Clinical Reasoning:
A 47-year-old woman with left shoulder pain after a fall

SECTION 1
A 47-year-old right-handed woman fell to the ground while dancing. She hit her head and neck. However, she did not lose consciousness and continued to dance. Three days later, she developed severe sharp and burning left shoulder pain radiating into her left arm. The pain was associated with weakness and numbness. She also noticed right facial numbness. On review of systems, she had no visual, swallowing, speech, or bowel/bladder disturbances. Prior to the incident, she was in good health and took no medications. She drank alcohol only socially, and had a remote history of social smoking.

Examination 5 weeks later revealed marked left deltoid, left infraspinatus, and left biceps weakness. Left biceps and brachioradialis reflexes were absent. Sensation to pinprick was decreased in the first 2 digits of the left hand. An MRI of the cervical spine showed no disc herniation, cord lesion, or foraminal stenosis. EMG and nerve conduction studies (NCS) showed fibrillations and loss of motor unit potentials in the C5-6 innervated muscles. Sensory potentials were intact, consistent with a radiculopathy rather than a plexopathy. The working diagnosis was left cervical radiculitis and the patient was prescribed gabapentin, hydrocodone, and prednisone.

Three weeks later, the patient’s left shoulder pain and weakness had worsened. The pain prevented her from having good quality sleep. She also had new right shoulder pain and difficulty lifting her right shoulder. The combination of prednisone, gabapentin, and hydrocodone only transiently improved her symptoms. Examination now also revealed weakness in the right deltoid, right biceps, and right infraspinatus.

Question for consideration:
1. What is the differential diagnosis for progressive bilateral arm weakness associated with pain and numbness?
SECTION 2
This patient presented with progressive bilateral arm weakness, arm numbness, and shoulder pain (left greater than right). The anatomical distribution given the symmetrical deltoid, biceps, and infraspinatus weakness was consistent with bilateral C5-6 radiculopathies. The differential diagnosis of bilateral cervical radiculopathies can be divided into compressive and noncompressive etiologies (table). Because the patient presented with progressive, painful, bilateral, asymmetric weakness after a fall in a specific anatomical distribution, cervical disc prolapse and neoplasm remained diagnostic considerations. However, another differential diagnosis was traumatic root avulsion. This was believed to be less likely given the 3-day interval between the injury and the onset of symptoms and the subsequent progressive nature of the contralateral weakness.

Question for consideration:
1. What is the next step in the management of this patient’s symptoms?

<table>
<thead>
<tr>
<th>Cervical radiculopathy causes</th>
<th>Etiologies</th>
<th>Red flags to identify</th>
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</thead>
<tbody>
<tr>
<td>Compressive</td>
<td>Herniated disc</td>
<td>Radiating neck pain into the upper limb with numbness, tingling, and weakness</td>
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<td></td>
<td>Nerve root avulsion</td>
<td>Acute onset, associated with trauma</td>
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<td></td>
<td>Thoracic outlet syndrome</td>
<td>Weakness of muscles in lower trunk of brachial plexus, ulnar nerve sensory loss</td>
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<td>Cervical spondylosis</td>
<td>Neck, shoulder suboccipital pain and headache, radicular symptoms, and cervical spondylotic myelopathy</td>
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<td>Noncompressive inflammatory</td>
<td>Peripheral nerve sheath tumor</td>
<td>Palpable (or radiographically visible) mass involving a peripheral nerve, loss of nerve function, or pain; movement of limb can exacerbate pain</td>
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<td>Diabetes</td>
<td>History of diabetes; monophasic pain followed by weakness; involves motor, sensory, and autonomic fibers; begins focally and often evolves into a multifocal condition10</td>
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<td></td>
<td>Brachial plexitis (Parsonage-Turner, postvaccination reaction)</td>
<td>Shoulder and arm pain; rapid and severe atrophy follows weakness approximately 3–4 weeks later; typically does not follow a single root or nerve distribution</td>
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<tr>
<td>Noncompressive infectious</td>
<td>Sarcoïdosis</td>
<td>Rare; can have rapid response to steroids</td>
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<td></td>
<td>Giant-cell arteritis</td>
<td>Headache, occipital pain, neck pain, temporal pain, good response to steroids</td>
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<tr>
<td>Noncompressive neoplastic</td>
<td>Cytomegalovirus</td>
<td>Usually immunocompromised patients with HIV</td>
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<td>Varicella-zoster virus (herpes zoster)</td>
<td>Painful vesicular rash (shingles) in a dermatomal distribution; deep, burning, or aching electric-like pain that is often associated with paresthesias, dysesthesia, and hypoesthesia</td>
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<td>Lyme disease</td>
<td>Untreated late-stage Lyme disease</td>
</tr>
<tr>
<td>Noncompressive neoplastic</td>
<td>Lymphoma</td>
<td>Aching, burning pain (resulting in insomnia and lack of appetite), asymmetric distribution, progressive, unrelenting onset, and rapid evolution</td>
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<tr>
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<td>Carcinomatous meningitis</td>
<td>Cerebral involvement (headache, lethargy); cranial nerve involvement; spinal root involvement with nuchal rigidity and neck and back pain, or invasion of the spinal roots</td>
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<td></td>
<td>Melanoma</td>
<td>Can occur in same distribution as herpes zoster with similar dermatologic appearance</td>
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</table>
SECTION 3
Given the rapid progression and severe pain, the patient was admitted to the hospital. Strong narcotics were required to control her pain. EMG/NCS were repeated, showing bilateral C5-6 radiculopathies. Complete blood count, biochemistry, serum lactate dehydrogenase, and cytomegalovirus, varicella-zoster virus, HIV, and Lyme serology were all normal. Erythrocyte sedimentation rate was normal but C-reactive protein was elevated at 2.3 mg/dL (normal <0.5 mg/dL). CSF examination revealed an increased lymphocyte count (17 nucleated cells/mm³ with 14 lymphocytes/mm³) with normal protein, glucose, and angiotensin-converting enzyme. CSF cytology showed rare large atypical lymphocytes with nuclear folding and multiple nucleoli. CSF flow cytometry was suspicious for a clonal B-lymphocyte population but was not sufficient for diagnosis. Flow cytometry performed on peripheral blood showed no clonal B-lymphocyte population. A repeat cervical MRI showed an enhancing mass along the left C5 nerve root, consistent with a neurogenic tumor (figure, A and B). The lesion was restricted on diffusion-weighted imaging and dark on apparent diffusion coefficient mapping, consistent with lymphoma (figure, C and D).

Figure Primary neurolymphomatosis and CNS lymphoma

(A) Precontrast axial T1-weighted image shows thickening of the left C5 nerve root (red arrow). (B) Postcontrast axial T1-weighted image with fat saturation shows greater enhancement of the left C5 nerve root (red arrow), relative to the right C5 nerve root. (C) Axial diffusion-weighted image demonstrates restricted diffusion in the area of the left C5 nerve root (red arrow). (D) Axial apparent diffusion coefficient (ADC) map reveals a low ADC value (524 μm²/s) in the area of the left C5 nerve root (red arrow). (E) Axial fluid-attenuated inversion recovery image of the brain shows left periventricular hyperintensity (white arrow). (F) Postcontrast axial T1-weighted image with fat saturation demonstrates enhancement of the left periventricular lesion (white arrow). (G) Axial diffusion-weighted image reveals restricted diffusion of the left periventricular lesion (white arrow) with an associated low ADC value (484 μm²/s) (not shown). (H) Coronal PET scan demonstrates abnormal metabolic uptake in the left cervical spine (black arrowhead). (I) Immunoperoxidase stain for CD20 (B-cells) of the left C5 nerve root biopsy shows diffuse positivity of the tumor cells and absent staining in the ganglion cells and nerve roots. (J) Hematoxylin & eosin stain of the left C5 nerve root biopsy reveals ganglion cells (black arrow) infiltrated by diffuse large B-cell lymphoma.
An MRI of the brain showed left periventricular and callosal hyperintensities with faint enhancement and diffusion restriction (figure, E–G). Given the cervical localization, the imaging results, and the clinical presentation, lymphoma was an important consideration. A biopsy of the left C5 nerve root lesion showed changes consistent with diffuse large B-cell lymphoma (figure, I and J). CT of the chest, abdomen, and pelvis was unremarkable. PET scan from brain to mid-thigh showed increased uptake only in the left cervical neuroforamina (figure, H). Bone marrow biopsy was normal. The final diagnosis was primary neurolymphomatosis (NL) and CNS lymphoma. Although no abnormal uptake was seen in the PET scan of the brain, retrospective review of the MRI cervical spine showed possible abnormal uptake in the right cervical nerve roots, suggesting bilateral dissemination to the nerve roots. Chemotherapy was initiated with Hyper CVAD A (cyclophosphamide, vincristine, Adriamycin, and dexamethasone) and Hyper CVAD B (intrathecal cytarabine and methotrexate).

**DISCUSSION** Typically, peripheral neuropathy associated with lymphoproliferative disorders is a result of a paraproteinemia (mostly immunoglobulin M). Lymphoma directly causing a polyneuropathy by infiltration along nerve sheaths is rare. Primary NL refers to neurotropic neoplastic cells infiltrating nerves in the setting of a hematologic malignancy as the first manifestation of the malignancy. The initial description by Lhermitte and Trelles of peripheral neuropathy due to lymphomatous invasion of the peripheral nerves was published in 1934. A later study described 10 cases with nervous system involvement out of 7,000 autopsies on patients with lymphoma. Most lymphomatous invasions are difficult to diagnose. In a study over a 16-year period, only 30% of patients were identified within the first 8 years of symptoms.

Non-Hodgkin lymphoma (NHL) is classified as B-cell or T-cell type, with B-cell types being more common. NHL uncommonly causes peripheral and CNS complications. NHL can infiltrate cranial nerves, roots, plexi, and peripheral nerves from a regional focus or hematogenously. The site of the initial lesion is often unknown when lymphoma presents as NL. Proposed mechanisms of this presentation seen in 7% of patients include possible lymphoma cell neurotropism, which could infiltrate from adjacent lymph nodes and spread along nerves. The incidence of concomitant CNS involvement in cases of NL is seen in 10% of patients with NL. Common features that may suggest NL include severe aching, burning pain (resulting in insomnia and lack of appetite), asymmetric distribution, progressive, unrelenting onset, and rapid evolution. Bilateral symptoms are suggestive of the diagnosis, as seen in this case. Patients often present in their 50s or 60s. NL presents in 4 distinct patterns: painful radiculopathy, cranial neuropathy (± pain), painless peripheral polyneuropathy, and a mononeuropathy (± pain). Lumbosacral (L4-S1) and cervical (C8-T1) root involvement have been reported. In some cases, a significant delay between the onset of NL and dissemination of lymphomatous disease has been reported.

Diagnosing NL is challenging because it can occur in patients with no relevant medical history, can present with a variety of clinical manifestations, and has a wide differential diagnosis. Imaging studies are especially useful for the diagnosis of NL. MRI can yield abnormal findings in 80% of patients; however, the findings are not always specific. Our case was successfully detected by diffusion-weighted MRI, as in a previous report. Although the administration of steroids has been effective to alleviate acute radicular pain in the short term, steroids can mask or delay appropriate diagnosis, especially in the case of lymphoma, by resolving enhancement on imaging. We were able to diagnose the lymphoma despite prior steroid use. A recent decrease in the rate of postmortem diagnoses has been reported. This is probably due to improved imaging techniques. PET-CT is highly sensitive in diagnosing NL. CSF examination is an important diagnostic tool, but it may have to be repeated up to 3 times before tumor cells can be detected. If imaging and CSF findings are indeterminate, a nerve biopsy should be considered.

Aggressive B-cell lymphomas present typically with radiculopathies and have the poorest prognosis. The overall median survival of unilateral presenting NL was reported as 10 months after diagnosis. Favorable outcomes have been seen in demyelinating neuropathy and multiple mononeuropathy in the presence of a T-cell lymphoma.

The most appropriate treatment regimens are unknown as there is no standard regimen of therapy. Typically, treatment involves high-dose IV methotrexate and systemic chemotherapy with high-dose cytarabine. Radiotherapy can help with unremitting neuropathic pain. When NL is properly diagnosed and treated, complete resolution of symptoms can occur, but the overall prognosis remains poor.

**AUTHOR CONTRIBUTIONS**

Dr. Jerath: design, conceptualization of the study, analysis and interpretation of the data, drafting and revising the manuscript. Dr. Reddy: design, conceptualization of the study, analysis and interpretation of the data, drafting and revising the manuscript. Dr. Moritani: design, conceptualization of the study, analysis and interpretation of the data, drafting and revising the manuscript. Dr. Gutmann: design, conceptualization of the study,
analysis and interpretation of the data, drafting and revising the manuscript.

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REFERENCES
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