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CASE STUDY

Pulmonary hypertension associated with POEMS syndrome

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Pulmonary hypertension associated with POEMS syndrome. S. Ribadeau-Dumas, I. Tillie-Leblond, C. Rose, F. Saulnier, J.L. Wemeau, P.Y. Hatron, B. Wallaert. ©ERS Journals Ltd 1996.

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.

Two patients, one female and one male, were hospitalized for dyspnoea. Both had a history of POEMS syndrome a few years previously. PH was diagnosed from cardiac catherization, and complete investigations did not reveal other underlying disease.

In Case No. 1, mean pulmonary artery pressure was 40 mmHg and pulmonary vascular resistance was 775 dyne·s·cm^{-5}·m^2, with a significant reversibility to vasodilators. Nifedipine and fluindrone treatment was initiated. The patient was still alive 18 months later. In Case No. 2, mean pulmonary artery pressure was 28 mmHg and pulmonary vascular resistance was 243 dyne·s·cm^{-5}·m^2, with a slight reversibility to vasodilators. The patient died 6 months later.

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.

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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 thrombocythaemia, 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. Dysglobulinaemia (monoclonal gammopathy of undetermined significance immunoglobulin A (IgA) lambda paraprotein) and albuminocytological 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 (prednisone 0.5 mg·kg^{-1}·*q.d.*) and levothyroxin (100 ng·*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-nucleaic 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 (P_{a,O_2}) 9.2 kPa (69 mmHg) and arterial carbon dioxide tension (P_{a,CO_2})

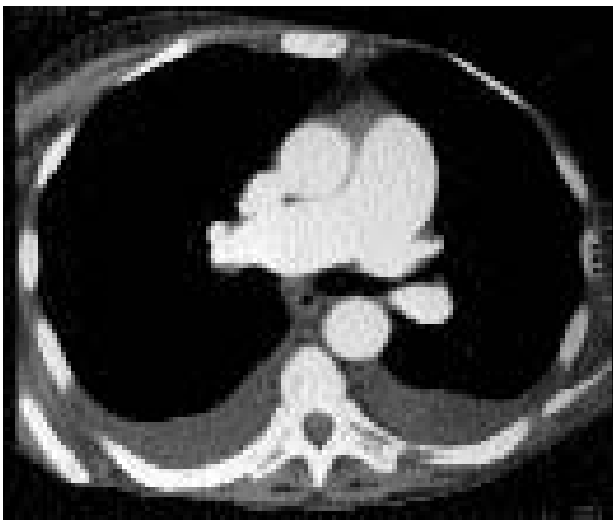

Fig. 1. – High resolution computed tomography (CT) scan with injection showing prominence of the main pulmonary arteries and bilateral pleural effusion. No mediastinal lymph nodes are seen on this section.

4.5 kPa (34 mmHg). Search for schistosome eggs in stools was negative. Human immunodeficiency virus (HIV) serodiagnostic test was negative. Chest roentgenogram and high resolution computed tomography (CT) scan with thin sections showed prominence of the main pulmonary artery, mediastinal lymph nodes and a bilateral pleural effusion (fig. 1). No parenchymal abnormality was observed. Bilateral pleural effusion was probably due to POEMS syndrome itself [8], but evaluation of pleural fluid was not performed. 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 triscupid 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.

Case 2

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 immunoelectrophoretic 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 develo-ped gynecomasty associated with hypotestosteronaemia. In June 1992, he developed cutaneous haemangioma and hypertrichosis with hepatosplenomegaly, adenomegaly and hypothyroidism. POEMS syndrome was diagnosed at this time.

Chest 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 $mm \cdot h^{-1}$, and C-reactive protein 5 $mg \cdot L^{-1}$, 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,O_2} 9.3 kPa (70 mmHg) and P_{a,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. Doppler echocardiography revealed major dilation of the right ventricle, with tricuspid insufficiency and a systolic pulmonary artery pressure of 60 mmHg. Cardiac catheterization, performed with a Swan Ganz® catheter, confirmed the precapillary pulmonary hypertension. Pharmacodynamic test with prostacyclin was performed and showed slight but significant modification in pulmonary pressure (table 1). Ventilation perfusion scintigraphy and contrast venography were normal. Diagnosis of PH associated with the POEMS syndrome was made. After a 6 month treatment with steroids (prednisone 0.5 $mg \cdot kg^{-1} \cdot q.d.$) and levothyroxin (100 ng·*q.d.*), the patient died following multiple organ failure and cachexia.

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),

Table 1. – Haemodynamic measurements

Variable	Case 1				Case 2		
	Baseline	NO 10 ppm	10min post NO	Prostacyclin 0.25 $\mu g \cdot min^{-1}$	Baseline	Prostacyclin 0.25 $\mu g \cdot min^{-1}$	10 min post injection
Right atrial mean pressure mmHg	10	7	10	5	5	6	6
Pulmonary artery systolic pressure mmHg	75	60	80	65	44	37	39
Pulmonary artery diastolic pressure mmHg	25	20	27	20	20	17	15
Pulmonary artery mean pressure mmHg	40	36	47	39	28	24	23
Total pulmonary resistance index unit	12.6	8.4	15.8	8.9	5.38	3.8	3.4
Pulmonary vascular resistance $dyne \cdot s \cdot cm^{-5} \cdot m^2$	775	520	975	551	243	171	153
Pulmonary capillary pressure mmHg	8	8	8	8	14	12	14
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	3.3	4.3	3.2	4.5	4.6	5.6	4.7
Systemic vascular resistance index unit	13.7	11.7	13.4	11.2	21.1	18.6	30
Systemic artery mean pressure mmHg	75	75	80	59	83	83	103
Heart rate $beats \cdot min^{-1}$	75	60	80	65	44	37	39

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 glomenular 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 (IL)-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 λ 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 [1]. 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.

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