POEMS Syndrome In a Patient Presenting with Chronic Inflammatory Demyelinating Polyneuropathy

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Peripheral neuropathy is a common diagnosis seen frequently by both neurologists and primary care physicians. Neuropathies can involve sensory, autonomic or motor pathways, and any combination of the above. Sensory involvement is most common, and patients usually present with pain, numbness, and/or paresthesias in the hands and feet, though patients with motor involvement may also complain of weakness. Worldwide, the most common cause of peripheral neuropathy is leprosy, but this is rarely seen in the United States, where the most common cause is diabetes. However, the list of possible etiologies for neuropathy is extensive, and a cause cannot be determined in over 25% of patients. No matter the patient presentation, physicians need to screen all patients for treatable causes of neuropathy.

This patient presented with the initial complaints of numbness and weakness and was at first thought to have chronic inflammatory demyelinating polyneuropathy (CIDP). Further workup, however, revealed an underlying malignancy and led to a completely different treatment regimen. This case emphasizes the importance of complete evaluation of any patient presenting with neuropathy.

CASE REPORT

This 51 year old man presented with numbness and weakness in his legs. His problems began one year prior with numbness on the lateral aspect of the right calf. Over the next several months he noticed numbness and tingling in his toes bilaterally. By two months prior to presentation, his sensory complaints had become much worse, and he was having trouble moving. Marching in a Memorial day parade, he had difficulty finishing the route because of weakness. He also experienced sexual dysfunction with loss of morning erections and difficulty attaining an erection. One month prior to presentation, he had trouble walking, climbing stairs, and getting in and out of cars. The sensory disturbance continued to worsen in his legs and involved his hands as well. He began to limp and could barely walk unassisted one week prior to presentation. Two days before presentation, he fell on a staircase landing and was unable to get up. He finally presented to the emergency department and was admitted for increasing weakness in his legs and a suspected demyelinating polyneuropathy.

The patient's past medical history was significant for hypertriglyceridemia and degenerative joint disease. He also had a 17 pack-year history of tobacco use and admitted to daily alcohol intake. There was no family history of neuromuscular disease.

At the time of his initial ER presentation, he was afebrile with a heart rate of 102 and a blood pressure of 151/83. His mental status and cranial nerves were within normal limits. Motor exam revealed strength to be 5/5 (MRC scale; 5=normal) in the upper extremities, 4/5 in the arms and legs, and 5/5 in the hands and feet. Bulk and tone were normal. Sensation was decreased to light touch and pinprick in the hands and below the hips bilaterally. Sensation was mildly decreased to vibration and temperature in the distal lower extremities. Coordination was intact to finger-to-nose testing, rapid alternating movements, and heel-to-shin testing. He was areflexic, and no Babinski signs were present. He could walk, but his gait was wide-based and unsteady. Lumbar puncture revealed a CSF protein of 107 mg/dL (normal < 45) with no cells. EMG/NCS was consistent with a diffuse demyelinating polyneuropathy. ESR, B12, folate, TSH and RPR were all within normal limits. CBC was within normal limits except for an elevated platelet count of 672,000. The patient was HIV negative. Serum protein electrophoresis was ordered but was still pending at the time of discharge. The patient was thought to have CIDP and was treated with a course of intravenous immunoglobulin (IVIG), which led to some improvement. He was discharged to a rehabilitation facility able to walk with a walker.

The patient initially did well at rehab but soon complained of worsening numbness and dysesthesias in his feet as well as increased weakness in his lower extremities and, to a lesser degree, in his upper extremities. A trial of oral prednisone (60 mg/day) did not lead to any improvement. He became bedbound and was re-admitted to Rhode Island Hospital three weeks after discharge.

At the time of his second admission he was nonambulatory. His strength was 4-5/5 in the upper extremities and 1-2/5 in the lower extremities. Sensory exam revealed decreased light touch and vibration in the legs bilaterally, decreased proprioception in the right leg, and intact pinprick and tem-
perature. Deep tendon reflexes were still absent. The patient had no remarkable skin lesions and no abnormal pigmentation or hair growth. A repeat LP showed no cells, but CSF protein remained elevated at 117 with a glucose of 67. A repeat ESR was 100. Serum protein electrophoresis from his first admission revealed a monoclonal protein spike with an IgG of 2810, and immunofixation showed a monoclonal IgG protein with lambda light chains. This study was repeated and revealed an IgG of 3220. Anti-GBM and anti-Hu antibodies were negative. A magnetic resonance imaging (MRI) of his L/S spine showed enhancement of the cauda equina, and a follow-up MRI showed a destructive mass with sclerotic edges at the S2-S3 level.

A biopsy of the mass was consistent with plasma cell myeloma, and bone marrow aspirate showed 18.8% of cells to be mature plasma cells consistent with plasma cell myeloma. Evaluation of his impotence complaint led to the diagnosis of hypogonadism with an abnormally low testosterone level. He was also found to have hepatosplenomegaly by CT. Upon further discussion, he admitted to orthostatic dizziness and thought his skin had become drier, rougher and his palms darker, though these skin changes could not be appreciated on exam. This constellation of symptoms was consistent with a diagnosis of POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome.

After the discovery of the plasma cell myeloma, the patient was treated with local radiation, steroids, and cyclophosphamide. Over a six-month period, his monoclonal protein decreased and eventually disappeared. With treatment of his malignancy, his neuropathy slowly improved. A second electrodiagnostic study confirmed the severity of his neuropathy and predicted a prolonged, likely incomplete, recovery. Seven months after diagnosis, the patient described a significant improvement in his sensory symptoms and mild motor improvement: arm strength improved to 4-5/5 and leg strength was approximately 3/5. The patient’s reflexes returned. However, he remained non-ambulatory.

**DISCUSSION**

This patient provides a classic example of a plasma cell dyscrasia and POEMS syndrome presenting as a chronic peripheral neuropathy. The case illustrates the clinical and laboratory similarities between CIDP and POEMS syndrome, the difficulty in diagnosis, and the importance of a complete workup in identifying the underlying cause of any neuropathy. POEMS syndrome is most closely associated with osteosclerotic myeloma (OM), but it can occur rarely in patients with multiple myeloma (MM), often with some osteosclerotic features. Our patient’s clinical and laboratory presentation was classic for POEMS syndrome associated with OM, but his bone marrow analysis was more typical of MM.

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Patients with POEMS syndrome often present with symptoms similar to CIDP. Both disorders begin with distal sensory complaints that are followed by progressive, ascending weakness. In POEMS patients, sensory complaints are typically the initial symptom and are usually present for a median of 1 1/2 years before the diagnosis is made. Beginning in the feet and progressing proximally, complaints of numbness, tingling, coldness and dyesthesias are common. As in the case of our patient, sensory loss usually affects light touch, vibration, and proprioception more than pain and temperature, consistent with involvement of large myelinated neurons. Motor involvement follows the sensory disturbance and eventually becomes the most pronounced feature. Weakness starts distally and progresses proximally over a period of months, and over one half of OM patients eventually experience severe motor impairment with trouble climbing stairs and walking. Cranial nerves are not involved except for occasional papilledema. One half of patients are areflexic.

Unlike CIDP, POEMS syndrome involves multiple organ systems, but non-neurologic symptoms are often mild and may be missed on initial presentation. Autonomic symptoms are not associated with POEMS, but complaints of sexual dysfunction are common, likely due to endocrine dysfunction. Endocrine problems can also lead to testicular atrophy, gynecomastia, amenorrhea, diabetes and thyroid dysfunction. Other non-neurologic features of POEMS syndrome include organomegaly, which most often affects the liver but can involve the spleen or lymph nodes. Patients frequently have skin changes such as hypertrichosis, hyperpigmentation, white nail beds, clubbing, skin thickening, and hemangiomas. Pulmonary hypertension has been reported as another systemic manifestation.

Like CIDP, the neuropathy of POEMS syndrome is predominantly demyelinating. Although nerve conduction studies can show a mixed picture with both axonal and demyelinating features, the decrease in conduction velocities is usually greater than the reduction in CMAP amplitudes, and the findings remain most consistent with demyelination. EMG is consistent with a neurogenic process and shows signs of denervation. Nerve biopsy shows axonal degeneration with secondary segmental demyelination. CSF protein is almost always elevated, and values over 100mg/dl are common. This increased protein is not accompanied by an increase in cellularity, and the finding of cytologic dissociation can mistakenly lead to a diagnosis of CIDP.

In patients with OM, a monoclonal protein is present in the serum of about 75% of patients, and it is present in 80-90% of patients with a plasma cell myeloma and POEMS syndrome. The identification of such a protein is usually the key to the correct diagnosis. The paraprotein can sometimes be obscured by other proteins, however, and immunofixation or electrophoresis may be necessary for detection. As in our patient, the M-protein is usually
IgG or IgA with lambda light chains, and Bence Jones proteins are rare. Bone marrow biopsy is normal or shows a less than 5% increase in normal appearing plasma cells. Over 50% of patients have thrombocytosis, and both polycythemia and leukocytosis are also common. In contrast to MM, renal insufficiency and hypercalcemia are rare.

Radiologically, OM is always associated with a sclerotic lesion, although lytic lesions may also be present. The sclerotic lesions can be single or multiple and most often involve the spine, pelvis or ribs. However, lesions involving the skull and extremities have been reported.

Our patient’s clinical history and laboratory findings were most consistent with a diagnosis of OM. However, his bone marrow biopsy was more consistent with MM, and his case illustrates the overlap between the two disease entities. In contrast to OM, patients with MM have a greater than 10% increase in plasma cells on bone marrow biopsy. The monoclonal protein is usually IgM or IgG and kappa light chains predominate in MM. There is also a greater amount of paraprotein in patients with MM, and protein is commonly detected in the urine. Radiological workup reveals primarily lytic lesions. Clinically, MM patients are older and typically present with bone pain, weakness, and fatigue. Neuropathy is uncommon, occurring in only 5-10% of patients. When present, it is primarily axonal and may be due to amyloidosis. Clinical presentation of the neuropathy is variable and may include a relapsing-remitting illness, a chronic sensorimotor polyneuropathy, a pure sensory syndrome, or a more typical amyloid neuropathy with sensory complaints, neuropathic pain, and autonomic involvement.

The prognosis in OM is better than in MM. There is a 60% survival rate at 5 years compared to 20% for patients with MM. If osteosclerotic lesions are limited, local radiation, or sometimes surgery, is the primary treatment. More widespread lesions require chemotherapy, usually a combination of melphalan and prednisone. Prednisone alone is relatively ineffective. Unfortunately, relapse is common, and only 1/3 of patients remain disease-free long term. Though conversion may take up to 20 years, about 2/3 of patients eventually develop MM.

The treatment for the neuropathy associated with OM is treatment of the tumor. In addition to the above therapies, there have been case reports of treatment with plasmapheresis, IVIG, interferon alpha-2b, chlorambucil and other chemotherapeutic agents, but the neuropathy usually responds poorly to medical treatments unless the underlying tumor is removed. With treatment of the malignancy, about one half of POEMS patients experience significant neurologic recovery. Improvement is usually slow, however, and may only become noticeable over 3-6 months, consistent with axonal loss and eventual nerve regrowth. Some patients continue to experience improvement for up to two years after treatment. Worsening or recurrence of neuropathy can indicate recurrent malignancy. In POEMS cases refractory to more conventional treatments, bone marrow transplantation has been beneficial.

Our patient’s course was typical of POEMS syndrome associated with OM. With radiation and chemotherapy, his M protein disappeared and his neuropathy slowly improved. His case emphasizes the importance of a complete workup in all patients presenting with neuropathy. Most patients with OM come to medical attention because of their neuropathic symptoms, and diagnosis is often made only as a result of a neuropathy evaluation. Other systemic problems associated with POEMS syndrome can be absent or very mild and may not alert the clinician to an underlying disorder. Moreover, POEMS syndrome can easily be mistaken for CIPD or another form of neuropathy. Thus, all patients presenting with neuropathy should undergo evaluation with serum protein electrophoresis and immunoelectrophoresis or immunofixation.

REFERENCES

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