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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.
Pachyonychia Congenita: A Clinical Study of 12 Cases and Review of the Literature

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Abstract: Twelve cases of pachyonychia congenita were reviewed. The mode of inheritance was autosomal dominant. The clinical features of these patients included thickened nails, hyperkeratosis of the palms and soles, thinning of hair or alopecia, painful bullae or ulcerations of the palms and soles, leukokeratosis oris, verrucous lesions of the extremities, hyperhidrosis, premature eruption of teeth, paronychial infections, epidermal cysts with milia, and corneal dyskeratosis at times associated with cataracts. Biopsy from the plantar lesions usually revealed marked hyperkeratosis, acanthosis, moderate hypergranulosis, and minimal dermal inflammatory infiltration. Treatment with keratolytic agents and lubricants is indicated to areas of palmar and plantar hyperkeratosis but usually produces only transient benefit. Squamous cell carcinoma developed in one of the patients over the site of chronic plantar ulcerations. Areas of chronic bullous formation or ulceration should be observed for possible skin malignancy.

Pachyonychia congenita (PC) is a rare, heritable disorder of the skin first described by Jadassohn and Lewandowsky (1) in 1906. When Schönfeld reported two patients in 1980, he had found reports of about 150 other cases in the literature (2). We reviewed the cases reported since then (3–30) and studied another 12 who were seen at the Mayo Clinic between 1945 and 1987, bringing the total number to at least 250 cases in the world literature. Several different names have been applied to this entity; Jadassohn-Lewandowsky syndrome is most commonly used.

MATERIALS AND METHODS

The present clinical investigation consists of 12 patients (5 females, 7 males), from 10 families, with pachyonychia congenita. Their ages when they were first seen at the Mayo Clinic ranged from 1 month to 43 years. In 10 (83%) of the patients the clinical manifestations were either present at birth or by age 6 months (Table 1). The familial cases were a mother and son in two different families.

RESULTS

Nail changes (Figs. 1 and 2) were seen in all 12 patients. The consistency of these clinical manifestations conforms to their prevalence in other reported series. Keratoderma (Fig. 3) and leukokeratosis oris
TABLE 1. Age at Onset of Clinical Manifestations of Pachyonychia Congenita*

<table>
<thead>
<tr>
<th>Age at Onset</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present at birth</td>
<td>4</td>
</tr>
<tr>
<td>Within 1 mo of birth</td>
<td>3</td>
</tr>
<tr>
<td>Within 1–6 mo</td>
<td>3</td>
</tr>
<tr>
<td>6 mo to 17 yrs</td>
<td>2</td>
</tr>
</tbody>
</table>

* Four of 12 cases occurred in successive generations.

Figure 1. Distal two-thirds of nail bed and hyponychium are thickened with subungual keratinous mass, which pushes the nail plate upward.

Figure 2. Abnormal thickening and dystrophy of toenails.

Figure 3. Keratoderma of soles, which often causes pain on walking.

Figure 4. Leukokeratosis oris with white, opaque thickenings at the lateral aspect of the tongue. No malignant degeneration.

DISCUSSION

From a clinical point of view, three separate types of the syndrome can be distinguished, as shown in the following classification originally proposed by Kummer and Loos in 1935 (31) and later modified by Joseph in 1964 (32):

Type I—Symmetric keratoses of the palms and soles with follicular keratoses of the body

Type II—Like type I but with leukokeratosis oris (Riehl type); most common form

Type III—Includes the characteristics of types I and II and, in addition, corneal dyskeratosis

Other classifications have been proposed (2,29).
Genetics

The abnormality of the nails, being the most consistent clinical feature of this syndrome, is the most suitable marker for following genetic transmission. The syndrome is the expression of a mutant autosomal gene with dominant effect but variable expression and, occasionally, what seems to be incomplete penetrance. Rarely, autosomal recessive inheritance has been reported (25). A high frequency was noted in Yugoslavians (33) and Jews (34). A few series have had an excess of males, but in our series, as in several others, the numbers of males (5) and females (7) were almost the same.

In some families, the disorder has occurred in multiple generations. Akesson (35) described 18 patients in 6 consecutive generations and Kummer and Loos (31) reported a family with 23 patients in 5 consecutive generations. Our series included two families with affected persons in three successive generations. Figure 6 shows the pedigree of two such patients. The index patient was a 1-month-old male whose mother was known to be affected, and whose two maternal aunts and maternal grandfather were reliably reported to be similarly affected. This pedigree could be interpreted as showing X-linked inheritance, but in other families male-to-male transmission has been observed. Interfamilial variation in expression could be owing to genetic heterogeneity, either different mutations at the same genetic locus, or mutations at different genetic loci.

Clinical Manifestations

Clinical features of PC in our 12 patients are listed in Table 2. The picture is one of widespread ectodermal dysplasia. In the skin, symmetric hyperkeratoses of the palms and soles are manifested by localized or diffuse keratoderma (see Fig. 3). Sometimes these lesions have a verrucoid or exophytic appearance. Painful bullous lesions occur most commonly over sites of friction and pressure on the palms and soles. Aggravating factors include warm weather, trauma, and badly fitting shoes. The bullae often rupture and may become secondarily infected, with consequent areas of chronic erosion and deep ulcerations. Callosities with painful fissuring make walking uncomfortable. Hyperkeratotic follicular papules are present most often on the extensor surfaces of the arms and legs and on the buttocks. Verrucous lesions (see Fig. 5) usually appear on the elbows, knees, and lower legs. Epidermoid cysts, acneiform lesions, and steatocystoma multiplex (36,37) may occur on the face, neck, or trunk. Hyperhidrosis of the palms and soles and generalized astenotasis resembling ichthyosis vulgaris have also been reported. More rarely, reticulated hyperpigmentation (28) and keratotic striae are present.

At birth or soon after, the nails are thick, pigmented distally, and dystrophic. The proximal por-

<table>
<thead>
<tr>
<th>Table 2. Clinical Manifestations of 12 Cases of Pachyonychia Congenita</th>
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<tbody>
<tr>
<td>Manifestation</td>
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<tr>
<td>Nail changes</td>
</tr>
<tr>
<td>Keratoderma</td>
</tr>
<tr>
<td>Leukokeratosis oris</td>
</tr>
<tr>
<td>Keratosis pilaris</td>
</tr>
<tr>
<td>Xerosis</td>
</tr>
<tr>
<td>Bullae, callosities</td>
</tr>
<tr>
<td>Verrucous lesions</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Alopecia</td>
</tr>
<tr>
<td>Paronychial infections</td>
</tr>
<tr>
<td>Premature teeth</td>
</tr>
<tr>
<td>Acneiform lesions</td>
</tr>
<tr>
<td>Angular lesions</td>
</tr>
<tr>
<td>Dental malformations, caries</td>
</tr>
<tr>
<td>Epidermoid cysts</td>
</tr>
<tr>
<td>Laryngeal, esophageal leukokeratosis</td>
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<tr>
<td>Associated skin carcinoma</td>
</tr>
</tbody>
</table>
tions are smooth and normally attached to the lateral and proximal nail folds. Thus, the pathologic abnormality occurs in only the distal two-thirds of the nail bed. This distal portion may increase to 6 times the normal thickness, producing a subungual keratinous mass (see Figs. 1 and 2) that pushes the nail plate upward, arching it transversely, folding it longitudinally, and elevating it distally. When severe, these changes may impair fine movements of the fingers. The nails are commonly shed and re-grow with similar but more severe lesions. Their projection from the nail beds makes the nails susceptible to trauma with consequent chronic paronychial infections.

Oral lesions are almost always present in PC. They take the form of white, opaque thickenings; these may be focal striations (see Fig. 4) involving only a portion of the buccal mucosa and tongue, or they may be generalized plaques covering the entire mucosa of the tongue, lips, and cheeks. Malignant degeneration of these plaques has not been reported. Cheilitis, angular cheilosis, and atrophy of the tongue may occur and may be complicated by herpetic and candidal infections.

In PC the teeth may erupt prematurely; sometimes they are even present at birth. These natal teeth and the oral leukokeratosis may be the earliest clinical manifestations (38). Malformed teeth, multiple caries, and thinning of the incisor teeth have been reported. Congenital alopecia may be present; later there may be diffuse thinning of the hair and a dry, lusterless texture. One of our patients had premature teeth, leukokeratosis in the mouth, and an epidermoid cyst on the back.

Ectodermal dyskeratosis may affect the eyes, ears, nose, and larynx in these patients. In the eyes, corneal dyskeratosis may lead to partial blindness (39); leukokeratosis of the tympanic membrane may cause partial deafness (35). The nose may be the site of mucosal leukokeratosis; leukokeratosis of the larynx can cause permanent hoarseness (40,41).

More rarely observed features of this disorder include increased joint mobility, abnormally long bones, osteomas of the frontal bones (42), colonic polyps (36), and mental subnormality.

A skin malignancy developed over an area of recurrent bullous formation and ulceration on the plantar surface in one of our patients. One area of ulceration did not heal despite several skin-grafting procedures. A subsequent biopsy of the affected skin revealed a squamous cell carcinoma. Thus, areas of chronic bullous formation or ulceration in these patients should be closely observed for possible skin malignancy.

Histopathologic Changes

The primary histopathologic changes of the skin in PC are marked hyperkeratosis, acanthosis, moderate hypergranulosis of the epidermis (Figs. 7 and 8), and, occasionally, focal parakeratosis and follicular plugging (2,43). If the skin is injured, intraepidermal bullae may develop. A slight lymphocytic infiltrate is usually present in the upper dermis. Melanophages and epidermoid cysts sometimes are also seen within the dermis.

The nail plate and proximal nail matrix appear histologically normal, whereas the nail bed shows marked hyperkeratosis. Hard keratin arises irregularly from the nail folds. The distal nail matrix is hyperplastic and papillomatous, producing large quantities of horny material mixed with periodic acid-Schiff-positive hyalin. Consequently, the deformed nail resembles a miniature horse's hoof (44).

Pathogenesis

Three key points should be considered in a discussion of the pathogenesis of PC. First, mutations of a gene controlling the specific biochemical conversion of normal metabolic precursors could cause changes in structures of ectodermal origin. Second, in PC as in other congenital ectodermal disorders, this defect probably involves multiple ectodermal cellular structures. Finally, these defects account for the inherent structural weaknesses and lowered resistance of the skin and mucous membranes to pressure, irritation, and friction that are responsible for the clinical manifestations.

Figure 7. Biopsy specimen of nail shows thickening of nail bed and hyponychium as well as marked hyperkeratosis. (Hematoxylin & eosin; magnification 16×)
Figure 8. Biopsy specimen of sole shows hyperkeratosis and acanthosis of skin from patient with keratoderma. (Hematoxylin & eosin; magnification 51 x)

Treatment

Many kinds of treatment have been tried in PC with various degrees of success. Treatment is only palliative, however, with attempts directed at improving symptoms that cause significant disability.

In our patients the use of various lubricants and emollients, keratolytics in the form of salicylic acid plaster, protective footwear made from specially fitted rubber-base foot molds, and the combination of antibiotics and antiseptic wet dressings for secondarily infected areas produced the best treatment results. Radical excision of the nail, nail matrix, and nail bed, followed by vigorous curettage and electrodesication of nail matrix and nail bed, and skin implantation to site of nail removal can improve function and appearance (11). Systemic retinoic acid, such as isotretinoin, and aromatic retinoids have also improved the lesions (5,15-21).

SUMMARY

Pachyonychia congenita is a rare genodermatosis with an autosomal-dominant pattern of inheritance. Nail changes and keratoderma were seen consistently in all 12 of our patients. A biopsy specimen from a typical plantar lesion shows marked hyperkeratosis, acanthosis, moderate hypergranulosis, and minimal dermal inflammatory infiltration. Treatment is palliative; lubricants, keratolytics, and protective footwear were the most beneficial in our patients. Systemic retinoid treatment can be considered for severe cases.

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