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

Rud syndrome

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

Conradi 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.

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.
Thost-Unna palmoplantar keratoderma is autosomal dominantly inherited. Localized diffuse lesions with a red halo form on the palms and soles of infants. Thickening of the horny cell layer and epidermis is seen. In recent years, cases with mutation in the keratin 1 gene have been reported. The palms and soles of patients with Thost-Unna palmoplantar are usually hyperhidrotic.

2. Vörner palmoplantar keratoderma

It is autosomal dominantly inherited. Differentiation from Thost-Unna palmoplantar keratoderma can be made by histopathological detection of granular degeneration; such differentiation is impossible from clinical findings. Mutation in the keratin 9 gene is found in half of all patients with Vörner palmoplantar keratoderma.

3. Mal de Meleda

Synonym: Meleda disease

This autosomal recessively inherited disease is often seen in offspring of consanguineous marriages. It hardly ever occurs in Asians. Hyperkeratosis accompanied by flush appears immediately after birth. Keratinization progresses and extends as the patient ages. In many cases, not only are the palms and soles affected, but so are the dorsal hands and feet, arms and legs. It is progressive until the patients become elderly. Mental retardation may occur.

4. Dominant Meleda palmoplantar keratoderma

Relatively mild reddening and keratinization affect the dorsal hands and feet.

**Table 15.4 Major types of palmoplantar keratoderma.**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance pattern</th>
<th>Age of onset</th>
<th>Eruptions</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thost-Unna keratoderma</td>
<td>AD</td>
<td>Babyhood, infancy</td>
<td>Diffuse keratotic eruption with a red-halo in the periphery localized on the palms and soles</td>
<td>Hyperhidrosis on the palms and soles</td>
</tr>
<tr>
<td>Vörner keratoderma</td>
<td>AD</td>
<td>Babyhood, infancy</td>
<td>Thost-Unna keratoderma-like eruption</td>
<td>Granular degeneration (histologically)</td>
</tr>
<tr>
<td>Mal de Meleda</td>
<td>AR</td>
<td>Babyhood</td>
<td>Hyperkeratosis accompanied by flushing, spreading to the dorsum of hands and feet with age</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>Dominant Mal de Meleda keratoderma</td>
<td>AD</td>
<td>Infancy, early childhood</td>
<td>Resembles eruption in Mal de Meleda; however, keratosis and flushing are milder</td>
<td></td>
</tr>
<tr>
<td>Keratosis palmoplantaris transgrediens Nagashima</td>
<td>AR</td>
<td>Babyhood, infancy</td>
<td>Mild keratosis on the dorsum of hands and feet</td>
<td></td>
</tr>
<tr>
<td>Keratosis palmoplantaris linearis/ striata</td>
<td>AD</td>
<td>Infancy, early childhood</td>
<td>Linear, band-like, or round hyperkeratosis on the palms and soles</td>
<td></td>
</tr>
<tr>
<td>Punctate palmoplantar keratoderma</td>
<td>AD</td>
<td>Early childhood to elderly</td>
<td>Multiple, firm, punctate keratotic papules on the palms and soles</td>
<td>May be accompanied by nail deformity resulted from malnutrition</td>
</tr>
</tbody>
</table>

(AR: autosomal recessively inherited, AD: autosomal dominantly inherited).
A. Hereditary keratoses

The symptoms are relatively mild, similar to those of Mal de Meleda. Keratinization is mild. It is autosomal recessively inherited. The pathogenesis has not been identified.

It is autosomal dominantly inherited. Linear, band-like or round hyperkeratosis is present in the palms and soles. Mutations in the desmoglein 1 and desmoplakin genes are found in some families.

It is autosomal dominant inherited. Punctuate keratinization is seen in the palms and soles.

Keratosis occurs in the palms and soles, which leads to strangulation obstruction in fingers and toes (Fig. 15.16). Star-shaped keratinized plaques develop on the dorsal surfaces of the hands and feet and on the kneecaps. Mutation in the loricrin gene has been reported.

Flush and hyperkeratosis occur on the palms, soles, the dorsal surfaces of hands and feet, and the extremities. The syndrome is

5. Keratosis palmoplantaris transgrediens Nagashima

The symptoms are relatively mild, similar to those of Mal de Meleda. Keratinization is mild. It is autosomal recessively inherited. The pathogenesis has not been identified.

6. Keratosis palmoplantaris linearis/ striata

It is autosomal dominantly inherited. Linear, band-like or round hyperkeratosis is present in the palms and soles. Mutations in the desmoglein 1 and desmoplakin genes are found in some families.

7. Punctate palmoplantar keratoderma

It is autosomal dominant inherited. Punctuate keratinization is seen in the palms and soles.

8. Keratosis palmoplantaris mutilans (Vohwinkel)

Keratosis occurs in the palms and soles, which leads to strangulation obstruction in fingers and toes (Fig. 15.16). Star-shaped keratinized plaques develop on the dorsal surfaces of the hands and feet and on the kneecaps. Mutation in the loricrin gene has been reported.

9. Papillon-Lefévre syndrome

Flush and hyperkeratosis occur on the palms, soles, the dorsal surfaces of hands and feet, and the extremities. The syndrome is

Fig. 15.15-2 Palmoplantar keratoderma.

Fig. 15.16 Keratosis palmoplantaris mutilans (Vohwinkel).

Fig. 15.17-1 Papillon-Lefévre syndrome. Flushing and the hyperkeratosis are present.
characterized by periodontal disease (Figs. 15.17-1 and 15.17-2). It is autosomal recessively inherited.

### 10. Richner-Hanhart syndrome

The three major characteristics are painful palmoplantar keratinosis, photophobia, and mental retardation. It is autosomal recessively inherited. The pathogenesis is a reduced activity of tyrosine aminotransferase.

### 11. Náxos disease

Keratosis, cardiac myopathy of the right ventricle, cardiac enlargement, and palmoplantar keratosis are present. Cases with mutation in the plakoglobin gene have been reported.

#### c. Other hereditary keratoses

### 1. Darier’s disease

Synonym: Keratosis follicularis

#### Outline

- Keratotic papules of 2 mm to 5 mm in diameter appear, mainly on seborrheic and intertriginous areas. The condition is aggravated by perspiration in summer.
- The pathogenesis is genetic mutation in SERCA2, the calcium pump of keratinocytes. It is autosomal dominantly inherited.
- The characteristic pathological findings are acantholysis, lacunae, corps ronds, and grains.

#### Clinical features

Darier’s disease first occurs in infancy and continues through adolescence. Multiple dark brown keratotic papules of 2 mm to 5 mm in diameter covered by thick crusts occur in the seborrheic and intertriginous areas such as the neck, axillary fossae, sternal region, inframammary region, abdomen and groin (Figs. 15.18-1 and 15.18-2). The papules may be moist and give off a bad odor. On the perspiratory intertriginous areas, papules coalesce and condyloma-like proliferation occurs. The following occur: keratosis in the palms and soles, verrucous keratosis in the dorsal surfaces of hands and feet, punctuate depression in the palms, enanthema, deformity of nails, and sometimes nervous symptoms such as mental retardation and epilepsy. Bacterial or viral infection (e.g., Kaposi’s varicelliform eruption) may occur secondarily.

#### Pathogenesis

Darier’s disease is caused by mutation in the ATP2A2 gene, which codes for the SERCA2 calcium pump. That pump controls the calcium concentration in the cytoplasm of keratinocytes.