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Postmortem Identification of Vascular Ehlers-Danlos Syndrome in a Lung Transplant Recipient

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Ehlers-Danlos syndrome (EDS) is a group of rare genetic disorders that occur because of abnormalities in collagen and extracellular matrix. The vascular subtype of EDS (vEDS) is an autosomal dominant disorder characterized clinically by arterial dissections, spontaneous intestinal perforations, and spontaneous pneumothoraces.[1] We present a unique case of postmortem identification of vEDS in a 60-y-old female after bilateral sequential lung transplantation.

CASE DESCRIPTION

A 60-y-old woman with a 35-pack-year smoking history underwent bilateral sequential lung transplantation for Global Initiative for Chronic Obstructive Lung Disease stage IV chronic obstructive pulmonary disease. She had a history of several uncomplicated surgeries early in her life, including a thyroidectomy, colostomy placement, and subsequent reversal for bowel perforation. However, her transplant surgery was complicated intraoperatively. The initial observation by the transplant surgeon upon implantation of the donor lungs was evidence of extremely friable recipient tissues and vascular structures with resultant profuse bleeding. The pulmonary artery was noted to be extremely thin walled, requiring placement of the patient on venoarterial extracorporeal membrane oxygenation (ECMO) from venovenous ECMO (VV-ECMO) during implantation of the transplanted lung. Further difficulty was encountered with the recipient tissues while securing the left atrial anastomosis. This necessitated the conversion to cardiopulmonary bypass with fibrillatory arrest. At the conclusion of the surgery, continued oozing and coagulopathy ensued, and the patient's chest was left open. She was returned to the intensive care unit with plans for delayed chest closure. Despite the intraoperative complications, the graft function was excellent, with mild primary graft dysfunction (score of 1 at time 0). The chest was closed on postoperative day 1 and the patient was extubated 48 h later to high flow nasal cannula (FiO_2 50%) and slowly weaned to 4 L of supplemental oxygen therapy.

Unfortunately, 3 d after extubation, she developed hypoxic respiratory failure and required intubation. The intubation was uncomplicated, with adequate visualization of placement of the endotracheal tube. However, a significant air leak was noted in one of the chest tubes after intubation, and emergent bronchoscopy was performed, revealing a large posterior tracheal wall tear (Figure 1A). Subsequent computed tomography (CT) of the chest demonstrated a large tracheal diverticulum in the posterior membrane of the trachea (Figure 1B, C). To prevent further tracheal injury, the patient was extubated the following day to nasal cannula with efforts to continue with gentle pulmonary hygiene. However, she decompensated further and was placed on VV-ECMO without pursuing intubation and mechanical ventilation for acute hypoxic and hypercapnic respiratory failure. Despite manipulation of VV-ECMO settings and cannula repositioning, the patient's respiratory parameters did not improve and fiberoptic endotracheal intubation was necessary. Postintubation, the patient became hemodynamically unstable with a precipitous acute drop in hemoglobin, requiring resuscitation with blood products. A CT of the abdomen revealed a massive

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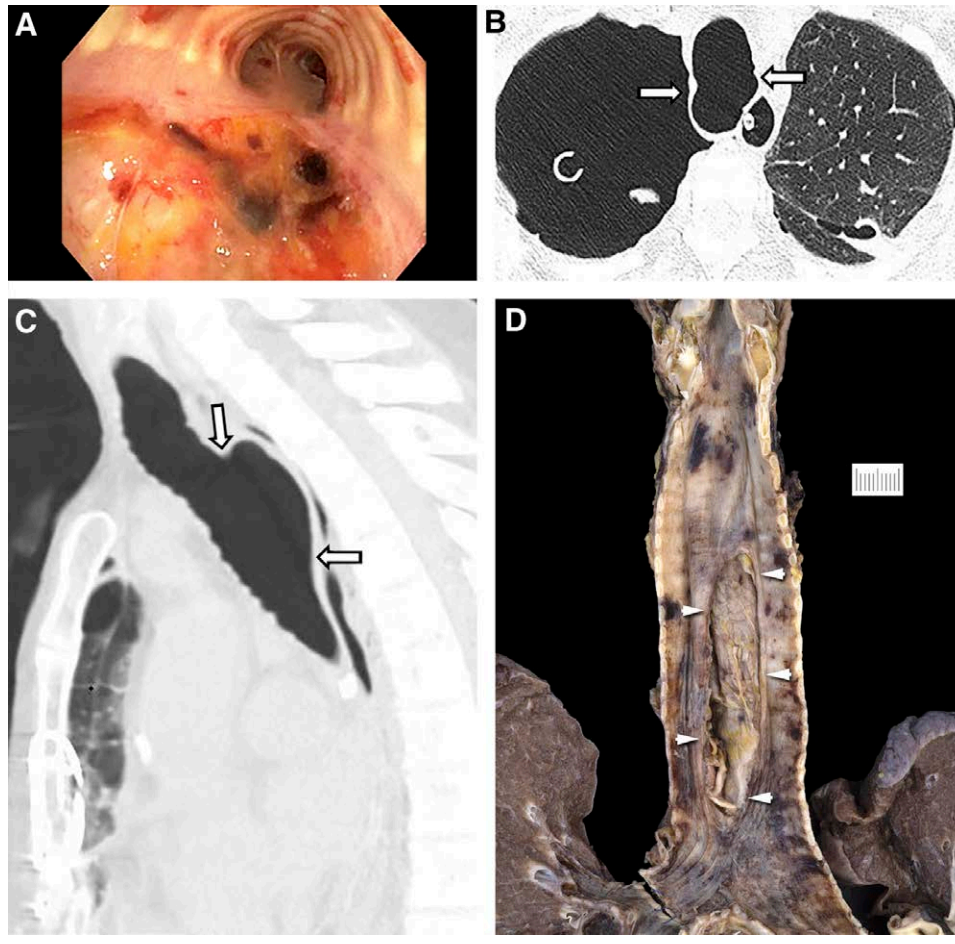

FIGURE 1. A, Bronchoscopy image demonstrating diverticulum in the posterior (membranous) wall of the trachea. B and C, Post–lung transplant axial and coronal HRCT demonstrate a wide-based diverticulum or outpouching of the posterior (membranous) wall of the intrathoracic trachea measuring 47 × 22 × 21 mm in maximal craniocaudal, anteroposterior, and transverse dimensions (between the white arrows). D, The trachea on autopsy is opened anteriorly to demonstrate the tear in the posterior (membranous) wall of the trachea (indicated by the white arrows). The adventitia of the esophagus is visible underneath the tear. HRCT, high-resolution computed tomography.

hemoperitoneum and retroperitoneal bleeding. An emergent exploratory laparotomy was performed, revealing no major vascular injury but profuse bleeding from all raw surfaces of the peritoneum and retroperitoneum. While packing the abdomen, a capsular tear was noted in the spleen, and a splenectomy was performed. Despite aggressive measures to control the bleeding and volume resuscitation, the patient had a cardiac arrest and cardiopulmonary resuscitation was initiated. Further bleeding was noted in the chest cavity because of a right ventricular tear needing an emergency pericardial patch repair. She was also noted to have ongoing abdominal bleeding and was found to have a liver laceration. Severe coagulopathy, hemorrhagic, and cardiogenic shock ensued, which led to bowel ischemia. The patient expired in the operating room because of profound shock. An autopsy was granted by the next of kin.

On postmortem examination, the body was thin. Facial features were notable for bluish sclerae, thin nose, thin lips, and gingival recession. The connective tissue and skeletal muscles were extremely friable and easily torn with blunt dissection. There were no chest wall abnormalities, but the chest wall musculature and diaphragm were thin. A right ventricular outflow tract myocardial rupture with an intact pericardial patch, tracheal rupture (Figure 1D), and liver lacerations were present. Additionally, chronic dissections of the right and left renal arteries were found with severe left renal artery stenosis that led to left renal atrophy. Given the findings of extreme tissue fragility, an antemortem blood sample was sent for genetic testing with family consent, which revealed a likely pathogenic variant in the *COL3A1* gene, [COL3A1 c.1826G>A (p.Gly609Glu)], consistent with a diagnosis of vEDS.

DISCUSSION

This case highlights a rare presentation of vEDS in a patient with no prior history of intraoperative complications, poor wound healing, joint hypermobility, or spontaneous pneumothoraces.

EDS is a spectrum of rare genetic disorders with several different inheritance patterns and is characterized by defective synthesis or processing of collagen or extracellular matrix. The vascular subtype of EDS (vEDS) is an autosomal dominant disorder that occurs because of defective processing of type III procollagen and leads primarily to vascular complications such as arterial dissection (iliac, aortic, renal, mesenteric) and visceral rupture (including intestinal perforation and uterine rupture in gravid females).[1-3] Although our patient had a history of intestinal perforation, she underwent a colostomy and revision with no wound-healing issues and

also other operations in her 20s and 30s without notable complications.

vEDS is potentially the most life-threatening of the EDS with a median age of survival of 48 y.[2] The true prevalence of vEDS is unknown because of the underdiagnosis of the milder forms of the disease and is estimated to lie between 1 in 50 000 and 1 in 200 000.[4]

The phenotypic features that may be found in vEDS patients include large prominent eyes, thin translucent skin with increased venous visibility, thin lips, a narrow nose, and a wide forehead.[1] Our patient had similar phenotypic features but no history of wound healing or frail tissues from any previous surgeries. After her passing, focused interviewing of her family members by a genetic counselor revealed that she had experienced a lifelong history of easy bruising, gingival fragility, which led to her requiring dentures at the age of 34, severe varicose veins requiring stripping surgery in her 40s, and hypermobile thumbs, which are other features that have been described in vEDS.[1]

A recent case series examined 136 patients with vEDS who had CT chest performed, demonstrating pulmonary abnormalities in 78 patients (57.4%), with the most commonly identified abnormality being emphysema.[5] Other abnormalities included linear opacities, clustered micronodules, and cavitating nodules.

Examination of the explanted lungs, in this case, revealed severe emphysema but was not suspicious for possible uncommon causes of emphysema (Figure 2). In particular, there were no excess hemosiderin-laden macrophages, organized hematomas, fibrous nodules, or pleural fibrosis as previously described in a series of vEDS patients.[6] This is in keeping with the absent history of hemoptysis or hemothorax in our patient.

Upper airway manifestations of EDS include dysphonia, airway collapse, and obstruction.[7,8] Our patient had a history of fluctuating hoarseness and developed a tracheal tear in the membranous portion after straightforward intubation. Tracheal rupture after a straightforward single-attempt intubation, in this case, was attributed to vEDS. We were unable to identify any other contributing factors, such as multiple forceful attempts, cuff hyperinflation, improper endotracheal tube size, or positioning. Based on a review article, although the tracheal cartilage is composed of type II collagen, which is not typically involved in EDS, there have been reports of tracheobronchomalacia in patients with EDS.[7,8]

In regard to lung transplant and vEDS, there has been only 1 other case described in the literature. Saez et al[3] described a case of a 29-y-old female with emphysema and vEDS who underwent successful bilateral lung transplantation despite her intraoperative course being complicated by severe coagulopathy, bleeding, and friable tissues. In this patient's case, the history

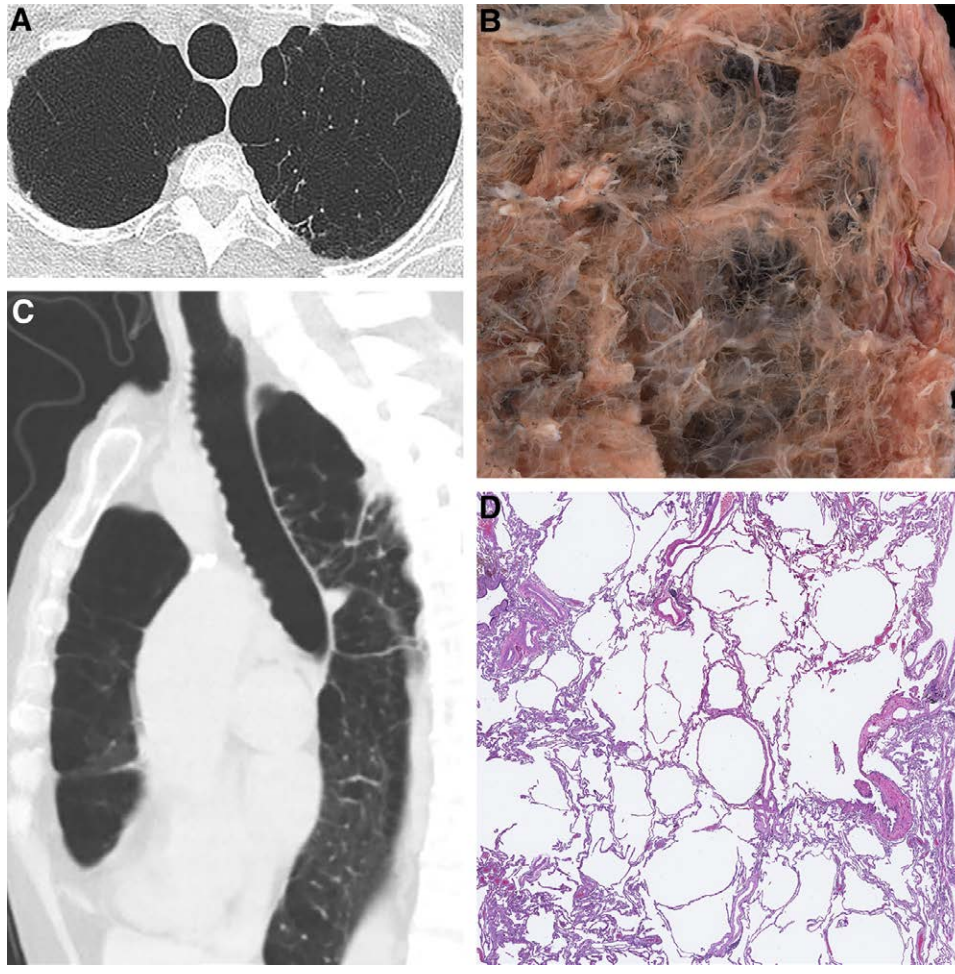

FIGURE 2. A and C, Pre–lung transplant axial and coronal HRCT demonstrating normal caliber trachea and emphysematous changes in lung parenchyma. B and D, Gross pathology and histopathology of the explanted lung demonstrating severe emphysematous changes. HRCT, high-resolution computed tomography.

of vEDS was known before surgery, which led to preparedness among surgeons while handling her tissues intraoperatively and optimum management of her coagulopathy. Additionally, her surgery was performed under cardiopulmonary bypass from the beginning. Despite a protracted hospitalization, she was eventually discharged home with good lung function.

In summary, we presented a case of vEDS with emphysema who underwent sequential bilateral lung transplantation and later succumbed to retroperitoneal bleeding complicated by multiple organ rupture. Because of its rarity and heterogenous clinical manifestations, the diagnosis of vEDS is often missed before a catastrophic event occurs. However, it is important to establish the diagnosis postmortem by genetic testing because of the need for screening, surveillance, and management of affected family members.

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