Case report

Chronic thromboembolic pulmonary hypertension: take care to a "favourable" apparently evolution. A case report

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Abstract. Chronic thromboembolic pulmonary hypertension (CTEPH) caused by intraluminal thrombus organization and fibrous stenosis or complete obliteration of pulmonary arteries, is a not rare but life-threatening complication of acute pulmonary embolism. The prognosis of medically treated patients with CTEPH is poor and worsens as pulmonary hypertension exacerbates. We describe the case of a 43-years old with a history of progressive shortness of breath, hemoptysis, chest discomfort and syncope. Echocardiographic and imaging studies showed changes consistent with chronic thromboembolic pulmonary hypertension. Further work-up showed only moderate increase of homocysteine level with negative features for lupus and others primary thrombophilic disease. The patient was managed adequately with thrombolytic and inotropic therapy; oral anticoagulation was started with improvement of his clinical status and was screened for pulmonary thrombo endarterectomy, but he refused. The case presented despite its evolution 'temporarily' positive perhaps related to the reduction of hemodynamic overload through bronchial arteries, reiterates the importance of early surgical intervention, before it establishes the hypertensive vasculopathy. Abnormal pulmonary function at rest and after exercise stress test associated to non invasive echocardiographic measurements are an excellent tool to identify the bad prognosis patients in CTEPH. We discuss the pathophysiology and conclude that in selected cases, pulmonary thromboendarterectomy is the best therapy,but only if executed early. (www.actabiomedica.it)

Key words: chronic thromboembolic pulmonary hypertension, echocardiography, cardiopulmonary test

Introduction

Pulmonary artery hypertension is defined as a mean pulmonary artery pressure higher than 25 mmHg at rest; pulmonary capillary wedge or left ventricular end-diastolic pressure <15 mmHg, and pulmonary vascular resistance >3 Wood units (1). Chronic thromboembolic pulmonary hypertension caused by intraluminal thrombus organization and fibrous stenosis or complete obliteration of pulmonary arteries, is a rare but life-threatening complication of acute pulmonary embolism, represents the fourth group in DANA POINT classification (Fig. 1).

The prognosis of medically treated patients with CTEPH is poor and worsens as pulmonary hypertension exacerbates. Patients with pulmonary artery pressure of >30 mmHg have a 30% 5-years survival rate, and those with mean pulmonary artery pressure exceeding 50 mmHg have only a 10% 5-years survival rate. Despite the forward strides in the diagnosis and management of patients with CTEPH, there are yet considerable gaps in our understanding of the epidemiology and natural history of this disease (2). The evolution from an acute pulmonary embolus to chronic thromboembolic residual that becomes incorporated into the wall of the pulmonary vessel is incompletely understood (3).

1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/or hypoxaemia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 = activin receptor-like kinase 1 gene; APAH = associated pulmonary arterial hypertension; BMPR2 = bone morphogenetic protein receptor, type 2; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Figure 1. Chronic thromboembolic pulmonary hypertension represents the fourth group in DANA POINT 2008 classification

Case report

A 43 years old man was admitted for increasing dyspnea and syncope. At the entrance he was in cardiogenic shock (EGA: pO_2 40, pCO_2 28, pH 7:32; D-dimer 4100; Tn-I 1.72). ECG: sinus tachycardia, BAV first degree, right ventricular hypertrophy and strain.

Transthoracic Echocardiography (EcoTT): dilatation and severe right-sided hypokinesia, right atria/ventricle gradient 120 mmHg, TAPSE 8 mm, Actpo 42 ms. A 64 computed tomography pulmonary angiogram was immediately performed, showing evidence of massive TEP, increased pulmonary artery trunk diameter (47 mm) (Fig. 2), the picture is confirmed from transesophageal echocardiography (EcoTE) showing bilateral thrombosis with almost complete obstruction of the main branches and dilatation of the pulmonary artery (Fig. 3).

A lung perfusion scintigraphy was'nt performed, because TEE confirmed pulmonary embolism.

The patient was treated with rt-PA 100 mg and intravenous heparin UFH, dobutamine and furosemide ev; he began also an oral anticoaugulant therapy.

Three days after admittance, the patient was submit to a right heart catheterization, pulmonary an-

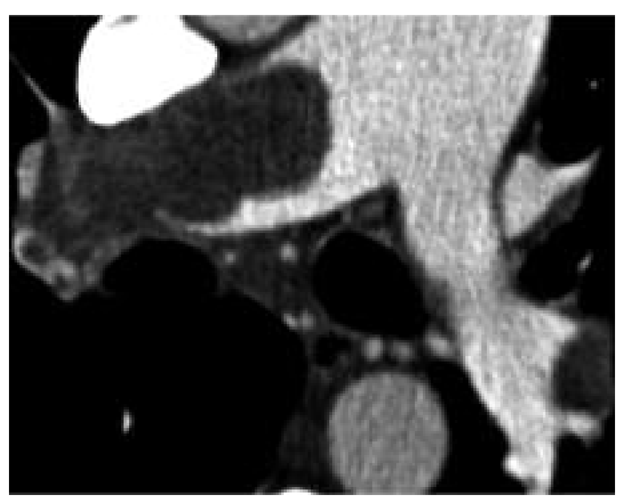

Figure 2. CT angiography was immediately performed, showing evidence of massive TEP, increased pulmonary artery trunk diameter (47 mm)

giography (Fig. 4) and coronary angiogram showing severe precapillary pulmonary hypertension not vasoreactive (AP 78 mmHg, RVP 9.4 UW) and normal coronaric function.

It was also repeated an EcoTT confirming PAPs of 75 mmHg, TAPSE 12 mm, Actpo 60 msec. The reviews pre-discharge also diagnosed an intermediate grade hyperhomocysteinemia (31 uM/L), in which the patient is discharged in good clinical condition with Folina plus furosemide, Coumadin (INR 2-3).

The patient was checked three months after admittance: it showed dyspnea under effort of medium

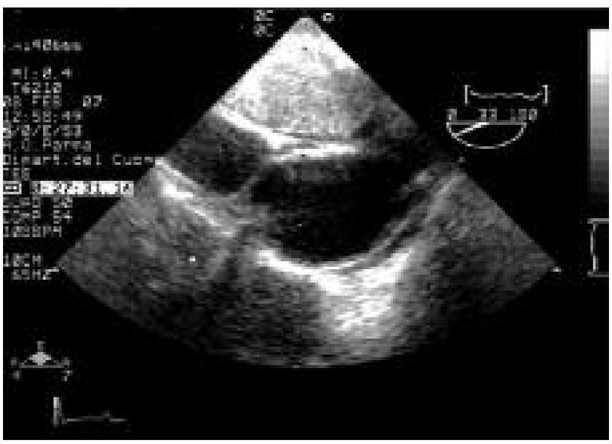

Figure 3. EcoTE showing bilateral thrombosis with almost complete obstruction of the main branches and dilatation of the pulmonary artery

Figure 4. After admittance, the patient was submit to a right heart Catheterization and pulmonary angiography

intensity (NYHA II) and the framework of the echocardiographic angiographic proved the same. Cardiopulmonary test showed a reduction in functional capacity (VO2 max 19.6 ml/kg/min, O_2 pulse 12, $VEVCO_2$ 30).

It was proposed to the patient to undergo pulmonary thromboendarterectomy(TEA), but he refused.

Checks are made out-patient at one year and two years after the patient showing a stable framework for the clinical and echocardiography, supported by a good tricuspid annular post systolic elongation value (TAPSE 20).

Although, the cardiopulmonary exercise test shows a further reduction in cardiopulmonary functional capacity (VO_2 max 17 ml/kg/min, O_2 pulse 10, $VEVCO_2$ 38); angiographic recanalization of the pulmonary vessels with evidence of slight thrombotic stratification to vascular wall, reducing the diameter of the pulmonary trunk (40 mm) (Fig. 5),was showed at CT scan.

A scintigraphy perfusional scan was normal.

Discussion

A single episode of pulmonary embolism does not lead to pulmonary hypertension in man or other species, while close embolic relapses could cause it (3, 4).

Early experience with CTEPH patients led to the estimate that 0.1 to 0.5% of acute embolic survivors would develop this disease. More recent data would suggest that this conservative estimate may in fact be a significant underestimate of the prevalence of this disease worldwide (4, 5).

In CTEPH, patological lesions are characterized by organized thrombi tightly attached to the pulmonary arterial medial layer in the elastic pulmonary arteries, replacing the normal intima. These may completely occlude the lumen or form different grades of of stenosis. In the non-occluded areas, a pulmonary arteriopathy indistinguishable from that PAH can develop. Collateral vessels from the systemic circulation can grow to reperfusion at least partially the areas distal to complete obstructions.

Pulmonary thromboembolism or in situ thrombosis may be initiated or aggravated by abnormalities in either the clotting cascade, endothelial cells, or platelets, all of witch interacte in the coagulation

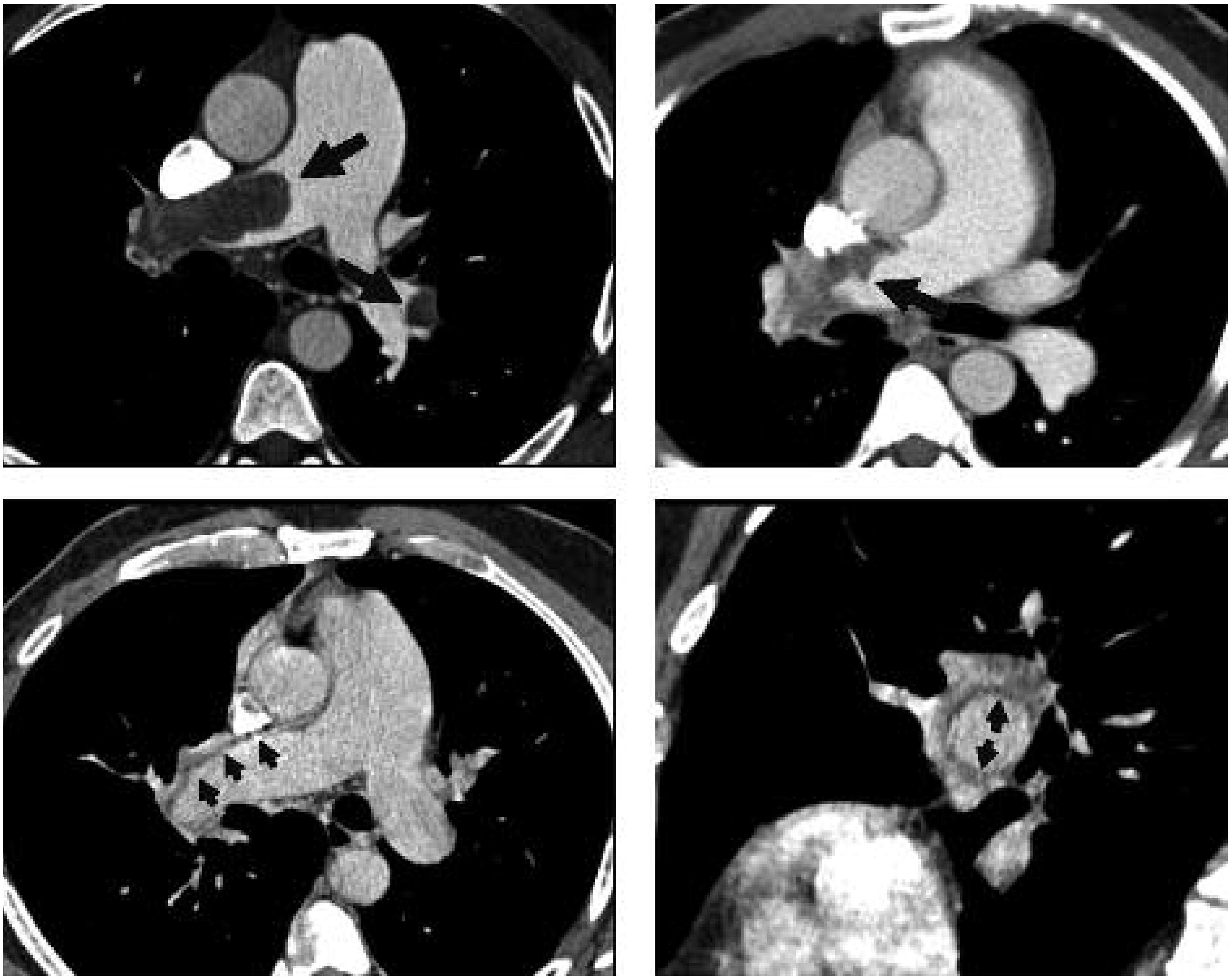

Figure 5. CT from the standpoint of angiographic recanalization of the pulmonary vessels with evidence of thrombotic stratification to vascular wall, reducing the diameter of the pulmonary trunk

process. Platelet abnormalities and biochemical features of a procoagulant environment within the pulmonary vasculature support a potential role for local thrombosis in initiating the disease in some patients. In most cases, it remains unclear whether thrombosis and platelet dysfunction are a cause or consequence of the disease. Thrombophilia studies have shown that lupus anticoagulant may be found in 10% of such patients, and 20% carry antiphospholipid antibodies, lupus anticoagulant, or both. The obstructive lesions observed in the distal pulmonary arteries of non-obstructed areas may be related to a variety of factors, such as shear stress, pressure, inflammation, and the release of cytokines and vascular mediators.

Both clinical and haemodynamic assessments by echocardiography, yeld important prognostic information which may guide clinical management.

The primary goals in the evaluation of patients for chronic thromboembolic disease are to determine the degree of PAH and cardiac compromise present, to differentiate between large and small-vessel pulmonary vascular disease, in the setting of large-vessel involvement, to confirm the diagnosis of chronic thromboembolic disease and to establish surgical accessibility of the chronic thromboembolic residua, and as a result, whether the patient is a potential candidate for pulmonary TEA surgery (6, 7).

Transthoracic echocardiography commonly provides the initial objective evidence for the presence of PAH. Available technology allows for estimates of pulmonary artery systolic pressure, from tricuspidal regurgitant jet velocity; tricuspid annular post systolic elongation (TAPSE) has been reported to be of prognostic value, as we showed in this case .

Despite being supplanted by computed tomographic angiography in the diagnostic pathway for acute pulmonary embolism, ventilation/perfusion scintigraphy continues to play a valuable role in the evaluation of patients with PAH. In chronic thromboembolic disease, at least one, and more commonly several segmental or larger mismatched perfusion defects are present. In disorders of the distal pulmonary vascular bed, perfusion scans are either normal as it has been reported by Auger et al[8] and detected in this case. Furthermore, the magnitude of the perfusion defects in chronic thromboembolic disease often understate the extent of the actual degree of pulmonary vascular obstruction determined angioghraphically or at surgery.

Pulmonary TEA has proven to be effective for patients with CTEPH; however, this operation is a technically and surgical experience demanding procedure associated with an increased operative mortality rate of around 10% (7, 8). Residual pulmonary hypertension is the major complication associated with perioperative mortality. Follow-up studies show significant improvement in prognosis and clinical functional status with relief of symptoms in patients undergoing pulmonary TEA (8-10).

Conclusions

There are still some unresolved issues that are also suggested by case reports, such as a dissociation between the degree of angiographic obstruction and its hemodynamic consequences. Fundamental changes have been described in hypertensive pulmonary arteries of type "obstructed" but also in the "open" with consequent hemodynamic progression and development of pulmonary arterial hypertension despite the removal or lysis of the thrombus.

The case presented despite its evolution 'temporarily' positive perhaps related to the reduction of hemodynamic overload through bronchial arteries, reiterates the importance of early surgical intervention, before it establishes the hypertensive vasculopathy.

Abnormal pulmonary function after exercise stress test (CPET) associated to non invasive echocardiographic measurements are an excellent tool to identify a bad prognosis patient with CTEPH.

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