Chronic Thromboembolic Disease in a 43-Year-Old Man

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The overall incidence of pulmonary embolus in the United States is approximately 650,000 cases per year.[1] It is estimated that 0.1% to 0.5% of those with pulmonary embolus (650–3,250 cases) develop recurrent thromboembolic pulmonary hypertension each year.[2]

Case Report

A 43-year-old man was admitted to the hospital complaining of nonproductive cough, progressive shortness of breath, increasing dyspnea on exertion, and fatigue of approximately 3 months' duration. The patient stated he could no longer walk without shortness of breath. He denied syncope, lightheadedness, palpitations, chest pain, wheezing, hemoptysis, fever, weight change, or night sweats.

Other than having the sickle cell trait, the patient related no additional medical or surgical history. He had never smoked tobacco and denied use of alcohol. One month earlier he returned from reserve military duty, where he had served for 8 months as an F-14 naval flight officer. While flying, the patient was exposed to immobility and excess gravitational forces. At the time of admission he was a full-time student. His family history was notable for hypertension. He had no known drug or food allergies and was not taking any medications, herbal supplements, or vitamins.

The patient was visibly short of breath walking into the Emergency Department. His temperature was 99.1°F, heart rate 93 beats per minute, respiratory rate 20/min, blood pressure 130/92 mm Hg, and oxygen saturation 89% on room air. His oxygen saturation increased to 98% on 4 L of oxygen while using a nasal cannula.

Findings during the patient's physical examination were normal, except during the cardiac examination. He had a regular rate and rhythm, with a fixed, split S_2, and a prominent pulmonary component (P_2). There was no murmur or gallop. Stool was negative for occult blood. There were no palpable cords in the lower extremities, and there was no lower extremity edema. Arterial blood gas on room air was pH 7.441, $PaCO_2$ 32 mm Hg, PaO_2 67 mm Hg, bicarbonate 21.3 mEq/L, and a base excess of −1.7, findings consistent with chronic respiratory alkalosis and metabolic compensation. The alveolar-arterial gradient was 42 mm Hg.

His chest radiograph showed prominent right central pulmonary arteries, but was otherwise unremarkable, and there was no evidence of effusion, infiltrate, or pneumothorax. An electrocardiogram showed a normal sinus rhythm at 79 beats per minute, and there were inverted T waves in leads II, III, aVF, and V_1 through V_5, consistent with right heart strain. A ventilation-perfusion scan showed multiple, bilateral, moderate-to-large, segmental, mismatched perfusion defects and was read as high probability for pulmonary embolus.

A sonogram of the lower extremities showed extensive chronic intraluminal thrombi in the left superficial femoral and proximal popliteal veins and collateralization by the left superficial vein. The right lower extremity had no thrombi. An echocardiogram showed severe pulmonary hypertension with right ventricular pressure overload findings and right ventricular hypokinesis. The estimated systolic pulmonary artery pressure was 92 mm Hg (normal 14–30 mm Hg). The right atrium and right ventricle were enlarged, and the intraatrial septum was bulging into the left atrium.

Severe pulmonary arterial hypertension was evident on a pulmonary angiogram, with pulmonary arterial pressures reaching 87/33 mm Hg (mean of 52 mm Hg) at their highest levels. There were

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multiple weblike pulmonary artery stenoses and marked pruning of branches. There was marked truncation of a left lower lobe medial branch vessel, indicative of acute thromboembolism superimposed on chronic thromboembolic disease. During the pulmonary angiogram an inferior venacaval filter was placed (Greenfield device).

Laboratory studies for the following were later returned as negative: factor V Leiden, activated protein C, prothrombin gene mutation (G20210A), protein S deficiency, protein C gene mutation, antithrombin III deficiency, hyperhomocystinemia, antinuclear antibody, and lupus anticoagulant. The hemoglobin electrophoresis showed the sickle cell trait with 36% hemoglobin S.

The patient was given intravenous unfractionated heparin and coumadin. Within 48 hours, his hemoglobin oxygen saturation increased to 96% on room air and the alveolar-arterial gradient dropped to 28 mm Hg; clinically, the patient was able to complete his activities of daily living without shortness of breath. Once coumadin reached therapeutic blood levels, the patient was released to home. When he had a follow-up echocardiogram after 10 weeks of anticoagulation therapy, his estimated systolic pulmonary artery pressure improved to 35 mm Hg. The patient's complaint of shortness of breath and coughing had resolved, but he continued to have exertional dyspnea. He returned to student status.

Discussion

Chronic thromboembolic disease is thought to be the result of small, recurrent pulmonary emboli that develop slowly until vascular occlusion is sufficient to result in pulmonary hypertension.[3] This underlying pathophysiologic condition is presumed to have occurred in the case described here. The patient had a long-standing left femoral thrombus, with collateralization of vessels evident on sonography. Most likely this thrombus had dislodged clots through the venous system and the right side of the heart to the lungs for many months, resulting in progressive pulmonary hypertension and accounting for the patient's long-standing symptoms of fatigue, cough, shortness of breath, and progressive dyspnea on exertion. The fixed, split S_2 with the prominent pulmonary component (P_2) on cardiac examination and the echocardiographic findings were consistent with chronic pulmonary hypertension. Given the patient's symptoms, degree of pulmonary hypertension, and right ventricular hypokinesis, it is possible he would not have survived any additional acute pulmonary thromboembolism.

Patients with chronic thromboembolic pulmonary hypertension suffer from exercise intolerance and progressive dyspnea. They experience deterioration with intermittent stabilization,[4] and they might have right ventricular ischemia as the right ventricle hypertrophies and exceeds its blood supply. Syncope can occur as a result of sudden decreases in right ventricular preload during a Valsalva maneuver. Lower extremity edema caused by right heart failure or the postphlebitic syndrome can occur.[2] A prominent P_2 can be heard during the examination, and the arterial blood gas will usually show a widened alveolar-arterial gradient. Chest radiographs are often read as normal but in retrospect can show signs consistent with pulmonary hypertension.

Chronic thromboembolic disease is often mistakenly diagnosed as coronary artery disease, cardiomyopathy, interstitial lung disease, asthma, deconditioning, or psychogenic dyspnea. Some patients have been enrolled in an exercise program or advised to seek psychiatric help.[2] An echocardiogram showing elevated pulmonary artery pressures is important in narrowing the differential diagnosis. Any mismatched defect on a ventilation-perfusion scan in a patient with complaints of progressive shortness of breath and exercise intolerance should prompt consideration of pulmonary angiography.[2]

Treatment is generally with anticoagulation using heparin and coumadin and placement of an inferior vena cava filter. There have not been any trials of patients with proven pulmonary hypertension using low-molecular-weight heparin.[2] Thrombolytic therapy can be considered in acute pulmonary embolism for patients who are hemodynamically unstable. Thrombolysis is not indicated for chronic pulmonary embolisms because of clot endothelialization in the pulmonary vasculature. Thromboendarterectomy can be considered for those patients who have considerable hemodynamic or ventilatory impairment at rest or with exercise, for patients whose thrombi are accessible by current surgical methods, and for those who have few serious comorbid conditions that might affect the outcome of the procedure.

Operative and perioperative mortality rates are high, and it is important that patients considered for this procedure be selected carefully. In the case described here, the patient's symptoms improved noticeably with medical therapy alone, and thromboendarterectomy was not necessary. Lung transplantation is an option for patients who do not respond to medical therapy and who are not candidates for thromboendarterectomy.

Conclusion

Chronic thromboembolic disease is not rare, and the consequences of a missed diagnosis can be deadly. All physicians should be aware of the subtle symptoms and signs of chronic thromboembolic disease and consider it in the differential diagnosis of any patient complaining of unexplained shortness of breath and dyspnea on exertion.

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