48-Year-Old Woman With Bilateral Lower Extremity Paresthesias and Weakness

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A 48-year-old woman presented to the emergency department with a 3-week history of bilateral lower extremity paresthesias, weakness, and progressive dyspnea. Her symptoms began with numbness in her feet and gradually progressed proximally to involve her knees and hands. Eventually, progressive weakness developed in the same distribution. She had difficulty climbing stairs and going from a seated to a standing position. Her most recent symptoms included exertional dyspnea, now present at rest. She had not experienced diplopia, slurred speech, dysphagia, difficulty holding her head, or back pain. She had no recent infections, vaccinations, or outdoor exposures. Her medical history included sleep apnea, hypertension, hypothyroidism, diabetes, obesity, and breast cancer treated with bilateral mastectomy and adjuvant chemotherapy without evidence of recurrence. Her medications included triamterene with hydrochlorothiazide, levothyroxine, metformin, and letrozole.

On physical examination, she appeared to be in moderate respiratory distress and was noted to have rapid, shallow breathing. She was afebrile with a temperature of 36.8°C, tachycardic with a heart rate of 104 beats/min, normotensive with a blood pressure of 120/72 mm Hg, tachypneic with a respiratory rate of 27 breaths/min, and hypoxic with an oxygen saturation of 85% while breathing room air. Pulmonary examination revealed accessory muscle use, and cardiovascular examination was notable for 1+ lower extremity pitting edema without jugular vein distention. Skin examination revealed a palpable 3.5-cm firm, semimobile, nontender mass over the right side of her neck, mild diffuse skin sclerosis, hypertrichosis, and digital clubbing. Neurologic examination revealed normal cranial nerves, marked motor weakness (3/5) affecting both hands and distal lower extremities, and hyporeflexia throughout. Sensory examination revealed decreased pinprick and vibration sense distally.

Laboratory testing revealed the following (reference ranges provided parenthetically): mild normocytic anemia (hemoglobin, 10.4 g/dL [12.0-15.5 g/dL]; mean corpuscular volume, 82 fL [81.6-98.3 fL]); white blood cell count, 7.5 × 10^9/L (3.5-10.5 × 10^9/L); and platelet count, 390 × 10^9/L (150-450 × 10^9/L). Her electrolyte panel revealed a sodium level of 135 mmol/L (135-145 mmol/L), potassium level of 4.6 mmol/L (3.6-5-2 mmol/L), random glucose concentration of 175 mg/dL (70-140 mg/dL), creatinine level of 0.7 mg/dL (0.6-1.1 mg/dL), bicarbonate level of 29 mmol/L (22-29 mmol/L), albumin level of 3.4 g/dL (3.5-5.0 g/dL), and total protein level of 6.5 g/dL (6.3-7.9 g/dL). Arterial blood gas while the patient breathed room air revealed a pH of 7.36 (7.35-7.45), $PaCO_2$ of 54 mm Hg (35-45 mm Hg), and a PaO_2 of 83 mm Hg (80-100 mm Hg), findings consistent with acute hypercapnic respiratory failure. Examination of cerebrospinal fluid from lumbar puncture revealed a glucose level of 151 mg/dL (50-75 mg/dL or 60% of the plasma/serum concentration), protein level of 190 mg/dL (0-35 mg/dL), red blood cell count of 0/μL (<0/μL), and a white blood cell count of 2/μL (0-5/μL). Electromyography identified low-amplitude motor and sensory responses as well as diffusely slow conduction velocities with prolonged sensory latencies. Conduction block was seen in all motor nerves. Magnetic resonance imaging (MRI) of the brain and spine revealed no abnormalities.

1. Which *one* of the following diagnoses is the *most likely* explanation for this patient's presentation?

a. Neoplastic epidural spinal cord compression
b. Tick paralysis

See end of article for correct answers to questions.

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c. Transverse myelitis
d. West Nile flaccid paralysis
e. Demyelinating polyneuropathy

Neoplastic epidural spinal compression can present with lower extremity weakness preceded by sensory deficits. However, it is usually asymmetric and associated with back pain, and MRI abnormalities are present. Our patient did not have back pain, and spinal imaging findings were unremarkable. Tick paralysis causes flaccid ascending paralysis with paresthesias that progress within hours to days. Our patient's symptoms evolved over the course of weeks, and she reported no outdoor activities or recent tick bites to suggest this as a cause. Transverse myelitis also presents with ascending paralysis and paresthesias. It occurs after an infection, and physical examination findings include a definite sensory level, autonomic abnormalities (eg, bladder dysfunction), and hyperreflexia, and MRI abnormalities are also present. This scenario is inconsistent with our patient's presentation. West Nile neuroinvasive disease presents as an asymmetric flaccid paralysis with lower motor neuron signs resembling poliomyelitis. Sensory loss is uncommon. The presence of ascending sensory and motor symptoms is suggestive of a peripheral neuropathy. Electromyographic findings are suggestive of a diffuse demyelinating process.[1] Therefore, a demyelinating polyneuropathy is the most likely diagnosis in this patient.

To further clarify the etiology of her profound weakness, a sural nerve biopsy and computed tomography of the chest were obtained. Pathologic examination confirmed the presence of diffuse axonal degeneration, demyelination, and scattered epineurial perivascular inflammatory infiltrates. Computed tomography revealed multiple prominent mediastinal lymph nodes. Because of concern about neoplasia, an excisional biopsy of her right neck mass was performed, revealing angiofollicular hyperplasia consistent with Castleman disease (CD).

2. Which *one* of the following tests should be performed *next*?

a. Human herpesvirus (HHV) 8, human immunodeficiency virus (HIV), and protein electrophoresis
b. Abdominal ultrasonography
c. Endobronchial ultrasonography for mediastinal lymph node biopsies
d. Bone marrow (BM) biopsy and peripheral blood smear
e. Aerobic, anaerobic, and fungal blood cultures

Castleman disease is a lymphoproliferative disorder often associated with HHV-8, HIV, and monoclonal gammopathies. A diagnosis of CD should prompt evaluation for HIV, lymph node HHV-8, and monoclonal gammopathies, particularly in the setting of peripheral neuropathy.[2] Computed tomography rather than ultrasonography can be used in patients with CD to define the extent of the disease and the presence of osteosclerotic lesions. The presence of prominent mediastinal lymph nodes is suggestive of multicentric rather than unicentric (single lymph node group) CD, and therefore, no additional biopsies would be indicated. Despite CD's association with other hematologic malignancies, BM biopsies or peripheral blood smears should be done only after other testing results are suggestive of malignancy. Blood cultures have no role in the diagnosis of CD.

Lymph node biopsy for HHV-8 and HIV serologic testing yielded negative results. Serum electrophoresis revealed an M spike in the gamma region. Serum immunofixation confirmed the presence of monoclonal IgG-λ. Immunoglobulin serum free light chains revealed an elevation of κ (8.38 mg/dL [0.33-1.94 mg/dL]) and λ (8.11 mg/dL [0.57-2.63 mg/dL]) light chains, but the κ/λ ratio was normal at 1.03 (0.26-1.65). Bone marrow biopsy revealed megakaryocyte hyperplasia, less than 1% plasma cells, and the presence of clonal λ plasma cells. These findings were suspicious for POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

3. Which *one* of the following statements about the suggested diagnosis in this patient is *true*?

a. The diagnosis is unlikely; she does not meet all the features of the acronym
b. Sclerotic bone lesions would not be expected
c. Plasma and/or serum vascular endothelial growth factor (VEGF) levels are expected to be elevated
d. Skin changes are unrelated to her diagnosis

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e. Nerve biopsies would likely show endoneurial inflammatory cells and large onion bulbs

The diagnosis of POEMS syndrome is based on the presence of 2 mandatory criteria (polyneuropathy and monoclonal plasma cell proliferative disorder), 1 major criteria (eg, CD), and 1 minor criteria (eg, skin changes). Diagnosis can be made without the presence of all of the acronym features.[3] Sclerotic bone lesions occur in up to 80% of patients and are a major feature of the disease.[4] Both plasma and serum VEGF levels are markedly elevated in patients with POEMS syndrome and are considered a major diagnostic criterion. Skin changes such as hypertrichosis, sclerosis, or digital clubbing have been reported in 68% to 89% of patients. Patients with POEMS syndrome are often misdiagnosed with chronic inflammatory demyelinating polyradiculopathy (CIDP); however, nerve biopsies in patients with POEMS rarely show onion bulb formation or an inflammatory component. If inflammation is present, it is mostly scant with epineurial and perivascular infiltration, rather than the endoneurial and perivascular inflammation seen with CIDP.[5]

Plasma VEGF levels were elevated in our patient at 1101 pg/mL (≤96.2 pg/mL). Bone survey did not reveal the presence of sclerotic lesions. Given the polyneuropathy and monoclonal plasma cell proliferative disorder in conjunction with CD, elevated VEGF, skin changes, and volume overload, POEMS syndrome was diagnosed.

4. Which *one* of the following is *true* regarding treatment in this patient?

a. The presence of BM involvement will change the therapeutic approach
b. Radiation therapy can be curative
c. Radiation therapy is indicated despite the absence of bone lesions
d. Serial follow-up of VEGF levels does not add any value to her care
e. Her neurologic symptoms are expected to improve rapidly with therapy

Treatment differs depending on the presence of BM involvement. If there is no BM involvement and only a few isolated bone lesions are present, radiation therapy alone can control symptoms and may be curative.[5] In patients with disseminated disease (BM involvement or more than 2 skeletal lesions), radiation therapy is not considered curative, and the mainstay of treatment is based on alkylating agents with or without stem cell transplant.[5] For large bone lesions, however, radiation therapy may be used as an adjuvant treatment.[5] Our patient did not exhibit bone lesions. The VEGF levels correlate best with disease activity, and VEGF trends can be used to monitor response to therapy.[5] Neurologic recovery is often slow and may take up to 6 months before improvement is seen.[6]

Our patient had BM involvement consistent with disseminated disease. She was started on systemic therapy with cyclophosphamide and dexamethasone and completed 5 cycles. Adjuvant radiotherapy was not indicated because she did not have bone lesions. Three months after therapy, her VEGF levels decreased to 55 pg/mL. Six months later, her weakness and paresthesias improved.

5. Which *one* of the following factors would *not* influence the prognosis in this patient?

a. Renal function
b. Pulmonary hypertension
c. Young age
d. Elevated VEGF levels
e. Number of POEMS features

Some of the factors that correlate with poor prognosis include poor renal function, pulmonary hypertension, and advanced age.[7] These variables would influence the prognosis in this patient. The VEGF levels not only correlate with disease activity but also with poor response to therapy. Therefore, low VEGF levels (<1500 pg/mL) can predict a better response to therapy.[8] Survival does not seem to correlate with the number of POEMS features.[3]

Despite her age and normal renal function, 12 months after initial response to treatment, her VEGF levels began to increase, and there was concern about recurrence.

DISCUSSION

POEMS syndrome is a rare paraneoplastic syndrome secondary to an underlying plasma cell

dyscrasia. Its true incidence is unknown, but it occurs more often in men (63%) between their fifth and sixth decade of life.[3]

The acronym stands for some but not all of the clinical features of the disease, including polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes. A diagnosis of POEMS syndrome is made with the presence of all mandatory criteria (polyneuropathy and monoclonal plasma cell proliferative disorder), plus one major criterion (CD, sclerotic bone lesions, VEGF elevation) and one minor criterion (organomegaly, volume overload, endocrinopathy, skin changes, papilledema, thrombocytosis/polycythemia).[5]

*P*olyneuropathy is the dominant clinical feature of the disease. It presents as a progressive and symmetric peripheral neuropathy. Paresthesias or dysesthesias are common, although pain has been reported as the main feature in 15% of patients.[5] Muscle weakness typically follows sensory symptoms, resulting in difficulty climbing stairs, rising from a chair, or grabbing objects firmly. Over time, motor involvement may become severe enough to confine a patient to a wheelchair.[6] Other features may include a steppage gait, areflexia, and muscular atrophy responsible for weight loss seen in these patients. Papilledema occurs in at least 30% of patients and may be asymptomatic or associated with headaches, scotomas, or blurry vision.[3] Autonomic function and cranial nerves are unaffected.[5] Cerebrospinal fluid samples often include elevated protein levels (>50 mg/dL) and normal cell counts.[3] Electromyography reveals slow nerve conduction consistent with polyneuropathy and demyelination. Findings are similar to those of CIDP; however, there is diffuse nerve involvement with more axonal loss and damage to intermediate nerve segments. Additionally, nerve biopsies lack large onion bulb formations.[5,9]

*O*rganomegaly including splenomegaly, hepatomegaly, or lymphadenopathy occurs in up to 50% of patients.[3] Lymphadenopathy, when present, can be due to multicentric CD (angiofollicular lymph node hyperplasia), a lymphoproliferative disorder that is often associated with POEMS syndrome.[2]

*E*ndocrinopathy is present in up to 84% of patients.[10] It commonly manifests as hypogonadism followed by hypothyroidism, diabetes, and adrenal insufficiency.[11]

Protein electrophoresis reveals an *M* spike that is small, usually due to IgG or IgA, that is almost always λ type.[5] Free light chains are elevated in up to 90% of patients, and the ratio is normal in up to 18% of cases.[5,12]

*S*kin changes occur in up to 89% of patients and may include hyperpigmentation, hemangiomas, hypertrichosis, sclerosis, acrocyanosis, white nails, and digital clubbing. Extravascular volume overload can also occur, resulting in peripheral edema, ascites, and pericardial/pleural effusions.[5]

Other organ systems may also be affected. Pulmonary involvement can occur in 28% of patients, causing pulmonary hypertension, restrictive lung disease, cough, or neuromuscular weakness, occasionally leading to respiratory failure.[10] Renal dysfunction with proteinuria or elevated creatinine is rare but more likely to occur if CD is present.[6] Osteosclerotic lesions are present in up to 80% of patients and can be seen on computed tomography.[4,5] Finally, patients with POEMS syndrome are at a high risk of both arterial and venous thromboses and thus have an increased risk for stroke, myocardial infarction, limb gangrene, and Budd-Chiari syndrome.[3]

Laboratory work-up often reveals thrombocytosis and polycythemia, but anemia and thrombocytopenia may be seen if CD is present.[6] Thrombocytosis and BM infiltration have both been associated with an increased risk of cerebrovascular accidents.[13] Bone marrow biopsy findings include megakaryocyte hyperplasia and clustering with less than 5% of plasma cells. Clonal plasma cells are almost always (91%) λ type.[14] Serum and plasma VEGF levels are elevated and correlate with the disease activity. Serum levels are 10 to 50 times higher than plasma levels. This difference is thought to be secondary to VEGF release from platelets during in vitro processing; however, it is unclear which test is preferred.[5] Vascular endothelial growth factor likely plays a role in many clinical features of POEMS syndrome including organomegaly, edema, hemangioma formation, and increased vessel permeability. Vessel permeability could facilitate the leakage of toxic substances like thrombin and complement into nerves, inducing nerve injury.[6]

The treatment of POEMS syndrome depends on the extent of disease. In patients

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with no BM involvement and less than 2 bone lesions, radiation therapy alone can provide symptomatic relief and be potentially curative. In patients with BM involvement or more than 2 bone lesions, radiation therapy is not curative but can be used in conjunction with systemic therapy for large bony lesions.[5] Systemic treatment in POEMS syndrome is similar to that for other plasma cell dyscrasias (eg, multiple myeloma). Melphalan with dexamethasone has a reported 81% hematologic response rate and a 100% neurologic response rate.[5] Corticosteroids alone provide response in half of patients. Unfortunately, their effects are usually short lived.[5] Alternative regimens include cyclophosphamide with dexamethasone, thalidomide, lenalidomide, or bortezomib. Intravenous immunoglobulin and plasmapheresis have no proven benefit and are not supported by the literature. Although anti-VEGF therapy with bevacizumab has been attempted, it has no role in therapy.[5] The use of high-dose chemotherapy with autologous stem cell transplant is effective and safe and should be considered as first-line therapy in eligible patients.[5]

The VEGF levels, hematologic values, imaging, and reported symptoms are used to assess response to treatment. Skin manifestations are expected to improve within 1 month of therapy, whereas VEGF levels and neurologic symptoms can take at least 3 months.[5] Substantial clinical benefit does not always correlate with a complete hematologic response.[6]

The 10-year overall survival of patients with POEMS has improved since 2003 from 55% to 79%, likely due to evolving therapeutic and diagnostic tools.[15] The number of POEMS features does not correlate with prognosis.[3] A recently validated score identified age greater than 50 years, estimated glomerular filtration rate less than 30 mL/min per 1.73 m^2, pulmonary hypertension, and pleural effusions as poor prognostic markers.[7] Other factors like clubbing and respiratory symptoms are also associated with shorter overall survival.[6,10] Conversely, albumin levels greater than 3.2 g/dL, younger age, and complete hematologic response have been associated with better outcomes.[15]

Despite its rarity, POEMS syndrome is a diagnosis that should be considered by clinicians in patients presenting with peripheral neuropathy. The disease has a high morbidity and mortality that can be greatly impacted with early recognition and intervention.

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REFERENCES

1. Watson JC, Dyck PJ. Peripheral neuropathy: a practical approach to diagnosis and symptom management. *Mayo Clin Proc*. 2015;90(7):940-951.
2. Dispenzieri A, Armitage JO, Loe MJ, et al. The clinical spectrum of Castleman's disease. *Am J Hematol*. 2012;87(11):997-1002.
3. Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. *Blood*. 2003;101(7):2496-2506.
4. Kourelis TV, Buadi FK, Gertz MA, et al. Risk factors for and outcomes of patients with POEMS syndrome who experience progression after first-line treatment. *Leukemia*. 2016;30(5):1079-1085.
5. Dispenzieri A. POEMS syndrome: 2017 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2017;92(8):814-829.
6. Dispenzieri A. POEMS syndrome. *Blood Rev*. 2007;21(6):285-299.
7. Kourelis TV, Dispenzieri A. Validation of a prognostic score for patients with POEMS syndrome: a Mayo Clinic cohort. *Leukemia*. 2017;31(5):1251.
8. Scarlato M, Previtali SC, Carpo M, et al. Polyneuropathy in POEMS syndrome: role of angiogenic factors in the pathogenesis. *Brain*. 2005;128(pt 8):1911-1920.
9. Mauermann ML, Sorenson EJ, Dispenzieri A, et al. Uniform demyelination and more severe axonal loss distinguish POEMS syndrome from CIDP. *J Neurol Neurosurg Psychiatry*. 2012;83(5):480-486.
10. Allam JS, Kennedy CC, Aksamit TR, Dispenzieri A. Pulmonary manifestations in patients with POEMS syndrome: a retrospective review of 137 patients. *Chest*. 2008;133(4):969-974.
11. Gandhi GY, Basu R, Dispenzieri A, Basu A, Montori VM, Brennan MD. Endocrinopathy in POEMS syndrome: the Mayo Clinic experience. *Mayo Clin Proc*. 2007;82(7):836-842.
12. Wang C, Su W, Zhang W, et al. Serum immunoglobulin free light chain and heavy/light chain measurements in POEMS syndrome. *Ann Hematol*. 2014;93(7):1201-1206.
13. Dupont SA, Dispenzieri A, Mauermann ML, Rabinstein AA, Brown RD Jr. Cerebral infarction in POEMS syndrome: incidence, risk factors, and imaging characteristics. *Neurology*. 2009;73(16):1308-1312.
14. Dao LN, Hanson CA, Dispenzieri A, Morice WG, Kurtin PJ, Hoyer JD. Bone marrow histopathology in POEMS syndrome: a distinctive combination of plasma cell, lymphoid, and myeloid findings in 87 patients. *Blood*. 2011;117(24):6438-6444.
15. Kourelis TV, Buadi FK, Kumar SK, et al. Long-term outcome of patients with POEMS syndrome: an update of the Mayo Clinic experience. *Am J Hematol*. 2016;91(6):585-589.

CORRECT ANSWERS: 1. e. 2. a. 3. c. 4. a. 5. e.