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Junctional epidermolysis bullosa with extensive lung involvement in three patients with a *LAMB3* Mutation

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Abstract

Junctional epidermolysis bullosa (JEB) is characterized by skin and mucous membrane fragility leading to easy blistering. Blistering may be the result of multiple genetic mutations, including the *LAMB3* gene encoding a subunit of laminin 332, an important protein in the basement membrane zone. The clinical presentation of JEB includes blistering and granulation tissue forming anywhere on the skin including around oral and nasal cavities, fingers, toes, and within mucous membranes such as the upper respiratory tract. Lung pathology associated with JEB is less commonly reported; we describe three children with *LAMB3* pathogenic variants with extensive lung injury contributing to decline in clinical status and likely leading to their demise early in life.

Keywords

epidermolysis bullosa; genetic diseases/mechanisms

1. Introduction:

Junctional epidermolysis bullosa (JEB) is a genetic condition characterized by skin and mucous membrane fragility that presents with easy blistering. The incidence of disease is rare at approximately 3.6 to 6.7 per million per year.[1,2] Pathogenic variants in the *LAMB3* gene, which encodes a subunit of the protein laminin 332, a component of the dermal-epidermal junction, are among the notable mutations causing JEB. Cutaneous findings of the JEB severe subtype include large areas of blistering skin with friable granulation tissue, especially around mucous membranes. Other findings include failure to thrive, poor wound healing, and recurrent infections. Mucosal involvement of the upper respiratory tract is also common, and accumulation of granulation tissue around the airway can lead to respiratory distress.[3] Treatment is usually focused on palliative care and given the rarity, alternate treatment strategies such as gene therapy are not well established. Consequently, survival is limited and mean life span of patients with JEB due to a *LAMB3* mutation has been reported

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at 10.8 months in one study.[2] Less well documented is JEB-associated lung pathology; we report three patients with JEB due to a *LAMB3* mutation involving extensive airway and lung injury.

2. Cases:

2.1. Patient 1:

Patient 1 was a 41-week gestation male, evaluated in the NICU on day of life two, noted to have abrasions on the left elbow and multiple bullae and erosions on the face that had been present since birth. He was discharged and subsequently diagnosed with generalized severe JEB due to *LAMB3* mutation (Table 1).

Notable medical history over the next 5 months of life included frequent blistering at sites of friction or minor trauma, gastroesophageal reflux, glottic stenosis, hoarseness, and chronic respiratory stridor. At approximately 6 months of age, he presented with an episode of acute respiratory distress that continued to worsen. Microlaryngoscopy and bronchoscopy showed exophytic lesions of the posterior true vocal cords and glottis, with narrowing of the glottic inlet. Based on the severity of lesions and refractory respiratory distress, a tracheostomy was placed. He was slow to wean off ventilatory support, and despite successful transition to CPAP at postoperative day 10 and focus on lung-protective ventilation to minimize barotrauma, he subsequently had progressive hypoxemic hypercapnic respiratory failure, requiring escalating ventilatory support. After several weeks of positive pressure ventilation, he developed recurrent pneumothoraces. Chest radiograph and chest CT demonstrated diffuse parenchymal disease with cystic lesions and blebbing (Figures 1, 2 A, B). At 7 months of age, the decision was made to withdraw support given the level of disease and associated complications.

Respiratory system pathology on autopsy demonstrated denudation of the bronchial epithelium with reactive changes, reactive pneumocytes as well as dilatation and ulceration of airways, along with some organizing fibrosis. Airway and lung parenchyma were filled with mucin pools containing macrophages and neutrophils, and evidence of patchy pneumonia was seen. Subpleural foci of intra-alveolar thrombi were also noted.

2.2. Patient 2:

Patient 2 was a 39-week gestation female admitted to the NICU on day of life two with intermittent stridor and skin denudation on bilateral fingers. She was discharged within one week and diagnosed with generalized severe JEB due to a *LAMB3* pathogenic variant.

She re-presented at 1.5 months of age with increasingly labored breathing. Her medical history included noisy breathing, cough, and blood-tinged saliva. During her hospital stay, hypovolemia, ulceration of the supraglottis, and blunting of the vocal cords were noted. She required intubation and mechanical ventilation for 7 days. Approximately one week after extubation, her respiratory status acutely worsened with respiratory distress. She underwent microlaryngoscopy and bronchoscopy which showed inflammation, swelling, and edema of the larynx with inward collapse of the arytenoids and epiglottis as well as limited size of the glottis inlet leading to intubation. Chest radiograph while intubated demonstrated

mild increased opacities of the right upper lobe and left lung, consistent with subsegmental atelectasis.

At 3 months of age, she was transitioned to comfort care, given ongoing respiratory failure and JEB-associated complications, and expired shortly after a desaturation episode.

Respiratory system pathology on autopsy demonstrated extensive laryngo-tracheobronchial tree ulceration, acute and chronic inflammation, granulation tissue formation, and squamous metaplasia (Figure 3). The patient's lungs also showed increased alveolar macrophages, foci of alveolar fibrin deposition, hemosiderin pigment deposition as evidence for chronic bleeding, and dilated airspaces.

2.3. Patient 3:

Patient 3 was a full-term female noted on the first day of life to have moderate erosions of the periumbilical region, hands, and feet. She was subsequently discharged and diagnosed with generalized severe JEB due to a *LAMB3* mutation. She was admitted to the PICU at approximately 3 months of age for wheezing, and then again for an extended stay at approximately 4.5 months of age for respiratory distress with stridor and more extensive skin blistering. During the latter admission, chest CT showed no focal abnormalities. Flexible bronchoscopy demonstrated laryngomalacia, with endoscopic findings indicative of laryngeal scarring including the aryepiglottic folds and early supraglottic stenosis.

She then re-presented at 9 months of age due to respiratory distress and fever. She was admitted and intubated due to clinical evidence of sepsis. She was unable to achieve sustained respiratory improvement and therefore unable to be extubated. Her clinical status continued to decline as she suffered from repeated episodes of septic shock and significant bleeding. She was transferred to comfort care measures and expired at 12 months of age.

Respiratory system pathology on autopsy demonstrated denuded laryngeal mucosa that had been replaced by granulation tissue and fibrosis. The trachea also demonstrated denuded epithelium with chronic inflammation and mild fibrosis. The lung parenchyma showed areas of congestion, regions of intra-alveolar hemorrhage, and widening of the alveolar space. Additionally, the right lower lobe showed findings consistent with focal pneumonia.

3. Discussion:

While EB predominantly affects the squamous epithelium of the skin, it is well documented that blistering can occur on many mucosal surfaces such as those found in the oral cavity, pharynx, and less often in the larynx, trachea, and bronchi.[3] As described in all three of these cases, exacerbation of respiratory distress was associated with mucosal damage in one of these areas. Ventilation by endotracheal tube or tracheostomy may have contributed to additional mucosal trauma to our patients' already fragile airways; patients 1 and 3 were each dependent on ventilatory support for >4 weeks, and patient 2 for approximately 2 weeks. Given each patient's JEB diagnosis, efforts were made to avoid intubation and mechanical ventilation, but due to our patients' respiratory distress and decline, these supportive modalities were unavoidable.

In addition to these findings, all three patients had pathological findings in the lung parenchyma, either during life or on autopsy. Specifically, patient 1's chest CT demonstrated cystic lesions and blebbing of the lung parenchyma. Additionally, all three cases demonstrated dilatation of airways or alveoli as well as features of inflammation involving the lung parenchyma. While respiratory findings are often reported in JEB patients, findings of lung parenchyma pathology on chest CT and autopsy are more limited in the literature.

Laminin-332 is an important anchoring protein found in the dermal-epidermal zone. This protein consists of the α3, β3, and γ2 polypeptide chains that are encoded by the *LAMA3*, *LAMB3*, and *LAMC2* genes respectively.[2] Previous studies have shown that the laminin γ2 chain, which is unique to laminin 332, is localized to airway epithelial basement membranes. While knockout variants of the γ2 polypeptide chain did not show any defects in branching morphogenesis, as originally suspected, knockout models showed distal airspace dilation. Further studies additionally suggested that laminin 332 may contribute to injury/disease process response.[4] According to data from the Human Protein Atlas, LAMB3 protein expression has been recorded in goblet cells and human basal cells.[5] Given the role of basal cells in airway regeneration after injury, in the context of heightened response to a triggering barotrauma injury in JEB, it is plausible that mutated components of the laminin protein could reduce reparative capacity and thus contribute to progressive respiratory compromise. These cases illustrate the severe lower airway and parenchymal complications that can occur in JEB in addition to the more commonly recognized upper airway mucosal involvement. A multidisciplinary approach that includes families in respiratory management decisions is paramount, as prolonged ventilatory support in generalized severe JEB is generally not well tolerated and may lead to additional morbidity and mortality. Future studies should prioritize understanding the molecular pathology underlying lower airway and parenchymal involvement associated with JEB which may contribute to the development of therapies that help to avoid the barotrauma of ventilatory support, including gene therapy.

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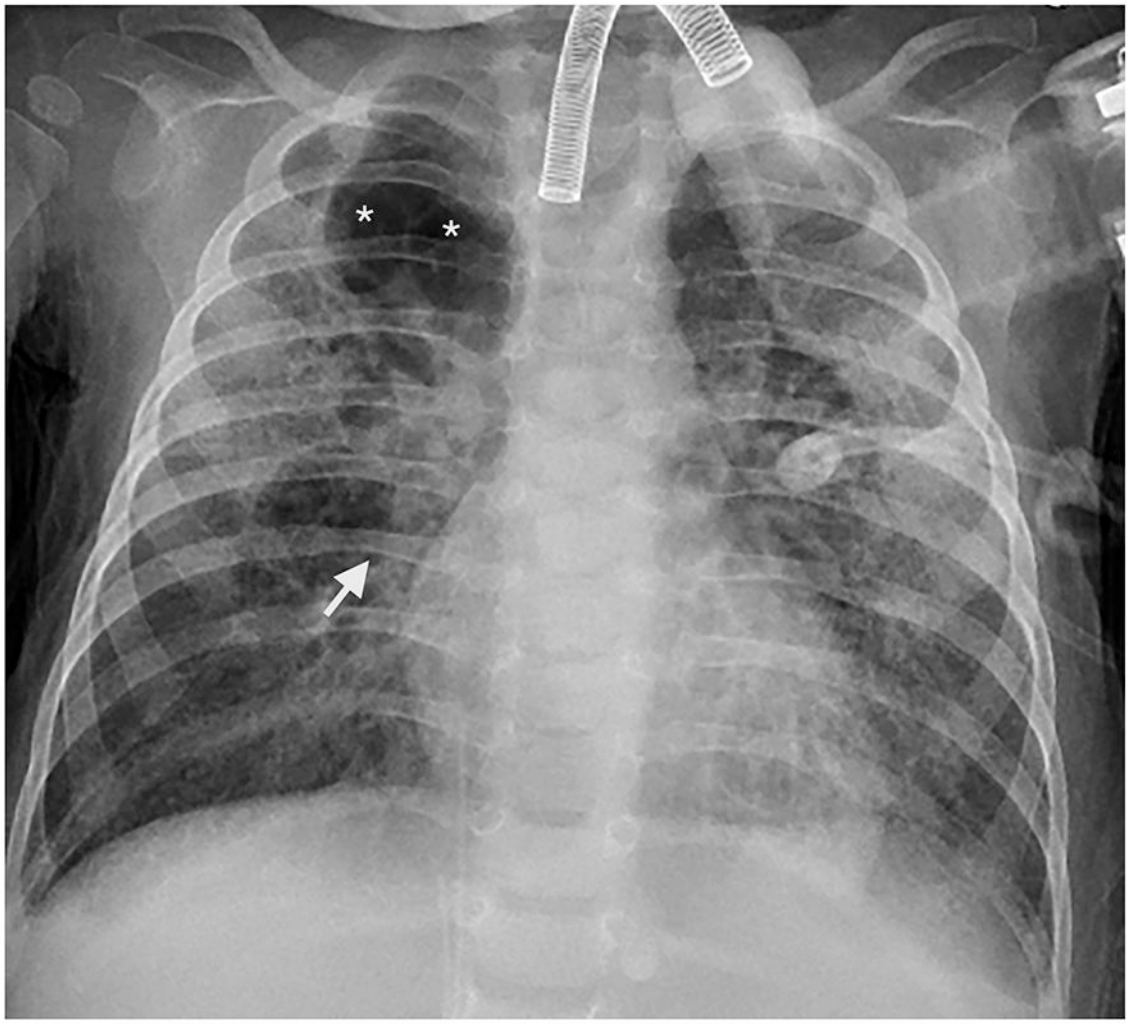

Figure 1.
Chest radiograph from Patient 1, one month after initial endotracheal intubation, demonstrates interval development of right sided large cystic lucencies (asterisks) along with bilateral, diffuse, hazy opacities and small perihilar locules of interstitial emphysema (arrow).

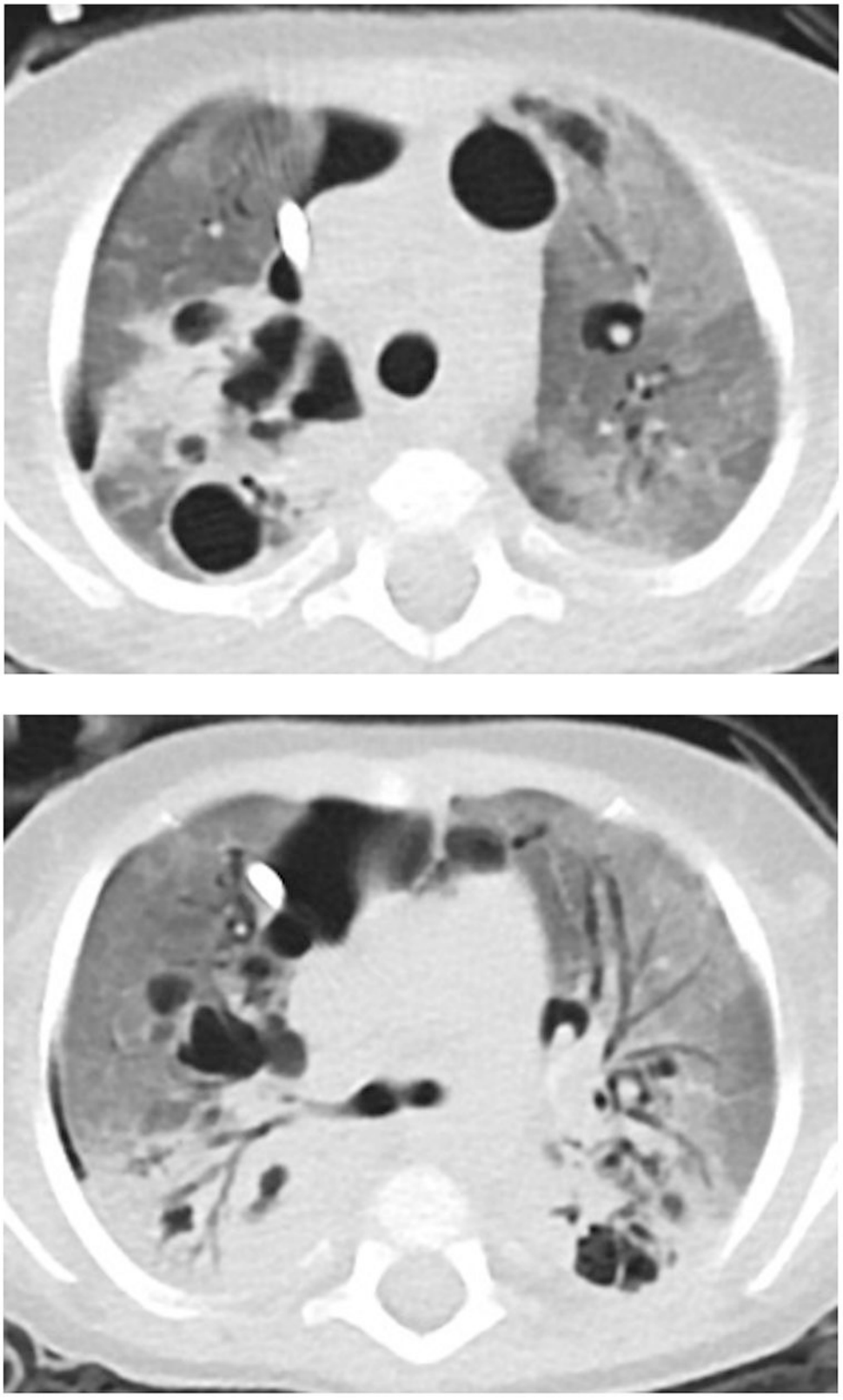

Figure 2.

Computed tomography (CT) axial image of the chest from Patient 1: **A)** at the level just above the carina and **B)** at the level of the carina. Images taken approximately one month after initial intubation. Findings include widespread, heterogeneous pulmonary ground glass opacity, extensive pulmonary interstitial emphysema, and multiple bilateral air-filled cystic spaces.

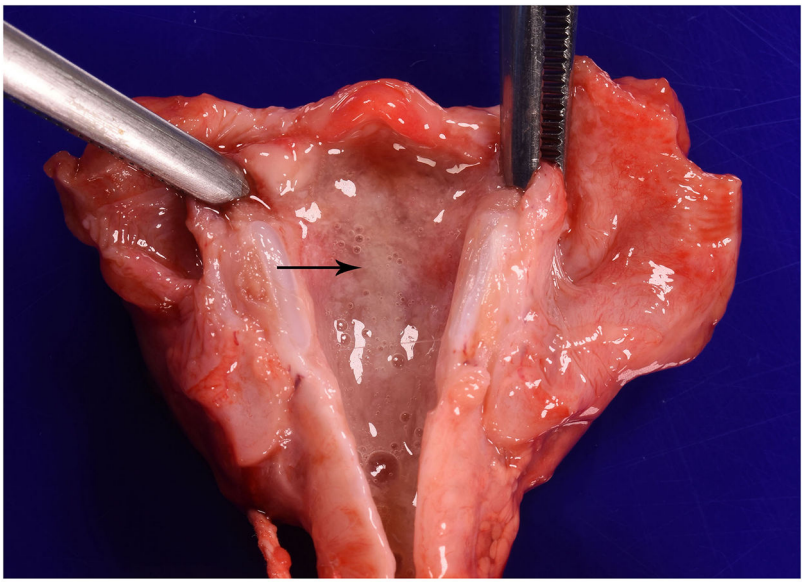

Figure 3.

Post-mortem examination of the opened larynx and upper trachea revealed copious amounts of intraluminal tan debris (black arrow), which was revealed later by microscopic exam to represent sloughed strips of mucosal epithelium admixed with inflammatory exudate.

Table 1:

Comparison of disease characteristics among the three reported cases

	Age at Respiratory Presentation	Age at Death	*LAMB3* Mutations	Notable Non-Pulmonary Complications
Patient 1	6 months	7 months	c.2288delG, c.2842delG	*Pseudomonas aeruginosa* (+ blood culture)
Patient 2	1.5 months	3 months	c.958_1034dup77, c.958_1034dup77	*Serratia marcescens (*+ respiratory culture), *Pseudomonas aeruginosa (+ wound cultures)*
Patient 3	9 months	12 months	c.1903C>T, c.958_1034dup77	*Pseudomonas aeruginosa* (+ respiratory and skin cultures), rhinovirus (+viral tracheal aspirate)