Case letter

An unusual cause of inguinal ulceration – dystrophic epidermolysis bullosa

Dear Editor,

Dystrophic epidermolysis bullosa (DEB) is a subtype of epidermolysis bullosa (EB) resulting from a mutation in collagen VII, which constitutes the anchoring fibrils in the basement membrane zone. It has both autosomal recessive and autosomal dominant inheritance patterns. The specific features of DEB are blistering of the skin and/ or mucosae, which heals with scarring and milia formation. According to the recent classification, recessive DEB has been categorised into severe, intermediate and rare variants like inversa, pruriginosa, and self-improving. Dominant DEB is sub-classified as intermediate, localised, pruriginosa and self-improving types. We herein describe a case of DEB presenting as inguinal ulceration.[1]

A 56-year-old lady presented with multiple non-healing ulcers on her upper medial thighs. Examination revealed multiple uniformly-spaced and uniform-sized linear ulcers present symmetrically around the inguinal creases in a peculiar disposition, strikingly perpendicular to the inguinal ligaments. These ulcers were arranged parallel to each other with areas of normal to slightly scarred skin in between, giving a ladder-like appearance. Also, ulceration and scarring was noted on the labia [Figure 1]. Inguinal lymph nodes were not enlarged. Histopathology revealed healing granulation tissue and no evidence of granulomatous inflammation. Interestingly, she was also found to have significant toe nail dystrophy and extensive cutaneous scarring over shins which she attributed to a childhood skin disease that resolved after a few months of treatment. She did not have any gastrointestinal complaints and had no family history of similar illness or nail dystrophy. The patient was hesitant for a repeat skin biopsy, and she denied immunofluorescence antigen mapping and transmission electron microscopy (TEM); hence, next-generation sequencing was performed with the suspicion of dystrophic epidermolysis bullosa. It

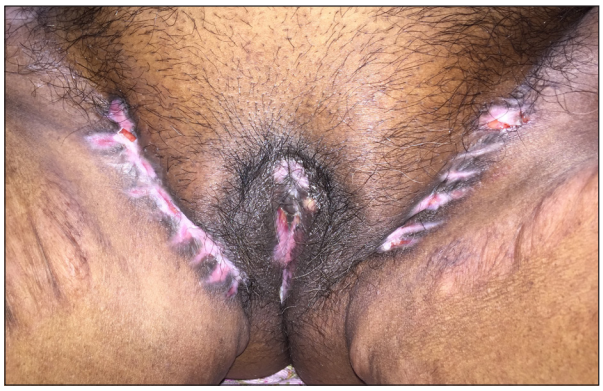

Figure 1: Multiple linear healing ulcers present symmetrically on both proximal inguinal areas in a step-ladder pattern.

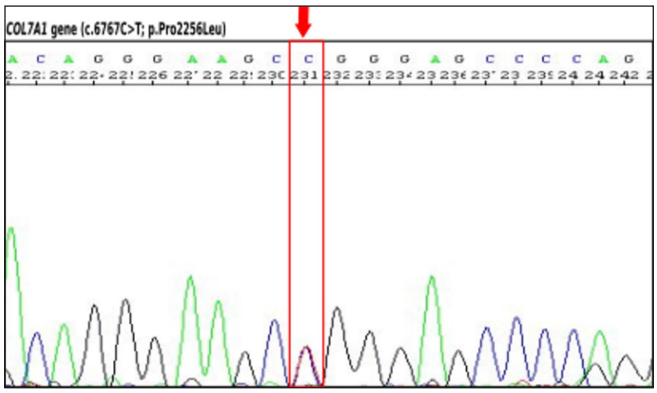

Figure 2: Validation of the observed variant by Sanger sequencing in the index patient: The PCR product for the observed variant was generated from the DNA sample of the index patient and subjected for Sanger sequencing. The green, blue, black and red line depicts adenine (A), cytosine (C), guanine (G), and thymine, respectively. Overlapping waves with two different colors with the same amplitude at the same location represent heterozygous inheritance. The chromatogram depicts the heterozygous mutation in the *COL7A1* gene at the coding position c.6767C>T, substituting Proline residue with Leucine at position 2256 in the protein sequence.

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demonstrated a heterozygous missense mutation c.6767C>T, in gene *COL7A1* on chromosome 3, exon 86 [Figure 2]. The identified variant (c.6767C>T, p.Pro2256Leu) may affect function of the expressed protein. Based on the literature search and *in silico* prediction tool scores, the particular variant was found to be disease-causing by mutation taster, damaged by Functional Analysis through Hidden Markov Models (FATHMM) and damaging by Functional Analysis through Hidden Markov Models (FATHMM)-Math Kernel Library (MKL). The variant has been reported in the dbSNP database and in the Genome Aggregation Database (gnomAD) with an allele frequency of 0.00003193. Based on American College of Medical Genetics and Genomics (ACMG) guidelines and literature review, this particular variant can be classified as a variant of uncertain significance (VUS). Data reanalysis did not reveal any second mutation, and hence, the diagnosis of dystrophic EB was proffered. Due to financial constraints and poor follow up, we were unable to test this mutation in the siblings and parents of the index case; hence, we were unable to conclusively establish the inheritance and pathogenicity of this mutation.

To the best of our knowledge, the index case could be the first case of DEB described with an inversa-like phenotype presenting with a unique pattern of inguinal ulceration. Recessive Dystrophic Epidermolysis Bullosa (RDEB)-inversa is one of the rare variants of DEB, with a predisposition to developing blisters and erosions in flexures like the axilla, inguinal region, neck, and lower back. In one of the largest case series of 20 patients of RDEB-inversa, a typical course of generalised blistering followed by localisation of the lesions to the flexures with advancing age was observed.[2] Of the 20, four patients also had localised absence of skin at birth, a condition known as aplasia cutis, which has been associated with both dominant and recessive forms of DEB.[2,3] Similarly, our patient experienced localised blistering/absence of skin on her leg at birth, for which she received a skin graft that led to disease remission. However, she relapsed later in adulthood with typical nail dystrophy, erosions, and fibrotic scars on her groins, which led us to consider the sabre-cut ulcers of Crohn's disease as a differential diagnosis.[4] There was a lack of severe mucosal involvement, which is a feature of RDEB-inversa.[2] In genetic analysis, we found proline replaced by leucine at position 2256 unlike the typically observed arginine and glycine substitutions in the triple helix domain of type VII collagen in RDEB-inversa.[2] Apart from the inguinal ulceration, the absence of widespread blistering, scarring, and milia with typical nail dystrophy and mutations favoured DEB. Mild blistering, atrophy, and nail dystrophy are often attributed to trauma that has occurred in childhood and are often missed by the patient as well as the caregiver as age advances. It is prudent to consider genodermatosis in an individual in the presence of unusual patterns of blistering and ulceration, as was seen in this case.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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