Peripheral Nerve Dysfunction Secondary to Lymphomatous Infiltration of the Nervous System by Non-Hodgkin’s Lymphoma

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Peripheral Nerve Dysfunction Secondary to Lymphomatous Infiltration of the Nervous System by Non-Hodgkin’s Lymphoma

Sean Grimm1, Marc Chamberlain2

Abstract: Lymphomatous meningitis (metastasis of lymphoma cells into the cerebrospinal-fluid spaces [CSF]) and neurolymphomatosis (lymphomatous infiltration of a peripheral nerve or root) are neurologic complications of non-Hodgkin’s lymphoma (NHL) that frequently result in significant neurologic dysfunction. Leptomeningeal metastases most commonly present as cerebral dysfunction (hydrocephalus causing headache or apraxia of gait, encephalopathy, or seizures), cranial neuropathy (diplopia, facial weakness, vertigo, hearing loss, and tongue weakness), and spinal-nerve root dysfunction (incomplete cauda equina syndrome — asymmetric lower-extremity weakness, sensory loss, or incontinence). Diagnosis is made by finding leptomeningeal enhancement on magnetic resonance imaging (MRI) of the brain or spine or demonstration of lymphomatous cells by CSF cytology or flow cytometry. Treatment consists of focal radiotherapy for areas of bulky disease followed by intra-CSF chemotherapy or systemic chemotherapy. Neurolymphomatosis typically presents as a painful, sensorimotor peripheral neuropathy affecting multiple limbs in an asymmetric fashion with rapid evolution although variability in presentation can occur. Diagnosis is made by demonstration of enhancement of nerve roots on MRI of the brachial or lumbosacral plexus or peripheral nerves or by increased hypermetabolic activity following the course of affected nerves on fluorodeoxyglucose positron emission tomography (FDG-PET). Treatment of neurolymphomatosis consists of focal radiotherapy (if significant neurologic dysfunction is present) and high-dose intravenous methotrexate therapy. Standard systemic chemotherapy agents are not effective since they do not penetrate the physiologic “nerve-blood barrier”. Other disorders that must be differentiated from these entities include peripheral-nerve or nerve root compression and paraneoplastic neuropathy.

Key words: lymphoma, neurolymphomatosis, lymphomatous meningitis, leptomeningeal lymphoma, intravascular lymphomatosis

Introduction

Patients with systemic NHL may experience dysfunction of the peripheral nervous system by a variety of mechanisms including leptomeningeal metastases, nerve root or peripheral-nerve invasion (neurolymphomatosis), nerve root and peripheral-nerve compression, and as a complication of paraneoplastic peripheral neuropathies or intravascular lymphomatosis. This review primarily focuses on lymphomatous meningitis and neurolymphomatosis; metastatic complications that result from direct lymphomatous infiltration of the nervous system.

Lymphomatous Meningitis

Lymphoma cells that spread to the subarachnoid space (CSF space) and leptomeninges (pia and arachnoid membranes) are referred to as leptomeningeal metastases or lymphomatous meningitis (LM). The CSF space is the most common site of central nervous system (CNS) metastasis of systemic lymphoma with a clinical incidence of 6 % [1, 2]. Histology is the most important risk factor for metastasis of lymphoma to the CSF. The incidence of LM is greatest in Burkitt’s lymphoma (BL) and lymphoblastic/acute lymphoblastic lymphoma (ALL) and, to a lesser extent, in diffuse large B cell lymphoma [3]. LM is rare in indolent lymphomas such as follicular or marginal zone lymphoma. Other risk factors include high serum lactate dehydrogenase (LDH), younger age, ≥ 2 extranodal sites, B symptoms, low albumin concentration, and specific sites of extranodal disease such as bone marrow, skin, testis, epidural space, retroperitoneum, orbit, paranasal sinus, and lung. Patients with BL, ALL, and diffuse B-cell lymphoma with multiple risk factors (particularly high LDH, ≥ 2 extranodal sites, and disease in bone marrow, testis, epidural space, orbits, palate, paranasal sinuses, or bone marrow) are often treated with prophylactic intra-CSF chemotherapy [4]. LM presents with a variety of symptoms and signs (Table 1). The anatomic regions affected by LM can be separated into (1) brain, (2) cranial nerves, (3) spinal cord and nerve roots.

Brain Dysfunction

LM may cause brain dysfunction by several mechanisms including increased intracranial pressure (ICP), superficial invasion and neuronal injury, mass effect, and ischaemia by

Table 1. Common presenting symptoms and signs of leptomeningeal metastases

<table>
<thead>
<tr>
<th>Symptom/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>New-onset seizures</td>
</tr>
<tr>
<td>Unexplained encephalopathy</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Gait unsteadiness (apraxic or “magnetic” gait)</td>
</tr>
<tr>
<td>Blurred vision (optic neuropathy)</td>
</tr>
<tr>
<td>Diplopia</td>
</tr>
<tr>
<td>Face numbness (“numb chin”)</td>
</tr>
<tr>
<td>Face weakness – “bells palsy” (unilateral or bilateral)</td>
</tr>
<tr>
<td>Vertigo</td>
</tr>
<tr>
<td>Hearing loss</td>
</tr>
<tr>
<td>Radicular pain</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Foot drop</td>
</tr>
<tr>
<td>Leg weakness</td>
</tr>
<tr>
<td>Bowel or bladder incontinence</td>
</tr>
</tbody>
</table>

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Peripheral Nerve Dysfunction Secondary to Lymphomatous Infiltration

small-vessel occlusion. LM may also cause impaired flow and outflow obstruction of CSF at any site within the CSF compartment (most commonly at the level of the ventricles, basal cisterns, spinal subarachnoid space, and superior sagittal sinus), resulting in hydrocephalus and increased ICP. It is important to recognise that CSF flow disruption and associated ICP may be present, even in patients without evidence of hydrocephalus by CT or MRI neuroimaging. CSF flow disruption is best assessed by radioisotope CSF flow studies in patients with LM being considered for intra-CSF chemotherapy. LM by invading superficial brain may result in an encephalopathy manifesting as confusion or focal hemispheric deficits. Either subarachnoid or ventricular nodules can be of sufficient size to result in mass effect and corresponding topographic specific focal deficits. Small-vessel occlusion by LM is a consequence of invasion by a tumour of the vasa nervorum, small vessels that perfume nerves, resulting in infarction.

Brain-Associated Clinical Symptoms

Headache

Headache is a common complaint in patients with LM. It is usually non-specific and diffuse and may be associated with nausea, vomiting, or lightheadedness. The severity of headaches varies from severe and quality-of-life-interfering to low-grade and noxious.

Gait Dysfunction

Patients with LM often have a gait disturbance which may reflect either hemispheric disturbance or spinal-cord dysfunction. Some patients may develop the “apraxia of gait” or “magnetic gait” that is seen in patients with normal-pressure hydrocephalus; urinary incontinence is a frequent associated feature.

Encephalopathy

Patients may experience diffuse cognitive dysfunction which resembles delirium or a confusional state. LM must be considered in lymphoma patients with altered mental status particularly if no other cause is demonstrable, ie electrolyte disturbance or medication effect.

Episodic Loss of Consciousness

Seizures are the most common cause of loss of consciousness in patients with LM. Both non-convulsive focal and generalised seizures may occur. Episodic, transient increases in intracranial pressure secondary to CSF flow obstruction may result in the phenomena of “plateau waves”. Transient impairment of consciousness is a common sign from plateau waves.

Cranial-Nerve (CN) Dysfunction

The cranial nerves travel through the subarachnoid space before exiting the CNS and innervating peripheral targets. LM may infiltrate or cause ischaemia in an exiting cranial nerve, causing symptoms.

Any cranial nerve may be affected by LM. Common complaints include blurred vision (CN II) binocular diplopia (CN III, IV, or VI), face numbness (CN V), facial weakness (CN VII), vertigo or hearing loss (CN VIII), and tongue weakness (CN XII).

Spinal Nerve Root Dysfunction

Any spinal root can be affected by LM, although the involvement of the cauda equina is most common. Patients often present with asymmetric lower-extremity weakness and dermatomal sensory disturbance that ultimately evolves into a complete cauda equina syndrome (paraparesis, sensory loss, and incontinence). Subtle lower-extremity weakness is often the only evidence of LM affecting the spine. LM may infiltrate exiting nerve roots causing radicular pain, ie a radiculopathy. Nuchal rigidity, common in infectious meningitis, is rarely present in LM despite the presence of inflammation in the subarachnoid space.

Diagnosis

Neurologic Exam

The hallmark of LM is dysfunction of the nervous system separated in space; patients suspected of harbouring LM should be examined carefully for neurologic abnormalities that may not be associated with symptoms. A classic example is the finding of a lower-extremity monoparesis (early cauda equina syndrome) or in a patient complaining of diplopia and manifesting as an abducens (cranial nerve VI) cranial-nerve palsy.

Neurological-examination findings suggestive of LM include cranial neuropathies such as extra-ocular muscle dysfunction (cranial nerve VI > III > IV), facial sensory loss, facial weakness, hearing loss, alteration of gag reflex, tongue deviation, extremity weakness (in a lower-motor neuron nerve pattern), confusion, and gait disorder. The finding of a cranial neuropathy in patients with NHL is most suggestive of LM. Similarly, finding communicating hydrocephalus without an obstructing mass suggests the diagnosis of LM. As mentioned above, signs or symptoms of cauda equina dysfunction are characteristic of LM when there is no evidence of epidural spinal cord compression.

Imaging

Patients suspected of harbouring LM should undergo MRI of the brain and complete spinal axis (cervical, thoracic, and lumbar) if being considered for treatment. In the appropriate clinical setting, abnormal leptomeningeal enhancement is consistent with a diagnosis of LM. Classic MRI brain findings include cortical leptomeningeal enhancement (often focal), cerebellar folia enhancement, ventricular enhancement, enhancement of the brainstem surface, and nodular enhancement of cranial nerves. Subtle hydrocephalus may be present (< 10 %) and may only be appreciated if a prior imaging study is available for comparison. Computerised tomography (CT) of the head may show similar findings, although it is less sensitive than MRI.

The classic finding on spine MR is nodular contrast enhancement of the cauda equina nerve roots. Patients may also have clumping of nerve roots or enhancement of the spinal cord surface.

CSF Analysis

CSF examination should be performed in all patients suspected of having LM. CSF assessment should include measurement of opening pressure, cytology (to determine if pathologically malignant lymphoma cells are present), flow cytome-
try (more sensitive and less volume-dependent than cytology), cell count, protein, glucose, and Epstein Barr Virus polymerase chain reaction (in those with lymphoma secondary to immune-compromise).

**Opening Pressure**

Opening pressure measurement should be obtained with the patient in the lateral decubitus position. Measurements obtained in the sitting or prone (eg procedures under fluoroscopic guidance) position may under- or over-estimate ICP. Elevated CSF pressure measured by lumbar puncture is defined as > 20 cm H₂O (normal is approximately 12 cm H₂O).

**Protein**

Elevated protein is the most common CSF abnormality found in patients with LM. The finding is non-specific and not required for diagnosis. Normal CSF protein in the lumbar space and ventricle is < 45 mg/dl and < 25 mg/dl, respectively.

**Pleocytosis**

Patients with LM often have an increased CSF white count with lymphocyte predominance. CSF leukocytosis is defined as > 4/mm³. The number of CSF white blood cells in patients with LM is usually between 5–50 cells/mm³. A higher number of leukocytes or neutrophil predominance should raise the possibility of infectious meningitis.

**Glucose**

Low CSF glucose (hypoglycoracchia) is a common finding in patients with LM. Glucoracchia is defined as CSF glucose < ½ of serum glucose. Because patients may have rapidly fluctuating serum glucose and it takes several hours for serum glucose to equilibrate with CSF glucose, an absolute value < 40 mg/dl is considered low in patients without diabetes mellitus.

**Cytology and Flow Cytometry**

The demonstration of malignant lymphoma cells in the CSF is pathologically diagnostic of LM. Differentiating between a reactive versus malignant lymphocyte can be difficult on histological analysis. Flow cytometry is an analysis of cell surface markers by fluorescent probes to identify a monoclonal population of tumour cells. It is more sensitive than CSF cytology in patients with lymphoma [5]. The identification of a monoclonal population of lymphocytes in a CSF sample (predominantly B-cells) distinguishes neoplastic from reactive cells (overwhelmingly T-cells). A negative cytology does not rule out the diagnosis because of a high false negative rate (40%). The poor sensitivity results from a combination of sampling error and difficulty with specimen processing. Sampling error occurs because of a small number of cancer cells circulating in CSF and the random event of capturing suspended tumour cells in a comparatively large fluid volume. LM cells adhere at various locations in the CSF compartment, diminishing the number of suspended cells available for analysis. The yield of cytology is improved by sending a large volume of CSF for analysis, ideally > 10 millilitres. The entire CSF cytology sample is centrifuged to concentrate the available cells for analysis. The CSF collected should be processed immediately or mixed with a preservative to prevent cell lysis. In some cases, a cervical puncture may improve yield (especially in patients where the LM are predominantly located along the brainstem). In a patient with an intraventricular device (ie an Ommaya reservoir), a sample can be obtained from the ventricle as well. Even with correct specimen processing, the false negative rate is still high; up to 50% of patients with eventual positive CSF cytology have a negative initial examination. Minimal benefit is obtained from a third CSF specimen if the first 2 CSF samples are negative for malignant cells. Importantly, nearly half of all patients with LM have persistently negative CSF cytology, suggesting positive CSF cytology is not the only parameter that defines LM. Neuroimaging (nearly 50% of all studies are negative for LM) and clinical examination often provide the only evidence for LM.

**Treatment**

A physiologic blood-CSF barrier (analogous to the blood-brain barrier) excludes water-soluble substances, such as most systemic chemotherapy agents, from entering the CSF. Chemotherapy can be administered directly into the CSF space or systemically at high doses (methotrexate [MTX] 3–8 g/m² or cytarabine > 2–3 g/m²). The intra-CSF chemotherapy agents most commonly used for LM are MTX, thio-TEPA, cytarabine (including liposomal cytarabine), and corticosteroids. The doses and schedules of these drugs are displayed in Table 2. Patients are typically treated with single-agent MTX or liposomal cytarabine, MTX alternating with cytarabine, or triple therapy with MTX, cytarabine, and corticosteroids. The optimal agent, dose, frequency or whether combination therapy is advantageous has never been established in prospective clinical trials. A small randomised trial suggested that liposomal cytarabine is more effective than free cytarabine when administered intra-CSF in patients with NHL and LM [6]. There is limited data to suggest intra-CSF rituximab (a monoclonal antibody directed at malignant CD20-expressing B-lymphocytes) either alone or combined with liposomal cytarabine may be safe and effective for lymphomatous meningitis [7, 8]. Intra-CSF chemotherapy may be administered either intralumbar, ie intrathecal therapy or by intraventricular injection through a ventricular access device, eg an Ommaya or Rickham reservoir and intraventricular catheter. There is a sin-

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**Table 2. Frequently used drugs for intrathecal instillation**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
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<tbody>
<tr>
<td>Methotrexate</td>
<td>12 mg</td>
<td>MTX/cytarabine twice weekly for 3 weeks, then alternate once a week until cytologic response, then alternate monthly</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>30–60 mg</td>
<td>MTX/cytarabine twice weekly for 3 weeks, then alternate once a week until cytologic response, then alternate monthly</td>
</tr>
<tr>
<td>DepoCyt (liposomal cytarabine)</td>
<td>50 mg</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Methotrexate/ cytarabine</td>
<td>12 mg/50 mg</td>
<td>MTX/cytarabine every 2 weeks, then alternate once a week until cytologic response, then monthly</td>
</tr>
<tr>
<td>Thiopeta</td>
<td>10–15 mg</td>
<td>Twice weekly for 3 weeks, then weekly for 4 weeks, then monthly</td>
</tr>
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Peripheral Nerve Dysfunction Secondary to Lymphomatous Infiltration

In patients with NHL and manifesting these symptoms should undergo a diagnostic evaluation as summarised above. Involved-field radiotherapy (to sites of symptomatic disease, bulky disease as defined radiographically, and sites of CSF flow obstruction) and either high-dose systemic or intra-CSF chemotherapy are the main treatment modalities for patients with NHL and LM.

Neurolymphomatosis

Lymphomatous infiltration of a nerve root, peripheral nerve, cranial nerve, or multiple peripheral/cranial nerves is known as neurolymphomatosis (NL). NL is a rare neurologic complication of systemic lymphoma that is poorly recognised by oncologists and neurologists.

The predominant malignant cell type is diffuse large B-cell, although rare cases secondary to follicular lymphoma, peripheral T-cell lymphoma, and mantel cell lymphoma have been reported [12].

Clinical Presentation

NL classically presents as a painful, sensorimotor peripheral neuropathy affecting multiple limbs in an asymmetric manner with relatively rapid evolution [12]. Other patterns of presentation include cranial neuropathy with or without pain, painless involvement of peripheral nerves, and painless or painful involvement of a single peripheral nerve [12, 13].

This neurologic complication typically presents several months after successful treatment of systemic lymphoma. Another classic presentation is a patient successfully treated with intra-CSF chemotherapy for leptomeningeal lymphoma that develops a painful polyneuropathy. Rarely, the disorder presents prior to a diagnosis of lymphoma or is the sole manifestation of lymphoma. NL is frequently misdiagnosed as a paraneoplastic/inflammatory neuropathy, particularly if there is an initial response to steroids. Other misdiagnoses include LM, peripheral nerve compression, and chemotherapy-induced peripheral neuropathy.

Imaging

Brain or spine MRI or CT imaging often fails to show nerve root or peripheral nerve abnormalities in patients with NL, further potentiating the difficulty in making the diagnosis. Contrast-enhanced MRI of the brachial plexus, lumbosacral

The advantage of intra-CSF treatment is that tumourocidal CSF drug concentrations can be achieved at doses that do not usually cause systemic toxicity. The predominant toxicity of intra-CSF chemotherapy is the induction of transient chemical aseptic meningitis manifested by headache, nausea, vomiting, CSF pleocytosis, and occasionally confusion. It can usually be differentiated from infection without obtaining CSF cultures as the symptoms of aseptic meningitis occur within hours after injection, too soon for an iatrogenic bacterial infection. Aseptic meningitis usually resolves within 1–5 days and can be treated with oral antipyretics, antiemetics, and corticosteroids. Rare side effects of intra-CSF chemotherapy include acute encephalopathy, myelopathy, and subacute encephalopathy (reversible stroke-like syndrome). Prolonged survivors of LM may be at risk for developing a late leukoencephalopathy (dementia, urinary incontinence, and gait apraxia), especially if they are treated with concurrent MTX and whole-brain radiotherapy or receive MTX following whole-brain radiotherapy. Similar delayed late neurotoxicity may be seen with the use of intra-CSF liposomal cytarabine.

Although intra-CSF chemotherapy is the mainstay treatment for LM, there are several limitations. First, intra-CSF chemotherapy should not be administered to patients with CSF obstruction or impaired flow dynamics as demonstrated on a radionucleotide ventriculography study. Impaired CSF flow dynamics is more common in leptomeningeal metastases from solid tumours although it is seen in nearly 15 % of patients with LM and is more common when bulky subarachnoid disease is present [10, 11]. Impairment of the normal CSF circulation leads to stasis of fluid in the ventricles and other regions. Chemotherapy injected into a blocked CSF compartment does not circulate and consequently does not treat the entire CSF space. Furthermore, the administered intra-CSF drug is effectively concentrated in the blocked compartment resulting in increased drug exposure and potentially enhanced neurotoxicity. Involved field radiotherapy to the site of CSF flow obstruction/bulky disease may alleviate obstruction and permit safe intra-CSF drug administration.

In addition, administration of intra-CSF chemotherapy is not always straightforward. Intra-CSF chemotherapy can be delivered into the lumbar space by repeated lumbar punctures (intrathecal therapy) or into the ventricle via an Ommaya reservoir (an intraventricular catheter attached to a subgaleal reservoir) as mentioned above. Both routes of intra-CSF drug delivery have limitations. Chemotherapy delivered via lumbar puncture is limited by patient discomfort, time required to perform the procedure, thrombocytopenia (platelets > 50,000 are required to reduce the risk of an iatrogenic epidural haematoma), and coagulopathy. In addition, the drug is often (approximately 15 %) injected into the subdural or epidural space so intrathecal therapy is not administered. Finally, even with successful intrathecal injection, therapeutic drug concentrations in the ventricular space may not be reliably achieved in nearly ½ of patients.

Because an Ommaya reservoir avoids these issues, it is employed in the majority of patients that are treated with intra-CSF chemotherapy in the United States. Treatment with a ventricular access device is not without complications; the device is subject to infection (nearly 10 %) and may occasionally be misplaced at the time of surgical implantation. Finally, placement of a ventricular access device requires a surgical procedure that is associated with risks of any neurosurgery procedure.
plexus, or limb may show contrast enhancement of peripheral nerves with associated enlargement and nodularity [14, 15]. Infiltrated nerves may appear hyperintense on STIR and T2-weighted images reflecting lymphoma and peritumoural oedema. Caution must be made in interpreting the MRI as radiation plexopathy and other non-metastatic lesions may have a similar appearance. In addition, cases of biopsy-proven NL exist in which MR images displayed no abnormality [12, 14, 15]. Hypermetabolic activity along the course of a nerve root or peripheral nerve on FDG-PET supports a diagnosis of NL in patients with the appropriate clinical history with or without an abnormal MR imaging [12, 14–16]. Figure 1 displays typical MR and FDG-PET imaging for a patient with NL.

The only certain diagnostic test is biopsy, although patients with the classic clinical history of NL and abnormal PET imaging are usually treated empirically given the difficulty in making a histological diagnosis. The yield of a positive biopsy is dependent upon sampling a clinically or radiographically involved nerve. Because NL may not involve the entire peripheral nerve, blind nerve biopsies of affected nerves and non-involved sural nerve biopsies (the common site for a peripheral nerve biopsy) are frequently negative for lymphomatous infiltration [17]. In addition, treatment with steroids may result in a false-negative biopsy given their lytic effect on lymphoma. FDG-PET/CT may assist in identifying a target for biopsy in a patient in which a biopsy is necessary, such as those without a history of lymphoma.

Electrophysiological Studies
Nerve conduction studies reveal some degree of reduced compound muscle and sensory action potentials and demyelinating features may be present [18]. Patients with NL may meet the electrodiagnostic criteria of definite chronic inflammatory demyelinating polyneuropathy (CIDP), so caution must be taken to avoid misdiagnosis of an immune-mediated neuropathy [18].

Staging Work-Up
After establishing a diagnosis of NL, patients should undergo a staging work-up that includes a contrast-enhanced MRI of the brain (to evaluate for leptomeningeal or parenchymal involvement), CSF analysis (flow cytometry to evaluate for leptomeningeal involvement), and CT of the chest, abdomen, and pelvis with contrast (to evaluate for systemic lymphoma).

Treatment
Given the rarity of the disease, prospective clinical trials evaluating potential treatments are lacking. Treatment is challenging as a physiologic “nerve-blood barrier,” analogous to the “blood-brain barrier,” excludes water-soluble chemotherapeutic agents from entering the nerves. Treatment with corticosteroids may initially result in a radiographic response and improve symptoms, although NL typically recurs or progresses as the malignancy develops resistance. As with central nervous system lymphoma, high-dose methotrexate chemotherapy achieves cytotoxic concentrations in the peripheral nerve and is the treatment of choice for most patients either alone or in combination with involved-field radiotherapy. Radiotherapy is particularly useful in patients with significant neurologic dysfunction since it may rapidly improve or stabilise symp-

toms. Given the rarity of the disease, prognosis is not well-established, although limited reports suggest a poor outcome. A retrospective study of 50 patients with NL reported a median survival of 10 months with 12-month and 36-month survival proportions of 46 % and 24 %, respectively [12]. The poor outcome is partially related to the frequent difficulty and delay in making the diagnosis. Limited reports suggest that consolidation with autologous stem cell transplantation following response to high-dose methotrexate may be an effective option [19].

Summary
Neurolymphomatosis classically presents as a painful, sensorimotor peripheral neuropathy affecting multiple limbs in an asymmetric manner several months after successful treatment of systemic lymphoma. This neurologic complication is poorly recognised by neurologists and oncologists and frequently misdiagnosed as a chemotherapy-induced or paraneoplastic/inflammatory neuropathy. Contrast-enhanced MRI of the brachial plexus, lumbosacral plexus, or limb may show contrast enhancement of peripheral nerves with associated enlargement and nodularity, or may be unremarkable. FDG-PET is useful in supporting the diagnosis in patients with the appropriate clinical history and normal MRI, to localise an appropriate nerve to biopsy, and to monitor response to therapy. High-dose systemic methotrexate alone or in combination with focal radiotherapy (in those with significant neurologic dysfunction) is the most common treatment. Although limited data regarding prognosis is available in the literature, there is a consensus that it is typically poor.

Unusual Causes of Peripheral Nerve Dysfunction
Epidural spinal cord metastases (ESCM) usually arise from the vertebral body or, less commonly, the vertebral lamina, pedicle, or spinous process. Epidural lymphoma causes neurologic dysfunction via spinal-cord, cauda equina, or nerve root
compression. Pain is the earliest and most common symptom of epidural metastases. Other symptoms include sensory loss or muscle weakness in a dermatomal or myotomal pattern. Treatment typically consists of focal radiotherapy or systemic chemotherapy. ESCM is a risk factor for the development of LM so appropriate patients should be screened.

Presumed paraneoplastic neuropathies that have been reported in patients with NHL include demyelinating neuropathy (resembling CIDP), sensory ganglionopathy, and vasculitic neuropathy [18, 20, 21]. The CIDP-type neuropathy typically presents subacutely as a painless, symmetric sensorimotor polyneuropathy. Electrophysiological studies display prolongation of distal latency and reduction of the conduction velocity. Sural nerve biopsy may show segmental demyelination without lymphomatous involvement. Patients with sensory ganglionopathy typically present with ataxia in the extremities from loss of proprioceptive sense. Electrophysiological studies reveal reduction of sensory nerve action potentials. A sural nerve biopsy reveals predominant large-fibre loss. Autopsy studies reveal loss of neurons in the dorsal-root ganglia with the preservation of motor neurons in the spinal cord and absence of lymphomatous infiltration. Vasculitic paraneoplastic neuropathy presents clinically as mononeuropathies, not as a diffuse symmetrical nerve dysfunction typical of peripheral neuropathies [20]. Electrophysiological studies reveal asymmetric axonal neuropathy. Nerve biopsy, which reveals occlusion of small vessels in the epineurium with inflammatory cellular infiltration without an atypical cellular appearance, is necessary to prove the diagnosis [18]. Intravenous immunoglobulin, plasma exchange, and rituximab may be an effective treatment in some patients, particularly those with CIDP-type or vasculitic-type paraneoplastic neuropathies. Other immunosuppressants such as steroids, mycophenolate, cyclophosphamide, and azathioprine may also be effective.

Intravascular lymphoma (IL), also known as angiotropic large-cell lymphoma or malignant angioendotheliomatosis, is a rare subtype of extranodal, diffuse large-B-cell lymphoma characterised by occlusion of small vessels by malignant lymphomatous cells [22]. 75–85% of IL patients present with neurological symptoms [23]. The 4 most common neurological presentations include multiple-focal cerebrovascular events, spinal-cord and nerve-root vascular syndromes, subacute encephalopathy, and cranial-nerve or peripheral neuropathies [22]. The primary mechanism of nerve injury in the neuropathic presentation is ischaemic infarction caused by the proliferation of neoplastic lymphoid cells and immune-complex deposition within the walls of the vasa nervosum, leading to vessel occlusion. Ischaemic lesions accumulate randomly along the course of peripheral nerves, typically causing a painful, predominantly distal, asymmetric neuropathy. Long myelinated fibres are most susceptible, however, with disease progression, the pattern of damage becomes more diffuse with smaller unmyelinated fibres also being affected. With multiple-neuror nerve-root involvement, mononeuropathy multiplex [24, 25] or lumbosacral polyradiculopathy (cauda equina syndrome) [26] may be the presenting syndrome. In those with peripheral nervous system manifestations, diagnosis can be made by biopsy of an affected nerve or nerve root. The highly varied presentation frequently results in diagnostic confusion, highlighted by the fact that the diagnosis is established at autopsy in most published cases.

**Conclusions**

LM and NL are 2 neurologic complications of NHL that are associated with significant neurological disability. Other neurologic complications of NHL affecting the peripheral nervous system include epidural spinal cord metastasis with nerve-root compression (after the nerves have exited from the subarachnoid space), compression of a peripheral nerve by a focal tumour, and paraneoplastic neuropathies.

**Conflict of Interest**

The authors report no conflicts of interest in relation to the subject matter of this review.

**References:**