

# Chronic Thromboembolic Pulmonary Hypertension Successfully Treated in a Six Year Old with Asthma

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June 15, 2020

## Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but serious, sequela of acute pulmonary embolism. Symptoms can be subtle and non-specific and the prognosis is poor if severe pulmonary hypertension (PH) and right ventricular dysfunction are present. While PH-targeted therapies are often used, there is only one FDA approved therapy, and only for disease that is deemed inoperable. The greatest chance for potential cure and long-term survival is surgical pulmonary endarterectomy. We report a 6-year-old male with a history of asthma and two unprovoked deep venous thromboses who presented with syncope. Chest x-ray showed cardiomegaly and an echocardiogram showed severe PH with severely decreased right ventricular (RV) function. Ventilation-perfusion scan showed mismatched perfusion defects involving the right lower lobe, and CT of the chest showed right lower lobe subsegmental pulmonary thrombus, suspicious for chronic thromboembolism. Given his clinical presentation and the severity of his right ventricular dysfunction, he was started on ambrisentan, sildenafil and subcutaneous treprostinil. Bilateral pulmonary endarterectomy was performed with resection of level 2 to 3 disease and he was successfully weaned off all PH therapy. Four months post-op, he is clinically asymptomatic and his echo shows normal RV function without PH. In conclusion, CTEPH is a rare but likely underdiagnosed disease process in pediatrics. Clinicians should have a high index of suspicion for at risk patients with unexplained dyspnea. Even if right ventricular dysfunction and severe PH are present, surgical pulmonary endarterectomy can be performed successfully in young children.

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Grants/Financial Support: None

Meetings: Presented at the 13<sup>th</sup> International Conference Neonatal and Childhood Pulmonary Vascular Disease

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Keywords: CTEPH, pulmonary hypertension, pulmonary thromboendarterectomy

Abbreviated title: CTEPH in a six year old with asthma

Introduction:

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by incomplete resolution of pulmonary thromboemboli and the subsequent development of pulmonary hypertension (PH). In adults, it is estimated to occur in 0.5% to 3% of acute pulmonary embolism survivors<sup>1</sup>, and in children is even less common. We present a case of the youngest known patient in the United States to have undergone successful pulmonary thromboendarterectomy (PTE) and review the literature on diagnosis and management of this rare condition.

Case Report

Our patient was a 6-year-old male with a history of moderate persistent asthma and a remote history of multiple unprovoked deep vein thromboses (DVTs), for which a thorough hypercoagulability work up had been performed and was found to be normal. After initial treatment for his DVTs, he was maintained on chronic prophylactic subcutaneous heparin injections. Prior to acute presentation, he was seen twice in a general pediatric pulmonary clinic for several months of worsening exertional dyspnea that was attributed to poor medication adherence to his prescribed asthma medications. He was in his usual state of health and visiting relatives on the day he presented to an out-of-state emergency department with syncope.

In the emergency department, a chest X-ray suggested cardiomegaly and prompted an echocardiogram that showed severe pulmonary hypertension based on a moderately dilated right ventricle with severely decreased function, dilated pulmonary arteries, and an interventricular septum that bowed in to the left ventricle. His pulmonary regurgitation Doppler estimated an end diastolic pulmonary artery pressure of 30 to 40 mmHg. Clinically, he was dyspneic but with clear lung sounds; he required 3 liters of nasal cannula oxygen to achieve normal oxygen saturations. Upon transfer to our facility for further expert evaluation and management of severe pulmonary hypertension, cardiac catheterization hemodynamics confirmed the diagnosis of PH with mean pulmonary artery pressures >40mmHg and a pulmonary vascular resistance index of 8.83 Units x m<sup>2</sup> (Figure 1). A ventilation-perfusion scan showed multiple mismatched perfusion defects involving both right and left lungs, suspicious for chronic thromboembolism. Computed tomography (CT) of the chest showed right lower lobe subsegmental pulmonary thrombus, confirming the diagnosis of CTEPH.

Given his worrisome clinical presentation with acute syncope and the severity of his right ventricular dysfunction, he was started on triple therapy including subcutaneous treprostinil, a selective phosphodiesterase inhibitor, and an endothelin receptor antagonist. His case was promptly reviewed by the multidisciplinary team of CTEPH experts at UC San Diego and he was deemed a candidate for surgical PTE. Within 4 weeks of presentation, he was transferred to San Diego and underwent bilateral PTE with resection of level 2 to 3 disease (Figure 2) via the surgical technique described in prior reports<sup>2</sup>. He was weaned off all PH therapy while in the operating room in an effort to avoid reperfusion pulmonary edema, a well-known complication

of PTE. Repeat ventilation-perfusion scan prior to discharge showed significant improvement with symmetric perfusion in both lung fields. After returning home, an evaluation 4 months post-surgery exhibited a clinically asymptomatic boy and an echocardiogram with normal RV size and function without any signs of PH. A pulmonary function test was also repeated and confirmed the prior diagnosis of asthma, showing mild obstruction with reduced forced expiratory volume/forced vital capacity ratio and notable scoop to the flow-volume curve and expiratory flows were found to significantly improve after bronchodilator administration. He continues to be followed by hematology and is maintained on warfarin for anticoagulation with a goal INR of 2 to 3.

## Discussion

CTEPH is a rare, although possibly underdiagnosed, entity seen in all age groups. Symptoms can be subtle and non-specific, making the diagnosis challenging in the presence of other underlying conditions such as asthma and the prognosis poor if severe pulmonary hypertension and right ventricular dysfunction are present. While PH-targeted therapies are often used, riociguat is the only FDA approved therapy for inoperable disease in adults. The greatest chance for long term survival is surgical PTE, with the lowest mortality and best immediate surgical results at the highest volume centers such as UC San Diego<sup>3</sup>.

As is common for many patients with CTEPH, our patient's non-specific symptoms mimicked a more common and more likely diagnosis of chronic asthma, and he went undiagnosed for several months despite having recurrent lower extremity thromboses—a known risk factor for the development of CTEPH—and multiple physician encounters in the outpatient and emergency room settings. While a normal ventilation-perfusion scan makes the diagnosis of CTEPH unlikely, an abnormal study warrants additional images via angiography or CT to confirm or exclude the diagnosis of CTEPH and aid in surgical planning. It has been suggested that for patients with operable CTEPH, medical optimization with PH-targeted therapy to improve hemodynamics can unduly delay potentially curable surgical treatment,<sup>4</sup> however we were able to stabilize our patient with triple PH-targeted therapy without delaying the referral and transfer process to a center who could confirm our diagnosis and perform PTE. Clearly, for our patient, prophylactic subcutaneous heparin was not adequate anti-coagulation to prevent recurrent thromboemboli, and a recent study in adults with CTEPH suggests lower risk of recurrent venous thromboemboli in those patients receiving vitamin K antagonists.<sup>5</sup>

In conclusion, our patient is the youngest reported case of surgically treated CTEPH in the United States. Providers must maintain a high index of suspicion for at risk patients with unexplained dyspnea to allow for prompt diagnosis and evaluation for surgical treatment.

Even if right ventricular dysfunction and severe pulmonary hypertension are present, surgical pulmonary endarterectomy can be performed successfully in young patients.

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