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Case Report

Treatment of Pulmonary Hypertension in POEMS Syndrome with Autologous Stem Cell Transplantation

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ABSTRACT

POEMS, a rare paraneoplastic syndrome, can cause pulmonary hypertension (PH). PH, diagnosed through echocardiogram in patients with POEMS, is known to improve after autologous stem cell transplantation (ASCT). However, similar accounts of PH, diagnosed through right heart catheterization (RHC), the gold standard diagnostic test for PH, do not exist. We report the case of a 65-year-old female who presented with dyspnea and burning pain in feet. Physical examination was unremarkable, while basic investigations revealed an elevated protein-albumin gap. This prompted further tests that led to the diagnosis of POEMS syndrome. Echocardiogram was additionally obtained and raised concern for PH. RHC was hence performed and confirmed the diagnosis of PH secondary to POEMS syndrome. The patient was treated with ASCT following which her dyspnea got better and repeated RHC revealed improved hemodynamics. This report highlights the first case of PH secondary to POEMS syndrome, which demonstrated improvement in hemodynamics, measured by RHC, following ASCT.

Introduction

POEMS is a rare paraneoplastic syndrome that occurs secondary to a plasma cell dyscrasia (PCD) and is characterized primarily by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (Table 1). Along with affecting various other organs, POEMS is associated with significant pulmonary morbidity. In addition to changes in lung function such as restriction and decrease in diffusing capacity, patients with POEMS can also be affected by, WHO Group V Pulmonary Hypertension (PH) [1, 2]. Management of patients with POEMS syndrome is aimed at treating the underlying PCD. This has historically been achieved successfully through different treatment modalities such as chemotherapy and radiotherapy. These methods of treatment, have in various cases, also been associated with improvement in PH seen with POEMS syndrome [3, 4]. Autologous stem cell transplantation (ASCT) is another viable option for treating PCD [5]. However, due to poor pulmonary function being a relative contraindication for the procedure, patients with POEMS may often be precluded from undergoing ASCT.

Table 1: Diagnostic criteria for POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes). Diagnosis requires the presence of both mandatory majors, at least 1 other major and 2 minor criteria.

MANDATORY MAJOR CRITERIA	Polyneuropathy
	Monoclonal plasma proliferative disorder
OTHER MAJOR CRITERIA	Sclerotic bone lesions
	Castleman disease
	Elevated serum Vascular Endothelial Growth Factor (VEGF) levels
MINOR CRITERIA	Papilledema
	Organomegaly (splenomegaly, lymphadenopathy etc.)
	Extravascular volume overload (pleural effusion, peripheral edema etc.)
	Skin changes
	Endocrinopathy (adrenal, thyroid, pituitary etc.)
KNOWN ASSOCIATIONS	Thrombocytosis

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Of note, rare accounts of ASCT being used to manage PH associated with POEMS syndrome do exist. However, PH in these patients was diagnosed and monitored through echocardiogram (ECHO), which is known to be less precise and accurate than right heart catheterization (RHC) [6]. We thus report the first case of a patient with POEMS syndrome and associated PH, diagnosed through RHC, who demonstrated an improvement in her PH after undergoing ASCT.

Case Description

A 65-year-old female with no prior medical history was evaluated in the clinic for worsening pain in bilateral feet over the past one year. She described the pain as burning in nature, radiating from toes to her ankles with no associated weakness, neurological deficits or correlation with activity. On questioning, she also endorsed swelling in lower extremities (LE) and new onset of shortness of breath (SOB) on moderate exertion (NYHA Class III). She further denied experiencing any concurrent chest pressure, dizziness or syncope with her symptoms. On cardiovascular examination, the patient was noted to have normal heart sounds with no jugular venous distension. Lung auscultation was remarkable for equal air entry in all lung fields with no added sounds. She was, however, noted to have 1+ pitting edema bilaterally on her LE with no tenderness to palpation and preserved sensory and motor function. An additional exam also revealed Raynaud's changes in the fingers of her upper extremities along with inguinal lymphadenopathy.

Given the non-specific physical exam findings, further diagnostic tests were ordered to determine the etiology of the patient's presenting complaint. EMG of the LE was performed and confirmed demyelinating peripheral neuropathy. Concurrently, basic blood tests were obtained with a protein albumin gap elevation to 5.2 g/dL on comprehensive metabolic panel and thrombocytosis to 508,000/µL on complete blood count, being noted. To further investigate the increased protein-albumin gap, serum protein electrophoresis (SPEP) was performed and proved to be remarkable for the IgA band and lambda restriction. In light of the neuropathy, Raynaud's changes, inguinal lymphadenopathy and positive SPEP results, suspicion for monoclonal gammopathy and possible POEMS syndrome arose. For this reason, vascular endothelial growth factor (VEGF) levels were obtained and were found to be elevated to 6227 pg/mL. Concurrently, bone marrow biopsy (BMB) was performed with pathology revealing hypercellular marrow along with atypical megakaryocytic hyperplasia and lambda-restricted plasma cells, that comprised 15% of cellularity. Following confirmation of PCD and neuropathy, on BMB and EMG respectively, diagnosis of POEMS syndrome was made and further affirmed through PET scan, which demonstrated sclerotic foci in the patient's spine and pelvic bones.

Given complaint of SOB and LE edema along with the known high prevalence of PH in patients with POEMS syndrome, an ECHO was subsequently performed; the results of which were notable for elevated pulmonary artery (PA) systolic pressure (PASP) to 60 mm Hg with no valvular abnormalities and normal biventricular size and function (Figure 1). Concern for PH thus increased, leading to right heart catheterization (RHC) being performed (Table 2). Results of RHC revealed hemodynamic measurements consistent with vasoreactive pre-capillary PH. To further delineate the etiology of PH, pulmonary function tests were obtained and were notable for normal lung volumes and spirometry with moderately reduced diffusion capacity to 32%. Simultaneously, a computed tomography (CT) scan of the chest was performed and was found to have no parenchymal changes. Due to no other identifiable cause for PH on the aforementioned extensive workup, the patient was diagnosed with WHO Group V PH secondary to POEMS syndrome.

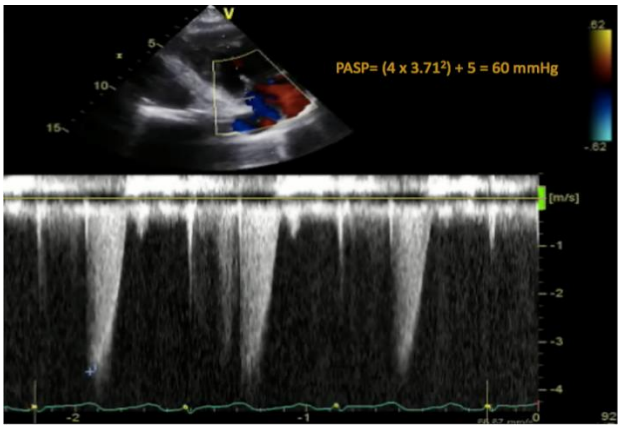

Figure 1: Tricuspid regurgitation signal on echocardiogram showing a peak velocity of 3.71 m/s and pulmonary artery systolic pressure (PASP) of 60 mm Hg.

Table 2: Hemodynamic parameters obtained during right heart catheterization before and after autologous stem cell transplant.

	RHC BEFORE ASCT	RHC AFTER ASCT
RA PRESSURE (mm Hg)	5	3
RV PRESSURE (mm Hg)	73/6	45/5
PA PRESSURE (mm Hg)	70/20	45/15
MEAN PA PRESSURE (mm Hg)	42	27
PA WEDGE PRESSURE (mm Hg)	8	8
PA PRESSURE AFTER NO (mm Hg)	42/11	-
MEAN PA PRESSURE AFTER NO (mm Hg)	27	-
PVR (woods units)	7	3.8
CARDIAC OUTPUT (L/min) (FICK)	4.9	5
CARDIAC INDEX (L/(min-m^2)) (FICK)	2.84	2.95

RA: Right Atrium; RV: Right Ventricle; PA: Pulmonary Artery; PVR: Pulmonary Vascular Resistance; RHC: Right Heart Catheterization; ASCT: Autologous Stem Cell Transplant.

Following the diagnosis of PH, the patient was started on vasodilator therapy with sildenafil 20 mg thrice daily. After the initiation of sildenafil, during follow-up evaluation, the patient reported improved exercise tolerance and was further noted to have preserved right ventricular function on ECHO. Two weeks following the repeated ECHO, the patient was admitted to the hospital and successfully underwent ASCT for the treatment of her PCD.

Following ASCT, the patient was monitored closely as an outpatient and continued to do well. Repeat VEGF levels obtained four months after transplant were noted to be elevated to 795 pg/dL with a remarkable decline relative to those obtained prior to transplantation. Due to the persistently increased VEGF levels, BMB was however performed again and revealed decreased cellularity of lambda restricted plasma cells to 5%. At the same time that these repeat studies were performed, the patient reported remarkable improvement in her dyspnea on exertion (NYHA Class II) and LE edema. ECHO was hence repeated and

revealed PASP to 42 mm Hg. In light of overall progress noted on ECHO and symptoms, sildenafil was discontinued and RHC was repeated a week after stopping the medication (Table 2). While hemodynamic parameters on repeat RHC were still consistent with mild pre-capillary PH, they did demonstrate a marked improvement from those obtained prior to ASCT. After the repeated evaluation, the patient was restarted on the same dose of sildenafil as before and had since then continued to do well, such that she has returned to work and is independent with activities of daily living.

Discussion

PH can occur in 27-48% of patients with POEMS syndrome [1, 3, 7]. Pathogenesis of PH in these patients is however still unclear. It is postulated that the overexpression and production of inflammatory cytokines is likely the cause of plexiform lesions and subsequent vasculopathy noted in PH associated with POEMS syndrome [2, 8-10]. VEGF, a key pro-inflammatory cytokine in POEMS syndrome, is known to cause endothelial proliferation, activation of smooth muscle cells and dysfunction of the vascular endothelium in patients with idiopathic pulmonary arterial hypertension (PAH). It is for the same reasons that it is implicated in causing PH in patients with POEMS syndrome [8, 11-15]. Another factor that supports this hypothesis is the improvement in PH in patients with POEMS syndrome who were treated with the anti-VEGF antibody, bevacizumab [16, 17]. Idiopathic PAH, characterized by remodeling of the distal pulmonary arteries and subsequent increase in pulmonary vascular resistance, is more often than not relatively incurable, such that most patients warrant lifelong treatment with PAH-specific pulmonary vasodilatory medications. PH associated with POEMS, however, appears to be a form of the disease outside this norm; with reports of cases demonstrating resolution of PH after treatment of the underlying PCD with radiotherapy or chemotherapy [3, 4].

Another modality utilized to treat PCD is ASCT, which has also been demonstrated to be successful in managing patients with POEMS syndrome [5]. While ASCT has been validated to be a potential therapeutic option for POEMS syndrome, there are rare accounts of it being used to treat PH associated with this syndrome. Furthermore, the cases in the past that detailed improvement in PH with ASCT, all used ECHO to diagnose and monitor these patients [6]. Unlike ECHO, RHC is known to be more accurate in detecting changes in hemodynamics and is hence the gold standard for diagnosis of PH [18, 19]. It is thus important to note that our case is the first to report the use of ASCT to successfully manage both POEMS syndrome as well as associated PH, that was diagnosed through RHC. As demonstrated in our case, ASCT did not only help to treat the underlying PCD but also led to the improvement in the patient's PH and associated symptoms. While the patient's hemodynamic parameters did improve remarkably after transplantation, the PH did not resolve completely and she still required low dose pulmonary vasodilator therapy. It is our hypothesis that this is likely due to her incomplete response to ASCT with residual disease and PCD, which was still evident on repeat BMB and led to the subsequently elevated VEGF levels and persistent PH.

Patients with POEMS syndrome have high morbidity and mortality with those who have concurrent PH being predisposed to worse outcomes and survival. The median survival of patients with PH secondary to POEMS syndrome was reported to be 54 months by one study while another reported a hazard ratio for the survival of 3.99 in these patients [7, 20]. However, swift treatment of the underlying PCD is associated with better outcomes, such that patients who are treated with ASCT have improved survival, with one study reporting a 5-year overall survival of 94% in patients with POEMS syndrome treated with ASCT [21]. While ASCT has been proven to be a life-prolonging treatment option for POEMS syndrome, our case demonstrates that in patients with PH secondary to POEMS syndrome, it may assist in doing so by also treating the associated PH. Thus, in patients with POEMS syndrome and PH, who are appropriate candidates for transplantation, we propose that ASCT be strongly considered as a treatment option.

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