Neurolymphomatosis: diagnosis, management, and outcomes in patients treated with rituximab

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Neurolymphomatosis (NL) is an uncommon syndrome of peripheral or cranial nerve root dysfunction secondary to infiltration by B-cell non-Hodgkin’s lymphoma (NHL). A high index of suspicion is required as presenting symptoms are varied, conventional radiology has only modest sensitivity, and pathological diagnosis is often difficult. Treatment with chemotherapy alone has an objective response rate of 82%, although long-term outcomes are highly variable. This case series describes outcomes in four patients whose management incorporated PET scanning and the use of rituximab in combination with chemotherapy. PET scanning could often diagnose NL where other diagnostic modalities were non-diagnostic. Although combination therapy with rituximab and chemotherapy has been shown to be superior to chemotherapy alone in other forms of NHL, this does not appear to be the case in patients with NL. This may reflect the inability of rituximab to adequately penetrate into the central and peripheral nervous system. This is supported by the common finding that patients will relapse solely with NL despite on-going complete remission at sites outside the nervous system. The prognosis of these patients is poor, with the disease often following a progressive course despite treatment.

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Neurolymphomatosis (NL) is an uncommon syndrome characterized by a direct invasion of the peripheral nervous system by lymphoma, nearly always B-cell non-Hodgkin’s lymphoma (NHL). A high index of suspicion is required as the presenting symptoms of this condition are varied (including plexopathy, mononeuritis multiplex, footdrop, radiculopathy, cranial nerve palsies) and a number of differential diagnoses need to be considered (eg, leptomeningeal lymphomatosis, nerve damage from herpes zoster, chemotherapy, nerve root compression, radiotherapy, lymphoma-associated vasculitis, and paraneoplastic syndromes). Many cases of NL are painful. Treatment with chemotherapy alone has an overall response rate of 82%, with disease control lasting from 2 weeks to 9 years. We present 4 cases of NL diagnosed in 126 new cases of intermediate/high-grade NHL treated at our institution between 2005 and 2007 inclusive (for an annual incidence of 3 cases of NL per 100 new cases of intermediate/high-grade B-NHL) and report on the utility of PET scanning and rituximab therapy in the diagnosis and management of these patients.

Case Report 1

A 56-year-old woman was diagnosed with Stage IV diffuse large B-cell lymphoma (DLBCL) after presenting with hypercalcemia, widespread lymphadenopathy, and bone marrow involvement. She was treated with 8 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) and achieved a complete remission. Three months later, she presented with a right wrist drop and a right Bell’s palsy. MRI of the brain and spine were non-contributory (Fig. 1). However, PET scan showed evidence of recurrent lymphoma in the brachial plexus of the right arm (Fig. 1). She was commenced on high-dose methotrexate (8 gm/m² every 2 weeks) for NL. Her disease continued to progress despite treatment, with persistence of her initial neurological problems and development of new left cranial nerve IX/X palsies. After consultation with...
Case Report 2

A fit 75-year-old woman presented with dyspnea and a painful radiculopathy of the right leg in an L4-5 distribution. A V-Q scan was consistent with pulmonary emboli and she was anticoagulated. She was also found to have Stage IV DLBCL with involvement of the liver, spleen, bone marrow, and multiple lymph node fields. MRI scans of her spine showed longstanding degenerative spinal disease but no abnormality of the central spinal cord or the lumbosacral nerve roots. CSF examination was unremarkable. PET scanning revealed fluorodeoxyglucose (FDG)-avid lesions at the sites of lymphoma listed above but no lesion of the spinal cord or nerve roots. The patient was treated with R-CHOP and prophylactic intrathecal methotrexate. Interval re-staging showed a complete response at all sites. However, after the fourth cycle of R-CHOP, the patient developed a new and painful radiculopathy of her right arm in the C8-T1 distribution. MRI of her neck and spine showed evidence of cervical spondylosis and a small, non-specific lesion in her brachial plexus (Fig. 2). A repeat PET scan showed intense FDG uptake in the brachial plexus abnormality seen on MRI and also a second lesion in the upper arm (Fig. 2). No other FDG-avid lesions were seen, consistent with persisting disease control elsewhere. A diagnosis of NL was made and the patient’s treatment changed to...

Fig. 1. Coronal T1 MRI images of right brachial plexus showing no mass lesion (A) and normal enhancement pattern (B). Intense abnormal FDG uptake in the right proximal arm (black arrow) on coronal PET scan (C).

Fig. 2. (A) Coronal and (B) transverse images on MRI scan show a small non-specific lesion in the axilla (white arrows) but (C) coronal and (D) transverse images on PET scan show intense FDG uptake at the same site, and more distally, consistent with neurolymphomatosis (white arrows).
high-dose methotrexate (8 g/m²) every 2 weeks. The patient’s neurological condition stabilized for 1 month but she then developed further weakness of her legs and right arm which rendered her quadriparetic. The patient continued to deteriorate with bulbar dysfunction despite treatment with high-dose methylprednisolone (500 mg IV daily for 3 days) and DICE-R (dexamethasone, ifosfamide, cisplatin, etoposide, rituximab). Active treatment was withdrawn after discussion with the patient and family. The patient died 4 months after her initial diagnosis of NL.

Case Report 3
A 68-year-old man presented with Stage IIB DLBCL involving the right testes and retroperitoneal nodes. He achieved a complete remission with 6 cycles of R-CHOP and concurrent intrathecal methotrexate. Two months later, he developed sudden onset of “blurry” vision in the left eye. CT scans showed no evidence of recurrence. However, sampling of his vitreous fluid showed evidence of recurrent lymphoma. Despite treatment with intrathecal methotrexate and radiotherapy (36 Gy) to the left orbit, he lost the vision in that eye. The patient then developed a right lower-motor neuron ulnar neuropathy. CT of the axilla showed no evidence of nerve root compression and MRI of the spine showed only mild cervical spondylosis. A clinical diagnosis of NL was made. The patient declined further investigation or treatment and died 3 months after relapse.

Case Report 4
A 64-year-old man presented with 1 month of thoracic back pain and 1 week of left leg weakness. MRI spine showed a soft-tissue mass causing pathological fracture of the T2 vertebra and cord compression. Open biopsy at the time of a C7-T4 posterior fusion was consistent with DLBCL. Staging showed he had Stage 1AE disease. He achieved a complete remission with 6 cycles of R-CHOP, intrathecal methotrexate, and consolidation radiotherapy (30 Gy) to the T2 region. He relapsed 7 months later with an isolated cutaneous lesion over the right scapula and left footdrop consistent with peroneal neuropathy. CT and MRI scans showed no overt disease. A provisional diagnosis of NL was made and he commenced treatment with R-ICE (rituximab, ifosfamide, carboplatin, etoposide). However, he continued to deteriorate despite treatment, with the advent of bilateral leg weakness and multiple cranial nerve palsies. His treatment was changed to ESHAP (etoposide, methylprednisolone, cytosine arabinoside, and cisplatin). However, the patient continued to deteriorate and died of pneumonia 3 months after his diagnosis of NL.

Discussion
We describe 4 cases of NL that illustrate several useful points. We provide a contemporary estimate of the incidence of NL at a tertiary referral hospital (~3 cases per 100 new intermediate or high-grade NHL patients annually). The mean age of these 4 patients was 66 years. Two of these patients had evidence of NL at diagnosis, whereas the others relapsed with NL despite complete remission elsewhere. The presenting complaints were diverse, including painful plexopathy (Patient 1), cranial nerve palsies (Patients 1 and 2), mononeuropathy (Patient 3), and footdrop (Patient 4). This is very similar to that described by Baehring et al.1 previously.

The diagnosis of NL can be difficult and may be delayed for months to years after the first onset of symptoms.1,7,9 Baehring et al.1 reported that the sensitivity of nerve biopsies was 80%, of MRI was 40%, and of CSF examination was 21%. Similar to other reports,3,6,10 we found that PET scanning (in Patients 1 and 2) was a useful diagnostic modality for patients with suspected NL where a diagnosis by other means was inconclusive. Although systematic series are not available in NL, PET is unlikely to be 100% sensitive and at least one report of a false-negative PET scan has been published.9 This may reflect the limitations of PET in detecting small-volume disease. However, data from other patient groups are reassuring. In patients with malignant peripheral nerve sheath tumors, the only group wherein systematic/prospective data are available about PET scanning for malignant peripheral nerve lesions, the efficacy of PET-scanning was good. In these patients, PET scans had a sensitivity of 89%–100%, specificity of 72%–95%, positive predictive value of 71%–87%, and negative predictive value of 95%–100%.13–15

The treatment of NL is difficult. Steroids alone only provide short-lived symptom control.1 Chemotherapy alone has a response rate of 82%, although many responses were not durable.1 Recently, the addition of rituximab to chemotherapy has been shown to significantly improve the survival of patients with DLBCL,16,17 and combination therapy has become the standard of care. However, our case series and those of others5,10,12 strongly suggest that rituximab therapy does not substantially improve outcomes in NL. All of these patients relapsed with NL either during or shortly after treatment with rituximab and systemic chemotherapy, often without evidence of disease elsewhere. It seems likely that the blood-brain barrier18 and the blood-nerve barrier19 present a barrier to the entry of large molecules such as cyclophosphamide, doxorubicin, vincristine, and rituximab into these areas. Furthermore, prognosis was generally poor once patients developed NL. Despite a number of salvage treatments, all patients in our series were dead 4 months after diagnosis of NL. One group reported that their patient remained relapse-free at 1 year after salvage ESHAP therapy (etoposide, methylprednisolone, cytosine arabinoside, and cisplatin) followed by BEAM (BCNU, etoposide, cytarabine, melphalan) chemotherapy with stem-cell transplant.
In summary, NL occurs in a minority of patients (3 per 100 intermediate or high-grade NHL patients annually) and can present in diverse ways, both at initial diagnosis of NHL or after treatment. PET scanning is often a useful diagnostic modality in these patients. Unfortunately, the prognosis of patients with NL remains poor despite treatment with chemotherapy and rituximab.

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References