A 65-Year-Old Man With Weight Loss, Peripheral Neuropathy, and Lower Extremity Swelling

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CASE PRESENTATION: A 65-year-old man with no past medical history sought treatment at the hospital with lower extremity swelling, pain, tingling in a stocking-glove distribution, and syncope. He reported a 23-pound unintentional weight loss. He felt unsteady walking with a couple of falls, and his exercise tolerance was limited to several hundred feet. He did not report vision changes, dysphagia, bowel or bladder problems, tremor, orthopnea, light-headedness, or chest pain. He did not report any history of substance misuse, high-risk sexual behavior, or concerning exposures. The patient was admitted for further workup.

Physical Examination Findings
Vital signs were pertinent for a heart rate of 140 beats/min and BP of 92/48 mm Hg, but otherwise were normal. Cardiopulmonary examination revealed tachycardia, irregularly irregular rhythm, no murmurs, and clear lungs. The abdomen was benign without organomegaly. He had 1+ lower extremity edema bilaterally. Neurologic examination revealed normal cranial nerves; motor examination pertinent for 4+/5 throughout the right arm, 3/5 plantarflexion, and 1/5 dorsiflexion; sensory examination pertinent for diminished sensation to pinprick bilaterally below the knees and loss of proprioception in the left foot; reflexes absent throughout, but with normal plantar reflex; normal cerebellar examination findings; and high steppage gait.

Diagnostic Evaluation
Laboratory investigations revealed normal basic metabolic panel, complete blood count, and hepatic function panel findings. Thyroid-stimulating hormone, cortisol, thiamine, vitamin B12, folate, copper, and zinc levels were normal. HIV, hepatitis C, and syphilis serologic examination results were negative. Serum protein electrophoresis showed a monoclonal IgA λ protein 0.2 g/dL with positive immunofixation.

Chest radiography showed enlargement of the pulmonary arteries, but the findings otherwise were normal. ECG showed rapid atrial fibrillation with a right bundle branch block. Brain natriuretic peptide was elevated at 196 pg/mL (normal, 0-100 pg/mL). Echocardiography showed normal left ventricular size and function, flattened interventricular septum, mildly dilated right ventricle with normal function, and an estimated right ventricular systolic pressure of 78 mm Hg (normal, < 39 mm Hg). Right heart catheterization revealed a pulmonary artery pressure of 62/24 mm Hg, with a mean pulmonary artery pressure of 36 mm Hg. The pulmonary artery wedge pressure was 7 mm Hg (normal, < 15 mm Hg), and the calculated...
Figure 1 – Fluorodeoxyglucose (FDG) PET images. Increased FDG uptake (arrows) of sternum (A), 10th rib (B), T12 vertebral body (C), and right 11th rib (D). No FDG-avid disease or adenopathy in the chest, abdomen, or pelvis.

Figure 2 – A-D. Photomicrographs of rib biopsy samples showing plasma cell neoplasm. A, Hematoxylin and eosin slide showing sheets of plasma cells (original magnification, ×100). B, Immunohistochemical study for CD138 labeling plasma cells. C, Immunohistochemical study for CD56 labeling plasma cells (aberrantly expressed in plasma cell neoplasms). D, Lambda light chain in situ hybridization study; kappa light chain in situ hybridization study showed negative results in the plasma cells.
pulmonary vascular resistance was elevated at 5.5 Woods units (normal, < 3 Woods units). Electromyography showed subacute severe sensorimotor length-dependent axonal and demyelinating peripheral polyneuropathy. Cerebrospinal fluid demonstrated 9 WBCs (monocyte predominance), protein of > 300 mg/dL (normal, 12-60 mg/dL), glucose of 56 mg/dL, cytologic findings negative for malignant cells, and negative results on a paraneoplastic panel. CT imaging showed mixed sclerotic and lytic lesions in the right eleventh rib, L3 and T12 vertebral bodies, sternum, pelvis, and sacrum. Whole body PET scanning showed multiple intensely Fluorodeoxyglucose (FDG) avid lytic lesions (correlating with CT scan findings), no nonosseous FDG avid disease, and no organomegaly (Fig 1). Bone marrow biopsy showed 4% clonal plasma cells, and rib biopsy pathologic features confirmed plasma cell neoplasm (Fig 2). The vascular endothelial growth factor (VEGF) level was 109 pg/mL (normal, 9-86 pg/mL).

What is the diagnosis?
Diagnosis: Pulmonary hypertension (group 5) secondary to polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (POEMS) syndrome

Discussion

POEMS syndrome is a paraneoplastic syndrome secondary to an underlying plasma cell disorder. POEMS syndrome is a rare disorder that usually presents in the fifth to sixth decade of life with an estimated prevalence of 0.3 per 100,000 people. The pathogenesis of POEMS syndrome is understood poorly, but overproduction of VEGF, a cytokine involved with angiogenesis and vascular hyperpermeability, has correlated with disease activity. A serum VEGF level of > 200 pg/mL has 95% sensitivity and 68% specificity for POEMS syndrome.

The diagnosis of POEMS syndrome requires a constellation of criteria that must include polyneuropathy and plasma cell proliferation, whereas all of the components of the acronym POEMS are not required for diagnosis (Table 1). Common symptoms in addition to polyneuropathy include peripheral edema, splenomegaly, and skin hyperpigmentation. Given the rarity of POEMS syndrome and its varied presentations, the diagnosis is often delayed.

The natural history of untreated POEMS syndrome is characterized by varied development of additional signs and symptoms, with progressive sensorimotor polyneuropathy being one of the most debilitating comorbidities. The number of POEMs features that develop does not correlate with increased mortality. Before treatment with chemotherapy and stem cell transplantation, individuals with POEMS syndrome show an estimated median survival of 100 months and a 60% 5-year survival.

It is important to distinguish POEMS syndrome from monoclonal gammopathy of unknown significance, smoldering myeloma, and multiple myeloma (MM) because myeloma spectrum diseases often can be surveilled actively, whereas POEMS syndrome warrants immediate treatment. Although MM and POEMS syndrome have several overlapping clinical and pathologic features, neuropathy is present in MM in only < 10% of patients. The neuropathy associated with POEMS syndrome typically is symmetrical, peripheral, ascending, and with both sensory and motor deficits. MM is characterized by painful lytic bone lesions and rarely with sclerotic bone lesions. Conversely, patients

TABLE 1 ] POEMS Syndrome Diagnostic Criteria

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<tr>
<th>Criteria</th>
<th>Details</th>
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<td><strong>Mandatory major criteria (both required)</strong></td>
<td>1. Polyneuropathy (typically demyelinating)</td>
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<td>2. Monoclonal plasma cell-proliferative disorder (almost always λ)</td>
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<td><strong>Other major criteria (one required)</strong></td>
<td>3. Castleman disease</td>
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<td>4. Sclerotic bone lesions</td>
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<td><strong>Minor criteria (one required)</strong></td>
<td>5. Vascular endothelial growth factor elevation</td>
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<td>6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy)</td>
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<td>7. Extravascular volume overload (edema, pleural effusion, or ascites)</td>
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<td>8. Endocrinopathy (adrenal, thyroid, a pituitary, gonadal, parathyroid, pancreatic)</td>
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<td>9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)</td>
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<td>10. Papilledema</td>
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<td>11. Thrombocytosis or polycythemia</td>
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<td><strong>Other symptoms and signs</strong></td>
<td>Clubbing, weight loss, hyperhidrosis, pulmonary hypertension or restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B12 values</td>
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Diagnosis requires both major criteria, one of the three other major criteria, and one of the six minor criteria. POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes; VEGF = vascular endothelial growth factor.

aDiabetes mellitus or thyroid abnormalities alone are not sufficient to satisfy the minor criteria of endocrinopathy, given their relatively high prevalence in the general population. Adapted from Dispenzieri (2019) with permission.
with POEMS syndrome have painless bone lesions, which either are entirely sclerotic or mixed sclerotic and lytic lesions. Survival in MM is worse compared with POEMS syndrome, with 10-year survival rates with treatment grossly estimated at 30% and 55% to 89%, respectively.

Pulmonary hypertension (PH) is present in 27% to 48% of patients with POEMS syndrome. POEMS syndrome is classified under World Health Organization group 5 PH: PH with unclear multifactorial mechanisms. Other causes of World Health Organization group 5 PH include hematologic disorders (ie, sickle cell disease, myeloproliferative disorders), systemic disorders (ie, sarcoidosis), metabolic disorders (ie, thyroid disease), and chronic renal failure. Histologic analysis of postmortem lungs of patients with POEMS syndrome who demonstrate PH have revealed either plexiform lesions (characteristic of idiopathic pulmonary arterial hypertension) or plasmocytic infiltration. It has been postulated that elevated levels of VEGF stimulate endothelial proliferation, which results in endothelial dysfunction and thereby overgrowth of vascular smooth muscle, in turn causing PH.

The primary treatment of PH secondary to POEMS syndrome is directed at the underlying plasma cell dyscrasia and may result in resolution of PH. Long-term follow-up echocardiographic data are missing in most studies. Pulmonary vasodilators in patients with World Health Organization group 5 PH may improve hemodynamic measurements, but survival benefits have not been demonstrated. If pulmonary vasodilators are initiated in patients with POEMS syndrome, they may be weaned off of them if the plasma cell dyscrasia goes into remission.

The optimal treatment of POEMS syndrome depends on the presence or absence of disseminated bone marrow infiltration. Systemic therapy is indicated for those with disseminated bone marrow involvement, whereas those with isolated bone lesions are treated with curative intent radiation. Systemic treatment may include alkylator-based therapy and steroids, immunomodulatory agents, or autologous stem cell transplantation. Anti-VEGF medications (ie, bevacizumab) have shown some success, albeit less than therapies directly targeting the underlying plasma cell dyscrasia. In a recent cohort of patients with POEMS syndrome, treatment led to a 72% rate of 6-year progression-free survival and an 89% rate of 10-year survival.

**Clinical Course**

After right heart catheterization showed moderate precapillary PH, alternative causes of PH, including autoimmune disease, parenchymal lung disease, OSA, and chronic thromboembolic PH, were ruled out. Given that the patient was assigned New York Heart Association functional class 2, tadalafil therapy was initiated. After receiving a diagnosis of POEMS syndrome, he was treated with three cycles of lenalidomide and dexamethasone, but a rash developed, leading to discontinuation. He subsequently underwent autologous stem cell transplantation. More than 1 year after autologous stem cell transplantation, he continues to show sustained remission with complete normalization of lesions on PET scanning, normal serum protein electrophoresis levels, and bone marrow with no clonal plasma cells. The neuropathy has improved from a motor standpoint, but distal pain persists. He presently is assigned New York Heart Association functional class 1 and is no longer receiving tadalafil, and the right ventricular systolic pressure on echocardiography has normalized.

**Clinical Pearls**

1. **POEMS syndrome is a rare paraneoplastic syndrome secondary to an underlying plasma cell disorder with protean manifestations.**
2. **PH occurs in 27% to 48% of patients with POEMS syndrome, yet a high index of suspicion is required to diagnose PH because patients’ exercise limitations may be impaired by debilitating polyneuropathy.**
3. **The primary treatment of PH in patients with POEMS syndrome is targeted at the underlying plasma cell neoplasm, which involves systemic therapy and may include steroids, chemotherapy, and stem cell transplantation.**
4. **Pulmonary vasodilators may be beneficial in instances of moderate to severe PH, although they can often be weaned off if patients go into remission.**

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**Suggested Readings**


