Case report

Life-saving pulmonary endarterectomy for a young female with primary antiphospholipid syndrome complicated by severe chronic thromboembolic pulmonary hypertension

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Summary

Background: Prothrombotic state and impaired clot dissolution can contribute to the occurrence of chronic thromboembolic pulmonary hypertension in primary antiphospholipid syndrome. Pulmonary endarterectomy – the surgical removal of the organized thromboembolic material from the proximal pulmonary arteries – is the procedure of choice and potentially a curative option for patients with chronic thromboembolic pulmonary hypertension, including patients with antiphospholipid syndrome. We report an exceptionally severe and complicated case with favourable outcome.

Case presentation: We present a case of a successful high risk pulmonary endarterectomy in a 29-year-old female with primary antiphospholipid syndrome and end-stage chronic thromboembolic pulmonary hypertension. Despite highly complicated perioperative course an impressive improvement in symptoms and functional status was achieved.

Conclusion: We hope that this complicated but successfully managed case of a combination of two rare diseases will arouse earlier suspicion and timely diagnosis for such patients and will encourage physicians to promptly refer the suitable patients to a pulmonary endarterectomy team.

It is important to remember that severe thrombocytopenia may occur in patients with antiphospholipid syndrome.

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Keywords: chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, antiphospholipid syndrome

Background

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease, caused by obstruction of the pulmonary artery branches (PA) after single or recurrent episodes of pulmonary embolism without complete resolution despite adequate anticoagulation. These chronic vascular obstructions lead to an increased pulmonary pressure and vascular resistance, eventually resulting in right ventricular failure, high morbidity and early mortality [1,2]. Antiphospholipid syndrome (APS) is an autoimmune disease, pathophysiologically characterized by the presence of at least one type of autoantibody, known as antiphospholipid antibody (aPL), in the plasma and by one or more clinical manifestations, the most common being arterial and/or venous thrombosis or recurrent miscarriages [3]. Prothrombotic states and impaired clot dissolution can contribute to the occurrence of CTEPH in primary APS [4]. Pulmonary endarterectomy (PEA) – the surgical removal of the organized thromboembolic mate-

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rial from the proximal PA – is the procedure of choice and potentially a curative option for patients with CTEPH, including patients with APS [1]. We report a case of high risk pulmonary endarterectomy with favourable outcomes in a patient with antiphospholipid syndrome and very severe CTEPH.

Case presentation

A 29-year-old female, suffering of severe dyspnoea, low exercise tolerance and fatigue, was referred to our Pulmonary Hypertension Centre with a suspicion of CTEPH. At the age of 17 years at the local hospital she was diagnosed with idiopathic primary APS. Diagnosis was based on the clinical and laboratory criteria: deep venous thrombosis of the lower extremities and repeatedly positive blood tests for anticardiolipin antibodies (aCL) in solid-phase immunoassay [3]. Despite anticoagulation therapy with warfarin (international normalized ratio (INR) value ranged between 1.7 and 2.8, therapeutic interval was reached in approximately 80% of tests according records) patient continued to suffer from recurrent pulmonary embolism (PE). Patient mentioned numerous hospitalisations to the local hospital due to pneumonia. The last documented episode of acute PE was diagnosed 2 years before referral to our centre and signs of pulmonary hypertension (PH) were found on echocardiogram. Patient had two pregnancies at the age of 19 and 21 years. First pregnancy was complicated with stillbirth at 7th month of gestation. The second pregnancy was finished in tertiary centre with in-term spontaneous vaginal delivery of healthy boy. She was anticoagulated with low molecular weight heparin, aspirin was added in the first and last semesters of the pregnancy. Symptoms of PH progressed gradually, signs of right heart failure manifested and highly elevated biomarker N-terminal pro-brain natriuretic peptide (NT-proBNP – 2267 ng/L) was found.

At presentation to our PH centre the patient was in World Health Organization (WHO) functional class III: slight tachypnea (20 breaths/min), tachycardia (100 beats/min), normal blood pressure (120/80 mmHg) and constitution, no cyanosis and peripheral edema were found. During 6-minute walk test (6 MWT) she developed severe dyspnoea (6 grade according Borg scale index); oxygen saturation dropped from 93 to 88% (Table 1). Her lung sounds were normal, but she had an accentuated second heart sound in the second left intercostal space and systolic tricuspid insufficiency murmur. Electrocardiogram revealed right atrial and ventricular hypertrophy. The pulmonary function tests (PFT) demonstrated mild obstruction, and decreased gases diffusion (DLCO 66% of predicted). Blood sample analysis demonstrated elevated haemoglobin level (161 g/L), mild thrombocytopenia (platelet count was 188 $\times 10^9$/L), normal liver enzymes and creatinine levels. Echocardiography showed moderate dilatation of right chambers and pul-

Table 1.
Patient data before and after pulmonary endarterectomy

	Before PEA: I visit/preoperatively	1 week after PEA	6 mo after PEA	2 years after PEA
WHO FC	III/IV	II	I–II	I
6 MWT (meters)	400/Bed-dependent	475	441	525
Echocardiography:				
Right heart chambers	Severe dilated	Mildly dilated		
Tricuspid insufficiency (grade)	III	I–II		
PFT				
FEV_1 (% predicted)	71		91	
FEV_1/FVC	67		75	
DLCO (% predicted)	66		54	
TLC (% predicted)	106		109	
VC (% predicted)	93		106	
RV (% predicted)	139		119	
RHC				
mPAP (mmHg)	73		25	
PAWP (mmHg)	12		10	
PVR (Wood Units)	20		2.35	
CI (l/min/m^2)	1.56		3.4	

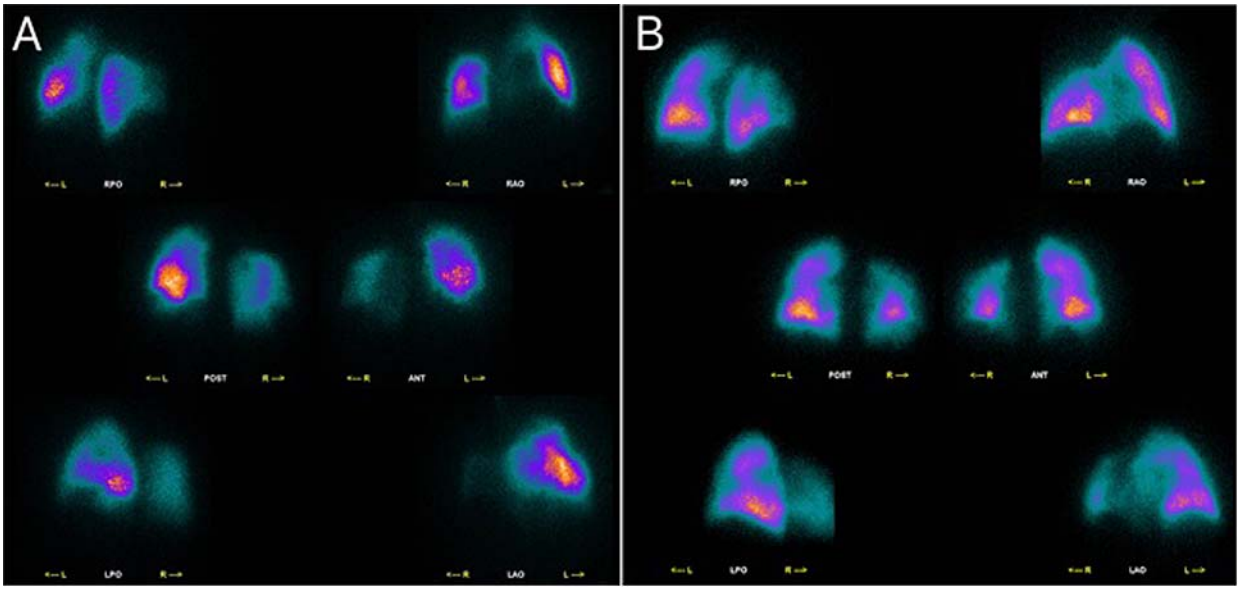

Figure 1. Lung ventilation-perfusion scintigraphy (A) before PEA shows only a small region of normally perfused parenchyma in the right lung and segmental perfusion defects in the left lung. 6 months after PEA (B) improved perfusion is evident in both lungs.

monary artery, hypertrophy and poor right ventricular function, normal left ventricle function with the ejection fraction of 56%, moderate-to-severe tricuspid valve regurgitation and signs of severe PH (systolic pulmonary artery pressure ~100 mmHg). Lung perfusion scintigraphy was diagnostic for chronic pulmonary thromboembolism (Fig. 1A). The computed tomographic pulmonary angiography (CTPA) revealed bands and webs in lobar and segmental pulmonary arteries, chronic occlusion of the right upper lobe pulmonary artery and right ventricular dilatation (Fig. 2A–D).

CTEPH was suspected after investigations and patient was scheduled (after two weeks) for right heart catheterisation (RHC) and invasive pulmonary angiography. Warfarin was stopped 5 days before planned procedure and bridging with therapeutic dosage of low weight heparin was performed. The patient developed syncope, with blood pressure drop (80/60 mmHg) and increased dyspnoea (respiratory rate 30/min) and was transferred to our Intensive Care Unit. Hemodynamic was stabilised with oxygen therapy, inotropes (dobutamine, milrinone) and pulmonary vasodilator sildenafil.

RHC revealed severe pre-capillary pulmonary hypertension with extremely high pulmonary vascular resistance (PVR); very low cardiac output was found as well (Table 1). Invasive pulmonary angiography revealed thrombosis of right PA segmental branches and left PA subsegmental and distal branches (Fig. 3A).

The patient was in very poor condition: breathlessness even at rest, completely dependent on the oxygen therapy – desaturation (arterial pO_2 65–70 mmHg) and repeated syncope occurred immediately after oxygen mask removal. Episodes of paroxysmal supraventricular tachycardia (heart rate up to 180 beats/min) were registered on ECG with blood pressure drops below 80/60 mmHg. We stabilised her hemodynamic with inotropes, vasopressors (adrenaline), combined target pulmonary arterial hypertension treatment (sildenafil and inhalations of iloprost), antiarrhythmic agent amiodarone, infusion therapy, diuretics. During multidisciplinary discussion it was decided to prepare patient for surgical treatment – PEA – according to vital indications, though the risk was very high. Low molecular weight heparin was switched to unfractionated heparin infusion. After 3 days severe thrombocytopenia developed (platelet count decreased from 127×10^9/L to 39×10^9/L). Heparin-induced thrombocytopenia was suspected and alternative anticoagulation with anti-Xa agent fondaparinux was started. However, no autoantibodies directed against platelet factor 4 complex with heparin was found using microcolumn gel immunoassay (serotonin release assay was not performed). Moreover, patient experienced a further sharp drop in platelet count (up to 6×10^9/L). Specific therapy for immune thrombocytopenia with glucocorticoids as well as high dose intravenous immunoglobulin (total dose 2 g/kg) was applied. Due to the risk of clinically important bleeding during forthcoming surgery platelet transfusions were used as well. Adequate platelet count response to therapy was achieved, in five days platelet count had reached 54×10^9/L. Daily platelet count monitor-

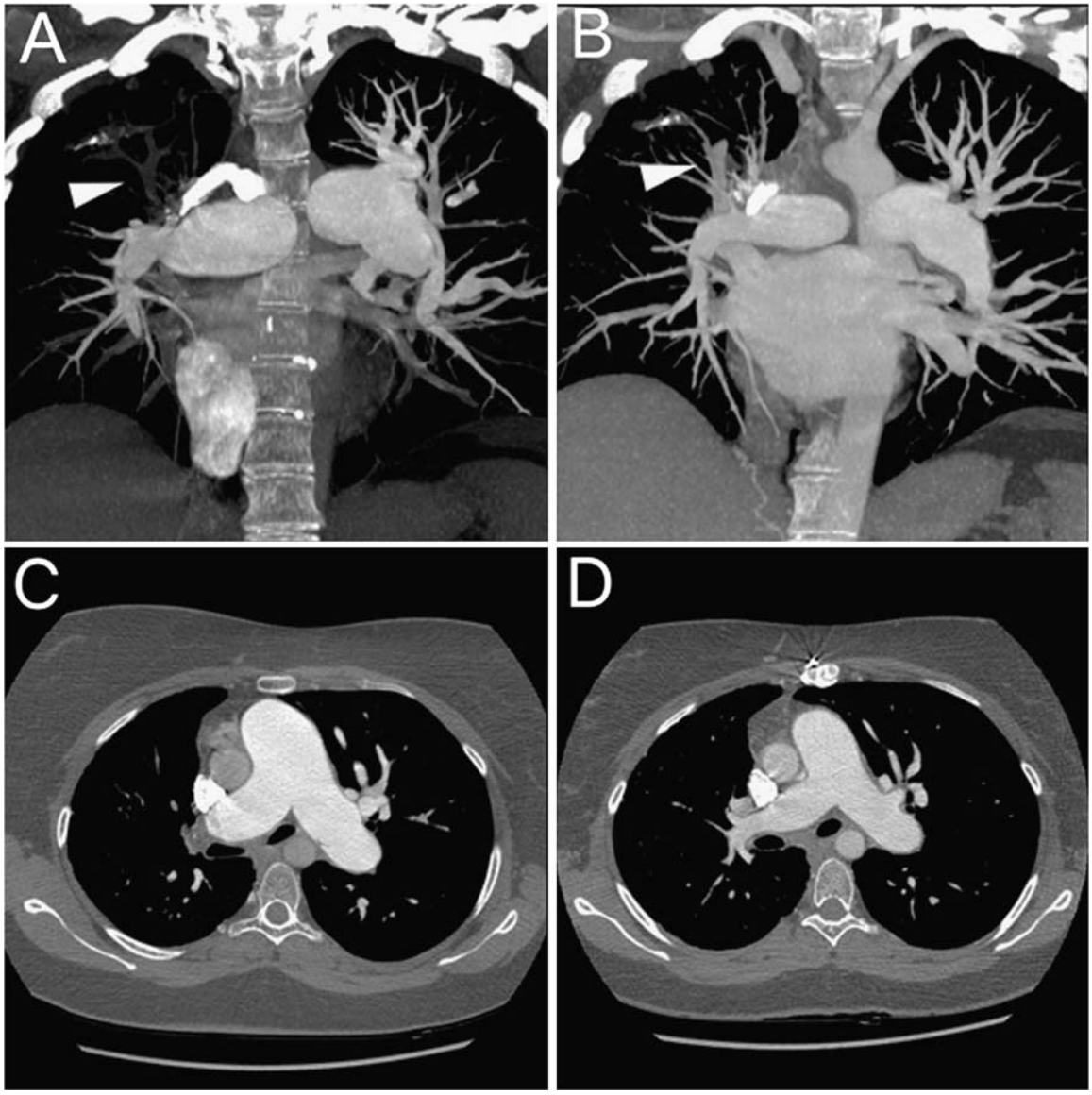

Figure 2. Computed tomographic pulmonary angiography (CTPA). Coronal maximum intensity projection view showing occluded right upper lobe pulmonary artery (A, arrowhead) and contrast enhancing right upper lobe pulmonary artery after successful recanalization (B, arrowhead). Axial CTPA images showing marked dilatation of pulmonary arterial trunk (C) and reduction in diameter after PEA (D).

ing was applied until a relatively safe numbers of 168×10^9/L was achieved, and then PEA (in accordance with the previously reported technique [5] using cardiopulmonary bypass, crystalloid cardioplegia, profound hypothermia (19°C) and limited total circulatory arrest) was performed. Old organized thrombi with the thickened intima were removed from the right and left pulmonary arteries (lobar and further subsegmental branches). The surgically removed material is shown in Fig. 4. PA pressure dropped immediately after PEA and was found to be between 50 and 60% of systemic. Extubation was performed on the second postoperative day and only low dose catecholamine therapy (noradrenaline 0.1 mcg/kg/min) was required for 3 days. Anticoagulation with fondaparinux was bridged to warfarin 1 week after the surgery (targeting an INR 2.5–3.5). Postoperative course was complicated with urinary infection, successfully managed with antibacterial treatment. Only mild residual PH was observed 1 week after surgery, treatment with sildenafil was continued, and the patient was moved to rehabilitation on the eighteenth postoperative day (Table 1).

Dramatic improvement in functional and hemodynamic state was observed during postoperative follow-up (Table 1). V/Q (Fig. 1B), CTPA (Fig. 2B), PFT and RHC (Fig. 3C, D) were repeated 6 months after the surgery and treatment with sildenafil was gradually discontinued after 1 year.

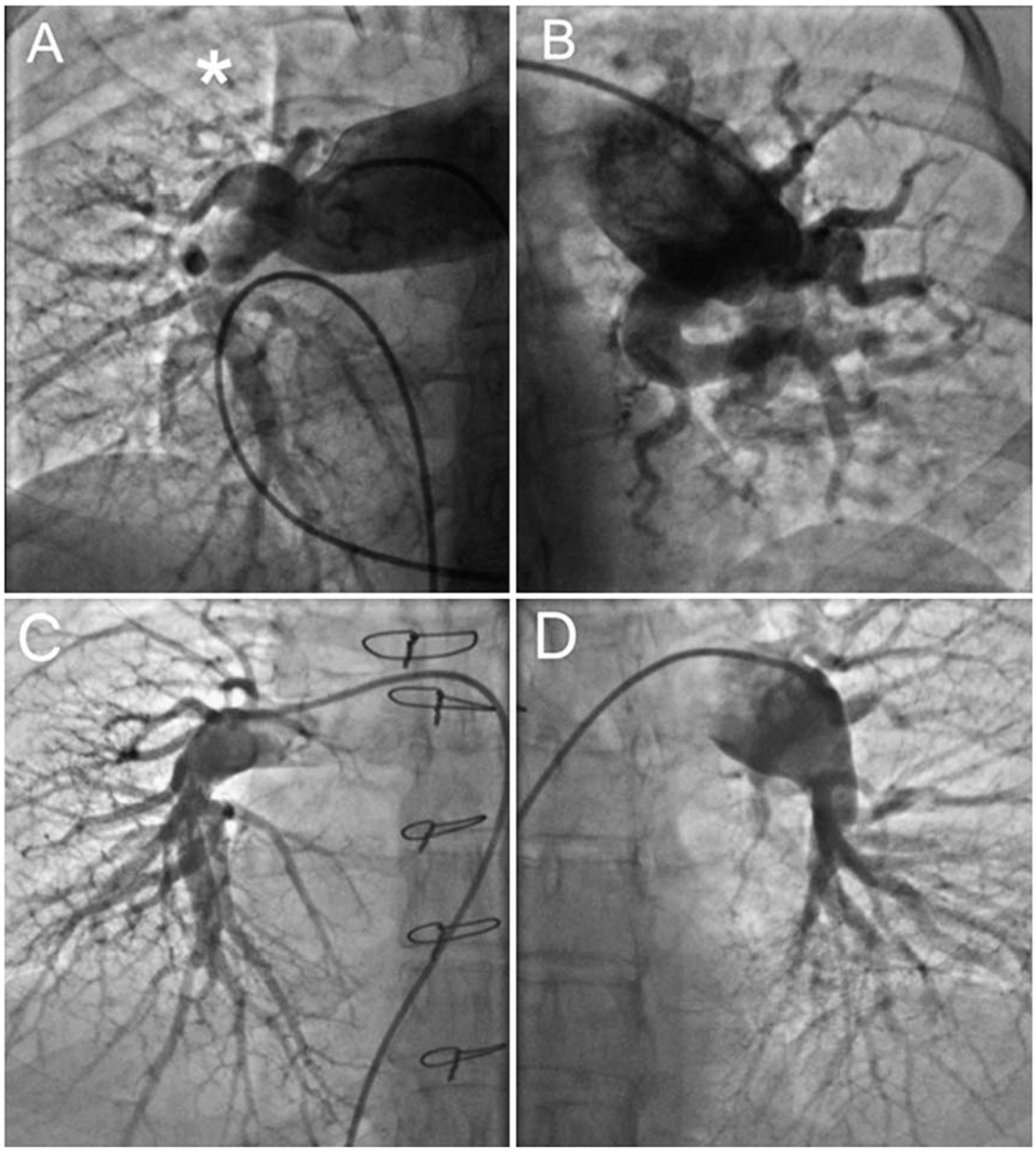

Figure 3. Invasive pulmonary angiography. Before PEA: A – right pulmonary artery (marked oligaemia in the right upper lobe – asterisk), B – left pulmonary artery. After PEA: C – contrast material filling in the right upper lobe pulmonary artery is affirmative of successful recanalization (postoperative sternal wires are visible), C and D images show decreased pulmonary arterial tortuosity, reduction in diameters of the right and left pulmonary arteries.

Discussion

Antiphospholipid syndrome is known to be strongly involved in pathogenesis of thrombosis and thromboembolic complications. CTEPH has been reported with a cumulative incidence of 0.1–9.1% within the first 2 years after a symptomatic PE event [6]. In the International CTEPH Registry a history of acute PE was reported for 74.8% of patients and thrombophilic disorders (including antiphospholipid syndrome) in 31.9% of cases [7]. Prevalence of high a-PL antibodies titre (HAPT) in patients undergoing PEA has been reported to be as high as 10–15% [8].

The diagnosis of CTEPH is based on findings (mean PAP $\geq$ 25 mmHg with PAWP $\leq$ 15 mmHg, mismatched perfusion defects on lung scan (Fig. 1) obtained after at least 3 months of effective anticoagulation) [1]. Specific diagnostic signs for CTEPH on angiography (CT or conventional) are ring-like stenosis, webs/slits and chronic total occlusions (pouch lesions or tapered lesions) [1] as are seen in our patient (Fig. 2).

Pulmonary function testing is most useful in evaluating for coexisting parenchymal lung disease or airflow obstruction. The typical functional picture of these patients demonstrates normal lung volumes, normal or slightly reduced

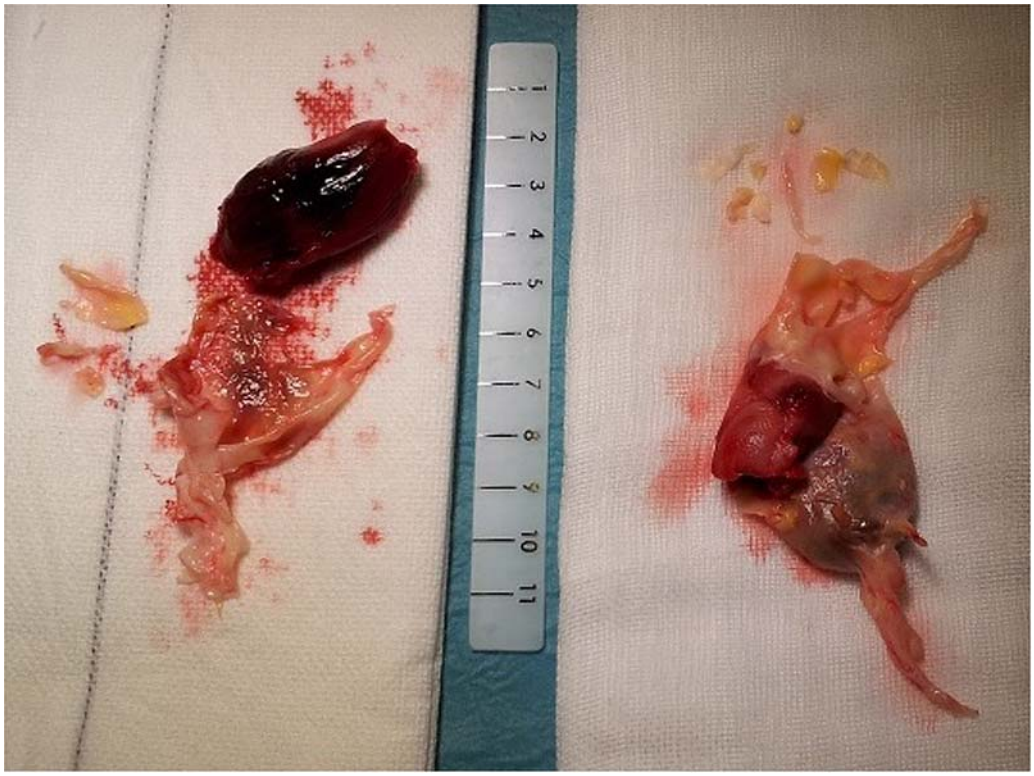

Figure 4. Pulmonary endarterectomy (PEA). Surgically removed material.

DLCO and mild hypoxemia with hypocapnia [9]. Approximately 20% of CTEPH patients with parenchymal scarring from prior lung infarction, a mild to moderate restrictive defect may be detected [10]. Our patient before surgery had mild bronchial obstruction as well as mild gas diffusion disorder and normal lung volumes. After PEA procedure obstruction disappeared. This can be explained by the fact that the obstruction before PEA was caused by small bronchiolar lumen narrowing due to pulmonary edema. An unexpected finding was that despite the improvement in functional status after surgery the gas diffusion decreased by 12%. This significant reduction in DLCO should raise concerns that the distal pulmonary vascular bed is significantly compromised.

CTEPH is a severe progressive disease with high morbidity and mortality, patient survival depends on severity of PH (correlates with the extent of PH) [1]. Diagnosis of CTEPH was delayed in our patient until extremely high PVR and advanced heart failure developed. Early diagnosis remains a challenge in CTEPH, with a median time of 14 months between symptom onset and diagnosis [11]. We estimate that a referral of our patient was delayed more than 20 months.

Surgical PEA offers the possibility of a cure for CTEPH patients and is the treatment of choice. Despite growing experience worldwide, the approach and criteria for patient selection are variable, related to the expertise of the surgical team and available resources [1]. In general PEA is indicated for symptomatic patients with PVR > 3.75 WU, surgical accessible thromboembolic lesions and absence of severe comorbidities [1,12]. Although there is no PVR threshold that can be considered to preclude PEA [1], the patients with a PVR $\geq$ 12.5 WU have a 2.4 times higher mortality risk during the perioperative period than patients with a lower PVR [13]. Patients with supra-systemic pulmonary artery pressures and excessive elevation of PVR (>18.75 WU) could also be accepted for surgery, although the operative risk is significantly increased [14,15].

The use of sildenafil or iloprost in operable patients with severe hemodynamic compromise as a bridge to PEA has not been supported by scientific evidence [1]. However, we believe that these selective pulmonary arteriolar vasodilators as well as oxygen therapy helped our patient to maintain remains of pulmonary circulation and to survive until PEA was performed.

Early transient neurological complications and recurrence of thrombotic events are more common in patients with APS after PEA [16,17]. They did not occur in our patient. Lifelong anticoagulation is essential for CTEPH patients, even after PEA. Though no data exist on the efficacy and safety of new oral anticoagulants (oral factor Xa inhibitor) [1], anticoagulation with warfarin (with target INR 2.5–3.5) with bridging to thera-

peutical dosages of low molecular weight heparin (if required) was advised to our patient. Careful and strict anticoagulation was applied later. Compared with the controls, the patients with APS have significantly lower platelet counts [16]. Thrombocytopenia is reported with prevalence's between 30% and 46% in patients with primary APS [18], but it is usually moderate ($>50 \times 10^9$/L) and not require intervention. Also preoperative platelet count could be significantly lower in patients with APS; no specific guidelines are available for managing thrombocytopenia in these patients [19]. While one of possible explanations for the aetiology of thrombocytopenia in APS could be the presence of autoantibodies to platelet surface membrane glycoproteins, same as in idiopathic thrombocytopenic purpura, patients are usually given similar treatment such as steroids, intravenous immunoglobulins, plasma exchange or splenectomy [16,19]. In this case, the time of severe platelet count drop-off was approximately 6 days after heparin prescription and caused the suspicion of heparin-induced thrombocytopenia; heparin was replaced by fondaparinux. Both the negative laboratory test for specific antibodies and the positive response to autoimmune treatment denied the initial idea. After successful management of preoperative thrombocytopenia we did not see platelet count drop after surgery.

After PEA, significant and persistent decrease of PA pressure and pulmonary vascular resistance was observed in our patient like in a large majority of published cases [5]. Oral soluble guanylate cyclase stimulator riociguat [20] is recommended for patients with persistent PH after PEA [1]. As this medication was not available to our patient, for the first year after surgery we applied off-label use of phosphodiesterase type 5 inhibitor sildenafil – medication acting in the similar pathway as riociguat.

Conclusions

We hope that this complicated but successfully managed case of a combination of two rare diseases will arouse earlier suspicion and timely diagnosis for such patients and will encourage physicians to promptly refer the suitable patients to a pulmonary endarterectomy team.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LG, MM, RS, LK and RK were involved in diagnostics and treatment of the patient. EP, VS, RM and LG interpreted the patient's data and drafted the manuscript. MM and RK prepared illustrations and figures. All authors contributed to writing and editing the manuscript for important intellectual content. All authors read and approved the final manuscript.

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