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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-Associated Alopecia. A Microscopic Analysis Using Transverse Section Technique
[Case Reports]

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Abstract

Pachyonychia congenita (PC) is a rare genodermatosis with characteristic nail abnormalities and occasional palmoplantar keratodermia and leukokeratosis oris; alopecia may occur (10% of patients). This report is the first microscopic description of a patient with PC-associated alopecia. Transverse section histologic features include diminished follicular density with preservation of follicular units, prominent miniaturization of follicles, dyskeratosis of outer root sheath keratinocytes, and moderate parakeratotic and orthokeratotic follicular hyperkeratosis. These microscopic features may be seen individually in other nonscarring alopecias, but the combination may be unique to PC-associated alopecia. Differential diagnoses include alopecia areata, androgenetic alopecia and traction alopecia/trichotillomania.

Pachyonychia congenita (PC) is a rare genodermatosis of autosomal dominant inheritance initially described by Jadassohn and Lewandowsky (1). Characteristic yellow-brown nails, marked distal subungual hyperkeratosis, and elevation of the nail plate are the primary diagnostic findings of this syndrome (2-5). Other minor diagnostic criteria include palmoplantar keratodermia, leukokeratosis oris (6), follicular keratosis, bullae on the palms and soles, and laryngeal leukokeratosis (7).
Hair abnormalities, such as diffuse alopecia and hair shaft abnormalities, may occur in some patients (8), and although hypotrichosis of the scalp is present in 10% of patients, it has not been characterized histologically. The transverse section technique is advantageous in evaluating alopecia (9,10), and this report is the first histologic analysis of alopecia in a patient with PC.

CASE REPORT

The patient is a 26-year-old Caucasian man with thickened nails since childhood and diffuse hair loss. He takes no medications and has no history of anemia. He has normal perspiration, dentition, buccal membranes, and patella. By history, the patient's father, one sister, and two brothers have similar thick nails; one brother has normal nails. The father and sister have near complete alopecia and are described as only having fine vellus scalp hairs.

On examination, all nails are thickened with subungual hyperkeratosis. Longstanding diffuse alopecia, more prominent on the sides of the scalp than the vertex, is present. A 4 mm punch biopsy from the lateral scalp was obtained.

The submitted specimen was grossly dissected, then sectioned using transverse section methods (9,10). Histologically, a moderate decrease in follicular density was observed, ~17 terminal follicles and seven follicular units were present in the 4 mm punch biopsy specimen (normal, 20-50 follicles and 10-14 follicular units) (9,10). The follicular units were largely intact with a normal number (two-three) of terminal hairs per unit and unremarkable sebaceous glands and arrector pili muscles. The follicular units were more widely spaced than usual and were separated by normal reticular dermal collagen. The anagen/telogen ratio was normal (Fig. 1).

<size=25>FIG. 1. A moderate decrease in follicular density with preservation of follicular unit morphology is seen at scanning power. Miniaturization of follicles is evident.</size=

Prominent miniaturization of follicular epithelium and hair shafts was present (Figs. 2 and 3). The diminutive follicles were small terminal follicles (shaft diameter greater than inner root sheath thickness) and vellus hairs (hair shaft diameter less than or equal to the inner root sheath thickness). Some of these miniaturized follicles were typical vellus hairs confined to the upper and mid reticular dermis with a small tricholemma, while others extended to the deep reticular dermis and superficial subcutis with a larger tricholemma.
The hair shafts had a normal round-to-oval shape. The bulbs were normal except for some miniaturization, and the inner root sheath showed typical trichohyaline keratinization. Dyskeratosis of the outer root sheath was present from the level below the entry of the sebaceous duct to the level of tricholemmal keratinization. Scattered individual dyskeratotic...
keratinocytes were more numerous in the outer root sheath below the sebaceous duct (Figs. 3 and 4). One dysmorphic catagen bulb and shaft was present (Fig. 5). The follicular infundibula were unremarkable; dyskeratosis was not present in this zone of the follicle. Follicular hyperkeratosis, both parakeratotic and orthokeratotic, was present in the distal infundibulum and acrotrichium of many follicles (Fig. 6). A rare dyskeratotic keratinocyte was noted at the dermal epidermal junction, but no true interface dermatitis was present.

FIG. 4. Dyskeratosis in the outer root sheath just above the level of the sebaceous duct (loss of inner root sheath and tricholemmal keratinization of outer root sheath).
FIG. 6. Parakeratotic and orthokeratotic hyperkeratosis of the distal follicular infundibulum.

**DISCUSSION**

The primary microscopic features in this patient with PC-associated alopecia are (a) diminished follicular density with preservation of follicular units, (b) prominent miniaturization of follicles, (c) dyskeratosis of outer root sheath keratinocytes, and (d) moderate parakeratotic and orthokeratotic follicular hyperkeratosis. None of these individual features are unique, and some may be seen in other nonscarring alopecias such as alopecia areata, androgenetic alopecia, and chronic traction alopecia/trichotillomania (Table 1). Except for the lack of peribulbar lymphocytic infiltrates and more numerous telogen bulbs, the histology of PC-associated alopecia is very similar to that of chronic-persistent or regrowth phase alopecia areata.
Histologic features of oral, skin, and nail lesions include prominent hyperkeratosis, acanthosis, and hypergranulosis. Intracellular edema and vacuolization of keratinocytes in the upper stratum malpighii has been described in vesicular lesions of the palms and soles (2,4-6). Ultrastructure studies have revealed increased tonofilaments in the peripheral cytoplasm of epidermal keratinocytes (3). However, dyskeratotic keratinocytes, seen in the outer root sheath of our patient, have not been reported in skin, nail, or oral lesions.

Recent genetic techniques have shown a missense mutation of keratin 16 in a sporadic Jadassohn-Lewandowsky PC patient, and a missense mutation of keratin 17 in a large family with the Jackson-Lawler type of PC (11,12). These keratins are usually associated with hyperproliferation, which correlates with clinically observed nail hypertrophy and hyperkeratosis of palmar, plantar, oral, and laryngeal lesions. In addition, increased expression of keratin 16 causes acantholysis and dyskeratosis of the epidermis and outer root sheath in a transgenic mouse model (13). Therefore, it is possible that the reported mutations of keratin 16 and 17 or other as yet to be determined keratin(s) result in apoptosis of the outer root sheath as well as occasional dysmorphic follicles and hair shafts. This intrinsic follicular abnormality would likely prevent full development of the follicular epithelium and hair shaft, thus leading to the prominent miniaturization observed in our patient.

REFERENCES


http://gateway2.ovid.com/ovidweb.cgi


Key Words: Alopecia; Pachyonychia congenita; Dyskeratosis; Apoptosis; Outer root hair sheath; Alopecia areata

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