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Dominant Dystrophic Epidermolysis Bullosa Albopapuloidea Pasini – Ultrastructural Observations of Albopapuloid Lesions and A Type VII Collagen DNA Polymorphism Study of a Family

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We describe a case of dominant dystrophic epidermolysis bullosa (DDEB) albopapuloidea Pasini. The patient was a 42-year-old female with albopapuloid lesions on her back, which had developed when she was 17. Histological examination of the albopapuloid lesions showed prominent proliferation of immature collagen bundles and deposition of amorphous material, which stained positively with Alcian blue. Electron microscopy of her albopapuloid lesions revealed marked nodular proliferation of collagen bundles from just beneath the basal lamina to the mid-dermis. In the light of these findings, we speculate that such albopapuloid lesions result from a reactive accumulation of collagen and glycosaminoglycan occurring on the EB skin. A *Pvu*II and *Alu*I polymorphism study of type VII collagen DNA from the patient's family suggests that the candidate gene for DDEB in her pedigree could be the type VII collagen gene. *Key words: Pasini type; glycosaminoglycan; anchoring fibrils; dermal collagen.*

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Dominant dystrophic epidermolysis bullosa (DDEB) is divided into three major subtypes, Cockayne-Touraine, pretibial and the albopapuloid variant Pasini (1). The albopapuloid variant is characterized by ivory-white papules occurring on the trunk and lumbosacral regions. Although several studies have demonstrated the histological, histochemical and biochemical characteristics of the Pasini variant (2–5) its specificity and identity are still unclear. In this report, we describe a patient with DDEB albopapuloidea Pasini, whose albopapuloid lesions were observed ultrastructurally. In addition, a type VII collagen DNA polymorphism study of the patient's family was performed.

PATIENT AND METHODS

A 42-year-old female (Fig. 1, I–2), had developed blisters and erosions on her extremities 7 days after birth, and during childhood she had suffered from blister formation and sometimes intense itching. The frequency of blister formation then diminished gradually with age but recurred during her three pregnancies. At the age of 17, she had noticed multiple white papules on her back, not caused by previous trauma. Her third, 2-year-old, son (Fig. 1, II-3), developed blisters 3 days after birth, but neither her parents, siblings nor other two sons suffer from any blistering disease. Physical examination revealed erosions and erythematous atrophic scars on her knees and feet; her nails were turbid and hypertrophic, and she had multiple, white, flat, soft papules on her back and lumbosacral regions (Fig. 2). Her affected son, however, had no similar lesions on his trunk or lumbosacral regions. Light microscopy of routine biopsy specimens from her albopapuloid lesions showed marked proliferation of immature collagen bundles and deposition of amorphous material, which stained positively with Alcian blue, in the upper half of the dermis. The epidermis was flattened. At the lateral margin of the albopapuloid lesions, rete ridges tended to extend downward and seemed to surround the albopapuloid lesions (Fig. 3).

RESULTS

Electron microscopic findings

Separation occurred just beneath the basal lamina, and the anchoring fibrils were rudimentary and diminished in number in a specimen from near a bulla. In the albopapuloid lesions (Figs. 4,5), prominent nodular proliferation of immature collagen bundles was observed from just beneath the basal lamina to the mid-dermis, and the papillary dermis was filled with numerous collagen bundles. In the dermis, the collagen bundles formed large nodules and showed subtle disorganization, and in traverse sections, the fibrils were slightly irregular in shape (Fig. 5). The anchoring fibrils were also rudimentary and diminished in number at the basement membranes of the albopapuloid lesions (Fig. 4, inset). The number of elastic fibers was not increased, and no myofibroblasts were observed in the proliferative collagen bundles.

On the basis of the above clinical and electron microscopic findings, the patient was diagnosed as having DDEB albopapuloidea Pasini. Her affected son was diagnosed as having DDEB, but DDEB Pasini was not diagnosed, since he had no albopapuloid lesions.

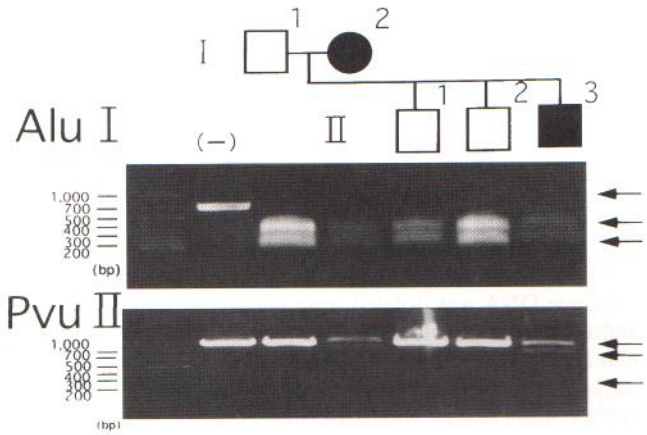

Fig. 1. Pedigree and type VII collagen DNA polymorphism study. Digestion of the PCR products by AluI (*upper panel*) and digestion of the PCR products by PvuII (*lower panel*). *Left lane*: DNA size marker; (−): undigested PCR product.

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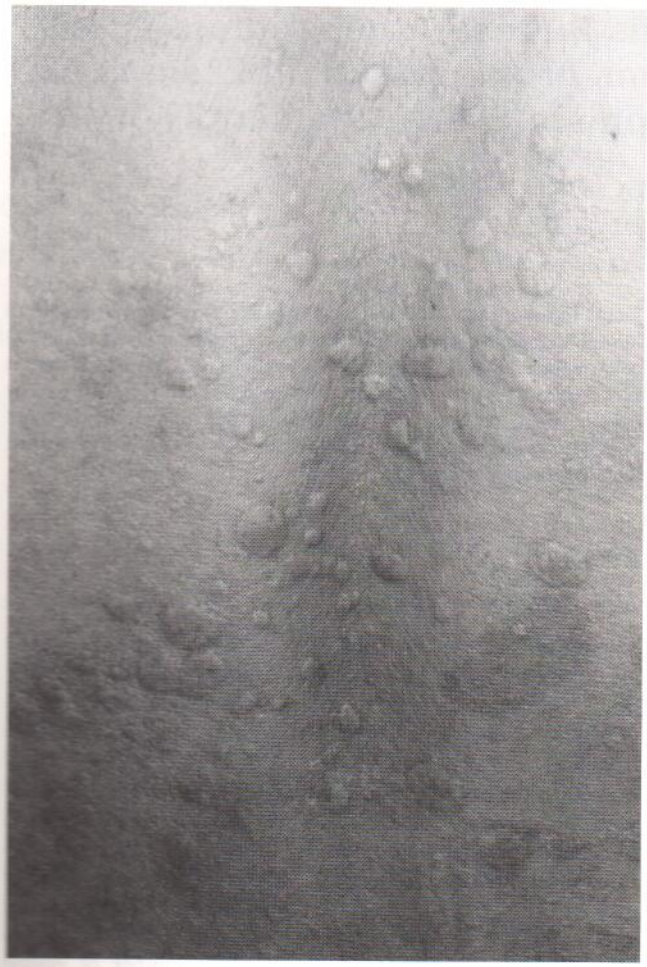

Fig. 2. Albopapuloid lesions on the lumbosacral region.

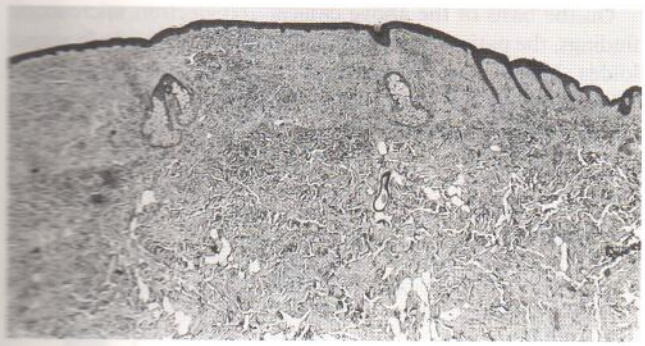

Fig. 3. Light micrograph of an albopapuloid lesion (HE staining, ×100).

Type VII collagen DNA polymorphism

Genomic DNA was isolated from peripheral blood of affected and unaffected individuals of the patient's family. The restriction enzyme *Pvu*II and *Alu*I polymorphic sites in the type VII collagen gene were amplified by the polymerase chain reaction (PCR), using specific oligonucleotide primers, with the following nucleotide sequences: 5′-CGATGAGGCACCAGATACTA-3′(sense) and 5′-GTCCACCACCACGTAGTTCAAT-3′ (antisense), for *Pvu*II site (6) and 5′-ATACTGCCATGTCCCACATC-3′(sense) and GGTCTGAAAGAGCAATGGAG-3′ (antisense), for *Alu*I site (7). The PCR products were digested with a *Pvu*II or *Alu*I and separated by electrophoresis on a 1% agarose gel. Digestion of the PCR products by PvuII resulted in the replacement of a band of approximately 1,200 bp by two fragments of 900 and 300 bp in this family. Unaffected individuals were homozygous for the 1,200-bp band, whereas affected individuals were heterozygous for the 1,200- and 900/300-bp bands. Digestion of the PCR products by *Alu*I showed that all the individuals of this family were homozygous for 420/300-bp bands (Fig. 1).

Fig. 4. Electron micrograph of an albopapuloid lesion. *Arrows* indicate basal lamina in the dermo-epidermal junction (×5,800). *Inset*: the anchoring fibrils were rudimentary and diminished in number at the basement membrane of the albopapuloid lesion.

DISCUSSION

Earlier reports have indicated that DDEB albopapuloidea Pasini is a different variant from the Cockayne-Touraine type clinically, biochemically and electron microscopically (2–5). Clinically, the most characteristic features of the Pasini variant are albopapuloid lesions, which are characterized by ivory white papules appearing during adolescence. They are independent of the bullae and occur most commonly in the lumbosacral region. The electron microscopic studies of Hashimoto et al. (2) and Anton-Lamprecht & Hashimoto (3) demonstrated the presence of structural defects of the anchoring fibrils in clinically normal skin from nonpredilection areas, whereas reduced numbers of anchoring fibrils were

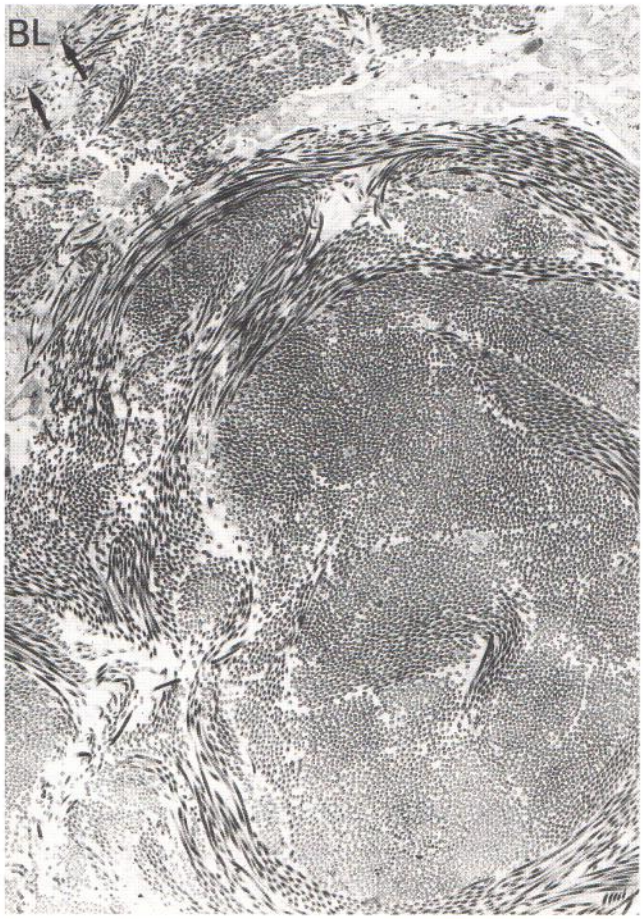

Fig. 5. Electron micrograph of an albopapuloid lesion. In the dermis, prominent nodular proliferation of immature collagen bundles is evident, and on the left upper side, the basal lamina (*BL*) can been seen (*arrows*) (×5,800).

noted only in predilection sites of patients with Pasini type DDEB. Conversely, Tidman & Eady (8) reported no significant ultrastructural differences between the anchoring fibrils in the Pasini and Cockayne-Touraine types. As far as we know, only a few ultrastructural studies on these albopapuloid lesions have been published. We observed prominent nodular proliferation of the collagen bundles from just beneath the basal lamina to the mid-dermis of our patient's albopapuloid lesions and found that the anchoring fibrils in both the nonpredilection areas and the albopapuloid lesions had a similar appearance. Histochemically, Sasai et al. (4) demonstrated increased amounts of degraded chondroitin sulfates in the papillary and subpapillary layers of albopapuloid lesions and suggested that some disturbance of acid mucopolysaccharides catabolism occurred in the lesions. In our patient, amorphous, Alcian blue-positive material was observed in the upper dermis, supporting their observation. Bauer et al. (5) reported increased synthesis and excretion of chondroitin sulfate containing glycosaminoglycans, particularly hyaluronic acid, by fibroblasts in culture. In contrast, Priestley (9) demonstrated no consistent differences between the amounts of glycosaminoglycan. Taking these findings together, we speculate that the albopapuloid lesion results from a reactive accumulation of collagen and glycosaminoglycan occurring on epidermolysis bullosac (EB) skin and is neither a simple scar nor lichenification following minor trauma.

Incidentally, albopapuloid lesions have sometimes been observed in other types of EB. Kero reported that 3 members of two families among 8 Finnish dystrophic EB families had the generalized form of Pasini, and one family had a member with both limited Pasini and Cockayne-Touraine EB (10). Ramelet & Boillat reported 3 cases of recessive dystrophic EB with albopapuloid lesions and concluded that the presence of such lesions is not necessarily a definite criterion for diagnosing the Pasini type of EB (11). Our proband had albopapuloid lesions, but her son currently has none, and it will be interesting to see whether he will develop them.

Type VII collagen is the major component of anchoring fibrils in the dermo-epidermal junction. Recent cDNA cloning of type VII collagen gene enabled us to search for molecular defects associated with dystrophic EB. Indeed, a strong genetic linkage to the type VII collagen gene was first reported in Finnish DDEB families (12). Subsequently, British (13), Japanese (14) and Dutch (15) families with DDEB were proved to be linked to the type VII collagen gene. Recently, a similar significant linkage was established in a Belgian family with the pretibial type of DDEB (16). Moreover, DNA mutation was detected in the gene coding the triple-helical domain of the type VII collagen in a Finnish DDEB family (17). Interestingly, some members of this family had albopapuloid lesions. We tried to analyze type VII collagen DNA polymorphism in this family, but the linkage between type VII collagen and this family was not informative, since the pedigree is too small to calculate the lod score. However, our results are not inconsistent with the concept that the candidate gene for DDEB in this family is the type VII collagen gene. Moreover, the mutation in this family may be on the allele possessing the *Pvu*II cleavage site. Collectively, Pasini, pretibial and Cockayne-Touraine type, or almost all DDEB patients, may have a causative mutation in the type VII collagen gene.

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