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Diagnosis of Ehlers-Danlos Syndrome in an Adolescent Who Presents with Recurrent Pneumothoraces and Hemoptysis

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Abstract

This is a case report describing a 17-year-old, non-smoker, adolescent male with a history of asthma who was initially evaluated for chronic cough, dyspnea, hemoptysis, and recurrent pneumothoraces requiring multiple chest tube placements and eventually was diagnosed with vascular Ehlers-Danlos Syndrome (EDS) via genetic testing. It is challenging to establish a diagnosis, especially in pediatric patients who do not have a known family history of vascular EDS. This case report emphasizes the importance of high clinical suspicion to make an early diagnosis to inform the patient and family of the prognosis of this condition and to coordinate the specialty care for future management.

Keywords: Vascular Ehlers-Danlos Syndrome; Adolescent; Pneumothorax; Hemoptysis; Hereditary disease; COL3A1 gene

Abbreviation: EDS- Ehlers-Danlos Syndrome; CT- Computed tomography

Introduction

Ehlers-Danlos Syndrome (EDS) is a heterogeneous group of rare hereditary connective tissue disorders characterized by clinical signs such as skin hyperextensibility, joint hypermobility, or tissue fragility. Vascular EDS is one of the subtypes of EDS [1]. The diagnosis is confirmed by genetic testing or biochemical analysis identifying pathogenic variants of the COL3A1 gene which encodes the pro-alpha 1 chain of type III procollagen. Abnormal synthesis of type III collagen leads to arterial, intestinal, or uterine fragilities. Vascular EDS is a rare genetic disorder with an estimated prevalence of 1:50,000-1:200,000. However, recognizing this condition is crucial as its complications can be life-threatening. Some of the major ones include arterial dissection, arterial aneurysm, arterial rupture, intestinal rupture, or uterine rupture during pregnancy. Pneumothorax or hemothorax is often associated with vascular EDS, but those are not part of the major diagnostic features [2]. Most individuals present with arterial or intestinal complications, and more than half of the pediatric patients who are diagnosed with vascular EDS before the age of 18 are identified due to their known family history [3,4]. This article describes an atypical case of a pediatric patient who presented with associated pulmonary involvements but without a known family history of vascular EDS or symptoms that are highly indicative of the connective tissue disorder.

Case Presentation

Case Presentation: This is a 17-year-old, non-smoker, adolescent male with a history of intermittent asthma, otherwise previously healthy, who was

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initially evaluated for chronic cough, dyspnea, and hemoptysis that had progressively worsened over six months. His primary pediatrician obtained a chest x-ray, and he had a left-sided pneumothorax, which required chest tube placement in the local hospital emergency department. A CT scan of the chest was performed and showed bilateral consolidation with mild calcification and a cavitary mass within his left upper lobe with a mural nodule (Figure 1).

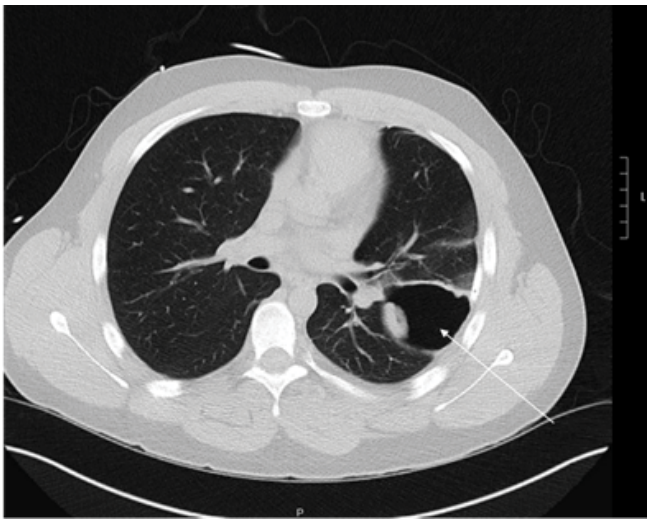

Figure 1: Chest CT scan without contrast: Cavity mass within the left upper lobe with a mural module.

After his recovery from the chest tube placement, he was discharged home with outpatient referrals to thoracic surgery and pediatric pulmonology. Within two months, he developed recurrent pneumothoraces on the bilateral sides of his lungs (Figure 2). He was admitted again and treated with bilateral chest tube placements. During this admission, a thoracic surgery team was involved given the recurrence of pneumothorax. They recommended video-assisted thoracoscopic surgery and pleurodesis in the outpatient setting. However, the patient subsequently returned to the emergency department after this last admission due to his persistent hemoptysis and dyspnea. This time, CT angiography excluded the diagnosis of pulmonary embolism as an underlying cause, but the scan did show new development of multiple pulmonary nodules with cavitary lesions and atelectatic change at the bases of the lungs.

Eventually, the patient's outpatient pediatric pulmonary team admitted him for a comprehensive evaluation and workup for broad differential diagnoses. Initial blood labs were unremarkable with normal inflammatory markers including white blood cell counts, C-reactive protein level, and erythrocyte sediment rate. Venous blood gas, hemoglobin level, coagulation studies, and d-dimer were also grossly within normal range.

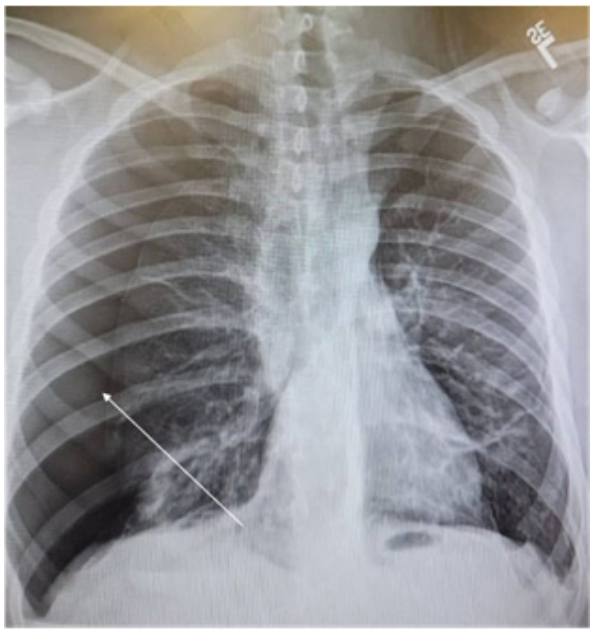

Figure 2: Chest Xray: Pneoumothorax on the right side

To rule out bleeding from his upper airway, otorhinolaryngology performed a flexible laryngoscopy which showed normal anatomy and did not demonstrate any evidence of underlying upper airway etiology.

There was a low clinical suspicion for systemic or respiratory infection given the chronic nature of the symptoms and unremarkable clinical findings i.e. afebrile, normal oxygen saturation, and normal inflammatory markers. Nonetheless, suspected infectious etiologies such as tuberculosis, nontuberculous mycobacterial infection, and fungal infection could not be completely ruled out due to radiological findings on CT scans (cavitary lesions, multiple pulmonary nodules, consolidations). The interventional pulmonary team proceeded with a diagnostic bronchoscopy that revealed bloody secretions in the right upper lobe and bronchus intermedius and a cavitary lesion in the right lower lobe. The bronchoalveolar lavage demonstrated numerous hemosiderin-laden macrophages and inflammatory cells, and the transbronchial biopsy of the right lower lobe nodule did not show malignant cells. Bronchoalveolar lavage culture did not grow any organisms. Other infectious workups including blood bacterial culture, fungal culture, and Acid Fast Bacillus smear with culture were all negative for growth.

On admission, the patient's family history was notable for recurrent spontaneous pneumothorax and bowel perforation in his maternal side of the family. His significant family history and initial presentation at a young age raised suspicion of genetic connective tissue disease. After collecting the blood sample for the genetic panel, he was discharged home with outpatient follow-up appointments. Afterward, genetic sequencing analysis revealed a heterozygous pathogenic

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variant in the COL3A1 gene (c.3338G>A, p.Gly1113Asp), which led to the final diagnosis of vascular EDS.

Discussion

Identification of the pathogenic variants of the COL3A1 gene through genetic testing confirms the diagnosis of vascular EDS cases and distinguishes this condition from other hereditary connective disorders. Our patient's genetic variant is a missense mutation, one of the known pathogenic variants that substitutes glycine for aspartic acid. It results in abnormal synthesis or mobility of type III collagen chains that leads to increased post-translational modification, which consequently causes vascular or tissue fragilities [5]. Most individuals present with vascular or intestinal complications at the time of testing. Per Shalhub et al., spontaneous pneumothorax and hemothorax frequently precede arterial and intestinal ruptures. Pneumothorax or hemothorax is one of the clinical manifestations associated with the vascular subtype of EDS [6]. However, the differential diagnosis for pneumothorax or hemothorax is broad. Hence, establishing a diagnosis of vascular EDS in atypical cases can be challenging for a clinician, given the rare nature of the disease.

The significance of this case was that the patient was an adolescent, a 17-year-old male, who did not have an established family history of vascular EDS and presented with only nonspecific respiratory symptoms. The majority of the patients present for the first evaluation after experiencing one of the associated complications which are not common in children. In the study done by Pepin et al., 25% of the index patients experienced their first complications by the age of 20 years [7,8]. Therefore, it requires a high clinical suspicion to deduce a diagnosis of vascular EDS on the initial presentation, especially in index patients without suggestive physical findings. However, as discussed earlier, vascular EDS may result in pulmonary or vascular complications that can be fatal and have a significant impact on the patient's quality of life. Our patient was evaluated by numerous specialty providers with different tests to reach the final diagnosis [9]. He was instructed to be routinely evaluated by vascular surgery and cardiology teams for frequent surveillance including non-invasive imaging and blood pressure monitoring. Especially in a pediatric population, it is important to make a diagnosis early on to arrange and establish care with specialists for screenings or surveillance of the complications [10]. Educating the family on the prognosis and providing guidance on future plans such as surgery or pregnancy are crucial parts of the management. Timely diagnosis with judicious workup may reduce the mental or emotional burden of the patient and their family.

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Conflicts of Interest: The authors do not have potential conflicts of interest with any companies or organizations whose products or services may be mentioned in this article.

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