An Atypical Case of Neurolymphomatosis

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Abstract
The diagnosis of neurolymphomatosis can be highly challenging requiring a high index of suspicion. This paper discusses a clinical case and workup for secondary neurolymphomatosis. A patient with a history of diffuse large B-cell lymphoma presented as an acute, ascending, progressive neuropathy mimicking acute inflammatory demyelinating polyradiculopathy with subtle differences. No response to intravenous immunoglobulins was seen though he had transient improvement after concurrent plasmapheresis and oral steroids. Extensive work-up eventually lead to a diagnosis of neurolymphomatosis by sural nerve biopsy. Multiple case reports suggest encouraging results from chemotherapy combinations which include high-dose methotrexate.

Introduction
Neurolymphomatosis is characterized by a direct infiltration of the peripheral nervous system by lymphomatous cells.1 Nervous system involvement by Non-Hodgkin (NH) lymphoma is seen in approximately 10-25% of cases, however, peripheral neuropathy associated with NH lymphoma is much rarer, affecting 0.1-2% of all cases.2 Patients can present with different patterns including a painful plexopathy or radiculopathy, cranial neuropathy, or peripheral neuropathy (painful or painless).3 In most reported cases, workup usually consists of some form of non-invasive imaging--either MRI or positron emission tomography (PET) scan--or cerebrospinal fluid (CSF) analysis. Median time to diagnosis has ranged from 2 weeks to 9 years depending on the study.4 Most patients had abnormal electromyography, typically an axonal neuropathy, rarely demyelinating.

Case Presentation
A 72-year-old Caucasian male with a history of diffuse large B-cell lymphoma (negative PET scan 2 months prior to presentation and last chemotherapy one year prior), presumed interstitial lung disease secondary to chemotherapy, and hypertension presented with acute-onset of bilateral burning foot paresthesias which progressed to ascending foot numbness and weakness over the course of four days. He had concurrent worsening shortness of breath present over the preceding two weeks, to the point of requiring continuous nasal cannula oxygen. There was no history of gastrointestinal illness, but he reported intermittent fevers and chills during the prior three months. The history of ascending numbness, weakness, and shortness of breath was highly suspicious for acute inflammatory demyelinating polyneuropathy (AIDP). However, the neurologic exam was less suggestive of AIDP initially as he was hyperreflexic at the knees and ankles. MRI imaging of the entire spine with and without IV contrast revealed degenerative disc disease causing moderate spinal cord compression at C4-5, severe spinal cord compression at L2-3 and foraminal narrowing at L4-5. Of note, no enhancing lesions were identified on that scan. As his clinical status deteriorated with worsening respiratory status and weakness, neurosurgical intervention for the spinal stenosis was deferred until he medically stabilized. Nerve conduction studies (NCS) of the lower extremities on day 7 after presentation revealed decreased conduction velocities, prolonged F waves and decreased action potentials suggestive of a demyelinating process. Needle electromyography (EMG) revealed decreased recruitment in the gastrocnemius and peroneal longus but no fibrillations. CSF sampling revealed 255 red blood cells, 14 nucleated cells (53% polymorphonuclear cells, 43% lymphocytes), protein of 106 and glucose of 49 (serum 120) with no abnormal morphology.
He was started on intravenous immunoglobulin (IVIG) for presumed AIDP. Despite the IVIG, his weakness progressed to complete paralysis in the lower extremities, absent reflexes, and bilateral hand weakness. He underwent another EMG/NCS in week 3 which revealed decreased conduction velocities in the bilateral upper extremities and prolonged F waves with absence of response in the bilateral lower extremities. Needle EMG demonstrated fibrillations in the right anterior tibialis and decreased recruitment in the left anterior tibialis, gastrocnemius, and vastus lateralis.

At this point, the workup was broadened to include a paraneoplastic panel (serum and CSF), full body CT imaging for investigation of primary malignancy, paraproteinemia labs, and bone marrow biopsy (for additional blood dyscrasia evaluation). All of this additional workup ended up being negative. A five-day course of plasmapheresis was then started. Several days into the plasmapheresis, the patient was also started on oral steroids (prednisone) to treat his presumed interstitial lung disease. He briefly showed some clinical improvement—increased strength in the bilateral lower extremities and return of 1+ patellar reflexes—but his symptoms worsened again shortly after completing the courses of plasmapheresis and prednisone.

Given the continued progressive neuropathy, more directed testing was obtained to attempt to link the patient’s history of B-Cell lymphoma with his symptoms. Peripheral flow cytometry revealed peripheral blood involvement by a lambda-restricted CD5+ B-cell lymphoma. A sural nerve biopsy revealed a marked axonal neuropathy with clusters of endoneurial, CD20- and PAX5-positive, atypical lymphocytes infiltrating the nerve, confirming the diagnosis of neurolymphomatosis (NL) (Figure 1).

Fluorodeoxyglucose (FDG)-PET revealed increased metabolism in the spleen but was otherwise unremarkable. As his respiratory status continued to decline, the patient elected to transition to hospice prior to any further treatment with chemotherapeutic agents.

Discussion

The case above demonstrates a NL B-cell lymphoma presenting as an AIDP mimic. CSF findings are neither sensitive nor specific; pleocytosis and elevated protein are present in only 60% of NL cases. EMG findings can be consistent with a demyelinating process which may lead to workup and management of presumed AIDP. NL patients have been reported as having symptomatic improvement on immunomodulating therapy, which can falsely “confirm” a diagnosis of AIDP as was seen in our patient. Even imaging such as FDG-PET with positivity rates as high as 87-91% was negative for nerve involvement in our case. In the setting of disease progression and non-diagnostic testing (including advanced imaging modalities), the importance of tissue diagnosis cannot be overstated.

Even if a diagnosis of NL is obtained, management decisions are purely anecdotal in the literature. Current systemic chemotherapy treatment options include intravenous high dose methotrexate, high dose cytarabine, or combination chemotherapy including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. Intrathecal chemotherapy treatment with methotrexate is also considered for patients with cranial nerve, spinal nerve, or high CSF cell count. A recent article suggests relatively improved outcomes with high-dose methotrexate, and an alkylating agent in a retrospective evaluation of 5 patients with histologically proven NL. With the typical association with aggressive B-cell lymphomas, overall survival is on the order of months to a few years regardless of treatment modality. Given the rarity of this diagnosis, it is possible there is a selection bias with a predilection of diagnosing patients with more rapidly progressive disease and potentially under-diagnosing patients with a more indolent course, especially considering the
broad spectrum of pathogenesis within the NH lymphomas.

Conclusion

Despite advances in imaging techniques and serologic studies, neurolymphomatosis remains a difficult diagnosis even when there is clinical suspicion. In some situations, like the one described above, a biopsy may be the only definitive option to obtain the diagnosis when other testing is inconclusive.

References