

## Ehlers-Danlos Syndrome with Recurrent Spontaneous Pneumothoraces and Cavitory Lesion on Chest X-ray as the Initial Complications

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### Abstract

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A 17-year-old-man developed left-sided pneumothorax in 1995. Chest computed tomography (CT) showed a thick-walled cavity in the left lower lobe. Video-assisted thoracic surgery was performed, and pathologic findings of the resected lung showed a cavity, organizing hematoma, and a fibrous nodule. Fragility of connective tissue was suspected, and biochemical and molecular analysis showed reduction of type III collagen production and point mutation of the *COL3A1* gene. The patient was diagnosed as having vascular-type Ehlers-Danlos syndrome (EDS). From 2002, the patient developed hemoptysis and bloody sputum once a year. Chest CT detected several nodules and cavities, which were regarded as hematomas with or without excretion. Several vascular changes including aneurysmal formations have been found since 2002, and an aneurysm of the left ulnar artery was resected. The patient continues to be followed regularly on an outpatient basis. We report a rare case of vascular-type EDS who developed pulmonary symptoms as an initial complication.

**Key words:** Ehlers-Danlos syndrome, vascular type, lung, pneumothorax

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### Introduction

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Ehlers-Danlos syndrome (EDS) is characterized by the clinical signs of skin hyperextensibility, joint hypermobility, and generalized connective tissue fragility. The frequency of this syndrome is reported to be 1 in 10,000 (1). It is known that vascular-type EDS (vEDS) has the worst prognosis. The frail walls of major vessels, the colon, and the pregnant uterus are all vulnerable to rupture, leading to sudden death in the third or fourth decade of life. Arterial tears are the most serious complication of vEDS, and the diagnosis is often made only after the occurrence of a catastrophic com-

plication or at postmortem examination.

Respiratory manifestations of vEDS, although not always common, have been described and include recurrent hemoptysis, bulla and bleb formation, and spontaneous pneumothoraces. We encountered a 17-year-old man with vEDS who presented in 1995 with a pneumothorax as the initial complication and whom we have been following since then. As the most frequent initial complication of vEDS is arterial dissection or rupture or colon rupture (2), this case is rare because the initial complication was limited to the lungs. Vascular complications did not occur until 7 years after the initial pulmonary manifestation. Although rare, vEDS patients can present at the hospital with pulmonary manifesta-

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tions as an initial complication without evident vascular or colon complications. We report on this patient's clinical course over the past 13 years and include the histologic findings from his lungs.

### Case Report

A 17-year-old man presented to our hospital in November 1995, with sudden onset of left anterior chest pain and dyspnea on effort. He was a high school student and had never smoked. He was not taking any medications, was not a drug abuser, and had no risk factors for HIV. His father and mother were healthy at 47 and 45 years of age, respectively, without vascular or skin disorders. His family had no relevant past medical history.

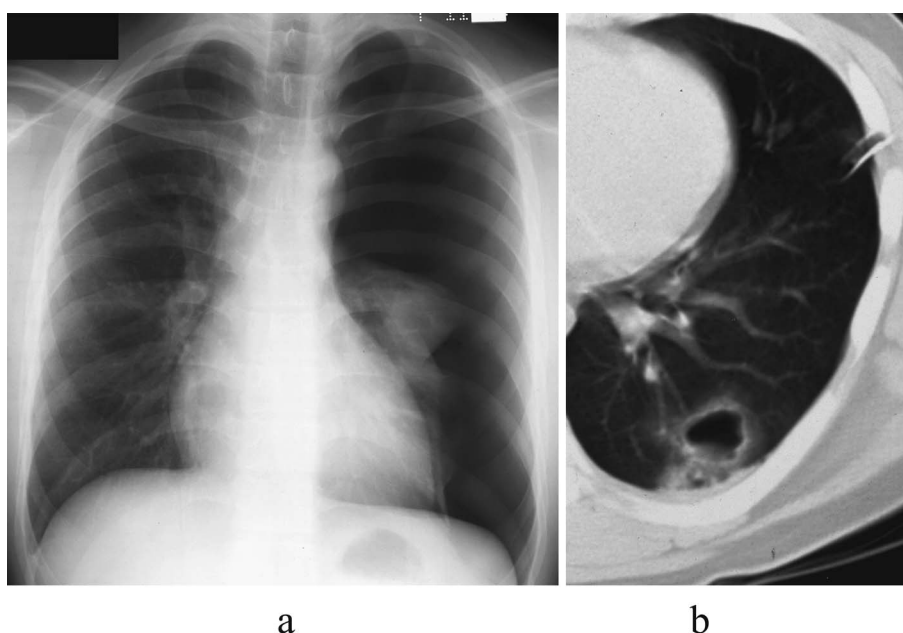
On admission, height was 171 cm, body weight 65 kg, body temperature 36.4°C, blood pressure 117/65 mmHg, heart rate 70 beats per minute, and respiratory rate 25 breaths per minute. Examination of the heart, abdomen, and neurologic system was normal. On chest examination, the patient had decreased air entry in the left lung field but no rales. His skin was found to be thin and translucent (Fig. 1). Characteristic facial appearance was not evident. The small joints of his extremities were slightly hyperextensive. A blood count revealed a white blood cell count of 8,500/ $\mu$ L, hemoglobin of 12.1 g/dL, and platelet count of 346,000/ $\mu$ L. Serum creatinine level was 0.7 mg/dL, and blood urea nitrogen level was 12.0 mg/dL. Liver-function tests, erythrocyte sedimentation rate, and C-reactive protein level were all within normal limits. Testing for HIV was negative. A chest X-ray revealed a left pneumothorax (Fig. 2a). A chest tube was inserted, and chest computed tomography (CT) showed

a left lower-lobe cavity (12×9 mm) surrounded by ground glass opacity (Fig. 2b). The cavity was resected via video-assisted thoracotomy. There were no evident complications including delayed healing during and after this thoracotomy, and no evident vascular changes were noted in his major vessels. After discharge, a right-sided pneumothorax developed in 1996 and was treated via thoracotomy. In 2002, the



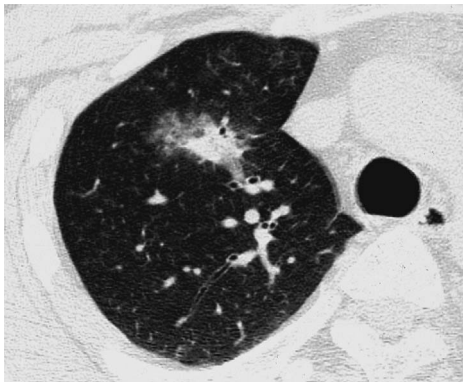
**Thin skin with visible veins**

**Figure 1.** Translucent skin. Skin examination showed thin and translucent skin.



**Figure 2.** Chest X-ray on admission and CT after chest tube insertion. a: Chest X-ray on admission showed nodules in the middle lung field of the right lung. b: Chest CT showed a thin-walled cavity in the left lower lobe.

patient developed bloody sputum, and chest CT revealed patchy consolidation in the right upper lobe (Fig. 3), which disappeared of its own accord. The patient also developed bloody sputum in 2003, and cavitory nodules in the right upper lobe were detected (Fig. 4), most of which also disappeared without treatment, leaving a small scar-like shadow. We suspected vEDS and reevaluated the resected lung specimen. An approximately 1.5 cm cavitory lesion containing blood and a 2.5 mm fibrous nodule were present (Fig. 5a). The wall of the cavity was composed of granulation tissue lacking normal lung structure (Fig. 5b). The fibrous nodule contained bone tissue (Fig. 5c) and also lacked lung tissue (Fig. 5d). Hemosiderosis was noted in the lung tissue around the cavity and nodule. Because no lung tissue was present in the cavity wall and fibrous nodule, we concluded that the cavity was an organizing hematoma with absorption or excretion of blood, and the nodule originated from the organized hematoma with complete excretion of blood and



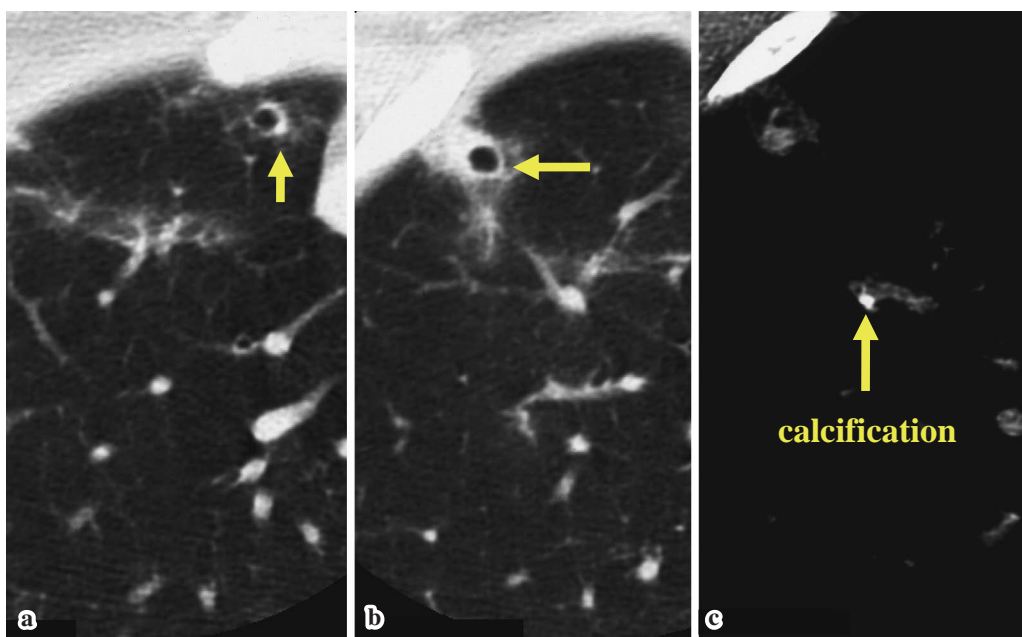
**Figure 3.** Chest CT obtained in 2002. Chest CT shows consolidation in the right upper lobe.

closure of cavitation. These findings suggested that lung laceration had occurred and that a hematoma was repeatedly developing because of connective tissue fragility, which led us to suspect EDS pathologically. A skin sample from a punch skin biopsy was performed to cultivate dermal fibroblasts for biochemical analysis of type III collagen production. The results showed remarkably reduced production of type III collagen in contrast to normal type I collagen production (Fig. 6). Analysis of the type III collagen gene *COL3A1* was then performed after obtaining the informed consent of the patient. A missense mutation in exon 29 at c.1,925 of the *COL3A1* gene from guanine to adenine (c.1,925 G>A) was detected (Fig. 7). This mutation substituted glycine for aspartic acid at amino acid position 603 (P. Gly 603 Asp). This mutation was not found in 100 normal controls and therefore the patient was diagnosed as having vEDS.

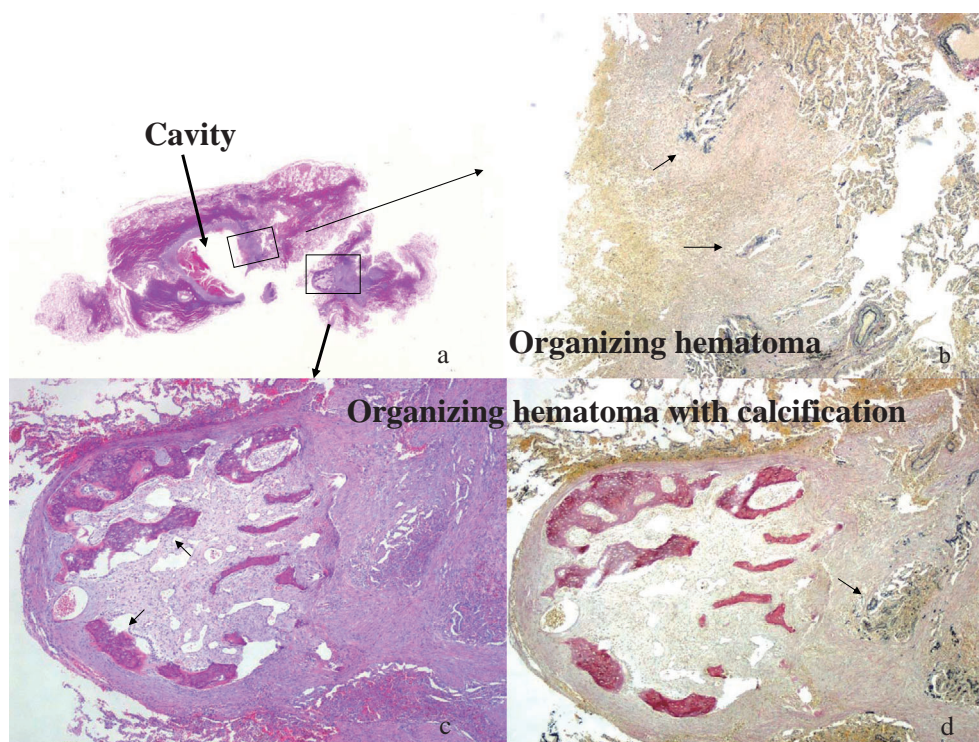
The patient has also been followed for vascular changes. An aneurysmal formation of the left ulnar artery developed in 2002 and was resected. Aneurysmal formation or arterial dilation of the right ulnar artery, celiac artery, and left iliac artery (Fig. 8) developed in 2007, and since then, he has been maintained on strict control of blood pressure by the cardiovascular department of a different hospital.

## Discussion

EDS is an uncommon inherited disorder of the connective tissue. Six types are classified by their clinical features: classical type, hypermobility type, vascular type, kyphoscoliosis type, arthrochalasia type, and dermatosparaxis type (3, 4). The present case is classified as vascular-type, which was previously called EDS type IV (Berlin nosology). This type



**Figure 4.** Chest CT obtained in 2003. Small cavitory lesions are shown in the right upper lobe (a, b). Calcification was also found (c).



**Figure 5.** Pathologic findings of the lung resected via video-assisted thoracotomy. a: A panoramic view shows a 1.5 cm cavitory lesion (left) and a 2.5 mm nodule together with blood of secondary artificial origin. Hematoxylin and Eosin staining. b: The wall of the cavity within the box in (a) shows granulation tissue lacking ordinal lung tissue. Arrows indicate remaining elastic tissue of the lung. Elastica Van-Gieson (EvG) stain,  $\times 40$ . c: The fibrous nodule within the box in (a) contained bone tissue (arrows). Hematoxylin and Eosin staining,  $\times 40$ . d: The fibrous nodule lacked lung structure. The arrow indicates the remaining lung tissue. EvG stain,  $\times 40$ .

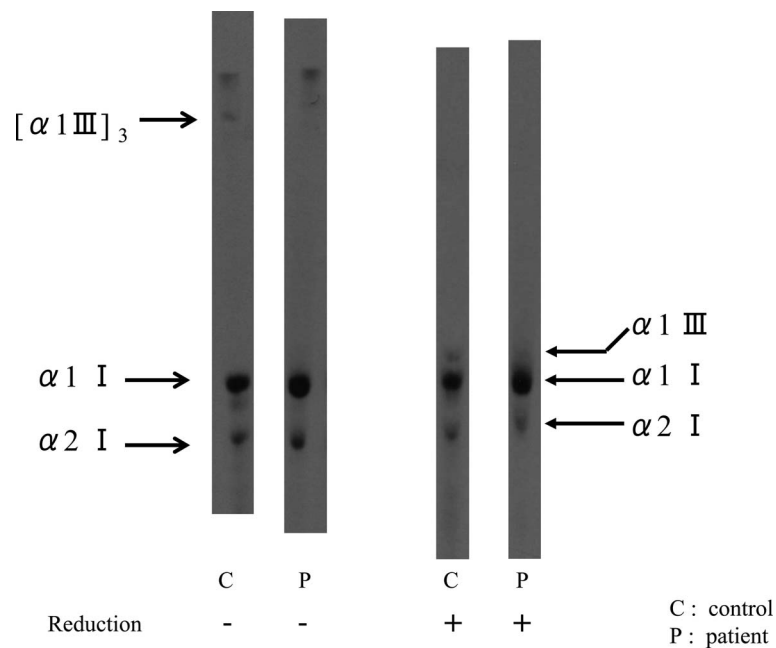
accounts for <4% of EDS patients (5) and results from deficient or defective type III collagen, which is an important component of skin, blood vessels, and other organs. The genetic defects primarily involve the *COL3A1* gene, which encodes type III procollagen. In the present case, dermal fibroblasts cultured from the patient were analyzed for production of types I and III collagen. Because type III collagen production was found to be reduced, the *COL3A1* gene was analyzed, and a point mutation from guanine to adenine was detected in exon 29 at c.1,925 of the *COL3A1* gene.

Pepin et al reported that most of the initial complications in vEDS patients were arterial dissection or rupture (65.4%) or gastrointestinal rupture (30.1%) (2). Initial complications stemming from other organs were seen in only 5% of cases. To our knowledge, only 2 cases of patients developing pulmonary symptoms as an initial manifestation have been reported (11, 12). In the present case, the initial complication was spontaneous pneumothorax, and vascular complications occurred 7 years after the initial pulmonary complication. The reason for the initial manifestations in the present case being limited to the lung is unclear. Although there was a report suggesting a relation between the location of the gene mutation and its phenotype (11), the location of the mutation in the present case (P.Gly 603 Asp) was remote from that in the previous report (11), and further studies are

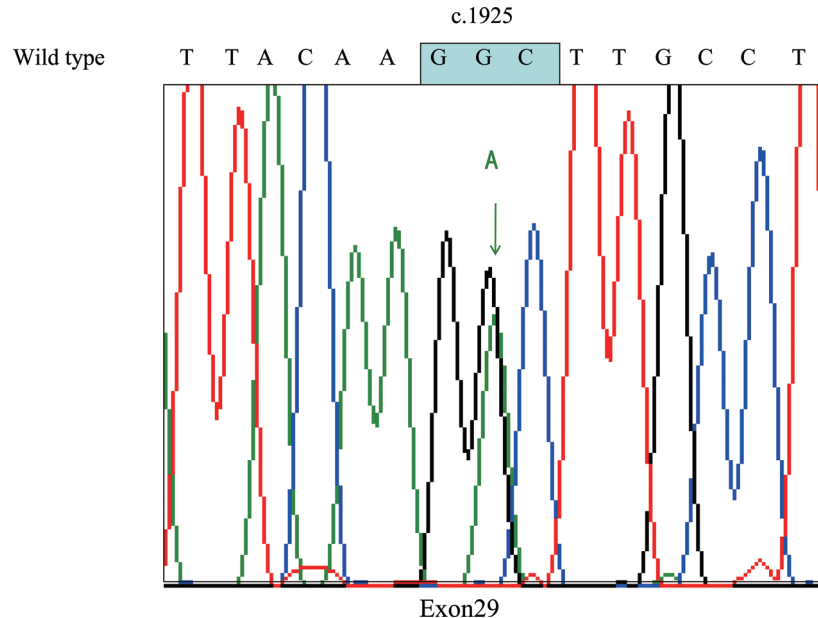
needed to clarify this matter.

In the present case, recurrent pneumothoraces and pulmonary consolidation and cavities, which probably resulted from rupture of blebs and lung, were seen. It has been shown that type I and type III collagen are the major collagens in the lung and that the amount of type III collagen in the lungs of patients with vEDS is significantly lower than that of normal controls (6). Lungs of vEDS patients are vulnerable to lacerate, which is suggested to manifest initially as acute hematoma, followed by organizing to organized hematoma. We speculate that when blood is absorbed or excreted through the airways, a cavity is then formed, and this might result in the creation of a fibrous nodule, as reported previously (7-11). Fragility of the pleural tissue may cause the formation of blebs, the rupture of which may lead to pneumothoraces. The incidence of spontaneous pneumothorax in vEDS is reported to be 16% (4). Other thoracic manifestations of vEDS include bullous lung disease, panacinar emphysema, pulmonary cysts, tracheobronchomegaly and bronchiectasis (9).

It is known that vEDS has the worst prognosis of the various types of EDS. Rupture of the frail walls of medium-sized abdominal arteries, the sigmoid colon, and the pregnant uterus can result in sudden death during middle age. Arterial tears are the most serious complication of vEDS.



**Figure 6.** Fluorograms of sodium dodecyl sulphate-polyacrylamide gel electrophoresis of pro-collagen obtained from dermal fibroblasts of the patient and from those of an age- and sex-matched normal volunteer. Both fibroblasts were cultured in appropriate medium with 5  $\mu\text{Ci/mL}$  of 2,3- $[\text{}^3\text{H}]$  proline. After collagen samples were treated with 0.1% pepsin, they were separated by SDS/5% polyacrylamide gel electrophoresis in the presence (reduction +) or absence (reduction -) of 2-mercaptoethanol. Then, the gels were exposed to X-ray films. Type III collagen secreted by the cells from the patient (P) was much less than that secreted by the control cells (C).

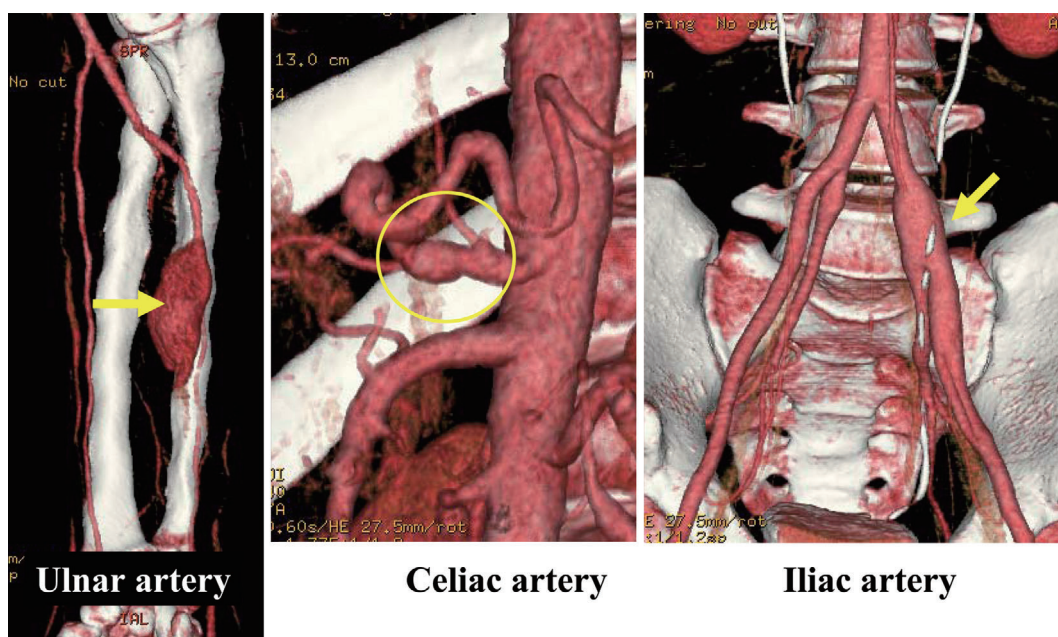


**Figure 7.** Genetic analysis examining the mRNA coding sequence of cultured dermal fibroblasts from the patient. A point mutation from guanine (G) to adenine (A) was detected in exon 29 at c.1925 of COL3A1.

Vascular changes involving several arteries have occurred in the present patient, and careful follow-up is needed.

Pulmonary manifestations in the present case of vEDS included spontaneous pneumothorax, hemoptysis and bloody sputum, and recurrent development of thick- and thin-walled

pulmonary cavities that probably resulted from lung laceration. Vascular disorders were not evident on initial presentation but developed 7 years after the pulmonary complications. When encountering similar cases, connective tissue disorders including that of vEDS should be suspected.



**Figure 8.** Vascular changes. Aneurysmal changes of the right ulnar artery (arrow), celiac artery (circle), and left iliac artery (arrow) were seen.

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