A previously healthy 17-year-old boy awoke with left-sided pleuritic chest pain. He also noticed mild dyspnea on exertion during track-and-field practice but reported no sputum production, fever, chills, or recent trauma.

Pleuritic chest pain reflects inflammation, irritation, or stretching of sensory-nerve fibers in the parietal pleura. Often, the process primarily involves the pleura, as in the case of pneumothorax, a pleural inflammatory or infectious process, or a tumor with pleural involvement. Alternatively, pleuritic pain can result from a pulmonary parenchymal process that extends to the visceral pleural surface and secondarily involves the parietal pleura, especially in the case of pneumonia or pulmonary embolus. The acute onset of pleuritic chest pain in an otherwise healthy teenager suggests spontaneous pneumothorax or the relatively acute onset of pneumonia, although the absence of fever, chills, or sputum production makes the latter diagnosis less likely.

The patient was evaluated by his primary care provider and told that chest radiography revealed a dislocated rib but was otherwise normal. Over the course of the next four months, progressive exertional dyspnea developed; dyspnea then occurred when the patient was at rest and was accompanied by three-pillow orthopnea.

I am uncertain what is meant by a “dislocated rib” and would explore the rib finding to confirm whether an abnormality is really present. Progressive dyspnea has become the predominant symptom, and its severity and progression are quite striking. Pulmonary disorders that might progress at this rate include pulmonary parenchymal disease (a broad spectrum, ranging from disseminated tumor to pulmonary alveolar pro-

tcnosis and Goodpasture’s syndrome), airway disease (e.g., asthma or obliterative bronchiolitis), or pulmonary vascular disease (e.g., primary pulmonary hypertension or occult thromboembolic disease). The presence of orthopnea raises the possibility of underlying cardiac disease associated with high left atrial pressure, as might be seen with mitral-valve disease or a cardiomyopathy.

On the day of admission to his local hospital, the patient had lightheadedness on standing that was followed by an episode of syncope when he was leaving the bathroom. At the time of hospital admission, he also reported having had an intermittent dry cough for two years with occasional hemoptysis and was noted to have lost 9 kg (20 lb) over a period of several months.

Lightheadedness and syncope are not typical symptoms of either pulmonary parenchymal disease or airway disease. Rather, I would lean toward either pulmonary vascular or cardiac disease, leading to obstruction of forward flow, diminished cardiac output, and impaired systemic perfusion. The intermittent dry cough and hemoptysis are more suggestive of pulmonary vascular than cardiac pathology, with the possible exceptions of mitral stenosis or a disorder mimicking mitral stenosis (such as cor triatriatum or left atrial myxoma). Although it is uncommon, any primary pulmonary vascular disorder associated with pulmonary hypertension could produce this constellation of symptoms, including chronic (or recurrent) pulmonary thromboembolism, tumor embolism, primary pulmonary hypertension, pulmonary venoocclusive disease, or mediastinal fibrosis producing pulmonary venous obstruction, pulmonary arterial obstruction, or both. The coexistence of orthopnea with the other symptoms suggests a postcapillary rather than precapillary origin of pulmonary hypertension and might therefore favor a diagnosis of pulmonary venoocclusive disease or mediastinal fibrosis with pulmonary venous obstruction.

The patient was not receiving any medications and indicated that he did not use tobacco or recreational drugs. He reported occasional alcohol use. He had not received a blood transfusion and said he had not engaged in sexual activity. He lived on a farm in Michigan with his mother and brother. He was a junior in high school, played football, and competed in the discus throw for the track-
and-field team. His great-aunt had had a pulmonary embolism at 40 years of age.

The patient’s temperature was 36.7°C, his heart rate was 110 beats per minute, his respiratory rate was 24 per minute, his blood pressure was 101/67 mm Hg, and his oxygen saturation was 88 percent while he was breathing room air. He had an athletic build and appeared to be in no acute distress. On cardiovascular examination, he was noted to have tachycardia, with a prominent S₂. He had no murmurs and no jugular venous distention. His lungs were clear bilaterally, and he had no clubbing. The remainder of the physical examination was normal.

The physical examination is helpful, with major findings being abnormal vital signs accompanied by a prominent S₂. This pattern of findings is consistent with pulmonary hypertension, although there are no other findings on examination to suggest a specific cause. However, additional historical information provides some tantalizing clues. Causes related to drugs or the human immunodeficiency virus seem unlikely. Residence on a farm in the Midwest raises the specter of either chronic hypersensitivity pneumonitis or histoplasmosis (a potential cause of fibrosing mediastinitis). Although a great-aunt is a rather distant relative, the possibility of one of the inherited thrombophilias should also be considered.

In addition to basic laboratory tests, I would initially order chest radiography, pulmonary-function tests, electrocardiography, and echocardiography. He will also need computed tomography (CT) of the chest — preferably CT angiography that would allow us not only to view his pulmonary parenchyma, but also to assess his pulmonary vessels and the possibility of subclinical, recurrent thromboembolism.

The white-cell count was 8100 per cubic millimeter, the hematocrit 47 percent, the platelet count 288,000 per cubic millimeter, the partial-thromboplastin time 39 seconds (normal range, 19 to 30), and the international normalized ratio for the prothrombin time 1.6. The serum aspartate aminotransferase level was 35 U per liter, the serum alanine aminotransferase level 81 U per liter, and the serum albumin level 3.3 g per deciliter. Electrocardiography revealed a pattern of right ventricular strain, and chest radiography demonstrated mild cardiomegaly and clear lung fields. Surface echocardiography suggested pulmonary hypertension, with an estimated right ventricular systolic pressure of 76 mm Hg, right ventricular enlargement, diminished right ventricular function, and slightly diminished left ventricular function.

The echocardiogram confirms the presence of pulmonary hypertension. The demonstration of clear lung fields on chest radiography and the absence of substantial cardiac pathology suggest that we should focus on primary pulmonary vascular disease. The differential diagnosis now revolves around precapillary and postcapillary forms of pulmonary hypertension. The presence of orthopnea is suggestive of a postcapillary form of pulmonary hypertension (such as pulmonary venoocclusive disease), whereas the finding of clear lung fields on chest radiography is suggestive of a precapillary origin (such as primary pulmonary hypertension or recurrent thromboembolic disease). The patient also has mildly abnormal results on coagulation studies that are currently unexplained and that warrant further characterization.

A spiral CT scan of the chest demonstrated multiple acute pulmonary emboli in the posterobasilar and anterior segments of the right lower lobe and left upper lobe, a nonocclusive thrombus in the left upper lobe, and prominent pulmonary arteries.

The spiral CT scan confirms the presence of thromboembolic disease as the cause of pulmonary hypertension. In the absence of any underlying reason for thrombosis in the arms or abdomen, large veins of the legs are the likely source of thromboemboli. Pulmonary emboli are quite unusual in adolescents and, in the absence of trauma or pregnancy, suggest an underlying thrombophilic state. Apart from antiphospholipid antibodies (of the lupus-anticoagulant type), inherited or acquired thrombophilic states generally are not associated with prolongation of either the prothrombin time or the partial-thromboplastin time. Because both are slightly prolonged, I would consider the possibility that a lupus anticoagulant is present. Although the lupus-anticoagulant phenomenon traditionally causes prolongation only of the partial-thromboplastin time, the prothrombin time may also be affected in some cases.

CT scans of the head, abdomen, and pelvis did not reveal evidence of cancer. Doppler ultrasonography of the veins in the arms and legs did not reveal thrombus. An evaluation for hypercoagulability (including measurement of the level or activity of protein C, protein S, antithrombin III, plasminogen, fibrinogen, heparin cofactor II, and hagemostyseine), gene analysis for factor V Leiden, prothrombin gene 20210, and methylenetetrahydrofolate reductase mutations, and immunologic analysis for antinuclear antibodies, antithrombophilic antibodies, and lupus anticoagulant were negative.

Heparin therapy was initiated, and the patient also received thrombolytic therapy with reteplase.
He was transferred to the pediatric intensive care unit at a tertiary care hospital for further evaluation of the cause of pulmonary emboli.

When dealing with an unusual case of pulmonary embolic disease, the clinician is faced with two issues: where are the clots coming from, and is there any predisposition to clot formation? In this case, the usual suspects have been rounded up, but none of them has yet been proved guilty. Even though the ultrasonographic examination of the arms and legs was negative, it is still possible that the arms or, more likely, the legs were the source of the emboli but that all identifiable clots had already embolized. Alternatively, ultrasonography could have missed a clot that was either too proximal or too distal to be detected, or a clot could still be originating from an intraabdominal source or from the right atrium or ventricle. Finally, we may be dealing with another type of embolic disease — specifically, tumor emboli.

A pulmonary angiogram was obtained that demonstrated elevated pulmonary arterial pressures (67/33 mm Hg). Multiple bilateral diffuse segmental and subsegmental filling defects consistent with the presence of acute and subacute pulmonary emboli were found (Fig. 1). The inferior vena cava was patent, with normal anatomy. Evaluation of the right subclavian vein demonstrated wall irregularities and a nonocclusive thrombus underlying the clavicle and first rib, without collateral flow (Fig. 2). The patient’s dyspnea and oxygenation improved over the next several days, and he was weaned to room air. He continued to receive heparin while warfarin therapy was initiated, and he was discharged from the hospital with a therapeutic prothrombin time; he was given oxygen for home use during activity, and a plan was made for him to return in three months for surgical decompression of the thoracic outlet.

Imaging studies confirm the presence of “spontaneous” thrombosis of the axillary subclavian veins, also called the Paget–Schroetter syndrome. This syndrome has been associated with exertion of the arms, and hence the term “effort thrombosis” has also been used. The patient’s track-and-field activities could certainly have contributed to the thrombosis in his arms. However, the additional feature often present is extrinsic venous compression by the first rib or by a cervical rib. In retrospect, the “dislocated rib” seen on initial chest radiograph might have provided a clue if the anomaly was in the region of the thoracic outlet. Surgical decompression, typically including resection of the first rib, is an important component of treatment when venous compression is present.
One week after the patient was discharged from the hospital, vomiting and abdominal pain developed, and re-admission was required. He had an oxygen saturation of 95 percent when breathing 5 liters of supplemental oxygen and appeared to be moderately ill. Echocardiography revealed a right ventricular systolic pressure of 100 mm Hg. Pulmonary angiography revealed a marked increase in filling defects in both pulmonary arteries as compared with the previous study (Fig. 3). Mechanical thrombectomy was performed and intra-arterial reteplase administered without improvement in pulmonary-artery flow. After the procedure was terminated because of hypotension and increasing hypoxemia, cardiac arrest occurred. The patient was resuscitated, and a circuit for extracorporeal membrane oxygenation was established. However, the patient had inadequate tissue perfusion, and when extracorporeal membrane oxygenation was discontinued, he died. Autopsy revealed numerous recent and organizing pulmonary emboli bilaterally, hypertensive changes in the pulmonary arteries, a large organizing infarct in the right lower lobe, and right ventricular hypertrophy and dilatation without mural thrombi or evidence of endocarditis. The inferior vena cava and superior vena cava were patent and without thrombi.

**COMMENTARY**

When a patient unexpectedly dies of a catastrophic illness, it is natural to review the clinical decisions that were made in order to verify that they were sound. Retrospectively, the physician tries to reaffirm that he or she made no errors in judgment that might have contributed to the death. This inspection is conducted with even greater scrutiny when the death was, at least in theory, preventable.

A possible misstep in this case was the delay in suspecting and confirming the diagnosis of pulmonary thromboembolic disease. Four months elapsed from the time the patient first sought medical attention for pleuritic chest pain to the hospital admission leading to appropriate studies and interventions. Many adolescents, especially boys, are reluctant to seek medical attention; often, our only interactions with members of this population come when physical examinations are required for participation in sports or school enrollment. Male adolescents may be more stoic than other patients and less likely to report symptoms; in addition, they may have an inflated sense of their own invincibility. This patient, however, sought medical attention early in the course of his illness, and therefore the delay in diagnosis cannot be attributed to procrastination in seeking care.

The physical examination may have been misleading. The patient was noted to have no jugular venous distention even at a time when his right ventricular and pulmonary arterial pressures were markedly elevated. Clinical assessment of jugular venous pressure is notoriously poor. In three studies comparing the prediction by physicians of central venous pressure with simultaneous pressure measurements obtained with an indwelling central venous catheter, the overall accuracy was only 56 percent. Connors and colleagues reported a sensitivity of 49 percent for the detection of elevated central venous pressure. When the clinical assessment is inaccurate, central venous pressure is more frequently underestimated than overestimated.

The physician may harbor a presumption that adolescent athletes are healthy. Although athletic activity may exacerbate or unmask serious conditions such as hypertrophic cardiomyopathy or asthma, athletic participation is not usually harmful in a healthy teenager. The notion that athletic participation may cause catastrophic illness is foreign to most of us.

The diagnosis was most likely delayed because a physically robust patient presented in an atypical fashion with an uncommon disease. Although the incidence of pulmonary embolism among adults is esti-
mated at 1 in 1000 per year, it is rare among children and adolescents. Bernstein and colleagues have estimated that 7.8 per 10,000 hospital admissions of adolescents or young adults are the result of pulmonary embolism — an incidence much lower than that among older adults. The incidence does appear to be higher among adolescents than among younger children. In addition, although the signs and symptoms of pulmonary embolism are similar in children and adults, adolescents may present with less dyspnea and tachypnea than adults, possibly reflecting better physiological tolerance.

Primary thrombosis of the axillary subclavian vein was described in 1875 by Sir James Paget and in 1884 by Leopold von Schroetter. The term “effort thrombosis” was later coined to acknowledge the role of unusual exertion of the arms. Paget–Schroetter syndrome usually develops in young, healthy persons with a history of repetitive motion of the arms. Spontaneous thromboses in the arms have been reported in athletes such as golfers, football players, weight lifters, baseball players, wrestlers, tennis players, and cheerleaders, as well as in painters and beauticians. The majority of patients are affected in the dominant arm. Unlike this athlete, most patients present with symptoms of venous obstruction such as pain, swelling, bluish discoloration, and venous collaterals. Nonocclusive thromboses, as seen in this patient, may not present with local symptoms, instead becoming symptomatic only after embolization.

Repetitive shoulder–arm motion, extrinsic compression of the subclavian vein, and in some patients, a hypercoagulable state may contribute to the development of primary thrombosis of the subclavian vein. Repetitive motion of the shoulder and arm predisposes persons to thrombosis by a number of mechanisms. Lateral abduction of the arm leads to compression of the subclavian vein, causing turbulence or obstruction.

Figure 4. Anatomical Factors Predisposing Persons to Paget–Schroetter Syndrome. Venous compression may occur as a result of abnormality or hypertrophy of the anterior scalene or subclavian muscles, complete or incomplete cervical ribs, fibromuscular bands, and callus from old clavicular fractures.
of flow. In addition, microscopic intimal damage may occur, stimulating the coagulation cascade. Repetitive motion may also contribute to anatomical stricture of the thoracic outlet through hypertrophy of the tendon of the subclavian muscle, the anterior scalene muscles, or both. Other possible sites of external compression include the first rib, complete or incomplete cervical ribs, fibromuscular bands, and callus from old clavicular fracture (Fig. 4). Lifting of heavy objects may lead to depression of the shoulder, which further narrows the costoclavicular space. Patients with an underlying hypercoagulable state may have more refractory thrombosis. In this patient, the abnormal coagulation results on presentation, the family history, and the progression of thromboemboli despite adequate anticoagulation all suggest a superimposed, yet unidentified, thrombophilia.

Historically, treatment of this syndrome consisted of elevation and anticoagulation, but long-term complications were common. More recently, catheter-directed thrombolytic therapy followed by decompression of the thoracic outlet has become the standard of care. The rates of vessel patency and of symptom-free survival approach 100 percent, although patients who do not undergo thrombolysis early have worse outcomes. The incidence of pulmonary embolism in patients with Paget–Schroetter syndrome varies from 10 to 30 percent, depending on how the diagnosis is made; most emboli are probably clinically silent.

Once this patient presented with pulmonary hypertension and syncope, the diagnosis of pulmonary thromboembolic disease secondary to Paget–Schroetter syndrome was made expeditiously. Despite thrombolysis and anticoagulation, new thromboemboli, progressive pulmonary hypertension, and right heart failure developed. Although management was consistent with the known standards of care, the outcome was disastrous. Although rare, the unusual suspect known as Paget–Schroetter syndrome should be considered whenever a person with repetitive arm motion presents with pulmonary hypertension or thromboembolic disease.

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REFERENCES


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