Pulmonary hypertension complicating multiple myeloma

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Abstract: Pulmonary hypertension (PH) is an infrequently reported complication of multiple myeloma (MM). PH has been more commonly associated with amyloidosis, myeloproliferative diseases, and the POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome. PH in MM is typically mild to moderate and may be secondary to a variety of conditions, which include left ventricular dysfunction, high-output cardiac failure, chronic kidney disease, treatment-related toxicities, and precapillary involvement. We describe 3 patients with MM and severe PH. Each patient underwent right heart catheterization. All patients demonstrated elevated pulmonary pressures, transpulmonary gradients, and pulmonary vascular resistance. Each patient was ultimately treated with pulmonary vasodilator therapy with improvement in cardiopulmonary symptoms. Additional studies are needed to define the prevalence, prognosis, and pathogenesis of PH in this complex population and to help clarify who may benefit from targeted PH therapy.

Keywords: pulmonary hypertension, multiple myeloma, pulmonary vasculature, amyloidosis.

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Multiple myeloma (MM) is a hematological malignancy characterized by the neoplastic proliferation of plasma cells within bone marrow and extramedullary sites. It is distinguished from other disorders of plasma cell proliferation by the presence of CRAB features, defined as hypercalcemia, renal insufficiency, anemia, and lytic bone lesions.[1] Although cardiovascular pathology has been frequently associated with MM, pulmonary hypertension (PH), which is characterized by elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), is not a commonly recognized complication. We report the clinical and hemodynamic features of 3 patients with established MM and severe PH. We also provide a review of the literature and discuss the different pathways for development of PH in this mixed population.

CASE DESCRIPTION

Case 1

Patient 1 was a 72-year-old man who presented to the PH clinic with exertional dyspnea. His medical history was significant for immunoglobulin A (IgA) κ MM treated with hematopoietic autologous stem cell transplantation (HSCT) 3 years earlier. At the time of presentation, the patient was receiving maintenance chemotherapy with lenalidomide to help extend clinical remission. In addition, he had a history of permanent atrial fibrillation and severe aortic stenosis. Physical examination revealed a 3/6 crescendo-decrescendo murmur at the upper sternal base radiating to the carotids and a soft 1/6 holosystolic murmur at the lower sternal base. Transthoracic echocardiography (TTE) revealed an ejection fraction (EF) of 62%, a dilated left atrium (LA), pulmonary artery systolic pressure (PASP) of 83 mmHg, flattening of the interventricular septum, a severely dilated right ventricle (RV) and right atrium (RA), mildly reduced RV function, and an aortic valve area of 0.73 cm^2. A right heart catheterization (RHC) showed PAP of 96/32 mmHg (mean, 53 mmHg) with a left ventricular (LV) end-diastolic pressure of 7 mmHg, and cardiac output (CO) of 4.96 L/min (Table 1). With addition of inhaled nitric oxide (iNO), pulmonary pressures decreased to 83/26 mmHg (mean, 45 mmHg) with pulmonary arterial wedge pressure (PAWP) remaining stable at 9 mmHg. A ventilation/perfusion (V/Q) scan showed only small, subsegmental, peripheral perfusion defects. There was no computed tomography (CT) evidence of interstitial lung disease or pulmonary embolism. A pulmonary angiogram was not suggestive of chronic thromboembolic disease. Cardiac magnetic resonance imaging showed normal LV systolic function, normal RV systolic function (RV EF, 50%), RV hypertrophy, biatrial enlargement, and an absence of evidence for cardiac amyloid deposition.

Given his advanced symptoms, compatible with World Health Organization (WHO) functional class (FC) III, the patient initiated therapy with sildenafil, which was uptitrated to a dosage of 40 mg 3 times daily. Because of persistent FC III symptoms and severe PH on repeat TTE, ambrisentan, administered at a dosage of 5 mg daily, was later added to the patient's regimen, which resulted in gradual improvement in symptoms. The patient's repeat RHC showed a decrease in pulmonary pressures to 81/22 mmHg (mean, 42 mmHg) with PAWP of 13 mmHg. His atrial fibrillation was treated with metoprolol succinate (50 mg daily) and digoxin (0.125 mg daily). The patient was evaluated for transvalvular aortic valve replacement and ultimately underwent the procedure without complications via a transfemoral approach. Repeat RHC showed a PAP of 70/23 mmHg

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Table 1. Baseline characteristics for each patient

Variable	Patient 1	Patient 2	Patient 3
Age, years	72	69	69
Sex	Male	Female	Female
Pretreatment WHO FC	III	III	III
Pretreatment echocardiogram finding			
LV EF	62	62	64
PASP (mmHg)	83	77	65
RV size	Dilated	Dilated	Dilated
RV function	Reduced	. . .	Reduced
RA size	Dilated	Dilated	Dilated
Septal flattening	Present	Present	Absent
Tricuspid regurgitation	2+	1+	1+
Pretreatment hemodynamic characteristic			
mRA, mmHg	4	8	9
PAP, systolic/diastolic (mean), mmHg	96/32 (53)	71/26(41)	61/28(39)
CO Fick, L/min	4.96	2	2.42
CI, L/min/m^2	2.5	1.36	1.48
PAWP, mmHg	7	17	12
PVR, Wood units	9.3	14.2	9.9
Medication			
Oxygen	No	No	Yes
Diuretics	No	Bumetanide	Furosemide
Warfarin	Yes	Yes	No
Digoxin	Yes	No	No
PDE5 inhibitor	Sildenafil	Sildenafil	Sildenafil
ERA	Ambrisentan	No	No
Prostacylin	No	No	No
Repeat echocardiogram finding			
No. of months since initial echocardiogram	15	18	3
LV EF	74	60	63
PASP, mmHg	44	58	42
RV size	Dilated	Dilated	Normal
RV function	Normal	Reduced	Normal
RA size	Dilated	Dilated	Normal
Septal flattening	Absent	Present	Absent
Tricuspid regurgitation	1+	2+	1+
Repeat WHO FC	2	2	2

Note: CI: cardiac index; CO: cardiac output; EF: ejection fraction; ERA: endothelin receptor antagonist; LV: left ventricle; mRA: mean right atrial pressure; PAP: pulmonary artery pressure; PASP: pulmonary artery systolic pressure; PAWP: pulmonary arterial wedge pressure; PDE5: phosphodiesterase type 5; PVR: pulmonary vascular resistance; RA: right atrium; RV: right ventricle; WHO FC: World Health Organization functional class.

(mean, 39 mmHg) with PAWP 18 mmHg. The patient's dyspnea improved after the procedure. An attempt at de-escalation of pulmonary vasodilator therapy resulted in clinical worsening; therefore, the patient continued to receive dual therapy and had stable WHO FC II symptoms (Table 2).

Case 2

Patient 2 was a 69-year-old woman who presented to the PH clinic with worsening dyspnea on exertion. Her medical history was significant for MM treated with HSCT 8 years earlier, which was in clinical remission at the time of presentation without ongoing che-

motherapy. In addition, the patient had amyloid light-chain (AL) amyloidosis with biopsy-proven cardiac and renal involvement, nephrotic range proteinuria, non-dialysis-dependent chronic kidney disease (CKD), and paroxysmal atrial tachyarrhythmias. Physical examination was notable for an RV heave, an accentuated P2 component, and a 3/6 systolic murmur at the left lower sternal base. Transthoracic echocardiography showed an EF of 62%, concentric LV hypertrophy, a dilated LA, a restrictive LV filling pattern, PASP of 77 mmHg, flattening of the interventricular septum, and a mildly dilated RV and RA. RHC showed a PAP of 71/26 mmHg (mean, 41 mmHg) with a PAWP of 17 mmHg, CO of 2.00 L/min, and PVR of 12 Wood units (WU). Use of nipride in the laboratory resulted in pulmonary pressures of 67/31 mmHg (mean, 43 mmHg) with PAWP of 14 mmHg. After addition of iNO, there was a decrease in pulmonary pressure to 58/28 mmHg (mean, 38 mmHg) with a PAWP of 14 mmHg. Pulmonary function testing demonstrated normal lung volumes (total lung capacity: 86%) with a reduction in carbon monoxide diffusion capacity (57%). There was no CT evidence of interstitial lung disease. A V/Q scan showed no mismatched defects, with small matched defects in several segments of both lobes. After a progressive decline in cardiopulmonary status, consistent with WHO FC III symptoms, the patient initiated sildenafil at a dosage of 20 mg administered 3 times daily, which was slowly up-titrated. In addition, the patient was treated with bumetadine at a dosage of 1 mg daily and warfarin. Her atrial fibrillation was rate controlled with metoprolol succinate administered at a dosage of 50 mg daily. Her symptoms improved, and her functional capacity afterward remained stable at WHO FC II. Repeat TTE showed a decrease in PASP to 58 mmHg (Table 1).

Case 3

Patient 3 was a 69-year-old woman who presented to the PH clinic with exertional dyspnea. Her medical history was significant for hypertension, diabetes, and IgA κ MM treated with HSCT 6 years earlier, with subsequent relapses treated extensively with multiple lines of chemotherapy using standard as well as experimental regimens (Table 2). Physical examination at presentation showed no features concerning for PH. TTE showed a PASP of 49 mmHg and normal RV size and function. RHC was performed with a PAP of 51/21 mmHg (mean, 31 mmHg) with a PAWP of 7 mmHg, with a decrease in mean PAP (mPAP) to 23 mmHg after a challenge with iNO. The patient initiated therapy with amlodipine, which had to be discontinued because of lower extremity edema. Her dyspnea was relatively stable for the next few years, but then deteriorated to the point of extreme shortness of breath after walking 2 blocks. After admission to the hospital for a syncopal episode, a repeat TTE showed an EF of 64%, eccentric LV hypertrophy, a dilated LA, a dilated RV and RA, reduced RV function, 1+ tricuspid regurgitation, and a PASP of 65 mmHg. RHC showed a PAP of 61/28 mmHg (mean, 39 mmHg) with a PAWP of 12 mmHg, cardiac output of 2.42 L/min, and PVR of 9.9 Wood units. A V/Q scan demonstrated a single, matched, segmental defect in the left upper lobe. There was no CT evidence of interstitial lung disease or pulmonary fibrosis. The patient initiated sildenafil therapy (20 mg 3 times daily) and portable oxygen. Over the next 6 months, she noted an improvement in her dyspnea consistent with WHO FC II. Repeat TTE demonstrated normalization of RV size and function as well as a PASP of 42 mmHg. However, 7 months later, the patient returned to the hospital with severe dyspnea on exertion. Repeat TTE again showed a dilated RV and a PASP of 74 mmHg. Ambrisentan therapy (5 mg daily) was started in addition to treatment with sildenafil. Over the next 3 months, the patient again noted gradual improvement in symptoms. Repeat TTE showed a PASP of 37 mmHg and normal RV size and function. On the basis of serial IgA levels and free light-chain ratios, there was no apparent correlation between myeloma activity and PH severity (Table 2).

DISCUSSION

We have described 3 cases of severe PH in patients with MM. Although PH in MM has been reported only rarely, these cases illustrate the complexity of this population and how an elevation in pulmonary pressure may be seen for a variety of reasons. Elucidation of this mixed PH phenotype must take into account the comorbidities related to MM, which may include CKD, AL amyloid deposition, and high-output states. Moreover, MM may be complicated by treatment-related toxicities, including pulmonary dysfunction and heart failure. We have reviewed selected comorbid conditions and their potential impact on the development of PH.

AL amyloidosis

AL (primary) amyloidosis is a systemic disorder characterized by the deposition of immunoglobulin light-chain fragments to form β-pleated sheets in organs. AL amyloid complicates up to 15% of cases of MM.[2] Cardiac involvement is present in at least 50% of patients and most commonly manifests with heart failure. Classic findings on echocardiogram include thickened ventricular walls, prominent biatrial enlargement, a restrictive filling pattern based on transmitral Doppler, and thickened valves. Patients are frequently intolerant to heart failure therapy, and in the absence of treatment, the natural history is rapidly progressive. Moderate PH, with PASP in the range of 40–50 mmHg, can occur and is usually secondary to LA hypertension in the setting of a perturbed LV end-diastolic pressure volume relationship.[3] PH that is out of proportion to left-sided filling pressures has been less commonly reported.

There are a limited number of cases of AL amyloidosis where pulmonary vascular amyloid deposition causing severe PH has been described.[4] In 4 of these patients who underwent RHC, the mean PAP was 51 mmHg. There was no evidence of cardiac amyloid in these patients, and each presented with evidence of RV failure. Rapid clinical deterioration occurred in most of them. Amyloidosis can affect up to 90% of vasculature in an affected organ; however, PH is a rarely reported complication.[5] In the heart, coronary blood flow reserve can be affected by amyloid infiltration in the microvasculature.[6]

Although patient 2 had a biopsy-proven diagnosis of cardiac amyloid and elevated left-sided filling pressures, she had only a slightly elevated PAWP (17 mmHg) at the time of RHC. In addition, she had a high transpulmonary gradient (24 mmHg), diastolic

PAP-PAWP gradient (9 mmHg), and PVR, which were suggestive of additional pulmonary vascular disease.

High-output heart failure and other cardiac disease

MM can also be associated with high-output heart failure, which most likely is secondary to multiple arteriovenous fistulas in the setting of extensive bony involvement.[7] Chronic anemia may also contribute to high-output states. McBride et al.[8] evaluated 34 patients with MM and RHC, and 8 (24%) were found to have a cardiac index >4.0 L/min/m^2. Severe bony involvement was significantly more common among these patients. High-output heart failure as a cause of PH has been reported in patients with CKD, cirrhosis, myeloproliferative states, sickle cell disease, and other hemoglobinopathies.

Although few studies have focused on the incidence of PH in the setting of high-output heart failure, there is a clear, physiologic rationale (mean PA pressure = cardiac output × PVR + LA pressure) that an inappropriately high cardiac output, especially in the setting of a noncompliant LV, will promote LA hypertension and subsequent PH.[9] Although the hemodynamic evaluation of our 3 patients ruled out high–cardiac output states, patients 1 and 3 did demonstrate evidence of left-sided heart disease in the absence of known cardiac amyloidosis. Patient 1 had severe aortic stenosis, and patient 3 had features suggestive of heart failure with preserved EF (HFpEF). Although the hemodynamic characteristics in both cases were consistent with active PH (PH out of proportion), both may have had at least some component of a group 2 PH phenotype, in which elevated left-sided filling pressures first cause passive PH and later promote pulmonary vascular remodeling and vasoconstriction. Although 2 of the patients had normal PAWP at the time of catheterization, it is possible for patients with diastolic heart failure to have elevated PAP with normal left-sided filling pressures at catheterization, and provocative measures may be needed to confirm pulmonary venous hypertension. The recognition of a group 2 PH phenotype in the MM population is not unexpected given that the majority of these patients receive a diagnosis at an age greater than 65 years, and the introduction of new treatments has extended overall survival times.[10] PH associated with heart failure is the most prevalent form in the United States today.[11] Up to 83% of patients with HFpEF are found to have PH.[12] Among the most common clinical characteristics of these patients are renal insufficiency and anemia, which are also defining features of MM, thereby providing explanation for an overlap in these patient populations.[13]

PH and renal disease in MM

Involvement of the kidneys is common in MM. The underlying pathophysiology is complex and related to multiple mechanisms that include myeloma cast nephropathy, renal amyloidosis, immunoglobulin deposition disease, tubulointerstitial nephritis, hypercalcemia, hypovolemia, plasma cell infiltration, and drug-induced nephrotoxicity.[14] Studies have shown that approximately 10% of patients with MM will require hemodialysis.[15] The clinical impact of CKD in this population is of considerable interest, because observational studies have reported a high prevalence of PH in CKD, particularly among patients with hemodialysis.[16]

The PH of CKD also represents a mixed phenotype with multiple potential causes. Persistent volume overload, secondary hypertension, and myocardial ischemia are commonly associated with CKD and can predispose to decreased LV compliance, valvular disease, and LV systolic dysfunction. For these reasons, the PH of CKD often exhibits a WHO group 2 phenotype. High cardiac output in the setting of arteriovenous fistula creation may also contribute to elevated pulmonary pressures, although studies of PH in association with arteriovenous fistula use have yielded conflicting results.[17-20]

The uremic milieu of CKD may also promote pulmonary vasculopathy via endothelial dysfunction with increased levels of endothelin-1 and reduced bioavailability of nitric oxide.[21] Additionally, increased pulmonary vascular calcification as a result of CKD or hypercalcemia in the setting of myeloma has been postulated as a mechanism of PH but has not been confirmed in research studies.[22]

Pulmonary vasculopathy and MM

Although it is reasonable to conclude that patients with MM represent a mixed population who can have elevated pulmonary pressures for a variety of reasons, it should be emphasized that, despite elements of left-sided heart disease in each of our patients, all 3 had normal to only slightly elevated filling pressures at the time of RHC, all had elevated transpulmonary gradients and PVR, and all demonstrated improvement in cardiopulmonary symptoms after initiation of pulmonary vasodilator therapy. Thus, despite evidence to support WHO group 2 pathophysiology, there was still strong suspicion of a component of pulmonary arteriopathy in each case. The mechanisms that lead to pulmonary arteriopathy may be inherent to the myeloma itself or may be a function of the various therapies employed in this population.

Treatment-related vasculopathy

The goal of therapy in MM is to induce remission with the use of chemotherapeutic regimens, with the goal of extending overall survival. For standard and intermediate-risk patients with newly diagnosed myeloma, the preferred approach is induction therapy to reduce tumor mass followed by autologous hematopoietic stem cell collection and transplantation for consolidation. Agents commonly used to treat MM include proteasome inhibitors (bortezomib and carfilzomib), immunomodulatory agents (thalidomide, lenalidomide, and pomalidomide), corticosteroids (most commonly dexamethasone), and occasionally alkylating chemotherapy (cyclophosphamide, melphalan, and liposomal doxorubicin).[23] Specific chemotherapy decisions and the choice of whether to undergo HSCT are tailored to the patient's comorbidities and specific tumor characteristics.

Pulmonary venoocclusive disease is a very rare and unusual cause of PH, which has been increasingly reported after HSCT in a variety of hematological malignancies, including at least 1 reported case of MM.[24] The pathologic hallmark of the disease is diffuse occlusion of the pulmonary veins by fibrous tissue. The PH is secondary to pulmonary venous hypertension as well as direct fibrous involvement of pulmonary arterioles. The triad of PH, pulmonary

Table 2. Treatment course and myeloma disease activity for each patient

Patient, event	Disease course and symptoms	Treatment course	IgA (units)	FLC ratio
Patient 1				
1	MM diagnosed	Multiple cycles of lenalidomide-dexamethasone; remission achieved; received HSCT 1 year after remission; continued maintenance lenalidomide	. . .	. . .
2	PH diagnosed 3 years after HSCT; FC III symptoms; RHC (RA = 4 mmHg; PAP = 96/32 [53] mmHg; LVEDP = 7 mmHg; CO = 4.96 L/min)	Sildenafil initiated; lenalidomide continued; ambrisentan added 3 months later for persistent FC III symptoms	. . .	. . .
3	FC improves; repeat RHC (RA = 9 mmHg; PAP = 81/22 [42] mmHg; PAWP = 13 mmHg; CO = 5.69 L/min)	TAVR performed given severe AS	. . .	. . .
4	Remains stable at FC II; repeat RHC (RA = 9 mmHg; PAP = 70/23 [39] mmHg; PAWP = 18 mmHg; CO = 5.53 L/min)	Continued sildenafil and ambrisentan; continued maintainance lenalidomide	. . .	. . .
Patient 2				
1	MM and AL amyloidosis diagnosed	Received HSCT the same year; does not receive subsequent chemotherapy	. . .	. . .
2	Cardiac amyloidosis diagnosed 5 years later	. . .	. . .	. . .
3	PH diagnosed 3 years after amyloidosis diagnosis; FC III symptoms; RHC (RA = 8 mmHg; PAP = 71/26 [41] mmHg; PAWP = 17 mmHg; CO = 2.0 L/min)	Sildenafil initiated	. . .	. . .
4	FC improves to class II; repeat TTE with lower measured PASP	Continued to receive sildenafil	. . .	. . .
Patient 3				
1	MM diagnosed	Received thalidomide-cyclophosphamide-dexamethasone; received bortezomib-dexamethasone; remission achieved; received HSCT	. . .	. . .
2	Relapse of myeloma 7 months after HSCT	Received multiple cycles of lenalidomide-dexamethasone for 1 year with POD; received carfilzomib-lenalidomide-dexamethasone for 2 years with POD	. . .	. . .
3	PH first diagnosed; FC II symptoms: RHC (RA = 6 mmHg; PAP = 51/21 [31] mmHg; PCWP = 7 mmHg; CO = 3.3 L/min)	Amlodipine started; discontinued because of lower extremity edema	406	1.7
4	Persistent MM	Received bendamustine-bortezomib-dexamethasone for 1 year with POD; received clarithromycin-pomalidomide-dexamethasone for 1 year with POD; received carfilzomib-pomalidomide-dexamethasone for 1 year with POD	. . .	. . .
5	PH worsens; FC III symptoms: RHC (RA = 9 mmHg; PAP = 61/28 [39] mmHg; PCWP = 12 mmHg; CO = 2.42 L/min)	Sildenafil initiated 4 years after initial diagnosis	3,360	29.9

Table 2 (*Continued*)

Patient, event	Disease course and symptoms	Treatment course	IgA (units)	FLC ratio
6	Persistent MM	Received clarithromycin-bortezomib-lenalidomide-dexamethasone for 1 cycle with POD	. . .	. . .
7	FC improves to class II; repeat TTE with improved RV function and lower measured PASP of 42 mmHg	. . .	3,760	17
8	Persistent MM	Received doxorubicin-bortezomib-dexamethasone for 6 months with POD; initiated monoclonal antibody elutuzumab and pomalidomide	. . .	. . .
9	PH symptoms worsen 7 months after last TTE; repeat TTE with more RV dilation; PASP is 74 mmHg	Ambrisentan added	4,800	128
10	FC improves to class II; repeat TTE with improved RV size and lower measured PASP of 38 mmHg	Continued sildenafil and ambrisentan; continued monoclonal antibody elutuzumab and pomalidomide	4,740	130

Note: AL: amyloid light chain; AS: aortic stenosis; CO: cardiac output; FC: World Health Organization functional class; FLC: free light chain; HSCT: hematopoietic autologous stem cell transplant; IgA: immunoglobulin A; LVEDP: left ventricular end-diastolic pressure; MM: multiple myeloma; PAP: pulmonary artery pressure, expressed as systolic/diastolic pressure (mean pressure); PASP: pulmonary artery systolic pressure; PAWP: pulmonary arterial wedge pressure; PH: pulmonary hypertension; POD: progression of disease; RA: right atrium; RHC: right heart catheterization; TAVR: transcatheter aortic valve replacement; TTE: transthoracic echocardiography.

edema, and normal PAWP, although not pathognomonic for the disease, is certainly suggestive.[25] Symptoms usually develop days to weeks after HSCT, and a surgical lung biopsy is sometimes needed to confirm the diagnosis. Although none of our patients had diagnostic lung biopsies performed, the temporal delay between HSCT and the development of PH (Table 2) and the absence of features consistent with pulmonary edema or pleural effusions argued against pulmonary venoocclusive disease.

There is a higher-than-average incidence of venous thromboembolism (VTE) in patients with MM.[26] Immunomodulatory agent-based regimens, which may impair endogenous anticoagulation, are associated with an even higher risk of VTE in these patients.[27] Despite an increased incidence of pulmonary embolism, chronic thromboembolic PH (CTEPH) has not been commonly reported in the MM population. Although none of our 3 reported patients had normal V/Q scan findings, pulmonary angiography ruled out CTEPH in 1 patient, and the findings on V/Q scans were subtle and not felt to be consistent with a diagnosis of CTEPH in the other 2 patients. PH in the absence of thromboembolism has been sporadically reported in association with thalidomide use in MM. There are 4 reports in the literature that suggest such a correlation.[28-31] In each series, patients showed clinical and echocardiographic features of PH after days to months of thalidomide therapy. In most cases, there was improvement in pulmonary pressures after discontinuation of thalidomide. Hatori et al.[29] described a patient who developed symptomatic PH 6 months after initiation of thalidomide therapy for relapsing MM. The patient ultimately died of RV failure. Autopsy results showed plexogenic pulmonary arteries with intimal and medial thickening, which are pathologic features of PAH. A prospective study by Lafaras et al.[31] monitored 82 patients with thalidomide-treated MM with serial echocardiography and identified 4 patients with echocardiographic evidence of PH. One of these patients developed symptomatic RV failure and experienced improvement after thalidomide discontinuation. In our series, only patient 3 was briefly exposed to thalidomide, and this was after PH was first detected. Patients 1 and 3 were maintained on thalidomide derivatives (lenalidomide and pomalidomide), agents which have not previously been implicated in the development of PH. Of note, carfilzomib has been associated with a rate of PH of approximately 3%, with 1% of patients having severe PH.[32] Patient 3 was treated with numerous chemotherapeutic agents, including carfilzomib both before and after PH was detected (Table 2).

Although the underlying pathogenesis of treatment-related pulmonary vasculopathy is poorly understood, both HSCT and thalidomide use may lead to dysfunction in the endothelial-derived vasoconstrictor/vasodilator system at the level of the pulmonary artery. Thalidomide has a wide spectrum of biological effects that include altered cytokine expression and decreased synthesis of nitric oxide.[33] Additionally, thrombotic arteriopathy and in situ thrombosis are pathologic features of PH that may occur as complications of MM treatment.

Role of inflammation and POEMS syndrome

Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome is a rare condition that has been commonly associated with PH and may provide some insight

into the underlying pathobiology of PH in plasma cell disorders. A diagnosis requires the presence of 2 mandatory criteria (polyneuropathy plus monoclonal plasma cell disorder), 1 major criteria (osteosclerotic bone lesions, Castleman disease, or increase in serum vascular endothelial growth factor [VEGF] levels), and 1 minor criteria (organomegaly, volume overload, endocrinopathy, skin changes, papilledema, or thrombocytosis).[34] Although PH is not one of these criteria, it has been frequently reported in cases of POEMS syndrome, with a prevalence based on varying echocardiographic definitions as high as 40%.[35] In limited cases, biopsies have demonstrated findings of plexogenic pulmonary arteriopathy with intimal fibrosis and medial hypertrophy, consistent with pathologic features of idiopathic PAH. In one report of POEMS syndrome, direct infiltration of the pulmonary vasculature by plasma cells was also reported.[36]

Although none of our 3 patients exhibited characteristic features of POEMS syndrome, the underlying mechanisms of angiogenesis and inflammation in this disease may help elucidate the pathogenesis of PH in MM. The POEMS syndrome is associated with elevated VEGF levels, and this has been incorporated into the diagnostic criteria for the disease. VEGF has also been found to play an important role in sustaining angiogenesis in MM.[37] Although VEGF is abundant in the lungs, and plasma levels of VEGF are elevated in patients with severe PAH, its role in the underlying pathogenesis of PAH is not well understood.[38]

Aside from VEGF, patients with POEMS syndrome and associated PH have markedly increased levels of inflammatory mediators that include tumor necrosis factor α, interleukin (IL) 2, IL-6, and interferon α.[39,40] Similarly, patients with idiopathic PAH can have markedly elevated IL-1 and IL-6 serum levels.[41] Elevated levels of inflammatory cytokines have also been observed in PAH associated with connective tissue disease,[42] human immunodeficiency virus infection,[43] and sickle cell disease.[44] Although the implications of inflammatory cytokines in PH remain the focus of active research, they likely have critical effects on pulmonary arterial endothelial function and perturb the delicate equilibrium between vasodilators and vasoconstrictors.

MM is similarly characterized by aberrant production of cytokines like IL-1b and IL-6, which is associated with the pathogenesis of the malignancy.[45] The existence of an aberrant proinflammatory cytokine milieu may have partially contributed to PH in each of our patients. Notably, each one demonstrated some degree of pulmonary vasoreactivity in response to iNO, suggesting that pulmonary vasoconstriction and underlying endothelial dysfunction played at least some mechanistic role. Additionally, the altered cytokine profile found in MM does not necessarily normalize once the disease is in remission.[46] This could explain the absence of a consistent relationship between myeloma activity and the existence of PH. Fenstad et al.[47] recently described 2 patients with reversible PH in the setting of smoldering MM (patient 1: mPAP, 40 mmHg; PAWP, 10 mmHg; and PVR, 4.72 Wood units; patient 2: mPAP, 52 mmHg; PAWP, 6 mmHg; and PVR, 9.93 Wood units). Both were treated with chemotherapy, HSCT, and pulmonary vasodilator therapy, ultimately with resolution of symptoms and normalization of pulmonary pressures. Although each of our patients clearly benefited from judicious use of pulmonary vasodilators, there was no clear relationship between PH and malignancy status. Patients 1 and 2 were in clinical remission when PH was diagnosed and subsequently treated. Although patient 3 had persistent myeloma activity refractory to multiple lines of therapy, there was no clear relationship between disease progression and PH severity (Table 2).

Conclusions

Severe PH characterized by an elevated PVR can occur in MM. The etiology in most cases is likely to be multifactorial, although a complete understanding of the underlying pathobiology is lacking at this time. Recognition of PH in the setting of MM is important, because pulmonary vasodilator therapy, when carefully selected, may be beneficial in certain cases. Larger studies are required to better elucidate the prevalence, prognosis, and pathophysiology of PH in this population and to help define more effective treatments.

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