

# An atypical case of pediatric epidermolysis bullosa acquisita: Review of diagnosis and pitfalls



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## INTRODUCTION

Epidermolysis bullosa acquisita (EBA) is a rare autoimmune blistering disorder, with <50 pediatric cases reported to date.<sup>1</sup> Presentation is categorized into 2 subtypes—classic mechanobullous and inflammatory. Here we present a case of EBA with mixed clinical phenotype with an atypical presentation of erythema multiforme-like eruption.

## CASE REPORT

A 13-year-old male presented for evaluation of a 3-week history of a blistering rash, which had emerged on the hands and arms with associated abdominal cramps and diarrhea. He had recently re-introduced gluten into his diet. Although the gastrointestinal symptoms subsided, the rash progressed to his back and thighs, prompting a visit to urgent care, where he was diagnosed with erythema multiforme and prescribed hydrocortisone 1% cream and cetirizine 5 mg. Ten days later, he presented to dermatology for progressive rash. Patient examination revealed a polymorphous eruption consisting of tense vesicles on the hands and feet, smooth pink papules diffusely distributed on the trunk and extremities, tense vesicles on the vermilion lips extending into the mucosa (Fig 1, A), and deep red atypical targetoid macules on both hands (Fig 1, B-D). We made a presumptive diagnosis of herpes simplex virus-induced erythema multiforme and prescribed valacyclovir 2 g daily for 5 days, and a 14-day taper of prednisone, starting at 40 mg daily for a week and subsequently 20 mg daily for the second week. Two weeks later, he had improved but continued to develop new blisters in areas of trauma on the hands, feet, and lips; the previous blisters

### Abbreviations used:

BSLE:	bullous systemic lupus erythematosus
DIF:	direct immunofluorescence
EBA:	epidermolysis bullosa acquisita
SLE:	systemic lupus erythematosus

healed with atrophic scars (Fig 2). Complete blood count and comprehensive metabolic panel were normal, and no herpes virus antibodies were found. The anti-*Mycoplasma* IgG antibody titer was high, whereas anti-*Mycoplasma* IgM antibodies were absent, indicating a past infection.

Biopsy revealed a subepidermal split with neutrophils within the split and along the dermal-epidermal junction (Fig 3, A). Direct immunofluorescence (DIF) of adjacent normal skin displayed linear deposits of IgG and C3 along the basement membrane zone (Fig 3, B) with indirect immunofluorescence on salt-split skin localizing to the dermal side. Indirect immunofluorescence for collagen VII detected 0.1 unit (positive >6 units). Additional laboratory tests were requested to rule out systemic lupus erythematosus (SLE). All tests, including C3, C4, urine analysis, antinuclear, double stranded-DNA, anti-SSA/Ro, and anti-SSB/La antibodies, were within normal limits. Workup for IgA deficiency, celiac disease, and inflammatory bowel disease revealed normal IgA levels, and upper gastrointestinal endoscopy and colonoscopy revealed normal histopathology.

Clinical and laboratory findings favored a diagnosis of EBA. Our patient was started on dapsone 100 mg daily with significant reduction in the rate of new blister formation.

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**Fig 1.** **A**, Tense vesicles on the vermilion lips (*white arrows*) extending into the mucosa. **B-D**, Deep red atypical targetoid macules on both hands mimicking erythema multiforme (*black arrows*).

## DISCUSSION

Our patient exhibited a mixed clinical phenotype of EBA. He had urticarial papules and oral involvement suggesting inflammatory EBA, and, over time, he developed mechanobullous lesions in the form of tense blisters in areas of trauma and healing with scars. In addition to this mixed presentation, he had both typical and atypical targetoid lesions, suggesting possible overlap with erythema multiforme. Although the atypical and evolving presentation cannot be fully explained, the authors have several theories.

One theory may be epitope spreading, which has been studied in other cutaneous autoimmune disorders. This is the theory that various epitopes on the N-terminal domain of collagen VII are attacked by circulating antibodies, leading to different clinical phenotypes.<sup>2</sup> Another possible theory may be

antigen mimicry. Our patient initially had a gastrointestinal infection, which could have led to unveiling of collagen VII in the gut with antibody formation. These antibodies then attacked collagen VII in the skin, via antigen mimicry. It is important to note that IgG antibodies in EBA are the IgG1 and IgG4 subclasses; however, in inflammatory bowel disease they are IgG3 subclass.<sup>3</sup> Antigen mimicry thus suggests that there must be isotype switching of antibodies, leading to attack of collagen VII in more than one location. This theory may also explain the relationship between EBA and inflammatory bowel disease.<sup>4,5</sup>

Neither of these theories, however, fully explains our patient's atypical targetoid eruption. The patient may have had inadequately treated erythema multiforme, which could have led to an inflammatory cascade and susceptibility of the skin proteins to

antigen-presenting cells. However, several underdiagnosed or under-reported phenotypes may exist.<sup>6</sup> Mixed classic and inflammatory EBA presentations have been reported, one of which was also an erythema gyratum repens-like presentation.<sup>7</sup> To our knowledge, this is the first patient to have an overlapping EBA phenotype in conjunction with erythema multiforme-like eruption.

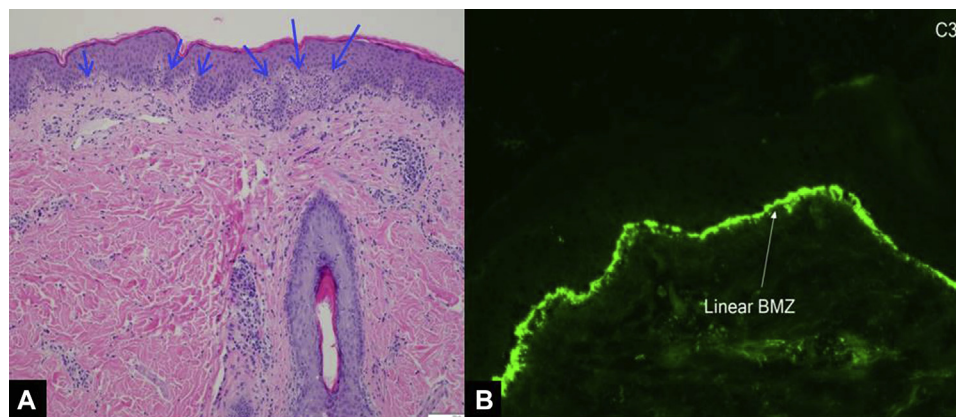


**Fig 2.** Two weeks later, we observed continued development of new blisters on areas of trauma on the dorsal aspects of the hands, and prior blisters had healed with atrophic scars (*yellow arrows*).

Making a diagnosis of EBA requires 2 biopsies—one for hematoxylin-eosin staining and one for DIF. Although a subepidermal split with neutrophils on hematoxylin-eosin staining is characteristic of EBA, several other autoimmune blistering disorder can exhibit a similar histology (*Fig 4*). In our case, DIF revealed linear IgG/C3 staining, which helped to narrow the differential diagnosis down to bullous pemphigoid, EBA, or bullous SLE (BSLE). DIF on “salt-split skin” showed deposition on the dermal side of the basement membrane zone. Although this helped to rule out bullous pemphigoid, without enough serum antibody levels, the test can result in a false negative.

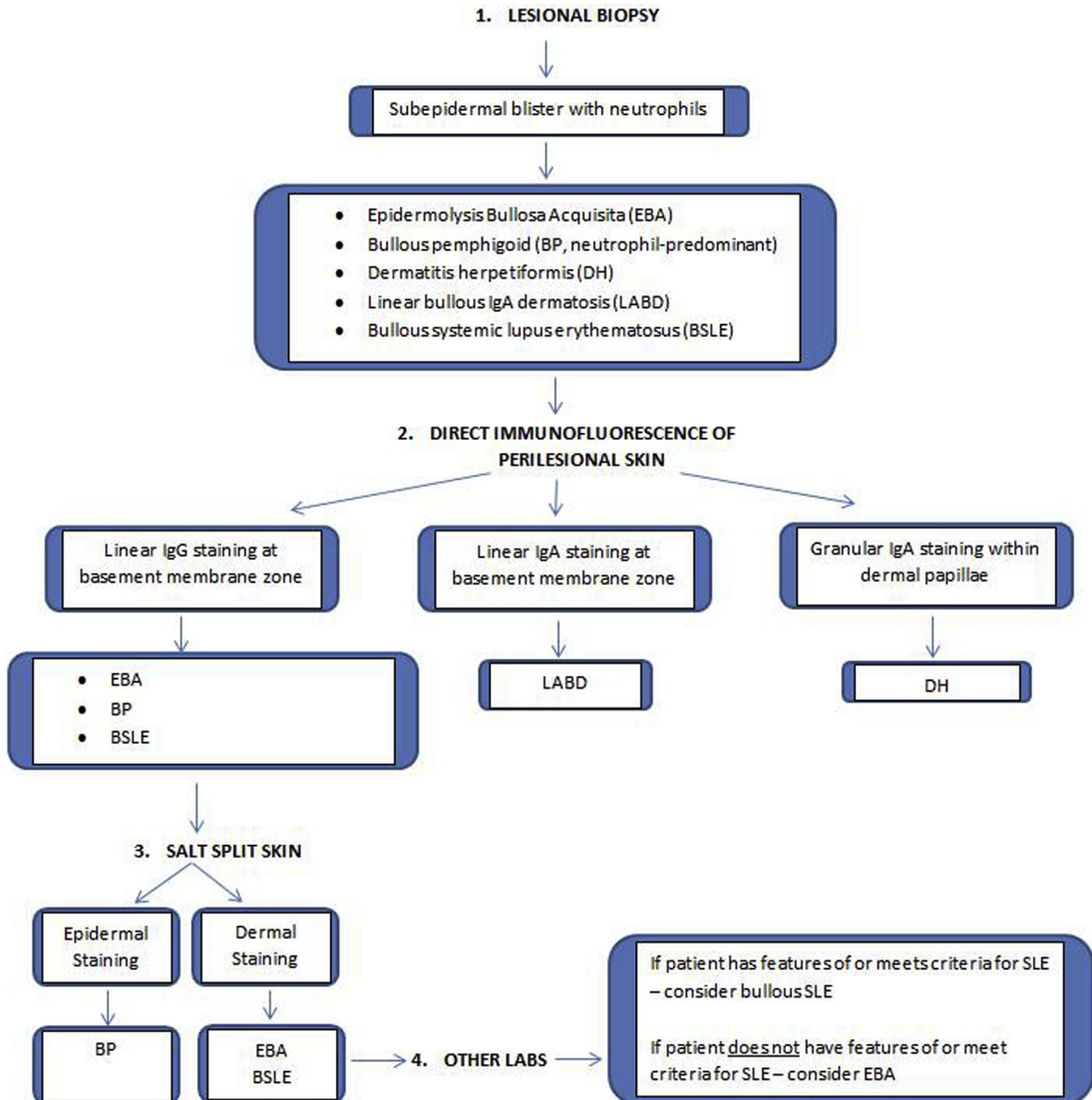
Another test that also relies on serum antibody levels is type VII collagen-specific enzyme-linked immunosorbent assay test. Our patient likely lacked enough serum antibodies to test above the positive threshold of 6 units, and instead was only detected at 0.1 unit. Additionally, antibodies toward collagen VII are also found in serum from patients with BSLE. Criteria exist to establish a diagnosis of BSLE, including rheumatologic criteria for SLE,<sup>8,9</sup> which our patient did not have, rendering a diagnosis of BSLE less likely. The most definitive way to diagnose EBA is via electron microscopy of the DIF specimen, which will show high-resolution antibody deposits within the anchoring fibril zone.<sup>10</sup> Electron microscopy is not available at most clinical laboratories, leaving the diagnosis dependent upon clinical correlation with histology, DIF, and serology.

After diagnosis, our patient was prescribed dapsone 100 mg daily, and 8 months later, he had ongoing skin fragility but no vesicles. This case highlights the clinical features and immunological pitfalls that may occur in the workup and diagnosis



**Fig 3.** **A**, Hematoxylin-eosin staining reveals a subepidermal split with neutrophils within the split (*blue arrows*) and along the dermal-epidermal junction. **B**, DIF reveals linear staining with C3 localized to the dermal side of the split. *DIF*, Direct immunofluorescence.





**Fig 4.** Algorithmic approach to diagnosing EBA and avoiding the pitfalls leading to other differential diagnoses.

of a rare entity with atypical clinical presentation and highlights the need for further careful study of under-diagnosed or under-reported phenotypes of EBA.

**Conflicts of interest**

None disclosed.

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