Ichthyosis Hystrix of Curth-Macklin

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Ichthyosis hystrix of Curth-Macklin (IHCM) is an extremely rare keratinization disorder, with verrucous to hystrix-like hyperkeratotic plaques of varying extent. The diagnosis is based on a distinctive pattern of epidermolytic hyperkeratosis and the presence of binucleate cells under light microscopy, as well as unique electron microscopic findings of continuous perinuclear tonofilbril shells in the suprabasal keratinocytes. We present the clinical manifestation and light and electron microscopic findings in a 23-year old male patient with IHCM. (Dermatol Sinica 22 : 239-242, 2004)

Key words: Ichthyosis hystrix, Epidermolytic hyperkeratosis

INTRODUCTION

Ichthyosis hystrix is a descriptive name for a heterogeneous group of keratinization disorders sharing similar features of massive, spiky or verrucous hyperkeratosis clinically and epidermolytic hyperkeratosis histologically.1 With electron microscopy and a further understanding of keratin genes, a rare but distinct entity called ichthyosis hystrix of Curth-Macklin (IHCM) can now be recognized.2-3 It has unique ultrastructural findings and genetic mutations very different from other histologically categorized epidermolytic hyperkeratoses.2-4

IHCM is an extremely rare type of epidermolytic hyperkeratosis. To date, only three families and some isolated patients with IHCM have been described.4 In this article, we describe our observations in a solitary case of IHCM and discuss the genetic and molecular basis of keratin disorders resulting in such pathologic findings.
CASE REPORT

A 23-year-old man patient had healthy skin at birth, without history of blistering or erythema. At the age of 8 months, ichthyotic skin changes appeared and progressed to involve most body parts. Dark-brown verrucous hyperkeratotic plaques were present on the trunk and back and were most prominent over the nipples in a cobble-stone to hystrix-like pattern (Fig. 1A-1C). The extensor surfaces of the knees, ankles, and wrists were particularly involved with obvious furrowed linear hyperkeratosis (Fig. 1D). Face and flexural areas were dry and scaly. Traumatic bleeding occurred occasionally due to friction from rough clothing. Otherwise, there was no other obvious skin fragility. His general health had been good and he was mentally normal. Nails and hair were uninvolved. No other family members had a history of a keratinization disorder. Treatment with salicylic acid 2.5% ointment, and other keratolytic agents, such as urea cream and lactic acid lotion were tried and resulted in soothing of the affected skin. However, the patient refused systemic treatment.

Skin biopsies of the lesions were performed. Under light microscopy, the epidermis showed acanthosis, papillomatosis and sustained hyperkeratosis with crest-like projections into the horny layer (Fig. 2). The basal cells appeared to be normal, but the suprabasal keratinocytes were round and pathologically enlarged, especially in the granular layer, where prominent vacuolar changes were clearly observed.

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observed. Approximately 10% of the suprabasal keratinocytes were binucleate (Fig. 2, inset).

Electron microscopic examination of the suprabasal keratinocytes revealed a continuous perinuclear dark shell formed of irregularly oriented keratin intermediate filaments lacking the normal tendency to form bundles (Fig. 3A & 3B). This tonofibril shell seemed to be retracted peripherally away from the nucleus, which it encircled at a distance (Fig. 3A). The shell hence divided the cytoplasm into three compartments: ① the inner compartment, a perinuclear halo, contained some particles representing ribosomes and polysomes; ② the shell itself; and ③ the outer compartment with a few keratin filaments that formed normal bundles to terminate on desmosomes. The number of desmosomes was not decreased. Electron microscopic examination focused on the binucleate cells revealed the one shell enclosing both nuclei (Fig. 3C).

DISCUSSION

IHCM was first described by Curth and Macklin in 1954, who noted the disorder in a family. Since then, only three families and a few sporadic cases have been reported. Because of the clinical and histopathologic resemblance to epidermolytic hyperkeratosis, it was once thought to be a variant of bullous congenital ichthyosiform erythroderma that lacks a tendency to blister. It was only because of the electron microscopic investigation of Curth’s original family that this peculiar keratinization abnormality became evident to be distinctly different from other historically categorized forms of epidermolytic hyperkeratosis.2

The onset of IHCM is usually in childhood, and the disorder progresses into adulthood. The clinical expression varies greatly, even within families, from localized keratoderma to severe generalized involvement with hyperkeratotic and papillomatous coalescent papules distributed extensively and bilaterally in whorled arrays of thickened, darkened, hystrix-like velvety lesions anywhere on the skin surface. Palmoplantar involvement is variable. But there are no episodes of blistering or skin fragility.1, 4

Histologically, the lesions have obvious perinuclear vacuolization of the suprabasal keratinocytes, with irregular cellular boundaries and increased number of keratohyaline granules in the background of crest-like compact hyperkeratosis and papillomatosis, as well as acanthosis with elongation of the rete ridges. This striking histologic picture is referred to as epidermolytic hyperkeratosis or granular degeneration of the epidermis.6, 7 This same process was first recognized in cases of bullous congenital ichthyosiform erythroderma. In IHCM, however, true epidermal separation does not occur,7 but a high percentage of binucleate suprabasal keratinocytes is present.8

In was not until the 1970s that these peculiar ultrastructural abnormalities of IHCM were clearly detected by electron microscopy:2 Pinkus and Nagao in 1970 and Anton-Lamprecht et al. in 1973 respectively reported a unique shell surrounding the nucleus of suprabasal keratinocytes observed in IHCM. With later structural analysis, the shell was found to be composed of 10nm filaments that were immunoreactive to keratin antibodies.3 These individual keratin intermediate filaments were disordered and failed to form normal bundles. Rather, they aggregated into concentric continuous shells that were retracted peripherally from the nucleus, leaving a clear halo. Electron microscopic examination of binucleate keratinocytes reveals an interesting picture of one shell enclosing both nuclei, indicating a disturbed post-mitotic division, most likely from interference by the keratin shell. In contrast to what is seen in epidermolytic hyperkeratosis, tonofilament clumps do not occur in IHCM.2, 8

Interestingly, these abnormalities are only observed in the suprabasal keratinocytes. The basal cells are normal. Such ultrastructural findings suggest molecular defects in keratin genes expressed by differentiated keratinocytes.4

Recent genetic studies and molecular analysis have disclosed reasons for the observed morphologic findings.3, 5, 8-10 Keratin intermediate
filaments, the cytoskeleton characteristic of keratinocytes, normally organize in bundles from the peri-nucleus and course peripherally to terminate at the desmosomes. They are composed of different keratins sharing a similar backbone structure of a classical alpha-helical rod domain flanked by non-helical variable end domains. In the skin, K1 is the major keratins expressed in differentiating keratinocytes. Keratinization disorders, among them, the epidermolytic hyperkeratosis, result from mutations affecting the keratin gene rod domain, which is believed to be crucial for the normal assembly of keratin filaments and thus for cell integrity. However, a mutated rod domain, keratin clumping, and epidermolysis have not been observed in ICMH.

In 2001, Sprecher et al. finally identified a novel mutation site for ICMH, not within the rod domain. A frameshift mutation 1609-1610delGGinsA in the V2 tail domain of K1 results in a different carboxy-terminal sequence, including the structurally and functionally important glycine loop motifs of K1, replaced by an aberrant, truncated peptide of 76 residues tail. Although the keratin intermediate filament assembly is not inhibited by this mutation, a higher supra-molecular structural organization is disturbed and an entangled shell formed.

Epidermal differentiation and keratinization are controlled by a large series of genes, mutations of which may induce a large variety of disturbances in the keratinization pathway and cell-cell integrity. Such keratinization disorders are highly heterogenous, although the resultant patterns may seem superficially similar, with common skin manifestations such as hyperkeratosis or blistering. However, phenotypic heterogeneity and ultrastructural differences may reveal distinct and specific abnormalities that are dependent on the precise underlying nature of the mutation. IHCM is one such disorder which furthers our understanding in the fascinating world of keratins.

REFERENCE