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Ehlers–Danlos syndrome presenting as cystic lung disease with recurrent pneumothorax: a case report

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Cystic lung disease, differential diagnosis, Ehlers–Danlos syndrome, recurrent pneumothorax.

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Abstract

A 19-year-old male patient was referred to our hospital for recurrent pneumothorax. He previously experienced seven episodes of pneumothorax refractory to conventional treatment including pleurodesis and wedge resection. On admission, chest computed tomography scan showed multiple cystic lesions with surrounding ground-glass opacities and several nodules in both lungs. Detailed history revealed that the patient experienced haemoptysis whenever pneumothorax developed and had a family history of sudden death. Physical examination showed large eyes with conjunctival injection, hypermobile joints, and hyper-extensive and easily bruised skin. All these findings led to the suspicion of vascular Ehlers–Danlos syndrome (EDS). Genetic testing for the diagnosis of vascular EDS was performed and a heterozygous mutation in *COL3A1* gene, c.1662+1G>A (IVS23(+1) G>A), was confirmed. Clinicians should consider vascular EDS as the differential diagnosis of cystic lung disease with recurrent pneumothorax.

Introduction

Ehlers–Danlos syndrome (EDS) refers to a group of connective tissue disorders due to mutation in the genes involved in the structure and/or biosynthesis of collagen [1,2]. EDS is classified into 13 subtypes and is characterized by skin hyperextensibility, joint hypermobility, and generalized connective tissue fragility [2]. EDS type IV, also called vascular EDS, is the most severe form and arises as a result of a mutation in the type III collagen gene (*COL3A1*) [3]. Affected patients have extremely frail major vessel walls and hollow viscera and uterus, vulnerable to rupture leading to sudden death [1,4].

Herein, we describe the case of a 19-year-old male patient presenting with cystic lung disease with recurrent pneumothorax and haemoptysis, eventually diagnosed with vascular EDS.

Case Report

A 19-year-old male patient presenting with cystic lung disease with recurrent pneumothorax was referred to our pulmonology department. Eight months ago, the first pneumothorax of the right lung developed and was treated with closed thoracotomy at another hospital. Chest computed tomography (CT) revealed right-sided pneumothorax, multifocal ill-defined nodules in both lower lobes, and consolidation in the right upper lobe (RUL) (Fig. 1A). Six months ago, the right pneumothorax recurred, and he was re-treated with a closed thoracotomy. Five and half months ago, the right pneumothorax recurred again. Because of the repeated recurrence of pneumothorax, wedge resection of the RUL using video-assisted thoracoscopic surgery was performed. Five months ago, the right pneumothorax recurred and chest CT revealed a newly developed cystic lesion in the RUL, with suspected *Paragonimus westermani* infection (Fig. 1B). Percutaneous needle biopsy of the RUL nodular lesion was performed, and histopathological findings showed organizing pneumonia with no evidence of malignant tumours or infections such as *P. westermani*. One month ago, pneumothorax developed on the left side and was treated

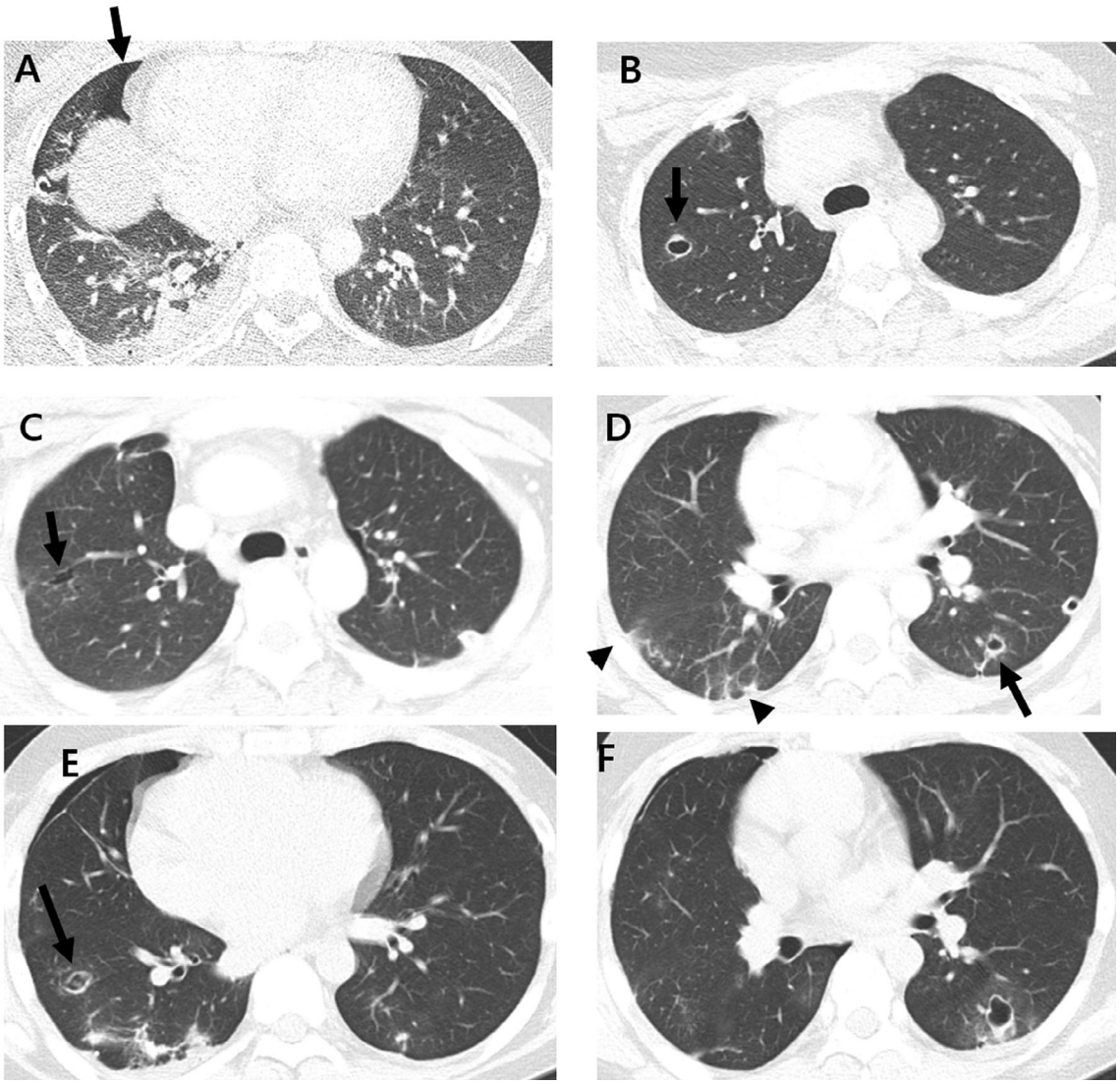

Figure 1. High-resolution chest computed tomography (CT) images. (A) Initial axial chest CT image shows right pneumothorax (arrow) with chest tube insertion and collapse and consolidation in the right lower lobe. (B) Three months after the initial chest CT, the patient had another episode of recurrent pneumothorax. Axial chest CT image shows newly appearing cystic lesion with eccentric wall thickening with surrounding ground-glass opacities in the right upper lobe (RUL, arrow). (C, D) Seven months after the initial chest CT, pneumothorax recurred in the left hemithorax. (C) Axial chest CT image shows improved state of the previously noted cystic lesion in the RUL with cicatricial emphysema (arrow). (D) Axial chest CT image also shows a new cavitary nodule in the left lower lobe and ill-defined subpleural consolidation and faint nodules with ground-glass opacities in the right lower lobe (triangles). (E, F) High-resolution chest CT images on admission. (E) Axial chest CT images show a newly developed cystic lesion with eccentric wall thickening and containing secretion in the right lower lobe (arrow). CT also shows consolidation and linear opacities in the right lower lobe and another ill-defined nodule with surrounding ground-glass opacities in the left lower lobe. A small right pneumothorax is demonstrated. (F) Axial chest CT shows increase in size of the previously noted cavitary nodule with internal fluid and surrounding ground-glass opacities in the left lower lobe. Right pneumothorax is also seen on CT.

with closed thoracotomy. Chest CT showed a new cavitary nodule in the left lower lobe and improvement of the previously shown cystic lesion in the RUL (Fig. 1C, D). Because of cystic lung disease with repeated pneumothorax, he was referred to our hospital for further diagnostic evaluation.

The patient was a non-smoker and complained of intermittent cough and blood-tinged sputum whenever pneumothorax developed. He was not on any medication and denied a history of infectious disease and travel abroad. Two years ago, he underwent ligament repair for right shoulder dislocation. He also had a history of easy bruising

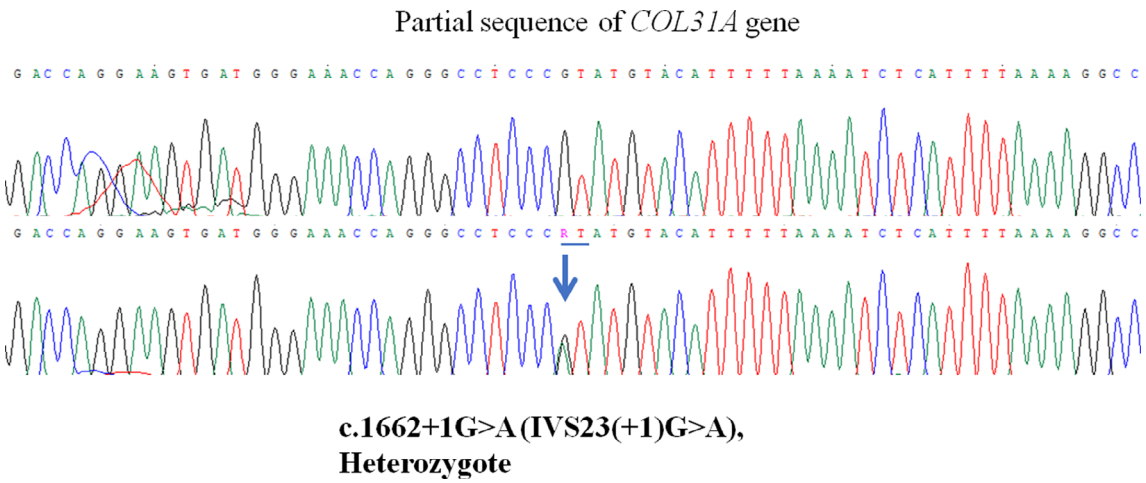

Figure 2. Partial sequences of the *COL3A1* gene; the patient carries a heterozygous splice-site mutation, c.1662+1G>A.

and a family history of sudden death, with his father dying of a brain haemorrhage. His father also had a history of surgery for an unexplained hepatic arterial rupture.

Physical examination revealed deep-set eyes with infraorbital creases, and the skin surface was thin with increased venous visibility. Chest auscultation was normal.

Laboratory tests showed white blood cell count 7000/μL (neutrophils 62.4%, lymphocytes 22.9%, and eosinophils 6.0%) and haemoglobin level 15.5 g/L. Chest CT revealed

Table 1. Diagnostic criteria for vascular EDS [2].

Diagnostic criteria for vascular EDS*
Major criteria
(1) Family history of EDS with a documented causative variant of the *COL3A1* gene
(2) Arterial rupture at a young age
(3) Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology
(4) Uterine rupture during the third trimester in the absence of previous caesarean section and/or severe peripartum perineal tears
(5) Carotid-cavernous sinus fistula formation in the absence of trauma
Minor criteria
(1) Bruising unrelated to identified trauma and/or in unusual sites, such as the cheeks and back
(2) Thin, translucent skin with increased venous visibility
(3) Characteristic facial appearance
(4) Spontaneous pneumothorax
(5) Acrogeria
(6) Talipes equinovarus
(7) Congenital hip dislocation
(8) Hypermobility of small joints
(9) Tendon and muscle rupture
(10) Keratoconus
(11) Gingival recession and gingival fragility
(12) Early onset varicose veins (younger than 30 years and nulliparous if female)

*Minimal criteria suggestive of vascular EDS: A family history of the disorder, arterial rupture or dissection in individuals less than 40 years of age, unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of other features consistent with vascular EDS should all lead to diagnostic studies to determine if the individual has vascular EDS. Testing for vascular EDS should also be considered in the presence of a combination of the other "minor" clinical features listed above.

EDS, Ehlers–Danlos syndrome.

right-sided pneumothorax and multiple cystic/cavitary lesions with surrounding ground-glass opacities and multiple ill-defined nodules in both lungs, suggesting vasculitis with haemorrhage, cystic lung disease, or *P. westermani* infection (Fig. 1E,F).

To differentiate Birt–Hogg–Dubé syndrome, an *FCLN* gene test was conducted, but no mutations were found. Serological tests for parasites, including *P. westermani*, were negative. The upper normal limit of the number of eosinophils and pulmonary infiltrates on chest CT suggested the possibility of Churg–Strauss syndrome. However, he had no other symptoms or signs suggesting vasculitis or asthma. All autoantibody tests were negative.

Considering all results including family history, the possibility of vascular EDS was strongly suggested. Therefore, a genetic test for vascular EDS was performed with a polymerase chain reaction-based sequencing analysis of the 51 exon and exon–intron boundaries of *COL3A1*. Heterozygosity was found for the previously reported splice-site variant, c.1662+1G>A (IVS23(+1) G>A), causing an aberrant splicing at the exon 23–intron 23 boundary of *COL3A1* (Fig. 2) [1]. Considering the fatal arterial complications of this disease, the patient was evaluated for vascular changes for the intracerebral artery, abdominal arteries, and thoracic arteries, and all arteries were normal. Currently, he is being monitored on an outpatient basis.

Discussion

Vascular EDS is characterized by thin skin that bruises easily and arterial complications (arterial aneurysms, dissection, or rupture), spontaneous intestinal perforation, and uterine rupture [5]. Vascular EDS was suspected due to the patient's history of recurrent pneumothorax, physical characteristics, and his father's sudden death.

The 2017 international classification of vascular EDS includes major and minor clinical criteria that suggested the diagnosis (Table 1) [2]. Our patient met four criteria: thin and translucent skin with increased venous visibility, spontaneous pneumothorax, characteristic facial appearance, and bruising unrelated to trauma. The diagnosis of vascular EDS is confirmed by demonstrating cultured fibroblasts that synthesize abnormal type III procollagen molecules or by identification of a mutation in the type III procollagen gene [1].

Consensus recommendations for the management of pneumothorax in vascular EDS have not been made. Although a conservative approach is recommended as much as possible, closed tube thoracotomy and pleurodesis can be performed if necessary, and it should be noted that lethal complications such as massive haemorrhages may occur in such cases. Surgical intervention should be avoided, except in life-threatening situations such as massive bleeding because of the risk of bleeding complications due to fragile tissue [5].

In conclusion, this case highlights the importance of detailed history-taking, physical examination, and clinical suspicion of vascular EDS when encountering recurrent pneumothorax cases refractory to conventional therapy.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Author Contribution Statement

Conceptualization: Jin Woo Song. Data curation: Min Jee Kim, Jooae Choe, Beom Hee Lee, Jin Woo Song. Writing—original draft: Min Jee Kim, Jin Woo Song. Writing—review and editing: Min Jee Kim, Jooae Choe, Beom Hee Lee, Jin Woo Song.

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