An unusual case of keratinopathic ichthyosis: a diagnostic conundrum

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Abstract

Epidermolytic ichthyosis (EI) is a rare inherited ichthyosis related to heterozygous mutations in *Keratin 1* or *Keratin 10* genes. Because of the broad phenotypic spectrum, it is sometimes difficult to differentiate EI from other keratinopathic ichthyoses (KI) in clinical practice. We report an intriguing case of KI presenting as generalized ichthyosis in a reticulate pattern surrounding islands of normal skin, epidermolytic hyperkeratosis and binucleate cells on histopathology, and heterozygous mutation in *KRT10*. Through this case, we would like to demonstrate the importance of genetic studies and genotype-phenotype correlation in diagnosing such challenging cases.

Keywords: epidermolytic hyperkeratosis, keratin 10, keratinopathic ichthyosis

Introduction

Keratinopathic ichthyoses (KI) are a rare group of non-syndromic ichthyosis related to mutations in keratin genes (*KRT*), [1,2]. There are 6 major types with overlapping clinical and histopathological features. Owing to the expanding genotypic and phenotypic spectrum of KI, accurate classification in clinical practice can be challenging [2,3]. We present one such intriguing case of KI with ichthyotic scaling in a reticulate pattern and histopathology resembling congenital reticular ichthyosiform erythroderma (CRIE). However, genetic testing favored the diagnosis of epidermolytic ichthyosis (EI).

Case Synopsis

An 11-year-old girl presented with itching, scaling, and thickening of skin over the elbows and knees from six months of age. The cutaneous abnormalities became generalized by one-and-a-half years of age. Mother gave history of thick scales that peel off leaving behind normal skin, suggestive of a molting phenomenon, but was uncertain about the age of onset of this phenomenon. There was no history of collodion membrane, erythroderma, or blistering at birth. Although there were mild exacerbations during summers, the symptoms generally worsened in winter. She was the firstborn of a non-consanguineous marriage by full-term uncomplicated vaginal delivery, with a birth weight of 2.7 kg. The antenatal and perinatal periods were uneventful and there were no visible abnormalities at birth. Her psychomotor development was normal. Except for myopia, there was no other history to suggest extracutaneous involvement. There was no family history of similar complaints. She was treated with acitretin for a year, which was moderately effective in the control of her skin symptoms. Treatment was discontinued 8 months before presenting to us.

At presentation, her height was 1.48 m (75^{th}-97^{th} centile) and weight was 30 kg (50^{th}-75^{th} centile). She had generalized dull erythematous scaling and hyperpigmentation interspersed with variably-sized islands of normal appearing skin. The patches of normal appearing skin were smaller with few being confetti-like on the chest (**Figure 1A)** and larger over the rest of the trunk and extremities (**Figures 1B, 2**),

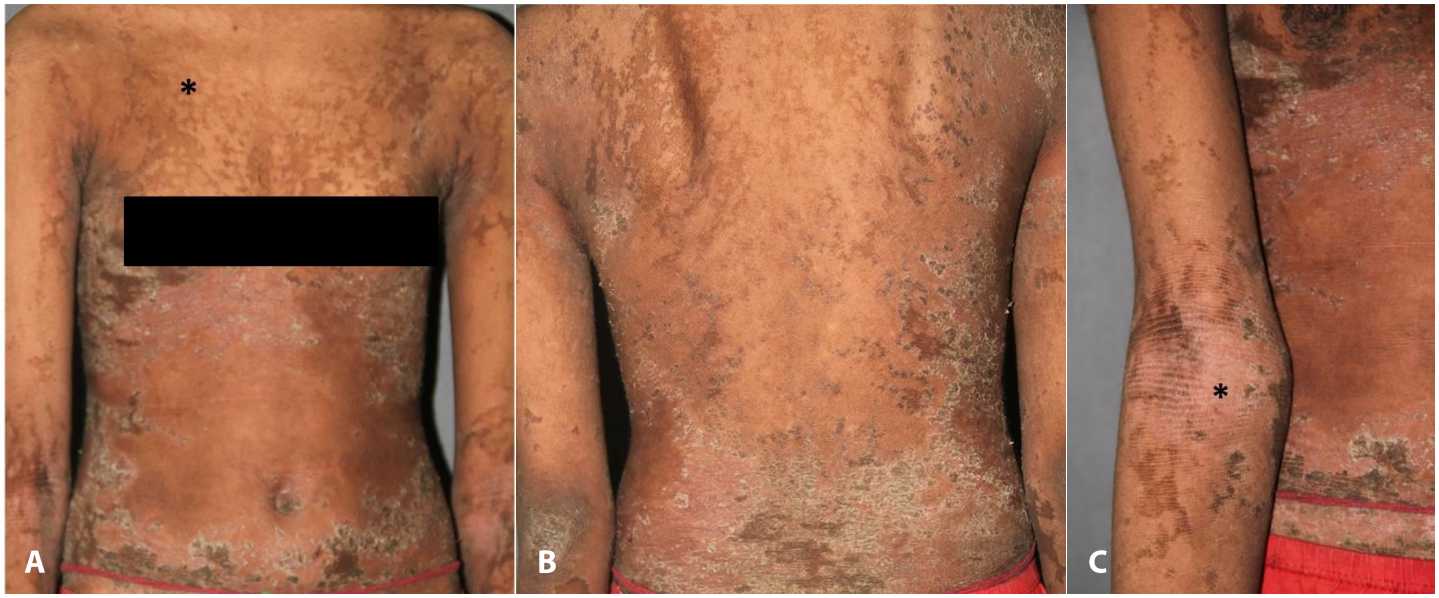

Figure 1. ***A, B)*** *Dull erythematous scaling and hyperpigmentation in a reticulate pattern around islands of normal skin involving the trunk and extremities, with few confetti macules of normal skin over the chest (asterisk).* ***C)*** *Ridged hyperkeratosis over the right cubital fossa (asterisk).*

lending a reticulate configuration to the adjacent ichthyotic skin. There was ridged hyperkeratosis, typical of KI, over the flexures (**Figure 1C)**, diffuse thick scaling on the scalp, and mild diffuse palmoplantar keratoderma (PPK). There was relative sparing of the central face. Hair, nails and mucosae were normal on examination.

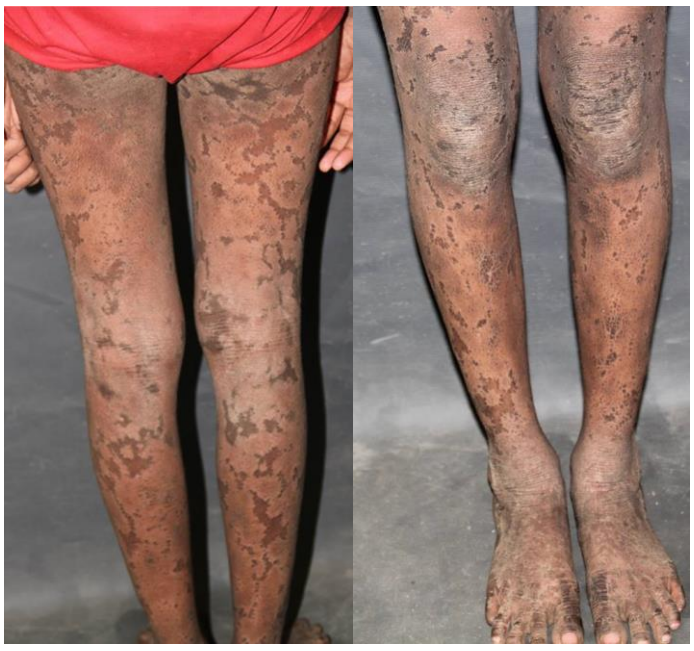

Figure 2. *Ichthyotic scaling in a reticulate pattern around islands of normal skin over bilateral lower limbs.*

Histopathological examination of the affected skin showed epidermolytic hyperkeratosis (**Figures 3, 4**), which was consistent with our clinical diagnosis of KI. Binucleate keratinocytes that are classically described in CRIE and ichthyosis Curth-Macklin (ICM) were also seen [4]. However, massive PPK and thick, verrucous, hyperkeratotic plaques over large joints, extremities, and trunk, characteristic of ICM were absent in our patient.

After obtaining informed consent from the parents, peripheral blood was sent for next-generation sequencing using an ichthyosis panel, which revealed a heterozygous, likely pathogenic variant in exon 6 of the *KRT10* (c.1301_1303del, p.Gln434del). This in-frame deletion leads to loss of a highly conserved glutamine residue in the 2B rod domain and has been previously reported in a patient affected with EI [5]. Missense mutations in *KRT1/KRT10* are seen in most cases of EI, whereas frame-shift mutations in the tail domain of *KRT10/KRT1* are seen in all cases of CRIE reported to date [2,6]. Mirza et al., were the first to report an in-frame trinucleotide deletion in *KRT10* identical to that seen in our patient. The genetic testing aided in the diagnosis of EI in this child, but we were unable to validate the results in the asymptomatic parents.

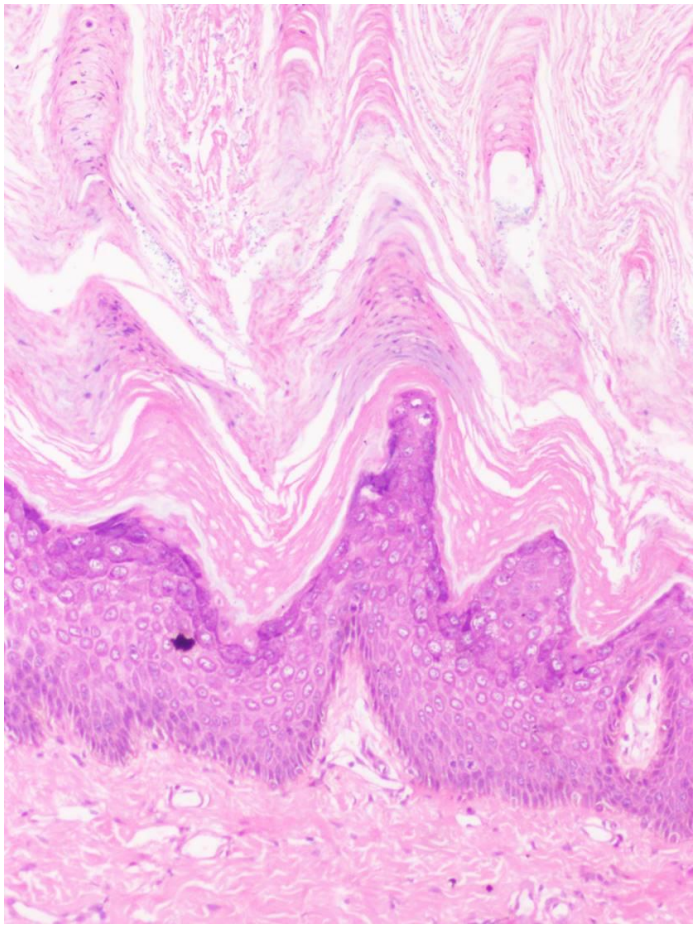

Figure 3. *Papillomatous hyperkeratosis with tiers of parakeratosis and vacuolated suprabasal keratinocytes. H&E, 40×.*

Her vitamin D level was 16.75nmol/l (normal >75nmol/l) which was adequately treated. She was treated with emollients and topical keratolytic agents (10% propylene glycol, a cream containing 10% urea, and 15% glycolic acid) with which she had moderate, symptomatic relief. She was started on isotretinoin during the follow-up visit.

Case Discussion

Keratin intermediate filaments (KIF) maintain the structural integrity of the epithelial tissue and mutation in keratin genes can have a myriad of presentations ranging from blistering to scaling clinically and epidermolytic hyperkeratosis on histology [3,5]. These are seen, albeit in varying severity, in all KI, which includes EI/ bullous ichthyosiform erythroderma of Brocq, superficial EI (SEI)/ ichthyosis bullosa of Siemens, annular EI (AEI), ichthyosis with confetti (IWC)/CRIE, ICM, and autosomal recessive EI (AREI), the key features of which are outlined in **Table 1** [1,7]. Although clinical examination and a comprehensive evaluation with skin biopsy for histopathology, immunopathology, and ultrastructural analysis can aid in the diagnosis, mutational analysis helps in nailing the diagnosis and is considered the gold standard to diagnose ichthyosis in many countries [1,7].

Epidermolytic ichthyosis is a rare autosomal dominant, inherited ichthyosis related to mutations in *KRT1* or *KRT10*, with an incidence of one case per 200,000 to 300,000 live births [3,8,9]. Around 50% of

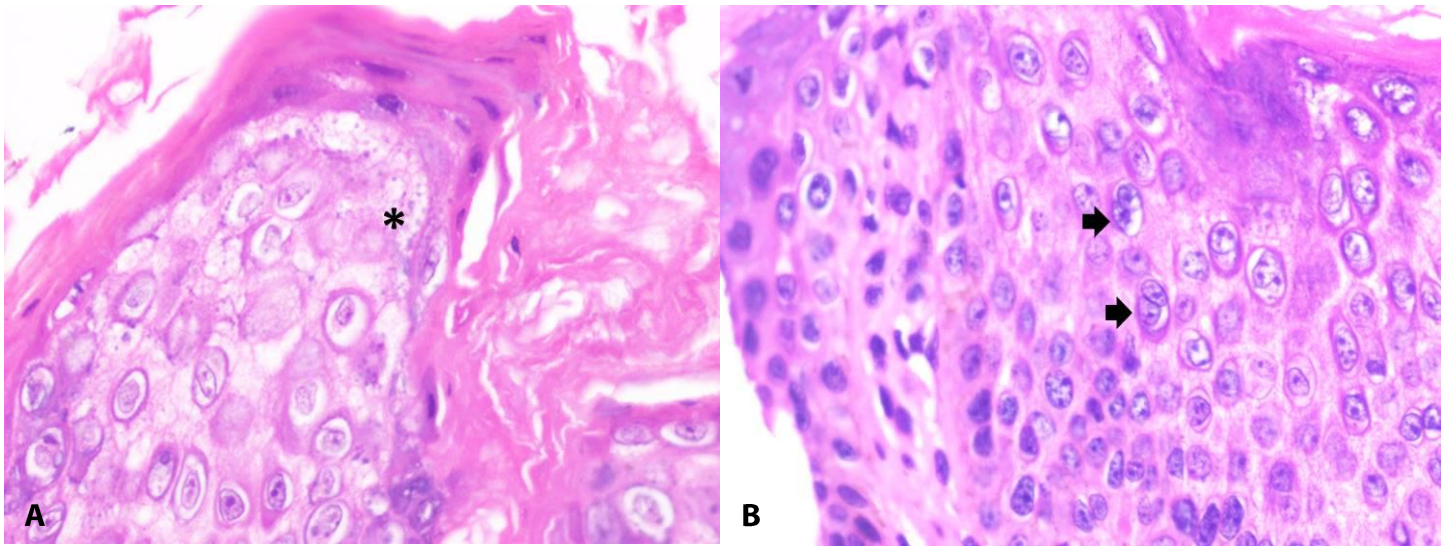

Figure 4. ***A)*** *Vacuolated keratinocytes with coarse keratohyaline granules (asterisk). H&E, 200×.* ***B)*** *Vacuolated binucleate keratinocytes (arrow). H&E, 400×.*

Table 1. *Summary of clinical and histopathological features of keratinopathic ichthyosis [1,3,4,7].*

Type of keratinopathic ichthyosis	Mode of inheritance	Gene	Clinical features	Histology	Electron microscopy
Epidermolytic ichthyosis	AD/AR	*KRT1/ KRT10*	At birth: Bullae and erosions overlying erythrodermic skin Later: Generalised ichthyotic scaling, corrugated hyperkeratotic scaling over the flexures +/- PPK	EH	EH Aggregation and clumping of KIF in suprabasal cells Cytolysis
Superficial epidermolytic ichthyosis	AD	*KRT2*	At birth: Bullae and erosions overlying erythrodermic skin Later: Hyperkeratosis predominantly over the joint extensors, molting/ Mauserung phenomenon PPK absent	Superficial EH	Superficial EH Cytolysis in granular cells No clumping of KIF
Annular epidermolytic ichthyosis	AD	*KRT1/ KRT10*	At birth: Bullae and erosions overlying erythrodermic skin Later: Cyclic annular and polycyclic hyperkeratotic plaques over trunk and extremities +/- PPK	EH	EH Aggregation and clumping of KIF in suprabasal cells
Ichthyosis Curth-Macklin	AD	*KRT1*	Thick, spiny, hyperkeratotic plaques over joints and hyperkeratotic papules over trunk and extremities Worsening PPK	Perinuclear vacuolization Binuclear keratinocytes	Concentric perinuclear shells of KIF Binuclear keratinocytes
Ichthyosis with confetti	AD	*KRT10/ KRT1*	At birth: Erythroderma Later: Develop confetti like spots of normal skin on the background erythroderma +/-PPK	Perinuclear vacuolization Binuclear keratinocytes	Perinuclear shells of granular material in vacuolized superficial keratinocytes Binuclear keratinocytes

AD, autosomal dominant; AR, autosomal recessive; EH, epidermolytic hyperkeratosis; KIF, keratin intermediate filaments; KRT1, keratin1 gene; KRT10, keratin 10 gene; PPK, palmoplantar keratoderma.

cases are sporadic and autosomal recessive inheritance is rarely seen [8,9].

Often, the affected infants present at birth or soon thereafter with erythroderma, blistering, and skin fragility which eventually improves and is replaced by hyperkeratotic scaling [1,6]. Nonetheless, our patient was unaffected at birth and developed generalized ichthyotic scaling later in life, indicating a milder phenotype. Incidentally, a case of EI described by Mirza et al., with the very same mutation as our patient, also did not have erythroderma/blistering at birth; the age of onset of ichthyosis in that patient was unavailable [5]. The prominent scaling over the neck, hands, feet, and joint flexures, aptly described as ridge-like/corrugated hyperkeratosis, a striking feature of EI, was seen in our patient as well; however, she never had blistering [3]. Though she had history suggestive of molting, which is classically described in SEI, the generalized involvement of skin including the palms and soles and *KRT10* mutation was incompatible with this diagnosis [1,7]. Although the

peculiar pattern of reticulate ichthyotic scaling seen in our patient made us consider CRIE, the areas of normal appearing skin were larger than the confetti macules classically seen in CRIE and the erythema that has been described in the previous cases was absent in our patient [6]. In this patient, the shedding of large plates of superficial epidermis is probably responsible for the reticulate configuration of the adjacent ichthyotic skin. Although palmoplantar keratoderma is usually associated with *KRT1* mutation, it can be seen with *KRT10* mutation as evident from this case [2,5].

Epidermolytic hyperkeratosis is the prominent histopathological feature seen in EI and the feature of the binucleate keratinocyte is classically but not exclusively seen in CRIE and ICM as evident from this case [4,10]. In EI, immunohistochemistry reveals defective expression of keratin 1 (K1) or keratin 10 (K10) and electron microscopy shows KIF clumping in suprabasal keratinocytes [1,3]. Although both are useful diagnostic tools, their use is limited by the cost, need for expertise, and poor accessibility and was not done in our case.

We considered AEI, a rare clinical variant of EI, in our differential diagnosis because of the milder phenotype and *KRT10* mutation. The absence of characteristic flares of erythematous, annular, polycyclic, scaly plaques over trunk and extremities, interspersed by periods of near-complete clearing and lack of prominent acantholysis in histopathology were incompatible with AEI [1,11].

Genetic testing helps not only to confirm the diagnosis but also predicts the severity of the disease and is crucial for genetic counselling and prenatal diagnosis. In EI, point mutations affecting the alpha-helical rod domain of *KRT1/KRT10* result in defective KIF, disrupting the keratin cytoskeleton in suprabasal keratinocytes [2,5]. The severity of the disease is influenced not just by the site of mutation, but also by the degree of mutated allele expression and the functional implications of amino acid substitution in the keratin gene [3]. Thus, genotype-phenotype correlation in patients with KI is considered to be complex and disease severity is found to be proportional to the degree of disruption of K1-K10 dimer interactions [2,3,5]. The milder phenotype seen in our patient can be explained by the results of the study by Mirza et al. They compared the K1-K10 polymer structure in wild and mutant states and noted that the particular mutation, seen in both our patients, affects the surface-exposed residues of K10, which are not directly involved in inter- or intramolecular interactions. Consequently, the resulting KIF are collapsed but do not form cytotoxic keratin aggregates, explaining the milder phenotype [5].

Conclusion

Epidermolytic ichthyosis is a congenital ichthyosis characterized by blistering and erosions on an erythrodermic skin. We report an additional case of this entity presenting with ichthyotic scaling in a reticulate pattern, binucleate keratinocytes in histology, and in-frame deletion in *KRT10*, which are unusual in EI. Through this case we would like to demonstrate the importance of genetic studies, comprehension of the molecular mechanisms, and knowledge of genotype-phenotype correlation in diagnosing such challenging cases of inherited ichthyosis.

Potential conflicts of interest

The authors declare no conflicts of interests.

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