A rare case of recessive dystrophic epidermolysis bullosa with aplasia cutis and pyloric stenosis

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INTRODUCTION

Epidermolysis bullosa (EB) encompasses a phenotypically and genetically heterogeneous group of inherited skin disorders. Mutations in genes encoding structural proteins in the epidermis and dermis result in marked mechanical fragility, leading to widespread blisters, erosions, and nonhealing wounds following minor trauma.[1] EB can be divided into 4 major types, EB simplex, junctional EB, dystrophic EB, and Kindler EB, based on the level of tissue separation in the skin. EB can be further subdivided based on phenotypic features, mode of inheritance, targeted protein and expression in the skin, and identification of mutation(s) present.[1] Dystrophic EB (DEB) is caused by mutations in the type VII collagen gene (*COL7A1*).[2] The gastrointestinal tract is often affected in patients with autosomal recessive DEB (RDEB), and this most typically manifests with nutritional deficiencies, failure to thrive, constipation, and the development of esophageal strictures over time. The occurrence of pyloric stenosis (PS) with EB has been described almost exclusively in patients with junctional EB (JEB).[3] We present an uncommon case of PS in a patient with RDEB and review the literature regarding the coexistence of these rare conditions.

Abbreviations used:

DDEB:	dominant dystrophic epidermolysis bullosa
DEB:	dystrophic epidermolysis bullosa
EB:	epidermolysis bullosa
JEB:	junctional epidermolysis bullosa
PS:	pyloric stenosis
RDEB:	recessive dystrophic epidermolysis bullosa

CASE REPORT

A 1-day-old male infant presented to our children's hospital with congenital absence of skin involving the left lower extremity and multiple bullae and superficial erosions concerning for EB. The family history was negative for skin conditions. Cutaneous examination revealed a large, circumferential, well-demarcated erosion with clean borders on the left lower extremity (Fig 1, *A*). Additional smaller erosions, vesicles, and bullae were seen on the left leg, bilateral buttocks, right heel, and chest. There was evidence of skin fragility with the development of new lesions over the first days of life. Blistering involved the oral mucosa, and the infant had notable bilateral eyelid edema (Fig 1, *B*). Wound care with emollients and nonadhesive protective dressings was instituted. The Haberman nipple was recommended to reduce oral trauma. Ophthalmologic evaluation of the periorbital swelling revealed corneal haze without concern for inflammation or infection. Genetic testing revealed heterozygous pathogenic variants in the *COL7A1* gene (c.5261delC, not previously reported but thought to be pathogenic based on the nature of the mutation; c.6501 G>A, previously reported in dominant dystrophic epidermolysis bullosa [DDEB] and RDEB), consistent with a diagnosis of DEB, most likely RDEB.

At 3 weeks of life, the patient was readmitted to our children's hospital for dehydration in the setting of a 1-week history of nonbloody, nonbilious emesis

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Fig 1. RDEB. **A**, Circumferential, well-demarcated erosion on the left lower extremity. **B**, Significant periorbital edema bilaterally as well as scattered erosions periorally and on the mucosal lips. *RDEB*, Recessive dystrophic epidermolysis bullosa.

concerning for PS. The physical examination was unremarkable, with the exception of bullae and erosions in various stages of healing. There was no palpable mass in the abdomen, and the initial abdominal ultrasound was unremarkable. Repeat ultrasound 3 days later revealed interval thickening of the muscular portion of the pylorus measuring up to 5 mm (previously 2 mm) and pyloric channel length up to 25 mm (previously 12 mm), consistent with PS. Pyloromyotomy was performed without complications. The patient had 1 postoperative episode of emesis after feeding but subsequently appeared to feed well with adequate oral intake. Six days later, the patient was readmitted for poor feeding secondary to pain from persistent intraoral blistering. Bottle feeding with fortified expressed maternal milk and donor milk was initiated and breastfeeding discontinued. Tylenol and oxycodone were given as needed for pain control. Feeding and weight gain improved at follow-up.

DISCUSSION

We present a rare case of PS in a patient with RDEB. DEB can be inherited in an autosomal dominant or recessive manner. Several hundred distinct mutations have been described in the *COLA7A1* gene, which is responsible for encoding collagen VII, the main constituent of anchoring fibrils in the basement membrane zone of the skin and mucosa.[2] The diagnosis is made with immunofluorescence mapping, transmission electron microscopy, and/or mutational analysis. DDEB is usually associated with missense and splice site mutations, whereas RDEB is typically associated with missense, nonsense, deletion, insertion, and splice site mutations.[2,4] The type of mutation may influence the phenotype of the patient.[5] There is a spectrum of genotypic and phenotypic variants; however, RDEB is typically more severe than DDEB.[1] The most severe form of RDEB, formerly called Hallopeau-Siemens type, is caused by premature termination codon mutations on both *COL7A1* alleles. The milder forms of RDEB are often caused by compound heterozygous mutations, as in our patient.[5] Because of the heterogeneity of phenotypes and overlap of clinical findings among subtypes, it may be difficult to precisely determine the diagnosis during the newborn period or early infancy.[4] Based on mutational analysis, we believe that our patient likely had RDEB, although targeted carrier testing of both parents would be needed to confirm this.

The gastrointestinal tract can be involved with varying degrees of severity in patients with different EB subtypes, particularly in DEB, JEB, and Kindler EB.[3] Gastrointestinal complications often occur in patients with RDEB, with esophageal strictures seen almost exclusively in this subtype.[6] PS has been primarily linked to patients with JEB,[3] and we could not find any cases of PS in patients with DEB confirmed by immunohistochemical or molecular techniques.[7-9] In contrast, there several reports of DEB in association with pyloric atresia. However, it is

important to note that EB with PS is distinct from EB with pyloric atresia; the latter often presents within a subtype of JEB caused by mutations in $\alpha_6\beta_4$ integrin, a component of hemidesmosomes.[10] Although the pathogenesis of PS is unclear and is rarely familial,[11] several risk factors, including genetics, may play a role in its development.[12] It is unclear whether patients with EB have a predisposition to PS, and the mechanism of development is unknown.

This report details an unusual case of coexisting RDEB and PS. The occurrence of both in our patient may be coincidental, although given the strong associations between EB and gastrointestinal tract manifestations, we postulate that the 2 conditions are related. This case report highlights the importance of being aware of not only the extracutaneous manifestations in EB subtypes but also the occurrence of coincidental or as yet unassociated conditions.

Conflicts of interest

Dr Funk has received institutional study support from AbbVie Inc and Palvella Therapeutics, and honoraria for consulting from Sanofi Genzyme and Regeneron and Palvella Therapeutics. Author Sawka and Dr Dhossche have no conflicts of interest to declare.

REFERENCES

1. Has C, Bauer JW, Bodemer C, et al. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol*. 2020;183(4):614-627.
2. Hovnanian A, Rochat A, Bodemer C, et al. Characterization of 18 new mutations in COL7A1 in recessive dystrophic epidermolysis bullosa provides evidence for distinct molecular mechanisms underlying defective anchoring fibril formation. *Am J Hum Genet*. 1997;61(3):599-610.
3. Fine JD, Mellerio JE. Extracutaneous manifestations and complications of inherited epidermolysis bullosa: part I. Epithelial associated tissues. *J Am Acad Dermatol*. 2009;61(3):367-386.
4. 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(6):931-950.
5. Dang N, Murrell DF. Mutation analysis and characterization of COL7A1 mutations in dystrophic epidermolysis bullosa. *Exp Dermatol*. 2008;17(7):553-568.
6. Freeman EB, Köglmeier J, Martinez AE, et al. Gastrointestinal complications of epidermolysis bullosa in children. *Br J Dermatol*. 2008;158(6):1308-1314.
7. Dereure O, Vailly J, Lagrange B, Meneguzzi G, Ortonne JP, Guillot B. Dominant dystrophic epidermolysis bullosa associated with pyloric stenosis and congenital absence of skin. *Arch Dermatol*. 2001;137(5):665-666.
8. Prakash R, Puri A. An unusual cause of dysphagia in a child: gastrointestinal manifestations of epidermolysis bullosa. *Indian J Med Res*. 2018;147(3):321.
9. Ben Dhaou M, Ammar S, Louati H, Zitouni H, Jallouli M, Mhiri R. Epidermolysis bullosa with hypertrophic pyloric stenosis in a newborn. *J Neonatal Surg*. 2015;4(4):47.
10. Pulkkinen L, Uitto J. Mutation analysis and molecular genetics of epidermolysis bullosa. *Matrix Biol*. 1999;18(1):29-42.
11. Fonkalsrud EW, DeLorimier AA, Hays DM. Congenital atresia and stenosis of the duodenum: a review compiled from the members of the surgical section of the American Academy of Pediatrics. *Pediatrics*. 1969;43(1):79-83.
12. MacMahon B. The continuing enigma of pyloric stenosis of infancy: a review. *Epidemiology*. 2006;17(2):195-201.