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Epidermolytic Hyperkeratosis With Ichthyosis Hystrix

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Epidermolytic hyperkeratosis (EH) is a congenital, autosomal-dominant genodermatosis characterized by blisters.[1,2] Shortly after birth, the infant's skin becomes red and may show bullae. The erythema regresses, but brown verrucous hyperkeratosis persists, particularly accentuated in the flexures. This condition is also known as bullous ichthyosiform erythroderma.

The disorder of keratinization has varied clinical manifestations in the extent of cutaneous involvement, palmar and plantar hyperkeratosis, and evidence of erythroderma. We describe 5 patients, 4 with EH (one of whom had it in localized form and one of whom had an unusual type of ichthyosis hystrix described by Curth and Macklin[3-7]).

Case Reports

Patient 1—A 7-year-old girl with a cutaneous eruption since birth characterized by flaccid bullae varying in size. The palms and soles had intense diffuse keratosis from 1 year of age. Her nails, hair, teeth, and mental state were normal. The patient's mother (Patient 2) had a similar disorder. Skin biopsy specimens showed the changes of EH, with pronounced cellular vacuolation of the middle and upper portions of the malpighian stratum and large, clear, irregular spaces. Cellular boundaries were indistinct. A thickened granular layer was evident with large, irregularly shaped keratohyalin granules. Ultrastructural study showed tonofilament clumping of the malpighian layer and cytolysis. Generalized erythema and desquamation with bullae formation were intense and persistent (Figure 1). Systemic vitamin A therapy was used, with mild to moderate improvement observed.

Patient 2—The 36-year-old mother of Patient 1 presented with hyperkeratotic dry scaling skin, presumably present since birth. Its onset was as flaccid bullae varying in size from 3 to 40 mm in diameter. From age 1, the patient's palms and soles showed intense diffuse keratosis. Her nails, hair, teeth, and mental state were normal. Generalized erythema and

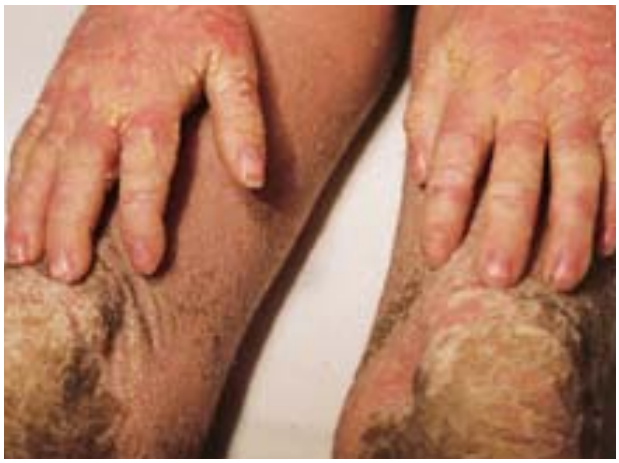

FIGURE 1. Seven-year-old girl with EH, demonstrating erythema and verrucous hyperkeratosis (Patient 1).

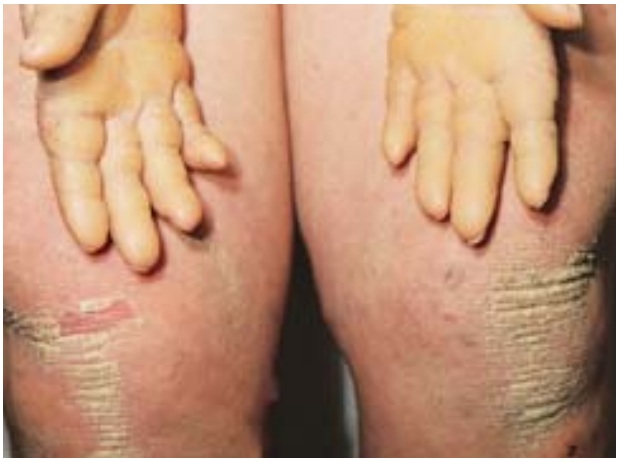

FIGURE 2. Thirty-six-year-old mother of Patient 1, showing erythema and verrucous hyperkeratosis (Patient 2).

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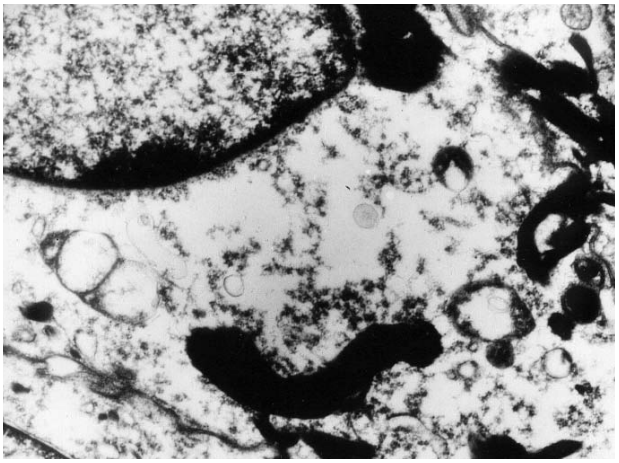

FIGURE 3. Skin biopsy specimens showed tonofibrillar clumping in a patient with EH (x18,000).

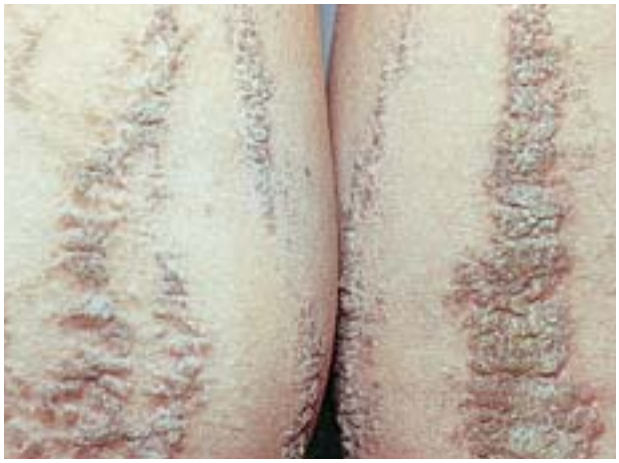

FIGURE 4. Five-year-old boy with verrucous back hyperkeratosis in bandlike distribution (Patient 4).

desquamation with bullae formation was especially intense up to 15 years of age. Her daughter was the only family member affected with a similar eruption. Physical examination showed thick, gray-brown, often verruciform plaques that were particularly prominent on the flexures, antecubital, popliteal fossae, and extensor sites of the palms and soles (Figure 2).

Skin biopsy specimens showed the light and electron microscopic changes of EH, as described for patient 1 (Figure 3). Generalized erythema and desquamation with bullae formation were intense and persistent. Systemic vitamin A therapy was used, with mild improvement observed.

Patient 3—A 5-year-old boy had erythema and blister formation since birth with no family history of keratinization disorders. Blister formation was prominent at pressure points and areas of friction. Diffuse hyperkeratosis of the palms and soles developed from the age of 4 months. The patient's skin was diffuse, scaly, and hyperkeratotic. Nails, hair, and teeth were normal. Skin biopsy specimens and ultrastructural studies showed the changes of EH as described above. Systemic vitamin A therapy was used, with mild improvement seen.

Patient 4—A 5-year-old boy was seen for evaluation of symmetrically distributed, bandlike, hyperkeratotic, black, verrucous skin involving the extensor sites slightly more than the flexor sites (Figure 4). The onset of the eruption was at age 4 to 6 months. Hyperkeratosis was present without visible blister

Table I.

Differential Diagnostic Criteria of Epidermolytic Hyperkeratosis

Condition	Clinical Picture	Inheritance
Epidermolytic hyperkeratosis	Thick, gray-brown, often verruciform scales but prominent with blister formation and keratosis palms and soles	Autosomal dominant
Localized epidermolytic hyperkeratosis (ichthyosis hystrix)	Hystrixlike ichthyosis without visual blisters; formation from 5–6 months of age, without keratosis of palms and soles	Autosomal dominant
Curth-Macklin type of ichthyosis hystrix	Hystrixlike ichthyosis without blister formation; palms and soles affected	Autosomal dominant
Ichthyosis bullosa of Siemens	Blisters, superficial cutaneous peeling, hyperkeratosis of limbs	Autosomal dominant

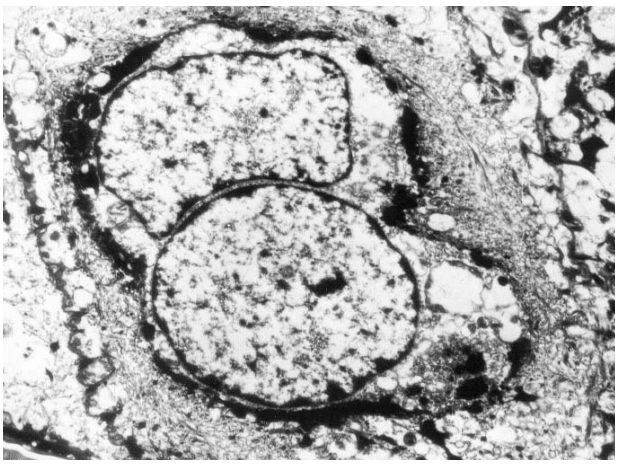

FIGURE 5. Perinuclear shell of tonofilaments in Curth-Macklin type of ichthyosis hystrix (Patient 5).

formation, and the facial skin was dry and scaly. The palms and soles were unaffected. There was no family history of a similar disorder. Skin biopsy specimens showed extreme ichthyosis, hystrixlike hyperkeratosis, acanthosis, and papillomatosis. Granular degeneration with acanthokeratolysis was evident from the suprabasal region to the granular layer. Melanocytes were reduced considerably in number. There was a mild perivascular lymphocytic infiltrate. Ultrastructural studies showed tonofilament clumping with acantholysis. Systemic vitamin A therapy was employed, with moderate improvement observed.

Patient 5—A 42-year-old woman was seen for hyperkeratotic skin that was presumably evident since birth. Her skin was dry and scaly without vesicle formation. Velvety keratinization was evident, especially in the extensor of the palms, the flexural areas, and the elbows and knees. The palms and soles showed markedly diffuse hyperkeratosis with fissuring and contractures. The patient's nails, hair, teeth, and mental state were normal, and there was no family history of keratinization disorders.

Skin biopsy specimens showed hyperkeratosis, parakeratosis, and papillomatosis with no degeneration from the suprabasal layer to the stratum corneum and no vacuolation and large irregular spaces separating well-outlined cells and groups of cells. Binucleate cells were evident, and shell formation was seen in the malpighian stratum. There was a mild lymphocytic perivascular infiltrate evident in the papillary dermis. Ultrastructural study showed that the shells were composed of tonofibrillar bundles (Figure 5). The aggregated tonofilaments concentrated perinuclearly formed shells. Between the shells and nuclei was a cytoplasmic zone without fibrils. No tonofibrillar clumps or acantholysis was evident. The diagnosis was Curth-Macklin type of ichthyosis hystrix. Systemic vitamin A therapy was employed, with moderate improvement noted.

Discussion

EH is an important form of ichthyosis, also known as bullous ichthyosiform erythroderma due to its clinical features.[1,2] Histologically, epidermolytic hyperkeratosis is a good description due to granular layer hyperkeratosis and clefts in the upper epidermis. Ultrastructural findings are characterized by tonofilament clumping, cytolysis, and blister formation in suprabasal keratinocytes. Treatment is usually symptomatic with retinoid therapy such as etretinate employed in severe cases.[1]

Localized forms of EH have been described. However, the histology of EH is not specific because it occurs in unrelated disorders such as epidermal nevus and actinic keratosis. In addition, localized forms of EH may resemble the type of ichthyosis hystrix described by Curth and Macklin.[3-7] The latter is similar clinically and by light microscopic examination, although it lacks true cell lysis with associated intraepidermal blister formation. Ichthyosis hystrix is autosomal dominant, but differs from EH ultrastructurally with aggregation of cytoplasmic components, perinuclear tonofilament shells, binuclear keratinocytes, and atypical parakeratosis. Ultrastructural evaluation showed Patient 4 fits best into the latter category. Histologically, ichthyosis hystrix is similar to nonepidermolytic palmoplantar keratoderma.[8] However, the genetic basis of neither has been established.[8,9]

Several keratin 1 (K1) and keratin 10 (K10) point mutations have been identified as the molecular basis of EH.[10-15] These keratins appear predominantly in the suprabasal layers of the epidermis. In fact, the tonofilament aggregates associated with EH are composed of K1 and K10. One recent report described a severe EH phenotype in an individual with a novel base pair substitution from tyrosine to serine at residue 14 within the 1A region of K10.[10] Such alterations produce defects in filament assembly and stability. Inappropriate amino acid substitutions cause collapse of the keratin filament network, producing cytolysis of keratinocytes. Clinical phenotypic expression of EH may result from K1 mutations at different sites, producing clinically distinct variants. One such variant is a cyclic EH with dramatic episodic flares of annular, polycyclic, erythematous plaques that coalesce to involve most of the cutaneous surface.[15] Variants of classical EH need to be distinguished clinically from ichthyosis bullosa of Siemens.[16] Diagnostic criteria for EH are indicated in Table I.

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