Pearls & Oy-sters: POEMS Syndrome
An Eloquent Acronym for a Rare Disease You Don’t Want to Miss

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Pearls
• POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) must be considered for patients with chronic inflammatory demyelinating polyradiculopathy (CIDP) not responding to corticosteroids, IV immunoglobulin (IVIg) therapy, or plasmapheresis.
• Thrombocytosis and polycythemia in patients with polyneuropathy should prompt further evaluation for POEMS syndrome.
• Consider non-neurologic signs and symptoms when evaluating a patient with a neuropathy to ensure you do not miss a multisystemic disease such as POEMS syndrome.

Oy-sters
• Many patients with POEMS syndrome are initially misdiagnosed with CIDP. A comprehensive review of systems inquiring about skin abnormalities, endocrine symptoms, and visual changes are key to expanding beyond the common diagnosis of CIDP.
• Vascular endothelial growth factor (VEGF) and platelet counts can be artificially normal with steroid treatment.

A 51-year-old woman, with a medical history significant for stage IIA ER+/HER2- breast cancer, presented with a 1-year history of progressive ascending length-dependent sensorimotor peripheral neuropathy. Initial symptoms were paresthesias in her feet that quickly progressed to mid-calf bilaterally. Over the next 6 months, she developed bilateral foot drop, profound proximal muscle weakness, and leg atrophy. Due to worsening balance, strength, sensory disturbances, and inability to ambulate without assistance, she was admitted for evaluation. Review of systems was notable for a 40-pound unintentional weight loss over 12 months, nightly fevers, mottling rash on her legs, and hyperpigmentation on her face and upper chest. She reported no visual symptoms or headaches.

Outside work-up was largely unremarkable except for a new diagnosis of hypothyroidism, vitamin B12 level of 271, and elevated antinuclear antibody (titer unknown). Outside non-contrasted MRI of brain, cervical, thoracic, and lumbar spine was unremarkable.

The patient’s breast cancer was in remission, having been treated 2.5 years previously with lumpectomy, radiation, and tamoxifen. Nerve conduction studies 3 months prior to admission demonstrated absent peroneal and tibial motor responses and low amplitude median and ulnar motor responses bilaterally. Sural sensory responses were low amplitude with prolonged distal latency bilaterally. EMG demonstrated fibrillation potentials and positive sharp waves in bilateral distal lower extremities associated with decreased recruitment. These findings were consistent with an active sensorimotor polyneuropathy with mixed axonal and demyelinating features.
Neurologic examination upon admission was notable for lower extremity atrophy and Medical Research Council Muscle Power Scale strength of 4+/5 bilateral hip flexion, 4/5 bilateral knee extension and flexion, 4/5 plantar flexion, and 2/5 bilateral dorsi flexion. Deep tendon reflexes were absent throughout except 1+ right brachioradialis. Sensation was intact to temperature and light touch but vibration was absent below the knees and proprioception was absent at the hallux bilaterally. Bilateral steppage gait was observed. Mental status, cranial nerves, and coordination were intact. The patient’s general examination was unremarkable except for areas of hyperpigmentation on her face and upper chest, acrocyanosis, and trace bilateral lower extremity edema.

CSF studies demonstrated an elevated protein level of 128 mg/dL with normal opening pressure, white blood cells, red blood cells, and glucose, and negative oligoclonal band profile, infectious panels, and cytology. Initial laboratory studies were notable for thrombocytosis (455 k/μL), β2 microglobulin level of 4.0 mg/L (normal 1.1–2.4 mg/L), elevated C-reactive protein (5.8 mg/L), and elevated serum kampa free light chains at 3.1 mg/dL (normal 0.33–1.94 mg/dL) and lambda free light chains at 2.82 mg/dL (normal 0.57–2.63 mg/dL) with a normal ratio of 1.10. Ganglioside panel showed elevated GQ1B immunoglobulin G/immunoglobulin M antibodies at 124 IV (normal 0–50 IV). Repeat EMG performed during admission demonstrated increased demyelinating findings in upper extremities as well as more severe and widespread active denervation consistent with progression of the previously demonstrated sensorimotor polyneuropathy. MRI lumbar spine showed prominent periaortic and retroperitoneal lymph nodes with diffuse enhancement of cauda equina nerve roots and the distal conus. Given the EMG findings, an initial diagnosis of CIDP was made and the patient was treated with IVIg 2 g/kg while awaiting immunofixation electrophoresis and VEGF results. Due to lack of improvement with IVIg therapy and patient’s breast cancer history, she underwent further imaging with CT abdomen and pelvis, which showed mild splenomegaly and subtle areas of sclerosis involving the anterior column of the left acetabulum. CT neck showed scattered enhancing cervical lymph nodes and ill-defined sclerotic lesions within cervical spine. Serum protein electrophoresis demonstrated broadening of complement component in the beta region and a faint immunoglobulin A lambda. VEGF was elevated at 490 pg/mL (normal 9–86 pg/mL); interleukin-6 was normal. Bone marrow biopsy showed increased megakaryocytes without evidence of plasma cell dyscrasia suggestive of either a reactive process or a myeloproliferative neoplasm. Due to her growing constellation of additional systemic findings, ophthalmology was consulted and found bilateral disc edema with peripapillary hemorrhages on fundoscopic examination (Figure 1).

Our patient was diagnosed with POEMS syndrome as she met mandatory criteria (polyneuropathy, monoclonal gammopathy), major criteria (sclerotic bone lesions and elevated VEGF), and minor criteria (organomegaly, endocrinopathy, skin changes, and thrombocytosis). She was discharged with close outpatient follow-up with hematology, where she was given 4 cycles of dose-reduced bortezomib, cyclophosphamide, and dexamethasone. Her VEGF levels decremented from 1,095 to 49 pg/mL. Despite improvement in motor strength, there was no sensory improvement. After completion of chemotherapy, the patient underwent autologous stem cell transplant (ASCT). At day 100 post-transplant, her VEGF level remains in the normal range, her platelet count normalized, her splenomegaly, endocrinopathy, skin changes, and papilledema have all resolved, and she continues to show slow improvement in motor strength.

Discussion

POEMS is an elegant acronym describing a rare, multiorgan, paraneoplastic syndrome including polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes resulting from an underlying plasma cell neoplasm. The estimated prevalence of POEMS is 0.3 per 100,000 with a peak incidence occurring during the fifth and sixth decades of life.
The association of neuropathy with other conditions, notably hyperpigmentation and plasmacytomas, was initially traced back to an autopsy evaluation in 1938. While the POEMS acronym reminds us of the common diagnostic criteria for the disease, subtle presentations create challenges for both initial diagnosis and timely treatment.

Diagnosis of POEMS syndrome requires presence of both mandatory criteria of polyneuropathy and evidence of a plasma cell proliferative disorder, 1 of the major criteria (Castleman disease, sclerotic bones lesions, increased levels of VEGF), and 1 of the minor criteria (organomegaly, signs of extravascular volume overload, endocrinopathy, skin changes, papilledema, thrombocytosis). Additional non-criteria findings can include digital clubbing (Figure 2), weight loss, hyperhidrosis, pulmonary hypertension/restricted lung disease, thrombotic diathesis, diarrhea, and low vitamin B12 values.

The diagnostic challenge to early recognition in POEMS is the ubiquity of its initial presenting symptom, polyneuropathy, which leads to a broad differential. Screening for a plasma cell disorder is critical in the diagnostic work-up of any neuropathy. Pattern recognition can also aid in early diagnosis. POEMS is marked by a subacute, symmetric, often painful, sensorimotor neuropathy frequently with pronounced weakness. In cases of symmetric distal polyneuropathy, the American Academy of Neurology provides guidelines for evaluation.

The pathophysiology of POEMS syndrome is unknown. VEGF levels are seen as a specific marker of disease activity and are monitored as a response to treatment. Augmented VEGF has been shown in animal models to lead to increased microvascular permeability ultimately resulting in endoneurial edema and the presence of serum components toxic to nerves. The multitude of additional symptoms in POEMS and their connection to one another remains a mystery.

POEMS syndrome is a malignant disease with widespread complications. Pulmonary hypertension and severe renal impairment (estimated glomerular filtration rate <30 mL/min) due to cytokine-induced endothelial malfunction and renal capillary collapse respectively are common complications. Another association with POEMS is cerebral ischemia. A study by Dupont et al. found the 5-year risk of ischemic stroke to be 13.4%. Increased platelet count and plasma cell hyperplasia further increased this risk and increased fibrinogen levels are also an independent risk factor for cerebral ischemia. The University College London Hospital POEMS registry reported 30% of their patients with POEMS had an arterial and/or venous thrombotic event (VTE) before and during treatment, with the highest risk during active disease, which they defined as VEGF levels >1,000 pg/mL. Their findings highlight the importance of developing VTE prophylactic strategies for suspected and treated patients.

Although there are no randomized controlled trials, treatment for POEMS is based on treating the underlying plasma cell neoplasm with myeloma-adapted regimens. Radiation therapy is first line for limited disease (isolated bone lesions), whereas chemotherapy, with or without adjuvant radiation therapy, is standard for disseminated plasma cell disease. In practice, first-line therapies may include lenalidomide/dexamethasone and bortezomib/cyclophosphamide/dexamethasone. Thalidomide and bortezomib have both been associated with chemotherapy-induced peripheral neuropathy. Our patient was started on low-dose bortezomib combination therapy without evidence of worsening neuropathy. Chemotherapy with ASCT is an option for selected patients with POEMS, with a 5-year overall survival rate of 94% and 5-year progression-free survival of 75%. Interestingly, patients' age (<50) was also associated with an increased risk of relapse ($p = 0.01$). As discussed above, VTE prophylaxis is an important consideration. While the ideal antithrombotic regimen is unknown, the POEMS registry investigators recommend prophylactic low molecular weight heparins in addition to a single antiplatelet agent until VEGF levels fall below 1,000 pg/mL. Further studies are needed to create a POEMS-specific VTE prophylaxis guideline both before and during treatment. VEGF levels are an important marker of disease activity and treatment response. Our patient demonstrated remarkable normalization of VEGF levels with medical therapy.
Early diagnosis of POEMS syndrome can have profound effects on patient disability. A 20-year retrospective review of patients with POEMS found that 35% were either wheelchair- or bed-bound at time of diagnosis. Patients diagnosed within 6 months of symptoms had significantly lower Overall Neuropathy Limitations Scale scores compared to those with a later diagnosis.11

Although rare, this syndrome should be remembered. By keeping POEMS on your radar as a possible diagnosis in patients presenting with sensorimotor polyneuropathy and systemic symptoms, you have the opportunity to reduce long-term disability and improve survival through prompt diagnosis and treatment initiation.

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### Appendix (continued)

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### References

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