

# Bothersome Blisters: Localized Epidermolysis Bullosa Simplex

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## PRACTICE POINTS

- Localized epidermolysis bullosa simplex (formerly Weber-Cockayne syndrome) presents with flaccid bullae and erosions predominantly on the hands and feet, most commonly related to mechanical friction and heat.
- It is inherited in an autosomal-dominant fashion with defects in keratin-5 and keratin-14.
- Biopsy of a freshly induced blister should be examined by transmission electron microscopy or immunofluorescence mapping.
- Treatment is focused on wound management and infection control of the blisters.

To the Editor:

Epidermolysis bullosa (EB) was first described in 1886, with the first classification scheme proposed in 1962 utilizing transmission electron microscopy (TEM) findings to delineate categories: epidermolytic (EB simplex [EBS]), lucidolytic (junctional EB), and dermolytic (dystrophic EB).<sup>1</sup> Localized EBS (EBS-loc) is an autosomal-dominant disorder caused by negative mutations in keratin-5 and keratin-14, proteins expressed in the intermediate filaments of basal keratinocytes, which result in fragility of the skin in response to minor trauma.<sup>2</sup> The incidence of EBS-loc is approximately 10 to 30 cases per million live births, with the age of presentation typically between the first and third decades of life.<sup>3,4</sup> Because EBS-loc is the most common and often mildest form of EB, not all patients present for medical evaluation and true prevalence may be underestimated.<sup>4</sup> We report a case of EBS-loc.

A 26-year-old woman with no notable medical history presented to the dermatology clinic for evaluation of skin blisters that had been intermittently present since infancy. The blisters primarily occurred on the feet, but she did occasionally develop blisters on the hands, knees, and elbows and at sites of friction or trauma (eg, bra line, medial thighs) following exercise. The blisters were worsened by heat and tight-fitting shoes. Because of the painful nature of the blisters, she would lance them with a needle. On the medial thighs, she utilized nonstick and gauze bandage roll dressings to minimize friction. A review of systems was positive for hyperhidrosis. Her family history revealed multiple family members with blisters involving the feet and areas of friction or trauma for 4 generations with no known diagnosis.

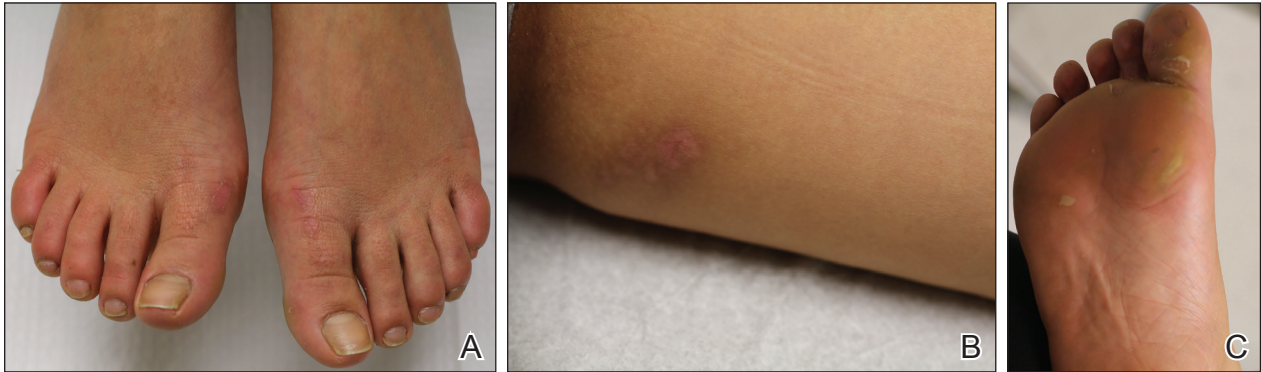
Physical examination revealed multiple tense bullae and calluses scattered over the bilateral plantar and distal dorsal feet with a few healing, superficially eroded, erythematous papules and plaques on the bilateral medial thighs (Figure 1). A biopsy from an induced blister on the right dorsal second toe was performed and sent in glutaraldehyde to the Epidermolysis Bullosa Clinic at Stanford University (Redwood City, California) for electron microscopy, which revealed lysis within the basal keratinocytes through the tonofilaments with continuous and intact lamina densa and lamina lucida (Figure 2). In this clinical context with the relevant family history, the findings were consistent with the diagnosis of EBS-loc (formerly Weber-Cockayne syndrome).<sup>2</sup>

Skin manifestations of EBS-loc typically consist of friction-induced blisters, erosions, and calluses primarily on the palms and soles, often associated with hyperhidrosis and worsening of symptoms in summer months and hot temperatures.<sup>3</sup> Milia, atrophic scarring, and

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**FIGURE 1.** Healing, superficially eroded, erythematous papules and plaques of localized epidermolysis bullosa simplex. A, Bilateral medial dorsal feet. B, Bilateral medial thighs. C, Intact blisters and callus on the plantar foot.



**FIGURE 2.** Electron microscopy of a biopsy specimen showed lysis within the basal keratinocytes through the tonofilaments with continuous and intact lamina densa and lamina lucida (original magnification  $\times 20,000$ ). Labels indicate dermis (D), epidermis (E), basement membrane (arrow), and intracellular lysis (star).

dystrophic nails are uncommon.<sup>1</sup> Extracutaneous involvement is rare with the exception of oral cavity erosions, which typically are asymptomatic and usually are only seen during infancy.<sup>1</sup>

Light microscopy does not have a notable role in diagnosis of classic forms of inherited EB unless another autoimmune blistering disorder is suspected.<sup>2,5</sup> Both TEM and immunofluorescence mapping are used to diagnose EB.<sup>1</sup> DNA mutational analysis is not considered a first-line diagnostic test for EB given it is a costly labor-intensive technique with limited access at present, but it may be considered in settings of prenatal diagnosis or in vitro fertilization.<sup>1</sup> Biopsy of a freshly induced blister

should be performed, as early reepithelialization of an existing blister makes it difficult to establish the level of cleavage.<sup>5</sup> Applying firm pressure using a pencil eraser and rotating it on intact skin induces a subclinical blister. Two punch biopsies (4 mm) at the edge of the blister with one-third lesional and two-thirds perilesional skin should be obtained, with one biopsy sent for immunofluorescence mapping in Michel fixative and the other for TEM in glutaraldehyde.<sup>3,5</sup> Transmission electron microscopy of an induced blister in EBS-loc shows cleavage within the most inferior portion of the basilar keratinocyte.<sup>2</sup> Immunofluorescence mapping with anti-epidermal basement membrane monoclonal antibodies can distinguish between EB subtypes and assess expression of specific skin-associated proteins on both a qualitative or semiquantitative basis, providing insight on which structural protein is mutated.<sup>1,5</sup>

No specific treatments are available for EBS-loc. Mainstays of treatment include prevention of mechanical trauma and secondary infection. Hyperhidrosis of the palms and soles may be treated with topical aluminum chloride hexahydrate or injections of botulinum toxin type A.<sup>2,6</sup> Patients have normal life expectancy, though some cases may have complications with substantial morbidity.<sup>1</sup> Awareness of this disease, its clinical course, and therapeutic options will allow physicians to more appropriately counsel patients on the disease process.

Localized EBS may be more common than previously thought, as not all patients seek medical care. Given its impact on patient quality of life, it is important for clinicians to recognize EBS-loc. Although no specific treatments are available, wound care counseling and explanation of the genetics of the disease should be provided to patients.

#### REFERENCES

1. Fine JD, Eady RA, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *J Am Acad Dermatol.* 2008;58:931-950.

2. Bologna JL, Jorizzo JL, Schaffer JV, eds. *Dermatology*. 3rd ed. Philadelphia, PA: Elsevier Limited; 2012.
3. Eichenfield LF, Frieden IJ, Mathes EF, et al, eds. *Neonatal and Infant Dermatology*. 3rd ed. New York, NY: Elsevier Health Sciences; 2015.
4. Spitz JL. *Genodermatoses: A Clinical Guide to Genetic Skin Disorders*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
5. Epidermolysis bullosa. Stanford Medicine website. <http://med.stanford.edu/dermatopathology/dermpath-services/epiderm.html>. Accessed April 3, 2019.
6. Abitbol RJ, Zhou LH. Treatment of epidermolysis bullosa simplex, Weber-Cockayne type, with botulinum toxin type A. *Arch Dermatol*. 2009;145:13-15.