Annular epidermolytic ichthyosis: An exceptional mild subtype of epidermolytic ichthyosis without genotype and phenotype correlation

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INTRODUCTION

Annular epidermolytic ichthyosis (AEI) is a rare subtype of epidermolytic ichthyosis (EI) characterized by recurrent flares of erythematous and scaly lesions alternating with periods of almost normal skin with or without associated palmoplantar keratoderma (PPK).1 We report on 2 different patients with AEI showing pathogenic variants in the KRT1 and KRT10 genes respectively, and review the main clinical, histologic and molecular findings of this exceptional subset of EI.

CASE REPORTS

Case 1

A 6-month-old boy was brought for consultation because of blisters and erosions since birth. The child had been born at term by vaginal birth to a healthy mother. Maternal family background was unremarkable, and paternal family history could not be tracked. On physical examination, there were annular erythematous and scaly lesions on the diaper area and proximal lower extremities. There was mild hyperkeratosis on the armpits, elbows, and intergluteal fold, as well as superficial blisters on the palms and soles. Pathologic analysis showed hyperkeratosis on the armpits, elbows, and intergluteal fold, as well as superficial blisters on the palms and soles. Pathologic analysis showed hyperkeratosis with epidermal detachment within the granular layer and acantholysis in the upper spinous layers. Targeted DNA sequencing of the KRT1 gene from peripheral blood identified a heterozygous missense variant c.1436T>C; p.(Ile479Thr) in KRT1. After 2 years of follow-up, the patient developed diffuse PPK and continues to show recurrent crops of transient annular scaly lesions on the lower portion of the trunk (Figs 1 and 2).

Case 2

A 3-month-old boy, born at term to healthy, nonconsanguineous parents, was brought for consultation for recurrent crops of cutaneous lesions. Large areas of blisters and erosions over the genital area and limbs were observed shortly after birth. On physical examination, there were transient annular polycyclic erythematous plaques over the trunk, knees, ankles, and lateral aspects of the feet and upper limbs (Figs 3 and 4). Palms and soles were uninvolved. Periods of almost complete clearing were observed. Biopsy of an erythematous and scaly lesion on the trunk showed thick hyperkeratosis with foci of parakeratosis, hypergranulosis with prominent and coarse keratohyalin granules,
and vacuolar degeneration of the superficial spinous and granular layers. Targeted DNA sequencing from peripheral blood identified the pathogenic variant c.467G>A;p.Arg156His in the KRT10 gene in heterozygosis. After 1 year of follow-up, the boy continues to have waxing and waning annular and polycyclic erythematous scaly lesions and shows mild hyperkeratosis on knees, elbows, and major folds.

DISCUSSION

AEI was included as a minor variant of epidermolytic ichthyosis (EI) in the last consensus classification of congenital ichthyosis. The name was coined in 1992 by Sahn et al, who reported the first family with AEI. Although the researchers did not provide genetic testing, their patient showed palmoplantar involvement consistent with a KRT1 gene variant. Since then, only 16 additional cases due to either KRT1 or KRT10 gene pathogenic variants, belonging to 7 different families, have been published in the literature (Table I).

AEI clinical findings are distinctive and relatively easy to recognize. The condition is characterized by intermittent flares of annular and polycyclic erythematous and scaly plaques over the trunk and extremities from early infancy or, more rarely, from childhood or adult life. Blistering and superficial erosions are commonly present at birth, with or without accompanying erythema. Inconstant diffuse hyperkeratosis in the flexural areas and extensor surfaces is seen. KRT1 gene variants are associated with PPK, whereas KRT10 variants result in sparing of the palms and soles. Unlike major forms of EI, periods of almost complete clearing are possible, except for PPK in patients with KRT1 gene variants. Histologically, orthokeratotic hyperkeratosis, prominent acantholysis, and a thickened granular layer with coarse keratohyalin granules are common findings, whereas vacuolar degeneration appears in both in AEI and major forms of EI, in EAI it appears in upper layers of the epidermis.

Like all keratins, KRT1 and K1RT0 are composed of a globular head and a tail domain with an alpha helical central rod domain composed of 4 distinct segments (1A, 1B, 2A, and 2B) separated by non-helical linkers (Fig 5). Pathogenic variants in KRT10 are located in the 2B segment of KRT10 and in the 1A rod domain of the gene. Keratin gene variants
Table I. Phenotypic and genotypic findings of all reported cases of AEI

| Reference            | Case Number | Age/Sex | Clinical Features | Mutation            | Treatment                        |
|----------------------|-------------|---------|-------------------|---------------------|----------------------------------|
|                      |             |         | Blistering at Birth | Migratory Anular Erythematosus Scaly Plaques | PPK | KRT Gene | Genetic Locus; Protein |                          |
| Sybert et al (1999)3 | 1           | 3 years/M | +                  | +                   | +             | KRT1 2B segment (case 1) | c.1436T>C; p.(Ile479Thr) | Emollients              |
|                      | 2           | 18 years/M | -                  | +                   | +             | KRT1 2B segment (cases 2, 3, and 4) | c.1435A>T; p.(Ile479Phe) | Emollients              |
|                      | 3 (mother of case 2) | NS/F | -                  | -                   | +             | KRT1 2B segment (cases 2, 3, and 4) | NS                          |
|                      | 4 (aunt of case 2) | NS/F | -                  | +                   | +             | KRT1 2B segment (cases 2, 3, and 4) | NS                          |
| Michael et al (1999)5 | 5, 6, 7, 8 (same family) | NS | +                  | +                   | +             | KRT1 2B segment (cases 2, 3, and 4) | c.1435A>T; p.(Ile479Phe) | Emollients              |
| Zaki et al (2018)4   | 9           | 5 years/F | +                  | +                   | +             | KRT1 2B segment (cases 2, 3, and 4) | c.1436T>C; p.(Ile479Thr) | Emollients + topical keratolytics + topical steroids |
| Case 1               | 17          | 6 months/M | +                  | +                   | +             | KRT1 2B segment (cases 2, 3, and 4) | c.1436T>C; p.(Ile479Thr) | Emollients + topical keratolytics |
| Joh et al (1997)6    | 10 (father of case 11) | 33 years/M | +                  | +                   | -             | KRT10 2B segment (cases 2, 3, and 4) | c.1264_1265delinsGA; p.(Arg422Glu) | Emollients + acitretin |
|                      | 11 (daughter of case 10) | 2 months/F | +                  | +                   | -             | KRT10 2B segment (cases 2, 3, and 4) | c.1264_1265delinsGA; p.(Arg422Glu) | Emollients + acitretin |
| Suga et al (1998)7   | 12          | 11 years/M | -                  | +                   | -             | KRT10 2B segment (cases 2, 3, and 4) | c.1337T>C; p.(Ile446Thr) | NS                        |
|                      | 13 (mother of case 12) | NS/F | -                  | -                   | -             | KRT10 2B segment (cases 2, 3, and 4) | c.1337T>C; p.(Ile446Thr) | NS                        |
|                      | 14 (sister of case 12) | NS/F | -                  | -                   | -             | KRT10 2B segment (cases 2, 3, and 4) | c.1337T>C; p.(Ile446Thr) | NS                        |
| Yoneda et al (1999)9 | 15          | 18 years/M | +                  | +                   | -             | KRT10 1A segment (cases 2, 3, and 4) | c.472G>C; | Emollients, etretinate |
|                      | 16 (mother of 15) | 48 years/F | +                  | +                   | -             | KRT10 1A segment (cases 2, 3, and 4) | c.472G>C; | Emollients, etretinate |
| Case 2               | 18          | 3.5 months/M | +                  | +                   | -             | KRT10 1A segment (cases 2, 3, and 4) | c.472G>C; | Emollients, etretinate |

AEI, Annular epidermolytic ichthyosis; F, female; KRT, keratin; M, male; NS, not stated; PPK, palmoplantar keratoderma.
affecting the residues at the ends of the central rod domains of the keratin proteins (helix initiation and termination motifs), such as the variant c.467G>A (p.Arg156His) in the 1A rod domain found in our patient (case 2), interfere with proper keratin intermediate filament assembly and function, resulting in skin fragility and/or hyperkeratosis. Although this pathogenic variant has previously been reported in patients with major forms of EI, to our knowledge, our patient is the first to show an AEI phenotype. Only 2 different keratin (KRT) 1 (KRT1) gene pathogenic variants resulting in the AEI phenotype have been reported to date: c.1435A>T; p.Ile479Phe and c.1436T>C; p.Ile479Thr. Both pathogenic variants are located in the 2B segment of KRT1 and predict a change of amino acids located in the same codon (codon 479) in the highly conserved 2B helix-termination motif. Interestingly, the c.1436T>C; p.Ile479Thr pathogenic variant has also been reported in multiple families with major forms of EI, suggesting a lack of direct correlation between genotype and phenotype.

Because 14 of the 16 previously reported cases occurred in children, no conclusions can be drawn about the course of the disease. Although nearly all patients show large blisters and erosions at birth, making them indistinguishable from those with major forms of EI, it seems that the degree of cutaneous involvement is considerably milder in AEI except for the palms and soles, which show progressive thickening in patients with KRT1 pathogenic variants. The variable phenotypic expression of similar KRT1 and KRT10 variants led us to hypothesize that patients with major forms of EI might have additional cis- or trans-regulatory changes affecting the expression of the wild-type allele. However, tissue expression studies are needed to further investigate this hypothesis.

There is no definitive therapy for AEI. Symptomatic therapy includes daily use of emollients, topical keratolytics, and systemic retinoids, but treatment response varies considerably among patients and families. Thus, although retinoid therapy is particularly effective in patients with KRT10 pathogenic variants, those with KRT1 variants may experience an exacerbation.

In summary, we add to the phenotypic and genotypic findings of all reported cases of AEI, an extremely uncommon subtype of EI, and we add 2 new cases of AEI due to mutations in KRT1 and
KRT10, respectively. The lack of genotype and phenotype correlation supports the idea that AEI is a milder phenotype of EI rather than a true subtype, an important fact that must be addressed when providing genetic counseling.

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