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Case Report
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A Rare Cause of Subglottic Stenosis; CARMI Syndrome

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Abstract

Epidermolysis Bullosa (EB) is a rare heritable disease of the skin, manifests at birth, early childhood, or adults with different subtypes (simplex, recessive, dystrophic, and junctional) that cannot be separated clinically. Junctional EB (JEB) divided into three subgroups: Herlitz, non-Herlitz, and JEB with Pyloric Atresia (JEB-PA). JEB-PA, also known as CARMI syndrome, is an autosomal recessive disease, divided into two variants, non-lethal and lethal, because of mutations in ITGB4 and ITGA6. Upper airway obstruction that can be fatal is one of the important complications. There is no cure treatment, and additionally, it has a poor prognosis.

Keywords: Carmi; Congenital; Epidermolysis bullosa; Skin fragility; Subglottic stenosis

Introduction

Epidermolysis Bullosa (EB) is a rare hereditary disease that seems with or without trauma as blistering or erosion of the skin and tissue layer. The precise prevalence of epidermolysis bullosa is unknown [1]. EB classified into four major groups, looking at the level of skin involvement: EB Simplex (EBS) involving the intra-epidermal layer, Junctional EB (JEB) involving the lamina lucida, Dystrophic EB (DEB) involving the sublamina densa; and Kindler syndrome involving multiple layers of the epidermis. Junctional EB is divided into three subgroups: Herlitz, Non-Herlitz, and JEB with Pyloric Atresia (JEB-PA). JEB- PA is an autosomal recessive blistering disease, which can be fatal in early infancy even after the correction of PA. It is usually diagnosed in the neonatal age [2]. JEB-PA has a high mortality rate of up to 75% because of infection and nephritic impairment [3]. Besides the skin lesions, other common extra-cutaneous manifestations are corneal erosions, dental, nail, and hair abnormalities, along with tracheal and urinary tract involvement. JEB has a higher incidence of airway obstruction compared to other types of epidermolysis bullosa. The incidence rate of laryngeal stenosis, stricture, or obstruction around 40% for Herlitz-JEB by the age of 6% and 13% for non- Herlitz –JEB by the age of 9 [2].

In this case report, we tend to present a toddler's history with Carmi syndrome complicated with subglottic stenosis. Parents' consent was obtained for publishing all the required data for the case.

Case Presentation

A 6-month-old Baby girl referred to us with a chief complaint of recurrent chest infection and persistent stridor for investigations. She was managed as croup in the other facility with nebulizer epinephrine, dexamethasone orally, in addition to topically applied medications for skin lesions. Despite all management, stridor did not resolve. She was born as preterm 33 weeks and admitted to the NICU because of respiratory distress and pyloric atresia, which needed a surgical operation at the age of two days. Moreover, she was observed to have skin lesions; given the EB's positive family history, she was diagnosed with the disease (EB). Her family history was significant. Her sister had Epidermolysis Bullosa and pyloric atresia, but she died in the early neonatal period. Also, her cousin has been died before reaching her first birthday, suffering from Epidermolysis Bullosa. Unfortunately for both patients, there is no genetic study done.

On admission, physical examination revealed well appearance; no dysmorphic features, with blisters on her face, and nails junctions. There are audible stridor and mild respiratory distress with symmetric air entry. The rest of the examinations is unremarkable. Chest X-ray and the blood test was normal, except CRP slightly increased.

Bronchoscopy at the age of 6-month was showing laryngeal swelling and laryngomalacia, mild subglottic stenosis, fragile mucosa, with granulation, and easily bleed.

A genetic study showed, JEB with pyloric atresia the homozygous variant c.3674>A, p.

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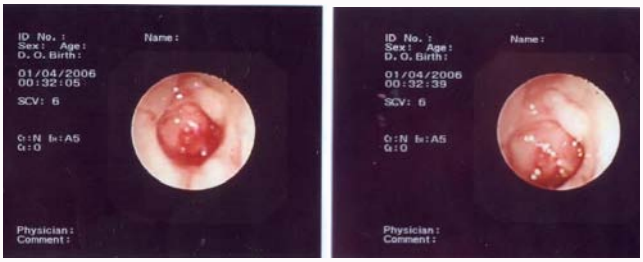

Figure 1: Bronchoscopy at age one year.

(Arg1225His) in ITGB4 (OMIM:147557) is a rare form of EB with multisystem involvement.

Because of the increase of upper airway obstruction symptom (persistent stridor), a repeated bronchoscopy at the age of 1 year showed;

The glottis is swelling, with mild bleeding. Sub glottis anterior mass (white, smooth) obdurate the trachea's whole entrance around 90%, we couldn't pass through it with the bronchoscope (Figure 1).

CT neck with contrast ordered but issued after three months from bronchoscopy, and it showed: Mild Laryngeal stenosis, possibly due to edema (Figure 2).

She is regularly followed in the outpatient, the stridor was moderate to severe during the first year, but she gradually improved during the second year. For that reason, the third bronchoscopy was done at the age of 2 years, and it showed: The glottis appears normal with mild swelling in the anterior part of the glottis. No subglottic stenosis was seen. The rest of the bronchoscopy was normal. In conclusion, improve subglottic stenosis spontaneously comparing the last bronchoscopy (Figure 3).

Discussion

JEB with pyloric atresia, the homozygous variant c.3674>A, p. (Arg1225His) in ITGB4 (OMIM:147557) is a rare form of EB with multisystem involvement. 7 out of 10 bioinformatic in silico programs predict a pathogenic effect for this variant. Parallel analysis for parental WES data revealed both parents are heterozygous carriers of the detected variant in ITGB4. This confirms the homozygosity of the detected variant in the index. The variant is found in 0.0032% of the overall population.

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The variant has been described in the literature by Nakano et al. [4] in a 13-year-old female with a non-lethal type of Epidermolysis

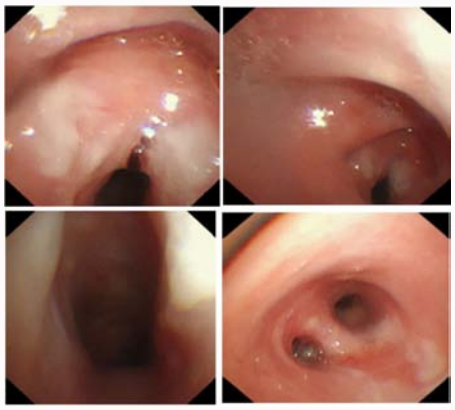

Figure 3: Bronchoscopy at age of 2 years.

Bullosa with urologic obstruction, ocular involvement, scarring on legs, hypoplastic enamel, laryngeal obstruction [4].

Swinburne and Kohler were the first to describe the disease in 1967 at the 13th Annual Pediatric Pathology Society in England and published the corresponding paper in 1968 [1]. Carmi has first described the condition, so also called "Carmi syndrome" [5]. The accurate prevalence of the subtype Carmi is unknown, approximately <1:1,000,000. There are 100 cases documented worldwide [6]. Diagnosis can be approach prenatally by a genetic study from amniotic fluid or chorionic villi. Also, skin biopsy guided by ultrasound or fetoscopy is another option to reach the diagnosis prenatally [7,8].

JEB is impacted on the larynx and trachea has been described, but because of the disease rarity, all studies were with few numbers of patients and included all types of EB [9-13]. Signs and symptoms are weak or hoarse cry, inspiratory stridor, and edema, blistering of the mucosa, thickening and scarring of the vocal cords, cicatricial lesions or severe upper airway stenosis. The most common complication is partial or complete obstruction of the airways, typically occur from subglottic stenosis, which can be life-threatening. Diagnosis relies on clinical symptomatology, histopathology, electron microscopy, and genetic studies [2].

There is no cure treatment for Carmi syndrome. Genetic therapies are a promising treatment for the future, but it has not been applied. Current therapies rely on symptomatic treatment [14]. For the patient who has airway disease, there is very little data written relating to the care of the airway, the safety of airway bronchoscopy, and outcomes [15]. Despite all management as well as surgical correction for PA, Carmi syndrome is fatal in most cases. The prognosis is poor because of prematurity, extensive skin blistering with electrolyte and fluid imbalance, respiratory morbidities, malnutrition, sepsis, and association with another organ disease. One hundred cases reported

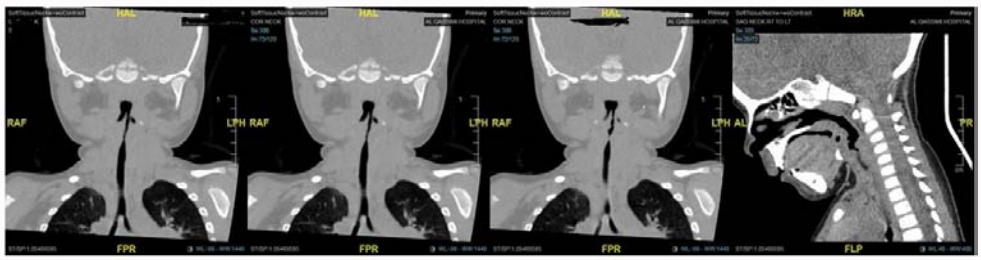

Figure 2: CT neck soft tissue.

in 2018, 70 patients out of 94 patients died (74.5%) with a median time of age 30 days [3].

Conclusion

Carmi syndrome is a rare non-treatable condition and has a poor prognosis. It is a multi-systemic disease in addition to other systems can affect the whole respiratory tract, especially the larynx, as subglottic stenosis, and cause life-threatening obstruction episodes. But in a few cases, the subglottic stenosis can improve spontaneously, like our case. The diagnosis and management of children with these disorders are very difficult. Each case has to take in the individual. Deciding on tracheotomy should not be taken lightly but requires thorough consideration. The treatment needs a multidisciplinary approach.

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