

Epidermolysis Bullosa Pruriginosa Masquerading as Psychogenic Pruritus

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Background: Epidermolysis bullosa pruriginosa is a rare clinical subtype of dystrophic epidermolysis bullosa characterized by intense pruritus, secondary scratching-induced lesions, and pronounced scarring.

Observations: We describe a patient with epidermolysis bullosa pruriginosa who was misdiagnosed as having psychogenic pruritus for several years. Except for nail (toenail) dystrophy, no features of the disease were evident among his immediate family members. An underlying new heterozygous donor splice-site mutation in the type VII collagen gene (IVS55 + 1G>C) was found in both the patient and his family members with nail dystrophy.

Inheritance was autosomal dominant. The patient was treated with cyclosporine and experienced significant reduction in pruritus, with subsequent improvement of the skin condition.

Conclusions: Pruritus is an important factor in the development of epidermolysis bullosa pruriginosa and is the focus of management. Patients with this inherited skin disorder can be easily misdiagnosed as having psychogenic pruritus, and this article aims to make physicians aware of this diagnostic pitfall.

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EPIDERMOLYSIS BULLOSA PRURIGINOSA (EBP) ([OMIM] 604129) is a rare clinical subtype of autosomal dominant (and occasionally autosomal recessive) dystrophic epidermolysis bullosa (DEB) (OMIM 131850).^{1,2} DEB is a group of inherited mechanobullous disorders characterized by mutation in the *COL7A1* gene (OMIM 120120) (encoding type VII collagen), which results in anchoring fibril dysfunction at the dermo-epidermal junction and blistering beneath the lamina densa of the epidermal basement membrane. In addition to trauma-induced blisters, milia, scars, and nail dystrophy in DEB, EBP is characterized by severe localized or generalized pruritus, scratching-induced secondary skin lesions, and pronounced scarring. Disease onset does not usually occur at birth, and symptoms and signs often do not manifest for several decades. These typical skin lesions, consisting of linear pruriginous or lichenified plaques associated with deep excoriations, are dermatologic evidence of intense scratching, and the clinical appearance frequently imparts an impression of underlying psychogenic self-mutilation. Because of the rarity of EBP, patients are often misdiagnosed as having psychogenic pruritus. Other incorrect diagnoses include nodular prurigo, lichen

simplex chronicus, pemphigoid nodularis, and hypertrophic lichen planus. In this article, we describe a family with EBP resulting from a new mutation in *COL7A1* and illustrate the diagnostic difficulties.

REPORT OF A CASE

A 14-year-old boy was seen with an 8-year history of a worsening pruritic eruption on his legs. He had previously been diagnosed as having hypertrophic lichen planus, along with a severe neurodermatitis component. The itch and scratching were severe and had greatly affected his daily activities. There was no history of consanguinity, and he was born after an uneventful full-term pregnancy; none of his immediate family members were similarly affected. He had previously been treated with high-potency topical and intralesional corticosteroids and antihistamines, which resulted in only short-term improvement. His family had consulted more than 20 physicians, including psychiatrists who treated him for obsessive-compulsive disorder with a regimen of fluoxetine hydrochloride, sertraline hydrochloride, and quetiapine fumarate. His condition remained refractory.

Examination revealed profound hypertrophic scarring associated with linear ero-

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Figure 1. Hypertrophic scars with superimposed linear erosions, vesicles, and milia. Lesions prominently involving the knees and shins of the patient (A). Magnified view (B) showing hypertrophic scars, linear excoriations, a vesicle, and milia.

sions, milia, and vesicles on the extensor aspects of the patient's lower legs and forearms (**Figure 1**). Dystrophy of all toenails was noted. Findings of numerous skin biopsy specimens prompted various diagnoses, including scar, milia, lichen planus, and vascular proliferation. A subsequent biopsy specimen demonstrated a cell-poor subepidermal blister with a sparse superficial perivascular lymphocytic infiltrate (**Figure 2**). Direct immunofluorescence performed on perilesional skin was negative for IgG, IgA, IgM, and complement C3. Results of a complete blood cell count and comprehensive metabolic panel were normal.

We requested clinical examination of the patient's family members and found that his mother and younger sister had nail dystrophy in most of their toenails. A pedigree was constructed to track the presence of nail dystrophy and probable blistering skin disease, and it revealed a pattern suggestive of an autosomal dominant disorder (**Figure 3**). Peripheral blood samples were obtained from the patient and his younger sister, parents, and older half sister (from his father's previous marriage). From the samples, DNA was extracted, and polymerase chain reaction amplification of *COL7A1* was performed. A donor splice-site mutation consisting of a heterozygous single-nucleotide substitution in intron 55 (IVS55 + 1G>C) was found in the patient, his younger sister, and his mother (all of whom have nail dystrophy) (**Figure 4**).

In addition to high-potency topical corticosteroids and topical tacrolimus, cyclosporine (300 mg [3.5 mg/kg]) was started in 2 divided doses daily. He responded with significant reduction in pruritus and concomitant healing of erosions (**Figure 5**). He was weaned off all psychotropic medication and is on a maintenance regimen of low-dose cyclosporine.

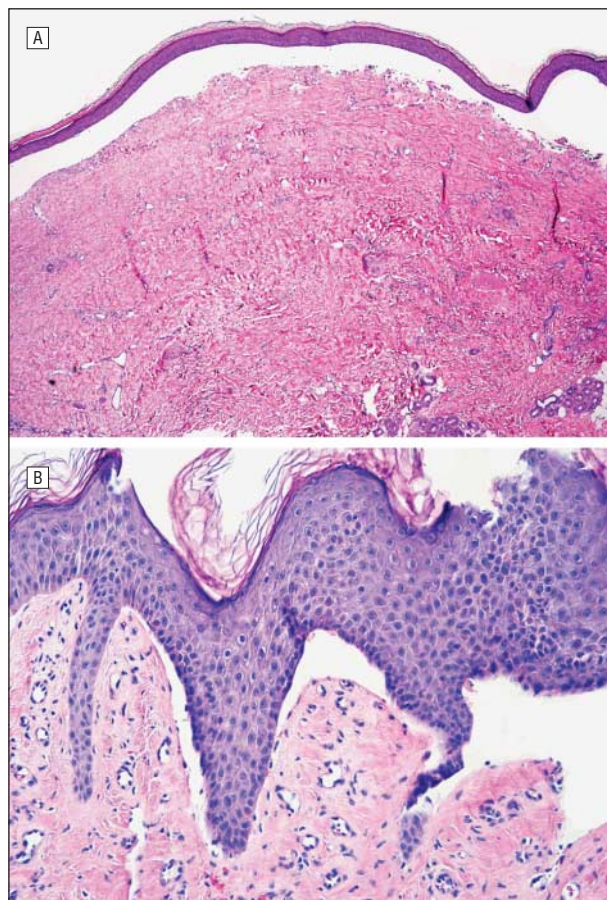


Figure 2. Cell-poor subepidermal blister (A) with minimal inflammatory cellular infiltrate (hematoxylin-eosin, original magnification $\times 4$ [A] and $\times 20$ [B]).

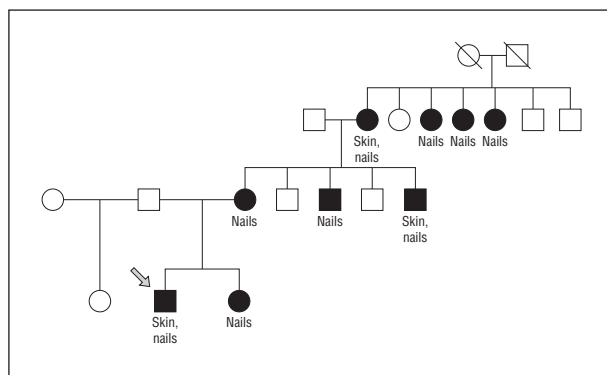


Figure 3. Family members affected with nail dystrophy and probable blistering skin disease in an autosomal dominant pattern. Square indicates male individual; circle, female individual; shading, affected individual; slash, deceased individual; and arrow, proband.

COMMENT

The various subtypes and clinical manifestations of DEB have been shown to result from different combinations of missense, nonsense, frameshift, and splice-site mutations in *COL7A1*. However, genotype-phenotype correlation in EBP is not clear-cut. Although Saito et al³ pointed out that skipping of exon 87 in *COL7A1* can be associated with the dominantly inherited form of EBP, other findings indicate that the nature of the *COL7A1* mutations in EBP does not.

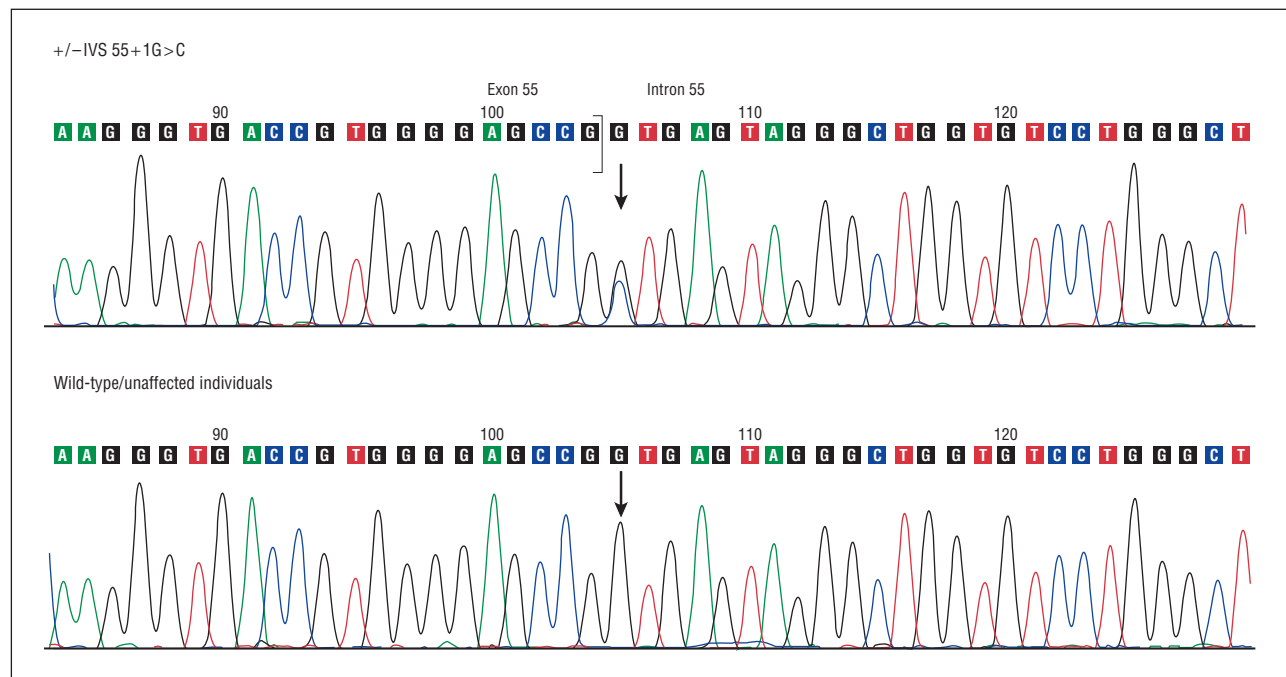


Figure 4. A guanine-to-cytosine heterozygous mutation at the donor splice-site mutation in intron 55 (arrows) is expected to result in an inframe skipping of exon 55.



Figure 5. Marked reduction in excoriations and erythema and flattening of hypertrophic scars 4 months after treatment with cyclosporine.

in general, differ from that in other types of DEB; moreover, identical mutations have resulted in both EBP and other forms of DEB.⁴⁻¹⁴ Therefore, potential disease modifiers resulting in EBP have been examined, including IgE levels, atopy, biochemical and endocrinological abnormalities, iron deficiency, filaggrin mutations, and matrix metalloproteinase 1 gene promoter polymorphisms.^{1,5,14,15} However, these factors were not found to be universal factors in the pathogenesis of EBP.

Most cases of EBP are inherited in an autosomal dominant manner, but autosomal recessive and sporadic inheritance patterns have also been described. Including the mutation described herein, 32 different mutations in *COL7A1* have been detected in EBP so far, including 22 missense mutations, 7 splice site mutations, and 3 small nucleotide deletions.^{4,5,10,11,14,16,17} In our patient, the heterozygous single-

nucleotide substitution in intron 55 with resultant donor splice-site mutation (IVS55 + 1G>C) would be expected to result in an inframe skipping of exon 55 (deletion of 15 amino acids). The abnormal polypeptides produced likely cause dominant-negative interference by destabilizing the triple helix structure of collagen fibrils.

In a previous study,¹¹ all 7 patients with EBP had a typical mild DEB phenotype until the onset of pruritus. This highlights that pruritus, in addition to being a characteristic feature of EBP, may have an important role in the pathogenesis of EBP and suggests that early control of pruritus may prevent progression of DEB to EBP.³

The pathogenesis of EBP and the mechanism of pruritus in EBP are unknown. A possible pathogenetic mechanism is the healing of erosions and the formation of scars, which typically occurs in DEB. Normal scars and pathological (hypertrophic and keloid) scars are frequently itchy, but the cause is unknown.¹⁸ Protease-activated receptor 2 (PAR-2) is a type of G protein-coupled receptor that is expressed in cells active in scar formation, and it may be involved in the development of pathological scars.¹⁹ Also, PAR-2 is an essential component of itch signaling.²⁰ An aberrant wound repair process associated with increased PAR-2 expression may explain and provide the link between the severe scarring and itching seen in EBP, although no data exist to support this possible disease mechanism. What is clearly evident is that severe pruritus leads to frequent and aggravated scratching, and further damage to the already fragile skin in DEB results in more scars and secondary pruriginous and lichenified skin changes. Scars that are more hypertrophic and protruding, as seen in our patient, also tend to promote the development of pruriginous lesions.

Potent topical and intralesional corticosteroids have been reported to reduce pruritus in some cases of EBP but do not produce sustained improvement.¹ Neverthe-

less, the role of inflammation in the pathogenesis of EBP is supported by several studies in which anti-inflammatory agents resulted in rapid improvement of itch. These anti-inflammatory agents, including cyclosporine,²¹ thalidomide,²² and topical tacrolimus,²³ may work by modulating the healing and scarring processes and reducing pruritus. However, the effectiveness of tacrolimus is questionable, as it was subsequently reported that only 1 in 8 patients treated experienced significant itch relief, and this response rate was similar to that of other patients treated with topical corticosteroids.¹⁴ The effectiveness of cyclosporine treatment in a previous study²¹ and in our patient points to a probable causal role of T-cell-mediated inflammation in EBP. Interleukin 31 (IL-31), a cytokine mainly produced by helper T cells (type 2), was recently found to be a mediator of pruritus²⁴ and was implicated in the pathogenesis of familial primary cutaneous amyloidosis.²⁵ Although a recent study²⁶ found that IL-31 gene polymorphisms were unassociated with EBP, IL-31 expression and signaling in EBP skin and the potential of using IL-31 antibodies in the treatment of EBP remain to be explored.

Marked excoriations and skin lesions from aggravated and chronic scratching in EBP often give physicians the impression of psychogenic pruritus (in particular, neurotic excoriation and dermatitis artifacta). In general, organic causes should be ruled out before attributing a disease to psychogenic causes. A diagnosis of prurigo nodularis in younger children should be questioned, as this condition rarely occurs in this age group. Clinical clues that suggest EBP include trauma-induced blisters, nail dystrophy, milia, and more pronounced involvement of the shins.^{1,27,28} The absence of an obvious family history of blistering skin disease and the onset of EBP later in life, as seen in our patient, may divert attention from an underlying genetic disorder. Family members should be screened when an inherited disorder is suspected, and in the case of EBP, nail (toenail) dystrophy should be checked for because it occurs in most patients,^{26,29} even in those with minimal or no skin lesions. Skin biopsy specimen findings may be inconclusive or may need repeating, but *COL7A1* screening offers the best route to an accurate diagnosis of EBP.

Chronic pruritus negatively influences a patient's psychosocial well-being, especially in EBP, for which the symptoms are debilitating and the signs disfiguring. Management should address not only the dermatologic condition but also the associated psychological comorbidities, such as anxiety, depression, and social issues.

In conclusion, we describe a new donor splice-site mutation (IVS55 + 1G>C) in *COL7A1* among a family with EBP. Pruritus is a characteristic and pathogenetic feature in EBP and serves as a therapeutic focus of management. Patients with EBP are frequently misdiagnosed as having psychogenic pruritus, and this article aims to make physicians aware of this potential diagnostic pitfall.

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