Case Report

Chronic thromboembolic pulmonary hypertension: diagnostic limitations*

Hipertensão pulmonar associada ao tromboembolismo pulmonar crônico: limitações diagnósticas

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Abstract

Chronic thromboembolic pulmonary hypertension is the only potentially curable form of pulmonary hypertension, assuming that surgical treatment is possible. However, there are hindrances to making a definitive, noninvasive diagnosis. We present the case of a 40-year-old female patient with idiopathic pulmonary arterial hypertension, confirmed in 1994. This patient developed thrombi in pulmonary vessels (as an overlap syndrome) mimicking chronic thromboembolic pulmonary hypertension. The identification of these conditions, which present high intraoperative mortality and unsatisfactory surgical resolution, is quite difficult in clinical practice. We discuss the current approach to candidate selection for surgical treatment of chronic thromboembolic pulmonary hypertension and the possible repercussions of inappropriate selection.

Keywords: Hypertension, pulmonary/diagnosis; Hypertension, pulmonary/therapy; Pulmonary embolism; Endarterectomy.

Resumo

A hipertensão pulmonar associada ao tromboembolismo pulmonar crônico é a única forma potencialmente curável de hipertensão pulmonar, desde que o tratamento cirúrgico seja possível. Existem, entretanto, limitações para o diagnóstico não-invasivo definitivo. Apresentamos o caso de uma paciente de 40 anos, com diagnóstico confirmado de hipertensão arterial pulmonar idiopática desde 1994, a qual evoluiu com sobreposição de trombos em vasos pulmonares simulando hipertensão pulmonar associada ao tromboembolismo pulmonar crônico. O reconhecimento dessas condições, as quais apresentam alta mortalidade intra-operatória e baixa resolutividade cirúrgica, é muito difícil na prática clínica. Discutiremos a abordagem atual para a seleção de candidatos para o tratamento cirúrgico da hipertensão pulmonar associada ao tromboembolismo pulmonar crônico e as possíveis repercussões da seleção inadequada.

Descritores: Hipertensão pulmonar/diagnóstico; Hipertensão pulmonar/terapia; Embolia pulmonar; Endarterectomia.

Introduction

Pulmonary arterial hypertension is a rare disease that can occur idiopathically or in combination with various clinical conditions. It is characterized by progressive pulmonary vascular remodeling with an increase in pulmonary vascular resistance (PVR), leading to right ventricular insufficiency and, consequently, death.[1] Among the causes of pulmonary hypertension, profiles associated with chronic thromboembolism are particularly important, since they are potentially curable, assuming that surgical treatment (pulmonary thromboendarterectomy) is possible.[2]

Therefore, appropriate preoperative patient selection is essential for the success of this treatment, since the leading cause of procedure-related death is the persistence of increased PVR in the postoperative period.[3] The current strategy used in order to minimize this risk consists of preoperative evaluation (imaging studies) of the mechan-

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ical obstruction of the central circulation and its proportionality with preoperative PVR, as well as its surgical accessibility.[2-4]

However, the presence of an extensive, centrally located thrombus does not definitively rule out the possibility of in situ thrombosis associated with idiopathic pulmonary arterial hypertension (IPAH), a rare but increasingly recognized condition.[5,6] It is likely that the anatomical similarity between this condition and chronic thromboembolic pulmonary hypertension (CTEPH) is responsible for its low recognition, which must certainly play a role in the treatment failure seen in some cases treated by thromboendarterectomy.[5,6]

Case report

A 40-year-old female patient with IPAH, confirmed in 1994, presented with dyspnea upon moderate exertion (functional class II/New York Heart Association). Using an echocardiogram, we estimated the systolic pulmonary artery pressure to be 126 mmHg. We found significant right ventricle dilatation and dysfunction, without involvement of the left chambers. Right heart catheterization and pulmonary arteriography showed no flow impairment consistent with CTEPH, as well as serving to confirm the vascular pressures in the pulmonary circulation (Table 1). Ventilation/perfusion scintigraphy revealed homogeneous radiotracer uptake in the perfusion mapping (Figure 1). Nonspecific treatment was started, using digitalis and anticoagulation therapy.

In April of 2004, the patient presented progressive functional worsening, reaching functional class IV. Angiotomography of the chest revealed eccentric parietal thrombi, predominantly in the pulmonary artery trunk (from the main branches to the subsegmental branches, bilaterally), with calcifications peripheral to the thrombi (Figure 2). There was also mosaic perfusion in the pulmonary parenchyma, together with bronchial artery dilatation. Tests for deep vein thrombosis and thrombophilia were negative. Despite the functional class worsening, the distance covered on the six-minute walk test (6MWT)—used to assess functional capacity—was 414 m, a dissociation that has previously been described in patients with IPAH.[7] The patient remained adequately anticoagulated throughout the treatment period. The tomographic images were fully consistent with the diagnosis of CTEPH. Fortunately, our knowledge of the previous diagnosis (IPAH) allowed us to opt for clinical treatment with 75 mg/day of sildenafil. There was a favorable clinical response, and, after a few weeks, the patient returned to functional II status.

Another right heart catheterization, performed in July of 2007, revealed a slight decrease in cardiac output and maintenance of the pressure levels, as compared with those observed during the catheterization performed at the time of diagnosis of IPAH. At this writing, the patient maintained functional class II status and was covering 404 m on the 6MWT.

Table 1 - Invasive hemodynamic evaluation at the onset of the disease (1995) and after the diagnosis of embolism and initiation of treatment (2007).

	1995	2007
PAP: S × D (M)	115 × 45 (68) mmHg	139 × 26 (67) mmHg
PWP	12 mmHg	12 mmHg
RAP	3 mmHg	9 mmHg
Cardiac output	4.66 L/min	4.0 L/min
PVR	960 dynes • s^{-1} • cm^{-5}	1,096 dynes • s^{-1} • cm^{-5}

PAP: pulmonary arterial pressure (S: systolic, D: diastolic, and M: mean); PWP: pulmonary wedge pressure; RAP: right atrium pressure; and PVR: pulmonary vascular resistance.

Discussion

In the diagnostic evaluation of pulmonary hypertension, the diagnosis of CTEPH is classically based on ventilation/perfusion scintigraphy and pulmonary arteriography findings. In recent years, the role of angiotomography of the chest as a noninvasive diagnostic tool has grown, since it has good sensitivity for detecting involvement of central pulmonary circulation, and the use of arteriography has therefore become increasingly restricting.[8]

However, as in other clinical situations, imaging methods have limitations for characterizing thromboembolic disease as the cause of pulmonary hypertension, as well as for determining operability if used in isolation. An imaging finding consistent with a chronic central thrombus does not rule out the existence of distal arteriolar disease, nor does it allow us to infer the occurrence of in situ thrombosis, which has been increasingly associated with

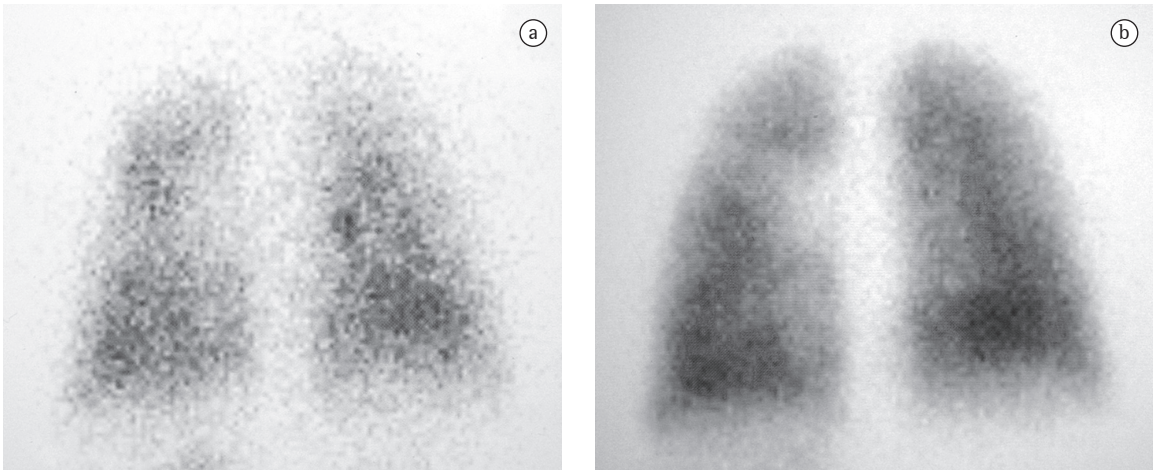

Figure 1 - Mapping of the (a) inhalation and (b) perfusion; posterior view revealing homogeneous and consistent radiotracer uptake.

IPAH.[9] If the patient in this report had sought treatment presenting the current profile, and we had not known about the initial profile, we would have relied on angiotomography findings alone, our diagnosis would have been CTEPH, and thromboendarterectomy would have been indicated. This underscores the fundamental role of clinical evaluation in such cases. It has recently been suggested that some demographic and functional characteristics, such as advanced age and increased diffusing capacity of the lung for carbon monoxide, can help differentiate between patients with CTEPH and those with IPAH.[9]

In 2005, one group of authors attempted to correlate preoperative tomographic findings with hemodynamic improvement in the postoperative period of thromboendarterectomy in 60 patients diagnosed with CTEPH.[10] Postoperative PVR was found to present a negative correlation with preoperative presence and extent of central thrombi, as well as with preoperative dilated bronchial arteries. In addition, 60% of the patients without central thrombi visible on tomography scans presented inadequate hemodynamic response, compared with 4% of the patients with visible central thrombi. Although these findings confirm the hypothesis that central thrombi suggest a good surgical outcome, our case shows that this should not be the only criterion considered.

Pulmonary thromboendarterectomy remains the treatment of choice for symptomatic patients with CTEPH.[3] The currently accepted criteria for its identification are as follows[11,12]: symptoms consistent with functional classes III or IV; preoperative PVR > 300 dynes • s^{-1} • cm^{-5}; surgically accessible thrombi in lobar or segmental arteries; and absence of severe comorbidities. Other factors that should be considered are the technical feasibility of endarterectomy and the experience of the team.[4]

In patients properly selected and in facilities with experienced teams, the procedure can be performed with low perioperative mortality, resulting in great hemodynamic benefits, symptom relief, increased survival,[3] and significant improvement in the quality of life.[13]

Persistent pulmonary hypertension accompanied by high postendarterectomy PVR is still the principal marker of postoperative mortality or failure of the procedure. In the largest series published (500 patients operated between 1998 and 2002), 77% of the deaths were related to high pressures or residual PVR in the postoperative period. Preoperative PVR is also an important marker of postoperative mortality, 30-day mortality being 10.1% among patients with values higher than 1,000 dynes • s^{-1} • cm^{-5}, compared with 1.3% for patients with lower values.[3] This factor was also confirmed in a study conducted in France, in which preoperative PVR > 1,200 dynes • s^{-1} • cm^{-5} was associated with higher mortality.[4]

These results underscore the role of preoperative evaluation. The proximal obstruction component should not be used as a single indicator of the need for surgery, and the contribution that the distal

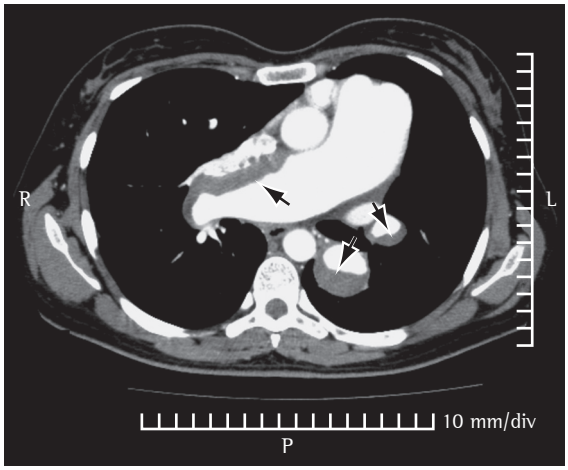

Figure 2 - Angiotomography of the chest (2004) at the level of the pulmonary artery trunk revealing dilated bronchial arteries and eccentric parietal thrombi extending to the segmental branches (black arrows).

microvascular component makes to patient PVR can be a determining factor in evaluating operability. Unfortunately, in this aspect, there is no consensus regarding the best way to preoperatively classify and select patients. Some authors suggest considering the location and degree of the proximal obstructions (arteriography), the proportionality between basal hemodynamic data and imaging findings (as an indirect way to assess distal vascular involvement), and the preoperative PVR values. In patients with CTEPH, PVR is determined by three factors: the chronic thromboembolic disease itself; concomitant small vessel arteriopathy; and right ventricular function (cardiac output). Increased preoperative PVR, in the absence of substantial central thromboembolic disease (arteriography), suggests that there is concomitant small vessel arteriopathy.[2]

Pulmonary capillary pressure, as determined through analysis of pulmonary artery pressure decay curves, has been suggested as a prognostic factor in patients with CTEPH. By determining pulmonary capillary pressure, it is possible to separate PVR into large artery (area of accelerated decay) and small blood vessel (area of slow decay) components.[14] In a recent study of 26 cases, PVR in the area of accelerated decay was shown to correlate strongly with mean postoperative PVR (R^2 = 0.79). All postoperative deaths occurred in patients with large artery component PVR values below 60%, indicating a significant slow decay component and, therefore, predominant involvement of small blood vessels.[15] Although promising, the use of this technique is still limited, and further studies are needed in order to corroborate its true role in the preoperative evaluation.

The pathogenesis of microvascular disease in CTEPH has yet to be fully characterized, although it probably shares mechanisms with IPAH,[16] since individuals for whom surgery is not indicated present some degree of response to specific treatments for pulmonary hypertension, even in the presence of a more accentuated mechanical component.[17,18] Abnormalities in the endothelium, as well as in the coagulation cascade, platelet function, and fibrinolysis, can contribute to a prothrombotic environment, particularly in nonoccluded sites, and there is biological evidence that intravascular coagulation is a continuous process in several forms of pulmonary hypertension.[4,19] However, it is not known for certain whether such coagulation results from genetic predisposition or from endothelial and platelet dysfunction secondary to pulmonary vascular injury.[20] All of these factors can contribute to the occurrence of in situ thrombosis or to the progression of the distal microvascular disease, even in cases of IPAH.

In conclusion, CTEPH is a unique form of pulmonary hypertension due to the possibility of surgical treatment, and even cure, in selected cases. Currently, candidate selection for surgery places great emphasis on the anatomical evaluation of the distribution of accessible central thrombi, which, in isolation, can significantly limit surgical success. The main factor of poor postoperative prognosis is the persistence of elevated PVR, which occurs mainly due to concomitant small vessel arteriopathy and central obstructions. The case presented here underscores the need to combine detailed clinical evaluation with existing imaging methods, as well as the fact that there is a lack of appropriate techniques for the evaluation of the most peripheral pulmonary vascular region. It is possible that the functional study of pulmonary vessels might be found to represent an alternative to this evaluation.

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