Epidermolysis Bullosa Pruriginosa

A Case With Prominent Histopathologic Inflammation

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Importance: Epidermolysis bullosa (EB) pruriginosa is a rare variant of dystrophic EB. It may manifest late in life and is characterized by intense pruritus, resulting in a phenotype resembling acquired inflammatory dermatoses. Dermatopathology textbooks include hereditary forms of EB among the “cell-poor” list of subepidermal blistering disorders.

Observations: We report a case of dominant dystrophic EB pruriginosa with late-onset cutaneous manifestations. A biopsy specimen showed subepidermal blistering with prominent inflammatory cells, including numerous eosinophils. Unfamiliarity with the distinctive clinicopathologic features of EB pruriginosa led to an initial erroneous histopathologic diagnosis of an acquired autoimmune blistering disorder. Direct immunofluorescence study results were negative for immune reactants. A strong clinical suspicion of hereditary EB pruriginosa led to mutation analysis of COL7A1, which confirmed a novel, heterozygous nonglycine missense mutation. Subsequently, 2 other family members who had nail dystrophy were also correctly diagnosed as having dominant dystrophic EB, highlighting the clinical spectrum of the disorder and the intrafamilial variability in disease presentation.

Conclusions and Relevance: The clinical features of EB pruriginosa are becoming more widely recognized, but dermatologists, dermatopathologists, and histopathologists should be aware that inflammatory infiltrates and late presentation are potential pitfalls in correctly diagnosing this subtype of hereditary EB.


E PIDERMOLYSIS BULLOSA (EB) IS a mechanobullous genodermatosis characterized by skin fragility and trauma-induced blisters. Dystrophic EB (DEB) is a clinically heterogeneous subgroup of EB caused by mutations in COL7A1 (OMIM 120120), which encodes type VII collagen, giving rise to reductions in the number of and in structurally defective anchoring fibrils at the dermoeidermal junction, as well as sublamina densa blistering as a consequence.1 Epidermolysis bullosa pruriginosa (EBP) is an unusual clinical subtype of DEB characterized by severe pruritus, resulting in scratching-induced secondary linear pruriginous or lichenified plaques and marked scarring, especially on the shins.2 The signs and symptoms of EBP often develop in adulthood, unlike most inherited disorders. Common clinical misdiagnoses include dermatitis artefacta, psychogenic pruritus, hypertrophic lichen planus, lichen simplex chronicus, cutaneous amyloidosis, keratosis lichenoides chronica, nodular prurigo, pemphigoid nodularis, and immunobullous disorders.2,4 Intact blisters are rare, adding to the diagnostic difficulties.2 Misdiagnosis of EBP as an acquired immunobullous disorder often occurs because the disease may manifest only in adulthood and because skin biopsy can reveal a conspicuous inflammatory cell infiltrate on light microscopy, a histological contrast to what is written in most dermatopathology textbooks that simply list hereditary EB as a group of “cell-poor” blistering skin disorders.5,6 We report a case of dominant dystrophic EB pruriginosa caused by a novel, non-glycine missense mutation, which highlights this diagnostic pitfall.

REPORT OF A CASE

A 26-year-old woman was seen with a 3-year history of an intensely pruritic skin eruption and lifelong dystrophy of both hallux nails. The pruritus affected her daily activities and was unresponsive to potent...
Topical corticosteroid therapy. She had no history of atopy or other conditions predisposing to pruritus, and the family was nonconsanguineous. However, there was a strong autosomal dominant family history of dystrophic nails across 5 generations (Figure 1). The proband was unaware of any other family members with cutaneous disease.

Physical examination revealed lichenified, violaceous plaques, containing intact blisters, milia, and scarring on her shins. Linear albopapuloid lesions were noted on her trunk. The hallux nails were dystrophic, but all other toenails and fingernails were normal (Figure 1). A clinical diagnosis of EBP was made, and a hereditary form was favored because of the family history of dystrophic nails.

A physician who was not involved with the initial consultation obtained a biopsy specimen from a lesion on the shin. The request form queried a diagnosis of EB, and the presence of dystrophic nails was included in the clinical information, but the family history of the latter was omitted. Histological features included subepidermal blistering, vascular proliferation, subtle fibrosis, milia, marked lichenification, and mild to moderate perivascular lymphocytic infiltrates. A few eosinophils were noted in the blister cavity, with more numerous eosinophils in the upper dermis, below the blister (Figure 2). Because of the adult presentation and the degree of inflammation on the skin biopsy specimen, 2 experienced dermatopathologists (R.A.C. and S.M.T.) considered the case on histopathologic grounds to be commensurate with an immunobullous disorder, including EB acquisita. The presence of prominent eosinophils also raised the possibilities of bullous pemphigoid and lichen planus pemphigoides. However, direct immunofluorescence study findings were negative for immune reactants.

In view of the strong clinical suspicion of hereditary EBP, mutation analysis of the COL7A1 gene was performed. This demonstrated a novel, heterozygous nonglycine missense mutation involving the substitution of glutamine to arginine, (+/−) c.6215A>G, p.Gln2072Arg, in exon 74 (Figure 2). This mutation has not been reported previously but was excluded as a common nonpathogenic polymorphism by screening 200 ethnically matched control chromosomes. Although most pathogenic mutations in type VII collagen in dominant dystrophic EB comprise heterozygous glycine substitutions within the collagenous triple helix, several other pathogenic nonglycine missense mutations (including in exon 74) have been reported. The molecular pathology in this case represents a further example of this type of mutation in COL7A1 and fully supports a clinical and molecular diagnosis of dominant dystrophic EB pruriginosa.

We treated our patient with twice-daily applications of tacrolimus, 0.1%, ointment to the shins, which resulted in a reduction in pruritus and in minor improvement in clinical appearance (Figure 3). However, our patient desires a better cosmetic outcome, and we are considering treatment with cyclosporine. We have also re-
ferred her to a surgical team for permanent avulsion of the dystrophic nails.

Following the diagnosis of EBP, our patient’s niece and cousin, who had been seen in our department with congenital nail dystrophy several years previously, were reevaluated. The proband’s 10-year-old niece gave a history of mild, trauma-induced blisters on her elbows and knees. Clinical examination revealed dystrophy of most of her toenails and the right pollex nail but no scarring. The proband’s 20-year-old cousin gave a history of a blistering eruption affecting her pubic region, genitalia, and scalp. Clinical examination revealed bilateral dystrophic hallux nails, albobapuloid lesions on the nape of her neck, and vesicular, excoriated papules on her scalp, as well as violaceous, excoriated papules on her pubic region and labia majora. Mutation analysis in the niece and cousin revealed the same mutation as that in the proband, confirming dominant dystrophic EB. The cousin clinically has the pruriginosa subtype, despite a lack of typical cutaneous features on her shins. These findings highlight the intrafamilial variability that can occur in EBP and other forms of DEB.

Epidermolysis bullosa pruriginosa is a distinct subtype of DEB characterized by milia, excoriations, skin fragility, nail dystrophy, intense pruritus, lichenified plaques, albobapuloid lesions, violaceous linear scarring, and nodular prurigolike lesions.1 Albopapuloid lesions are small, grouped hypopigmented papules often located on the trunk of patients with DEB, especially dominant variants thereof.8 The pruritic, pruriginous, lichenified plaques and scarring are often localized to the shins and forearms, with relative sparing elsewhere. Intact blisters are rarely seen because of damage during scratching.2 Toenail dystrophy has usually been present since infancy and is seen in almost all cases of EBP,1,9 providing a clue to the underlying diagnosis and the hereditary nature of the condition. The proband herein has typical features of EBP, including rare intact blisters.

Pruritus is a recognized feature in all types of EB. In EBP, intense pruritus has been reported to accompany9 or predate2 the cutaneous manifestations by several years.

Figure 2. Incisional biopsy specimen stained with hematoxylin-eosin. A, Subepidermal blistering, vascular proliferation, and subtle fibrosis. B, Milia. C, Lichenification and mild to moderate perivascular lymphocytic infiltrates. D, A few eosinophils in the blister cavity. E, Numerous eosinophils in the upper dermis. F, Novel, nonglycine missense mutation of COL7A1. Original magnification ×50, ×100, ×100, ×400, and ×400 for A, B, C, D, and E, respectively.

DISCUSSION
Light microscopy typically performed in cases of suspected EBP to exclude other conditions. EBP is a rare disorder, and the diagnosis is often made after other skin conditions have been ruled out. Light microscopy may be performed to confirm the diagnosis of EBP.

It has been suggested that perhaps it is not the level of pruritus that is abnormal in EBP, but rather the patient's response. Studies have excluded other associated or triggering pathologic conditions as potential phenotype modifiers in EBP, including atopy, raised IgE levels, iron deficiency, and renal, liver, and thyroid dysfunction, as well as matrix metalloproteinase 1 gene polymorphisms, filaggrin gene mutations, and interleukin 31 gene haplotype. The cause of the pruritus and the pathophysiology of EBP remain unknown.

Epidermolysis bullosa pruriginosa is commonly inherited in an autosomal dominant manner, but autosomal recessive and sporadic cases have also been reported. Numerous mutations in COL7A1 have been implicated in all forms of DEB, including EBP. Other genetic, behavioral, and environmental factors likely contribute to the pruriginosa phenotype because additional pedigrees with clinical variability have been described, despite the presence of identical COL7A1 mutations. Dominant dystrophic EB pruriginosa is usually caused by glycine substitutions. Although non-glycine substitutions have previously been reported, the missense mutation of glutamine to arginine in the present family is new. Some studies report consistent clinical features among individuals within certain families with EBP. Equally, other studies found significant intrafamilial variability. These articles demonstrate that there is no clear genotype-phenotype correlation in EBP.

Mutation analysis is the gold standard investigation for suspected hereditary EB. Light microscopy may be performed in cases of suspected EBP to exclude other common pathologic skin conditions, such as hypertrophic lichen planus or, in the case of a clinically unsuspected hereditary EB, because of the frequent late clinical presentation of the cutaneous manifestations of EBP. Epidermolysis bullosa pruriginosa has been reported to manifest as late as age 71 years. Light microscopy typically demonstrates subepidermal blistering, hyperkeratosis, fibrosis, milia, and a few lymphocytic infiltrates. In the major textbooks, hereditary EB is listed with the cell-poor blistering disorders. The experience of the EB laboratory at St John’s Institute of Dermatology, London, England, and the detailed literature suggest that eosinophilic infiltrates are common findings in EB, including EBP. However, the observation of prominent inflammatory infiltrates, including eosinophils, in hereditary EB is almost certainly an underappreciated feature by most histopathologists. Certainly, unfamiliarity with this finding in our case by 2 experienced dermatopathologists led to a favored histopathologic diagnosis of an acquired immunobullous blistering disorder rather than hereditary EBP. Although it is tempting to postulate that the inflammatory infiltrates are responsible for the pruritus, pruritus was a prominent feature in some cases of EBP in which inflammatory infiltrates were absent histologically.

Treatment of EBP should be aimed at reducing pruritus, preventing scarring, and improving the patient’s quality of life. With varying results, therapeutic efforts have included antihistamines and topical, intraskeletal, and systemic corticosteroids, as well as UV-B, dapsoine, thalidomide, topical tacrolimus, cyclosporine, and cryotherapy. There is a need for more effective treatment.

We have described a typical case of late-onset EBP and the value of molecular studies for diagnosis. The presence of prominent inflammatory infiltrates, including numerous eosinophils, led to alternative histopathologic diagnoses because hereditary EB is traditionally regarded as a cell-poor subepidermal blistering disorder. We propose that future dermatopathology textbooks should include hereditary EB in the lists of blistering disorders with accompanying inflammatory cells (eg, subepidermal blistering with eosinophils), as well as the hitherto more commonly recognized inclusion within the cell-poor subepidermal blistering conditions.

Accepted for Publication: January 11, 2013.
Published Online: April 24, 2013. doi:10.1001/jamadermatol.2013.155
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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Carr and Taibjee. Acquisition of data: Vivehanantha, Madhogaria, and Ilchyshyn. Analysis and interpretation of data: Carr, McGrath, Taibjee, and Ilchyshyn. Drafting of the manuscript: Vivehanantha, Carr, Taibjee, Madhogaria, and Ilchyshyn. Critical revision of the manuscript for important intellectual content: Carr, McGrath, Taibjee, and Ilchyshyn. Administrative, technical, or material support: Vivehanantha and Madhogaria. Study supervision: Taibjee and Ilchyshyn.

Conflict of Interest Disclosures: Dr McGrath serves as consultant to Lotus Tissue Repair.

Additional Contributions: Lu Liu, PhD, performed the mutation analysis.
REFERENCES


