Chapter 15 Disorders of Abnormal Keratinization

The mechanisms of keratinization have been clarified in recent years. The genes responsible for many hereditary disorders of abnormal keratinization have been identified, but the pathogenesis of some disorders remain unknown. It is expected that these will be elucidated in the near future.
Disorders of abnormal keratinization are classified as hereditary keratoses (e.g., ichthyosis, Darier's disease) and acquired diseases. The acquired diseases are subclassified as inflammatory diseases, whose main symptom is inflammation accompanied by itching (e.g., psoriasis, lichen planus), and non-inflammatory keratoses (e.g., clavus, callus). This chapter discusses typical disorders of keratinization, based on that classification.

A. Hereditary keratoses

a. Ichthyosis ★★

Ichthyosis is the clinical condition in which the whole body skin dries and becomes coarse, resulting in scaling. It is caused by abnormality in keratinization and exfoliation of the horny cell layer. The skin is covered with what appear to be fish-like scales. Patients with ichthyosis have a congenital abnormality in keratinization and scaling, and most cases are classified as hereditary keratoses. However, some may appear later in life as acquired conditions; these cases often accompany malignant tumors. Ichthyosis is classified by clinical features, inheritance pattern, and affected sites into more than ten subtypes (**Table 15.1**). This section introduces typical types of ichthyosis.

1. Ichthyosis vulgaris ★★

Outline

- It is caused by mutation in the gene coding for filaggrin, a key protein involved in skin barrier function. This is the mildest form of ichthyosis. The main symptoms are dryness and scaling of the skin.
- The onset is early childhood. Dryness, and scaling of the skin are present, mostly on the extensor surfaces of extremities and trunk. It subsides during summer.
- It is the common inherited disorder of keratinization.
- Inheritance is semidominant.
- Symptomatic therapies including application of moisturizer are the main treatments.

Clinical features

The onset is early childhood. It is progressive until the patients reach about the age of 10, the symptoms subsiding in adolescence

Table 15.1 Classification of ichthyosis.

Congenital ichthyosis
Ichthyosis vulgaris
X-linked ichthyosis
Bullous congenital ichthyosiform erythroderma (BCIE)
Nonbullous congenital ichthyosiform erythroderma (NBCIE)
Lamellar ichthyosis
Harlequin ichthyosis
Ichthyosis accompanied by internal organ lesion (Ichthyosis syndrome)
Sjögren-Larsson syndrome
Netherton syndrome
KID syndrome
Dorfman-Chanarin syndrome
Refsum syndrome
Rud syndrome
Conradi syndrome
Acquired ichthyosis
Acquired ichthyosis

Fig. 15.1 Ichthyosis vulgaris.
The skin dries, and pityriasis-like lamellar exfoliation occurs.

in most cases. The skin dries, appearing pityroid and lamellar. The extensor surfaces of the legs and the back region are the most commonly affected; the flexure of joints in the extremities, axillary fossae genitals and thoraco-abdominal region are unaffected (**Fig. 15.1**). Subjective symptoms and itching are rarely observed. The symptoms subside during the summer and aggravate during the winter, when the skin tends to dry. Filaggrin mutation is a major predisposing factor for atopic dermatitis, and atopic disorders are strongly associated with ichthyosis vulgaris.

Pathogenesis

The causative gene has recently been identified as the filaggrin gene (FLG). As a result of a decrease in the production of filaggrin, which moisturizes the epidermis, there is abnormal exfoliation of horny cells and dryness and scaling of the skin (Chapter 1). Ichthyosis vulgaris is semidominantly inherited (homozygous patients have more severe symptoms than heterozygous patients) and often runs in families.

Pathology

There is thickening of the horny cell layer and reduction or loss of keratohyaline granules and granular cell layer because of loss or reduction of filaggrins.

Laboratory findings, Diagnosis

Ichthyosis vulgaris is diagnosed by the clinical and pathological features, family history and filaggrin gene mutation.

Differential diagnosis

In other hereditary ichthyoses, the onset is the time of birth, and the flexures of the joints in the extremities are often involved (**Table 15.2**). Acquired ichthyosis can be differentiated from ichthyosis vulgaris by the age of onset, the clinical course, and the presence of malignant tumor in the case of the former.

Table 15.2 Comparison between types of ichthyosis.

		Ichthyosis vulgaris	X-linked ichthyosis	Bullous congenital ichthyosiform erythroderma (BCIE)	Nonbullous congenital ichthyosiform erythroderma (NBCIE), lamellar ichthyosis	Harlequin ichthyosis
Frequency		Common	Uncommon	Rare	Rare	Very rare
Inheritance pattern		SD (semidominant)	XR	AD	AR	AR
Age of onset		Babyhood, infancy	At birth or early after birth	At birth or early after birth	At birth	At birth
Skin symptom	Site	Extremities, trunk (back > abdomen), intertriginous sites, extensor surface > flexor surface	Abdomen > back, intertriginous sites, extensor surface = flexor surface	Whole body	Whole body	Whole body
	Form	Fine scales	Large, dark brown scales	Severe hyperkeratosis	Flushing, fine or dark brown (NBCIE) large scales (lamellar ichthyosis)	Markedly thick hyperkeratosis, deep fissures, ectropion
Pathology		Hyperkeratosis, thinned granular cell layer	Hyperkeratosis, almost normal granular cell layer	Degeneration of granular cell layer	Hyperkeratosis (with or without parakeratosis)	Severe hyperkeratosis
Causative gene		Filaggrin (FLG)	Steroid sulfatase	Keratin 1 or keratin 10	Transglutaminase 1 in some cases	ABCA12

(AD: autosomal dominantly inherited, AR: autosomal recessively inherited, XR: x-linked recessively inherited, SD: semidominantly inherited).

Treatment, Prognosis

Treatments are symptomatic. Moisturizer, urea ointments, salicylic acid petrolatum, and vitamin D_3 ointments are applied. The symptoms subside after adolescence.

2. X-linked ichthyosis

Outline

- It is caused by loss or marked reduction of steroid sulfatase, resulting in delayed exfoliation of the horny cell layer. It is X-linked recessively inherited.
- The symptoms are severer than those of ichthyosis vulgaris. Eruptions also appear on the flexures of joints.

Clinical features

X-linked ichthyosis manifests shortly after birth and does not improve with age. The cutaneous symptoms are severe; the scales are large and dark brown (**Fig. 15.2**). The whole body of newborns may be encased in a translucent covering (collodion baby). Not only the extensor surfaces but also the flexures of extremities are affected. The abdomen is most severely affected. Corneal opacification may occur as a complication. As with ichthyosis vulgaris, X-linked ichthyosis aggravates during the winter and subsides during the summer.

Pathogenesis

It is caused by mutation in the steroid sulfatase gene on X-chromosome. Steroid sulfatase is the enzyme that breaks down cholesterol sulfate, a substance which promotes intercellular adhesion in the horny cell layer. The lack of steroid sulfatase causes accumulation of cholesterol sulfate, leading to delayed exfoliation of horny cells and hyperkeratosis (Chapter 1). X-linked ichthyosis is recessively inherited and occurs in males.

Pathology, Laboratory findings

Thickening of the horny cell layer, and normal or mildly thickened granular and suprabasal cell layers are present. Follicular keratinization is rarely found. Absence or marked reduction of steroid sulfatase is observed in the horny cell layer, peripheral leukocytes, and fibroblasts. Estriol in the urine decreases in the mothers (carriers) of children with X-linked ichthyosis.

Differential diagnosis, Treatment

Ichthyosis vulgaris is differentiated from X-linked ichthyosis by the decrease of steroid sulfatase in the case of the latter. The treatments are symptomatic and the same as those for ichthyosis vulgaris.

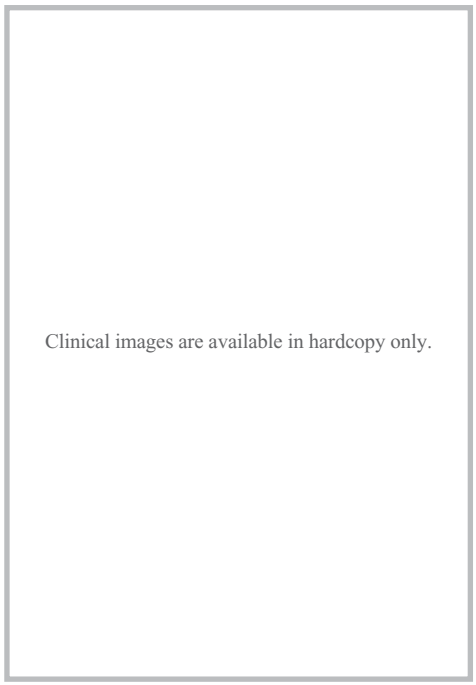

Fig. 15.2 X-linked ichthyosis.
Relatively large scales are present. The symptoms are severer than those of ichthyosis vulgaris.

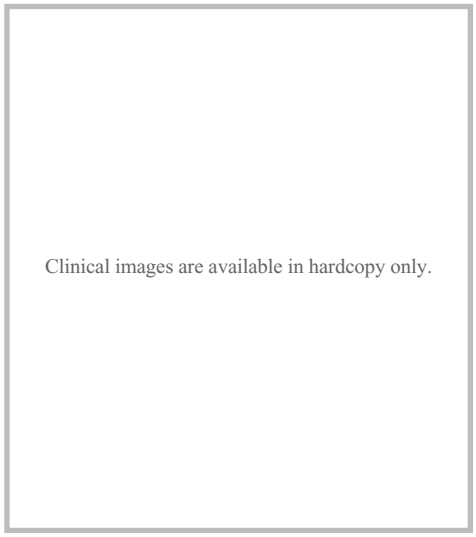

Fig. 15.3-1 Bullous congenital ichthyosiform erythroderma.
Skin lesions accompanied by flushing and thick keratinization occur on the whole body surface.

Fig. 15.3-2 Bullous congenital ichthyosiform erythroderma.
Flushing appears on the whole body. Severe, dark keratinization with a dirty appearance occurs on the hands and feet (often in cases of mutation in the keratin 10 gene).

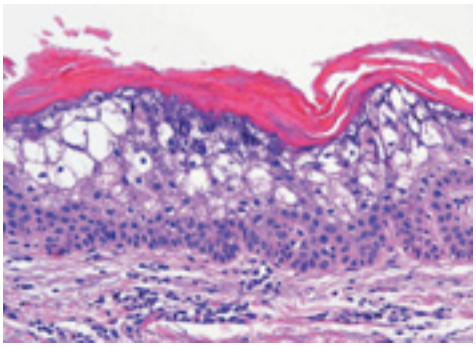

Fig. 15.4 Histopathology of bullous congenital ichthyosiform erythroderma.
Granular degeneration occurs in the epidermis.

3. Bullous congenital ichthyosiform erythroderma (BCIE) ★

Clinical features

Patients with bullous congenital ichthyosiform erythroderma (BCIE) are sometimes born as collodion babies. Diffuse flushing and blistering recur for several weeks after birth. Scales gradually thicken, leading to severe keratinization in later childhood (**Figs. 15.3-1** and **15.3-2**). The thickly keratinized plaques are accompanied by flush and a characteristic odor. The whole body including the flexures of joints and extremities appear erythrodermatic and dark rose in color. The prognosis is good.

Pathogenesis

The cytoskeleton (intermediate filament) of suprabasal cells is

composed of keratin 1 and keratin 10. Because of mutation in the keratin 1 or keratin 10 gene, abnormal keratin fiber formation, cytoskeleton distortion, and epidermal blistering occur, leading to secondary thickening of the horny cell layer (**Fig. 1.14**). BCIE is autosomal dominantly inherited.

Pathology

The horny and suprabasal cell layers thicken, keratin fibers aggregate, and there are vacuolated cells containing large keratohyaline granules in the granular and suprabasal cell layers (granular degeneration, **Fig. 15.4**).

Differential diagnosis, Treatment

Blistering is marked, particularly in newborns. It is necessary to differentiate BCIE from epidermolysis bullosa, incontinentia pigmenti and impetigo contagiosa by the pathological findings. The treatments are oral retinoid and application of moisturizer.

4. Ichthyosis bullosa of Siemens ★

It is caused by mutation in the keratin 2e gene. The clinical features are similar to those of the mild type of bullous congenital ichthyosiform erythroderma; nonetheless, erythroderma is not present in ichthyosis bullosa of Siemens (**Fig. 15.5**). Localized granular degeneration is histopathologically seen in part of the uppermost prickle layer and granular layer where keratin 2e is expressed in the epidermal granular layer.

5. Nonbullous congenital ichthyosiform erythroderma (NBCIE) ★

Clinical features

Most of the patients are born as collodion babies. Two to three days after birth, the collodion covering exfoliates, leaving the whole body surface with diffuse flushing and scaling (**Figs. 15.6-1** and **15.6-2**). The affected sites include the flexures of joints. Ectropion of eyelids may also occur. There are minor changes in the symptoms with season. NBCIE progresses until the age of 10, at which point it stops and subsides. The clinical manifestations range from mild to severe.

Pathogenesis

It is autosomal recessively inherited. The pathogeneses are various. Six or more genes are thought to be associated with occurrence of NBCIE. A certain mutation in the ABCA12 gene, the causative gene for harlequin ichthyosis, also causes NBCIE. The transglutaminase 1 gene, the causative gene for lamellar ichthyosis, can also cause NBCIE. Complete absence of transglutaminase 1 activity causes typical lamellar ichthyosis; severe reduction in such activity leads to NBCIE. The mechanism of

Clinical images are available in hardcopy only.

Fig. 15.5 Ichthyosis bullosa of Siemens.
The clinical symptoms are milder than those of bullous congenital ichthyosiform erythroderma. Flushing and hyperkeratosis are present.

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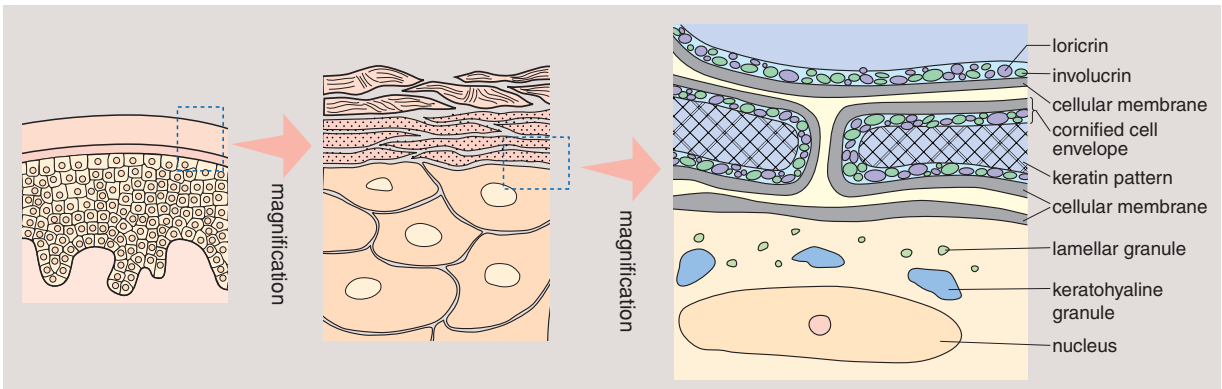
Fig. 15.6-1 Nonbullous congenital ichthyosiform erythroderma.
Erosive flushing and fine scales are seen on the whole body. Blistering does not occur.

Fig. 15.6-2 Nonbullous congenital ichthyosiform erythroderma.



Cornified cell envelopes cover the horny cell membrane in the horny cell layer. They play an important role in increasing the strength of the horny cell layer against physical and chemical stimuli.

Fig. 15.7 Cornified cell envelope.

NBCIE is known to be a marked decrease in physical and functional strength of keratin (**Figs. 15.7** and **1.16**).

Treatment

Oral retinoid (a vitamin A derivative) is effective. The skin should be kept clean to prevent secondary infection.

6. Lamellar ichthyosis ★

In approximately half of all cases of lamellar ichthyosis, the cause is an absence of transglutaminase 1; however, its activity is normal in some cases. Transglutaminase 1 is a calcium-dependent enzyme that is necessary for the formation of cornified cell envelopes in keratinocytes. The pathogeneses of lamellar ichthyosis are various. The scales in lamellar ichthyosis are clinically rough and large in most cases, dark brown, and plate-like or lamellar; these characteristics distinguish the scales from those in nonbullous congenital ichthyosiform erythroderma (NBCIE) (**Fig. 15.8**).

7. Harlequin ichthyosis ★

Synonym: Harlequin fetus

The patient is covered with an extremely thick stratum corneum at birth. Cracks in the skin, ectropion of eyelids, protrusion of lips, and difficulty of opening the mouth are so severe that most patients die within 2 weeks after birth (**Fig. 15.9**). In 2005, a Japanese dermatologist identified ABCA12 as the causative gene. ABCA12 is a lipid transporter in the lamellar granule, and the lack of ABCA12 leads to marked reduction of lipid content in the horny layer. There is abnormality of the lamellar granules in harlequin ichthyosis. It is autosomal recessively inherited, and DNA-based prenatal diagnosis is clinically applied.

8. Ichthyosis syndrome ★

Ichthyosis syndrome is a general term for congenital ichthyosis accompanied by involvement of certain organs. Most of the cutaneous symptoms resemble those of nonbullous congenital ichthyosiform erythroderma (NBCIE). The most frequently occurring types of ichthyosis syndrome are listed in **Table 15.3**.

①Sjögren-Larsson syndrome

It is autosomal recessively inherited. The main characteristics are congenital ichthyosiform erythroderma, spasmodic acroparalysis, and mild to moderate mental retardation (**Fig. 15.12**). There is abnormality in the gene that codes for fatty aldehyde dehydrogenase (FALDH/ALD). The condition is caused by absence of FALDH.

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Fig. 15.8 Lamellar ichthyosis.
Large, dark brown scales are characteristic of lamellar ichthyosis.

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Fig. 15.9 Harlequin ichthyosis.
There is marked hyperkeratosis on the whole body surface. Ectropion of the eyelids results in reddening over the eyes. Normal eyeballs are present underneath.

Table 15.3 Major ichthyosis syndromes.

Disease	Inheritance pattern	Eruptions	Other symptoms
Sjögren-Larsson syndrome	AR	Nonbullous congenital ichthyosiform erythroderma	Mental retardation, spastic quadriplegia
Netherton syndrome	AR	Atopic dermatitis-like eruption, bamboo hair	Atopic diathesis
KID syndrome	AD	Spiny hyperkeratosis in the extremities and face	Hearing impairment, keratitis
Dorfman-Chanarin syndrome	AR	Nonbullous congenital ichthyosiform erythroderma	Lipid droplets in leukocytes, hepatic steatosis, cataract, neurologic manifestation
Refsum syndrome	AR	Lamellar ichthyosis-like skin	Retinitis pigmentosa, polyneuropathy, cerebellar ataxia, inner-ear deafness
Rud syndrome	AR	Nonbullous congenital ichthyosiform erythroderma	Seizure, mental retardation, low height, gonadal hypofunction
Conradi syndrome	AD or AR	Nonbullous congenital ichthyosiform erythroderma	Skeletal defects, cataract, punctate shadow at bone ends, quadriplegia

(AR: autosomal recessively inherited, AD: autosomal dominantly inherited).

Fig. 15.10 Netherton syndrome.
a: It is accompanied by atopic dermatitis-like eruptions and nonbullous congenital ichthyosiform erythroderma-like eruptions. b: The scalp hair becomes knotted and easily breaks at the knots, resulting in short hair (bamboo hair).

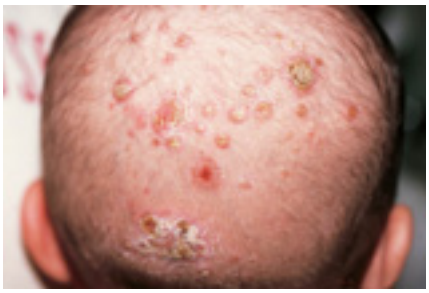
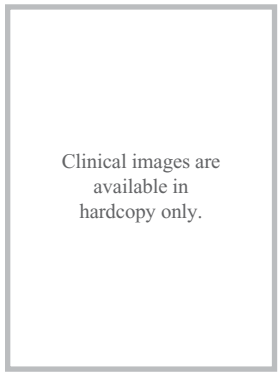


Fig. 15.11 KID syndrome.
Prickle keratotic macules on the scalp.



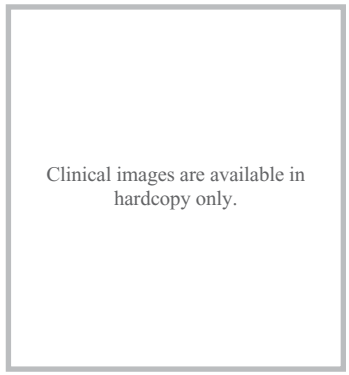


Fig. 15.12 Sjögren-Larsson syndrome.
Nonbullous congenital ichthyosiform erythroderma-like eruptions occur.

②Netherton syndrome

Autosomal recessively inherited, it is caused by a mutation in the SPINK5 gene, which codes for serine protease inhibitor. The eruptions resemble atopic dermatitis or nonbullous congenital ichthyosiform erythroderma (**Fig. 15.10**). Scalp hair becomes knotted, short and easily broken (bamboo hair).

③Keratitis, ichthyosis and deafness (KID) syndrome

It is autosomal dominantly inherited. The main symptoms are keratitis, ichthyosis and deafness. Papillomatous or prickle keratotic lesions occur mainly on the face and extremities (**Fig. 15.11**).

④Dorfman-Chanarin syndrome

It is an autosomal recessively inherited metabolic disorder of neutral lipids, caused by mutation in the CGI-58 gene, which codes for an enzyme that regulates metabolism of phospholipids. Triacylglycerol accumulates in the cytoplasma of various cells to form lipid droplets. The disorder may be accompanied by ichthyosis, liver disorder, hearing loss, mental retardation, cataract and nystagmus (**Figs. 15.13** and **15.14**).

⑤Refsum syndrome

It is autosomal recessively inherited. In addition to lamellar-ichthyosis-like eruptions, there is night blindness caused by

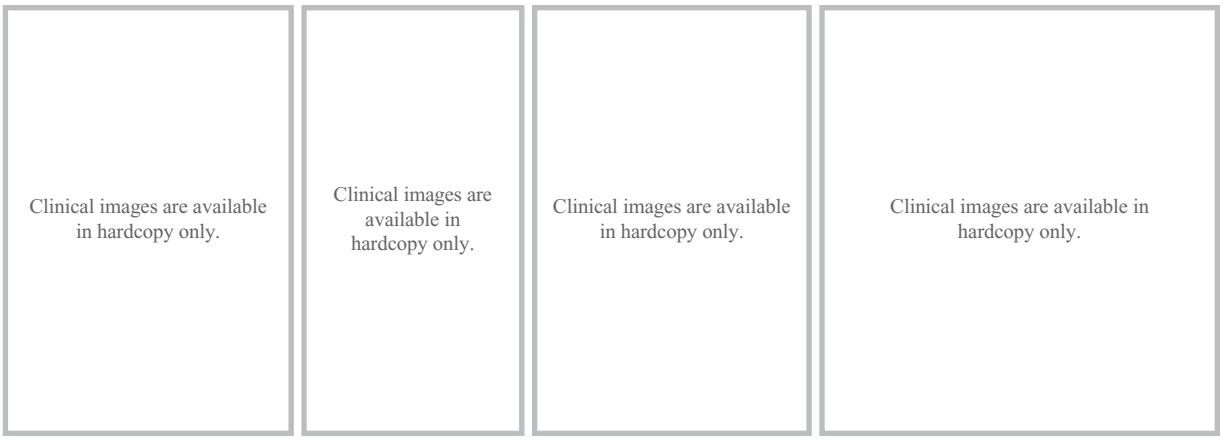


Fig. 15.13 Dorfman-Chanarin syndrome.

retinitis pigmentosa. Cerebellar ataxia, multiple neuritis polyneuritis, and sensorineural deafness are present. Levels of phytanic acid in the blood increase from congenital metabolic disorder.

⑥Rud syndrome

It is known to be autosomal recessively inherited; boys are more commonly affected than girls, and most cases are sporadic. Congenital ichthyosiform erytheoderma-like skin manifestations, epilepsy, mental retardation, gonadal hypofunction and short stature may occur as complications.

⑦Conradi syndrome (Conradi-Hünermann-Happle syndrome)

The symptoms of nonbullous congenital ichthyosiform erythroderma, abnormal formation of bones, cataract, and paralysis in all extremities occur. Conradi syndrome is X-linked dominantly inherited. Males die prenatally. The cause is mutation in the emopamil binding protein (EBP) gene at Xp11.22-p11.23.

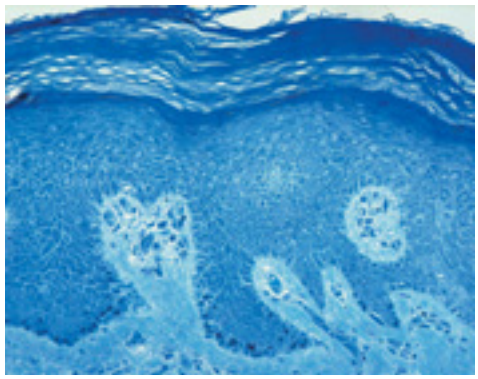


Fig. 15.14 Histopathology of Dorfman-Chanarin syndrome.

b. Palmoplantar keratoderma ★

Definition, Classification

Palmoplantar keratoderma is a generic term for diseases that hereditarily cause hyperkeratosis in the palms and soles. It is subclassified by clinical features and patterns of inheritance (**Figs. 15.15-1** and **15.15-2; Table 15.4**). Genetic mutation is identified in some cases. Further clarification is necessary for exact classification of palmoplantar keratoderma. The main types of palmoplantar keratoderma are shown below.

Treatment

There is no effective treatment for any types. Oral retinoid (a vitamin A derivative) and topical application of petrolatum salicylate or moisturizer are the main treatments.