

Congenital absence of the skin secondary to the self-improving subtype of dystrophic epidermolysis bullosa with recurrent lesions throughout early childhood



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INTRODUCTION

Epidermolysis bullosa (EB) is a group of inherited blistering disorders with an estimated prevalence of 11 per million in the United States.¹ The self-improving subtype of dystrophic EB (SI-DEB), previously known as bullous dermolysis of the newborn, is a rare form characterized by generalized blisters at birth that rapidly improve during the first days or months of life.^{2,3} SI-DEB is caused by the transient retention of type VII collagen (a key component of anchoring fibrils) in the cytoplasm of basal keratinocytes, leading to sublamina densa blistering due to weakened anchoring fibrils.⁴ SI-DEB is associated with mutations in *COL7A1*, the gene encoding type VII collagen.⁵ Diagnosis of SI-DEB is confirmed through the identification of granular intraepidermal type VII collagen by immunofluorescence mapping and electron-dense stellate bodies on ultrastructural examination.² In SI-DEB, blistering improves as type VII collagen distribution normalizes.⁴

Congenital absence of the skin (CAS), or aplasia cutis congenita, is a clinical sign associated with many subtypes of EB.^{3,6,7} Formerly known as aplasia cutis congenita type VI or Bart syndrome, EB with CAS typically presents at birth, with large areas of aplasia cutis on the bilateral dorsal aspect of the feet and legs, although upper extremity and trunk involvement has also been reported.⁶ The specific

Abbreviations used:

CAS: congenital absence of the skin
EB: epidermolysis bullosa
SI-DEB: self-improving subtype of dystrophic epidermolysis bullosa



Fig 1. Skin findings during infancy. Absence of skin along the left lower extremity at birth.

mechanism of CAS in EB is not known, but in utero friction is the most cited hypothesis.⁶ Similar to the blistering in SI-DEB, CAS generally heals by the end of infancy.⁶

In this report, we describe an unusual case of EB with CAS secondary to SI-DEB with recurrent blisters throughout early childhood. We also review the few cases in the literature of SI-DEB failing to resolve during infancy. To the best of our knowledge, this is only the second case of SI-DEB presenting with CAS

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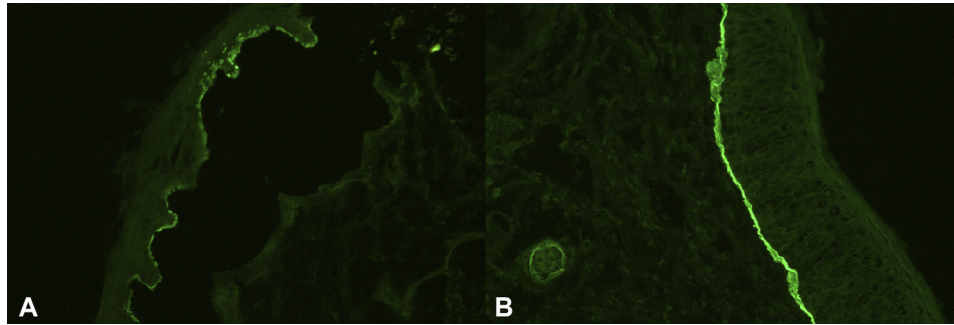


Fig 2. Immunofluorescence mapping. **A**, Type VII collagen as granules in the epidermis and weaker reactions in the BMZ of the roof. **B**, Type VII collagen in normal skin control (original magnification: $\times 200$). *BMZ*, Basement membrane zone.

at birth with persistent blistering lesions past 3 years of age.

CASE REPORT

A newborn African American girl was evaluated for the absence of skin on the left lower extremity following an uncomplicated pregnancy and delivery at 36 weeks. She had 3 half siblings on her paternal side with no history of skin or blistering disorders.

At birth, she had absence of skin on the anteromedial aspect of the lower portion of the left leg extending down through the dorsum of the foot and toes (Fig 1). She also had several ulcerations on the face, anterior aspect of the right wrist, dorsum of the left hand, and abdomen. The primary lesion on her leg was treated conservatively with antibiotic ointment and gentle wound care. No nail or mucous membrane abnormalities was noted. On day 15, multiple new erosions appeared on her face, trunk, hands, and feet. Immunofluorescence mapping studies on a biopsy specimen of an induced lesion revealed cytoplasmic granular deposits of type VII collagen in basilar and suprabasilar cells (Fig 2). On day 36, keratinization was noted in the primary leg lesion.

From infancy through age 5, she has had recurring blistering episodes on her bilateral lower extremities 3 or 4 times per year. The lesions tend to develop following minor mechanical trauma and typically self-resolve with minimal scarring. In sum, the initial presentation at birth, biopsy with immunofluorescence mapping, and subsequent clinical course favor a diagnosis of CAS secondary to SI-DEB with recurrent blisters throughout childhood. Her family was offered genetic sequencing but refused.

DISCUSSION

This case of EB deviates from the classic description of SI-DEB, given the continued blistering

present throughout early childhood. To our knowledge, there have been only 4 previously reported cases of SI-DEB with continued blistering past age 3 (Table I). With the addition of our case, such cases account for 9.6% of known SI-DEB cases (5 of 52).⁵ However, clinical follow-up was inconsistently reported for many cases, which raises the question of how often SI-DEB truly resolves in infancy. Among these 5 cases, no clear demographic or clinical pattern was identified, with the exception of continued blistering associated with mechanical trauma. The specific genetic defect within *COL7A1* was unique in each of the 3 cases for which sequencing data were reported (Table I).

This case was also associated with unilateral lower extremity CAS. Unilateral CAS accounts for a minority of CAS cases of EB, with most cases presenting bilaterally.⁶ The often-cited mechanism for CAS in EB is trauma of sensitive skin caused by crossing of the legs of the fetus in utero.⁶ Genetic causes have also been hypothesized; there is an association between the specific location of missense mutations in *COL7A1* and CAS phenotype³ and the higher odds of CAS in recessively inherited SI-DEB.⁷ CAS in EB has also been thought to follow the lines of Blaschko, a manifestation of cutaneous mosaicism.⁶ Interestingly, recent studies have identified revertant mosaicism, when inherited mutations self-resolve in groups of somatic cells, in patients with EB.⁸ Revertant mosaicism may be especially common in DEB.⁹ Unfortunately, we know of no studies assessing mosaicism in EB with CAS or SI-DEB specifically. Given these data, both genetic and environmental mechanisms are likely implicated in the transient nature and phenotypic heterogeneity of EB with CAS, as well as SI-DEB more generally.

In conclusion, to our knowledge, this is only the second report of SI-DEB presenting with both CAS at birth and recurrent blistering throughout early

Table I. BDN with recurrent lesions past 3 years of age

Case no.	Reference	Sex	Race/ethnicity	Inheritance pattern	Genetic defect	Disease extent at diagnosis	Disease extent at last follow-up
1	Fine et al 1993 ⁴	F	Not reported	AD*	Heterozygous c.4120-1G>C; splice acceptor variant resulting in skipping of exon 36	9 mo: generalized blistering	Age 11 y: blistering following mechanical trauma
2	Hatta et al 1995 ¹¹	F	Japanese	Unknown	Unknown	Birth: RLE CAS; generalized blistering; mucosal and nail disease	Age 4 y: mild blistering
3	Boccaletti et al 2015 ¹⁰	F	Pakistani	AR [†]	Homozygous p.Pro2259Leu, c.6776C>T, missense variant in the second THD domain	Birth: generalized blistering and superficial ulcerations; mucosal and nail disease	Age 3 y: blistering following mechanical trauma
4	Diociaiuti et al 2016 ⁷	M	Not reported	AD [‡]	Heterozygous p.Gly2431Val, c.7292G>T, missense variant in the second THD domain	1 mo: vesicles and erosions on the hands, subungual hemorrhages	Age 3 y: blistering on extremities, typically occurring in summer
5	Current report	F	African American	Unknown	Unknown	Birth: LLE CAS; generalized blistering	Age 5 y: blistering of the bilateral lower extremities following mechanical trauma

Note: Case 1 did not have diagnostic IF mapping reported; in cases 2-5, diagnostic IF mapping revealed type VII collagen within basilar and suprabasilar keratinocytes. In case 2, resolution of IF mapping findings was noted at age 4 years.

AD, Autosomal dominant; AR, autosomal recessive; BDN, bullous dermolysis of the newborn; CAS, congenital absence of the skin; IF, immunofluorescence; LLE, left lower extremity; RLE, right lower extremity; THD, triple helix domain.

*The mother had mild blistering that started at age 13 years and presented with a few focal atrophic scars and small hypopigmented papules at age 37 years.

[†]The younger brother also presented with blistering at birth, although the presentation was milder and mostly resolved by 10 months of age.

[‡]The mother had similar blistering lesions during infancy that resolved by age 10 years.

childhood. Since both the presentation of CAS and diagnosis of EB can be difficult for new parents, it is critical for clinicians to be aware of the heterogeneity and potential prognoses of EB with CAS. When EB is suspected, the subtype should be determined through molecular characterization and, if the family is amenable, genetic sequencing. Our case shows that although CAS with EB is often associated with more severe forms of DEB, it can also be associated with SI-DEB, which has a more benign clinical course. Furthermore, although SI-DEB often resolves in infancy, it can have a more prolonged, albeit mild, course. Our case emphasizes the need for continued evaluation throughout childhood to monitor disease progression following a diagnosis of SI-DEB. This report provides further evidence for the phenotypic heterogeneity of self-limited variants of EB, emphasizing the need for further study of the genetic

and environmental factors that affect disease presentation.^{10,11}

Conflicts of interest

None disclosed.

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