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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Chapter 34
Disorders of Keratinization

W.A.D. GRIFFITHS, M.R. JUDGE & I.M. LEIGH

Ichthyosis: general principles

Congenital ichthyoses
Ichthyosis vulgaris
X-linked recessive ichthyosis
Multiple sulphatase deficiency
Collodion baby
Non-bullous ichthyosiform erythroderma
Lamellar ichthyosis
Harlequin ichthyosis
Bullous ichthyosiform erythroderma
Ichthyosis bullosa of Siemens
Ichthyosis hystrix
Netherton’s syndrome
Sjögren-Larsson syndrome
Refsin’s disease
IBIDS
X-linked dominant ichthyosis
Neutral lipid storage disease
KID syndrome
CHILD syndrome
Ichthyosis follicularis with alopecia and photophobia

Congenital ichthyosis variants

Isolated genetic syndromes with ichthyosis
Acquired ichthyoses
Pityriasis rotunda
Peeling skin syndromes
Acquired peeling of the palms

Congenital peeling skin syndromes

Erythroderma
Erythroderma variabilis
Symmetrical progressive erythroderma
Progressive partially symmetrical erythroderma with deafness
Erythroderma en cocardes
Localized erythroderma
Erythroderma with periorificial lesions
Annular migrating erythroderma

Discrete keratotic disorders
Follicular disorders
Darier’s disease
Transient and persistent acantholytic dermatosis
Acrokeratosis verruciformis
Perforating keratotic disorders

Porokeratosis

Miscellaneous circumscribed keratotic disorders
Waxy keratoses of childhood
Facial Afro-Caribbean childhood eruption
Florid cutaneous papillomatosis
Keratosis circumscripta
Florid oral papillomatosis and keratoderma
Hyperkeratosis of the nipple

Knuckle pads
Familial dyskeratotic comedones
Disseminate and recurrent infundibulofolliculitis

Filiform keratoses
Multiple minute digitate hyperkeratoses
Minute aggregate keratoses

Classification of keratodermas

Palmoplantar keratodermas
Diffuse hereditary keratodermas
Focal keratodermas
Punctate keratodermas
Marginal and inverse keratodermas
Other keratoderma syndromes

Keratodermas and associated disorders

Acquired keratodermas
Keratoderma climactericum
Keratoderma and myxoedema
Palmoplantar keratoderma and cancer
Acrokeratosis paraneoplastica
Acanthosis nigricans
Lymphoedematous keratoderma
Keratodermas due to other dermatoses

Confluent and reticulate papillomatosis

**Ichthyosis: general principles**

**Definition and nomenclature.** Ichthyosis describes dry, rough skin with persistent, visible scaling over much of the body that may resemble fish scale (ichthys, fish from the Greek). The ichthyoses are a heterogeneous group of skin disorders whose major cutaneous feature is ichthyosis. Several congenital forms exist, and they can be divided into the major types occurring as primary ichthyotic disorders, a number of rarer variants classified as ichthyosiform or ichthyotic syndromes, and case reports of congenital ichthyosis that do not fit a recognized syndrome. Acquired ichthyosis is a rare complication of several systemic or malignant diseases. A simple classification, reflecting the frequency of various forms of congenital ichthyosis in the population, is shown in Table 34.1.
focal areas of hyperkeratosis and orthokeratosis with no dermal infiltrate. Odland bodies are present on electron microscopy of lesional skin.

**REFERENCES**


**Classification of keratodermas**

The taxonomy of keratodermas is confusing. Attempts have been made to base classifications on clinical features, eponymous labels, epidermal kinetics, modes of inheritance, consecutive numbering, and most recently genetic mutations. None of these is entirely satisfactory. For the purposes of this book, the approach adopted has been for the practising clinician, and an attempt has been made to clarify as far as possible where useful information from recent findings correlate with the clinical expression of the diseases (Table 34.8). Grouping and sequence has been adopted which places commoner disorders before those rarely seen. This is not therefore to be regarded as a classification of keratodermas. For further study of the difficulties of arriving at a unified classification, the reader is directed to the classifications suggested by Greither [1], Salamon [2], Zemstov and Veitschegger [3], Lucker et al. [4], Itin and Lautenschlager [5], Stevens et al. [6] and Ratnavel and Griffiths [7].

**REFERENCES**


**Palmoplantar keratodermas**

Palmoplantar keratodermas are a clinically diverse group of hereditary and acquired skin disorders predominantly affecting palmoplantar epidermis. Some have additional features in non-glabrous skin, which complicates the clinical diversity. A considerable biological heterogeneity of disease mechanisms underlies the clinical heterogeneity, but many hereditary keratodermas have been found to be caused by abnormalities in structural proteins of the epidermal keratinocyte (Table 34.9).
<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Eponym</th>
<th>Other terms</th>
<th>Inheritance</th>
<th>Onset (year)</th>
<th>Hyperhidrosis</th>
<th>Transgredient? (spreading to extensor surface)</th>
<th>Red border</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse</td>
<td>Thost–Unna</td>
<td>Keratoma palmarum et plantarum hereditarium</td>
<td>Autosomal dominant</td>
<td>2–5, occ. later</td>
<td>++</td>
<td>No</td>
<td>+</td>
<td>Commonest type, Sporadic cases common</td>
<td>[11]</td>
</tr>
<tr>
<td>Mutilating</td>
<td>Vohwinkel</td>
<td>Keratoma hereditaria mutilans</td>
<td>Autosomal dominant</td>
<td>infancy –</td>
<td>Yes</td>
<td>+</td>
<td></td>
<td>Honeycomb palms; starfish extensor keratoses; high-tone deafness</td>
<td>[3,14,15]</td>
</tr>
<tr>
<td>Meleda disease (Mijet)</td>
<td>Mal de Meleda</td>
<td>–</td>
<td>Autosomal dominant (irregular) or autosomal recessive</td>
<td>0–3</td>
<td>+</td>
<td>Yes</td>
<td>+</td>
<td>Remission possible but usually progressive; atopic eczema and secondary infection</td>
<td>[2,13,18]</td>
</tr>
<tr>
<td>Greither's disease</td>
<td>Greither</td>
<td>Keratosis extremitarum hereditaria progresiens; progressive keratoderma</td>
<td>Autosomal dominant</td>
<td>3–8</td>
<td>+</td>
<td>Yes</td>
<td>+</td>
<td>Regression by 60 years</td>
<td>[5,9]</td>
</tr>
<tr>
<td>Epidermolytic hyperkeratosis</td>
<td>Vorner</td>
<td>–</td>
<td>Autosomal dominant</td>
<td>0–3</td>
<td>+</td>
<td>No</td>
<td>+</td>
<td>Appearance identical to diffuse-type but histology distinctive</td>
<td>[1,6,8,20]</td>
</tr>
<tr>
<td>Punctate</td>
<td>Buschke-Fischer</td>
<td>Keratodermia maculosa disseminata palmaris et plantaris</td>
<td>Autosomal dominant and sporadic</td>
<td>10–45</td>
<td>–</td>
<td>No</td>
<td>–</td>
<td>For associated disorders see Table 34.11</td>
<td>[12,16]</td>
</tr>
<tr>
<td>Brauer–Brunauer–Fuhs</td>
<td>–</td>
<td>Keratoderma hereditarium dissipatum palmaris et plantare</td>
<td>–</td>
<td>15–30</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>(Focal, areata/stripata)</td>
<td>Siemens</td>
<td>Keratosis palmarum plantaris areaeta; keratoderma en aires</td>
<td>Autosomal dominant</td>
<td>4–10</td>
<td>+/-</td>
<td>No</td>
<td>–</td>
<td>Striate on palms, islands on feet; varians type marked intrafamilial variation of phenotypic expression</td>
<td>[17]</td>
</tr>
<tr>
<td>(Focal, areata/stripata)</td>
<td>Varians</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>[10]</td>
</tr>
<tr>
<td>Papuloverrucous</td>
<td>JAKAC–Wolf</td>
<td>Polykeratosis of Touraine</td>
<td>Autosomal recessive</td>
<td>2–6</td>
<td>+</td>
<td>No</td>
<td>+</td>
<td>Disseminated follicular keratoses; teeth dysplastic</td>
<td>[19]</td>
</tr>
</tbody>
</table>
Diffuse hereditary keratoderma

Non-epidermolytic palmoplantar keratoderma

SYN. THOST-UNNA KERATODERMA

Aetiology. The condition is inherited as an autosomal dominant with high penetrance and expressivity.

Molecular biology. The original description of non-epidermolytic palmoplantar keratoderma by Unna and Thost has been complicated by a reappraisal of the original Thost family, and rediagnosis as epidermolytic palmoplantar keratoderma, due to K9 gene mutations [1]. There are, however, a number of strands of evidence that non-epidermolytic palmoplantar keratoderma exists as a distinct entity, characterized by even, thick, waxy, yellow hyperkeratosis over the whole palm and sole, present from early infancy. An extensive histopathological appraisal of 91 biopsies in northern Sweden showed no evidence of epidermolysis, but suggested that vesiculation due to secondary dermatophyte infection might be a confounding factor [2]. A single family was shown to have a mutation in the VI domain of K1, a region thought to be important in interactions with loricrin [3], although this mutation has been excluded in many other families. A further study using linkage analysis of two families generated lod scores compatible with linkage to the keratin cluster on chromosome 12, i.e. excluding K9 as the target gene (as it maps to chromosome 17) [4]. A further study that mapped a Ukrainian family to chromosome 17 unfortunately did not include detailed morphological studies to exclude epidermolysis [5]. It seems likely that non-epidermolytic palmoplantar keratoderma can result from keratin mutations, which subtly interfere with keratin interactions

Table 34.8 Continued.

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Eponym</th>
<th>Other terms</th>
<th>Inheritance</th>
<th>Onset (year)</th>
<th>Transgredient? (spreading to extensor surface)</th>
<th>Red border</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal acral hyperkeratosis</td>
<td>–</td>
<td>Acrokeratolaxeliosis without elastorhexis</td>
<td>Autosomal dominant</td>
<td>Peak in 3rd decade</td>
<td>No</td>
<td>–</td>
<td>Afro-Caribbean; umbilicated puncta at margins of palms and soles; palmar crease lesions common</td>
<td>[4,7]</td>
</tr>
</tbody>
</table>

REFERENCES TO TABLE 34.8

with other cellular proteins, without disrupting filament assembly and without producing filament clumps or tangles. However, the evidence is currently small and other candidate genes must be considered, especially those restricted to palmoplantar epidermis. These mutations cannot be in K9 the palm- and sole-restricted keratin, as it has been excluded by linkage and mutational analysis.

Pathology. Orthokeratotic hyperkeratosis is associated with hypergranulosis or normogranulosis and moderate acanthosis [2]. There is usually a mild perivascular infiltrate. These changes are common to many varieties of keratoderma. Unless a biopsy is performed, the more specific changes of epidermolytic palmoplantar keratoderma will be missed. Re-examination of Thost’s original family suggests that they had the epidermolytic variety [6]. Epidermolytic histological changes were not found in cases from Sweden [2], nor in the majority of the author’s (W.A.D.G.) material. These findings, taken with genetic data described above, suggest that epidermolytic and non-epidermolytic palmoplantar keratodermas are distinct from each other, but share similar phenotypic expression.

Clinical features [7–9]. The condition may present in the first few months of life and is usually obvious by the age of 4 years. It rarely appears in the third decade. An even, very thick, yellow hyperkeratosis occurs over the whole of the foot, starting on the heel and anterior arch, spreading later to the palms (Fig. 34.46). There is a sharp cut-off at the wrist, and there is no tendency to spread to the extensor surfaces (not transgrediens). The margins show a vivid red border, which can be seen also to underly the hyperkeratosis. Heavy manual labour worsens the hyperkeratosis. Marked hyperhidrosis is usual, and dermatophyte infections and pitted keratolysis are frequently found. Cases appearing later in life represent spontaneous mutations or are acquired keratodermas. The nails are usually normal, but may be thickened without evidence of dystrophy. Hair and teeth are normal, and

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Definite target gene</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse PPKs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermolytic PPK</td>
<td>K9</td>
<td>Linkage/mutations</td>
</tr>
<tr>
<td>Non-epidermolytic PPK</td>
<td>K1</td>
<td>Mutations single family</td>
</tr>
<tr>
<td></td>
<td>?Type 1 keratin</td>
<td>Linkage keratin cluster 12q</td>
</tr>
<tr>
<td>Focal PPKs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striate</td>
<td>?Desmosomal cadherin</td>
<td>Linkage to 18q12</td>
</tr>
<tr>
<td>Focal + oral hyperkeratosis</td>
<td>K16 (and 6)</td>
<td>Mutations in two families</td>
</tr>
<tr>
<td>Pachyonychia congenita 1</td>
<td>K6/16</td>
<td>Mutations in multiple families</td>
</tr>
<tr>
<td>Howell Evans (fyllosis</td>
<td>?</td>
<td>Linkage to 17q30 (not keratin)</td>
</tr>
<tr>
<td>and oesophageal cancer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pachyonychia congenita 2</td>
<td>K17</td>
<td>Mutations</td>
</tr>
<tr>
<td>Vohwinkel’s</td>
<td>Loricrin</td>
<td>Linkage 1q21/mutations</td>
</tr>
</tbody>
</table>

Table 34.9 Genetic mutations in palmoplantar keratodermas (PPK).

![Fig. 34.46 Thost-Unna keratoderma: even, yellow hyperkeratosis of sole with red border.](image)

![Fig. 34.47 Woolly hair in a patient with the keratoderma, woolly hair and ventricular fibrosis syndrome. (Courtesy of Dr D.M. Macdonald, Guy’s Hospital, London, UK.)](image)

abnormalities of these structures suggest another diagnosis (Fig. 34.47). For further clinical associations, see Table 34.11.

Treatment. Many patients are helped by keratolytic therapy, such as 6% salicylic acid in white soft paraffin, or a gel of
6% salicylic acid in 70% propylene glycol. Occlusion with polythene for a few nights speeds the efficacy of these preparations. Benzocic acid compound ointment is mildly keratolytic, and is useful in reducing fungal and bacterial overgrowth and the resulting bad odour. Topical retinoids have little effect. Actretin may be effective for patients with marked functional impairment, but response is unpredictable and some patients find the loss of the thick keratin leaves the foot markedly hypersensitive.

REFERENCES


Norbotten type [1,2]

SYN. GAMBORG- NIELSEN’S KERATODERMA

In a series of studies of palmoplantar keratoderma in Sweden, a common autosomal dominant type was seen in which a medium thick, horny layer with a smooth, uniform surface was present. One-quarter of these cases showed a papular border. A second variety inherited as an autosomal recessive showed a thick mutilating keratoderma associated with knuckle pads. This may represent a variant of mal de Meleda.

REFERENCES


Epidermolytic palmoplantar keratoderma

SYN. VORNER’S KERATODERMA

Molecular biology. Vorner described a diffuse palmoplantar keratoderma with an autosomal dominant inheritance, with features of epidermolytic hyperkeratosis (EHK) confined to the palm and sole. Clinically, this could not be distinguished from Thost–Unna keratoderma, which was thought to be non-epidermolytic. The changes in Vorner’s epidermolytic palmoplantar keratoderma show marked epidermolytic change in suprabasal keratinocytes with large filament aggregates. The morphological appearance of keratin filament bundles in palmoplantar epidermis is different, with thicker bundles in a distinct orientation, so care must be undertaken in the assessment of filament aggregation [1]. The morphological changes suggested that keratin mutations were likely to cause epidermolytic palmoplantar keratoderma, as in bullous ichthyosiform erythroderma (BCIE), but as the EHK is site restricted in epidermolytic palmoplantar keratoderma, the target keratin must be predominantly restricted to those sites. A palm- and sole-specific type I keratin, K9, was described in 1986 [2], but the gene sequence was not known until 1994 [3]. Linkage of epidermolytic palmoplantar keratoderma to the K9 locus on chromosome 17 was reported [4] and followed by several reports of point mutations in highly conserved regions of K9, mostly in the 1A helix [1,5–7]. Many of these mutations affect the arginine residue of the helix initiation motif as found in keratins K1 and K10 in BIE, and would be predicted to reduce the resistance of the cytoskeleton to minor external trauma, increasing the likelihood of blistering and hyperkeratosis. Re-examination of 22 Vorner families showed, in addition to diffuse keratoderma with a sharp demarcation and erythematous edge, the presence of knuckle pads and nail changes [8]. Many of these families had K9 mutations. There is now good evidence that Vorner’s epidermolytic palmoplantar keratoderma results from a distinct genetic lesion, mutations in the highly conserved domain of the palm- and sole-specific K9; a good case of genotype–phenotype correlation.

Clinical features [9–11]. This autosomal dominant disorder is characterized by diffuse palmoplantar keratoderma identical to the autosomal dominant type (Thost–Unna), but with the epidermal vacuolation of EHK (BIE). Thost’s original family is believed to have been epidermolytic [12,13], but non-epidermolytic palmoplantar keratoderma is frequently seen. Its onset is in the first year, and there is little or no spread to dorsal surfaces, nor is it progressive. A family with the disorder is reported with the development of generalized annular and polycyclic lesions [14]. Possible autosomal recessive inheritance was reported in two children born to consanguineous parents [15]. There is no hyperhidrosis, and the hair, teeth and nails are normal. A history of blistering in the affected areas may point to the diagnosis [11]. A family with a tendency to develop internal solid tumours has been reported [16], and another with breast and ovarian cancer [17]. Response to retinoids is good, but excessive peeling may be a problem [18]. Topical calcipotriol has been helpful [19].
Progressive palmar plantar keratoderma [1,2]

SYN. GREITHER’S SYNDROME

Pathology. The changes on light microscopy are non-specific, with orthohyperkeratosis and absence of granular cell degeneration, in contrast to epidermolytic palmar plantar keratoderma. Immunohistochemical staining with the marker KI-67 showed pronounced proliferation of keratinocytes [3]. Beylot et al. [4] found numerous desmosomes and abnormal imbricated cell-to-cell junctions on electron microscopy.

Sybert keratoderma

A large family with a distinctive disorder inherited as an autosomal dominant was studied by Sybert et al. [1]. The condition appeared in the earliest years of life as palmar plantar erythema soon followed by a gross hyperkeratosis, with extension (transgressions) to the elbows, knees, backs of the hands, posterior aspects of the forearms, dorsa of the feet and anterior aspects of the legs. The groins and natal cleft were also involved. Spontaneous amputations of the digits had occurred, but the ‘starfish’ keratodases of the autosomal recessive mutilating keratoderma were not found. The severity of the condition, and the autosomal dominant inheritance, differentiate this disorder from mal de Meleda. Greither’s syndrome is less severe and has a later onset.

Lesional skin showed, on light microscopy, marked thickening of all epidermal layers and exaggerated rete ridges. There was an excessive accumulation of lipid-laden cells in the stratum corneum. The keratozyalin
granules were globular or irregular in shape. A moderate upper dermal infiltrate was found. Electron microscopy showed keratohyalin granules that were abnormal in distribution and structure. This, and the finding of abnormal filaggrin staining, suggested that the normal association of filaggrin and keratin filaments in the stratum corneum was defective.

REFERENCES


Palmoplantar keratoderma varians

**SYN. WACHTERS' KERATOderma**

Three families with an autosomal dominant condition affecting seven members was reported by Wachters [1]. The features included the onset towards the end of infancy of a palmoplantar keratoderma with marked variability of phenotypic expression, both between individuals and between families. Lesions seen were focal islands of hyperkeratosis, especially on pressure points, striae lesions on the palms, and flexor aspects of the fingers, or an even thin hyperkeratosis described as 'membranous'. An erythematous border was not seen. Similar features were reported in an unrelated family [2], among whom hyperhidrosis was noted in seven of the 16 affected members. The centre of the soles was always spared. A further three families were reported from Spain [3]. Of the seven affected members, the age at onset was 6-14 years in five and at 18 months in two. Epidermolysis was not seen histologically.

REFERENCES


Mal de Meleda [1-2] (Fig. 34.48)

**SYN. KERATOderma PALMOPlANTARIS TRANsgrediens; ACROerythroKeratoDermA**

This very rare syndrome takes its name from the Dalmatian island of Meleda (Mljet), where its relative frequency is the result of inbreeding. It has been reported from many countries. The keratoderma is characterized by extension onto the dorsal surfaces of the hands and feet and over the knees and elbows (transgrediens) (Fig. 34.49), by its association with eczema (often secondarily infected) and by its recessive or variable dominant
mode of inheritance. Redness of palms and soles in early infancy is soon followed by scaling and thickening, usually diffuse but sometimes in islands, extending to the dorsal surfaces in a glove-like distribution. The hyperkeratosis is often malodorous. The erythematosus component remains conspicuous. Perioral erythema and hyperkeratosis recall the changes of Olmsted’s syndrome and keratosis lichenoides chronica striata [3]. Hyperhidrosis, nail thickening or koilonychia can be seen. Some cases with pseudoainhum (digital constricting fibrous bands) have been reported [4,5]. The disease is slowly progressive. Associated features most commonly encountered are lingua plicata, synechiae teeth, hair on the palms and soles, high-arched palate and left-handedness [2]. A suggestion that the MNSs and Kk blood groups show an abnormality was reported by Salamon et al. [6]. A family with some similarities to this disorder was reported by Sybert et al., but was inherited as an autosomal dominant (see Sybert type above). Etratinate may improve the hyperkeratosis but not the erythema [1,5], and isotretinoin was superior to etretinate in a further case [7].

REFERENCES

Focal keratoderma

Pachyonychia congenita

A number of classifications of this disorder have been proposed, and that suggested by Shonfeld on clinical features is the most widely adopted [1]. Localized areas of hyperkeratosis on the palms and soles with gross thickening of the nails characterizes the disease. Subtypes include other features listed below. A purely clinical classification does not correlate satisfactorily with the observed phenotypic expression of all cases observed, and recent molecular biological findings also throw doubt on the accuracy of such a clinical classification (see below).

Molecular biology. The diagnostic clinical feature of pachyonychia congenita (PC) is the presence of thickened, wedge-shaped nails, but the other clinical characteristics fit into two major patterns: the Jadassohn–Lewandowsky syndrome (PC-1) with additional focal palmoplantar hyperkeratosis and some localized foot blistering, follicular hyperkeratosis and oral leukokeratosis; and the Jackson–Lewler syndrome (PC-2), which has nasal teeth, cutaneous cysts, and hair abnormalities but no oral lesions or significant keratoderma. Linkage analysis of a large PC-2 family showed linkage to the keratin gene cluster on chromosome 17 [2], and subsequently keratin gene mutations were found in keratins K6/K16 and K17 [3]. The pattern of pachyonychia correlates well with the keratin gene mutation. Keratins K6 and K16 are expressed in mucosal epithelia, follicular keratinocytes and palmoplantar epidermis [4]. A point mutation in the highly conserved 1A domain of K16 has been reported in one patient with PC-1 [3], and a heterozygous 3bp deletion in exon 1 of a K6 isoform (K6a) in a PC-1 family from Slovenia [5]. In contrast, K17 is constitutively expressed in the pilosebaceous unit and basal appendage keratinocytes, with some basal expression in palmoplantar skin [6]. Point mutations in the conserved 1A domain of K17 gene have been reported from multiple families with PC-2 characterized by keratin and vellus hair cysts of the pilosebaceous unit [3]. There have been identical mutations of K17 in steatocystoma multiplex [7], where predominantly sebaceous and keratin cysts reflect expression in the sebaceous gland as well as hair follicle. Steatocystoma may therefore be considered a limited form of PC-2. The prominent nail involvement of pachyonychia reflects the extensive expression of K6/K16 and K17 in the nail matrix.

Pathology. The epidermis shows gross hyperkeratosis with alternating ortho- and para-keratosis. Acanthosis is present with patchy hypergranulosis, in which large and misformed keratohyalin granules are present [8].

Clinical features [9-11]. Most cases are inherited as an autosomal dominant, with erythema of the nailbed appearing in the first year or two of life, followed by thickening of zones of the palms and soles [9]. Cases with onset in the second and third decade have been described as pachyonychia congenita tarda [12,13].

Rarely, an autosomal recessive pattern of inheritance has been recognized [14].

Type 1 (Jadassohn–Lewandowsky type). Thick, yellow keratoses are found on sites of pressure (Fig. 34.50), associated with gross step-like thickening of all finger- and toe-nails (Fig. 34.51), keratosis pilaris and follicular keratoses on the knees and elbows. Occasional blister formation may be seen. Patchy or streaky white thickened areas are seen on the tongue and oral mucosa (oral leukokeratosis). Involvement of the larynx may produce hoarseness. Hair
Type III (Schafer-Brunauer type) consists of the findings of type I plus leukokeratosis of the cornea.

Involvement of the nails alone has been reported in two families [15,16]. Isolated reports of additional features have appeared: impaired immunological response to Candida antigen [17], polyneuropathy and signs of neurofibromatosis [18], tuberous sclerosis [19], mottled hyperpigmentation and amyloid deposition [20], hidradenitis suppurativa [21] and squamous carcinoma in a persistently ulcerated area [9].

Prognosis. The condition is progressive, with the hyperkeratosis producing marked pain on walking.

Treatment. Emollients and keratolytics are usually prescribed with improvement in the milder cases. Acitretin 25–35 mg/day make the keratin more flexible and less pronounced without complete clearing [22,23]. Retinoids produce a reasonable degree of flattening of the nails if given for prolonged periods. Surgical excision of the keratotic masses is sometimes attempted, but recurrence around the margins is frequent.

REFERENCES

Tylosis

In 1958, Howell Evans described two families in which autosomal dominantly inherited palmpoplantar keratoderma was associated with the later development of oesophageal cancer [1]. Although originally described as tylosis or diffuse, non-epidermolytic palmpoplantar keratoderma, reappraisal of this family has shown that the lesions predominantly affect the pressure points of the sole, not the palm, and therefore the lesions should be considered as a focal palmpoplantar keratoderma [2]. There was also variable oral leukokeratosis and follicular prominence. Thirty-seven per cent of affected family members developed oesophageal cancer 30–40 years later. Although the pattern of lesions follows the distribution of keratins K6 and K16 in normal epithelia, linkage analysis excluded the keratin gene clusters, but found a highly significant lod score to a locus on chromosome 17q23 [3], a site of no known candidate genes and labelled the TOCG locus (for tylosis with oesophageal cancer). A further extensive German–American family has been reported, also with an increased (38-fold) risk of oesophageal cancer and a focal keratoderma with oral leukokeratosis. Recombination events have narrowed the TOCG locus to a single polymorphic marker D17S1603 [4]. Positional cloning is in progress, but clearly an identical clinical picture can result from K16 mutations and the TOCG gene.

REFERENCES


Keratosis palmoplantaris areata/striata [1,2] SYN. SIEMENS’ SYNDROME

Molecular biology. Linkage analysis of a pedigree for striated form of palmpoplantar keratoderma has localized the locus to chromosome 18q, near the desmosomal cadherin gene cluster [3].

Clinical features. There is marked variability of phenotypic expression in this disorder, which is paralleled by recent findings of genetic heterogeneity [3–5]. The condition is inherited as an autosomal dominant. The earliest sign is palmar or plantar erythema, followed by islands of, or linear, hyperkeratotic lesions [7]. The onset may be delayed to the second decade, but considerable intrafamilial variation occurs. Furthermore, in some kindreds, including that reported by Siemens, some individuals show areate or striate lesions, while others have diffuse keratoderma. In some reports, the large keratotic masses are referred to as ‘focal keratoderma’ (Fig. 34.52), while others record the presence of more punctate lesions, often referred to by the eponymous title Brunauer–Fuhls keratoderma. Separation of a variants-type on this basis has been suggested [7]. Lesions may be insular on the soles and linear on the palms (Fig. 34.53). Histologically, the condition is indistinguishable from many other keratodermas, but in one case [8] there was complete absence of a granular
major envelope protein loricrin, are somewhat puzzling [5]. Loricrin is widely expressed in the epidermis and yet Vohwinkel's is a localized disease; also, the honeycombing and mutilating change need to be explained biologically. This serves to illustrate that finding gene mutations does not always explain the disease phenotype.

**Clinical features.** This syndrome is inherited as an autosomal dominant. Palmoplantar keratoderma is present from infancy; it is diffuse, but honeycombed by small depressions. From the fourth or fifth year, but sometimes as late as the third decade, constricting fibrous bands lead to progressive strangulation of the digits. There may be gross mutilation of the hands and feet from loss of digits (Fig. 34.54). Starfish-shaped keratoses on the dorsa of the fingers and knees are distinctive (Fig. 34.55) [6]. Associated features may include alopecia, deafness, spastic paraplegia, myopathy and ichthyosiform dermatoses [7-9]. Isolated cases have occurred in which the mode of inheritance may have been different, and was possibly of autosomal recessive type [10]. In another patient [11], there was grossly mutilating keratoderma in association with keratosis of the groins and perianal skin and sparse dystrophic hair.

Constriction of the digits may occasionally complicate the keratoderma in mal de Meleda, Olmsted syndrome and pachyonychia congenita; it also occurs in ainhum, leprosy and scleroderma. The cases reported in a black family that showed features resembling papuloverrucous keratoderma demonstrate the difficulties of precise classification [12].

**References**

Congenital palmoplantar and perioral keratoderma [1]
S Y N. O L M S T E D S Y N D R O M E

Nine cases have now been reported of this syndrome [2–9], and a possible tenth with corneal dystrophy [10]. All patients have been male. In one, a maternal uncle was affected [8], and in another the mother [6]. Identical twins with simultaneous onset were reported [9].

The onset is in the first year of life. Symmetrical, sharply defined palmar and plantar keratoderma surrounded by erythema appears with flexion deformities of the digits, leading to constriction or spontaneous amputation (Fig. 34.56). Other abnormalities include periorificial erythema and warty hyperkeratosis (Fig. 34.57). Striking linear keratoses on the flexor forearms were seen in Poulin's case [4]. Universal alopecia, nail and tooth anomalies and joint laxity have been reported in several. The condition can be confused with acrodermatitis enteropathica, hidrotic ectodermal dysplasia of the Clouston type, mal de Meleda and mutilating keratoderma (Vohwinkel).

Fig. 34.56 Olmsted syndrome: gross keratoderma with striate features. (Courtesy of Professor R.K. Winkelmann, Mayo Clinic, USA.)

Fig. 34.57 Olmsted syndrome: periorificial hyperkeratosis. (Courtesy of Professor R.K. Winkelmann, Mayo Clinic, USA.)

Etretinate has been used in several cases with only modest or no improvement. Topical tretinoin slightly improved the keratosis but proved irritant in Poulin's case [4].

REFERENCES

Papillon–Léfèvre syndrome [1,2] (Figs 34.58 & 34.59)

Definition. An inherited disorder of keratinization characterized by redness and thickening of the palms and soles, associated with periodontosis and a tendency to frequent pyogenic skin infections.

Aetiology. The condition is inherited as an autosomal recessive, affecting both sexes equally and all races.

Fig. 34.58 Papillon–Léfèvre syndrome: diffuse plantar hyperkeratosis.
Fig. 34.59 Papillon-Léfevre syndrome: loss of dentition.

Parental consanguinity is common. The prevalence has been estimated as one to four per million [1].

**Pathology.** Leukocyte function is disordered. Decreased neutrophil phagocytosis [3] and impaired reactivity to T- and B-cell mitogens [4,5] with only minimal changes in monocyte function [6] might account for the prominent gingival and cutaneous infections. Immunological tests may, however, be normal [7]. Virulent Gram-negative organisms invade the alveolar socket, usually including *Actinobacillus actinomycetemcomitans* [8]. Non-infective mechanisms of disruption of the gingival fibroblast and cementoblast function have also been considered [9]. Histopathological changes are non-specific, but show hyperkeratosis with irregular parakeratosis and a moderate perivascular infiltrate. Electron-microscopic findings include lipid-like vacuoles in the comeocytes and granulocytes, reduction in tonofilaments and irregular keratohyalin granules. These changes improve during retinoid therapy [10].

**Clinical picture.** The condition associates three elements:

1. transgredient palmoplantar keratoderma;
2. periodontal disease leading to shedding of primary and secondary dentition;
3. recurrent cutaneous and systemic pyoderma.

Erythema precedes the keratoderma, which appears in the first year of life, and spreads to the dorsal surfaces and up the Achilles tendon (transgrediens). Psoriasiform plaques on the knees and elbows are common in older patients.

Associated hyperhidrosis causes an unpleasant odour [11]. The hair is usually normal but may be sparse. Frequent pyogenic infections of the skin and internal organs occur [12].

Periodontosis resulting in severe gingivitis leads to the loss of teeth by the age of 4 or 5 years unless treated. The permanent teeth may be lost in the same fashion. The mechanisms have been reviewed [2]. Dural calcification, especially in the attachment of the tentorium and choroid, has been noted in some cases.

**Treatment.** Before the advent of retinoids, dental clearance and antibiotic therapy was advised. Etretinate [12–14], isotretinoin [15] and acitretin [10] have all been successful in improving the keratoderma, lessening the gingival inflammation and saving the teeth.

A variant syndrome combining the classical features with arachnodactyly and acro-osteolysis has been described [16,17].

The Schopf–Schulz–Passarge syndrome combines hydrocystomas, hypotrichosis, hypodontia and palmoplantar keratoderma [18,19].

**REFERENCES**

Oculocutaneous tyrosinaemia [1–5]
SYN. TYROSINAEMIA TYPE II; RICHERH–HANHART SYNDROME

Definition. An inherited deficiency of the enzyme tyrosine aminotransferase associated with palmoplantar keratoderma, dendritic corneal ulcers and progressive mental impairment.

Molecular biology. The condition is caused by a deletion of the tyrosine aminotransferase gene at 16q21.1–q22.3 [6].

Aetiology. Inheritance is by an autosomal recessive gene that causes deficiency of tyrosine aminotransferase, leading to increased levels of serum tyrosine [6–8]. Urinary reducing substances and aminocaciduria are found.

Pathology. Biopsy shows acanthosis with hyperkeratosis and hypergranulosis. At ultrastructural level, the keratinocytes contain clumped tonofilaments with adherent globoid keratohyalin granules resembling ‘dew drops on a blade of grass’ [9]. Slit-lamp examination of the ocular lesions shows crystals of tyrosine [10].

Clinical features (Fig. 34.60). In the first year of life, photophobia and corneal ulcers occur. At this stage, slit-lamp examination may permit the diagnosis to be made.

A year or two later, erythematous areas appear on the pressure-bearing areas of the soles, soon to be followed by extremely painful circumscribed hyperkeratoses, making the child walk on the toes. The onset of the keratoderma may be delayed to the second decade [11]. The keratoses vary from gross keratoderma to dry lamellar patches. Bullous lesions and hyperhidrosis are sometimes seen. Unless correctly treated, behavioural problems arise within a few years and progressively worsen, ending in inanition or death. Chitayat et al. [15] reported a family in which two siblings both had hypertyrosinaemia, but only one showed signs of the Richner–Hanhart syndrome [15]. It is difficult to explain this observation.

Treatment. Early institution of a low phenylalanine and tyrosine diet causes prompt resolution of the ocular and cutaneous symptoms and prevents the development of mental disorder [4,8,12–14].

REFERENCES

Punctate keratodermas
The punctate keratodermas cause much confusion because of an impossibly varied nomenclature and differing usage of the terms. Whatever name is applied to the various

Fig. 34.60 Oculocutaneous tyrosinaemia (Richner–Hanhart syndrome). Callosity-like hyperkeratoses.
disorders, it should be realized that different types of lesion may be found; on some occasions, a whole family may show only one type of lesion, on others there is much interindividual variation in the lesions observed. In Fig. 34.61 some of the types of lesion are shown diagrammatically. The variation can be clearly seen in figure 2 of reference [1], where in the same individual the lesions are papular on the palms and soles (or areata) on the soles. Whether each morphological pattern justifies a different name is doubtful. Genetic linkage studies will undoubtedly give further help in elucidating the problem.

A large clinical study in Croatia has clearly demonstrated that the terms papulosa, punctata and disseminata should be regarded as synonymous, and that the older complex morphological terms should be discarded [2]. For convenience, Table 34.10 lists many of the terms used in the literature. Where the pattern is entirely that of small lesions (Fig. 34.61a), punctate porokeratosis should be excluded by histopathological examination.

REFERENCES

11. Kehall DJ, Stevers HP, Rainavel R et al. Genetic linkage studies in non-

**Table 34.10** Terms used in the literature for punctate keratoderma.

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Disseminated clavus of hands and feet (Davies-Colley)</td>
<td>Focal acral hyperkeratosis</td>
</tr>
<tr>
<td>Focal acral hyperkeratosis</td>
<td>Hereditary painful callusitis</td>
</tr>
<tr>
<td>Hereditary palmar-translucent acrokeratoderma</td>
<td>Keratoma dissectum hereditarium palmare et plantare (Brauer)</td>
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<tr>
<td>Keratosis punctata palmoplantaris</td>
<td>Keratoderma palmoplantar papulosa (Buschke-Fischer)</td>
</tr>
<tr>
<td>Keratoderma palmoplantar papulosa</td>
<td>Keratoderma punctata hereditaria</td>
</tr>
<tr>
<td>Keratoderma maculosa disseminata symmetrica palmaris et plantaris</td>
<td>Keratosis palmoplantar papulosa seu maculosa</td>
</tr>
<tr>
<td>Keratosis palmoplantar papulosa seu maculosa</td>
<td>Multiple minute palmoplantar digitate hyperkeratosis</td>
</tr>
<tr>
<td>Porokeratosis palmoplantar papulosa</td>
<td>Porokeratosis palmipalemaire palmaire et plantaire (Mantsou)</td>
</tr>
<tr>
<td>Porokeratosis palmipalemaire</td>
<td>Porokeratosis punctuée palmoplantaire</td>
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<tr>
<td>Porokeratosis punctuée palmoplantaire</td>
<td>Punctate keratoderma of the palmar creases</td>
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<tr>
<td>Punctate keratoderma of the palmar creases</td>
<td>Palmoplantar keratosis acuminata</td>
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<tr>
<td>Palmoplantar keratosis acuminata</td>
<td>Spiny keratoderma of the palms and soles</td>
</tr>
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**Punctate keratoderma** [1–3]

**SYN.: BRAUER–BUSCHKE–FISCHER KERATODERMA**

The condition is inherited as an autosomal dominant. The sexes are equally affected with an incidence reported as 1.17 per 100,000 [2]. The onset of the condition is much later than the diffuse hereditary keratomas with lesions appearing in the later teens, twenties or later. Pin-point, hard, keratotic papules initially rather translucent and later opaque and warty, appear on the palms and soles (Fig. 34.62). In many families, small and large lesions coexist, and the finding of broader focal callous-like lesions on the soles has been mentioned. In contradistinction to diffuse hereditary keratoderma, there is no associated hyperhidrosis. Lesions can be picked out leaving a small depression, which on occasion may bleed. New lesions reform. Lesions are more florid in manual workers. Two patients in the report by Salamon et al. [4] also suffered from neutropenia and neutropenomalacia. These authors list a number of other reported congenital associations. To these can be added spastic paralysis [5], anodontia [6], HLA-B27 associated arthropathy [7], and freckle-like hyperpigmentation on the dorsa of the hands and feet [8]. Several families have been reported in association with diverse Lynch type II malignancies [9,10].

**Molecular biology.** The possibility of a keratin gene mutation being responsible for this pattern of keratoderma has been excluded by linkage analysis in two unrelated pedigrees, who had multiple cancers. A lod score of −2.3 for the keratin cluster on chromosome 17, and −3.26 for chromosome 12 cluster, at least means that other mechanisms than keratin mutations are responsible for punctate keratoderma [11]. A genome search is being undertaken to further characterize the disease gene.

**Treatment.** Topical retinoids and calcipotriol have only a slight effect on softening the keratoses but may be tried. Results with systemic retinoids are better but variable. Etretinate 0.5–1 mg/kg/day produced good results in three patients, moderate in four and no effect in two patients [12]; acitretin was rapidly effective in another case [3].
Fig. 34.61 Morphological patterns seen in palmoplantar keratoderma. (a) Small, even papules; (b) predominantly larger papules; (c) mixture of small and large papules; (d) focal or areate; (e) mosaic; (f) linear; (g) striate; inset shows linear keratoses ‘Kung-sign’ Chinese character Kung; (h) and (i) transgressions (spreading beyond confines of palms and soles).


**Spiny keratoderma**

**SYN. MUSIC BOX SPINE KERATODERMA**

In recent years, a number of papers have appeared in which keratotic lesions have been variously described as filiform, spiked, spiny, minute digitate, minute aggregate, musc-box spine and possibly others. They are characterized by keratotic lesions, which are fine and project a millimetre or so from the surface. The terms used mask enormous morphological differences between cases, see for example the fine lesions in [1] and those in [2], both referred to as spiny. The taxonomy of these conditions is debatable, as
it appears from the reports that there are quite a number of different aetiologies. Attempts have been made to provide a unifying clinical classification based on clinical and histological features [3–5], (Table 34.11). Only those conditions affecting the palms and soles are described here (see also disseminated varieties and porokeratosis).

Lesions may be inherited as an autosomal dominant, when they appear in the second or third decade [6]; they may also involve the trunk or occur alone, and may be of late onset and sporadic, lacking a family history. In addition, they may show compact orthohyperkeratosis, patchy or pronounced parakeratosis, or features somewhat resembling porokeratosis. Finally, some cases fulfill all the histological criteria for being porokeratotic. Tosti et al. [7] found dyskeratotic foci in the nail matrix. The cases of Anderson et al. [1], a mother and daughter, both had in addition polycystic kidneys and liver cysts. Other associations reported include Darier’s disease [3], epidermodysplasia verruciformis [2], nodular melanoma [5], renal failure [8] and tuberculosis [9].

Mention should be made of profuse filiform keratoses associated with multiple myeloma and with HIV-associated pityriasis rubra pilaris.

Treatment. Keratolytics are usually prescribed but are rarely successful. Etretinate gave variable slight improvement [2] or good results [7]. Topical 5-fluorouracil ointment cleared the lesions temporarily in one patient [10] but failed in another [1].

REFERENCES


Acquired punctate palmar keratoses and cancer

The association between arsenic ingestion, keratoses and malignancy is well known (Chapter 36), but it is likely that other carcinogens may also predispose to the development of palmar keratoses. One survey showed that palmar keratoses occur four to five times more frequently in patients with cancer than in controls [1] and, although this has been denied [2], other groups have confirmed an increased incidence of keratoses in patients with lung or bladder cancer [3,4]. The underlying link is obscure, but the incidence of keratoses was raised in patients who smoked [4]. Another possible link could be an infection with a type of human papillomavirus [3]. These keratoses can be separated histologically from arsenical keratoses [5]. Bennion and Patterson have reported hereditary punctate keratoderma in association with cancer of the colon [6].
Marginal and inverse keratodermas

Since the last edition of this book, there has been active discussion of the relationship and identity of several of the conditions described in this section, and the questions are by no means resolved. Jacyn and Smith [1], who described the mosaic keratoderma [1], pointed out that it is not a marginal keratoderma [2] and it is only included here for convenience.

Some confusion has arisen in relation to Costa’s collection of 13 cases on both morphological and histological grounds (see below). The problem is compounded by the fact that the lesions illustrated in the paper by Dowd et al. [3] are also seen in many of the illustrations of keratoelastoidosis in Costa’s thesis [4]. These lesions have been referred to as crateriform or cupuliform lesions. They are clearly marginal, but are not the lumpy papular lesions understood by the term acrokeratoelastoidosis, nor are they degenerative collagenuous plaques. This relationship has been discussed [2,5]. Figure 1 in the paper by Dowd et al. [3] shows that the patient has marked punctate keratoses of the palmar creases. Focal acral hyperkeratosis of Dowd et al. may therefore overlap with punctate keratoderma of the palmar creases. Further studies are required, more particularly on the status of the connective tissue in all of these disorders, those thought to be genetic as well as those attributed to solar or petrochemical damage [6].

1 Keratosis punctata of the palmar creases [7,8] (Figs 34.63 & 34.64). Hard, warty lesions of the finger and palm creases are seen, often with a clavus-like lesion at the medial border of the distal palmar crease. Largely but not solely found in Afro-Carribeans [9,10] and inherited as an autosomal dominant.

2 Focal acral hyperkeratosis [3,6]. Similar findings to the above, with similar distribution, but with the addition of oval or polygonal crateriform papules along the borders of the hands and feet. No solar damage or elastorrhexis was seen in these patients.

3 Acrokeratoelastoidosis of Costa [4,11–13] and focal acral hyperkeratosis [3] appear to be clinically similar, marginal keratodermas composed of cornified papules, some of which may become umbilicated, distributed along the borders of the hands and feet (Fig. 34.65). In the 13 cases described by Costa, fragmentation and rarefaction of elastic fibres in the dermis was noted in addition to focal hyperkeratosis. Only the latter feature was described in the 15 clinically identical cases reported by Dowd et al. (they included ultrastructural studies). Whether the elastic tissue changes are a genuine feature of this condition or whether they are a non-specific finding related to the site will not become clear until adequate controls are examined. In Costa’s group of 13 patients, eight were unequivocally identical to focal acrokeratoderma, while the details on four were inadequate for assessment. Case 13 [11] differed markedly, and showed widespread polygonal papular lesions over the ankles and shins. This latter case is similar to that reported by Jacyn and Smith under the title mosaic acral keratosis (see below) [1]. A similar case is illustrated in the review by Schulz [14].

4 Degenerative collagenuous plaques [4,15–17]. These are firm plaques, sometimes concave, forming a linear band principally around the web of the thumb and index finger at the margin of the volar and dorsal surfaces. There is marked clinical and histological evidence of solar damage. For a discussion of the significance of the histological findings see [18].

5 Porokeratosis of Mantoux. Regular crateriform lesions are seen all over the palms, not confined to the marginal areas. Careful attention to the genetic background, morphology and histology of the lesions may allow future clarification of the nosological relationship of these conditions.

REFERENCES

Other keratoderma syndromes

Palmoplantar keratoderma with leukoplakia

It is likely from recent studies that cases reported with this title represent a heterogeneous group including pachyonychia congenita, dyskeratosis congenita and focal keratoderma [1]. Florid oral papillomatosis also combines oral leukoplakia and a keratoderma [2].

Papillomatoverrucous palmoplantar keratoderma

The association of a florid, warty keratoderma, dysplastic teeth and follicular keratoses was reported in four siblings in one family, with a possible autosomal recessive mode of inheritance [3]. Baran and Juhlin [4] reported a similar case, which responded to etretinate.

REFERENCES


Keratoderma with scleratrophic of the extremities

SYN. HURIEZ SYNDROME

This autosomal dominant condition was reported in 44 of
156 members of three Belgian families. It was present from birth. Atrophic, parchment-like skin over the dorsal surface of the hands was associated with diffuse keratoderma, more marked on the soles than the palms. Dense hyperkeratosis giving a pseudosclerodermatous appearance, with nail atrophy, completed the picture. Squamous cell carcinomas of the affected skin developed in six cases, and internal malignancy was the cause of death in six out of 33 deaths recorded [1–5]. One of the original families was re-examined and reported in 1995 [6]. Additional findings were that the palms were more often affected than the soles, the keratoderma lacked an underlying erythema, the dermatoglyphics were often absent, and the nail changes consisted of overcurvature, longitudinal ridging, onychorrhexis and koilonychia. Only two of the 23 deaths in the family were due to internal malignancy. No evidence was found to support the earlier suggestion of a linkage of the disorder to the MNS blood group on chromosome 4. Biopsies of the keratoderma and the scleroatrophy lesions were taken. In the former, acanthosis, accentuation of the granular layer and orthohyperkeratosis were seen. There was no dermal infiltrate, and connective tissue was normal. On electron microscopy the dermo-epidermal junctions and desmosomes were normal, but dense bundles of tonofilaments were seen in all epidermal layers. The granular layer showed large, course, clumped keratohyalin. In the scleroatrophic area, similar changes were seen, with the addition of thinning of the elastic fibres, which on electron microscopy had irregular borders and looked non-homogeneous. Excision repair of UV damage to lymphocytes was normal. A case with some similarities was reported by Vahlquist et al. [7].

REFERENCES

Acral poikiloderma of Weary

A curious, dry, leather-grained appearance of the palms and popular keratotic lesions on the dorsa of the hands is seen in the Weary syndrome [1,2]. This condition overlaps with the Kindler syndrome and is thought to be variant of epidermolysis bullosa.

Dowling–Meara epidermolysis bullosa

This combines florid palmoplantar keratoderma and skin fragility and blistering, a further example of the overlap between epidermolysis bullosa and disorders of keratinization [3].

Keratosis multiformis

Under this title, Salamon and Marinkovic [4] presented a patient with gross warty palmoplantar keratoderma, shiny atrophic skin on the dorsa of the feet and hands, follicular keratoses, punctate pigmentation around the neck, forearms and buttocks, and skeletal abnormalities. The parents were consanguineous.

REFERENCES

Acro-osteolysis with keratoderma [1,2]

SYN. BUREAU-BARRIERE SYNDROME

Marked diffuse keratoderma is associated with osteolysis in the forefoot area, painless ulcers of the feet and a polyneuropathy of the lower legs. A sporadic case associated with benign symmetrical lipomatosis was reported [3]. Similar changes were reported in a patient who also had angiodysplasia [4].

Keratoderma, woolly hair and endomyocardial dysfunction (see Fig. 34.47)

Seven pedigrees from Greece were reported with this constellation of symptoms inherited as an autosomal recessive condition [5]. A similar family showed an autosomal dominant genotype and diffuse Thost–Unna phenotype [6].

Keratoderma, woolly hair, follicular keratoses and blistering

A possibly unique syndrome was reported in Ecuador, which shared many features with the previous condition [7].
Keratoderma with mental retardation and spastic paraplegia

This syndrome includes spastic paraplegia in the lower limbs (present in the first 2 years of life), striate keratoderma of the palms, diffuse keratoderma of the soles (appearing from 5–13 years) and mental retardation. A probable sex-linked inheritance was reported in four brothers. Pes cavus was also seen [1].

Symmetrical interdigital keratoderma of the hands

In this sporadic condition, thickening of the interdigital spaces occurs from the second decade. The absence of occupational or other factors, and the poor response to corticosteroids or keratolytics, were said to be features supporting the diagnosis [2,3].

Knuckle pads

While thickening over the knuckles may be seen to some degree in many keratodermas and in Dupuytren's contracture, isolated lesions without a history of trauma may sometimes be seen occurring both sporadically and inherited with leukonychia and deafness as an autosomal dominant condition [4–6]. The lesions should not be mistaken for pachydermodactyly, now thought to be traumatically produced and appearing as fusiform swelling around the knuckles rather than true knuckle pads.

REFERENCES


Keratodermas and associated disorders

With a large group of genetically determined diseases, it is not surprising that many associated disorders have been reported. Some are isolated cases, and probably fortuitous, but others that occur repeatedly may be significant. The task of recording these comprehensively is beyond the scope of this volume but Table 34.12 lists many of them, with references, according to the systems involved.

REFERENCES TO TABLE 34.12

18. De Kaninsky AR, De Kaninsky CA, Shaw M. Keratodermic genodermatosis with hydrocytomas, mililiary cysts, xanthelasmas, nail and dental
Table 34.12 Keratodermas and associated diseases.

<table>
<thead>
<tr>
<th>Bone and muscle</th>
<th>Metabolic</th>
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<tr>
<td>Arachnodactyly</td>
<td>Tyrosinaemia [31]</td>
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<tr>
<td>Pes planus</td>
<td>Myxoedema [42,77]</td>
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<td>Acro-osteolysis</td>
<td>Sphingomyelinuria [51]</td>
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<td>Clindactyly</td>
<td>Beta-glucuronidasaeemia [60]</td>
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<td>Ankyllosing spondylitis</td>
<td>Abnormal cystine metabolism [58]</td>
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<td>Albers-Schönberg</td>
<td>Cirrhosis [59]</td>
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<td>Amyotrophy</td>
<td>Internal malignancy</td>
</tr>
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<td>Craniofacial anomalies</td>
<td>Colon [6,7,20]</td>
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<td>Hyperostotic spondylisis</td>
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<td></td>
<td>Epithelioa cuticulatum [3]</td>
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<tr>
<td></td>
<td>Breast [7,105]</td>
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<td>Canities</td>
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<tr>
<td>Ornychogryphosis</td>
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<td>Ichthyosis [13,25,87]</td>
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<td>Lichen nitidus [107]</td>
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<td>Pseudo-ainhum [109]</td>
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<td>Squamous cell carcinoma [73,85]</td>
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<td>Eyes</td>
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21 Fitzsimmons JS, Fitzsimmons EM, McLauchlan JJ et al. Four brothers with mental retardation, spastic paraplegia and palmoplantar hyperkeratosis.

23 Franscascetti A, Jadassohn WA. À propos de l'inconstantia pigmenti; délinitation de deux syndromes différents figurant sous le même terme. Dermatologica 1953; 106: 129-56.
25 Gansberg-Nielsen F. A curious genetic coincidence found in a study of
Keratodermas and associated disorders


Acquired keratodermas

Keratoderma climactericum [1,2]

SYN. HAXTHAUSEN’S DISEASE

Clinical features. Skin lesions start on the soles in females over the age of 45 years. There is no antecedent personal or family history of skin diseases, including psoriasis or eczema. Pressure areas such as the heel and the forefoot are involved first (Fig. 34.66). Erythema and heavy hyperkeratosis with fissuring occur, making walking painful. There is little if any pruritus. The condition slowly extends to become confluent. Later, the central areas of the palms may be affected. Symptoms may be worse in winter. Many patients are obese. Deschamps et al. [2] examined ovarian, adrenal and pituitary function with negative results. He also excluded contact dermatitis, fungal infection and found normal serum vitamin A levels. The relationship to endocrine function remains uncertain. Wachtel [3] described three young female patients in whom an identical condition arose following bilateral

Fig. 34.66 Keratoderma climactericum.