Clinical Reasoning: Multifocal neuropathies in a patient with Waldenstrom macroglobulinemia and prior borreliosis

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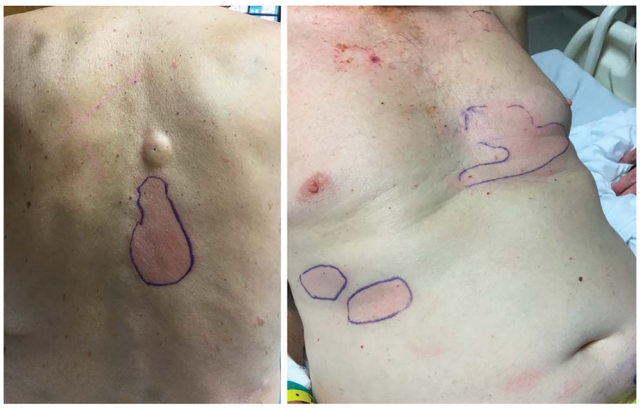
Section 1

A 77-year-old man presented with 1 week of back pain, night sweats, confusion, jaundice, and pruritus with patchy, blanchable erythematous lesions over his trunk (figure 1). Neurologic examination was normal, but a lumbar spine MRI showed diminished bone marrow signal. He was thrombocytopenic (13×10^9/L) and anemic (7.2 g/dL) with an immunoglobulin M (IgM) kappa monoclonal gammopathy and bone marrow biopsy consistent with Waldenstrom macroglobulinemia (WM). He was initiated on 60 mg prednisone daily and rituximab. Skin biopsy revealed nonspecific dermal edema with perivascular inflammation. Two weeks into admission, he developed left lower motor neuron facial droop, and was kept on the prednisone started 2 days prior for his WM. Shortly after that, it was noted that his *Borrelia burgdorferi* enzyme immunoassay (EIA) screen and supplemental *B burgdorferi* IgM immunoblot were positive, while the immunoglobulin G immunoblot was negative. Three weeks later, his facial palsy had resolved, but given extensive tick exposure history, he was treated with 3 weeks of doxycycline. CSF collection was deferred due to thrombocytopenia.

Nine months later, the patient presented to neurology with 3 weeks of progressive left ptosis, bilateral upper extremity weakness, and neuropathic pain in a C5 distribution. MRI head and cervical spine were unremarkable. CSF showed a mildly elevated protein of 65 mg/dL with normal cell count and glucose, 7 unique oligoclonal bands, and negative cytology. Because of the prior Lyme disease (LD), an LD CSF antibody index (AI) was performed, which was elevated at

Figure 1 Multifocal, blanchable, erythematous patches over the trunk, some with a dusky center



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6.0 (normal 0.6–1.2). He received IV ceftriaxone, but his condition declined, with the patient developing binocular horizontal diplopia and dysphagia, prompting admission.

Examination showed left ptosis, a pupil-sparing third nerve palsy, and left lower motor neuron facial palsy. Muscle testing revealed right greater than left weakness (4/5 range) in the deltoids, biceps, triceps, wrist and digit extensors, and interossei. In the lower extremities, the patient had 4/5 weakness in L5 innervated muscles. Reflexes were absent in the right upper limb and left triceps with hypoactive left biceps and brachioradialis reflexes. Ankle reflexes were absent with trace response at the knees. Toes were downgoing. He had mild length-dependent sensory loss in the feet with relative preservation in upper extremities. Electrodiagnostic studies showed a diffuse axonal-predominant sensorimotor polyradiculoneuropathy in the cervical segments and left L5 nerve root. MRI brain, orbits, and cervical spine were negative, but lumbar MRI showed thickening of the nerve roots with associated enhancement (figure 2A). Antineutrophil cytoplasmic antibodies, antinuclear antibodies, lactate dehydrogenase, HIV serology, repeat LD serology, and a paraneoplastic panel in serum and CSF were negative. Erythrocyte sedimentation rate was 114 mm/h and C-reactive protein was 87.4 mg/L.

Questions for consideration:

1. Where do you localize this process?
2. What is your differential diagnosis?
3. Did the patient have LD and is his latest presentation consistent with neuroborreliosis?

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Section 2

The patient presented with subacute weakness and diplopia. His examination, with patchy asymmetric weakness and hyporeflexia in multiple nerve root distributions, as well as relatively preserved sensation in spite of radicular pain, was suggestive of a polyradiculoneuropathy, which was confirmed by EMG. He also had multiple cranial neuropathies.

The patient's first neurologic symptom was an isolated left-sided facial palsy occurring 2 weeks into his original presentation. The differential diagnosis then included neurologic involvement of the newly diagnosed lymphoproliferative disorder (Bing-Neel syndrome), infectious neuritis, or idiopathic facial palsy. Given possible exposure in a Lyme-endemic region, LD testing was obtained, which demonstrated a positive LD EIA screen and IgM immunoblot, with a negative IgG immunoblot, suggesting acute infection. Diagnostic testing for LD relies on detection of antibodies to *B burgdorferi* using the standard 2-tiered testing algorithm, which starts with an initial EIA or immunofluorescence assay.[1] Positive samples require supplemental anti–*B burgdorferi* IgM or IgG immunoblot testing, depending on the duration of symptoms. The Centers for Disease Control and Prevention (CDC) requires detection of IgM antibodies to at least 2 of 3 antigens and detection of IgG class antibodies to at least 5 of 10 antigens to be considered positive. Importantly, an isolated positive IgM immunoblot result is only meaningful during the first 4 weeks of symptoms. For symptoms longer than 4 weeks, only the IgG immunoblot should be considered to determine the presence or absence of LD. Our patient met CDC criteria on initial presentation as he presented within 4 weeks of symptom onset. Although he did not have the classic erythema migrans, his rash had multiple red lesions with dusky centers, which is not uncommon in early borreliosis and spontaneous recovery without treatment has been reported.[2]

When the patient later presented with progressive deficits and a positive LD CSF AI, neuroborreliosis was considered. The problem with this diagnosis is the time course. Whereas his initial presentation with left-sided Bell palsy, rash, and a positive serum LD IgM could be consistent with neuroborreliosis, his symptoms had resolved and he had completed appropriate antibiotics. Neuroborreliosis is almost always monophasic and so emergence of new symptoms 9 months later would more likely be caused by reinfection, if truly due to LD. It is important to remember that the LD CSF AI can remain positive for years following adequate treatment.[3] Detection of *B burgdorferi* by real-time PCR (RT-PCR) in CSF would provide definitive evidence of active infection; however, a negative RT-PCR does not rule out infection, due to low sensitivity.[4] Thus recent Infectious Diseases Society of America draft guidelines for neuroborreliosis recommend against using RT-PCR for diagnosis.[4]

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is another consideration and the patient's CSF did demonstrate cytoalbuminologic dissociation. The asymmetric presentation and electrodiagnostic studies demonstrating primarily axonal changes would be atypical, but could be present in axonal forms of AIDP. Similarly, anti-myelin-associated glycoprotein peripheral neuropathy usually presents as a symmetric, primarily sensory demyelinating neuropathy with ataxia and tremor. Vasculitic neuropathies are usually multifocal and workup for systemic vasculitis was negative. Paraneoplastic disease was unlikely with negative antibodies in serum and CSF.

Although root enhancement on MRI can be seen with immune-mediated polyradiculoneuropathies, this is typically more diffuse; our patient's pattern of focal enhancement is suggestive of an infiltrative process, such as a neoplasm (figure 2, A–C). Neurosarcoidosis can also focally enhance; however, in this context, direct peripheral nerve involvement of lymphoma (neurolymphomatosis) is more likely.

Waldenstrom macroglobulinemia rarely infiltrates the peripheral nervous system,[5] but other lymphomas can present with multiple peripheral and cranial neuropathies. About 10% of patients with low-grade lymphomas undergo transformation to diffuse large B-cell lymphoma (DLBCL).[6] Although uncommon, this diagnosis explains all of the patient's findings.

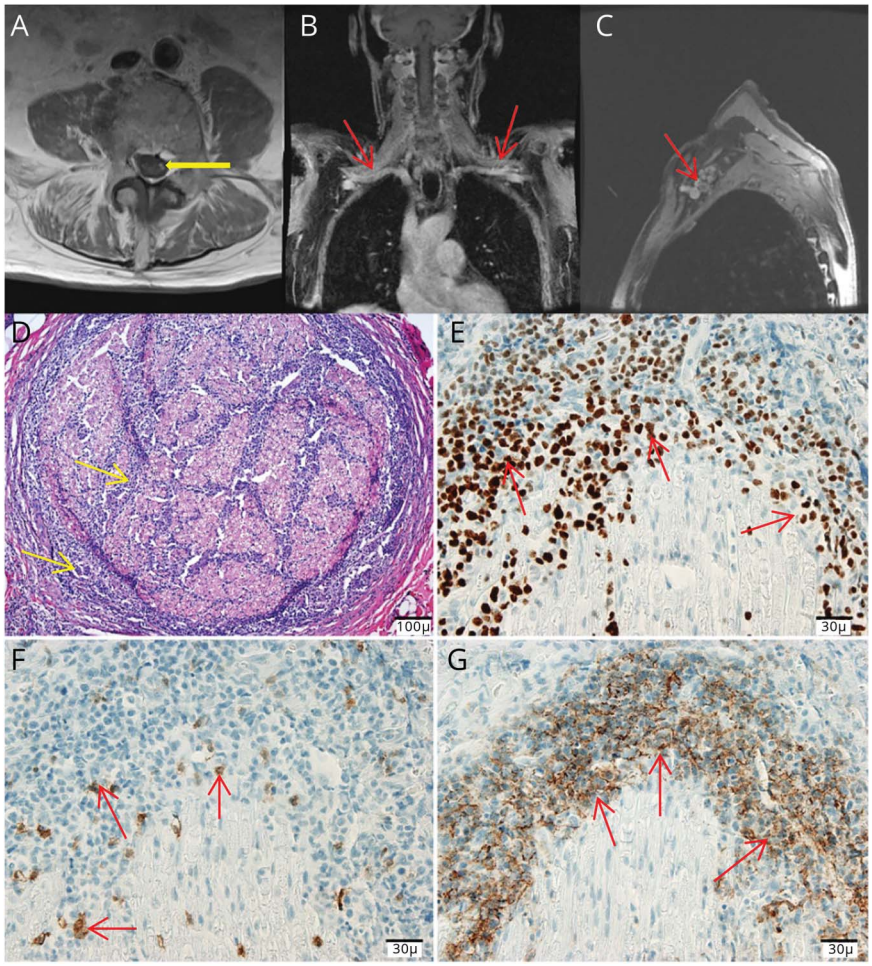
To further evaluate for neurolymphomatosis, an FDG-PET scan was ordered. FDG-PET is the most sensitive and specific imaging modality in detecting lymphoma; however, other inflammatory or infectious causes can be FDG-PET avid. Tissue pathology remains the gold standard in diagnosing lymphoma and is the only way to differentiate between low-grade vs DLBCL, which has treatment and prognostic implications.[7] Nerve biopsy is important in diagnosing amyloidosis, inflammatory disorders, infections, and neurolymphomatosis. Targeted fascicular biopsy should be considered in rapidly progressive neuropathies with electrophysiologic or radiographic evidence of disease.[8] PET CT showed moderate brachial plexus hypermetabolism. MRI of the brachial plexus was obtained to assist in biopsy planning, which demonstrated T2-hyperintense enlargement of both plexi with peripheral enhancement (figure 2, B and C). The patient underwent biopsy of the right lateral cord and radial nerve. Initial radial nerve pathology demonstrated lymphoplasmacytic lymphoma with large lymphoid cells, but was insufficient for DLBCL. The samples sent from the right lateral cord, however, demonstrated lymphocytes with cellular markers consistent with DLBCL (figure 2, D–G).

The question remained as to whether the patient ever had LD, given negative repeat serology. RT-PCR for *B burgdorferi* was performed on the remaining skin biopsy, which was positive. Collectively, this indicates that the patient did have an acute, disseminated LD infection during his initial admission, which manifested with skin lesions and facial palsy.

Discussion

This case illustrates several important points. First, LD CSF AI is very sensitive for neuroborreliosis, but must be

Figure 2 MRI and nerve biopsy results



T1 postgadolinium MRI of lumbar spine demonstrates focal enhancement (yellow arrow) and thickening of nerve roots at filum terminale and L5 (A). Postgadolinium coronal LAVA Flex Water MRI (B) and left sagittal spoiled gradient recalled acquisition MRI of brachial plexi (C). Diffuse enlargement of bilateral plexi is seen along with associated peripheral enhancement (red arrows). Transverse paraffin hematoxylin & eosin section demonstrates diffuse and dense mononuclear cell infiltrate in the endoneurium and perineurium (D, yellow arrows). Immunohistochemical preparations for PAX-5 (E), CD3 (F), and CD20 (G) highlight the B-cell predominance in the lymphocyte infiltrate (red arrows). The immunophenotypic profile supports the diagnosis of diffuse large B-cell lymphoma.

interpreted appropriately. The patient's initial facial palsy was likely due to neuroborreliosis, as the patient met the CDC criteria, and had a rash that tested positive by RT-PCR for *B burgdorferi*. The positive LD CSF AI documented 9 months later likely represented persistent intrathecal antibody production after adequate treatment—an important point for clinicians to consider.[3] Importantly, while CSF analysis is not required to establish neuroborreliosis in symptomatic seropositive patients, it may be helpful in select, clinically confounding cases.[9]

Notably, our patient's repeat serology was negative. Failure to seroconvert has been reported with early initiation of treatment during acute infection.[10] Rare cases of neuroborreliosis with a positive LD CSF AI result, yet negative serum serology has been reported in otherwise healthy individuals and in patients with acquired humoral deficiency.[11] In this case, the repeat negative serologic result is likely due to dissipation of the IgM antibodies, while the lack of IgG seroconversion could be due to acquired humoral deficiency from rituximab.

The second teaching point is that the emergence of multifocal peripheral neuropathies with or without pain in a patient with WM should prompt the consideration of neurolymphomatosis. Whereas neurolymphomatosis can rarely be caused by WM, DLBCL is the most common cause, and so transformation should be considered in these cases. Nevertheless, the diagnosis can be difficult to make and may be delayed by several years.[12]

Treatment and follow-up

The patient was treated successfully with high-dose methotrexate, rituximab, temozolomide, and ibrutinib. He experienced a relapse within a year, however, and eventually died of an opportunistic infection.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Benjamin Cox, MD	Mayo Clinic, Rochester, MN	Composed manuscript and figures
Michelle Mauermann, MD	Mayo Clinic, Rochester, MN	Manuscript editing, revision for intellectual content
Elitza Theel, PhD	Mayo Clinic, Rochester, MN	Manuscript editing, revision for intellectual content editing
Michel Toledano, MD	Mayo Clinic, Rochester, MN	Manuscript editing, revision for intellectual content

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