A Case of Recessive Dystrophic Epidermolysis Bullosa Associated Colitis

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INTRODUCTION

Epidermolysis bullosa (EB) is an inherited group of disorders of epithelial fragility caused by mutations in various genes encoding structural proteins that maintain the integrity of the dermal-epidermal junction. Recessive dystrophic epidermolysis bullosa (RDEB), generalized type, is a severe form of EB caused by mutations in the COL7A1 gene, which encodes for a critical component of type VII collagen required for maintenance of the dermal-epidermal junction. RDEB often presents at birth with clinical findings including diffuse skin fragility, blisters at sites of friction, and erosions (Fig. 1). Gastrointestinal complications of RDEB include recurrent esophageal strictures, gastroesophageal reflux disease, chronic constipation, protein-losing enteropathy, and undernutrition. Few studies have described EB-associated colitis. Here we present a case of EB-associated colitis in a patient with severe RDEB.

CASE

A 22-year-old nonambulatory male with a history of RDEB confirmed by genetic testing (compound heterozygous variants in COL7A1 gene) presented with several weeks of watery diarrhea progressing to hematochezia. The patient had been previously followed by pediatric gastroenterology for constipation, esophageal strictures requiring dilation, and management of enteral nutrition through gastrostomy for chronic undernutrition.

In the month before his presentation, he was diagnosed with cellulitis of the leg and back and was started on Cephalexin (500 mg 3 times daily). One week later, he developed nonbloody, watery diarrhea. Testing for Clostridium difficile toxin B polymerase chain reaction, stool ova and parasites, and bacterial stool cultures returned negative. Skin cultures were positive for Pseudomonas sp. and he was switched to levofloxacin. Ten days later, he developed hematochezia and was admitted to the hospital ward. Stools were passed 2–3 times per day, were loose to liquid in consistency, and contained visible blood. He had no associated nausea, vomiting, or abdominal pain. Hemoglobin remained stable, and hematochezia was attributed to antibiotic-associated colitis. He was discharged on levofloxacin and was started empirically on enteral budesonide (6 mg daily) for a 14-day course. His hematochezia resolved and his stools returned to formed consistency without visible blood.

Approximately 3.5 months later, hematochezia recurred. Unlike the prior occurrence, this episode was not preceded by any antibiotic use. Enteral budesonide (9 mg daily) was restarted without improvement. Infectious stool studies including Clostridium difficile toxin B polymerase chain reaction again returned negative.

Due to the patient’s preference to avoid general anesthesia and limit procedure time, flexible sigmoidoscopy was performed and revealed moderately active colitis (Fig. 2). Rectosigmoid biopsies showed moderately active colitis consisting of mixed lamina propria stromal inflammation, including prominent eosinophils and neutrophils (Fig. 3). Budesonide (9 mg daily) was continued and mesalamine

FIGURE 1. Gross image of skin (upper arm) of a 22-year-old male with RDEB demonstrating blistering, erosions, crusts, and scarring. RDEB = Recessive dystrophic epidermolysis bullosa.
(1000 mg 3 times daily) was started for treatment of EB-associated colitis. Hematochezia resolved within 2 weeks and budesonide was then discontinued. Mesalamine was continued for maintenance treatment of EB-associated colitis. He had no recurrence of diarrhea or hematochezia for 6 months of follow-up available.

**DISCUSSION**

Tissue-specific effects of RDEB include corneal blisters that can cause vision loss, skin ulcerations, denudation, and retracting scars which can lead to pseudosyndactyly, a high (>90%) lifetime risk of aggressive squamous cell carcinoma, oral mucosal involvement leading to progressive microstomia, and esophageal erosions leading to the formation of esophageal strictures causing dysphagia (3,4). Colitis is rare in most genetic forms of EB but is most prevalent in the RDEB subtype (2). Interestingly, epidermolysis bullosa acquisita, a related disorder caused by auto-antibodies against type VII collagen, is strongly associated with inflammatory bowel disease (5), however, the pathophysiology of the few reported cases of inflammatory bowel disease in RDEB appears to be unique (2). As a result of the low incidence, the risk factors, presentation, diagnostic approach, and management of colitis in patients with RDEB are not well defined.

This patient initially presented with hematochezia following antibiotic use, and when infectious testing returned negative, was diagnosed with antibiotic-associated colitis. The second episode of colitis was not preceded by a recent infection or antibiotic use;

**FIGURE 2.** Gross endoscopic images of the rectosigmoid mucosa demonstrating diffusely granular appearing and erythematous colonic mucosa with loss of vascularity consistent with colitis.

**FIGURE 3.** Histological examination of sigmoid biopsies: Moderately active colitis consisting of mixed lamina propria stromal inflammation, including prominent eosinophils and neutrophils. Acute cryptitis, acute crypt abscesses, focal superficial karyorrhectic debris within the lamina propria, and focal extravasated neutrophilic inflammation on the luminal colonic surface (A) as well as rare hemosiderin-laden macrophages (B).
however, concern remained about possible intestinal dysbiosis which may have contributed to the onset of EB-associated colitis. The intestinal effects of frequent antibiotic use in patients with RDEB are poorly defined. Studies of prophylactic probiotics have been inconclusive with regard to their efficacy in preventing dysbiosis due to antibiotic use (6). RDEB represents 1 example of a disease in which patients require recurrent and frequent exposure to antibiotics, however, the effect on the intestinal microbiome and whether this increases the risk of colitis remains unclear. Furthermore, the effects of the COL7A1 mutations on the integrity of the intestinal epithelium and barrier function are not well understood. A colorectal biopsy confirmed moderately active colitis (Fig. 3). Histopathological features including discrete petechiae and mucosal friability were noted in our patient and have been reported in other patients with EB-associated colitis (2). Similarly, rectosigmoid biopsies demonstrated findings consistent with EB-associated colitis including (1) moderately active colitis consisting of a mixed lamina propria stromal inflammation, including prominent eosinophils and neutrophils (2) superficial lamina propria karyorrhectic debris and (3) rare hemosiderin-laden macrophages. Importantly, and consistent with other reports, there was no evidence of epidermal clefting or separation as seen in the skin of EB patients (2). Biopsies from this patient also demonstrated acute cryptitis and acute crypt abscesses which are nonspecific and also seen in colitis due to inflammatory bowel disease (Fig. 3). Colorectal biopsy proved to be helpful in determining the next steps in the diagnosis and treatment of this patient, however, the diagnostic process for colitis in EB patients presents many obstacles. In this case, the risks associated with the endoscopic procedure included a history of complications with anesthesia and risks of further skin damage caused by procedure-related interventions (eg, Intravenous access, use of adhesives, and airway management) (7). Additionally, serum inflammatory markers may be difficult to interpret in the setting of chronic inflammation in RDEB. Prior reports of successful treatment of EB-associated colitis used 5-Aminosalicylates and corticosteroids when necessary (2). In this case treatment with a 5-Aminosalicylates (mesalamine) in combination with enteral budesonide was effective. This case highlights the significant morbidity of EB-associated colitis as well as the paucity of data available to guide treatment. Here we provide an example of successful treatment with mesalamine and budesonide, but further investigation is required to develop evidence-based guidelines for the prevention, diagnosis, and treatment of EB-associated colitis.

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REFERENCES