

# Case Report

## Systemic corticosteroids as first-line treatment in pulmonary hypertension associated with the POEMS syndrome\*

Corticoide sistêmico como tratamento de primeira linha da hipertensão pulmonar secundária a síndrome POEMS

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### Abstract

The POEMS syndrome is a rare plasma cell disease. Pulmonary hypertension is an infrequent respiratory complication of this syndrome and might be associated with increased levels of various cytokines, chemokines and growth factors as part of the inflammatory phenomena that involve the physiopathology of POEMS syndrome. We present the case of a 54-year-old woman diagnosed with POEMS syndrome and pulmonary hypertension, which were treated with corticosteroids as the first-line therapy. The patient presented with the classic symptoms of this syndrome: polyneuropathy (confirmed by electromyography), organomegaly, subclinical hypothyroidism and monoclonal gammopathy detected in urine, together with skin changes. Right heart catheterization revealed a mean pulmonary artery pressure of 48 mmHg, a cardiac output of 4.1 L/min and pulmonary vascular resistance of 8.05 Woods. The serum level of brain natriuretic peptide (BNP) was 150 pg/mL. No other underlying disease was found during the investigation. Prednisone (1 mg/kg for three months) was then initiated, with a dramatic improvement in the clinical and functional condition. Levels of thyroid hormones and urinary protein levels (as determined using electrophoresis) normalized. Mean pulmonary artery pressure decreased to 26 mmHg, cardiac output decreased to 3.8 L/min, and pulmonary vascular resistance decreased to 2.89 Woods. Serum levels of BNP dropped to 8 pg/mL. Our findings suggest that corticosteroids could play a role as a first-line treatment in pulmonary hypertension accompanied by POEMS syndrome. Due to the rarity of this presentation, a multicenter registry should be developed to allow the compilation of additional data to support this practice.

**Keywords:** POEMS syndrome; Hypertension, pulmonary; Glucocorticoids.

### Resumo

A síndrome POEMS é uma rara doença de plasmócitos. A ocorrência de hipertensão pulmonar como complicação respiratória da síndrome é pouco frequente e pode estar ligada ao aumento de várias citocinas, quimiocinas e fatores de crescimento como parte dos fenômenos inflamatórios que cercam a fisiopatologia da síndrome POEMS. Descrevemos o caso de uma mulher de 54 anos com síndrome POEMS e hipertensão pulmonar, que foi tratada com corticoide como terapia de primeira linha. Tratava-se de uma paciente com clássicos sintomas dessa síndrome: polineuropatia (confirmada por eletroneuromiografia), organomegalia, hipotireoidismo subclínico, gamopatia monoclonal em dosagem urinária e alterações cutâneas. A cateterização cardíaca direita revelou pressão arterial pulmonar média de 48 mmHg, débito cardíaco de 4,1 L/min e resistência vascular pulmonar de 8,05 Woods. O nível sérico de *brain natriuretic peptide* (BNP) foi de 150 pg/mL. Nenhuma outra doença foi encontrada durante investigação. Prednisona (1 mg/kg por três meses) foi iniciada, com dramática melhora clínica e funcional, além de normalização dos níveis dos hormônios tireoidianos e de proteína em urina por eletroforese. A pressão arterial pulmonar média caiu para 26 mmHg, o débito cardíaco para 3,8 L/min e a resistência vascular pulmonar para 2,89 Woods. O nível sérico de BNP caiu para 8pg/mL. Nossos achados indicam o potencial papel da corticoterapia como primeira linha de tratamento na hipertensão pulmonar associada à síndrome POEMS. Diante da raridade dessa apresentação, um registro multicêntrico deveria ser desenvolvido para permitir a aquisição de mais dados que suportem essa conduta.

**Descritores:** Síndrome POEMS; Hipertensão pulmonar; Glucocorticoides.

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## Introduction

The POEMS syndrome, also known as Crow-Fukase syndrome, is a multisystemic disorder commonly associated with blood diseases. Because it is a complex disease, criteria have been developed in order to diagnose it.<sup>(1)</sup> There are two major criteria and seven minor criteria for a diagnosis of POEMS syndrome. Patients are classified as having the syndrome if meeting both of the major criteria and at least one of the minor criteria. The major criteria are polyneuropathy and monoclonal immunoglobulin deposition. The minor criteria are as follows: sclerotic bone lesions; Castleman's disease; organomegaly (splenomegaly, hepatomegaly or lymphadenomegaly); fluid accumulation (peripheral edema or cavity effusion); endocrinopathy (affecting the adrenal glands, thyroid, pituitary gland, gonads, parathyroid glands or pancreas); skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomas or white nails); and papilledema. The combination of POEMS syndrome and pulmonary hypertension is uncommon, and the exact mechanism of such co-occurrence is unknown.<sup>(1,2)</sup>

The co-occurrence of these two clinical conditions might be linked to increased levels of proinflammatory cytokines.<sup>(3-7)</sup> The potential relation between the inflammatory process and the development and modulation of pulmonary hypertension<sup>(8)</sup> is confirmed by a significant response to immunosuppressants when the clinical condition associated with the development of pulmonary hypertension is predominantly inflammatory, e.g., systemic lupus erythematosus and mixed connective tissue disease.<sup>(9)</sup> Such findings provide the theoretical basis for the use of immunosuppressive therapy in pulmonary hypertension accompanied by POEMS syndrome.

We present a case of pulmonary hypertension associated with POEMS syndrome and initially treated with systemic corticosteroids, which evoked clinical, hemodynamic and functional responses.

## Case report

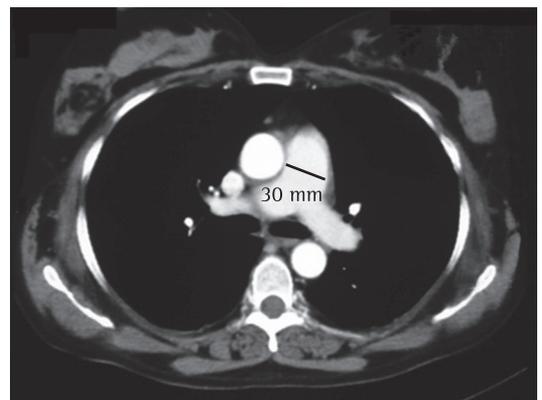
A 54-year-old female sought treatment complaining of abdominal distension, lower limb edema and progressive dyspnea on exer-

tion. She also complained of bilateral paresthesia of the hands and feet. Clinical examination revealed skin lesions on the upper limbs and torso, characterized as hyperpigmented brownish macules. Abdominal palpation revealed hepatosplenomegaly.

Echocardiography showed severe tricuspid insufficiency and an estimated pulmonary artery systolic pressure of 75 mmHg, with no signs of left ventricular dysfunction (systolic or diastolic). Electromyography was performed, and the results were consistent with chronic inflammatory demyelinating polyneuropathy with secondary axonal involvement. Thyroid hormone levels revealed subclinical hypothyroidism. Urine immunofixation electrophoresis revealed a monoclonal increase in IgA with an increase in kappa. Screening for thromboembolic disease was negative, and angiotomography of the chest showed that the pulmonary artery trunk was 30 mm in diameter at its widest point, without flow impairment (Figure 1).

Right heart catheterization confirmed the presence of pulmonary hypertension (Table 1), without acute response to NO inhalation. The serum level of brain natriuretic peptide (BNP) was 150 pg/mL. Rheumatologic tests and parasitological stool examination, as well as serology for HIV and hepatitis, all yielded negative results, and the patient had no history of chronic drug use that would be implicated in the onset of pulmonary hypertension.

The clinical data, together with the complementary tests, led to the hypothesis of POEMS syndrome with pulmonary hypertension.



**Figure 1** - Angiotomography of the chest: pulmonary artery trunk at its widest point (30 mm in diameter), with no evidence of flow impairment.

**Table 1** – Clinical, hemodynamic and biochemical parameters.

Parameters	Pre-treatment	Post-treatment (3 months)
Functional class	III	II
Hemodynamic		
PASP (mmHg)	62	36
PADP (mmHg)	40	17
MPAP (mmHg)	48	26
PAOP (mmHg)	15	15
RAP (mmHg)	12	9
CO (L/min)	4.1	3.8
CI (L/min/m <sup>2</sup> )	2.41	2.23
PVR (Woods)	8.05	2.89
IRVP (Woods/m <sup>2</sup> )	4.73	1.70
Biochemical		
BNP (pg/mL)	150	8

PASP: pulmonary artery systolic pressure; PADP: pulmonary artery diastolic pressure; MPAP: mean pulmonary artery pressure; PAOP: pulmonary artery occlusion pressure; RAP: right atrium pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; and BNP: brain natriuretic peptide.

Treatment with a corticosteroid (prednisone, 1 mg/kg) was initiated, and the clinical response was good. A second right heart catheterization, performed three months later, revealed significant improvement in the hemodynamic profile (Table 1), the serum level of BNP having fallen to 8 pg/mL. Urine immunofixation results and thyroid hormone levels were within normal limits.

## Discussion

A rare blood disease, POEMS syndrome is characterized by the combination of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. For the diagnosis of POEMS syndrome, it is not necessary that patients present with all of the related manifestations; however, at least three typical findings have to be present.<sup>(1)</sup> The mean survival of these patients is greater than 10 years, far superior to that observed in cases of multiple myeloma.<sup>(1)</sup> Treatment has yet to be clearly defined. However, the principal treatment options are radiotherapy, alkylating agents, autologous bone marrow transplantation and corticosteroids.<sup>(1)</sup> Early detection of POEMS

syndrome is important for reducing the associated mortality.

Various forms of pulmonary impairment are related to POEMS syndrome. One group of authors recently conducted a retrospective study of 137 patients with POEMS syndrome. Of the 137 patients, 28% presented some type of respiratory symptom within the first 2 years after diagnosis, dyspnea being the most prevalent complaint, followed by chest pain, cough and orthopnea. Pulmonary hypertension was identified in 8.7% of the patients and, together with restrictive lung disease and respiratory muscle weakness, was one of the most prevalent types of lung impairment in these individuals.<sup>(2)</sup>

Various other studies have confirmed the relation between POEMS syndrome and pulmonary hypertension, although it should be borne in mind that this is a differential diagnosis. Therefore, it is essential to perform complementary tests in order to rule out other causes of pulmonary hypertension.<sup>(4,5,10-12)</sup> In the case reported here, the patient presented all clinical criteria for the diagnosis of POEMS syndrome and was submitted to right heart catheterization in order to confirm the diagnosis of pulmonary hypertension. In addition, the remainder of the investigation ruled out other clinical conditions that might have been associated with the development of pulmonary hypertension.<sup>(13,14)</sup>

The confirmation that pulmonary hypertension is associated with POEMS syndrome has prognostic implications, because the clinical evolution of such cases seems to follow a clinical course that is more benign than is that observed in other forms, such as the idiopathic form.<sup>(4)</sup> Another important aspect of this distinction lies in the treatment; due to the potential role of inflammation in the modulation of POEMS syndrome and accompanying pulmonary hypertension, the use of immunosuppressants should perhaps be regarded as the first-line treatment.<sup>(12)</sup> In the case reported here, there was a significant improvement in the hemodynamic pattern after the use of prednisone at a dose of 1 mg/kg for three months, as well as a marked decrease in the serum levels of BNP, an important prognostic marker related to the stress on the myocardial wall in patients with pulmonary hypertension.<sup>(15)</sup> Other studies have reported such dramatic response to corticosteroids. However, this was based only on subjective

data and on pulmonary artery pressure measured indirectly by echocardiography. In the case reported here, we confirmed the efficacy of corticosteroid treatment in POEMS syndrome through direct hemodynamic measurements and specific biochemical data before and after treatment.<sup>(4,11,12)</sup>

The response to corticosteroids is probably linked to the inflammatory etiology that characterizes POEMS syndrome. Patients with POEMS syndrome markedly show high levels of serum cytokines, particularly TNF- $\alpha$ , IL-6, IL-1 $\beta$  and vascular endothelial growth factor (VEGF).<sup>(4,6,7)</sup> More recently, one group of authors reported a case in which VEGF was determined before and after the initiation of corticosteroid treatment and noted that the serum levels of this cytokine decreased significantly.<sup>(5)</sup>

The expression of VEGF is intimately related to the formation of plexiform vascular lesions in the lungs of patients with severe idiopathic pulmonary arterial hypertension and in those patients with pulmonary arterial hypertension of other causes. This cytokine contributes to angiogenesis, increased vascular permeability and pulmonary microvasculature alterations, characterized by arteriolar and capillary wall thickening. Taken together, such alterations culminate in increased vascular resistance and, consequently, increased pressure in the pulmonary vascular bed.<sup>(16)</sup>

In conclusion, these data suggest that patients with pulmonary hypertension induced by POEMS syndrome present alterations in the production and regulation of inflammatory cytokines, which in turn cause alterations in the pulmonary vessels that increase pulmonary vascular resistance. In addition, corticosteroids inhibit the production of these cytokines and therefore have a potential for use as the first-line treatment in this subgroup of patients. The rarity of this form of presentation makes it difficult to conduct prospective studies that might provide sufficiently significant evidence on which to base such a hypothesis. However, the evaluation of treatment response through variables that are less influenced by a potential placebo effect, such as invasive hemodynamic variables or even serum levels of natriuretic peptides, as reported here, might aid in providing such a basis over time.

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