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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.
Jadassohn-Lewandowski Syndrome
(Pachyonychia Congenita)

Patrick R. Dahl, Mazen S. Daoud, and W.P. Daniel Su

Pachyonychia congenita is an uncommon autosomal dominant disorder with variable expression. Symmetrical nail hypertrophy, present in nearly all cases, is accompanied by dyskeratosis and dysplasia of other ectodermal tissues. This article reviews the genetics, clinical manifestations, histopathology, and treatment of pachyonychia congenita. Many clinical features have been reported in association with this syndrome. From a review of the literature, we propose criteria for the diagnosis of pachyonychia congenita using the more important of these clinical manifestations.

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<table>
<thead>
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<th>Essential Components of Jadassohn-Lewandowski Syndrome</th>
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<td>Major criteria</td>
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<tr>
<td>Classic nail changes*</td>
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<td>Minor criteria</td>
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<tr>
<td>Autosomal dominant inheritance</td>
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<tr>
<td>Palmoplantar keratoderma</td>
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<td>Leukokeratosis oris</td>
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<td>Follicular keratosis</td>
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<td>Bullae on palms/soles</td>
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<td>Laryngeal leukokeratosis</td>
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<td>The diagnosis of pachyonychia congenita can be definitively made when the characteristic nail changes occur in association with at least one minor criterion.</td>
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<td>* The distal two-thirds of the nails are yellow-brown, thick, and dystrophic; distal subungual keratinous material elevates and transversely arches the nail plate.</td>
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In 1906 Jadassohn and Lewandowski described a 15-year-old girl with abnormally thick fingernails and toenails that had been present since birth, palmoplantar hyperkeratosis, leukokeratosis oris, and follicular hyperkeratosis of the elbows and knees. The description of the nails as "pachyonychia congenita" has subsequently been used to designate the entire syndrome. Since then, many case reports and several series of pachyonychia congenita have been published.

GENETICS

The syndrome is an autosomal dominant genodermatosis with variable expression and a high degree of penetrance. Kumer and Loos described a family with 23 patients in five generations, and Åkesson in 1967 reported 18 affected members in six generations. These and other large pedigrees support an autosomal dominant mode of inheritance. As the most striking and consistent clinical feature of pachyonychia congenita, nail dystrophy is the best marker for following genetic transmission of the disease. Rarely, autosomal recessive inheritance has been reported.

Although the phenotypic expression is variable in extent and severity, differences seem to be more pronounced between unrelated families than within the same kindred. Within the affected families reported in the literature, the clinical characteristics are nearly identical among affected members of the same kindred.

CLASSIFICATION

Several classifications of pachyonychia congenita have been proposed based on the clinical features present. The following classification was proposed by Kumer and Loos in 1935:

Type I. Hypertrophy of the nails with symmetrical palmoplantar keratoderma and follicular keratoses on the body.
Type II. Like type I but also with leukokeratosis oris (Riehl type). This is the most common form.
Type III. Includes the characteristics of type II and, in addition, corneal dyskeratosis.

Whether these subdivisions have unique genotypes or reflect variable phenotypic expression of a single disease entity is not known.

CUTANEOUS MANIFESTATIONS

The unique nail changes are the most striking feature of pachyonychia congenita and are present...
in 97% to 100% of cases (Table 1). The distal two thirds of the nails are thick, dystrophic, and yellow-brown in color. The dorsal surface is smooth, and the nail has normal attachment to the proximal and lateral nail folds. The distal subungual keratinous material elevates the nail plate and causes a transverse arching of the nail and formation of an angle of 30 to 40 degrees with the axis of the phalanx (Fig 1). The nail plates may shed spontaneously, but they then regrow with similar pathology. The elevated nails can interfere with digital dexterity, and they are easily traumatized; chronic paronychia consequently develops.

Although the nail changes are so unusual that it is difficult to confuse pachyonychia congenita with other diseases, thickened nails may also be caused by psoriasis, pityriasis rubra pilaris, Darier's disease, fungal infections, and onychomycosis.

Symmetrical hyperkeratosis of the palms and soles produces a keratoderma (Fig 2). The extent of involvement varies from discrete, small keratotic papules to involvement of the entire palmar and plantar surfaces with thick, hyperkeratotic plaques. Callosities with painful fissures are frequently present. Painful plantar bullae and oozing often develop at sites of friction and pressure. Hyperkeratotic follicular papules and verrucous lesions exist most often on the extensor surfaces of the arms and legs and on the buttocks (Fig 3). Hyperhidrosis of the palms and soles is frequently present and is in marked contrast to the rest of the skin, which is asthenic and may resemble the skin in ichthyosis vulgaris.

Multiple cutaneous cysts may be present on the face, neck, or trunk of patients with pachyonychia congenita. These may be epidermoid in na-

Table 1. Clinical Features Associated With Pachyonychia Congenita

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<th>Feature</th>
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<tr>
<td>Angular chalosis</td>
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<td>Bullae on palms/soles</td>
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<td>Corneal dyskeratosis</td>
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<td>Cutaneous cysts</td>
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<tr>
<td>Follicular keratosis</td>
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<td>Laryngeal leukokeratosis/noisness</td>
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<td>Leukokeratosis oris</td>
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<tr>
<td>Natal or neonatal teeth</td>
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<tr>
<td>Palmoplantar keratoderma</td>
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<tr>
<td>Plantar hyperhidrosis</td>
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<td>Thick nails</td>
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Fig 1. Distal two thirds of nail beds are thickened, with a subungual keratinous mass that elevates the nail plate.

Fig 2. Hyperkeratosis of soles. Painful fissures and bullae often develop.

ature or of the steatocystoma multiplex type. Hair manifestations have been reported from dry and kinky to thick and exuberant, to thin with alopecia.

Sufficent physical findings for the diagnosis of pachyonychia congenita were present at birth in 33% of the 12 patients reported by Su et al. By 6 months of age, the characteristic clinical manifestations had developed in 83%. Although the nail dystrophy is usually apparent by infancy, onset in adolescence has been reported.

A squamous cell carcinoma developed within an area of recurrent bullous formation and chronic ulceration in one of the patients reported by Su et al.

EXTRACUTANEOUS MANIFESTATIONS

Oral lesions are almost always present in pachyonychia congenita (Fig 4). White, opaque thickenings may occur focally, involving only a portion
of the buccal mucosa and tongue, or there may be generalized plaques covering the entire mucosa of the tongue, lips, and cheeks.\textsuperscript{21,22} Although candidal superinfection may occur, malignant degeneration of these plaques has not been reported.\textsuperscript{23,24} Cheilitis and angular stomatitis may be present.\textsuperscript{8,14,23}

The teeth in patients with pachyonychia congenita may be present at birth (natal teeth) or erupt prematurely in the neonatal period.\textsuperscript{10,19} In the cases reported by Jackson and Lawler,\textsuperscript{10} neither natal nor neonatal teeth had an adverse effect on the development of the secondary teeth.

Ectodermal dyskeratosis may affect the eyes, ears, nose, and larynx\textsuperscript{25} in patients with pachyonychia congenita and interfere with the function of these organs. Corneal dyskeratosis may lead to blindness,\textsuperscript{26,27} and leukokeratosis of the tympanic membrane may cause a conductive deafness.\textsuperscript{26} Leukokeratosis of the larynx can cause hoarseness\textsuperscript{21,10,11,21,28,29} and, if severe, laryngeal obstruction requiring tracheostomy.\textsuperscript{6}

The likelihood that one of these unusual sites will be involved depends, for the most part, on the pedigree under study. A rare presentation in one pedigree may stand out as a common finding in another.\textsuperscript{3,25,28}

**HISTOPATHOLOGICAL CHANGES**

The nail plate and proximal nail matrix seem histologically normal, whereas the nail bed shows marked hyperkeratosis. There is hyperplasia and papillomatosis of the distal nail matrix, with production of excessive amounts of hard keratin (Fig 5).\textsuperscript{14,23,30,31} This produces a condition similar to that of a horse’s hoof.\textsuperscript{31}

Histological examination of the keratotic follicular lesions shows irregular acanthosis, hyperkeratosis without parakeratosis, and horny plugs in the follicular orifices.\textsuperscript{16,24}
The plantar callosities (Fig 6) show irregular acanthosis, extensive parakeratosis, and hypergranulosis.\textsuperscript{4,14,32} The blisters that may be seen beneath and around these lesions arise in the upper layers of the stratum malpighii through increasing intracellular edema and vacuolization.\textsuperscript{4} Unlike friction blisters and epidermolysis bullosa of the hands and feet (Cockayne), there are no areas of epidermal necrosis.\textsuperscript{4}

The oral and laryngeal lesions show epithelial acanthosis and parakeratosis with extensive intracellular vacuolization, as seen in white sponge nevus.\textsuperscript{19,21,28,32}

**DIAGNOSIS**

No diagnostic criteria have previously been established. From a review of the literature, we propose the diagnostic criteria outlined in the "Diagnostic Criteria" section of this article.

Pachyonychia congenita is a rare autosomal dominant disorder characterized by widespread ectodermal dysplasia. The unique nail changes are the sine qua non of pachyonychia congenita. Although many tissues may be affected (Table 1), the most consistent associated findings are palmoplantar hyperkeratosis, leukokeratosis oris, follicular keratosis, palmoplantar bullae, and laryngeal leukokeratosis. Therefore, these associated features make up the minor diagnostic criteria that we have proposed.

**TREATMENT AND PROGNOSIS**

The structural and functional defects in pachyonychia congenita persist for life. Numerous treatments have been tried with various degrees of success. As treatment is only palliative, it should be directed toward improving symptoms that cause significant disability.

Painful fissures and blisters on the soles may prohibit walking. Custom-fitted footwear offers protective support. Although the improvement is often only temporary, vigorous use of topical lubricants and keratolytics combined with antiseptic wet dressings for secondarily infected areas provides good results.\textsuperscript{14} Hydrocolloid dressings over the fissures may reduce the pain and accelerate healing.

Simple avulsion of the distorted nails is inadequate because the dystrophic nail regrows.\textsuperscript{9,10,30} Curettage and electrofulguration of the nail matrix and bed or surgical excision of the matrix and bed can improve function and appearance.\textsuperscript{30}

Systemic retinoid therapy produces variable and inconsistent results.\textsuperscript{33-35} Isotretinoin (2 to 3 mg/
kg/d) cleared the keratotic papules and leukokeratosis in two patients but did not affect the keratoderma or nail dystrophy, which tend to be the major sources of morbidity. Etretinate (0.7 mg/kg/d) for 5 months resulted in marked improvement of plantar hyperkeratosis and fissuring in one adult case, but symptoms recurred on discontinuation of therapy.

Laryngeal lesions can result in hoarseness and laryngeal obstruction. Surgical excision of a focal, hyperplastic epithelial mass resulted in improvement of hoarseness. However, in the case reported by Cohn et al., the laryngeal lesions recurred after 7 months, and additional microsurgery was necessary.

ADDITIONAL

In a recent study by McLean et al., pachyonychia congenita was associated with heterozygous missense mutations in the highly conserved helix initiation peptide sequences of keratins K16 and K17 in one family each. Further studies into the physiology, distribution, and function of these intermediate filaments are necessary to correlate these molecular defects with the clinical phenotype in patients with pachyonychia congenita.

REFERENCES