A 26-year-old white man presented to our referral hospital with a 1-month history of persistent cough productive of white sputum, which was occasionally tinged with blood. He reported mild pleuritic chest pain but no dyspnea, fever, chills, night sweats, or weight loss. The patient had had no epistaxis or episodes of sinusitis. One week before presentation, his cough had been treated with an empirical course of azithromycin with no resolution of his symptoms.

A key feature when evaluating a patient with cough is symptom duration. Acute cough lasts less than 3 weeks and is usually caused by a respiratory tract infection. Cough lasting longer than 8 weeks is considered chronic and is most often due to postnasal drip, asthma, or gastroesophageal reflux disease. Hemoptysis, however, suggests diseases of the airways — particularly bronchitis and bronchiectasis, although other causes must also be considered. A young man is unlikely to have bronchogenic carcinoma, although he could have metastatic testicular cancer or bronchial carcinoid. Kaposi’s sarcoma involving the airways may cause hemoptysis in patients infected with the human immunodeficiency virus (HIV). Hemoptysis can also arise from the lung parenchyma. Autoimmune disease, cocaine inhalation, and infections (including tuberculosis, bacterial pneumonia, and lung abscess) are potential culprits. A last consideration is that hemoptysis can arise from the pulmonary vasculature as a result of pulmonary embolism, pulmonary arteriovenous malformation, mitral stenosis, and severe left heart failure.

Five years before this presentation, the patient had been treated for a right-sided spontaneous pneumothorax. At that time, his hospital course was complicated by multiple chest-tube insertions on the right side, thoracotomy, and pleurodesis. Three years before presentation, he had had left-sided flank pain and was found to have a spontaneous left renal-artery dissection with renal infarction. He had received care elsewhere, and medical records were not available.

The patient worked as a graphic designer. He was monogamous and had no risk factors for infection with HIV. He neither smoked nor used illicit drugs. His outpatient medications consisted only of a multivitamin. His mother died at 52 years of age from a presumed pulmonary embolus; the family history was otherwise unremarkable.

Since the patient’s medical history is notable for two relatively uncommon diagnoses — pneumothorax and renal-artery dissection — it is tempting to find a single disease that provides a unifying diagnosis for these previous illnesses and the recent hemoptysis. Spontaneous pneumothorax can usually be managed with simple aspiration or tube thoracostomy; that this patient’s condition did not respond to the
usual therapy and required surgical intervention suggests that his pneumothorax occurred as a result of an underlying disease that was not appreciated at the time. Arterial dissection and pneumothorax can occur with Marfan’s syndrome, the Ehlers–Danlos syndrome, and rarely, homocystinuria. A hypercoagulable state can be seen with the latter and would be consistent with the family history of pulmonary embolism. Pulmonary and bronchial arterial aneurysms can occur in patients with Marfan’s syndrome and the Ehlers–Danlos syndrome and could explain the hemoptysis. Cocaine use is another possible cause of hemoptysis, pneumothorax, and arterial dissection. It should be investigated despite the patient’s report of no substance abuse. A toxicology screen and a careful physical examination with particular focus on the patient’s body habitus, skin, joints, and chest will be useful. Attempts should be made to verify the cause of death of the patient’s mother and any underlying disease she might have had.

The patient appeared comfortable and was in no acute distress. His body habitus appeared normal. The temperature was 36.2°C, the heart rate 63 beats per minute, the respiratory rate 18 breaths per minute, the blood pressure 127/73 mm Hg, and the oxygen saturation 98% while the patient was breathing ambient air. Examination of the abdomen, heart, and neurologic system revealed no abnormalities. On chest examination, the patient had rales and decreased air entry posteriorly in the left lower lung zone. The skin examination revealed no rashes, ecchymoses, or hyperextensibility. The patient had generalized joint hypermobility involving both small and large joints, but there was no joint swelling or synovitis.

The findings on lung examination are consistent with consolidation. In the absence of tachypnea, fever, or tachycardia, pneumonia is unlikely. There are no telangiectasias to suggest systemic arteriovenous malformations, and there is no arthritis or other evidence of a collagen vascular disease. Joint hypermobility is a hallmark of Marfan’s syndrome. However, there is no mention of arachnodactyly, scoliosis, or anterior chest deformity, findings that would increase the likelihood of Marfan’s syndrome. The joint findings could be consistent with the Ehlers–Danlos syndrome, but the patient’s skin is not hyperextensible. In most cases of the Ehlers–Danlos syndrome, the skin appears thin or even transparent. However, skin findings can be subtle in some subtypes of this syndrome, and at this point, I believe that one of these subtypes is the most likely diagnosis.

A complete blood count revealed a white-cell count of 5400 per cubic millimeter, with a differential count of 69% granulocytes, 16% lymphocytes, 12% monocytes, 2.5% eosinophils, and 0.1% basophils. The hemoglobin level was 12.3 g per deciliter (7.6 mmol per liter), and the platelet count was 212,000 per cubic millimeter. The serum creatinine level was 1.1 mg per deciliter (97.2 μmol per liter), and the urea nitrogen level was 11 mg per deciliter (3.9 mmol per liter). The results of liver-function tests, the erythrocyte sedimentation rate, and the C-reactive protein level were normal. Testing for HIV was negative. A chest radiograph (Fig. 1) revealed a left lower-lobe cavity with an
air–liquid level, small left-sided apical pneumothorax, and left hydrothorax.

Lung cavities are air-containing lesions with a wall thickness greater than 4 mm. (In contrast, cysts have thin walls that measure 4 mm or less.) The main causes of cavities include neoplasm, infection, and collagen vascular disease. The patient’s age and absence of smoking history make bronchogenic carcinoma unlikely. Lymphoma and metastases may cavitate, but in the absence of other systemic symptoms or examination findings, these possible diagnoses are unlikely. Bacteria and fungi can cause cavities, but generally are associated with fever, leukocytosis, and elevation of the C-reactive protein level. Hydatid disease is another infectious possibility, except that patients are generally quite ill when a cavity ruptures into the pleural space. A primary infection, therefore, seems unlikely. Cavitary nodules can be seen with Wegener’s granulomatosis and rheumatoid arthritis, occasionally as the initial manifestation of disease. Septic emboli and thromboemboli may also occasionally cavitate, but the cavities are generally smaller than those here and multiple. Computed tomography (CT) of the chest is warranted.

Chest CT (Fig. 2) revealed a left lower-lobe cavity with an air–liquid interface as well as a left-sided hydropneumothorax. There was an area of consolidation adjacent to the fluid-containing cavity in the left lower lobe. Subcentimeter nodules with surrounding haziness were seen in the left upper lobe, lingula, and right lower lobe. A left chest tube was placed and drained bloody serosanguineous fluid. The patient received 14 days of intravenous ampicillin–sulbactam to treat a presumed lung abscess. Findings from pleural fluid staining as well as cultures for bacteria, fungus, and mycobacteria were negative. The chest tube was removed after 9 days, and the patient was discharged home with close follow-up on a prescribed course of 28 days of oral amoxicillin–clavulanate.

Although the findings on chest CT are consistent with a bacterial abscess, a primary infection is unlikely since the patient does not have any apparent risk factors for aspiration (such as impaired consciousness, dysphagia, or esophageal dysfunction), which is the usual cause of bacterial abscess formation in the lungs. If he does have an infection, it is likely to be with a pathogen that has secondarily occupied a preexisting cavity or an uncommon agent such as a species of rhodococcus or paragonimus, or Entamoeba histolytica. Given the multiple nodules found on the chest CT, I am more concerned about a systemic process than localized infection. Pulmonary vasculitis — microscopic polyangiitis, the Churg–Strauss syndrome, and Wegener’s granulomatosis — may cause this radiographic finding. None of these diseases, however, would readily explain the patient’s history of spontaneous pneumothorax and renal-artery dissection. The Ehlers–Danlos syndrome, as mentioned, could provide us with a unifying diagnosis. Lung cavities can occur with some of the variants of the Ehlers–Danlos syndrome, in which spontaneous pneumothorax and arterial dissection are common.

At this point, I would order serologic tests and a urinalysis to look for evidence of a collagen vascular disease. I doubt that the patient’s lung cavity and nodules will respond to antibiotics, and I would readily proceed with a lung biopsy.

The patient returned after 5 weeks for an outpatient chest CT (Fig. 3). He reported that his cough had improved and he no longer had blood-tinged sputum. On chest CT, there appeared to be inter-
val improvement in the left lower-lobe cavity; however, multiple cavitary pulmonary nodules as well as irregular hazy opacities were noted. The nodules appeared different from those seen on the previous chest CT (obtained 5 weeks earlier). Whereas some nodules had improved or disappeared entirely, new nodules and hazy opacities were visible.

Waxing and waning pulmonary nodules can occur with several conditions. Sarcoidosis is one possible diagnosis, but hilar and mediastinal adenopathy would typically be seen in conjunction with waxing and waning nodules in a patient with sarcoidosis. Patients with rheumatoid arthritis can also have cavitary nodules that relapse and remit in concert with systemic disease activity, but the absence of joint manifestations in this case makes this diagnosis unlikely. Whereas the appearance of the pulmonary lesions is consistent with those seen in Wegener’s granulomatosis, isolated pulmonary disease is uncommon. Chronic thromboembolic disease can cause waxing and waning pulmonary infiltrates, but the patient’s course has been atypical of this condition. The Ehlers–Danlos syndrome remains a possibility.

Twelve weeks later, the patient presented with massive hemoptysis. Over the preceding 3-week period, hemoptysis (which had transiently resolved after his earlier hospitalization) increased gradually from 5 to 25 ml per day to as much as 200 ml in 1 day. He was readmitted for further treatment. Another chest CT was performed and the results compared with the two previous chest CT scans (obtained 12 and 17 weeks earlier). The rounded opacity in the left lower lobe, noted in the region of the initial fluid-containing cavity, appeared to be unchanged. New cavitary pulmonary nodules as well as irregular hazy opacities (more in the right lung than in the left) were noted. A comparison of the three chest CT scans indicated waxing and waning of individual nodules (Fig. 4).

Tests for antinuclear antibody, antineutrophil cytoplasmic antibody, antcardiolipin antibody, anti–glomerular basement membrane antibody, anti-Ro and anti-La antibodies, anti–Jo antibody, anti–Scl-70 antibody, and anti–smooth-muscle antibody were negative. Levels of complement C3 and C4 were normal.

The patient underwent fiberoptic bronchoscopy. No endobronchial lesions were seen. Culture of the lavage fluid was positive for Aspergillus fumigatus.

Specimens obtained by transbronchial biopsy of the right lower lobe showed hemosiderin-laden macrophages and no evidence of cancer.

Massive hemoptysis has developed, which is associated with a high risk of death. Bronchoscopy and high-resolution chest CT may be useful in localizing the site of bleeding. Determining when to perform these procedures depends on the patient’s condition and the tempo of the bleeding.

It is unlikely that the aspergillus found in the bronchoalveolar lavage is pathogenic. Common risk factors for invasive aspergillosis include severe neutropenia, hematopoietic stem-cell and solid-organ transplantation, HIV infection, and chronic granulomatous disease; the patient has none of these. Aspergillus species are ubiquitous in the environment, and growth in respiratory cultures often represents contamination rather than infection. A lung biopsy is needed for definitive diagnosis.

The patient underwent lung biopsy by means of video-assisted thoracoscopic surgery. Left upper-lobe and left lower-lobe wedge specimens revealed alveolated lung tissue with emphysematous chang-
es; no signs of vasculitis or tumor were seen. The left lower-lobe mass was found to be a well-circumscribed, organizing hematoma. Hemosiderin-laden macrophages were noted in the surrounding lung parenchyma (Fig. 5).

The lung biopsy is helpful in that aspergillosis and vasculitis have been ruled out. Unfortunately, a diagnosis is still lacking. The challenge is to find a unifying diagnosis that might account for the history of spontaneous pneumothorax and arterial rupture, moderate joint hypermobility, subacute development of hemoptysis, cavitary lung lesions and hemopneumothorax, and histologic evidence of emphysema. A connective-tissue defect that involves the joints, blood vessels, and lung parenchyma must be present.

A variant of the Ehlers–Danlos syndrome is most likely. The vascular type results from a defect in synthesis or structure of type III procollagen, a critical component of blood-vessel walls and pulmonary parenchyma. Patients with this condition often have arterial rupture and spontaneous pneumothorax. My main concern about the appropriateness of this diagnosis is the absence in this patient of two other common features of the syndrome, namely excessive bruising and thin, translucent skin.

A skin sample was submitted for genetic testing. A punch-biopsy specimen of skin was cultured to determine whether either type I or type III collagen, produced by dermal fibroblasts, was abnormal. Type III procollagen showed two bands (rather than one) on polyacrylamide-gel electrophoresis, and therefore, the gene that encodes this peptide, COL3A1, was sequenced. The patient was heterozygous for a missense mutation, confirming the diagnosis of the Ehlers–Danlos syndrome type IV (the vascular type). Repeat skin examination was performed in light of the diagnosis and revealed thin, atrophic scars (known as “cigarette-paper” scars) over the patient’s knees and shins at sites of minor trauma. Family members were referred for genetic testing. One year after the diagnosis was established, the patient reported that he was well with the exception of an anterior cruciate ligament tear in the left knee.

**Commentary**

The Ehlers–Danlos syndromes are a heterogeneous group of heritable disorders of connective tissue. Most of the disorders involve defects in the primary structure or post-translational processing of fibrillar collagen. The six types are differentiated by their clinical features. All types of Ehlers–Danlos syndrome share some involvement of both skin and joints. Skin can show easy bruising, hyperextensibility, abnormal thinness, fragility, and dystrophic scarring. Joints can be hypermobile, unstable, or both. The most serious form—the Ehlers–Danlos syndrome, vascular type—is also associated with fragility of the arterial walls and hollow viscera. Spontaneous perforation of the co-

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**Figure 4. Chest CT Scans Obtained without Intravenous Contrast Material, at Three Time Points.**

The CT images shown were obtained at initial presentation (Panel A), 12 weeks after initial presentation (Panel B), and 17 weeks after initial presentation (Panel C). They were taken at similar levels of the chest, higher than the levels of the images in Figures 2 and 3. The scans show waxing and waning nodules with areas of surrounding haziness. Panel A also shows left hydropneumothorax.
Ehlers and Danlos independently described the clinical features of the syndrome a century ago, but it was not until the late 1960s that a subgroup of patients with the Ehlers–Danlos syndrome who had vascular fragility was identified. Previously called Ehlers–Danlos syndrome type IV, this variant is now termed the vascular type.3 This form of the Ehlers–Danlos syndrome results from deficient or defective type III collagen, which is an important component of skin, blood vessels, and organs. The genetic defects primarily involve the gene COL3A1, which encodes type III procollagen. Inheritance is autosomal dominant; patients are heterozygous for one mutant allele.

To confirm the diagnosis, fibroblasts cultured from a specimen obtained by skin-punch biopsy are analyzed for production of types I and III collagen. If an abnormality of amount or migration of type III procollagen or collagen is seen, then the COL3A1 gene is analyzed to determine the specific mutation. Once the mutation in the proband is determined, relatives can be screened.2 Recently, some patients with a phenotype suggestive of the vascular type of Ehlers–Danlos syndrome have been found to have mutations in a receptor for transforming growth factor β.4

Arterial tears are the most serious complication of the Ehlers–Danlos syndrome, vascular type. Approximately half of all arterial complications (including tears, dissections, and aneurysms) affect arteries within the abdomen and thorax; the renal artery is commonly affected.2,5 Pulmonary manifestations include hemoptysis from pulmonary-artery rupture or tears in lung parenchyma, thick-walled cavities resulting from previous lung rupture, pneumothoraces, bullous lung disease, panacinar emphysema, pulmonary cysts, and bronchiectasis.6-8

In retrospect, the patient presented with multiple clues to the diagnosis. The medical history included two unusual conditions that are recognized to occur in patients with the vascular type of Ehlers–Danlos syndrome: spontaneous renal-artery dissection and spontaneous pneumothorax. On initial examination, the patient had joint hypermobility. Skin findings were not initially appreciated, but focused skin examination after the diagnosis was made revealed subtle dystrophic scarring. The patient’s hemoptysis, waxing and waning pulmonary cavitary nodules, and well-organized hematoma on lung biopsy are consistent with pulmonary parenchymal tears, also reported in this syndrome. Although the patient’s mother reportedly died of pulmonary embolism, medical records were not available to confirm the diagnosis, and it is possible that she died from a pulmonary manifestation of the Ehlers–Danlos syndrome.

Both the discussant and the clinical team did what experienced diagnosticians often do when confronted with a patient whose illness does not lend itself to a simple diagnosis: try to find the connection between the present illness and past abnormalities. Only after taking a step back and considering the patient’s history did the connection — a relatively rare connective-tissue disorder — become apparent.

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