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CLINICAL REPORT

Congenital Reticular Ichthyosiform Erythroderma — Ichthyosis Variegata: a Case Report and Review of the Literature

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We present a 32-year-old white patient with congenital reticular ichthyosiform erythroderma, also known as ichthyosis variegata. The patient had typical clinical features with areas of normal appearing skin surrounded by erythematous hyperkeratotic patches. The smaller "confetti-like" patches were mostly present on the trunk, while the larger areas forming a reticular pattern predominated on the extremities. Ultrastructural findings demonstrated perinuclear vacuolization, binuclear cells and filamentous deposits compatible with congenital reticular ichthyosiform erythroderma. Besides presenting the case, we review the literature on this rare disorder of keratinization.

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A well-defined classification of ichthyosis congenita (IC) is complicated by their great heterogeneity (1–4). Congenital reticular ichthyosiform erythroderma (CRIE) is a rare type of IC (5, 6). Four isolated cases have been reported to date (5–8), but it is possible that additional cases have been described (9–12). It is characterized by slowly enlarging islands of normal skin surrounded by erythematous ichthyotic patches in a reticulated pattern. The condition starts as a lamellar ichthyosis with small islands of normal skin resembling "confetti" appearing in late childhood and puberty (7). Hence the name "ichthyosis en confetti" has been suggested in the French literature (6). The term ichthyosis variegata (9) was recently proposed in order to describe the clinical picture better, since "confetti-like" patches correspond to normal skin with a typical ultrastructural finding present in the surrounding erythematous scaly areas.

The most important histopathological findings include band-like parakeratosis, psoriasiform acanthosis, vacuolization of the keratinocytes with binuclear cells in the upper epidermis and deposits of the amyloid in the dermis (6, 7). The peculiar ultrastructural abnormality is the presence of perinuclear shells built from a three-dimensional network of fine filaments in vacuolized keratinocytes of the upper epidermis (5, 7, 10, 13). The filamentous material is probably formed by glycoproteins, although its exact nature has not been identified (13).

We report an additional case of this rare type of IC and also review the literature on previously published patients with typical clinical features and ultrastructural abnormalities of CRIE.

CASE REPORT

A 32-year-old white male presented to our clinic with a history of red, scaly skin since birth. Over several years his skin findings remained stable and his psychomotor development was normal. At the age of 10 he started developing white spots on the trunk and extremities, which enlarged slowly but constantly over the next 10 years. His skin was especially sensitive in winter, with pruritus, dryness and irritation, and fewer symptoms in the summer. Treatment with emollients and 12% ammonium lactate was moderately effective in the control of his dryness. The patient was a full-term born baby after an uneventful pregnancy from a non-consanguineous marriage. He was the only child and the family history for ichthyosis was negative. Past medical history was consistent with hypospadia surgery in early childhood, but was otherwise non-contributory.

Physical examination showed a diffuse intense erythema on the face, trunk and extremities with fine scaling and discrete hyperkeratotic patches on the upper trunk and back. Patches of apparently normal skin ("confetti-like") surrounded by erythema and scaling were present on the abdomen, upper chest and back (Fig. 1). On the arms and lower legs the areas of normal unaffected skin were interspersed with erythematous scaly patches forming the reticulated pattern (Fig. 2). Orange-red hyperkeratosis was present on palmo-plantar surfaces with increased palmar skin markings. Extracutaneous abnormalities were not detected and all laboratory tests, including androgen profile, were within normal limits.

Histopathological findings from the affected erythematous skin on the back showed hyperkeratosis, thick granular layer, acanthosis, paranuclear vacuolization in some keratinocytes in the upper layers of the epidermis and dilatation of dermal blood vessels with a sparse

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Fig. 1. Presence of confetti-like islands of normal skin surrounded by ichthyosis on the chest.

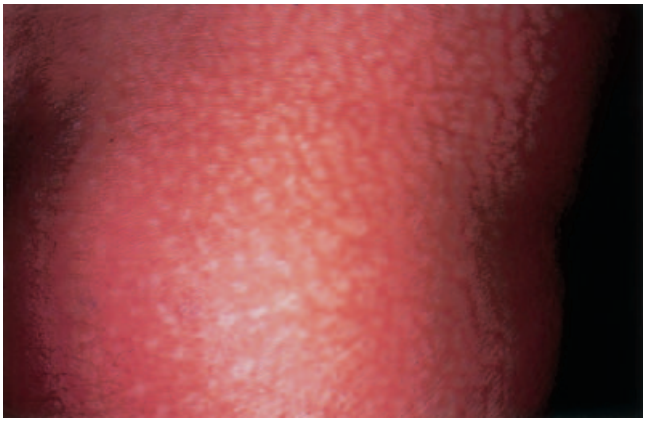


Fig. 2. Reticular arrangement of areas of erythema and scaling interspersed with areas of normal skin on the legs.

perivascular mononuclear infiltrate in the superficial dermis (Fig. 3). At the ultrastructural level, the most significant finding was the presence of binuclear cells (Fig. 4a) and granular paranuclear material (Fig. 4b) in

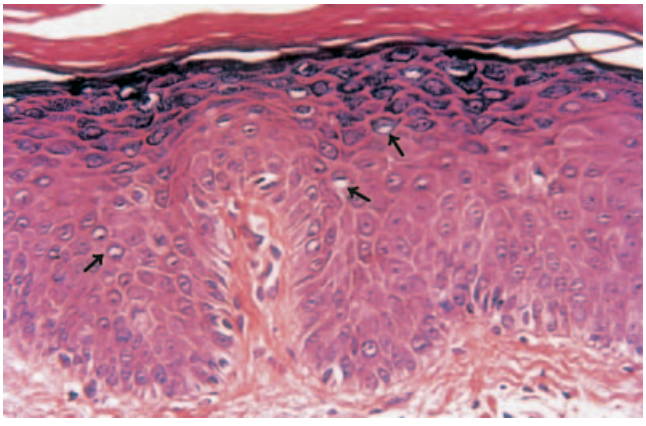


Fig. 3. The affected skin shows hyperkeratosis and acanthosis. Several keratinocytes in the upper layers of the epidermis show vacuolar change (arrows) (H&E : original magnification $\times 100$).

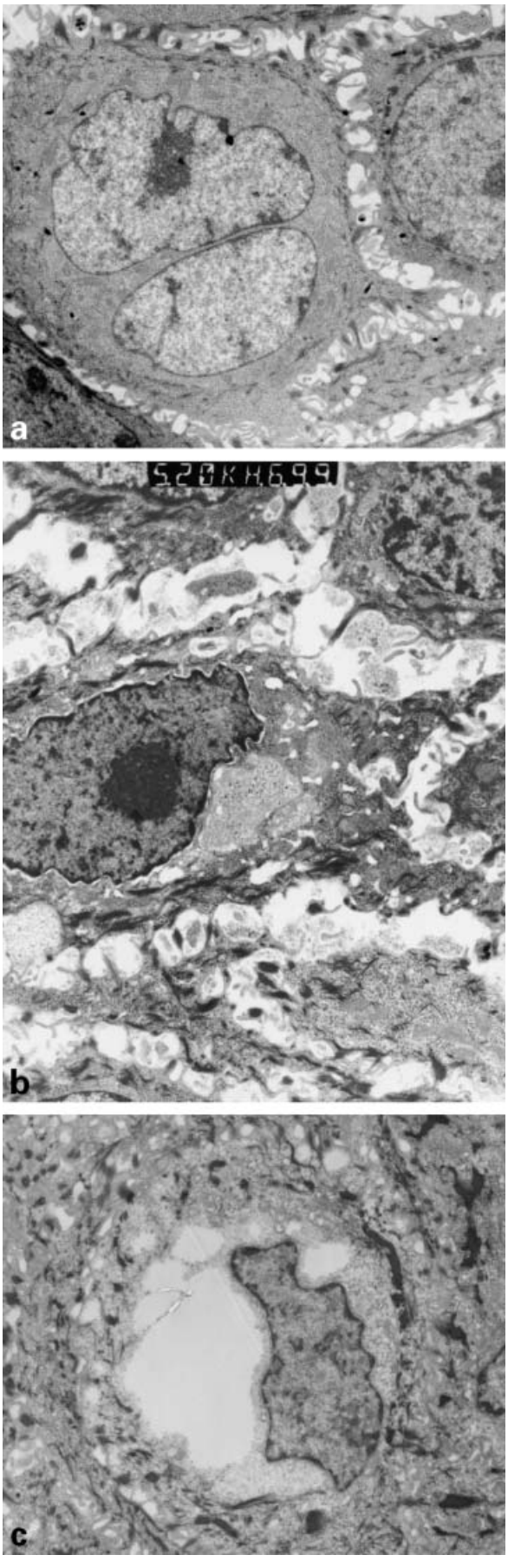


Fig. 4. Electron micrograph of the affected skin: some suprabasal keratinocytes show binuclear features (a), while others have a deposition of finely granular material in the perinuclear area of cells without (b) and with (c) vacuoles.

the vacuolized superficial keratinocytes (Fig. 4c). On closer examination, the material was composed of thin filaments.

DISCUSSION

We believe that our patient presents an additional case of the rare CRIE condition with clinical features of islands of normal skin surrounded by ichthyosis as well as pathognomonic ultrastructural features of binuclear keratinocytes and perinuclear shells of filamentous material. Compared to other reported cases, our patient demonstrated neither extensive psoriasiform acanthosis nor band-like parakeratosis under the light microscope. Nor were other reported findings, such as lipid droplets and amyloid (5, 10), significant in our patient, which is similar to the case reported by Brusasco et al. (7, 8).

A careful search of the literature revealed a total of six cases with clinical, histological and/or ultrastructural findings suggestive of CRIE (Table I). Two patients in the earlier reports did not have ultrastructural studies of the skin, although clinical and histological findings were highly consistent with CRIE (6, 9, 12). The four remaining cases had typical electron microscopic features of CRIE with perinuclear shells of filamentous material (5–8, 10, 11). The 5-year-old patient of Ruffli et al. (10) and the 19-year-old male patient of Arnold et al. (11) had lamellar erythrodermic ichthyosis with fine scaling rather than characteristic islands of unaffected skin. In the former case especially, we can at least speculate that the patient was still too young and the "confetti-like" pattern had yet to occur.

Oral retinoids have been reported effective in several cases of CRIE with enlargement of the areas of white skin in regard to the erythematous ichthyotic skin (5, 6, 10). Our patient refused this option, so the standard treatment with emollients was continued. Perhaps the absence of marked hyperkeratosis may be consistent with long-term use of lactic acid for skin hydration prior to presentation to our clinic (14).

The identification of only a small number of sporadic cases leaves the problem of inheritance unresolved. Our patient was the only child and had no relatives affected by ichthyosis. The extensive analysis of the pedigree of two families of reported patients revealed no other siblings affected. The authors suggested the occurrence of a new dominant mutation as a cause of the condition (5, 8, 11, 13). The somatic mutations resulting in the genetically different cell lines (mosaicism) suggested earlier (15) were strongly disputed in the later reports (8).

In conclusion, CRIE/ichthyosis variegata may be considered a separate entity in its clinical appearance and ultrastructural abnormalities. It differs from four classic types of IC. The specific pattern of presentation with uninvolved skin surrounded by ichthyosis is not clearly understood. Attempts to establish CRIE as a type of classical IC were abandoned after it was learned that the filamentous material shows similarities with glycoproteins but not tonofilaments (11). Further immunohistochemical studies and possible additional cases may help to resolve these questions. So far, CRIE presents further proof of the relevance of electron

Table I. *Reported cases with clinical and/or ultrastructural findings consistent with congenital reticular ichthyosiform erythroderma - ichthyosis variegata*

Case (ref.)	Age	Sex	Clinical findings	Histology	Electron microscopy	Additional findings
1 (6)	14	Male	Confetti-like patches of normal skin enclosed with ichthyosis	Acanthosis with orthokeratosis and parakeratosis	Not performed	
2 (6, 7, 8)	12	Female	Same	Acanthosis with orthokeratosis and parakeratosis, agranulosis, perinuclear vacuoles, rare binuclear cells	Perinuclear cup-shaped filamentous deposits, vacuolized keratinocytes	Black hyperpigmented macules on extremities developed 10 years later; hypertrichosis
3 (5)	57	Female	Reticular pattern of normal skin interspersed with ichthyosis	Same as case 2, but more binuclear cells and amyloid deposits	Similar as case 2	
4 (10)	5	Female	Non-bullous ichthyosiform erythroderma	Same as case 2	Same as case 2	
5 (11)	19	Male	Erythroderma with fine scaling	Similar to case 2 with lipid droplets in the horny layer	Same as case 2	Hypogonadism and growth retardation
6 (9, 12)	17	Male	Islands of normal skin surrounded with ichthyosis	Same as case 2	Not performed	Micropinna, alopecia, ectropion, squamous cell carcinoma
7 (our case)	32	Male	Confetti-like pattern on the trunk, reticular pattern on extremities	Similar to case 2, but mostly orthokeratosis, and thickened granular layer	Same as case 2	

microscopic studies in the diagnosis, classification and identification of inherited disorders of keratinization with such a tremendous clinical heterogeneity.

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