CLINICAL VIGNETTE

Persistent Dyspnea After Pulmonary Embolism

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Chronic thromboembolic pulmonary hypertension (CTEPH) is diagnosed when pulmonary artery pressures remain elevated many months after expected resolution of acute pulmonary embolism (PE). This condition is frequently overlooked because many patients report no history of overt pulmonary embolism. Patients usually have an initial 'honeymoon period' after acute PE during which symptoms are absent. As pulmonary hypertension worsens, patients present with dyspnea, hypoxemia, and right ventricular dysfunction. Echocardiography showing elevated pulmonary pressures is often the initial diagnostic test. Further testing with chest computed tomography angiogram (CTA) and/or ventilation perfusion (VQ) scan can confirm the diagnosis. Once CTEPH is suspected, referral to a specialized center for further invasive testing including pulmonary angiogram and right heart catheterization is warranted to assess surgical candidacy. For appropriate surgical candidates, thrombo-endarterectomy is the treatment of choice. Medical therapies are being investigated with encouraging results for nonsurgical candidates. We present a case of CTEPH that developed in a patient several months after acute PE.

Case Report

A 65-year-old retired mathematician suffered from severe bilateral hip pain from advanced osteoarthritis. Due to his symptoms, he was confined mainly to a wheelchair for several months and was considering hip replacement surgery. While using the toilet one evening, he developed sudden onset left sided weakness. He was taken to an outside hospital where brain imaging showed an acute right-sided middle cerebral artery stroke and he was treated with recombinant tissue plasminogen activator (t-PA). His left sided deficit resolved, but he was noted to have persisting hypoxemia during his hospital stay. Chest CTA showed a right lower lobe PE. Echocardiography reportedly showed normal chamber sizes and normal pulmonary artery pressure. Subsequently, the patient was discharged home on supplemental oxygen and warfarin anticoagulation.

Several weeks later, the patient was admitted at our hospital for persistent exercise intolerance and dyspnea. His weakness had become so pronounced he was "unable to get out of bed". He remained hypoxic with oxygen saturations of 80% on room air. Repeat chest CTA showed chronic appearing PE in multiple distributions in the right lung that was essentially unchanged when compared to the outside scan (**Figure 1**). The lung parenchyma on this scan was otherwise normal. Lower extremity Doppler ultrasound revealed acute and chronic appearing clots in the right and left lower extremities. An inferior vena cava (IVC) filter was placed to try to prevent any further PE and the patient was discharged home.

On follow-up several weeks later, the patient was noted to have persistent hypoxemia with oxygen saturations in the low 90% range despite oxygen supplementation at 4L/minute by nasal cannula. Repeat echocardiogram showed marked tricuspid regurgitation (5.21 m/sec and calculated pulmonary artery systolic pressure >100 mm Hg) with a slightly enlarged and hypokinetic right ventricle. A follow-up 'bubble' echocardiogram showed an "obvious" right to left shunt consistent with a patent foramen ovale (PFO). A VQ scan was consistent with chronic thromboembolic disease, and a subsequent pulmonary angiogram showed proximal dilation of the right pulmonary arteries and segmental defects in the pulmonary circulation (**Figure 2**).

Right heart catheterization showed elevated direct pulmonary artery pressure measurements of 84/19 mm Hg. The diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) was confirmed with associated PFO and marked hypoxemia. Subsequently, the patient underwent surgical thromboendarterectomy and closure of his PFO. After surgery, his pulmonary artery pressures normalized on direct catheter measurement, and a hypercoaguable workup was negative for any identifiable thrombophilia. Also, his hypoxemia improved postoperatively and he was successfully weaned off oxygen and discharged home. Several months later the patient underwent bilateral hip replacement surgery without complications. At his last orthopedic follow-up the patient noted that he "wanted to take up golfing again".

Discussion

Chronic thromboembolic pulmonary hypertension (CTEPH) has been formally defined as mean pulmonary artery pressure greater than 25 mm Hg that persists for 6 months after diagnosis of acute pulmonary embolism[1]. The diagnosis of CTEPH is often delayed or overlooked. In fact, large CTEPH registries report nearly half of the patients had no reported history of overt pulmonary embolism prior to their diagnosis of pulmonary hypertension. This suggests there may be many patients in which this disease is not recognized[2]. No medical therapy except anticoagulation at the time of PE has been shown to help prevent CTEPH. In patients with submassive PE some studies showed fibrinolytic therapy given in addition to standard anticoagulation within 2 weeks after acute PE may reduce the frequency of CTEPH. This issue has been controversial[3]. The true frequency of CTEPH following pulmonary embolism is unknown and estimates of disease prevalence have varied. Some prospective series have reported incidence as high as 2-4% following unprovoked pulmonary embolism.[4] Diagnostic delays are common and this condition is usually discovered when patients present with dyspnea, hypoxemia, and right ventricular dysfunction in the months and years following pulmonary embolism. Echocardiography typically shows elevated pulmonary pressures and chest CTA or VQ scan confirm pulmonary emboli. If CTEPH is diagnosed, referral to a specialized center for further invasive tests is warranted to determine whether the patient is a surgical candidate. Surgical thromboendartectomy is the treatment of choice. For nonsurgical candidates, several medical therapies are being investigated[1, 2].

CTEPH results not only from obstructing thrombi, but also from multiple subsequent changes in the vascular biology of the pulmonary microcirculation. In most cases of acute pulmonary embolism the patient will go on to resolve any pulmonary pressure elevation within a few weeks to months of the incident event. A small perscentage of vulnerable patients, however, will go on to develop severe and persistent hypertension in their pulmonary vasculature. In fact, many of the vascular changes seen on pathologic specimens of the lungs taken from patients with CTEPH are in areas not directly involved by the obstructing thromboemboli[1]. Additionally, it has been reported that patients with CTEPH have some response to pulmonary vasodilators, which would not be expected if the obstructive lesions were fixed emboli. These observations suggest pulmonary hypertension seen in patients with CTEPH is not simply related to obstructed flow from embolic thrombi, but reflects complex changes in vascular biology. In addition to persistent macrovascular obstruction, there is also a vasoconstrictor response that leads to a secondary small-vessel arteriopathy and further adverse vascular remodeling[1, 2]. Marked small vessel abnormalities (medial hypertrophy, microvascular thrombosis, and plexiform-lesion formation) that are similar to the pathologic features seen in 'idiopathic' pulmonary hypertension have been noted in patients with CTEPH[5]. The combination of these factors produces pulmonary pressures and right ventricular dysfunction that far exceeds the level expected from just macrovascular obstruction[2]. Researchers speculate that unknown factors tip the balance toward a pathologic vasculopathy, rather than fibrinolyisis and healing of the vascular bed in pulmonary embolism patients who are susceptible to CTEPH. To date, though, no clear fibrinolytic or other biologic defect has been identified in patients who develop CTEPH[6].

The presenting symptoms of CTEPH are typically indolent and diagnostic delays are common. Dyspnea along with exercise intolerance and fatigue are the most commonly reported symptoms. Dyspnea is thought to occur as a result of increasing ventilatory "dead space" and limited cardiac output brought on by loss of effective pulmonary circulation, and the pulmonary hypertension and subsequent right heart dysfunction resulting from the changes in vascular biology of the pulmonary circulation[1, 2]. Interestingly, patients with CTEPH often have a 'honeymoon' period during which they are asymptomatic between the initial pulmonary embolism and symptomatic disease discovered many months later. Several factors are known to be increase the risk of developing CTEPH (see **Table 1**)[1, 4, 7]. Severe hypoxemia is rare in CTEPH, unless there is an associated right to left shunt. In is speculated that elevated pulmonary pressures can accentuate a "shunt" of deoxygenated blood through a PFO. A PFO is an embryologic remnant which closes after utero in the majority of people, although remain at least "probe patent" in up to 25% of patients in autopsy studies. "Bubble" echocardiogram studies have reported similar prevalence in pulmonary hypertension patients and in patients with pulmonary embolism[8, 9]. Observational studies have shown its significance varies, but in theory can contribute to a sizable "shunting" of deoxygenated

blood, particularly when elevated pulmonary artery pressures are present[10].

As it is often not suspected on history and physical examination, testing with echocardiography typically provides the first indication of CTEPH. It is important to note, however, that some studies show that echocardiographic measurements can both underestimate and overestimate pulmonary artery pressures. Also it should be remembered that while echocardiogram is reasonably sensitive for the detection of pulmonary hypertension, it is not specific for the diagnosis of CTEPH[11]. Common echocardiographic findings of pulmonary hypertension include right ventricular dilation or dysfunction, intraventricular septal deviation toward the left ventricle during systole indicating right ventricular pressure overload, and tricuspid regurgitation[2]. Once pulmonary hypertension is confirmed, VQ scanning is useful in differentiating CTEPH from other causes of pulmonary hypertension and normal findings on a VQ scan practically rule out the diagnosis[12]. Chest CTA is also useful in showing the anatomical location of clots for surgical planning. Referral to specialized centers for additional invasive testing such as right heart catheterization with vasodilator challenge and pulmonary angiography is warranted if diagnosis of CTEPH is suspected after the above noninvasive tests. These tests are the gold standard for establishing the diagnosis and determining candidacy for operation[1, 2].

Pulmonary thromboendarterectomy is the definitive and most effective treatment for patients with established CTEPH[13]. In those who are not surgical candidates, medical therapy, which includes any medical intervention in addition to anticoagulation, is considered. Patients who undergo thromboendarterectomy generally experience significant improvement of their hemodynamics as well as clinical symptoms. Surgery is complex and should be performed at experienced centers. The 30-day mortality can be as low as 4-7% in these centers[14]. Patient selection is important in surgical outcomes. Thistlethwaite and colleagues have classified CTEPH into four types that predict the surgical outcome. Type I disease has fresh thrombus in the main or lobar pulmonary arteries that are visible and can reasonably be removed. Type 2 shows intimal thickening and fibrosis with or without organized thrombus proximal to segmental arteries. Type 3 has fibrosis, intimal webbing, and thickening with or without organized thrombus within distal segmental and subsegmental arteries. Type 4 has microscopic distal arteriolar vasculopathy without visible thromboembolic disease. Patients with type 1 and 2 diseases have the most success whereas type 3 and 4 disease patients have more persistent postoperative pulmonary hypertension, pulmonary vascular resistance, tricuspid regurgitation, perioperative mortality, and longer postoperative inotropic support and hospitalization time[15]. In addition, patients with higher preoperative pulmonary vascular resistance tend to have higher perioperative mortality. Patients with pulmonary vascular resistance (PVR) greater than 1100 dyn-s/cm^5 have postoperative mortality between 20-41% compared to patients with less than 1100 dyn-s/cm^5 have 4-6% postoperatively mortality[16]. Lastly, patients with multiple medical comorbidities may not be appropriate surgical candidates and may have increased postoperative complications and mortality.

Approximately 40% of patients with CTEPH are not candidates for pulmonary thromboendarterectomy, or have persistent pulmonary hypertension despite surgical treatment[17]. In these patients, medical therapy is considered. Several medications have been investigated including pulmonary vasodilators such as bosentan, sildenafil, prostacyclin analogues, and endothelin-receptor antagonists. Early studies have shown favorable results for several of these agents. For example, bosentan has shown to improve pulmonary vascular resistance, cardiac index, levels of pro-brain-type natriuretic peptide, and dyspnea. Long-term use of sildenafil at 50mg three times per day improves pulmonary vascular resistance, cardiac index, 6-minute walk distance and the World Health Organization (WHO) function. Treprostinil, a prostacyclin analogue, showed similar improvement to sildenafil in hemodynamics and clinical symptoms[1]. Patients with a diagnosis of CTEPH should be referred to a specialized center where advanced therapies and clinical trials are available. Also, it is important to note that patients with CTEPH should remain on anticoagulation in addition to any other medical therapies to prevent future thromboembolic disease.

In conclusion, CTEPH is a frequently under diagnosed condition following PE. This condition results not only from macrovascular obstruction from thrombi, but also from subsequent changes in the vascular biology of the pulmonary microcirculation. Patients often present with indolent symptoms such as dyspnea and exercise intolerance. Echocardio-graphy showing pulmonary hypertension is the initial clue to the diagnosis for the majority of patients. Further imaging to detect chronic pulmonary emboli

and subsequent referral to a specialized center for more invasive testing and possible surgery is warranted. While surgical thromboendarterectomy remains the treatment of choice, several promising medical therapies are being studied for non-surgical candidates. The patient we presented had a more complicated course that included severe hypoxia due to his PFO and subsequent right to left shunt. However, with proper diagnosis followed by thromboendarterectomy and PFO closure, he had an excellent outcome and was subsequently able to undergo hip replacement surgery with remarkable improvement in his quality of life.

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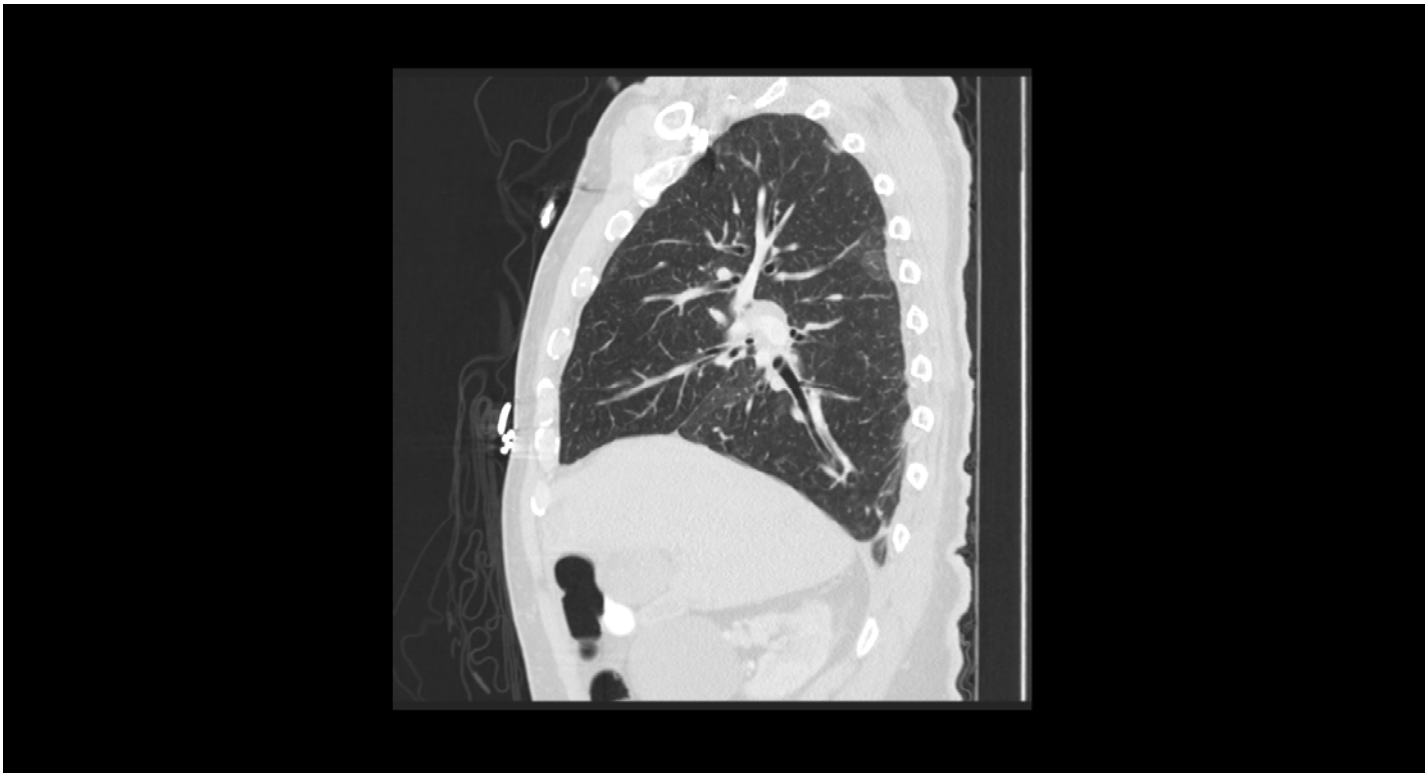

Figure 1. CT angiogram sagital view of R pulmonary artery: Nonocclusive clots adherent to the wall of the right inferior pulmonary artery, right lower lobe posterior basal segmental branches, right main pulmonary artery, inferior division of the right pulmonary artery and right upper lobe posterior segmental branch.

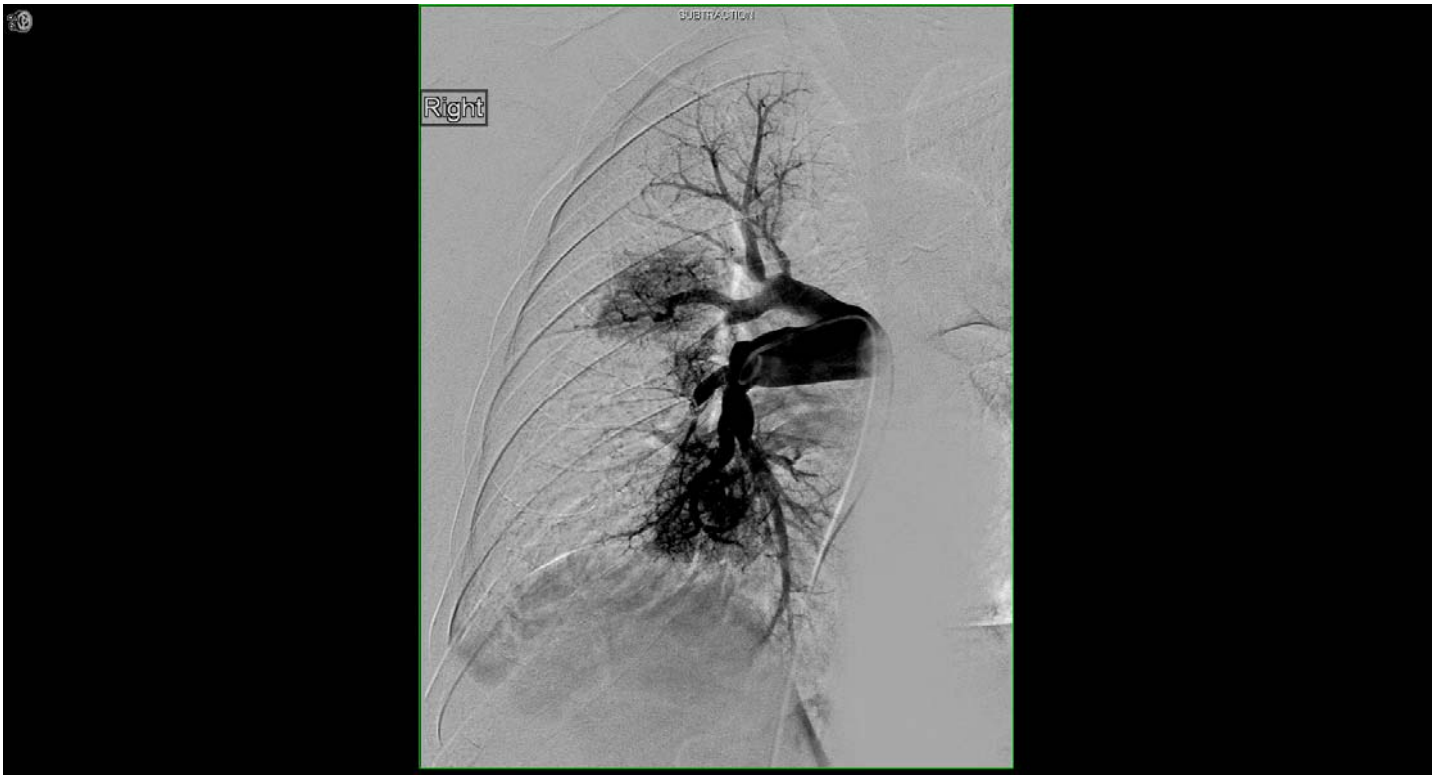

Figure 2. Pulmonary angiogram of the right lung. The proximal arteries are enlarged, however distal pruning is noted with small pulmonary arteries noted in the periphery. Multiple areas of segmental defects are noted consistent with oligemia from chronic thromboembolism.

Table 1. Selected Risk Factors for CTEPH*

A. Characteristics of initial PE
    a. Recurrent or idiopathic PE
    b. Large perfusion defects
    c. Pulmonary pressure > 50 mm Hg when PE is diagnosed
    d. Persistent pulmonary hypertension seen on echocardiogram 6 months after PE
B. Chronic medical illnesses
    a. Thyroid disorders
    b. Cancer
    c. postsplenectomy
C. Thrombophilias
    a. Antiphospholipid antibodies
    b. dyfibrinogenemia
D. Genetic factors
    a. ABO blood groups other than O
    b. Abnormal endogenous fibrinolysis

* adapted from Piazza G, Goldhaber SZ. Chronic thromboembolic pulmonary hypertension. The New England Journal of Medicine. 2011;364:351-60.