Volume 4 (2014) // Issue 2 // e-ISSN 2224-3453

European Association of NeuroOncology Magazine

Neurology · Neurosurgery · Medical Oncology · Radiotherapy · Paediatric Neuro-oncology · Neuropathology · Neuroradiology · Neuroimaging · Nursing · Patient Issues

Lymphoma Nerve Infiltration

Baehring JM

European Association of NeuroOncology Magazine 2014; 4 (2) 61-64

Homepage

www.kup.at/journals/eano/index.html

Online Database Featuring Author, Key Word and Full-Text Search

THE EUROPEAN ASSOCIATION OF NEUROONCOLOGY

Member of the DOAJ

Indexed in EMBASE

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz, Austria

Lymphoma Nerve Infiltration

Joachim M Baehring

Abstract: Neurolymphomatosis (NL) denotes the invasion of cranial nerves, nerve roots, plexus, or nerves by Non-Hodgkin lymphoma (NHL) or leukaemia. This occurs in the absence (primary NL) or presence (primary NL) of systemic NHL. Clinical patterns include a painful polyneuropathy or polyradiculopathy, cranial neuropathy, painless polyneuropathy, and peripheral mononeuropathy. Integration of clinical information, imaging findings, as well as histopathologic examination of involved nerves or non-neural tissue, and cerebrospinal fluid analysis are needed to establish the diagnosis. Timely recognition of the disease and its exact neuroanatomical extent is the basis for successful therapy using systemic chemotherapy and localized irradiation of bulky disease sites. More complex regimens are required when cerebrospinal fluid and systemic disease sites are affected. **Eur Assoc NeuroOncol Mag 2014; 4 (2): 61–4.**

Key words: neurolymphomatosis, NHL, lymphoma, leukaemia

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.

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.

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 autoreactive 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

Received on December 12, 2013; accepted after revision on February 10, 2014; Pre-Publishing Online on March 26, 2014

From the Section of Neuro-Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT, USA

Correspondence to: Joachim M Baehring, MD DSc, Section of Neuro-Oncology, Yale Cancer Center, 15 York Street, LLCI 920, New Haven, CT 06510, USA; e-mail: joachim.baehring@yale.edu

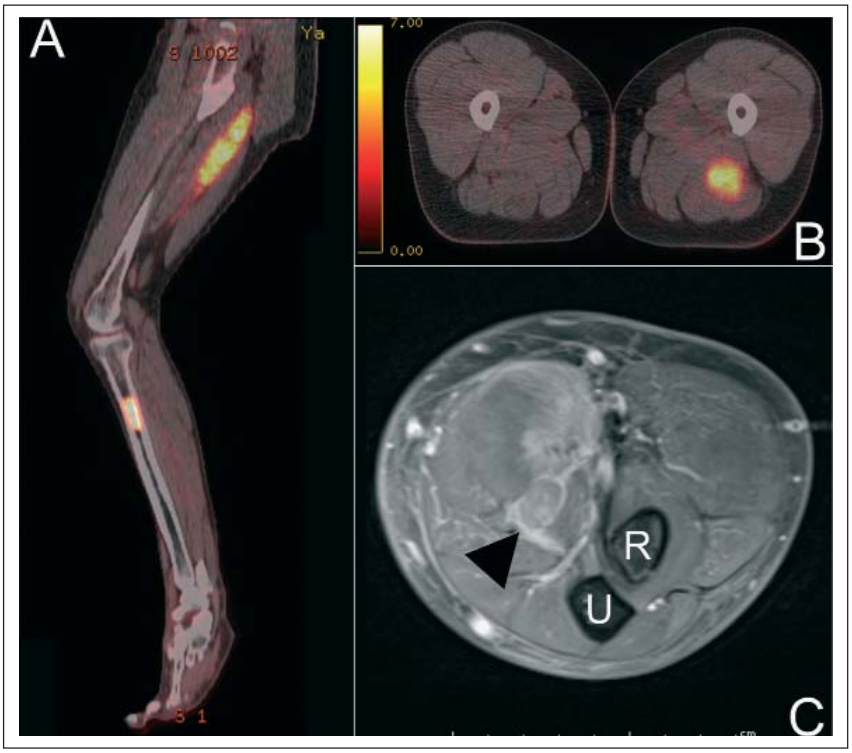

Figure 1. A 54-year-old man with a history of mantle cell lymphoma presented with tingling along the palmar surface of his left thumb. Then the left thumb, first and second digit started feeling *"inflamed, swollen, about to explode"*. The pain awakened him at night. At the same time, he felt a burning pain along the heel, lateral and anterior plantar surface of the right foot. Work-up revealed neurolymphomatosis. Multiple mass lesions were identified within the peripheral nervous system including the left sciatic nerve (**[a, b]** 18-FDG-PET), the left median nerve (arrow head in **[c]**; axial T1-weighted MRI of the left forearm; note infiltration of the flexor musculature by tumour), right brachial plexus, right sciatic nerve, and left tibial nerve (not shown). Biopsy of the soft tissue mass in the right forearm revealed a mantle cell lymphoma.
R: radius; U: ulna

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 afflicted than cervical or thoracic ones. Neuropathic pain is followed by an ascending sensorimotor polyradiculoneuropathy resulting in more or less symmetric paraparesis or quadriparesis. 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].

NL presenting as painless peripheral neuropathy is characterised by paresthesias, numbness, and loss of deep-tendon stretch reflexes followed by weakness. Asymmetric or patchy onset or early proximal limb weakness reflecting plexus invasion are rare.

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, oculomotor, 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–

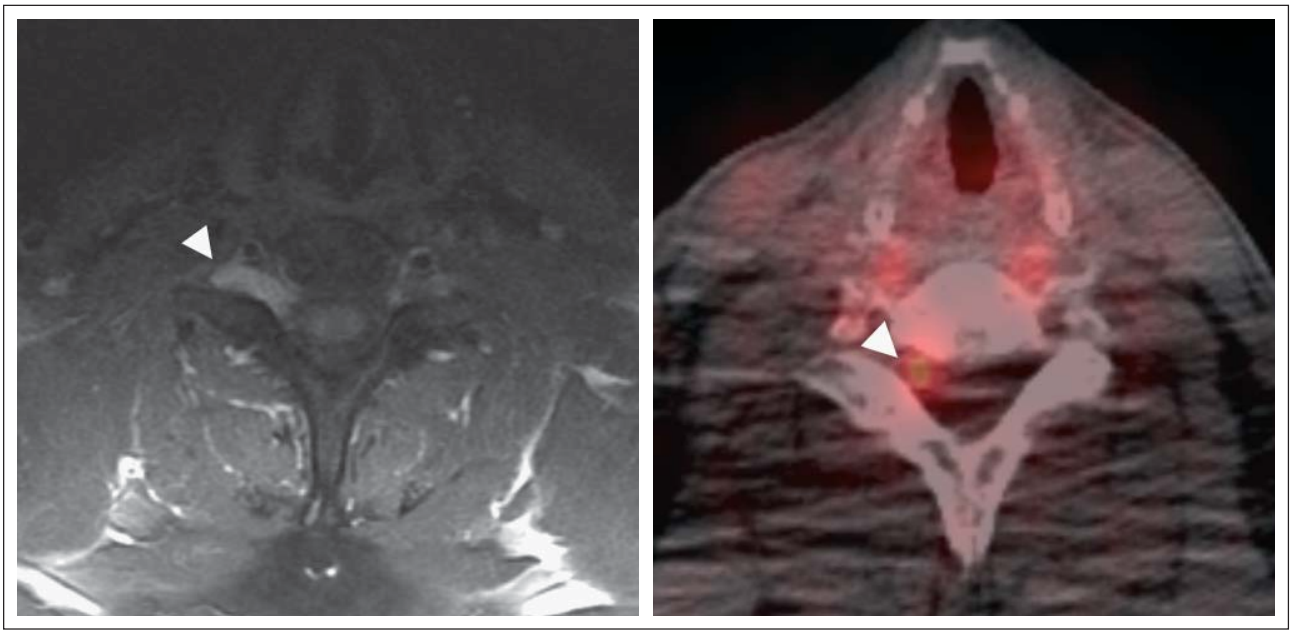

Figure 2. Magnetic resonance imaging shows a thickened and enhancing lower cervical nerve root in a patient with primary neurolymphomatosis (**[a]** T1-weighted sequence after administration of gadolinium). 18-Fluorodeoxyglucose positron emission tomography reveals increased tracer uptake within the affected nerve root (**[b]** arrow head).

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/m^2, 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].

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 penetrance through the blood-nerve barrier. There remains a need for improvement of diagnostic tools and novel therapeutic strategies.

Conflict of Interest

None.

References:

1. Jellinger K, Radiaszkiewicz T. Involvement of the central nervous system in malignant lymphomas. Virchows Arch A Pathol Anat Histol 1976; 370: 345–62.

2. Currie S, Henson RA. Neurological syndromes in the reticuloses. Brain 1971; 94: 307–20.

3. Gan HK, Azad A, Cher L, et al. Neurolymphomatosis: diagnosis, management, and outcomes in patients treated with rituximab. Neuro Oncol 2010; 12: 212–5.

4. Hollender A, Kvaloy S, Lote K, et al. Prognostic factors in 140 adult patients with non-Hodgkin's lymphoma with systemic central nervous system (CNS) involvement. A single centre analysis. Eur J Cancer 2000; 36: 1762–8.

5. Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in paediatric leukaemia. Lancet Oncol 2008; 9: 257–68.

6. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10–29.

7. Baehring JM, Damek D, Martin EC, et al. Neurolymphomatosis. Neuro Oncol 2003; 5: 104–15.

8. Gherardi R, Gaulard P, Prost C, et al. T-cell lymphoma revealed by a peripheral neuropathy. A report of two cases with an immunohistologic study on lymph node and nerve biopsies. Cancer 1986; 58: 2710–6.

9. Jellinger K, Kothbauer P, Weiss R, et al. Primary malignant lymphoma of the CNS and polyneuropathy in a patient with necrotizing vasculitis treated with immunosuppression. J Neurol 1979; 220: 259–68.

10. Abdel Aziz KM, van Loveren HR. Primary lymphoma of Meckel's cave mimicking trigeminal schwannoma: case report. Neurosurgery 1999; 44: 859–62.

11. Borit A, Altrocchi PH. Recurrent polyneuropathy and neurolymphomatosis. Arch Neurol 1971; 24: 40–9.

12. Pages M, Marty-Double C, Pages AM. Sensory neuropathy as revealing symptom of neurolymphomatosis: report of a case with a 15-year duration. Eur Neurol 2004; 52: 57–8.

13. Tajima Y, Sudo K, Matumoto A. Malignant lymphoma originating in the cauda equina mimicking the inflammatory polyradiculoneuropathy. Intern Med 2007; 46: 1029–32.

14. Grisariu S, Avni B, Batchelor TT, et al. Neurolymphomatosis: an International Primary CNS Lymphoma Collaborative Group report. Blood 2010; 115: 5005–11.

15. Hochberg FH, Baehring JM, Hochberg EP. Primary CNS lymphoma. Nat Clin Pract Neurol 2007; 3: 24–35.

16. Pals ST, de Gorter DJ, Spaargaren M. Lymphoma dissemination: the other face of lymphocyte homing. Blood 2007; 110: 3102–11.

17. Bashir R, Coakham H, Hochberg F. Expression of LFA-1/ICAM-1 in CNS lymphomas: possible mechanism for lymphoma homing into the brain. J Neurooncol 1992; 12: 103–10.

18. Albelda SM. Role of integrins and other cell adhesion molecules in tumor progression and metastasis. Lab Invest 1993; 68: 4–17.

19. Aho R, Kalimo H, Salmi M, et al. Binding of malignant lymphoid cells to the white matter of the human central nervous system: role of different CD44 isoforms, beta 1, beta 2 and beta 7 integrins, and L-selectin. J Neuropathol Exp Neurol 1997; 56: 557–68.

20. Huang K, Geoffroy JS, Singer MS, et al. A lymphocyte homing receptor (L-selectin) mediates the in vitro attachment of lymphocytes to myelinated tracts of the central nervous system. J Clin Invest 1991; 88: 1778–83.

21. Kern WF, Spier CM, Hanneman EH, et al. Neural cell adhesion molecule-positive peripheral T-cell lymphoma: a rare variant with a propensity for unusual sites of involvement. Blood 1992; 79: 2432–7.

22. Misdraji J, Ino Y, Louis DN, et al. Primary lymphoma of peripheral nerve: report of four cases. Am J Surg Pathol 2000; 24: 1257–65.

23. Cheung C, Lopes D, Hung KN, et al. Neurolymphomatosis: role of positron emission tomography in diagnosis. Ann Hematol 2012; 91: 1313–4.

24. Kosa SC, Peller PJ, Klein CJ. T-cell neurolymphomatosis involving cauda equina and sciatic nerves. Neurology 2009; 72: 98.

25. Koyama T, O'Uchi T, Matsue K. Neurolymphomatosis involving the trigeminal nerve and deep peroneal nerve in a patient with relapsed intravascular large B-cell lymphoma. Eur J Haematol 2010; 85: 275–6.

26. Nishio M, Tamaki T, Ochi H, et al. Intraspinal canal neurolymphomatosis detected by FDG-PET/CT. Clin Nucl Med 2009; 34: 610–2.

27. Peruzzi P, Ray-Chaudhuri A, Slone WH, et al. Reversal of neurological deficit after chemotherapy in BCL-6-positive neurolymphomatosis. Case report. J Neurosurg 2009; 111: 247–51.

28. Shima K, Ishida C, Okino S, et al. A linear lesion along the brachial plexus on FDG-PET in neurolymphomatosis. Intern Med 2008; 47: 1159–60.

29. Suga K, Yasuhiko K, Matsunaga N, et al. F-18 FDG PET/CT findings of a case of sacral nerve root neurolymphomatosis that occurred during chemotherapy. Clin Nucl Med 2011; 36: 73–6.

30. von Falck C, Rodt T, Joerdens S, et al. F-18 2-fluoro-2-deoxy-glucose positron emission tomography/computed tomography for the detection of radicular and peripheral neurolymphomatosis: correlation with magnetic resonance imaging and ultrasound. Clin Nucl Med 2009; 34: 493–5.

31. Wan MY, Ardeshna KM, Bomanji J. Neurolymphomatosis in a patient with lymphoblastic lymphoma. Br J Haematol 2012; 156: 691.

32. Ye BS, Sunwoo IN, Suh BC, et al. Diffuse large B-cell lymphoma presenting as piriformis syndrome. Muscle Nerve 2010; 41: 419–22.

33. Abrey LE, Batchelor TT, Ferreri AJ, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol 2005; 23: 5034–43.