Severe reversible pulmonary hypertension in smoldering multiple myeloma: two cases and review of the literature

Wayne L. Feyereisn,¹ Eric R. Fenstad,² Robert B. McCully,² Martha Q. Lacy³

¹Division of General Internal Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; ²Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; ³Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA

Abstract: An association between pulmonary hypertension (PH) and POEMS syndrome (characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) as well as other plasma cell dyscrasias, including multiple myeloma (MM), has been shown to exist. Recent case reports have identified a reversible form of PH that occurs outside of previously identified etiologies. We report two cases of PH in the setting of smoldering MM (SMM) that resolved with chemotherapy and stem cell transplantation. Although other features were individualized among the cases (dermatomyositis, scleromyxedema), treatment of MM and SMM resulted in a normalization of right ventricular systolic pressure and improvement in right ventricular dysfunction that was previously unresponsive to PH therapies. The magnitude and sustained nature of reversibility in these four cases could offer clues about the pathophysiology and treatment of PH.

Keywords: hypertension pulmonary, multiple myeloma, outcomes.

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CASE DESCRIPTION

The two recent updates to the clinical classification of pulmonary hypertension (PH)^{1,2} state that hematologic disorders—and, more specifically, myeloproliferative disorders—can be associated with PH (group 5.1). It has been reported that PH can occur in the chronic myeloproliferative disorders of myeloid metaplasia with myelofibrosis, polycythemia vera, and essential thrombocythemia.³ PH can also occur in patients with plasma cell dyscrasias, including those with POEMS syndrome (characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes)⁴ and amyloidosis,⁵ as well as after thalidomide treatment of multiple myeloma (MM).⁶ PH occurs in 27%–48% of patients with POEMS syndrome and may resolve after POEMS treatment.⁷ The mechanism of PH associated with myeloproliferative disorders is not known. Recently, we identified two patients with smoldering MM (SMM) who developed severe, symptomatic PH that resolved after treatment of their SMM.

Case 1

A 63-year-old man presented with dyspnea on exertion (World Health Organization [WHO] functional class III)

and an increase in his abdominal girth. Serum protein electrophoresis and immunofixation revealed an immunoglobulin G (IgG) λ of 2.1 g/dL and a λ immunoglobulin free light chain of 53.6 mg/dL (reference range, 0.57–2.63 mg/dL). A 24-hour urine protein was 737 mg, with a urine M-spike of 35 mg/dL on protein electrophoresis. A workup for POEMS syndrome was negative. Bone survey was negative for lytic or sclerotic bone lesions. Bone marrow biopsy showed 20%–30% plasma cells, while renal biopsy was consistent with membranoproliferative glomerulonephritis (Table 1). He was diagnosed as having SMM. Echocardiography showed evidence of severe PH. The estimated right ventricular systolic pressure (RVSP) by Doppler was 84 mmHg, the right ventricle was moderately to severely enlarged, there was mild RV systolic dysfunction, and there was severe tricuspid regurgitation. He had a left ventricular ejection fraction of 65% without pericardial effusion. Echocardiographic and hemodynamic catheterization parameters are presented in Table 2. Mild mitral regurgitation and moderate pulmonary regurgitation were present. At right heart catheterization, right atrial pressure was 15 mmHg, right ventricular end diastolic pressure was 21 mmHg, mean pulmonary arterial

Address correspondence to Dr. Wayne L. Feyereisn, Division of General Internal Medicine, Department of Medicine, Gonda 5, Mayo Clinic, 200 First Street Southwest, Rochester, MN 55905, USA. E-mail: feyereisn.wayne@mayo.edu.

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Table 1. Cases of reversible pulmonary hypertension (PH) with multiple myeloma (MM) or smoldering MM (SMM)

Case	Age at diagnosis, years	Diagnosis date		MM type	Plasma cells, %	M-spike, g/dL	Other	PH (RVSP), mmHg
		SMM or MM	PH					
1	63	9/19/2007	2007	IgG λ	20–30	2.1	Sleep apnea, membranoproliferative glomerulonephritis	84
2	59	4/28/2003	2004	IgG κ	10	1.4	Scleromyxedema	106
3 ^a	58	11/11/1996	1996	IgG κ	10–15	1.02	Dermatomyositis	105
4 ^b	31	3/2003	2003	IgG λ	80	3.3	...	80

Note: RVSP: right ventricular systolic pressure; IgG: immunoglobulin G.

^a Previous Mayo Clinic case.

^b Italy case.

pressure (mPAP) was 40 mmHg, pulmonary capillary wedge pressure (PCWP) was 10 mmHg, left ventricular end diastolic pressure was 11 mmHg, cardiac index (CI) was 2.51 L/min/m², and pulmonary vascular resistance (PVR) was 5.51 Wood units (WU). With administration of nitric oxide at 80 ppm, mPAP increased slightly to 42 mmHg, PCWP increased to 16 mmHg, CI increased to 3.55 L/min/m², and PVR decreased to 3.90 WU, consistent with a negative vasodilator response. A right ventricular endomyocardial biopsy showed no evidence of cardiac amyloid. The N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) level was 4,392 pg/mL (normal, <92). With aggressive diuresis, he lost 48 pounds over 6 weeks. Initial treatment of the SMM was with bortezomib and dexamethasone. He was also started on PH-specific medication, ambrisentan. His M-spike and λ free light chain levels decreased to 0.4 mg/dL and 5.66 g/dL, respectively. His NT-pro-BNP level decreased to 201 pg/mL. On echocardiography, RVSP decreased to 43 mmHg, right ventricular systolic function improved, and the tricuspid regurgitation resolved. By that time, the patient was ambulating without dyspnea.

Three years later, his MM relapsed. His M-spike level was 1.3 gm/dL, and his λ free light chain level was 25.2 mg/dL. The RVSP had increased to 75 mmHg (Fig. 1), indicating recurrence of severe PH. He was treated with bortezomib and dexamethasone again and remained on the pulmonary vasodilators. He responded to treatment once more, and he had no detectable M-spike and normalization of λ immunoglobulin free light chains at the 100-day follow-up. Four months later, he underwent stem cell mobilization after repeat right heart catheterization. Right atrial pressure was 7 mmHg, RVSP was

72 mmHg, mPAP was 35 mmHg, PCWP was 13 mmHg, CI was 3.12 L/min/m², and PVR was 3.53 WU. Sildenafil three times daily was added. He underwent autologous stem cell transplantation following conditioning with high-dose melphalan and met criteria for complete remission 4 months later,⁸ with no detectable M-protein and normalization of his bone marrow biopsy. NT-pro-BNP was 140 pg/mL, and RVSP was 51 mmHg. His functional capacity improved to his baseline prior to MM and PH diagnosis (WHO functional class I). To date, he has remained dyspnea-free, with RVSP levels of 30–40 mmHg on yearly follow-up echocardiograms (Fig. 1). At the most recent cardiology follow-up visit in the fall of 2011, he remained symptom-free, and sildenafil was discontinued. On the basis of mail correspondence, the patient remained dyspnea-free in 2014.

Case 2

A 59-year-old man presented with a 2-year history of symptoms of a peripheral neuropathy, skin thickening, and progressively worsening weight loss, diarrhea, difficulty swallowing, and exertional dyspnea (WHO functional class III). Serum protein electrophoresis showed an M-spike of 1.13 g/dL monoclonal IgG κ . A skeletal survey was negative for lytic lesions. Bone marrow biopsy showed 12% plasma cells and was negative for Congo red stain. Rectal biopsy was negative for amyloid. Blood counts were within normal limits. He was diagnosed with SMM. He was treated with one cycle of melphalan and prednisone followed by a single cycle of high-dose dexamethasone. A second opinion was obtained at a tertiary referral hematology center because of progressive skin thickening and sclerosis unresponsive to treatment. He

Table 2. Characteristics of three patients with pulmonary hypertension (PH) and multiple myeloma (MM) or smoldering MM

	Patient 1	Patient 2	Patient 3 ^a
Clinical			
Sex	Male	Male	Male
Pulmonary function testing			
FEV ₁ , %	70	104	76
FEV ₁ /FVC	93.5	88.4	84.8
DLCO, %	36	67	56
Index echocardiogram			
Ejection fraction, %	65	65	64
e', m/s	0.09	0.07	ND
Medial E/e'	18.0	7.1	ND
E : A ratio	1.8	1.0	ND
Left atrial volume index, cc/m ²	53	38	ND
Estimated RA pressure, mmHg	20	20	14
Estimated RVSP, mmHg	84	105	106
Right ventricular enlargement	Moderate/severe	Moderate/severe	Severe
Right ventricular systolic dysfunction	Moderate/severe	Moderate/severe	Moderate
Right ventricular strain, mean, %	ND	ND	-12
TV lateral annulus systolic velocity, m/s	0.10	0.10	ND
Pulmonary acceleration time, ms	ND	ND	ND
Most recent follow-up echocardiogram			
Estimated RA pressure, mmHg	5	5	5
Estimated RVSP, mmHg	36	41	32
Right ventricular enlargement	Mild	Mild	Normal
Right ventricular systolic dysfunction	Normal	Normal	Normal
Right ventricular strain, mean, %	-23	-25	ND
TAPSE, mm	17	19	ND
TV lateral annulus systolic velocity, m/s	0.14	0.13	0.14
Cardiac index, L/min/m ²	2.72	2.71	5.33
Right heart catheterization			
RA pressure, mmHg	15	6	13
RVSP, mmHg	70	87	79
mPAP, mmHg	40	53	52
PCWP, mmHg	10	10	6
PVR, Wood units	4.72	4.40	4.03
Vasodilator reversibility	Negative	Negative	Negative

Note: FEV₁, forced expiratory volume in first second of expiration; FVC: forced vital capacity; DLCO: diffusion capacity; ND: not done; RA: right atrial; RVSP: right ventricular systolic pressure; TV: tricuspid valve; TAPSE: tricuspid annular plane systolic excursion; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance.

^a Case previously published by Yaqub et al.⁹

was diagnosed with scleromyxedema. His M-spike was 1.4 g/dL, and his IgG λ level was 1,750 g/dL (Table 1). Two months later, he was started on intravenous immunoglobulin treatments for scleromyxedema. He received three monthly treatments (5 days each) at a dose of

400 mg/kg (30 g/day for 5 days) without symptomatic improvement. Plans were made to proceed with high-dose chemotherapy and autologous stem cell transplantation.

An echocardiogram performed prior to transplantation demonstrated severe PH with an RVSP of 106 mmHg,

Figure 1. Patient 1 right ventricular systolic pressure trends over time with medical therapy changes.

moderate to severe right ventricular enlargement, moderate to severe RV systolic dysfunction, and ventricular septal flattening during systole and diastole. Left ventricular end diastolic dimension was 43 mm, with an ejection fraction of 64% and tiny pericardial effusion (Table 2). He had documented a normal RVSP 1 year previously. The findings on right heart catheterization were consistent with pulmonary arterial hypertension (Table 2), with right atrial pressure of 13 mmHg, mPAP of 52 mmHg, PCWP of 6 mmHg, CI of 2.28 L/min/m², and PVR of 9.93 WU. Vasodilator study with epoprostenol infusion was negative, as mPAP was 49 mmHg, PCWP increased to 17 mmHg, CI increased to 2.76 L/min/m², and PVR decreased to 6.57 WU. He was diuresed with furosemide, and intravenous epoprostenol was initiated for PH. He returned for his stem cell transplantation after 1 month of epoprostenol treatment and was conditioned with melphalan at 140 mg/m² prior to his stem cell transplantation. The epoprostenol was continued through the peritransplant period but was tapered off over the next 3 months as sildenafil three times a day and extended-release diltiazem were initiated. Diltiazem once daily was initiated after transplantation because of symptomatic atrial flutter with rapid ventricular rates up to 153 bpm. When he returned 3 months later for his 100-day checkup, his M-spike was 1.4 g/dL, and his bone marrow plasma cells were unchanged. His RVSP remained high at 105 mmHg. He was then started on thalidomide at 200 mg daily with dexamethasone on days 1–4, 9–12, and 17–20. He stopped the dexamethasone 2 months later and continued thalidomide for 9 months. One year after transplantation, he was in complete remission. During that time his scleromyx-

edema resolved; over the next 4 years his RVSP gradually decreased to as low as 30 mmHg, and it has remained <45 mmHg on yearly follow-up echocardiograms on pulmonary vasodilator therapy (Fig. 2). On stress echocardiography, the patient exercised for 5 minutes on a Bruce protocol (64% functional aerobic capacity) with an appropriate pulmonary pressure response to exercise (RVSP of 34 mmHg at rest, 49 mmHg at peak exercise). Given the normalization of his right-sided pressures and recovery of right ventricular function, sildenafil was discontinued at his most recent follow-up visit with plans for biannual evaluation and transthoracic echocardiography.

DISCUSSION

Unexplained PH can occur in the setting of hematologic and myeloproliferative disorders, including MM. Two other cases of reversible PH associated with MM have been reported.^{9,10} One of them, a patient at Mayo Clinic, was reported in 2004. It was a case of a 58-year-old man with a rash who had dyspnea on exertion, arthralgias, and myalgias and who ultimately was determined to have dermatomyositis, PH, and MM.⁹ The other case, from Italy, was that of a 31-year-old man who presented with abdominal tenderness, distension, and dyspepsia.¹⁰ He was ultimately diagnosed with PH and MM. In the current study, we report two new cases of a reversible form of PH associated with SMM. Neither case had features of POEMS syndrome. Of these four cases, two had IgG κ and two had IgG λ abnormalities, although a wide range in the M-spike was present (1.02–3.3 g/dL). All four patients had significant PH on echocardiography, and three patients had elevated pulmonary vascular resistance at right heart

Figure 2. Patient 2 right ventricular systolic pressure trends over time with medical therapy changes.

catheterization (range, 4.0–4.7 WU). Their mPAPs ranged from 32 to 53 mmHg. All patients had a dramatic improvement in their dyspnea and PH following treatment of MM or SMM. Three of the four cases identified were diagnosed as a result of a multidisciplinary team approach by internal medicine, hematology, and cardiology. There was a high index of suspicion after the first case was reported in 2004.⁹ Since SMM by definition has absence of end organ damage (lytic bone lesions, anemia, hypercalcemia, or renal failure), it is generally a condition that is followed clinically rather than treated, and the majority of patients lack symptoms. The natural history of the disease suggests progression to symptomatic MM or amyloidosis in 59% of patients with a median time to progression of 4.8 years with the greatest overall risk of progression in the first 5 years (10% per year).¹¹ Recently, a randomized trial of 119 patients with high-risk SMM investigated disease progression and outcomes of early treatment with lenalidomide and dexamethasone.¹² The authors demonstrated a delay in disease progression and improved 3-year survival. Although promising, the National Comprehensive Cancer Network recommends further investigation into treating high-risk SMM before adopting it as a national guideline. It is likely that neither of the two cases described above would have been considered for chemotherapeutic treatment if the association with PH was not felt to be a possibility. Therefore, heightened clinical awareness is recommended. The presented cases raise the question of whether PH in the setting of SMM is truly a rare occurrence or whether this association is overlooked in clinical practice. Population-based studies have not been

undertaken to investigate this relationship. Although the aforementioned cases at Mayo Clinic had other autoimmune features, including scleromyxedema, dermatomyositis, and membranoproliferative glomerulonephritis, the treatment of myeloma resulted in hemodynamic improvement and resolution or near normalization of PH in all cases. Although the pathophysiology of PH development in this setting is unclear, the association with autoimmune features suggests involvement of a cytokine or humoral mechanism because a dramatic improvement in the PH occurred with myeloma treatment. PH associated with POEMS is postulated to occur due to overexpression of vascular endothelial growth factor, interleukin 6 (IL-6), IL-1 β , tumor necrosis factor α , or transforming growth factor α (TGF- α) or to dysregulation of TGF- β , but the exact etiology remains unclear.^{4,7,13-15} However, the literature is limited to case reports and raises more questions than answers regarding prevalence, pathophysiology, and optimal treatment. This would require a population-based study. Further research is needed to determine the prevalence of this association. Further assessments of biomarkers and cytokines may also further understanding of the etiology and ultimately aid in the diagnosis and potential treatments.

Described here are four cases of reversible PH occurring in patients with SMM or active MM. Clinicians should consider screening for monoclonal proteins when working up a patient with unexplained PH. Future study is necessary to better delineate the association of this hematologic malignancy with PH and determine the pathophysiologic mechanism by which PH can occur in this disease.

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