Laryngeal stenosis associated with epidermolysis bullosa simplex

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INTRODUCTION

Inherited epidermolysis bullosa is a heterogeneous group of rare genetic diseases characterized by cutaneous or mucosal fragility. The diseases are caused by the mutation of genes encoding the constituent proteins of the dermal-epidermal junction. There are 4 major types of inherited epidermolysis bullosa: epidermolysis bullosa simplex, junctional epidermolysis bullosa, dystrophic epidermolysis bullosa, and Kindler syndrome. A new classification system[1] published in 2014 considers the type, mode of inheritance, phenotype, immunofluorescence antigen mapping findings, and mutation(s) present in each patient. The prognosis depends on the type of epidermolysis bullosa, the extent of lesions, and the potential mucosal damage.

Laryngeal lesions are frequently observed in junctional epidermolysis bullosa and dystrophic epidermolysis bullosa[2] but are uncommon in epidermolysis bullosa simplex, except in epidermolysis bullosa simplex with plectin gene deficiency. Laryngeal involvement is associated with a potential risk of airway occlusion and death.

Here, we report an atypical case of generalized intermediate epidermolysis bullosa simplex associated with laryngeal stenosis.

CASE REPORT

A male infant was born at term from nonconsanguineous parents after an uncomplicated pregnancy. His mother had a diagnosis of generalized intermediate epidermolysis bullosa simplex with typical clinical features (blisters on palms and soles during childhood, and nail lesions) and histologic features (intraepidermal cleavage within basal keratinocytes). Immunofluorescent antigen mapping result was positive for keratin and laminin 5. Molecular analysis revealed a heterozygous mutation of *KRT14* on exon 1. This mutation predicts an amino acid change from arginine to cysteine at codon 125 (R125C) of the protein.

At birth, the infant had blisters on the palms and soles (Fig 1) and around the mouth. Oral mucosa showed slight erythema and erosion. The diagnosis of generalized intermediate epidermolysis bullosa simplex was retained. Since birth, the child had had permanent dysphonia, with hoarse screaming. When

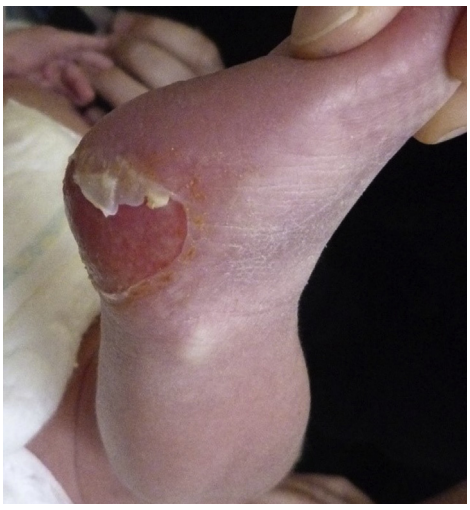

Fig 1. A blister on the heel of the child at birth.

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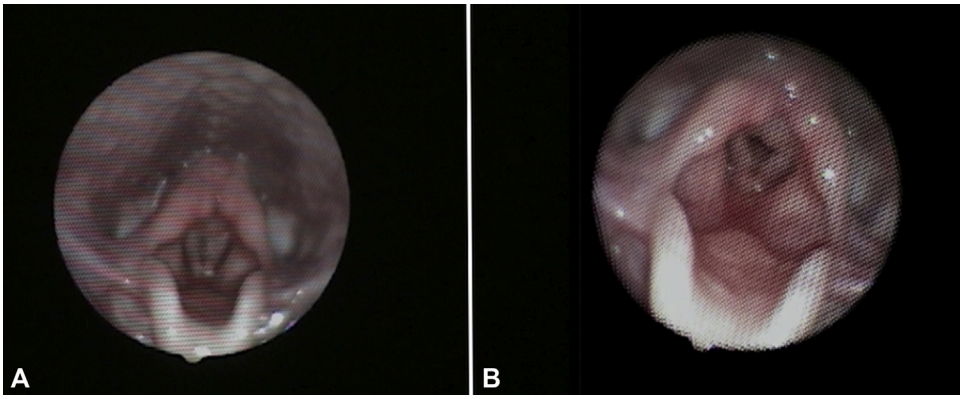

Fig 2. **A**, Laryngoscopy showing the laryngeal stenosis. **B**, Laryngoscopy showing only minor defects of the larynx 2 months later.

the infant was aged 8 months, the otolaryngologist performed fibroscopy apart from any infectious context. Erythema and erosions were observed on both sides of the larynx, on the vocal cords, and on the posterior aspect of the commissure. The glottic airway was greatly reduced, with laryngeal stenosis at 80% (Fig 2, *A*). The dysphonia was not associated with severe respiratory symptoms or interference with feeding; specialized surveillance by a pediatric otolaryngologist was started. Nebulized corticosteroids were started immediately in case of upper airway infection to avoid aggravation of the hoarse screaming.

The symptoms gradually decreased during follow-up. At aged 10 months, the child underwent repeated fibroscopy, which did not show any anomaly (Fig 2, *B*). Congenital dysphonia completely disappeared at aged 12 months. With a follow-up of more than 2 years, the child was in good general health without dysphonia, and with normal height and weight. Blisters were still appearing all over the body, especially on the palms and soles. There is currently no more mucosal involvement.

DISCUSSION

Laryngeal lesions are usually absent in epidermolysis bullosa simplex, except in epidermolysis bullosa simplex with plectin gene deficiency, a form frequently associated with muscular dystrophy. Our report describes an atypical case of generalized intermediate epidermolysis bullosa simplex associated with laryngeal stenosis.

Laryngeal stenosis is associated with risk of airway occlusion, asphyxia, and death, so it must be detected as early as possible. Clinical warning signs, particularly of obstructive upper airway bubbles, are inspiratory dyspnea (stridor), weak or hoarse screaming, and dysphonia. These signs require urgent examination by an otolaryngologist.

A retrospective study to define the frequency of upper airway complications in epidermolysis bullosa included 3,280 cases from the National Epidermolysis Bullosa Registry.[2] The study also assessed the cumulative risk of laryngeal stenosis in patients. Laryngeal complications occurred most frequently in junctional epidermolysis bullosa types. In epidermolysis bullosa simplex, it was a rare complication, with a cumulative risk by aged 8 years of 0% in generalized severe, generalized intermediate, and localized epidermolysis bullosa simplex and 0.43% in other types.

We found reports of 6 cases of epidermolysis bullosa simplex with plectin gene deficiency (with or without muscular dystrophy) associated with laryngeal stenosis, with poor prognosis and the need for tracheotomy in 3 cases.[3-7]

A mutation on the *KRT14* gene, which is a known cause of epidermolysis bullosa simplex,[8] is described in our case report.

We found 2 other cases similar to ours: Shemanko et al[9] and Diociaiuti et al[10] reported an association between laryngeal involvement and *KRT14* gene mutation in patients with generalized severe epidermolysis bullosa simplex. The disease was caused by a mutation on codon 125 of *KRT14*, as in our patient, for the 2 cases. In the study by Diociaiuti et al,[10] the mutation was the same as in ours, and in the report by Shemanko et al,[9] the mutation resulted in a predicted change from arginine to histidine.

Vocal cords are made of a stratified squamous epithelium, which contains keratin 14, so the few observations of laryngeal involvement in epidermolysis bullosa simplex with *KRT14* mutation may be surprising. One explanation for the 3 cases reported is that the location of the mutation on the gene is disruptive to keratin intermediate filament.

The reports by Shemanko et al[9] and Diociaiuti et al,[10] like ours, showed favorable disease evolution. We suggest that spontaneous regression of laryngeal stenosis in these 3 cases may explain this underreported complication in epidermolysis bullosa simplex and that respiratory symptoms should be monitored, but managed conservatively.

To conclude, we present an atypical case of laryngeal stenosis associated with generalized intermediate epidermolysis bullosa simplex. Hoarse screaming and dysphonia must alert physicians to the possibility of laryngeal lesions in inherited epidermolysis bullosa, even in simplex forms. Given the potential risk of sudden airway occlusion and death, meticulous surveillance by a pediatric otolaryngologist is a critical part of the overall management of infants and children with epidermolysis bullosa with laryngeal involvement, even those with epidermolysis bullosa simplex.

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