

# Neurolymphomatosis: the challenge of diagnosis and treatment

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Neurolymphomatosis (NL) is the infiltration of the peripheral nervous system by lymphomatous lymphocytes. Four types of peripheral nerve involvement in NL are known: painful or painless mononeuropathy, cranial neuropathy, painful radiculopathy, and peripheral polyneuropathy. We report a case of neurolymphomatosis in a woman with non-Hodgkin's lymphoma (NHL) who presented with lumbosacral and brachial plexopathy and was successfully treated with four cycles of high-dose systemic methotrexate.

**S**ystemic non-Hodgkin's lymphoma (NHL) may directly infiltrate the peripheral nervous system at various levels. Beside the leptomeninges, malignant lymphocytes can infiltrate the neuromuscular junctions, peripheral nerves, and nerve roots.<sup>1</sup>

Neurolymphomatosis (NL) is a rare neurologic syndrome in lymphomas; it has been previously reported to infiltrate peripheral nerves and rarely the brachial and lumbar plexuses.<sup>2,3</sup> It is important to distinguish NL from other types of neuropathies, particularly infectious and inflammatory conditions. However, it is difficult to isolate a cancer-related inflammatory vasculitis and mononeuritis multiplex without definitive histopathologic examination. In this report, we describe a case of NHL presented as relapsing NL. Malignant lymphocytes infiltrated both lumbosacral and brachial plexuses bilaterally and were treated successfully with four cycles of high-dose methotrexate.

## Case report

A 73-year-old woman presented with a new onset of progressive abdominal distention worsening over 4 weeks. General physical examination showed evidence of ascites without organomegaly or lymphadenopathy. CT (computed tomography) scans of the chest, abdomen, and pelvis confirmed the ascites. Ascitic fluid cytology showed atypical lymphoid cells suggestive of malignant lymphoma. Flow cytometry of the lymphoid cells demonstrated a monoclonal kappa, CD10-positive B-cell large cell lymphoma. Bone marrow biopsy was hypocellular (5%–15%), with large B-cell lymphoma cells that were positive for CD10 and

CD20 markers and negative for BCL-2 marker. 18-Fluorodeoxyglucose-positron emission tomography (FDG-PET) showed hypermetabolic activity in the peritoneum consistent with malignancy.

She was finally diagnosed with NHL stage IV (Ann Arbor clinical staging system), with intermediate risk by the International Prognostic Index (IPI = 3) and a predicted 5-year survival of 43%. Six cycles of rituximab (Rituxan) and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) were administered. Restaging FDG-PET after chemotherapy showed no evidence of active disease.

Three months later, she presented with progressive pain in both lower extremities, but mostly in the left hip radiating to the left anterolateral and lateral leg. She had diffuse hyperesthesia in the left leg without definite sensory or motor loss. Pain progressed over a week, and she was hospitalized for pain control; she was commenced on strong narcotic analgesics, with minimal response.

Meanwhile, weakness in the left lower extremity was noted, and she lost bowel and bladder sphincter control. Neurologic examination showed weakness in the left ankle flexors and extensors (Medical Research Council [MRC] = 3) and slight weakness in the ipsilateral thigh abductors (MRC = 4). Motor

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examination elsewhere was normal. Deep tendon reflexes were depressed throughout the upper and lower extremities without asymmetry, and the plantar responses were flexor. Sensory perception was decreased to light touch, and vibratory sensation diminished in both distal lower extremities. Cranial nerve examination and mental status were normal. She was able to walk with high stepping in the left lower extremity. Preliminary diagnoses included mononeuritis multiplex versus bilateral L5–S1 radiculopathies. MRI (magnetic resonance imaging) of the brain was normal, with normal repeated cerebrospinal fluid examinations. An immunofluorescent study showed that the deposits consisted of immunoglobulin (Ig) M-monoclonal kappa Ig. The anti-Hu antibodies were negative.

One week later, electrodiagnosis showed active denervation in the lower extremities, more severe in the left, consistent with an active lower motor neuron process. Repeated FDG-PET (Figure 1A) showed extensive hypermetabolic activity in the regions of both brachial and lumbosacral plexuses, with no evidence of lymph node involvement or other extranodal areas.

An open biopsy of the left sciatic nerve revealed large atypical diffuse B-cell lymphoma positive for CD20

and CD10 markers. The immunostain with antisera against CLA (common leukocyte antigen) was positive for IgM heavy chain and kappa light chain. There was no evidence of inflammatory changes or vasculitis (no vasonecrosis or fibrinoid changes). Final diagnosis of NL of both brachial and lumbosacral plexuses was made.

Four cycles of intravenous high-dose methotrexate (8 g/m<sup>2</sup>), given at 2-week intervals, resulted in a dramatic recovery of the plexopathies. FDG-PET performed 4 weeks after the final methotrexate infusion showed resolution of the previously seen hypermetabolic activity (Figure 1B). Pain medications were discontinued after methotrexate treatment, and she was able to ambulate with the support of a walker. In addition, full bladder and rectal sensory perception and sphincter function returned to normal. Six months after finishing the treatment, our patient was still asymptomatic, with no signs of relapse.

## Discussion

In NHL, the nervous system may be affected by direct spread of the disease or by a paraneoplastic mechanism.<sup>4</sup> Direct nervous system tumor invasion commonly involves the leptomeninges. Less commonly, intracranial lesions, dural involvement, and dif-

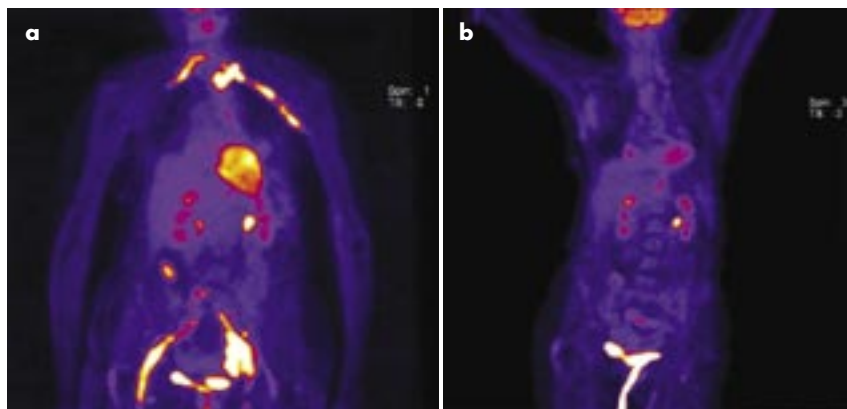
fuse infiltration of the proximal nerve roots (neurolymphomatosis) may occur.<sup>5</sup> NL usually develops in patients with widespread NHL and may be the first manifestation of a relapse.<sup>6,7</sup>

NL should be considered in the diagnostic evaluation of peripheral neuropathy of unclear etiology, especially in patients with a history of lymphoma. Appropriate diagnosis of NL and early therapy may prevent considerable morbidity and perhaps mortality. In one series of 25 patients, the time from initial symptoms to diagnosis ranged from 2 weeks to 4 years; in the same series, the peripheral nerve enlargement and/or enhancement was observed on MRI in 18 of 25 patients.<sup>8</sup> However, nerve root enhancement or thickening on MRI is not a specific diagnostic finding for NL, and abnormal enhancement can also be present in a variety of processes, including acute and chronic neuritis and peripheral nerve sheath tumors.

Definitive diagnosis of NL usually requires biopsy of the nerve.<sup>2,3,9</sup> Biopsy has been diagnostic in 84% of suspected cases, whereas in 16%, it has revealed nonspecific findings.<sup>9</sup>

Following chemotherapy, residual tumor masses on CT may show false-positive results due to tissue fibrosis or a nonviable tumor, possibly being labeled a partial remission. FDG-PET is complementary to anatomic imaging in assessing metabolic activity. In particular, FDG-PET plays an important role in diagnosing relapses of NHL.<sup>10</sup> As in our patient, FDG-PET can be an essential diagnostic tool in evaluating peripheral nerve involvement with malignancy and the extent of NL.<sup>11,12</sup>

Treatment of NL includes resection of peripheral nerve masses and chemotherapy with or without radiation therapy. Standardized criteria to measure the response to therapy in NL are not yet available. However, only a few cases have shown adequate response to chemotherapy.<sup>13,14</sup> These responses were short-lasting, and relapse was the rule. Poor response to chemotherapy



**FIGURE 1** (a) FDG-PET scan shows extensive hypermetabolic activity in the regions of the brachial and lumbosacral plexuses, with a bulky focus in the left sacroscliac notch. (b) Follow-up FDG-PET scan after high-dose methotrexate shows resolution of the hypermetabolic foci. Physiologically excreted activity in the urinary bladder and Foley catheter are noted in both figures.

in NL may be explained by the extreme difficulty in achieving cytotoxic concentration of the drugs within the peripheral nerves.

In one published series, 5 of 25 patients treated with high-dose methotrexate succeeded in achieving a durable response and good functional outcome, with minimal toxicity.<sup>8</sup> Despite the lack of information regarding the optimal duration of therapy in responding patients, Baehring et al observed a meaningful clinical improvement after the sixth cycle of methotrexate infusion.<sup>8</sup> Our patient had 4 cycles of high-dose methotrexate, which appeared to be effective.

High-dose methotrexate may be an effective method of treatment in some patients with NL. However, randomized clinical trials comparing high-dose methotrexate with previously established treatment modalities are needed to define the optimal dose and duration of therapy and to determine long-term outcomes.

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*Conflicts of interest:* None to disclose.