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Resolutive pulmonary endarterectomy in a non-compliant patient with systemic lupus erythematosus and antiphospholipid syndrome

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Abstract
Patients with chronic thromboembolic pulmonary hypertension (CTEPH) have poor prognosis, and pulmonary endarterectomy (PEA) is considered the treatment of choice for this condition. We report a case and review the literature of successful PEA for CTEPH due to antiphospholipid syndrome associated with systemic lupus erythematosus. The definitive and decisive approach needed to treat this high-risk patient with a history of comorbidity, long-term illness and poor compliance was found with a therapy of PEA.

Keywords Pulmonary endarterectomy, Systemic lupus erythematosus, Antiphospholipid syndrome.

Introduction

Antiphospholipid syndrome (APS) is characterized by venous or arterial thromboses accompanied by a persistence in antiphospholipid antibodies in patients' serum, namely anticardiolipin (aCL), antibeta2GPI (anti-b2-GPI) or lupus anticoagulant (LA). Fifty per cent of APS patients have an associated connective tissue disease, mainly systemic lupus erythematosus (SLE) [1]. Pulmonary complications, especially pulmonary arterial hypertension (PAH), may aggravate both of these conditions: 0.5–14% in SLE [2] and 0.5% in APS [3]. PAH may be due to chronic pulmonary thromboembolism as a pulmonary manifestation of the APS. Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as a mean pulmonary arterial pressure (PAP) greater than 25 mmHg persistent for more than 6 months which occurs in 2–4% of patients after the diagnosis of pulmonary embolism [4]. CTEPH results in persistent vascular obstruction and vasoconstriction leading to further abnormal remodelling of the vessels. Patients with CTEPH have poor prognosis, and pulmonary endarterectomy (PEA) is considered the treatment of choice for this condition [4, 5]. We report a case of successful PEA for CTEPH due to APS associated with SLE. Of note, the definitive and decisive approach needed to treat this highrisk patient with a history of comorbidity, long-term illness and poor compliance was found with a PEA therapy.

Case report In 2009, a 30-year-old male patient with SLE and APS presented to our attention for further investigations for spontaneous lower extremity deep venous thrombosis (DVT) that had occurred 15 days earlier. At the time, the patient was being treated with low-molecular weight heparin (LMWH). The patient had been followed up from the age of 12 till the age of 28 by our centre, when he voluntarily interrupted any medical control and therapy. Past medical history was significant for a diagnosis of SLE when he was 12 with the following manifestations over the years: arthritis, leucopoenia, severe and prolonged thrombocytopenia (minimum 1,000/mm3), nephritis (not biopsy proven because of the haemorrhagic risk in the course of thrombocytopenia), serositis, positive serology for antinuclear antibodies (ANA), antiDNA, LA. The patient had been treated with multiple immunosuppressive therapies (steroids, intravenous immunoglobulin, cyclosporin, azathioprine, danazol, IV cyclophosphamide, mycophenolate). The diagnosis of APS was based on 2 episodes of DVT (at the age of 12 and 13) in triple positivity for antiphosholipid antibodies at high titre. The patient had been on oral anticoagulant therapy (OAT) since the age of 15. Of note, a 2-year-long period of complete autointerruption of immunosuppressive, OAT and followup occurred at the age of 23, which resulted in the reactivation of the autoimmune disease. Comorbidites included: arterial hypertension, obesity (BMI 39), osteoporosis, recurrent infections, prothrombin polymorphism, heterozygosity and homozygosity for the A1298C mutation in the MTHFR (methylenetetrahydrofolate reductase) gene.
On admission, he reported suffering from exertional dyspnoea for the past 8 months, pain and swelling of the right lower limb due to the recent DVT. Physical examination revealed a blood pressure of 150/100 mmHg, heart rate of 120 bpm and oxygen saturation in room air 94%. An ulcerated lesion with erythema and oedema in the lower third region of the right leg was present. A cardiopulmonary examination revealed a split of S2, holosystolic murmur at the left sternal

border. The lungs were clear with respiratory sound reduced bilaterally. No hepatosplenomegaly was found. Laboratory and instrumental findings are shown in the Table 1. Based on these findings, the patient was diagnosed with CTEPH in APS. The patient denied rash, photosensitivity, fever, arthritis, mucosal ulcerations and chest pain. In the absence of signs or symptoms suggestive for lupus reactivation, the patient was treated with warfarin, with no immunosuppressive therapy. The patient was then discharged asymptomatic, with an estimated systolic PAP of 70 mmHg. After 6 months, we evaluated his cardiopulmonary parameters with non-invasive procedures. The angio-CT imaging concluded for the persistence of CTEPH despite full oral anticoagulation treatment. The patient was, therefore, referred to the CTEPH-PEA Reference Center, where he completed the diagnostic work-up for a surgical evaluation (pulmonary arterial angiogram and right heart catheterization) (Table 1) which concluded for an operable CTEPH. Given the association of CTEPH with SLE and a thrombophilic tendency, a permanent inferior vena cava filter was placed before surgery. Thus, the patient underwent bilateral PEA (on the right: upper, median and lower lobes; on the left: lingular and lower lobes) (see Fig. 1). Surgery was performed through standard median sternotomy under total cardiopulmonary bypass. Some technical solutions were taken in order to reduce invasiveness. Given the APS [6], moderate hypothermia (23C) was preferred to deep hypothermia, and short periods (7 min) of intermittent circulatory arrest were performed, interrupted by periods ([5 min) of reperfusion, for a total circulatory arrest time of 67 min (27 min during right PEA and 40 min during left PEA). The patient's course was uneventful, he was weaned from mechanical ventilation on postoperative day 1, and cycles of helmet cPAP were performed. The patient was discharged from the ICU on postoperative day 2. The results of the postoperative exams (Table 1) proved the success of the bilateral PEA (Fig. 1). The patient was dismissed asymptomatic on full oral anticoagulation therapy (target INR 3) on postoperative day 10. He continued regular follow-up at our centre. During the next months, no reactivation of SLE was observed. 15 months after surgery, the patient is asymptomatic (WHO functional class I) and the transthoracic echocardiogram proved the steady hemodynamic improvement, showing an estimated systolic PAP of 25 mmHg. Given the relief from cardiopulmonary symptoms, he was able to carry out physical activities and achieved a significant reduction of his BMI, from 39 to 30 (starting from 108 to 85 kg).

Discussion

We report our experience in a case of resolutive PEA in a patient with CTEPH, in APS and SLE, previously not compliant to medical therapy. To our knowledge, in the previous 27 cases described (Table 2) none presented with inherited thrombophilic state associated with APS. Moreover, our patient was particularly complicated for the underlying chronic medical conditions, as metabolic syndrome and SLE. His SLE-state was diagnosed in paediatric age with major organ involvement and was treated with large cumulative doses of immunosuppressive drugs. The thromboprophylaxis in lupus patients with autoimmune thrombocytopenia and antiphosholipid antibodies may be a real challenge for physicians. In our case, the lower-dose prophylaxis used due to the concomitant severe and prolonged thrombocytopenia could explain the first thrombotic events at the age of 12 and 13. At the time of surgery, he had high anesthesiological risk for cardiac and pulmonary complications, thrombosis, infections and catastrophic antiphosholipid syndrome; favourable factors included low organ damage score and no lupus activity and immunosuppressive therapy at the time. Of note, in our patient, the diagnosis of CTEPH was made timely, and the patient was correctly evaluated and directed to a tertiary referral centre with a large experience, where PEA surgery and perioperative bridging therapy in a patient with high thrombotic risk were carefully and successfully performed. No serious perioperative complications occurred. After surgery, the hemodynamic and functional improvements were remarkable. This case confirms that a multidisciplinary diagnostic work-up and a collaborative clinical management are mandatory when surgical treatment is planned, especially, where major surgery is concerned. A further interesting aspect in our patient was his noncompliance to medical therapy which had twice led to the interruption of therapy and to the reactivation of lupus, and the second time also to an acute thromboembolic event. Non-adherence to medication regimen in SLE, especially in juvenile patients [7], is a very common problem [8], as in other chronic conditions, even more during the quiescent phases of the disease [9]. At the time of the transition to our adulthood care unit, attention was paid to establish a direct relationship with this young patient without parental intervention. Much time was spent trying to involve him directly, listening to his difficulties as well as explaining the goals and risks of the therapy involved. A good provider–patient relationship was consequently reached. In the subsequent years, close monitoring of medication intake and personal lifestyle adjustments were attempted. Probably, a low level of personal resources [10] could justify difficulties in finding motivation and promoting the use of active coping strategies to face distressful situations. Psychological support was refused by the patient. After surgery, a significant change in the patient's attitude was noticed, and he is now aware of his current well-being and more conscious of the risks he has taken. This has determined a reinforcement of healthy behaviour and compliance aimed at better global functioning.

Conclusions

We reported a case of successful PEA for CTEPH due to APS associated with SLE. Of note, the PEA treatment represented in this experience a valid opportunity, in a patient at high risk because of comorbid, long-term illness and a poor compliance, which made a definitive approach needed.

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Table 1
clinical and laboratory findings on admission, after 6 months and post-PTEA

	On admission 8/2009	6 months later 2/2010	Post-PTEA 3/2010
Laboratory data	Normal: white cell and red cell counts, myocardial markers, complement, antiDNA, homocysteine. LA positive, aCL IgG/IgM 370/0, anti-β2-GPI IgG/IgM 156/0.D-dimer 1.82 (<0.5); NT-proBNP 760 (<125 UI)	Normal: white cell and red cell counts, myocardial markers, complement, antiDNA, homocysteine. LA positive, aCL IgG/IgM 290/2, anti-β2-GPI IgG/IgM 75/1. NT-proBNP 1029	Normal: white cell and red cell counts myocardial markers NT-proBNP 540
Arterial blood gas	pH pO_2 79 mm Hg, pCO_2 29 mm Hg	pH 7.41; pO_2 82 mm Hg, pCO_2 32 mm Hg	No
ECG	Signs of chronic right ventricle overload: right-axis deviation, pulmonary P waves, incomplete right bundle branch block, and inverted T wave in leads V2–V5	Unchanged	Incomplete right bundle branch block
Transthoracic echocardordiography	Overload of the right ventricle with tricuspid valve regurgitation and an estimated sPAP of 87 mmHg; LVEF 59% with normal morphology and function	sPAP 75 mm Hg; LVEF 56%	sPAP 25 mmHg; LVEF 60%
Lung scintigram	Multiple perfusion defects in the right superior lobe and the left inferior lobe	The perfusion ratio 53% on the left and 47% on the right	Reequilibration of the perfusion between the two lungs. The perfusion ratio 34% on the left and 65% on the right

Angio-CT scan	Perfusion defects in the right proximal pulmonary artery, consistent with organized thrombus	Complete occlusion of the right upper branch of the pulmonary artery, and anarchic rechanalization in the discendent branch. Reduced the changes in the discendent branch of the left artery. Persistence of CTEPH despite full oral anticoagulation	Revascolarization of the previously obstructed pulmonary arteries
Pulmonary arterial angiogram	No	Occlusion of the right upper lobe artery, reduced flow in the lower lobe and severe stenosis of the left lower lobe vessels	No
Right heart catheterization	No	PAP 89/55/30 mmHg; CO 4.52 L/min; PVR 885 dyne s cm^{-5}; RVEF 28%	PAP 33/22/13 mmHg (−60%); CO 5.77 L/min (+28%); PVR 236 dyne s cm^{-5}(−73%); RVEF 39%. (+39%)
WHO	III	III	I

Fig. 1 Surgical specimen from bilateral pulmonary endarterectomy

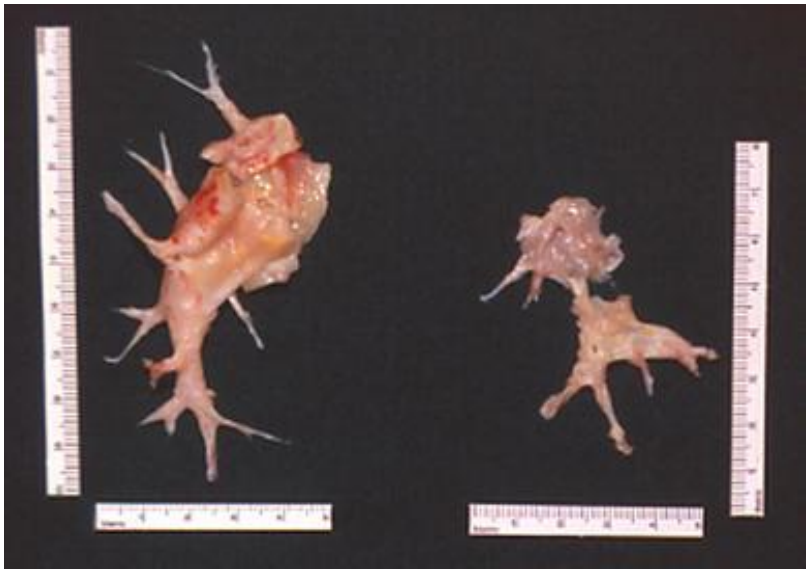

Table 2 Case reports of PTEA for CTEPH in APS patients

Author	Year	Number of patients	Gender	Age	Notes
Nakagawa	1992	1	M	43	CTEPH in aPL +
Coignard	1995	1	M	25	CTEPH in APS
Sandoval	1996	3	F	19	CTEPH in APS
			M	30	
			F	40	Died in postoperative period
Cucurull	1996	1	N/a	N/a	CTEPH in APS
Ando	1998	5	M	44	APS
			F	22	APS in SLE
			F	56	APS
			M	21	APS
			M	38	APS
Sato	2000	3	N/a	N/a	APS in SLE
Kamezaki	2004	1	M	19	CTEPH in primary APS
Peng	2006	1	F	19	CTEPH in previous APS and SLE diagnosed during

Author	Year	Number of patients	Gender	Age	Notes
					hospitalization for CTEPH
Colorio	2007	10		41 average	TEA for CTEPH in APS has better prognosis than for CTEPH without APS (survival 56 mo vs. 33 mo)
Porres-					
Aquilar	2008	1	M	40	CTEPH as first presentation of APS

N/a not available