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Retinoid Acid in the Treatment of Hyperkeratosis lenticularis perstans Flegel

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Received March 16, 1981

Abstract. Successful treatment with oral retinoid acid (Ro 10-9359) in a case of Hyperkeratosis lenticularis perstans Flegel is reported. Membrane coating granules (Odland bodies) could be demonstrated in all sections of lesional epidermis.

Key words: Hyperkeratosis lenticularis perstans Flegel; Keratinization disorder; Odland bodies; Oral retinoid acid treatment

Hyperkeratosis lenticularis perstans (HLP), first described in 1958 by Flegel (1), is probably an autosomal dominant keratinization disorder. It occurs as small foci on the skin, preferring the distal parts of the lower extremities. The lesions persist indefinitely.

Cases of HLP not only aroused interest because of their rarity—up to 1980 only about 40 cases of HLP have been published—but also because of a unique process of keratinization occurring in the absence of membrane-coating granules (MCG, Odland bodies) as postulated by Frenk & Tapernoux (2).

So far, fluoro-uracil (9) and dermabrasion have been found to be helpful in treating HLP. For the first time, clinical effectiveness of a systemic retinoid treatment (Ro 10-9359, all-trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3-7-dimethyl-2,4,6,8-nonatetraenoate, Roche) is reported.

CASE REPORT

Three years ago, a 71-year-old Austrian housewife observed the appearance of asymptomatic, horny papules on the dorsa of her feet. Within a few weeks new similar lesions were detected on the whole circumference of the lower legs and, less distinctly, on the thighs and on upper arms.

The patient was in fairly good health and had an uneventful personal history. Her parents, her six brothers and sisters and her son were reported to be free of similar lesions.

Examination of the affected skin revealed small reddish-brown horny papules, 1–5 mm in diameter, which could easily be removed in one piece, leaving a brilliant epidermis, with punctiform bleeding areas accentuating a psoriasiform aspect (Fig. 1). No inflammatory halo could be found around the numerous non-follicular hyperkeratoses. On palms and soles no pinpoint-sized depressions interrupting the papillary lines (as described by Kocsard, 9) were seen. Hair, nails and mucous membranes were normal.

Previous *therapeutic trials* with locally applied retinoid acid and urea had failed. Initial systemic treatment consisted of aromatic retinoid (Ro 10-9359) with a daily dose of 1 mg/kg/day. This dosage was reduced to 0.6 mg/kg/day after 10 days. Because of side effects such as headaches, and burning palms and soles, retinoid therapy had to be terminated after 6 weeks, when skin lesions had improved markedly. Within a 7-week period without treatment, the condition recurred, and a second series of treatment with oral aromatic retinoid was therefore tried. Further improvement of the hyperkeratoses could subsequently be observed.

Skin biopsies for *light microscopy* of two lesions of the lower leg were performed before retinoid treatment was started. In all sections the hyperkeratosis was mainly of

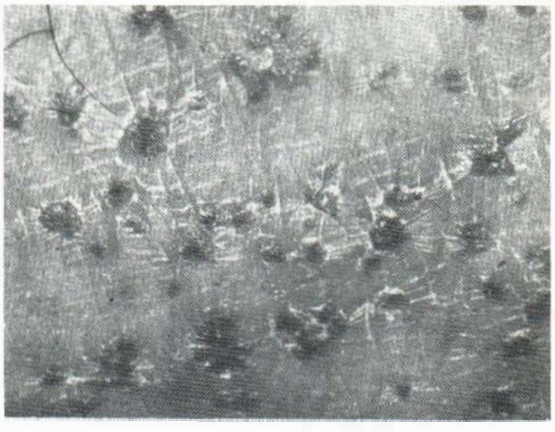

Fig. 1. Hyperkeratosis lenticularis perstans Flegel.

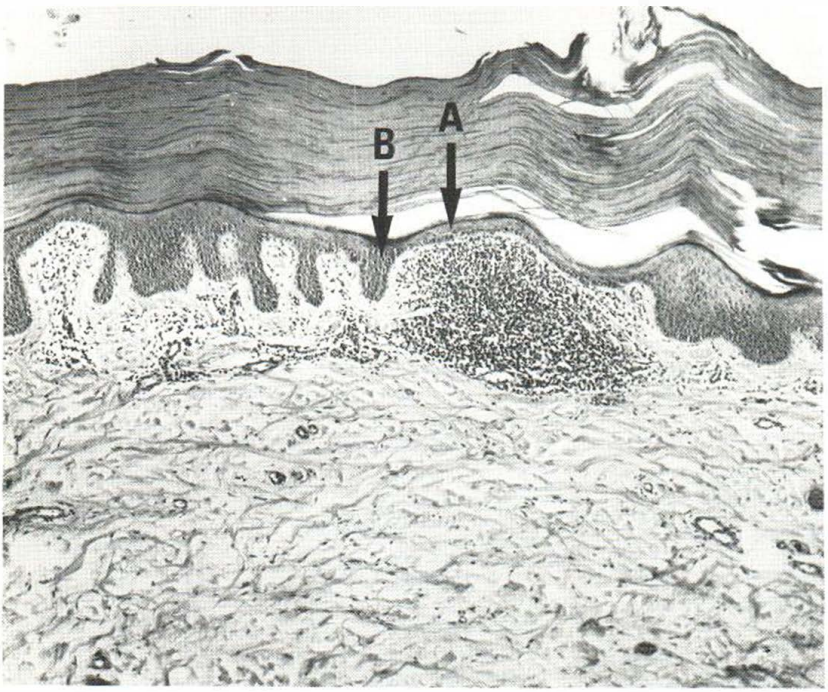

Fig. 2. HE-stained histological section. Arrows indicate zones of interest (A and B) examined by electron microscopy.

the orthokeratotic and only rarely of the parakeratotic type. The underlying epidermis appeared slightly atrophic. In some sections of the papular lesions, especially below the atrophic epidermal areas, there was a well circumscribed band-like upper dermal infiltrate, localized to the papillary and subpapillary layer, containing mainly lymphocytes and histiocytes. There was an increased number of capillaries with thickened endothelia seen in this zone. Its lower margin was rather sharply demarcated and paralleled the skin surface.

For *electron microscopy* a skin biopsy from the lower leg was obtained 7 weeks after discontinuation of systemic retinoid treatment. The material was fixed in glutaraldehyde, postfixed in O_sO_4 and embedded in Epon 812. Ultrathin sections were stained with uranyl acetate and lead citrate and examined in a Jeol 100 S electron microscope.

Two regions of interest were investigated, indicated by arrows in Fig. 2: (*a*) a section of slightly flattened epidermal layers and overlying hyperkeratotic mass above the dense dermal infiltrate; (*b*) The neighbouring normal epidermis underlying the horny papule.

In the atrophic epidermis (*a*) Odland bodies were encountered in reduced numbers, but of normal shape. MCG increased in numbers approaching the area (*b*) where these organelles were present in normal distribution. The persistence of desmosomal structures between the corneocytes up to the middle parts of the compact stratum corneum could be more frequently observed in areas (*a*) and (*b*), than in orthokeratotic skin. Arsenic in hair or nails could not be found by means of electron microscopic element analysis.

DISCUSSION

Skin lesions from patients with Flegel's disease have been reported to lack membrane-coating granules (2, 8), whereas numerous granules were present in the paralesional epidermis (2, 7).

Frenk & Tapernoux (2) were able to study 2 cases of Flegel's disease, correlating the lack of Odland bodies in lesional skin with the persistence of desmosomal discs throughout the shole stratum corneum. Subsequently, HLP was viewed as a biological model for keratinization occurring in the absence of MCG.

Two years later, Squier et al. (7) used this model for an ultrastructural tracer study of 4 patients with HLP disease. The authors could not detect lamellate MCG in lesional skin, but encountered the presence of small vesicles in the granular layer, similar in size and shape, but lacking a lamellate internal structure. Without giving detailed data, Ralfs et al. (6) presented another case of HLP, reporting Odland bodies present in normal amounts.

In contrast to the findings of Frenk & Tapernoux (2) and Van des Staak (8), Odland bodies were found in lesional skin in our investigations. It is possible that MCG are encountered regionally in varying degrees (3), since sections from HLP biop-

sies are histologically not uniform. There are distinct variations in the extent of the band-like dermal infiltrate, in the grade of epidermal atrophy above the infiltrate, and in the mass of hyperkeratosis.

One might speculate that Ødland bodies may be reduced in number or may be absent in areas of distinct epidermal atrophy, where keratohyalin is reduced and/or where persistence of the desmosomal discs in the layers of the compact stratum corneum is encountered. Observations that parakeratosis is more pronounced in areas where the underlying epidermis is atrophic and the infiltrate particularly dense (5), give support to this idea. It would seem unlikely that the retinoid acid could account for the presence of Ødland bodies in the lesions, since specimens for investigations were taken 7 weeks after discontinuation of systemic retinoid acid treatment, but it cannot be excluded that the medication had influenced the outcome.

During the last few years, oral retinoids have been found to exert a beneficial therapeutic effect on dermatoses showing hyperproliferation and disturbed keratinization. Both these features appear to be present in HLP. As has been found in the treatment of other keratinization disorders, oral aromatic retinoid has proved to be an effective agent during the time of application.

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