Chronic Thromboembolic Pulmonary Hypertension in a 69-Year-Old Man

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially life-threatening consequence of acute and recurrent pulmonary embolism (PE).[1] It is characterized by pulmonary hypertension (mean pulmonary artery pressure [PAP] > 25 mm Hg at rest or > 30 mm Hg with exercise[2]) and right heart failure. CTEPH represents an infrequent and underrecognized secondary cause of pulmonary hypertension. Failure to recognize CTEPH often results in a delay in diagnosis, and this condition has a poor prognosis if left untreated.[3] However, CTEPH can be treated successfully with surgical intervention in appropriately selected patients. This article reports the case of a 69-year-old man who presented with an 8-month history of progressive dyspnea on exertion and syncope. The patient, who had a history of prior episodes of acute PE, was subsequently diagnosed with CTEPH. A review of the approach to diagnosing and treating this entity is also provided.

CASE PRESENTATION

History and Initial Evaluation

A 69-year-old man presented to the emergency department with symptoms of exertional syncope and shortness of breath. The patient reported an 8-month history of progressive dyspnea on exertion and syncope. While traveling outside of the United States 8 months ago, the patient presented to a hospital with a chief complaint of syncope and subsequently was diagnosed with acute PE. He was managed with intravenous heparin followed by 6 months of warfarin anticoagulation to a target international normalized ratio (INR) of 2 to 3. His past medical history was significant for recurrent episodes of deep vein thrombosis (DVT) and PE as well as secondary pulmonary hypertension that occurred 5 years earlier, for which he was receiving long-term anticoagulation therapy with warfarin (target INR, 2–3). At this time, a limited thrombophilia panel was completed and reported as normal. Because the patient was receiving warfarin, it was recommended that this therapy should be interrupted after 6 months to complete the thrombophilia panel, but this was not done.

The current physical examination revealed a hemodynamically stable patient with jugular venous distension at 15-cm H_2O, a right ventricular (RV) lift, and persistently split S_2 sound with an increased pulmonic component. Laboratory studies including a complete and differential blood count, blood urea nitrogen, serum creatinine, an electrolyte panel, and a liver function panel were ordered, which were all within normal limits. Arterial blood gases revealed a low partial pressure of oxygen and saturation of 88% on room air. Supplemental oxygen was administered, and the patient was admitted to a monitored telemetry bed in the general service for further evaluation.

Diagnostic Work-up

After admission, the patient underwent electrocardiography, which showed deep symmetric T-wave inversion in the precordial leads suggesting RV strain. A subsequent transthoracic echocardiogram revealed a small left ventricle with a D configuration caused by flattening of the interventricular septum from high right-sided blood pressures (**Figure 1**); a normal left ventricular ejection fraction at 71%; severe pulmonary hypertension (estimated right ventricular systolic pressure [RVSP], 87 mm Hg; systemic blood pressure, 130/78 mm Hg) with RV hypertrophy; severely reduced RV systolic function; and moderate tricuspid regurgitation. Ventilation-perfusion (V/Q) lung scan revealed multiple bilateral

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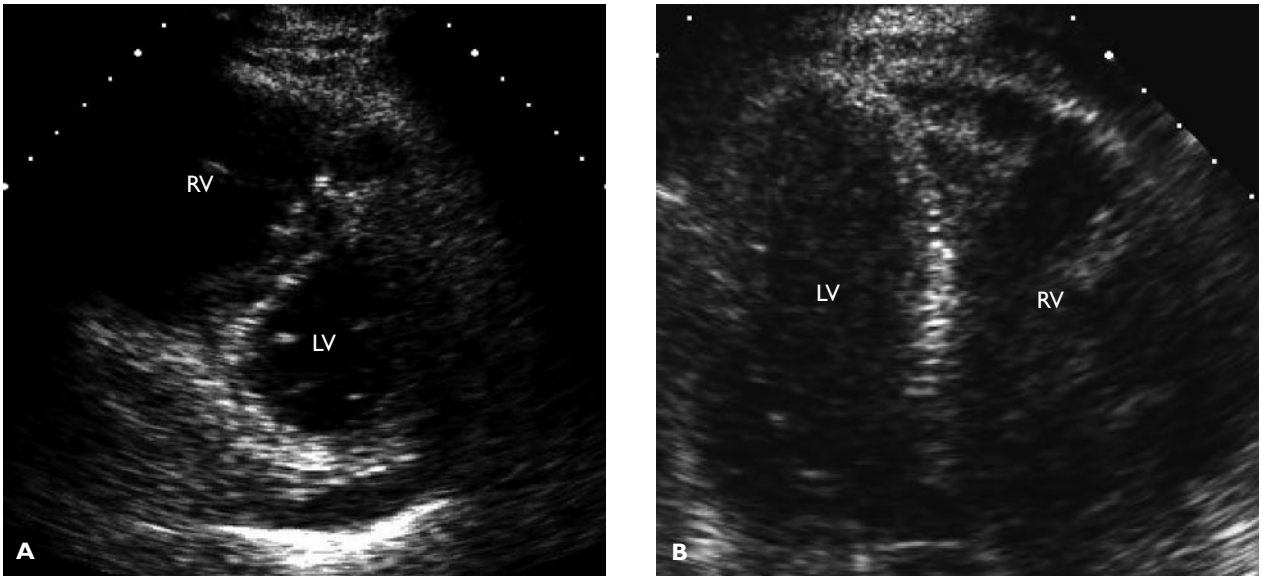

Figure 1. (**A**) A parasternal long-axis echocardiogram demonstrating a small left ventricle (LV) with a D configuration due to flattening of the interventricular septum and high right-sided pressures. (**B**) A 4-chamber–view echocardiogram demonstrating an enlarged right ventricle (RV).

wedge-shaped perfusion defects and normal ventilation with high probability for PE (**Figure 2**). Computed tomography (CT) angiogram findings were consistent with chronic PE in the left lower lobe pulmonary artery, the right upper lobe pulmonary artery, bifurcation of the right upper and lower lobes, and subsegmental branches of pulmonary arteries of the left and right lower lobes, with no evidence of acute pulmonary emboli (**Figure 3**). Right heart catheterization revealed a right atrial pressure of 21/20 mm Hg, RVSP of 102/19 mm Hg, PAP of 105/55 mm Hg, and pulmonary capillary wedge pressure of 15/12 mm Hg. Nitroprusside infusion had no effect on pulmonary blood pressures or vascular resistance during right heart catheterization. Based on the results of these studies and the patient's history and physical examination findings, the patient was diagnosed with CTEPH.

Treatment and Hospital Course

Bilateral pulmonary thromboendarterectomy was performed on hospital day 6. Pathology specimens confirmed old organized thrombus and recent degenerating thrombus (**Figure 4**). RVSP decreased to 30 mm Hg postoperatively. The patient developed atrial fibrillation and volume overload requiring aggressive diuresis on hospital day 8. On postoperative day 3 (hospital day 9), the patient was extubated and remained hemodynamically stable. An intercurrent urinary tract infection with *Enterobacter cloacae* was diagnosed on hospital day 9 and was treated with antibiotics for 5 days. Elective cardioversion was completed to restore sinus rhythm on hospital day 10. The patient began ambulating on hospital day 11 and was discharged on warfarin (target INR, 2–3) for 4 weeks postcardioversion on hospital day 15.

CTEPH

In most patients with acute PE, the thrombosis resolves, leaving behind minimal to no residua. Pulmonary hypertension related to a large nonresolved or recurrent small pulmonary emboli may occur but typically resolves with dissolution of the thrombus.[1,2,4] In contrast, CTEPH results from obstruction of large pulmonary arteries by acute and recurrent pulmonary emboli with subsequent organization of the thrombi.[1] Both the extent of proximal occlusion of pulmonary arteries due to nonresolved thrombus and secondary small-vessel arteriopathy from vascular remodeling contribute to high pulmonary vascular resistance (PVR).[3,5,6] The reason the thrombus does not resolve in patients with CTEPH is unknown. The presence of thrombotic risk factors, such as antithrombin III, protein C, or protein S activity, as well as factor II and factor V Leiden mutations was not different between CTEPH and primary pulmonary hypertension or control subjects.[6,7] However, antiphospholipid antibodies and elevated levels of factor VIII are seen more commonly in CTEPH patients,[7,8] which suggests that an underlying hypercoagulable state may be responsible for CTEPH.

The actual incidence of CTEPH is unknown. Each year, approximately 500 to 2500 US patients are diagnosed with this condition, accounting for 0.1% to

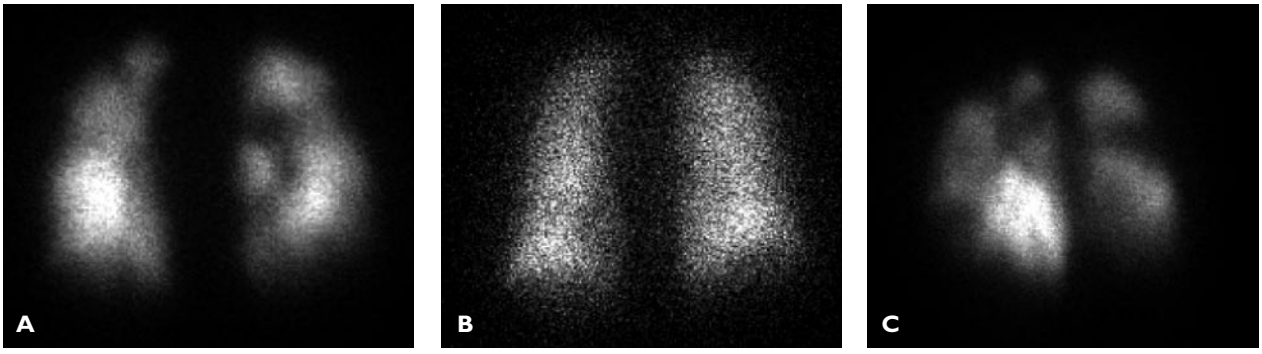

Figure 2. Posterior ventilation-perfusion lung scans showing (**A**) multiple bilateral perfusion defects and (**B**) normal ventilation. Ventilation-perfusion scan of the left posterior oblique lung revealed (**C**) bilateral multiple wedge-shaped perfusion defects.

0.5% of patients with pulmonary emboli who survive.[9] However, these figures are thought to underestimate the true incidence of CTEPH. In 1 study that enrolled 223 patients with PE, the cumulative incidence of symptomatic CTEPH was 1.0% of cases occurring 6 months after an acute episode of PE, 3.1% at 1 year, and 3.8% at 2 years.[4]

Clinical Features

In patients with CTEPH, the past medical history may be significant for previous episodes of acute PE. In these patients, an asymptomatic period following the thromboembolic event precedes the development of progressively worsening symptoms. However, it is estimated that more than half of all patients with PE remain undiagnosed.[1] In 1 series that included 434 DVT patients with or without signs of PE, only 88 (54%) of 164 patients diagnosed with PE had clinically apparent PE at presentation. Of the 346 DVT patients who had no signs or symptoms of PE, 76 (22%) were found to have silent PE on scintigraphy.[10] Therefore, nearly two thirds of CTEPH patients may not have a history of acute PE, which may result in diagnostic delays.[11] Patients without a history of PE have a clinical course similar to that of primary pulmonary hypertension.[12] However, some patients may provide a history that is consistent with acute PE.[13]

Presenting features of CTEPH may include progressive dyspnea, chest pain, exercise intolerance, syncope, hemoptysis, or right heart failure. Typically, patients present with an advanced degree of pulmonary hypertension.[3] Because CTEPH usually presents with nonspecific symptoms that can resemble numerous cardiac or pulmonary conditions, diagnostic delays may occur.[3] Physical examination reveals signs of pulmonary hypertension with an RV heave and a palpable P_2. Cardiac auscultation may reveal loud split S_2, tricuspid regurgitation or pulmonic insufficiency murmurs, or an RV S_3 or S_4 gallop. With untreated and progressive pulmonary hypertension, RV dysfunction and right heart failure will supervene. The physical findings at this time may also include jugular venous distention, hepatomegaly, ascites, peripheral edema, and chronic venous stasis dermatitis.[3] A high peripheral pulmonary bruit (representing turbulent flow through partially occluded or recanalized thrombi) is heard in approximately one third of patients presenting with CTEPH.[3] These bruits are nonspecific for CTEPH and are also audible in other causes of proximal pulmonary artery narrowing (eg, pulmonary artery sarcoma, congenital pulmonary artery stenosis, and pulmonary arteritis[14]) but not in primary pulmonary hypertension.[15]

Diagnostic Evaluation

Findings obtained from laboratory studies are nonspecific for CTEPH, and the results of these studies vary depending on the stage of disease and the degree of thromboembolic obstruction and cardiac dysfunction.[13] Given that the patient presentation may suggest an underlying cardiac etiology, chest radiograph and electrocardiogram are often ordered. Chest radiograph may be normal or show hilar enlargement with oligemic lung fields, or parenchymal opacities that represent infarcts; right atrial or RV enlargement may be seen on the lateral views.[13,14] Electrocardiogram usually demonstrates RV hypertrophy, rightward QRS axis deviation, right bundle branch block, and nonspecific ST-segment abnormalities.[14] A normal electrocardiogram is rare.[14] Echocardiography, which is typically the initial diagnostic study when pulmonary hypertension is suspected, may show a hypertrophied, dilated, or hypokinetic right ventricle. Tricuspid regurgitation and elevated PAPs are usually present to a variable degree.[15] The presence of a mean PAP exceeding 40 mm Hg on echocardiography in a patient with a history of pulmonary

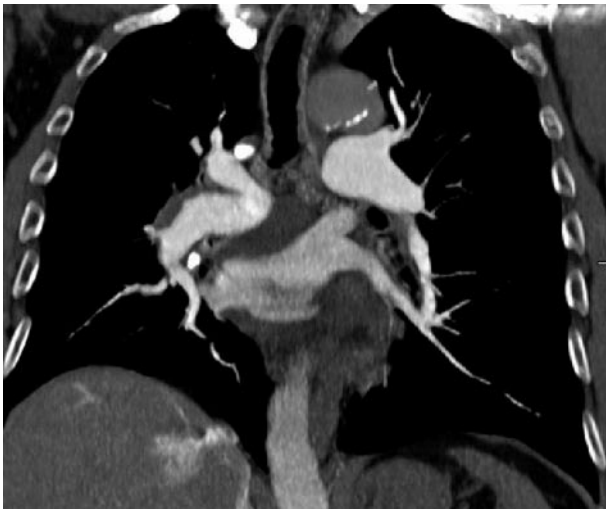

Figure 3. Helical computed tomography angiogram findings consistent with chronic pulmonary embolism in subsegmental branches of pulmonary arteries of the left and right lower lobes with no evidence of acute pulmonary emboli.

emboli supports a diagnosis of CTEPH.[1,11] Echocardiography also may provide prognostic information for patients with CTEPH.[16] Increased age (> 70 yr) and a systolic PAP exceeding 50 mm Hg at the time of diagnosis are independently associated with an increased risk of persistent pulmonary hypertension and RV dysfunction.[17] Patients with a systolic PAP exceeding 50 mm Hg at admission are 3 to 4 times more likely to have persistent pulmonary hypertension and RV dysfunction at 6 weeks and a lower 5-year survival than younger patients with lower systolic PAP.[16] Goldhaber[16] proposed that these patients are more likely to benefit from more aggressive management of acute embolus; however, Pengo et al[4] present evidence to the contrary.

Imaging techniques such as V/Q scanning, helical CT angiography, magnetic resonance imaging (MRI), pulmonary angiography, and right heart catheterization are important components in diagnosing patients with suspected CTEPH.[3] A completely normal V/Q scan excludes the diagnosis of CTEPH. A V/Q scan that reveals multiple perfusion defects is highly suggestive of CTEPH; however, other conditions may create these findings and further evaluation is required to confirm the diagnosis. A V/Q scan also underestimates the extent of disease.[3] Pulmonary angiography remains the gold standard for confirming the diagnosis of pulmonary artery hypertension. The angiographic findings in CTEPH include sharply defined intraluminal defects and are similar to those of acute PE. Findings more specific to CTEPH

Figure 4. Pathology specimens confirming old organized thrombus and recent degenerating thrombus.

and suggesting organized thromboembolic material include pouch defects, pulmonary artery webs, intimal irregularities, abrupt narrowing of the major pulmonary arteries, and obstruction of lobar or segmental vessels at their point of origin, with complete absence of blood flow.[18] Helical CT angiography can identify partial obstruction and abnormal thickening of the artery and is adjunctive to right heart catheterization in assessing surgical candidacy.[19] In a study that compared helical CT angiography with MRI in 55 CTEPH patients, the investigators collated the radiologic findings with surgical specimens and found that helical CT may be superior to MRI in detecting central lesions and segmental vessel disease.[20] Right heart catheterization, which is typically performed with pulmonary angiography, also rules out pulmonary venous hypertension, defines the degree of hemodynamic impairment, and helps select a therapeutic strategy.[19] Riedel et al[21] demonstrated that mean PAP higher than 30 mm Hg on right heart catheterization is associated with a poor prognosis in untreated CTEPH patients. Five-year survival with a mean PAP of 30 mm Hg is 30%; with a mean PAP of 50 mm Hg, the 5-year survival is only 10%.[21] Concomitant RV dysfunction also affords a worse prognosis.[22–24]

Treatment

All patients with CTEPH should receive lifelong anticoagulation prophylaxis with warfarin (target INR, 2–3) to prevent recurrent thromboembolic events, but regression of pulmonary hypertension due to anticoagulation therapy is unlikely.[3] In patients with mild disease (ie, mild pulmonary hypertension, little to no clinical impairment, and normal RV function), watchful waiting and anticoagulation are recommended.[3] However, the definitive treatment of patients with symptomatic CTEPH is surgical.

Thromboendarterectomy. Thromboendarterectomy has improved the prognosis in selected patients with an average mortality rate of 10.9% (range, 4%–20%).[1] Patients undergoing pulmonary endarterectomy experience marked symptomatic improvement early after surgery and in the long term.[1,9,22,25] Perioperative risk is related to preoperative hemodynamic data. The mortality rate is 4% when the PVR is below 900 dynes.s.cm^{-5}, 10% when the PVR is between 900 and 1200 dynes.s.cm^{-5}, and 20% when the PVR exceeds 1200 dynes.s.cm^{-5}.[1] A reduction in PVR exceeding 50% is usually seen after successful surgery and translates into improved functional status of the patient. Six-year survival postsurgery was approximately 75%.[22] Predictors of successful outcome are a prior history of PE or DVT; a period of months to years between the acute embolic event and the development of clinical symptoms of CTEPH; angiographic lesions located proximally in pulmonary arteries or lobar branches that provide easier surgical access to thrombi; correlation between PVR and anatomic obstruction; absence of hemodynamic impairment; and the surgeon's level of expertise.[26]

The decision to perform pulmonary endarterectomy is not only dependent on hemodynamic data but also on the clinician's opinion on the greatest potential benefits for these patients, which includes consideration of factors such as thrombi access, severity of hemodynamic/ventilatory impairment, and patient comorbidities.[26] Intravenous epoprostenol has been used with varying results to achieve hemodynamic stabilization prior to surgery, with some patients showing significant hemodynamic and clinical improvement.[3,27–29] Postoperatively, anticoagulation should be started as soon as possible. Because there is a high risk for PE recurrence, postoperative prophylaxis with unfractionated or low-molecular-weight heparin should be considered for the period during which the INR is less than 2 for warfarin.[30] Adding heparin should be weighed against the risks of bleeding postoperatively as compared with the morbidity and mortality risk associated with venous thrombosis and PE.[31]

Transplantation. Lung or heart-lung transplantation is indicated in patients with a life expectancy less than 1 year, New York Heart Association (NYHA) stage III/IV disease, and recent worsening of dyspnea and hemodynamic parameters (right atrial pressure > 12 mm Hg, PAP > 60 mm Hg, a cardiac index < 2.2 L·min^{-1}·m^{-2}, or indexed pulmonary resistance > 30 UI).[1] When thromboendarterectomy is not feasible, lung or heart-lung transplantation is the only option in eligible candidates with a 7-year survival of 40%.[9] Balloon atrial septostomy is palliative for inoperable cases of CTEPH in patients with advanced NYHA class III/IV disease or with recurrent syncope and/or right heart failure despite maximal medical management.[32] Atrial septostomy appears to improve hemodynamic parameters and survival in severe pulmonary hypertension refractory to vasodilator therapy, but the risks of the procedure are high.[33] For most patients, this procedure may not contribute significant survival benefit, and it is considered to be a bridge to lung transplantation.[33] There is a risk of complications and death during atrial septostomy, especially in inexperienced hands.[32,34]

Experimental approaches. Several experimental and clinical observations have suggested that an iatrogenic interatrial defect may be beneficial in patients with severe pulmonary hypertension, but data on this intervention are not robust.[23,24] The role of medical therapy is also being studied in patients with CTEPH. To date, phosphodiesterase-5 inhibitors and the endothelin receptor antagonist bosentan have shown potential benefit in CTEPH patients who are poor surgical candidates for endarterectomy.[3,35–38] Thus far, the Aerosolized Iloprost Randomization Study is the only controlled clinical trial that included CTEPH patients in evaluating the role of a vasodilator in pulmonary hypertension, but a post hoc subgroup analysis failed to show significant benefit of inhaled iloprost on hemodynamics or exercise capacity in patients with severe pulmonary hypertension.[3,39]

Prevention. The best approach to decreasing the morbidity and mortality as well as the large medical burden and expense associated with CTEPH[15] is to prevent this condition. CTEPH is among the long-term sequelae of PE;[9,13,15] however, most cases of PE are not diagnosed.[1] Ultimately, prevention of DVT and PE with prophylaxis agents when possible as well as proper treatment of acute PE and prevention of recurrent events with anticoagulation may result in fewer cases of CTEPH.[40–44] As noted earlier, the role of aggressive management of acute embolus with thrombolytic therapy for prevention of CTEPH is still unclear.[4]

CONCLUSION

CTEPH is a leading cause of severe pulmonary hypertension and frequently occurs as a consequence of acute and chronic PE. The diagnosis of CTEPH is typically delayed until the degree of pulmonary hypertension is severe and, in many cases, RV dysfunction supervenes. Multimodality noninvasive imaging is usually needed to make the diagnosis, to define the etiology and degree of pulmonary hypertension, and to determine accessibility for surgical intervention. Pulmonary thromboendarterectomy is the primary form of therapy. Team experience and expertise in evaluating

disease burden and providing surgical as well as postoperative care are important for successful management of patients with CTEPH. **HP**

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