

Hyperkeratosis lenticularis perstans (Flegel's Disease)

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A 62-year-old female with a 20-year history of small horny papules on the skin of the legs is described. Light microscopy revealed a hyperkeratotic papule with atrophic epidermis and a dense dermal inflammatory cell infiltrate with many cerebriform lymphocytes not earlier described in connection with hyperkeratosis lenticularis perstans (HLP). The electron-microscopic picture showed membrane-coating granules (MCG) and keratohyalin located in different cells, indicating that the disorder of keratinization in HLP is possibly caused by reduced co-operation between these cells and that the keratinization process occurs in the absence of MCG. Perpetual treatment with oral retinoid was successful. (Received November 16, 1982.)

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Hyperkeratosis lenticularis perstans (HLP) is a rare disorder of keratinization occurring in elderly people and probably transmitted by an autosomal dominant gene (1). In 1958 Flegel first described the clinical picture of HLP characterized by small hyperkeratotic papules on the skin of the extremities (3). In addition to their own case, Frenk & Tabernoux reviewed the literature on 34 cases of HLP in 1976 (4). We described here a case of HLP which was successfully treated with oral retinoid. Electron microscopy was used to study membrane-coating granules and their relation to keratinization.

CASE REPORT

Clinical history. A 62-year-old female observed about 20 years ago the appearance of small stationary, horny papules on her legs. Her relatives (mother, father, two sisters, one brother, two children) do not have similar skin lesions. Thirteen years later the patient suffered a coronary heart attack and for 2 years she has had transient ischemic attacks.

Examination of the skin revealed small, flat, red-brown, hyperkeratotic papules, 1 to 2 mm in diameter, on the skin of the legs and dorsum of the feet (Fig. 1). A few smaller lesions were also noted symmetrically on the lateral aspects of the thighs, upper arms and lower arms. There were no pits on the palms or soles. Hair, nail and mucous membranes were normal.

Histopathology. Two representative hyperkeratotic papules were removed from the right leg and processed by standard histology procedures. From serial sections two distinct patterns emerged: (1) An active lesion consisting of a hyperkeratotic, slightly parakeratotic, papule with atrophic epidermis and dense dermal inflammatory cell infiltrate where the lymphocytes often had cerebriform nuclei (Fig. 2); and (2) another, probably a fully developed lesion consisting of a hyperkeratotic horny layer with slight parakeratosis, a flattened Malpighian stratum, and papillomatous elevations at the margins. There were some dilated capillaries in the upper dermis but only occasional lymphocytes were seen (Fig. 3).

Electron microscopy. A hyperkeratotic papule was removed from the skin of the patient's right leg. This sample was cut into small pieces and fixed in phosphate-buffered glutaraldehyde, pH 7.4, for 24 hours, post-fixed in OsO₄, dehydrate in graded ethanol, and embedded in Epon 812. Semithick (1 µm) sections were stained with toluidine blue and ultrathin (60 nm) sections with uranyl acetate and lead citrate. Electron microscopic examinations were made in Jeol 100C and 100U electron microscopes.

In the atrophic area of the epidermis above the lymphocytic infiltrate only a few cytoplasmic organelles were found which could be interpreted as membrane-coating granules (MCG). In the peripheral area of the lesion where the Malpighian stratum was 5 to 7 cells thick, the nucleated epidermal cells, located immediately below the fully keratinized layer, contained abundant keratohya-

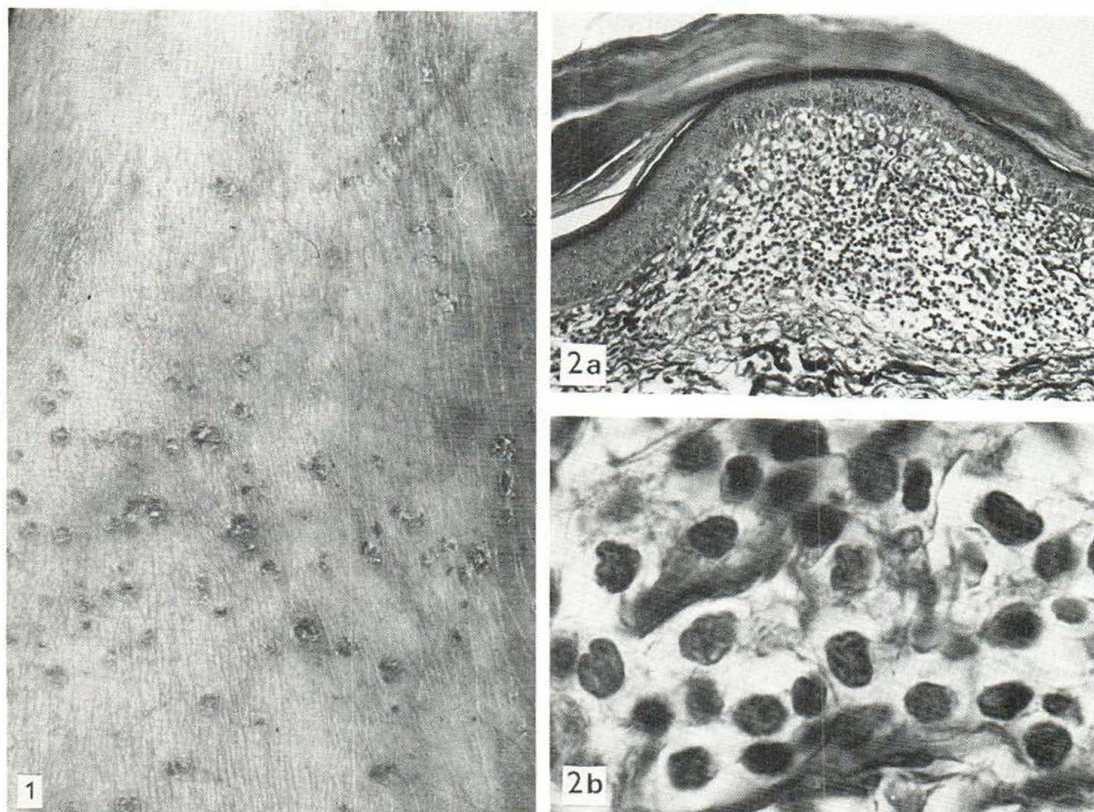


Fig. 1. Numerous small papules with horny scales on the lateral aspect of the leg.

Fig. 2. An active HLP lesion. (a) A hyperkeratotic papule with atrophic epidermis and dense lymphocytic dermal infiltrate. Herovici. $\times 100$. (b) A higher magnification of the dermal infiltrate shows lymphocytes, many of which have cerebriform nuclei. Herovici. $\times 1000$.

lin but no MCGs, whereas the cells deeper down had many MCGs but no keratohyalin (Fig. 4). Electron microscopy confirmed the cerebriform morphology of the lymphocyte nuclei (Fig. 5).

Treatment. The patient was treated with aromatic retinoid (Ro 10-9359, Tigason®). The dosage was 0.8 mg/kg/day for 4 weeks, whereafter it was reduced to 0.4 mg/kg/day for 8 weeks. Hyperkeratotic lesions disappeared completely, leaving small pitted scars, but when the dosage was reduced to 0.1 mg/kg/day the lesions began to reappear. After cessation of the treatment the condition recurred fully in 4 weeks. Perpetual therapy (0.4 mg/kg/day) was necessary to maintain the therapeutic effect.

DISCUSSION

The possible role of membrane-coating granules (MCG) in the pathogenesis of HLP has been discussed in several papers. In some studies (4, 5, 9) a lack of MCGs in the lesional area had been observed and consequently HLP had been considered to be a pattern of keratinization occurring in the absence of MCG. In other studies MCGTs have been found in normal (8) or reduced (7) numbers.

In these studies, where the MCGs had been observed to be missing or reduced in the atrophic epidermis above the inflammatory cell infiltrate, such organelles were found paralesionally in normal distribution (4, 7, 9) or even in increased numbers (5). In our case keratohyalin and MCGs were located in different cells, indicating that the disorder of

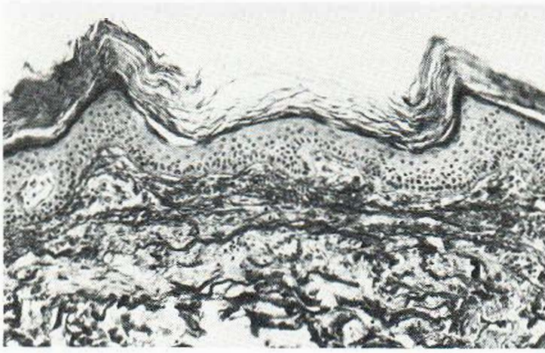


Fig. 3. A fully developed HLP lesion consisting of a hyperkeratotic horny layer with slight parakeratosis, a flattened Malpighian stratum, and papillomatous elevations at the margins. Herovici. $\times 40$.

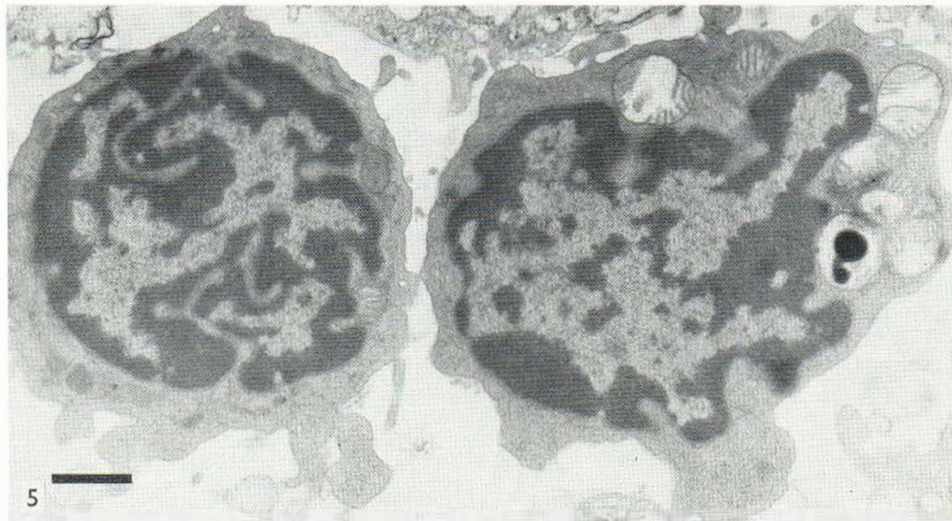
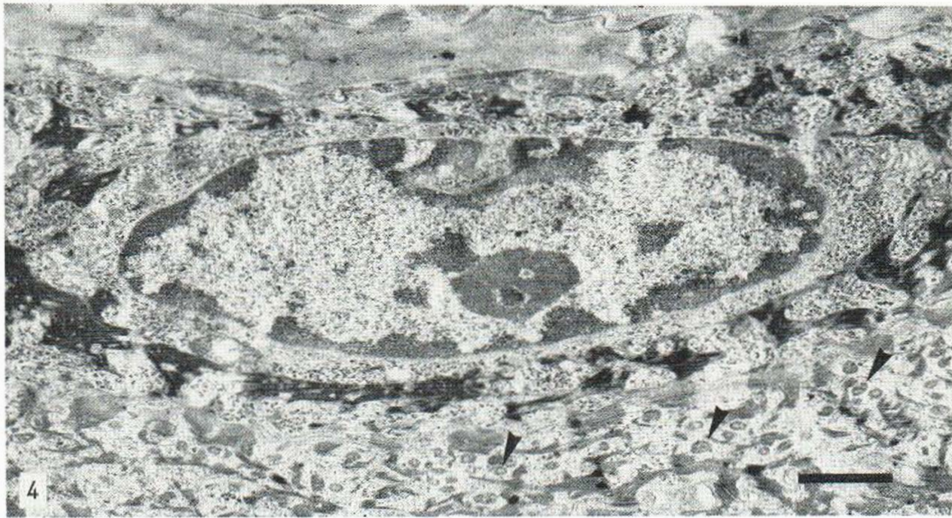


Fig. 4. A nucleated cell beneath the fully keratinized layer. This cell contains keratohyalin but no membrane-coating granules, whereas the cell deeper down has many MCGs (arrowheads) in its cytoplasm. $\times 14\,300$. Bar = $1\ \mu\text{m}$.

Fig. 5. Two lymphocytes with cerebriform nuclei in the inflammatory cell infiltrate in the upper dermis. $\times 12\,000$. Bar = $1\ \mu\text{m}$.

keratinization in HLP is probably connected with reduced co-operation between these cells.

Electron microscopic findings of the present study are in favour of the view of Frenk & Tabernoux (4) that in HLP, keratinization occurs in the absence of MCG. Ultrastructurally the disorder appears to manifest itself at the level of the uppermost nucleated epidermal cells laying below a fully keratinized layer.

In the dermal inflammatory cell infiltrate we found many cerebriform lymphocytes which were similar to the cells seen in mycosis fungoides and Sézary's syndrome and are known to exhibit T lymphocyte characteristics in lymphocyte marker studies (6). To our knowledge this is the first report on the presence of cerebriform lymphocytes in an HLP lesion and serves as an additional example of the possibility of finding this cell type also in non-lymphomatous dermatoses (2).

In many skin diseases characterized by abnormal keratinization—for example in psoriasis, various kinds of ichthyosis and Darier's disease—aromatic retinoid (Ro 10-9359) has opened up new therapeutic prospects (10). We have found only one earlier report of successful treatment of hyperkeratosis lenticularis perstans with oral retinoid (7). Perpetual administration of aromatic retinoid is required to maintain the therapeutic effect in HLP.

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