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Acute Respiratory Failure Secondary to Persistent Lobar Atelectasis in Ehlers-Danlos Syndrome Patient and the Role of Connective Tissue Disease in Altering the Mechanical Properties of the Lungs

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Abstract Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective-tissue disorders characterized by joint hypermobility, cutaneous fragility, and hyperextensibility. The collagen defect has been identified in at least six of the many types of Ehlers-Danlos syndrome. Changes in the mechanical properties of the bronchial airways and lung parenchyma may trigger the observed increased tendency of the airways to collapse and lung atelectasis. This is a case of a 33 year old Caucasian female who presented with acute hypoxic respiratory failure secondary to persistent right lower lobe atelectasis despite optimal medical management, pulmonary toilet, and multiple bronchoscopies. She also had an incidental finding of lung arteriovenous malformation (AVM) which can occur in EDS patients.

Keywords: *Ehlers-Danlos, atelectasis, respiratory failure, collapse, connective tissue, asthma, pneumothorax, arteriovenous malformation, hemoptysis*

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1. Introduction

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective-tissue disorders characterized by joint hypermobility, cutaneous fragility, and hyperextensibility. The collagen defect has been identified in at least six of the many types of Ehlers-Danlos syndrome [1,2,3]. In most types of EDS, the underlying pathophysiology involves inherited alterations in genes affecting the synthesis and processing of different forms of collagen, which are important in the structure of many tissues and organs, including the skin, ligaments, tendons, vasculature, skeleton, and eyes [3]. Multiple pulmonary complications in EDS have been reported in the medical literature including spontaneous pneumothoraces, recurrent pneumonia, recurrent sinusitis and tracheobronchiomegaly, in addition to abnormalities in lung function which mainly include raised gas transfer coefficient, and increased tendency of upper and lower airways to collapse [6,7].

2. Case Presentation

A 33 year old Caucasian female with a history of hepatitis C, bipolar disorder, hypertension, hypothyroidism, classical Ehlers-Danlos syndrome and reactive airway disease presented with worsening resting and exertional dyspnea of 2 days duration shortly after being discharged from hospital after a ventral hernia repair. Her dyspnea was associated with productive cough. She denied any fever, chills, wheezes, hemoptysis, chest pain, orthopnea or paroxysmal nocturnal dyspnea. She denied any previous cardiac diseases. Her surgical history was significant for hysterectomy, tubal ligation and ventral hernia repair. She denied current or past exposure to allergens, irritants, noxious gases or chemicals. She smokes 1 pack of cigarettes a day. Her medications include lithium, verapamil, metoprolol, budesonide inhaled, bupropion, citalopram, and montelukast. She had a recent outpatient pulmonary function test that showed FEV1 2.83 L, FEV1/FVC of 70%, and reversibility after administration of beta-2 agonist suggesting asthma hyper-reactive airway. The lung volumes showed mild hyperinflation and mild air trapping.

Upon presentation her blood pressure was 126/78 mmHg, heart rate 105 beat/minute, temperature of 97.6 F, respiratory rate of 20 breaths/minute, oxygen saturation of 93% on 3 L nasal oxygen. Cardiovascular examination revealed normal S1 and S2 with no added sounds or murmurs. Lung examination revealed decreased breath sound on right lower zone, rhonchi in the right middle zone and dullness to percussion in the right lower zone.

Abdominal examination revealed a clean recent ventral hernia repair surgical wound.

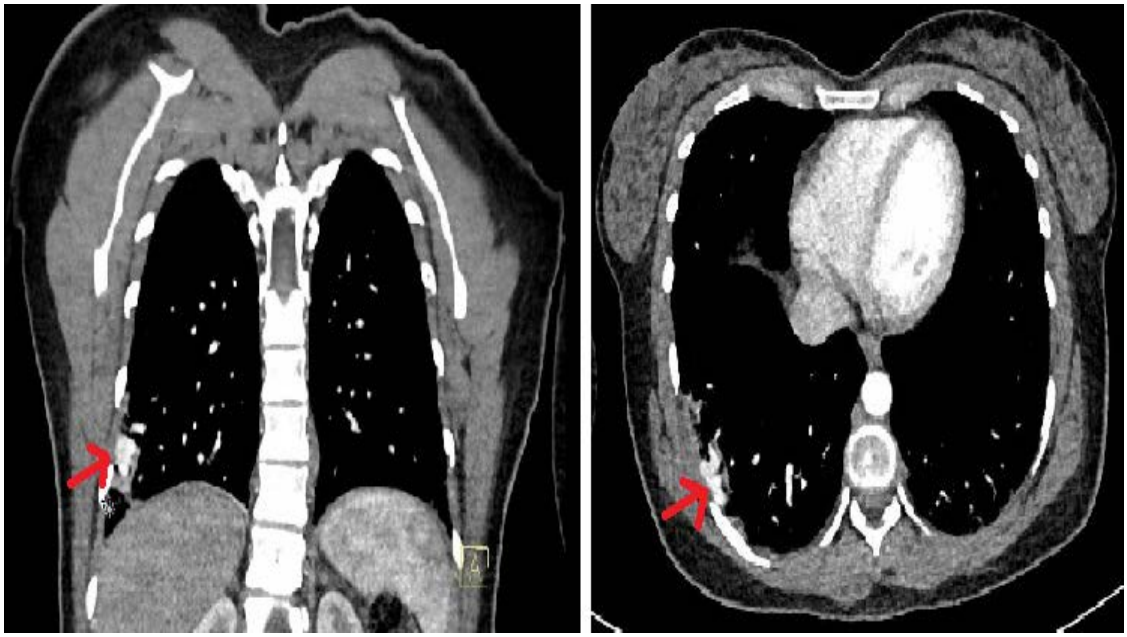

Figure 1. Chest CT, Right lower lobe AVM

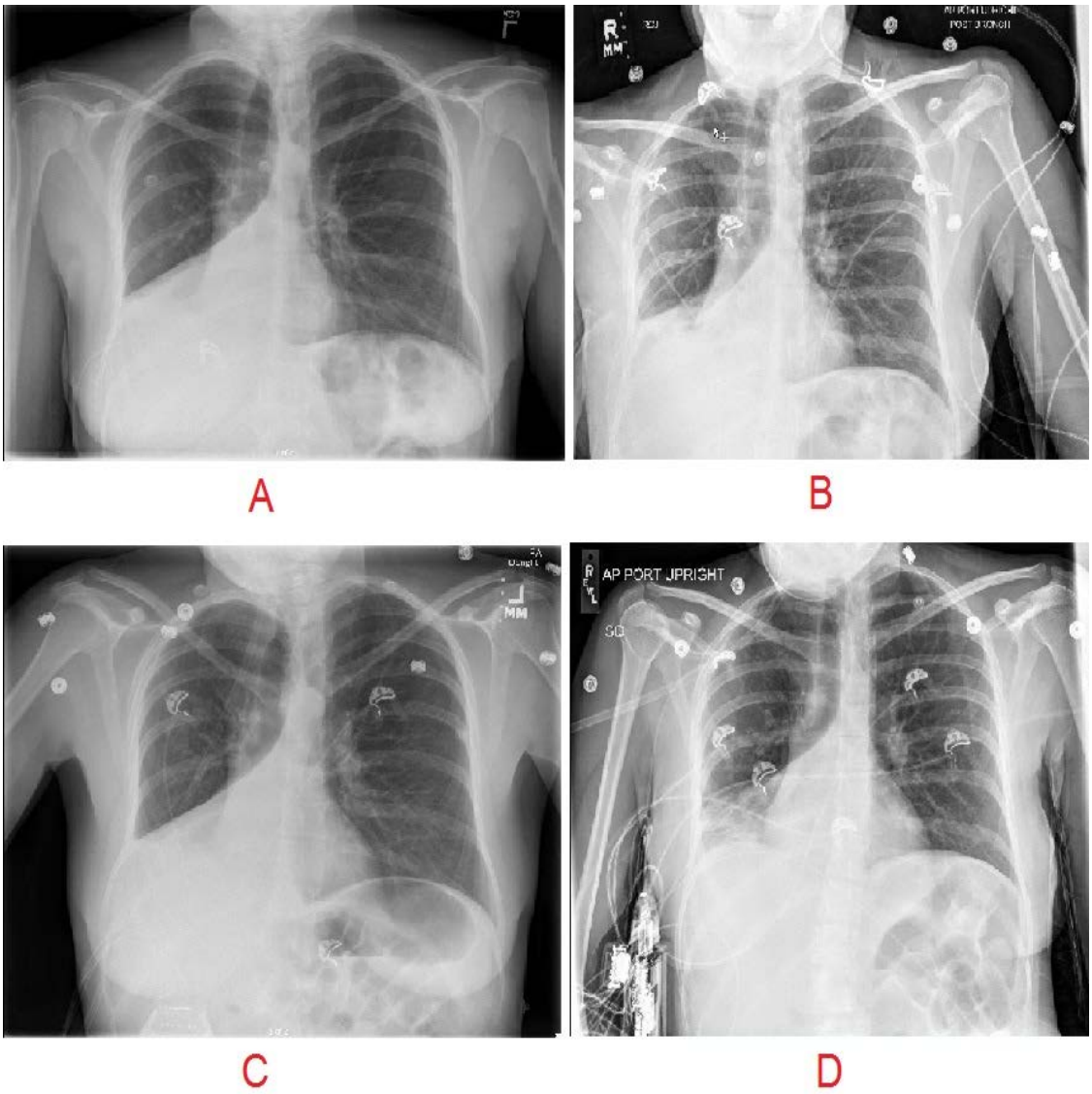

Figure 2. Chest X-rays Findings

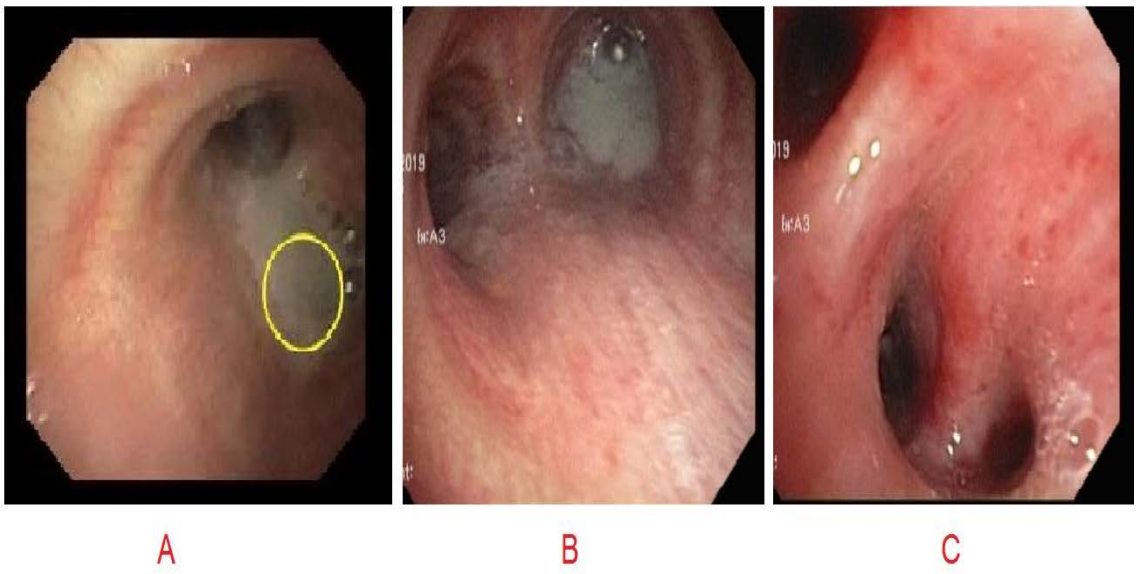

Figure 3. Bronchoscopies Findings

Later her oxygen requirements increased to 6 L via facemask and she desaturated to 70% with ambulation. Laboratory workup on admission showed normal complete blood count, normal basic metabolic profile, negative troponins, procalcitonin of 0.12 ng/mL. Chest computed tomography showed prominent serpiginous vascular structure within the peripheral right lower lobe with surrounding consolidative changes representing arteriovenous malformation (AVM) (Figure 1). Abdomen computed tomography revealed pneumoperitoneum due to recent surgery. Pneumonia work up including streptococcus urinary antigen, legionella urinary antigen, mycoplasma PCR, and respiratory viral panel were all negative. Blood cultures did not show any growth. Transthoracic ECHO revealed an ejection fraction of 55-60%, normal left ventricular systolic function and no valvular abnormalities. ECG didn't show any acute ST-T segments changes.

She was started on conservative management with oxygen therapy, pulmonary toilet, chest physiotherapy, bronchodilators and flutter valve but she had minimal symptoms relief. Patient continued to require 5-6 L of oxygen and desaturating quickly on ambulation. Repeat chest x-ray showed persistent atelectasis of the right lower lobe without improvement from 1 day previously, clear left lung, normal heart size and pulmonary vascularity (Figure 2: A). Decision was to proceed with the first bronchoscopy which showed right lung copious thick mucus plugging of the bronchus intermedius with normal underlying mucosa (Figure 3: A). Bronchial washings grew normal flora. Acid fast smear and culture were both negative. Fungal culture was negative.

The Patient continued to have significant resting and exertional shortness of breath after the procedure and repeat chest x-ray showed again persistent atelectasis of right lower lobe not significantly changed from prior study (Figure 2: B). The formal cardiology evaluation concluded that her dyspnea is of pulmonary origin.

The patient continued to require 5 to 6 L of oxygen and became more tachypneic despite all interventions, so repeat chest x-ray to follow clinical response was ordered and showed marked volume loss in right lower lung again (Figure 2: C).

Due to continued clinical deterioration; a second bronchoscopy was performed and showed mucus plugging of the right bronchus intermedius again with underlying inflamed mucosa (Figure 3: B & C). Bronchial samples were sent for the second time. Acid fast smear, fungal culture, respiratory viral panel, HSV and CMV PCR were all negative again, but this time the bacterial culture grew Haemophilus influenzae, so she was started on ceftriaxone. Repeat chest x-ray post the second bronchoscopy showed improved aeration of the right lung base and mild patchy air space disease (Figure 2: D). Her dyspnea improved slightly and her oxygen requirement decreased to 3 L via nasal cannula after the second bronchoscopy. However the next day her oxygen requirement increased again and her dyspnea got worse mainly on ambulation, so repeat chest x-ray was obtained and showed recurrence of the right lower lung field opacification suggesting lobar collapse. At this point Sniff test was ordered to evaluate the function of the diaphragm and it came back normal.

She continued to improve slowly over the next few days of her hospital stay and her oxygen requirements decreased down to 2 L via nasal cannula; so she was discharged home with oxygen therapy and close outpatient clinic follow up.

3. Discussion

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of inherited connective-tissue disorders characterized by joint hypermobility, cutaneous fragility, and hyperextensibility. The collagen defect has been identified in at least six of the many types of Ehlers-Danlos syndrome [1,2,3].

In most types of EDS, the underlying pathophysiology involves inherited alterations in genes affecting the synthesis and processing of different forms of collagen, which are important in the structure of many tissues and organs, including the skin, tendons, vasculature, ligaments, skeleton, and eyes [3].

Classical EDS is inherited as an autosomal dominant disorder. Mutations are found within the collagen genes

COL5A1 and COL5A2 in about 90 percent of patients who are diagnosed clinically. Type V collagen molecules, encoded by the genes in which the mutations reside, interact with type I collagen molecules during collagen fibrillogenesis [4,5]. Type I collagen is an integral component of the connective tissue, forming skin, tendons, ligaments, bones, and the aorta.

The diagnosis of Ehlers-Danlos syndrome should be suspected when a patient presents with joint hypermobility, multiple joint dislocations, poor wound healing, translucent skin, easy bruisability, and unusual scars. Also it should be suspected in case of a spontaneous rupture of an organ (eg, gut or uterus) or dissection of a major blood vessel.

Pulmonary complications in EDS include pneumothoraces, recurrent pneumonia, recurrent sinusitis, hemoptysis and arteriovenous malformations. Abnormalities of the lung function include raised gas transfer coefficient due to increased pulmonary blood volume or intrapulmonary hemorrhage; as the various collagen defects responsible for the different types of EDS may alter the permeability or distensibility of blood vessel walls. Other striking abnormalities include increase in lung volumes (Total Lung Volume, Vital Capacity, Residual Volume) [6,7].

Patients can also present with hemoptysis due to intrapulmonary hemorrhage or arteriovenous malformations, as it was incidentally discovered on imaging in this case [7]. (Figure 1)

Studies have shown increased prevalence of asthma in EDS population because the genes contributing to asthma and EDS may be in linkage disequilibrium and thus tend to be co-inherited [8]. Alternatively, one of the genes contributing to EDS may play a direct role in asthma pathogenesis. In this case, subtle modifications of matrix proteins may alter tissue biomechanics, repair and remodeling responses following epithelial damage, or in the binding of growth factors that may influence cellular functions and cytokine biological activities [9,10,11].

Changes in the mechanical properties of the bronchial airways and lung parenchyma may underlie the observed increased tendency of the airways to collapse and lung atelectasis [6,7]. Many individuals appeared to have alterations in the mechanical properties of their lungs, resulting in both increased distensibility and an increased tendency of the airways to collapse [6,7].

The increased tendency of the airways to collapse is believed to be caused by inadequate connective tissue support to the small airways by the lung parenchyma. Other alternative explanation could be secondary to gas trapping and emphysema.

Life threatening upper airway obstruction due to hypermobility of the suprahyoid suspensory soft tissues have been reported [12]. In a case series of 3 patients with EDS who had respiratory symptoms of shortness of breath, wheezing, cough, stridor, and abnormal voice that was exacerbated after recent elective surgery, respiratory infection, or trauma. It was found that these symptoms were due to arytenoid cartilage and upper airway collapse that occur during the respiratory cycle. This collapse was visualized with direct bronchoscopic airway examination and it was evident on pulmonary function testing. It occurs because of an increase in tissue distensibility with inadequate connective tissue support to the airways, leading to redundancy as a result of the connective tissue defect [13].

The presence of upper-airways collapse and coexistence of multiple defects in many individuals support that connective tissue defects in EDS alter the mechanical properties of the lungs, thus resulting in increased airway distensibility with an increased tendency to collapse [12,14].

This is a unique case that demonstrates multiple pulmonary complications that can be associated with EDS. All of these complications and associations have been described and reported sparsely in the medical literature.

i) The first is the increased prevalence of asthma among EDS population, which was shown on her pulmonary function test.
ii) The second is the increased prevalence of pulmonary arteriovenous malformations (AVMs), which was found incidentally on her chest tomography.
iii) The third is the increased tendency of airways to collapse and atelectasis, which was her main presentation.

Multiple factors may have been implicated in the patient's persistent right lower lobe atelectasis despite the optimal medical treatment, pulmonary toilet and multiple bronchoscopies. These include: recent surgery and anesthetics use, her history of asthma and mild air trapping, the Haemophilus influenzae infection that showed in her second bronchoscopy, and the increased tendency of her airways to collapse because of her connective tissue disease and its effect in altering the mechanical properties of the lungs.

4. Conclusion

This is a unique case that demonstrates multiple pulmonary complications that can be associated with Ehlers-Danlos syndrome. All of these complications and associations have been described and reported sparsely in the medical literature. The case will help to increase the awareness of physicians about the increased propensity for pulmonary complications in Ehlers-Danlos syndrome patients, mainly in the critical postoperative period.

Abbreviations

EDS: Ehlers-Danlos syndrome
COL5A1: Collagen alpha-1 (V) chain
COL5A2: Collagen alpha-2 (V) chain
AVM: Arteriovenous malformation.

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