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Histologic and Ultrastructural Features of the Ichthyotic Skin in X-linked Dominant Chondrodysplasia punctata

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The ichthyotic skin in X-linked dominant chondrodysplasia punctata was investigated in a four-week-old baby and a fourteen-year-old girl. Histologically, the ichthyosiform erythroderma of the newborn and the ichthyosis of the older child presented as a retention hyperkeratosis with several distinctive features such as calcification of the keratotic follicular plugs, atrophy of the hair follicles and focal hyperpigmentation of the basal keratinocytes. On ultrastructural examination, small to medium sized vacuoles were regularly seen in the thinned granular layer. Some of these vacuoles contained needle-like calcium inclusions. The histologic and ultrastructural findings are therefore characteristic for this rare type of ichthyosis. *Key words: Congenital ichthyosiform erythroderma; Ichthyosis; X-chromosomal dominant inheritance; Follicular atrophy; Follicular calcium deposits; Vacuolization of granular cells.* (Received December 6, 1983.)

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Chondrodysplasia punctata is a modern term for a rare congenital bone defect which has been called Conradi-Hünermann syndrome in the past. The latter term is no longer applicable, since three different types of the disease have been identified more recently, namely the rhizomelic or autosomal recessive type (1), the X-linked dominant type (2), and a third type which may be inherited as an autosomal dominant trait (3). The three types of chondrodysplasia punctata differ with regard to severity of bone involvement and to associated extraosseous anomalies. They can be differentiated by the presence or absence of typical cutaneous and ocular anomalies.

The X-linked dominant type of chondrodysplasia punctata is characterized by ichthyotic skin lesions which are distributed in a mosaic pattern (4). At birth, the affected girls suffer from ichthyosiform erythroderma which clears spontaneously during the first months of life (5, 6). Later on, systematized follicular atrophoderma and mild ichthyosis are observed. In order to further delineate the morphological features of this ichthyosis with X-linked dominant inheritance, we have examined skin biopsies from a four-week-old baby and a fourteen-year-old girl, using light and electron microscopic methods.

PATIENTS AND METHODS

The four-week-old baby and the fourteen-year-old girl both showed the typical clinical features of X-linked dominant chondrodysplasia punctata. The diagnosis was confirmed by the demonstration of epiphyseal stippling on X-ray examination (7). The skin anomalies of the baby consisted of erythematous lesions covered with thick adherent scales which were distributed in a patchy and linear arrangement. In the older girl, there were hyperkeratoses in a blotchy and whorled arrangement on the trunk and the extremities. In addition, the skin of this patient showed systematized atrophoderma which involved primarily the hair follicles and resulted in a circumscribed alopecia of the scalp.

Skin specimens were taken from the ichthyotic areas by punch biopsy. For ultrastructural examination, the tissue was fixed in 2.5% glutaraldehyde (0.114 M S-collidin buffer, pH 7.4) and postfixed in

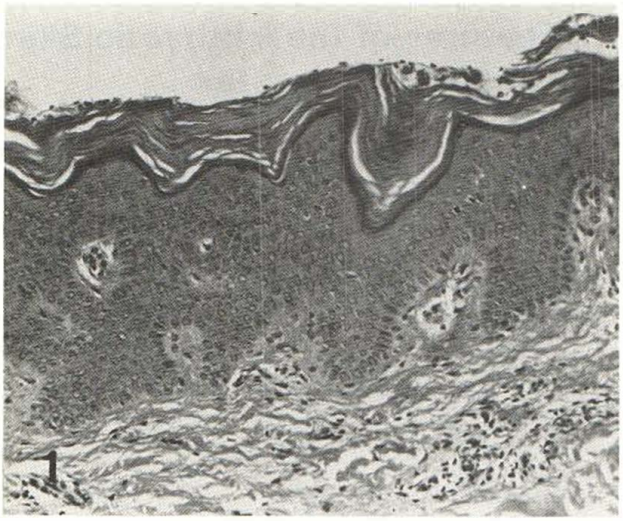


Fig. 1. Ichthyosis in X-linked dominant chondrodysplasia punctata. Note marked hyperkeratosis, follicular plugging, and thinned granular layer. H&E, ×130.

1.33% osmic acid (0.05 M phosphate buffer, pH 7.4). Ultrathin sections stained with uranyl acetate and lead citrate were examined with a Philips EM 301 electron microscope.

RESULTS

The ichthyotic skin of the two patients showed similar light and electron microscopical changes which were somewhat more pronounced in the older girl.

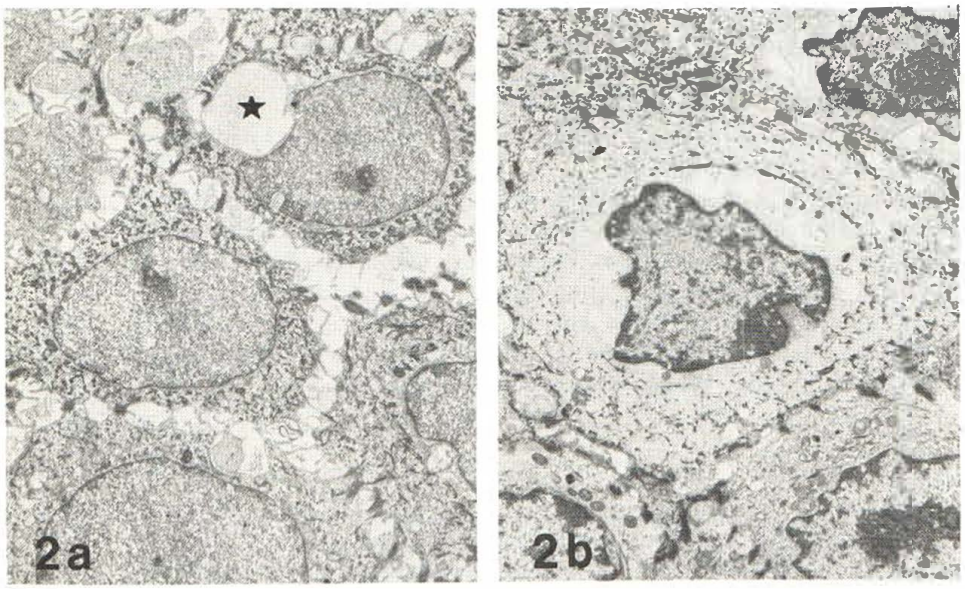


Fig. 2a. Electron micrograph of the lower spinous keratinocytes. Note widened intercellular spaces and perinuclear vacuole (asterisk). ×5200.

Fig. 2b. Cytolytic keratinocytes in the follicular epidermis. The cells are characterized by an edematous cytoplasm with reduced amount of organelles and tonofilaments. ×4700.

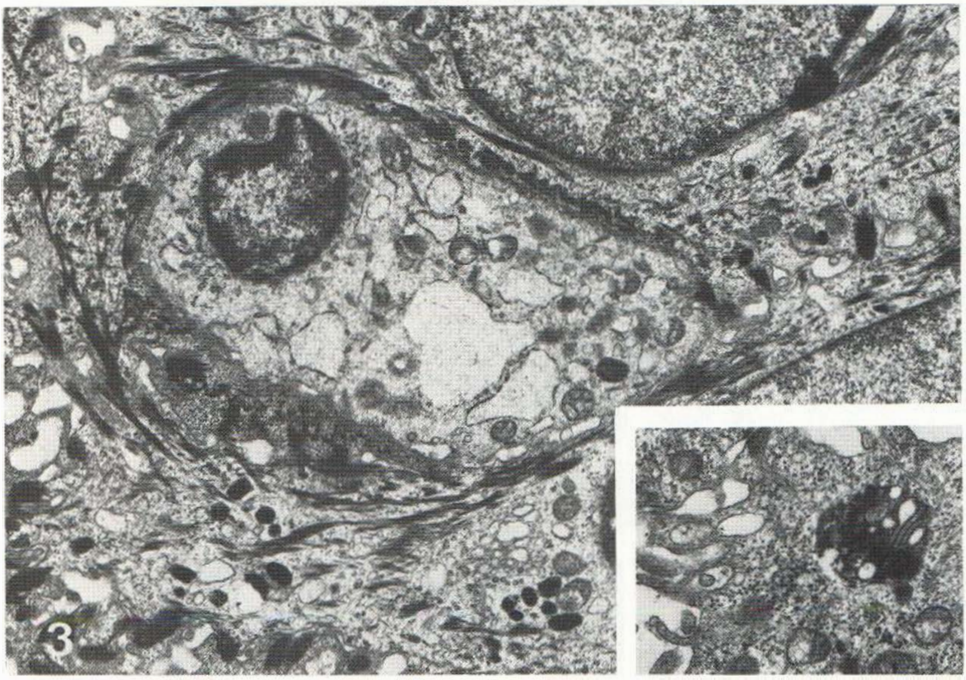


Fig. 3. Degenerative Langerhans cell with cytoplasmic edema, endoplasmic vacuolization, and pyknotic nucleus. ×12 500. *Inset:* Keratinocyte phagolysosome with Birbeck granules. ×20 100.

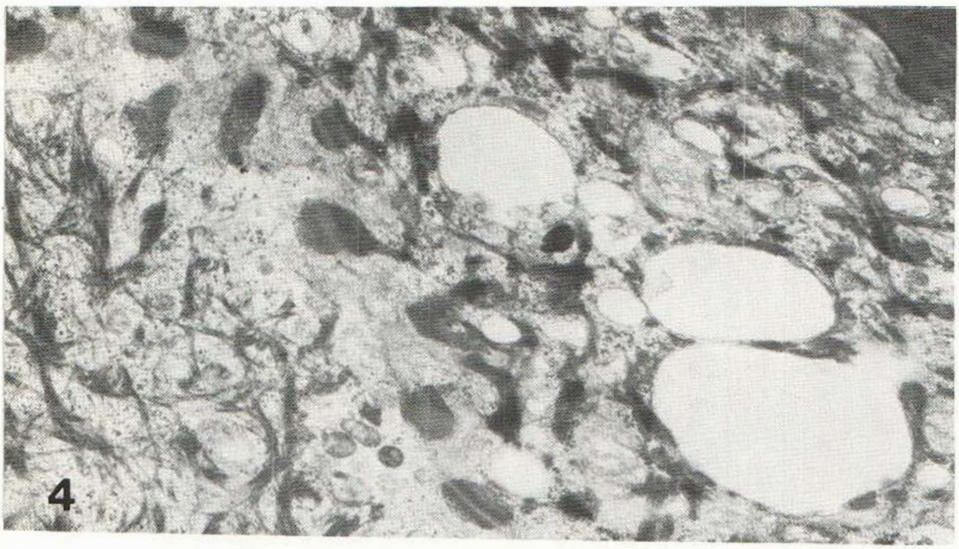
Light microscopy

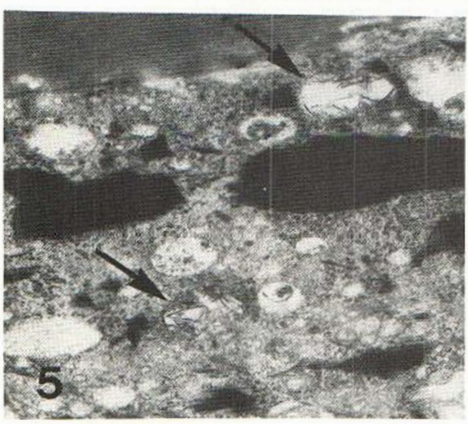
Histological examination (Fig. 1) revealed a moderately thinned epidermis with prominent rete ridges. There were marked hyalinized to laminated hyperkeratosis and minimal focal parakeratosis. The thickened keratinous layer extended into the dilated ostia of the pilosebaceous units, resulting in follicular plugging. In the ichthyosiform erythroderma of the newborn, the keratotic plugs contained lumps which gave a positive reaction with the von Kossa staining for calcium. The stratum granulosum was thinned, but there was no evidence for structural abnormalities of keratinization. The basal and suprabasal keratinocytes often displayed focal hyperpigmentation. In the dermis, some mononuclear inflammatory cells and macrophages surrounding the blood vessels were seen. The hair follicles showed signs of atrophy which was in an early stage in the four-week-old baby and fully developed in the fourteen-year-old girl. The other adnexal structures appeared normal.

Electron microscopy

On electron microscopic examination, the basal and suprabasal keratinocytes showed only few alterations of their fine structure. The tonofilaments and the tonofilament-desmosome complex appeared normal, but the intercellular spaces were slightly widened and often displayed myelin-like inclusions (Fig. 2*a*). The basal keratinocytes contained an increased number of regularly structured melanosomes. The endoplasmic reticulum was often vacuolized, and some spinous keratinocytes showed membrane-bound, electron-lucent vacuoles with diameters up to 5 μm (Fig. 2*a*). These vacuoles were mostly found near the nuclei which were invaginated by the vacuoles.

In the pilosebaceous units, groups of cytolytic keratinocytes with an edematous cytoplasm were found (Fig. 2*b*). The cells contained fewer mitochondria which were some-





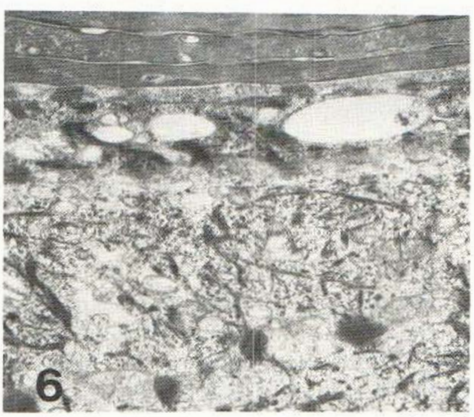


Fig. 4. Interfollicular stratum granulosum showing electron-lucent cytoplasmic vacuoles and reduced number of keratohyaline granules. ×20 300.

Fig. 5. Granular layer of follicular ostium. Some vacuoles contain needle-like inclusions (arrows), the keratohyaline amount is regular. ×15 800.

Fig. 6. Survey of interfollicular granular layer and horny layer. Note preserved desmosomal discs between the horny lamellae. ×13 400.

times swollen, and a markedly reduced number of tonofilaments. The nuclei were of irregular shape, and heterochromatin often accumulated at the nuclear margin.

Vacuolization of the endoplasmic reticulum occurred in some Langerhans cells (Fig. 3). In addition, these cells showed a pale, less electron-dense cytoplasm with a reduced number of mitochondria and Birbeck granules. The nuclei demonstrated pyknotic changes. Remarkably, the keratinocytes close to these Langerhans cells sometimes exhibited Birbeck granules in phagolysosomes (Fig. 3).

The keratinocytes of the thinned granular layer contained numerous small to medium sized vacuoles measuring between 0.4 and 1.5 μm in diameter (Fig. 4). The vacuoles were round or oval-shaped and mostly surrounded by a unit membrane. Most of them showed

an electron-lucent matrix, but some of them contained needle-like inclusions (Fig. 5). These inclusions were predominantly found in the granular layer of the follicular ostia. The keratohyaline granules did not show a structural defect. Their number was reduced in the interfollicular granular layer, but not in the follicular ostia (Figs. 4, 5). The desmosomal discs between the horny lamellae were often preserved in the thickened horny layer, especially in its lower portions (Fig. 6). Pathologic inclusions or vacuolization of the horny material were not observed in the interfollicular portions. The follicular horny plugs exhibited some small electron-lucent vacuoles.

DISCUSSION

The results show that the ichthyosis observed in X-linked dominant chondrodysplasia punctata is characterized by distinctive histologic and ultrastructural features, and that these features are present in newborns as well as in older patients.

On histological examination, this X-linked dominant type of ichthyosis presents as a retention hyperkeratosis. So far, retention hyperkeratosis has been taken as a typical feature of autosomal dominant ichthyosis vulgaris and is characterized by moderate to marked hyperkeratosis, diminishing of the granular layer, and keratotic follicular plugging (8, 9). In X-linked dominant ichthyosis, in contrast, follicular plugging is usually associated with atrophy of the hair follicles leading to follicular atrophoderma and circumscribed alopecia in the older children (2, 4, 6). The calcification of the follicular plugs observed is another unique feature of this type of ichthyosis and may be attributed to a pathomechanism similar to that resulting in premature calcificaton of the epiphyses. Moreover, the X-linked dominant type of ichthyosis exhibits focal hyperpigmentation of the lowermost keratinocytes and a slight increase in dermal macrophages. These findings may explain the clinical observation of hyperpigmented scaly lesions (2).

The ultrastructural features of inherited ichthyoses have been thoroughly studied during the last years, and structural defects in keratinization have been found in types with dominant inheritance such as ichthyosis vulgaris, bullous ichthyosiform erythroderma, and ichthyosis hystrix of the Curth-Macklin type (10, 11, 12). The ichthyotic skin of X-linked dominant chondrodysplasia punctata does not show specific changes of the tonofilaments and the keratohyaline. There is only a slight reduction of the amount of keratohyaline in the interfollicular granular layer. Vacuolization of the granular cells and the appearance of needle-like calcium crystals within these vacuoles are however characteristic features of this type of ichthyosis. On ultrastructural grounds, these vacuoles most likely represent enlarged cisternae of the endoplasmic reticulum also found in the spinous and basal keratinocytes. In the lower layers of the epidermis, the presence of these vacuoles is less characteristic, since this finding is observed likewise in several other types of ichthyosis as well as in other skin diseases (see for example 13, 14). The deposition of calcium in the granular cell vacuoles, especially in the follicular ostia, apparently corresponds to the calcificaton of the follicular plugs seen on light microscopic examination.

Other ultrastructural changes of X-linked dominant ichthyosis comprise cytolytic keratinocytes in the follicular epidermis and degeneration of Langerhans cells. While the former alteration indicates an early degree of follicular atrophy, the nature of degeneration of Langerhans cells remains unclear. A destruction of these cells is usually found in contact dermatitis (15), but has not been described in the various types of ichthyosis previously examined.

In conclusion, the ichthyosis observed in X-linked dominant chondrodysplasia punctata is characterized by a retention hyperkeratosis with calcification of the keratotic follicular plugs, atrophy of the hair follicles, and focal hyperpigmentation of the basal keratinocytes.

At the subcellular level, a vacuolization of the granular layer and calcium deposits within these vacuoles are found. Taken together, the histologic and ultrastructural features allow one to distinguish this skin disorder from all other ichthyoses known so far.

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