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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.
Autosomal Recessive Pachyonychia Congenita

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We report the second and third cases of pachyonychia congenita inherited as an autosomal recessive disorder. Our cases were unusual, with the fingernails showing a striking leukonychia and appearing clinically as Terry’s nails. These patients were originally diagnosed as having epidermolysis bullosa simplex because of a history of a life-long blistering disorder. The clinical features and inheritance of pachyonychia congenita, as well as the reasons for the long delay in diagnosis of our cases, are discussed.

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Pachyonychia congenita (PC) has typically been reported to be an autosomal dominantly inherited condition. We have recently seen two brothers in whom pachyonychia congenita was inherited in an autosomal recessive manner.

REPORT OF CASES

CASE 1.—A 23-year-old man presented with a diagnosis of epidermolysis bullosa simplex that had been made in infancy. At the age of 3 months, he developed blisters, primarily on his hands and feet but also occasionally on other parts of his body, which healed without scarring. The blistering of his hands and feet was worse in the summer. This blistering problem was much more severe during childhood but has gradually improved over the years, and at the present time, blisters are extremely infrequent. Blisters have never occurred in the patient’s mouth. He has been seen over the years by several dermatologists who concurred with the diagnosis. Therapy with oral vitamin E in the past was of no benefit.

At the age of 3 months, the patient was noted to have a whitish thickening of the tongue and also of the buccal mucosa. These whitish areas varied in severity but never completely cleared. A chronic angular cheilitis has been a problem, and treatment with topical betamethasone 17-valerate cream has not been helpful. Discrete yellowish thickenings appeared on the patient’s palms when he was 9 years old. A more diffuse yellowish thickening has occurred on both soles. The patient’s fingernails have been noted to have a whitish appearance since he was 12 years old and have not changed significantly with time. His teeth have always been normal, and there is no history of ocular problems.

The patient has one brother who is also affected in the same manner. Two sisters and a third brother have no similar problems, and both parents are normal. There is a strong history of consanguinity between the parents; this is discussed below in detail under “Genetics.”

Physical examination revealed one intact bulla on the plantar surface of the fifth toe of the left foot. The fingernails were remarkable for a proximal area of leukonychia with obliteration of the lunulae and 3 to 4 mm of normal pink distal nail bed, giving the fingernails an appearance of Terry’s nails (Fig 1). In a few fingernails, more of the distal nailbed appeared normal, and these nails resembled half-and-half nails. No onycholysis was seen in the fingernails. The toenails showed mild onycholysis, with slight elevation of the nail plates by a small amount of yellowish subungual debris. There were macerated areas in the webbed spaces of the toes. A punctate keratoderma with 2- to 3-mm yellowish firm papules was seen on the palms bilaterally, while the soles displayed a diffuse yellowish keratoderma. Hyperkeratotic papules were seen on the dorsa of the toes and fingers. The patient’s tongue had a thick well-demarcated whitish coating on the dorsum (Fig 2), with whitish areas on both buccal mucosal surfaces. Angular cheilitis was evident bilaterally. The patient’s teeth appeared normal, and no cysts were seen on his skin. He has been assessed by an ophthalmologist and has no evidence of any corneal abnormality.

The constellation of features, with leukokeratosis of the tongue and buccal mucosa, keratoderma of the palms and soles, keratotic papules on the toes and fingers, bullae, and unusual nail changes, was felt to be compatible with a diagnosis of PC rather than epidermolysis bullosa simplex.

Laboratory studies revealed a normal complete blood cell count and normal hepatic and renal functions. A swab

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from the mouth yielded a few yeast cells on culture. Fungal scraping from the right first and fourth toenails yielded *Trichophyton mentagrophytes*. Both *T. mentagrophytes* and *Corynebacterium minutissimum* were isolated from the cultures of the webbed spaces of the toes. No fungus grew on cultures of the fingernails.

**CASE 2.**—The 28-year-old brother of patient 1 has had similar clinical features and was believed to have epidermolysis bullosa simplex. At the age of 3 months, he was noted to have a whitish coating on his tongue. Blisters on his hands and feet developed later, around the age of 3 years, but are very infrequent at the present time. The yellowish thickenings of his palms and soles were noted at the age of 10 years. The patient has also had white nails for as long as he can remember, but the exact age of onset is uncertain.

Physical examination revealed no intact bullae but one erosion on the dorsum of the right big toe. All fingernails showed an almost total leukonychia, except for the distal 2 to 3 mm, which appeared pink, giving the nails the appearance of Terry’s nails. There was mild onycholysis, with a small amount of subungual debris of the fingernails. The toenails appeared yellowish, with some distal onycholysis and subungual hyperkeratosis (Fig 3). A punctate keratoderma of the palms was evident, with a diffuse yellowish keratoderma of the soles. Many hyperkeratotic papules were present on the dorsum of the toes and fingers, with several follicular hyperkeratotic papules present on the left knee (Fig 4). An extensive whitish plaque covered the dorsum of the patient’s tongue. His teeth were within normal limits. The clinical diagnosis was PC.

**PATHOLOGY**

A skin biopsy specimen was obtained from the dorsum of one foot of patients 1 and 2 after preheating the skin in water at 40°C and then rubbing the area for five minutes with a cotton swab, to rule out the possibility of epidermolysis bullosa coexisting with PC. Both skin biopsy specimens were examined under the electron microscope. The specimen from patient 1 showed no evidence of bulla formation and no pathologic change. The specimen from patient 2 showed a separation in the mid epidermis associated with some degenerative changes of the adjacent keratinocytes and was believed to be compatible with a friction blister.

A biopsy specimen was also obtained from one of the follicular hyperkeratotic papules on the left knee of patient 2. It was routinely processed and stained with hematoxylin-eosin and examined under the light microscope. The specimen revealed a parakeratotic plug above the infundibular portion of a hair follicle. This resembled a cornoid lamella but was
more diffuse. The granular layer of the epidermis was absent below the parakeratotic area (Fig 5). No actual perforation into the dermis was seen.

GENETICS

There is a strong history of consanguinity in this family. The parents of the two affected children are first cousins once removed on one side and second cousins on the other side. The parents' families originate from the same small town in southern Italy. There is no family history of PC. Both parents were examined and were found to have no clinical features of this condition. The family's pedigree is shown in Fig 6. The parents' coefficient of kinship was determined to be 3/64.

COMMENT

Pachyonychia congenita is a rare genodermatosis that was first described by Jadassohn and Lewandowsky1 in 1906. They described a patient with dystrophic nails, palmar and plantar hyperkeratosis, hyperhidrosis, blistering of the feet during the summer, and leukokeratosis of the tongue.

In 1935, Kumer and Loos2 attempted to classify cases of PC into three types: Type I consists of the typical nail changes as well as symmetrical keratosis of the hands and feet and follicular keratosis of the body. Type II (Riehl type) is like type I, but, in addition, oral leukokeratosis is seen. Type III includes the features of type I, as well as corneal dyskeratosis.

More recently Schönfeld3 divided the PC syndrome into three types. Type I (Jadassohn-Lewandowsky syndrome) consists of the following: (1) symmetrical hard thickening of all finger and toenails; (2) keratosis palmaris et plantaris; (3) palmar and plantar hyperhidrosis; (4) follicular keratosis, especially on knees and elbows; (5) blister formation, especially
under and around callosities; (6) leukokeratosis of the oral mucosa and occasionally of the laryngeal mucosa, which can produce hoarseness; and (7) hair abnormalities. Type 2 (Jackson-Sertoli syndrome) has the same clinical features as type 1, but, in addition, has the additional features of associated leukokeratosis of the cornea.

Pachyonychia congenita is transmitted as a simple mendelian dominant disorder with variable expressivity. There are many family studies in the literature to support a dominant inheritance pattern, and McKusick lists two types of PC as autosomal dominants. To our knowledge, there is only one report of PC with autosomal recessive inheritance in the literature. This was a 4-year-old Malaysian girl with type 1 (Jadassohn-Lewandowsky syndrome) PC. The child was the product of a marriage between two first cousins, and, because of this, the PC was believed to be inherited as a recessive trait. However, the authors acknowledge the possibility that a spontaneous mutation could have occurred.

To our knowledge, our patients represent the second report and the second and third cases of PC inherited in an autosomal recessive manner. The history of consanguinity, as well as the occurrence of two affected brothers in a family of five children with normal parents, makes autosomal recessive inheritance extremely likely. Identical spontaneous mutations in brothers are very unlikely. A germ-cell mutation in one of the mother’s autosomes or X chromosomes is a possible explanation for two affected children. However, this is an extremely rare occurrence and, in view of the history of consanguinity, autosomal recessive inheritance is probable.

There are several other aspects of our cases that are noteworthy. Our patients had most of the usual features of Schönfeld’s type 1 PC, except for the typical nail findings. Classically in PC, the nail bed becomes hyperkeratotic and elevates the nail plate. The nail plate appears yellow or brown and assumes a progressively wedge-shaped appearance. Histologic study has confirmed that the pathologic process in PC occurs in the nail bed, with the nail plate showing no abnormality. Zaias, in analyzing two biopsy specimens from the nail bed in a mother and daughter with PC, showed that keratinization of the nail bed was completely abnormal, with individual cell keratinization of cells in the malpighian layer. It should be remembered that, although abnormal nails are characteristic for PC, they are not necessary for the diagnosis of this syndrome. Moldenhauer and Ernst reviewed 93 cases of PC and found pachyonychia was absent in three cases. In PC, the nails are usually normal at birth but become progressively discolored and thicken within the first year of life. The nails in our autosomal recessively inherited patients were remarkable because of the unusual clinical appearance and the late age of development of abnormal nails around 12 years of age. The leukonychia of the fingernails, with an appearance resembling Terry’s nails, has not to our knowledge been previously reported in PC.

Whether these unusual nail changes are a specific feature of autosomal recessive PC or merely represent a variation of the more severe changes usually seen in autosomal dominant PC is uncertain. Future case reports of autosomal recessively inherited cases are needed to answer this question. In the only other reported case of autosomal recessive PC, the nails were described as markedly hyperkeratotic, deformed, and dystrophic, an appearance similar to that of dominantly inherited cases.

It appears that a spectrum of nail changes can occur in PC, ranging from no obvious clinical abnormality, as demonstrated in the study of Moldenhauer and Ernst, in which pachyonychia could be totally absent, to the more typical PC nails, in which marked thickening of the nail bed occurs. It would have been of interest to know what the results of a nail biopsy would show in our cases, in view of the unusual clinical findings. Unfortunately, our patients declined to have this performed. We postulate that the leukonychia of the fingernails was due to a minor degree of dyskeratosis of the nail bed. The apparent late onset of the nail changes in our patients may be explained by a delay in appreciation of a nail abnormality being present, in view of the subtness of the nail changes.

The presence of T. mentagrophytes in two nails of the right foot in case 1 is interpreted as a secondary dermatophyte infection in an already abnormal nail. A tongue swab from this patient also yielded a few yeast cells. An associated Candida albicans infection superimposed on the leukokeratosis of the tongue and oral mucosa in PC has been previously described.

Several cases of PC have been previously reported as presenting as epidermolysis bullosa. The reason for misdiagnosis can be understood, when one considers that PC can have significant blistering of the palms and soles and the blistering is often worse in the summer, a similar history to that obtained in recurrent bullous eruption of the hands and feet (Weber-Cockayne) and epidermolysis bullosa simplex. Usually, the typical nail changes should make the diagnosis of PC obvious, as nail changes do not normally occur in recurrent bullous eruption of the hands and feet or epidermolysis bullosa simplex. The absence of the classic nail changes in our patients most likely accounts for the long delay in making the correct diagnosis.

We were unable to perform a biopsy on any new spontaneous blisters because these now occur very infrequently in our patients. Therefore, in order to exclude the simultaneous occurrence of PC and epidermolysis bullosa, we attempted to induce blisters in our patients after first preheating the skin. In both recurrent bullous eruption of the hands and feet and epidermolysis bullosa simplex, induced bullae form by separation through the basal layer. In one
of our patients, the induced bulla formed in the mid epidermis, indicating this was a friction blister. In our other patient, no bulla was induced after rubbing the skin for five minutes. Therefore, our patients did not have coincidental epidermolysis bullosa along with their PC.

Vesicle formation is different in PC than in epidermolysis bullosa. In PC, the cells in the upper stratum malpighii show increasing intracellular edema with progressive perinuclear vacuolization, eventually leading to intraepidermal vesicle formation. The blister formation in PC is therefore believed to be due to the abnormal keratinization that is a feature of this disease.

The pathology of the follicular hyperkeratotic papule on the knee of patient 2 is interesting, in that it showed a parakeratotic plug above the infundibular portion of a hair follicle.

Previous reports of the pathology of these papules have shown hyperkeratosis without parakeratosis, a thick stratum granulosum, and acanthosis. There is one previous report of a keratotic papule in a patient with PC showing a cornoid lamella. Also, one report described the simultaneous occurrence of PC and Kyrle's disease in the same patient, because the pathology revealed large orthokeratotic and parakeratotic plugs penetrating the epidermis to the point of breaking into the dermis. We believe these two reports represent a phenomenon similar to the parakeratotic plug shown on the biopsy specimen of our patient 2 and is simply a manifestation of the widespread abnormality of keratinization that occurs in PC.

References