A 39-Year-Old Man With Hip Pain and Respiratory Failure*

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A 39-year-old man presented with progressive shortness of breath and a 1-day history of decreased urine output. He had a history of mild COPD for which he occasionally used albuterol inhalers. Over the prior 3 months, however, he had developed gradually increasing dyspnea and was using his inhalers several times a day with little relief. He also described 3 months of progressive lower extremity weakness. He had suffered a series of falls, the last resulting in continuous right hip pain. Prior to hospital admission, he had been in bed for 2 months because of weakness and pain. His sister brought him to the emergency department because of dyspnea. He had a 75-pack-year smoking history and a distant history of alcohol abuse.

Physical Examination

The patient was tachypneic with a respiratory rate of 26 breaths/min but could speak in full sentences. His heart rate was 113 beats/min, and BP was 138/80 mm Hg. He was afebrile. The patient’s hemoglobin oxygen saturation while breathing room air was 38%. His examination was also notable for jugular vein distention, a prominent S2, decreased breath sound intensity at the bases, and pitting edema. He had no skin lesions, lymphadenopathy, or murmurs, and the findings of his abdominal examination were normal. A neurologic examination demonstrated intact cranial nerves, moderate upper and severe lower extremity weakness that was more prominent distally, burning dysesthesias elicited with palpation of the lower extremities, decreased vibratory sense and proprioception, generalized muscle wasting, and areflexia.

Laboratory Findings

Initial laboratory data revealed a hematocrit of 56%, a WBC count of 13,900 cells/μL, and a platelet count of 198,000 cells/μL. Arterial blood gas analysis on room air showed the following: pH, 7.30; PaO₂, 36 mm Hg; and PaCO₂, 76 mm Hg. The results of basic metabolic testing were remarkable for the following: serum potassium level, 5.2 mEq/L; bicarbonate, 28 mEq/L; and BUN, 44 mg/dL. The results of measurements for creatinine, glucose, and calcium levels, testing of liver function, and urinalysis were normal. His ECG showed tachycardia, an incomplete right bundle-branch block, and a shortened PR interval. His chest roentgenogram revealed a right pleural effusion and a rightward shift of the mediastinum that was consistent with right lower lobe collapse (Fig 1).

The results of a lower extremity Doppler ultrasound were negative for deep venous thrombosis. An echocardiogram showed normal left ventricular function and right ventricular enlargement. Pulmonary function testing showed an FEV₁ of 0.51 L (11% of predicted), an FVC of 0.97 L (17% of predicted), and an FEV₁/FVC ratio of 53%. The patient’s maximum inspiratory pressure was 10 cm H₂O (8% of predicted), and his maximum expiratory pressure was 22 cm H₂O (10% of predicted). He had severe claustrophobia and initially refused a ventilation-perfusion scan and CT scan.

The patient was treated with broad-spectrum antibiotics, heparin, and bronchodilators. Two days after hospital admission, the patient became cyanotic with oxygen saturations of 40% while receiving high concentrations of O₂ via a 100% nonrebreathing mask; he had a heart rate of 40 beats/min and a
systolic BP of 50 mm Hg. He was intubated emergently, and thick purulent secretions were suctioned from his airway with improvement in his oxygenation. A chest roentgenogram showed total right lung opacification. A chest CT scan revealed a right pleural effusion, atelectasis, and no evidence of pulmonary embolus. A CT scan of the pelvis (Fig 2) showed a destructive lesion of the right ileum just above the acetabulum measuring 4 cm in the anteroposterior dimension. Electromyography and nerve conduction studies demonstrated a severe demyelinating polyneuropathy with axon loss and diffuse denervation in the upper and lower extremities. A biopsy of the lytic lesion was performed, and the results are shown in Figure 3.

What is the most likely diagnosis?
Figure 2. CT scan of the pelvis.

Figure 3. Image of biopsy specimen from the lytic lesion of the ileum (hematoxylin-eosin, original × 10).
Diagnosis: Chronic demyelinating polyneuropathy with phrenic nerve involvement associated with multiple myeloma

Multiple myeloma is the most common plasma cell dyscrasia and constitutes 10% of hematologic malignancies. The median patient age at diagnosis is 67 years, and there is an increasing incidence with increasing age. There is a slight male preponderance (1.3:1), and the disease is more common in African Americans. The classic clinical features of multiple myeloma include anemia, renal insufficiency, recurrent bacterial infections, and painful osteolytic lesions. Diagnostic features include marrow plasmacytosis, monoclonal spike on serum protein electrophoresis, and lytic bone lesions. Solitary plasmacytoma is a closely related plasma cell dyscrasia in which patients have Ig spikes and a solitary lytic lesion. Solitary plasmacytomas are amenable to radiation therapy, and the mean survival time with this condition is >10 years. By contrast, the median survival time of patients with multiple myeloma is 3 years with standard therapy, which includes either melphalan and prednisone (MP) or a combination of vincristine, doxorubicin (Adriamycin) and dexamethasone (VAD). While therapy with VAD does not prolong survival time compared to therapy with melphalan and prednisone, this regimen leads to more rapid induction of remission and spares the stem cells so that subsequent bone marrow transplantation can be offered. There is no cure for multiple myeloma, but bone marrow transplantation and thalidomide therapy are under study as possible curative strategies.

Neurologic complications in patients with multiple myeloma are common and include spinal cord compression, radiculopathies, cranial nerve involvement, cerebral disorders resulting from hypercalcemia or renal insufficiency, meningeal myelomatosis, hyperviscosity, and peripheral neuropathies. A review of patients with multiple myeloma reported clinical polyneuropathies in 13% of patients and electrophysiologic evidence of peripheral neuropathy in 39% of patients. Diaphragmatic weakness is an uncommon sequela of multiple myeloma that can be established with the measurement of reduced maximum inspiratory and expiratory pressures. In patients receiving mechanical ventilation, the measurement of negative inspiratory pressures will provide similar information. Fluoroscopic examination and phrenic nerve stimulation may confirm the diagnosis but are not essential in all cases.

There are few published reports of respiratory failure related to peripheral neuropathy from multiple myeloma. Pulmonary involvement has been reported more commonly in patients with peripheral neuropathy associated with monoclonal gammapathy of unknown significance. In a small series, one of three patients with monoclonal gammapathy and paraproteinemia experienced respiratory failure. Restrictive lung ventilatory defects that were confirmed by pulmonary function testing and decreased diaphragmatic excursion also have been associated with the presence of IgM monoclonal gammapathy and peripheral neuropathy. In addition, pleural effusions have been described in patients with multiple myeloma, and the diagnosis of multiple myeloma can be confirmed by the finding of plasma cells in pleural fluid.

Although the link between plasma cell dyscrasias and peripheral neuropathies is well-recognized, the pathophysiology of this relationship is still not fully understood. In chronic demyelinating peripheral polyneuropathies that are associated with plasma cell neoplasias, the serum paraprotein is thought to play an important role. Findings of deposition of M components along myelin sheaths, monoclonal antibodies binding to peripheral nerve myelin, and the passive transfer of human monoclonal antibodies to mice resulting in demyelination lend support to this theory.

In patients with multiple myeloma and demyelinating polyneuropathy, there are no standard treatment guidelines. The use of a VAD chemotherapy regimen in patients with preexisting neuropathy may be problematic because vincristine can cause axonal-type peripheral neuropathy. Moreover, chemotherapy alone does not help the polyneuropathy. The combination of chemotherapy with radiation therapy, plasma exchange, or IV Ig has been successful in some patients.

Clinical Course

The results of the current patient’s serum protein electrophoresis showed a monoclonal spike, and serum immuno fixation showed a band of restricted electrophoretic mobility in the IgG lane with a corresponding band in the lambda lane. A bone marrow specimen obtained during a biopsy of the hip opposite the lytic lesion was hypercellular with atypical plasma cells. The patient received a diagnosis of chronic demyelinating polyneuropathy associated with IgG multiple myeloma. A 5-day course of IV Ig therapy was initiated, which resulted in a slight improvement in strength but had no significant effect on diaphragmatic muscle strength. Overall, negative inspiratory pressures remained markedly diminished (range, 16 to 20 cm H₂O), and the patient remained ventilator-dependent throughout his hospital course. Chemotherapy with VAD was initiated despite the patient’s poor functional status,
with the hope that treatment of the underlying malignancy would result in an improvement of his paraproteinemia and polyneuropathy. However, he developed febrile neutropenia and, despite receiving broad-spectrum antibiotic therapy, died of pseudomonal sepsis.

An autopsy demonstrated bilateral pneumonias, a healing myocardial infarct, heart failure, pleural effusions, and splenic infarcts. The results of the testing of specimens from the peripheral nerves, heart, kidney, and lungs were negative for amyloid. The bone marrow showed bizarre plasmacytoid forms that stained positive for CD138, a plasma cell marker. Such cells were also present in the carinal and periaortic lymph nodes. Peripheral nerve specimens showed a moderate loss of large, myelinated axons in the sciatic nerve and severe loss of large myelinated axons in the tibial and popliteal nerves.

**Clinical Pearls**

1. *Peripheral neuropathy is a common complication of multiple myeloma. Phrenic nerve involvement with associated respiratory failure is an uncommon complication.*

2. *Electromyography and nerve conduction studies can help in the diagnosis of polyneuropathy associated with plasma cell dyscrasias.*

3. *Treatment with chemotherapy in conjunction with radiation therapy, plasma exchange, or IV Ig has been successful in some patients. Chemotherapy alone does not help the polyneuropathy, and the stability or progression of the neuropathy may be independent of the course of the multiple myeloma.*

4. *Hypercarbic respiratory failure in a young patient should prompt the consideration of diaphragmatic weakness as a possible etiology. Diaphragmatic weakness may be quantified noninvasively through the measurement of maximum inspiratory and expiratory pressures. A fluoroscopic evaluation of diaphragmatic movement or phrenic nerve stimulation may confirm the diagnosis if uncertainty persists.*

**Suggested Readings**


