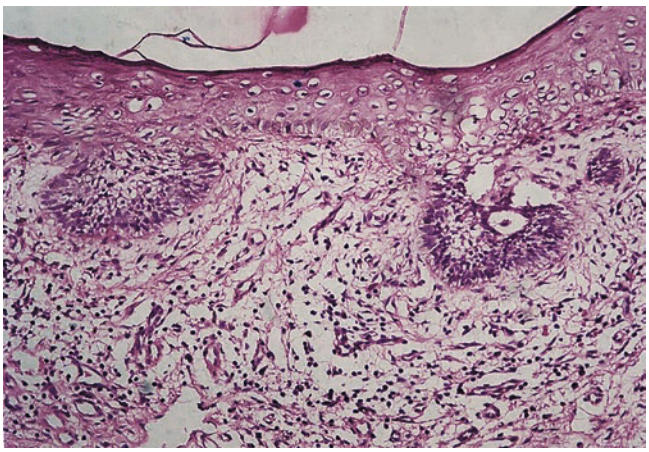
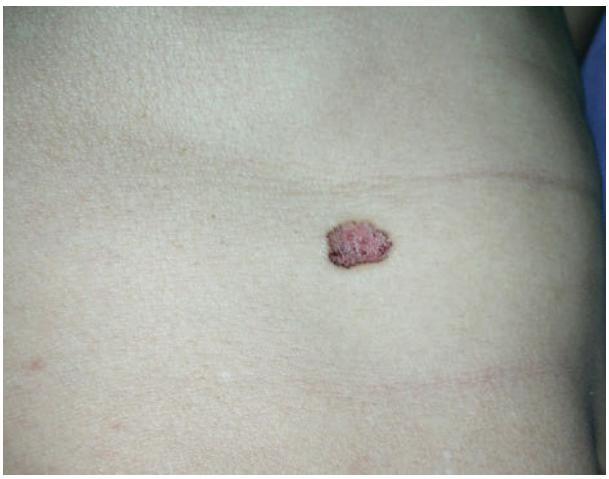
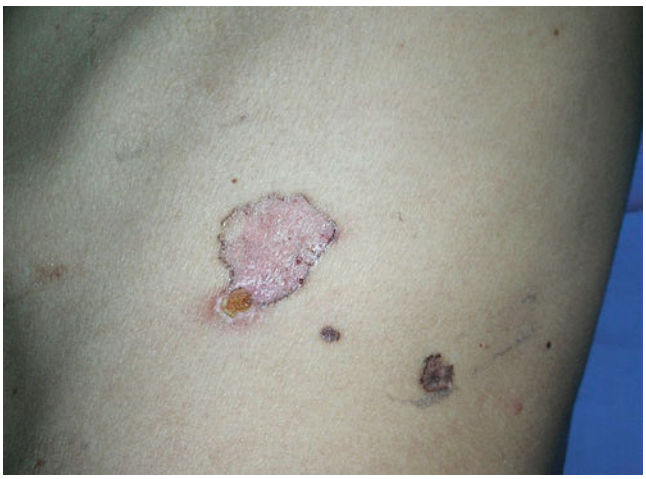


Fig. 27-11-2 The buds of tumor cells attached to the undersurface of the epidermis. The peripheral cells of the tumor show palisade arrangement (HE stain, ×200)

27.12 Fibroepithelioma of Pinkus [26, 27]

- Fibroepithelioma of Pinkus (FEP) is a rare cutaneous tumor. Multiple tumors of FEP are rather rare. FEP develops in persons aged between 40 and 60 years. FEP presents as a skin-colored, pink, red, or brown nodule or plaque, with occasional ulceration. But large pedunculated, polypoid, or ulcerated cases have also been reported.
- They usually are most frequently located on the trunk or extremities. However, lesions occurring on the head, abdomen, anus, penis, scrotum, and breasts have been reported.
- Only ten cases with multiple FEP have been described. Nine of them were associated with basal cell carcinoma (BCC). The presentation as a multiple BCC is rather rare. Prior radiotherapy is a predisposing factor in the onset of disease.
- There are very few reports of fibroepithelioma of Pinkus in continuity with a nodular BCC. The classification of fibroepithelioma of Pinkus is controversial and is considered as a variant of either BCC or trichoblastoma.





Figs. 27-12-1, 27-12-2 Four brown or erythematous maculae or patches with a brown-colored, elevated borderline in different sizes on two sides of the waist. Some dilated follicular orifices were seen in the fringe. The central parts of the patches were erythematous and slight atrophied without erosion and infiltration

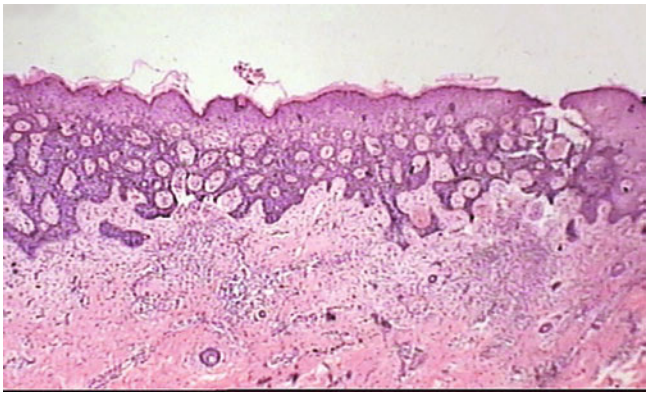


Fig. 27-12-3 Mild hyperkeratosis and acanthosis in the epidermis (HE stain, ×40)

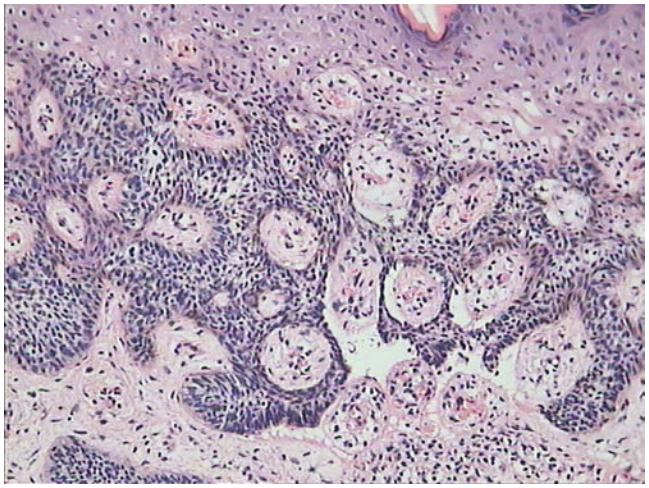


Fig. 27-12-4 Reticulated strands of basaloid cells extended into the dermis. The macronuclei of basal cells were deeply basophilic. There were more melanin granules in basal layers and the basement membrane was integrated. Hemangiectasia and numerous lymphocyte infiltrated in the mid-dermis (HE stain, ×200)

27.13 Marjolin's Ulcer of Squamous Cell Carcinoma Secondary to Radiation [28, 29]

- Marjolin's ulcer (MU) is the presentation of cutaneous malignant tumor over previous chronic inflammatory skin disorder.
- MU has a predilection for the scalp, trunk, and extremities.
- MU is usually induced by burns, snake bites, vaccination, radiation, venous stasis, osteomyelitis, and pilonidal abscesses. Commonly, it takes approximately 35 years for this kind of malignant transformation.
- Squamous cell carcinoma (SCC) is the chief pathological form of MU, followed by melanoma, basal cell carcinoma, and mesenchymal malignancy.
- It is more aggressive and usually shows a higher rate of regional metastasis than other skin cancers.
- Localized toxins, immunological depression, carcinogens, and poor lymphatic drainage are its potential etiological factors.

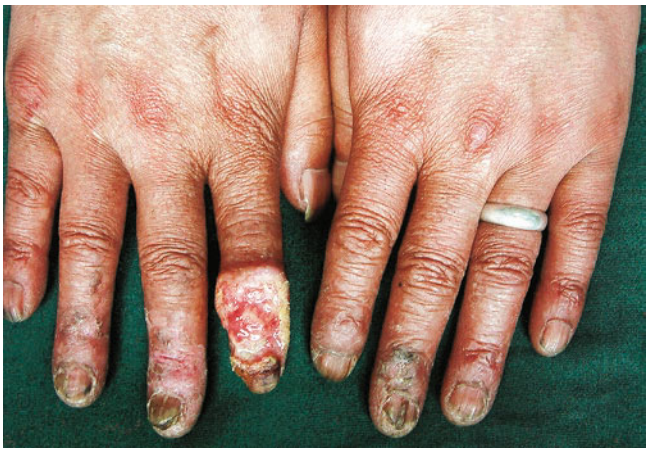


Fig. 27-13-1 Dryness, keratosis, peeling, hyperpigmentation, and slight atrophy on dorsa of the hands, several marked thickened brownish-yellow nails, an ulcer on the extensor of the first and second knuckles of the index finger

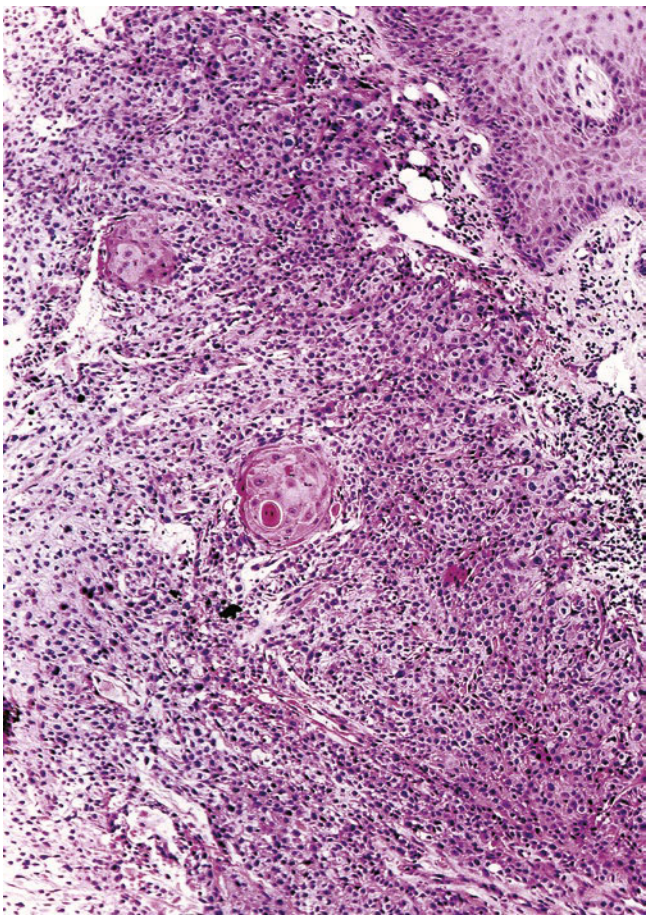


Fig. 27-13-2 Irregular hyperplasia epidermis, many tumor cell masses with marked atypical cells, mitotic figures, and atypical mitosis in the whole dermis (HE stain, ×100)

27.14 Cutaneous Clear Cell Squamous Cell Carcinoma [30, 31]

- Clear cell squamous cell carcinoma (SCC) typically shows lobular neoplastic cells separated by thin strands of fibrous stroma. These cells have an obviously clear cytoplasm with rounded, ovoid, or wrinkled nuclei.
- Tumor cells in type I resemble mature adipose cells, which have clear cytoplasm and peripheral nuclei. However, there are foci of pronounced keratinization and fibrotic stroma.
- Tumor cells in type II are disconnected from the overlying epidermis. These cells have reticulated clear cytoplasm without obvious keratinization or ductal or glandular differentiation.
- Type III is depicted as an extensive ulceration that is unrelated to the overlying epidermis. Nuclear pleomorphism is discernible with foci of squamous differentiation. There are distinctive dyskeratotic cells and pseudoglandular changes.
- Clear cell occurs in a variety of conditions, including clear cell hidradenoma, clear cell acanthoma, clear cell Bowen's disease, tricholemmoma, pagetoid squamous cell carcinoma in situ, Paget's disease, hidradenocarcinoma, sebaceous carcinoma, balloon cell nevus, and balloon cell melanoma.

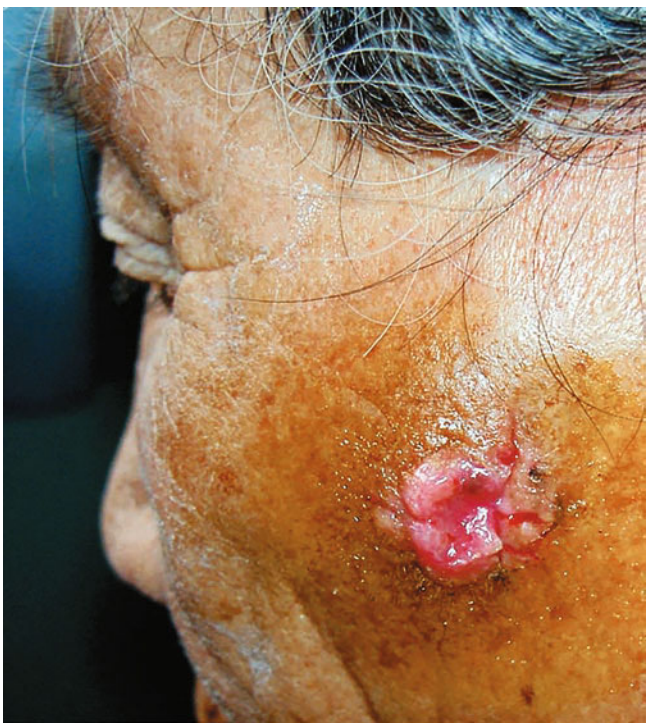
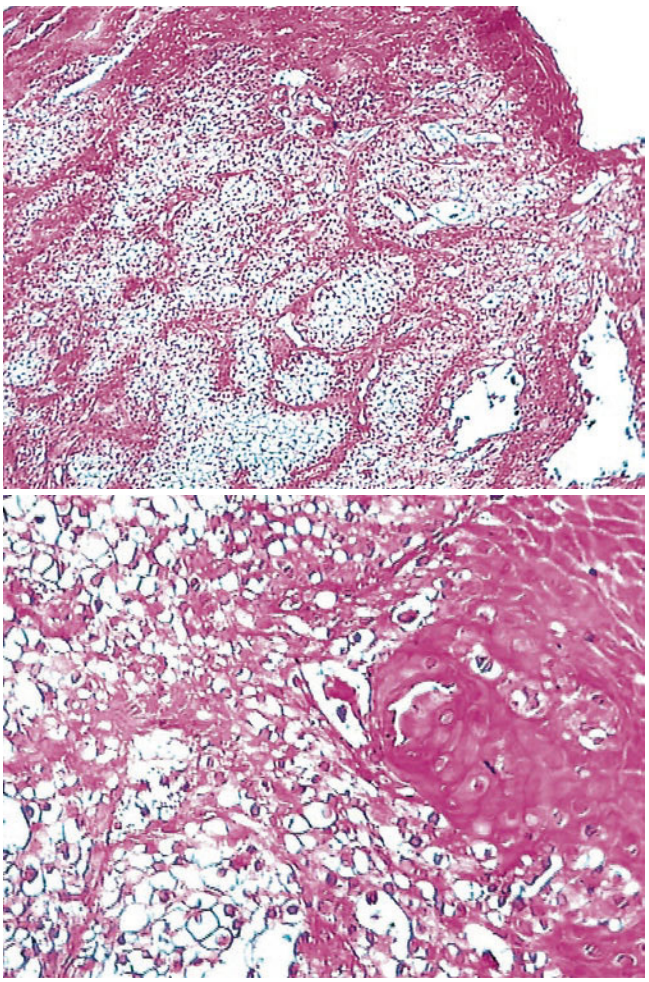


Fig. 27-14-1 A 2 × 2 cm nodular and ulcer on the left vizard



Figs. 27-14-2, 27-14-3 The tumor masses were consisted of normal squamous cells and of atypical squamous cells with clear cytoplasm and atypical nuclei (HE stain, (2) ×100; (3) ×400)

27.15 Milia En Plaque [32–34]

- Milia en plaque (MEP) is characterized by numerous grouped tiny milia circumscribing an erythematous plaque.
- MEP is most commonly located in the retroauricular region. Occasionally, the eyelids, the paranasal region, submandibular area, supraclavicular area, and mental crease have also been described.
- Histopathology is characterized by the presence of keratin-filled epidermal cysts surrounded by a variably mild to dense mononuclear infiltrate.
- MEP is associated with other diseases, such as pseudoxanthoma elasticum and discoid lupus erythematosus.

Fig. 27-15-1 White-yellow, cystic lesions scattered within slightly erythematous plaques symmetrically localized on the posterior aspects of both his ears

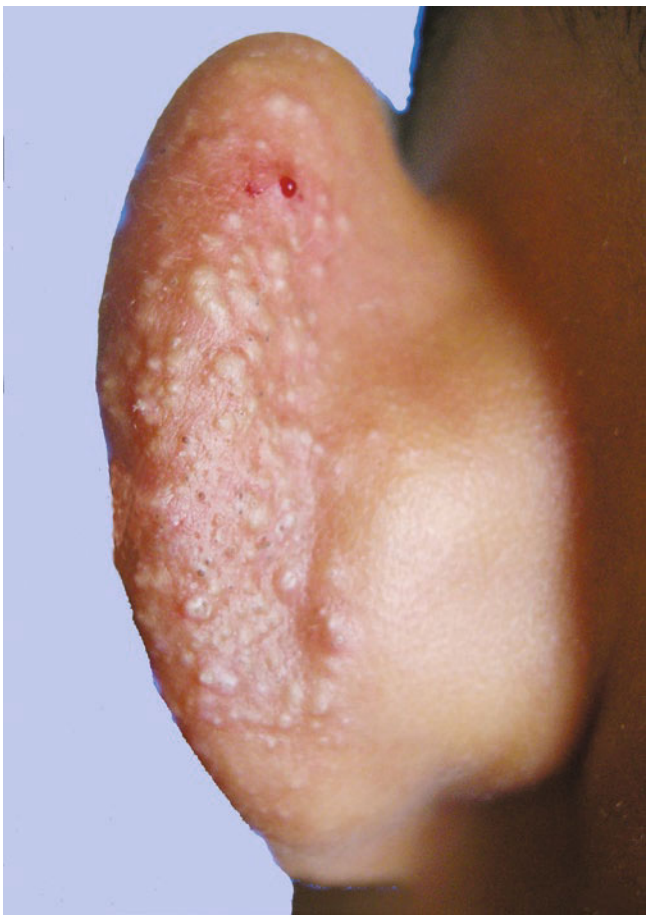


Fig. 27-15-2 Close view of the left ear. Multiple milia and a few open comedones overlaid the erythematous plaques

27.16 Eruptive Vellus Hair Cysts [35–37]

- Eruptive vellus hair cysts (EVHC) presents as multiple, small, dome-shaped, comedo-like papules with a smooth surface.
- EVHC preferentially affects the chest and face. Such a distribution seems to grossly overlap with that of pilosebaceous and apocrine units.
- The pathological hallmark of EVHC is the existence of multiple vellus hair shafts within the stratified squamous epithelial-lined cysts.
- EVHC and steatocystoma multiplex belong to two different entities. The nonexistence of attachment of sebaceous glands to the cyst wall, together with negative keratin 10 staining, facilitates this differentiation for EVHC.
- Other associations, such as keratosis pilaris, trichostasis spinulosa, acneiform eruptions, pilomatricoma, folliculitis, epidermoid cysts, molluscum contagiosum, and perforating dermatosis, have rarely been reported.

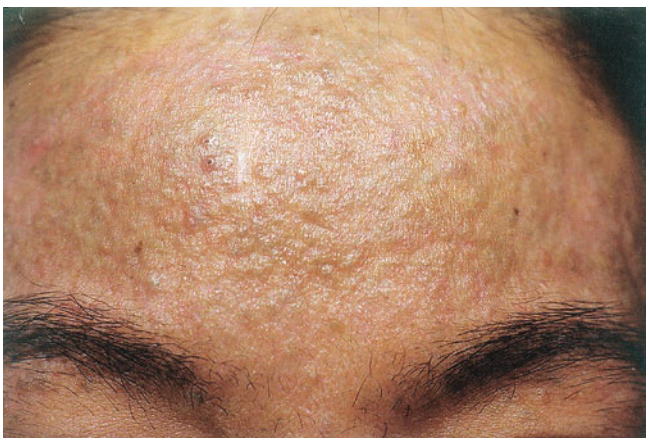


Fig. 27-16-1 Numerous blue hair follicle papules on the forehead, a few papules having umbilicated surface

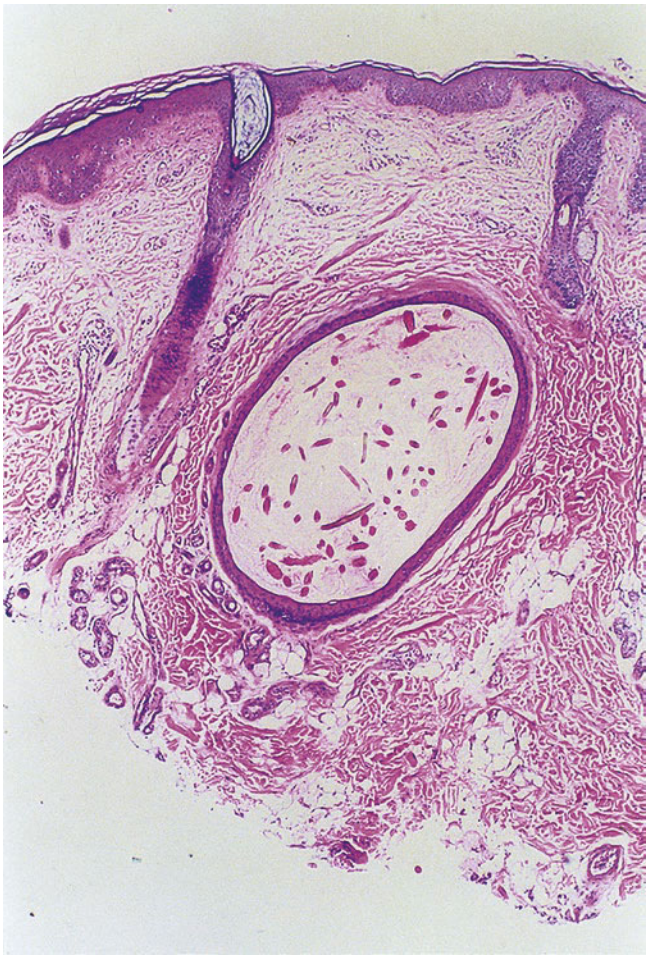


Fig. 27-16-2 Cysts in the upper and mid-dermis were lined by squamous epithelium, and the cysts contained numerous transversely or obliquely cut vellus hairs (HE stain ×40)

27.17 Nevus Comedonicus [38, 39]

- Nevus comedonicus (NC) presents clusters of follicular horny plugs that are predominantly located on the face and neck.
- Its lesions may be distributed in a unilateral, bilateral, linear, interrupted, segmental, or blaschkoid way.
- The first subtype of NC has only comedo-like eruptions, while the second has large cysts, papules, fistulas, abscesses, and scarring in different stages of development.
- Nevus comedonicus syndrome is defined if NC coexists with additional findings in ocular, skeletal, or neurologic abnormalities. Cataracts, fused vertebrae, scoliosis, delayed mental development, and spina bifida are the most common symptoms in NC.
- The skin tumors associated with NC syndrome are trichoepithelioma, dilated pore of Winer, syringocystadenoma papilliferum, keratoacanthoma, basal cell carcinoma, hidradenoma papilliferum, or squamous cell carcinoma.

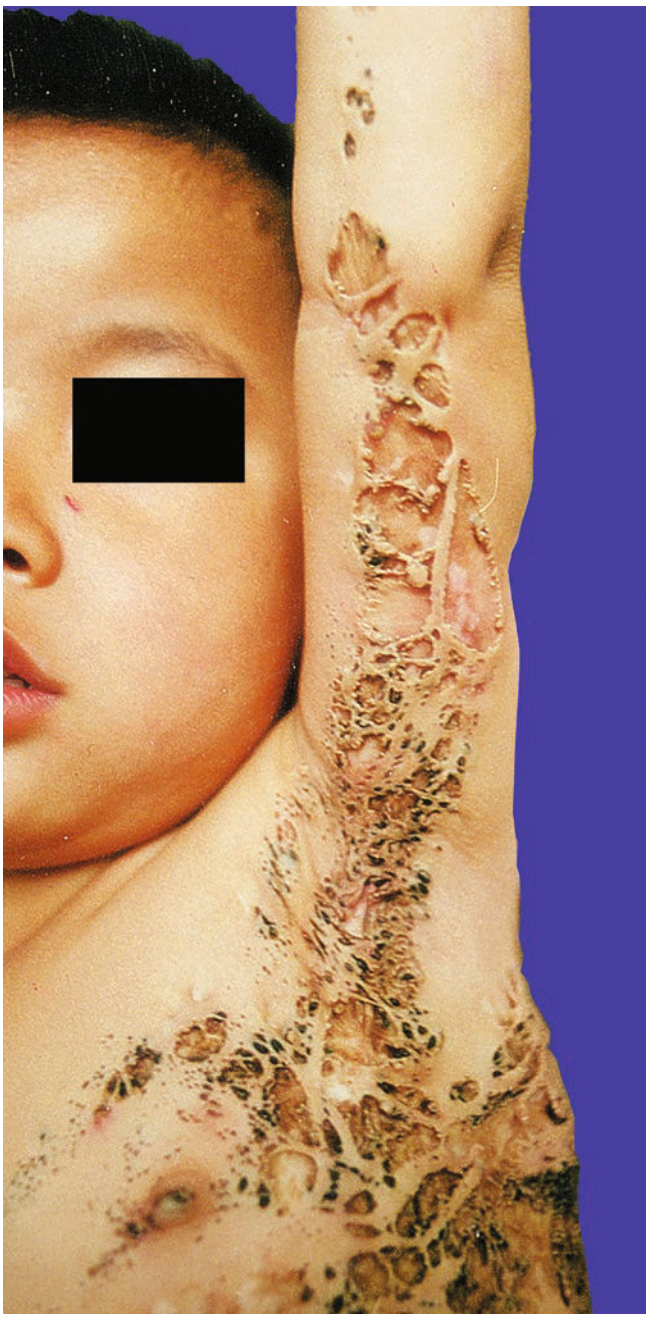


Fig. 27-17-1 Numerous "blackheads" distributed in band and on the left chest

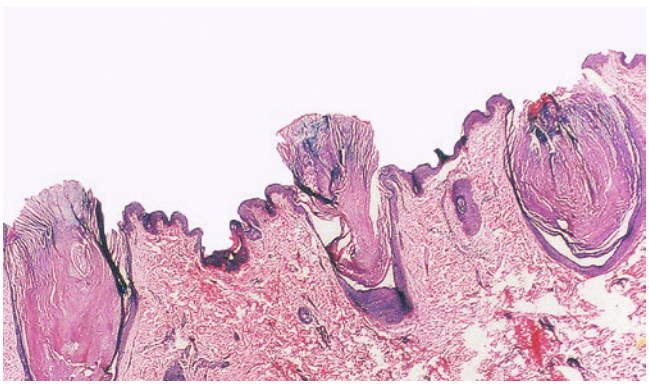


Fig. 27-17-2 There were three keratotic plugs located in dilated follicular orifice (HE stain, ×20)

27.18 Dilated Pore [40, 41]

- Winer's dilated pore (DP) is a rare specific neoplasm. The lesion of DP occurs on the face or upper trunk of an elderly individual.
- The typical lesion of DP presents as an enlarged pore and open comedo. Patients with DP usually have a single lesion. A few patients have two.
- Histological trait includes infundibular cyst lined by outer root sheath epithelium.

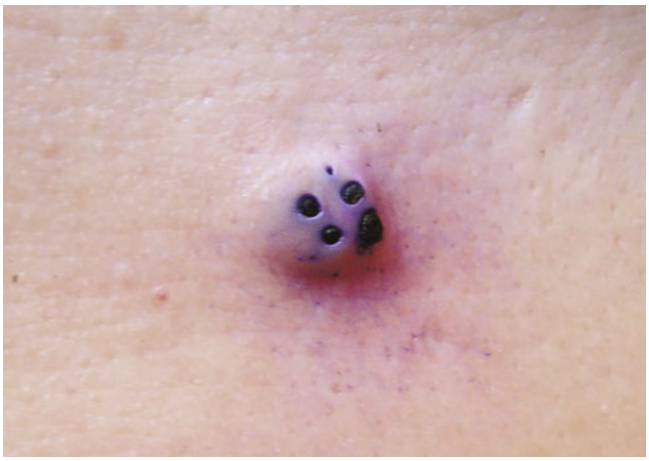


Fig. 27-18-1 A solitary papule with four open comedos on the trunk

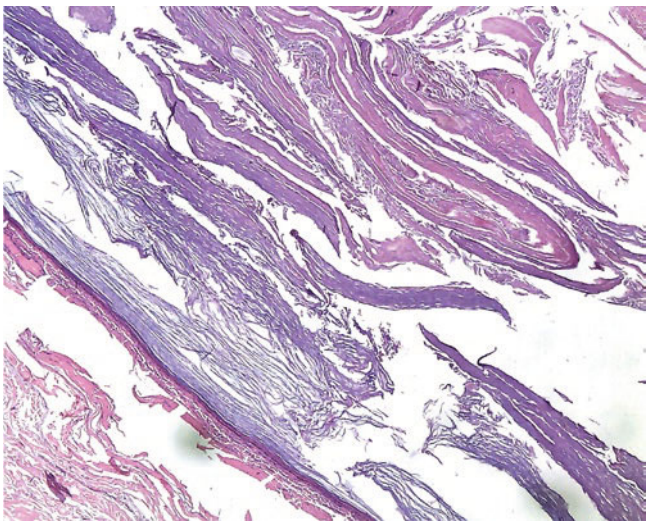


Fig. 27-18-2 A dilated pore was filled with lots of keratin (HE stain, ×100)

27.19 Inverted Follicular Keratosis [42, 43]

- Inverted follicular keratosis (IFK) results from an exoendophytic expansion of the infundibular portion of the hair follicle.
- The clinical features of IFK are quite variable, from pink papules to keratoacanthoma-like or papillomatous nodules. Its diagnostic confusion includes irritate seborrheic keratosis, warts, keratoacanthoma, adnexal tumor, basal cell carcinoma, and squamous cell carcinoma.
- Microscopy examination of IFK is a diagnostic step characterized by an endophytic tumor that has peripheral basaloid cells and central larger keratinizing cells with several circumscribed squamous eddies. The absence of atypia, mitotic activity, necrosis, or stromal invasion in IFK helps its differentiation with other dermatoses.
- The most typical dermoscopic presentation is central keratin encircled by hairpin vessels with a white halo.

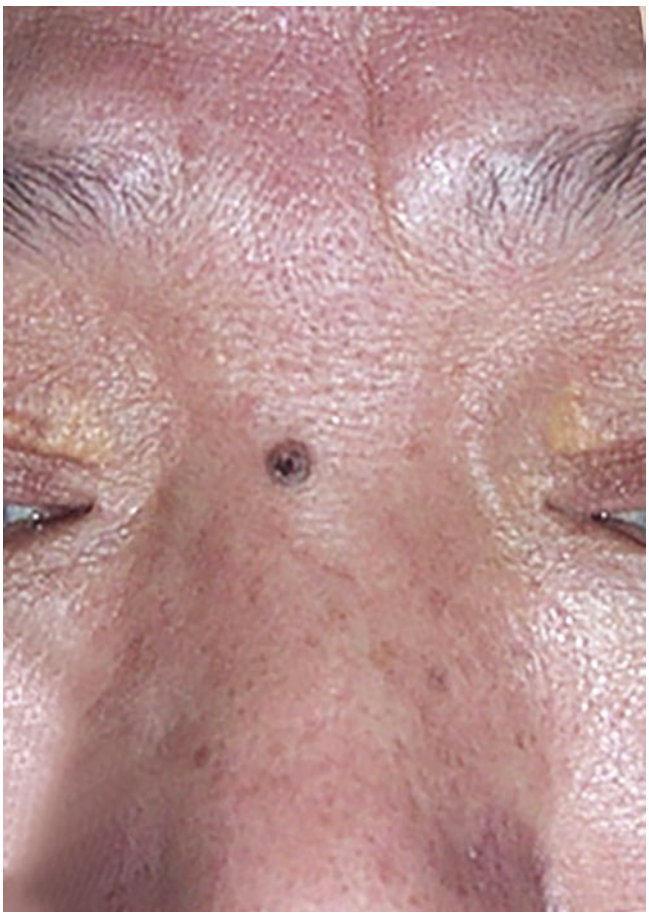


Fig. 27-19-1 A millet-sized, well-circumscribed, dust-colored papule with central erosions and black crust on the base of the nose bridge

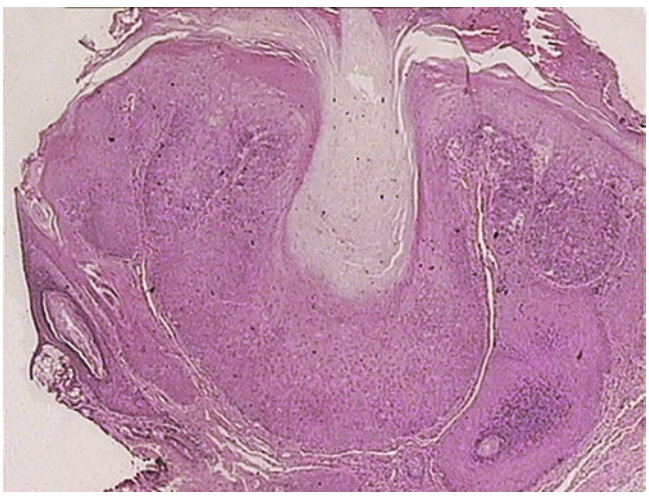


Fig. 27-19-2 Keratin-filled invaginations were covered with squamous epidermis, surrounded by basaloid cells, which formed squamous eddies, and there were follicular structures in hyperplastic tissue (HE stain, ×20)

27.20 Infundibulocystic Basal Cell Carcinoma [44, 45]

- Infundibulocystic BCC is a well-differentiated form of BCC that histopathologically shows circumscribed lobular and anastomosing cords of bland basaloid cells with multiple tiny infundibulocystic structures.
- Infundibulocystic BCC arises as a solitary papule on the face of elder people. Multiple lesions are commonly found in multiple hereditary infundibulocystic BCC syndrome (autosomal dominant inheritance without jaw cysts, palmar pits, or other signs of nevoid basal cell carcinoma syndrome).
- There is still debate whether infundibulocystic BCC is the same as trichoepithelioma and basaloid follicular hamartoma.
- It has been noted that infundibulocystic BCC may be established with a paucity of fibrocytes, in contrast to the abundant and highly fibrocystic stroma in trichoepithelioma.
- Infundibulocystic BCC and basaloid follicular hamartoma might be different names for the same entity, considering their identical morphology and equivalent diffuse distribution of CK20+ cells.

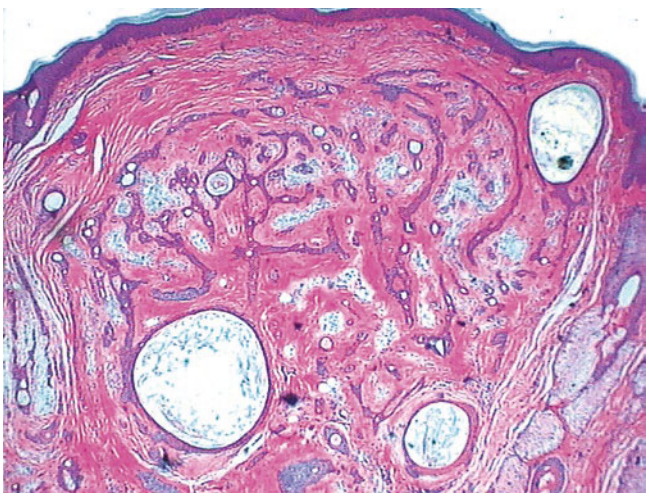


Fig. 27-20-1 A well-circumscribed, intradermal tumor was composed of many anastomosing cords and strands of epithelial cells with a reticulated pattern. There were multiple infundibular cystic structures scattered throughout the neoplasm (HE stain, ×40)

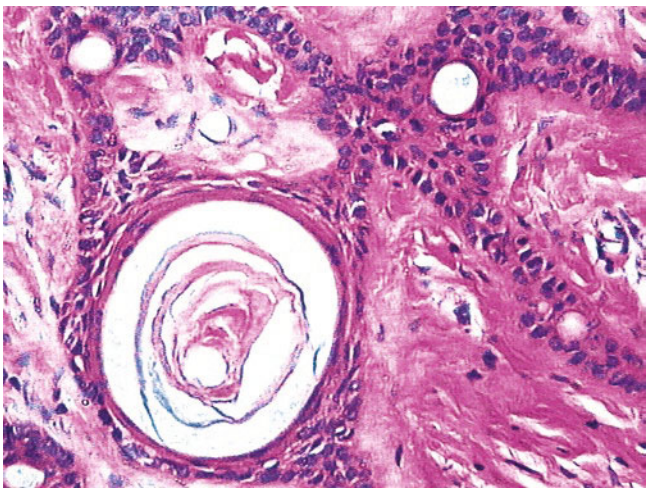


Fig. 27-20-2 Squamoid cells were present in the central of the tumor with oval pale nuclei, while peripheral cell layer was composed of basaloid cells with hyperchromatic, elongated nuclei in a palisade arrangement; the cysts containing corneocytes or wholly hair were lined by follicular infundibular epithelium; follicular bulbs and papillae were seen without mucin deposition (HE stain, ×200)

27.21 Trichofolliculoma [46]

- Trichofolliculoma typically appears as a central dilated pore with tufted hairs.
- Histologically, it has a central dilated infundibulum of a primary follicle and several secondary vellus hair follicles derived from it.

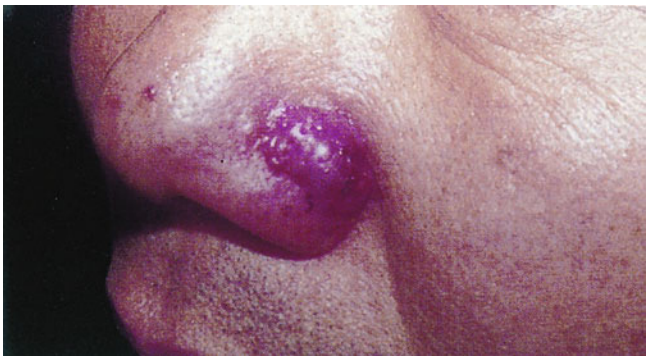


Fig. 27-21-1 Slightly reddish nodules on the left nasolabial folds with vellus hairs in a central pore

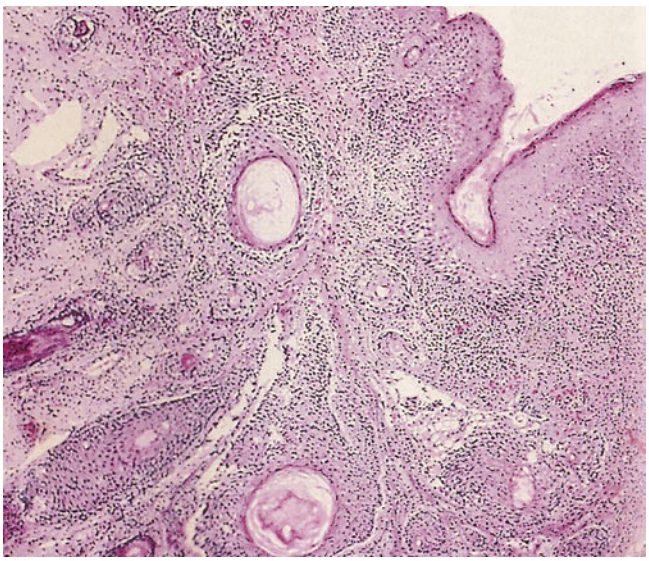


Fig. 27-21-2 Numerous keratinous cysts in the dermal, hair shaft with double refraction in the cysts (HE stain, ×50)

27.22 Trichoepithelioma [47–49]

- Trichoepithelioma (TE) is a benign trichogenic tumor derived from the hair follicle, and solitary, multiple, and dermoplastic TE are three distinctive variants.
- Microscopic observation of TE reveals basaloid epithelial cell islands, keratinous cysts, and abortive hair follicle structures characterized by follicular differentiation.
- Dermoplastic TE originates from the outer root sheath of the hair follicle. It usually manifests as a skin-colored, indurated papule or plaque with a peripheral annular ring and a depressed center. Islands of basaloid cells, dense fibrous stroma, and horn cysts serve as a dermatopathological triad for dermoplastic TE.
- CK20 and androgen receptor are the most reliable immunohistochemical biomarkers to distinguish dermoplastic TE from morpheaform basal cell carcinoma, which is considered potentially more aggressive than the benign nature of dermoplastic TE.
- Multiple TE may be cosmetically disfiguring, and it may rarely present in a linear configuration following Blaschko's lines.
- Trichoepitheliomas are part of a constellation of syndromes, including Brooke-Spiegler syndrome, Bazex syndrome, and Rombo syndrome.
- While solitary TE results from deletions at 9q22.3, multiple TE is associated with germline mutations in the CYLD gene mapped to chromosome 16q12–q13.
- Topical sirolimus, imiquimod, and tretinoin are proven to be beneficial in the management of multiple familial trichoepitheliomas.

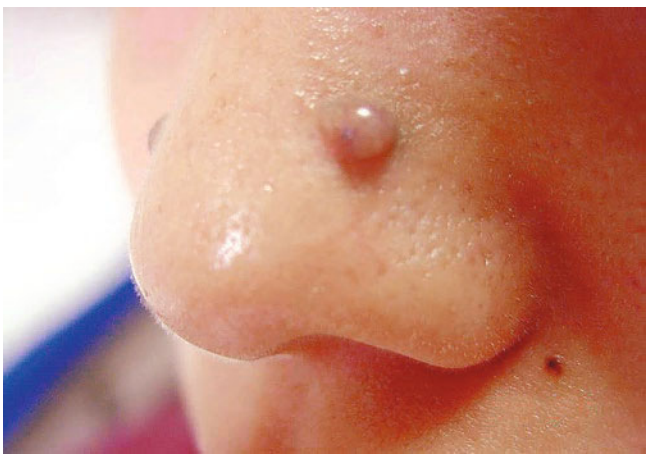


Fig. 27-22a-1 A mung bean-sized, half ball, light brown papule on the left nose wing

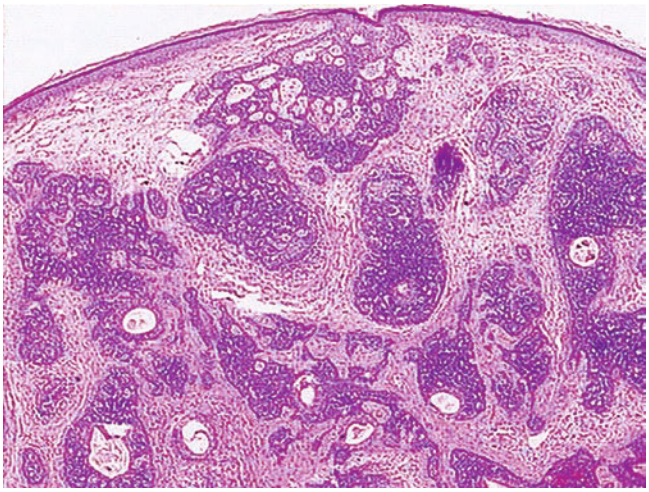


Fig. 27-22a-2 Numerous basaloid cell masses and cell cords containing horn cysts arranged in network in the dermis (HE stain, ×40)

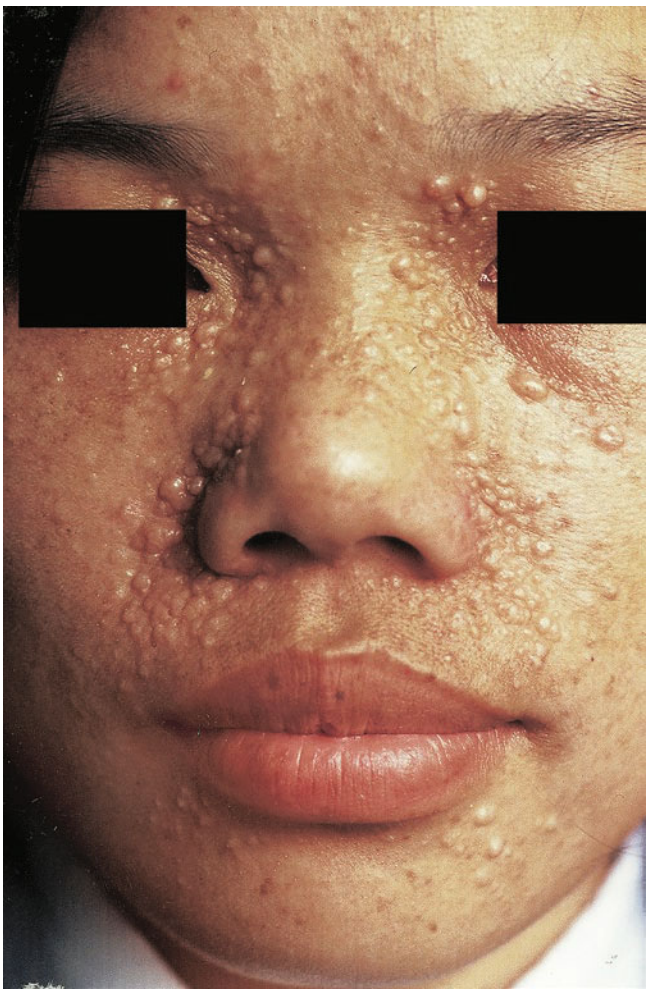


Fig. 27-22b-1 Multiple, varying-sized, rounded, shiny, slightly translucent, flesh-colored nodules on the face, especially on the central face

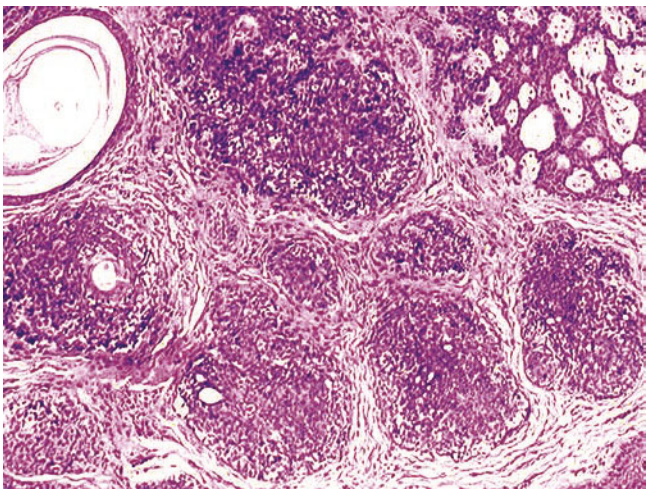


Fig. 27-22b-2 Numerous masses of basaloid cells in the dermis, keratinous cysts, and infantile follicle also observed (HE stain ×100)

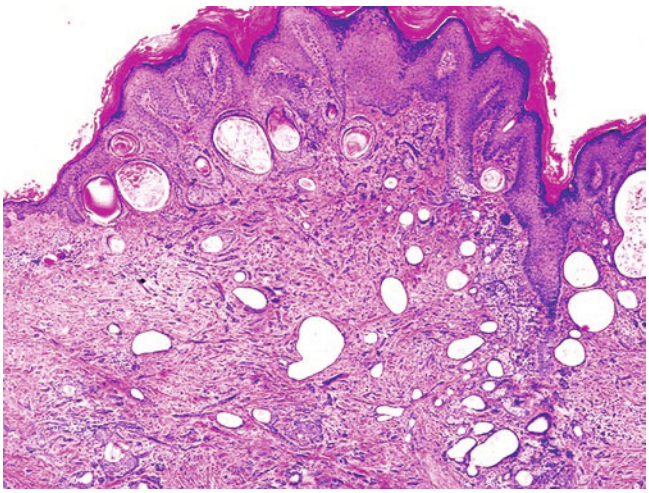


Fig. 27-22c-2 Horn cysts with various sizes, a strand of basaloid tumor cells in the upper dermis, and considerable amounts of collagen fibers (HE stain,×40)

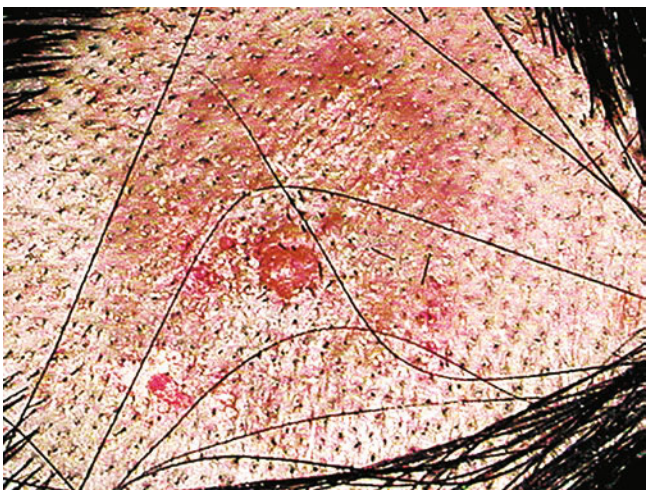


Fig. 27-22c-1 Damask, annular plaque with raised border and damask papules in the center of the scalp

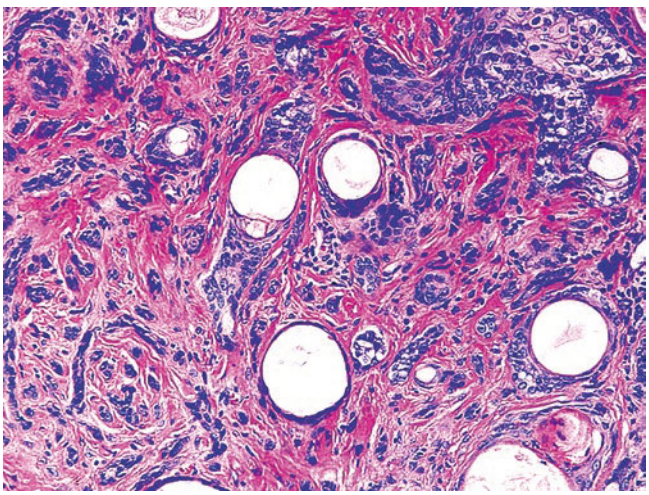


Fig. 27-22c-3 Numerous small horn cysts in the dermis, narrow strands of basaloid cells, and epidermoid cysts infiltrated a fibrotic stroma (HE stain, ×100)

27.23 Bullous Pilomatricoma [50, 51]

- Pilomatricoma is most seen as a solid, well-demarcated, and slow-growing dermal nodule with an overlying smooth surface. Many subtypes, including familial, bullous, perforating, multinodular, exophytic, anetodermic, and giant clinical types, have been previously reported.
- Bullous pilomatricoma typically arises as wrinkled, heavily folded, atrophic skin appearance with a predilection for the upper arm and shoulder.
- Skin biopsy of pilomatricoma exhibits basaloid hair matrix cells, transitional cells, and eosinophilic amorphous ghost cells. The bullous variant additionally features a marked reduction of elastic fiber and prominent dermal edema between the solid tumor and the covering epidermis.
- The bullous appearance is accredited to the hindrance of lymphatic fluid circulation by the hard central tissue.

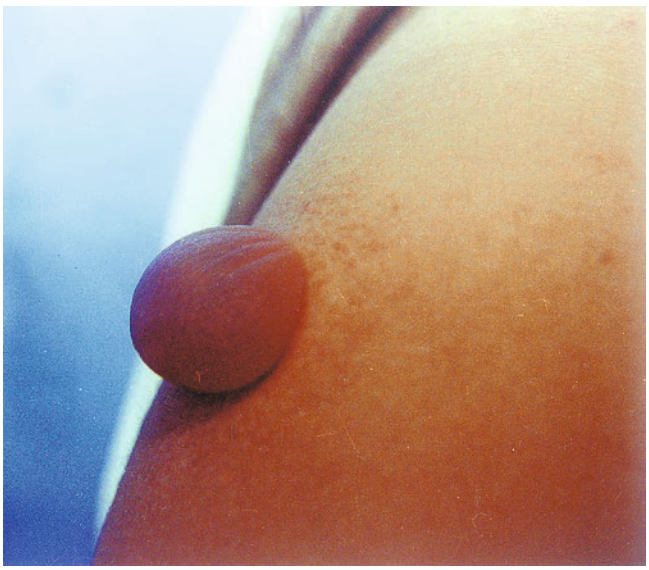


Fig. 27-23-1 A wrinkled, purplish, thick-walled, translucent, bulla 2.0 × 2.5 cm in diameter on the left upper arm

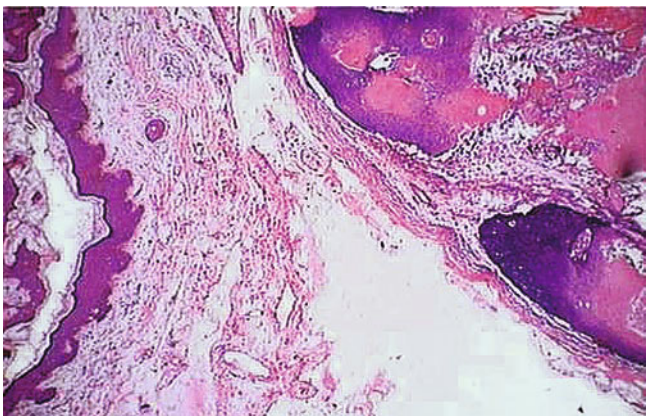


Fig. 27-23-2 The marked edema between the epidermis and tumor, markedly dilated thin-walled lymph vessels filled with fluid (HE stain, ×100)

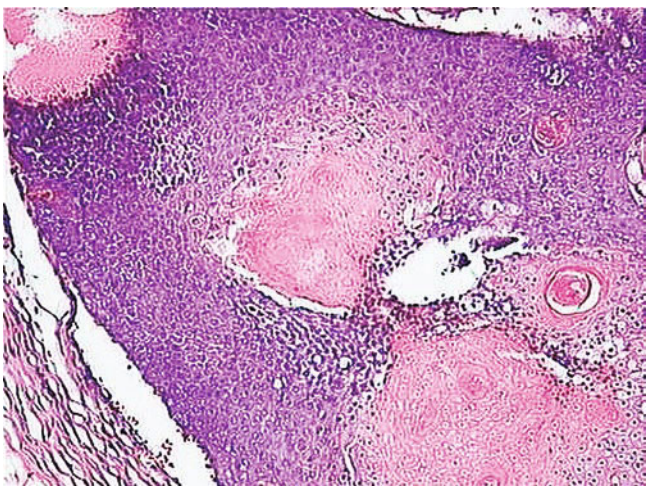


Fig. 27-23-3 The cell islands consisting of basophilic cells, transitional cells, and "shadow" cells with small calcifying areas (HE stain, ×400)

27.24 Areolar Sebaceous Hyperplasia [52–54]

- Sebaceous hyperplasia (SH) is a proliferation of the sebaceous gland.
- The most frequently affected area for SH is the face; the areola, nipples, penis, neck, and chest are atypical locations for it.
- Areolar SH presents as yellowish papules/plaque or diffuse thickening of the areola, either bilaterally or unilaterally.
- SH may lead to confusion with milia en plaque, nipple papilloma with sebaceous metaplasia, and Paget's disease.
- Giant, linear variants of SH have been documented.

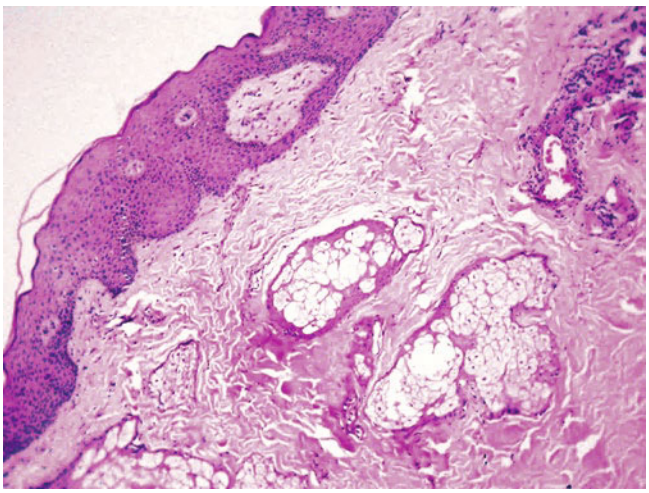


Fig. 27-24-2 Several enlarged sebaceous lobules in the upper dermis (HE stain, ×100)

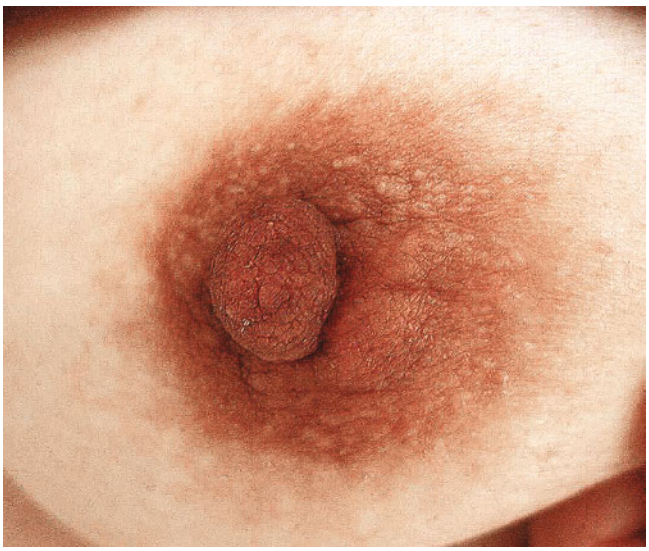


Fig. 27-24-1 Numerous skin-colored nodules around the right nipple

27.25 Nevus Sebaceous with Apocrine Cystadenoma [55–57]

- Nevus sebaceous (NS) is a demarcated, yellowish, hairless patch that commonly involves the scalp.
- NS and verrucous epidermal nevus may be the same entity, but they differ in locations. NS is designated to patches on the head and neck.
- NS is an innate hamartoma associated with epidermal, folliculosebaceous, and apocrine structures.
- The structures previously confirmed as BCC in NS may essentially be the benign tumor of trichoblastoma. Total excision is appropriate for those with a secondary tumor in NS.
- NS has a higher frequency of oncogenic HPV16 coinfection (39%).
- Apocrine cystadenoma (AC) is an adenomatous cystic proliferation rather than a simple retention cyst.
- This cystic tumor consists of layers of cuboidal cells showing decapitation secretion and underlying myoepithelial cells.
- A complete excision is recommended for AC, which is a real form of proliferation of the apocrine glands.

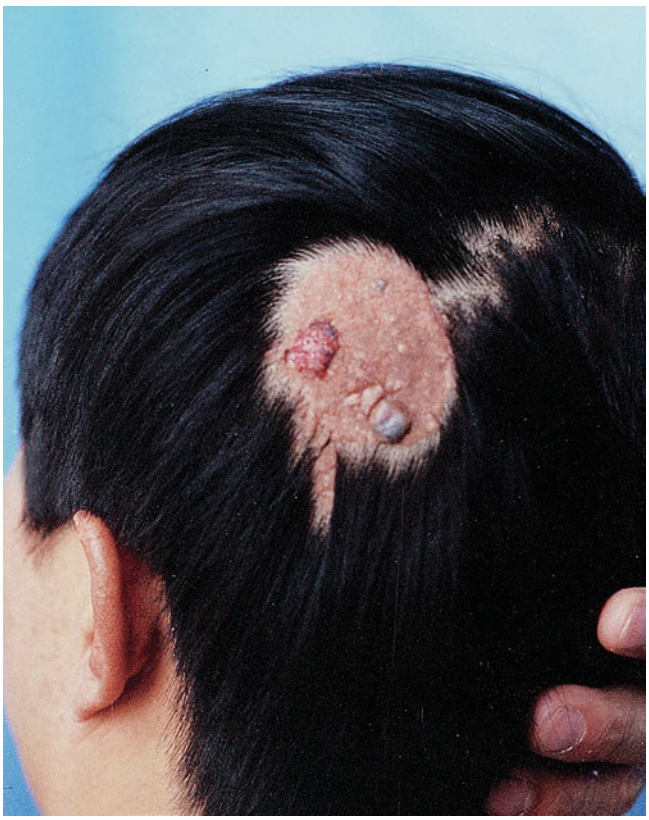


Fig. 27-25-1 A flaxen plaque with erosions on the scalp

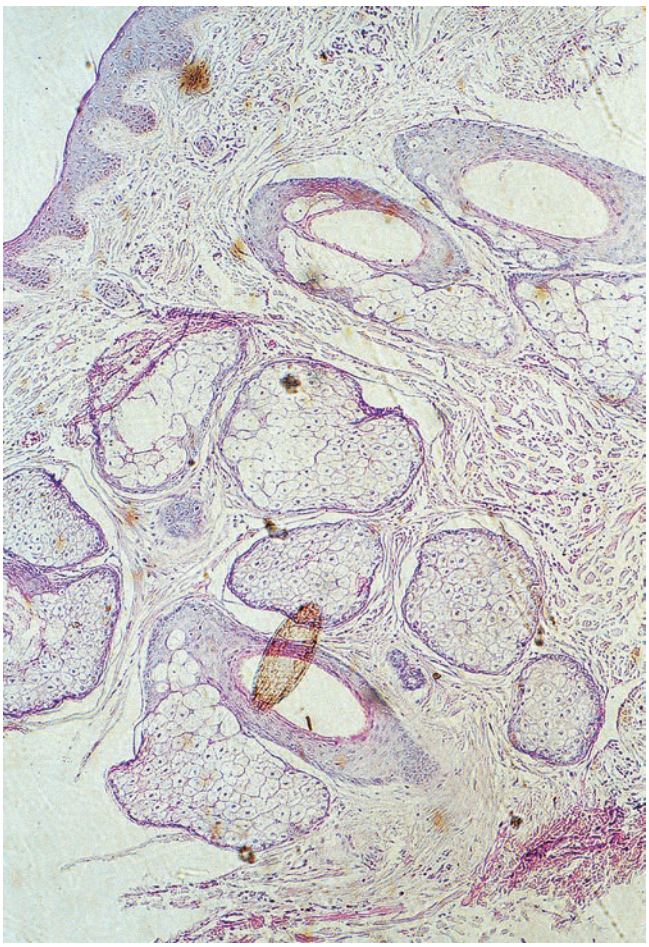


Fig. 27-25-2 Numerous mature sebaceous glands in the upper dermis (HE stain,×100)

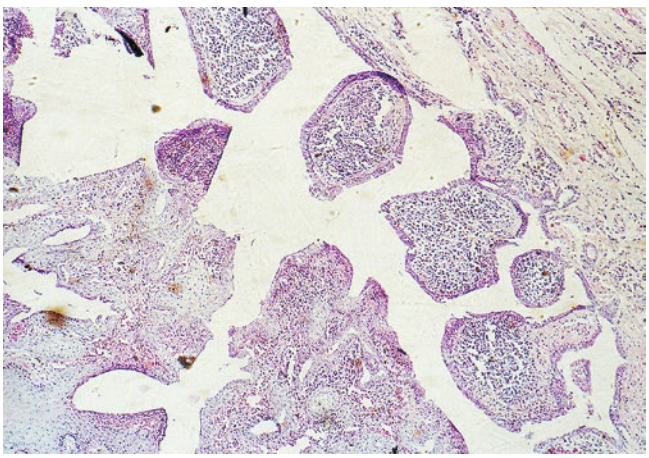


Fig. 27-25-3 Papillomatosis in the epidermis, a cystic invagination lined by two rows of cells, decapitation of the nearest luminal cells (HE stain, ×100)

27.26 Linear Nevus Sebaceous Syndrome [58, 59]

- Linear nevus sebaceous syndrome (LNSS) is within the spectrum of epidermal nevus syndrome or overlaps with neurocutaneous syndrome.
- Sebaceous nevus is the hallmark of LNSS, and it presents as linear, yellowish plaque, mainly on the midline facial skin. Seizures and mental retardation are its common extracutaneous defects, and they are sometimes difficult to control.
- The ophthalmologic defects of LNSS are composed of coloboma of the iris, lipodermoid, cataract, ptosis, degenerated retina, detachment of retina, and so on.
- In addition, there is also a diverse group of abnormalities in the structures of the pulmonary, cardiovascular, skeletal, renal, and gastrointestinal systems.
- Malignant transformation is likely to occur in LNSS.

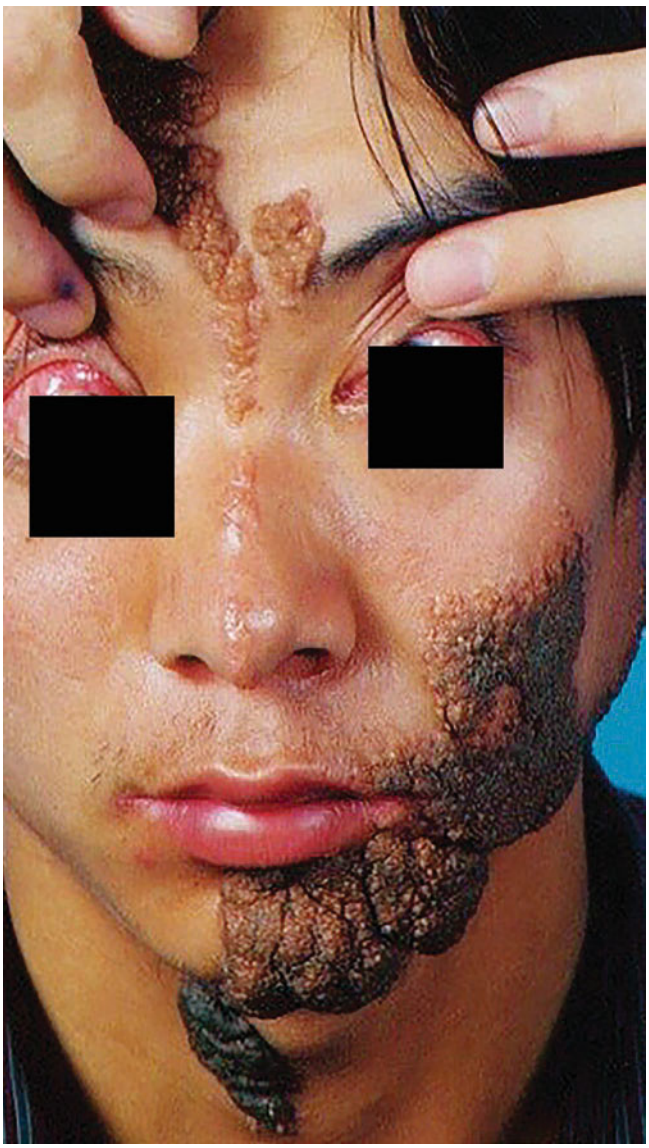


Fig. 27-26-1 Lesions of nevus sebaceous located in the midline of the scalp and on both sides of the face, pterygium of bilateral conjunctivae with high myopic retina (Reproduced with the permission from [58, 59])

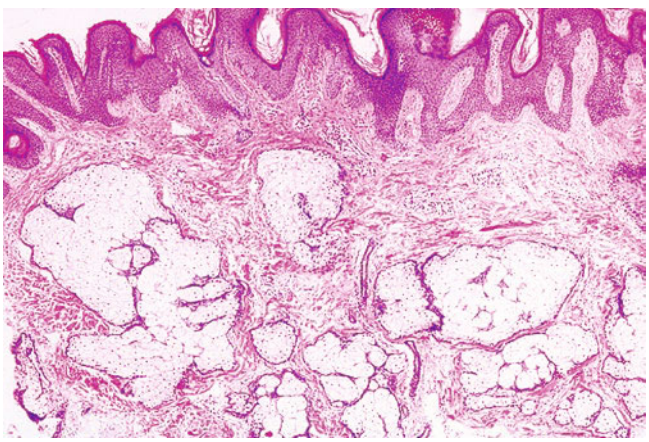


Fig. 27-26-2 A large number of sebaceous glands and papillomatous hyperplasia of the epidermis with hyperkeratosis (HE stain, ×100)

27.27 Apocrine Hidrocystoma [60, 61]

- Apocrine hidrocystoma (AH) is a translucent nodular lesion that affects the face, head, and neck.
- The color of AH varies from flesh-colored to blue, brownish, or even black.
- AH and apocrine cystadenoma (AC) are both described as a cystic proliferation of apocrine glands.
- AC is not a simple retention of cyst apocrine; it has papillomatous hyperplasia of the apocrine, which projects into the cystic lumen. Apocrine papillary cystadenoma is regarded as a variant of AC with enormous papillary projections.
- There is prevailing belief that cystic apocrine neoplasm without papillary projections into the cystic cavity should be diagnosed as apocrine hidrocystoma.

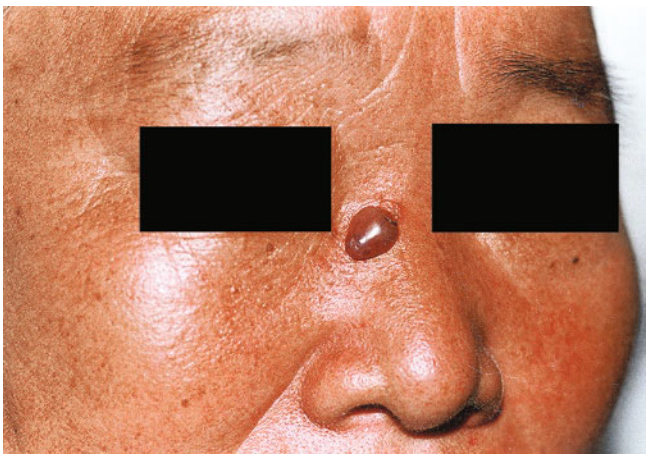


Fig. 27-27-1 A rufous translucent nodule of cystic consistency on the right of the nose bridge

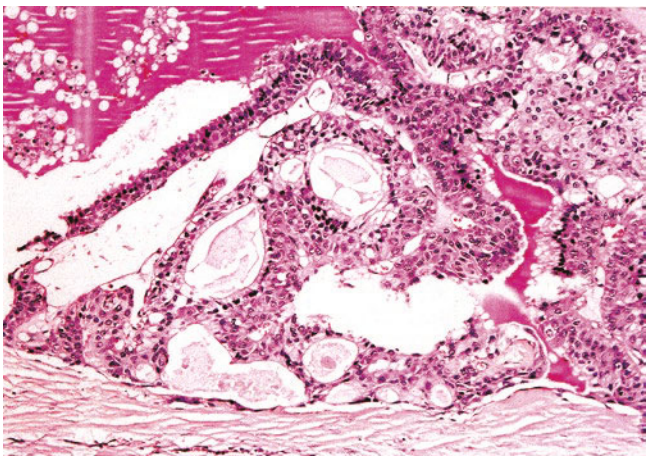


Fig. 27-27-2 The dermis contained several large cystic spaces into which papillary projections often extended; the inner surface of the wall and the papillary projections were lined by a row of secretory cells of variable height showing "decapitation" secretion indicative of apocrine secretion (HE stain, ×100)

27.28 Eccrine Angiomatous Hamartoma [62, 63]

- Eccrine angiomatous hamartoma (EAH) is abnormal proliferation of the skin eccrine and blood vessels, and it usually has a predilection for the extremities.
- Approximately half of the patients develop EAH at birth, and 3/4 of the remaining patients develop EAH in adolescence.
- Lesions in EAH are quite variable, including red, yellow, brown, skin-colored papules or plaque. Hyperkeratotic, verrucous variants are also seen.
- Some patients may complain about obvious hyperhidrosis, pain, or hypertrichosis.
- Histological observation reveals a tubular and glandular structure within an enriched vascular structure.

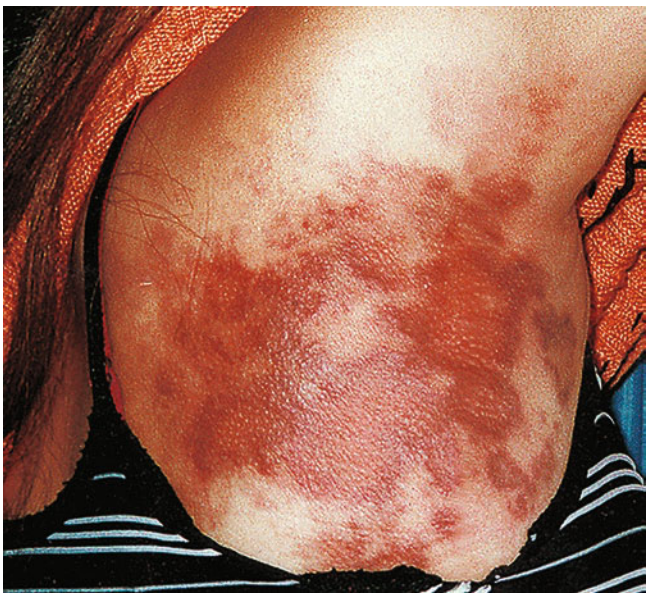


Fig. 27-28-1 Bluish multi-annular macules with elevated edges and numerous follicular papules in the lesions

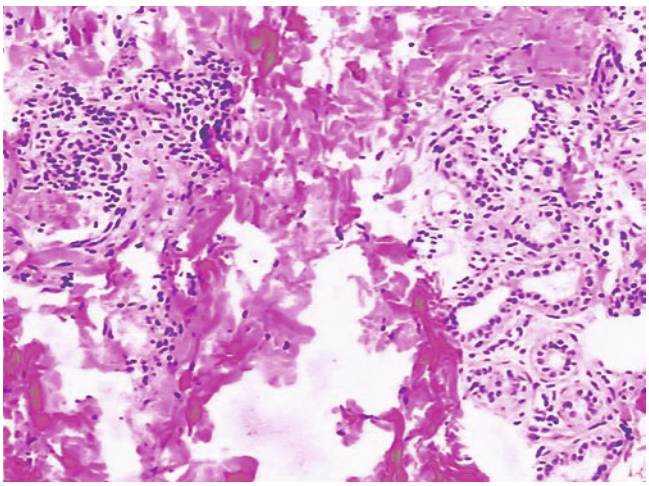


Fig. 27-28-2 Dilated blood vessels in the lower dermis, nearby numerous dilated ducts of eccrine glands (HE stain, ×400)

27.29 Syringocystadenoma Papilliferum [64–66]

- Syringocystadenoma papilliferum (SCAP), in the majority of cases, appears on the scalp, neck, or face in females.
- SCAP clinically arises as a solitary papule, nodule, or plaque. These lesions are verrucous or exudative. Rarely, it may be present in a linear configuration.
- A unifying pathological feature of SCAP is the presence of a cystic and papillary projection of scaly epithelium and rich infiltration of plasma cells in the stroma. There are two types of tumor cells. In the outer layer, there are cuboidal cells characterized by round nuclei and scarce cytoplasm. The inner layer is comprised of decapitated columnar cells.
- SCAP is most contiguous with an organoid nevus comprised of basal cell carcinoma, nevus sebaceous, and trichilemmoma.

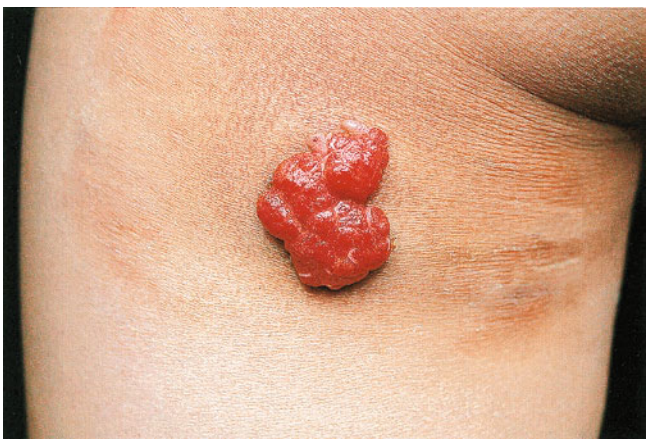


Fig. 27-29-1 A solitary red tumor on the flexor aspect of the left leg

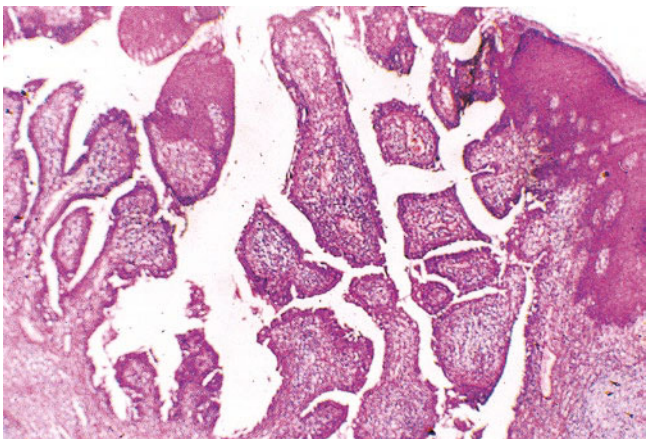


Fig. 27-29-2 Numerous papillary projections into the lumina of the invaginations (HE stain, ×100)

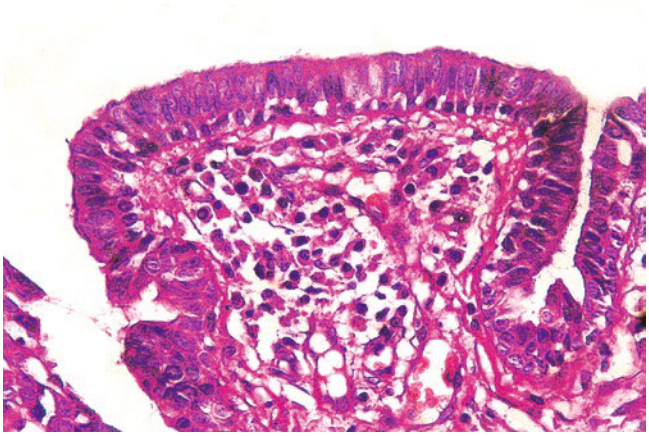


Fig. 27-29-3 The invaginations were lined by glandular epithelium consisting of two rows of cells (HE stain, ×400)

27.30 Eruptive Milium-Like Syringoma [67, 68]

- Syringoma appears as multiple, firm, flesh-colored, or brownish papules, 1–3 mm in diameter.
- Friedman et al. proposed that syringoma can be classified into four clinical subtypes: localized, familial, Down syndrome-related, and generalized variants.
- Skin biopsy of syringoma reveals aggregations of nests, cords, or tubules, lined by single- to double-layered cuboidal epithelium, giving them a tadpole shape. Some ducts are dilated and contain eosinophilic materials.
- In localized syringoma, the periorbital, vulva, penis, scalp, and axillae are predominantly involved.
- Generalized syringomas tend to have multiple systemic associations, as shown in Brooke-Spiegler syndrome, Nicolau-Balus syndrome, and Costello syndrome.
- Eruptive milium-like syringoma occurs in successive crops of small papules with superimposed variable milia that are distributed extensively over the chest, axillae, neck, abdomen, and extremities.
- Lichen planus-like syringoma has lichenoid plaques caused by repetitive scratching.
- In comparison to classical syringoma, the onset of the eruptive type mostly occurs before or during puberty.
- Unilateral syringoma, urticarial pigmentosa-like syringoma, clear cell syringoma, and chondroid syringoma are its other demonstrations.
- The dermoscopic features of eruptive syringoma are comprised of a rosette structure and a nonspecific structure of the pigment network with a reddish tinge.

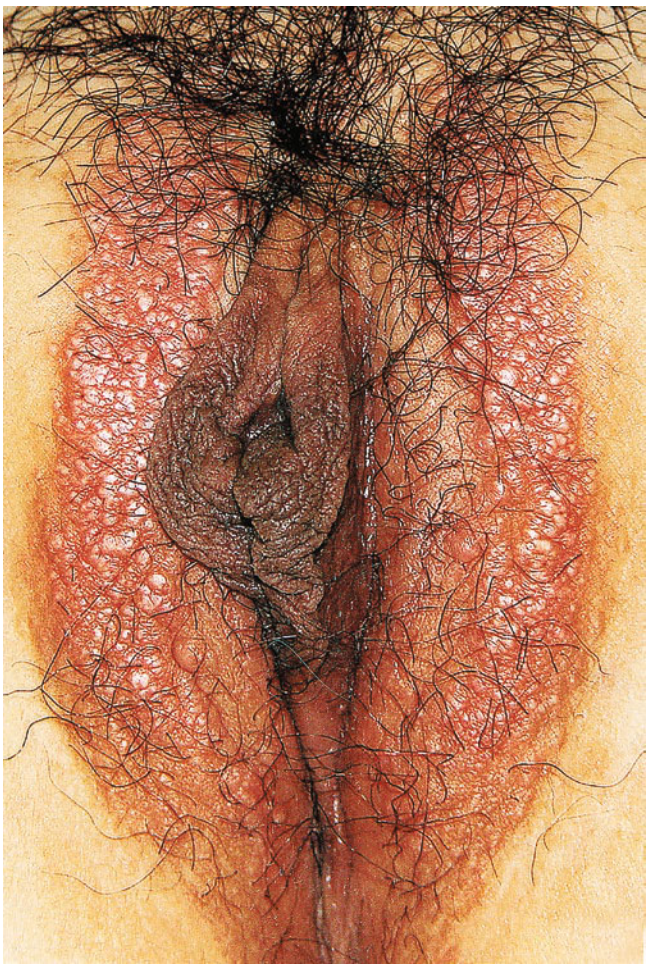


Fig. 27-30-1 Dense millet to mung bean-sized skin-colored papules on both of the labia majora

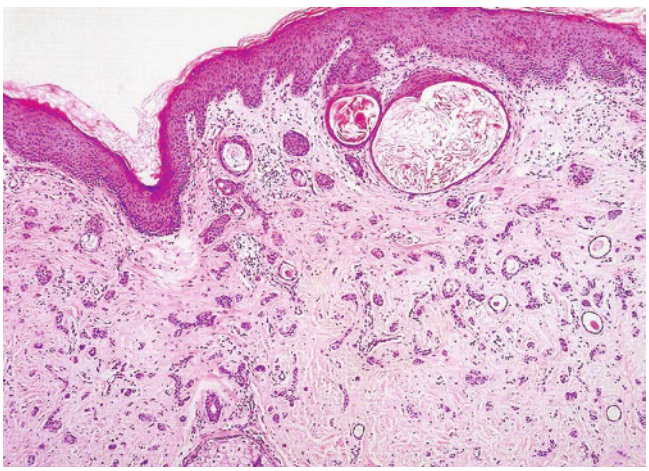
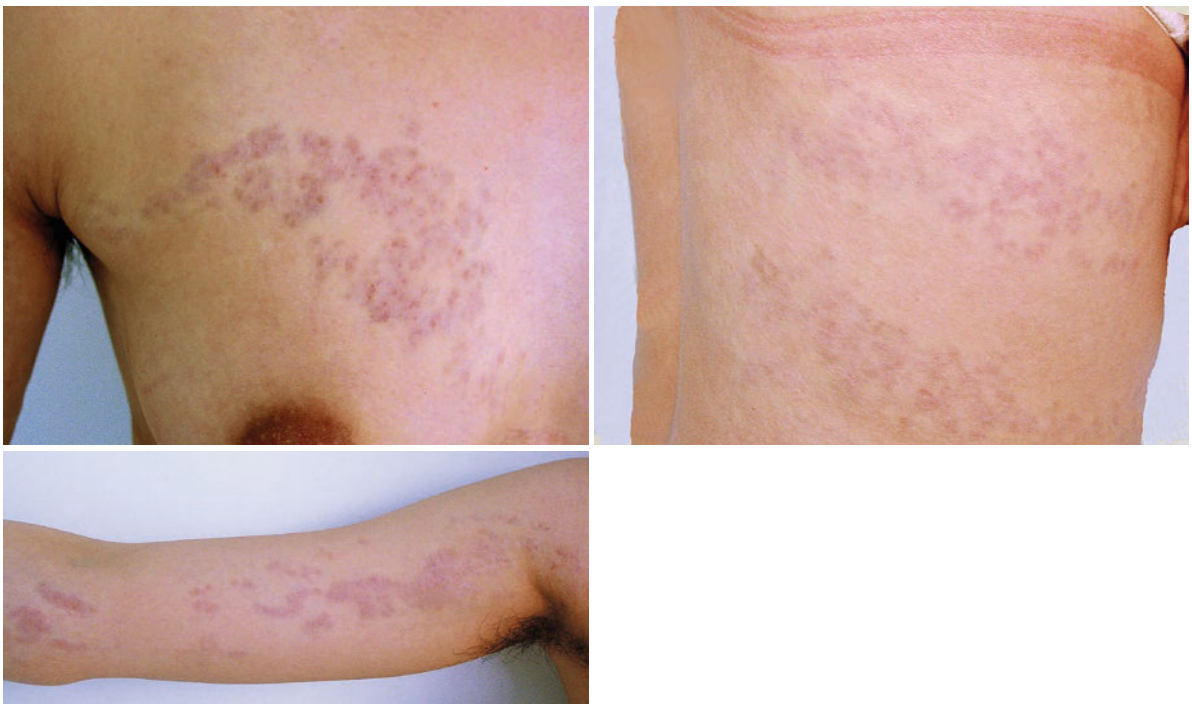


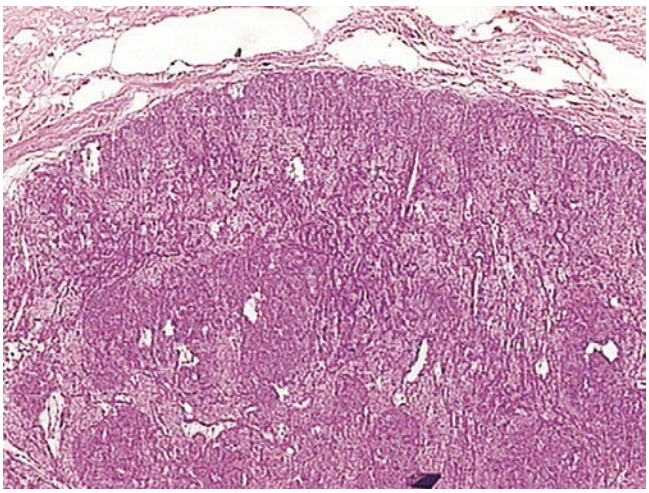
Fig. 27-30-2 Hyperkeratosis, keratin cysts in superficial dermis, cystic ductal lumina filled with acidophil, and many cell cords (HE stain, ×40)

27.31 Segmental Multiple Eccrine Spiradenomas [69–71]

- Eccrine spiradenoma (ES) usually occurs as subcutaneous papule or nodule ranging from 1 to 2 cm in diameter. An overlying pink or blue hue is highly suggestive of its diagnosis.
- ES is in the spectrum of painful skin disorders, including neuroma, leiomyoma, angiolipoma, dermatofibroma, endometrioma, neurilemmoma, granular cell tumor, and glomus tumor.
- Clinically, ES is classified as solitary and multiple variants. Histological classification of ES includes common, vascular, and cystic variants.
- ES is comprised of multiple, well-circumscribed, basophilic subcutaneous nodules surrounded by eosinophilic fibrous strands. Two types of distinct cells are clues for its diagnosis: larger, pale staining clustered cells at the center and smaller cells characterized with peripheral hyperchromatic nuclei. Duct-like structures may exist at the center.
- S-100, pancytokeratin, and CK7 are expressed on tumor cells in ES.
- Vascular eccrine spiradenoma, a rare variant of ES, contains abundant vascular stroma.
- In Brooke-Spiegler syndrome, spiradenomas commonly occur jointly with cylindromas and trichoepitheliomas.



Figs. 27-31-1, 27-31-2, 27-31-3 Zosteriform distribution of purple macules on the right chest, flexor side of upper limb, waist, and abdomen along the intercostal nerve or long axis of limb



Figs. 27-31-4 A large and well-circumscribed, dermal nodule comprised of tumors was surrounded by fibrous membrane (HE stain, ×100)

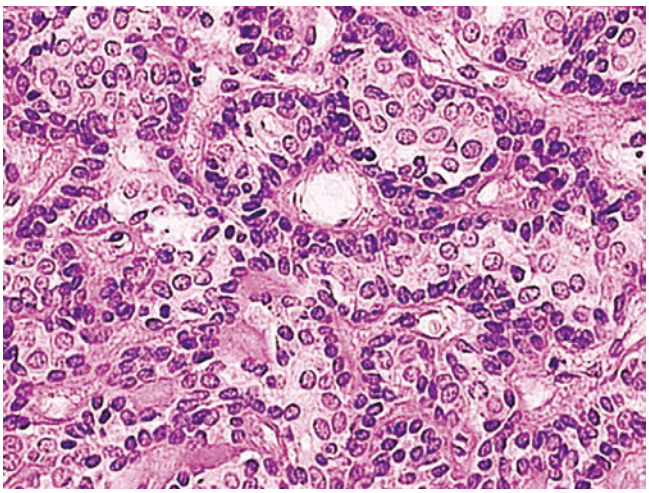


Fig. 27-31-5 Tumors were composed of cells with large, lightly stained nuclei located in the center of the tumor and some cells with small, darkly stained nuclei around the tumor. Some tumor cells were arranged in rose pattern with a few small lumina (HE stain, ×100)

27.32 Clear Cell Hidradenoma [72–74]

- Clear cell hidradenoma (CCH) is a benign neoplasm from a skin appendage. It usually presents as a solitary unencapsulated dermal nodule.
- Microscopic observation in CCH shows a grenz zone between the epidermis and tumor masses. CCH are composed of polyhedral cells with basophilic cytoplasm and oval cells with vacuolated cytoplasm.
- The oval cells have rich glycogen without lipid, and they stain positively with periodic acid-Schiff and diastase-resistant material.
- Metastatic renal cell carcinoma and other clear cell neoplasms should be cautiously excluded before the final diagnosis of CCH.
- Immunohistochemical studies are valuable in distinguishing CCH (CK5+, CK6+, CK7+) from renal cell carcinoma (vimentin+, CD10+).

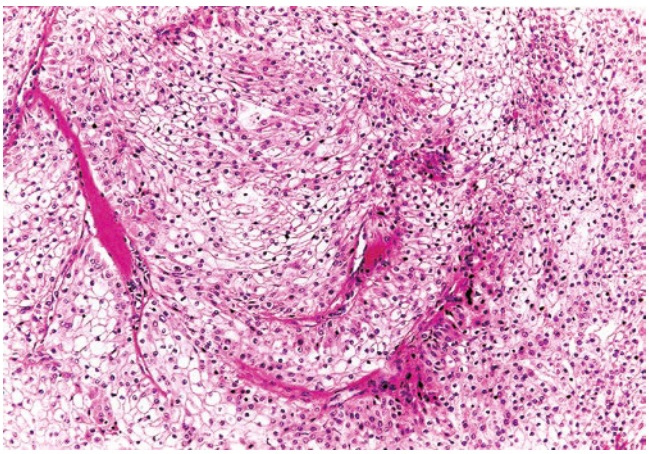


Fig. 27-32-2 The tumor consisting of polyhedral cells and clear cell, with transitional cells between these two varieties and cystic and lumina spaces also observed (HE stain, ×100)

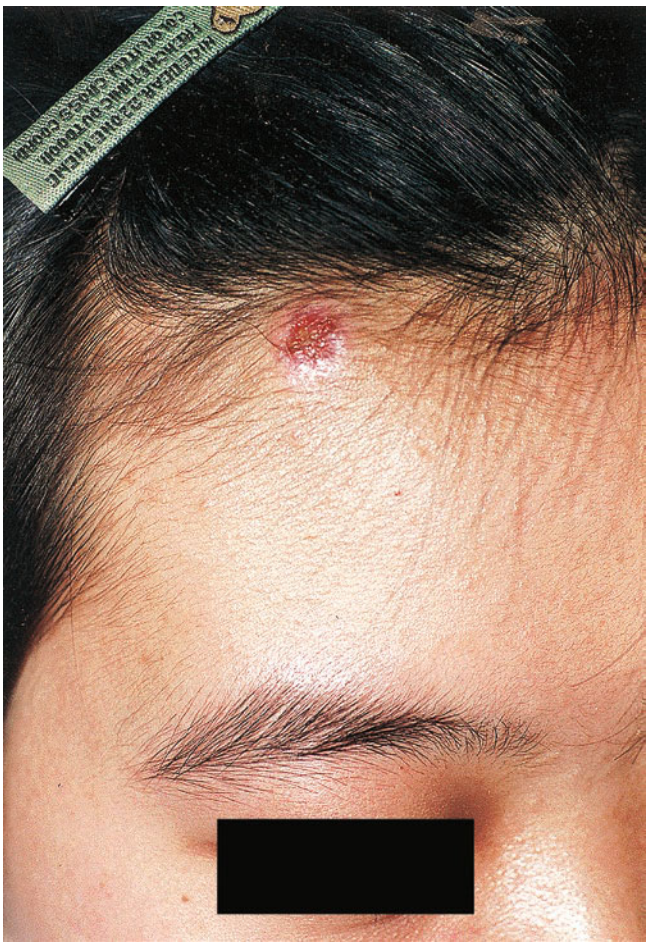


Fig. 27-32-1 A well-circumscribed, rosiness nodule with crust on the forehead

27.33 Malignant Eccrine Poroma [75–77]

- Malignant eccrine poroma (MEP) often appears as nodular, ulcerated, or polypoid, and it occurs on the intraepidermal eccrine duct.
- MEP arises spontaneously or from an eccrine poroma that has existed for a long time.
- The neoplasm consists of squamous cells, spindle cells, and differentiated clear cells. Pagetoid spreading of melanocytes is reported in MEP.
- The vacuolated cytoplasm, duct-like structures, and eosinophilic cuticles in MEP are signs of eccrine differentiation.
- The nuclei of these tumor cells are large. The cells have a higher mitotic rate (compared to normal cells) and clear cytoplasm, and they show EMA+, S-100 -, and CEA−.
- Histopathological findings of lymphovascular invasion, mitosis >14 per high-power field, depth of invasion >7 mm, and lymph node involvement are predictive of a fatal prognosis.

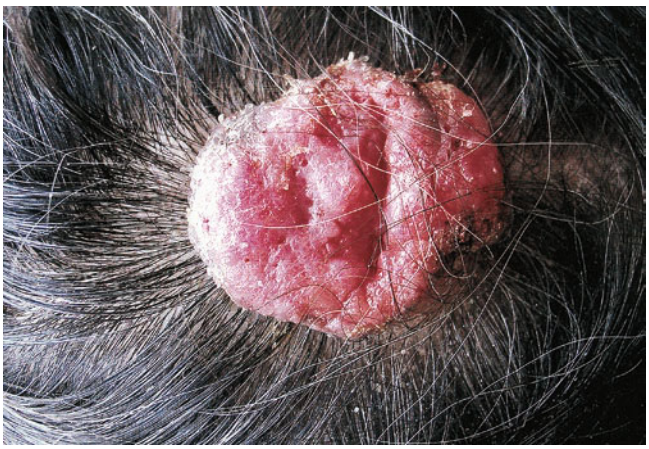


Fig. 27-33-1 A well-circumscribed, walnut-sized, brownish-red nodule with erosions and wet base on the scalp

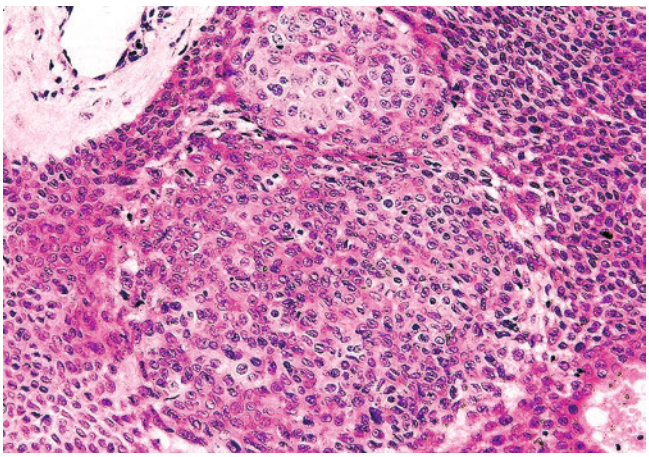


Fig. 27-33-2 Tumor located in the epidermis, composed most of basaloid cells and some atypically eosinophilic squamous cells scattered as masses (HE stain, ×200)

27.34 Microcystic Adnexal Carcinoma [78–80]

- Microcystic adnexal carcinoma (MAC) is a locally invasive neoplasm with pilar and eccrine gland differentiation that rarely metastasizes.
- MAC appears as a firm subcutaneous papule, nodule, plaque, or cystic lesion. It has a predilection for the central face or T zone.
- The report of numbness, paresthesia, burning, or pruritus at the tumor site indicates perineural invasion.
- The histological features in MAC are comprised of horn cysts and epithelial cells arranged in a nest strand or a cord pattern in the superficial dermis. Ductal structures are embedded in a desmoplastic matrix in the deep dermis.
- The lack of circumscription, deep dermal involvement, and perineural invasion are helpful diagnostic features.
- As radiation promotes MAC development, it should be discouraged in its management.

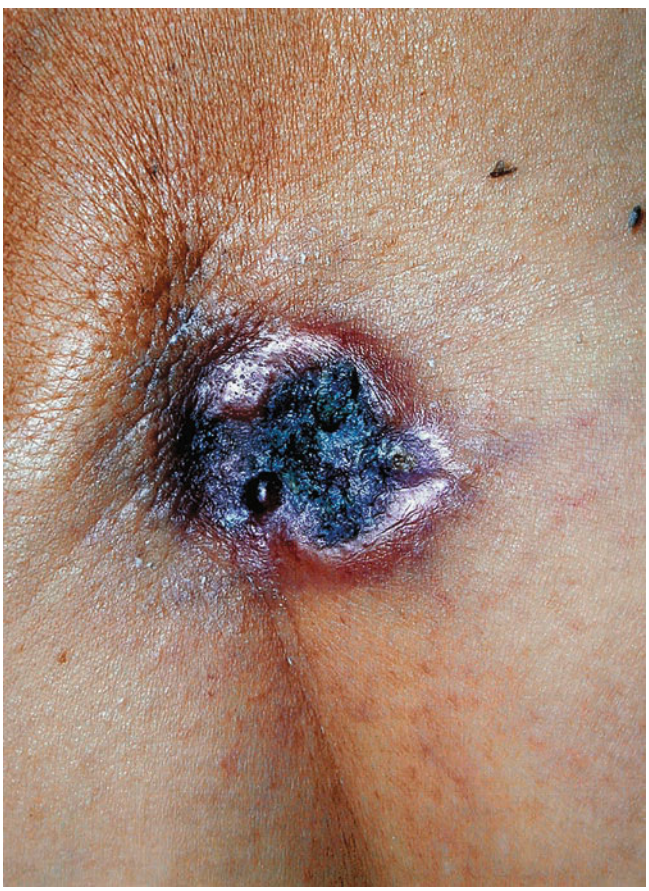


Fig. 27-34-1 An indurated and unmovable plaque with a black crust on its surface on the right chest

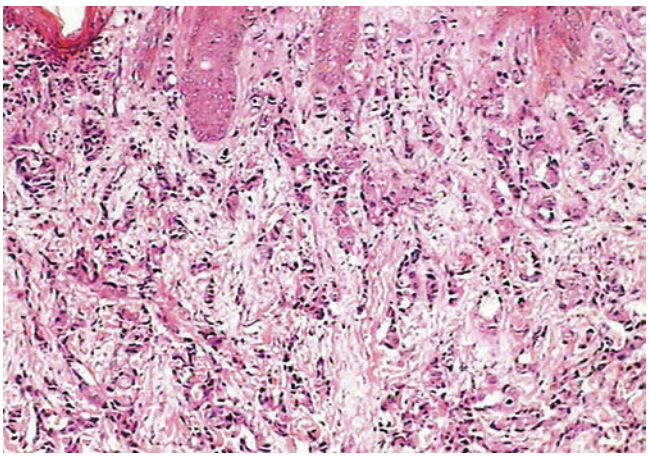


Fig. 27-34-2 Hyperkeratosis and tumor cell were arranged in funicular pattern, cord, and adenoid structures (HE stain, ×100)

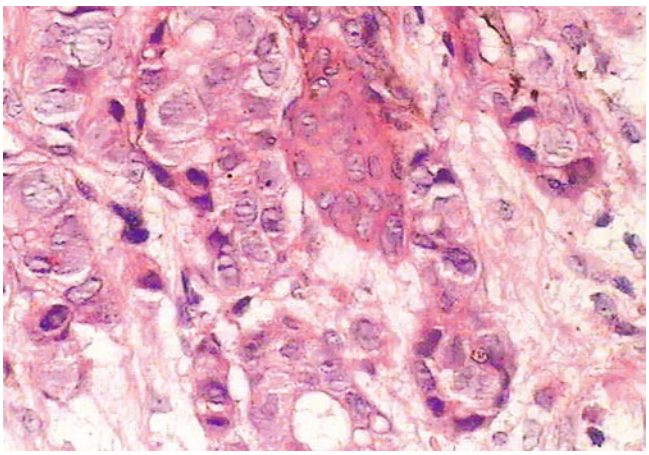


Fig. 27-34-3 Sparse solid islands of squamous cells surrounded by basaloid cells (HE stain, ×400)

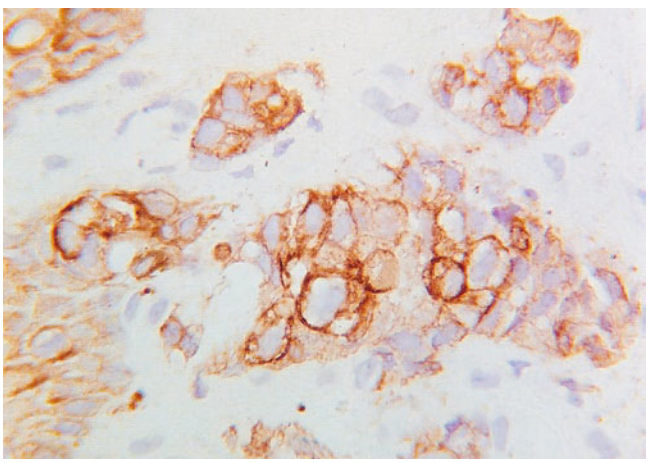


Fig. 27-34-4 Tumor cells AE1/AE3 positive (En Vision method, ×400)

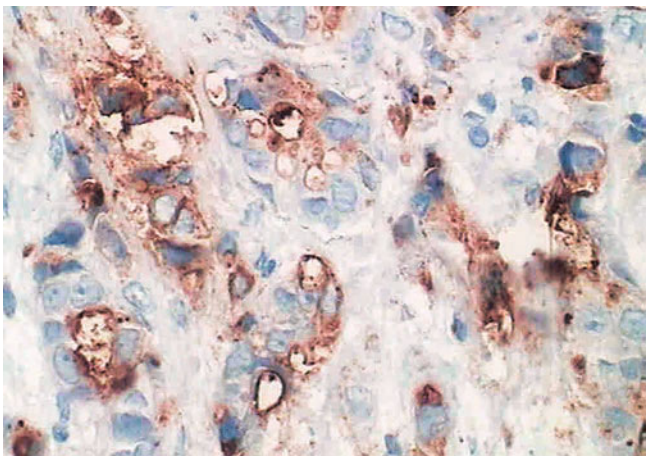


Fig. 27-34-5 Part tumor cells CEA positive (En Vision method, ×400)

27.35 Acquired Digital Fibrokeratoma [81, 82]

- Acquired digital fibrokeratoma (ADF) is a hyperkeratotic, fibrous periungual neoplasm.
- ADF clinically presents as a solitary, smooth, dome-shaped or fingerlike, flesh-colored papule of the extremities.
- Histologically, it features connective tissue proliferation with an overlying epidermal orthokeratosis or hyperkeratosis, papillomatosis, and acanthosis.
- Differentiation of ADF with the periungual tumors includes Koenen tumors of tuberous sclerosis, rudimentary supernumerary digits, endochondromas, and neurofibromas.
- APF is mainly different from acquired digital fibrokeratoma in the aspects of location, microscopic production of a pseudo-nail plate, and a requirement for meticulous surgery to preserve the germinal matrix.

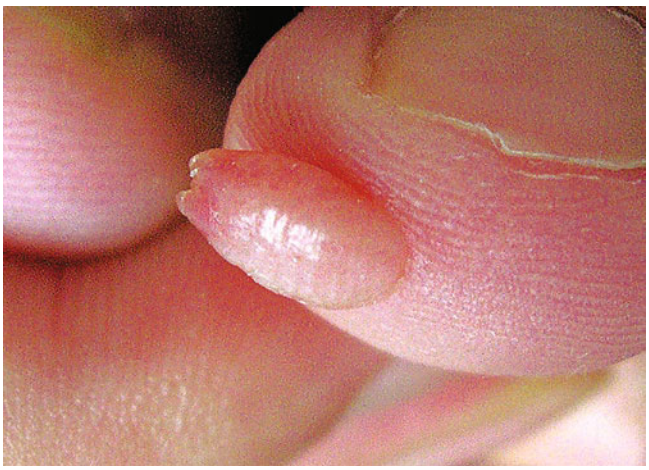


Fig. 27-35-1 A damask, digital neoplasm on the second toe tip of the right foot

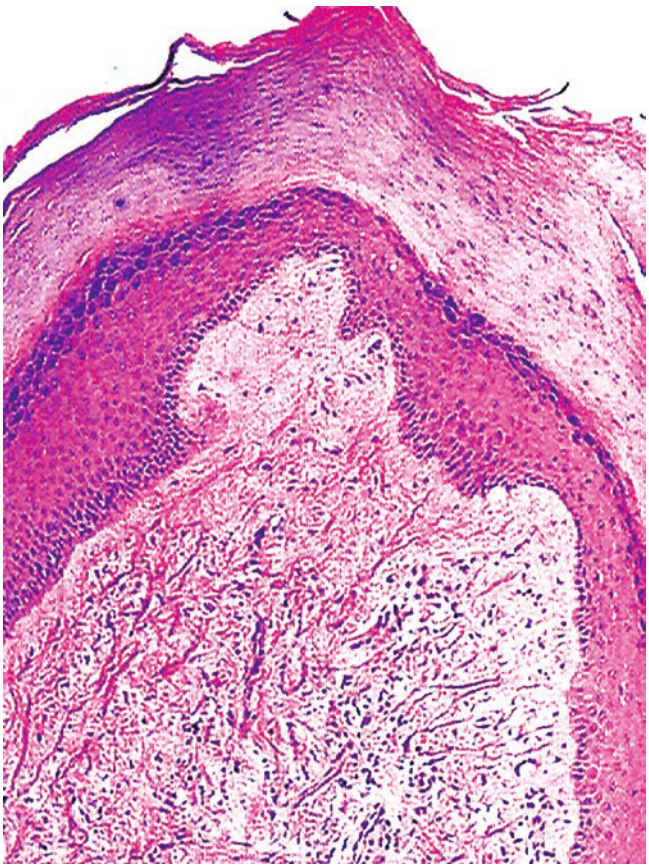


Fig. 27-35-2 The epidermis showed marked hyperkeratosis and acanthosis with thickened, branching rete ridges (HE stain, ×40)

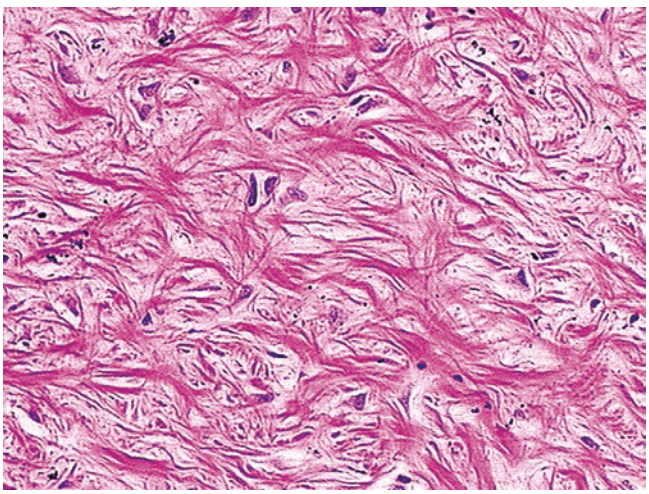


Fig. 27-35-3 Considerable amount of collagen fibers and fibroblasts in the dermis (HE stain, ×100)

27.36 Epithelioid Cell Histiocytoma [83–85]

- Fibrous histiocytoma has a densely cellular form (histiocytoma) or a dominant collagenous form (fibromas).
- Histiocytoma can be classified into following subtypes: classic, storiform, xanthomatized, monster cell, hemosiderotic, giant cell, and epithelioid cell histiocytoma (ECH).
- Several variants of fibroma have been proposed. They are classic, sclerotic, and hyalinized fibroma, as well as angiofibromas.
- Epithelioid cell histiocytoma can be single, multiple, or eruptive. It is made up of different proportions of proliferated histiocytes, fibroblasts, and collagen.
- ECH is dominantly an exophytic nodular lesion with a silhouette of pyogenic granuloma.
- The histological features of ECH include angulated epithelia embedded in massive vascular stroma. The cytoplasm is filled with eosinophilic materials. Spindle-shaped cells with ovoid or tapering nuclei are located underneath the deep dermis.
- Immunohistochemical stainings are XIIIa+, vimentin+, and al-antitrypsin+. The absence of S-100 and HMB-45 rules out melanocytic disorders.
- The granular cell variant of ECH has also been documented.

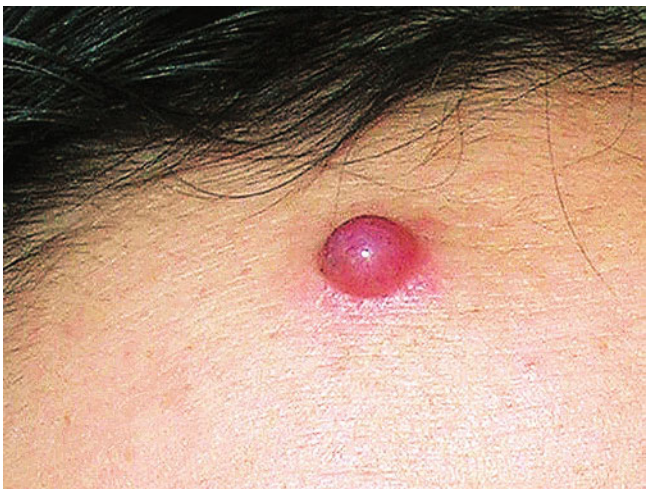


Fig. 27-36-1 A well-circumscribed protuberant violaceous nodule on the forehead

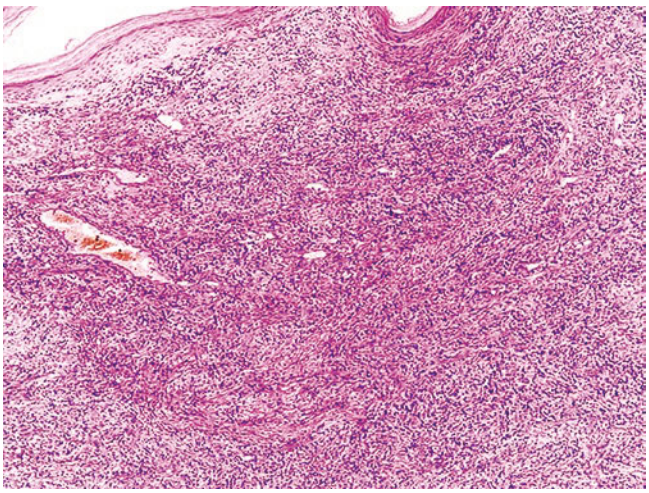


Fig. 27-36-2 Marked hyperplasia and dilated vessels in the tumor tissue and slight collagen fiber hyperplasia (HE stain, ×100)

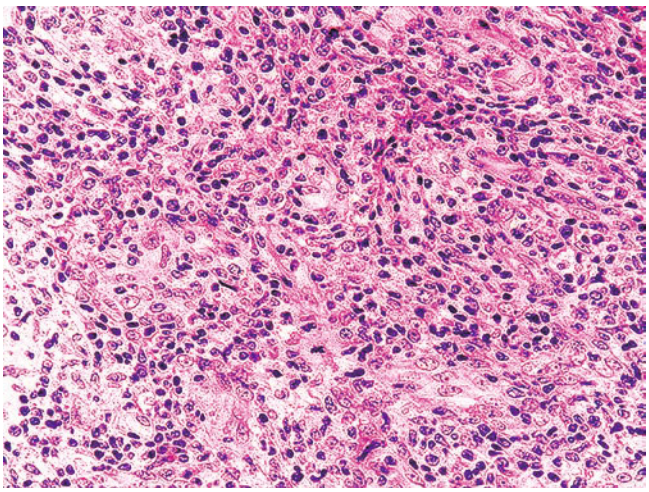


Fig. 27-36-3 The tumor was mainly composed of epithelioid cells and prominent plasma cells with nuclei mitoses (HE stain, ×400)

27.37 Multiple Eruptive Dermatofibromas [86–88]

- Multiple eruptive dermatofibromas are a rare clinical form of dermatofibroma, which is defined as the occurrence of no less than eight dermatofibromas within a 4-month period.
- There is a spontaneous regression of these lesions over several months.
- Histiocytosis X, juvenile xanthogranuloma, papular xanthoma, sinus histiocytosis with massive lymphadenopathy, urticaria pigmentosa, and benign cephalic histiocytosis should be excluded before MEDF is diagnosed.
- The relationship between the immunosuppressive level of the patient and the occurrence of MEDF has led to the speculation that MEDF is an additional sign of immunosuppression.

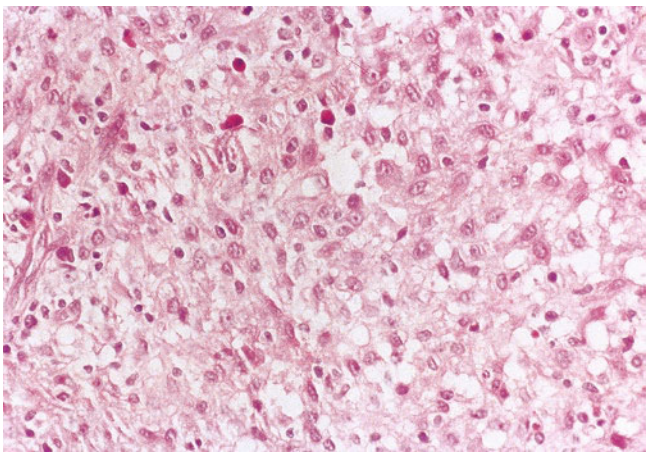


Fig. 27-37-2 Infiltrate composed of various types of histiocytes in the dermis (HE stain, ×400)

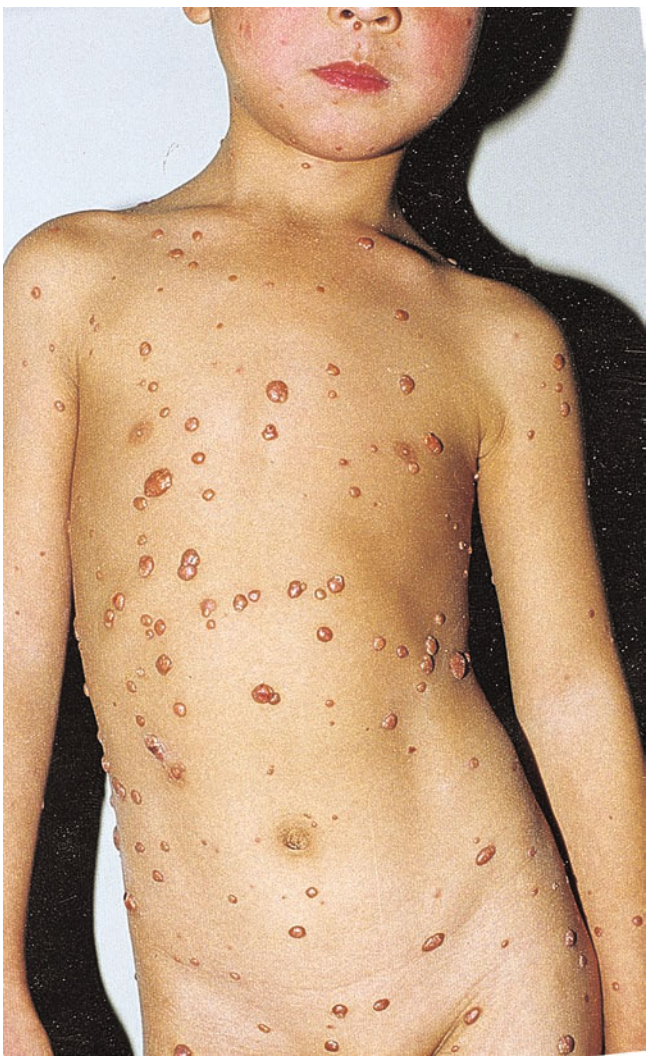


Fig. 27-37-1 Numerous flesh-colored to red papules on the trunk

27.38 Intradermal Nodular Fasciitis [89, 90]

- Nodular fasciitis (NF) is a benign myofibroblastic proliferation that commonly occurs in young adults.
- NS has a distinct predilection for subcutaneous (particularly the volar aspect of the forearms), intramuscular, fascial, or periosteal areas. Intradermal nodular fasciitis is extremely rare.
- It characteristically manifests as a rapidly growing, circumscribed tender nodule within a few weeks.
- Microscopic observation of NF reveals a loose myxoid stroma and numerous spindle cells with eosinophilic cytoplasm. It can be categorized into myxoid, cellular, and fibrous pathological variants, and the immunoprofile is SMA+, vimentin+, CD34−, and desmin−. In intradermal NF, fibroblast-like spindle cells deeply infiltrate into the subcutaneous skin.
- NF can be easily misdiagnosed as sarcoma owing to its rapid growth, abundant cellularity, mitotic activity, and contiguous tissue infiltration.
- Local excision or strict follow-up is appropriate management for the confirmed NF patient.

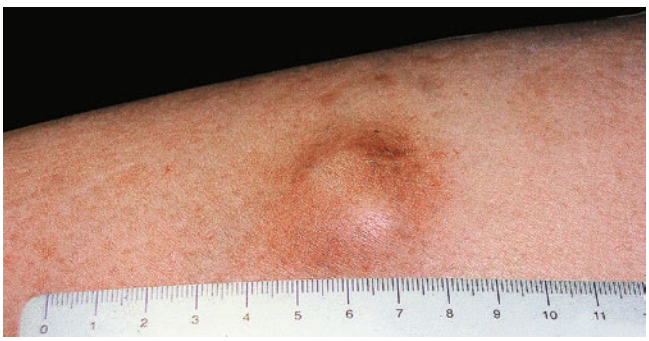


Fig. 27-38-1 A subcutaneous nodule without pain and ulcer on the left leg

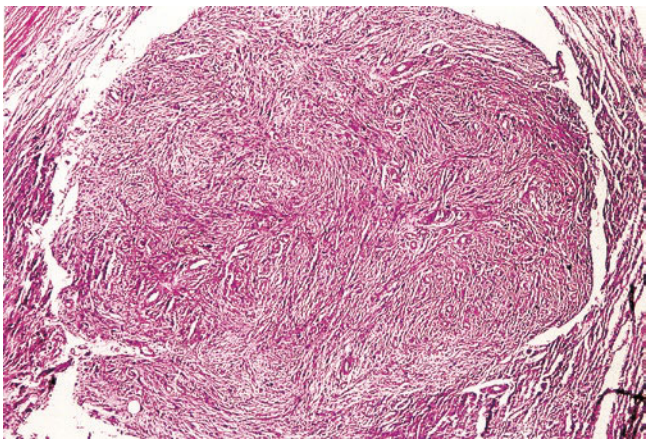


Fig. 27-38-2 Lots of fusiform cells in the dermis and hypodermis (HE stain, ×50)

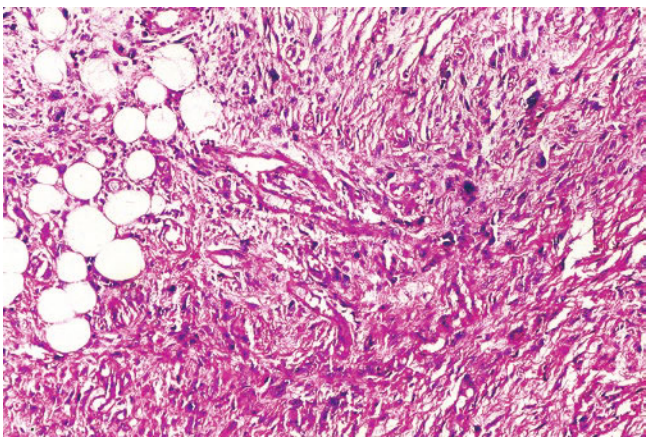


Fig. 27-38-3 Some fusiform cells had hyperchromatic and irregularly shaped nucleus (HE stain, ×250)

27.39 Dermatofibrosarcoma Protuberans [91–93]

- Dermatofibrosarcoma protuberans (DFSP) is a rare fibrohistiocytic tumor with a low-grade malignancy.
- Although DFSP can occur in children, a congenital case is considered a hamartoma, which is exceedingly rare.
- Classically, DFSP begins as a solitary, violaceous nodule or plaque on the trunk. It progresses to be multilobulated after years or decades. Atrophic DFSP most commonly appears as an atrophic, morphea-like plaque.
- Classical DFSP usually exhibits proliferated spindle cells with fingerlike projections deep in the dermis, forming a storiform as a pathological change.
- XIIIa, S100, and CD56 negativities will assist in making a differential diagnosis with XIIIa-positive dermatofibroma, melanoma, and neurogenic neoplasms.
- Congenital atrophic DFSP usually masquerades as medallion-like dermal dendrocyte hamartoma (ML-DDH), in which spindle cells express CD34, factor XIIIa, and fascin (dendritic cell markers). DFSP can easily be distinguished from ML-DDH considering its negative stain for factor XIIIa and the formation of the COL1A1-PDGFB fusion protein.
- Metastasis of DFSP is likely in patients whose skin specimen shows more than eight mitoses per high-power field.
- Excision with a 2 cm margin is the standard of treatment.

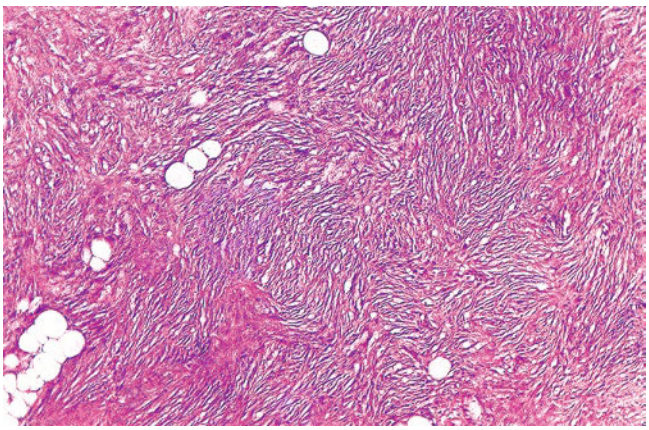


Fig. 27-39a-2 A. Dense, monotonous spindle cells were arranged in a storiform pattern (HE stain, ×100)

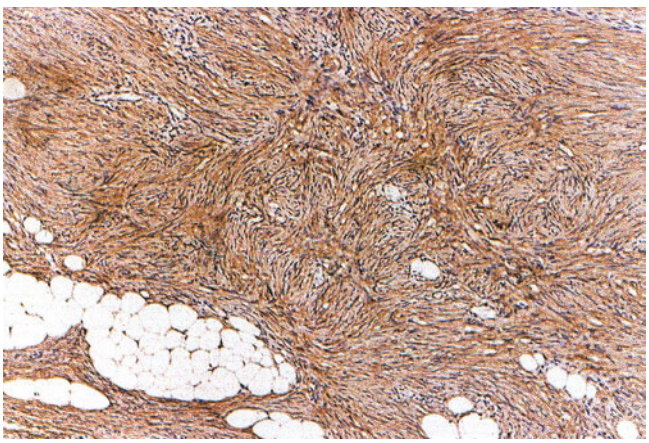


Fig. 27-39a-3 CD34 positive in the cytoplasm of tumor cell (SP stain, ×100)

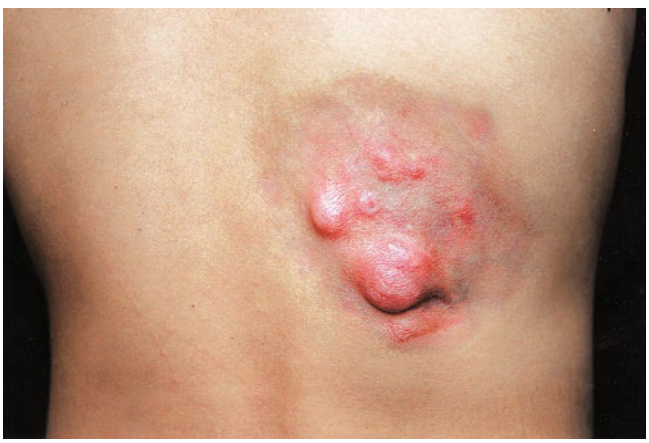


Fig. 27-39a-1 A large brown atrophic patch with six raised, reddish firm smooth nodules on the back

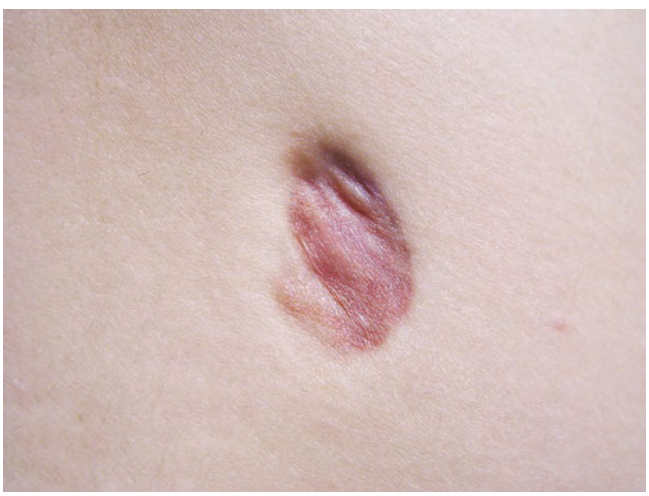


Fig. 27-39b-1 A 3 × 2.5 cm irregular dark erythema with atrophic surface on the right lower back

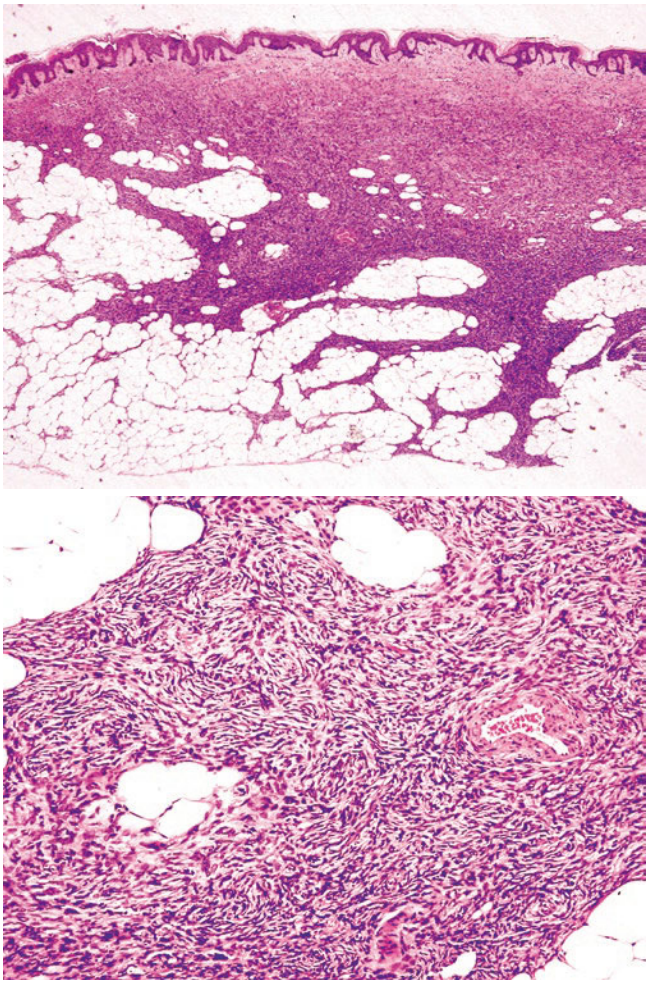


Fig. 27-39b-2, 27-39b-3 Monotonous spindle cells in the dermis and subcutaneous tissue, penetrating into the subcutaneous fat; some cells were arranged in cartwheel pattern; a few cells with larger and darker nuclei (HE stain, (2) ×40; (3) ×200)

27.40 Epithelioid Sarcoma [94–96]

- Epithelioid sarcoma (ES) is a malignant tumor with a high incidence of local recurrence and metastasis, and it arises in deep mesenchymal tissues.
- ES grows as solitary or multiple subcutaneous nodules with a woody, hard consistency, and it distributes along the fibrous sheaths of tendons or other fibrous structures over the extremities of the young people.
- ES is basically lethal, although it may easily be mistreated as a benign disease, both clinically and pathologically.
- Metastasis of ES has a propensity for the regional lymph node, lungs, and scalp, usually in a 5- to 10-year period. Locally recurrent ES appears as annular plaques.
- Microscopic observation reveals circumferential nodules, usually with central necrosis, that can easily be mistaken as a necrotizing granuloma. The tumor cells are mostly ovoid to polygonal and have rich cytoplasm.
- ES often expresses cytokeratin and epithelial membrane antigen, which help to differentiate it from other sarcomas, malignant fibrous histiocytoma, and melanoma. Meanwhile, it uniformly lacks common leukocyte antigens, myoglobin, and factor VIII-related antigen.
- Lesions in ES that are over 3 centimeters in diameter, deep infiltration of tumor cells, and focal necrosis are factors associated with a poor prognosis. The young female ES might have a better outcome than others.
- The extent of surgery does not show a substantial influence on the survival rate or local recurrence in ES populations.

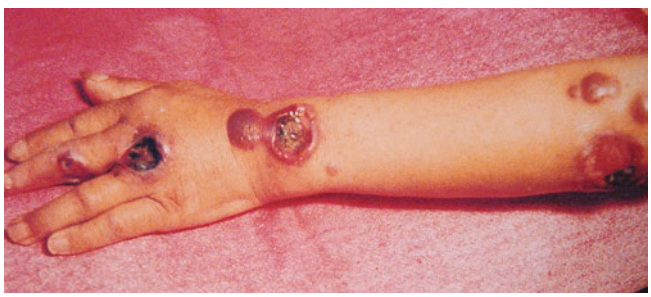


Fig. 27-40-1 Brownish nodules partly with ulcers on the upper limbs

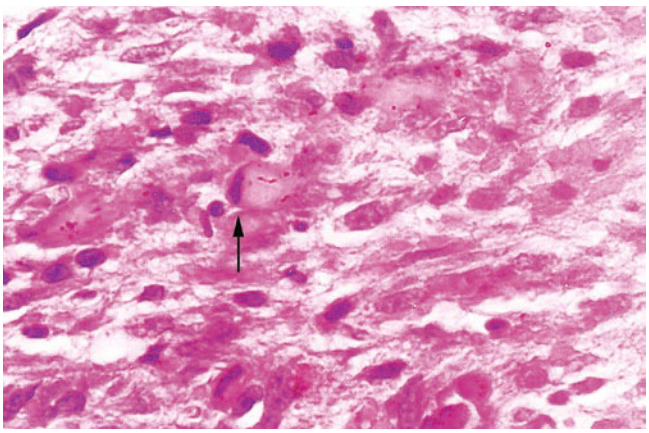


Fig. 27-40-2 Nodular atypical epithelioid cells with eosinophilic cytoplasm and atypical nuclear (↑) (HE stain, ×400)

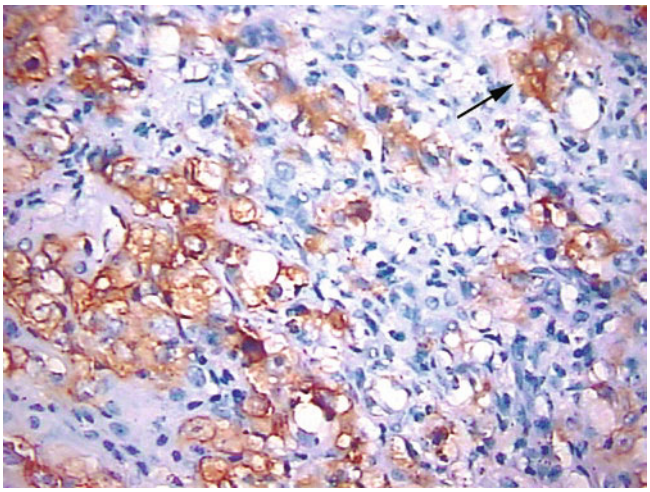


Fig. 27-40-3 Positive staining for cytokeratin (CK) in the tumor cells (LSAB, ×400)

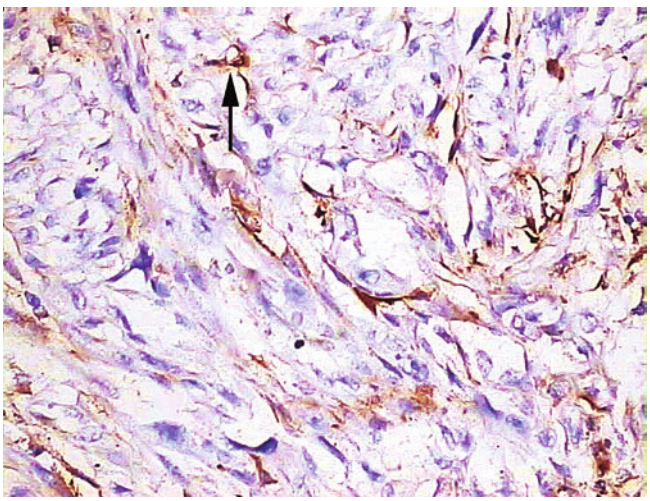


Fig. 27-40-4 Positive staining for epithelial membrane antigen (EMA) in the tumor cells (LSAB, ×400)

27.41 Superficial Angiomyxoma [97, 98]

- Myxoma consists of stellate cells in a loose mucoid matrix.
- Superficial angiomyxoma (SA) is a cutaneous myxoma that arises in the pronounced vascular component.
- Pathognomonic signs for the Carney complex consist of multiple cutaneous myxomas and SA, particularly on the external ear.
- SA displays a well-circumscribed, nodular lesion, which is usually bigger than 5 cm in diameter.
- Histological observation of SA reveals well-circumscribed multilobulated lesions consisting of numerous stellate fibroblasts, capillary-like vessels, and neutrophils in the dermal matrix.
- Both keratin cysts and thin strands of squamous cells in the epidermis are suggestive of a higher rate of local recurrence after surgery.
- The differential diagnosis in SA is very wide, including superficial acral fibromyxoma, intramuscular myxoma, aggressive angiomyxoma, nerve sheath myxoma, juxta-articular myxoma, angiomyofibroblastoma, focal mucinosis, myxoid neurofibroma, angiomyxolipoma, malignant myxomatous, and ganglion cysts.

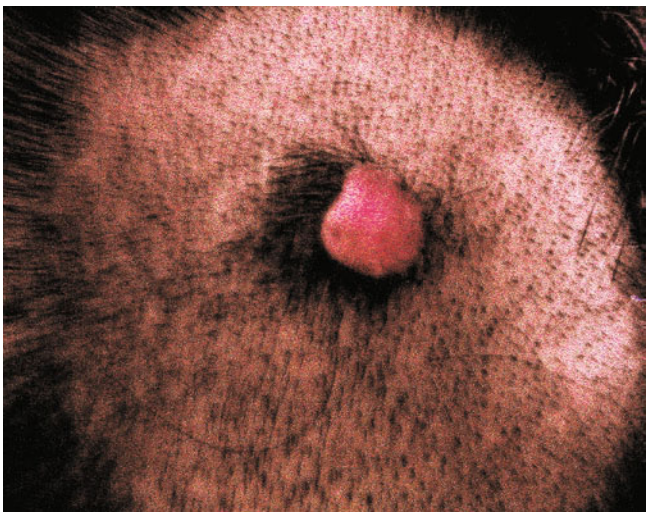


Fig. 27-41-1 A red nodule measuring 0.5 × 0.5 cm on the scalp

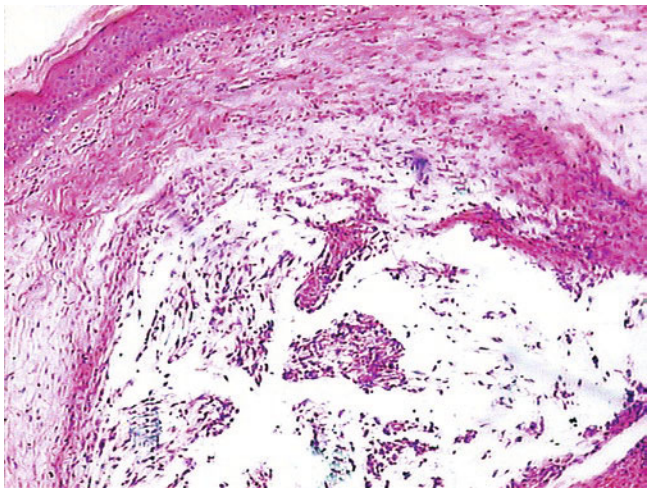


Fig. 27-41-2 The tumor located in the dermis and defined by thick collagen bundles (HE stain, ×40)

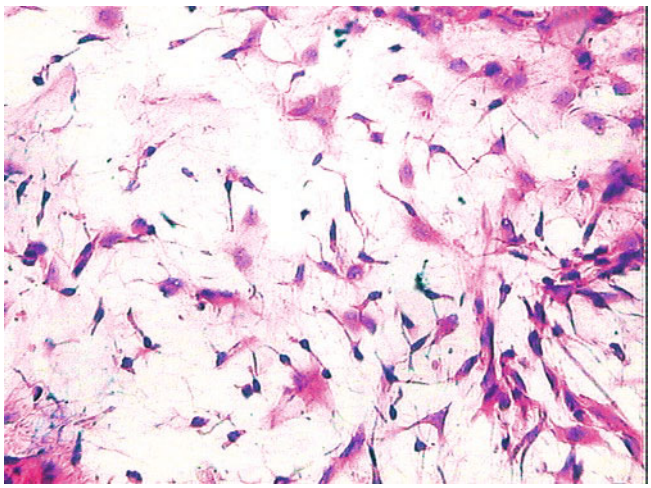


Fig. 27-41-3 Myxoid stroma filled the whole tumor, and starlike and spindle-shaped stromal cells were scattered throughout the tumor (HE stain, ×200)

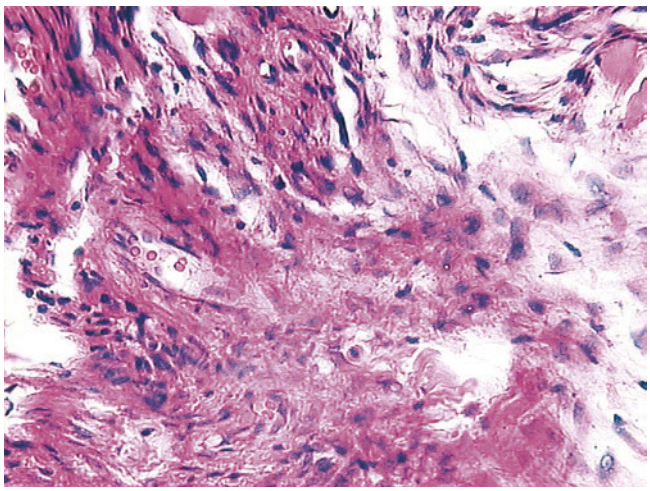
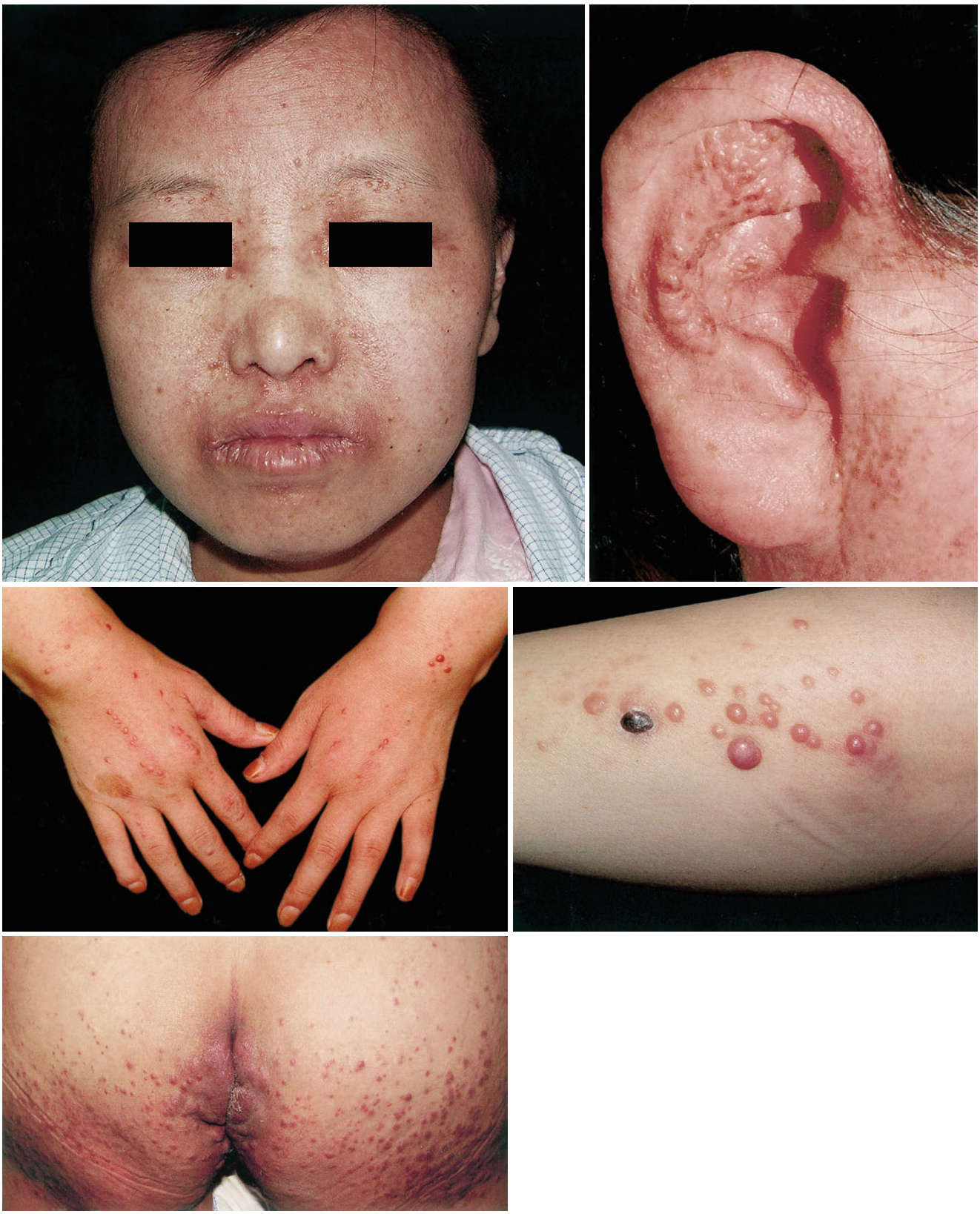


Fig. 27-41-4 Small, thin-walled blood vessels scattered in the tumor and fiber bundles (HE stain, ×400)

27.42 Multicentric Reticulohistiocytosis [99–102]

- Multicentric reticulohistiocytosis (MRH) is an uncommon histiocytosis that has extensive papulonodular lesions and severe arthropathy.
- Most MRH patients seek management of joint problems before their skin lesions manifest. Fatigue, weight loss, and fevers are concomitant symptoms with MRH.
- The musculoskeletal findings of MRH present as erosive arthritis, which is prone for the development of joint structural deformities. The younger the patient at the time of diagnosis, the higher the likelihood that the development of arthritis mutilans may appear.
- The skin lesions can be brown-reddish to flesh-colored papules and nodules, usually with residual atrophic scars or disfigurement. Coalesced lesions tend to have a cobblestone appearance. "Coral beads" is the pathogenic sign when the periungual area is involved.
- Approximately 25% of MRH has underlying malignant disorders, and treatment of these malignancies can only ameliorate its symptoms.
- Cardiopulmonary features include pleural effusions, pulmonary fibrosis, pericardial effusion, and congestive heart failure, and these features confer a grave prognosis.
- The gastrointestinal, urogenital, and hepatic systems are occasionally affected.
- Although spontaneous healing occurs in MRH within approximately 10 years, many individuals have already suffered from irreversible deforming arthritis by then.
- The pathological hallmarks of MRH diagnosis are comprised of abundant histiocytes with multinucleated giant cells and ground-glass-like cytoplasm. Immunohistochemical profiles are positive for vimentin, CD68, MAC387, HAM-56, CD3, and CD45, while they are negative for S100, CD1a, CD34, XIIIa factor, and CD19. Langerhans granules are not identified under electron microscopy.
- Bisphosphonates have shown promising results to inhibit osteoclast formation in MRH, and they are regarded as a promising effective modality for its treatment.



Figs. 27-42-1, 27-42-2, 27-42-3, 27-42-4, 27-42-5 There were papules and nodules on the face (1), ears (2), dorsa of the hands (3), elbows (4), and erythematous plaques on the buttocks (5)

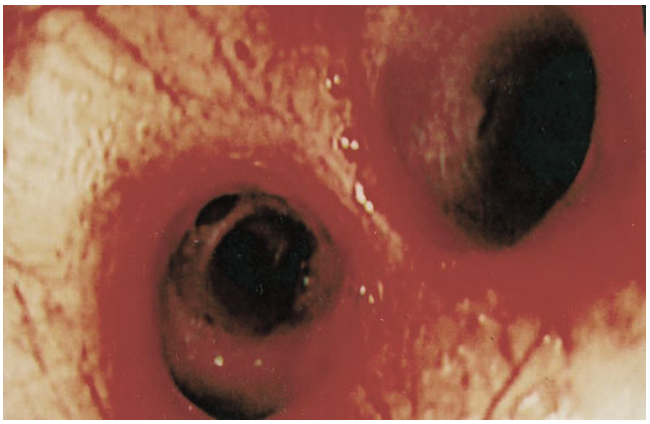


Fig. 27-42-6 Numerous nodules in the bronchus

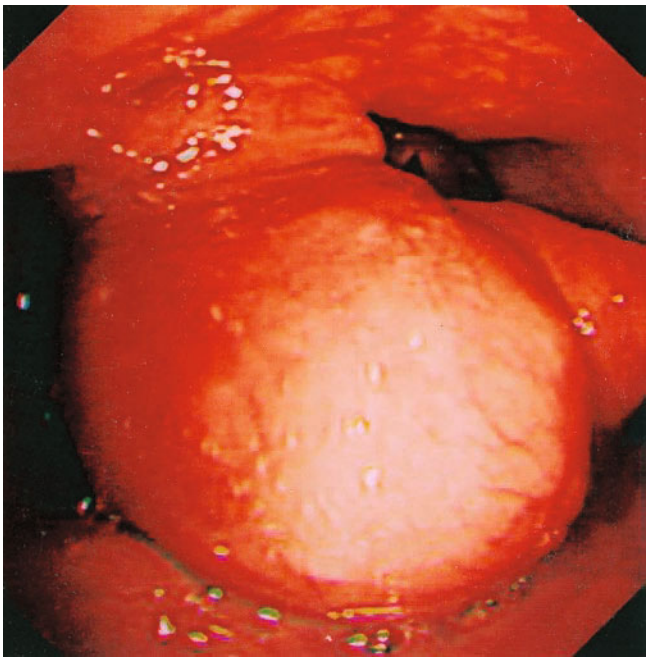


Fig. 27-42-7 A mass 1.5 × 2.0 cm in size on the left aryepiglottic fold

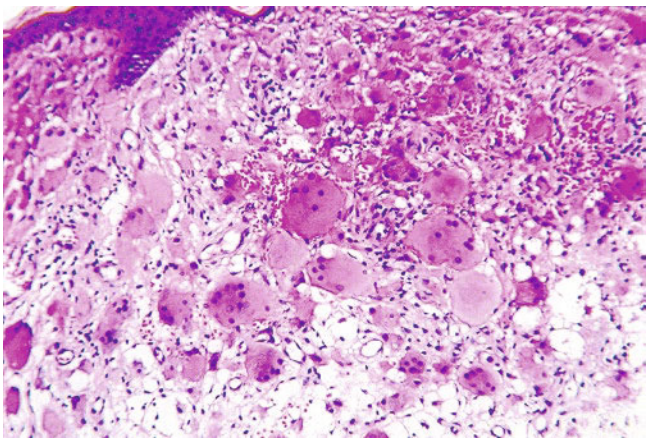


Fig. 27-42-8 Histiocytes and multinucleated giant cells with eosinophilic "ground-glass" cytoplasm in the dermis (HE stain, ×200)

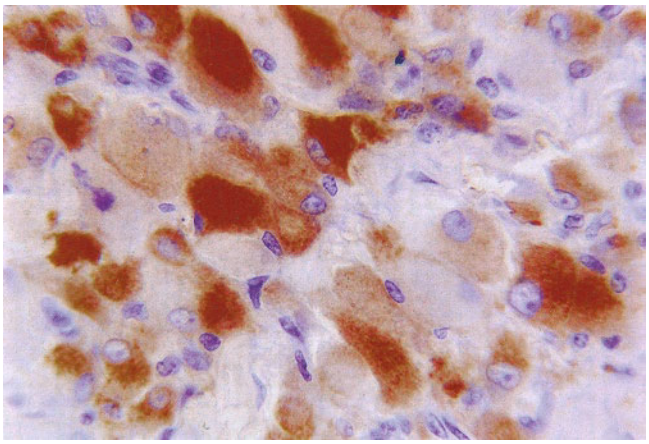


Fig. 27-42-9 Brown-yellow cytoplasm, CD68 positive (SP stain, ×200)

27.43 Letterer-Siwe Disease [103, 104]

- Histiocyte refers to a category of cells consisting of macrophages and other dendritic cells (antigen-presenting cells: dermal dendrocytes, Langerhans cells, and undetermined cells).
- Histiocytoses are a spectrum of histiocytic proliferations categorized into Langerhans cell histiocytoses (LCH), non-Langerhans cell histiocytoses, and malignant histiocytoses.
- Four well-defined variants of LCH have been recognized, namely, Hand-Schüller-Christian disease, Letterer-Siwe disease (LSD), Hashimoto-Pritzker disease, and eosinophilic granuloma.
- The incidence of dermal infiltrations of lymphomonocytic cells with reniform nucleus is highly suggestive of LCH. The diagnosis is established if the expressions of CD1a, S100, CD 207, CD68, and factor XIIIa are confirmed. Birbeck granules are pathognomonic of LC under electronic microscope.
- The mortality rate for LCH in children less than 2 years of age with multiorgan involvement tends to have a bad prognosis.
- Painful intertriginous cutaneous LCH lesions respond well to thalidomide.
- Crusted or scaly papules and papulovesicles are the most common lesions in skin folds in LSD.
- Rarely, nodular, vesicular, purpuric, erosion, granuloma, and pustular lesions are likely to display in crops in LSD.
- Poor prognostic features include younger age; involvement of the nail, gastrointestinal tract, lung, and liver; infections; and anemia.
- Emperipolesis and positive immunological staining for S100, CD68, and CD1a are the main features in Rosai-Dorfman disease (RDD).

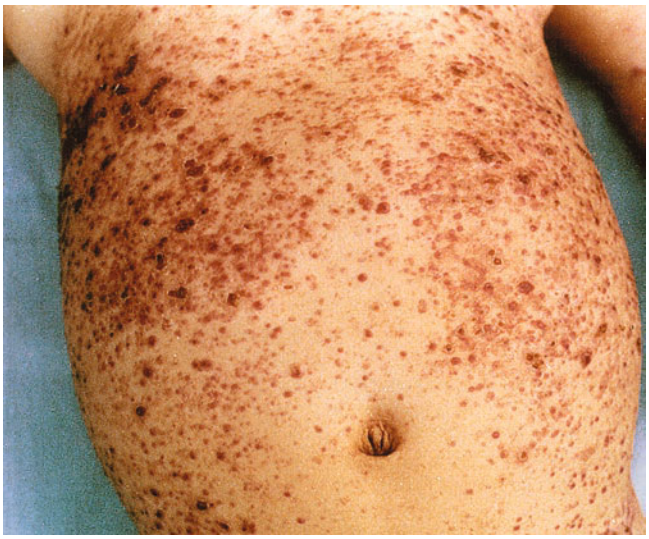


Fig. 27-43-1 The petechiae and brownish papules covered with crusts or scales on the chest and the abdomen

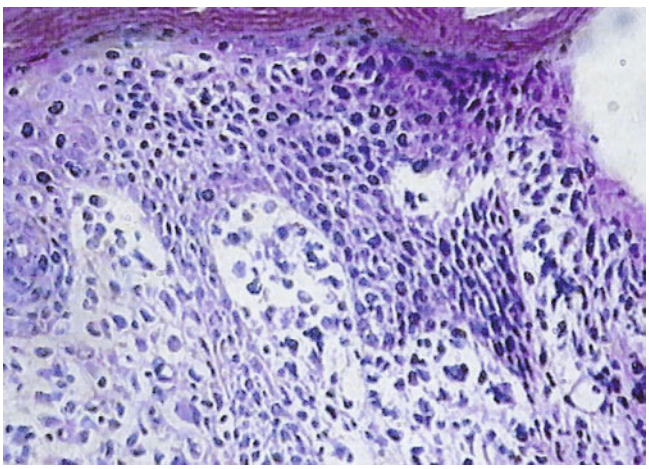


Fig. 27-43-2 There was a superficial dermal infiltration of mononuclear cells; some of them had invaded the epidermis (HE stain, ×200)

27.44 Cutaneous Rosai-Dorfman Disease [105, 106]

- Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a self-limited, multiorgan, non-Langerhans cell histiocytosis. It usually has systemic complications of fever, weight loss, night sweating, etc.
- Cutaneous Rosai-Dorfman disease (C-RDD) is a type of extranodal RDD that involves the skin.
- The clinical manifestations of C-RDD are quite variable, ranging from papules, nodules, and plaques to rare pustular or acneiform eruptions. However, the most typical lesion is a central nodule-plaque with surrounding satellite papules. The colors of the lesions are diverse, ranging from erythematous, brownish, gray-blue, violaceous, or yellowish in appearance.
- C-RDD is commonly seen in Asia and is divided into the papulonodular type, indurated plaque type, and tumor type.
- Histopathological features of C-RDD are comprised of the infiltration of lymphocytes, histiocytes, and plasma cells. Histiocytic morphology is highly characterized by vesicular nucleus and pale cytoplasm. The immunoprofile of these histiocytes is CD68+, S100+, CD1a−, Langerin−, Factor XIIIa−, and CD34−. Emperipolesis is the diagnostic pathognomonic finding in its differentiation from other histiocytoses.
- The engulfed cells seen in emperipolesis are intact and survive in the histiocytes, which differs from phagocytosis.
- C-RDD is the least responsive to corticosteroids, but surgical excision can be curative. However, commitment with widespread visceral damage usually has a fatal outcome.

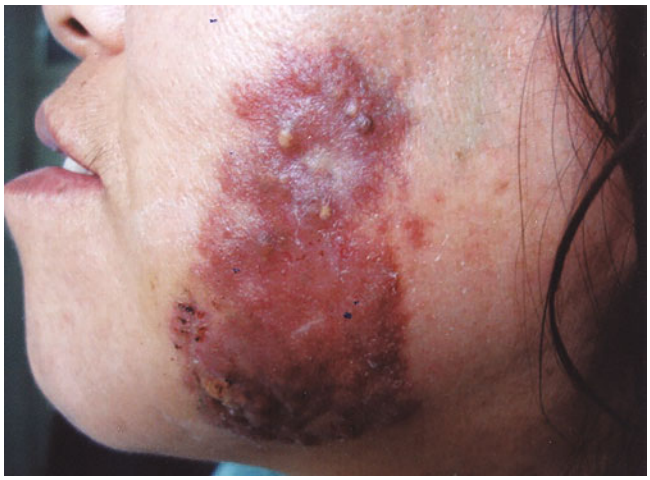


Fig. 27-44-1 A brown-red plaque 4.5–7.1 cm in size on the left cheek

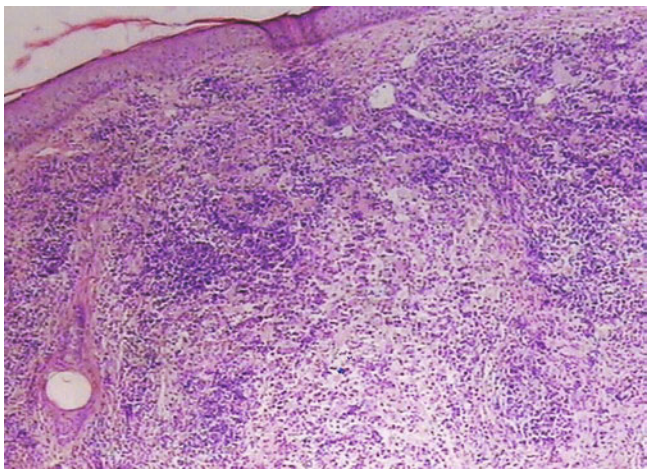


Fig. 27-44-2 Epidermal atrophy and many histiocytes, lymphocytes, and plasma cells associated with lymph follicular structure were present in the dermis (HE stain, ×100)

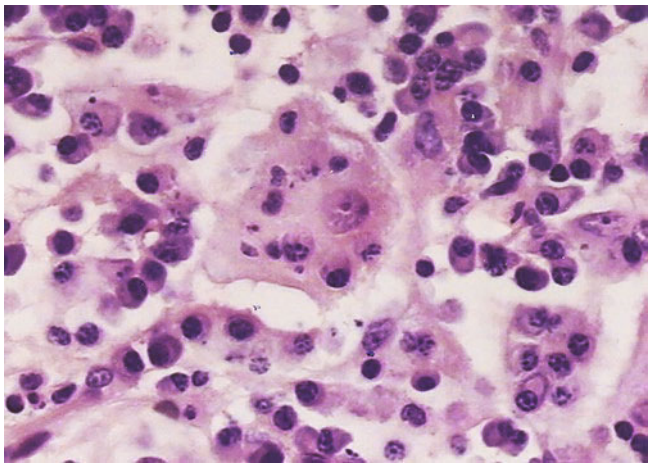


Fig. 27-44-3 The lymphocyte, plasma cell, and nuclear debris were phagocytosed in a big histiocyte around many plasma cells (HE stain, ×400)

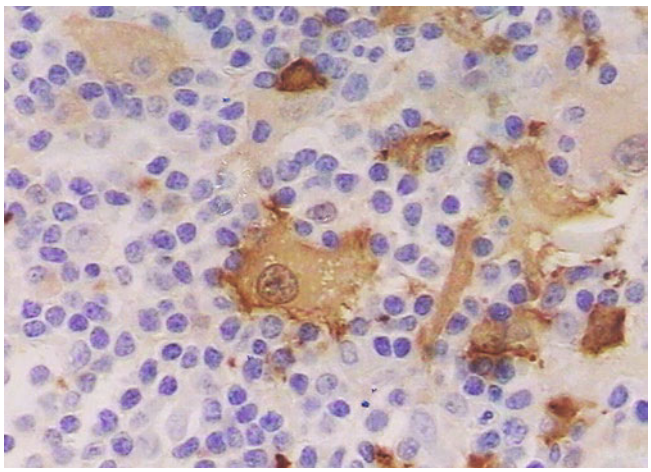


Fig. 27-44-4 S100 positive in histiocyte (Envision method, ×400)

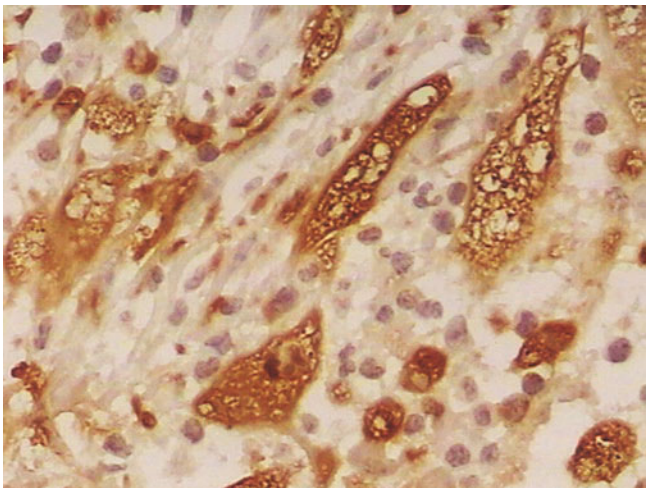


Fig. 27-44-5 CD68 positive in histiocyte (Envision method, ×400)

27.45 Phakomatosis Pigmentovascularis [107, 108]

- Phakomatosis pigmentovascularis syndrome (PPS) is the co-occurrence of cutaneous pigmentary abnormalities and vascular lesions.
- PPS can be classified into several types (shown in Table 27.27-1).

Table 27.27-1 Classification of phakomatosis pigmentovascularis

Type	Vascular nevus	Pigmentary changes
I a, b	Nevus flammeus	Nevus pigmentosus and verrucosus
I1 a, b	Nevus flammeus ± nevus anemicus	Mongolian spot
111 a, b	Nevus flammeus ± nevus anemicus	Nevus spilus
IV a, b	Nevus flammeus ± nevus anemicus	Mongolian spot, nevus spilus
V	Cutis marmorata telangiectatica congenita	Mongolian spot

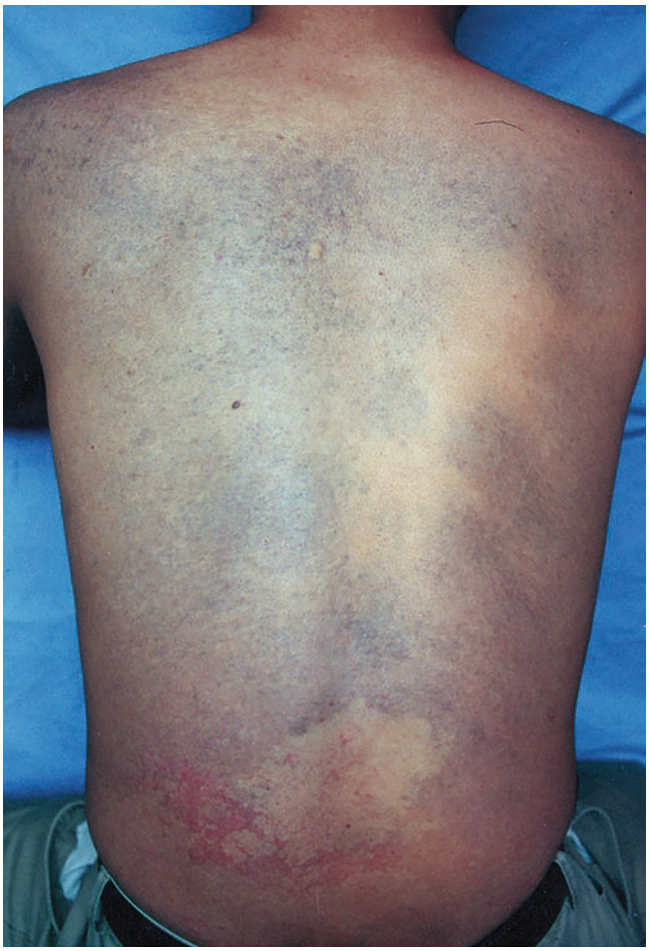


Fig. 27-45-1 A gray-blue spot about 40 × 25 cm on the back and a nevus flammeus about 16 × 10 cm on the left waist

27.46 Angiokeratoma Corporis Diffusum [109, 110]

- Angiokeratoma is characterized by vascular ectasia in the superficial dermis with acanthosis, hyperkeratosis, and other epidermal changes.
- Angiokeratoma corporis diffusum (ACD) belongs to a variant of angiokeratoma highlighted by numerous dark-red papules or plaques on the lower part of the trunk, buttocks, and legs.
- ACD is considered the cutaneous hallmark of Fabry's disease, fucosidosis type II, Kanzaki disease, mannosidosis, sialidosis, galactosialidosis, and aspartylglycosaminuria, which are caused by a defect of a certain lysosomal enzyme.
- Fabry's disease occurs as a result of a dysfunctional lysosomal enzyme named galactosidase A.

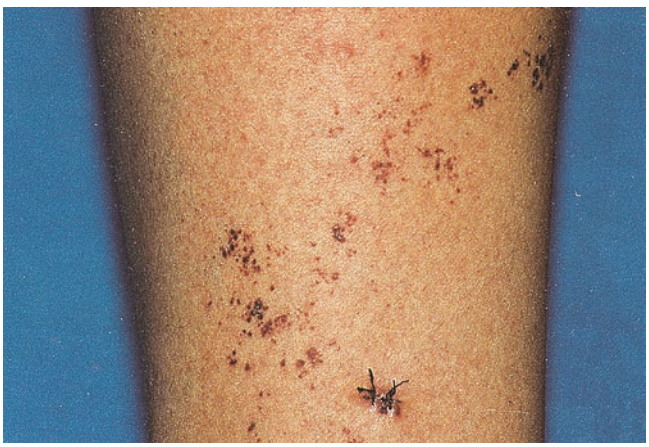


Fig. 27-46-1 Numerous clusters of tiny red papules on the left leg

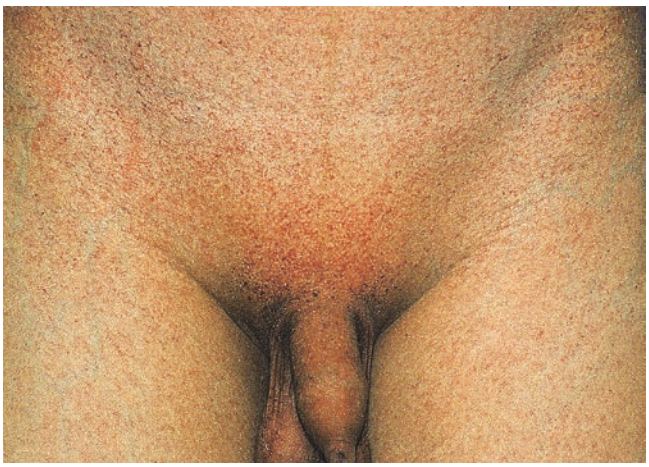


Fig. 27-46-2 Numerous tiny red papules on the lower abdomen

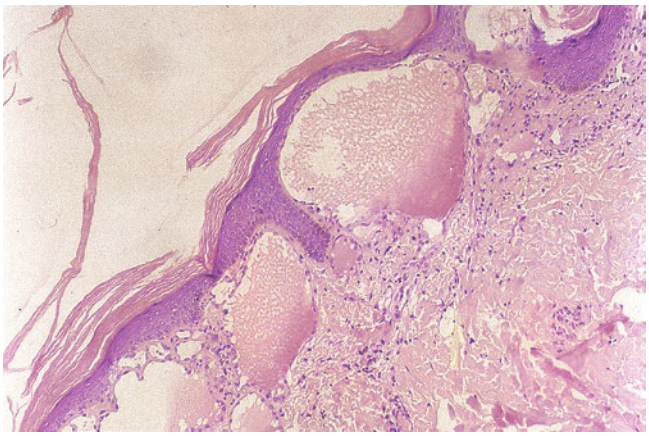


Fig. 27-46-3 Ectasia of blood vessels in the papillary dermis with overlying hyperkeratosis (HE stain, ×100)

Fig. 27-46-4 Lamellar bodies in the lysosome of the epithelium of renal glomeruli

27.47 Angiokeratoma of Fordyce [111, 112]

- Angiokeratomas display demarcated, verrucous papules with a red, blue, or black color.
- Histology of the lesion shows hyperkeratosis in the epidermis. In the reticular dermis, blood-filled vessels are notably dilated.
- Angiokeratoma of Fordyce is a localized variant, which is characterized by the involvement of the penis or vulva.
- Although angiokeratomas of the scrotum are common, unilateral distribution of the lesions is extremely rare.

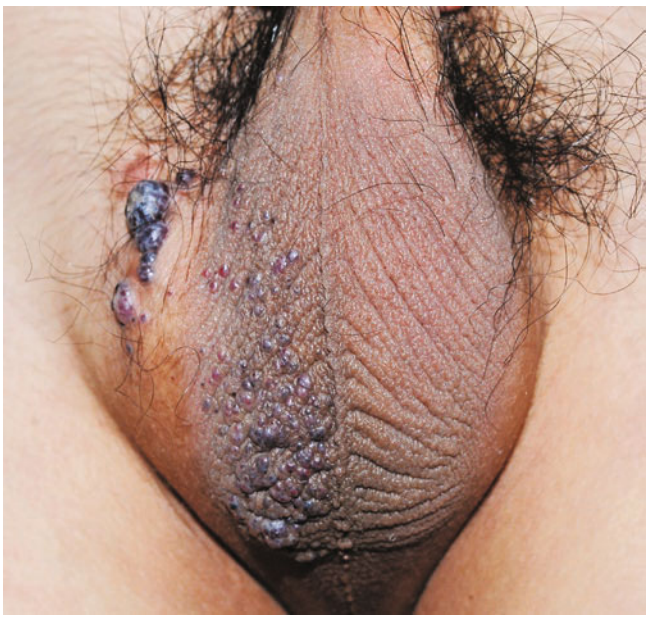


Fig. 27-47-1 Clusters of mauve papules on the right scrotum

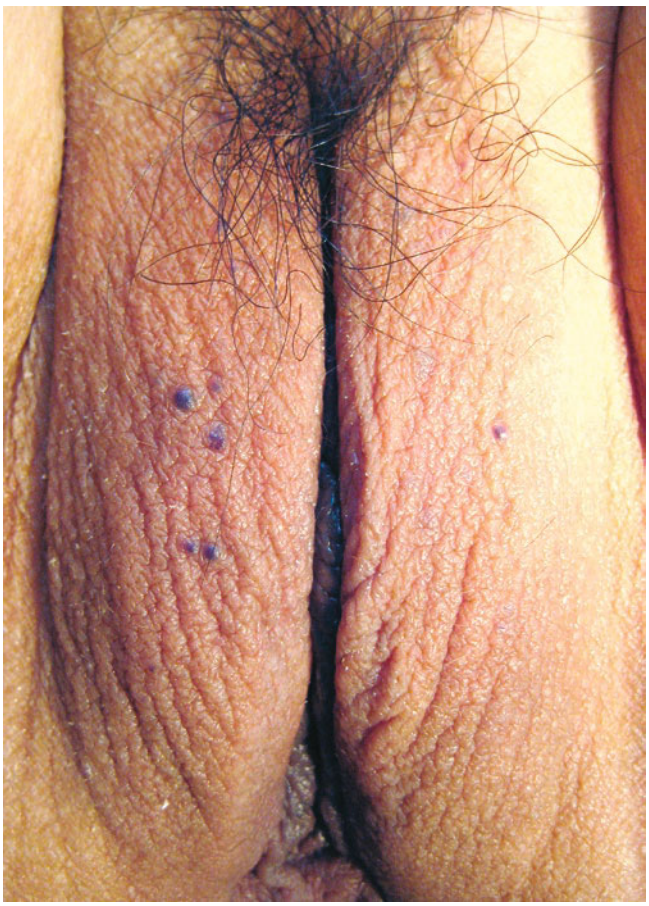


Fig. 27-47-2 A few small vascular papules on the vulva

27.48 Angioma Serpiginosum [113, 114]

- Angioma serpiginosum (AS) is a congenital capillary malformation characterized by capillary ectasias in the papillary dermis.
- Clinically, AS presents multiple, punctate, nonblanchable, and red macules arranged in a serpiginous pattern.
- Skin biopsy shows ectatic, congested, and tortuous capillaries without inflammation in the superficial dermis.

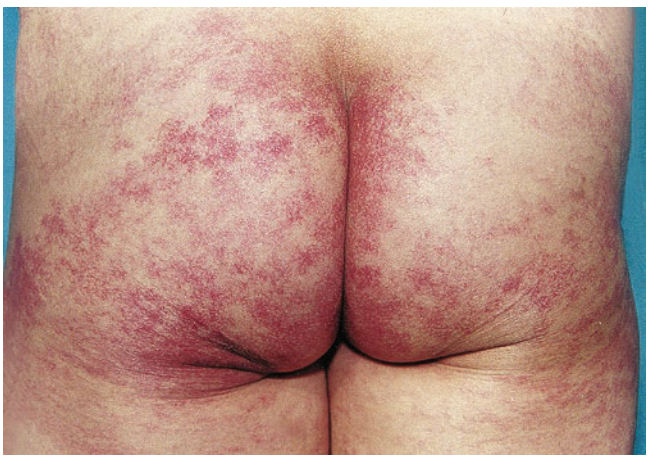


Fig. 27-48-1 Netlike pattern deeply red maculae and numerous violaceous spots on the buttock

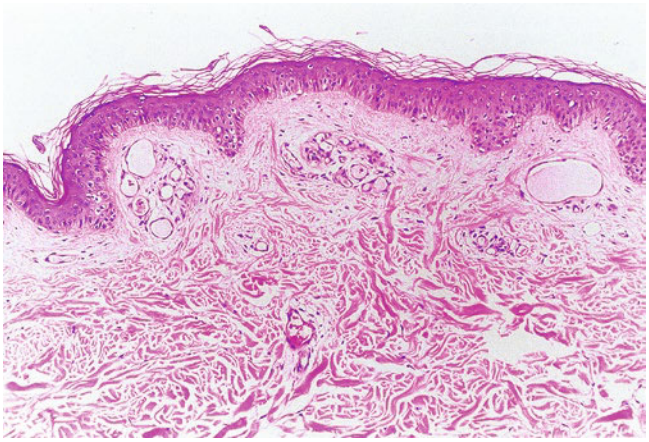


Fig. 27-48-2 Dilated capillaries in the papillae and reticular dermis (HE stain, ×100)

27.49 Reactive Angioendotheliomatosis [115, 116]

- Reactive angioendotheliomatosis (RAE) is a self-limiting disease. It is regarded as a benign proliferation of endothelial cells in the skin.
- Observation of the lesions reveals erythematous to violaceous patches, papules, or plaques that occasionally become ulcerated or blistered.
- Clinically, RAE resembles eruptive disseminated lobular capillary hemangioma, Kaposi's sarcoma, morphea/scleroderma, pyoderma gangrenosum, calciphylaxis, and angiosarcoma.
- It is usually associated with a wide spectrum of diseases, such as infections, cryoproteinemias, monoclonal gammopathies, and allergic disorders. Peripheral vascular atherosclerotic disease, pregnancy, and iatrogenic arteriovenous fistulas also correlate to RAE.
- Malignant angioendotheliomatosis is a counterpart of RAE, which is a fatal, B-cell intravascular lymphoma.

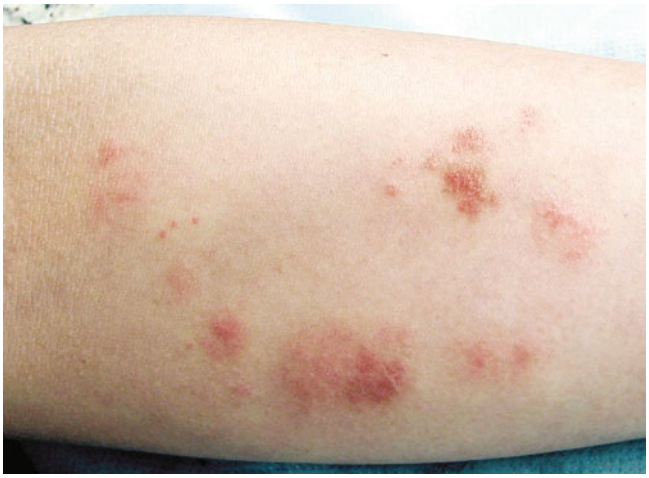


Fig. 27-49-1 There were six to eight patches of erythemas, papules, or plaques presented on the antecubital area, the biggest diameter of which was 4 cm. There were variable pin-sized hemacelinosis inside

27.50 Epithelioid Hemangioma [117, 118]

- Epithelioid hemangioma (EH) is a neoplasm of blood vessels involving the skin on the head and neck.
- EH is characterized by a solitary, round, erythematous papule, nodule, or plaque. Multiple lesions or zosteriform figurations are quite rare.
- Histologically, EH is characterized by an unclear lobular proliferation of epithelioid endothelial cells of various sizes. Variable lymphocytes and eosinophils can be seen around these vessels. Immunohistochemistry is positive for the endothelial biomarkers CD31 and CD34, and it is negative for epithelial markers (cytokeratins).
- The plump endothelial cells, stromal fibrosis, and distinctive clinical manifestations all differentiate Kimura's disease from EH.

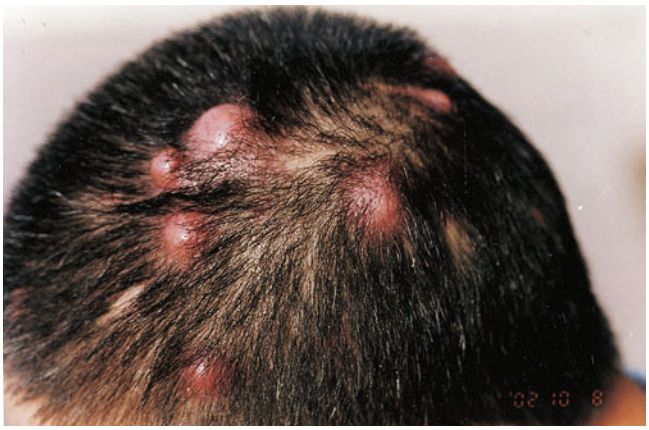


Fig. 27-50-1 Multiple brownish-red nodules with smooth surfaces on the left scalp

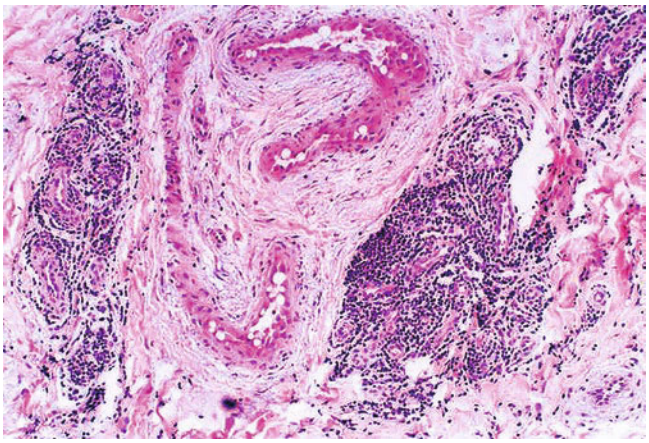


Fig. 27-50-2 Exuberant proliferation of vessels lined by cuboidal to endothelioid cells with inflammatory infiltration (HE stain, ×200)

27.51 Tufted Angioma [119–121]

- Tufted angioma (TA) is regarded as a benign vascular neoplasm commonly observed among children under 5.
- The clinical manifestation of TA is quite variable. It characteristically shows red-brownish, indurated nodules or plaques. TA in linear or annular arrangements has been reported. Rarely, there is hyperhidrosis and hypertrichosis overlying the lesion.
- Multiple lobular vascular proliferation occupying stroma in the dermis and subcutis (cannonball pattern) is highly suggestive of TA. The endothelial cells are plump with spindle-shaped pericytes.
- Oral mucosa and vermilion border are preferentially affected in adult TA.
- TA is occasionally related to systemic diseases, such as chronic coagulopathy, Kasabach-Merritt syndrome, and thrombocytopenia, and it usually has a poor cosmetic outcome.
- Juvenile capillary hemangioma lacks cannonball nests and glomeruloid structures, which differentiates it from TA.

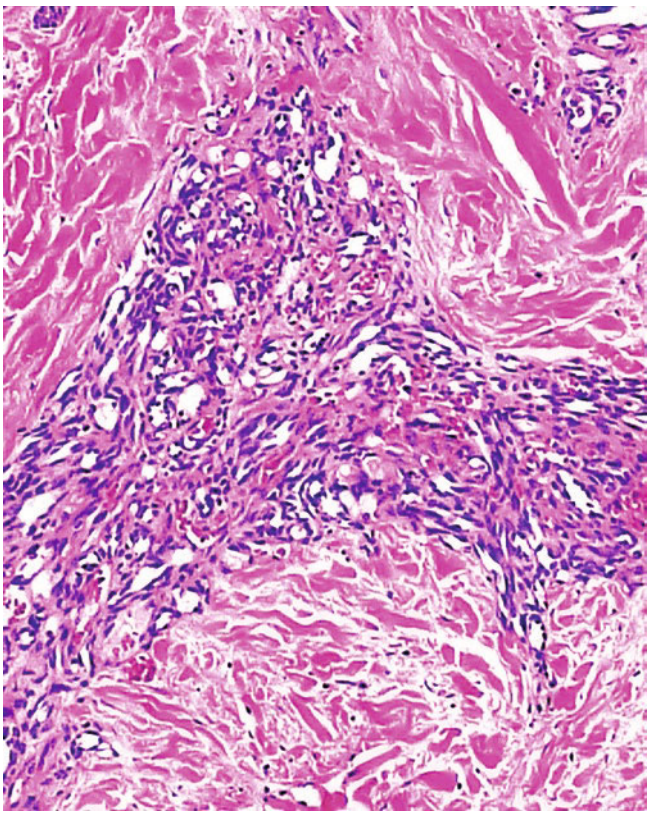


Fig. 27-51-2 Well-circumscribed capillary lobules in the dermis (HE stain, ×100)

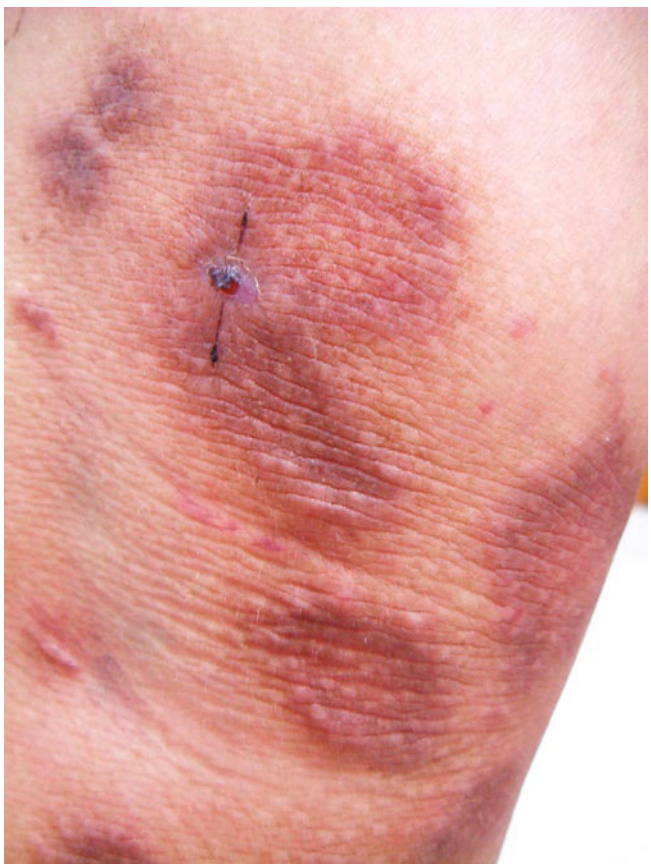


Fig. 27-51-1 Red-brown plaques with thick indurated border and a central depression similar to a doughnut

27.52 Verrucous Hemangioma [122, 123]

- Verrucous hemangioma (VH) represents a rare congenital vascular anomaly commonly found on the leg unilaterally.
- VH originally appears as a bluish-purple macule that progresses to a warty plaque or nodule. Its size varies from approximately 0.5 to 8 cm in diameter. These lesions can be solitary or multiple and are distributed in a linear or serpiginous pattern.
- Histopathologically, VH displays marked verruciform epidermal changes (papillomatosis, hyperkeratosis, and acanthosis) overlying delicate, ectatic thin-walled vessels. Meanwhile, thick-walled, small blood vessels extend deeply into the reticular dermis and subcutaneous tissue, which is a reliable feature for distinguishing VH from angiokeratoma.
- VH persists after excision, mainly due to deep subcutaneous involvement.

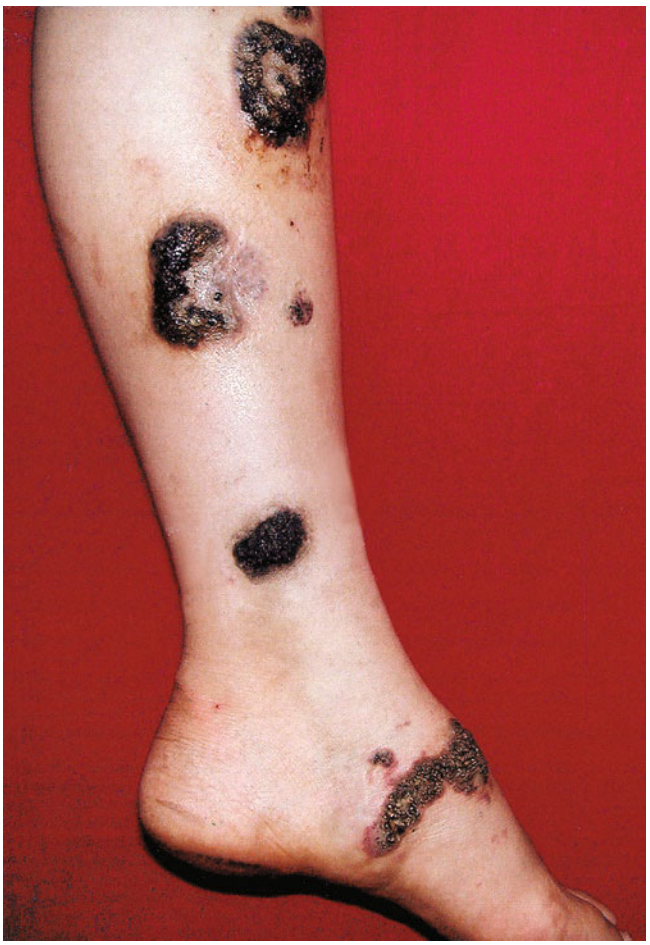


Fig. 27-52-1 A group of several well-circumscribed, hyperkeratotic, dark-red plaques were arranged linearly along the inside aspect of left lower extremity

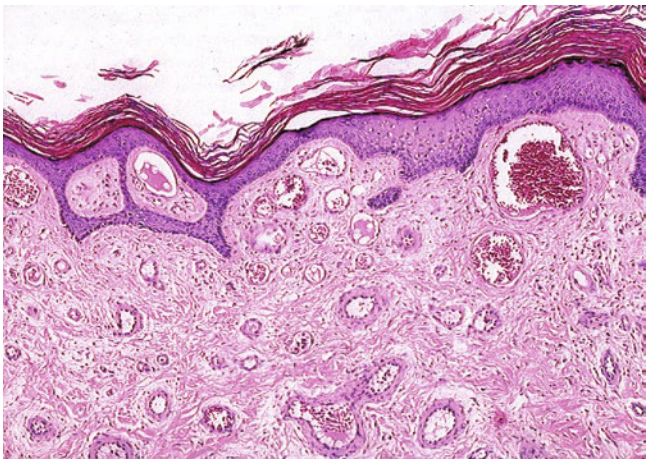


Fig. 27-52-2 Hyperkeratosis of the epidermis and multiple dilated vessels filled with red blood cells in the superficial dermis (HE stain, ×100)

27.53 Targetoid Hemosiderotic Hemangioma [124, 125]

- Targetoid hemosiderotic hemangioma (THH), or hobnail hemangioma, is a type of vascular proliferation occurring mostly in adult persons.
- THH classically presents as a solitary, brown to violaceous papule or plaque enclosed by a thin pale area and an outlying ecchymotic ring, giving a targetoid manifestation. However, this ecchymotic ring is not always present.
- A histopathological change of THH is a biphasic vascular proliferation pattern. Vascular channels in the papillary dermis are ectatic and lined by the hobnail-like endothelial cells. In the mid-dermis, collagen bundles are dissected by the slit-like or angulated vascular spaces. Abundant hemosiderin deposition, together with extravasated erythrocytes, is noteworthy.
- A low Ki-67 proliferation index and/or negative immunostaining for Wilms tumor-1 gene indicate a vascular malformation in THH rather than a proliferative nature.
- Mounting evidence shows that THH is of lymphatic origin: CD31+, CD34−, VEGFR-3+, and D2-40+.
- Occasionally, THH relapses after spontaneous resolution.

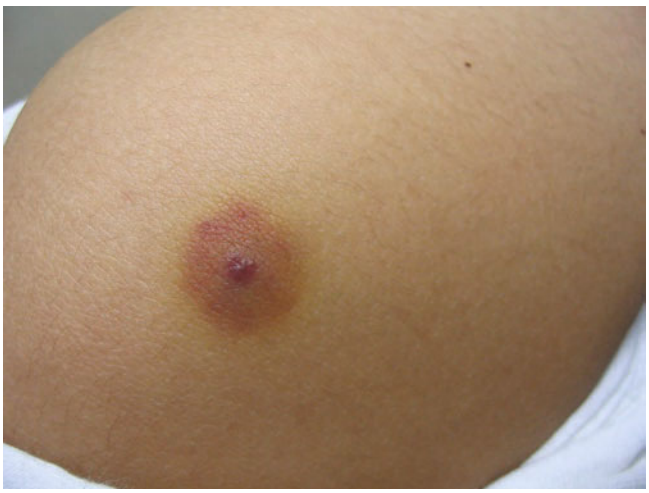


Fig. 27-53-1 A 1.7-cm-sized, targetoid violaceous papule with an annular violaceous and outmost yellowish ring was noted on the upper part of the left shoulder

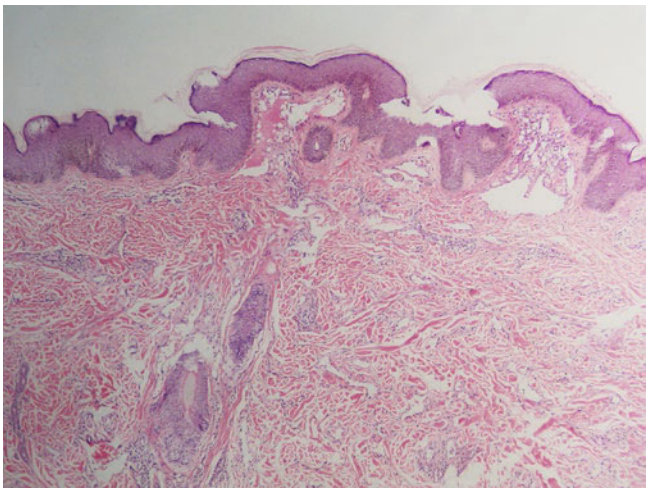


Fig. 27-53-2 Histologic evaluation revealed dilated and proliferated capillaries in the superficial dermis. Some highly dilated lumina were congested with eosinophilic, homogenous materials. Blood vessels or lymphatic vessels ran parallel to the surface of the skin. Slit-like vessels were located in the mid-dermis and dissected between collagen bundles (HE stain, ×100)

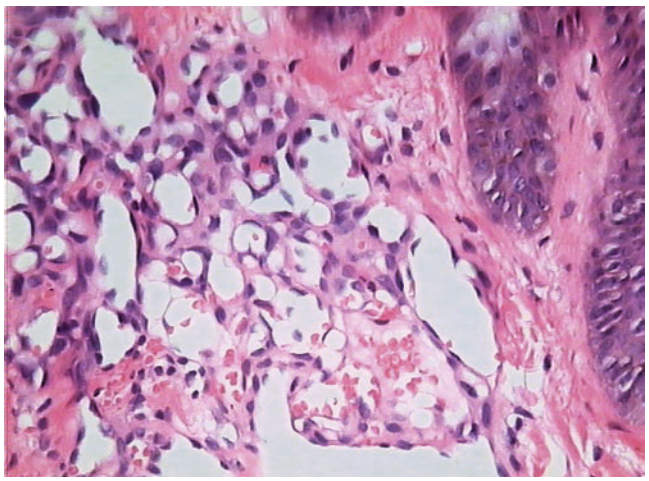


Fig. 27-53-3 Vessels were lined with plump, hobnail-like endothelial cells protruding into the lumen. Extravasated erythrocytes were obvious (HE stain, ×400)

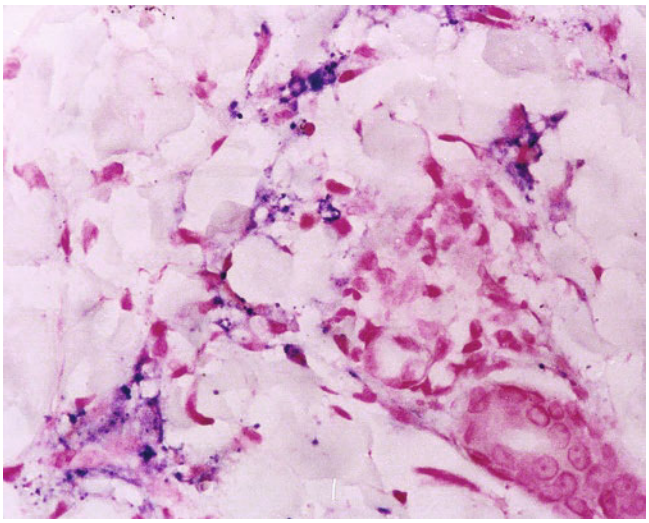


Fig. 27-53-4 Prussian blue stain for iron highlights, abundant hemosiderin deposition between collagen bundles (Prussian blue stain, ×400)

27.54 Microvenular Hemangioma [126, 127]

- Microvenular hemangioma (MH) is a benign proliferation of the blood vessels with a predilection for adults.
- It commonly occurs as a solitary papule or plaque with variable size and violaceous-to-red color.
- The development of MH may be associated with hormonal disturbances after the administration of contraceptive drugs or during pregnancy.
- Histopathologic findings include irregularly branching small-caliber venules with narrow lumina, which are distributed between the sclerotic collagen bundles. The endothelial cells are walled by pericytes. Cellular atypia, pleomorphism, or mitotic figures are absent.
- MH is CD31+, CD34+, factor VIII+, and SMA+ for the lesional pericytes but stains negatively for podoplanin.
- Angiosarcoma and Kaposi's sarcoma (KS) are distinguished from MH by the nonexistence of pericytes of the vessels and other characteristics.

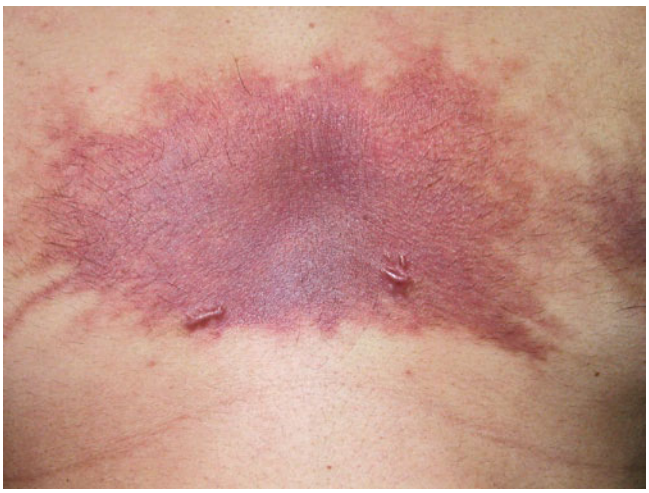


Fig. 27-54-1 A 7 × 18 cm erythema with irregular border on the chest

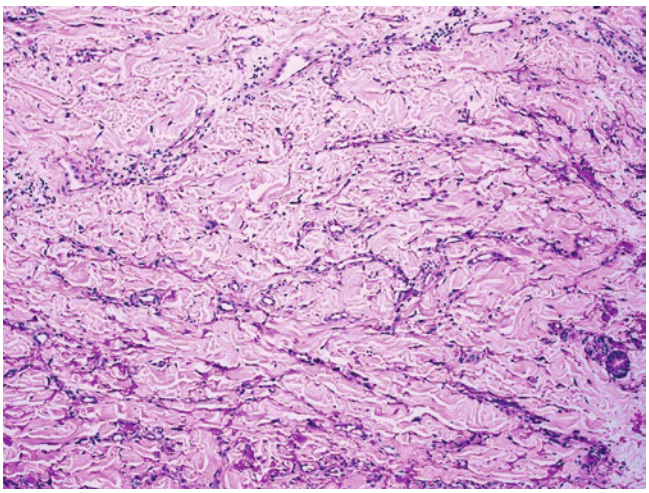


Fig. 27-54-2 Slit-like vascular channels in slightly collagenous stroma (HE stain, ×400)

27.55 Glomus Tumor [128, 129]

- Glomus tumor (GT) is recognized as a benign, vascular hamartoma that originated from the neuromyoarterial glomus unit. The tumor is made up of varying proportions of glomus cells, vascular tissue, and smooth muscle cells.
- Pinpoint pain, rigorous pain, plus cold hypersensitivity are the triad symptoms of GT. The presence of cold hypersensitivity may be useful to differentiate it from neuroma.
- Solitary GT presents as a painful purple nodule situated on the extremities, particularly in the nail bed. Histologically, the encapsulated mass consists of dilated capillary vessels encircled by numerous round glomus tissue that fills the spaces. Subungual GT is associated with previous localized trauma or neurofibromatosis.
- Multiple GTs are usually painless, and they distribute in any site. Microscopical observation reveals noncapsulated cavernous vascular spaces. The vessels are lined by flat endothelium and are peripherally encircled with glomus cells.

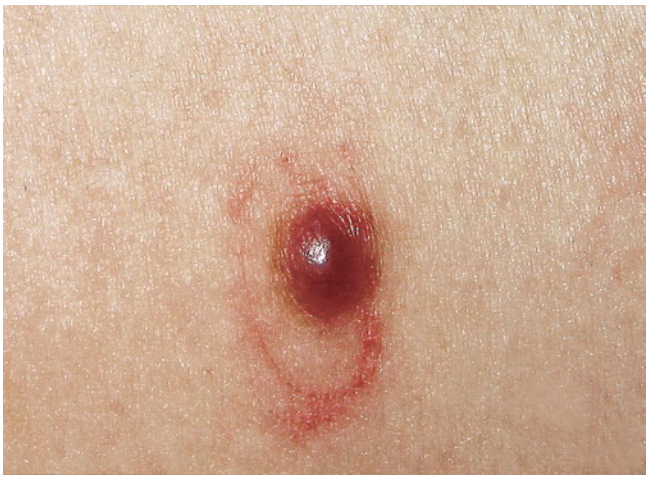


Fig. 27-55a-1 A soybean-sized purplish nodule with damask halation on the back of the left thigh

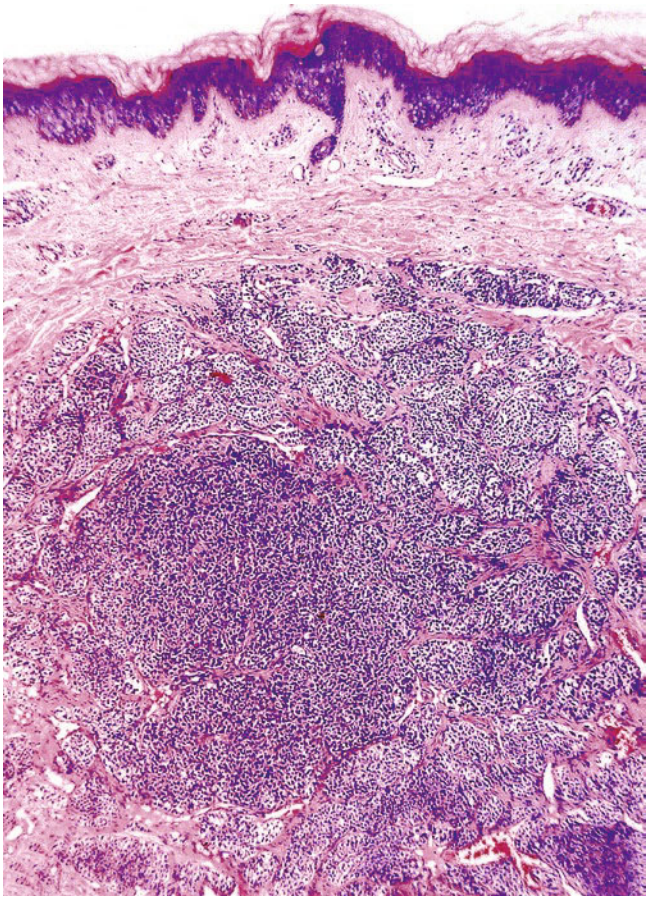


Fig. 27-55a-2 Circumscribed glomus tumors with a few vascular spaces in the dermis (HE stain, ×100)

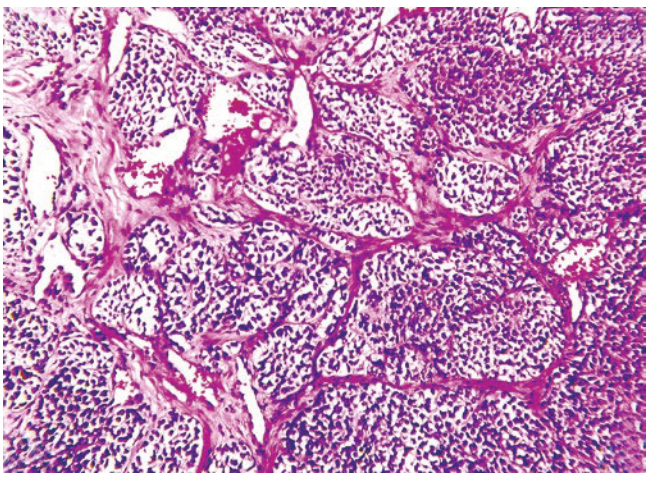


Fig. 27-55a-3 The glomus cells had a faintly eosinophilic cytoplasm and round to oval nuclei in the center. The glomus tumors were surrounded by a fibrous capsule and a few vascular spaces (HE stain, ×100)

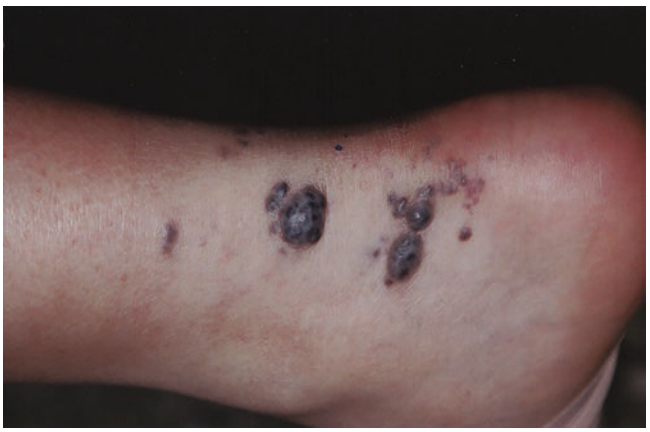


Fig. 27-55b-1 More than 30 purplish red papules or nodules with tenderness on the right ankle

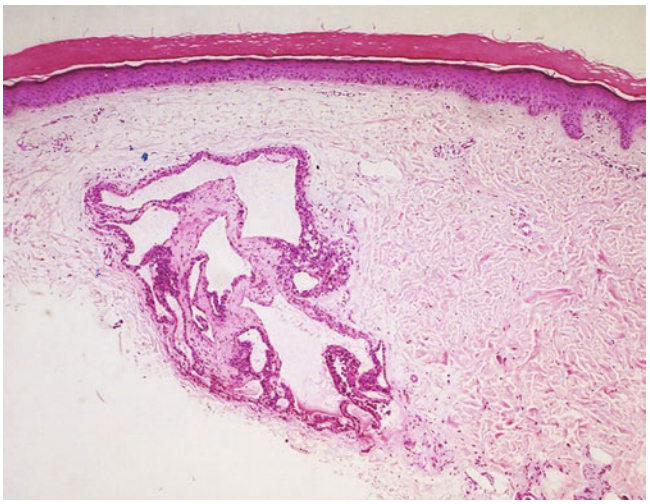


Fig. 27-55b-2 There were several narrow vascular lumina in masses of tumor cells (HE stain, ×40)

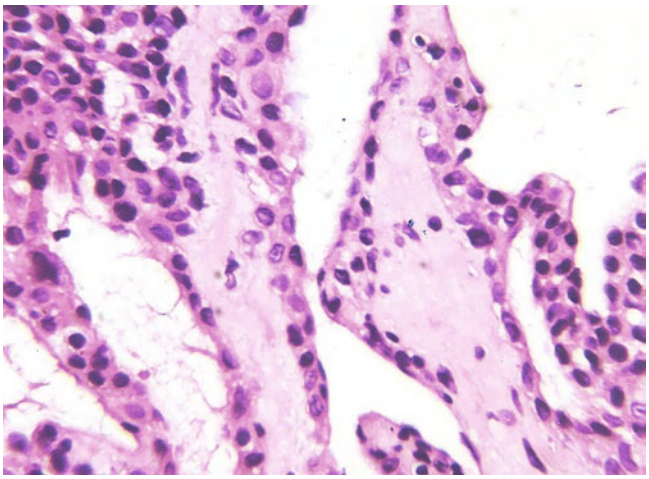


Fig. 27-55b-3 The vascular lumen lined by a single or many layers of glomus cells (HE stain, ×400)

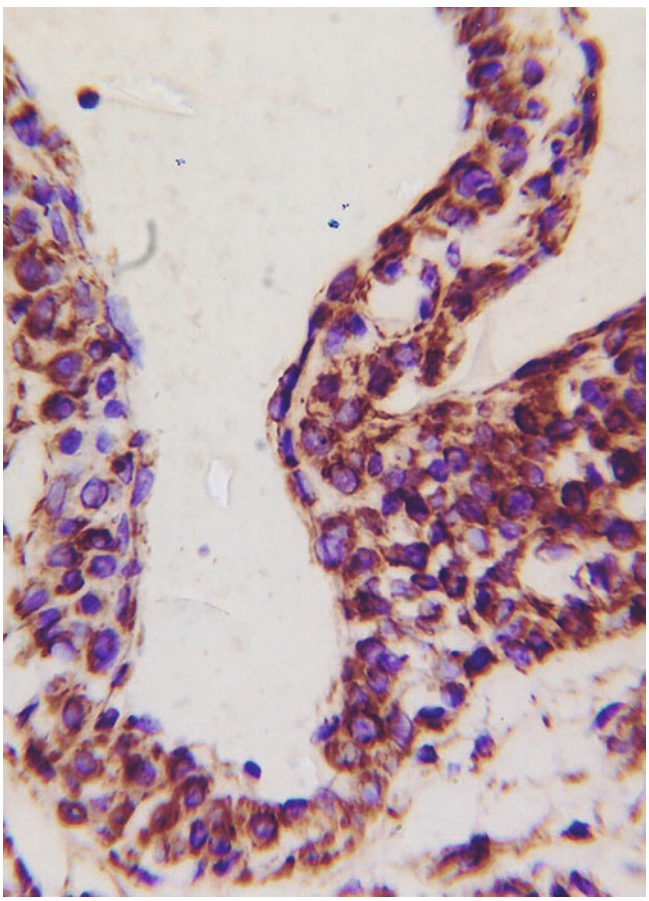


Fig. 27-55b-4 Vimentin positive in glomus cells (immunohistologic technique, ×400)

27.56 Spindle Cell Hemangioma [130, 131]

- Spindle cell hemangioma (SCH) is an uncommon reactive form of vascular malformation that usually develops during childhood or early adulthood. Patients with SCH tend to complain about pain and disfigurement.
- SCH arises in the skin, spinal cord, cervix, oral cavity, pancreas, spleen, and other viscera, presenting as a solitary, smooth, and firm nodule (spindle cell hemangioma) and as multiple lesions (spindle cell hemangiomatosis).
- Microscopically, SCH shows proliferations of thin-walled blood vessels within abundant spindle cell areas. There are thrombi or phleboliths in their lumina. No mitosis can be found.
- Although local wide local excision is the standard treatment, the reoccurrence rate is greater than 50%.
- Multiple SCH is related to Maffucci's syndrome, congenital lymphedema, Ollier disease, Klippel-Trenaunay syndrome, and early-onset varicose veins.

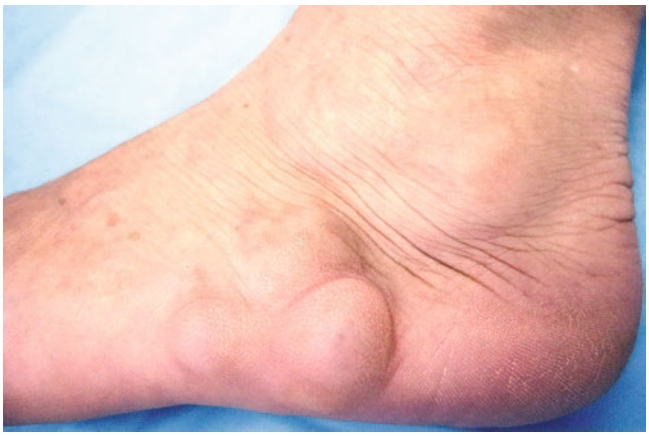


Fig. 27-56-1 Several skin-colored or reddish nodules on the fibular margin, external malleolus, and sole of the left foot

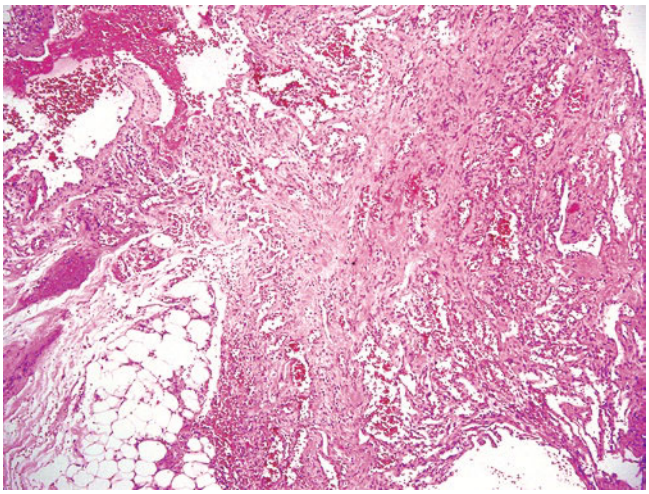


Fig. 27-56-2 The tumor composed of spindle tumor cells and cavernous blood vessels with irregular dilated thin-walled sinusoids lined with flattened endothelial cells in the middle and lower dermis (HE stain, ×100)

27.57 Kaposiform Hemangioendothelioma [132, 133]

- Kaposiform hemangioendothelioma (KHE) is an aggressive vascular neoplasm almost exclusively seen in infancy and childhood.
- KHE typically shows red to violaceous macules, nodules, and plaques. The appearance of telangiectatic papules is also likely to present. KHE usually occurs with Kasabach-Merritt syndrome, leading to intense thrombocytopenia and coagulopathy.
- Histologically, KHE has interconnecting sheets or nodules with slit-like or crescent-shaped vessels lined by spindled endothelial cells. In the focal vessel lumina, there are trapped RBCs, platelet thrombi, hyaline eosinophilic globules, and hemosiderin.
- KHE and tufted angioma reflect different stages in the evolution of the same entity, and they can be discriminated by positive stains with D2-40, Prox1, and lymphatic vessel endothelial hyaluronan receptor-1.
- Although KHE is histologically benign, it is considered to be a type of intermediate malignancy due to its invasion of local tissue and aggressive growth.
- The site and size of the lesion, invasive depth, and coagulopathy abnormality are associated with significant morbidity in some cases.

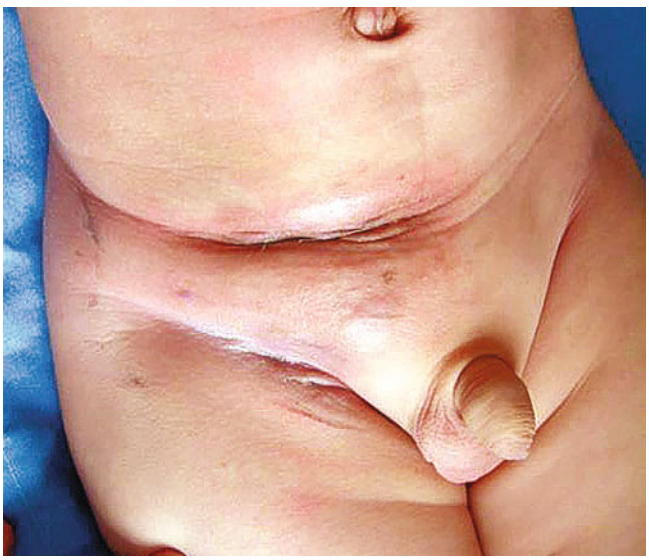


Fig. 27-57-1 Brown-red plaques on the right lower abdomen and groin area

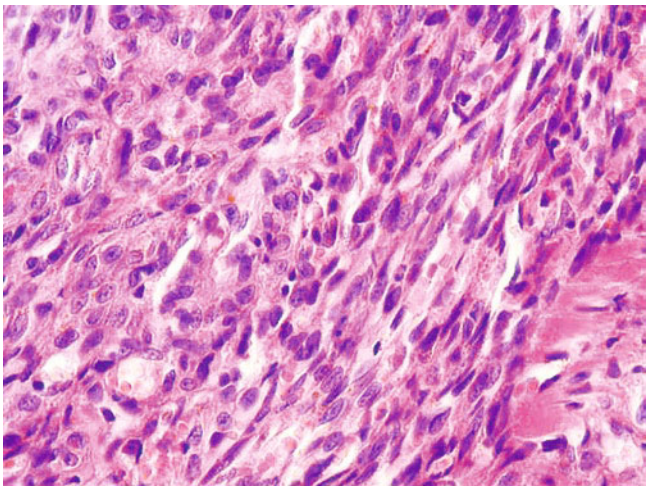


Fig. 27-57-2 Nodular aggregates of spindled cells and ovoid cells associated with vascular spaces, blood red cell, and hemosiderin in the dermis (HE stain, ×400)

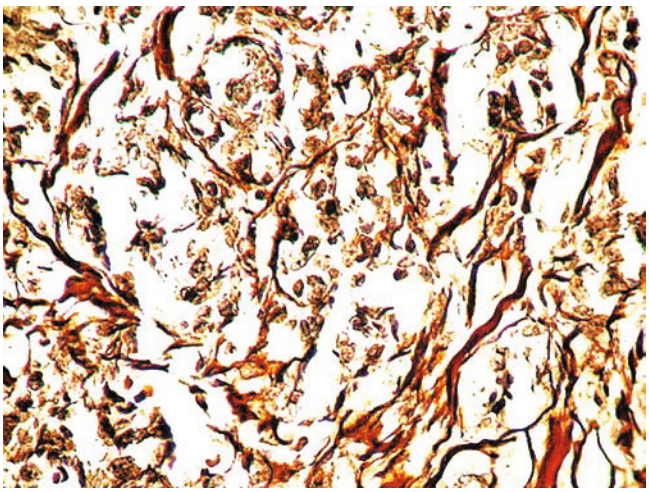


Fig. 27-57-3 Tumor was surrounded by dark reticular fibers in the dermis (Reticular fiber stain, ×400)

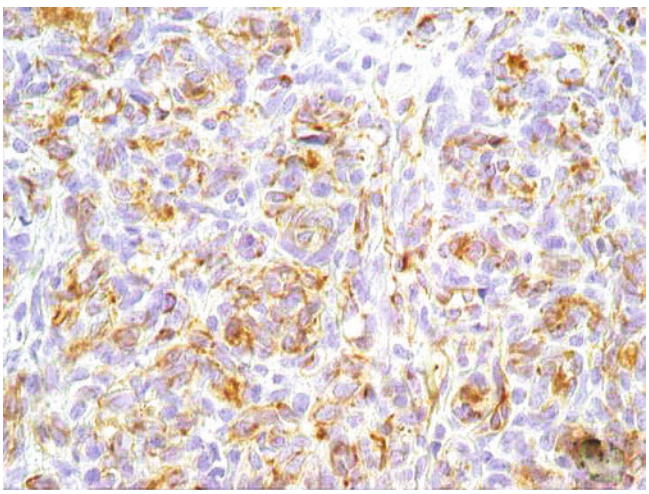


Fig. 27-57-4 CD31 positive (Vision, ×400)

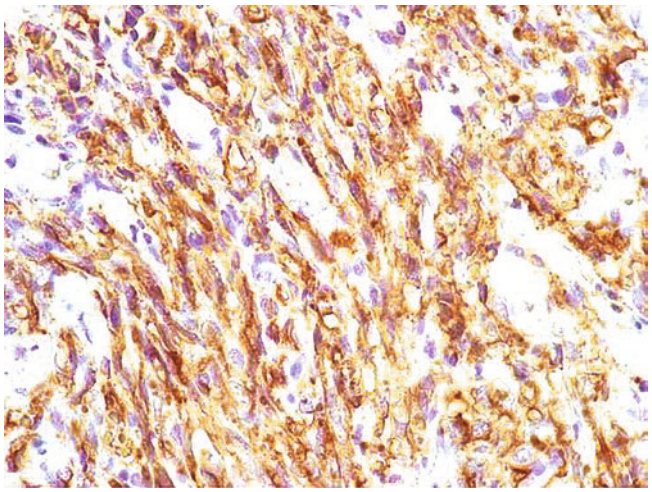
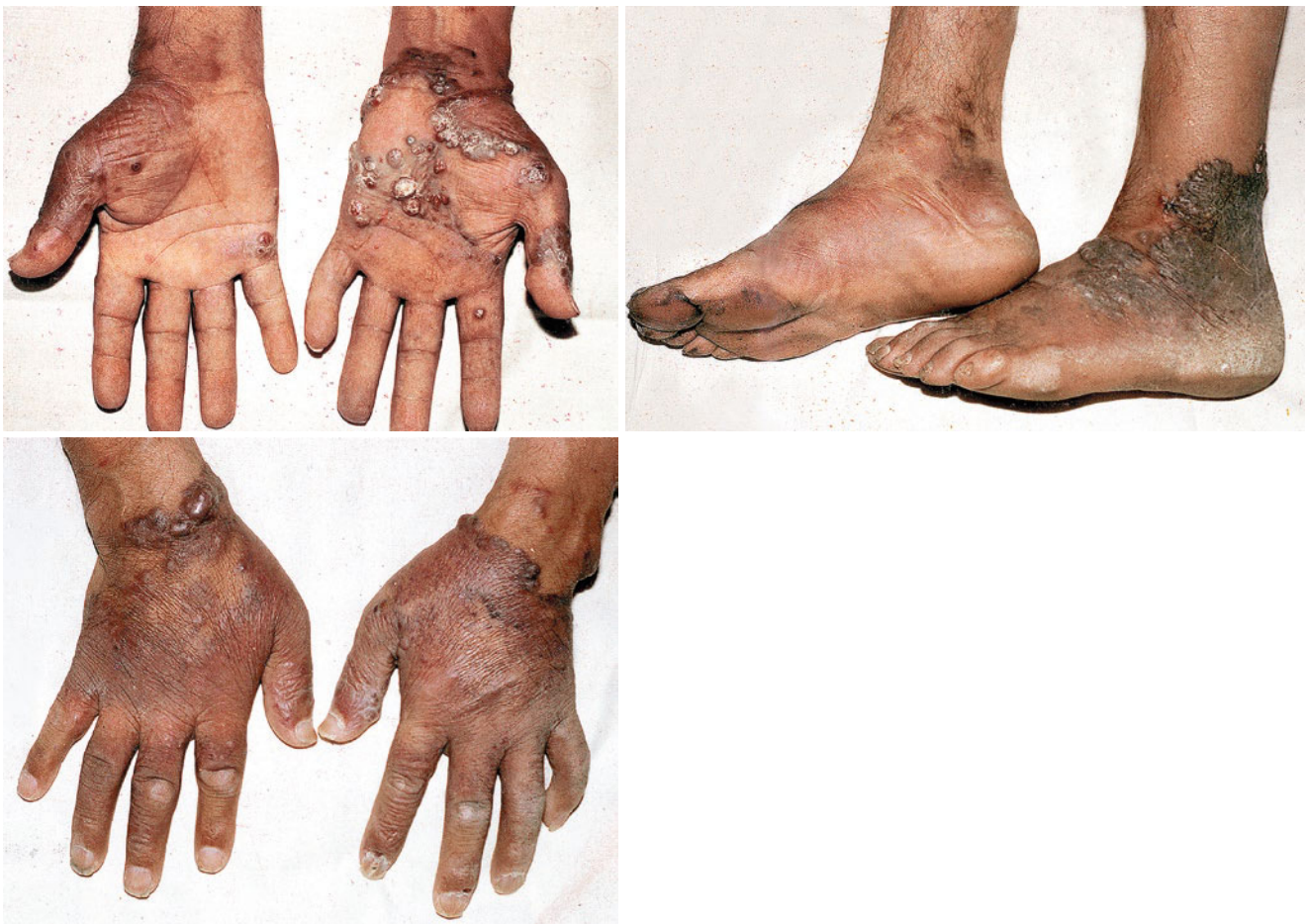


Fig. 27-57-5 CD34 positive (Vision, ×400)

27.58 Classic Kaposi's Sarcoma [134, 135]

- Kaposi's sarcoma is a mesenchymal tumor that is pathologically classified into four types: classic, African, iatrogenic, and AIDS-related.
- Most patients are Ashkenazi Jews or elder populations from Eastern European and Mediterranean countries.
- Classic Kaposi's sarcoma (CKS) presents as bluish-red macules or firm nodules on the lower extremities.
- Histology of the lesion typically shows the dermal proliferation of spindle cells. In addition, slit-like vascular spaces, hemorrhage, and extravasated red blood cells have also been reported.



Figs. 27-58-1, 27-58-2, 27-58-3 Three main lesions of KS including nodules, plaques, and patches distributed on the extremities: (1) on the dorsa of the hands, (2) on the palms, and (3) on the feet

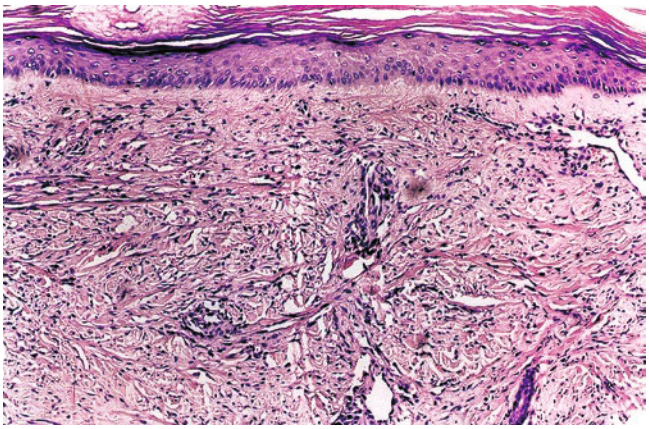


Fig. 27-58-4 Chronic nonspecific inflammation appeared in patch lesion (HE stain, ×100)

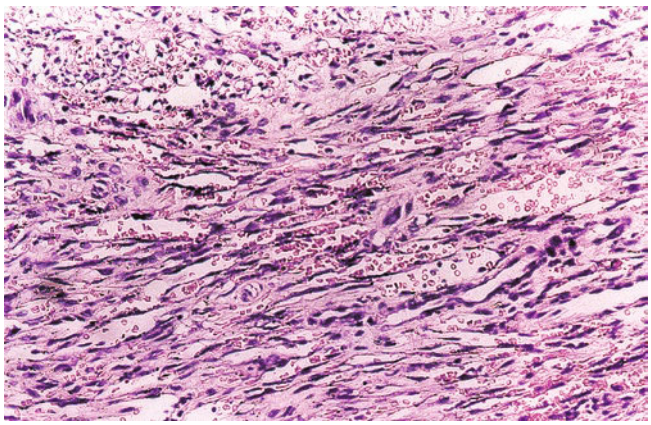


Fig. 27-58-5 RBC extravasation and abundant deposition of hemosiderin in the tissue (HE stain, ×200)

27.59 Cutaneous Angiosarcoma [118, 136]

- Cutaneous angiosarcoma (CA) is a highly malignant vascular neoplasm with a very poor prognosis.
- There are three subtypes of CA: radiation-induced angiosarcomas, head-and-neck-type angiosarcoma, and lymphedema-associated angiosarcoma.
- The initial presentation of head-and-neck-type CA is a purplish macule, nodule, or plaque that may ultimately become ulcerated and hemorrhagic.
- Well-differentiated CA shows "lightning-like" vascular slits that are often lined by flattened endothelial cells. For poorly differentiated angiosarcomas, the vascular channels are lined by multiple layers of epithelioid, spindled, or pleomorphic endothelial cells.
- CA typically expresses endothelial markers, including CD34, CD31, agglutinin 1, and VEGF.
- Tumors with a diameter larger than 5 cm tend to have a significantly worse prognosis.
- There are sporadic reports that pemphigus herpetiformis occurs with visceral malignancies, including lung cancer, esophageal carcinoma, prostate cancer, and herein cutaneous angiosarcoma.

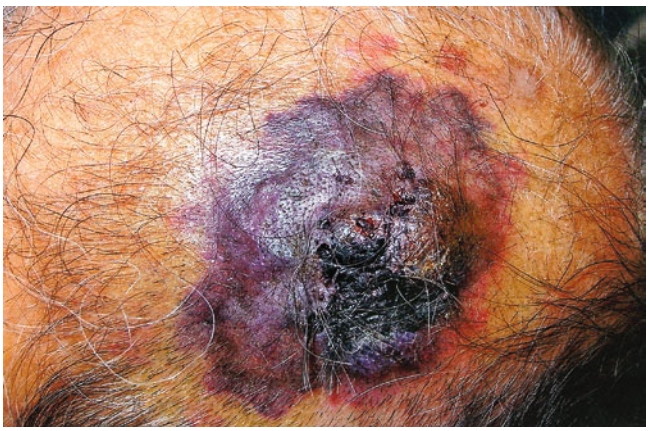


Fig. 27-59a-1 A big, purple-red, diffuse infiltrating mass covered with necrosis and crusts on the scalp

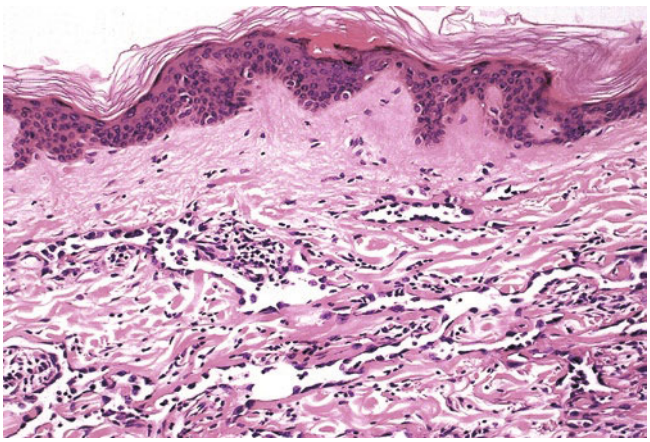


Fig. 27-59a-2 In the dermis, there were numerous lumens with variable sizes and configurations,and were lined by plump endothelial cells (HE stain, ×100)

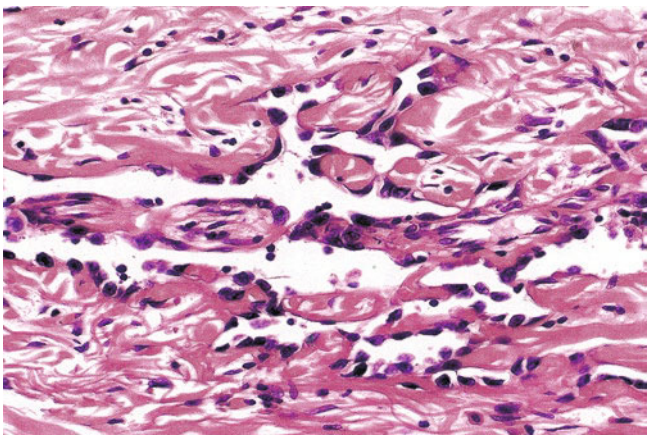


Fig. 27-59a-3 The vascular lumina was lined by atypical endothelial cells that were irregular in shape (HE stain, ×200)

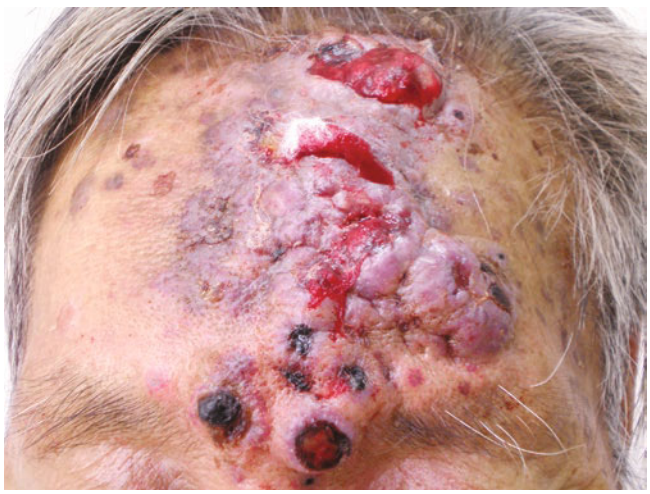


Fig. 27-59b-1 Purpuric papulonodular lesions with dotted ulceration and bleeding on the forehead (Reproduced with the permission from [137])

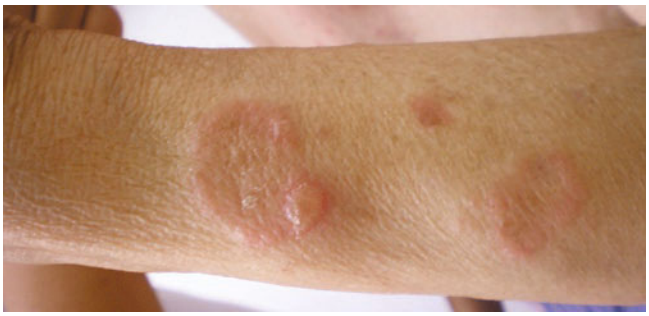


Fig. 27-59b-2 Numerous erythematous and edematous skin lesions in an annular arrangement, associated with small- to medium-sized blisters on the trunk and extensor aspects of the extremities, Nikolsky sign (−) (Reproduced with the permission from [137])

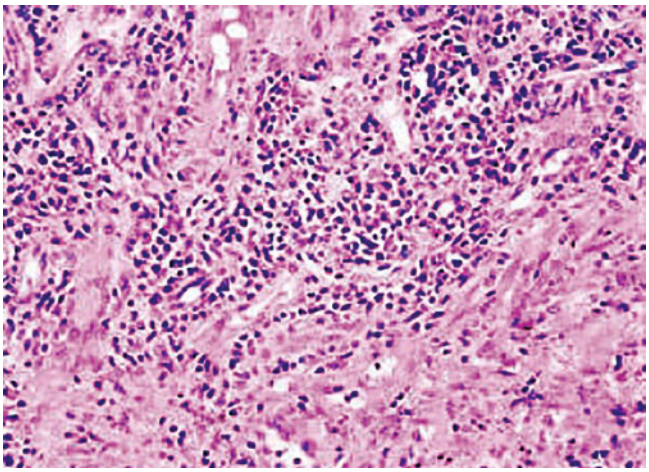


Fig. 27-59b-3 Vascular hyperplasia and sporadic atypical endothelial cells and moderate dense mononuclear infiltrated with irregular vascular channel formation and extravasation of erythrocytes (HE stain, ×200) (Reproduced with the permission from [137])

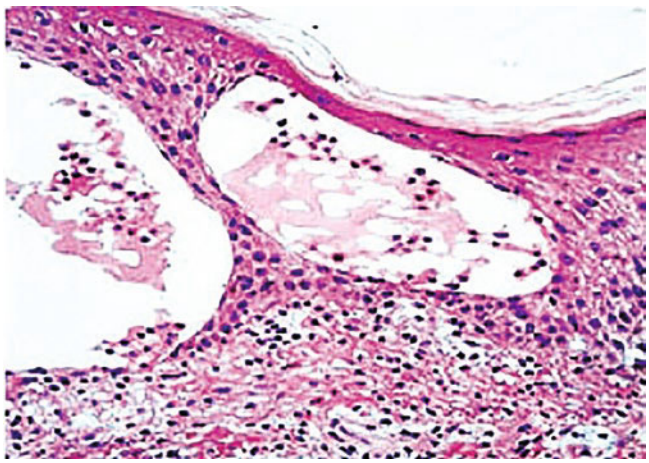


Fig. 27-59b-4 Intraepidermal acantholysis and blisters located in the mid- to lower epidermis with mixed infiltration of eosinophils and neutrophils (HE stain, ×200) (Reproduced with the permission from [137])

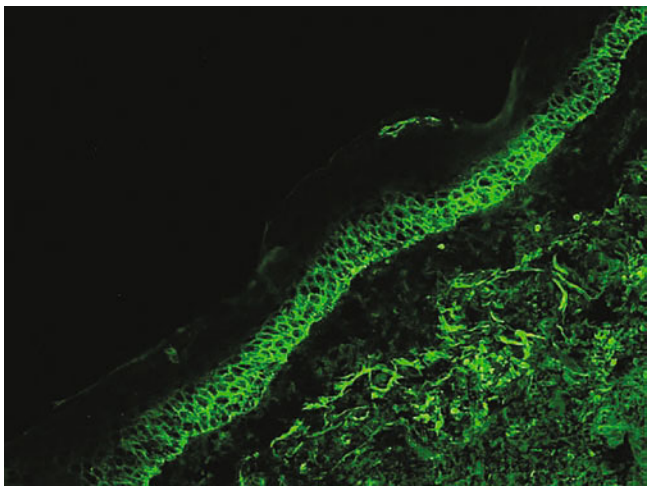


Fig. 27-59b-5 Direct immunofluorescence study showed intraepidermal deposition of immunoglobulin G localized to the lower upper epidermis (DIF, ×100) (Reproduced with the permission from [137])

27.60 Acquired Progressive Lymphangioma [138, 139]

- Acquired progressive lymphangioma (APL) is a rare disorder that occurs in childhood or adult time. APL is characterized by bruise-like lesions, red patches, or erythematous macules. APL occurs anywhere and grows slowly.
- Histopathology of the lesions shows numerous lumina that are dilated and randomly arranged. These lumina are lined by a single layer of endothelial cells with erythrocytes in them.

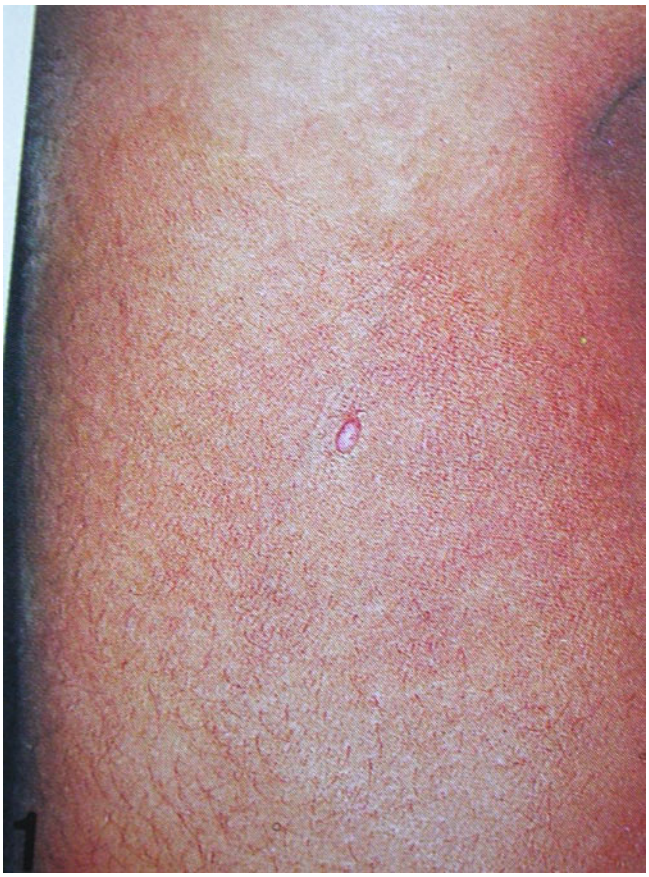


Fig. 27-60-1 Hyperpigmented, slightly indurated, irregular patches on the right calf (Reproduced with the permission from [140])

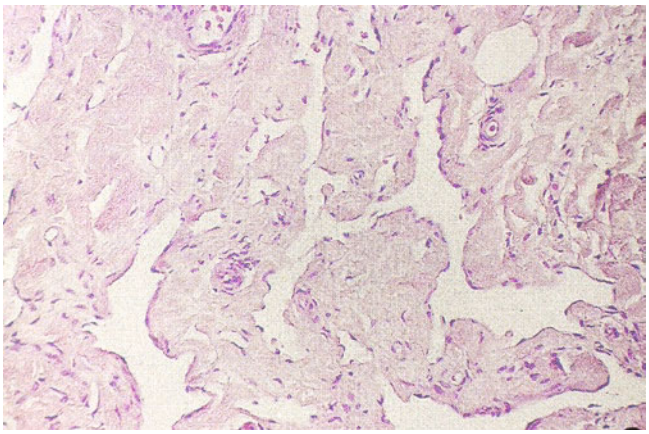


Fig. 27-60-2 Interlacing channels in the dermis, lined by vascular endothelium, that tended to coat collagen bundles (HE stain, ×200) (Reproduced with the permission from [140])

27.61 Lymphangioma [138, 141]

- Lymphangioma is an uncommon malformation of microcystic lymphatic vasculature involving the skin and subcutaneous tissues.
- Lymphangioma is divided into three types: circumscriptum lymphangioma, cavernous lymphangioma, and cystic lymphangioma. Circumscriptum lymphangioma is superficial, whereas the latter two are much deeper.
- The pathological features are comprised of dilated lymphatic vessels that are lined by endothelium and filled with clear fluid. These vessels express CD31 and D2-40, while they are negative for SMA.
- Lymphangioma circumscriptum (LM) occurs as clustered "frog spawn"-like vesicles that contain clear fluid. It begins congenitally or follows radiotherapy for cancers, treatment for cellulitis, and pelvic surgeries.
- Cavernous lymphangioma mostly presents on the trunk and occurs with Turner's syndrome or other malformative diseases.

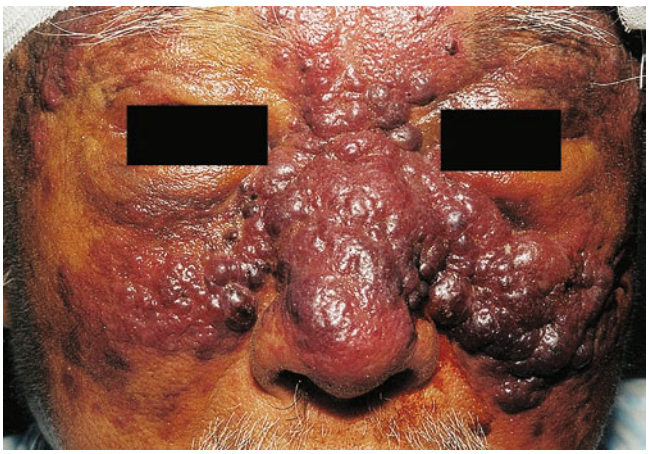


Fig. 27-61a-1 A great soft tumor with ulcers and bleeding on the frontal plane

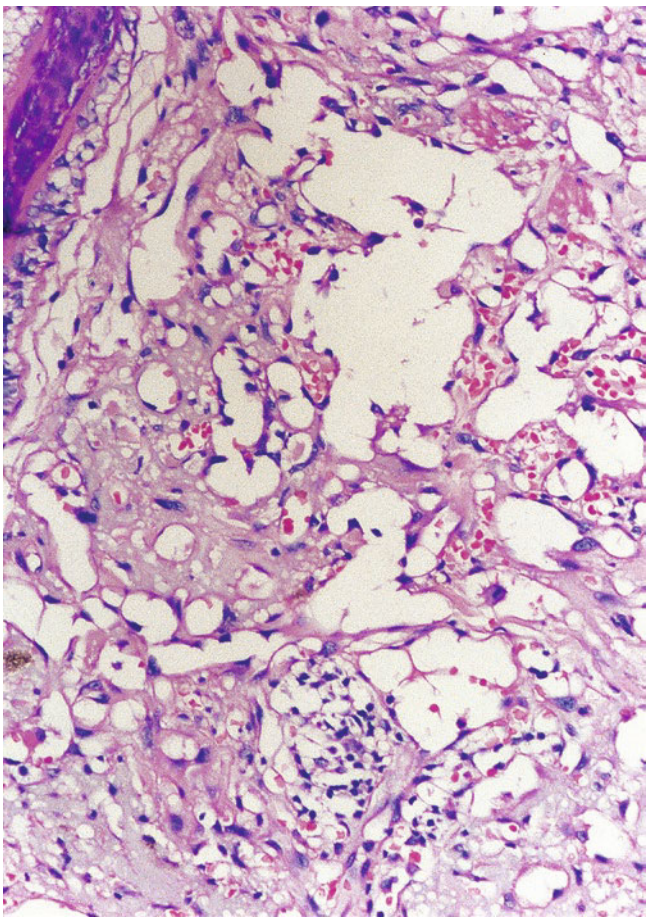


Fig. 27-61a-2 Dilated lymph tubes with endothelial cell swelling and a few lymphocytes infiltrated in the dermis (HE stain, ×400)

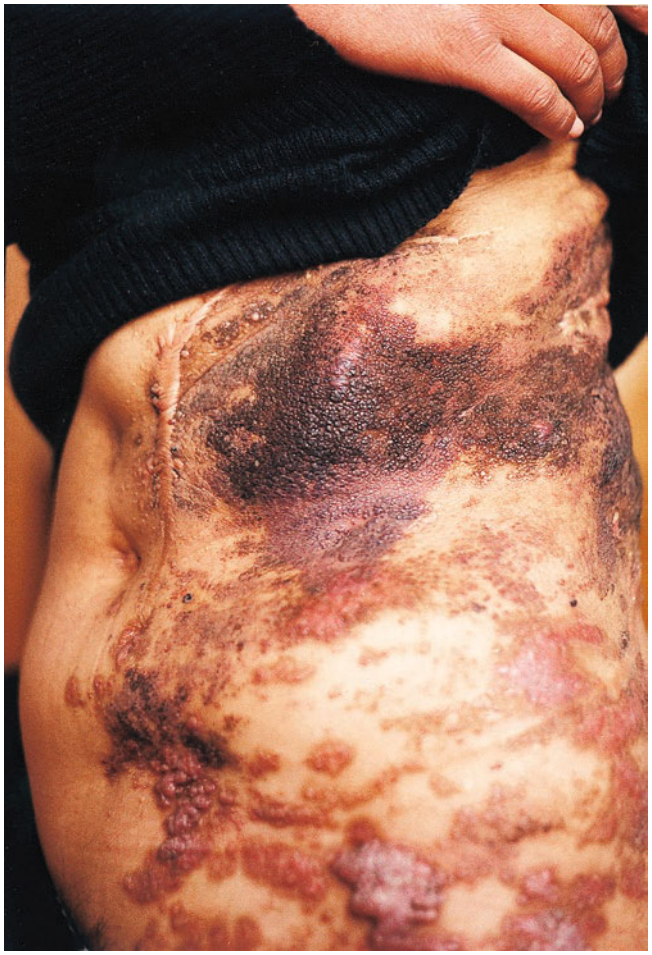


Fig. 27-61b-1 Varying-sized brown papules and verrucous and thick-walled vesicles in diffuse distribution on the left chest and abdomen

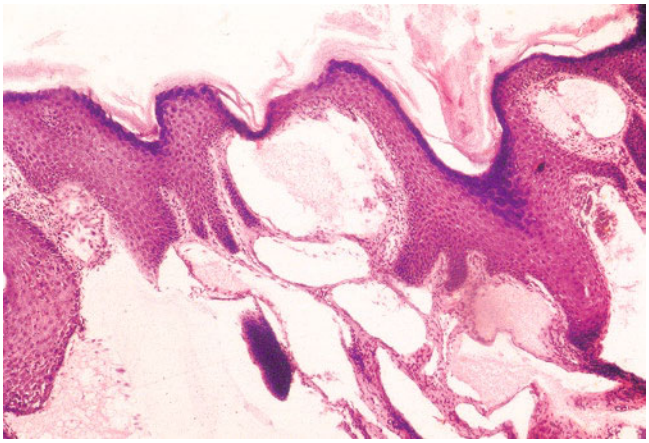


Fig. 27-61b-2 Hyperkeratosis and large irregular dilated lymph vessels lined by single-layer endothelial cells associated with hyperplastic capillaries and lymphocyte infiltrating in the dermis (HE stain, ×100)

27.62 Nevus Lipomatosus Superficialis [142, 143]

- Nevus lipomatosus superficialis (NLS) is a unique developmental anomaly or nevoid form of lipoma.
- Histopathology of NSL demonstrates isolated adipocytes or an ectopic deposit of mature adipocytes in the dermis.
- The classic variant presents as clustered, soft, cerebriform, pedunculated papules or nodules. They merge to form a plaque in a zonal pattern. The solitary form manifests as an isolated pedunculated papule. NLS with a scleroderma-like appearance is quite rare.
- Pigmentary anomalies, retractile testis, and folliculosebaceous cystic hamartoma are common associations with NLS.

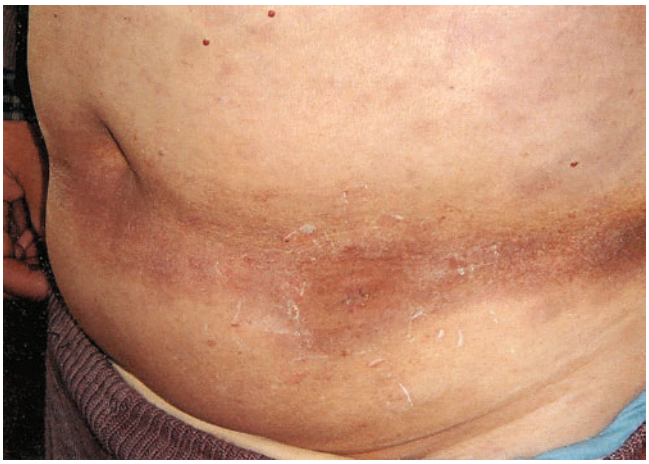


Fig. 27-62-1 Irregular hyperpigmentation on both aspects of the umbilicus

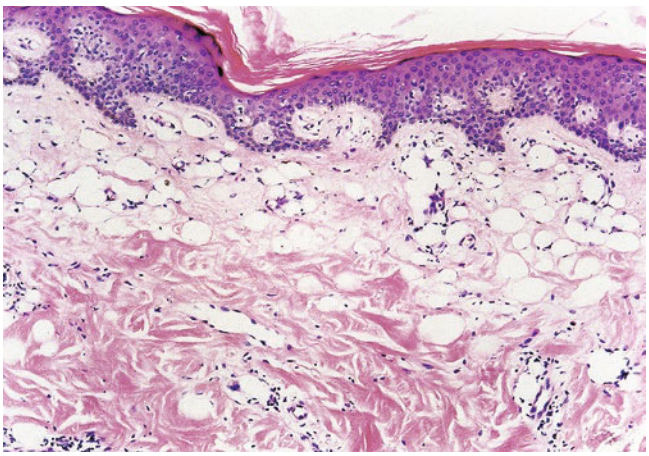


Fig. 27-62-2 Hyperkeratosis and acanthosis, numerous fat tissues, and collagen fiber in the upper dermis, similar to homogeneous change (HE stain, ×100)

27.63 Encephalocraniocutaneous Lipomatosis [144, 145]

- Encephalocraniocutaneous lipomatosis (ECCL) is an unusual syndrome with variable skin, ocular, and neurologic lesions.
- Dermatological presentations include alopecia, nevus psiloliparus, focal dermal hypoplasia, and lipoma over the frontotemporal area.
- Brain abnormalities in ECCL are comprised of agenesis of corpus callosum, hydrocephalus, calcification, lipoma, and cyst.
- Ocular lesions arise as microphthalmia, conjunctival tumors, iris dysplasia, ocular calcifications, and optic nerve pallor.

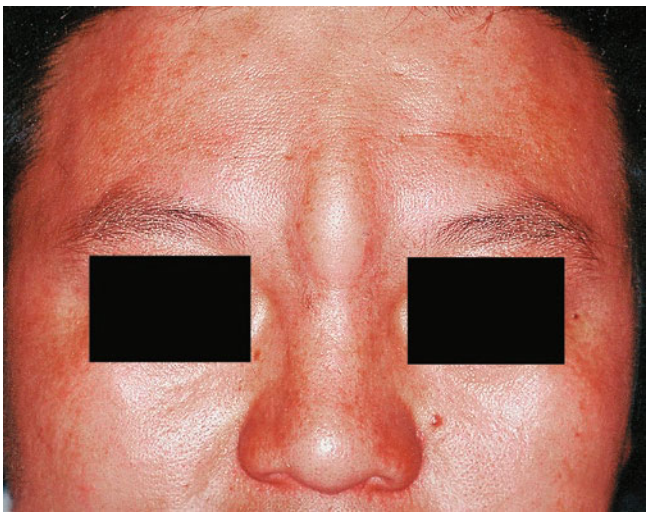


Fig. 27-63-1 Innate frontoparietal subcutaneous fat oncoma

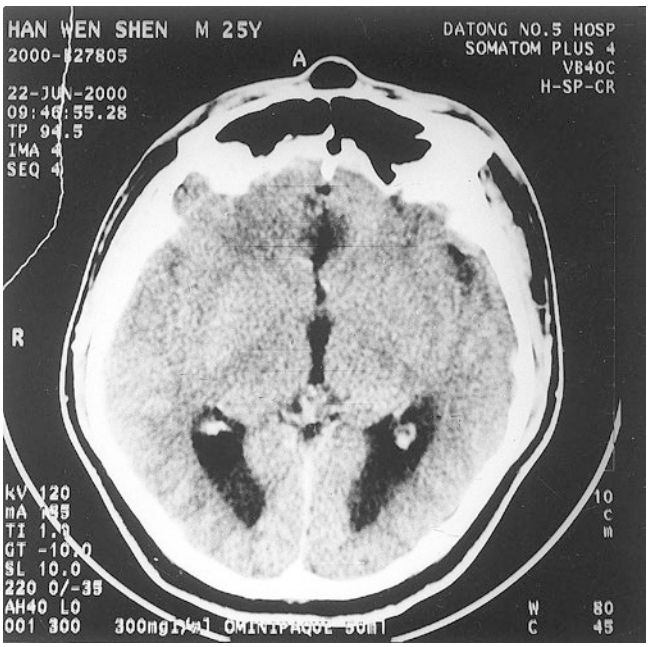


Fig. 27-63-2 A fat oncoma of cerebral flax

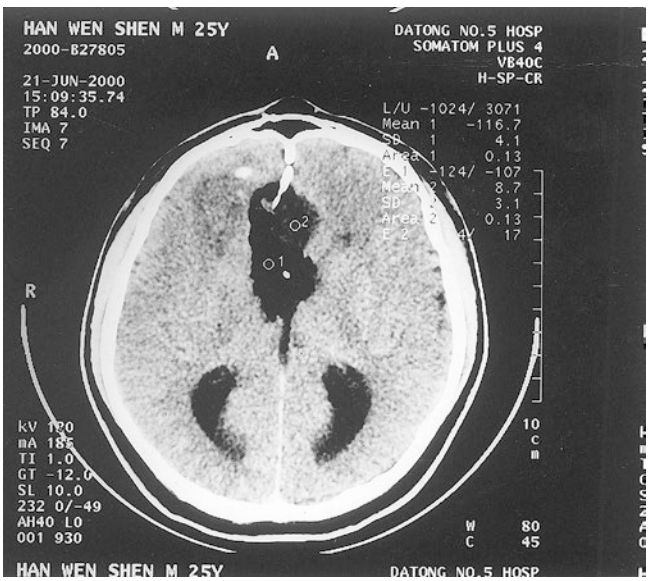


Fig. 27-63-3 Callosal dysplasia

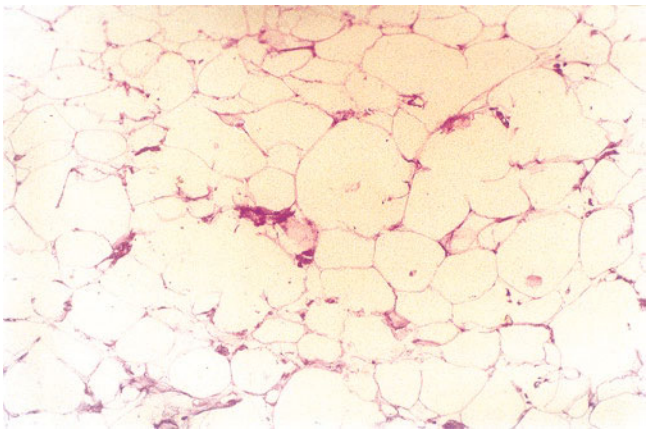


Fig. 27-63-4 Brown fat cell with good differentiation (HE stain, ×200)

27.64 Madelung Disease [146, 147]

- Madelung disease (MD) represents an uncommon metabolic disease characterized by the accumulation and enlargement of nonencapsulated adipose tissue. The face and neck are predilection sites of involvement.
- The contour of fat deposits in MD changes to different locations, and it may resemble a horse collar (the neck and nape), hamster's cheek (parotid regions), and pseudo-athletic appearance (the shoulder, back, and chest).
- Mounting evidence shows alcohol abuse in MD impairs adrenergic lipolysis and induces unusual fat accumulation. However, abstinence from alcohol shows no promising outcomes.
- MD is categorized into two types. Fat tissue in type I accumulates on the neck, nape, upper arms, and upper back. In type II, there is a diffuse deposit of fat over the entire body, giving the appearance of generalized obesity.

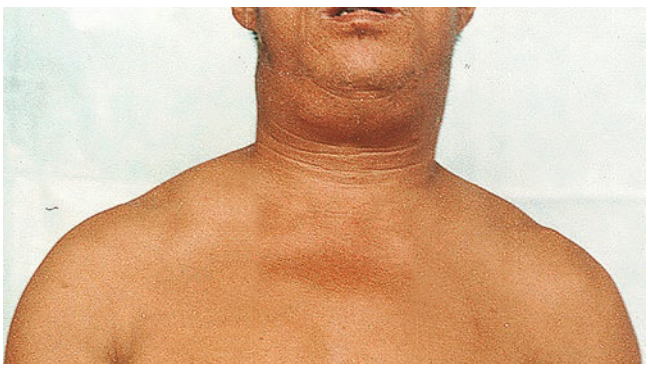


Fig. 27-64-1 Multiple massive lipomas were around the neck

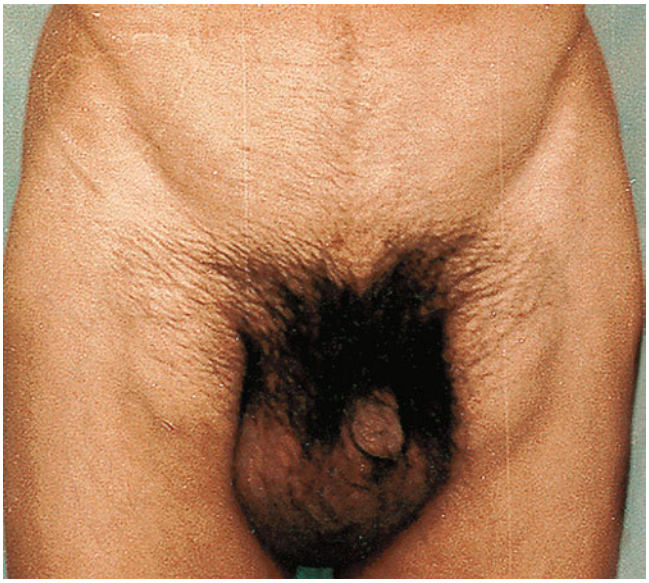


Fig. 27-64-2 Multiple massive lipomas were symmetrical in the groin

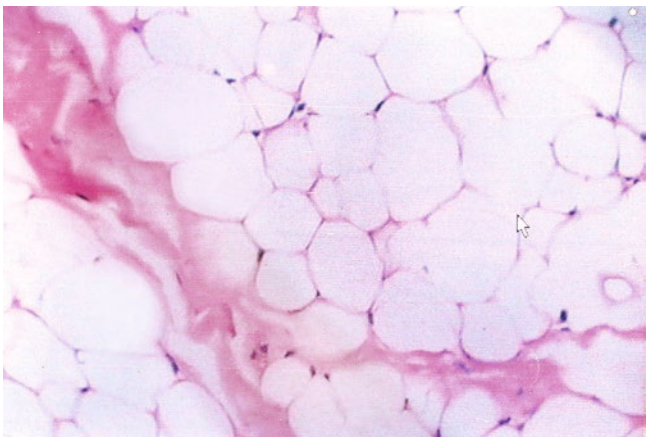


Fig. 27-64-3 Lipoma was composed of cells which did not differ from normal fat cells (HE stain, ×400)

27.65 Multiple Leiomyoma [148, 149]

- Cutaneous leiomyoma is the most common smooth muscle tumor, and it can be divided into three derivations: piloleiomyoma, genital leiomyoma, and angioleiomyoma.
- Paroxysmal or spontaneous pain is the most common complication in leiomyoma, followed by regional itching or burning sensations.
- Both genital leiomyoma and angioleiomyoma show a solitary nodule.
- Piloleiomyoma may be solitary or multiple. It usually consists of smooth, indurated, and red-brown papulonodules or plaques.
- Familial multiple leiomyomas have been reported with Reed syndrome, Gardner syndrome, dermatitis herpetiformis, and multiple endocrine neoplasia type I.
- Histological observation of leiomyoma reveals spindle cells distributed in an interlaced fascicular pattern. These nuclei are oval or cigar-shaped with blunt tips.

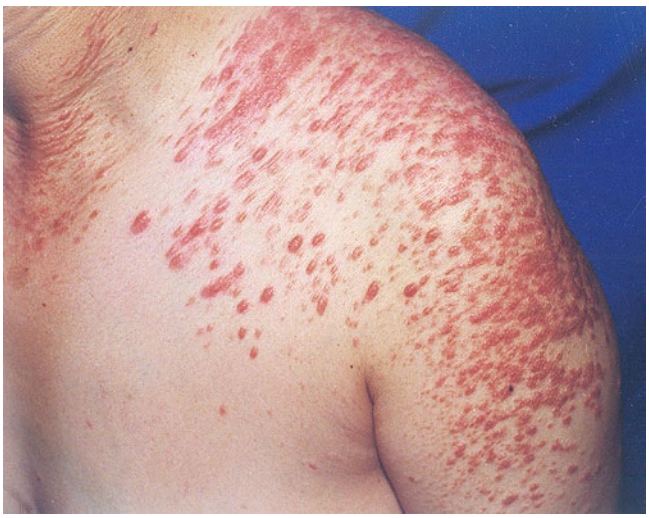


Fig. 27-65-1 Numerous amaranth papules and nodules on the left neck, chest, shoulder, and upper of arm; some of them were confluent

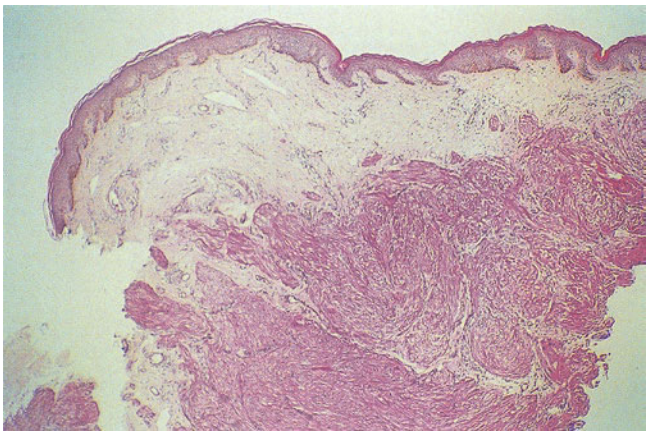


Fig. 27-65-2 Tumor was composed of smooth muscle fibers without encapsulation in the dermis (HE stain, ×40)

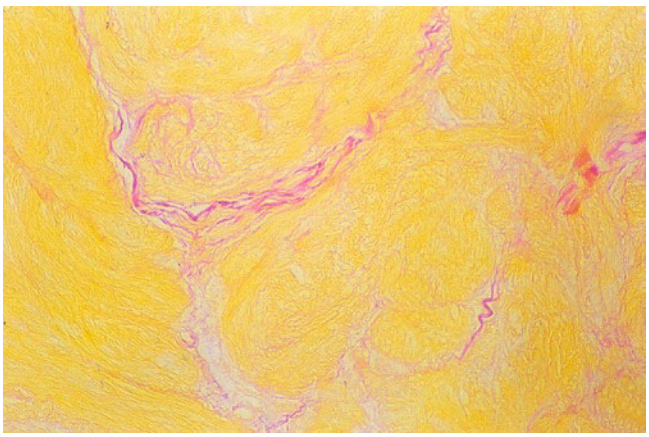


Fig. 27-65-3 Tumor was composed of massive yellow smooth muscle fibers and a few red collagen in the midst of them (van Gieson stain, ×100)

27.66 Cutaneous Leiomyosarcoma [150–152]

- Leiomyosarcoma is a kind of malignancy that arises from the smooth muscles of the extremities.
- Leiomyosarcoma is comprised of multiple or solitary nodules with a color range from normal to pink or brownish.
- Skin biopsy of CLS features fascicular proliferation of spindle-shaped cells in the dermis. The tumor cells have elongated, blunt-tipped, and anaplastic nuclei.
- Immunohistochemical stains for CLS are positive for vimentin, desmin, and actin.
- Tumor depth has a significant impact on its prognosis. Compared to the subcutaneous type, dermal leiomyosarcoma is more likely to recur with a much lower potential for distant metastasis.

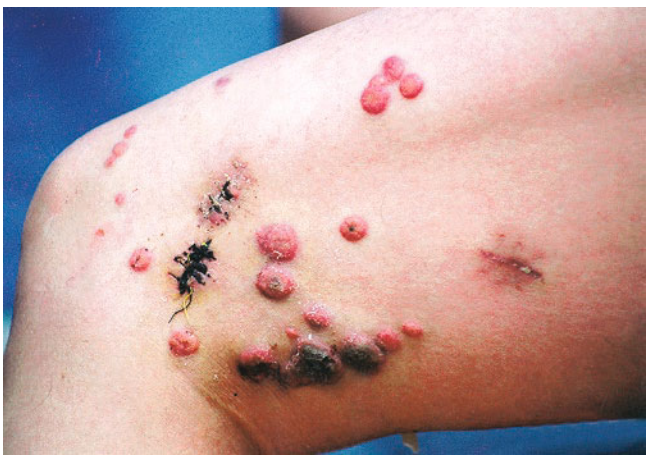


Fig. 27-66-1 Numerous turkey-red nodules on the outside of the left thigh

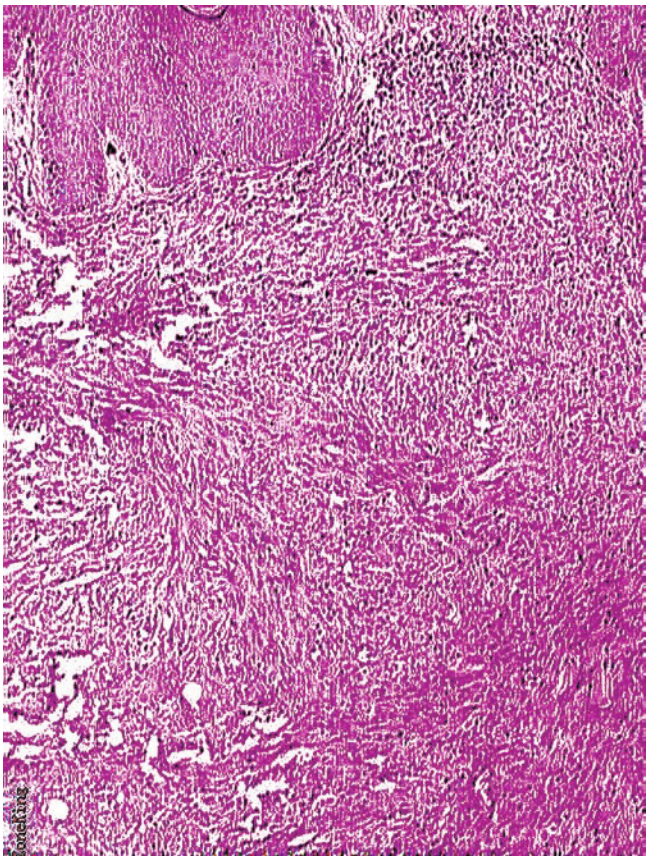


Fig. 27-66-2 Numerous pleomorphic elongated cells with atypical nuclei mitotic figures in the dermis (HE stain, ×40). The tumor cells were vimentin strong positive (unshown)

27.67 Subungual Exostosis [153, 154]

- Subungual exostosis (SE) is a relatively rare osteocartilaginous tumor that arises on the distal phalanges.
- SE is known as a painful, pink or flesh-colored, solid nodule involving the free edge of the nail. The overlying nail is usually deformed and elevated.
- A radiography should be performed prior to surgical excision, and it will tend to show bony excrescence from the distal phalangeal bone.
- Histopathologic evaluation typically reveals normal trabecular bone and a fibrocartilaginous cap.
- The cartilaginous cap should be completely excised to avoid recurrence.

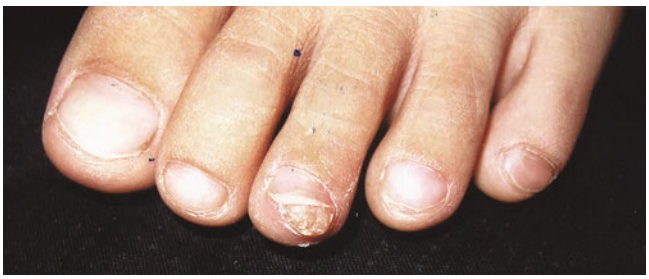


Fig. 27-67-1 A nodule on the nail edge of the left third toe

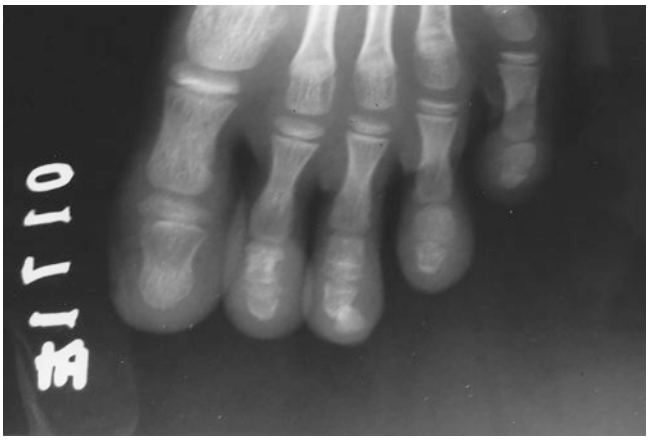


Fig. 27-67-2 X-rays exhibited a bone mass protruding from the third distal phalanx

27.68 Cutaneous Endometriosis [155, 156]

- Cutaneous endometriosis (CE) is an iatrogenic growth of endometrial tissue in the skin.
- Primary CE appears preferentially in the umbilicus area. In contrast, secondary CE generally develops by direct implantation of endometrial tissue on the scar following surgery to the abdomen.
- The typical clinical presentation of CE is a palpable mass with variable colors due to different underlying hemorrhage states. There may be a history of cyclic pain, swelling, or discharge in menstruation.
- Biopsy specimen of CE shows an endometrial gland-like lumen embedded in the highly vascular stroma in the dermis. The glandular tissue constitutes a single layer of columnar cells that typically shows decapitation secretion and is occasionally intermingled with clear cells.
- Immunoprofiles of CE are positive for CD10, estrogen, and progesterone receptors, which facilitates the diagnosis in atypical cases.

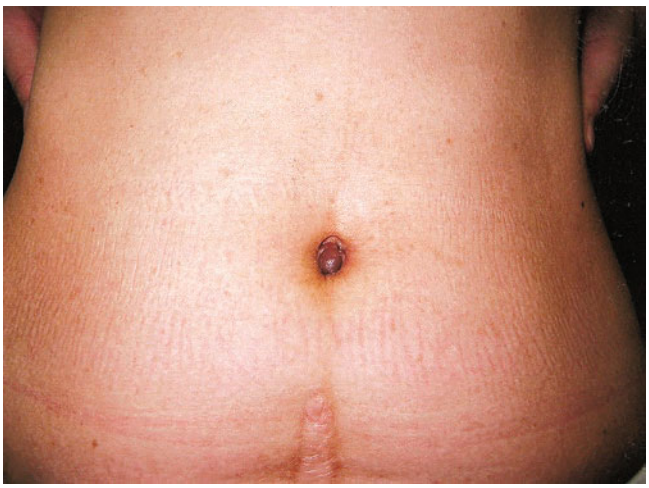


Fig. 27-68-1 A brown tumor on the lower part of umbilical

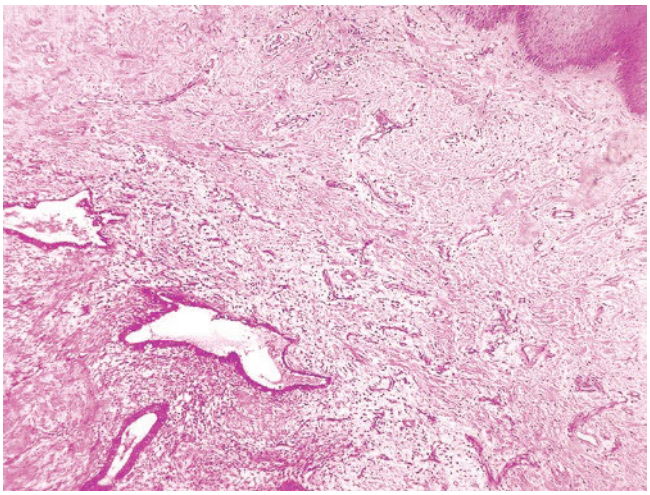


Fig. 27-68-2 Varying-sized glandular lumen around cellular and vascular stroma in the dermis (HE stain, ×40)

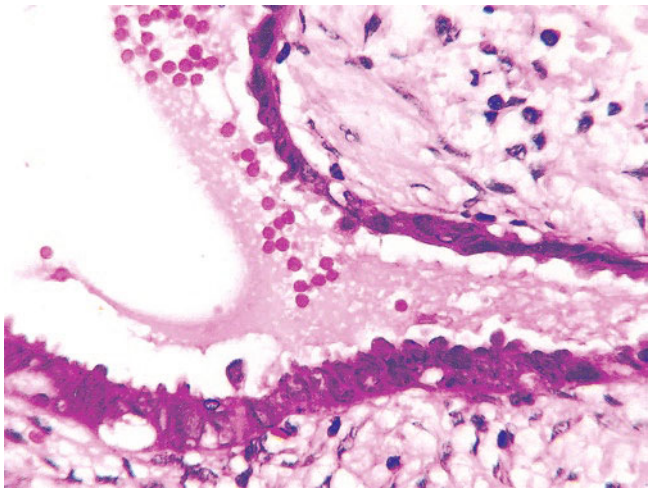


Fig. 27-68-3 Decapitation secretion at their luminal surfaces (HE stain, ×400)

27.69 Palisaded Encapsulated Neuroma [157, 158]

- Palisaded encapsulated neuroma (PEN) is characterized by proliferated Schwann cells and axons within a capsule.
- PEN typically presents as small, asymptomatic, dome-shaped papules that occur preferentially on the neck and oral mucosa.
- Microscopically, PEN shows intersecting fascicles separated by artifactual clefts and wavy hyperchromatic nuclei. Although Verocay bodies present in PEN, they are not seen as frequently as they are in schwannoma.
- Schwann cells can be shown after an S-100 stain. Axons are highlighted with neurofilament protein. The perineurial cells of the capsule can be distinguished by EMA.
- The absence of glial fibrillary acidic protein helps to differentiate it from schwannoma.

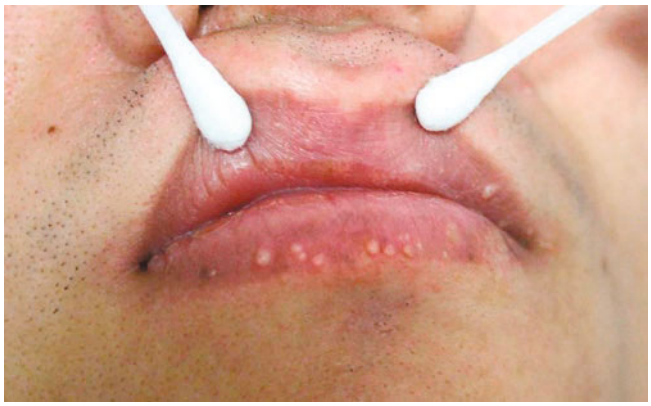


Fig. 27-69-1 Multiple creamy white, corn-sized papules diffused on the lower lip

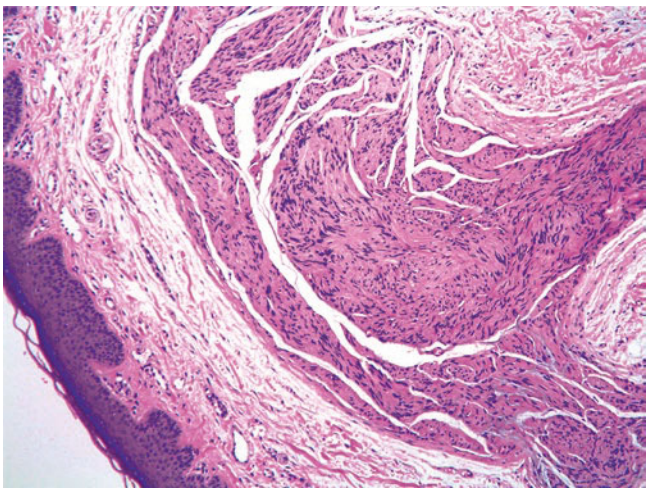


Fig. 27-69-2 The epidermis was normal. Some irregular cell masses with well-defined margin appeared in the dermis (HE stain, ×200)

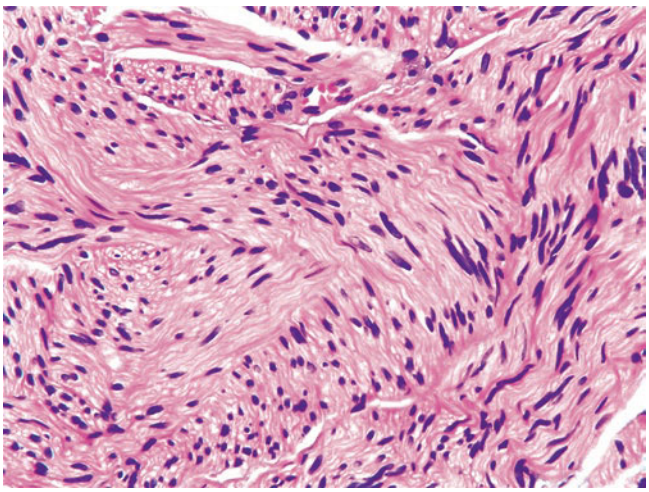


Fig. 27-69-3 The nucleus of Schwann cells was arranged in an irregular palisading and whirling pattern (HE stain, ×400)

27.70 Schwannoma [159, 160]

- Schwannoma, also referred to as neurilemoma, is a well-capsulated benign tumor of the Schwann cells of the peripheral nerve sheath.
- Cutaneous schwannoma (CS) is usually described as a solitary, glistening, and tender nodule deeply seated in the subcutaneous skin.
- Multiple schwannomas occur with neurofibromatosis in von Recklinghausen's disease.
- CS can be classified into the following clinicopathological patterns: classical, cellular, cranial nerve, plexiform, melanotic, ancient, granular cell, and palisaded encapsulated form.
- The tumors are well encapsulated and have a biphasic growth pattern of Antoni A regions and Antoni B regions. The Antoni A regions are highlighted with hyalinized acellular material sandwiched between two opposing rows of parallel nuclei, whereas the Antoni B areas consist of a loose meshwork of scattered spindled cells in a loose myxoid stroma.
- CS expresses S100 protein and collagen type IV. S-100 is much stronger in CS than other S-100 protein-positive neoplasms, such as melanoma.

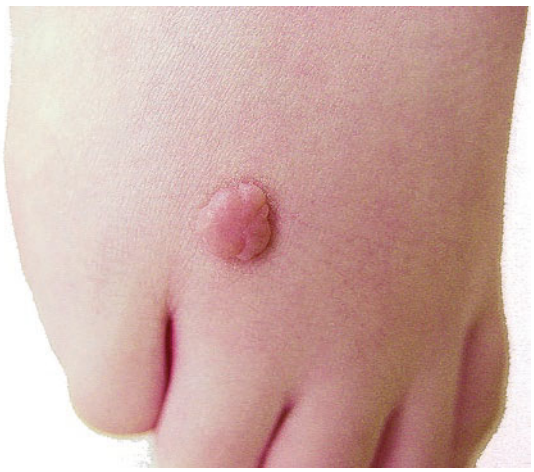


Fig. 27-70-1 A pink-gray and soft nodule on the dorsum of the right foot

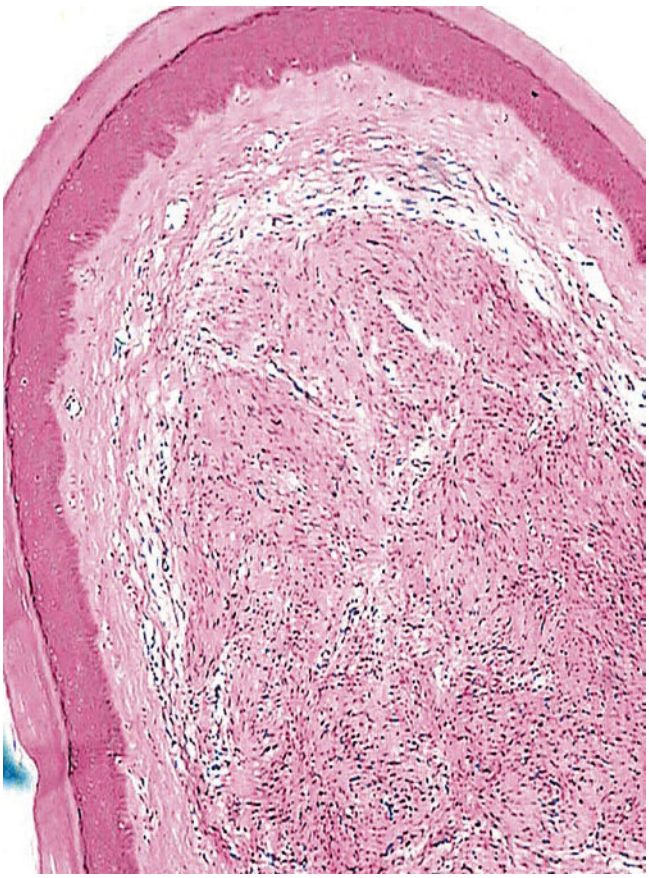


Fig. 27-70-2 A well-circumscribed and nonencapsulated tumor was situated in the dermis with fissures around them (HE stain, ×100)

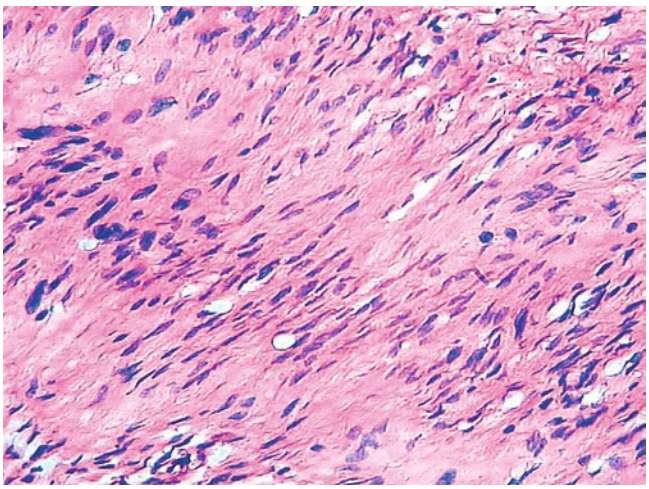


Fig. 27-70-3 The cells were spindle shaped with poorly defined cytoplasm and elongated basophilic nuclei, which were arranged in bands, which stream and interweave, the nuclei display palisading and were arranged in parallel rows with intervening eosinophilic cytoplasm in a typical appearance known as Verocay bodies (HE stain, ×400)

27.71 Cutaneous Merkel Cell Carcinoma [161, 162]

- Merkel cell carcinoma (MCC) is rare neuroectodermal neoplasm.
- Cutaneous MCC often occurs on UV-exposed regions, including the head and neck.
- At the time of presentation, 34% of MCC has nodal involvement or distant metastases.
- The lesions of MCC are not pathognomonic, and diagnosis can be confirmed by histopathology.
- Merkel cells are described as basophilic cells of small to medium size. They have round nuclei, scant cytoplasm, and granular or stippled chromatin. Nodular, infiltrative, and trabecular MCC are its three major histopathologic patterns.
- Paranuclear dot-like stains of cytokeratin 20 is a hallmark of MCC. In addition, CAM5.2 and neurofilaments are very sensitive and specific to MCC.
- Small cell lung carcinoma can be excluded immunohistologically without expressions of thyroid transcription factor 1 and cytokeratin 7.
- The detection of Merkel cell polyomavirus is highly suggestive of the diagnosis of MCC.

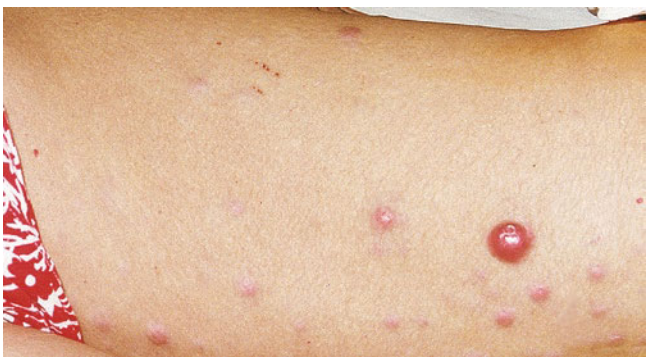


Fig. 27-71-1 Red-violet nodules with smooth surface on the left thigh

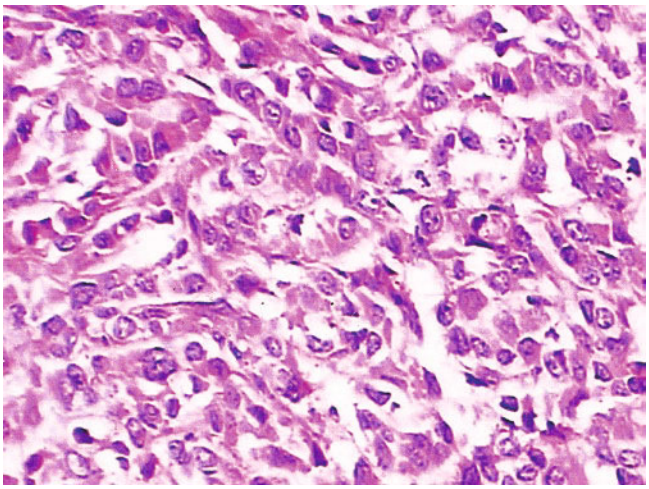


Fig. 27-71-2 The carcinoma cells with large nuclear in corium with the manner of mass (HE stain, ×200)

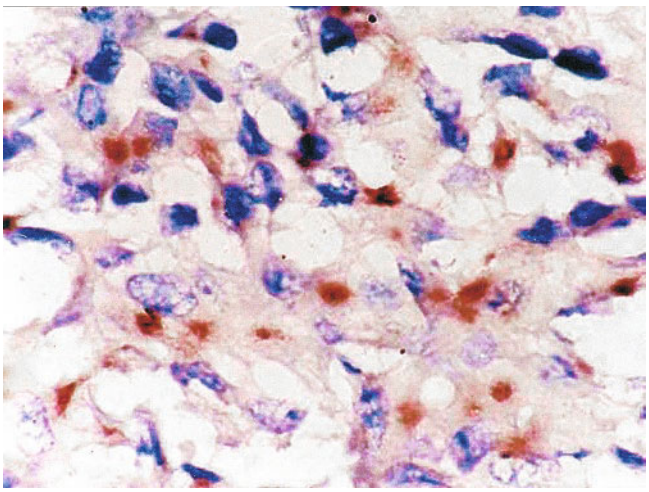


Fig. 27-71-3 Chromogranin A positive in cytoplasm of the carcinoma cells (SP method, ×400)

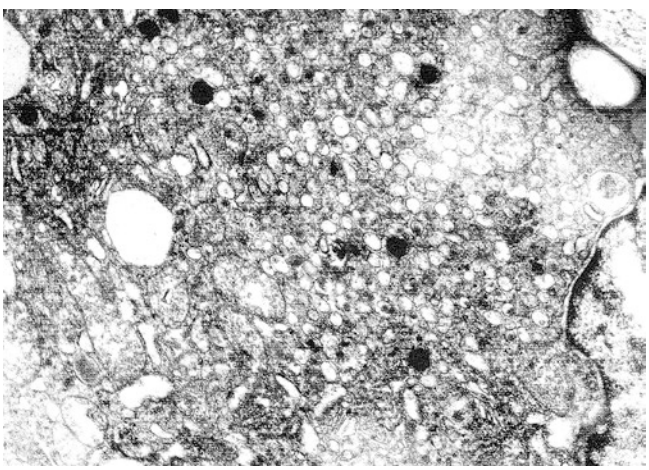


Fig. 27-71-4 Nerve secretion granules in cytoplasm of the carcinoma cells (TEM, ×20,000)

27.72 Agminated Spitz Nevus [163, 164]

- Spitz nevus (SN) appears as a shiny red or skin-colored papule at a young age.
- SN may present as disseminated or agminated multiple papules on a hyperpigmented, hypopigmented, or normal background skin color.
- Due to the likelihood of misdiagnosis between melanoma and SN, excision is often recommended for solitary SN.
- No case of conversion of multiple Spitz nevi to malignant melanoma has been reported.

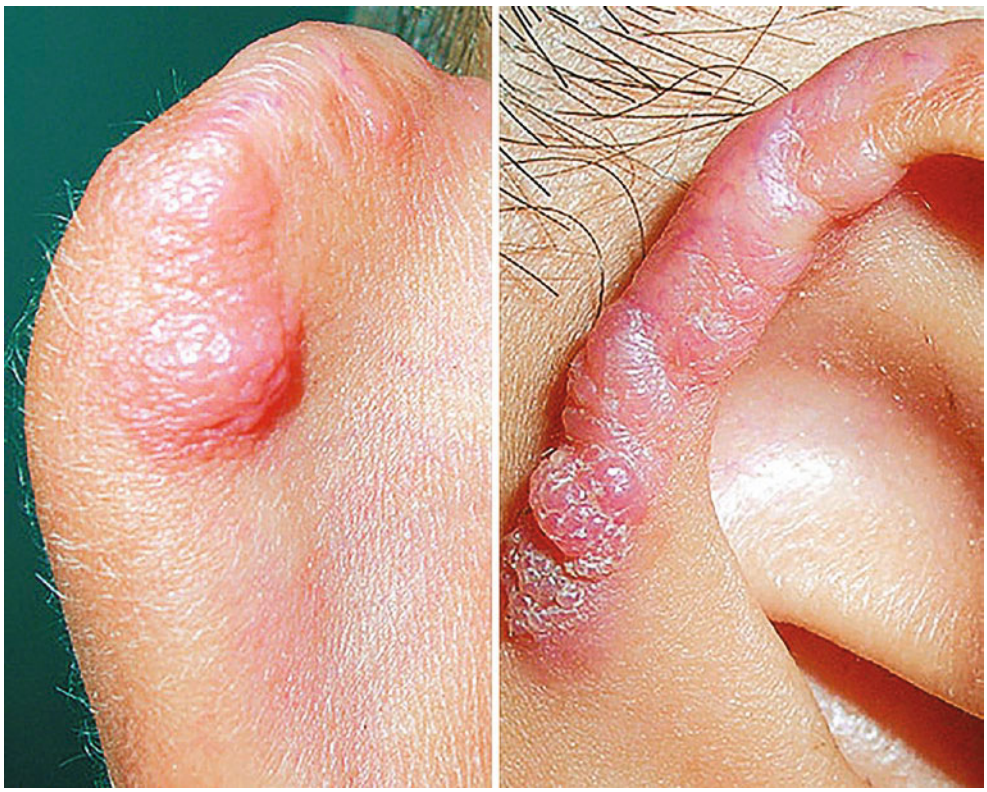


Fig. 27-72-1 Multiple pink, small papules confluenting to plaques on the left auricle; part papillary

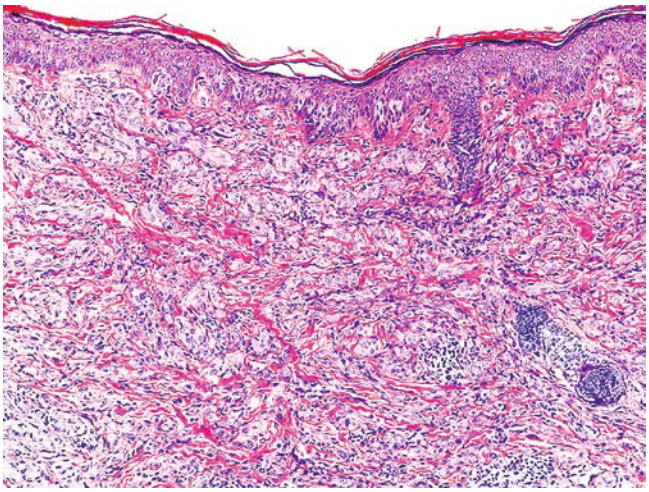


Fig. 27-72-2 Large amount of epithelioid cells were arranged in nests or funicular in the dermis (HE stain, ×100)

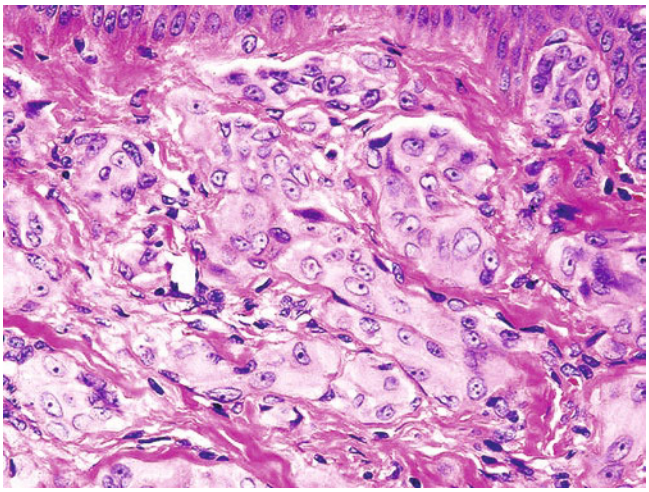


Fig. 27-72-3 Epithelioid tumor cells partly confluenting, artifactual clefts between the nests of nevus cells and the epidermis (HE stain, ×400)

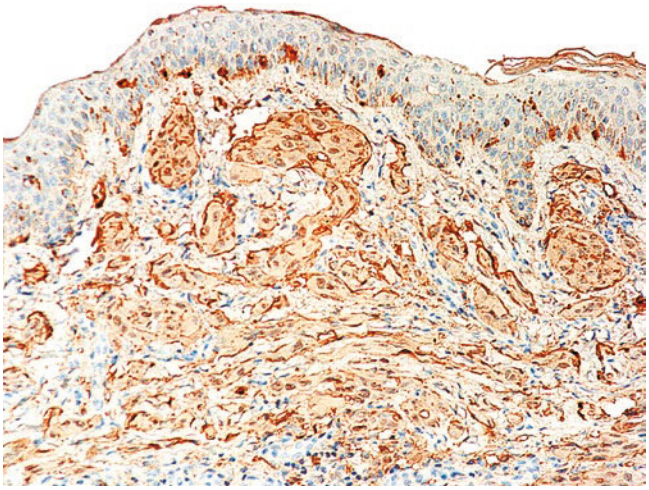


Fig. 27-72-4 S-100 strong positive in the membrane of tumor cells and nuclei (PV double stain,×100)

27.73 Subungual Melanoma [165, 166]

- Subungual melanoma (SM) has a higher morbidity among Asians than in other populations.
- SM affects the fingers more often than the toes.
- Nail plate loss, lifting off of the nail, Hutchinson's sign, a non-healing ulcer, a tumor nodule, or longitudinal melanonychia should lead to consideration of SM.
- SM can be amelanotic, and therefore any inexplicable dystrophy raises suspicion of SM.
- Dermatoscopic signs of longitudinal pigmented lines varying in width, interval, and color make biopsy appropriate.

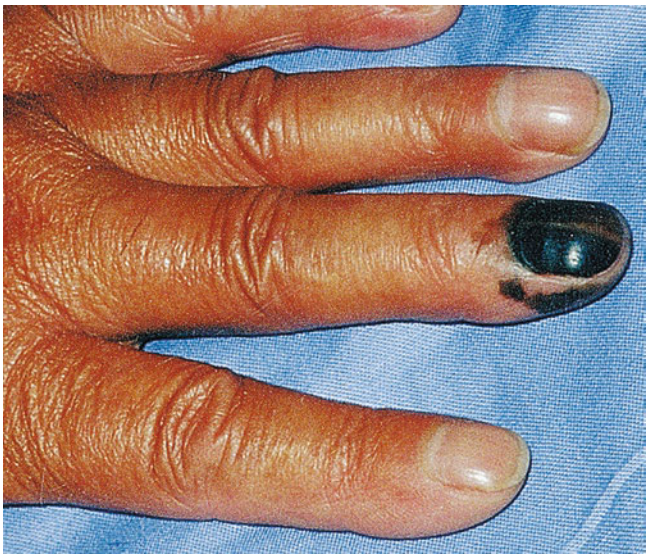


Fig. 27-73-1 Striated jet black spot on the left middle finger nail; irregular, varying color depth dark-brown macula around it

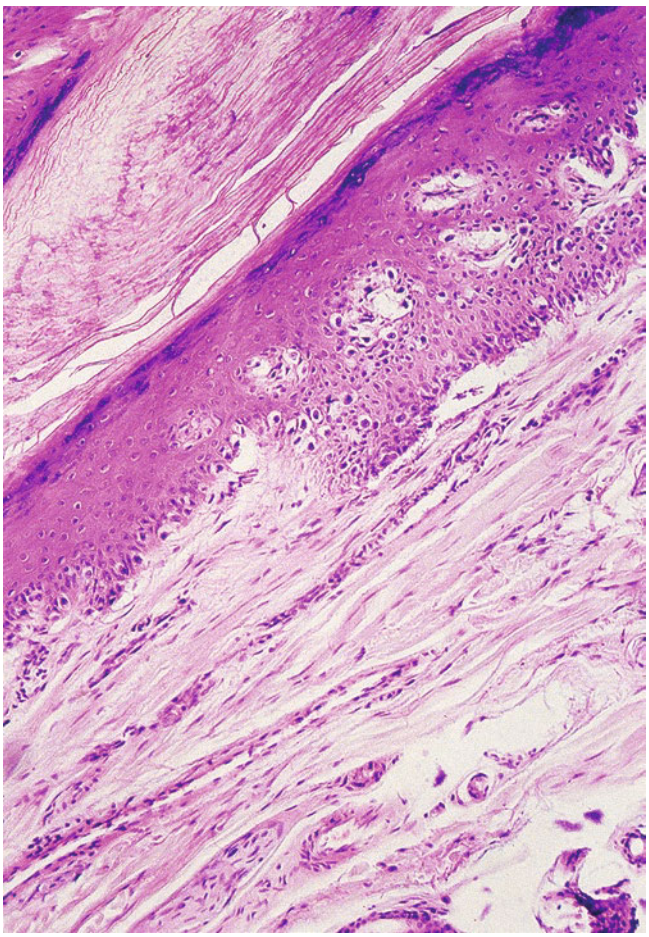


Fig. 27-73-2 Nest melanocytes in the epidermis (HE stain)

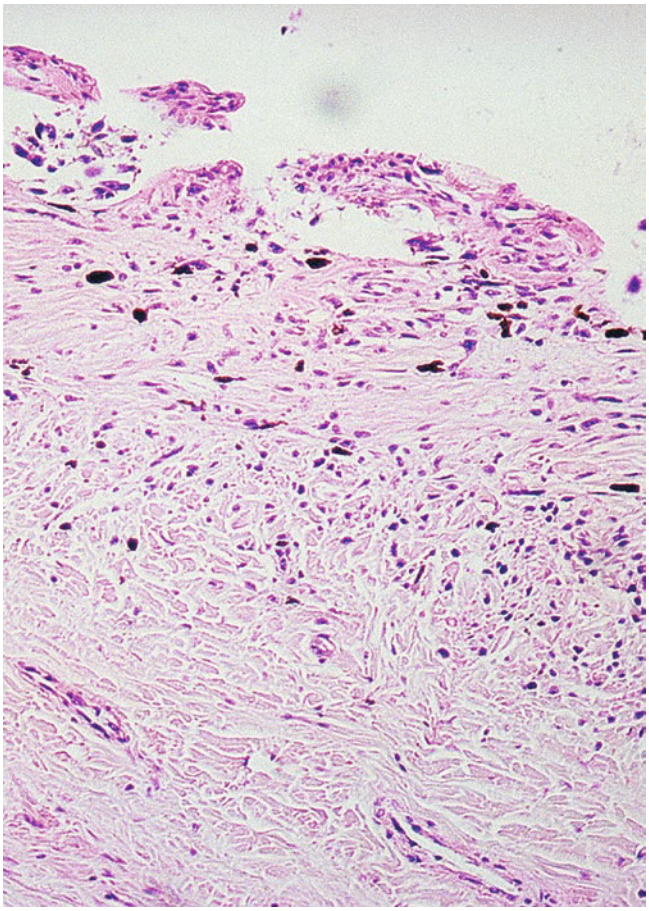


Fig. 27-73-3 Melanoma cells in the upper dermis, moderate perivascular lymphocyte infiltration (HE stain, ×100)

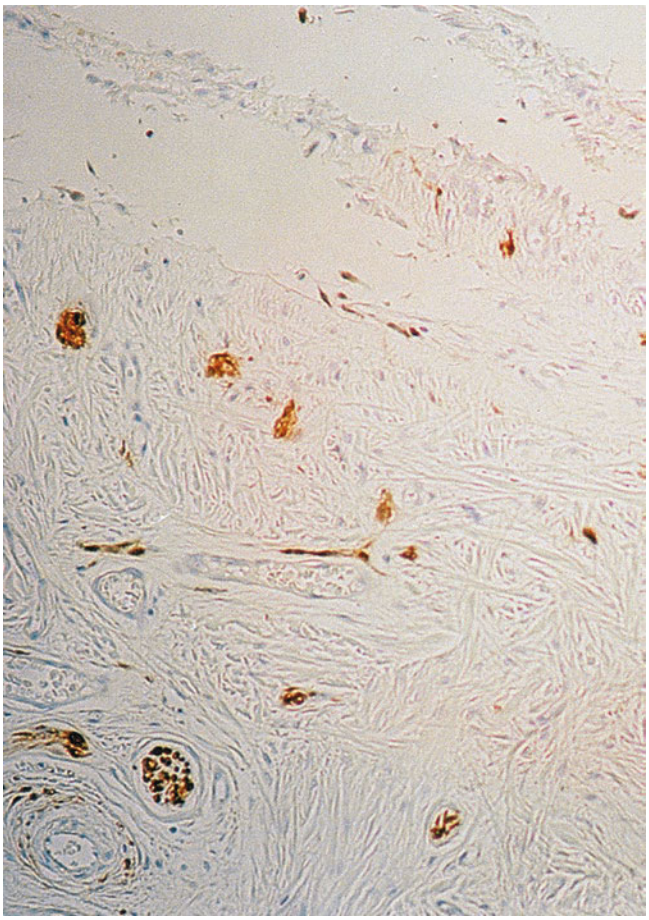
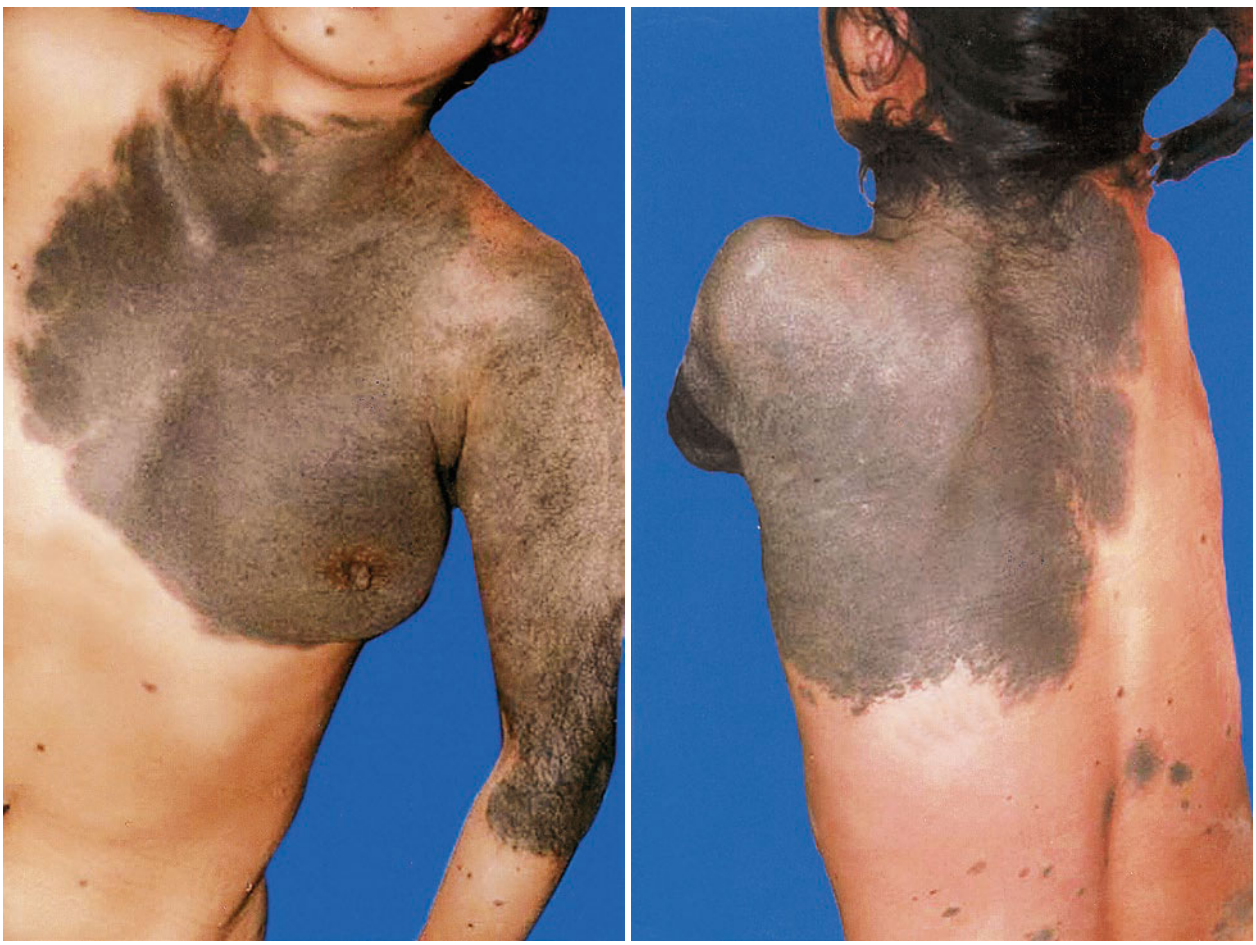


Fig. 27-73-4 Tumor cell S-100 positive in the dermis (S-100 stain, ×100)

27.74 Fatal Leptomeningeal Melanoma in Neurocutaneous Melanosis [167–169]

- Fox proposed a diagnostic criterion for neurocutaneous melanosis (NCM). It consists of the presence congenital melanocytic nevi (at least one is larger than 20 cm in diameter, and nevus of Ota is included), benign melanosis, or primary leptomeningeal melanoma (PLM).
- PLM normally occurs in the arachnoid and pia mater region, and its incidence peaks in the fourth decade of life.
- Initially, NCM presents with seizure, psychiatric disorder, and elevated intracranial pressure.
- To exclude malignant degeneration of the lesions in the central nervous system, MRI surveillance should be performed regularly.



Figs. 27-74-1, 27-74-2 Large black patches with black hair on the left chest, neck, shoulder, upper arm, and left nape

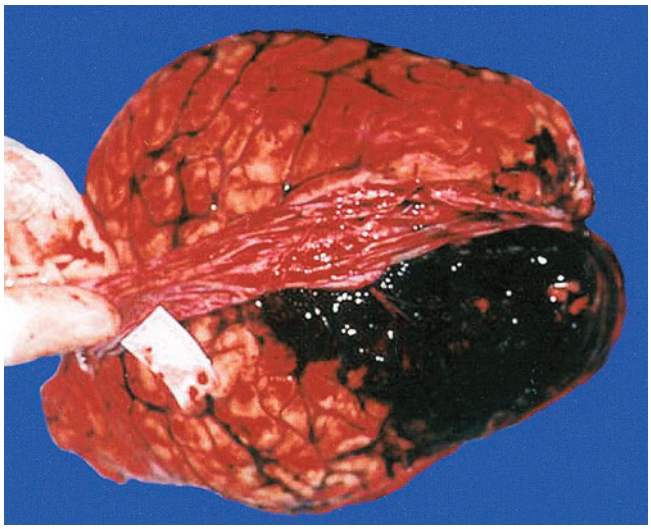


Fig. 27-74-3 Large black, irregular plaques on the pia mater encephali

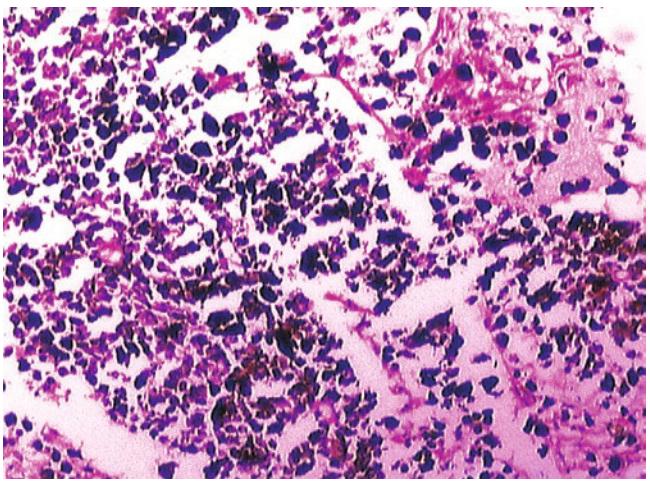


Fig. 27-74-4 Large numbers of atypical tumor cells with multiple melanin granules in the subarachnoid space (HE stain, ×100)

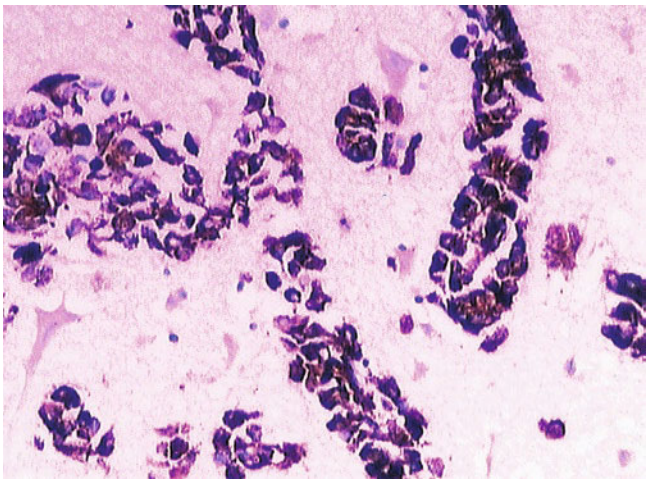


Fig. 27-74-5 HMB45 positive in tumor cells, brown granules in cytoplast (SP stain, ×400)

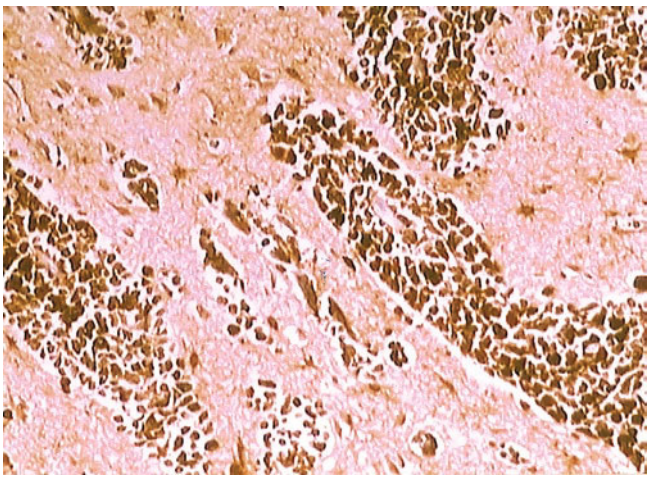


Fig. 27-74-6 S-100 positive in tumor cells, brown granules in cytoplast (SP stain, ×100)

27.75 Rare Forms of Cutaneous Melanoma [165, 170, 171, 172]

- Acral lentiginous melanoma (ALM) has a poorer prognosis than other subtypes of melanoma.
- ALM has a propensity for acral regions and shows radial lentiginous proliferation of large melanocytes along the dermoepidermal junction.
- According to Kuchelmeister's research, melanomas arise from the palmoplantar or subungual areas of the ALM type, and by comparison, melanomas located at the dorsum hands and feet were of the superficial spreading melanoma type.
- Balloon cell melanoma (BCM) is the rarest pathological variant of primary cutaneous melanoma in which more than 50% of the tumors cells are foamy cells.
- BCM may in fact have a dermal origin and is actually a vertical growth phase of melanoma.
- Ballooning change in BCM is due to progressive vacuolization of the melanosomes.
- Head and neck mucosal melanoma (HNMM) behaves aggressively and involves mucosa of the vermilion, nasal cavity, paranasal sinuses, oral cavity, laryngeal pharynx, and even esophagus.
- Amelanotic acral melanoma (AAM) is rare subtype of melanoma with little or no pigment.
- AAM can be easily mistaken as a non-melanocytic neoplasm, and therefore it poses a diagnostic challenge.
- The positive immunostaining for S-100 and HMB-45, the presence of pigment after Fontana-Masson stain, and electron microscopy observation confirm the diagnosis in certain AAM cases.

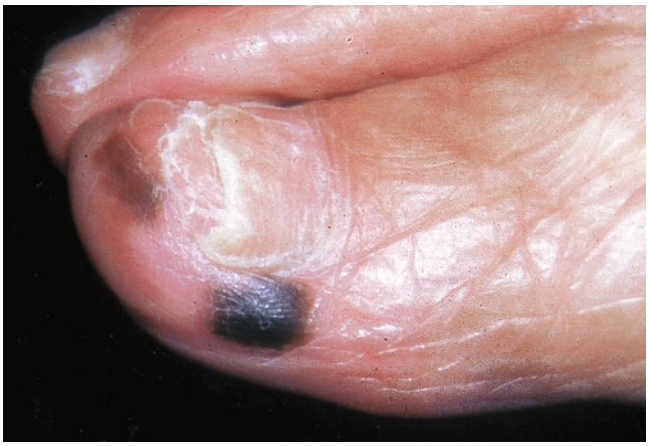


Fig. 27-75a-1 A black nodule on the periungual region of the right first toe

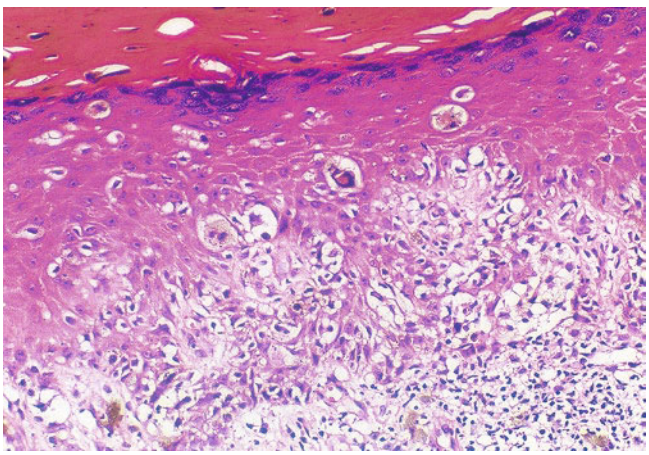


Fig. 27-75a-2 Many atypical nevus cells in the epidermis (HE stain, ×200)

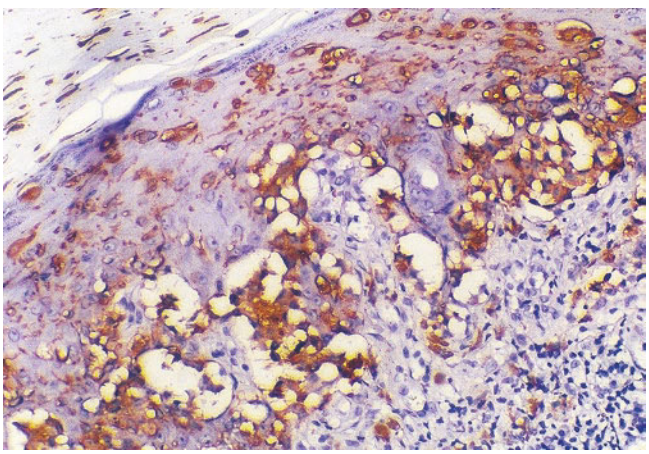


Fig. 27-75a-3 S-100 positive of atypical nevus cells in the epidermis (DAB stain, ×200)

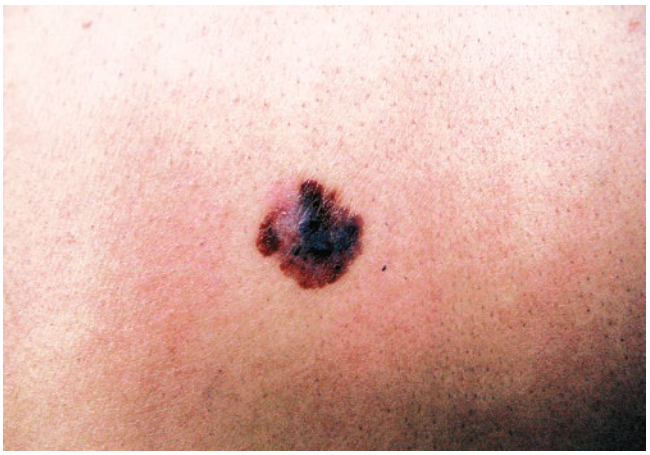


Fig. 27-75b-1 A jitney-sized brownish-red plaque on the back

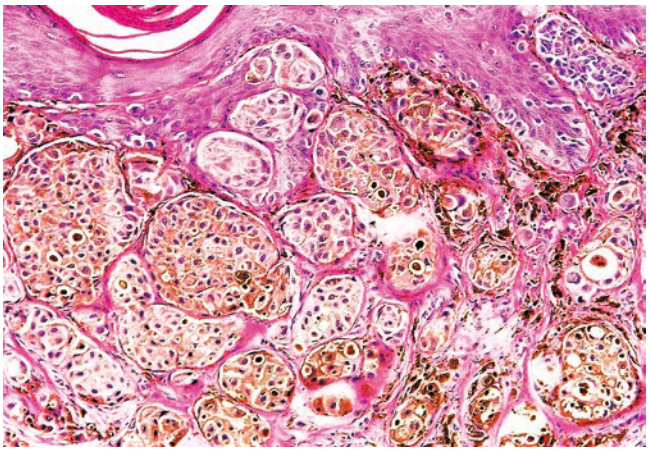


Fig. 27-75b-2 Balloon cells constituted the tumor (HE stain, ×200)

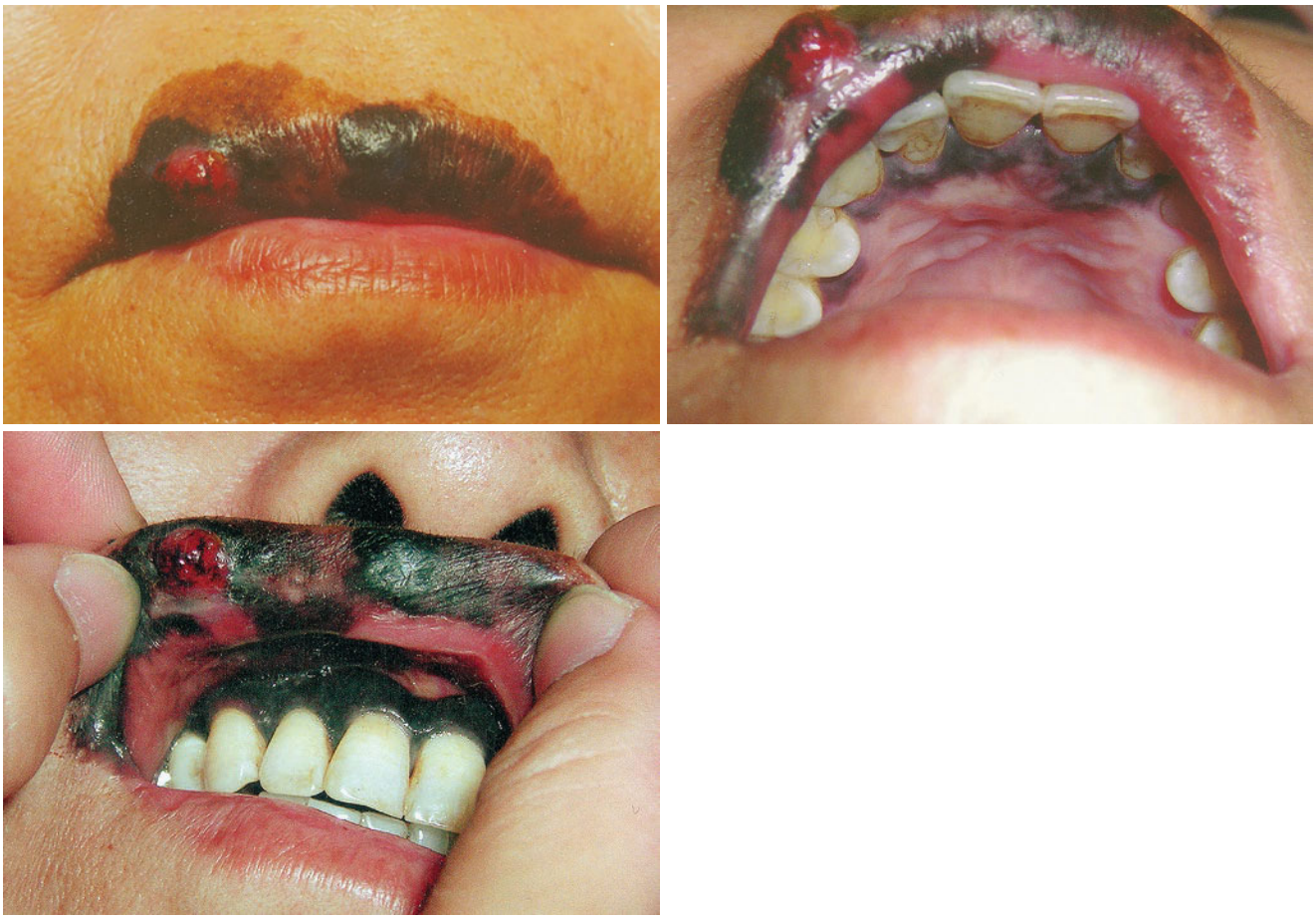


Fig. 27-75c-1, 27-75c-2, 27-75c-3 Extensive, black-pigmented, and irregularly bordered macules on the upper lip (1), gingival (2), and the palate (3); an amaranth mass 0.6 cm in diameter with blood crust on the right upper lip

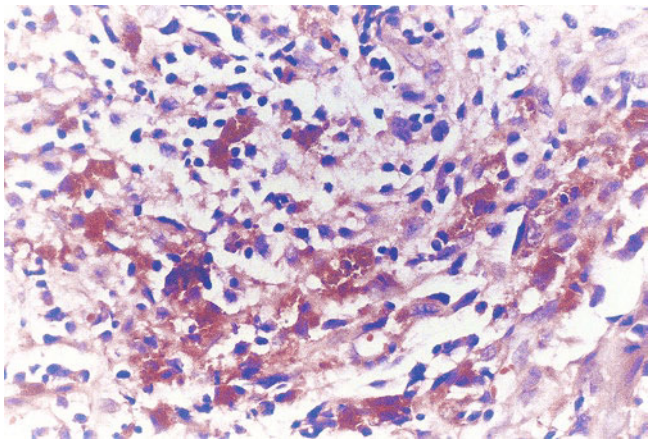


Fig. 27-75c-4 Rounded collections or nests of melanocytes filled the connective tissue. Tumor cells showed cellular pleomorphism and smudged nuclei (HE stain, ×400)

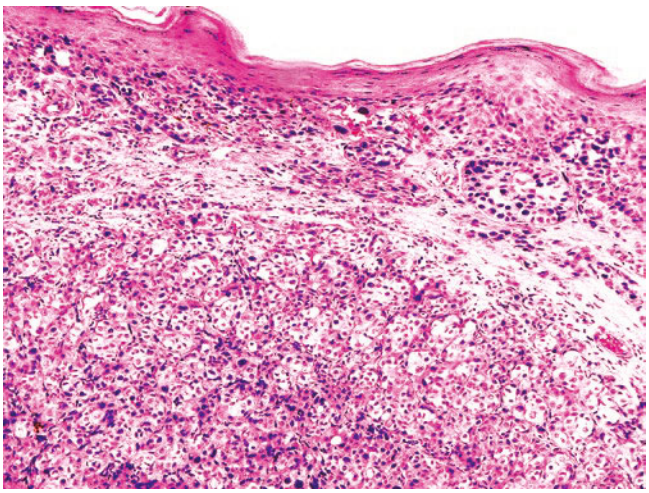


Fig. 27-75d-2 A mass of infiltrating tumor cells with large irregularly shaped and hyperchromatic nuclei in the reticular dermis (HE stain, ×100)

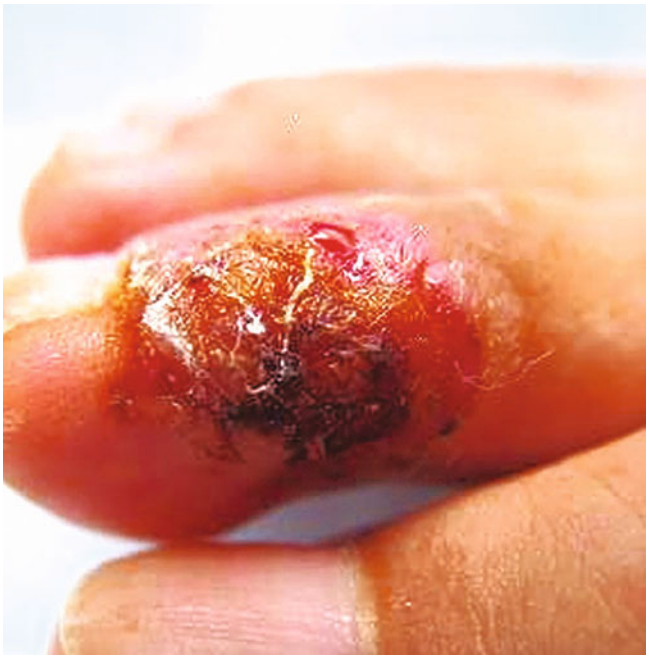


Fig. 27-75d-1 An infiltrating plaque with superficial erosion at the dorsal side of the second toe of the right foot

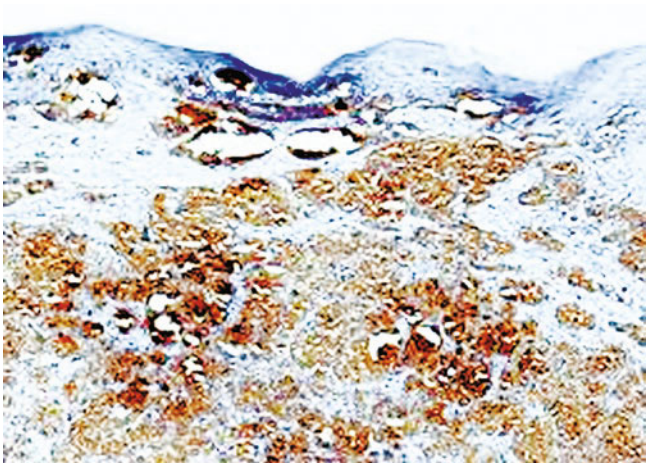


Fig. 27-75d-3 S-100 positive in the cytoplasm of tumor cells (SP stain, ×100)

27.76 Cutaneous Pseudolymphoma [173–175]

- Cutaneous pseudolymphoma (CPL) includes reactive lymphoproliferative disorders with T-cell and/or B-cell phenotypes, which simulates cutaneous lymphomas clinically and pathologically.
- CPL often presents a smooth flesh-colored to plum-red papule or nodule that predominantly locates on the face and neck.
- CPL develops in response to stimuli, such as arthropod bites, vaccinations, anemia, allergic reactions, medications, infections, or foreign agents.
- Biopsy specimen shows a polymorphous infiltration comprised of mixed T cells, B cells, eosinophilic cells, and histiocytes.
- T-cell CPL can be categorized pathologically into three forms: bandlike, nodular, and perivascular/periadnexal type. The absence of clonal T-cell rearrangements, normal T-cell phenotypes, epidermotrophism, and atypical lymphocytes in CPL warrants differentiation from most MF patients.
- Nodular infiltration is most commonly seen in B-cell CPL, followed by diffused and acral pseudolymphomatous angiokeratoma in children and a pseudolymphomatous-folliculitis-like pattern. A germinal center is commonly seen in the heavy multinodular CPL.
- Determination of its monoclonality is helpful for the final diagnosis of possible CPL patients.

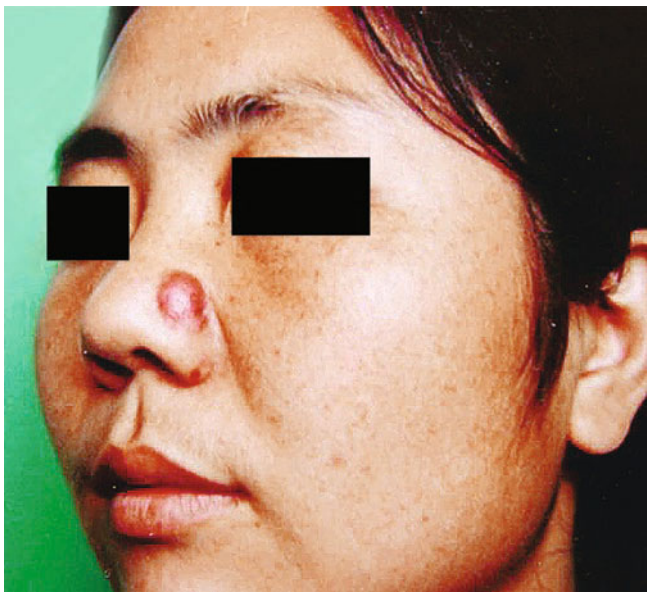


Fig. 27-76-1 A brownish-red nodule on the nose

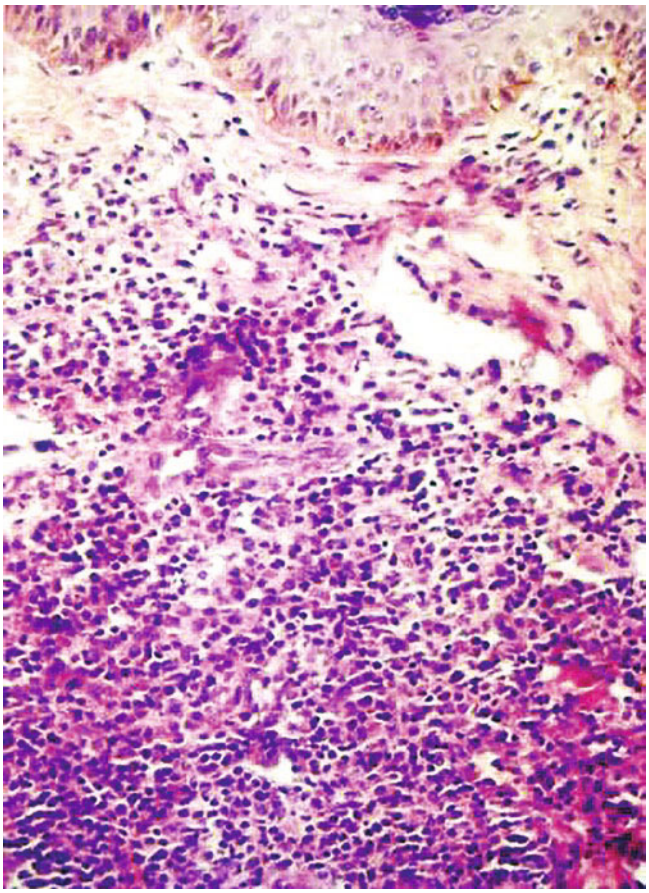


Fig. 27-76-2 There was a narrow free zone between infiltration of lymphocytes and the epidermis in the superficial dermis (HE stain, ×400)

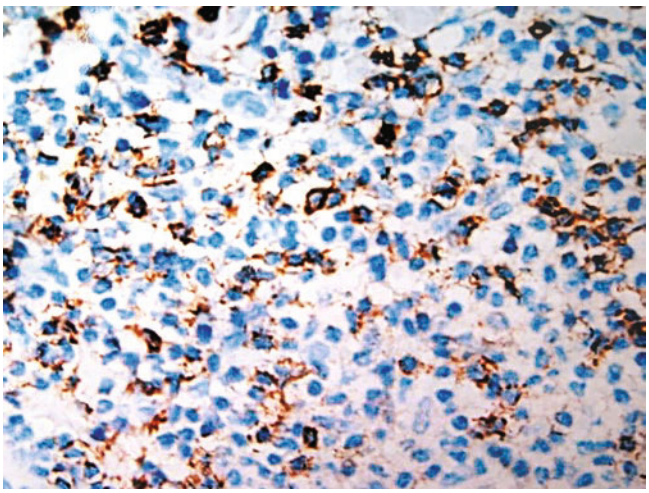


Fig. 27-76-3 CD45RO positive (SP, ×400)

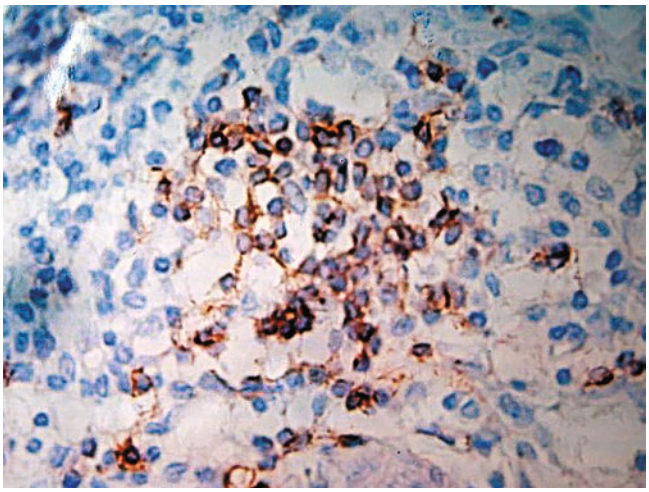


Fig. 27-76-4 CD20 positive (SP, ×400)

27.77 Jessner's Lymphocytic Infiltration of the Skin [176–178]

- Lymphocytic infiltration of the skin (LIS) presents in middle-aged adults. Although LIS predominantly affects the cheeks and earlobe, involvement of the upper trunk, neck, and proximal extremities has already been reported. The LIS is a persistent popular and indurated plaque which is photosensitive on the face.
- Investigation on LIS indicates that it is a benign cutaneous disorder predominantly of T-cell origin, although B-cell origin has uncommonly reported.
- Pathology of LIS is characterized by a heavy lymphocytic infiltration around the blood vessels or the adnexal structures.

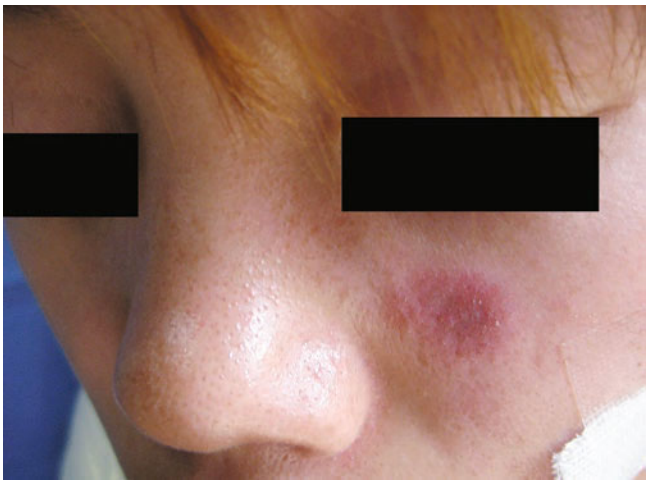


Fig. 27-77-1 A persistent plaque-like erythema on the left cheek

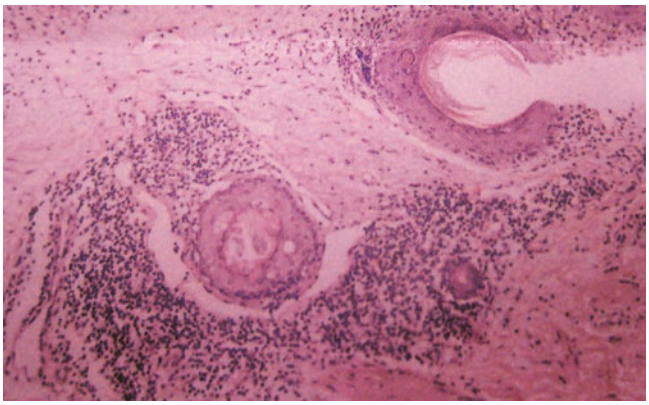


Fig. 27-77-2 Dense perivascular and diffuse lymphocytic infiltrated in the upper dermis

27.78 Ketron-Goodman Disease [179, 180]

- Localized pagetoid reticulosis (LPR) is considered to be a solitary indolent form of mycosis fungoides (MF) without extracutaneous spread or lethal outcome.
- LPR typically displays psoriasiform, erythematous, or verrucous plaques, which are predominantly located on the extremities.
- Ketron-Goodman (KG) disease is an aggressive disseminated form of LPR in contrast to the classical type.
- Histologically, it manifests acanthosis with striking pagetoid epidermotropism of atypical medium-sized lymphocytes, which are highlighted by the hyperchromatic nuclei and are surrounded by vacuolated cytoplasm.
- In addition, epidermotropism may similarly present in lymphomatoid papulosis, lymphomatoid drug reactions, melanoma, or epithelial neoplasia with pagetoid appearance.
- CD30 positivity is found in approximately 50% of cases with LPR, and 50–60% of cases have a presence of Ki-67 expression.
- Immunoprofiles of these atypical cells express all T-cell markers of CD3+, CD4+, and CD8+, or, rarely, they are double negative for CD4 and CD8. Clonal a/β TCR gene rearrangement is frequently identified on keratinocytes in ES. However, these ES immunoprofiles do not alter its prognosis.

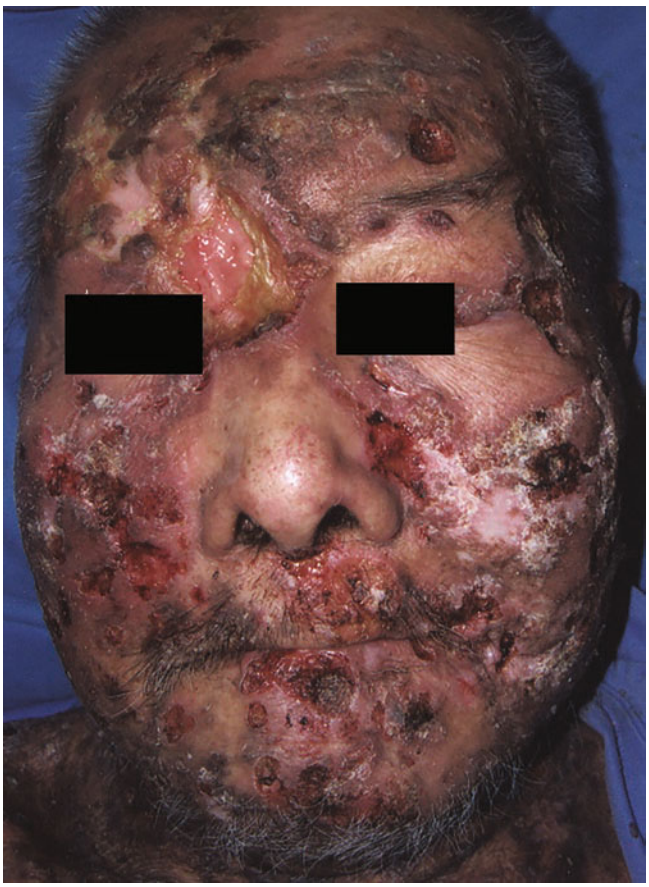


Fig. 27-78-1 Numerous dark-red plaques with scales and crusts on the face

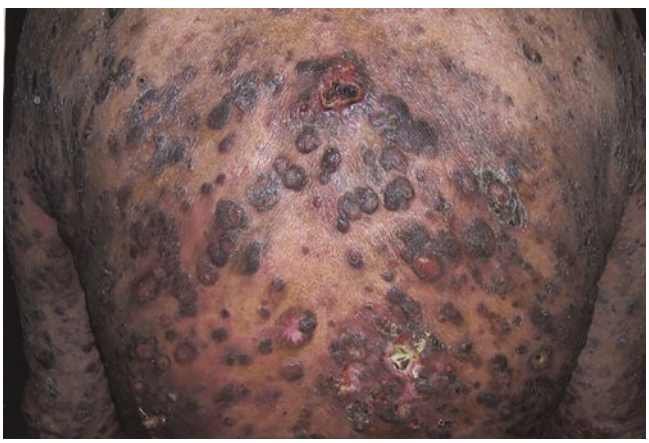


Fig. 27-78-2 Numerous brown plaques associated with ulcers on the back

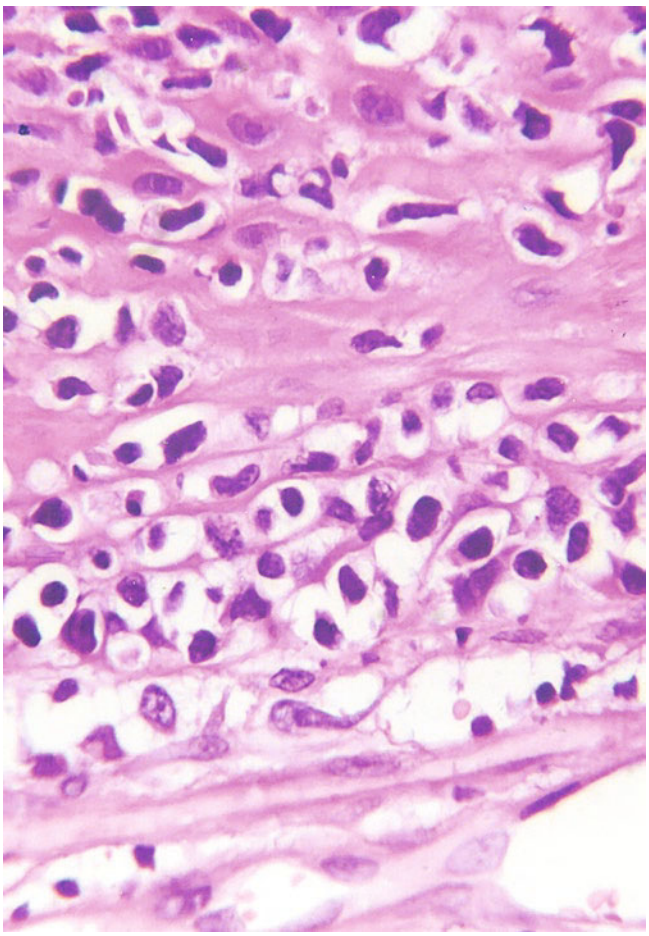


Fig. 27-78-3 Infiltration of atypical lymphocytes like pagetoid cells in the epidermis (HE stain, ×400)

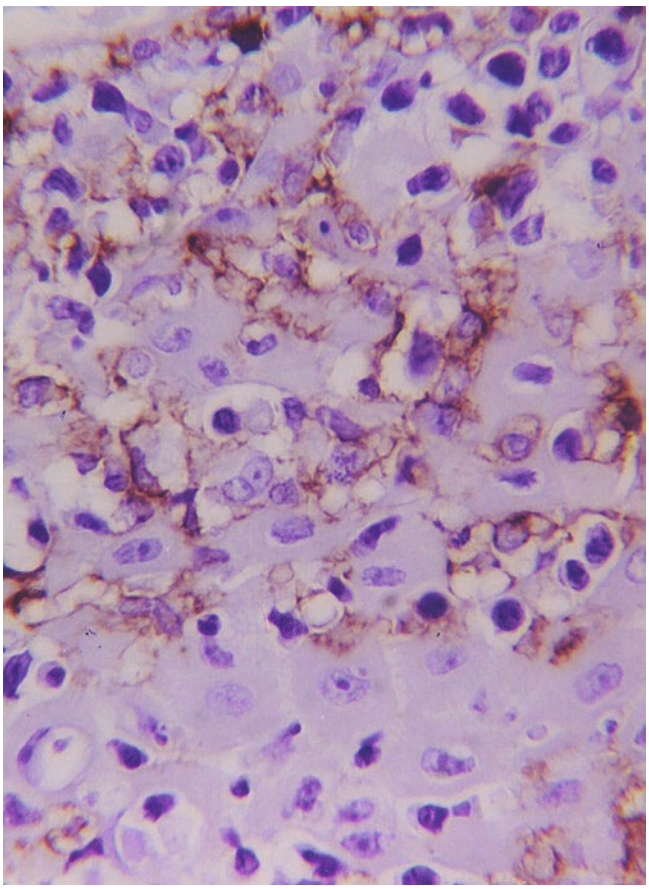


Fig. 27-78-5 CD45 RO is positive (ABC method, ×400)

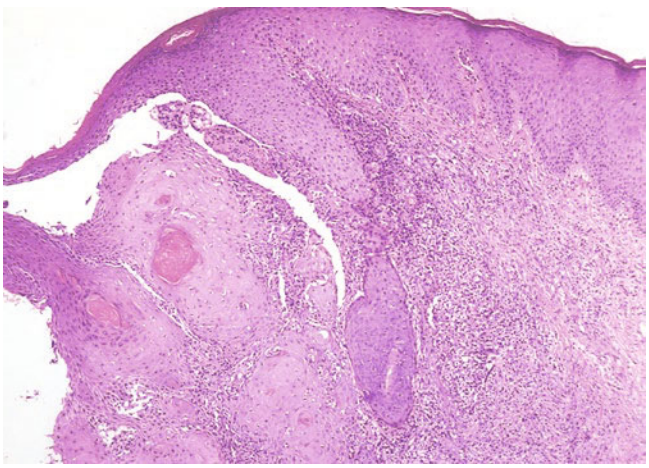


Fig. 27-78-4 Infiltration of numerous atypical lymphocytes in the upper and middle dermis (HE stain, ×40)

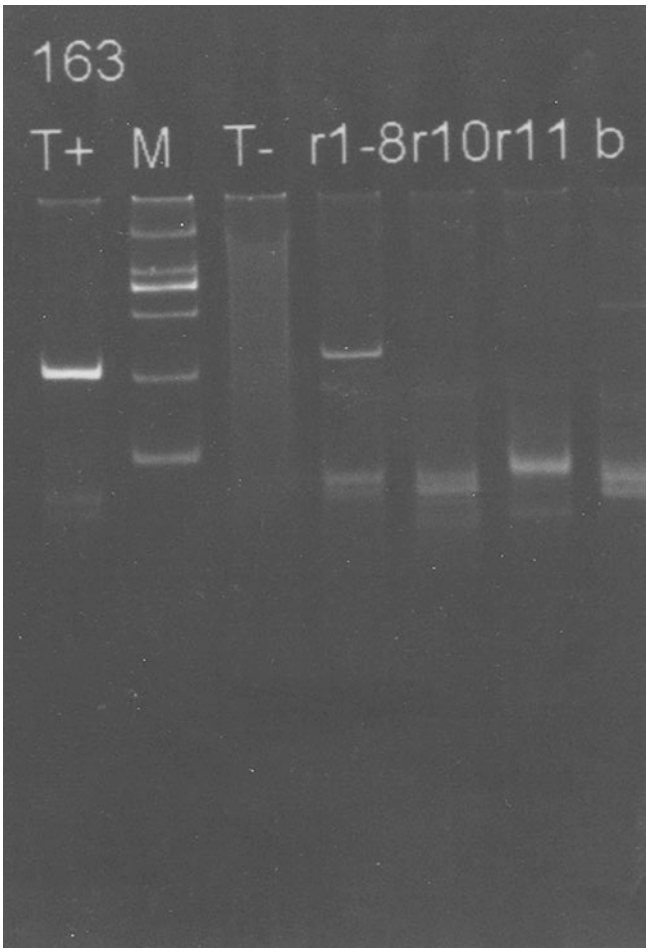


Fig. 27-78-6 T-cell receptor γ is positive

27.79 Mycosis Fungoides [181–186]

- Mycosis fungoides (MF) is a type of primary cutaneous T-cell lymphoma that can be categorized into three classical forms: patch stage, plaque stage, and tumor stage.
- MF has several distinct clinicopathologic subtypes, including folliculotropic, hypopigmented, hypopigmented, granulomatous, bullous and poikilodermatous, syringotropic, palmaris and plantaris, solitary, verrucous anetodermic, ichthyosiform, papular, pustular, interstitial, invisible, and CD8+CD56+ MF.
- The constellation of histological features in classical MF consist of atypical CD4+ cells that have haloed, cerebriform nuclei with typical alignment along the epidermal basal layer. Focal epidermotropism and formation of Pautrier microabscesses are considered hallmarks of MF.
- Ichthyosiform MF is a distinct variant of MF characterized by widespread ichthyosiform lesions and an indolent course.
- Rupioid lesions in MF may present in a large spectrum of skin diseases, including reactive arthritis, rupioid psoriasis, crusted scabies, histoplasmosis, and syphilis.
- Hyperpigmented MF manifests as diffuse hyperpigmented macules.
- MF has the phenotype of a T-helper memory cell (CD3+, CD4+, CD45RO+, CD8−, CD30−, CD56−). It rarely shows CD8− or CD4−CD8−. Transformation of MF into CD30+ large T-cell lymphoma is defined when less than 25% of the tumor cells are large, pleomorphic, anaplastic lymphocytes in an MF individual. CD2, CD5, and CD7 are known to be T-cell markers, and those molecules may be partially lost in some patients.
- The detection of thymocyte selection-associated high mobility group box gene in early MF distinguishes it from certain benign inflammatory dermatosis.

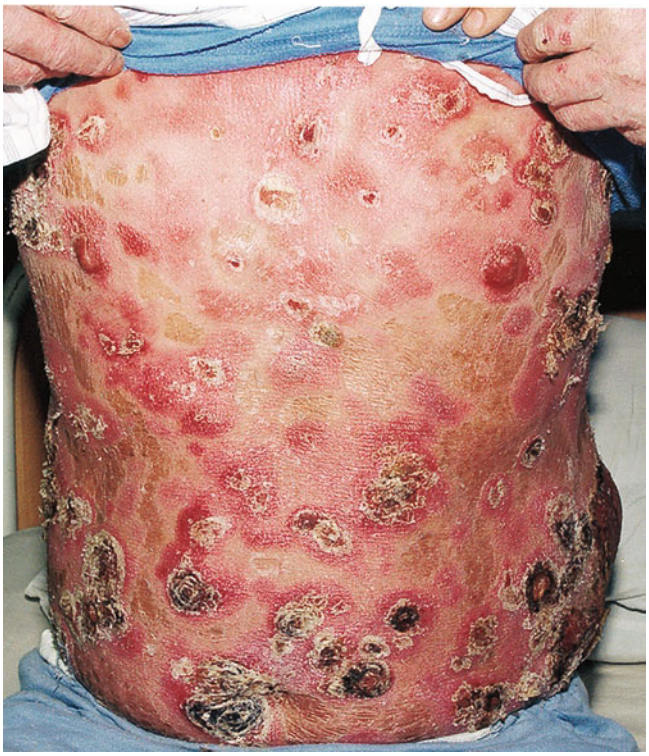


Fig. 27-79a-1 Erythematous, scaling patches and rupioid eruptions on the trunk

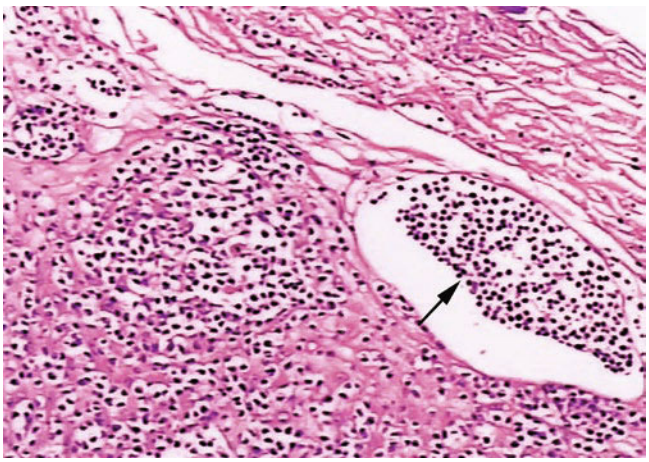


Fig. 27-79a-2 MF cell infiltrated within the epidermis and dermis, Pautrier microabscesses presented in the epidermis (HE stain, ×40)

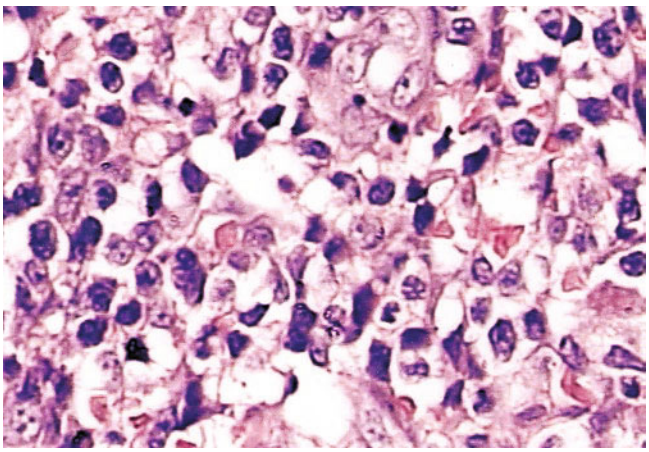


Fig. 27-79a-3 Diffuse tumor cells in the dermis (HE stain, ×400)

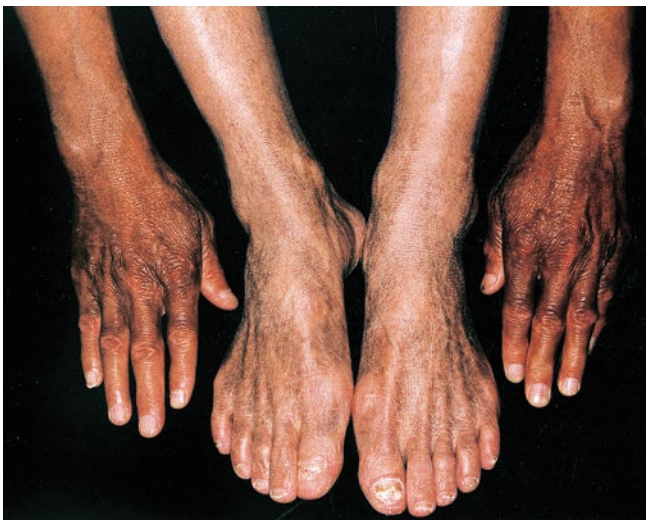


Fig. 27-79b-1 Dark-brown patches on dorsa of hands and feet, border of the lesions was unclear

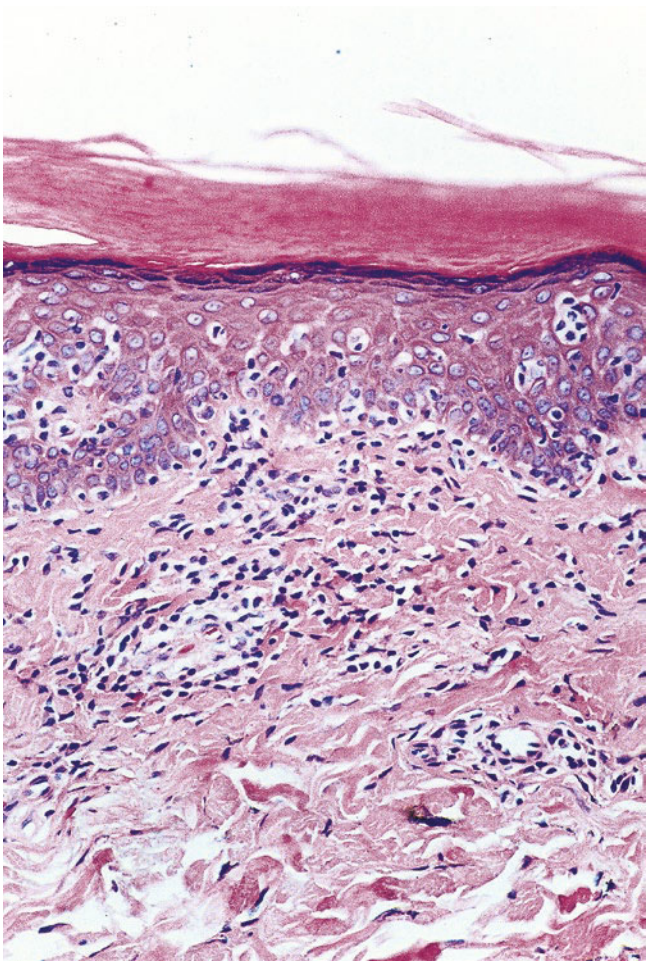


Fig. 27-79b-2 Pautrier microabscesses within the epidermis, a band-like lymphocyte infiltrated in the dermis (HE stain, ×100)

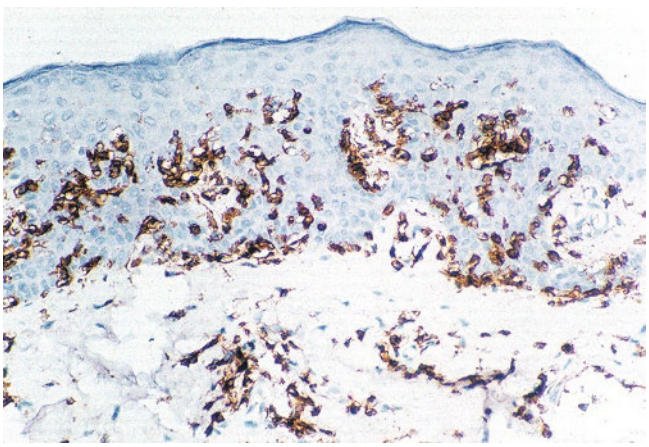


Fig. 27-79b-3 LCA positive in the lymphocytes of the epidermis and dermis (ABC stain, ×200)

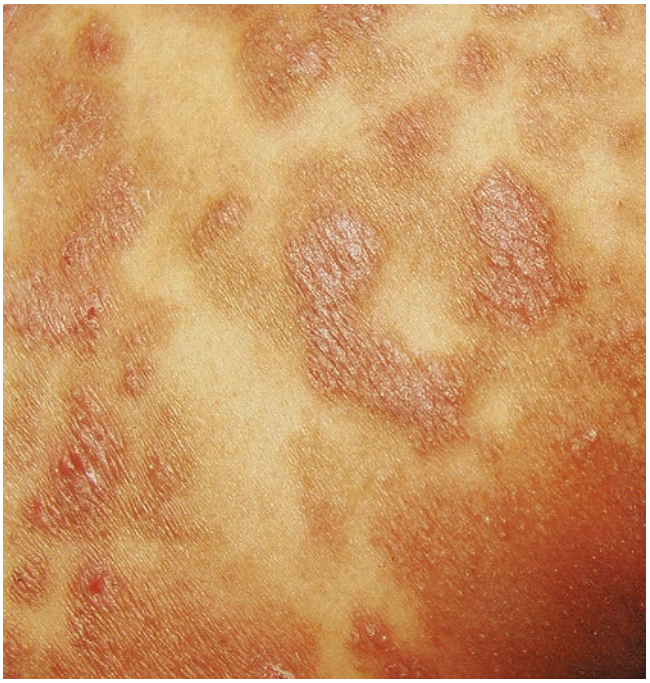


Fig. 27-79c-1 Lichenoid plaques on the buttocks

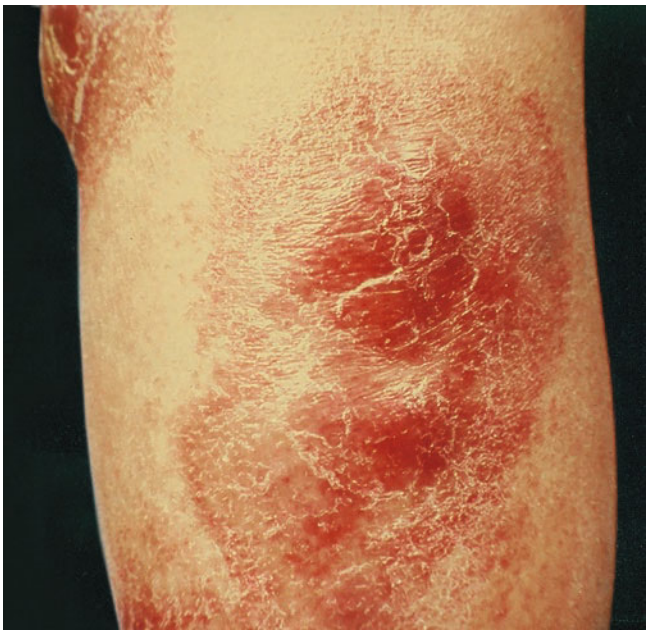


Fig. 27-79c-2 Brownish-red nodules on the extensor of the left calf

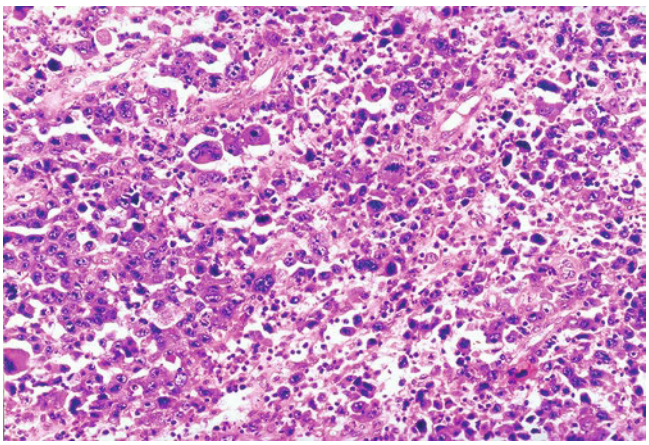


Fig. 27-79c-3 Diffuse tumor cell infiltrated in the dermis (HE stain, ×100)

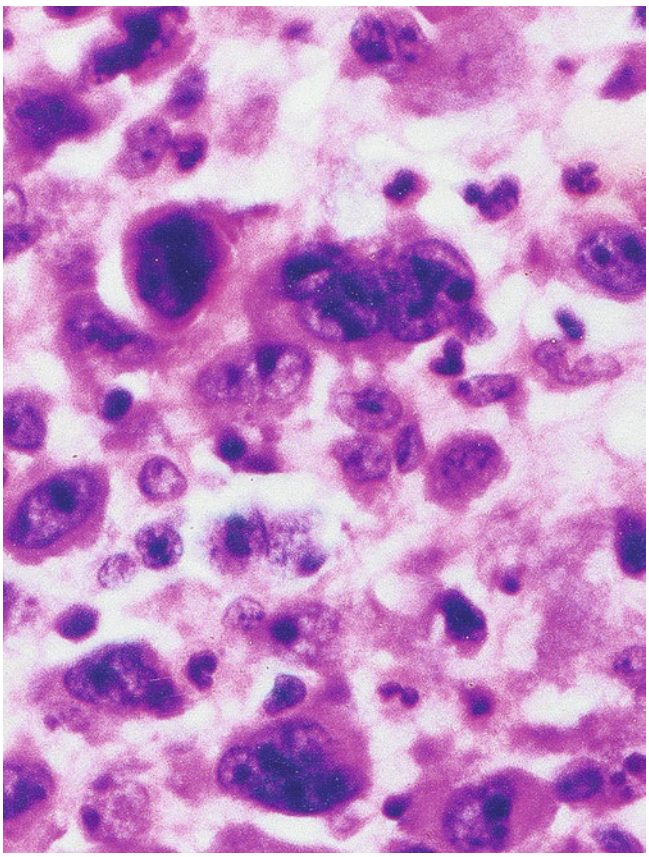


Fig. 27-79c-4 Tumor cell and multinucleated tumor giant cells (HE stain ×1000)

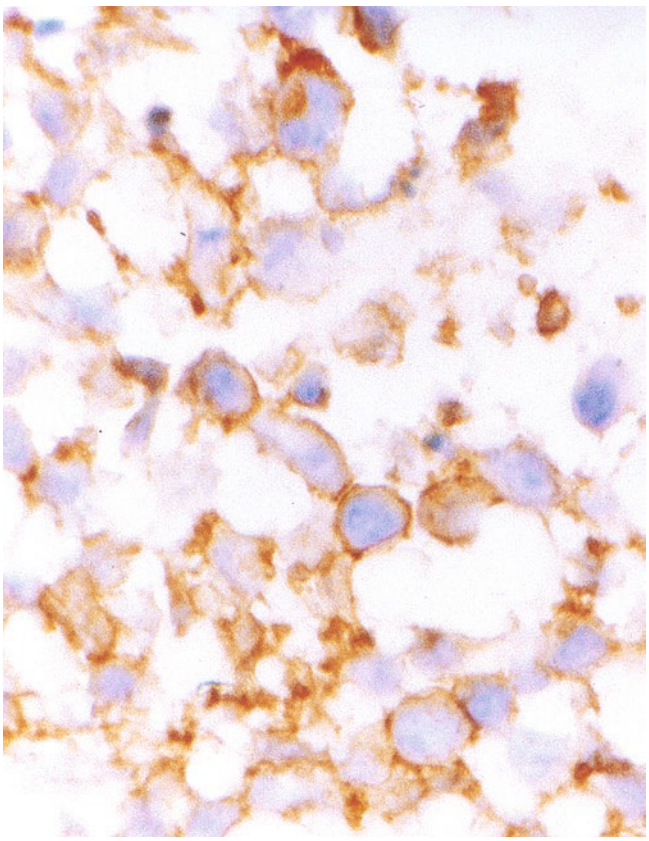


Fig. 27-79c-5 CD45RO-positive tumor cells (ABC method ×400)

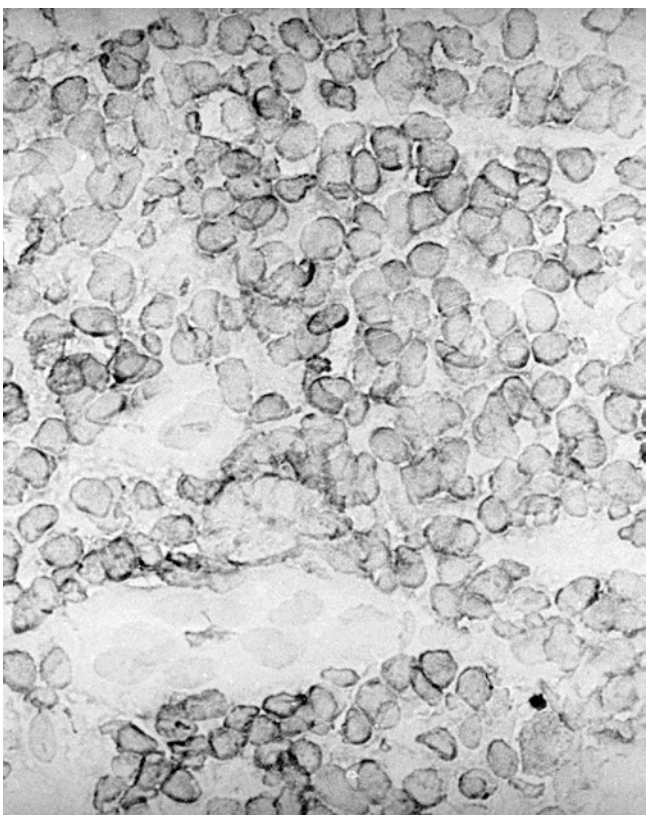


Fig. 27-79c-6 CD30-positive tumor cells (ABC method ×400)

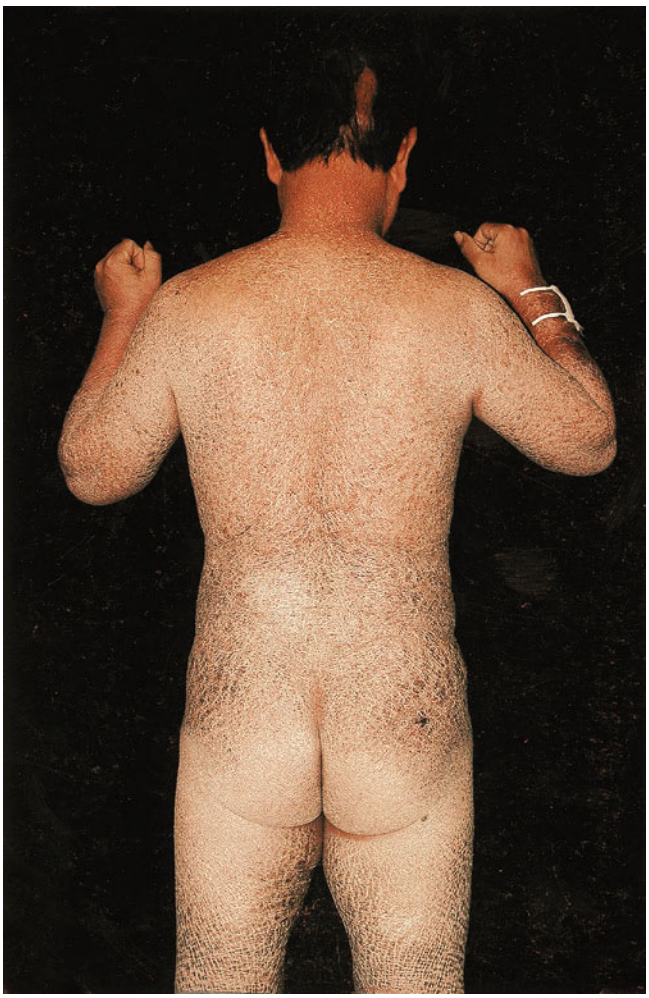


Fig. 27-79d-1 Dry skin over the whole body, covered with multiple coarse, whitish, large scales and crusts

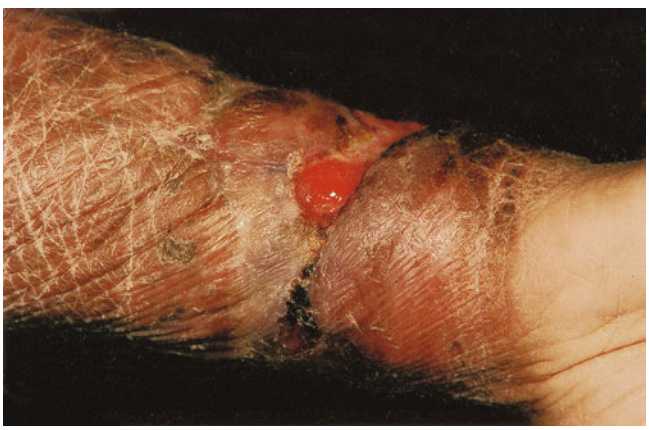


Fig. 27-79d-2 Marked swelling with an ulcer 6 cm in diameter in the center on the right forearm

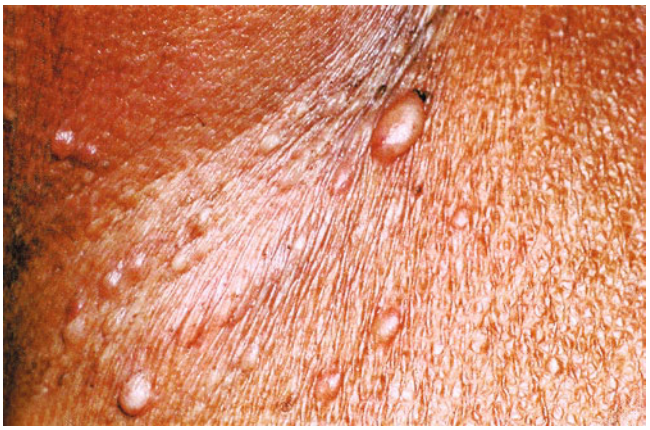


Fig. 27-79d-3 Numerous bean-sized, translucent, white papules and nodules on the axilla

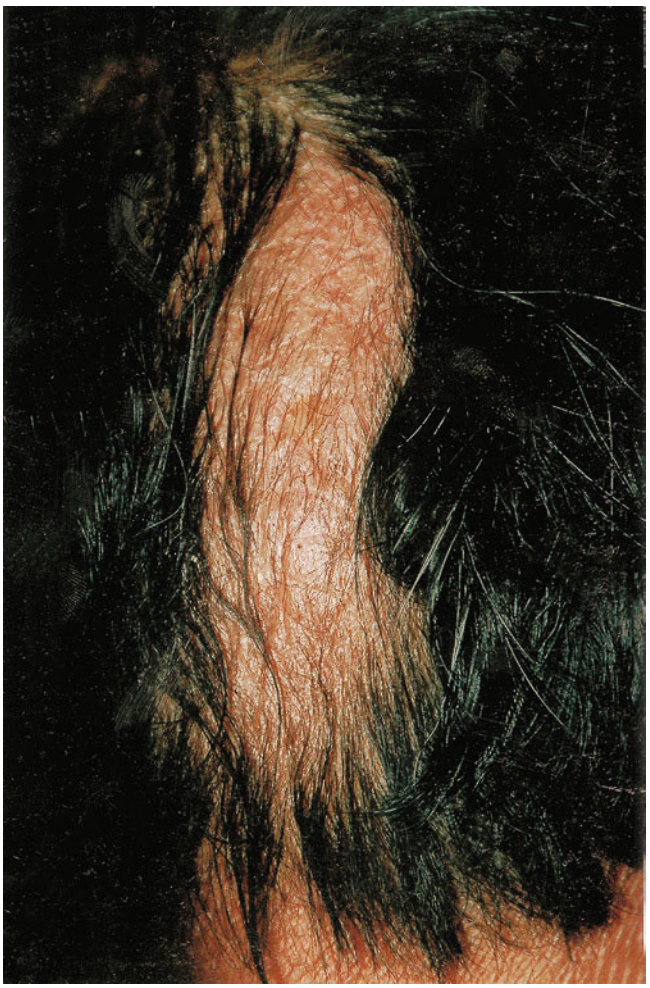


Fig. 27-79d-4 Strip and sheet bald plaques on the occiput, several hair follicle papules on the plaques, covered with a few adherent scales

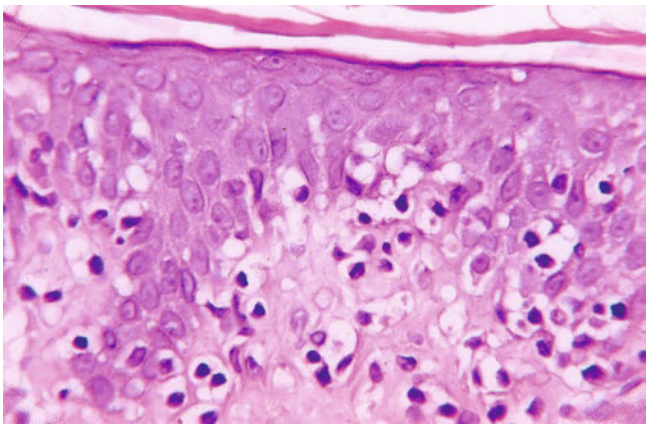


Fig. 27-79d-5 Epidermal atrophy had mononuclear cell infiltration presenting atypical Pautrier microabscess (HE stain, ×400)

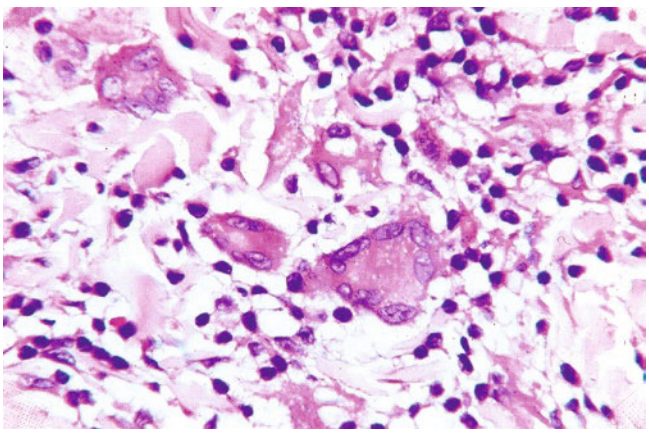


Fig. 27-79d-6 Multiple multinucleated giant cells in the dermis (HE stain, ×400)

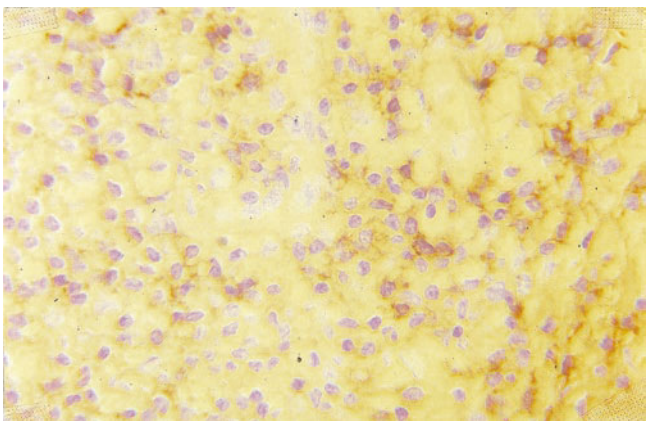


Fig. 27-79d-7 CD45RO positive (ABC stain, ×400)

27.80 Erythrodermic Cutaneous T-Cell Lymphoma [187–189]

- Erythrodermic cutaneous T-cell lymphoma (e-CTCL) mainly underlies the aggressive subtypes of cutaneous lymphomas, including erythrodermic mycosis fungoides and Sezary syndrome.
- e-CTCL, lymphadenopathy, and circulating cerebriform T cells are the triad of Sezary syndrome.
- Pruritus, a sensation of burning or chills, may precede the onset of skin lesions.
- The algorithm suggested by Dr. Russell-Jones provides valuable guidance in the management of e-CTCL.

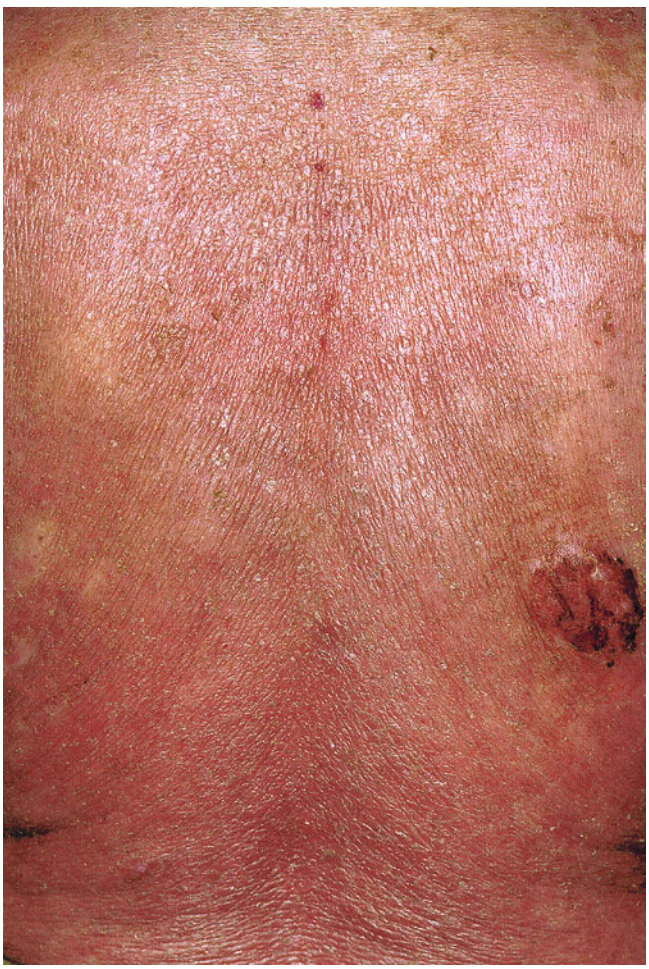


Fig. 27-80-1 Diffuse erythema all over the body

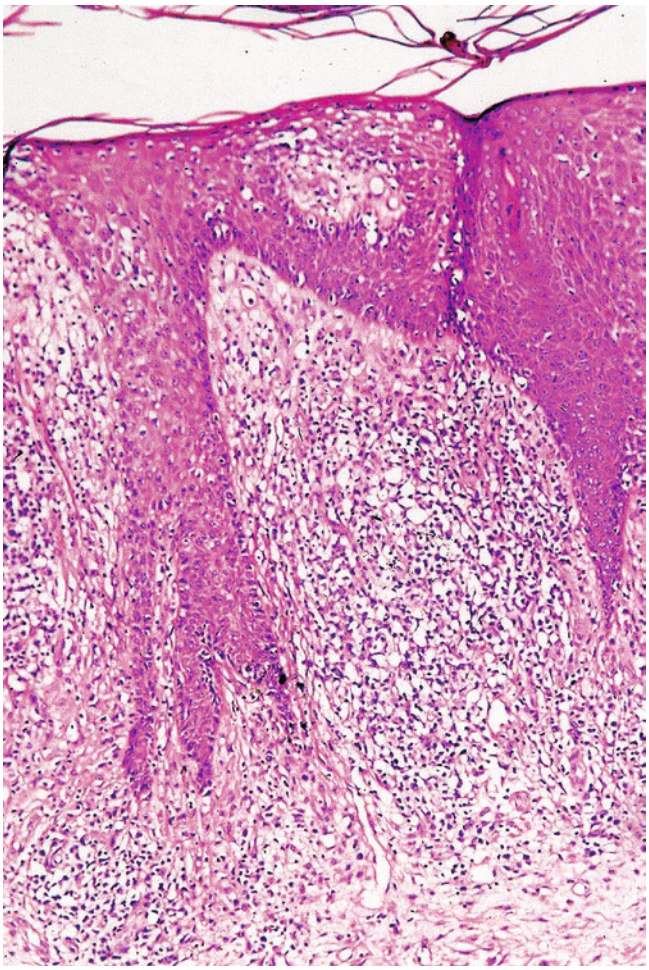


Fig. 27-80-2 A few masses of lymphocyte infiltrated with large nuclei in the epidermis (HE stain, ×150)

27.81 Subcutaneous Panniculitis-Like T-Cell Lymphoma [190, 191]

- Subcutaneous panniculitis-like T-cell lymphoma (SPTL) is a distinct subset of cutaneous T-cell lymphomas that preferentially involves subcutaneous fat of the leg.
- SPTL is usually mistreated as benign panniculitis for years before confirmation of the diagnosis.
- SPTL manifests as solitary or multiple deep-seated nodules or plaques. Localized lipoatrophy is likely to be seen after regression of the lesion.
- Fever, fatigue, weight loss, hemophagocytic syndrome, and autoimmune diseases are common systemic comorbidities with SPTL.
- Pleomorphic atypical T cells are scattered at the periphery of adipose lobules in SPTL. It is defined as CD8+ cytotoxic T-cell lymphoma and expresses α-/βT-cell receptors.

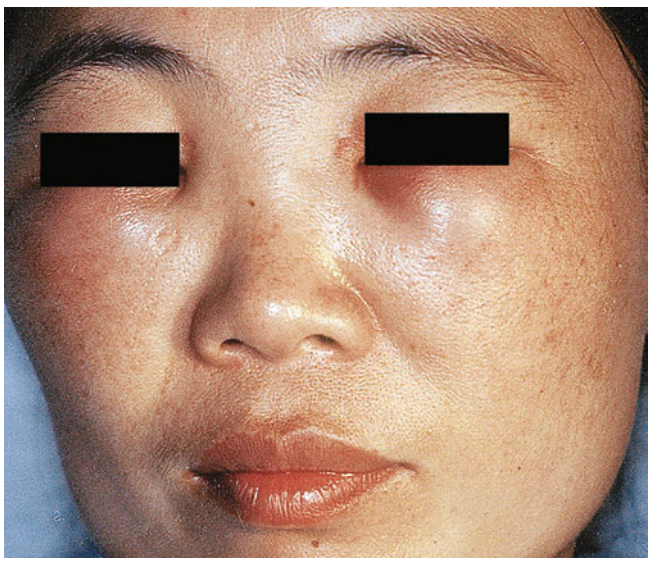


Fig. 27-81-1 Nodules on the face

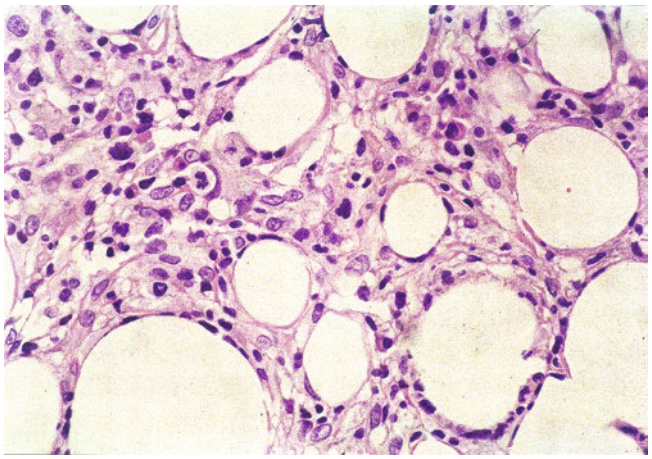


Fig. 27-81-2 The infiltration of small- or medium-sized lymphocytes in subcutaneous panniculus adiposus (HE stain, ×125)

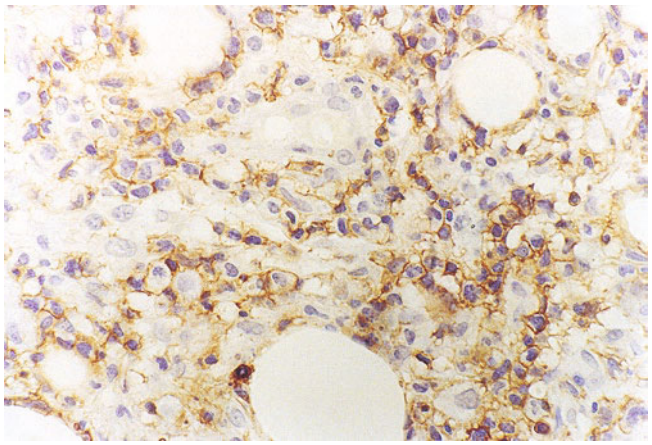


Fig. 27-81-3 CD45RO positive (SP stain, ×125)

27.82 Hydroa Vacciniforme-Like Lymphoma [192, 193]

- Hydroa vacciniforme-like lymphoma (HVLL) designates a rare Epstein-Barr virus-positive cutaneous T-cell lymphoma that clinically mimics hydroa vacciniforme.
- HVLL appears prone to development in children of Asia and Central America.
- Most patients complain of edematous face, vesiculopapules, hemorrhagic bullae, ulcerations, and pitted scars, which are mainly located on sun-exposed areas. Systemic complications of intermittent fever, hepatosplenomegaly, and lymphadenopathy have also been reported.
- Skin biopsy of the lesion reveals pleomorphic small- to medium-sized lymphocytes that infiltrate around blood vessels or the adnexal tissues with notable vasculitis, angiocentricity, or necrosis.
- Neoplastic cells usually show a CD8 cytotoxic T-cell phenotype, as well as positive expression of TIA-1, perforin, and granzyme B.
- For the HVLL patient who has high titers of antibodies to Epstein-Barr virus or a strong increase in CD30 expression, the ultimate progression of hemophagocytic syndrome or NK-/T-cell lymphoma is highly probable.

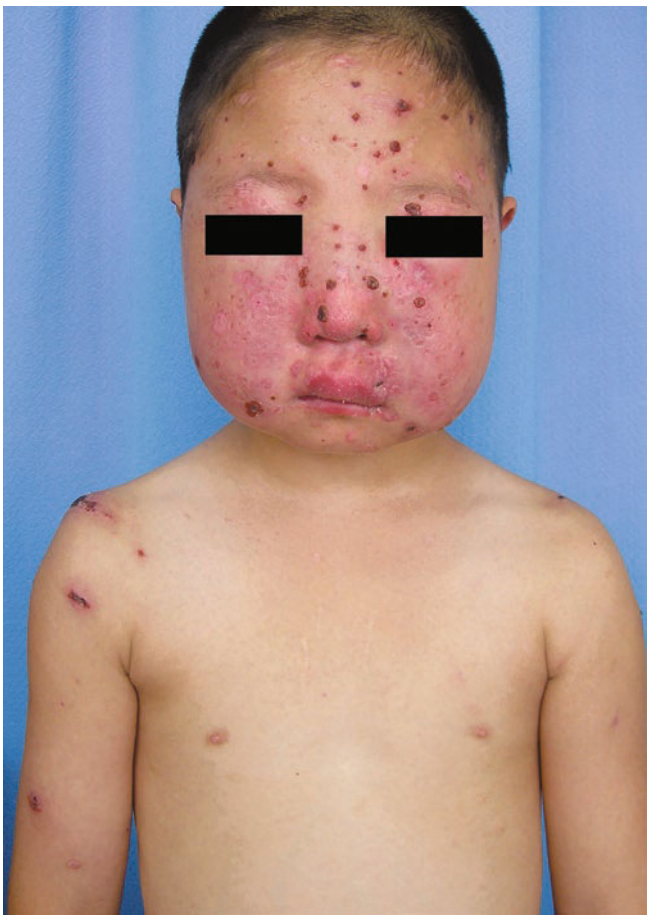


Fig. 27-82-1 Diffuse flushing edema, with some scattered blisters, crusts, and variola like atrophic scars, resembling hydroa vacciniforme on the face

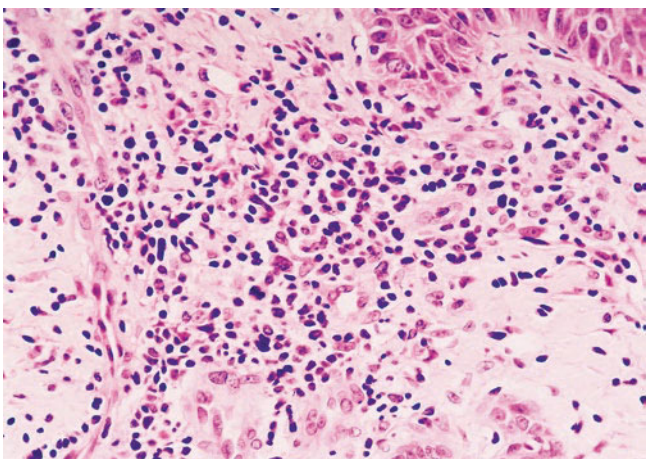


Fig. 27-82-2 Dermal lymphoid cell infiltration; atypical cells with irregular nuclei (HE stain, ×100)

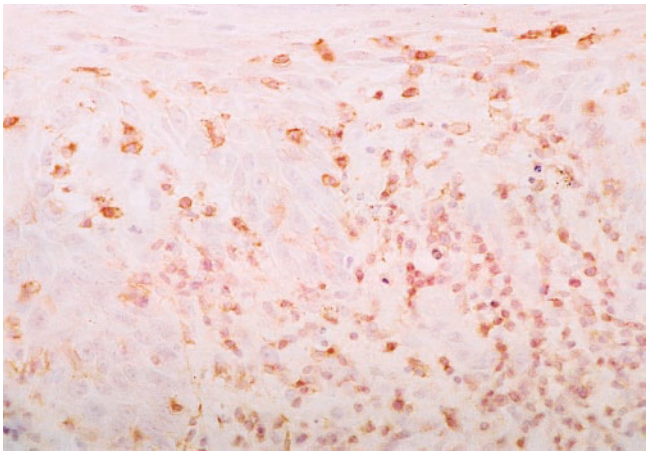


Fig. 27-82-3 Dermal infiltrating lymphoid cells showed positive for CD45RO

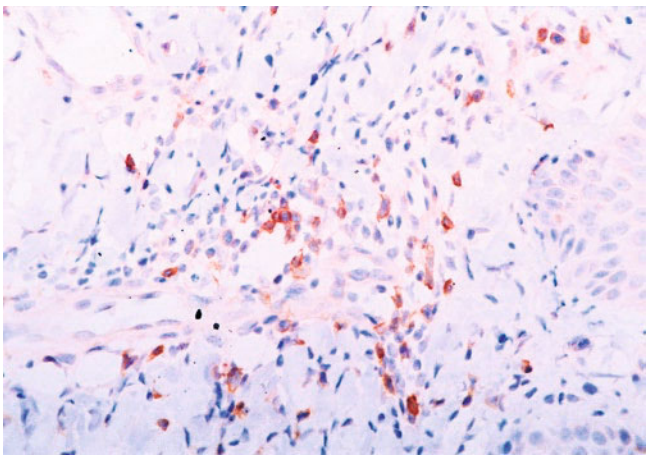


Fig. 27-82-4 Dermal infiltrating lymphoid cells showed positive for CD8

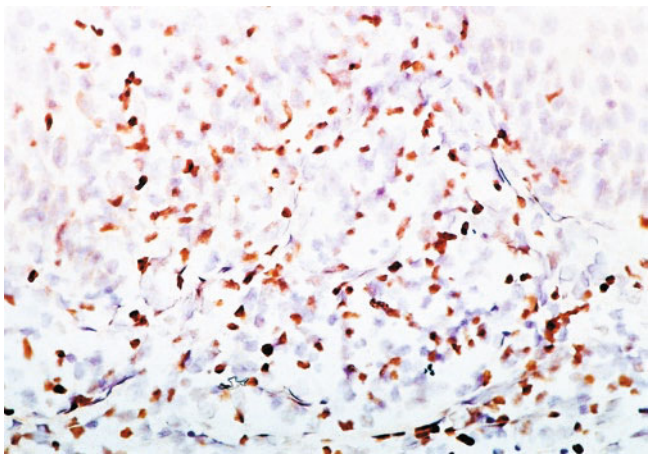


Fig. 27-82-5 By in situ hybridization, the majority of dermal lymphoid cells were positive for Epstein-Barr virus

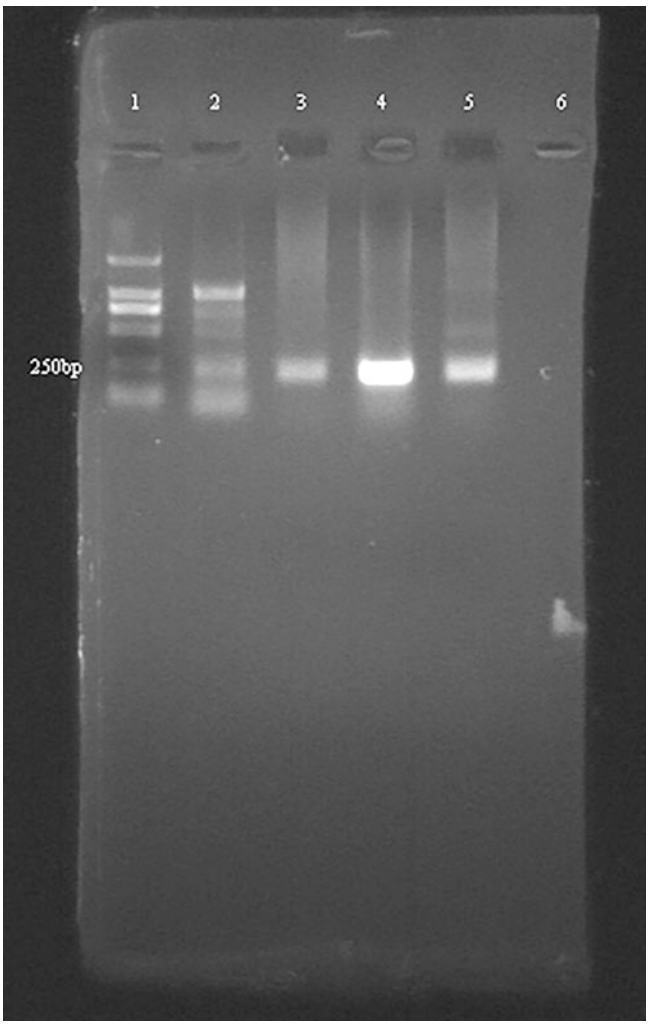


Fig. 27-82-6 Monoclonally rearranged TCR-γ gene (250 bp band) in the DNA from the specimens

27.83 Extranodal NK-/T-Cell Lymphoma [194–196]

- The spectrum of NK-cell lymphoma consists of extranodal NK-/T-cell lymphoma (ENTL, including nasal and extranasal types), intravascular NK-/T-cell lymphoma, NK-cell lymphoma, and NK-cell leukemia.
- ENTL has a facial predominance, often with midline facial destruction. The upper aerodigestive tract, testicles, and skin are similarly affected.
- Clinically, it occurs as nodules, cellulitis-like swelling, and erythematous to purpuric patches. However, cellulitis with persistent ulceration is highly suspicious for ENTL.
- Neoplastic cells infiltrate whole layers of the skin, with an angiocentric and angiodestructive growth pattern. The nuclei are ovate or irregular with pale cytoplasm. Angiocentricity and angiodestruction are often present with extensive necrosis.
- The typical immunophenotype for ENTL is CD2+, CD3ε+, CD56+, and cytotoxic proteins (TIA1+, GramB+, and perforin+), while it is negative for CD4, CD5, and CD8.
- Although ENTL is consistently associated with CD56 and Epstein-Barr virus, a CD56-negative variant has also been diagnosed with the prerequisite of detection of EBV and expression of cytotoxic proteins.
- The nasal type of ENTL has less skin involvement and a better survival rate.
- Intravascular lymphoma is defined as intravascular proliferations of large neoplastic cells. These tumor cells exhibit the phenotype of large B cell, CD30-positive anaplastic large T cell, and NK-/T-cell lymphoma (commonly cutaneous intravascular NK-/T-cell lymphoma).

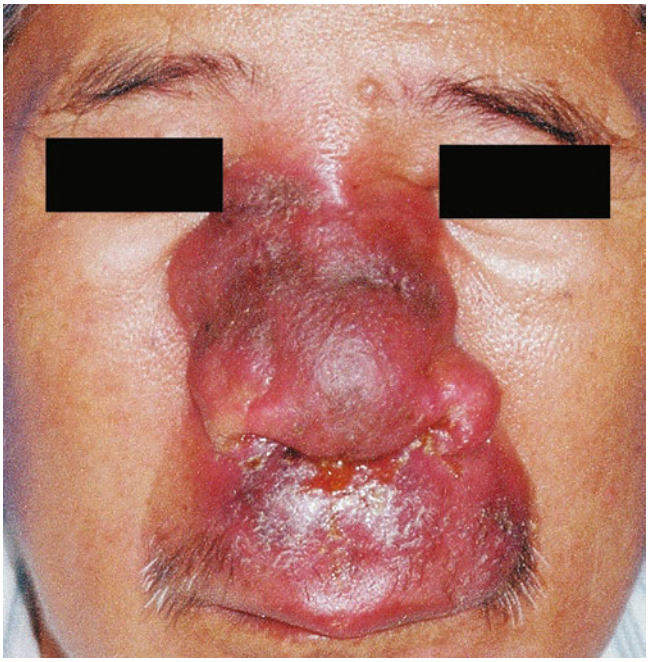


Fig. 27-83-1 Well-circumscribed plaques and nodules on the sides and bridge of the nose

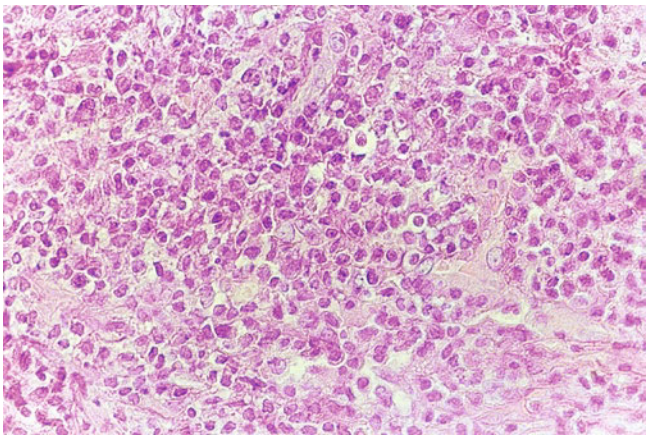


Fig. 27-83-2 Lymphoid cells with part atypical infiltrating in the dermis (HE stain, ×100)

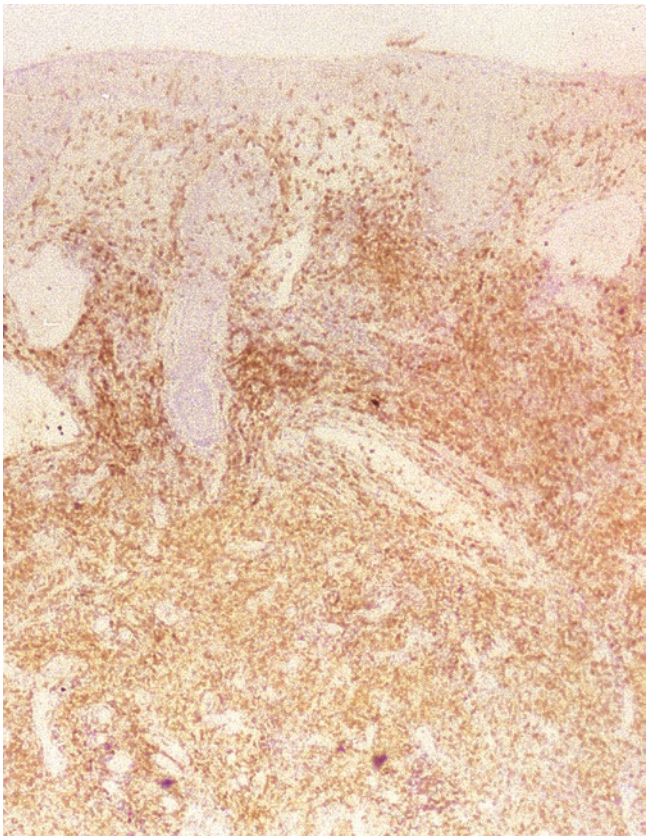


Fig. 27-83-3 Positive CD56 (ABC stain, ×100)

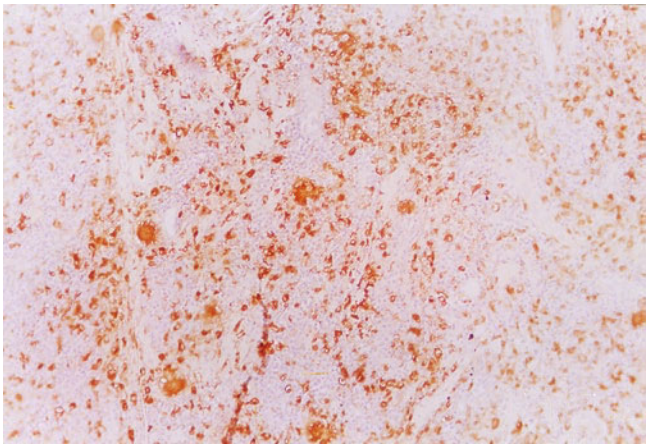


Fig. 27-83-4 Positive CD45RO (ABC stain, ×100)

27.84 Primary Cutaneous B-Cell Lymphoma [197, 198]

- Primary cutaneous B-cell lymphoma (PCBCL) represents a variety of lymphomas that originate from skin B lymphocytes in different stages. No extracutaneous manifestations can be found at the time of diagnosis.
- PCBCL typically manifests with solitary or multiple plum-colored papules, nodules, or plaques. The lesions have a predilection for the scalp, forehead, trunk, and foot.
- In PCBCL, the clinical characteristics are quite different between its subtypes. Unlike PCDLBCL-LT (primary cutaneous diffuse large B-cell lymphoma, leg type), PCMZL (primary cutaneous marginal zone lymphoma) and PCFCL (primary cutaneous follicle center lymphoma) are rather indolent, and there are quite a lot individuals with PCFCL who undergo spontaneous resolution.
- CD20 and CD79a immunophenotypes are characteristic of B-cell lymphoma. In addition, PCDLBCL-LT expresses BCL-2 and MUM-1, while diffuse large B-cell lymphoma (DLBCL) shows a positive stain for BCL-2 -and BCL-6. Systemic chemotherapy is likely to have a favorable prognosis in DLBCL patients with CD40 expression.

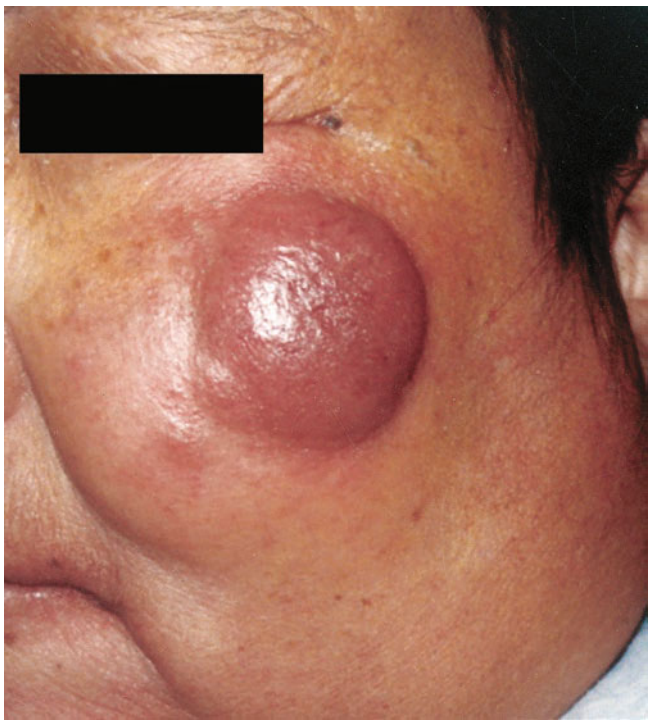


Fig. 27-84-1 Pigeon egg-sized, half ball, brownish-red tumor on the face

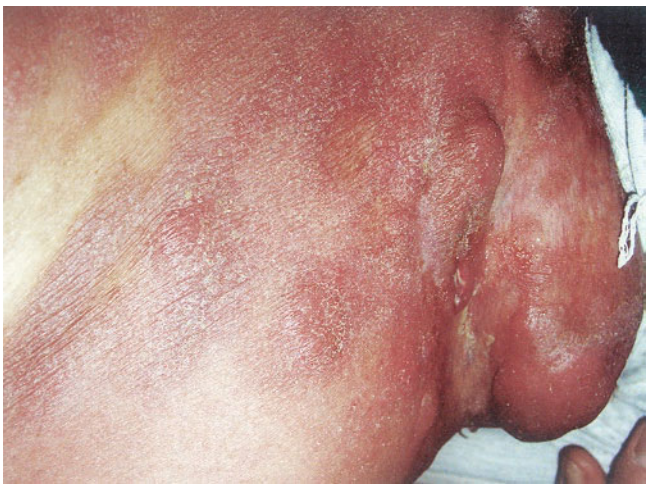


Fig. 27-84-2 Diffuse erythema and infiltrate plaques on the axilla

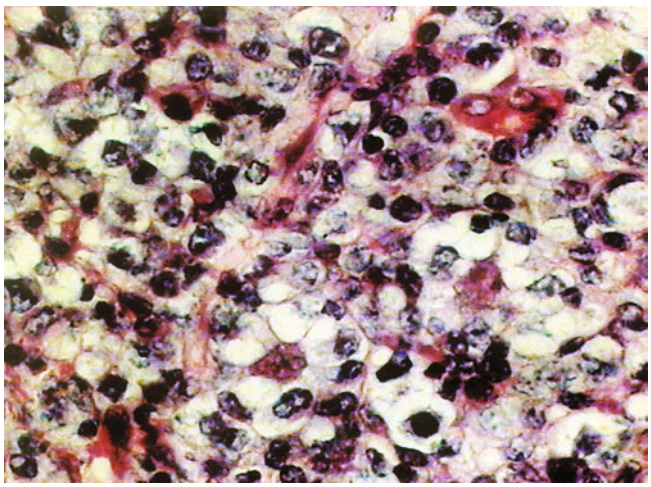


Fig. 27-84-3 Numerous atypical tumor cells

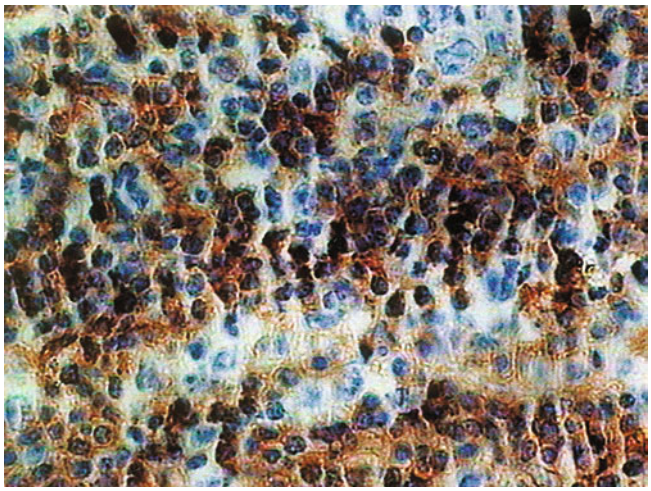


Fig. 27-84-4 Numerous CD20-positive cells

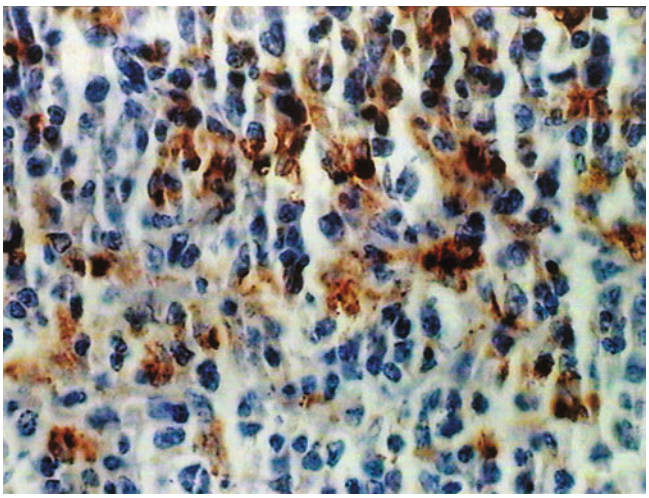


Fig. 27-84-5 A few CD68-positive cells

27.85 Maculopapular Cutaneous Mastocytosis [199, 200]

- Maculopapular cutaneous mastocytosis (MCM) consists of classical urticaria pigmentosa (UP), plaque UP, nodular UP, and telangiectasia macularis eruptiva perstans.
- Pediatric MCM presents with less numerous and more polymorphic maculopapules that are yellowish in color. The adult type presents with more numerous monomorphic reddish lesions.
- The onset of urticaria pigmentosa (UP) is a variable number of brown macules or papules that urticate with friction.

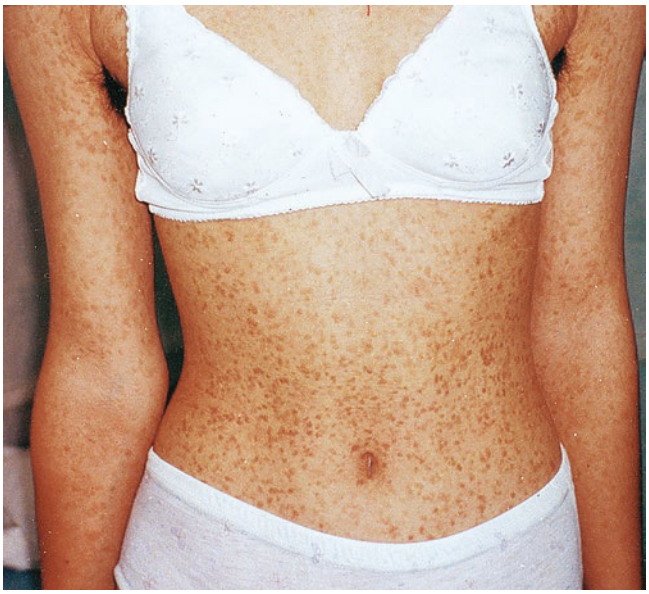


Fig. 27-85-1 Multiple brown papules on the trunk

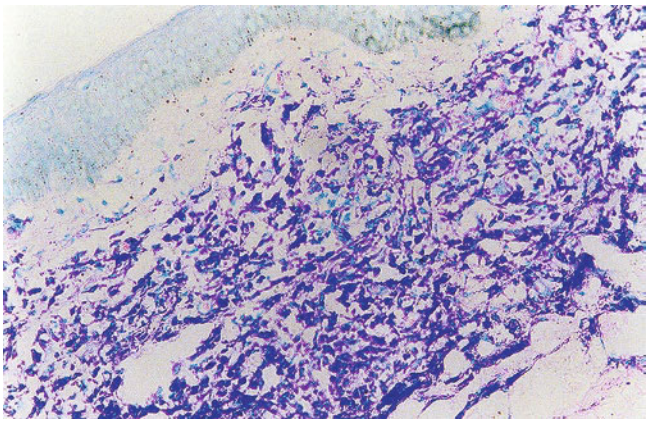


Fig. 27-85-2 Mast cell infiltrated in the upper dermis (Giemsa stain, ×200)

27.86 Diffuse Cutaneous Mastocytosis [200, 201]

- Most diffuse CM cases arise at birth or in early infancy, and they tend to be distributed over the trunk and the scalp. The lesions are quite variable from papules and blisters to hemorrhagic bullae.
- Diffuse CM is an anaphylactic disease with a potentially life-threatening outcome, and it particularly occurs at a young age due to the heavy load of mast cells in the skin.
- Diffuse CM mostly appears within 6 months postpartum. Hemorrhagic bullae and small vesicles are regarded as the typical features of diffuse CM.
- There is evidence showing that diffuse CM is prone to progress to systemic mastocytosis.

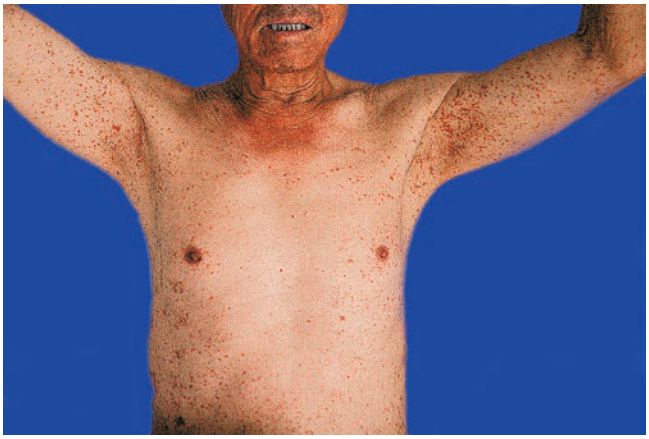


Fig. 27-86-1 Generalized red papules on the trunk and extremities

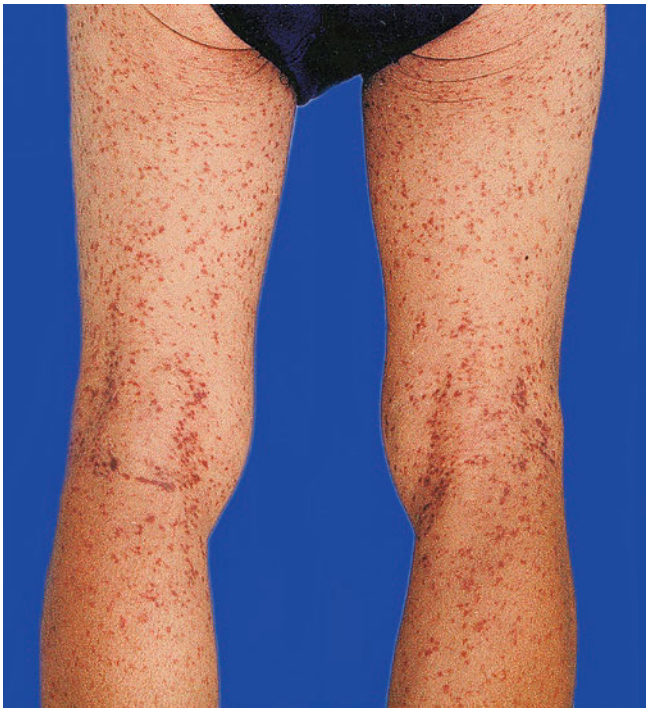


Fig. 27-86-2 Part bleeding lesions

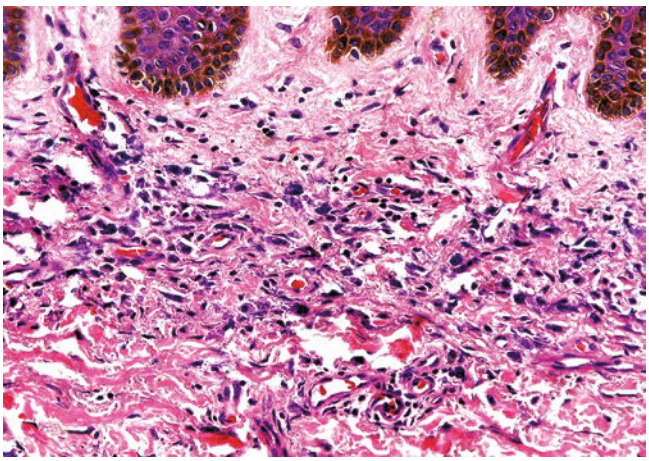


Fig. 27-86-3 Moderate infiltration of mast cells in the upper dermis, some of which showed an abnormal morphology (HE stain, ×200)

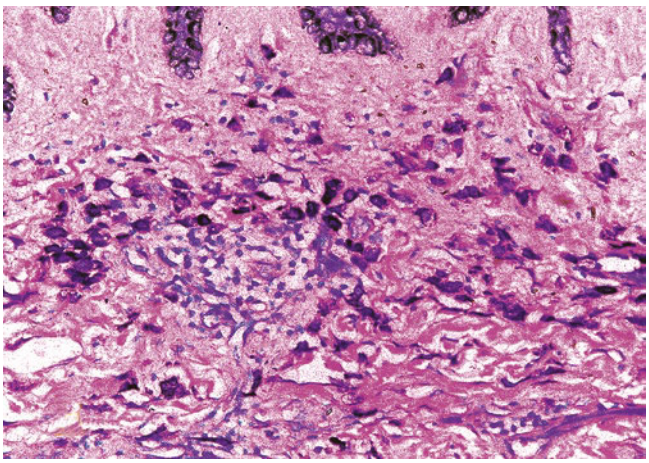


Fig. 27-86-4 Violaceous, metachromatic granules were found (Giemsa stain, ×200)

27.87 Mastocytoma [202–204]

- Cutaneous mastocytosis (CM) displays an increase and accumulation of mast cells in the dermis, which is distinctive to systemic mastocytosis.
- Urticaria pigmentosa (UP) is also called maculopapular CM. CM can be categorized into three types: UP, diffuse CM, and solitary mastocytoma.
- Mast cells can be stained immunohistochemically with azure A, CD25, Giemsa, kit (CD117), toluidine blue, and tryptase.
- Most mastocytoma develops in infants and children, and the majority resolve completely within 4–10 years.
- The clinical appearance of the mastocytoma is described as a reddish-brown papule, nodule, or plaque. Blistering, pruritus, and tenderness may also be noted. The diameter of the lesion ranges from several millimeters to 12 cm.
- Approximately 79% of mastocytomas demonstrate positive Darier's sign, which is evoked by rubbing the lesion.

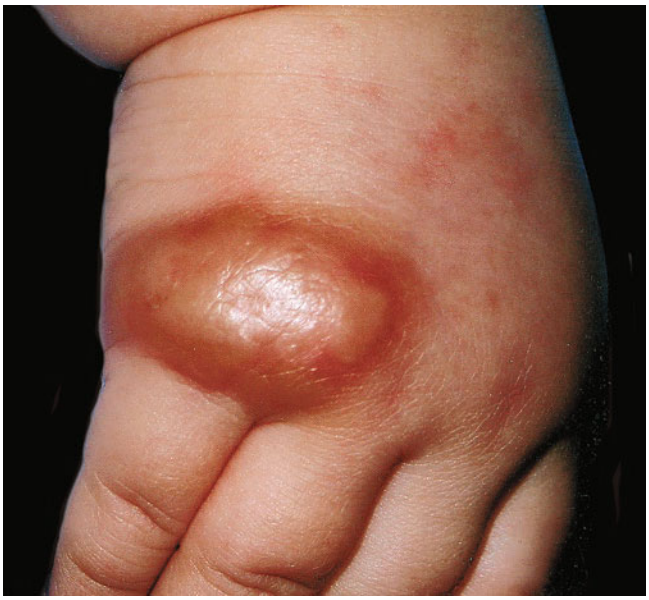
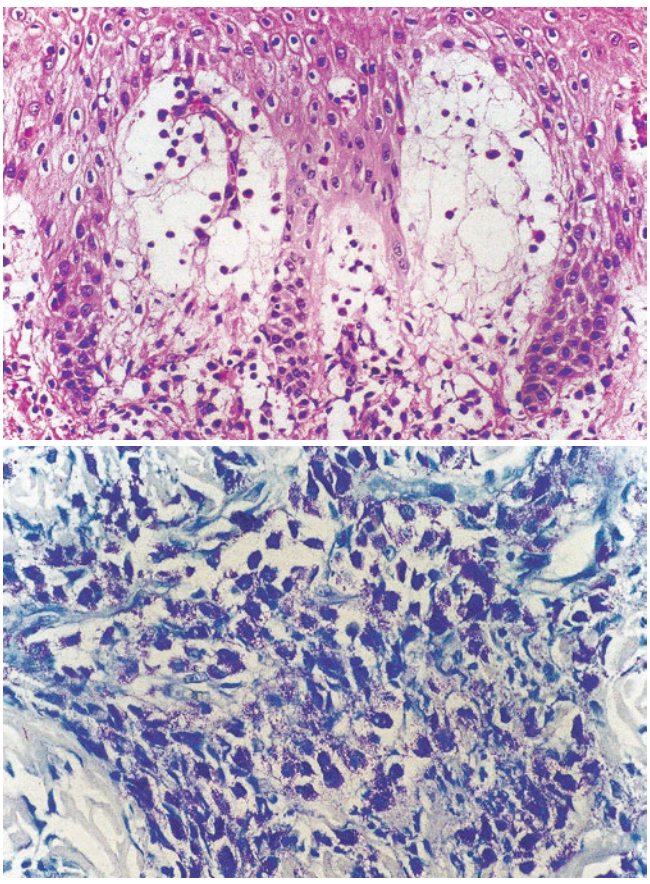


Fig. 27-87-1 A large skin-colored nodule with brown-red ring on the dorsum of the right hand



Figs. 27-87-2, 27-87-3 Lots of mast cells contained purple granules in the cytoplasm in the dermis ((2):HE stain, ×100; (3):Giemsa stain, ×400)

27.88 Cutaneous Plasmacytoma [205–207]

- Neoplasms of plasma cells are classified into four groups: classic plasma cell myeloma, extramedullary plasmacytoma, isolated plasmacytoma of bone, and plasma cell leukemia.
- Cutaneous plasmacytoma (CP) is a malignant transformation of plasma cells in the skin.
- CP arises on the scalp and neck, especially in the nasal cavity and nasopharynx.
- CP often masquerades as B-cell lymphoma, which displays solitary or multiple, smooth, dome-shaped plaques or nodules with a reddish, violaceous, or normal color.
- Biopsy specimens show a monomorphic population of atypical plasma cells distributed in a nodular or diffused pattern.
- The immunoprofiles for CP are CD38+, CD43+, CD56+, CD79a+, CD138+, and EMA+, and monoclonal cytoplasmic light chain expression favors the diagnosis of plasmacytoma.
- Primary CP is associated with organ transplantation, Epstein-Barr virus activation, and recurrent herpes simplex virus infection.
- Many CP patients develop local recurrence or visceral metastasis. Unique cases of transformations into multiple myeloma or CD30+ large B-cell lymphoma have also been described.

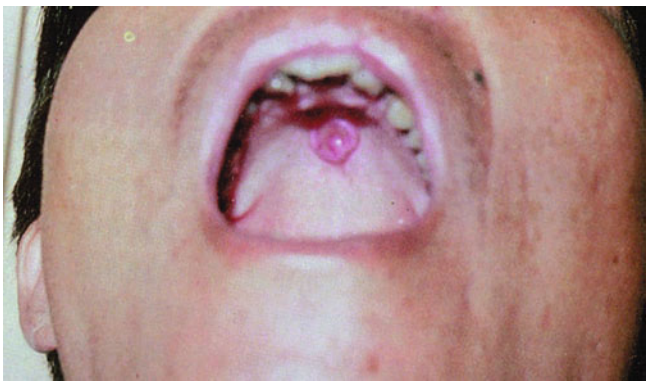


Fig. 27-88a-1 A solitary red nodule with ulcers in the center of the palate

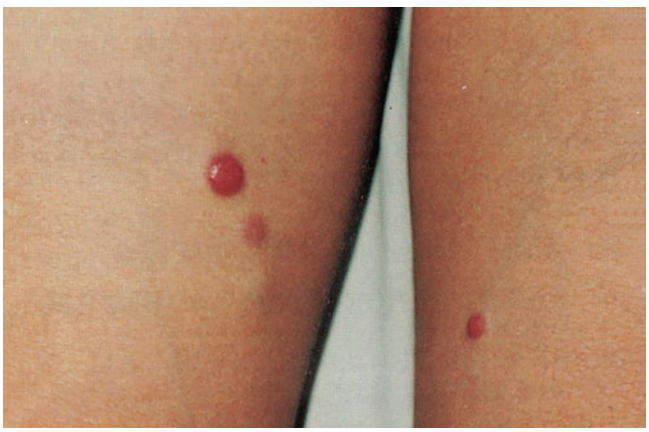


Fig. 27-88a-2 Numerous violaceous, skin-colored nodules on the internal aspect of both thighs

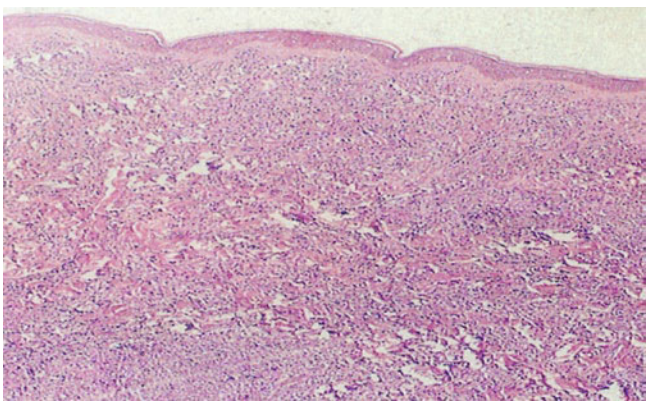


Fig. 27-88a-3 Diffuse infiltrates of plasma cells in the dermis and subcutaneous tissue (HE stain, ×40)

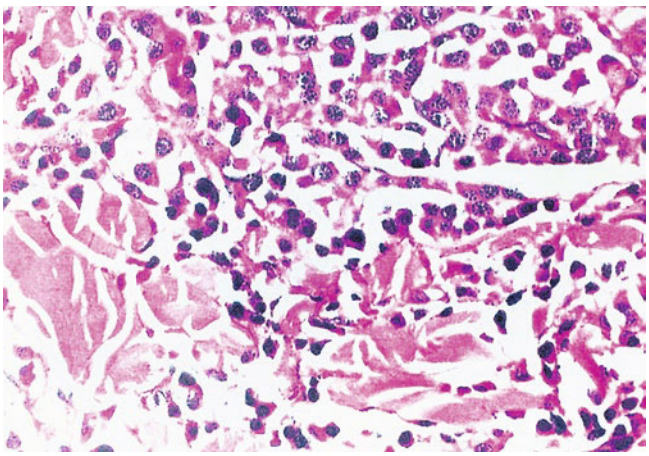


Fig. 27-88a-4 The plasmacytes varied from sizes and shapes due to clumping of chromatin associated with atypical mitotic figures (HE stain, ×400)

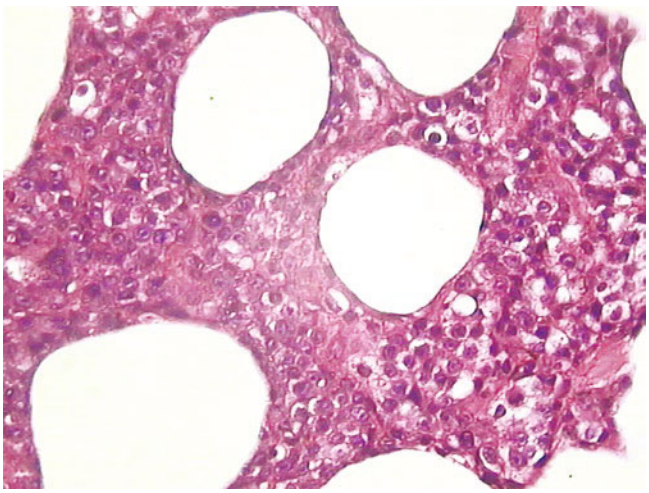


Fig. 27-88b-3 Tumor cells had hyperchromatic, irregularly shaped nuclei and atypical mitotic figures (HE stain, ×400)

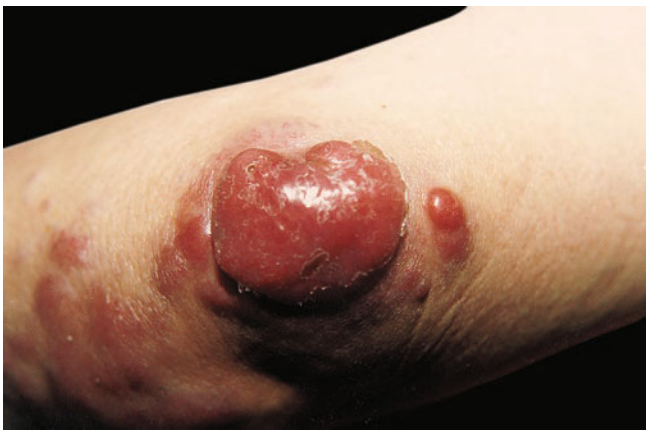


Fig. 27-88b-1 A big dark-red mass and many nodules on the left arm

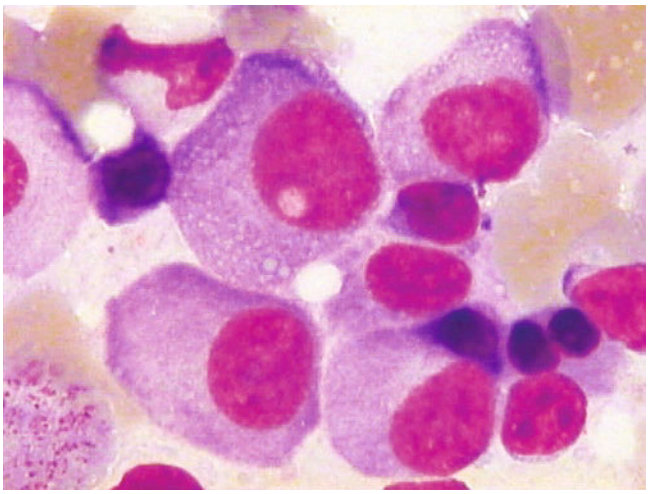


Fig. 27-88b-4 The bone marrow smear showed many plasmablasts, proplasmacytes, and binucleated plasmacytes (Wright's stain, ×1000)

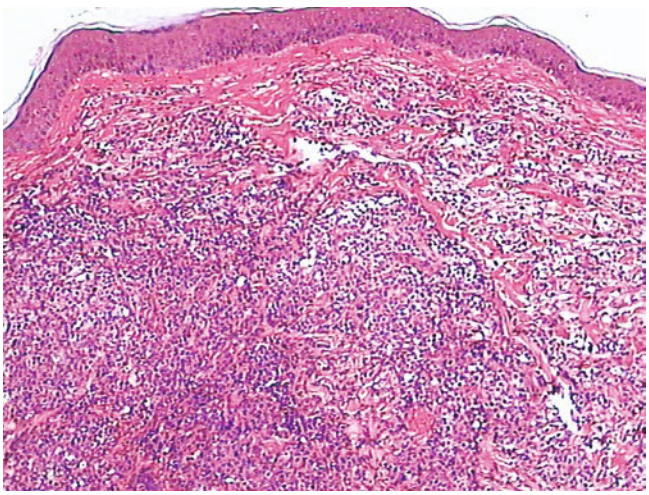


Fig. 27-88b-2 Lots of tumor cell in the dermis (HE stain, ×100)

27.89 Polycythemia Vera [208, 209]

- Polycythemia vera (PV) is a myeloproliferative disease characterized by a larger number of red blood cells.
- The most common cutaneous manifestations of PV include aquagenic pruritus, erythromelalgia, cyanosis, and purple coloration of the skin.
- These cutaneous manifestations are secondary to the microcirculatory disturbances that are common features of PV.

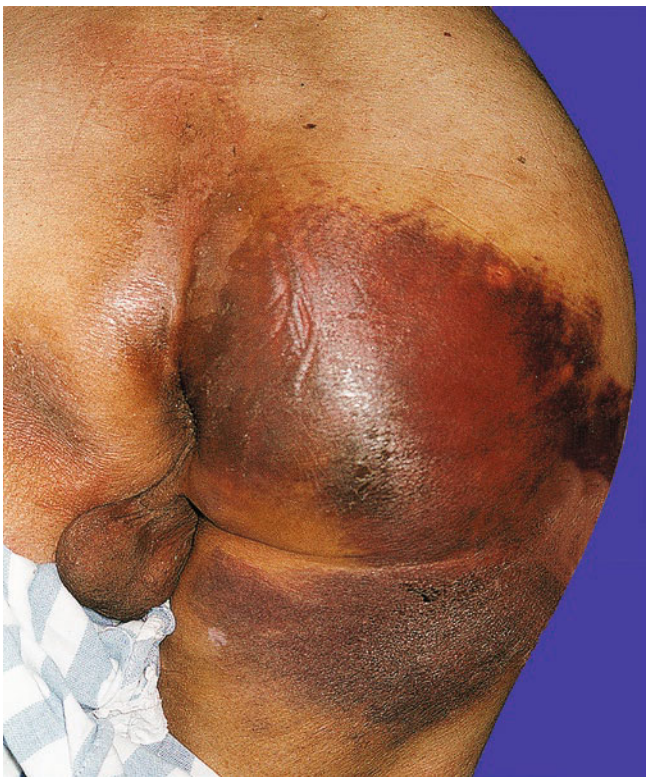


Fig. 27-89-1 Well-circumscribed violet maculae on the right buttocks, lower limbs, and scrotum

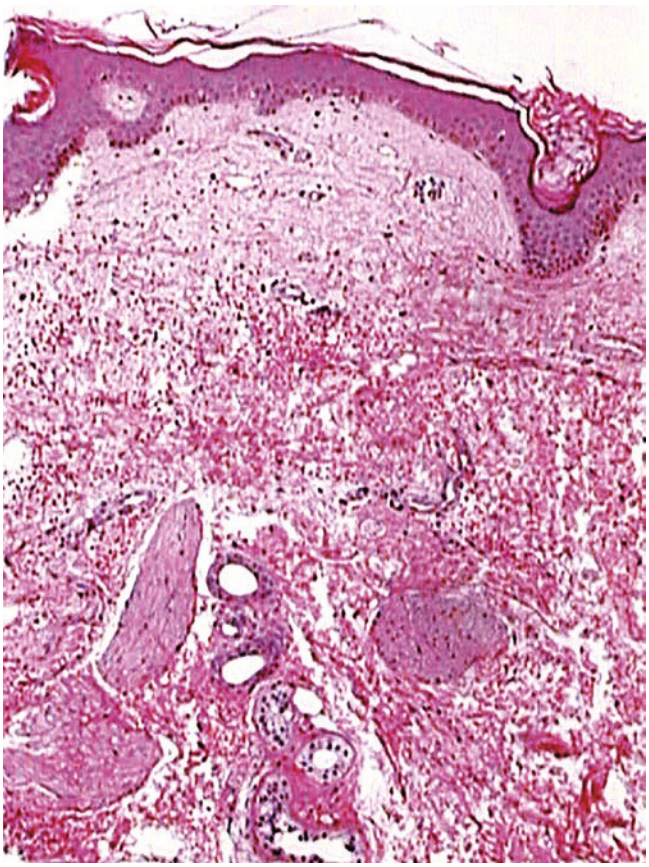


Fig. 27-89-2 Slight atrophy of epidermis, edema with many erythrocytes effusion, and perivascular inflammatory infiltration in the dermis (HE stain, ×40)

27.90 Leukemia Cutis [210–212]

- Leukemia cutis (LC) often arises from acute monocytic leukemia, acute myelomonocytic leukemia, chronic lymphocytic leukemia, and chronic myeloid leukemia.
- LC often presents with papules, nodules, or plaques of varying sizes. These lesions are brown, red, purplish, or hemorrhagic.
- LC may exist prior to demonstration in the bone marrow or peripheral blood.
- Clinical characteristics and critical investigation of the bone marrow and circulating blood are of equal importance in the diagnosis of LC.
- The pleomorphic leukemic cells infiltrate the dermis in a nodular, interstitial, or perivascular pattern. However, the upper papillary dermis is spared. The nuclei of these atypical cells are kidney-shaped, monomorphous, or cytologically bland.
- To determine the infiltrated cell type of LC, immunophenotypic staining and cytologic analysis should be performed.
- Detection of specific immunohistochemical markers and molecular genetic data is conducive to a correct diagnosis of LC.

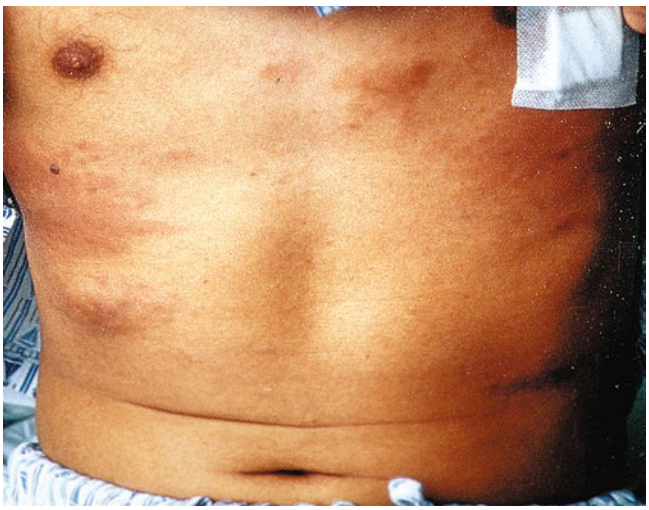


Fig. 27-90-1 Erythematous-to-violaceous nodules and plaques on the chest

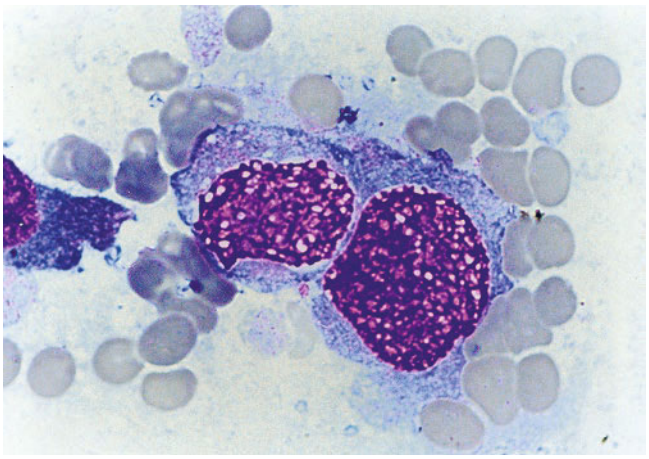


Fig. 27-90-2 Large naive monocytes in the bone marrow (Wright stain, ×1000)

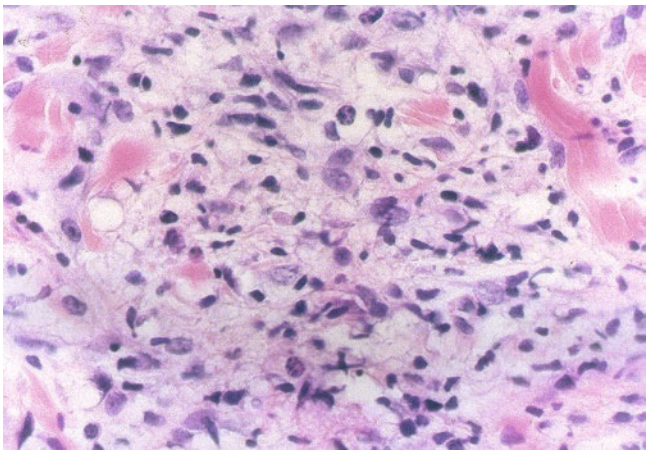


Fig. 27-90-3 Lots of small- to medium-sized histiocytes with hyperchromatic nuclei infiltrated in the perivascular area (HE stain, ×40)

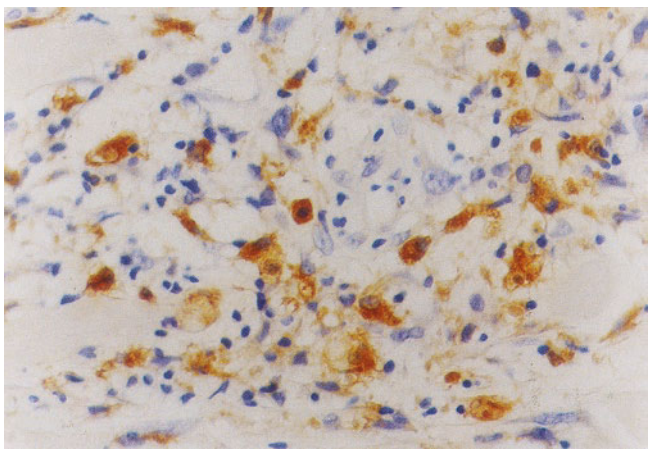


Fig. 27-90-4 CD68 positive in tumor cells (SP stain, ×40)

27.91 Cutaneous Metastasis for Lung Cancer [213]

- While the eyes are the window to the soul, the skin is the window to internal malignancies.
- The incidence of skin metastasis in lung cancer is approximately 0.2–3.1%, with the majority spreading to the scalp. Those in the upper lobes of the lung tend to metastasize more frequently to the skin. For oat-cell carcinoma, the back is the most common site of involvement.
- Lung cancer can be classified pathologically as squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, and undifferentiated carcinoma.
- Skin manifestations from lung malignancies are not characteristic. The most common are nodules, papules, and plaques with variable red to pink to violaceous color. Less frequently, these lesions resemble ulcers, herpes zoster, morphea, hemangioma, dermatofibroma, epidermal cysts, pyogenic granuloma, cellulitis, erysipelas, and bullae.
- Among male patients with lung cancer, skin metastases have a predilection for the chest, abdomen, upper lip, and back. The traumatic area after thoracotomy, needle aspiration, or burning may also be involved.
- The immunological phenotype of the metastatic cells is TTF-1+, CAM5.2+, CK7−, and CK20−.

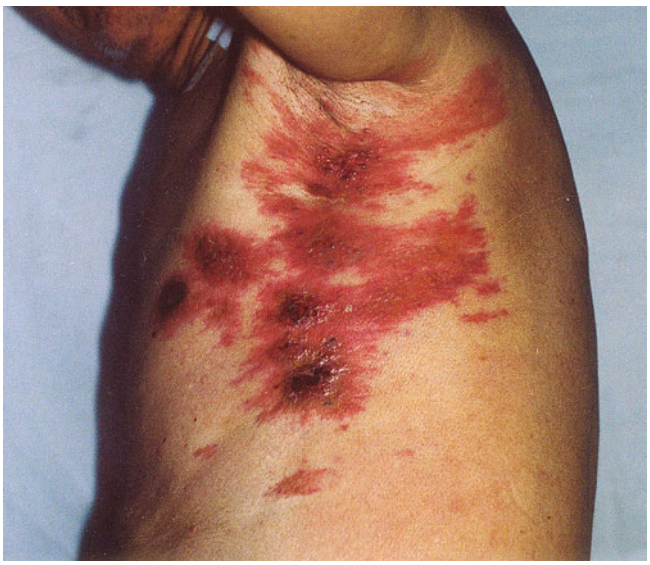


Fig. 27-91-1 Lesions on the left axilla, chest, back, and hypochondrium

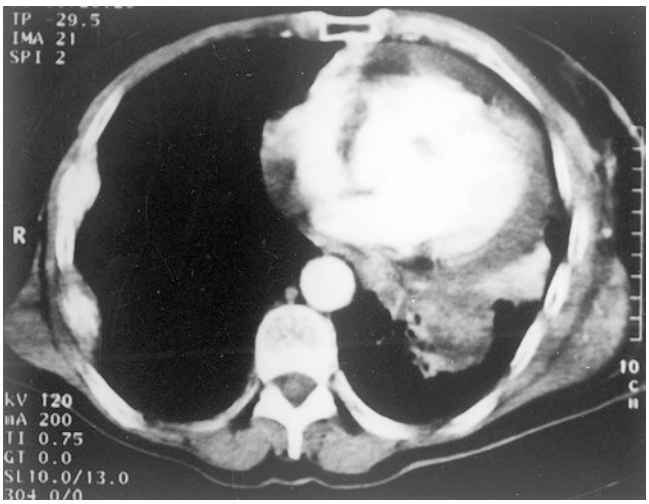


Fig. 27-91-2 A 4.5 × 4.0 cm tumor in left lower lung

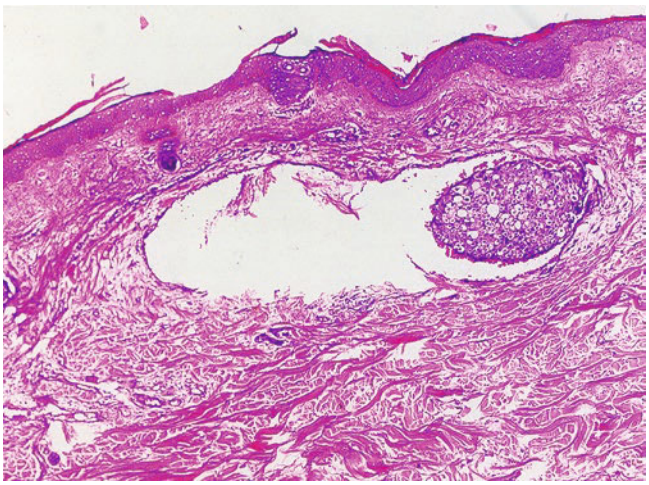


Fig. 27-91-3 Tumor embolism in the dermis (HE stain, ×160)

27.92 Cutaneous Metastasis of Gastrointestinal Malignancy [214, 215]

- The upper abdominal wall is the predilection site for skin invasion in gastrointestinal malignancies. A Sister Joseph nodule on the umbilicus is the underlying sign, especially for gastric adenocarcinoma.
- The cutaneous manifestations of gastrointestinal malignancy occur as dome-shaped, skin-colored, pink, whitish, or reddish nonspecific nodules.
- Skin metastases from colorectal neoplasms are associated with better outcomes compared to other gastrointestinal tumors.
- According to a survey in male patients, nearly 6% of all cutaneous metastases are from gastric adenocarcinoma.
- Tumor cells aggregate in the dermis to form clusters or strands of glands, embedded in a rich fibrous stroma. Signet-ring neoplastic cells may also present.
- Alcian blue and PAS stains are positive for the tumor cells. Meanwhile, expressions for CDX2, CK7, CK20, CEA, and EMA have already been demonstrated. Recently, HIK1083 was applied as a sensitive marker to label signet-ring cells of adenocarcinoma.

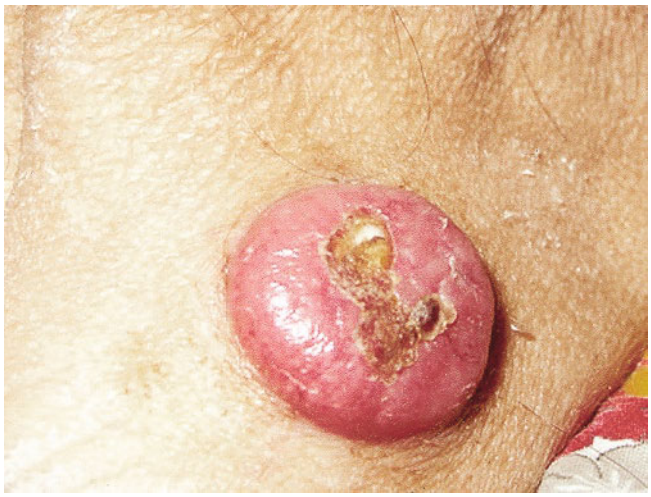


Fig. 27-92-1 A 2 × 2 × 1 cm tumor with depressed center on the back of the neck

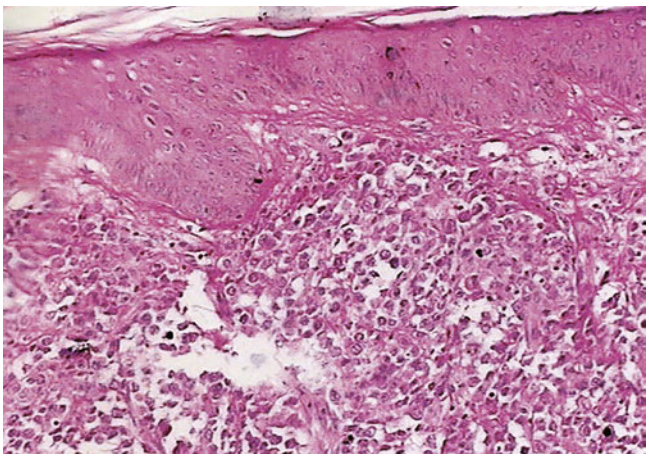


Fig. 27-92-2 Numerous tumor cells nest in the dermis (HE stain, ×100)

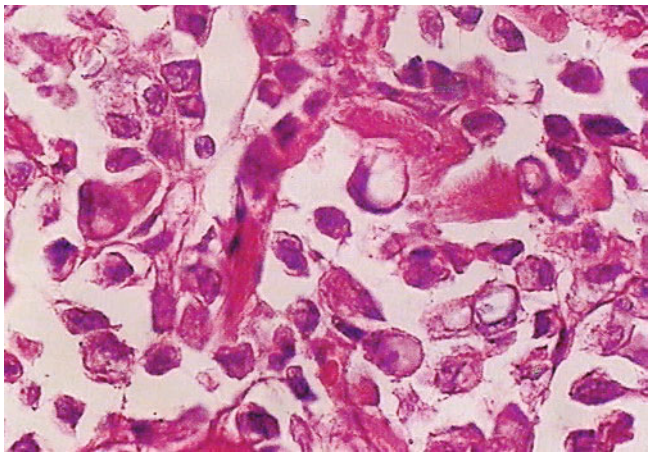


Fig. 27-92-3 Numerous signet-ring cells with variable sizes and shapes (HE stain, ×400)

27.93 Sister Mary Joseph's Nodule [216–218]

- Sister Mary Joseph's nodule (SMJN) is the umbilicus metastasis of abdominopelvic malignancy.
- SMJN often presents as an ill-defined, firm mass with overlying ulceration or necrosis. There is blood or purulent discharge in some lesions.
- The vast majority are metastatic adenocarcinomas that originate from the gastrointestinal tract, ovarian tissue, and bladder.
- The most common pathological type of SMJN is adenocarcinoma, which is then followed by squamous cell carcinoma, carcinoids, and undifferentiated tumors.
- The ovarian malignancy expresses CK-7 and Wilms' tumor gene products. Mucinous tumor of Müllerian origin is positive for estrogen and progesterone receptor stains. In primary peritoneal serous carcinomas, there is high expression of PAX-8. CDX-2 and CK-20 are diagnostic markers for urachal carcinoma.
- The overall survival of SMJN is 2–11 months in untreated patients.

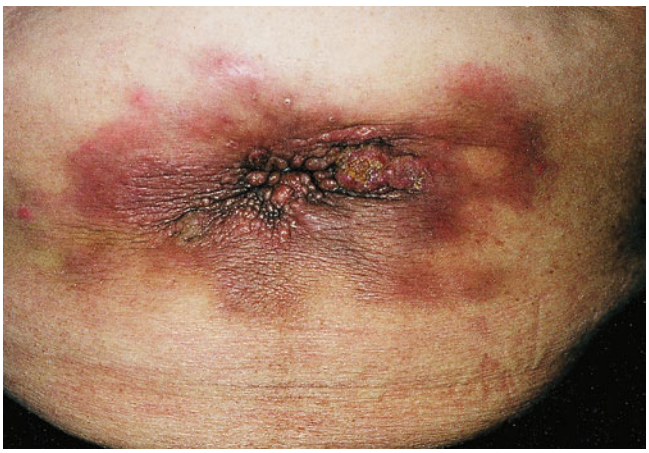


Fig. 27-93-1 An oval, well-circumscribed plaque 9–10 cm in diameter with hyperpigmentation and papules with papillomatous surface

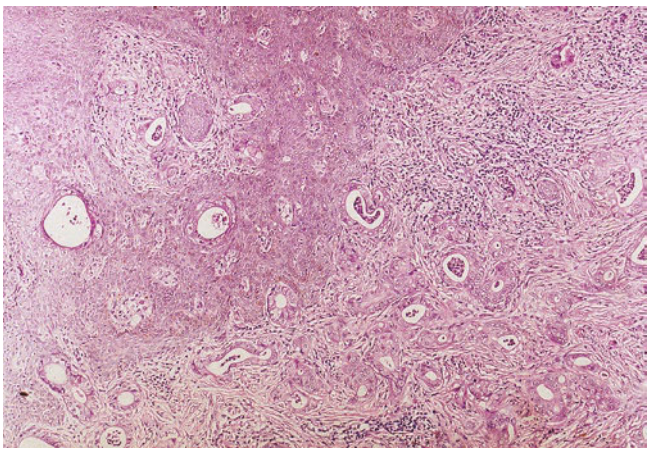


Fig. 27-93-2 Low-differentiated adenocarcinoma from umbilical-urethral canal remnant (HE stain, ×88)

27.94 Carcinoma en Cuirasse [219–221]

- Carcinoma en cuirasse (CC) refers to the armor-like induration resulting from tumor cell infiltration and reactive fibrosis.
- CC exhibits scattered, firm papulonodules that progress to be brawny hard and eventually merge into a sclerodermoid plaque, reminiscent of the encasement in armor of a cuirassier.
- The anterior chest is the most common site of involvement. The back, neck, abdomen, vulva, scrotum, and supraclavicular region can also be affected.
- The pathological changes of CC include extensive dermal fibrosis with interstitial infiltration of atypical epithelial cells in a nodular pattern or in a linear arrangement of dissecting collagen bundles (Indian filing).
- It is proposed that pleiotrophin, a multifunctional tumor promoter, leads to rapid tumor growth and progression to the scirrhous subtype of invasive carcinoma.
- Any treatment for CC is now palliative, and because the tumor cells cause extensive reactive fibrosis and decreased vascularity, chemotherapeutic agents may be unable to obtain tumoricidal concentrations locally.

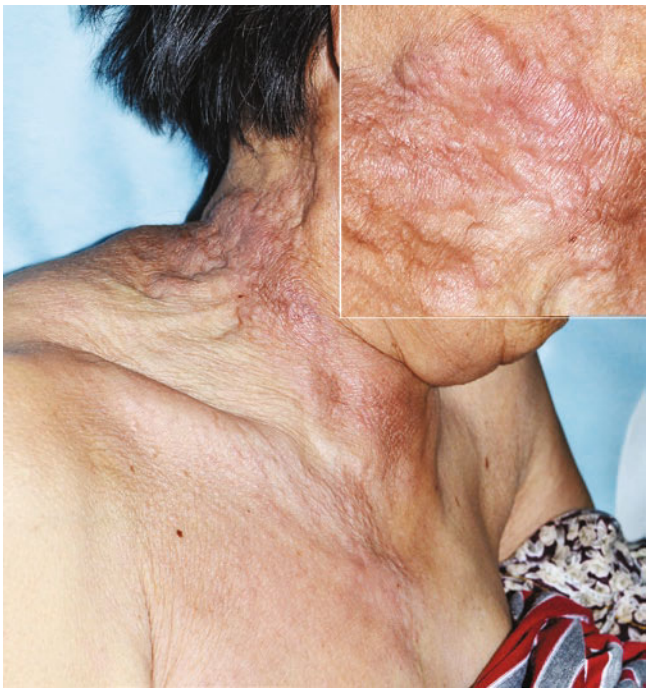


Fig. 27-94-1 Indurated plaque was found on the right side of the upper chest wall measuring 20 × 15 cm in size, and it extended upward to the right part of the neck over an area of 20 × 10 cm, which was grossly distorted and convolutional in shape. The underlying skin was woody hard and unpinchable (Reproduced with the permission from [221])

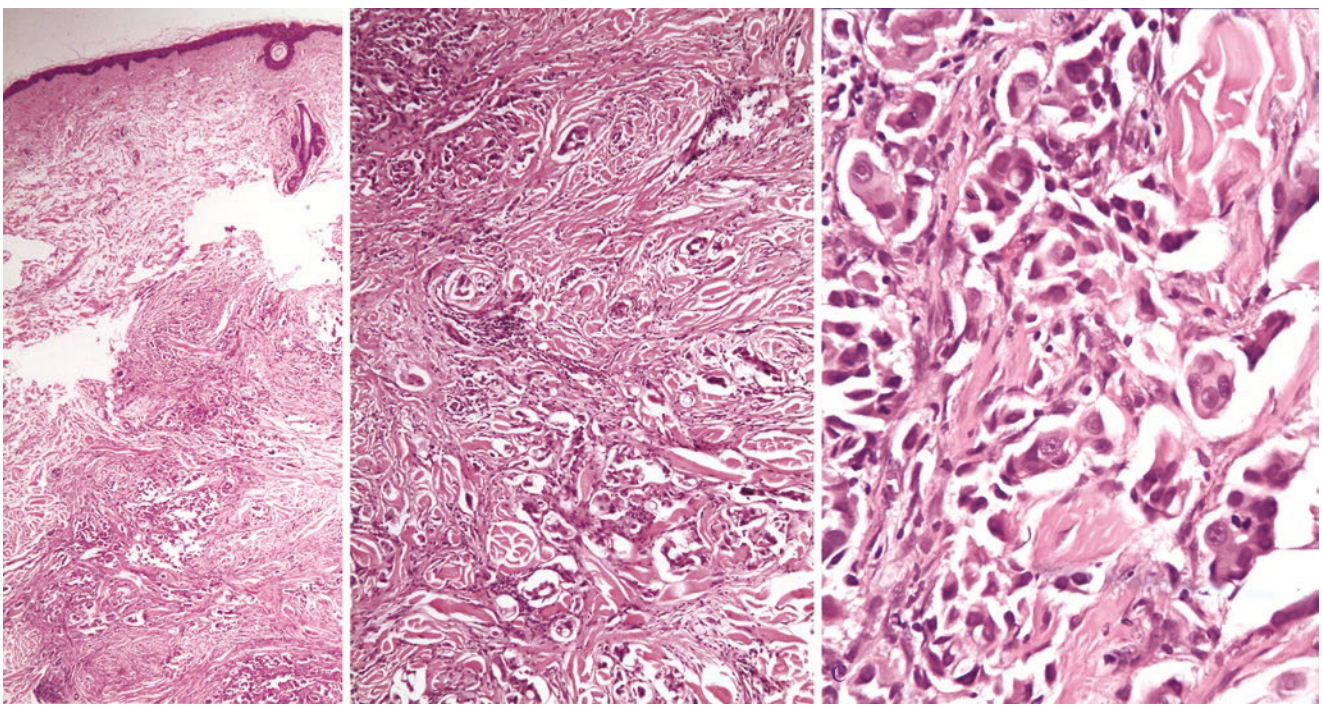


Fig. 27-94-2 Monomorphous tumor cells with a rich cytoplasm in vacuoles, presented singly or in small clusters between dense collagen bundles in the dermis (HE stain, (1) ×40; (2) ×100; (3) ×400) (Reproduced with the permission from [221])

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