Lymphoma Nerve Infiltration

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*European Association of NeuroOncology Magazine* 2014; 4 (2)
61-64
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Abstract: Neurolymphomatosis (NL) denotes the invasion of cranial nerves, nerve roots, plexus, or nerves by Non-Hodgkin lymphoma (NHL). Most commonly, NL occurs as a result of dissemination from systemic disease sites, brain or cerebrospinal fluid (secondary NL). NL in the absence of systemic NHL (primary NL) is exceedingly rare. NL has to be distinguished from the much more common chemotherapy-induced, inflammatory, or paraneoplastic neuropathies.

In this review, the clinical manifestations of NL are described. Current knowledge of the mechanisms of NHL dissemination into nerves is summarised and diagnostic procedures as well as treatment options are outlined.

Introduction

Neurolymphomatosis (NL) is defined as invasion of cranial nerves, nerve roots, plexus, or nerves by Non-Hodgkin lymphoma (NHL). Most commonly, NL occurs as a result of dissemination from systemic disease sites, brain or cerebrospinal fluid (secondary NL). NL in the absence of systemic NHL (primary NL) is exceedingly rare. NL has to be distinguished from the much more common chemotherapy-induced, inflammatory, or paraneoplastic neuropathies.

Epidemiology

NL appears to be the least common direct neurologic manifestation of NHL. The disease is slightly more common in men and manifests itself over a wide age range. However, population-based incidence data are not available. Relative frequencies ranging from < 1 % to 40 % have been reported in case series [1, 2]. The wide range is explained by varying definitions, variable inclusion of leukaemia cases, and differences in diagnostic material available for diagnosis (biopsy, autopsy, imaging only). In a small case series, the relative incidence of NL was estimated to be 3 % in patients with newly diagnosed intermediate or high-grade NHL patients annually [3]. The cumulative incidence of central nervous system (CNS) invasion by NHL ranges from 2.2–6.9 % (excluding Burkitt’s lymphoma in which it is substantially higher) and by acute leukaemia from 9–10 % [4, 5]. NHL dissemination into the peripheral as well as central nervous systems most commonly occurs with aggressive subtypes such as diffuse large B-cell lymphoma (DLBCL) or lymphoblastic histologies. Based on reported population-based incidence data (approximately 70,000 cases of NHL and 20,000 cases of acute leukaemia per year in the US [6]), it is estimated that there are < 2000 cases of NL per year in the US. Less than 10 % of these cases are primary NL.

Pathogenesis

NL patients, similar to patients with primary CNS lymphoma, have a history of idiopathic diseases of possible autoimmune aetiology (recurrent chorioretinitis, celiac disease, hypothyroidism, Bell’s palsy, Sjögren’s syndrome, systemic lupus erythematosus, erythema nodosum, erythema multiforme, allergic purpura) at a greater-than-expected rate [7–10]. Selected case reports with neuropathic symptoms for months to years preceding the diagnosis of NL suggest that lymphoma may arise in a subset of patients by malignant degeneration of an autoimmune B-cell clone targeting peripheral neural structures [7, 11–13]. We have observed several cases in which NL was preceded by lymphomatous invasion of cerebrospinal fluid. Clinical and radiographic signs of NL soon followed the initially successful eradication of tumour cells from CSF, suggesting that the intrathecally administered drug sufficiently eliminated freely floating tumour cells but failed to address tumour cell infiltration into proximal nerve roots and their intraneural spread.

The vast majority of NL cases consist of B-cell NHL [7, 14]. Based on autopsy data, systemic involvement by lymphoma is found in the majority of patients with NL. However, only 20 % are known to have systemic lymphoma at the time NL is diagnosed and in another 10 % systemic and peripheral nervous system involvement is found coincidentally although these numbers may represent a selection bias [7]. Given the morphologic similarities, it is likely that tumour cells in NL share molecular features with CNS lymphoma, for example, derivation from germinal centre or post-germinal centre B-cells [15]. Studies on molecular pathogenesis, the role of transforming viral pathogens, and chronic antigenic stimulation have not been performed in NL.

Site-specificity of NL in NHL reflects conserved physiological behaviour of the originating tumour cell. It is based on expression of a stimulating endogenous or exogenous antigen within the target organ and mediated through adhesion receptors [16]. Selectins (mediating tethering), integrins, and chemokines (mediating adhesion and migration) have been implicated in CNS dissemination of NHL [17–20], for example neural cell adhesion molecule (NCAM) expression (CD56) in peripheral
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T-cell lymphoma [21]. Yet a role of CD56 in the targeting of peripheral neural structures could not be confirmed [22]. Specific adhesion molecules as the basis for target organ selection in NL have yet to be identified.

## Clinical Presentation

NL presents most commonly as a painful polyneuropathy or polyradiculopathy, followed by cranial neuropathy, painless polyneuropathy, and peripheral mononeuropathy. Nervous-system involvement progresses over weeks to several months. A relapsing-remitting pattern of progression may be seen when the disease temporarily responds to empiric therapies for clinical diagnoses such as chronic inflammatory demyelinating polyneuropathy. At advanced disease stages, there is diffuse infiltration of peripheral neural structures as well as CSF and the substance of brain and spinal cord [7, 14].

In patients presenting with painful polyneuropathy or polyradiculopathy, lumbosacral roots or nerves are more often affected than cervical or thoracic ones. Neuropathic pain is followed by an ascending sensorimotor polyradiculoneuropathy resulting in more or less symmetric paraparesis or quadriplegia. Other patterns of progression such as mononeuropathy multiplex or isolated plexopathies have been observed. The disease usually evolves over weeks to months but hyperacute variants reminiscent of Guillain-Barré syndrome have been described [11].

In about 20% of patients with NL, the early disease course is characterised by isolated cranial neuropathy [7]. Peripheral facial nerve weakness, sometimes bilateral or recurrent, abducens, abducens, trigeminal neuropathy (including tic doloreux), hearing loss, and preauricular pain as well as vocal cord paralysis have been described.

Various mononeuropathies secondary to lymphomatous infiltration have been reported: sciatic, median, radial, and intercostal. Patients present with motor or sensory deficits, often in the absence of pain [7]. The mononeuropathy can remain isolated for months to years but the majority of patients develop more widespread lymphoma or have a history of prior systemic lymphoma.

## Diagnosis

The diagnostic gold standard for NL is histopathologic examination of an involved nerve biopsy. NL is characterised by tumour cell infiltration of endo- and perineurium. Tumour cells display B-cell-associated surface antigens (CD19, CD20) and a high proliferative index. However, the decision to biopsy a nerve or root does not come easily and the procedure is performed in less than half of patients. Thus, diagnosis often relies on integration of clinical information, imaging findings, CSF analysis, and biopsy of non-neural tissue (for an example see Figure 1). The diagnosis is often delayed, especially in the absence of systemic lymphoma. Not uncommonly, it is the response to empiric treatment (steroid therapy, intravenous immunoglobulin, plasmapheresis) – or lack thereof – that may lead the clinician to the correct diagnosis. The diagnosis remains elusive until autopsy in almost half the reported cases [7].

Magnetic resonance imaging is the most sensitive and specific non-invasive diagnostic tool. Nerves, roots, or plexus infiltrated by NHL are enlarged and enhance after gadolinium administration (Figure 2A) [7, 14]. The radiographic differential diagnosis includes acute or chronic inflammatory radiculoneuropathies and tumours of the peripheral nerve sheath.

18-fluorodeoxyglucose positron emission tomography is a useful adjunct to the diagnosis of NL and identification of possible biopsy sites (Figure 2B) [3, 23–32].

CSF cytopathologic evaluation may be a useful diagnostic tool when NL is accompanied by meningeal dissemination (20–
40% of patients) [7, 14]. The use of automated cell sorting and lymphocytic surface receptor gene rearrangement (immunoglobulin heavy chain gene, T-cell receptor gamma subunit gene rearrangement analysis) for clonality assessment increases the diagnostic sensitivity and specificity [14].

**Treatment**

The majority of patients with NL are treated with systemic chemotherapy alone or combined with intrathecal chemotherapy or external beam radiotherapy [7, 14]. Therapy must address both symptomatic and asymptomatic root and nerve involvements, as well as the coexistent dissemination into brain parenchyma, CSF, and systemic sites. The biggest challenge is the distinction between NL and meningeal lymphomatosis or the recognition of their coexistence as neurologic syndromes largely overlap. Accurate staging is of utmost importance and the guidelines established for PCNSL should be followed (slit lamp examination of the eyes, contrast-enhanced MR images of brain and spine, CT scans of chest, abdomen, and pelvis, bone marrow aspiration and biopsy) [33].

Systemic chemotherapy is the most promising approach to NL as it is best suited to address the multiple sites of involvement [7, 14]. Intravenous methotrexate in doses exceeding 3.5 g/m², either alone or in combination with other drugs, is provided as first-line treatment for cases with isolated nervous-system involvement. Polychemotherapy regimens such as CHOP, MCHOD (methotrexate, cyclophosphamide, doxorubicin, vincristine, dexamethasone), hyperCVAD (cyclophosphamide, doxorubicin, vincristine, dexamethasone alternating with methotrexate and cytarabine), VAC (vincristine, doxorubicin, cyclophosphamide), ProMACE (procarbazine, methotrexate, doxorubicin, cyclophosphamide, etoposide)/Cytabom (cytarabine, bleomycin, vincristine, methotrexate), and others are used for patients with concomitant systemic lymphoma. In the absence of systemic lymphoma, it is unclear whether polychemotherapy confers any survival benefit to patients with NL compared to methotrexate monotherapy as has been demonstrated in cerebral parenchymal disease. It remains to be shown if the addition of rituximab improves treatment outcomes in NL [3]. Intrathecal chemotherapy (methotrexate, cytarabine, rituximab) is used to eradicate leptomeningeal involvement by lymphoma but it cannot sufficiently treat nodular root infiltration. Its impact on treatment outcome is difficult to ascertain. It may be dispensable in patients receiving high-dose methotrexate or cytarabine-based regimens. Myeloablative chemotherapy with autologous stem cell transplantation is feasible and can be considered for consolidation in NL patients in complete remission after conventional chemotherapy.

Radiation therapy is provided either with curative intent or for palliation. As in systemic lymphoma, adjuvant radiotherapy may be particularly useful as localised consolidation of bulky disease.

Corticosteroids should be avoided prior to the diagnosis of NL since the lymphotoxic effects of these drugs may obscure the histopathologic findings. Moreover, clinical benefit from corticosteroid monotherapy is short-lived and disease progression is the rule, in spite of continuation of therapy or upon tapering.

Retrospective case series suggest response rates exceeding 50%, disease stabilisation in 25%, and disease progression with initial therapy in the remainder [7, 8]. Given the selection bias in reporting single cases and lack of uniform response criteria, the accuracy of these estimates is unclear.

Median overall survival of NL is 10 months from initial diagnosis. Patients with primary NL may have a more favourable outcome [7].

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*Figure 2. Magnetic resonance imaging shows a thickened and enhancing lower cervical nerve root in a patient with primary neurolymphomatosis ([a] T1-weighted sequence after administration of gadolinium). 18-Fluorodeoxyglucose positron emission tomography reveals increased tracer uptake within the affected nerve root ([b] arrow head).*
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**Conclusion**
Dissemination into the peripheral nervous system is an uncommon complication of NHL and acute leukaemia. Timely diagnosis, preferably based on biopsy or CSF analysis, and sufficiently thorough staging are prerequisites for successful therapy. Characteristic neuroimaging findings may be sufficient for diagnosis in secondary NL and for patients in whom tissue acquisition is not deemed possible. Treatment needs to address the often widespread dissemination of the disease. Most neuro-oncologists use intravenous chemotherapy regimens including high-dose methotrexate or cytarabine. Patients with CSF involvement may benefit from the addition of intrathecal chemotherapy. Adjuvant radiation is used for consolidation of bulky disease. Primary NL carries a worse prognosis than cerebral parenchymal lymphoma, likely a function of diagnostic delay and suboptimal drug penetration through the blood-nerve barrier. There remains a need for improvement of diagnostic tools and novel therapeutic strategies.

**Conflict of Interest**
None.

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**References:**