Inherited Disorders of Keratinization

7

Priyanka Karagaiah and Varsha M. Gowda

7.1 Introduction

Disorders of keratinization are those group of diseases in which there is abnormal differentiation and desquamation of the epidermis resulting in a defective cutaneous barrier. It includes ichthyosis, palmoplantar keratoderma, porokeratoses and a perforating group of disorders.

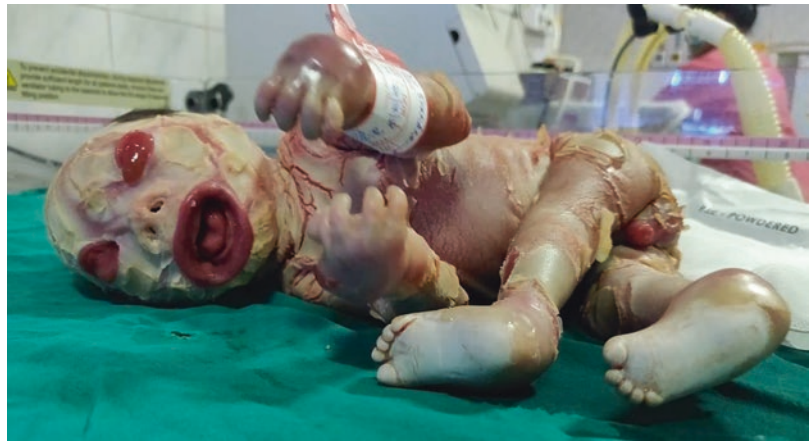
Ichthyoses are characterized by generalized scaling of skin with or without erythema. Conditions that are discussed include the most common disorders, ichthyosis vulgaris due to filaggrin deficiency and X-linked recessive ichthyosis due to steroid sulfatase deficiency. Non-syndromic conditions include keratinopathic ichthyoses and autosomal recessive congenital ichthyosis (ARCI) due to defect in epidermal lipid metabolism and transport. Various syndromic ichthyoses include Netherton syndrome, Sjogren-Larsson syndrome, ichthyosis associated lipid storage diseases and trichothiodystrophy. Understanding the underlying pathomechanisms becomes important for the development of targeted treatments.

Palmoplantar keratoderma (PPK) represents a large group of disorders of cornification which can be hereditary or acquired. Inherited PPK can be a component of other genodermatoses or a component of multisystem syndrome (e.g. deafness, cardiomyopathy). Acquired can be drug-induced or paraneoplastic. Patients suffer from hyperhidrosis, maceration, blisters, fungal infections, constricting keratotic bands (pseudoainhum), malodor and even severe pain. The underlying molecular defect may involve epidermal proteases or proteins of keratinocyte cytoskeleton, intercellular junctions or cornified envelope.

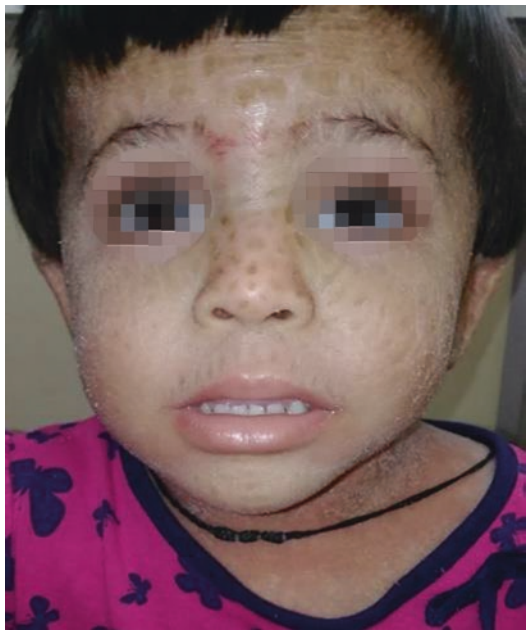
P. Karagaiah (✉) · V. M. Gowda
Bangalore Medical College and Research Centre, Bangalore, India

R. R. Ranawaka et al. (eds.), *Atlas of Dermatoses in Pigmented Skin*,
https://doi.org/10.1007/978-981-15-5483-4_7

Picture courtesy:
Dr Kavyashree Krishna, Bangalore Medical College and research centre, Bangalore, India



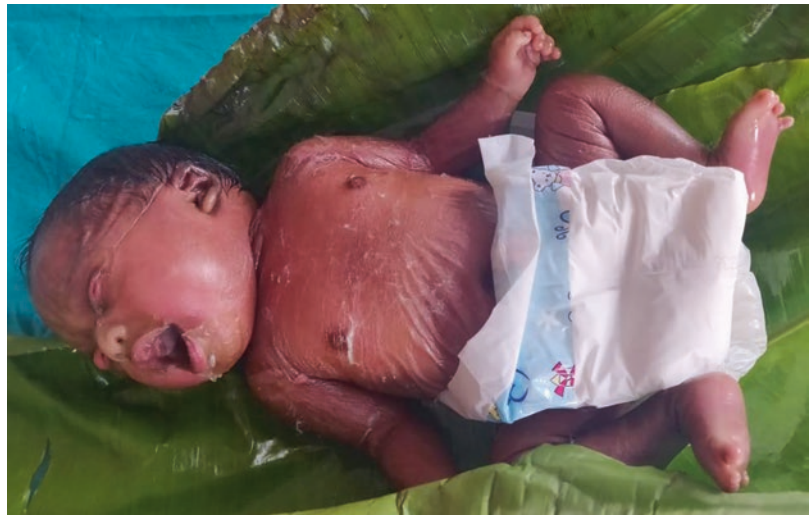
1. A full-term neonate was born with these skin lesions.
   (a) What is the diagnosis?
   (b) What is the gene mutation in this disorder?
   (c) What are the complications associated with this disorder?



(Picture courtesy: Dr Priyanka Karagaiah)

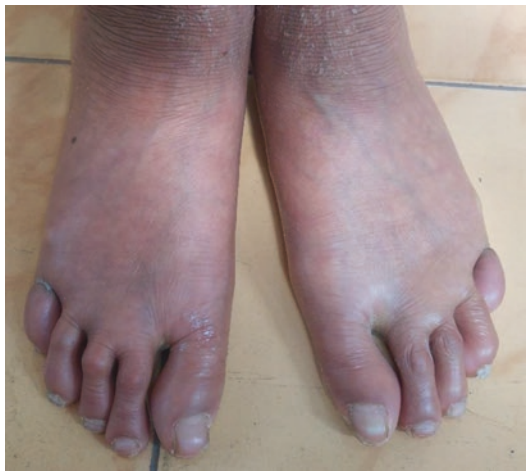
2. A 3-year-old boy came with dirty yellowish brown polygonal scales over the face and neck. Family history of similar lesions in maternal uncle.
   (a) What is the diagnosis?
   (b) What is the pattern of inheritance?
   (c) What is the enzyme deficient in the condition?

(Picture courtesy: Dr Kavyashree Krishna, Bangalore Medical College and research centre, Bangalore, India)

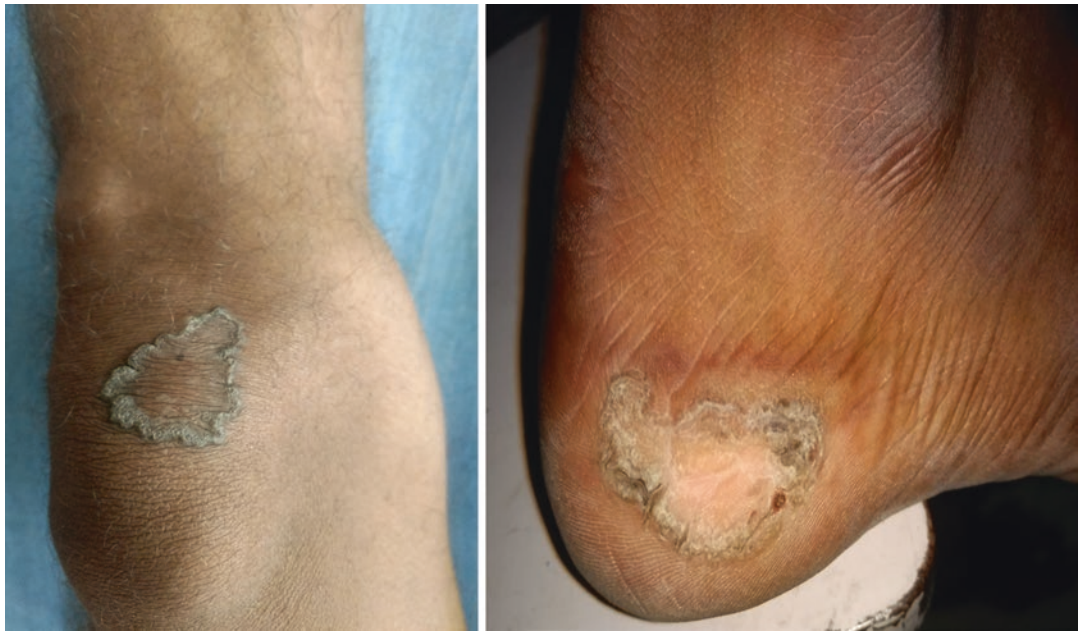


3. A 7-day-old neonate came with yellowish taut parchment-like skin with fissuring and associated ectropion.
   (a) What is the diagnosis?
   (b) What are the related complications?
   (c) What is the mainstay in the management of this condition?

4. A 20-year-old woman came with lesions over last digit of bilateral feet as shown in the picture with hyperkeratosis of both soles.
   (a) What is this lesion called?
   (b) What are the conditions associated with these lesions?
   (c) What are its complications?



(Picture courtesy: Dr Priyanka Karagaiah)



(Picture courtesy: Dr Priyanka Karagaiah)

5. A 25-year-old man came with itchy lesions since 2 years. On examination, two well-defined annular plaques with hyperkeratotic raised borders noted.
   (a) What is the diagnosis?
   (b) What are the differential diagnoses?
   (c) What is the typical histopathological feature?

Answers

1. Harlequin ichthyosis
   Nonsense and/or frameshift mutations in the ABCA12 gene
   Bilateral ectropion and eclabium causing difficulty in feeding and breathing, hypothermia and infections may even cause death
2. X-linked ichthyosis
   X-linked recessive inheritance
   Steroid sulfatase enzyme
3. Collodion baby
   Dehydration, hypoxia, malnutrition and pneumonia
   Barrier nursing in warm, humidified environment in an intensive care setup
4. Pseudoainhum
   Unna-Thost syndrome, Mal de Meleda syndrome, Vohwinkel syndrome, Olmsted syndrome and Bart-Pumphrey syndrome
   Infection, necrosis and finally autoamputation
5. Porokeratosis
   Granuloma annulare, tinea corporis, actinic keratosis and viral warts
   Hyperkeratotic stratum corneum and, at the raised border, a column of poorly staining parakeratotic stratum corneum cells – cornoid lamella

Disorders of keratinization are a group of disorders characterized by abnormal epidermal and appendageal differentiation, often accompanied by formation of aberrant cornified envelope, clinically presenting with hyperkeratosis and scaling. This group of disorders is now referred to as Mendelian disorders of cornification (MeDOC).

Based on the classical clinical features, disorders of cornification can be classified into ichthyoses, palmoplantar keratodermas and miscellaneous group of keratinization disorders, including porokeratosis and confluent reticulate papillomatosis.

7.2 Ichthyosis

Ichthyoses are disorders of keratinization with abnormal hyperproliferative differentiation and delayed desquamation of the epidermis. The word ichthyosis is derived from a Greek word 'ichthys', synonymous with fish, and refers to the characteristic fish-like scaling of the skin.

It is clinically characterized by hyperkeratosis with scaling of the skin. The condition may be either inherited or acquired.

Inherited ichthyosis can be classified clinico-genetically as:

(a) Non-syndromic ichthyosis
(b) Syndromic ichthyosis

7.2.1 Non-syndromic Ichthyoses

See Table 7.1.(Oji V et al 2010, Oji V et al 2016)

7.2.1.1 Ichthyosis Vulgaris

Ichthyosis vulgaris (IV) is the most commonly seen variant of ichthyosis and least severe of all types. It has an autosomal semidominant inheritance with variable penetrance and is caused by mutations in filaggrin gene (FLG) which encodes for profilaggrin resulting in abnormal keratinization and cornified envelope.

Clinical Features

Ichthyosis vulgaris usually manifests after the first 3 months of life and is characterized by dry, fine grey scales predominantly over the extensor aspect of the limbs and trunk with sparing of groin and flexures. The symptoms are more prominent in the winter season and subside in summer. It can be associated with hyperlinearity of the palms and soles and keratosis pilaris over the extremities and buttocks. Atopic eczema and allergic rhinitis may be seen in association with ichthyosis vulgaris in some cases. Diagnosis is mostly clinical and histopathology may aid in ruling out other conditions.

Management

- Adequate hydration of the skin with emollients immediately after showering is the mainstay in treatment of ichthyosis vulgaris and helps in reducing scaling.
- Patients without concomitant atopic eczema may benefit from 10 to 15% urea-containing creams or creams containing 12% lactic acid.
- Moisturizing cleansers and humidifiers may be beneficial in maintaining skin hydration.
- Systemic treatment with retinoids may rarely be required (Figs. 7.1, 7.2 and 7.3).

Table 7.1 Non-syndromic ichthyosis can further be classified as

Common ichthyoses	Autosomal recessive congenital ichthyosis (ARCI)	Keratinopathic ichthyosis (KPI)	Other non-syndromic forms
Ichthyosis vulgaris (IV)	Harlequin ichthyosis (HI)	Epidermolytic ichthyosis (EI)	Loricrin keratoderma (LK)
Non-syndromic recessive X-linked ichthyosis (RXLI)	Lamellar ichthyosis (LI)	Superficial epidermolytic Ichthyosis (SEI)	Erythrokeratodermia variabilis (EKV)
	Congenital ichthyosiform erythroderma (CIE)	Congenital reticular ichthyosiform erythroderma (CRIE)	Inflammatory peeling skin disease
	Self-healing collodion baby (SHCB)	Ichthyosis Curth–Macklin (ICM)	Keratosis linearis–ichthyosis congenita–keratoderma (KLICK)

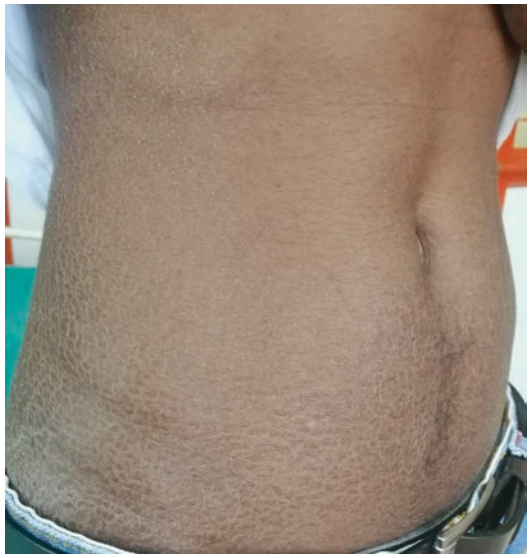


Fig. 7.1 Ichthyosis vulgaris in a 25-year-old man. Fine grey brown scales over the trunk (photographed by Dr. Priyanka Karagaiah)

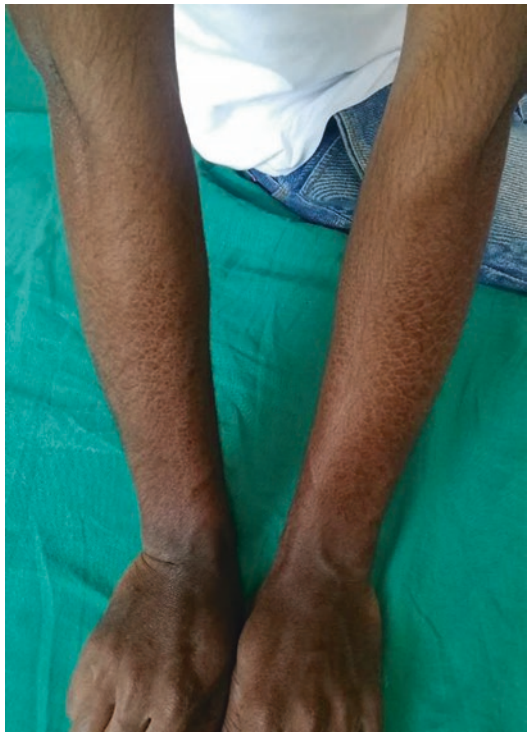


Fig. 7.2 Fine grey brown scales over the extensor aspect of the bilateral forearms (photographed by Dr. Priyanka Karagaiah)

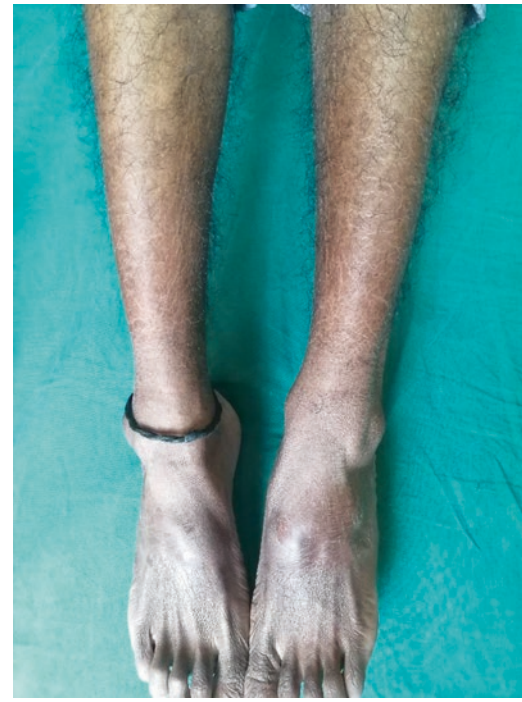


Fig. 7.3 Fine grey brown scales over the extensor aspect of the bilateral lower limbs (photographed by Dr. Priyanka Karagaiah)

7.2.1.2 Non-syndromic Recessive X-Linked Ichthyosis

X-linked ichthyosis (XLI) is caused by a mutation in STS gene encoding for steroid sulfatase enzyme, resulting in accumulation of cholesterol sulphate in the epithelium. It primarily affects males, with females being the carriers of the disease.

Clinical Features

Children may present with fine scaling immediately after birth, which often resolves spontaneously. Usually, large thick polygonal yellow-brown to dark brown scales involving the trunk, the extremities and the neck develop by 2–6 months of age, giving the baby a 'dirty look'. Flexures, palms and soles are usually spared as in ichthyosis vulgaris. It is associated with extracutaneous manifestations like corneal opacities, cryptorchidism, attention-deficit hyperactivity syndrome (ADHD) and autism.

Analysing STS gene mutation by fluorescent in situ hybridization (FISH) or comparative microarray analysis (CMA) may aid rapid diagnosis.

Management

- Recessive X-linked ichthyosis patients benefit from moisturizers containing glycerol.
- Low-dose systemic retinoids may be beneficial during periods of disease exacerbations (Figs. 7.4, 7.5 and 7.6).

7.2.1.3 Autosomal Recessive Congenital Ichthyosis (ARCI)

The term ARCI is an umbrella term including all non-syndromic autosomal recessive forms of congenital ichthyosis with no tendency toward blistering (Fishcer 2009). Thus the spectrum includes:

(a) Harlequin ichthyosis (HI)
(b) Collodion baby and self-improving congenital ichthyosis (SICI)
(c) Lamellar ichthyosis (LI)
(d) Bullous congenital ichthyosiform erythroderma (BCIE)

(a) Harlequin Ichthyosis (HI)

Harlequin ichthyosis is the most serious type of ARCI with an estimated prevalence of one in two million. Nonsense and/or frameshift mutations in the ABCA12 gene resulting in abnormal lamellar body formation, along with the defective transport of proteases such as kallikrein 5, 7 and 14 lead to retention hyperkeratosis.

Clinical Features

The disease presents with large plates of armour-like scales on the truncal skin in neonates and is often associated with bilateral ectropion and eclabium causing difficulty in feeding and breath-

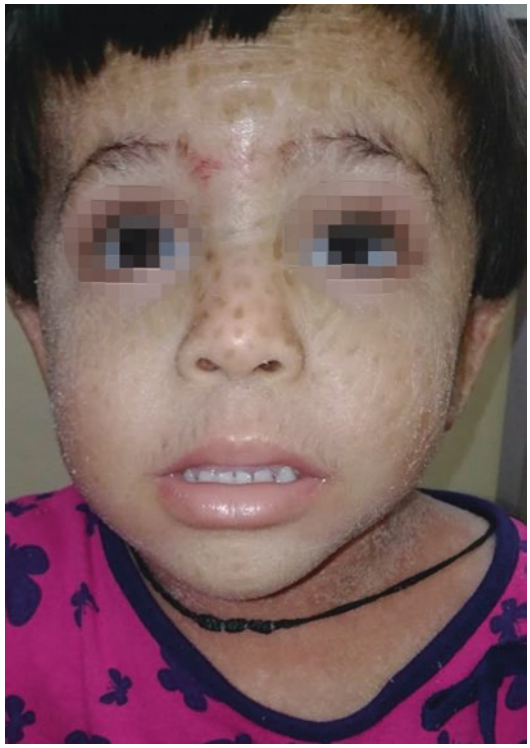


Fig. 7.4 X-linked recessive ichthyosis in a 3-year-old boy. Dirty yellowish brown polygonal scales over the face and neck (photographed by Dr. Priyanka Karagaiah)

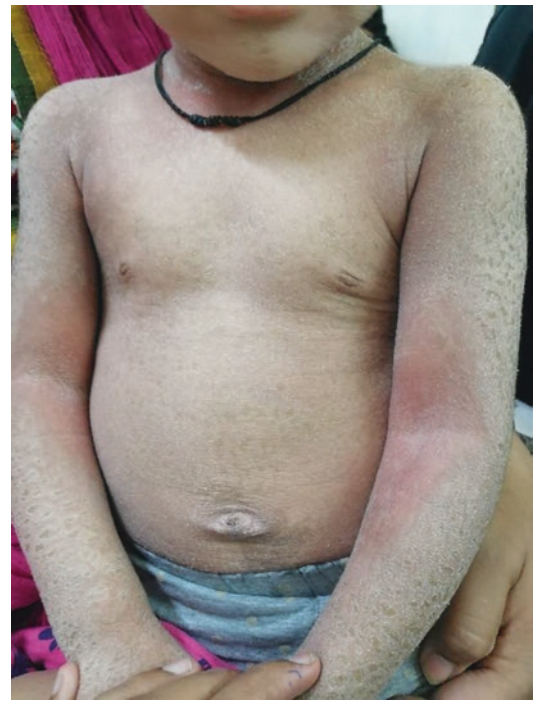


Fig. 7.5 Yellowish brown polygonal scales over the neck, trunk and extremities giving a dirty skin appearance (photographed by Dr. Priyanka Karagaiah)

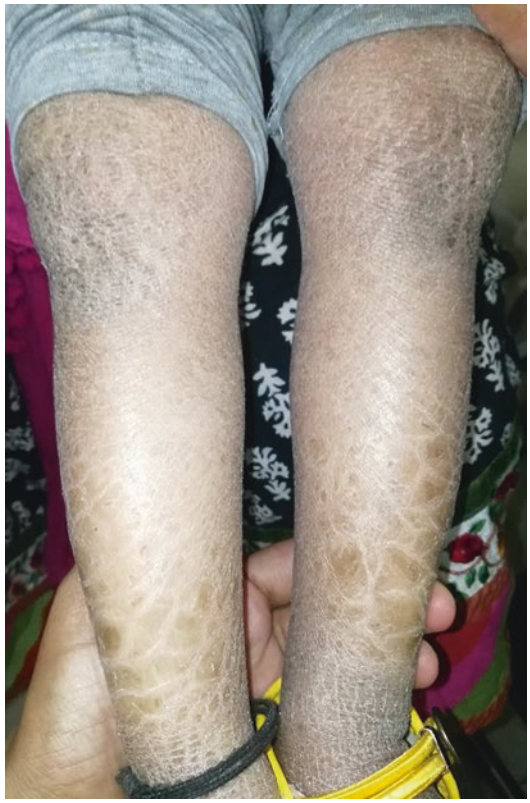


Fig. 7.6 Large yellowish brown polygonal scales over the bilateral lower extremities. Family history of similar lesions in maternal uncle (photographed by Dr. Priyanka Karagaiah)

ing. Hypothermia and risk of infection pose a grave problem in early infancy, and respiratory problems may even cause death. In children surviving the initial phase, some improvement with large lamellar scales and ichthyosiform erythroderma may be noticed. Persistent ectropion, failure to thrive and vitamin D deficiency can occur in later stages (Fig. 7.7).

(b) Collodion Baby and Self-Improving Congenital Ichthyosis

'Collodion baby' is a bracket term for a transient parchment-like appearance of neonates in a variety of inherited disorders including congenital ichthyosiform erythroderma, bathing suit ichthyosis, lamellar ichthyosis, Sjogren-Larsson syndrome, trichothiodystrophy (TTD), neutral lipid storage disease, chondrodysplasia punctata, loricrin keratoderma (LK), Gaucher disease, etc.

Clinical Features

The neonate is born encased in a shiny taut yellowish membrane with fissuring, associated ectropion and eclabium. Limb movements, sucking and pulmonary ventilation may be restricted due to taut membrane, resulting in dehydration, hypoxia, malnutrition and pneumonia. The membrane is shed in within 4 weeks of life, revealing

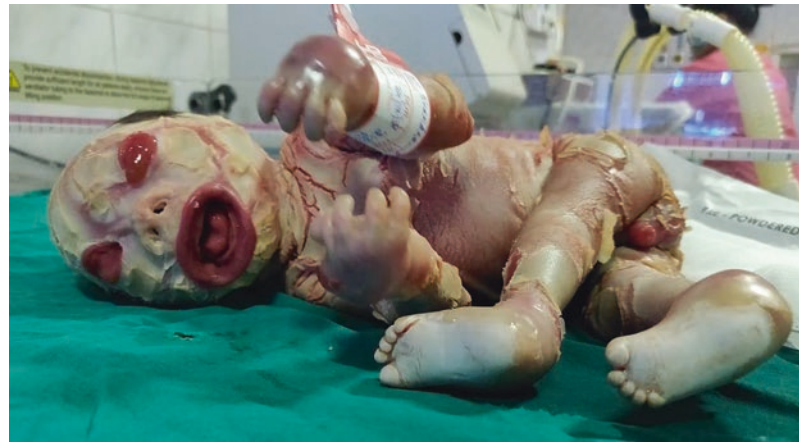


Fig. 7.7 Harlequin ichthyosis: Large armour-like scaly plaques in a neonate with notable ectropion, eclabium, flattened aural plates and nose and visible contractures of the fingers (photographed by Dr. Kavyashree Krishna, Bangalore Medical College and research centre, Bangalore, India)

the actual features of the inherent genetic disorders in 80% of the neonates. However, 10–20% of infants progress into self-healing collodion baby (SHCB).

Management of Collodion Baby

- Barrier nursing in a warm, humidified environment of an intensive care unit is the main stay of management in collodion babies.
- Bland emollient after cleansing with tepid water is applied to the thickened skin.
- Nasogastric feeding and fluid electrolyte balance have to be maintained.
- Ocular lubricants and release of contractures may be necessary to prevent complications.
- It is not advisable to manually remove the collodion membrane due to the increased risk of infections (Figs. 7.8 and 7.9).

(c) Lamellar Ichthyosis (LI)/Congenital Ichthyosiform Erythroderma (CIE)

Lamellar ichthyosis is a type of ARCI, most frequently caused by deficiency of transglutaminase 1 (TG1). Other genes involved in the pathogenesis of lamellar ichthyosis are ALOX12B, ALOXE3, NIPAL4 and CYP4F22 gene.

Fig. 7.8 Collodion baby. Yellowish taut parchment-like skin with fissuring and associated ectropion in a 7-day-old neonate (photographed by Dr. Kavyashree Krishna, Bangalore Medical College and research centre, Bangalore, India)

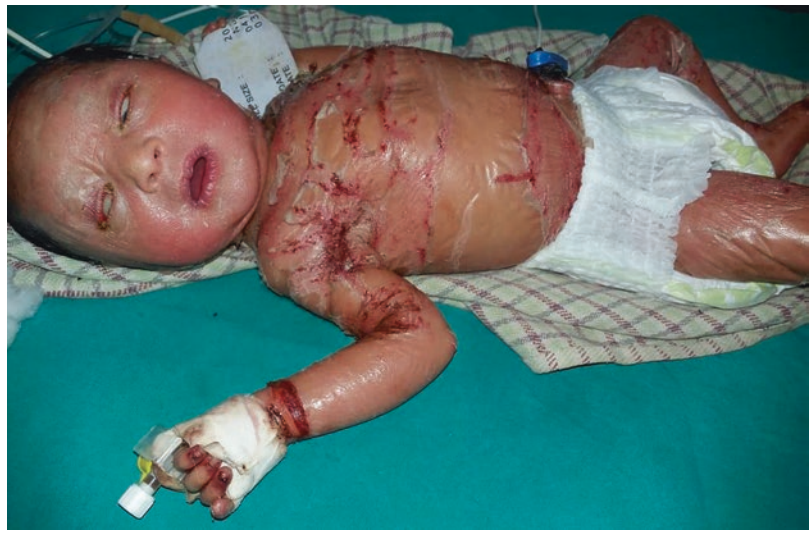


Fig. 7.9 Collodion baby. Gradual shedding of the taut shiny membrane in a 45-day-old infant (photographed by Dr. Reshma Tejaswi, Kurnool Medical College and Govt General Hospital, Kurnool, India)

Clinical Features

Lamellar ichthyosis is characterized by large brown hyperkeratotic plate-like scales with fissuring, covering the entire body and associated with mild palmoplantar hyperkeratoses. At the other end spectrum, ARCI presenting with fine whitish grey scales with marked erythroderma and palmoplantar keratosis has been referred to as congenital ichthyosiform erythroderma (CIE). Initial presentation at birth may be of mild collodion baby, which later improves to reveal the characteristic disease phenotype. LI/CIE may be associated with ectropion, marked palmoplantar hyperlinearity, pruritus and hypohidrosis.

Management

- Mechanical removal of detached scales with application of emollients should be advised.
- Topical keratolytics like 2–3% salicylic acid or 10% urea can be used but limited due to potential for irritation and systemic absorption.
- Topical tazarotene and calcipotriol have been reported to be effective in children (Figs. 7.10, 7.11 and 7.12).

(d) Epidermolytic Ichthyosis/Bullous Congenital Ichthyosiform Erythroderma (BCIE)

BCIE is an autosomal dominant disease characterized by mutation in KRT1 or KRT10 gene.

Clinical Features

At birth, the neonate usually presents with CIE associated with pronounced blistering, classically referred to as 'enfant brûlé/burned child'. Blistering often resolves in the first few months and later develops hyperkeratosis (Fig. 7.13). However, bouts of blistering can be caused by exposure to mechanical friction and high ambient temperature. Older patients usually present with rippled keratotic ridges on the knees, axilla and antecubital flexures. Palms and soles show marked keratoderma. However, KRT10 mutations show sparing of the palms and soles.

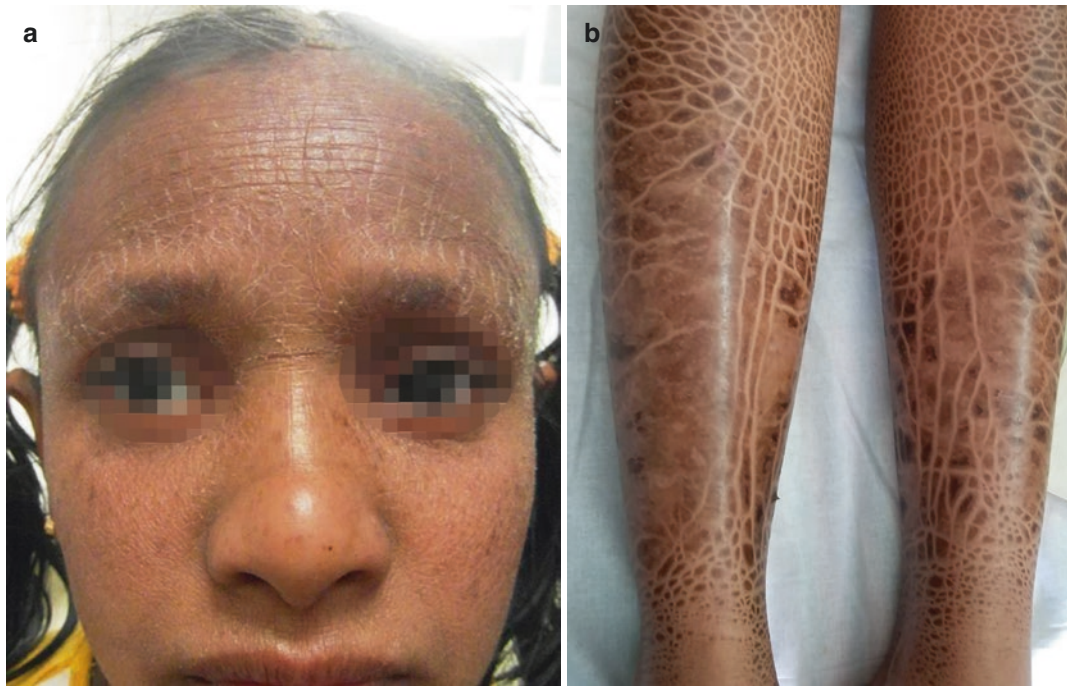


Fig. 7.10 (**a**, **b**) Lamellar ichthyosis in a 12-year-old girl. Large brown hyperkeratotic plate-like scales present over the face and bilateral lower limbs (photographed by Dr. Nayani Madarasinghe, Consultant Dermatologist, Teaching Hospital Anuradhapura, Sri Lanka)

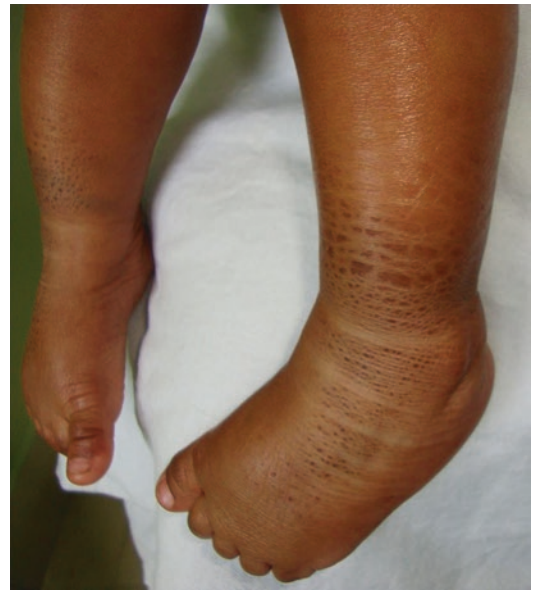


Fig. 7.11 Lamellar ichthyosis in a 15-month-old baby. Thick brown hyperkeratotic scales over the lower limbs (photographed by Dr. Ranthilaka R. Ranawaka)

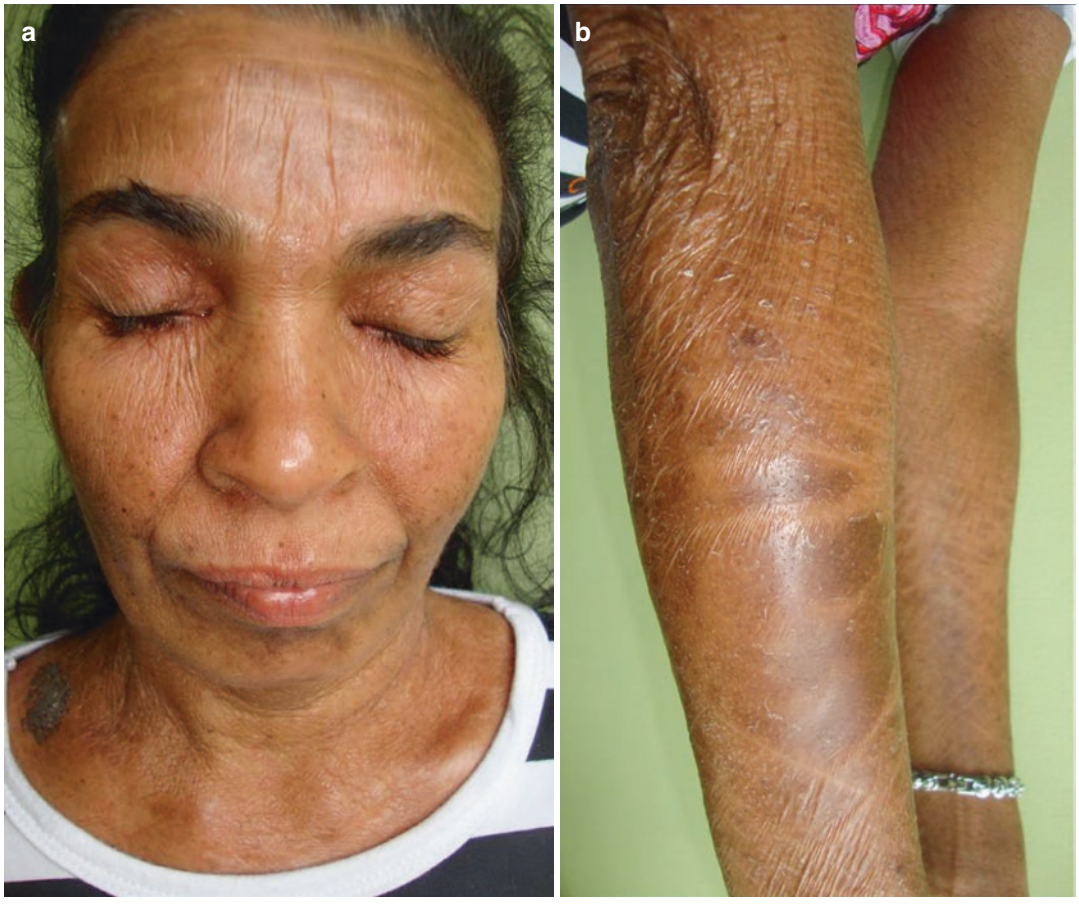


Fig. 7.12 (**a**, **b**) Lamellar ichthyosis in a 42-year-old woman. Large brown polygonal scales over the face and extensor aspect of bilateral forearms (photographed by Dr. Ranthilaka R. Ranawaka)

Histopathology shows marked hyperkeratosis and acanthosis of the epidermis, suprabasal splits along with multiple perinuclear vacuoles, and large aggregates of keratohyalin granules in the granular and spinous layer. These histopathologic changes are collectively termed as 'epidermolytic hyperkeratosis'.

Management

Treatment is similar to that of lamellar ichthyosis.

Other ichthyosis syndromes with epidermolysis on histopathological examination include:

- Superficial epidermolytic ichthyosis/ichthyosis bullosa of Siemens
- Annular epidermolytic ichthyosis
- Congenital reticular ichthyosiform erythroderma
- Ichthyosis Hystrix Curth–Macklin

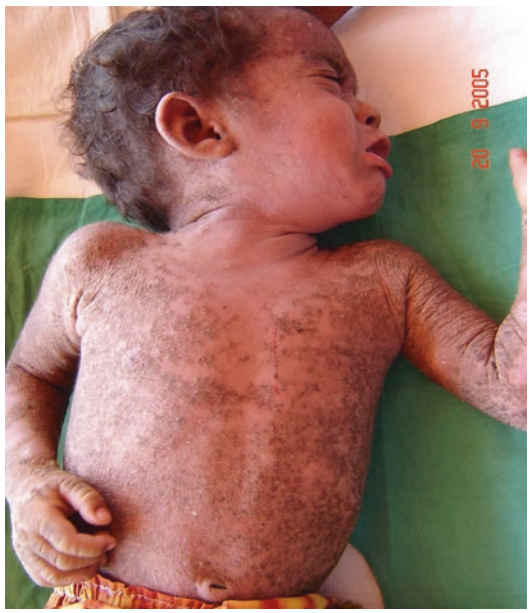


Fig. 7.13 Bullous ichthyosiform erythroderma in an 18-month-old baby. Greyish brown hyperkeratotic rippled ridges and plaques present on the trunk, flexors of the bilateral upper limbs, face and neck (photographed by Dr. Ranthilaka R. Ranawaka)

7.2.1.4 Ichthyosis Hystrix Curth–Macklin

Ichthyosis hystrix clinically differs from EI by having characteristic spiny hyperkeratosis ('hystrix'-like) covering the entire body and is caused by mutations in KRT1. Palms and soles are characteristically involved. Ridged hyperkeratosis or cobblestone-like pattern can be seen on large joints and in the skin.

Histologically it can be differentiated from EI by the presence of perinuclear vacuolization and binucleated cells, without keratin aggregates (Fig. 7.14).

7.2.1.5 Erythrokeratodermas

Localized ichthyotic conditions along with associated erythema and hyperkeratosis were termed as erythrokeratoderma or erythrokeratodermia (Rogers M 2005).

(a) Erythrokeratoderma Variabilis

Erythrokeratoderma variabilis (EKV) is a rare autosomal dominant disease characterized by

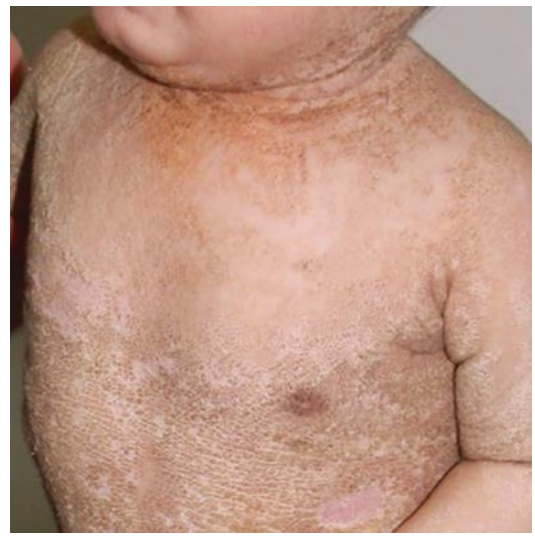


Fig. 7.14 Ichthyosis hystrix in a 3-month-old baby with nipple hyperkeratosis. Spiny hyperkeratotic coalescing ridges and scales resembling a porcupine present over the trunk and neck (picture courtesy: Katerina Damevska MSc, PhD. Clinic of Dermatology, Medical Faculty, University 'Ss Cyril and Methodius' Skopje, Republic of Macedonia)

migratory polycyclic erythematous hyperkeratotic patches/plaques. It is caused by mutations GJB3 or GJB4 encoding connexin 31 and 30, respectively.

Clinical Features

Disease usually manifests in infancy and usually presents with two types of lesions: One, a relatively well-demarcated fixed erythematous keratotic plaques on the extensors of the extremities, lateral trunk and buttocks and transient polycyclic erythematous macular lesions occurring at any site.

Management

Oral acitretin is the treatment of choice (Fig. 7.15).

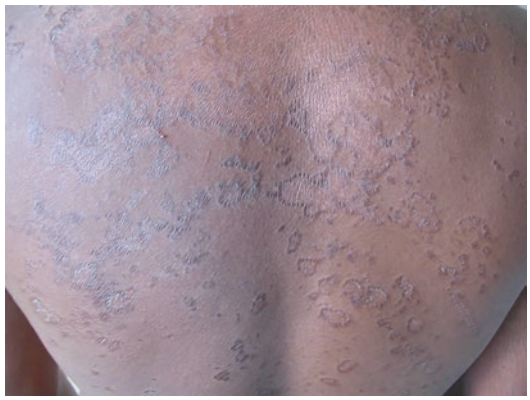


Fig. 7.15 Erythrokeratoderma variabilis in a 22-year-old male. Polycyclic migratory erythematous hyperkeratotic patches/plaques, with advancing border and central clearing on the back (photographed by Dr. Ranthilaka R. Ranawaka)

(b) Progressive Symmetrical Erythrokeratoderma

Progressive symmetrical erythrokeratoderma (PSEK) is a rare clinical variant of erythrokeratoderma characterized by large symmetrical erythematous fine scaly plaques appearing in infancy and is non-migratory in nature. It mostly affects the knees, elbows, shins, cheeks and buttocks. Keratoderma may be seen occasionally (Fig. 7.16a, b).

7.2.2 Syndromic Ichthyoses

See Table 7.2.

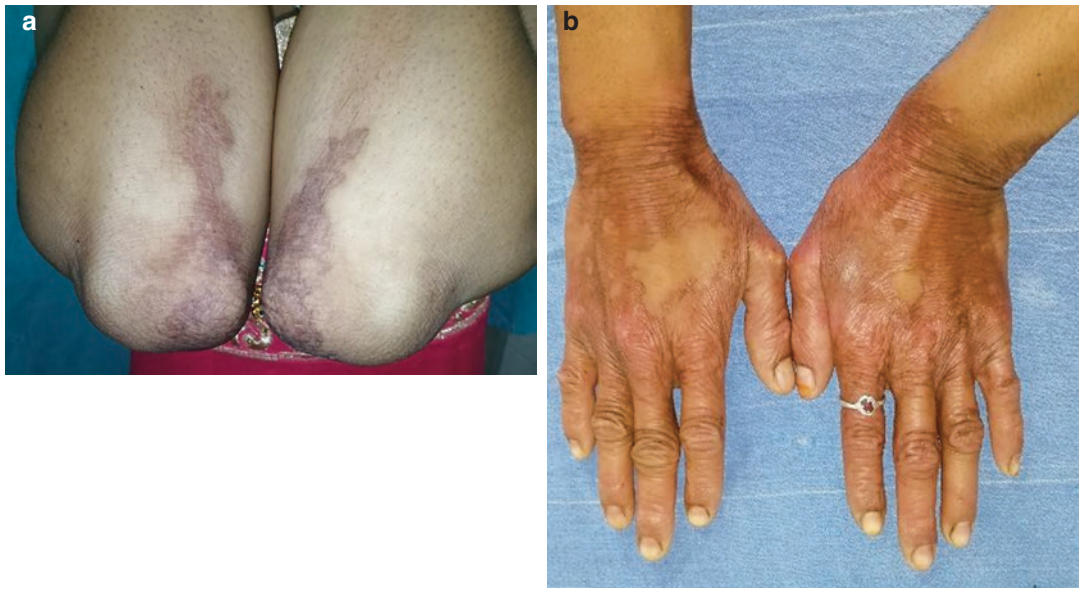


Fig. 7.16 (**a**, **b**) Erythrokeratoderma variabilis et progressiva in a 22-year-old woman. Fixed erythematous non-migratory symmetrical plaques with fine scaling present over the extensors of the elbow and dorsum of the hand (photographed by Dr. Priyanka Karagaiah)

Table 7.2 Classification of syndromic ichthyosis

X-linked ichthyosis syndromes	Autosomal ichthyosis syndromes with prominent hair abnormalities	Autosomal ichthyosis syndromes with prominent neurological signs	Autosomal ichthyosis syndromes with deafness
Recessive X-linked ichthyosis (RXLI)	Netherton syndrome (NS)	Refsum syndrome	Keratitis–ichthyosis–deafness (KID)
Ichthyosis follicularis alopecia photophobia (IFAP)	Severe dermatitis, multiple allergies, metabolic wasting (SAM)	Gaucher syndrome type 2	Mental retardation, enteropathy, deafness, neuropathy, ichthyosis, keratodermia (MEDNIK)
Conradi–Hünermann–Happle syndrome (CDPX2)	Ichthyosis with hypotrichosis	Sjögren-Larsson syndrome	ELOVL4 deficiency
	Neonatal ichthyosis–sclerosing cholangitis (NISCH)	Trichothiodystrophy (TTD)	
		Cerebral dysgenesis, neuropathy, ichthyosis, palmoplantar keratoderma (CEDNIK)	

7.2.2.1 Trichothiodystrophy (TTD)

Trichothiodystrophy is a group of rare heterogeneous neurocutaneous disorders with a common sulphur-deficient brittle hair defect. It is caused by mutations in the DNA repair/transcription factor IIH (TFIIH) in the photosensitive TTD group and mutations in the C7ORF11 gene in the non-photosensitive group.

Clinical Features

Photosensitive TTD is often associated with premature birth and collodion membrane or CIE-like presentation at birth. They may additionally present with elfin-like progeric face, eczema, palmoplantar hyperkeratosis, digital flexion contractures and hypoplastic aural cartilage. They may present with sparse, fragile, unruly shortened hair, with low cysteine content, in the scalp and eyebrows which often improves with age. Classical cases show 'tiger-tail appearance' on polarizing microscopy.

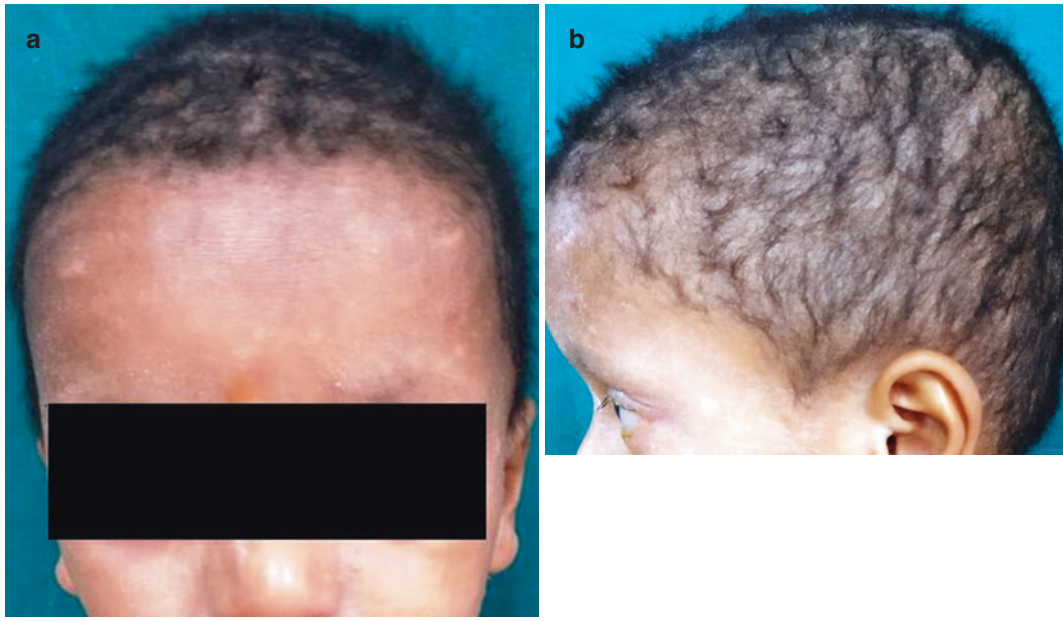
Management

- Emollients are essential for maintaining skin barrier.
- Strict sun protection with sunscreens and physical barriers are recommended for photosensitive TTD.
- Avoidance of physical hair treatment is necessary to reduce further damage (Figs. 7.17 and 7.18).

7.2.3 Acquired Ichthyosis

Acquired ichthyosis (AI) is rare form of ichthyosis associated with underlying disorders with disease onset at a later stage in life.

- Malignancies – Hodgkin's lymphoma, non-Hodgkin's lymphoma and mycosis fungoides
- Infections – Leprosy and AIDS
- Metabolic – Malnutrition, malabsorption, essential fatty acid deficiency and renal failure
- Endocrine disorders – Hypopituitarism, hypothyroidism and diabetes
- Connective tissue disorders – Systemic lupus erythematosus (SLE), dermatomyositis and eosinophilic fasciitis
- Drug induced – Cholesterol-lowering drugs, nicotinic acid, triparanol, clofazimine, hydroxyurea and allopurinol (Fig. 7.19)



7.17 (**a**, **b**) Diffuse sparseness of hair over scalp, eyebrows and eyelashes in a 6-year-old boy with TTD (photographed by Dr. Chandan, Paediatric dermatology fellow, Bangalore Medical College and research centre, Bangalore, India)

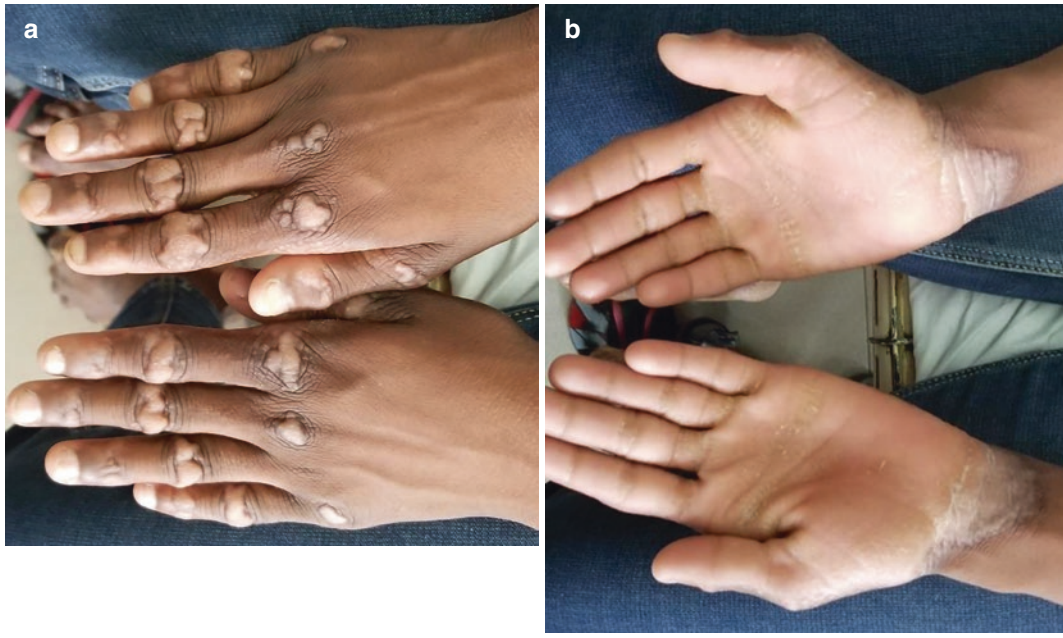


Fig. 7.18 (**a**, **b**) Keratoderma of the knuckles and palms extending up to the wrists in a 19-year-old man with TTD (photographed by Dr. Ranthilaka R. Ranawaka)

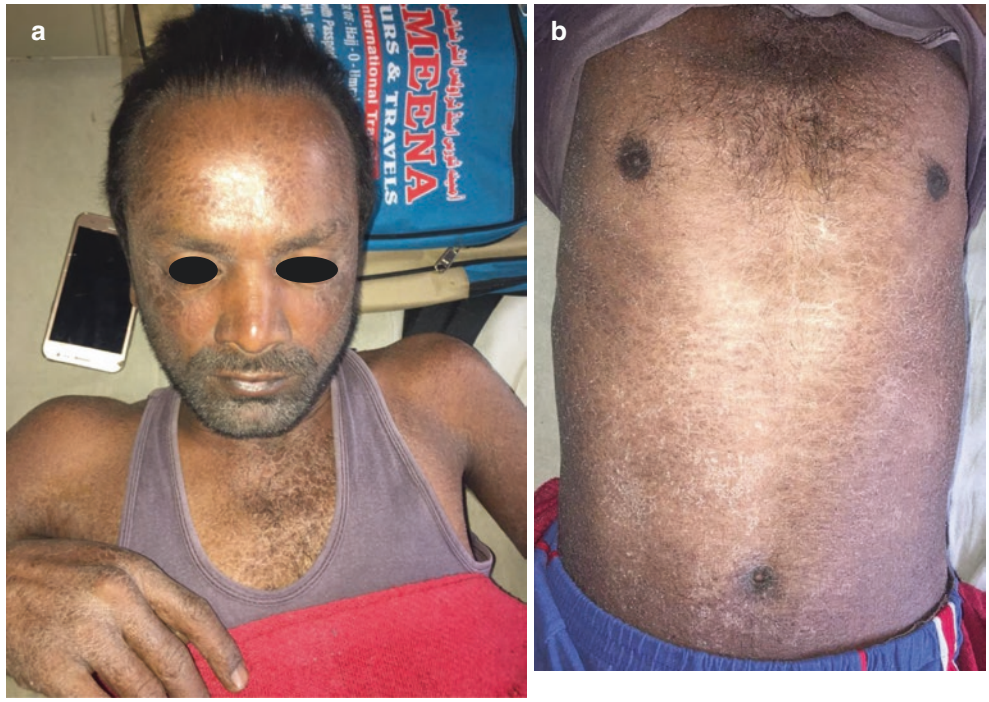


Fig. 7.19 (**a**, **b**) Acquired ichthyosis in a 42-year-old man with HIV. Diffuse brownish scales all over the body (photographed by Dr. Priyanka Karagaiah)

7.3 Palmoplantar Keratoderma

Palmoplantar keratodermas (PPK) form a heterogenous group of hereditary and acquired disorders of cornification characterized by excessive thickening of palms and soles.

Clinically, it can present as diffuse, focal, striate, punctate, papular, transgradient, confluent or cicatrizing keratodermas.

It can be syndromic or non-syndromic PPK.

7.3.1 Non-syndromic Keratoderma

7.3.1.1 Epidermolytic PPK/Unna-Thost Disease

It is an autosomal dominant disorder characterized by mutation in KRT 9 > KRT 1. Disruption of intermediate filament integrity reduces resilience of the cytoskeleton to minor trauma causing blistering, hyperkeratosis and also epidermolysis with tonofilament clumping.

Clinical Features

Clinically presents as diffuse keratoderma in infancy. In adult onset, there is confluent keratoderma sparing dorsal surfaces with sharp demarcation and erythematous edge. Hair, nail and mucosa are normal (Kuster and Becker 1992).

Limited transgradient lesions (e.g. at the dorsum of Achilles tendon) are termed – Greither keratoderma.

Histologically, it shows epidermolytic changes in suprabasal keratinocytes.

Management

- Mechanical debridement followed by lubrication with mild keratolytics.
- Oral retinoids/topical calcipotriol can also be tried (Figs. 7.20, 7.21 and 7.22).

7.3.1.2 Pachyonychia Congenita (PC)

PC is a group of autosomal dominant keratinization disorders caused by mutation in keratins 6A, 6B, 6C, 16 and 17.

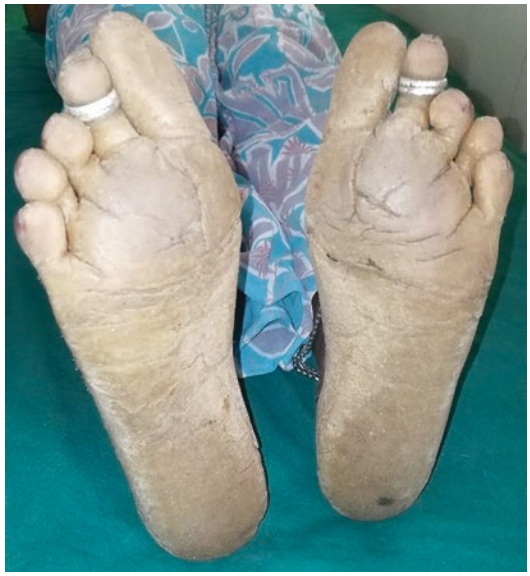


Fig. 7.20 Epidermolytic PPK in a 40-year-old woman. Hyperkeratosis of bilateral soles with fissuring (photographed by Dr. Priyanka Karagaiah)

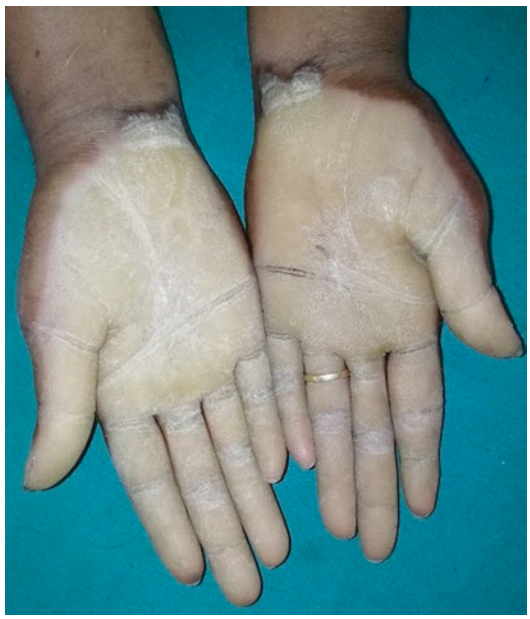


Fig. 7.21 Diffuse keratoderma with sharp demarcation at the borders (photographed by Dr. Priyanka Karagaiah)

Older classification:

PC Type 1 – Jadassohn-Lewandowsky – KRT 6A/16 mutation, associated with PPK and oral leukokeratosis

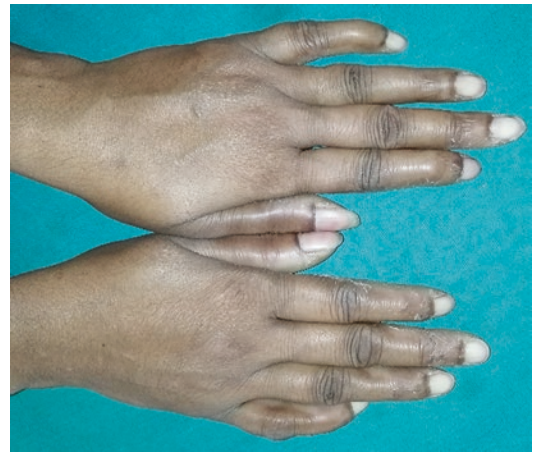


Fig. 7.22 Epidermolytic PPK with flexion deformity (photographed by Dr. Priyanka Karagaiah)

PC Type 2 – Jackson-Lawler – KRT 6B/17 mutation, associated with pilosebaceous cysts/steatocystomas and neonatal teeth

Because of significant overlap in genotype-phenotype features, current classification is based on the affected keratin: PC 6A, PC 6B, PC 6C, PC 16 and PC 17.

Clinically, three cardinal features: toenail dystrophy, plantar keratoderma and plantar pain.

Histologically, gross hyperkeratosis with ortho- and parakeratosis. Acanthosis with patchy hypergranulosis in which large and malformed keratohyalin granules are present.

Management

- Mechanical reduction of hyperkeratosis and of nails.
- Emollients and keratolytics help in milder disease. Botulinum toxin A may reduce hyperhidrosis
- Use of topical sirolimus or oral simvastatin is under investigation (Fig. 7.23).

7.3.1.3 Diffuse Non-epidermolytic Palmoplantar Keratoderma

It represents a heterogenous group of non-syndromic forms of PPK. It includes Bothnia, Kimonis, Nagashima and Mal de Melede (Table 7.3).

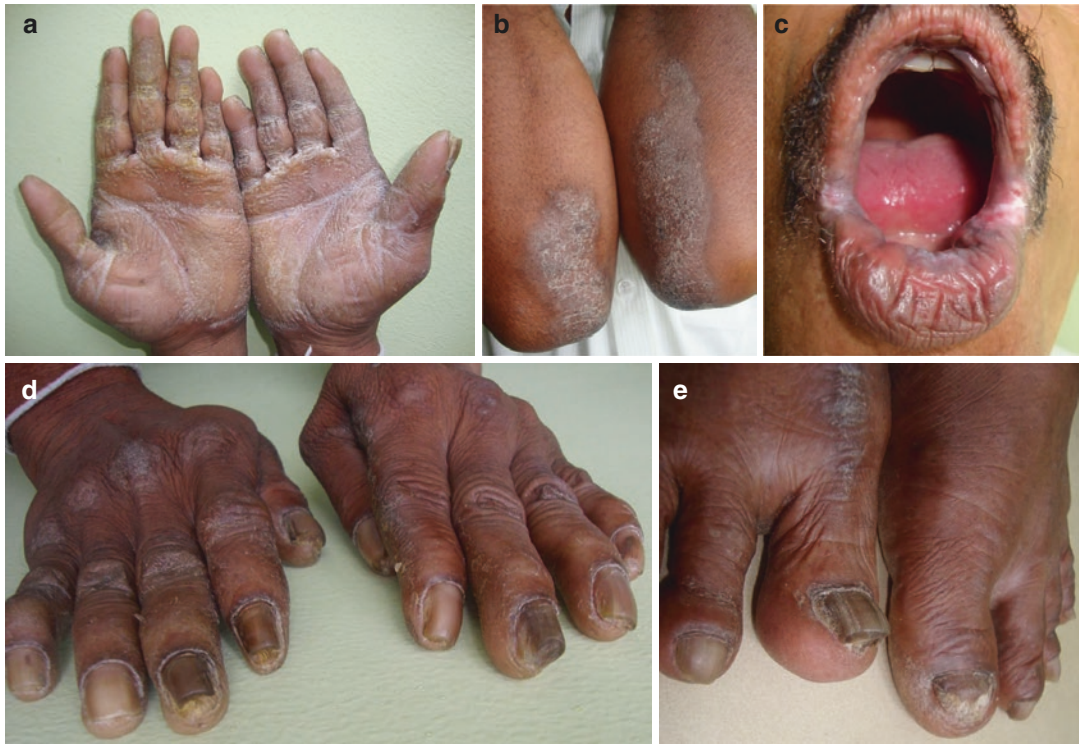


Fig. 7.23 (**a**, **b**, **c**, **d**, **e**) Pachyonychia congenita with palmoplantar keratoderma, nail dystrophy and oral leukokeratosis (photographed by Dr. Ranthilaka R. Ranawaka)

Table 7.3 ▮ Different types of non epidermolytic Palmoplantar Keratodermas

Disorder	Inheritance	Mutated gene	Protein products
Kimonis NEPPK	AD	KRT 1	Keratin 1 (V1 domain)
Bothnia NEPPK	AD	AQP 5	Aquaporin 5
Nagashima NEPPK	AR	SERPINB7	Serpin family B member 7
Mal de Meleda	AR	SLURP1	Secreted Ly6/PLAUR-domain containing 1

Clinically, manifests as thick skin with hyperhidrosis and frequent dermatophyte infections and pitted keratolysis.

Bothnia type features as white spongy appearance on exposure to water.

Mal de Meleda manifests as progressive transgredient hyperkeratosis and hyperhidrotic maceration. Hyperkeratosis of fingers may lead to sclerodactyly and digital constrictions (pseudoainhum).

Management

- Stronger keratolytics: 5–6% salicylic acid in 70% propylene glycol gel
- Low-dose acitretin (0.2–0.5 mg/kg daily): helpful in patients with functional impairment
- Oral erythromycin and topical tacrolimus may be helpful (Figs. 7.24 and 7.25)

7.3.1.4 Striate Palmoplantar Keratoderma (Sppk)

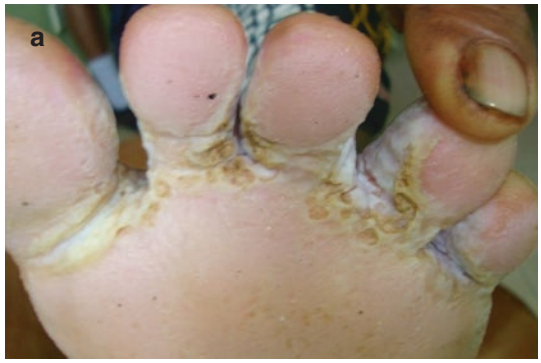
It is an autosomal dominant trait disorder with defects in at least three different genes:

SPPK1 – Desmoglein 1 gene mutation

SPPK2 – Desmoplakin gene mutation

SPPK3 – V1 domain of KRT 1 mutation

Clinically, characterized by striate hyperkeratosis on flexural site of fingers and palms, more



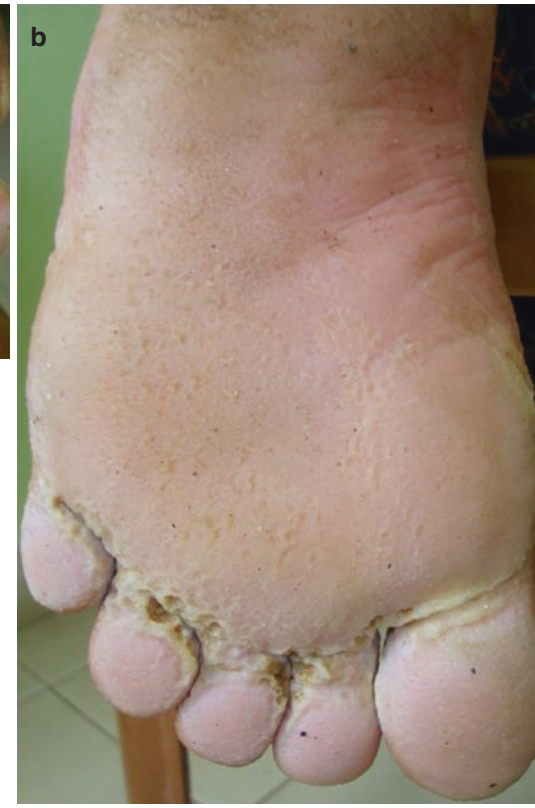


Fig. 7.24 (**a**, **b**) Non-epidermolytic palmoplantar keratoderma, thick skin with hyperhidrosis and frequent dermatophyte infections and pitted keratolysis. Note white spongy appearance on exposure to water in feet (photographed by Dr. Ranthilaka R. Ranawaka)

diffuse and focal changes on soles, triggered by manual work/mechanical stress.

SPPK2 can present with woolly hair.

Management Systemic acitretin treatment with topical urea creams are effective

7.3.1.5 Loricrin Keratoderma/Variant Vohwinkel Syndrome

It is caused by mutations in LOR gene encoding loricrin, a glycine-rich cornified protein envelope. Mutant loricrin is transported to the nucleus and is thought to interfere with regulation of cornification.

Generalized desquamation or features of collodion body may be evident at birth. Hyperkeratosis has a 'honeycomb' appearance with keratotic digital constrictions (pseudoainhum), knuckle pads and warty keratoses on extensor surfaces (Schmuth et al 2004).

Absence of deafness and presence of ichthyosis distinguish loricrin keratoderma from true Vohwinkel syndrome.

Histological features include hyperkeratosis, hypergranulosis and parakeratosis.

Electron microscopy shows dense intranuclear granules in granular cells and a thin cornified cell envelope with abnormal extracellular lamellae.

Immunoelectron microscopy reveals presence of loricrin in these nuclei.

Management Isotretinoin therapy has been tried with success. VEGF receptor 2 inhibitors are under trials (Figs. 7.26, 7.27, 7.28 and 7.29).

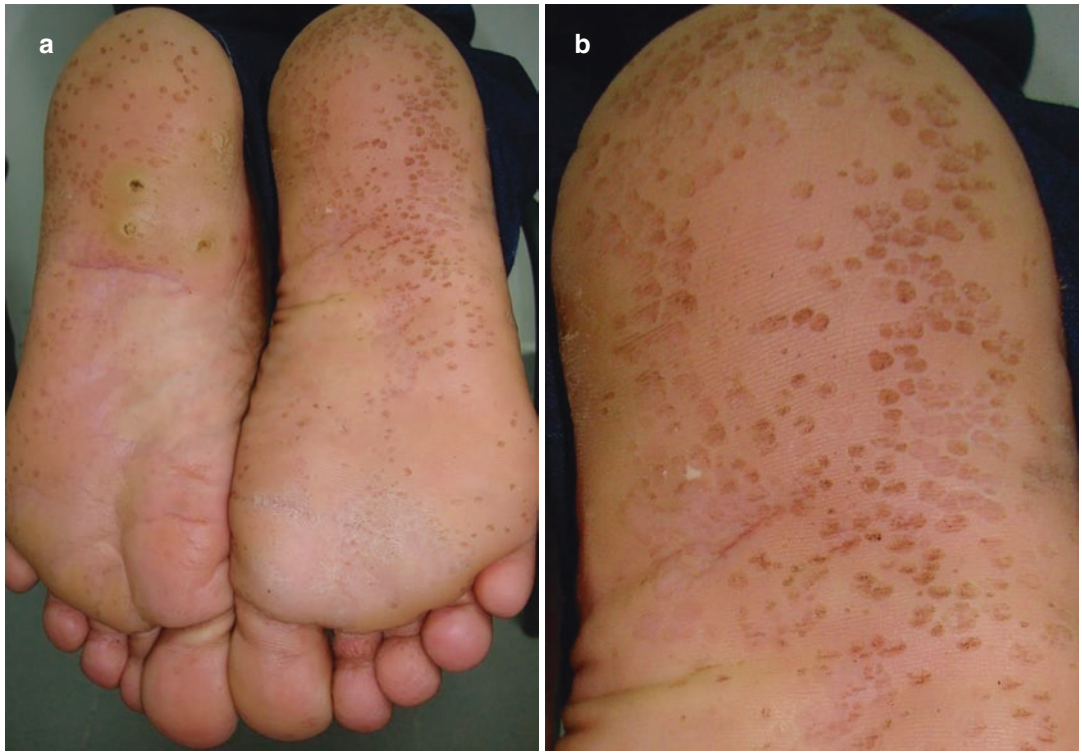


Fig. 7.25 (**a**, **b**) Non-Epidermolytic Palmoplantar keratoderma, thick skin with hyperhidrosis and pitted keratolysis (photographed by Dr. Ranthilaka R. Ranawaka)

Fig. 7.26 Loricrin keratoderma in a 20-year-old woman. Yellowish brown hyperkeratotic plaques over forehead and neck

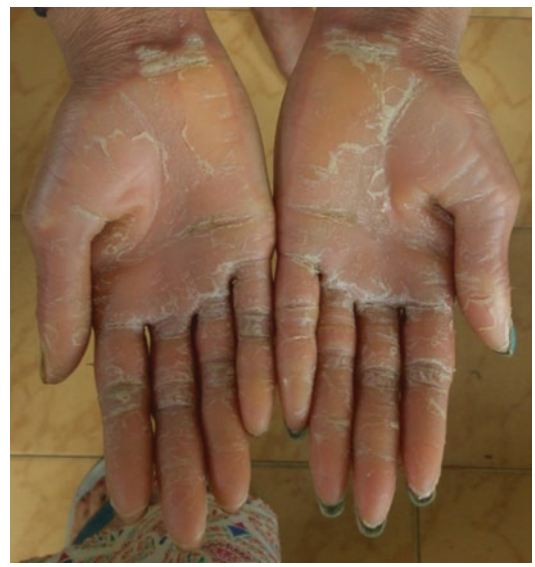


Fig. 7.27 Loricrin keratoderma, yellowish hyperkeratotic plaques over bilateral palms (photographed by Dr. Varsha C B, Bangalore Medical College and research centre, Bangalore, India)

7.3.2 Syndromic Keratoderma

Syndromic Keratodermas can be further classified based on the organ of involvement. See Table 7.4.

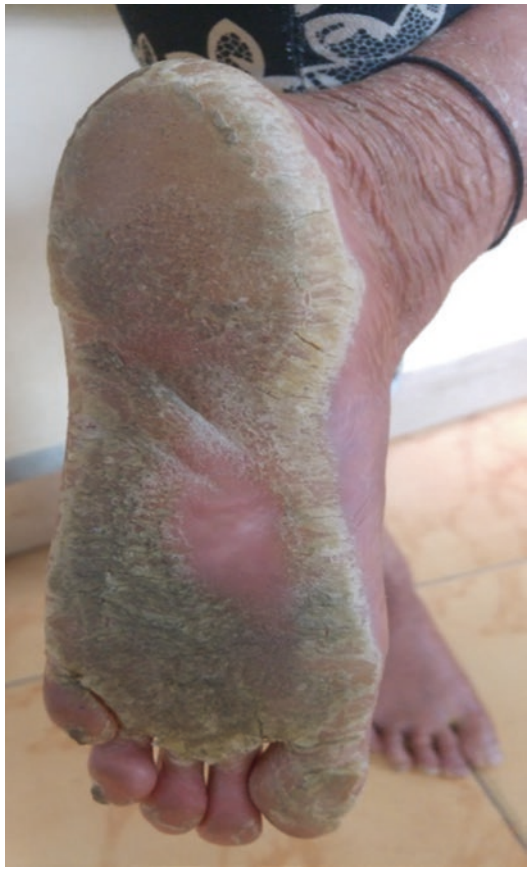


Fig. 7.28 Loricrin keratoderma, warty focal hyperkeratosis of soles resembling honey-combing pattern (photographed by Dr Varsha C B, Bangalore Medical College and research centre, Bangalore, India)

7.3.2.1 Papillon-Lefevre and Haim-Munk Syndrome

In Papillon-Lefevre syndrome, redness and thickening of palms and soles are associated with periodontitis and recurrent bacterial skin infections. Hyperkeratotic lesions can also affect elbows and knees, and pseudoainhum has also been described. Dural and choroid plexus calcification have also been described in this syndrome.

Haim-Munk syndrome is allelic with Papillon-Lefevre syndrome, with additional features of onychogryphosis, arachnodactyly and acro-osteolysis.

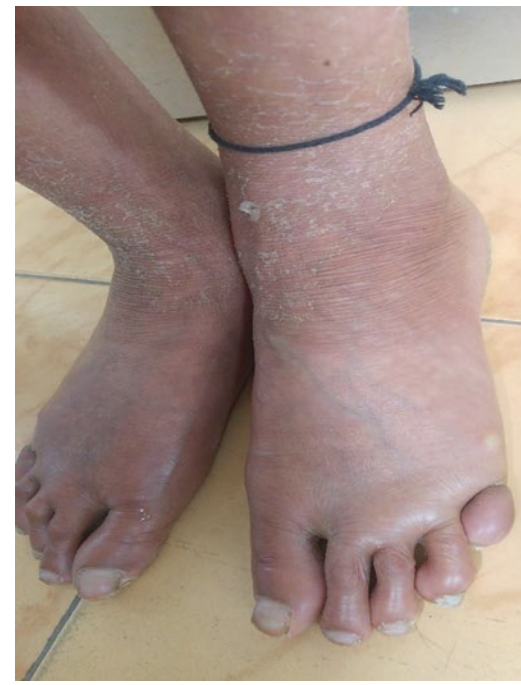


Fig. 7.29 Loricrin keratoderma, constriction band (pseudoainhum) over the last digit (photographed by Dr. Varsha C B, Bangalore Medical College and research centre, Bangalore, India)

Table 7.4 Classification of syndromic keratoderma

PPK and cardio myopathy	PPK and hearing impairment	PPK and cancer	PPK in ectodermal dysplasia	PPK and ophthalmic manifestations
Naxos syndrome	Vohwinkel syndrome	Huriez syndrome	Clouston syndrome	Oculocutaneous tyrosinemia
Carvajal-Huerta syndrome	Bart-Pumphrey syndrome	Tylosis oesophageal syndrome	Papillon-Lefevre syndrome	
	Keratitis-ichthyosis deafness (KID) syndrome		Haim-Munk syndrome	
			Olmsted syndrome	

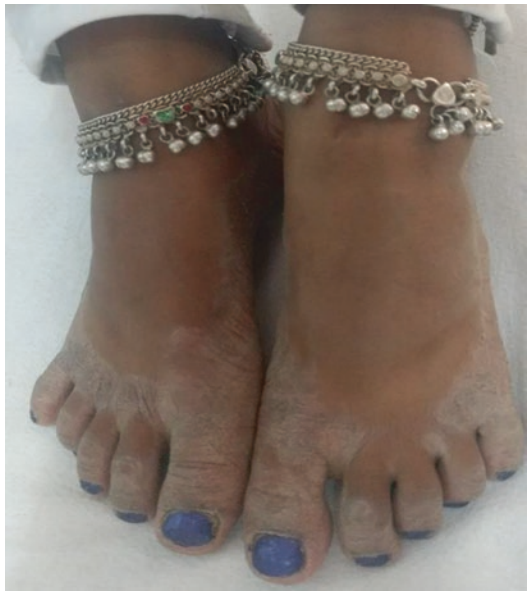


Fig. 7.30 Transgradient keratoderma extending over dorsum of bilateral foot (photographed by Dr Chandan, Bangalore Medical College and research centre, Bangalore, India)

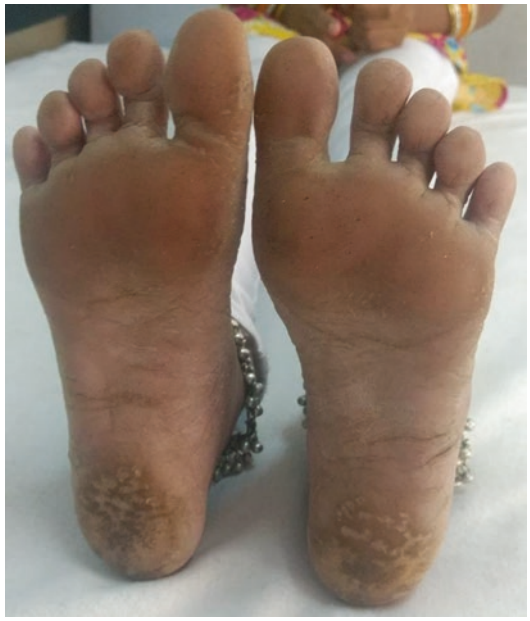


Fig. 7.31 Focal hyperkeratosis over bilateral soles (photographed by Dr. Chandan, Bangalore Medical College and research centre, Bangalore, India)

These conditions are caused by mutation in CTSC gene encoding for lysosomal protease cathepsin C. The main function of cathepsin C is

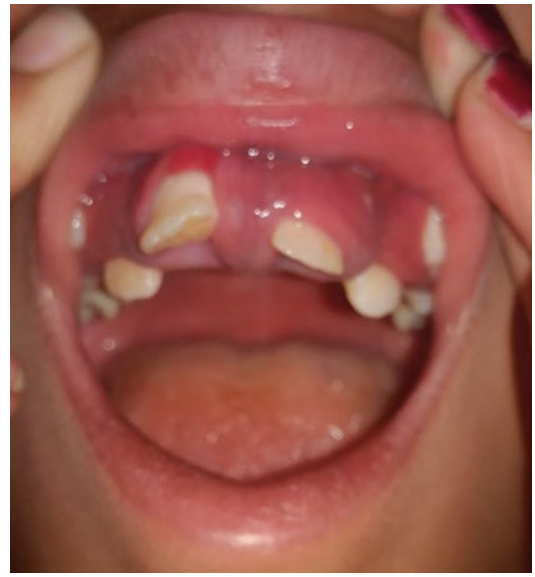


Fig. 7.32 Papillon-Lefevre syndrome showing loss of dentition (photographed by Dr. Chandan, Bangalore Medical College and research centre, Bangalore, India)

protein degradation and enzyme activation. Neutrophil phagocytosis and reactivity to T-cell and B-cell mitogens are impaired.

Severe gingivitis and periodontitis affect both deciduous and permanent dentition leading to total loss of teeth unless treated (Figs. 7.30, 7.31 and 7.32).

7.4 Porokeratosis

They refer to a heterogenous group of keratinization disorder, in which there is a presence of so-called cornoid lamella (column of parakeratotic keratinocytes) in the lesions.

Pathophysiology: It is known to be caused by mutation in the gene, MVK which encodes for mevalonate kinase, involved in the cholesterol biosynthesis. The enzyme also seemed to regulate keratinocyte differentiation.

The tumour suppressor gene p53 is known to be overexpressed in cornoid lamella.

An association of immunosuppression, possible infective aetiology by HPV types 66 and 14, has also been proposed.

Clinical variants are: (Sertznig et al 2012) 1. Disseminated Superficial Actinic Porokeratosis

2. Disseminated Superficial Porokeratoses of Immunosuppression 3. Disseminated Superficial Porokeratosis of Childhood 4. Porokeratosis of Mibelli 5. Linear Porokeratoses 6. Giant Porokeratoses 7. Porokeratoses Ptychotropica

7.4.1 Disseminated Superficial Actinic Porokeratosis

It is the most common presentation characterized by multiple lesions mostly over sun-exposed areas in middle-aged women.

The papules are surrounded by a finer keratotic ridge.

Photochemotherapy, radiotherapy is known to exacerbate the disease (Fig. 7.33).

7.4.2 Disseminated Superficial Porokeratoses of Immunosuppression

It has been reported in AIDS patients or after renal, hepatic, cardiac or bone marrow transplantation (Fig. 7.34).

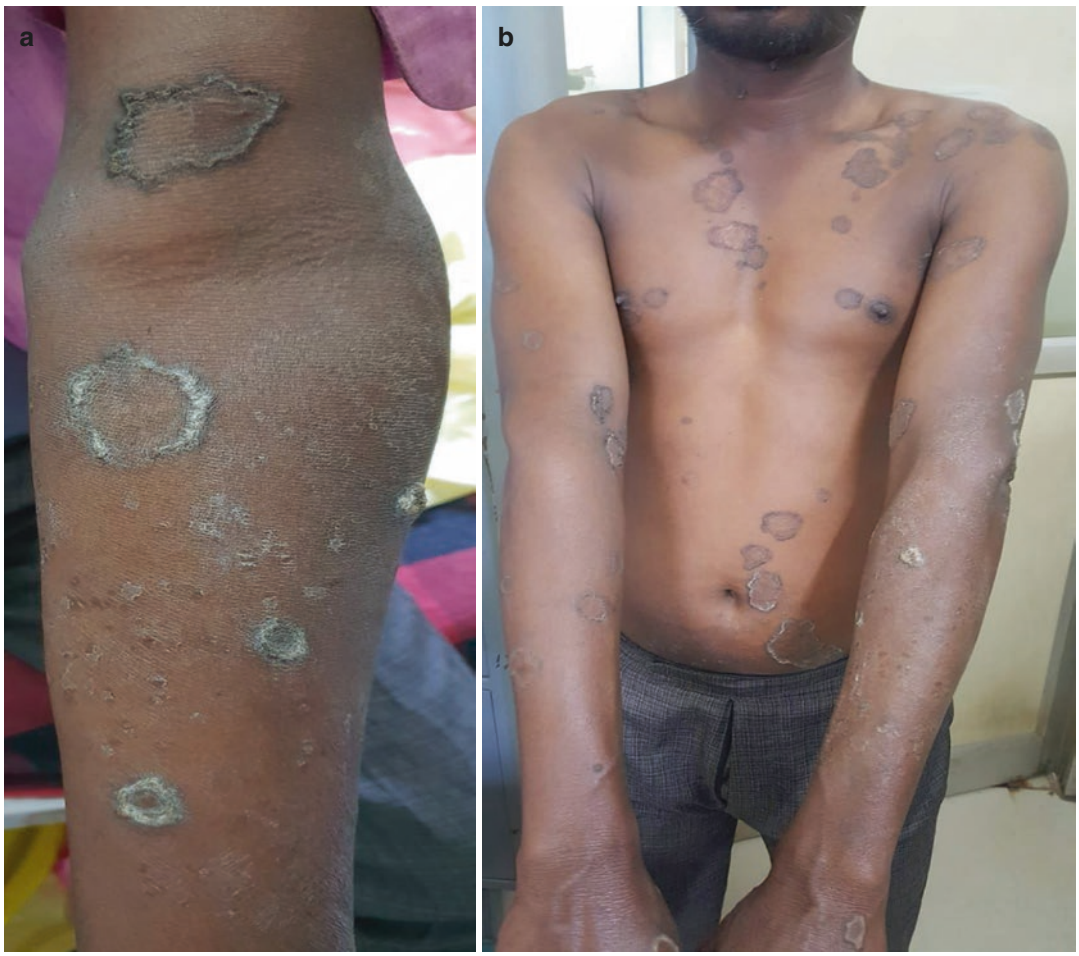


Fig. 7.33 (**a**, **b**) Disseminated porokeratosis in a 37-year-old man presenting as multiple well-defined annular plaques with hyperkeratotic borders (photograhed by Dr. Sowmya S Aithal, Bangalore Medical College and research centre, Bangalore, India)

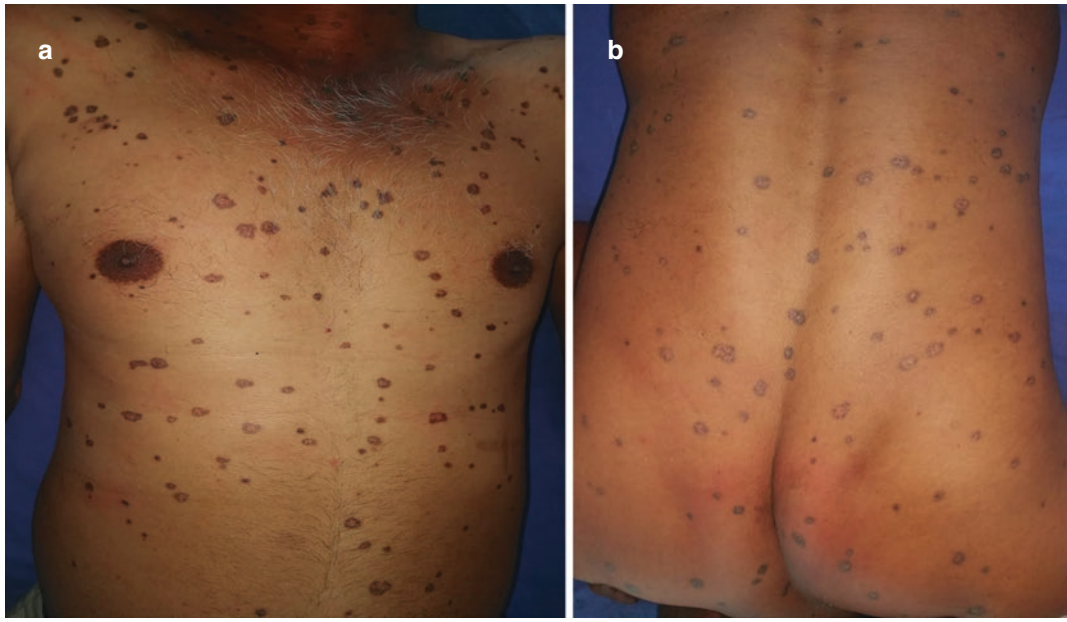


Fig. 7.34 Disseminated porokeratosis in a TB patient presenting as multiple well-defined hyperpigmented annular plaques (photograhed by Dr. Sowmya S Aithal, Bangalore Medical College and research centre, Bangalore, India)

7.4.3 Disseminated Superficial Porokeratosis of Childhood

It is mostly inherited as an autosomal dominant disorder. Widely disseminated flat lesions begin to appear at childhood. Maybe associated with diffuse palmoplantar lesions or other congenital abnormalities.

7.4.4 Porokeratosis of Mibelli

The term, 'Mibelli', has been referred only to single or scanty and larger lesions. They present as annular dry plaques surrounded by a raised fine keratotic elevated border with a central atrophic/hypertrophic groove. The face, scalp, nail and mucosae may be involved. It can either be inherited as an autosomal dominant fashion or can be sporadic with late-onset lesions (Fig. 7.35).

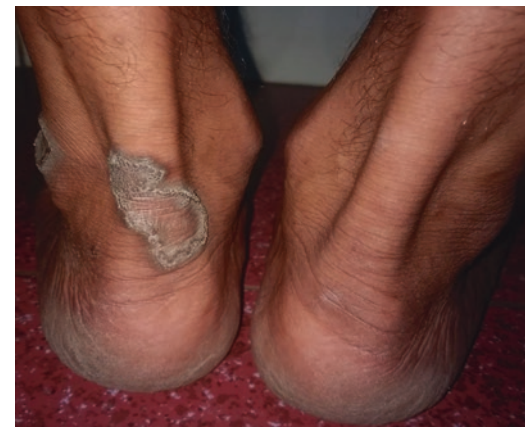


Fig. 7.35 Porokeratosis of Mibelli in a 25-year-old man presenting as a well-defined annular plaque with hyperkeratotic border (photograhed by Dr. Sowmya S Aithal, Bangalore Medical College and research centre, Bangalore, India)

7.4.5 Linear Porokeratoses

It exhibits typical cornoid lamellae along the lines of Blaschko. These lesions probably result from predisposition of an abnormal clone of epidermal precursors to porokeratosis. Malignant degeneration and metastasis have also been reported (Fig. 7.36).

7.4.6 Giant Porokeratoses

It measures up to 20 cm in diameter with a surrounding elevated edge of 1 cm.

Most commonly seen on the foot and has highest malignant transformation potential.

7.4.7 Porokeratoses Ptychotropica

This type is confined to body folds (ptyche = fold).

Brownish to reddish macules or plaques usually develop symmetrically over perianal region.

It can also manifest as verrucous lesions with expansile popular growth.

Histopathology: The characteristic findings are seen at the edge of the lesions. Stratum corneum is hyperkeratotic with a column of poorly staining parakeratotic cells – 'cornoid lamella'. The underlying keratinocytes are large and vacuolated, and some are dyskeratotic and pleomorphic. Absent granular layer. Dense lichenoid lymphocytic infiltrate may be present. Involvement of hair follicles, sweat pores are

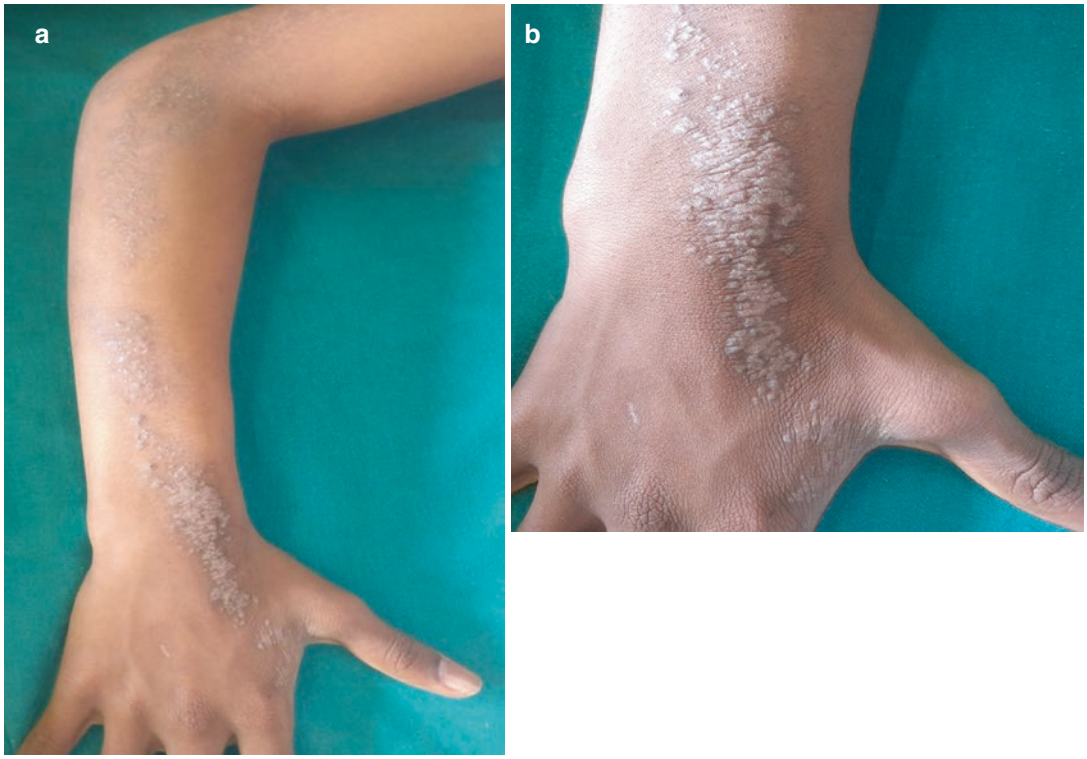


Fig. 7.36 (**a**, **b**) Linear porokeratosis in a 19-year-old man characterized by multiple papules and plaques arranged in linear fashion over extensor aspect of right forearm (photograhed by Dr. Sowmya S Aithal, Bangalore Medical College and research centre, Bangalore, India)

prominent. Papillary dermis is fibrotic and contains melanophages.

Treatment:

Photoprotection is recommended. Topical tacalcitol, topical retinoids, 5-flourouracil, imiquimod creams and oral etretinate may be effective. Cryotherapy, CO2 laser, pulsed dye laser and photodynamic therapy have variable results.

7.5 Perforating Keratotic Disorders

They are probably not true disorders of keratinization. They present as keratotic papules in the epidermis, probably secondary to a dermal disease.

Clinical features: It is characterized by follicular or non-follicular keratotic papules to nodules up to 1 cm in diameter mostly over limbs. Some have a central depression having an adherent necrotic plug. Most commonly associated with diabetes, patients on dialysis for renal failure, malignancy, infection or inflammatory conditions.

Histopathology: Broad or narrow ulcer craters with degenerate collagen, elastic tissue and keratin admixed with a clear material regarded as accumulation of a metabolite.

Management: Topical/intralesional steroids, NBUVB has shown effective results. Topical tretinoin may also reduce the lesions. Oral allopurinol/doxycycline is under trial.

Clinical variants: 1. Necrotizing Infundibular Crystalline Folliculitis 2. Elastosis Perforans Serpiginosa 3. Reactive Perforating Collagenosis

7.5.1 Necrotizing Infundibular Crystalline Folliculitis

It is characterized by transepidermal elimination of negatively birefringent needle-shaped crystals. It has been thought to occur due to initiation of crystal formation around microorganisms from follicular lipids at critical concentrations.

Clinically, multiple waxy papules develop at the forehead, neck and back.

Histology reveals necrosis of follicular epithelium with perifollicular neutrophilic infiltrate.

Crystalline deposits with yeasts and gram-positive bacteria can be found in the follicular ostia which are enclosed by parakeratotic columns.

7.5.2 Elastosis Perforans Serpiginosa

It presents as grouped arcuate or serpiginous keratotic papules and is associated with Down syndrome, connective tissue disorder or penicillamine therapy. Histologically, amorphous masses that bind elastic tissue stains are seen traversing the epidermis.

7.5.3 Reactive Perforating Collagenosis

It mainly affects children presenting as 2–5 mm papules on the extremities. Lesions in all stages of eruption and resolution are present simultaneously (Figs. 7.37, 7.38 and 7.39).

7.6 Confluent and Reticulated Papillomatosis

Confluent and reticulated papillomatosis (CARP) is an infrequent disorder of keratinization characterized by coalescent and reticulate hyperkeratotic papules and plaques presenting on the truncal skin. It is a disease of young adults and adolescents equally affecting both genders. An abnormal immune reaction to *Malassezia* and actinomycetes is believed to play a causative role.

Clinical Features

They present with multiple 1–2 mm wide hyperkeratotic papules, coalescing to form greyish plaques that are confluent at the centre and reticular at the periphery. The lesions initially begin on

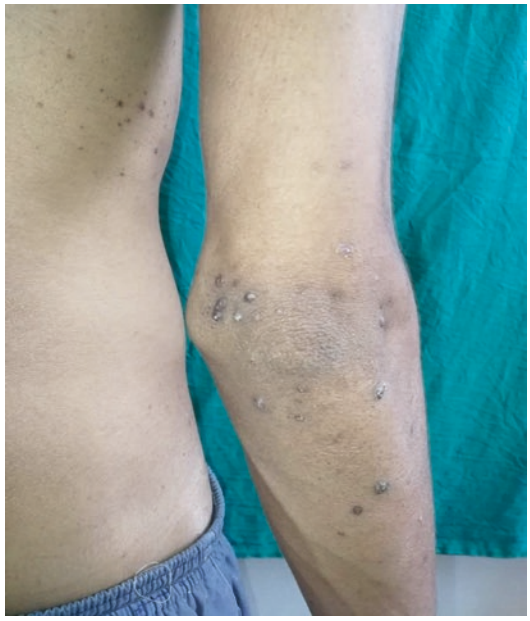


Fig. 7.37 Perforating collagenosis in a man with chronic kidney disease on dialysis (photographed by Dr. Priyanka Karagaiah)

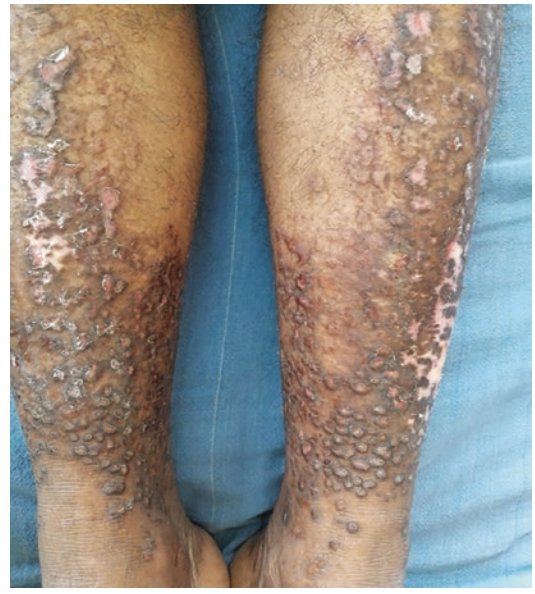


Fig. 7.39 Multiple hyperkeratotic confluent papules forming serpiginous plaques in a patient with chronic kidney disease and uncontrolled DM (photographed by Dr. Priyanka Karagaiah)

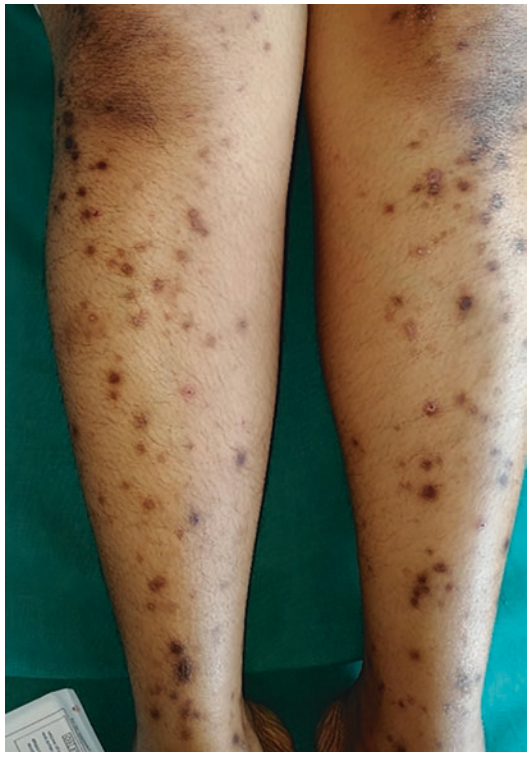


Fig. 7.38 Multiple papules with central keratotic core on the extremities of a diabetic patient (photographed by Dr. Priyanka Karagaiah)

the trunk and gradually progress to involve the lower abdomen and pubic areas, and mucous membranes are spared.

Management

- Oral minocycline or topical mupirocin ointment can be used.
- Topical and systemic antifungal agents like selenium sulphide shampoo have been used in some cases.
- Topical retinoids, vitamin D analogues and low-dose isotretinoin have been used (Fig. 7.40).

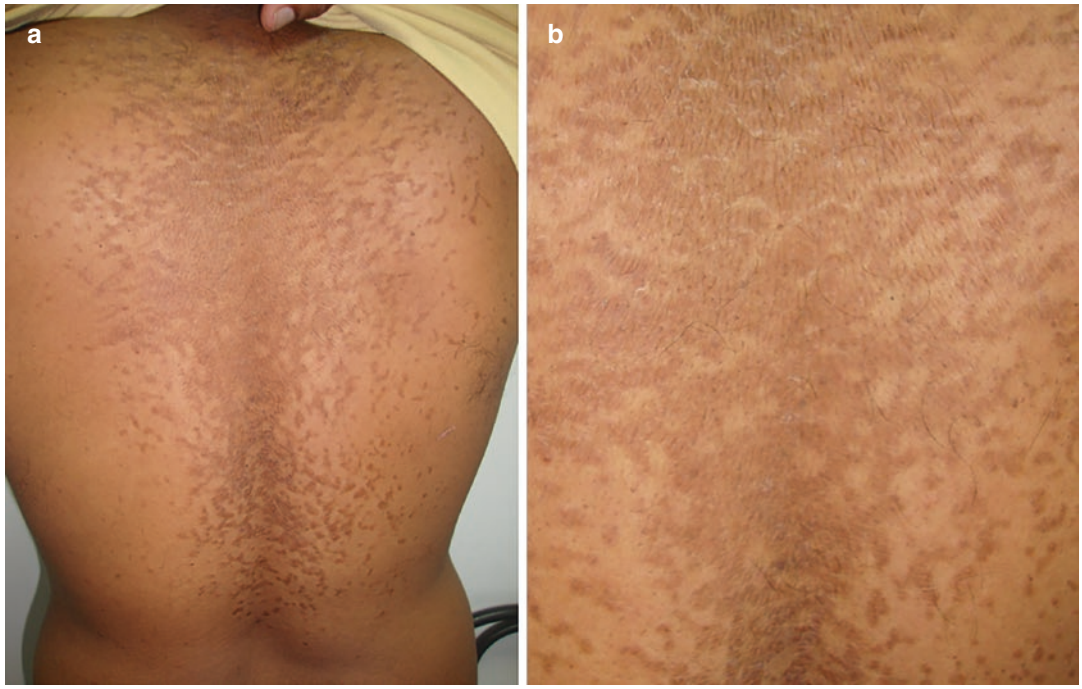


Fig. 7.40 Confluent reticulated papillomatosis (dirty skin appearance) in a 37-year-old man showing (**a**) the back of the trunk and (**b**) closer view (photographed by Dr. Ranthilaka R. Ranawaka)

References

Fischer J (2009) Autosomal recessive congenital ichthyosis. J Invest Dermatol 129:1319–1321

Kuster W, Becker A (1992) Indication for the identity of palmoplantar keratoderma type Unna–Thost with type Vörner. Acta Derm Venereol (Stockh) 72:120–122

Oji V, Tadini G, Akiyama M et al (2010) Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Sorèze 2009. J Am Acad Dermatol 63:607–641

Oji V, Metze D, Traupe H (2016) Inherited disorders of cornification. In: Griffith CEM, Barker J, Bleiker T, Chalmers R, Creamer D (eds) Rook's textbook of dermatology, vol 2, 9th edn. Blackwell Publishing, Oxford, p 65.1

Rogers M (2005) Erythrokeratodermas: a classification in a state of flux? Australas J Dermatol 46:127–141

Schmuth M, Fluhr JW, Crumrine DC et al (2004) Structural and functional consequences of loricrin mutations in human loricrin keratoderma (Vohwinkel syndrome with ichthyosis). J Invest Dermatol 122:909–922

Sertznig P, von Felbert V, Megahed M (2012) Porokeratosis: present concepts. J Eur Acad Dermatol Venereol 26:404–412