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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]



Spontaneous Hemothorax and Recurrent Hemoptysis in a 26-Year-Old Man With Skin Lesions

Bernardo Selim, MD; Charles R. Lane, MD; Ami N. Rubinowitz, MD;
and Jonathan M. Siner, MD

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A 26-year-old nonsmoking man was brought to the hospital for an episode of hemoptysis. On initial evaluation, a heart murmur was noted, and an echocardiogram showed mitral regurgitation. Chest radiography demonstrated a hydropneumothorax, prompting consultation to our service. Further history revealed intermittent production of blood-tinged sputum for the past 10 years. He described skin lesions on his right arm persisting over the last 4 years. On review of systems, he denied dyspnea, chest pain, fevers, night sweats, weight loss, and loss of consciousness. He also denied any history of recent trauma or practice of full contact sports. His father died suddenly at age 40 of unknown cause, and other paternal non-nuclear family members had cardiovascular events at young ages. He is currently enlisted in the armed forces and denies any exposure to dusts, chemicals, or asbestos. He has no risk factors for HIV, and he denies use of illicit drugs. His travel history is significant for a tour of duty in Panama.

Physical Examination

On physical examination, the patient appeared comfortable and in no acute respiratory distress. Vital

signs on presentation were significant for a heart rate of 100, a respiratory rate of 30, and oxygen saturation of 96% on 2-L nasal cannula. His body habitus was remarkable for short stature (5 ft 1 in), and his facial examination was significant for flattened nasal bridge and slightly low-set ears. Chest examination revealed dullness to percussion and decreased air entry over the lower half of the left hemithorax. Cardiac examination showed a soft S1 and a blowing holosystolic murmur best heard at the apex with radiation into the axilla. Examination of his extremities demonstrated tapered fingers and micronychchia of a few nails. No ecchymoses were found, but there were 2 × 2.5 cm pink-orange, scaly, serpiginous linear papules located on the extensor surfaces of right forearm (Fig 1). The patient did not have joint swelling or erythema. Examination of the abdomen and central nervous system was normal.

Laboratory Findings

CBC count, comprehensive metabolic panel, liver function tests, and coagulation times were within



FIGURE 1. Extensor surface of right forearm shows 2 × 2.5 cm scaly serpiginous linear papules.

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Affiliations: Department of Internal Medicine, Section of Pulmonary and Critical Care Medicine (Drs Selim, Lane, and Siner), and the Department of Radiology (Dr Rubinowitz), Yale University School of Medicine, New Haven, CT.

Drs Selim and Lane contributed equally to this work.

Correspondence to: Charles Lane, MD, Section of Pulmonary and Critical Care Medicine, Yale University School of Medicine, 300 Cedar Street, PO Box 208057, TAC 441 South, New Haven, CT 06520; e-mail: charles.lane@yale.edu

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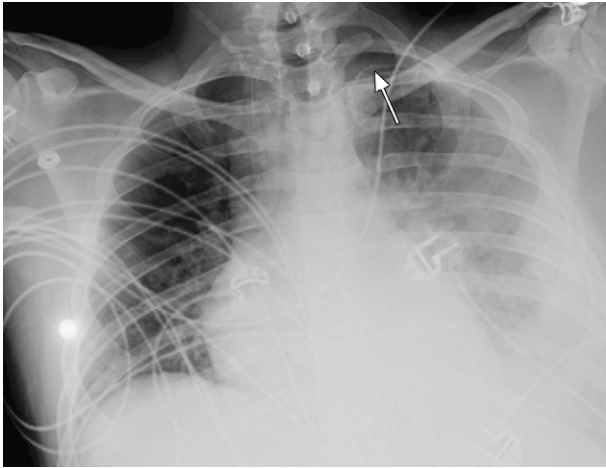


FIGURE 2. Anteroposterior chest radiograph demonstrates a moderate to large left-sided pleural effusion and a small pneumothorax (arrow).

normal range. Erythrocyte sedimentation rate was 76 mm/h, and C-reactive protein was 104 mg/L. Serology tests for antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor, double-stranded DNA, and HIV were negative.

Diagnostic Testing

Chest radiography (Fig 2) showed a left-sided hydropneumothorax. A diagnostic thoracentesis was performed and was grossly bloody, consistent with a hemothorax (3×10^6 RBC, 1,700 WBC). Chest CT (Fig 3A, 3B) confirmed the presence of a left hemopneumothorax. Following therapeutic drainage of pleural fluid, chest CT demonstrated cavitory lesions in the left lower lobe (Fig 4). Fiberoptic bronchoscopy was notable for multiple diffuse areas of friable mucosa and telangiectasias with no focal source of active bleeding. Cultures for bacteria, fungus, and mycobacteria from pleural fluid and BAL were negative,

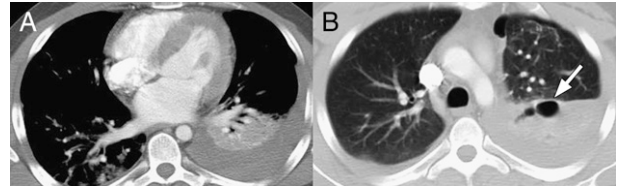


FIGURE 3. Chest CT imaged with lung windows (A) and soft tissue windows (B) shows a left-sided hemopneumothorax, including loculated pleural air within the superior aspect of the left major fissure (arrow). The pleural fluid had an attenuation value of 60 Hounsfield units compatible with acute hemorrhage.

and cytology from both samples was unremarkable. ECG revealed a rupture of the mitral valve chordae tendineae with preserved left ventricular function. Cardiac filling pressures were in normal range on right heart catheterization. A skin biopsy was consistent with elastosis perforans serpiginosa.

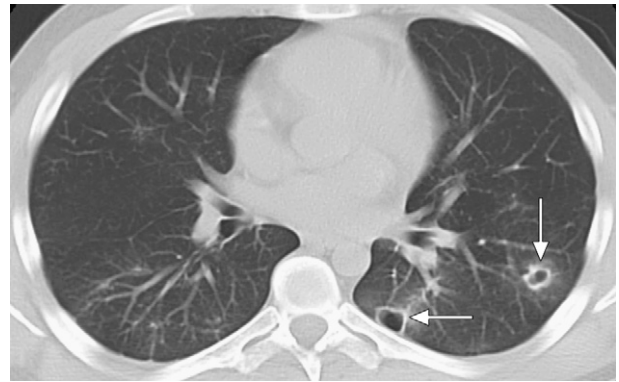


FIGURE 4. Chest CT imaged with lung windows obtained after drainage of the pleural fluid shows cavitory lesions in the left lower lobe (arrows).

What is the most likely diagnosis?

DISCUSSION

In most cases, hemothorax is the result of trauma or a complication of a procedure, such as placement of a central venous catheter or thoracentesis. Hemothorax, as a result of tearing of adhesions between pleural layers or rupture of highly vascularized bullae, can be a complication of spontaneous pneumothorax. Although rare, spontaneous hemothorax does occur (Table 1). After ruling out pneumothorax and necrotizing infections, the differential diagnosis of spontaneous hemothorax in an otherwise healthy young patient will be dominated by inherited and congenital disorders. These disorders include vascular diseases (Ehlers-Danlos syndrome [EDS] type 4, Osler-Weber-Rendu syndrome, neurofibromatosis type 1) and coagulopathies (hemophilia, Glanzmann thrombasthenia). Spontaneous hemothorax has been described as a complication of malignancies, such as from bone and soft tissues, germ cell tumors, and rarely metastatic hepatocellular carcinoma. Costal exostosis and pulmonary sequestration have also been reported to cause hemothorax.

Our patient presented with ruptured chordae tendineae, spontaneous hemothorax, recurrent intermittent hemoptysis, and skin findings that were compatible with type 4, or vascular-type, EDS. Type 4 EDS is a rare, but serious, inheritable connective tissue disorder, carrying the worst prognosis of all

subtypes of the syndrome. Reported prevalence ranges from one in 100,000 to one in 1,000,000, accounting for 5% to 10% of all EDS cases. In general, patients with type 4 EDS do not present with the joint hypermobility seen in other subtypes. Physical examination findings suggesting this diagnosis include skin hyperelasticity, serpiginous rash, extensive bruising, and facial findings such as pinched nose, low-set ears, and creasing of the nasolabial folds (acrogeria). Although arterial rupture is the most common cause of death in type 4 EDS, perforation of viscous organs as well as serious respiratory manifestations carry a high mortality. A study of 419 patients with EDS estimated the median survival to be 48 years.

The biochemical abnormality leading to vascular-type EDS is a defect in type 3 collagen, encoded by the COL3A1 gene. Type 3 collagen is a key element in the structure of arterial walls, viscous organs, and lung parenchyma. Many different mutations have been shown to result in the phenotype of type 4 EDS. No individual deficit has been shown to correlate with prognosis or predict the complications that a patient will develop. The mode of inheritance is autosomal dominant. In families identified on the basis of clinical complications, penetrance of the vascular EDS phenotype appears to be close to 100%; however, the age of detection of the phenotype may vary. Patients who present with a high degree of clinical suspicion should undergo a skin biopsy, with culture of fibroblasts to analyze the collagen fibrils. The abnormality may be detected by abnormal migration of the collagen protein on polyacrylamide gel electrophoresis, and confirmed by DNA sequencing.

The most common respiratory complication of vascular-type EDS is pneumothorax. Since type 3 collagen is synthesized not only in the vessel walls but also by fibroblasts within the lung parenchyma, hemoptysis from pulmonary artery rupture, or tears in the lung parenchyma is not uncommon. Additionally, thoracic arteries, such as the internal mammary artery, can rupture leading to hemothorax. Other well-described pulmonary findings include thick-walled cavities as a result of previous lung rupture, bullous lung disease, panacinar emphysema, pulmonary cysts, and bronchiectasis.

Arterial manifestations of type 4 EDS vary, ranging from aneurysms and dissections to ruptures and fistulas. Approximately half of all these vascular complications affect middle- to large-size arteries located within the thorax and abdomen. Approximately 80% of patients have experienced at least one arterial complication by the age of 40. The frequency of cardiac complications has not been precisely described; however, mitral valve prolapse, conduction abnormalities, and coronary aneurysms have been reported. Neurologic manifestations, such as epilepsy and

Table 1—Causes of Spontaneous Hemothorax

Class	Examples
Pneumothorax related	Ruptured bullae (eg, emphysema) Pleural adhesions (eg, postoperative)
Coagulation disorders	Drug related (eg, anticoagulation, fibrinolysis) Underlying hematologic disorders (eg, hemophilia, Glanzmann thrombasthenia)
Malignancy	Sarcoma and osteosarcoma Vascular tumors Germ cell tumors Hepatocellular carcinoma
Vascular and connective tissue anomalies	EDS type IV Marfan Syndrome Neurofibromatosis Hereditary hemorrhagic telangiectasia Aneurysm Coarctation of the aorta
Miscellaneous causes	Exostoses Extramedullary hematopoiesis Pulmonary sequestration Thoracic endometriosis Complicated pancreatic pseudocysts

EDS = Ehlers-Danlos syndrome.

temporary hemiparesis, have also been reported in EDS type 4. Microangiopathic changes and congenital malformations such as cortical dysgenesis could be the cause of these CNS manifestations, making them undetectable by current neuroimaging technology.

Clinical Course

In our patient, the diagnosis of vascular EDS was confirmed by DNA sequencing of the COL3A1 gene, which revealed a G727A transition in exon 47. This genotype has previously been reported in a patient who had an isolated hemothorax. Our patient was referred for genetic counseling to discuss the severity and frequency of complications, his prognosis, and ramifications for future family planning. The patient was also counseled to avoid lifestyle and work-related activities that pose an increased risk for trauma.

This case emphasizes the importance of considering uncommon developmental vascular and connective tissue abnormalities in young adults who present with spontaneous hemothorax. Extrathoracic findings, such as skin lesions and neurologic or cardiovascular manifestations, may also lend valuable clues to obtaining the correct diagnosis.

CLINICAL PEARLS

1. The presence of spontaneous hemothorax in a young, healthy patient should prompt an investigation for inherited coagulopathies, neoplastic disease, and vascular and connective tissue anomalies.
2. The vascular type of EDS is a rare but serious heritable defect in type 3 collagen expression encoded by the COL3A1 gene.
3. Despite a penetrance of 100%, the age of detection of type 4 EDS may vary from early childhood into adulthood.

4. During the physical examination, the vascular type of EDS does not usually present with diffuse skin hyperelasticity or joint hypermobility, which are common to the other types.

5. Thoracic manifestations, such as hemoptysis, pneumothorax, cavitory lung lesions, or hemothorax, may be the initial and only clinical presentation of vascular EDS.

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