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Recurrent 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 *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.

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Recurrent brachial neuritis attacks most commonly are associated with hereditary brachial plexus neuropathy (HBPN), an autosomal-dominant hereditary disorder due to mutations of the *SEPT9* gene.[1-3] When attacks are isolated and present as a sporadic disorder, Parsonage-Turner syndrome is diagnosed because the symptomatology is similar to that of HBPN. This is characterized by severe neuropathic pain, most commonly of a shoulder, followed by rapid onset of weakness and muscle atrophy. The pain is typically steroid-responsive and deficits spontaneously improve over a period of months. Nerve pathology is similar between HBPN and Parsonage-Turner cases, with large nonclonal mononuclear infiltrates noted.[4-6] Clinical involvement outside the brachial plexus, most commonly of the cranial and lumbosacral segments, is more frequent in HBPN.[2,3]

Case series of lymphomatous infiltration of the brachial plexus are reported to most commonly occur in the setting of known non-Hodgkin B-cell lymphoma.[7,8] However, reports of recurrent brachial plexus attacks as the presenting symptom of B-cell lymphoma are lacking. Neurolymphomatosis (NL) is defined as infiltration of the peripheral nervous system by lymphomatous cells in the setting of hematological malignancy and is most commonly seen in non-Hodgkin large B-cell lymphoma.[9-11] Typical presentations include neuropathy affecting peripheral nerves, the brachial or lumbosacral plexus, spinal nerve roots, or spinal or cranial nerves often associated with intense pain. In a recent case series of newly diagnosed intermediate/high-grade non-Hodgkin lymphoma, the relative incidence of NL was estimated to be approximately 3%.[12] In the largest detailed series describing NL, 24% of patients with NL had an initial diagnosis of primary central

nervous system (CNS) lymphoma.[11] Malignant cells were detected in the cerebrospinal fluid (CSF) in only 40% of patients studied.[11] Of note, NL appears to be the least common initial presentation of lymphoma.[10]

Diagnosis of NL is difficult because of the varied clinical presentations and broad differential diagnosis including inflammatory or paraneoplastic neuropathies, leptomeningeal lymphomatosis, nerve root compression, disc herniation, vasculitis, or secondary effects of chemotherapy or radiation.[12] In particular, diagnosis of NL can be elusive because lymphoma more often causes indirect immunological disorders of the peripheral nervous system such as inflammatory plexopathy or Guillain-Barre syndrome due to the immune perturbations that often accompany lymphoma.[13]

We report a case of NL presenting with several years of recurrent brachial plexus attacks, initially thought to be brachial neuritis Parsonage-Turner syndrome and negatively reviewed for *SEPT9* mutation, which eventually 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 prednisone therapy, with total or near-complete resolution of symptoms. The initial presenting episode was a right brachial plexitis, significant right upper limb pain, and weakness of the biceps and deltoid that developed over several weeks. Several months later, she developed 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 subsequently right cranial nerve VI palsy. Following this, she remained asymptomatic for approximately 2 years. She then developed another episode of right brachial plexitis with

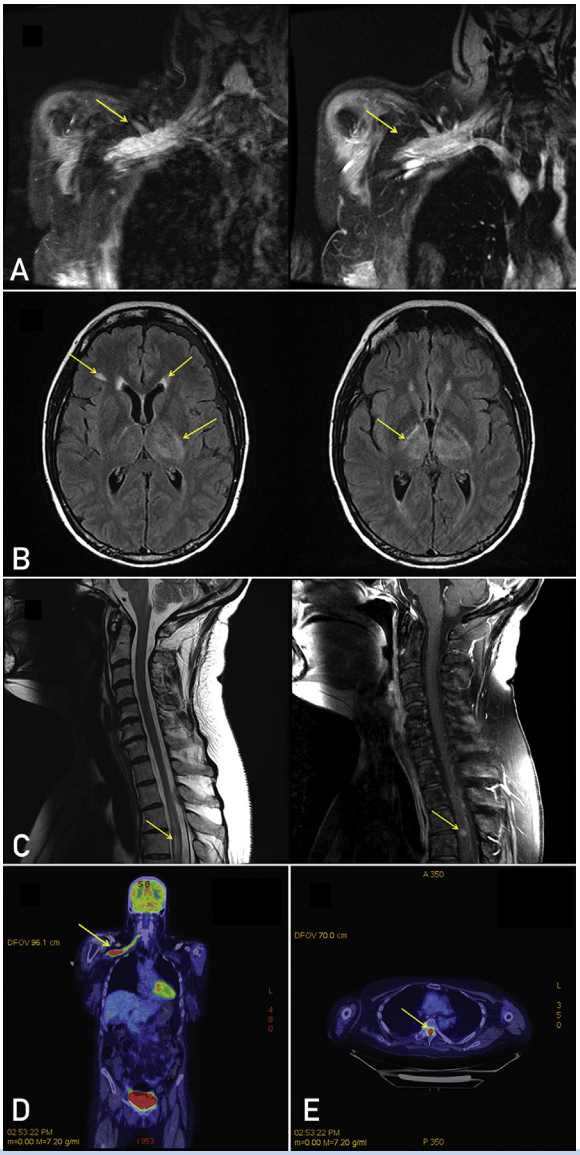

FIGURE 1. A, Coronal T2FS (left) and T1FS (right) postgadolinium MRI images of the right brachial plexus demonstrating diffuse T2 hyperintensity, enlargement, and enhancement involving most of the visualized right brachial plexus. B, Axial T2 FLAIR images of the brain showing numerous foci of increased 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 hyperintense 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.[2,3] 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.[6,14] 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.[15-19] Our patient did not have Sjogren syndrome or other systemic autoimmune conditions.

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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.[13] 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.[1,6] 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.[1] Cranial nerves are rarely affected, with less than 1% of facial nerve involvement reported in the literature.[1] 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.[4] 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.[11] 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.[9] 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.[20] Nerve biopsy remains the diagnostic criterion standard.[10]

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.[10] Various

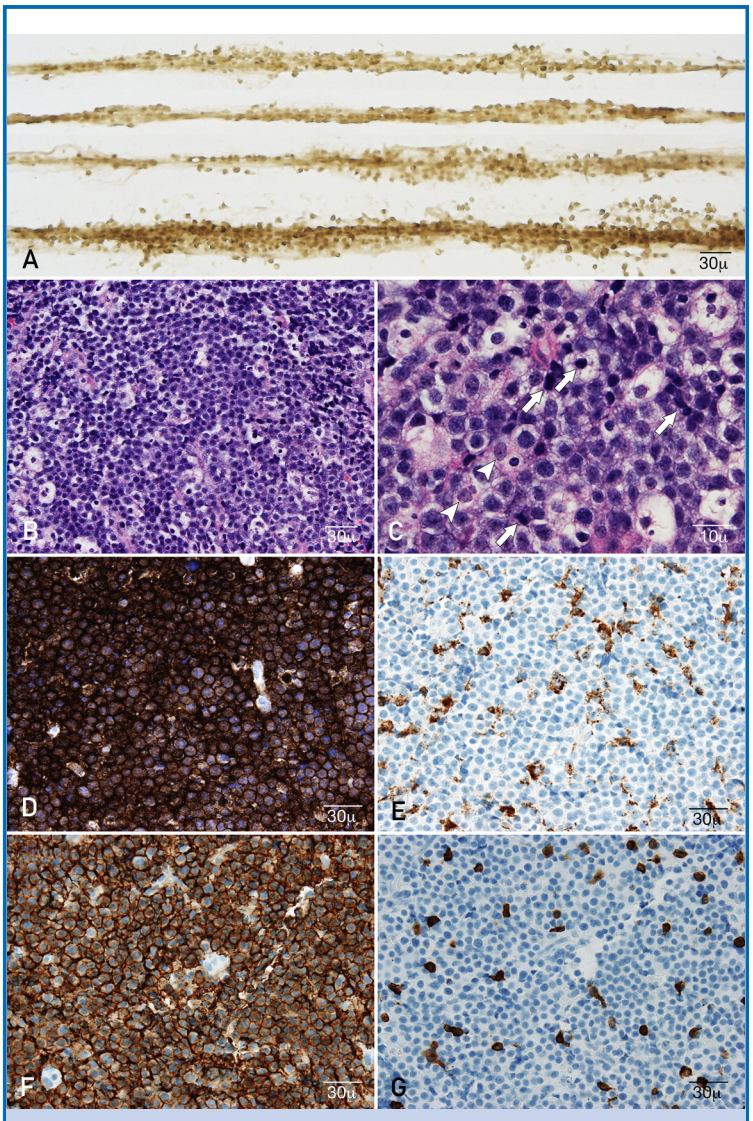

FIGURE 2. Targeted right infraclavicular posterior cord biopsy at site of MRI and PET imaging abnormality diagnostic of B-cell lymphoma without bone marrow biopsy abnormalities found. A, Closely approximated teased nerve fibers fixed with osmium tetroxide demonstrate marked cellularity with all fibers being unclassifiable without normal nodal or axonal architecture. B, Low-power hematoxylin and eosin stains demonstrate replacement of nerve fibers with tumor. C, High-power hematoxylin and eosin stains show frequent mitotic figures and prominent nucleoli. D, CD45 lymphocyte marker positivity throughout the nerve. E, CD68 macrophage marker sparse staining. F, CD20 B-cell marker staining showing diffuse positivity. G, CD3 T-cell sparse staining. MRI = magnetic resonance imaging; PET = positron emission tomography.

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.[10,21-24] Steroids have shown to provide symptom control, though this is often short-lived.[9] The overall prognosis for patients with NL is poor, with a median overall survival of about 10 months from initial diagnosis.[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.[10,11]

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

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