Acta Dermatovener (Stockholm) 50: 338–344, 1970

UNUSUAL CORNIFICATION IN ICHTHYOSIS-LIKE DERMATITIS

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Abstract. During recent years, a number of reports on a strange ichthyosis-like dermatitis have been presented in Japan. This is a type of contact dermatitis which is caused by the application of a certain kind of ointment containing alkyl-benzyl trimethyl ammonium chloride. The hypertrophic horny cells produced were found to contain numerous residual keratohyalin granules. Membrane-coating granules were also present in abundance in the intercellular spaces of the horny layer.

Recently, many cases of a peculiar type of ichthyosis—or xeroderma-like dermatitis—have been reported in various parts of Japan. This is a type of contact dermatitis that is caused by the application of a certain kind of ointment which consists of 0.3% alkyl-benzyl trimethyl ammonium chloride in polyethyleneglycol, a non-ionic emulsifier, etc. According to a statistical analysis of the cases examined, the majority of the patients were female (46 : 8 = ♀ : ♂); and most were quite young, 41 out of 54 cases were from 10 to 30 years of age. The site most commonly afflicted was the neck, 52 out of 54 cases; and the dermatitis occurred most frequently in the autumn and winter.

In this kind of dermatitis, the characteristic skin manifestation is well demarcated; it is skin colored or dirty brown; the exanthem is dry and scaly as in ichthyosis. Usually there is no subjective symptom except a slight irritation and stretching. The skin change usually appears 1–3 weeks after the ointment has been applied and it takes about 1 or 2 months until the skin condition disappears. The best treatment, as far as we know, is a topical application of a simple vaseline-based ointment.

This paper presents a typical case of this dermatitis and reports on the histological and electron microscopic studies done on the unusual cornification observed in this disease.

CASE HISTORY

A 22-year-old woman visited the hospital in May, 1969, because of some slightly itchy, dry, rough skin around her neck. She had had itchy skin trouble on her neck for about a year and had applied various topical ointments without any improvement. She had been using an ointment that contained of 0.3% alkyl-benzyl trimethyl ammonium chloride in polyethyleneglycol, a non-ionic emulsifier, for a week prior to coming in for treatment. As a result, increasingly itchy, dry, rough skin was brought out on her neck as shown in Figs. 1 and 2. There was a well demarcated, normal-to-brown colored, slightly erythematous dry, scaly skin lesion over the entire surface of her neck. The patient was treated with a 2% boric acid vaseline salve for a period of 4 months, with marked improvement in the skin lesions.

MATERIAL AND METHODS

Biopsy specimens of skin lesions were obtained from the neck of 3 patients with this skin disease and fixed in a chilled 2.5% glutaraldehyde phosphate buffered to pH 7.4 for 2 hours. Then they were fixed in a 1% osmium tetroxide phosphate also buffered to pH 7.4 for 2 hours. They were dehydrated through a graded series of alcohols and embedded in Epon 812. The specimens were cut with a Porter-Blum ultramicrotome Model MT-2 and stained with uranium acetate and lead citrate. Observations were carried out with a Hitachi 11 B electron microscope.

The skin specimens for the light microscopic examination were fixed in formalin, serially sectioned, and stained with hematoxylin and eosin and Feulgen stain.

RESULTS

Light microscopy

As shown in Fig. 3, the epidermis is slightly acanthotic and the rete ridges are lost. There is some intracellular edema in the spinous cell layer and in the basal cell layer also. In the dermis, a slight edema of the papillary layer and a slight

lymphocytic cell infiltration around the vessels are noted. The most characteristic finding is on the horny layer. This layer looks parakeratotic, but it differs distinctly from the typical parakeratosis seen in psoriasis. It contains numerous basophilic granules in various sizes, which are not residual nuclei but appear to be keratohyalin granules.

Electron microscopy

Observations were mainly carried out on the horny layer. In general, as shown in Fig. 4, the horny layer is highly heterogeneous and lacks its usual uniform appearance. The normal keratin pattern (1, 3) is not observed. There are numerous irregular high electron-dense masses in various sizes, polymorphic components displaying negative contrast, melanosomes, and lacunae in the cytoplasm. Fig. 5 shows less electron-dense homogeneous masses, which we assume are remnant nuclei. The nuclear membrane is not distinct and chromatin granules are seen as very fine homogeneous granules. Fig. 6 shows another view of the irregular dense masses in which low density filamentous structures can be recognized. Small opaque particles are scattered around the masses. A normal keratin pattern is not seen. The relationship between electron-dense masses and filaments is shown more clearly in Fig. 7. The wavy fascicles of tonofilaments are enclosed in irregular dense masses, which show to some extent angular profiles; small opaque particles are evenly scattered around them. Such an arrangement of filaments and granules indicates that these electron-dense masses might be keratohyalin granules. From these observations, it seems most reasonable to assume that these electron-dense masses found in horny cells are remnant keratohyalin granules.

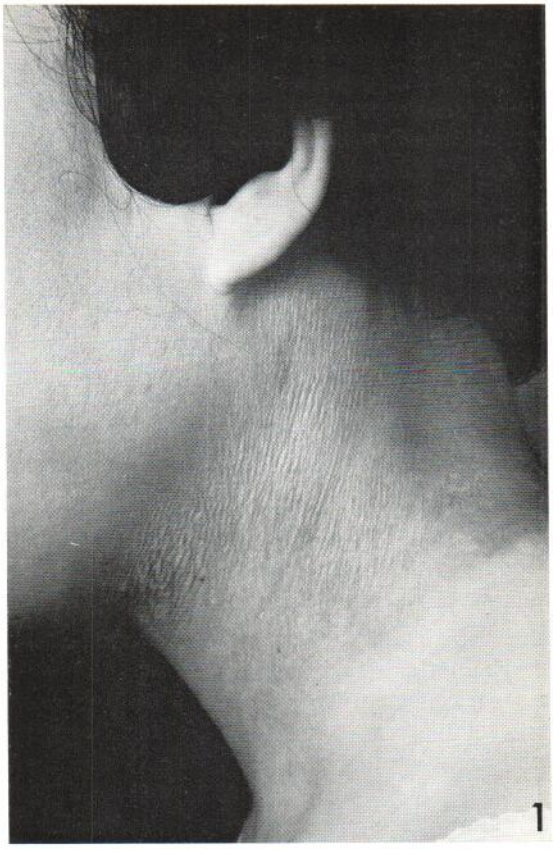

Fig. 1. Neck of a 22-year-old female patient. A well demarcated, dry, scaly lesion is noted.

Another prominent feature in the abnormal horny layer of this peculiar skin condition is a

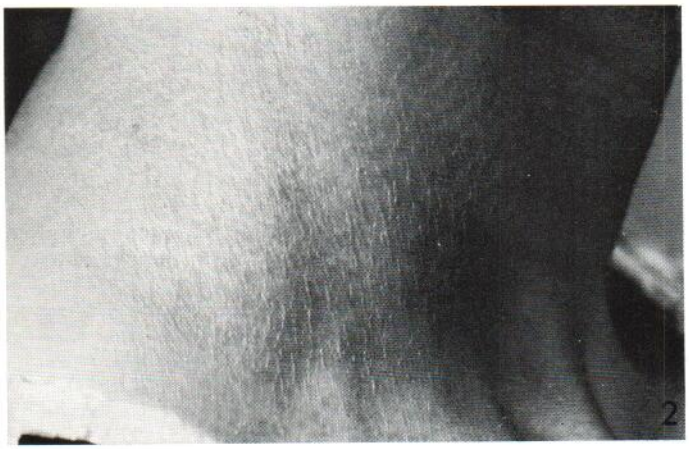

Fig. 2. Magnified view of the other side of the same patient's neck.

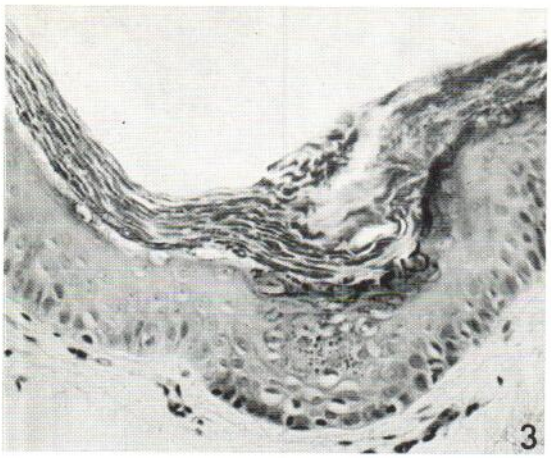

Fig. 3. Epidermis of the lesion of the neck. What appears to be a parakeratotic horny layer contains numerous basophilic granules in various sizes. Hematoxylin and eosin.

change in intercellular space. As shown in Fig. 8, the intercellular space appears distinctly, showing a conspicuous but irregular variation in width. In spite of this variation in width, the cell surfaces are rather even. Throughout their whole length the cells parallel the skin surface fairly well and the intercellular space in practically the whole horny layer is filled with a homogeneous, rather opaque substance. The distinct appearance of the individual cells is due to the occurrence of a clearly observed, unstained zone immediately outside the plasma membranes of the cells. It is impossible to recognize desmosomes, probably because of the presence of a homogeneous opaque substance in the intercellular spaces. The plasma membranes are not distinctly visible. Fig. 8 shows several sac-like pouches that leading off from an intercellular space and containing a conglomeration of many granules, some of which show clear lamellar structures. They are thought to be the membrane-coating granules (MCG) of Matoltsy (8). A few MCG are also observed in the slightly dilated intercellular spaces as well as in the cytoplasm.

The cytoplasm of the horny cells consists mainly of a less dense homogeneous substance with only slight, irregularly occurring variations in density. There are also irregular electron-dense masses and polymorphous components such as mitochondria, cytoplasmic membranes, MCG, etc., displaying negative contrast in the cytoplasm.

COMMENTS

The clinical skin manifestation of the dermatitis reported herein is peculiar and certainly differs from those seen in ordinary contact type dermatitis. Although this dermatitis certainly belongs to the contact type dermatitis, signs of inflammation such as erythema, edema and vesicle forma-

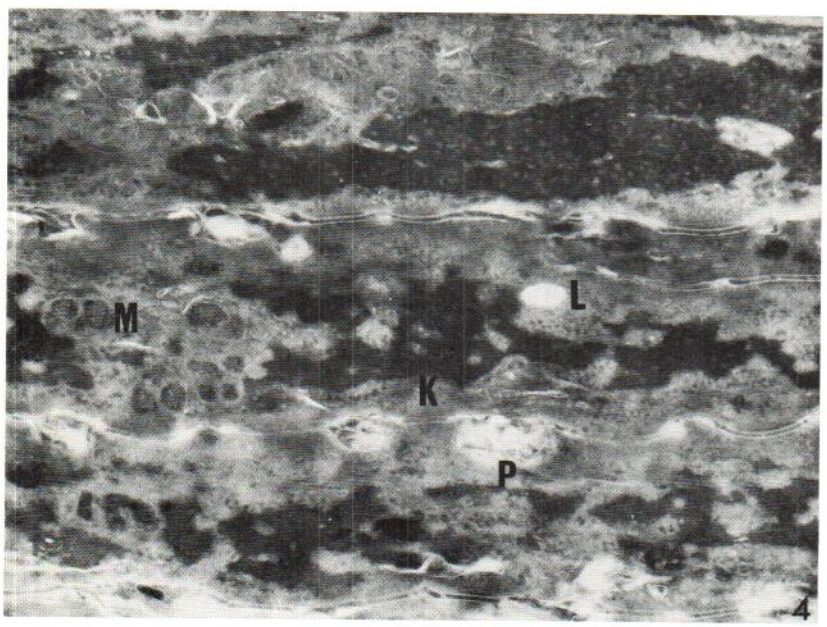

Fig. 4. Electron micrograph of the horny layer showing its heterogeneity and disuniformification. Numerous high electron-dense masses (*K*), polymorphic components (P), melanosomes (*M*) and lacunae (*L*) are observed. × 33 000.

Fig. 5. Horny layer. Less electron-dense homogeneous masses (*N*) assumed to be remnant nuclei are seen in the upper- and lower-parts of the photograph. × 29 000.

Fig. 6. Horny layer. Low density filamentous structures are observed in the highly electron-dense masses (*K*) and the small opaque particles around them. × 29 000.

Fig. 7. Horny layer. The relationship between electron-dense masses and filaments is shown clearly. × 66 000.

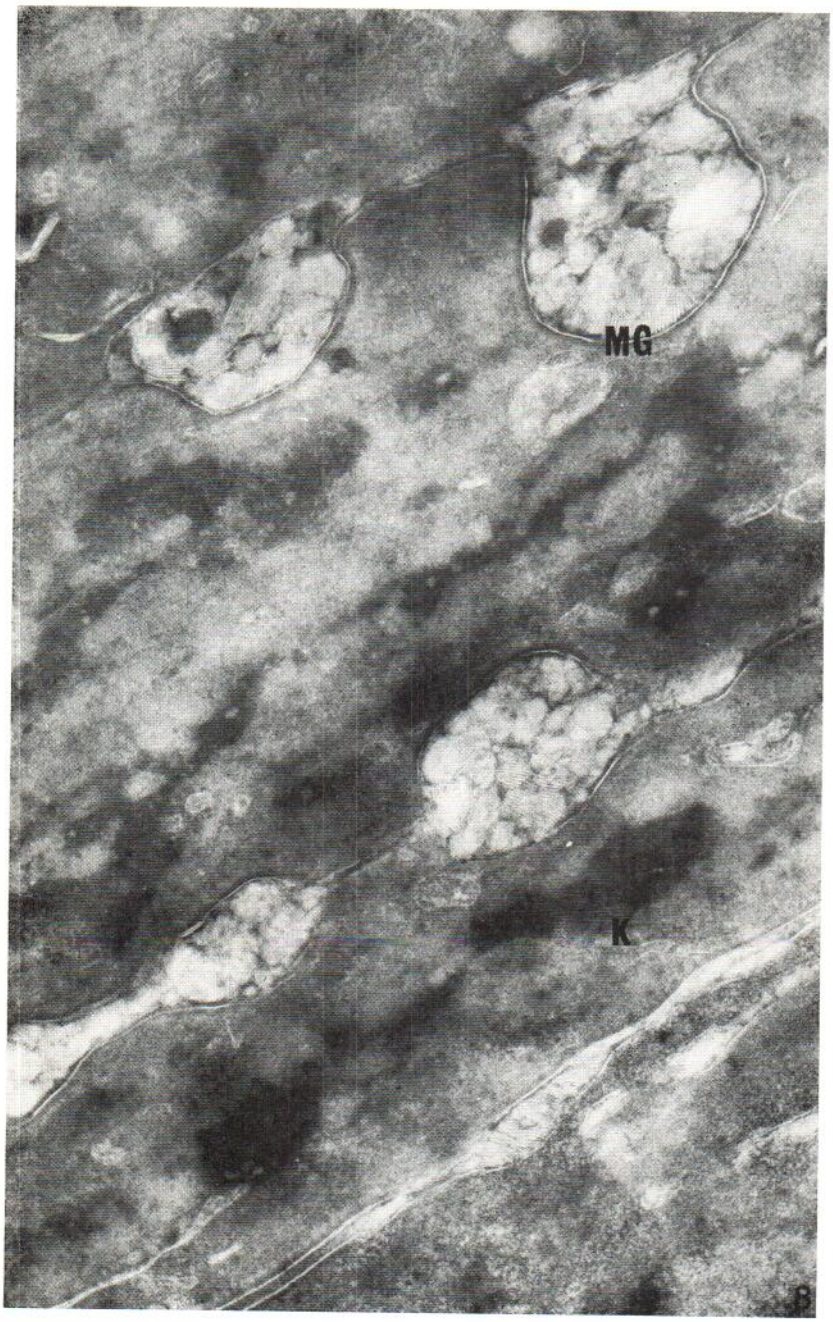

Fig. 8. High power view of the intercellular space of horny layer showing several sac-like pouches containing conglomerations of many granules, some of which show clear lamellar structures. × 66 000.

tion are hardly observed; dry scaly rough skin as seen in ichthyosis vulgaris or xeroderma is the typical skin manifestation.

A patch test was performed with 0.3% alkylbenzyl trimethyl ammonium chloride in polyethyleneglycol which was suspected to be the cause of the dermatitis.

The three cases tested all showed a positive reaction; that is, the typical dry, scaly skin lesion was reproduced on the skin area tested, when the closed patch test was performed repeatedly for about 2 to 3 weeks. A similar skin change is known to be produced on the normal skin by the application of cationic surface-active substances

(7). In that case, when a low concentration of cationic surface-active agent solution was applied, a dry, scaly rough skin was produced without any prior inflammation. Alkyl-benzyl trimethyl ammonium chloride is one of the cationic surface-active substances. The exact reason why and how such a peculiar contact dermatitis with abnormal cornification is produced is not known at the present time.

The aim of this report is not concerned with eliciting the cause of this dermatitis, but mainly with studying how the abnormal cornification is produced.

Under the light microscope, the histopathological changes in the dermis and epidermis are very slight except in the horny layer. Basophilic granules in various sizes are found in all the cells of the horny layer. These granules were negative in the Feulgen stain and appeared to be distributed evenly in the horny cells.

Under the electron microscope, the changes in the basal cells and spinous cells were not so remarkable, but there was a significant increase in the number of MCG in the upper spinous layer. Ribosomes, mitochondria, tonofilaments, and desmosomes in the spinous cells resembled very closely those of the normal human epidermis. The granular layer of two or three cells was observed and the ultrastructure of the cells bore some resemblance to that of the normal human epidermis. In this particular dermatitis, the most pronounced changes in the epidermis are the presence of numerous electron-dense masses in the horny cells and the numerous conglomerated MCG in the intercellular spaces of the horny layer and also within the horny cells. There are two kinds of electron-dense amorphous masses in the horny layer. One of these is assumed to be residual nuclei and the other, keratohyalin granules. The nuclear membrane is not clearly seen. The chromatin granules are seen as fine homogeneous granules with less electron opacity.

These findings observed through the electron microscope differ from those seen in the nuclei taken from the parakeratotic horny cells of psoriasis vulgaris (2). In psoriasis, nuclear membranes are distinctly recognized and chromatin granules, which exhibit high electron density, are located at the periphery. Therefore, the mechanism by which nuclei are retained in the horny cells of this dermatitis may not be the same as that of psoriasis. The other electron-dense masses can be identified quite accurately as keratohyalin granules from their high density, characteristic angular profiles, relations with fascicular tonofilaments and the fact that they are surrounded by small opaque particles. Not only are large numbers of keratohyalin granules retained, but the other cell organelles such as mitochondria, α-cytoplasmic membranes, MCG, lipid, etc. are also recognized by positive or negative images in the horny cells. The filamentous component was not recognized and the cytoplasm of the horny cell appeared to be homogeneous. The keratin pattern was not recognized. The fascicular architectures were recognized but it was not possible to distinguish the individual filaments. It is known that there are a large number of MCG in the upper part of the spinous layer in the case of psoriasis where the epidermal cell turnover is greatly increased (2). The existence of large numbers of MCG in the intercellular spaces as well as in the cytoplasm of the horny layer might possibly be interpreted as the result of an increased rate of epidermal cell turnover. These findings indicate that the cornification of the epidermis of this dermatitis is not entirely complete. It is not known, however, why only nuclei (but not keratohyalin) were disintegrated for a while.

In ichthyosis, whose clinical skin manifestation is very similar to that of this dermatitis, the ultrastructure of the cells of the epidermis bear some resemblance to that of the normal human epidermis. The keratohyalin granules are much smaller than those seen in the normal human epidermis and the normal keratin pattern is recognized in the horny cells although it is a small difference. Further, the epidermal cell in ichthyosis is assumed to have a lower metabolic activity and a reduced rate of epidermal cell turnover (6, 10). The incompletely cornified horny cells, where the keratohyalin granules remained intact have not been mentioned in the case of ichthyosis vulgaris.

Although extensive studies on keratohyalin granules (4, 5) are being carried out, their origin and exact role in the cornification mechanism have not been settled. The parakeratosis without keratohyalin, the parakeratosis with keratohyalin and hyperkeratosis, in which process keratohyalin always occurs, have been described in psoriasis (2). The pronounced granular layers and the per-

sistent keratohyalin materials in the horny layers have been observed in lichen planus (9). They showed that the increased amount of keratohyalin granules gave rise to persistent keratohyalin material in the horny layer. Further experimental work is needed before the nature of this incomplete cornification, which can be called "keratohyalin keratosis", is thoroughly understood.

ACKNOWLEDGEMENTS

We would like to record our sincere thanks to Mr H. Miyamoto, and Miss S. Nakajima, Tokyo Medical and Dental University, for assistance and cooperation throughout this study.

This work was supported by a research grant from the Japanese Ministry of Education, and in part by a grant from West Wood Pharmaceuticals, Buffalo, New York, USA.

Abbreviations. *K*, high electron dense mass (Keratohyalin granule); *L*, lacuna; *M*, melanosome; *MCG*, membrane coating granule; *N*, nucleus; *P*, polymorphic components displaying negative contrast.

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Received March 17, 1970

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