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Autosomal-Dominant Lamellar Ichthyosis: Ultrastructural Characteristics of a New Type of Congenital Ichthyosis

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Summary. Recently, autosomal-dominant lamellar ichthyosis (ADLI) has been shown to be a new genetic trait with clinical and histologic features similar to those of autosomal-recessive lamellar ichthyosis. In two patients affected with ADLI, the malpighian keratinocytes showed ultrastructural signs of increased cellular metabolism. The tonofilaments and keratohyaline granules were regular in structure and number. However, as a distinctive ultrastructural feature, a prominent transforming zone was found between the granular and horny layers. Moreover, a normal keratin pattern and only a limited number of lipid inclusions were observed in the stratum corneum. Thus, ADLI can be distinguished from the autosomal-recessive forms of lamellar ichthyosis, permitting a correct diagnosis when genetic counselling has to be given in sporadic cases.

Key words: Lamellar ichthyosis – Autosomal-dominant inheritance – Ultrastructure – Transforming cells – Genetic counselling

Introduction

Lamellar ichthyosis or non-bullous congenital ichthyosis has, up to now, been considered to be a monogenic entity with autosomal-recessive inheritance [7]. On the basis of lipid-chemical analysis, Williams and Elias [16, 17] have recently suggested that it is possible to distinguish an erythrodermic type from the non-inflammatory type of autosomal-recessive lamellar ichthyosis (ARLI). On the other hand, we have recently observed four patients with lamellar ichthyosis belonging to three consecutive generations of a family [14], thus providing genetic evidence for a third type of non-bullous congenital ichthyosis: autosomal-dominant lamellar ichthyosis (ADLI). So far, the diagnosis of ADLI has solely relied on its mode of inheritance, since its clinical and histologic features are similar to those of non-inflammatory ARLI.

Over the past 15 years, ultrastructural examination has become a powerful tool for the classification and diagnosis of the various types of ichthyosis [2]. In particular, distinct abnormalities of the tonofilaments and keratohyaline granules have been found in ichthyoses with a dominant mode of transmission. The present study demonstrates that ADLI does not exhibit a specific defect in these structural proteins, but shows ultrastructural features which distinguish this new ichthyosis from all other known types.

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Patients and Methods

Two patients suffering from ADLI – a 9-year-old girl and her 27-year-old mother – were studied. The family history and the clinical features of both patients have been described in detail elsewhere [14]. Skin biopsies were taken from a site of maximal scaling (lower back or buttocks, respectively) and were processed using routine methods for light microscopy. For ultrastructural examination, the tissue was fixed in half-strength Karnovsky's solution ([9]; 0.1 *M* cacodylate buffer, pH 7.4), post-fixed in 1.33% osmic acid (0.05 M phosphate buffer, pH 7.4) and finally embedded in Epon 812. Ultrathin sections stained with uranyl acetate and lead citrate were examined using a Philips EM-301 electron microscope.

Results

The ichthyotic skin of the two patients showed similar light and electron microscopic features.

Light Microscopy

Histologic examination revealed an acanthotic and slightly papillomatous epidermis covered by a marked hyperkeratosis with focal areas of parakeratosis

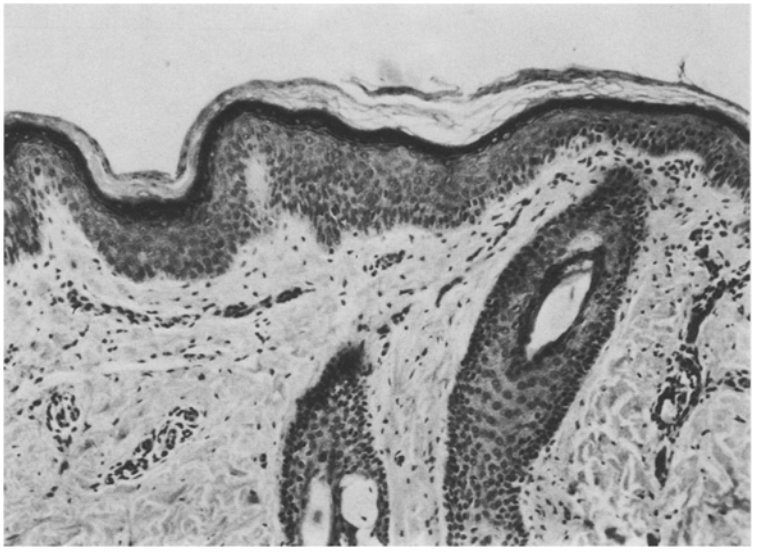

Fig. 1. Histologic appearance of ADLI in a 27-year-old patient, showing acanthosis, slight papillomatosis and hyperkeratosis of the epidermis, and few mononuclear inflammatory cells in the dermis. Note the parakeratotic areas associated with a broadened granular layer. H&E. ×100

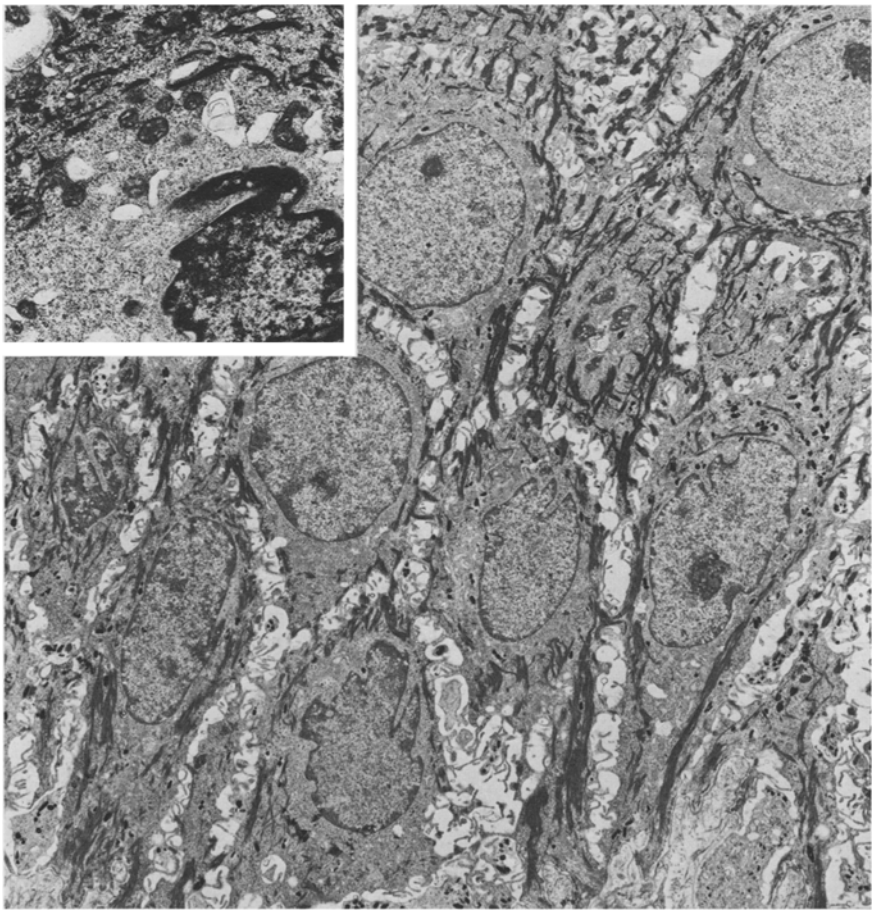

Fig. 2. Electron micrograph of the basal and suprabasal keratinocytes in a 9-year-old child with ADLI. Some cells exhibit indented nuclei, the cytoplasm of the cells contain numerous organelles, and there are widened intercellular spaces (×3,300). *Inset:* perinuclear cytoplasm of a suprabasal keratinocyte showing numerous free ribosomes, several mitochondria and cytoplasmic vacuoles with small myelin-like inclusions (×8,000)

(Fig. 1). The granular layer was increased in size, even in parakeratotic areas. In the basal cell layer, a few regular mitotic figures were noted. The dermis exhibited some mononuclear inflammatory cells located in a perivascular position.

Electron Microscopy

The basal and spinous keratinocytes exhibited slightly enlarged nuclei with some indentations and enlarged nucleoli (Fig. 2). The cytoplasm of the cells contained

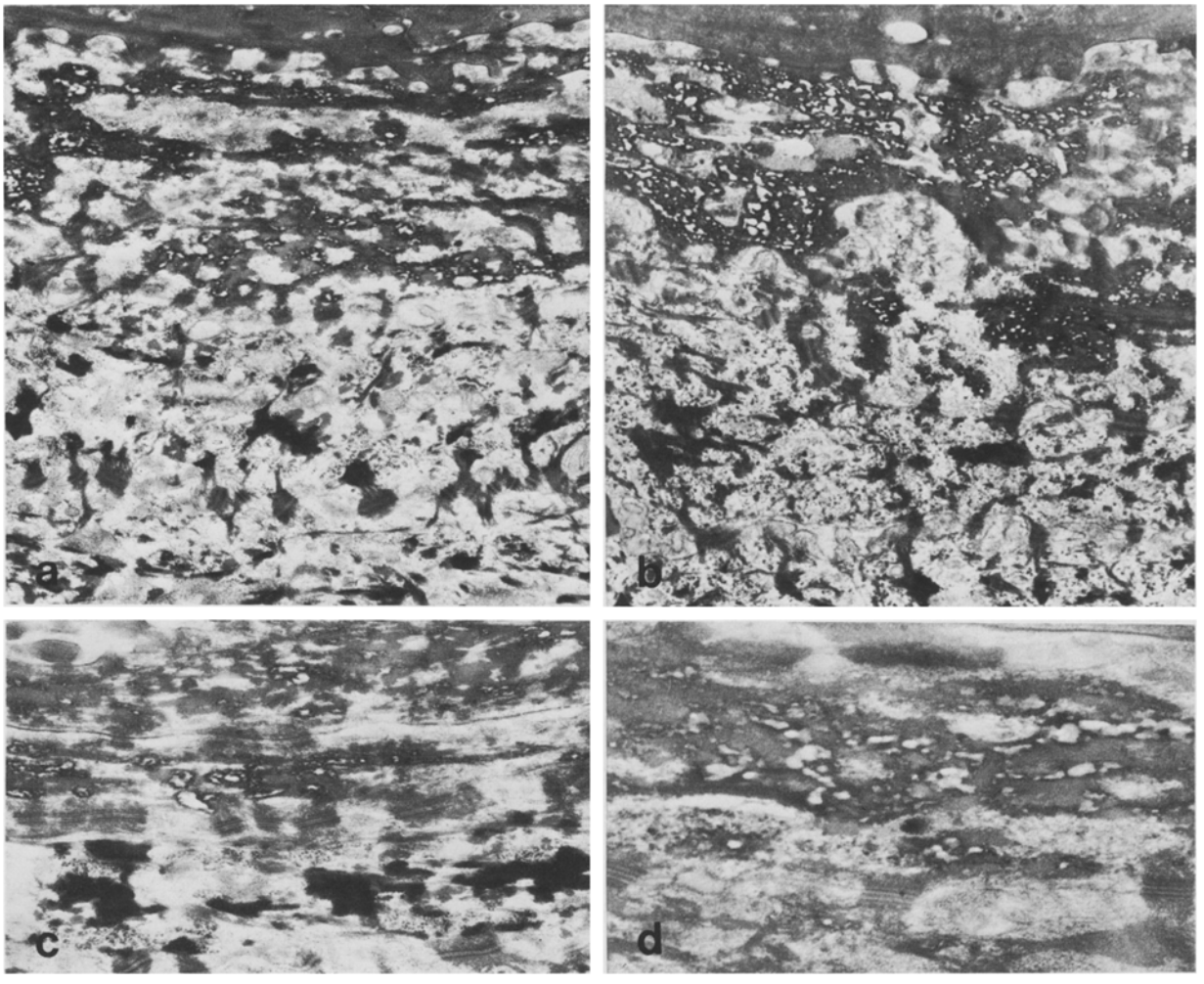

Fig. 3. Comparative micrographs of the transforming zones of a 9-year-old child **(a, c)** and a 27-year-old adult **(b, d)** with ADLI. **a, b** Survey of the granular layer, prominent transformed zone and lower horny layer showing the gradual conversion of compact keratohyaline granules to horny keratin. **c, d** Higher magnification of the transforming zone showing vacuolization, mixing and spreading of the tonofilament-keratohyaline complexes. **a** ×11,600; **b** ×11,000; **c** ×20,300; **d** ×30,800

numerous and frequently enlarged mitochondria, a well-developed Golgi area and an increased number of free ribosomes. Occasionally, small, myelin-like inclusions were found in a juxtanuclear position (Fig. 2). The intercellular spaces were widened, but there was no alteration in the tonofilaments or the tonofilament-desmosome complex. The melanocytes and Langerhans cells showed a normal structure and distribution.

The stratum granulosum was enlarged and consisted of typical granular cells in the lower part and two to six layers of transforming cells in the upper part (Fig. 3a, b). Both the granular and transforming cells contained an increased number of cell organelles, and nucleated keratinocytes were found even in the upper layers of transforming keratinocytes. In the granular cells, the keratohyaline granules appeared as electron-dense, round or stellate deposits in close relation to the regular tonofilaments. The flattened transforming cells (Fig. 3a–d) were initially characterized by less electron-dense tonofilament-keratohyaline aggregates with multiple electron-lucent inclusions. Subsequently, the keratohyaline granules increased in size, finally forming the filament-matrix complexes of the lower horny cells (Fig. 4a). During this transformation, the cell membrane became thickened, and the cell organelles underwent degradation.

The thickened stratum corneum was made up of more than 25 cell layers. The horny cells exhibited a regular keratin pattern (Fig. 4a). Apart from nuclear inclusions in the parakeratotic areas, the lower corneocytes sometimes exhibited small remnants of cell organelles (Fig. 4b). Electron-lucent lipid vacuoles were only rarely seen (Fig. 4c).

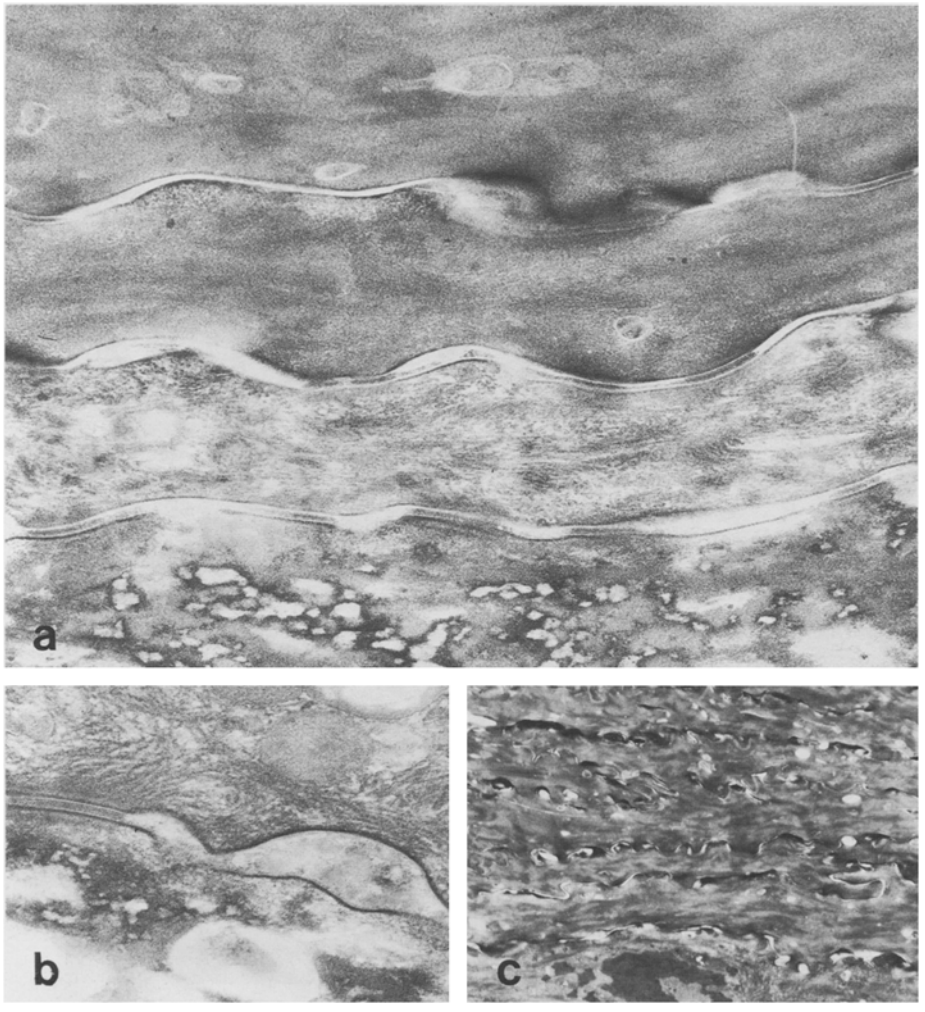

Fig. 4. a Upper transforming zone and lower horny layer with loosely and tightly packed filaments. The compact corneocytes display the typical keratin pattern (27-year-old patient; ×40,600). **b** Tonofilament-matrix complex of the lowermost horny layer showing some remnants of cell organelles (27-year-old patient; × 42,000). **c** Survey of the horny layer showing a parakeratotic inclusion, but only few electron-lucent lipid vacuoles (9-year-old patient; ×6,800)

Discussion

In contrast to the other ichthyoses with a dominant mode of transmission, ADLI does not display a specific defect in the tonofilaments or keratohyaline granules. The present results show that these structural proteins are regular in their structure and amount.

Most of the ultrastructural features observed in ADLI are similar to those of non-inflammatory ARLI [1, 15] and can be attributed to increased cellular metabolism of the keratinocytes. There are slightly enlarged nuclei that sometimes show prominent nucleoli, an increased number of mitochondria and numerous free ribosomes in the cells of the malpighian layer. The widened granular layer likewise contains numerous mitochondria, and nucleated keratinocytes are found even in the uppermost transforming keratinocytes. Furthermore, all types of lamellar ichthyosis show the histologic characteristics of proliferation hyperkeratosis, with acanthosis, hypergranulosis, and ortho- and parakeratosis [13]. In ARLI, these light and electron microscopic features are considered to be morphologic correlates of the increased epidermal cell turnover, as demonstrated by cell-kinetic [8] and grafting experiments [3].

However, ADLI differs from other ichthyoses due to the presence of a prominent transformation zone between the stratum granulosum and corneum, consisting of up to six cell layers. These layers reflect the structural and biochemical conversion of fully developed granular cells into horny cells [11, 12]. Ultrastructurally, the gradual transformation of tonofilaments and keratohyaline granules into horny keratin has only been described in detail in some stratified epithelia of experimental animals [4, 10, 11], but not in human epidermis, in which the transforming cells usually appear as single cells scattered beneath the corneocytes and do not form a continous layer [5].

ADLI may thus serve as a human model for studying this important step of cornification in detail.

The prominent appearance of transforming cells in ADLI indicates that the differentiation of the hyperproliferative keratinocytes is not faulty, but delayed. The concept of the complete differentiation of keratinocytes in ADLI is further supported by the ultrastructural features of the horny layers. Except for the focal areas of parakeratosis, the corneocytes show a normal keratin pattern [6]. This is in contrast to the recessive type of lamellar ichthyosis which, in addition to parakeratosis, is characterized by incomplete keratinization, with numerous remnants of degraded keratinocyte organelles and lipid inclusions [1, 15]. Whether this structural difference is also reflected by a different lipid composition of the horny layer is currently being investigated using scale-lipid analysis.

In conclusion, ADLI shows some ultrastructural similarities to ARLI, but it can be distinguished by a prominent and regularly structured transformation layer, a regular keratin pattern of the horny cells and the presence of only few lipid inclusions in the corneocytes. These characteristic features help to establish ADLI as a distinct type of lamellar ichthyosis and permit a correct diagnosis even in the absence of a positive family history. The ultrastructural delineation is therefore of great practical value when genetic counselling has to be given in sporadic cases of lamellar ichthyoses.

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