Epidermolysis Bullosa Simplex (Dowling-Meara Type) Associated with Pyloric Atresia and Congenital Urologic Abnormalities

Dong-Kun Kim¹, Soo-Chan Kim¹, Sung-Nam Chang², and So Yeon Kim³

Abstract

We report a case of epidermolysis bullosa simplex, Dowling-Meara type (EBS-DM), which was associated with congenital pyloric atresia (PA) and various urologic abnormalities, a diagnosis confirmed by immunofluorescence mapping and electron microscopic findings. Immunofluorescent mapping showed the serum from a patient with bullous pemphigoid faintly binding to the floor of the blister, and monoclonal antibodies against type IV and VII collagens were also stained on the floor of the blister. Electron microscopy showed epidermolysis cleavage and prominent clumping of tonofilaments in the basal and suprabasal keratinocytes. An abdominal radiograph and barium swallow showed a complete obstruction at the pyloric channel level. The widespread bullae healed without any scar formation and the bullae formation was localized on the extremities after 3 months of age without any specific treatment. Multiple urologic abnormalities such as bilateral hydronephrosis, hydroureter and a distended bladder with trabeculation were observed at 12 months of age. Currently, with the patient at 4 years of age, bullae still appear on the hands and feet and nail shedding can be observed. The patient’s father, a paternal uncle and a paternal aunt had had similar bullous eruptions in infancy, all of which had improved spontaneously by the age of one.

Key Words: Epidermolysis bullosa simplex, Dowling-Meara, pyloric atresia, urologic abnormalities

INTRODUCTION

Epidermolysis bullosa simplex, Dowling-Meara type (EBS-DM) is a rare type of epidermolysis bullosa simplex (EBS) and is characterized clinically by herpetiform clustering of blisters and palmo-plantar keratoderma.¹⁻⁵ Characteristic tonofilament clumping has been observed in basal keratinocytes in electron microscopy.²⁻⁸ Recent studies have demonstrated that EBS-DM results from mutations of the keratins, K5 and K14, of basal keratinocytes.⁹⁻¹⁵ The concomitant occurrence of inherited epidermolysis bullosa (EB) and congenital pyloric atresia (PA) has been reported mostly in junctional EB (JEB). This subgroup of EB is now known as the JEB-PA syndrome.¹⁶⁻¹⁸ Only two cases of EBS associated with congenital PA have been reported in the literature, but its subtype was undefined.¹⁹,²⁰ Urologic abnormalities were reported in recessive dystrophic EB (RDEB)²¹ and JEB,²² not in EBS. We report a peculiar case of EBS-DM associated with both PA and congenital urologic abnormalities.

CASE REPORT

A 2,400 g male infant was born at 37 weeks gestational age by spontaneous vaginal delivery. He had persistent, non bile-stained vomiting from birth. His abdomen was distended and bowel sound was increased. Multiple bullae and erosions were found on the head, anterior chest, hands, feet, and oral mucous membrane (Fig. 1). Nail dystrophy was observed on the right thumb.

Abdominal radiographs demonstrated distension of the stomach and a lack of air in the intestine. Barium swallow showed a complete obstruction at the pyloric channel level (Fig. 2A). An emergency gastrostomy was performed. Following the operation
the patient tolerated milk feeding with a satisfactory weight gain.

A biopsy taken from a bulla on the upper arm showed a subepidermal blister containing fibrin. A mild perivascular lymphohistiocytic infiltrate was present in the dermis (Fig. 3A). Direct immunofluorescence studies performed on the blister edge failed to reveal any deposits of IgG, IgM, IgA, C3, or fibrinogen. Immunofluorescence mapping showed serum from a the patient with bullous pemphigoid faintly binding to the floor of the blister (Fig. 3B), and monoclonal antibodies against type IV (DAKO, Copenhagen, Denmark) (Fig. 3C) and type VII collagens (Gibco, Gaithersburg, MD, USA) (Fig. 3D) were also stained on the floor of the blister. Transmission electron microscopy revealed a blister above the dermoeipidermal junction (Fig. 4A). Normal hemidesmosomes were seen associated with clumped keratin filaments (Fig. 4B). Basal and suprabasal keratinocytes undergoing cytolysis had clumps of keratin filaments (Fig. 4C).

The widespread bullae healed without any scar formation and the bullae formation was localized on the extremities after 3 months of age without any specific treatment. At 12 months of age, multiple urologic abnormalities such as bilateral hydronephrosis, hydroureret (Fig. 2B) and a distended bladder with trabeculation, all of which are suggestive of detrusor dyssynergia, were observed. At 4 years of age, bullous eruptions are still developing on the extremities and nail dystrophy can be observed.

The patient’s father, a paternal uncle and a paternal aunt had had similar bullous eruptions without any associated anomalies, all of which had improved spontaneously by the age of one.

**DISCUSSION**

EBS-DM is a rare genodermatosis inherited as an
autosomal dominant trait. Furthermore, the family history of the present case also strongly suggests autosomal dominant genetic transmission. EBS-DM usually presents at birth or in early infancy with a widespread herpetiform grouping of blisters, which follows a relatively benign course and a tendency to improve in later childhood or adult life. Blistering can be severe in early infancy and intraoral blistering is common. Esophageal erosions have also been reported. The present case shows the usual clinical manifestations; herpetiform bullae with erosions leaving no scars, and nail shedding, which are still developing at 4 years of age. The other family members who had suffered from this disease demonstrated a relatively benign course. They had had similar bullous eruptions in infancy, which had improved spontaneously by the age of one and showed no recurrence thereafter.

PA is a rare autosomal recessively inherited anomaly with an incidence of one per million at birth. Even though the etiological and pathogenic relationship between PA and inherited EB is still unknown, the simultaneous occurrence of congenital PA and inherited EB in a newborn seems to be a distinct association. Lestringant et al. provided an overview of the PA-EB association in world literature, in which 42 cases were reviewed. The EB subtypes were confirmed by transmission electron microscopy only in 24 patients and the results were as follows: JEB in 21 cases (87.5%), RDEB in 2 (8.3%) cases, and EBS in 1 (4.2%) case. They regarded the PA-JEB association as a distinct congenital syndrome because most patients with the PA-EB association also had...
JEB. Recently, mutations in the 4 or 6 integrin genes have been demonstrated in patients with the PA-JEB syndrome.\textsuperscript{23-25} The PA-EBS association has rarely been reported, and the subtype of EBS has not been verified.\textsuperscript{19,20} To our knowledge, this is the first report describing the association of PA with EBS-DM.

Genitourinary involvement has rarely been reported in RDEB\textsuperscript{21} and JEB,\textsuperscript{22} and not at all in EBS. In these cases, extensive erosions, edema, and fibrosis resulted in ureteral obstruction at the ureterovesical junction and the subsequent hydroureteronephrosis. Unexpectedly, the present case with EBS-DM showed evidence of multiple urologic abnormalities such as bilateral hydronephrosis, hydrourereter and a distented bladder with trabeculation, all of which are suggestive of detrusor sphincter dyssynergia.

It can also be hypothesized that this association of EBS-DM with urologic abnormalities represents the outcome of an epithelium at risk of responding to mechanical trauma. The scarring or mucosal adhesion which follows repeated trauma may play a role in the formation of the associated anomalies, even though the present case was a simplex type of EB which showed no scars in the skin after healing. It is also possible that the association was incidental or the result of an unknown mechanism. Further research will be necessary in order to understand the etiopathogenesis of this peculiar form of EBS-DM associated with congenital anomalies of multiple organs.

REFERENCES

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