Chronic Thromboembolic Disease: Underdiagnosis and Nonsurgical Options

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Chronic thromboembolic disease (CTED) remains an important exclusion in patients presenting with pulmonary hypertension. As illustrated by this case, however, exclusion must be rigorous with or without a suggestive history. Although it is a surgically treated disease, not all patients may be candidates for or elect surgery, leaving medical management as the only remaining option.

An 81-year-old man, a lifelong nonsmoker, was referred for evaluation of pulmonary hypertension and dyspnea. Historically, the patient had progressive dyspnea in retrospect for more than 3 to 5 years. He was diagnosed with chronic obstructive pulmonary disease (COPD) and an acute lower extremity deep vein thrombosis approximately 3 years ago but had little to no improvement with bronchodilators and inhaled corticosteroids. He was unable to participate in his regular sports and exercise program for the last 1 to 2 years. He was prescribed oxygen and furosemide approximately 6 months prior. The patient continued to note deterioration in exercise tolerance until he was referred with increasing symmetric peripheral edema. An outside computed tomographic (CT) scan showed a very small area of fibrosis in one lung and the patient underwent uneventful bronchoscopy at an outside institution. An outside echocardiogram revealed a dilated right ventricle with an estimated right ventricular pressure of 128 mmHg, which prompted referral.

Upon review, the past history was negative for HIV risks, anorexigen exposure, or illicit drug use. Past medical history was remarkable for:

- Systemic hypertension
- Benign prostatic hypertrophy
- Hyperlipidemia
- Type 2 diabetes
- Deep venous thrombosis diagnosed after onset of dyspnea
- Chronic renal insufficiency with baseline serum creatinine 1.8 to 2.0 mg/dL

Previous allergies and adverse medication reactions, which included muscle pain, were reported to cerivastatin. Family history was remarkable only for leukemia and systemic hypertension in his parents. There was no history of pulmonary hypertension or venous thromboembolism. There were no significant industrial, environmental, or social exposures. Incidental review of systems was positive only for dyspnea on exertion, symmetric peripheral edema. In particular the patient denied chest pain, hemoptysis, cough, palpitations, or syncope.

Physical examination was remarkable for a patient who appeared his stated age. He was in a wheelchair and receiving nasal cannula oxygen therapy. Jugular venous distension was 4 cm at 45 degrees. Heart rate was regular but had a split S2 with an accentuated pulmonic component. There was a II-III/VI systolic murmur best heard at the left lower sternal border and a suggestion of right ventricular lift. Abdomen was nontender without ascites or organomegaly. The extremities were free of deformity, telangiectasia, clubbing, or cyanosis; 1+ bilateral ankle edema was noted.

Initial Testing

• ***Echocardiography:*** Normal left ventricular and left atrial size and function. Normal aortic, pulmonic, and mitral

Key Words—Chronic thromboembolic disease, V/Q scanning, differential diagnosis, small vessel PAH, thromboendarterectomy.

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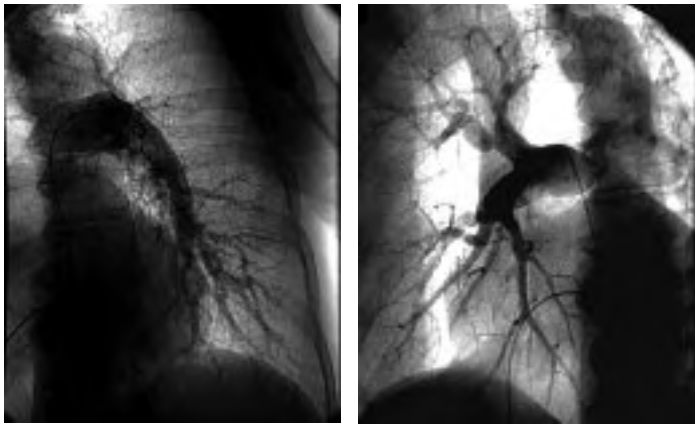


Figure 1. Fluoroscopic pulmonary angiograms show vascular irregularities typical of chronic thromboembolic disease.

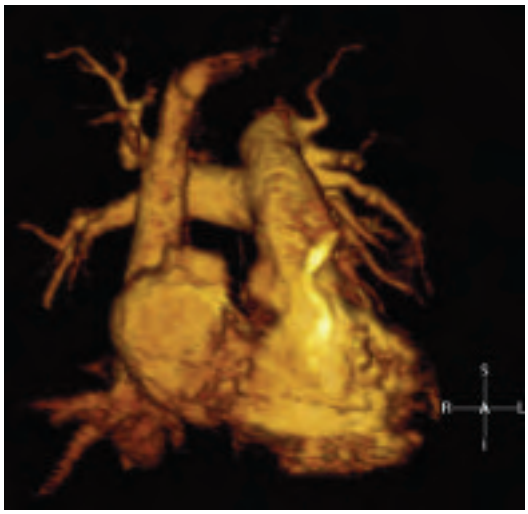


Figure 2. Magnetic resonance image of pulmonary vasculature in chronic thromboembolic disease.

valves; 2+ tricuspid regurgitation. Moderate to severe right atrial and right ventricular dilation with an estimated RVSP of 81 mmHg. Evidence of septal flattening.

• ***Spirometry:*** FVC = 87%, which improved to 98% predicted following bronchodilator; FEV1 = 84%, which improved to 99% predicted following bronchodilator; TLC = 127% predicted; RV = 136% predicted; DLCO = 100% predicted.

• ***Six-minute walk test:*** 290 meters in 6 minutes with desaturation to 92%.

Chemistries and blood counts were within normal limits except for a serum creatinine level of 2.0 mg/dL consistent with past medical history. Outside CT pulmonary angiogram was read as negative for thromboembolism.

At this point, the patient was referred for ventilation perfusion scanning, which showed unmatched perfusion defects in the right mid-lung zone and left upper lobe.

• ***Right heart catheterization:*** RAP = 10; PA = 105/14; PAOP = not obtainable; MvO2 = 62%; SpO2 = 96%.

Previous left heart catheterization showed trivial coronary artery disease with normal left ventricular end diastolic function.

Arterial blood gas analysis on room air, 7.48/28/75/20/96%; CBC, normal; BNP = 706 ng/L.

Clinical Course

Pulmonary thromboendarterectomy was declined by the patient. Therapy was started with sildenafil and bosentan after the patient declined infusion therapy with epoprostenol. Results of 6-minute walk testing remained relatively stable. His diuretic regimen was unchanged. Dyspnea was subjectively improved. However, 6-minute walk distance was relatively unchanged.

Discussion

Review of this case points out a number of important considerations for the diagnosis of CTED and illustrates the clinical problem of management of patients who either decline thromboendarterectomy or may not be candidates for the surgery.

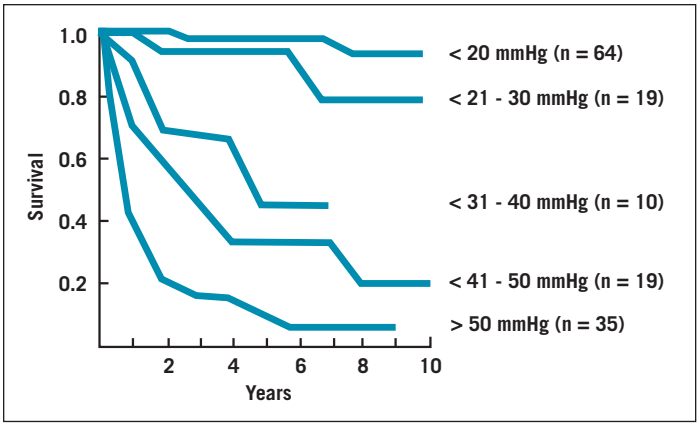
Some current estimates suggest that chronic thromboembolic pulmonary hypertension complicates pulmonary embolism in as many as 3.8 % of patients.[1] However, as many as 30% to 50% of patients with CTED do not have historical evidence of an intial venous thromboembolic event—underlining the importance of routine V/Q scanning of patients with documented pulmonary hypertension. This patient did have a history of recent peripheral venous thromboembolism but received initial evaluations that were inadequate to disclose all factors involved in the production of the pulmonary hypertension. Current guidelines for the diagnosis of pulmonary hypertension suggest that ventilation/perfusion scanning is the test of choice to exclude the entity of CTED.[2] CT pulmonary angiography, although reported to detect CTED, may at times lack sufficient diagnostic sensitivity. The reasons for this may include technical limitations of the technique and insufficient experience in interpretation of subtle changes that suggest CTED. The presence of at least one perfusion mismatch should prompt further diagnostic evaluation.

Angiographic findings in this patient are typical of CTED, demonstrating vascular webs, irregular caliber of vessels that should be uniformly arborizing, intimal irregularities, and acute vascular cut-offs (**Figure 1**).[3] Adjunct scanning with magnetic resonance imaging (MRI) technology yielded interesting similar vascular contours and perfusion abnormalities suggesting the diagnosis as well (**Figure 2**). The role of MRI in the evaluation of CTED is incompletely described at this time, but growing evidence suggests the possible utility in the diagnosis of this process.[4,5]

Selection criteria for pulmonary thromboendarterectomy once the diagnosis of CTED is established involve assessing:

- Distribution of the disease to determine surgical accessibility of the lesions
- Likelihood of significant clinical improvement
- Patient operability exclusive of the CTED with regard to age; concomitant illness such as coronary artery disease, renal insufficiency, and extensive parenchymal lung disease; and obesity

Perioperative mortality risks based on the degree of pulmonary hypertension and right heart dysfunction are further considerations in discussing the option of surgical thromboendarterectomy with patients. Several studies have dis-



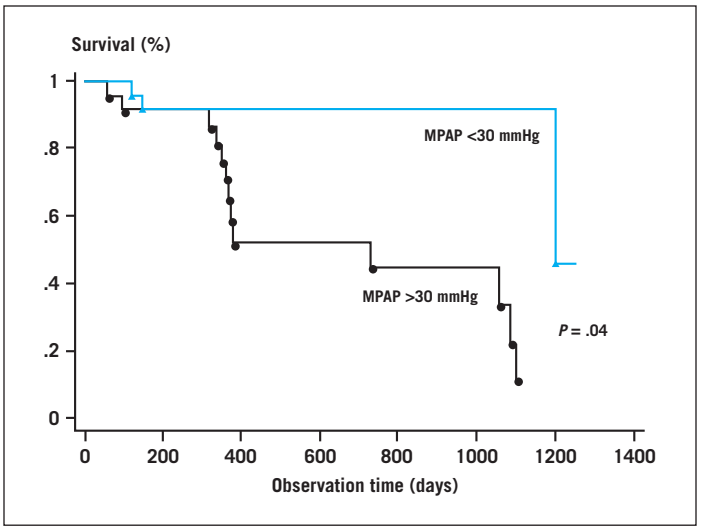


Figure 3. Natural history of chronic thromboembolic disease.

closed that preoperative PVRs greater than 1000 to 1100 dyn·s·cm^{-5} are associated with higher operative mortality rates. [6-8] However, the selection of appropriate patients for surgery, with its attendant risks, is offset by the potential for dramatic improvements in pulmonary hemodynamics and functional status postoperatively. With the endarterectomy of chronic thromboembolic material from the pulmonary vasculature, blood flow is restored to previously occluded lung regions. This results in a decline in pulmonary pressures and augmentation of cardiac output. Such a favorable outcome is obtained in the majority (>90%) of patients, results that have been reported from several centers throughout the world. [9-12]

For those CTED patients who have declined surgery or for those with inoperable disease, previous management strategies have been supportive. The placement of IVC filters has been advocated and lifelong anticoagulation is typically indicated. Oxygen and diuretic therapy are also used when indicated. However, with this approach, the natural history of this CTED remains deadly, especially for patients with very severe pulmonary hypertension (**Figure 3**).[13,14]

Recent advances in the medical management of pulmonary arterial hypertension have led to speculation that some of these treatments may also have some benefit for CTED patients with inaccessible disease, or who may not otherwise be surgical candidates. This concept is supported by the presence of small-vessel pulmonary arteriopathy coexisting in patients with CTED.[15] Several small, uncontrolled studies have anecdotally addressed this issue using bosentan, sildenafil, or intravenous prostacyclin, showing only modest pulmonary hemodynamic and functional status improvements.[16-19] Currently no PAH agents are approved for use in patients with CTED.

Key Points

- V/Q scanning is important in differentiating CTED from small-vessel pulmonary arterial hypertension.
- CTED should be considered in the differential diagnosis of pulmonary arterial hypertension in all patients, even in the absence of documented venous thromboembolism.
- Assessment for surgical therapy includes evaluation of the pulmonary vascular anatomy for proximal CTED (eg, conventional pulmonary angiography, or carefully performed CT angiography).
- Management of patients who cannot or will not undergo surgery is largely supportive. Whether patients may have some benefit from the treatment of small vessel components of the disease remains an open question.

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