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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.

Hereditary callosities with blisters

Report of a family and review

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A family with calluses of the soles associated with blistering is described. Electron microscopic study of a bulla showed an intraepidermal blister with cytolysis of keratinocytes and clumping of tonofilaments. Review of the literature and our own experience with keratoderma palmare et plantaris revealed no similar patients with this combination of findings. The appearance of the soles is similar to pachyonychia congenita, but the lack of nail and mucous membrane changes is not consistent with that disorder. Treatment with isotretinoin caused reduction in the size of the calluses but exacerbated the blistering. (J AM Acad Dermatol 11:409-415, 1984.)

Keratoderma palmare et plantaris is a relatively common cutaneous disorder that may be localized primarily to the hands and feet or associated with more generalized skin diseases. Both hereditary and acquired forms have been described. The former represent a diverse group of diseases that may be disabling because of the severity of involvement and the resulting loss of normal use of the hands and feet.

The best-known and most completely described hereditary diseases that are confined primarily to the palms and soles are listed in Table I. The
Table I. Classification of hereditary keratoderma palmaris et plantaris

<table>
<thead>
<tr>
<th>Classification</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unna-Thost</td>
<td>D</td>
</tr>
<tr>
<td>Howell-Evans</td>
<td>R</td>
</tr>
<tr>
<td>Mal de Meleda</td>
<td>R</td>
</tr>
<tr>
<td>Papillon-Lefèvre</td>
<td>D</td>
</tr>
<tr>
<td>Hereditary epidermolytic palmoplantar keratoderma</td>
<td></td>
</tr>
<tr>
<td>Keratosis punctata</td>
<td>D</td>
</tr>
<tr>
<td>Mutilating keratoderma</td>
<td>D</td>
</tr>
<tr>
<td>Keratosis striata</td>
<td>D</td>
</tr>
<tr>
<td>Progressive keratoderma</td>
<td>D</td>
</tr>
<tr>
<td>Keratoderma with skeletal deformity</td>
<td>R</td>
</tr>
<tr>
<td>Keratosis acuminata with sebaceous hyperplasia</td>
<td>D</td>
</tr>
<tr>
<td>Richner-Hanhart syndrome</td>
<td>R</td>
</tr>
<tr>
<td>Focal keratoderma and mucosal hyperkeratosis</td>
<td>D</td>
</tr>
<tr>
<td>Acral keratoderma</td>
<td>R</td>
</tr>
<tr>
<td>Painful calllosities</td>
<td>D</td>
</tr>
</tbody>
</table>

D: Dominant type of inheritance; R: autosomal recessive type of inheritance.

Fig. 1. Family with calluses and blisters. Closed circles and closed squares are affected members. Numbers are ages, and arrow indicates patient.

Unna-Thost type is the most common and has a relatively wide range of clinical expression. A number of other abnormalities have been reported in association with the keratoderma; some of these undoubtedly represent the chance association of two genetic diseases, whereas others appear to be distinct clinical and genetic entities.

This report describes a family with a dominantly inherited keratoderma in whom affected members have calluses and bullae of the soles. We have reviewed the literature on hereditary palmar and plantar keratoderma, as well as our own experience with these diseases, and have not uncovered similarly affected individuals.

CASE REPORT

A 28-year-old man was seen at the dermatology clinic of the Massachusetts General Hospital because of painful calluses of the feet that had their onset at 5 years of age. During the summer months he developed bullae at the edges of the calluses, and cellulitis with lymphangitis occurred on multiple occasions. Otherwise he has been in excellent health.

The patient’s maternal great-grandmother, maternal grandfather, mother, and one brother were reported to be similarly affected (Fig. 1). Only his brother was available for examination; he had calluses on his soles, although to a lesser extent than the proband. All affected family members had intermittent blister formation at the edges of some calluses.

The physical examination revealed a healthy young man except for numerous calluses primarily on the periphery of the soles and on the bottom and sides of several of the toes. At the initial visit no bullae were present, but tense bullae were observed at the edge of calluses on subsequent visits (Fig. 2, A and B). No bullae were observed (or reported by the patient) at sites other than at the edges of calluses. The palms, remainder of the cutaneous surface, nails, scalp, mucous membranes, and teeth were within normal limits.

Results of the following laboratory tests were negative or within normal limits: complete blood count, urinalysis, blood chemistry studies for alkaline phosphatase, aspartate aminotransferase, total bilirubin, total protein, albumin, blood urea nitrogen, creatinine, fasting blood sugar, phosphorus, calcium, uric acid, high-density lipoproteins, cholesterol, and triglycerides.

Over the years he had been treated, without much success, with a variety of topical preparations, including keratolytic agents containing salicylic acid. Paring down of the hyperkeratotic areas provided some symptomatic relief. He was given 10% glutaraldehyde, which he painted on the soles once a day; this regimen reduced hyperhidrosis but otherwise was of little help. He was placed on isotretinoin for 4 months at a dose of 2 mg/kg and this brought about a complete cure of the calluses.

MATE

Tissue obtained for histological examination showed 10% formalin fixation for 24 hours followed by embedding in paraffin at 60°C and sectioning 5 microns thick and stained to x 1, areas of necrosis with uranyl acetate.
2 mg/kg/day, which resulted in reduction in the size and thickness of the calluses. Unfortunately the blistering became more severe, and the patient had two episodes of cellulitis that resulted in our discontinuing the drug. After the patient had been off the drug regimen for several weeks, the blistering decreased but the calluses returned to their initial state.

MATERIAL AND METHODS

Tissue from the junction of a blister and callus was obtained by punch biopsy following adequate local anesthesia with 1% lidocaine (Xylocaine) without epi-
nephrine. Half of the biopsy specimen was fixed in 10% formalin solution and processed in a routine manner for light microscopy. Paraffin-embedded sections were stained with hematoxylin and eosin and the periodic acid–Schiff stain.

For ultrastructural examination, the remainder of the tissue was immediately fixed in a solution containing 2% paraformaldehyde, 2.5% glutaraldehyde, and 0.025% calcium chloride in 0.1 M cacodylate buffer. Following postfixation in 2% osmium tetroxide and dehydration in graded ethanol solutions, the tissue was embedded in an Epon-Araldite mixture. Sections, 1 μm thick, were stained with Giemsa reagent at pH 8.0 and examined by light microscopy at magnifications up to ×1,000. Ultrathin sections were cut from selected areas on a Porter-Blum MT-2 ultramicrotome, stained with uranyl acetate and lead citrate, and viewed with a Zeiss EM 109 electron microscope operated at 80 kv.

RESULTS

Light microscopy. The epidermis was moderately hyperkeratotic and hyperplastic with elongation of the rete ridges. Reticular and ballooning degeneration of keratinocytes (without viral-associated nuclear alterations) was most prominent in the midspinous region of the epidermis (Fig. 3). The granular layer was normal in appearance. Dyskeratotic cells were observed in and surrounding areas of ballooning and reticular degeneration (Fig. 4). Cellular debris and occasional erythrocytes were present in the interstices between degenerating keratinocytes. A slight, superficial, perivascular mononuclear inflammatory cell infiltrate was noted.

Electron microscopy. Lining the cavity of the intraepidermal blister were keratinocytes exhibiting nuclear and cytoplasmic organelle degeneration, intracellular edema, tonofilament clumping, and cytolysis with rupture of cell membranes (Fig. 6). Surrounding these degenerating cells there was slight to moderate intercellular and/or intracellular edema involving several layers of keratinocytes. Aggregates of clumped tonofilaments were found in some cells surrounding the blister cavity (Fig. 6), but not necessarily only in those also demonstrating intracellular edema. More distant from the blister cavity, intracellular edema of usually slight degree was observed in some keratinocytes. The basement membrane zone was intact; no abnormalities of the basal layer cells were noted in the numerous sections examined.

DISCUSSION

Review of the literature revealed several reports of individuals with keratoderma palmare et plan
taris associated with blistering, 1,16–20 and in all but
no evidence of epidermolytic hyperkeratosis by biopsy or focal involvement (calluses), were classified as the Unna-Thost type (Table II). Although biopsies were not obtained in all our patients with calluses, typical epidermolytic hyperkeratosis has been reported to be associated only with diffuse involvement. A recent report describes painful callosities demonstrating focal epidermolytic hyperkeratosis microscopically; however, the published photomicrographs are not convincing.

Some of our patients showed different degrees of involvement on the palms and soles, and variability in the clinical findings was also observed in different members of the same family (Table II). This lends further support to our classification of focal and diffuse involvement as Unna-Thost disease. However, as indicated in Table I, some authors have classified callosities as a separate entity.

Vesicles were observed in one of our patients with diffuse involvement of the palms and with calluses of the palms and soles (Case 1b in Table II). The lesions were pruritic, occurred on the diffusely involved area of the palms, and were 1-2 mm in diameter. They resembled the lesions of dyshidrotic eczema. None of our previous patients with calluses reported blistering of the normal skin or at the edge of the calluses.

The remaining ten patients with keratodermia palmaris et plantaris in our prior series included one each with the Papillon-Lefèvre and mal de Meleda types and four with the punctata type (two of whom were from the same family). Two other patients with diffuse keratodermia palmaris et plantaris had biopsies revealing epidermolytic hyperkeratosis. One of these patients reported that his father had blisters on the affected areas of the palms and soles, but details concerning the type of blistering could not be obtained. Finally, two patients had diffuse involvement of the palms and soles, but since no biopsy was obtained, the diagnosis of epidermolytic hyperkeratosis could not be excluded. Therefore these two patients' disorder remains unclassified as to subtype.

Our patient had been initially diagnosed as having epidermolyosis bullosa simplex (EBS), but neither he nor other affected and nonaffected family members had blistering of normal skin. Fur-
Fig. 4. Within and surrounding area of keratinocyte degeneration there are numerous dyskeratotic cells having darkly staining eosinophilic cytoplasm and pyknotic nuclei. Although occasional detached dyskeratotic keratinocytes were present within blister cavity, acantholytic cells were not observed. (Hematoxylin-eosin stain; original magnification, ×400.)

Fig. 5. Electron micrograph of keratinocytes at edge of blister cavity (C) reveals degeneration of nuclei (N) and cytoplasmic organelles, tonofilament clumping, and focal rupture of cell membrane (area within square) with release of cell contents. (Uranyl-lead stain; original magnification, ×7440.) Inset depicts area within square at higher magnification; focal cell membrane rupture (arrow) with release of cytoplasmic contents into blister cavity is observed. (Uranyl-lead stain; original magnification, ×30,500.)
thermore, calluses have not been reported in epidermolysis bullosa. Histopathologic differentiation of the intraepidermal blisters in our case from those of EBS of the Weber-Cockayne type may not be possible. According to Pearson,\textsuperscript{22} the blisters of the EBS-Weber-Cockayne type occur in the suprabasal area, where there is tonofilament clumping (dyskeratosis) followed by cell membrane rupture and cytolyis. However, recent experimental studies have provided ultrastructural evidence that blister formation in EBS-Weber-Cockayne type may occur in a manner identical to that observed in EBS of the generalized Koebner type.\textsuperscript{24} That is, the blisters begin between the basal layer cell nuclei and the dermoepidermal junction.\textsuperscript{24} If this finding is corroborated, then our case would not be compatible with a form of EBS.

Patients with pachyonychia congenita\textsuperscript{25} characteristically have calluses and blisters on the plantar surfaces that closely resemble the changes seen in our patient. The light microscopic appearance of one case of pachyonychia congenita was similar to that of our case. Within the stratum malpighii the keratinocytes showed ballooning resulting from intracellular edema, but unlike our case, dyskeratotic and/or necrotic (cytolytic) cells were not observed.\textsuperscript{25} Ultrastructural studies have not yet been reported. However, nail involvement is seen in virtually 100% of individuals with pachyonychia congenita, and that diagnosis is not possible in the family we have described.

Blistering following mechanical trauma is com-

<table>
<thead>
<tr>
<th>No. of cases*</th>
<th>Type of involvement</th>
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<tbody>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>Diffuse on palms and calluses on soles</td>
</tr>
<tr>
<td>1b</td>
<td>Diffuse on palms and calluses on palms and soles</td>
</tr>
<tr>
<td>2b,c</td>
<td>Calluses on palms and soles</td>
</tr>
<tr>
<td>4a,d</td>
<td>Linear bands on palms and calluses on soles</td>
</tr>
<tr>
<td>2c</td>
<td>Calluses on soles</td>
</tr>
<tr>
<td>No family history</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Diffuse on palms and soles</td>
</tr>
<tr>
<td>1</td>
<td>Diffuse on palms and soles but spares instep</td>
</tr>
<tr>
<td>1</td>
<td>Calluses on palms and soles</td>
</tr>
</tbody>
</table>

*The letters a, b, and c represent three different families, and it can be seen that the two affected members in each family had different manifestations. One of the patients (d) with linear bands on the palms and calluses on the soles had hyperkeratotic lesions on the corners of the mouth, with extension onto the adjacent mucous membranes.
mon, but there is considerable variation in the response among different individuals. However, our patient experienced blistering with ordinary activity, and it seems likely that his skin is more fragile than normal. In the case presented here, the intraepidermal blister closely resembled, by light and electron microscopy, a blister occurring as a result of friction, but it differs by having less pronounced intracellular and intercellular edema about the blister cavity. Furthermore, tonofilament clumping was prominent, even in areas lacking significant edema, suggesting that abnormal keratinization may play a role in blister formation.

The association of blistering and callus formation seems incongruous, and the mechanism underlying these changes is not readily apparent. One possible explanation is that these individuals are susceptible to injury with relatively mild trauma (possibly because of a keratinization abnormality), and callus formation is a protective mechanism. The callus, however, may produce pressure on the surrounding skin, causing a blister to form from trauma that would ordinarily evoke no reaction.

REFERENCES