Pretibial dystrophic epidermolysis bullosa associated with aberrant exon splicing of type VII collagen

Patricia Richey, MD,[a] Melia Holt, MD,[a] Sydney Crotts, BA,[a] and Ali Jabbari, MD, PhD[a,b,c]
Iowa City, Iowa

Key words: epidermolysis bullosa; exon skipping; lower extremity ulcers; RNA splicing.

INTRODUCTION

Epidermolysis bullosa (EB) is a group of genetic disorders characterized by blisters and erosions/ulcerations in response to otherwise benign mechanical forces applied to the skin. Pretibial epidermolysis bullosa (PEB) is a form of EB that most often presents with blistering, ulceration, scarring, and milia localized to the bilateral legs. We report a case of man in his 50s presenting with blistering and scarring of his bilateral legs caused by PEB found to be associated with a mutation in *COL7A1* that results in exon skipping.

CASE REPORT

A 57-year-old man with type 2 diabetes mellitus presented with a four-year history of blistering on the lower extremities. Every 2 to 3 weeks, he had burning, painful red plaques that blistered over the course of hours and eventually ruptured, leaving crusted erosions and eventually violaceous scars with milia. He denied oral ulcers or blisters of any other body region. No other family members were affected.

Prior biopsies found dermal fibrosis and dilated blood vessels as well as scar and regenerative changes. Before presenting at our site, his condition was treated with compression stockings, topical steroids, and a prednisone taper, none of which provided improvement. Previous laboratory tests included antinuclear antibody, anti-dsDNA, C3, C4, hepatitis B serologies, hepatitis C serologies, rheumatoid factor, angiotensin-converting enzyme, anti-CCP and anti-U1RNP, all of which were negative/normal. A lower extremity vascular Doppler ultrasound scan was performed and read as normal.

Abbreviations used:

DEB:	dystrophic epidermolysis bullosa
EB:	epidermolysis bullosa
PCR:	polymerase chain reaction
PEB:	pretibial epidermolysis bullosa

Physical examination found tense bullae and well-circumscribed violaceous plaques of varying sizes in the pretibial region as well as on the calves, some with milia and ulceration (Fig 1, *A-C*). Lower extremity nail plates showed miniaturization, thickening. and yellow discoloration.

A biopsy of a tense bulla on the right calf was performed. Subepidermal separation with dermal fibrin and underlying scar with inflammation were noted. Direct immunofluorescence microscopic studies showed linear trace IgG and C3 along the dermoepidermal junction. A split skin study was negative as were indirect immunofluorescence studies.

Whole exome sequencing was subsequently performed, showing a heterozygous splice mutation in *COL7A1* on chromosome 3p21.1, specifically the deletion of 2 nucleotides before coding exon 108 (c.7984-2delA). This alteration, which abolishes the native acceptor splice site, is consistent with a diagnosis of dystrophic epidermolysis bullosa (DEB) with autosomal dominant inheritance. Polymerase chain reaction (PCR) analysis of cDNA from our patient was consistent with loss of exon 108 in the mRNA from one of the patient's *COL7A1* alleles (Fig 2). The patient continues to report

From the Department of Dermatology,[a] Interdisciplinary Program in Immunology,[b] and the Holden Comprehensive Cancer Center,[c] University of Iowa.
Funding sources: None.
Conflicts of interest: None disclosed.
Correspondence to: Ali Jabbari, MD, PhD, 2110 Medical Laboratories, Iowa City, IA 52242. E-mail: ali-jabbari@uiowa.edu.

JAAD Case Reports 2019;5:779-81.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.06.032

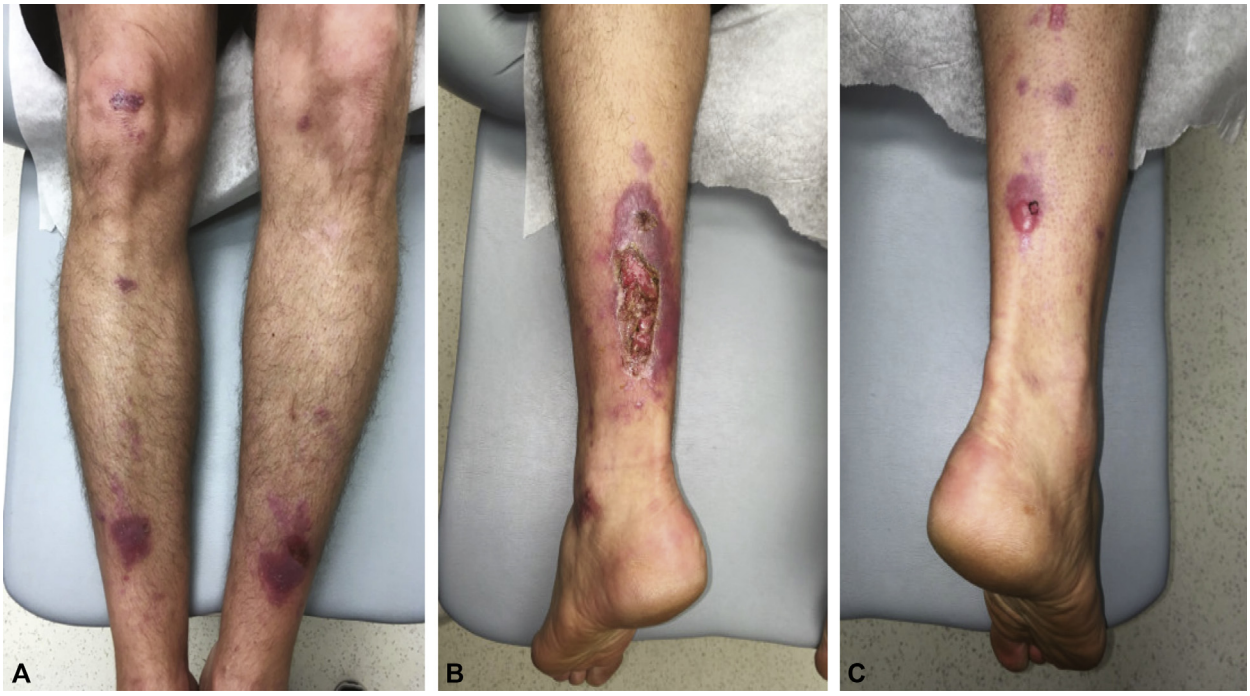

Fig 1. Clinical presentation. Physical examination found well-circumscribed violaceous plaques of varying sizes in the pretibial region (**A**) as well as on the posterior legs (**B** and **C**). Milia (**A**), ulceration (**B**), and tense bullae were noted (**C**).

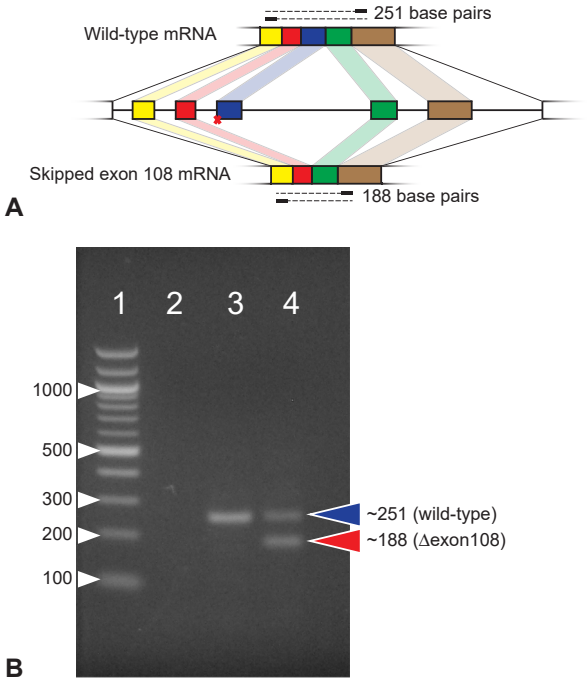

Fig 2. Dominant mutation causing exon skipping in *COL7A1*. **A**, Our patient's mutation, a c.7984-2delA splice site mutation, putatively affects pre-mRNA splicing, leading to skipping of exon 108 within collagenous domain 1 of procollagen VII. Depicted is the genomic DNA (*center*) with exons illustrated as boxes with intervening introns illustrated as a solid black line. A red X marks the expected variation site for our patient. The expected mRNA is depicted as labeled for wild type (*top*) and for mRNA with a skipped exon 108 (*bottom*). PCR amplification products (*dotted lines*) are shown with the primers that were used (*black boxes*); resulting product lengths are labeled. **B**, Products of indicated PCR reaction are shown. Lane numbers correspond to DNA ladder with white arrowheads indicating ladder band length size (*1*), no template PCR reaction (*2*), healthy control/wild-type genomic template (*3*), and PEB patient genome template (*4*). Blue arrowhead is shown at approximately 251 base pairs, where wild-type template product is expected. Red arrowhead is shown at approximately 188 base pairs, where exon108-skipped template product is expected.

waxing and waning of his disease with wound care and avoidance of trauma to the lower extremities.

DISCUSSION

The symptoms of DEB, a mechanobullous disease, are prompted by dysfunction of the anchoring fibrils within the basement membrane caused by a pathogenic mutation in type VII collagen.[1] When the skin fragility, blistering, and resultant scarring are localized to the pretibial region, often with pruritus and nail dystrophy (especially of the toenails), a diagnosis of PEB, a rare subtype of DEB, should be considered.[1]

As in our patient, this diagnosis may not be made until later in life, although PEB can also present in childhood.[2] The disease tends to be progressive, with some patients reporting worsening at the onset of puberty or in the heat or humidity.[3] Marked improvement in adulthood, however, has been reported in 2 female patients.[3]

Familial cases of dominant inheritance in Taiwan, Japan, China, Finland, and Belgium have been studied, with pedigrees displaying glycine substitution mutations in the C-terminal portion of *COL7A1*.[3-5] Recessive cases have been reported at about half the rate of dominant cases, with mutations alternatively distributed along the entire length of the *COL7A1* gene.[5] Two patients with splice site mutations prior to our patient have been reported.[5,6] We provide a previously unreported dominant mutation associated with exon skipping, supporting genomic investigations for similar dermatologic cases presenting during adulthood.

REFERENCES

1. Mahto A, McGrath JA, Deroide F, Rustin MH. Late onset pretibial recessive dystrophic epidermolysis bullosa. *Clin Exp Dermatol*. 2013;38(6):630-632.
2. Lee YY-J, Chen H-C, Lin S-J. Pretibial epidermolysis bullosa: a clinicopathologic study. *J Am Acad Dermatol*. 1993;29:974-981.
3. Rizzo C, Anandasabapathy N, Walters RF, et al. Pretibial epidermolysis bullosa. *Dermatol Online J*. 2008;14(10):26.
4. Naeyaert JM, Nuytinck L, De Bie S, Beele H, Kint A, De Paepe A. Genetic linkage between the collagen type VII gene COL7A1 and pretibial epidermolysis bullosa with lichenoid features. *J Invest Dermatol*. 1995;104(5):803-805.
5. Masunga T, Kubo A, Ishiko A. Splice site mutation in COL7A1 resulting in aberrant in-frame transcripts identified in a case of recessive dystrophic epidermolysis bullosa, pretibial. *J Dermatol*. 2018;45(6):742-745.
6. Betts CM, Posteraro AM, Costa AM, et al. Pretibial dystrophic epidermolysis bullosa: a recessively inherited COL7A1 splice site mutation affecting procollagen VII processing. *Br J Dermatol*. 1999;141:833-839.