Progressive Onset of Extracardiac and Myocardial Symptoms
Right Heart Failure and Cor Pulmonale in a Young Man With Debilitating Polyneuropathy and Monoclonal Gammopathy

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Foreword

Information about a real patient is presented in stages (boldface type) to expert clinicians (Drs Yee and Dudzinski), who respond to the information, sharing reasoning with the reader (regular type). A discussion by the authors follows.

A 34-year-old man with a 2-year history of unexplained steroid-refractory polyneuropathy, lower-extremity edema, and monoclonal gammopathy presented to our tertiary care center with 3 days of rapidly progressive dyspnea. The patient’s vital signs were notable for a temperature of 37.0ºC, heart rate of 122 bpm, blood pressure of 80/60 mm Hg, respiratory rate of 22 breaths per minute, and oxygen saturation of 94% on 2 L supplemental oxygen. Physical examination revealed a cachectic young man in mild respiratory distress with a jugular venous distention, a pulsus paradoxus of 6 mm Hg, regular tachycardic rhythm without murmur or gallop, but a prominent P2 sound with heave at the left sternal border, bilateral fine crackles, and decreased bilateral breath sounds. Abdominal examination revealed mild hepatomegaly. Peripheral examination was notable for warm and well-perfused lower extremities with 2+ pitting edema extending to the sacrum but without evidence of venous stasis disthropy, leg tenderness, erythema, warmth, or palpable cord. There was also mild, diffuse skin hyperpigmentation.

Dr Dudzinski: On this acute presentation with new dyspnea and hypotension, the onus is on the cardiologist to rapidly evaluate and exclude possible diagnoses such as pulmonary embolism (PE), myocardial infarction, pericardial tamponade, and decompensated heart failure. Jugular venous distention can be consistent with all of these diagnoses, but it importantly excludes other shock phenotypes such as distributive (eg, septic) or hemorrhagic shock. Pitting pedal and sacral edema may also be consistent with elevated central venous pressures; the lack of stasis dermopathy may argue for a relatively new overload syndrome, for example, heart failure or constrictive pericarditis. Bilateral crackles and decreased bilateral breath sounds could indicate pulmonary edema and pleural effusions. Despite tachycardia and hypotension with jugular venous distention, a pulsus paradoxus of 6 mm Hg argues against tamponade physiology; moreover, cardiac sounds were not obscured. The finding of a Kussmaul sign—failure of the jugular venous pressure level to decrease with inspiration—may be seen in a number of conditions, including constrictive pericarditis and restrictive cardiomyopathy, acute PE, acute right ventricular (RV) infarction, severe tricuspid valvulopathy, right-sided cardiac tumors, and acute sequelae of cor pulmonale that may result from primary pulmonary hypertension or congenital heart disease. The parasternal heave suggests RV dilatation; the augmented P2, elevated pulmonary pressures. Accordingly, acute PE is a possibility that must be considered, as well as acute-on-chronic right heart insults from congenital, shunt, or valvular lesions. Because the acuity of the examination findings of right heart dysfunction is not certain, comprehensive medical history, particularly regarding this young man’s comorbidities of polyneuropathy, edema, and gammopathy, will be a critical instrument of the diagnostic evaluation. Such information not only may help determine the proximal cause of the right heart dysfunction but also may direct initial management and possibly suggest a unifying pathophysiological process. Finally, hypotension and diffuse hyperpigmentation may raise concern of hypoadrenalism as a primary endocrinopathy.

Patient presentation (continued): The patient was well until 2 years previously when he developed insidious generalized extremity numbness with weakness and an unintentional 25-pound weight loss. Neurological evaluation at a community hospital was remarkable for elevated total protein in the cerebrospinal fluid. Electromyogram was consistent with a subacute immune-mediated demyelinating polyneuropathy initially thought to be Guillain-Barre syndrome. The presence of trace lower-extremity pitting edema was evaluated at that time with echocardiography, which

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revealed preserved RV and left ventricular size and function, no valvulopathy, and a small circumferential pericardial effusion without hemodynamic evidence of tamponade.

The patient was treated with intravenous immunoglobulin with initial improvement of his neuropathy, but symptoms recurred within 2 weeks. The lower-extremity edema worsened. Repeat echocardiography demonstrated an interval increase in the size of the pericardial effusion, although still without hemodynamic compromise, and was otherwise unrewarding. A sural nerve biopsy was performed, with histopathology consistent with a demyelinating polynuropathy. Serum protein electrophoresis was remarkable for mildly elevated IgA lambda monoclonal protein, 0.12 g/dL, which was consistent with monoclonal gammopathy of uncertain significance. Extensive medical evaluation was remarkable for hypothyroidism, with thyroid-stimulating hormone of 13.41 μU/mL (reference range, 0.50–4.00 μU/mL) and correspondingly low free thyroxine (T4) and triiodothyronine (T3). The patient’s weakness did not improve with thyroid hormone replacement therapy. No rheumatologic, neurologic, infectious, or oncological cause was identified.

Two additional courses of intravenous immunoglobulin were administered without clinical response. A regimen of methotrexate and high-dose pulse steroid therapy was then administered for presumed chronic inflammatory demyelinating polyneuropathy. The patient’s symptoms stabilized, but then he gradually deteriorated over the ensuing 1 ½ years from being physically active as a laborer to becoming bedridden and requiring nursing home care. Worsening bilateral lower-extremity edema was attributed to long-term steroid administration, prompting recent trials of steroid-sparing regimen that included azathioprine. The patient subsequently developed acute dyspnea and hypotension, prompting transfer to our cardiology service for further evaluation.

Dr Yee: The patient’s refractory course of polyneuropathy and the seemingly disparate constellation of findings, including peripheral edema, pericardial effusion, and monoclonal gammopathy, in this young patient are highly unusual and raise the possibility of an underlying syndromic condition. Monoclonal gammopathies are known to be associated with many common and rare diseases, which require methodical and critical evaluation. On the other hand, the presence of monoclonal gammopathies such as monoclonal gammopathy of unknown significance is relatively common in the older population, affecting 3.2% of individuals >50 years of age.

The assessment to date by prior providers should be carefully reviewed and conducted using primary data when possible. It is intriguing to consider whether the patient’s initial positive response to empirical corticosteroid therapy and decompensation after withdrawal of steroid therapy speak to an as-yet unidentified and underlying process mediated by inflammatory, immunological, or homeostatic mechanisms.

Dr Dudzinski: In addition to the acute evaluation of dyspnea and hypotension, parallel assessment of the chronic edema and pericardial effusion is vital. The progressive edema may reflect worsening cardiac dysfunction (right, left, or biventricular), but of note, the right side of the heart was echocardiographically normal on 2 recent occasions. Other causes may also contribute to chronic peripheral edema, including liver and renal disease, hypoalbuminemia, endocrinopathy, medication effects, venous thromboembolic disease, and inferior vena cava compression. Additionally, liver or renal disease, venous thromboembolic disease, or caval compression could theoretically arise from malignancy or inflammatory conditions. The patient’s history of indolent pericardial effusion may be relevant vis-à-vis the acute presentation and may point toward a unifying pathogenesis of systemic transudative fluid accumulation. Hypothyroidism itself could also account for peripheral edema and pericardial effusion, although generally not in mild disease.

On the basis of a current presentation with hypotension and the prior medical history, the initial cardiac evaluation will require ECG, laboratory studies, and echocardiogram to query possible PE, pericardial tamponade, or new cardiomyopathy with acute decompensated heart failure. Moreover, sequelae of acute myocardial infarction such as RV myocardial infarction or acute valvulopathy may be considered, as well as adrenal insufficiency, given the long-term corticosteroid use followed by recent withdrawal of these medications.

Patient presentation (continued): ECG showed sinus tachycardia, leftward axis, repolarization changes, and T-wave inversions most prominent in precordial leads V_{6} through V_{8} and 0.2- to 0.3-mV low-voltage QRS complexes in the limb leads without clear ischemic ST-segment and T-wave abnormalities (Figure 1). Laboratory studies were significant for troponin T of 0.08 ng/mL (reference range, <0.03 ng/mL), N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) of 16768 pg/mL (reference range, 0–450 pg/mL), serum albumin of 2.9 mg/dL (reference range, 3.3–4.8 mg/dL), and random cortisol of 7.2 μg/dL (reference range, 5–15 μg/dL). Other routine laboratory testing, including the remainder of hematology and chemistry studies, was unremarkable.

Contrast-enhanced chest computed tomography (CT) excluded PE but showed dilated pulmonary arteries and a small circumferential pericardial effusion. Dependent patchy ground-glass airspace opacities, pulmonary vascular congestion, and interlobular septal thickening, all compatible with interstitial pulmonary edema, were visualized, along with mild bilateral pleural effusions. The only other reported finding was multiple prominent lymph nodes.

Transthoracic echocardiography revealed new RV dilation, diffuse hypokinesis with relative sparing of the apex (Figure 2 and Movie I in the online-only Data Supplement), and an elevated estimated RV systolic pressure of 54 mm Hg (with assumed right atrial pressure of 10 mm Hg, given normal inferior vena cava size and respiratory variation). There was systolic and diastolic interventricular septal flattening, consistent with elevated RV pressure and volume, respectively. Left ventricular ejection fraction was 73% without regional wall motion abnormality, dilatation (end-diastolic dimension, 43 mm), or hypertrophy (interventricular septum and posterior wall thickness, 8 mm). An unchanged moderate circumferential pericardial effusion was present, again without echocardiographic evidence of tamponade physiology or elevated intrapericardial pressures.
Dr Dudzinski: Laboratory data and CT findings are consistent with marked volume overload requiring acute but judicious diuresis to restore hemodynamic stability. Random cortisol does not exclude adrenal insufficiency, and empirical stress-dose steroids could be reasonable at this early juncture in evaluating a hypotensive patient who recently stopped high-dose corticosteroids. Low voltage on the ECG implies attenuation of electric potential from pericardial effusion or myocardial infiltration and replacement, although increased wall thickness may be expected with the latter. The cause of the troponin elevation may be nonspecific without evidence of past infarction and acute ischemia on ECG, although the early precordial T-wave inversions could be consistent with Wellens syndrome. T-wave inversions in the early precordium of the ECG may in this case indicate RV subendocardial ischemia or strain.

Doppler echocardiography and ventricular septal geometry also confirm elevated pulmonary pressures, as had been inferred by examination. The echocardiographic findings of RV dilation and, in particular, the pattern of RV global hypokinesis with apical sparing are concerning for chronic or RV pulmonary hypertension and raise the specter of PE and acute RV myocardial infarction. RV myocardial infarction would be atypical in isolation without any left ventricular involvement, although a Kussmaul sign can be seen in this condition. However, this young patient has no major risk factors for ischemic heart disease, and the ECG, although showing early precordial T-wave inversions, does not have ST-segment elevation in lead V1.

In terms of the cause of right heart failure, left heart failure must always be considered. However, although dyspnea may be multifactorial, other symptoms of left heart failure such as orthopnea and signs such as left-sided S3 that suggest concomitant left heart failure were absent; the left ventricular size and systolic function were also normal on echocardiography.

In a young person who presents with acute right heart failure, decompensation from undiagnosed congenital shunts, valvulopathy, or other structural anomalies must be considered and, as in this case, excluded by echocardiography with careful color and spectral Doppler examination, although advanced imaging or invasive hemodynamics may be required. Even though the cardiac examination and echocardiographic findings could be consistent with acute or chronic PE, peripheral examination revealed no stigmata of peripheral venous thromboembolism. Acute PE is less likely with a negative CT, but the presentation and echocardiographic findings could be consistent with chronic thromboembolic disease; typically, this requires a ventilation-perfusion scan to detect chronic perfusion mismatch, which can evolve into chronic thromboembolic pulmonary hypertension.

The remaining differential diagnosis of a right heart failure syndrome with preserved left ventricular systolic function in this young man without congenital heart disease includes pulmonary hypertension secondary to chronic pulmonary processes or primary pulmonary arterial hypertension, pericardial constriction, restrictive cardiomyopathy, or a syndromic condition unifying his protean neurological and hematologic

Figure 1. Twelve-lead ECG obtained on presentation showing sinus tachycardia with early precordium repolarization changes consistent with right ventricular strain, left axis deviation, and low limb lead voltage. Compared with the most recent tracing obtained at another hospital 2 months earlier, the early precordial changes were new, although the low voltage and tachycardia were present previously.

Figure 2. Transthoracic echocardiogram with parasternal long-axis view (A), parasternal short-axis view at the papillary muscle level (B), and apical 4-chamber view (C) demonstrating right ventricular dilation and diffuse hypokinesis with apical sparing, as well as ventricular septal flattening in both systole and diastole, signifying both right ventricular pressure and volume overload.
findings. Thus, detailed review of the patient’s medical history for additional clues is critical. Pericardial constriction, which may result from prior radiation, chronic inflammation, infection, or infiltration such as metastatic disease, may mimic right heart failure in its marked edema, ascites, and hepatomegaly. Although there was no known history of malignancy, the patient had multiple prior echocardiograms dating back 18 months demonstrating chronic small to moderate pericardial effusion of unknown origin, which may theoretically result in pericardial thickening and fibrosis over time, causing constrictive physiology. The cause of this patient’s chronic, indolent pericardial effusion remains unknown at this point. The possibilities for such an effusion are vast and include connective tissue disorders, inflammation, malignancy, endocrinopathy, uremia, and drug toxicity. Chronic infectious causes such as tuberculosis and parasites may be entertained, and pericardial fluid sampling may be indicated for diagnostic purposes if another cause does not become apparent. The lack of hemodynamic consequence of the pericardial effusion suggests chronicity because the pericardium has had time to remodel and enlarge so that there is not significant ventricular interdependence.

Restrictive cardiomyopathy may present similarly with poorly compliant myocardium as a result of systemic infiltrative disease. Despite normal biventricular wall thickness on echocardiography, the presence of peripheral neuropathy and a monoclonal protein raises concern for amyloidosis, which is a plausible unifying diagnosis for right heart dysfunction, especially with heretofore unexplained pericardial effusion, low voltages on ECG, and hypotension. Pulmonary hypertension with right heart failure has been reported as a rare and late complication of amyloidosis in case series. Thus, laboratory testing to exclude amyloidosis, hemochromatosis, and other infiltrative myopathies could be considered as the first noninvasive step toward diagnosis.

Cardiac magnetic resonance imaging (MRI) is the preferred imaging technique for tissue characterization. The degree of fibrosis or infiltration can be quantified by measuring the extracellular volume fraction of the myocardium. The physiological significance of pericardial thickening and the presence or absence of adhesion can be assessed by measuring the motion and distortion of tag lines over the pericardium during systole. Invasive hemodynamics with simultaneous catheterizations of the left and right sides of the heart and endomyocardial biopsy could ultimately be necessary to conclusively differentiate constrictive pericarditis from restrictive cardiomyopathy if they became the foremost remaining diagnostic considerations.

**Patient presentation (continued):** The patient was felt to be total-body volume overloaded. Empirical diuretic therapy was thus administered, which rapidly improved his symptomatic, respiratory, and hemodynamic status. Both serum free κ and λ light chains were elevated at 49.9 and 105.5 mg/mL, respectively. Ventilation-perfusion scan was negative for both acute and chronic pulmonary thromboembolic disease.

Cardiac MRI confirmed RV dilation and dysfunction without late gadolinium enhancement (Figure 3 and Movie II in the online-only Data Supplement). There was no pericardial thickening or abnormal pericardial enhancement, and tagged cine analysis was normal. However, the kinetics of gadolinium in the myocardium and blood pool were abnormal. On the basis of the recovery curve of longitudinal magnetization (T1), higher levels of gadolinium were present in the myocardium than in the blood pool. There was no evidence of abnormal shunting on cardiac MRI.

Catheterization of the right side of the heart revealed a right atrial pressure of 11 mm Hg, an RV pressure of 63/11 mm Hg, a pulmonary artery pressure of 71/41 mm Hg (mean, 51 mm Hg), and a mean end-expiratory pulmonary capillary wedge pressure of 8 mm Hg (Figure 4A). Vasodilator challenge with 100% supplemental oxygen followed by addition of 80 ppm inhaled nitric oxide reduced the mean pulmonary artery systolic pressure to 35 and 31 mm Hg, respectively (Figure 4B). Cardiac output remained normal at 5.6 L/min. Concurrent coronary angiography was also performed, which excluded significant coronary artery disease.

**Dr Dudzinski:** The presence of significant pulmonary hypertension was first suggested on examination and echocardiography with elevated estimated pulmonary artery systolic pressure. Hemodynamic assessment by catheterization of the right side of the heart confirmed precapillary pulmonary hypertension, given the normal estimate of left-sided filling pressures.
pressures by pulmonary capillary wedge pressure. The vasodilator challenge to assess for vasoreactivity in pulmonary arterial hypertension is considered positive with a decrease in the mean pulmonary artery pressure by >10 mm Hg to an absolute value <40 mm Hg while maintaining the same cardiac output. The cause of the pulmonary hypertension does not appear to be lung disease absent a history of intrinsic pulmonary disease and normal imaging for acute and chronic pulmonary thromboembolic disease. Moreover, evaluation for rheumatologic and infectious causes such as collagen vascular diseases and human immunodeficiency virus, respectively, was known to have been negative. A final consideration is pulmonary veno-occlusive disease, a rare condition that often requires surgical lung biopsy for diagnosis and may be entertained if other more common causes are first excluded. Despite chronic pericardial effusion and probable concurrent inflammation, RV pressure tracings (Figure 4) did not demonstrate “dip and plateau” morphology, a finding which might have suggested constrictive or restrictive physiology. The normal pericardial imaging on cardiac MRI suggests no adherence of the visceral and parietal pericardium and makes constriction unlikely.

Although cardiac amyloidosis was considered to explain the MRI gadolinium kinetics results, several features of this case are atypical for amyloidosis. Although low voltage on ECG may be seen in infiltrative disease, there was no evidence ventricular wall thickening on either the echocardiogram or cardiac MRI, suggesting that the low voltage is likely attributable to the pericardial effusion. There was no elevation in the pulmonary capillary wedge pressure, as might be expected if there was impaired left ventricular lusitropy resulting from infiltration. Although abnormal gadolinium kinetics were present, diffuse subendocardial late gadolinium enhancement, which is classically seen in amyloidosis, was notably absent. Nevertheless, abnormal myocardial and blood-pool gadolinium kinetics have been reported with amyloidosis; however, any infiltrative process that markedly expands the extracellular space could produce a similar finding.

**Patient presentation (continued):** The patient underwent fat pad biopsy and bone marrow biopsy. Prior lymph node and nerve biopsy samples obtained during neurologic evaluation were also reviewed. All histological samples stained negative for amyloidosis. RV endomyocardial biopsy was deferred in the setting of right heart failure, severe pulmonary hypertension, and concern for increased procedural risk. Multiple negative biopsy samples for amyloidosis prompted evaluation for an alternative diagnosis.

Drs Dudzinski and Yee: This patient had progressive right heart failure of unknown origin, with virtually all causes excluded by the battery of testing. Clinicians re-evaluated the seemingly disparate group of signs, including relentless polyneuropathy, monoclonal gammopathy, and pericardial effusion, in the context of other protean abnormalities that initially appeared unrelated, such as splenomegaly and lymphadenopathy, hyperpigmentation, and hypothyroidism. In consultation with neurology and endocrinology colleagues, the profound polyneuropathy in the setting of monoclonal gammapathy raised suspicion for POEMS syndrome, classically characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammapathy, and skin changes. The diagnostic criteria were outlined by Dispenzieri et al (Table). The patient met both mandatory diagnostic criteria at the time of presentation: polyneuropathy and monoclonal gammapathy. He also exhibited several associated features, notably pulmonary hypertension and extravascular volume overload manifested as pericardial and pleural effusions and peripheral edema. Although rare, POEMS syndrome should be considered in the broad differential diagnosis of a patient with polyneuropathy and monoclonal gammapathy, particularly with other unexplained features such as endocrinopathy, pericardial effusion, and cor pulmonale. Other diagnostic considerations include chronic inflammatory polyadiculoneuropathy, amyloidosis, and Castleman disease, a rare lymphoproliferative condition associated with excess interleukin-6 production. The possibility of POEMS syndrome must be explored in the evaluation of idiopathic right heart failure, as in this patient, when other more common etiologies have been excluded. To complete the diagnostic criteria for POEMS
syndrome, 1 of 2 other major criteria, elevated vascular endothelial growth factor (VEGF) or the presence of sclerotic bone lesions, is required. The observation that elevated plasma VEGF levels are specific and sensitive for POEMS syndrome has been a significant advance toward making the diagnosis of POEMS syndrome and differentiating this disorder from other plasma cell disorders or causes of neuropathy.\(^{14}\) However, the VEGF assay is typically performed only in reference laboratories, and results may take days. Imaging with skeletal survey or positron emission tomography–CT to assess for sclerotic lesions is typically pursued. Furthermore, given the pleiotropic and multisystem nature of POEMS syndrome, a comprehensive review of systems is critical in further defining the syndrome and identifying minor criteria and other associated findings.

**Patient presentation (continued):** Positron emission tomography–CT was remarkable for bilateral axillary, hilar, mediastinal lymphadenopathy, bilateral pleural and pericardial effusions, and, notably, sclerotic bone lesions. A skeletal survey confirmed multiple 3- to 4-mm sclerotic bone lesions. Several minor criteria and associated conditions were identified through retrospective review of the patient’s medical history, imaging, and laboratory data, satisfying the full diagnostic criteria for POEMS syndrome: organomegaly as manifested by unexplained and episodic hepatomegaly, splenomegaly and lymphadenopathy incidentally imaged by CT, and cardiomegaly as shown on cardiac MRI and echocardiography. Skin changes were present as hyperpigmentation and hypertrichosis on examination. The patient was subsequently noted to have several, albeit mild, endocrinopathies in addition to hypothyroidism, including hypogonadism and hyperprolactinemia with bilateral gynecomastia. Plasma VEGF level was ultimately found to be markedly elevated to 1028 pg/mL (reference range, 31–86 pg/mL). Iliac crest bone marrow aspirate revealed normocellular histology with trilineage hematopoiesis. No monoclonal cell population or abnormal lymphocyte population was identified.

**Dr Yee:** POEMS syndrome belongs to a group of plasma cell disorders such as amyloidosis in which the systemic effects of the disease appear to be out of proportion to the size of the causal monoclonal plasma cell dyscrasia.\(^{15}\) Given that POEMS syndrome is a paraneoplastic plasma cell disorder, assessing the extent of this condition is centrally important to determine the most effective and targeted treatment. Bone marrow or multiple sites of systemic involvement typically require consideration of systemic therapy.\(^{13,16}\) One third of patients with POEMS syndrome do not show evidence of bone marrow involvement with a plasma cell disorder,\(^{17}\) as was the case with this patient. If restricted to a solitary plasmacytoma, external beam radiation is the treatment of choice.\(^{13,16,17}\) The patient did not have a solitary lesion, and multiple bone lesions were identified, thus necessitating systemic therapy. There are no randomized, clinical trial data to direct specific treatment for POEMS syndrome. Treatment recommendations are based on case series and guided by based on treatments for other plasma cell disorders such as multiple myeloma and light chain amyloidosis. Regimens typically include glucocorticosteroids and alkylator-based therapy. Interestingly, this patient initially received corticosteroids after initial diagnosis of chronic inflammatory

### Table. Criteria for the Diagnosis of POEMS Syndrome

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<th>Criteria for the Diagnosis of POEMS Syndrome</th>
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<tr>
<td>Mandatory major criteria</td>
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<td>Polyneuropathy (typically demyelinating)</td>
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<td>Monoclonal plasma cell proliferative disorder (almost always λ)</td>
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<tr>
<td>Other major criteria (1 required)</td>
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<tr>
<td>Castleman disease*</td>
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<td>Sclerotic bone lesions</td>
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<tr>
<td>VEGF elevation</td>
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<td>Minor criteria (1 required)</td>
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<tr>
<td>Organomegaly (spleenomegaly, hepatomegaly, or lymphadenopathy)</td>
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<td>Extravascular volume overload (edema, pleural effusion, or ascites)</td>
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<td>Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic)†</td>
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<tr>
<td>Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, and white nails)</td>
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<tr>
<td>Papilledema</td>
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<tr>
<td>Thrombocytosis/polycythemia§</td>
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<td>Other symptoms and signs</td>
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<td>Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B₁₂, values</td>
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The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, 1 of the 3 other major criteria, and 1 of the 6 minor criteria are present. The differential diagnosis of POEMS syndrome includes chronic inflammatory polyradiculoneuropathy, monoclonal gammopathy of undetermined significance (MGUS) neuropathy, immunoglobulin light chain amyloid neuropathy, and Castleman disease. POEMS indicates polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes; and VEGF, vascular endothelial growth factor. Reproduced from Dispenzieri et al\(^{13}\) with permission from the publisher. Copyright © 2014 Wiley Periodicals, Inc.

*There is a Castleman disease variant of POEMS syndrome that occurs without evidence of a clonal plasma cell dyscrasia that is not accounted for in this table. This entity should be considered separately.

†Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

‡Approximately 50% of patients will have bone marrow changes that distinguish it from a typical MGUS or myeloma bone marrow. Anemia and thrombocytopenia are distinctively unusual in this syndrome unless Castleman disease is present.
polyradiculoneuropathy, which temporarily stabilized his symptoms; presumably, without the underlying process being addressing, the disease invariably progressed. The extent of his cardiac dysfunction and poor baseline functional status further suggested that he would not tolerate treatment with high-dose chemotherapy and autologous stem cell transplantation. Instead, the patient was treated with lenalidomide and dexamethasone on the basis of a case series of 20 patients in which all patients responded initially, although 4 patients relapsed within 3 to 10 months.\textsuperscript{18,19} Fifteen of these 20 patients presented with peripheral edema, and 5 presented with pulmonary arterial hypertension. Treatment ameliorated symptoms and improved disease markers, including edema and pulmonary hypertension, and dramatically reduced VEGF levels, as was observed with this patient, with a reduction in VEGF from 1028 to 101 pg/mL (reference range, 31–86 pg/mL) 6 weeks after initiation of therapy. A subsequent phase II study of lenalidomide-dexamethasone in 27 patients with newly diagnosed POEMS syndrome showed similar benefit.\textsuperscript{20}

\textit{Dr Dudzinski:} Multiple reasons for this patient’s cor pulmonale and pulmonary hypertension were excluded, including left heart failure, valvulopathy, venous thromboembolic disease, and congenital heart disease. Right heart failure and pulmonary hypertension in this clinical scenario are consistent with the well-described association of POEMS syndrome with pulmonary arterial hypertension.\textsuperscript{21–24} Treatment of the underlying plasma cell dyscrasia in POEMS syndrome improves disease sequelae, including pulmonary hypertension. In addition, therapy with calcium channel antagonists or phosphodiesterase-5 inhibitors, specifically for pulmonary arterial hypertension, may be effective in POEMS syndrome,\textsuperscript{25} particularly for this patient because vasoreactivity testing was positive during catheterization of the right side of the heart.

\textit{Patient presentation (continued):} After stabilization of heart failure symptoms with diuresis, therapy for POEMS syndrome with daily lenalidomide and weekly dexamethasone was initiated. The patient did not tolerate calcium channel blockade because of profound hypotension and was instead started on the phosphodiesterase-5 inhibitor sildenafil for pulmonary hypertension, which was better tolerated. The patient was discharged to inpatient rehabilitation. Repeat echocardiogram 2 months after initiation of chemotherapy showed a significant reduction in pericardial effusion and normalization of RV size and function and estimated pulmonary artery systolic pressure. Repeat cardiac MRI confirmed significant improvement in RV size and function and normalization of the abnormal myocardial and blood-pool gadolinium kinetics. Late gadolinium enhancement was again absent.

Six months after starting chemotherapy, the patient had significant improvement in peripheral strength sufficient to permit him to mobilize by wheelchair. Echocardiogram 15 months after presentation showed an RV of normal size and function, trivial circumferential pericardial effusion, and estimated RV systolic pressure of 27 mm Hg. Heart failure symptoms, dyspnea, and hypotension did not recur.

\textit{Dr Yee:} Given the late stage at which the patient was diagnosed with POEMS syndrome, it is not unexpected that his profound polyneuropathy did not completely resolve. He will require close monitoring for relapse and treatment-related complications.

**Discussion**

POEMS syndrome is a paraneoplastic plasma cell disorder and a rare cause of isolated acute decompensated right heart failure. Although the chronic neuropathy and monoclonal gammopathy were initially thought to be unrelated, they are actually the defining characteristics of POEMS syndrome, also known in the literature as Takatsuki syndrome or Crow-Fukase syndrome. The acronym, first coined by Bardwick et al\textsuperscript{25} in 1980, provides a memorable construct to frame the syndrome. However, not all features of the acronym are required for diagnosis—only polyneuropathy and monoclonal gammopathy are necessary—and several other important sequelae have since been appreciated, notably sclerotic bone lesions, elevated VEGF levels, extravascular volume overload, and pulmonary hypertension. Our patient likely developed cor pulmonale with right heart failure secondary to the pulmonary hypertensive vasculopathy of longstanding, undiagnosed POEMS syndrome.

Pulmonary arterial hypertension is commonly associated with POEMS syndrome.\textsuperscript{21–24} Pulmonary hypertension occurs at a frequency of 36% on the basis of a pooled analysis of contemporary retrospective case reports.\textsuperscript{13} Presence of pulmonary hypertension is a late manifestation of this disease process and imparts poor prognosis, potentially because of the delay in the diagnosis of POEMS syndrome.\textsuperscript{24} Interestingly, pulmonary hypertension more likely occurs in patients with extravascular volume overload,\textsuperscript{13} possibly suggesting a shared vascular origin.

The varied manifestations of POEMS syndrome are thought to be mediated in part by dysregulation of paracrine signaling.\textsuperscript{21–24} A host of soluble signaling proteins are induced in POEMS syndrome, including the proinflammatory cytokines interleukin-1β, interleukin-6, and tumor necrosis factor-α,\textsuperscript{21,22} and the growth factor VEGF.\textsuperscript{26,27} Elevated circulating VEGF is a major diagnostic criterion and correlates with disease activity of POEMS syndrome.\textsuperscript{14,29,30} A plasma VEGF level >200 pg/mL is 95% specific and 68% sensitive for the diagnosis of POEMS syndrome in the right clinical context of patients presenting with multisystem illness.\textsuperscript{14} Other rare conditions associated with elevated VEGF levels include connective tissue disorders and vasculitis,\textsuperscript{14} which are typically easily discernible clinically from POEMS syndrome.

VEGF is a cytokine and well-known mediator in endothelial cell biology, inducing microangiopathy, neovascularization, and vasopermeability. The extravascular volume overload and multiple effusions observed in POEMS syndrome have been linked to the vasoactive effects of VEGF.\textsuperscript{24} Moreover, VEGF levels parallel the severity and treatment response of pulmonary hypertension, independently of other biomarkers, suggesting a role for VEGF in the pathogenesis of pulmonary arterial hypertension.\textsuperscript{31} VEGF has been hypothesized to mediate pulmonary hypertension by 2 complementary mechanisms.\textsuperscript{32} First, VEGF causes pathological vascular permeability within the pulmonary arterial bed,
causing interstitial and perivascular edema and increasing angioreistance. The resultant decline in gas diffusion capacity causes hypoxemia, which is a potent inducer of endothelial VEGF, thus completing a vicious cycle ultimately leading to pulmonary arterial hypertension. Corticosteroids are known to inhibit VEGF expression and to reduce vascular permeability experimentally, which is supported by empirical clinical experience. However, targeted therapy directed against circulating VEGF with the monoclonal antibody bevacizumab in POEMS syndrome has produced conflicting results without clear benefit, suggesting that VEGF may not be the central mediator in the pathogenesis of POEMS syndrome.

Conclusions

We present a case of POEMS syndrome manifesting acutely as right heart failure caused by pulmonary hypertension in a young man with antecedent polyneuropathy, monoclonal gammopathy, and extravascular volume overload. The patient’s marked improvement by clinical, imaging, and biochemical measures with treatment underscores the importance of identifying the underlying process to initiate a targeted, effective, and durable treatment. Although POEMS syndrome is classically described as a paraneoplastic syndrome encompassing hematology, neurology, and endocrinology, cardiovascular sequelae are common and thus are important considerations for the cardiologist in evaluating the differential diagnosis of cor pulmonale and unexplained pulmonary hypertension. Careful integration of multiple seemingly disparate clinical findings ultimately yielded the diagnosis. The case illustrates the key clinical, imaging, hemodynamic, and pathological findings characteristic of POEMS syndrome and associated cardiovascular manifestations.

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Disclosures

None.

References


Key Words: heart failure, hypertension, pulmonary paraneoplastic syndromes, pericardial effusion, polyneuropathies, pulmonary heart disease
Progressive Onset of Extracardiac and Myocardial Symptoms: Right Heart Failure and Cor Pulmonale in a Young Man With Debilitating Polyneuropathy and Monoclonal Gammopathy

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