Pulmonary hypertension associated with POEMS syndrome


ABSTRACT: Pulmonary hypertension (PH) is an uncommon but lethal complication of some connective tissue diseases. We describe two cases of PH associated with plasma cell dyscrasia, with polyneuropathy (P), organomegaly (O), endocrinopathy (E), M protein (P) and skin changes (S) described as POEMS syndrome.

Our observations suggest that pulmonary hypertension (PH) may be associated with the POEMS syndrome, and that patients suffering from the POEMS syndrome and dyspnoea should be tested for PH.


Primary pulmonary hypertension, also referred to as unexplained or idiopathic, is a clinical syndrome characterized by persistent pulmonary hypertension without identifiable underlying disease to explain the elevation in pulmonary vascular resistance [1]. Pulmonary hypertension (PH) may occur during the course of various connective tissue diseases, especially progressive systemic sclerosis and systemic lupus erythematosus [2]. The POEMS syndrome is characterized by the association of polyneuropathy (P), organomegaly (O), endocrinopathy (E), M protein (M) and skin changes (S) [3–7]. We report the cases of two patients with POEMS syndrome, who presented with progressive dyspnoea. Elevation in pulmonary artery pressure was definitely documented in both cases, and PH was defined as associated with POEMS syndrome by the absence of other secondary causes.

Case reports

Case 1

A 68 year old female was hospitalized in January 1994 for progressive dyspnoea which had appeared 3 yrs previously. She had a history of breast cancer treated by surgery and radiotherapy in 1967. In 1985, she presented with thrombocytopenia, and received treatment with the alkylating agent Pipobroman for 1 yr, which was stopped following onset of aplastic anaemia. By that time, Raynaud's syndrome had occurred. Between 1989 and 1992, the patient progressively developed hypothyroidism, hypopituitarism, Gougerot-Sjögren's syndrome, a four limbs sensorimotor polyneuropathy, hepatomegaly, splenomegaly, glomerulonephritis, diffuse osteosclerotic bone lesions and cutaneous haemangioma. Kidney biopsy was performed and demonstrated enlargement of glomeruli with proliferation of mesangial cells and accumulation of lymphoid cells within the interstitium. Dysglobulinemia (monoclonal gammapathy of undetermined significance immunoglobulin A (IgA lambda paraprotein) and aluminocytological dissociation of the cerebrospinal fluid were also present. Bone marrow aspiration was performed and did not reveal significant plasmocytosis (3.5%). The association of polyneuropathy (P), organomegaly (O), endocrinopathy (E), M protein (M) and skin changes (S) led to the diagnosis of POEMS syndrome. The patient was treated with steroids (prednison 0.5 mg·kg⁻¹·q.d.) and levothyroxin (100 mg·q.d.) with improvement of dyspnoea until November 1993. She secondarily developed fatigue, weight loss and dyspnoea. Physical examination showed a severe cachexia (body mass index (BMI) = 17 kg·m⁻²) and right heart failure. No cyanosis, digital clubbing or other chest abnormality were identified. There was no sign of portal hypertension. She received no medication except steroids and levothyroxin. Erythrocyte sedimentation rate (ESR) 16 mm·h⁻¹, and C-reactive protein, 3 mg·L⁻¹, were normal. Serum creatinine was 18 mg·L⁻¹, urea 0.96 g·L⁻¹, alkaline phosphatase 835 IU·L⁻¹ (<220). Serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), platelet count were within normal range. The search for rheumatoid factor, antinuclear antibodies (anti-deoxyribo-nucleic acid (DNA), anti-extractable nuclear antigens (ENA), anti-centromere and anti-scleroderma (SCL) antibodies) and circulating immune complexes was negative. Arterial blood gas analysis (room air) revealed pH 7.35, arterial oxygen tension (Pₐ,O₂) 9.2 kPa (69 mmHg) and arterial carbon dioxide tension (Pₐ,CO₂)
A 46 year old male was referred in November 1992 for progressive dyspnoea which had appeared 2 yrs previously. In May 1988, he presented a sensorimotor polyneuropathy with albuminocytological dissociation of the cerebrospinal fluid. Electrophoretic and immuno-electrophoretic analyses did not reveal an M component or a polyclonal increase of immunoglobulins [4, 7]. Diffuse osteosclerotic lesions were found on lumbar vertebral roentgenogram. In September 1989, the patient develope-ped gynecomastia associated with hypotestosteronemia. In June 1992, he developed cutaneous haemangiomia and hypertrichosis with hepatosplenomegaly, adenomegaly and hypothyroidism. POEMS syndrome was diagnosed at this time.

The examination was normal. No cyanosis, digital clubbing, chest abnormality, signs of right heart failure, or portal hypertension were identified. Cachexia and fatigue were noted. ESR 12 mm·h\(^{-1}\), and C-reactive protein 5 mg·L\(^{-1}\), were normal. Renal, hepatic tests and blood cell count were normal. Antinuclear antibodies, rheumatoid factor, parasitic research and HIV serodiagnosis were negative. Room arterial blood gas evaluation revealed pH 7.38, \(P_{a,\text{O}_2}\) 9.3 kPa (70 mmHg) and \(P_{a,\text{CO}_2}\) 5.1 kPa (38 mmHg). Chest roentgenogram and high resolution CT scan with thin sections showed prominence of the main pulmonary artery and mediastinal lymph nodes, and a normal interstitium. Pulmonary function tests and carbon monoxide transfer factor were normal. Night oximetry found no oxygen desaturation. Fingernail capillaroscopy was normal. Doppler echocardiography revealed a dilatation of the right ventricle with tricuspid insufficiency and a systolic pulmonary artery pressure evaluated at 75 mmHg. Left ventricular ejection fraction was 74%. Cardiac catheterization, performed with a Swan Ganz® catheter, confirmed the precapillary pulmonary hypertension. Pharmacodynamic tests with nitric oxide (NO) and prostacyclin (PGI\(_2\)) were performed and showed a positive response (table 1). Ventilation perfusion scintigraphy and venous Doppler echography were normal.

The diagnosis of PH associated with POEMS syndrome was retained and nifedipine (20 mg·q.d.) associated with fluindrone (20 mg·q.d.) was initiated. Three months later, dyspnoea improved, although systolic pulmonary artery pressure was still high (88 mmHg). The improvement of pulmonary symptoms was still present after 1 yr of therapy.

### Discussion

We describe two cases of pulmonary hypertension associated with POEMS syndrome. The POEMS syndrome, also called Takatsuki or Crow-Fukase syndrome, is a multiple system syndrome characterized by polyneuropathy (P),
organomegaly (O), endocrinopathy (E), M protein (M) and skin changes (S) [3–7]. Other lesions have been described, such as renal failure, thrombocytosis, sclerotic lesions with myeloma and albuminocytological dissociation in the cerebrospinal fluid [4, 6]. The association of PH and POEMS syndrome is very rare: one case was recently described by Iwasaki et al. [9] in a 60 year old female consulting because of severe dyspnoea. The characteristics of this observation were very similar to ours, including hypoxaemia, PH, cardiomegaly and right cardiac failure. In addition, several reports of micro-angiopathic glomerular lesions suggest that a pathogenic role might be played by a nonimmunoglobulin vasculotoxic component. Viard et al. [10] reported a case of POEMS syndrome with microangiopathic glomerular lesions and pulmonary arterial hypertension. Fam et al. [11] demonstrated a renal microangiopathy, with thickening and luminal reduction of the glomerular capillaries resembling that observed in diseases characterized by prominent renal microvascular abnormalities. One cannot exclude that such a microangiopathy might occur in lung vessels.

Recent reports support the hypothesis that endothelial cell dysfunction may account for systemic manifestations in the POEMS syndrome [12–14]. Indeed, increased capillary leakage responsible for oedema, sclerodermalike cutaneous lesions, and skin and kidney endothelial cell pathological lesions has been described [12, 13]. However, this hypothesis remains uncertain and little is known about the definite pathogenesis of this syndrome. Implication of proinflammatory cytokines, such as interleukin-1β, IL-6 and tumour necrosis factor-α (TNF-α) has been suspected [14, 15]. Interestingly, a role for these proinflammatory cytokines has recently been suggested in severe primary PH [16]. Some authors argue for a possible role of a light chain immunoglobulin or an unknown substance secreted by plasma cells which could be toxic to many organs [6, 17].

In our cases, the main respiratory symptom was dyspnoea. In one case, Raynaud’s syndrome was present and suggested abnormalities of endothelial cells. There was no chest pain, haemoptysis, syncope or palpitation. Thromboembolic disease was excluded in both cases. No cardiac disease was diagnosed. The pulmonary hypertension was not associated with other secondary causes. No toxic medication, portal hypertension or autoimmune abnormalities were found. Although pathological data were not obtained, it is well-known that the analysis of pulmonary vasculature is not necessary for diagnosis of primary PH [11]. In our observations, the mechanisms responsible for PH remain unknown; kidney biopsy was performed in one case and did not show microangiopathic abnormalities.

Regarding clinical outcome, the first patient, who had a significant decrease in the total pulmonary resistance index with the use of vasodilator agents was still alive 18 months after starting therapy. The second patient demonstrated a modest response to the vasodilators in comparison with the first patient and died 6 months later. However, there is probably no link between the acute response to vasodilators and the clinical outcome in our two cases.

The association of POEMS syndrome and pulmonary hypertension is rare. Although the link between these two disorders remains speculative, the rarity of both diseases suggests that the association might not be fortuitous. In conclusion, these cases suggest that patients suffering from the POEMS syndrome and dyspnoea should be tested for pulmonary hypertension.

References