

# Chronic Thromboembolic Pulmonary Hypertension as an Uncommon Presentation of Primary Antiphospholipid Syndrome

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Antiphospholipid syndrome is an autoimmune disease characterized pathophysiologically by the presence of antiphospholipid antibodies and  $\geq 1$  clinical manifestation, the most common being venous or arterial thrombosis. We describe the case of a 40-year-old male with unexplained severe pulmonary arterial hypertension with a seven-day history of progressive shortness of breath, hemoptysis, chest discomfort and bilateral pedal edema. Electrocardiographic, echocardiographic and imaging studies showed changes consistent with chronic thromboembolic pulmonary hypertension. Further work-up showed positive anticardiolipin antibodies and lupus anticoagulant with negative features for lupus with negative primary thrombophilic studies as well. The patient was managed adequately with oral anticoagulation with improvement of his clinical status and referred to a tertiary care center to be screened for pulmonary thromboendarterectomy. For patients meeting surgical selection criteria, pulmonary thromboendarterectomy has demonstrated positive outcomes with respect to survival, functionality and quality of life. We discuss the pathophysiology and treatment as well as novel therapies in nonsurgical candidates with chronic thromboembolic pulmonary hypertension in the setting of primary antiphospholipid syndrome.

**Key words:** lungs ■ pulmonary hypertension ■ antiphospholipid syndrome ■ pathophysiology ■ treatment

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## INTRODUCTION

**P**rimarily antiphospholipid syndrome (PAPS) is an autoimmune condition characterized by venous and/or arterial thrombosis, fetal loss and the presence of anticardiolipin antibodies, lupus anticoagulant or anti-beta<sub>2</sub> glycoprotein-I antibodies without the presence of other autoimmune process—lupus

being the most common coexistent entity when secondary antiphospholipid syndrome is suspected. Chronic thromboembolic pulmonary hypertension (CTPH) is an uncommon complication in PAPS, with very few cases published in the medical literature. Distinctive and specific pathophysiological mechanisms are involved in this entity with specific therapeutic approaches.

## CASE REPORT

A 40-year-old Hispanic male presented with progressive shortness of breath (New York Heart Association class 3) of several days' duration associated with minimal-to-moderate exertion accompanied by cough that was occasionally blood tinged and bilateral lower-extremity edema. He denied rash, fever or chills. His past medical history was remarkable for diabetes mellitus, systemic hypertension and two episodes of deep venous thrombosis—the first one 14 months ago and the latest one two months before to his current clinical presentation. An insertion of an inferior vena cava filter was placed following the most recent event. Daily medications included warfarin and supplemental home oxygen. No family history of blood disorders was noted. On physical examination, vital signs were within normal limits. Moderate jugular venous distention was noted, and cardiac exam revealed the presence of a 2/6 intensity diastolic murmur in the pulmonic area with accentuated S-2. The lower extremities had pedal edema bilaterally. Complete blood cell count was important for mild thrombocytopenia (113,000 U/L); prothrombin time was 24.2 seconds and international normalized ratio (INR) 2.0. Complete metabolic panel was normal and B-type natriuretic peptide (BNP) was significantly increased (1183 PG/ML). Chest x-ray demonstrated right atrial enlargement and large proximal pulmonary arteries. Electrocardiogram showed sinus rhythm, right-axis deviation and tall P waves consistent with right atrial enlargement in leads DII and V1. Transthoracic echocardiogram revealed severe dilated right-sided chambers with moderate tricuspid regurgitation, paradoxical motion of the interventricular septum and an estimated right ventricular systolic pressure (RVSP) of 90 mmHg. Contrast-

enhanced computed tomographic angiography of the chest showed specific patterns suggestive of CTPH (Figure 1). The patient underwent right heart catheterization, which showed the following significant hemodynamic parameters: mean right atrial pressure (mRAP) of 11 mmHg, right ventricular (RV) pressure of 94/15 mmHg, mean pulmonary arterial pressure (mPAP) of 61 mmHg (105/40 mmHg), mean pulmonary capillary wedge pressure (mPCWP) of 12 mmHg, cardiac output (CO) of 3.8 L/min by thermodilution, pulmonary vascular resistance (PVR) of 1,032 dynes/sec/cm<sup>5</sup> (13 Wood units) and a transpulmonary gradient (TPG) of 49 mmHg. Further investigation revealed that the patient's serum demonstrated the presence of IgG anticardiolipin antibodies, and lupus anticoagulant antibody was confirmed by the dilute Russell viper venom time without improvement with additional antiphospholipid. The patient was continued on lifelong oral anticoagulation, and loop diuretics were added with improvement of his lower-extremity edema. He was subsequently referred to a tertiary center to be evaluated for pulmonary thromboendarterectomy.

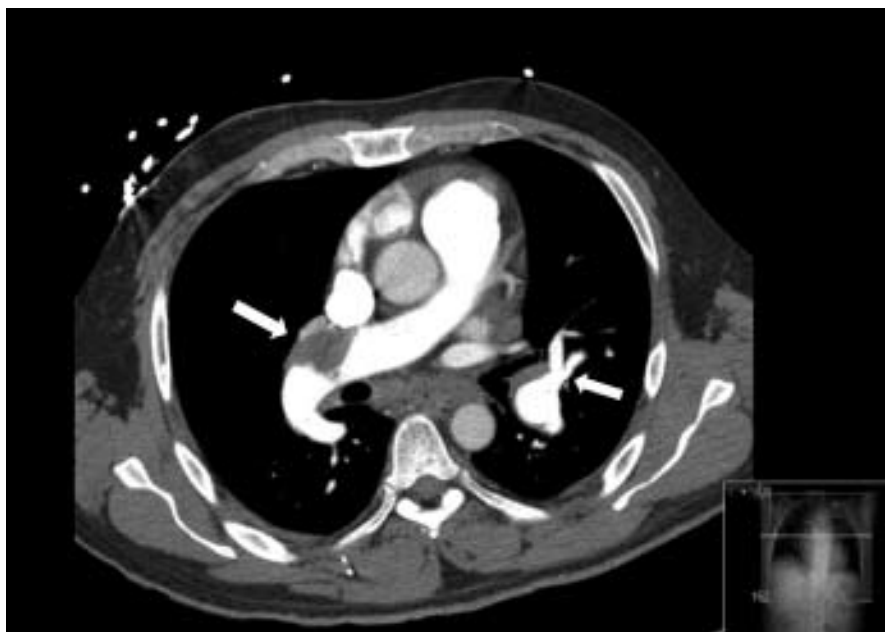
## DISCUSSION

The prevalence of PAPS is unknown, given the lack of large-scale epidemiological studies and only small descriptive case-series being reported in the literature, but these patients have been well characterized clinically by recurrent thrombosis, which may result in long-term complications.<sup>1</sup> In 1989, a clinical series was published that formally established the PAPS, including a group of patients in whom recurrent thrombosis, miscarriages

and thrombocytopenia were associated with anticardiolipin antibodies (aCL). None fulfilled classification criteria for the diagnosis of systemic lupus erythematosus (SLE).<sup>2</sup> The true incidence of CTPH is unknown; however, in a recent prospective follow-up study the cumulative incidence after two years of a first acute thromboembolic event was 3.8% with identifiable risk factors.<sup>3</sup> Recent studies have found the presence of anticardiolipin antibodies in 10–20% of patients with CTPH.<sup>3,4</sup> Hereditary thrombophilias such as protein C, protein S and antithrombin-III deficiencies cumulatively appear in <5% of patients; factor-V Leiden can be detected in 4–6.5% of CTPH patients.<sup>4,5</sup>

It is known that the antiphospholipid antibodies (aPLs) found in patients with PAPS are themselves pathogenic rather than mere markers. Current models for aPL-associated thrombosis are based in the activation of platelets followed by the binding of aPLs to platelet membrane phospholipid-bound proteins, initiating platelet activation, adhesion and thrombosis. These antibodies may inhibit certain reactions in the coagulation cascade catalyzed by phospholipids, such as inhibition of the activation of the protein C and protein S.<sup>1</sup> The pathophysiology of CTPH involves many likely mechanisms. Pulmonary vascular obliteration results from incomplete resolution of a venous thromboembolic episode, and secondary small-vessel arteriopathy occurs in both thrombosed and nonthrombosed vessels. Surprisingly, the whole pulmonary vascular bed may suffer arteriopathic changes. Another hypothesis is a primary role of in-situ thrombosis as a cause of pulmonary vascular occlusion especially

**Figure 1. Contrast enhanced computed tomographic angiography of the thorax showing a large organized thrombi in the main right pulmonary (left white arrow) with a 15 mm recanalized thrombi located in the basal anterior segment of the left upper lobe (right white arrow)**



in the setting of PAPS.<sup>6,7</sup> Inflammatory mechanisms have also been implicated in the pathophysiology of CTPH. Plasma levels of the proinflammatory cytokine macrophage chemoattractant protein-1 are elevated in patients with CTPH and correlate with the magnitude of pulmonary arterial hypertension (PAH).<sup>6</sup> As in other forms of PAH, the endothelin system is activated in patients with CTPH and may contribute to the pulmonary vasoconstriction as well as in the vascular remodeling process; however, further studies are required for a full understanding of the sequence of events that eventually result in pulmonary vascular remodeling.<sup>7</sup>

Similar to patients with other forms of pulmonary hypertension, patients may present with subtle and non-specific symptoms, and delay from months to years can occur until the confirmation of the diagnosis occurs in the latest stages of the disease (“honeymoon period”).<sup>6</sup>

Imaging studies, including ventilation/perfusion scanning, computed tomographic angiography (CT-angio) are fundamental part of the diagnostic work-up of patients with suspected CTPH. No prospective study has evaluated the most appropriate diagnostic approach to CTPH. There is consensus among experts that a normal ventilation-perfusion scan is normal; it practically rules out CTPH. If scintigraphy shows indeterminate results, the next diagnostic step is usually CT-angiography, which may reveal eccentric thrombotic material with the pulmonary arteries, subpleural densities and a characteristic mosaic pattern of the pulmonary parenchyma. Very proximal lesions on the right or left main pulmonary arterial trunks are well characterized, whereas the distal lesions are rarely visible. CT scanning is essential to exclude rare conditions that may present with similar symptoms, such as fibrous mediastinitis, mediastinal neoplasias and sarcoma of the pulmonary artery.<sup>6,7</sup> Matheus et al.,<sup>8</sup> in a Mexican prospective study, assessed the diagnostic usefulness of helical CT-angiography of the thorax in the setting of central or proximal CTPH, concluding that this is an excellent alternative approach for the diagnosis of proximal CTPH with high sensitivity, specificity and positive predictive value.

Pulmonary thromboendarterectomy represents an effective and efficacious therapy in patients with surgical accessibility (proximal disease confined within the main, lobar or segmental pulmonary arteries) and who have had an adequate preoperative period of oral anticoagulation. Unfortunately, very few centers have experience performing the procedure, with <3,000 operations performed worldwide.<sup>9</sup>

The current role of the insertion of an inferior vena cava filter in CTPH in the background of PAPS is controversial. Experts have mentioned that given the pathophysiological behavior of thrombosis in situ in patients with PAPS, the procedure will not be of benefit. Still, controversy exists regarding long-term benefit, and more studies are needed to design.

In regards to the predictors of outcome in CTPH, Bonderman et al.<sup>10</sup> demonstrated that predisposing medical conditions such as splenectomy, permanent central intravenous lines and certain inflammatory disorders predict poor survival in CTPH. Interestingly, the presence of aPL was not a negative predictor of survival.

## CONCLUSION

The patient described here presented with clinical and radiological features typical of CTPH with an underlying hypercoagulable state—in this case PAPS, which represents the most common hypercoagulable state in the setting of CTPH (10–20%). Important risk factors for the development of CTPH include young age, male gender, history of venous thrombosis and the presence of PAPS. Pulmonary thromboendarterectomy represents the gold standard of therapy in patients with surgical accessibility. For patients with inoperable (distal) CTPH, current treatment includes chronic oral anticoagulation and diuretics, but clinical trials testing new vasodilators and antiproliferative agents are needed at this point.

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