Pulmonary hypertension in POEMS syndrome: resolution following radiotherapy

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Abstract: Pulmonary hypertension (PH) is defined by the presence of a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg. It may be idiopathic or arise as a consequence of a number of diverse conditions. PH has been reported in association with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes), with reversal following systemic treatment with corticosteroids. We report a case of pulmonary hypertension associated with POEMS syndrome treated with radical radiotherapy locally to bone lesions with resolution of systemic disease.

Keywords: plasmacytoma, sildenafil, bosentan.

Pulm Circ 2014;4(4):732-735. DOI: 10.1086/678553.

Pulmonary hypertension (PH), defined by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, may be idiopathic or arise as a consequence of a number of diverse conditions. PH has been reported in association with POEMS syndrome, a rare paraneoplastic syndrome characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes. Reversal of PH with corticosteroids has been documented in the literature.¹⁻⁵ We report a unique case of PH associated with POEMS syndrome with poor initial response to PH-targeted therapy with pulmonary vasodilators, subsequently successfully treated with radical radiotherapy locally to bone lesions with resolution of PH at repeat right heart catheterization (RHC).

CASE DESCRIPTION

A 46-year-old female nonsmoker presented in September 2011 with a 3-month history of breathlessness. Her medical history consisted of treated hypothyroidism and benign intracranial hypertension. She was noted to have peripheral edema and a palpable supraclavicular lymph node.

Lung function was normal with the exception of a reduced carbon monoxide diffusing capacity, which was 40% of the predicted value. Chest radiograph findings (Fig. 1) indicated cardiomegaly. Transthoracic echocar-

diogram (TTE) suggested severe pulmonary hypertension (tricuspid regurgitant pressure gradient, 132 mmHg) with severe right ventricular (RV) dilatation and RV systolic impairment (tricuspid annular plane systolic excursion, 1.3 cm). A moderate pericardial effusion was present. Left ventricular function and left atrial size (13 cm²) were normal. Thrombocytosis was present with platelets of 492×10^9 cells/L.

Computed tomography (CT) pulmonary angiogram showed no evidence of thromboembolic disease but confirmed right heart dilatation, extravascular volume overload with subcutaneous edema, pericardial effusion, small left pleural effusion, and ascites. A 15-cm splenomegaly with widespread small volume lymphadenopathy (maximally measuring 15 mm in the mediastinum) was also present. Ventilation perfusion scan indicated low probability for thromboembolic disease.

PH was confirmed at RHC with mPAP of 70 mmHg (systolic PAP, 88 mmHg; diastolic PAP, 50 mmHg), right atrial pressure (RAP) of 20 mmHg, cardiac index (CI) of 2.5 L/min/m², pulmonary vascular resistance (PVR) of 13.8 Wood units, and pulmonary artery wedge pressure (PAWP) of 16 mmHg. The diastolic pressure gradient was significantly elevated, which suggests precapillary pulmonary vascular disease.⁶

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Submitted March 4, 2014; Accepted July 13, 2014; Electronically published October 16, 2014.

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Figure 1. Patient imaging. Chest radiograph (A) showing cardiomegaly, computed tomography (CT) pulmonary angiogram showing severe right heart dilatation (B), and left acetabular lesion identified on CT (C) and magnetic resonance imaging (D). Gross ascites are also seen.

Lymph node biopsy showed reactive tissue only, and bone marrow trephine was normal. Total serum immunoglobulin A was mildly elevated at 4.51 g/L (reference, 0.8–4.0 g/L) with normal protein electrophoresis. Bence Jones protein test results were negative. There was elevation of κ and λ free light chains (FLCs; 48.5 mg/L and 55.5 mg/L, respectively), but normal light chain ratio (0.874; reference ranges, 3.3–19.4 mg/L for κ and 5.7–26.3 mg/L for λ). CT and subsequent MRI (Fig. 1C, 1D) revealed an expansile lesion in the left acetabulum and the medial end of the left sixth rib with no increased uptake on bone scan. Biopsy of the acetabular lesion showed a plasmacytoma with a predominance of λ light chain expression in the plasma cell aggregates. Although there was no clinical history suggestive of neuropathy, nerve conduction studies confirmed peripheral polyneuropathy of demyelinating type with reduction in amplitude and velocity of sensory potentials and clear slowing of motor

velocities (e.g., peroneal, 26 m per second; typical normal range, 50–60 m per second) with decrease in amplitude in excess of 50%. This supported a diagnosis of POEMS syndrome.

In October 2011, the patient commenced sildenafil and diuretic therapy. However, due to poor clinical response with additional hospitalization requiring intravenous diuretics for refractory edema, increase in N-terminal prohormone of brain natriuretic peptide (NTproBNP) to 4,915 pg/mL, and static 6-minute walk distance (6MWD), this was increased to combination therapy with bosentan. In July 2012, sildenafil was titrated to 50 mg administered 3 times per day after a decrease in 6MWD to 458 m, again with little improvement.

In August 2012, the patient received radical radiotherapy (45 Gy, 20 fractions) to each of the bone lesions. Over subsequent months, her breathlessness improved, her ascites and edema resolved, and diuretics were withdrawn.

Serum FLC ratio improved to 1.03 (reference, 0.26–1.65). TTE showed resolution of the pericardial effusion. 6MWD increased from 478 to 582 m, NTproBNP decreased from 3,606 to 543.5 pg/mL, and the patient returned to work.

At repeat RHC in January 2013, dramatic resolution of PH was demonstrated (mPAP, 21 mmHg; RAP, 2 mmHg; CI, 3.7 L/min/m²; PAWP, 4 mmHg; PVR, 3.1 Wood units). At the most recent review in October 2013, the patient remained well and in New York Heart Association functional class II while continuing to receive dual oral vasodilator therapy.

DISCUSSION

POEMS syndrome is a rare clonal plasma cell disorder. Its pathogenesis is poorly understood, but vascular endothelial growth factor (VEGF) and overproduction of other inflammatory cytokines, such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor α have been suggested to play a role. These cytokines have recently been shown to be important in the prognosis of patients with idiopathic pulmonary arterial hypertension.⁷ Unfortunately, we did not have access to cytokine levels, which may have provided mechanistic insights in this case. Li et al⁴ demonstrated no difference in VEGF levels between patients with POEMS with and without PH, although a decrease in VEGF levels accompanied improvement in PH in patients treated for POEMS. In addition, anti-VEGF therapy with bevacizumab has not demonstrated clear clinical response, suggesting VEGF is not the sole mechanism relating PH to POEMS.⁸

The diagnosis is made on the basis of a composite of clinical and laboratory features requiring polyneuropathy and a monoclonal plasma cell-proliferative disorder (usually λ), one of three other major and one of six minor criteria (Table 1).⁹ Although our patient did not have a demonstrable paraprotein, she had proven plasmacytoma

with λ light chain clonality, which has been reported in previous literature regarding POEMS.¹⁰ Proportionately elevated κ and λ FLC levels have been reported and postulated to relate to extramedullary polyclonal plasma cell activation, related to organomegaly of the spleen and lymph nodes. In our patient, the FLC ratio increased after radiotherapy, indicating reduction in the λ light chain expression. Renal dysfunction could also explain proportionate FLC elevation; however, our patient had preserved urinary protein : creatinine ratio and estimated glomerular filtration rate.

Both precapillary and postcapillary PH have been described in the literature.^{1,2} The suggested prevalence of associated PH is 27%–48%, although these figures were obtained using TTE to estimate pulmonary artery pressure.^{3–5} In addition, thrombotic events can be associated with POEMS, with reports of an association with chronic thromboembolic pulmonary hypertension.¹ The survival of patients with pulmonary hypertension and POEMS is worse than those with POEMS alone, with median survival time of 54 months in large case series.⁴

Although reversibility of pulmonary hypertension has been reported with corticosteroids,^{1–5} this is, to our knowledge, the first case reported in which PH has resolved following radical radiotherapy to bone lesions. It is important to consider associated syndromes when a diagnosis of PH is made, because treatment of the underlying condition may lead to improvement in PH, not just in POEMS but in other conditions, such as human immunodeficiency virus infection and systemic lupus erythematosus.

Conclusions. In patients with pulmonary hypertension associated with POEMS syndrome, oncological treatment of the underlying plasma cell dyscrasia should be considered first-line therapy, because this may be followed by resolution of PH, whereas pulmonary vasodilator therapy showed little improvement in this case.

Table 1. POEMS syndrome diagnostic criteria

Criteria	Clinical feature
Mandatory major criteria	Polyneuropathy (typically demyelinating); monoclonal plasma cell proliferative disorder (usually λ)
Other major criteria (one required)	Castleman disease; sclerotic bone lesions; vascular endothelial growth factor elevation; organomegaly
Minor criteria (one required)	Extravascular volume overload; endocrinopathy; skin changes; papilledema; thrombocytosis/polycythemia

Note: POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes. Adapted from Allam et al.³

Source of Support: Nil.

Conflict of Interest: MJB reports travel grants from Actelion, GlaxoSmithKline, and Pfizer. MKJ reports grants from Actelion, GlaxoSmithKline, and Pfizer. ACC reports educational grants from Wellcome Trust and travel grants from Actelion, GlaxoSmithKline, and Pfizer. ST reports travel grants from Actelion, GlaxoSmithKline, and Pfizer. AJP sits on advisory boards for Actelion, Bayer, Eli Lilly, GlaxoSmithKline, Novartis, and Pfizer and has received honoraria and travel grants from Actelion, Bayer, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, and United Therapeutics. All other authors: none reported.

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