Recurrence Brachial Neuritis Attacks in Presentation of B-Cell Lymphoma

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Abstract

We describe a 51-year-old woman who over 5 years had 9 painful monophasic attacks affecting the brachial plexus before a fascicular plexus biopsy diagnosed large B-cell lymphoma. The initial attacks were responsive to steroids with clinical resolution. At last attack, magnetic resonance imaging showed multifocal T2 hyperintensities and nodular gadolinium enhancement in the right brachial plexus not seen previously. Also seen were similar changes in the thoracic spinal cord, basal ganglia, cerebellum, and brainstem. Positron emission tomography revealed marked hypermetabolic activity of the plexus facilitating targeted fascicular brachial plexus biopsy, making the pathological diagnosis. Neurolymphomatosis affecting the peripheral nervous system typically presents with insidious painful progressive infiltration of nerves, roots, or plexi. Recurrent idiopathic brachial neuritis attacks (ie, Parsonage-Turner syndrome) in contrast most commonly are seen in persons with a family history and a discoverable genetic cause by \textit{SEPT9} mutations, which tested negative in this patient. This case illustrates how neurolymphomatosis, which represents a malignant transformation of B cells within peripheral nerves, can sometimes present with paraneoplastic immune-responsive neuritis mimicking Parsonage-Turner syndrome. Recurrence, an immune-refractory course or insidious progressive involvement of the nervous system, should raise suspicion of neurolymphomatosis.
nervous system (CNS) lymphoma. Malig-
nant cells were detected in the cerebrospinal 
fluid (CSF) in only 40% of patients studied. Of note, NL appears to be the least common 
initial presentation of lymphoma.

Diagnosis of NL is difficult because of the 
varied clinical presentations and broad differen-
tial diagnosis including inflammatory or para-
neoplastic neuropathies, leptomeningeal 
lymphomatosis, nerve root compression, disc 
herniation, vasculitis, or secondary effects of 
chemotherapy or radiation. In particular, diag-
osis of NL can be elusive because lymphoma 
more often causes indirect immunological disor-
ders of the peripheral nervous system such as in-
flammatory plexopathy or Guillain-Barre 
syndrome due to the immune perturbations 
that often accompany lymphoma.

We report a case of NL presenting with 
several years of recurrent brachial plexus at-
tacks, initially thought to be brachial neuritis 
Parsonage-Turner syndrome and negatively 
reviewed for SEPT9 mutation, which eventu-
ally was diagnosed with lymphomatous 
involvement of both the central and peripheral 
nervous systems. Institutional review board 
approval and patient consent were obtained.

CASE PRESENTATION
A 51-year-old woman presented with 9 
distinct episodes of subacute-onset focal 
neuropathic symptoms over a 5-year time 
period. Each episode occurred separately, 
and all responded to short courses of predni-
sone therapy, with total or near-complete 
resolution of symptoms. The initial presenting 
episode was a right brachial plexitis, signifi-
cant right upper limb pain, and weakness of 
the biceps and deltoid that developed over 
several weeks. Several months later, she de-
veloped a left brachial plexitis, left upper limb 
pain, and weakness, again presenting over 
several weeks. She then developed a right 
Bell's palsy with no associated pain several 
months later. Several months after this, she 
developed right vocal cord paralysis with no 
associated pain. Over the next few months, 
she again presented with a subacute left 
brachial plexitis with associated pain, and sub-
sequently right cranial nerve VI palsy. 
Following this, she remained asymptomatic 
for approximately 2 years. She then developed 
another episode of right brachial plexitis with

FIGURE 1. A, Coronal T2FS (left) and T1FS (right) postgadolinium MRI images of the right brachial plexus demonstrating diffuse T2 hyperintensity, enlargement, and enhancement involving most of the visualized right brachial plexus. B, Axial T2 FLAIR images of the brain showing numerous foci of increased signal intensity in the periventricular white matter (left), posterior limb internal capsules (left), and thalami (right). C, Sagittal T2 MRI (left) of the cervical and upper thoracic spine showing abnormal hyperin-
tense intramedullary signal centered in the upper thoracic spine. Sagittal T1FS (right) images after gadolinium injection showing abnormal nodular intramedullary enhancement centered within the upper thoracic spine. D, Coronal PET CT image demonstrating marked hypermetabolic activity along the right brachial plexus, centered on the posterior cord. E, Axial PET CT image demonstrating a markedly hypermetabolic lesion centered within the upper thoracic spinal canal. CT = computed tomography; FLAIR = fluid attenuation inversion recovery; MRI = magnetic resonance imaging; PET = positron emission tomography.
associated pain and weakness in the right upper limb. This right brachial plexitis recurred again approximately 2 months later and subsequently once again after another 2 months.

There were no known precipitants or triggers for the episodes. Her medical history was negative for any autoimmune or neurologic disorders, and there was no family history of neurological disorders. Electromyography studies during the episodes of brachial plexitis showed findings consistent with brachial plexopathy of the respective limb during each attack. During her episode of right cranial nerve VI palsy, an extensive normal neurologic evaluation was performed including contrast magnetic resonance imaging (MRI) of the brain, cervical spine, and brachial plexus; body positron emission tomography (PET); laboratory testing for SEPT9 gene mutation, myasthenia gravis antibodies, paraneoplastic antibodies, HIV, and monoclonal proteins; and CSF analysis. Given her consistent response to steroids, she was followed clinically without long-term immunotherapy.

With her last episode of brachial plexitis, she presented with right arm pain and weakness that persisted over several months. Neurologic examination showed minimal activation and areflexia of all right upper limb myotomes. There was mild weakness of the distal left arm and proximal right leg with preserved reflexes. Unlike previous presentations, her weakness continued despite treatment with prednisone, intravenous methylprednisolone, and intravenous immunoglobulin. In addition, she had a 35 lb weight loss in the previous 3 months, had multiple falls, and at least 2 brief episodes of nonresponsiveness.

Electromyography studies revealed an acute, severe right brachial plexopathy, chronic neurogenic changes in the left upper limb, and normal findings in the right lower limb and thoracic paraspinals. Right brachial plexus MRI, brain and spine MRI, and body PET showed multiple abnormalities, further described in Figure 1. The CSF analysis showed a lymphocytic pleocytosis, increased protein, and lymphomatous cells on cytology. A targeted fascicular nerve biopsy of the right brachial plexus posterior cord revealed diffuse large B-cell lymphoma (Figure 2). Bone marrow biopsy was unremarkable. She was started on a systemic chemotherapy regimen of MRT (high-dose methotrexate, rituximab, and temozolomide). After 4 MRT cycles, approximately 4 months since diagnosis, she showed considerable functional improvement and is currently ambulating independently. However, she continues to have profound right upper limb weakness though with some improvement in supination. Repeat MRI of brain showed considerable interval improvement with resolution of enhancement. Repeat body PET showed complete resolution of pathological signal. She is currently undergoing evaluation for autologous stem cell transplant.

**DISCUSSION**

We describe a case of NL with multifocal nervous system involvement and an initial presentation of 5 years of recurrent neuropathic episodes that largely responded to short courses of prednisone. Initial imaging and laboratory studies were unremarkable as was genetic testing for the most common cause of recurrent brachial neuritis, HBPN from SEPT9 mutation. As time progressed, the patient developed symptoms unresponsive to steroids, leading to further workup and eventual diagnosis of NL. After treatment with systemic MRT, she showed considerable improvement. Unique to this case was the recurrent nature of neuropathic episodes in the setting of B-cell lymphoma and the central and peripheral nervous system involvement without additional systemic involvement.

Before diagnosis of NL, it was initially thought that the patient may have HBPN and subsequently Parsonage-Turner syndrome once SEPT9 testing result was negative given her recurrent episodes of brachial plexitis. Although the exact pathophysiology of HBPN is unknown, an inflammatory immune-mediated mechanism is suggested. Inflammatory neuropathies and their relationship with NL have not been extensively studied. However, systemic inflammatory conditions such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren syndrome, and Hashimoto thyroiditis have been well recognized as risk factors for non-Hodgkin lymphoma. Our patient did not have Sjogren syndrome or other systemic autoimmune conditions.
In the presence of existing lymphoma, inflammatory neuropathies can often occur secondary to a paraneoplastic syndrome likely due to antibodies derived from molecular mimicry of antigens in lymphoma cells. It may be difficult to differentiate paraneoplastic versus purely immune-mediated etiologies such as HBPN in cases of recurrent brachial plexitis, which is almost pathognomonic of HBPN. A unique and perhaps differentiating feature with our patient is that although most of her presenting episodes involved attacks of brachial plexitis, she did have 1 episode of Bell’s palsy, 1 episode of right vocal cord paralysis, and 1 episode of right cranial nerve VI palsy. With HBPN, nerves outside the brachial plexus have been reported to be affected in up to 56% of cases, most commonly in the lumbosacral plexus, phrenic nerve, or recurrent laryngeal nerve. Cranial nerves are rarely affected, with less than 1% of facial nerve involvement reported in the literature. In addition, most patients with HBPN tend to recover from their attacks, generally within 4 weeks, with 80% to 90% of patients having recovered completely after a 2- to 3-year follow-up. In our case, with the final presentation of right brachial plexitis the symptoms persisted and progressed insidiously over months despite treatment with immunomodulating therapies. This suggests a more infiltrative presentation as was evidenced by the eventual diagnosis of NL. In her case, it is possible that the multiple earlier attacks were paraneoplastic immune-mediated sentinel presentations of her underlying lymphoma.

Diagnosis of NL involves integration of clinical findings, imaging studies, and pathologic data. Given its rarity and varying presentation, diagnosis is often delayed. Magnetic resonance imaging is the most sensitive and specific imaging modality used in the diagnosis of NL, generally revealing abnormal enhancement or enlargement of involved nerves, similar to our case. The use of PET is playing an increasingly important role in NL, with recent reviews reflecting approximately 91% of patients with NL who underwent PET showing positive PET findings in involved NL sites. Nerve biopsy remains the diagnostic criterion standard.

Because of the infrequency of NL, treatment approaches have not been extensively studied. Generally, therapy follows similar approaches to that of primary CNS lymphoma. Systemic chemotherapy has shown the most promise, because it is well suited to address multifocal involvement. Intrathecal chemotherapy and radiation have also been reported.
studies have suggested that high-dose methotrexate-based chemotherapy be used as a standard component for primary CNS lymphoma, often in combination with other agents (eg, MRT) as used in our case.\textsuperscript{10,21-24} Steroids have shown to provide symptom control, though this is often short-lived.\textsuperscript{11} The overall prognosis for patients with NL is poor, with a median overall survival of about 10 months from initial diagnosis.\textsuperscript{10}

In summary, NL is a rare and frequently misdiagnosed presentation of hematological malignancy. In patients presenting with neuropathic symptoms associated with intense pain and poor response to other treatment modalities, neurolymphomatosis should be considered. Even in cases typical for inflammatory neuropathies/plexitis, one should consider NL if symptoms recur, persist, or fail to improve with passage of time or immunotherapy. Nerve biopsy remains the criterion standard for diagnosis. Early recognition and treatment may lead to improved outcomes.\textsuperscript{10,11}

Abbreviations and Acronyms: CNS = central nervous system; CSF = cerebrospinal fluid; HBPN = hereditary brachial plexus neuropathy; MRT = magnetic resonance imaging; MRI = magnetic resonance imaging; MRT = high-dose methotrexate, rituximab, and temozolomide; NL = neurolymphomatosis; PET = positron emission tomography

Potential Competing Interests: The authors report no competing interests.

Publication dates: Received for publication August 17, 2018; revisions received September 28, 2018; accepted for publication October 5, 2018.

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