Peripheral nerve neurolymphomatosis: clinical features, treatment and outcomes.

RUNNING TITLE: Peripheral nerve neurolymphomatosis

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Keywords

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/mus.27045

[181] Peripheral neuropathy, [216] Nerve tumour, [283] All clinical neurophysiology, [58] Natural history studies, [150] Haematologic

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Note statistical analyses were performed by the first author

Funding

Dr Keddie is funded by a Guarantors of Brain & Association of British Neurologists Clinical Training Research Fellowship.

Dr Rossor is funded by the Wellcome Trust.

Professor Lunn, Dr Carr, Dr Jaunmuktane and Professor Brandner are supported by the National Institute for Health Research, University College London Hospitals Biomedical Research Centre.

Professor Reilly is funded by the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases (U54NS065712) and the National Institute for Health Research, University College London Hospitals Biomedical Research Centre.

No authors received funding for the purposes relevant to the publication.

Ethics

We confirm we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflicts of interest

The authors report no competing interests.

Abstract

Introduction: This series characterises 9 patients with neurohistopathologically proven peripheral nerve neurolymphomatosis.

Methods: A search of the hospital neuropathology database from 2002-2019 identified biopsy proven cases. Clinical data, investigation modalities, treatments and outcomes were collated.

Results: Median age at neuropathy onset was 47 years, commonly as the initial disease manifestation. Most (8/9) presented with painful asymmetrical sensory disturbance, with additional cranial nerve involvement in three. Neurophysiology typically demonstrated multiple axonal mononeuropathies. Cerebrospinal fluid protein was often raised (6/8). Magnetic resonance imaging suggested peripheral nerve infiltration in 6/9 and positron emission tomography CT in 4/9. Bone marrow biopsy was abnormal in 6/8. Treatment involved systemic or intrathecal chemotherapy and radiotherapy. Median survival was 23 months.

Discussion: Neurolymphomatosis is a rare but important cause of neuropathy, particularly in those lacking systemic evidence of lymphoma as correct aggressive treatment can prolong survival. Nerve biopsy is essential to classify lymphoma type and rule out alternatives.

Introduction

Neurolymphomatosis (NL) is defined by direct infiltration of neurotropic malignant lymphoid cells into the peripheral or central nervous system (CNS) from a primary haematological malignancy.[1] The timing, location and extent of nerve infiltration is variable, reflected by the heterogenous and often unpredictable clinical phenotypes. Cerebrospinal fluid (CSF) analysis, magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging are useful investigations in peripheral nerve neurolymphomatosis (pNL), but may be inconclusive or normal.[2–4] Histological confirmation is definitive, but due to patchy nerve infiltration in pNL, biopsy findings may be non-diagnostic.[3]

Ascertaining the correct diagnosis of neuropathy in lymphoma is crucial and allows for appropriate treatment strategies.[5] The heterogeneity of the clinical findings, coupled with sub-optimal sensitivity of investigations can lead to misdiagnosis and delayed lymphoma targeted treatment. [6] This is of particular relevance, as pNL precedes systemic disease in approximately a quarter of patients, and early treatment favours better prognosis.[7,8] Of note, although pNL implies lymphoma, a single patient with nerve infiltration by a plasma cell leukaemia was also included in this cohort as this was considered a related entity.

Cohorts of patients with pNL confirmed with lymph node histology only, other than nerve biopsy, risk including cases where there are alternative causes of the neuropathy, such as antibody mediated, toxic, paraproteinemic or paraneoplastic. This paper presents a series of

neurohistopathologically defined patients with pNL, as opposed to all causes of neuropathy directly or indirectly caused by lymphoma.

Methods

Subjects

A retrospective search was made through the National Hospital for Neurology and Neurosurgery (NHNN) neuropathology database for all peripheral nerve biopsy samples from 2002 to present day with pathologically definite pNL. Endoneurial, epineurial, perivascular or intravascular lymphoma, neoplastic B-cell, T-cell or plasma cell infiltration or leukaemic nerve infiltration were eligible for the study. As the focus of the study was to consider the impact of nerve biopsy in identifying pNL and consequently improving survival, autopsy data were not included. Other forms of peripheral neuropathy associated with lymphoma, such as paraneoplastic, vasculitic, toxic, metabolic and drug related neuropathies were also excluded. All patients were presented at a multidisciplinary nerve biopsy meeting, with specimens interpreted by two peripheral nerve histopathologists and discussed amongst a team of peripheral nerve consultants.

Standard protocol approvals, registrations and patient consents

Ethics

Data were collected retrospectively by case note review of routine clinical practice and therefore covered by University College London Hospital (UCLH) Trust and National

Hospital audit policies. As per this guidance, no further approval of our ethics committee was required.

Clinical assessment

All patients were sequentially examined and investigated by a peripheral nerve specialist at the National Hospital for Neurology and Neurosurgery (NHNN), London, in conjunction with haematologists at UCLH. Time from presentation to diagnosis, clinical features, investigation results, treatment types and response were collated.

Assessment of sensory symptoms was standardised and symptoms defined based on the degree of alteration or intensity from normal, and the level of resulting disability graded from + (mild alteration/intensity, non-disabling), to +++ (high alteration/intensity, disabling). Any discrepancies were adjudicated by a third researcher and resolved by consensus decision. Motor impairment scores were categorised according to the most affected limb(s) from 'mild' as + (MRC power scale 4-5) to moderate (MRC grade 3 , ++) and 'severe' (MRC power scale 0-2, +++). Although graded descriptively in clinical notes, pain assessment was not standardised and was recorded as either present or absent. Functional status of patients was assessed pre and post treatment (between 6 months and 1 year) using the modified Rankin Scale (mRS) [9] and Overall Neuropathy Limitations Score (ONLS) [10], scored by two independent clinicians reviewing the patients' notes, based on clinical history and documented examination findings. Any discrepancies were adjudicated by a third researcher and resolved by consensus decision. Overall survival was defined as time from diagnosis of

pNL to follow up or death, and progression free survival as time from treatment initiation (following diagnosis of pNL) to follow up or progression.

Neurophysiological testing

Nerve conduction studies were performed in the Clinical Neurophysiology department at NHNN. The studies performed were tailored to the clinical question, including side-to-side comparison studies to enable assessment of length-dependence and were otherwise performed using standardised techniques.

The electrodiagnostic criteria documented in the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy were used as the criteria for determining potential demyelination.[11] Classification of length-dependence required nerve involvement to be demonstrated to affect distal muscles more severely than proximal muscles, specifically feet more affected than calves, with less or no involvement of the hands and proximal lower limbs for example. Non-length dependence included patients displaying significant side-to-side asymmetry or where nerve involvement was more consistent with discrete nerves or nerve roots. Side-to-side asymmetry was determined by either a greater than 50% difference in amplitude between each side, or if a given parameter was only abnormal unilaterally.

Results

Clinical features

Seven males and two females were identified as having pNL. The median age at onset of neuropathy was 47 years (range 36-67). Five of 9 patients were referred for neuropathic symptoms at presentation, without a pre-existing diagnosis of lymphoma. It took an average of 20 months for a biopsy proven diagnosis to be made, ranging from 3-36 months. In those with an existing diagnosis of lymphoma (4 of 9), the mean duration of lymphoma to onset of neuropathy symptoms was 24.3 months (range 3-65 months). Peripheral neurolymphomatosis types consisted of seven B cell lymphomas, and one T cell lymphoma. One patient with plasma cell leukemic infiltration was also included in the cohort which though not a lymphoma, is another rare example of haematologic peripheral nerve infiltration manifesting with a similar clinical pattern. See table 1 for details.

Neuropathy developed in a sub-acute fashion in five patients (four weeks to three months) compared to four with a chronic presentation (more than three months) (see table 1). Most patients (8/9) initially presented with a multiple mononeuropathy pattern of sensory disturbance. Patient 1 presented with a symmetrical multiple mononeuropathy involving the hands and feet. Patient 2 appeared length dependent with lower limb sensory loss and severe pain, but EMG revealed an asymmetrical multiple mononeuropathy pattern. Patient 3 presented with a mononeuropathy of the right common peroneal nerve (see Figure 1). Three patients developed additional cranial nerve involvement. Patient 7 had a unilateral cranial nerve VII palsy, and two patients had multiple cranial palsies.

Pain was a feature in all patients. There was no autonomic disturbance reported. Weakness was found in 8/9 patients, at a severity of moderate in four and severe in four in the territory of the affected nerves (see table 1). Seven patients were unable to walk without assistance or using a wheelchair at diagnosis, with a median ONLS score of 6/12. Of the five patients presenting with neuropathy without a pre-existing diagnosis of lymphoma, three were given an alternative diagnosis for neuropathy prior to referral at NHNN (see table 1).

Investigation results

Cerebrospinal fluid analysis

CSF examination was performed on all but one patient, ranging from one to thirteen lumbar punctures per patient. The pre-treatment CSF white cell count was raised in 5/8 patients (mean:11 cells/μL, range 2-22). CSF protein was raised in 6/9 patients (mean:1500mg/dl, range 300-3400). Abnormal cytology was detected in 4/9 patients, described as lymphocytosis (patients 1 and 5), atypical lymphocytosis with CD20+ cells on flow (patient 2), and plasma cells (patient 9) respectively (see table 2). CSF white cell count significantly decreased following treatment (p=0.015, 95% CI 3.2-18.5), as did protein levels (p=0.023, 95% CI 300-2300). The number of CSF examinations performed did not appear to improve detection of abnormal cells. Patients two and four received 11 and 13 lumbar punctures respectively looking for highly suspected abnormal cytology. Patient two was found to have abnormal flow cytometry with an abnormal population of CD20+ cells detected on the first lumbar puncture (with 21 white cells per mm^3 in the sample), but none following. When cytology was abnormal (4 of 9), this was detected from the first lumbar puncture. Flow

cytometry was performed in patients where atypical cells were detected on cytology, but reported as abnormal only in one patient (patient 2). CSF IgM levels were measured in 5 patients, with abnormally raised CSF:serum IgM ratio in all cases. MYD88 mutation was identified in the CSF of one patient demonstrating both central and peripheral neurolymphomatous involvement.[12]

Monoclonal protein testing

Serum protein electrophoresis was abnormal in 6/9 patients, with serum immunofixation confirming a monoclonal protein in 5/8 patients. Further information is shown in Table 2.

Imaging

MR imaging was abnormal in all patients prior to the diagnosis of pNL, with neuro-axis contrast enhancement of the meninges (1), cranial nerves (3), nerve roots (3), brachial plexus (1) and sciatic nerve (2) documented. Patient 8 was noted to have enlarged retroperitoneal lymph nodes (2) and Patient 9 spinal vertebrae lytic lesions (1). Some patients had multiple abnormalities (Table 2).

FDG-PET scanning was also abnormal in 8 of 8 patients examined, with avidity detected in nerve roots (1), brachial plexus (2), peripheral nerves (3), and lymph nodes (2). Bone infiltration was detected in two patients and splenomegaly in one. There was some discordance between MRI and PET imaging results, with MRI detecting nerve involvement in two patients (patients 2 and 7) where PET did not.

Neurophysiology

All patients had at least two studies during their disease course (mean number of studies per patient 3; time between consecutive studies 11 days to 5 years). Neurophysiological data from 9 patients included 27 separate studies.

Eight patients demonstrated multiple sensorimotor neuropathies while there was one patient with multiple sensory mononeuropathy (patient 8).

A primarily axonal pattern of neuropathy was demonstrated in eight patients. Primarily demyelinating features were seen in one patient (patient 7) and was non-length dependent. This was also the only patient in our cohort to meet EFNS/PNS criteria for a primary acquired demyelinating neuropathy [11].

Despite initial studies occasionally demonstrating apparent length-dependence and symmetry, follow-up studies in all patients clearly demonstrated non-length dependence. The most common picture was that of asymmetric, multiple mononeuropathies, becoming more confluent with disease progression with no definite demyelinating features.

An interesting subgroup was identified in two of the four patients with diffuse large B-cell lymphoma (DLCBL). Conduction block was reported in both (patients 4 and 6) in the absence of any other demyelinating features, but repeat studies at nine days and 18 months

demonstrated an absence of the previously seen conduction block and findings were consistent with secondary Wallerian axonal degeneration which is likely attributed to 'pseudo-conduction block'. It should also be emphasised that these two patients were classified neurophysiologically as axonal and were separate to the single patient who had persistent demyelinating findings (patient 7).

Bone marrow biopsy

Bone marrow biopsy was performed in eight patients, of which only two were reported histopathologically normal (table 2). One, with no abnormal cells, was positive for a MYD88 mutation on cytogenetic examination which is found in the majority of patients with lymphoplasmacytic lymphoma and is also seen in marginal zone lymphoma and more rarely in diffuse large B cell lymphoma [14]. This result prompted sural nerve biopsy, where histology confirmed an intravascular B cell lymphoma. Other bone marrow biopsies were diagnostic for lymphoplasmacytic lymphoma (patient 1), diffuse large B-cell lymphoma (patient 3), and an abnormal B/plasma cell clone (patients 5 and 9).

Nerve biopsy

Six sural nerve biopsies were performed, compared to four targeted lesion biopsies of the sciatic (2) and median nerves (2).

Of the sural nerve biopsies, one demonstrated intravascular large B cell lymphoma in the epineural blood vessels (Figure 2, b, b1, b2); two biopsies showed low grade B cell

lymphoma (lymphoplasmacytic lymphoma and chronic lymphocytic lymphoma) in the endoneurium (Figure 2, a, a1, a2); one biopsy confirmed T cell lymphoma in the walls of a large calibre epineural blood vessel and another demonstrated plasma cell leukaemia in the endoneurium. The remaining sural biopsy was non-diagnostic (patient 5) and targeted biopsy was subsequently performed.

Of the four targeted nerve biopsies, all confirmed diffuse large B cell lymphoma widely infiltrating in the endoneurium and perineurium (Figure 2, c, c1, c2).

All biopsies displayed a degree of fibre loss, although the severity of this varied, ranging from mild to severe (up to 80% loss) and involving myelinated and unmyelinated fibres. The level of axonal degeneration was similarly variable, ranging from occasionally seen (2/fascicle) to severe and widespread (over 30/fascicle) active degeneration. In three (patients 3, 5, and 6), quantification the nerve was overrun by lymphoma limiting further interpretation.

We retrospectively tested six nerve biopsy samples for the detection of MYD88 mutations through real time PCR assay (patients 2, 4, 6-9). DNA was of inadequate quality for the detection of a mutation of the MYD88 gene in all patients.

Treatment

All patients diagnosed with lymphoma prior to the development of neuropathy were treated with systemic chemotherapy as detailed in supplemental table 1 and below.

There is no consensus treatment regime for pNL. Treatment typically involves intensive chemotherapy with regimes intended to treat primary CNS lymphoma or relapsed lymphoma.[3,15–19] All patients received intensive systemic chemotherapy, but over the years of this study treatments varied. Two patients received radiotherapy, one for curative intent (patient 3), and the other disease control in a patient deemed to be palliative (patient 6). Five patients received intrathecal methotrexate. Three patients received autologous stem cell transplants. One patient who relapsed following autologous stem cell transplant received a sibling allograft. The details of treatments delivered are shown in supplemental table 1.

Outcome

Most patients responded well to initial chemotherapy, especially those in the DLBCL group who all achieved initial complete treatment response. Functional outcome following initial treatment was favourable. Of eight patients treated, three saw a 4 to 6 point improvement in ONLS. Two patients had a single point improvement and two were stable. Only a single patient had a worsening of ONLS score. Although the initial treatment was mostly effective in supressing the evolution of neuropathy, and often improving functional status in the short term, the long-term outcome was often poor. Seven patients have died, with an overall median survival of 23 months (range 1-78), with 12-month and 36-month survival at 77% and 44% (Supplemental Table 1 and Supplemental Figure 1). Of those who died, five had

relapse or progression of lymphoma, one experienced a combination of progressive lymphoma and pNL with severe pain and worsening neuropathy, and one had pNL progression and chemotherapy induced encephalopathy. Median progression free survival was 16 months (range 1-77 months) with 12-month and 36-month PFS at 55% and 22%. Two patients remain progression free at 60 and 77 months (patients 4 and 1), the remaining have relapsed disease or died.

Discussion

pNL is a challenge to diagnose. Clinical findings include severe pain, asymmetric distribution, and a rapid evolution of the neuropathy with poor response to immunomodulatory therapy. Even when clinical suspicion is high, diagnostic confirmation is challenging.

Electrophysiological features of neuropathy in pNL are varied without clear diagnostic criteria. The typical pattern was of asymmetrical, axonal sensorimotor multiple mononeuropathies. Bilateral nerve conduction studies are strongly recommended to distinguish between multiple mononeuropathies and symmetrical axonal polyneuropathies. Needle EMG will also aid in unmasking any false appearance of length-dependence from a previous confluence of mononeuropathies. Two patients (4 and 6) demonstrated initial findings of conduction block on neurophysiology which when repeated had disappeared and were replaced with axonal degeneration. This is atypical for true persistent demyelinating conduction block seen in acquired inflammatory neuropathies like CIDP or multifocal motor

neuropathy (MMN), and most likely represents 'pseudo-conduction block', which has been described before.[13] The pathophysiological mechanism of this neurophysiological phenomenon is thought to be secondary to focal infiltration within the nerve between proximal and distal stimulation sites causing demyelination, with subsequent macrophage infiltration and axonal degeneration distally.[6] The benefit of follow-up studies is again demonstrated here, where the initial finding of conduction block may mislead neurophysiologists to the diagnosis of CIDP. This highlights the utility of repeating studies to demonstrate reversal and secondary Wallerian degeneration. As in the case of patient 7, EFNS/PNS electrophysiological criteria may be positive and such situations may lead to misdiagnosis and delay of appropriate treatment.

CSF is often normal in isolated cases of pNL without root involvement,[20] but patients two and four had evidence of root infiltration on MRI and therefore cytological evidence of such was considered clinically relevant. CSF albumino-cytologic dissociation is often seen in pNL but is not a specific finding. Abnormal CSF cytology was seen in only a quarter of the patients in this study. Other studies suggest the volume and number of CSF samples sent increases diagnostic yield for all CNS or proximal nerve root involved malignancies, but this was not seen in our cohort [21]. If present, abnormal CSF cytology was detected on first examination. When cytology was normal, repeated lumbar punctures did not yield positive results.

MRI findings in NL include enlargement or enhancement of nerves or roots, or evidence of systemic involvement including the CNS with meningeal enhancement. Nerve root thickening is not specific for NL, and can be seen in inflammatory neuropathies such as CIDP and POEMS syndrome, demyelinating inherited neuropathies,, carcinomatous infiltration, nerve sheath tumours and neurofibromatosis, and so should be interpreted in light of clinical information and other investigations.. Imaging modalities can yield normal results in NL, and therefore cannot be used to rule out lymphomatous involvement. This study demonstrates discordance between MRI and PET imaging results, and we recommend that both imaging modalities be performed to investigate NL. Ultrasonography of peripheral nerves may also demonstrate focal nerve thickening with increased blood flow on Doppler,[22] but was not performed in any patients of this cohort.

Nerve biopsy allows for histologic confirmation of NL, with a reported diagnostic yield of 80% from cranial nerve, root or peripheral nerve biopsy.[1,23] This study only included biopsy defined patients, so cannot compare results. Choice of nerve biopsy location is not straightforward. Surgical accessibility, relatively large size and pure sensory function make the sural nerve a non-targeted nerve biopsy site of preference. However abnormal neurophysiology may be purely related to distal Wallerian degeneration secondary to NL rather than direct lymphomatous infiltration, rendering the biopsy histopathologically abnormal, but not displaying evidence of NL. Radiology can often provide detail for lesion biopsies, [24] but such biopsies may be technically difficult without causing significant motor and sensory deficits.

There exists little precedent for the treatment of NL. Little is known about the importance of penetrating the blood-nerve barrier. Haematologists extrapolate from experience of treating the same entity in marrow or nodal compartments by using combinations of effective anti-lymphoma agents whilst gauging clinical response, often with sequential imaging. In the setting of B cell lymphoma, clear guidelines exist and typically consist of chemotherapy in combination with rituximab and more recently other agents such as BTK inhibitors.[25,26] In T cell lymphomas, there are fewer targeted therapies available so therapy choices are limited to cytotoxic therapies of varying intensities depending on performance status.

Long-term outcome in pNL is typically poor. A series of 50 international patients from 1993-2008 reported a median survival of ten months, with 12-month and 36-month survival at 46% and 24% respectively [7]. The survival figures reported from this current cohort are significantly better. Although numbers are small in this study, this could reflect the fact that treatment following neurohistopathological confirmation of disease behind the blood-nerve barrier allows for a more targeted treatment regimen. More research needs to be undertaken to understand the reasons for the differences in survival, but time to diagnosis and modern treatment regimens from this cohort may contribute.

In summary, pNL is a diagnostic and therapeutic challenge, with poor long-term outcome. Neurophysiology often demonstrates an asymmetrical multiple mononeuropathy at presentation and occasionally ‘pseudo-conduction block’. Extensive imaging and pursuit of a

histological diagnosis through lumbar puncture and lesional peripheral nerve biopsy are critical to making a diagnosis. Long-term outcomes may be improving with earlier and more lymphoma type-specific diagnosis. There are no evidence-based therapeutic guidelines for NL, and therefore treatment should be determined in liaison with experienced haematological specialists.

Figure legend

Figure 1: Sensory loss distribution at presentation in peripheral nerve neurolymphomatosis

Distribution of sensory loss to pinprick is shaded. Patients 1 and 2 presented with symmetrical multiple mononeuropathies (patient 2 electrophysiologically determined) . Patient 3 presented with a mononeuropathy, and patients 4-9 asymmetrical multiple mononeuropathies.

Figure 2: Histopathological nerve biopsy findings of B cell neurolymphomatosis

Patient 1 (a, a1 and b2): Lymphoplasmacytic lymphoma. Haematoxylin and eosin (H&E) stained section (a and a1) demonstrates widespread subperineurial and endoneurial infiltration of small lymphocytes (red arrows). Immunostaining for CD20 confirms that the small endoneurial lymphocytes are B cells.

Patient 2 (b, b1, and b2): Intravascular large B cell lymphoma. H&E stained section (b and b1) shows large atypical lymphoid cells (blue arrows) in some of the epineural blood vessels. CD20 immunohistochemistry (b2) highlights dense epineural intravascular infiltrates of large atypical B lymphocytes.

Patient 6 (c, c1 and c2): Diffuse large B cell lymphoma. H&E section (c and c1) shows a nerve fascicle completely overrun by large atypical lymphoid cells (yellow arrows), all of which show diffuse immunolabelling for B cell marker CD20 (c2).

Scale bar: 200µm in a-c and 600µm in a1-c1 and a2-c2.

Statement of contributions

Dr Keddie was responsible for study concept and design, data collection, writing and data analysis. Dr Nagendran was responsible for neurophysiology data collection and interpretation, writing of neurophysiology and edits. Dr Cox was responsible for data collection and writing. Dr Bomsztyk was responsible for data analysis and revisions for intellectual content. Drs Jaunmuktane and Brandner were responsible for histopathological data analysis and write up Drs Manji, Rees, Ramsay and Rossor were responsible for design, data analysis and revisions. Dr D'Sa, Professor Reilly, Dr Carr and Dr Lunn were responsible for study conception and design, drafts and revisions.

Table 1 Clinical features of patients with neurolymphomatosis

Patient number	Sex	Age (yrs)	Malignancy classification	Duration of lymphoma until neuropathic onset (months)	Neuropathy progression	Neuropathy type	Additional cranial nerve involvement	Neuropathic features at presentation		Diagnosis prior to NL
								Sensory	Motor	
1	M	43	LPL+BN	21	Subacute	MM *	No	++	++	CIDP
2	M	47	IV DLBCL	-36	Chronic	MM *	No	+++	+++	CIDP
3	M	53	DLBCL	-3	Chronic	MM	VII, VIII, XII	++	+++	
4	M	47	DLBCL	8	Subacute	MM	No	+	++	
5	M	67	DLBCL	-15	Chronic	MM	II, III, IV, VII	+++	++	Neurosarcoid
6	M	36	DLBCL	-34	Chronic	MM	No	++	++	CIDP
7	F	67	BCL	65	Subacute	MM	VII	++	+++	
8	M	70	pTCL NOS	-5	Subacute	MM (sensory only)	No	+++	-	
9	M	43	Plasma cell leukaemia	3	Subacute	MM	No	++	+++	

LPL= lymphoplasmacytic lymphoma, BN= Bing Neel, IV DLBCL = intravascular diffuse large B cell lymphoma, DLBCL = diffuse large B cell lymphoma, BCL = B cell lymphoma, pTCL NOS= peripheral T cell lymphoma non-otherwise specified.
M= mononeuropathy, MM= multiple mononeuropathy
ND= not defined. NAD= nil abnormal detected
Duration of lymphoma until neuropathic onset: A negative number indicates the duration that onset of lymphoma symptoms preceded those of neurolymphomatosis
* Both cases display symmetrical multiple mononeuropathies. Case one with hand and feet involvement, case two appeared length dependent with lower limb sensory loss and severe pain, but EMG revealed an asymmetric multiple mononeuropathy pattern.

Table 2 Investigative findings for patients with neurolymphomatosis

Patient number	CSF results *					SPE	IF	MRI Brain and Spinal cord	FDG-PET	Bone Marrow	Nerve biopsy site	Nerve biopsy result
	Number of LPs	White Cells (mm^3)	Protein (mg/dl)	Cytology	Flow cytometry							
1	3	12 1 1	3400 800† 600†	Lymphocytosis	Normal	+	IgM kappa	Meningeal enhancement	ND	LPL	Sural	LPL
2	11	21 15 1	2600 300 500†	Atypical lymphoid cells	CD20+ve	+	NAD	Diffuse lumbosacral root enhancement	Splenomegaly	No abnormal cells Low level MYD88 mutation	Sural	Intravascular large B cell lymphoma
3	5	2 1	2500 1000†	No atypical cells	ND	–	NAD	Cranial nerve enhancement VII, VIII, IX	Multifocal bone and lung nodule, sciatic	DLBCL	Sciatic	DLBCL
4	13	5 1	300 200†	No atypical cells	ND	–	ND	Enhancement of R brachial plexus, L5 root	R sciatic nerve, left T12 nerve root	No abnormal cells	Median	DLBCL
5	3	6 18 1	2100 1700 1100†	Lymphocytosis	Normal	+	IgG kappa	Enhancing lesion left orbital apex, R sciatic nerve	L brachial plexus, R sciatic nerve, L thigh	5% malignant B cell infiltrate	Sural - Sciatic	DLBCL

6	1	2	600	No atypical cells	ND	–	NAD	Enhancing L sciatic nerve, R arm mass	R brachial plexus	Not done	Median	DLBCL
7	3	12 22 10	1200 1100 800†	No atypical cells	ND	+	IgG kappa	Enhancing nerve roots, lymph nodes, lacrimal glands	Mediastinal lymph nodes	No abnormal cells	Sural	SCLL
8	ND	ND	ND	ND	ND	+	IgM kappa	Retroperitoneal lymph nodes	Retroperitoneal lymph nodes	Reactive	Sural	Neoplastic T cell infiltration, CD2, CD3+ve, CD20, CD68-ve**
9	4	2	300	Plasma cells	Normal	+	IgG kappa	Lytic spinal lesions, brain/cord normal	Diffuse bone uptake	Plasma cell myeloma, gain in 1q	Sural	Plasma cell infiltration

LPL= lymphoplasmacytic lymphoma, DLBCL = diffuse large B cell lymphoma, SCLL= Small cell lymphocytic lymphoma, BCL = B cell lymphoma, SPE = serum protein electrophoresis, IF - immunofixation

ND= not done, NAD= nil abnormal detected, + = presence of paraprotein, – absence of paraprotein

For each case, biochemistry and microscopy was performed a maximum of 3 times (results displayed), and remaining CSF examinations were sent for cytology only. † Values are following treatment. Cytology descriptions were based on all samples received.

** Immunoprofile matched that of lymphoid cells from lymph node biopsy performed in parallel. Lymphoid cells showed positivity for CD3, CD4, CD5, CD7 and CD2 and increased proliferation fraction

NL - neurolymphomatosis

CNS – central nervous system

CSF – cerebrospinal fluid

MRI – magnetic resonance imaging

PET – positron emission tomography

NHNN – National Hospital for Neurology and Neurosurgery

UCLH – University College London Hospitals

MRC – Medical Research Council

mRS – modified Rankin score

ONLS – Overall Neuropathy Limitations Scale

EFNS – European Federation of Neurological Societies

PNS – Peripheral Nerve Society

MYD88 – myeloid differentiation factor 88

FDG-PET – fluorodeoxyglucose – positron emission tomography

DLCBL – diffuse large B-cell lymphoma

CIDP – chronic inflammatory demyelinating polyradiculoneuropathy

MMN – multifocal motor neuropathy

LPL – lymphoplasmacytic lymphoma

PCR – polymerase chain reaction

PFS – progression free survival

EMG - electromyography

POEMS – Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes

BTK – Bruton Tyrosine Kinase

SPE – Serum protein electrophoreses

IFE - Immunofixation

References

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

2 van den Bent MJ, de Bruin HG, Bos GM, *et al.* Negative sural nerve biopsy in neurolymphomatosis. *J Neurol* 1999;**246**:1159–63.

3 Shree R, Goyal MK, Modi M, *et al.* The diagnostic dilemma of neurolymphomatosis. *J Clin Neurol* 2016;**12**:274–81.

4 Kamiya-Matsuoka C, Shroff S, Gildersleeve K, *et al.* Neurolymphomatosis: A case series of clinical manifestations, treatments, and outcomes. *J Neurol Sci* 2014;**343**:144–8.

5 Lin M, Kilanowska J, Taper J, *et al.* Neurolymphomatosis--diagnosis and assessment of treatment response by FDG PET-CT. *Hematol Oncol* 2008;**26**:43–5.

6 Tomita M, Koike H, Kawagashira Y, *et al.* Clinicopathological features of neuropathy associated with lymphoma. *Brain* 2013;**136**:2563–78.

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

8 Briani C, Visentin A, Cavallaro T, *et al.* Primary neurolymphomatosis as clinical onset of chronic lymphocytic leukemia. *Ann Hematol* 2017;**96**:159–61.

9 Patel N, Rao VA, Heilman-Espinoza ER, *et al.* Simple and reliable determination of the modified rankin scale score in neurosurgical and neurological patients: The mRS-9Q. *Neurosurgery* 2012;**71**:971–5.

10 Graham RC, Hughes RAC. A modified peripheral neuropathy scale: the Overall Neuropathy Limitations Scale. *J Neurol Neurosurg Psychiatry* 2006;**77**:973–6.

11 Van den Bergh PYK, Hadden RDM, Bouche P, *et al.* European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating

polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripher. *Eur J Neurol* 2010;**17**:356–63.

12 Poulain S, Boyle EM, Roumier C, *et al.* MYD88 L265P mutation contributes to the diagnosis of Bing Neel syndrome. *Br J Haematol* 2014;**167**:506–13.

13 Park HJ, Shin HY, Kim SH, *et al.* Partial Conduction Block as an Early Nerve Conduction Finding in Neurolymphomatosis. *J Clin Neurol* 2018;**14**:73.

14 Hamadeh F, MacNamara SP, Aguilera NS, *et al.* MYD88 L265P mutation analysis helps define nodal lymphoplasmacytic lymphoma. *Mod Pathol* 2014;**28**:1–11.

15 Matsue K, Hayama BY, Iwama KI, *et al.* High frequency of neurolymphomatosis as a relapse disease of intravascular large B-cell lymphoma. *Cancer* 2011;**117**:4512–21.

Grisariu S, Avni B, Batchelor TT, *et al.* Neurolymphomatosis : an International Primary CNS Lymphoma Collaborative Group report. 2016;**115**:5005–12.

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

18 Correale J, Monteverde DA, Bueri JA, *et al.* Peripheral nervous system and spinal cord involvement in lymphoma. *Acta Neurol Scand* 1991;**83**:45–51.

19 Visentin A, Ferrari S, Briani C, *et al.* Primary neurolymphomatosis as clinical onset of chronic lymphocytic leukemia. *Ann Hematol* Published Online First: 2016

20 Grisold W, Klimpfinger M, Maehr B, *et al.* Peripheral nerve involvement in lymphoma: the meninges as the crucial barrier between meningoradicular spread and neurolymphomatosis. *J Peripher Nerv Syst* 2007;**12**:58–60.

21 Connor AO, McFeely O, Bermingham N, *et al.* Cerebrospinal Fluid (Csf) Cytology: Factors Impacting on Diagnostic Yield. *J Neurol Neurosurg Psychiatry* 2016;**87**:e1.107-e1.

22 Vijayan J, Chan YC, Therimadasamy A, *et al.* Role of combined B-mode and Doppler sonography in

evaluating neurolymphomatosis. *Neurology* 2015;**85**:752–5. 0

23 Duchesne M, Roussellet O, Maisonobe T, *et al.* Pathology of Nerve Biopsy and Diagnostic Yield of PCR-Based Clonality Testing in Neurolymphomatosis. *J Neuropathol Exp Neurol* 2018;**77**:769–81.

24 DeVries AH, Howe BM, Spinner RJ, *et al.* B-cell peripheral neurolymphomatosis: MRI and 18F-FDG PET/CT imaging characteristics. *Skeletal Radiol* 2019;**48**:1043–50.

25 Mcmillan A, Ardeshna KM, Cwynarski K, *et al.* Guideline on the prevention of secondary central nervous system lymphoma: British Committee for Standards in Haematology. *Br J Haematol* 2013;**163**:168–81.

26 Chaganti S, Illidge T, Barrington S, *et al.* Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol* 2016;**174**:43–56.

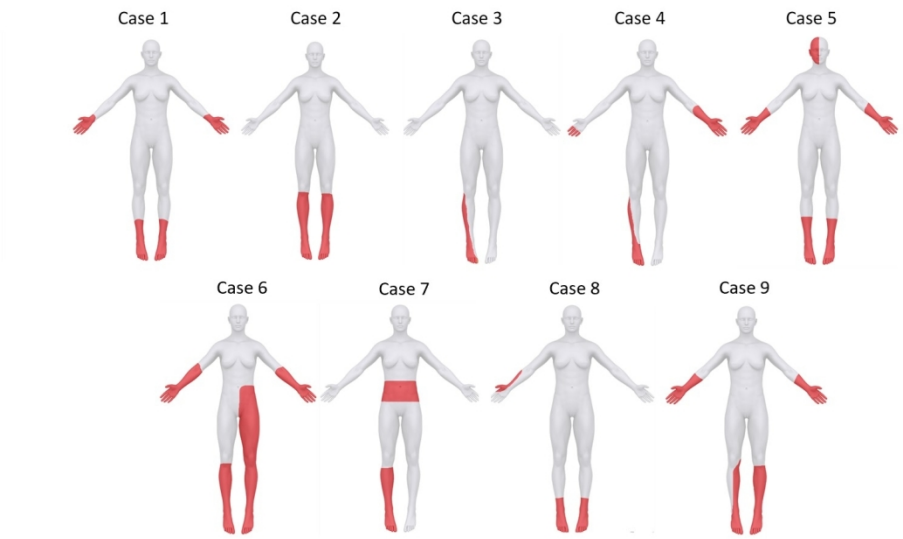

Figure 1: Sensory loss distribution at presentation in peripheral nerve neurolymphomatosis Distribution of sensory loss to pinprick is shaded. Patients 1 and 2 presented with symmetrical multiple mononeuropathies (patient 2 electrophysiologically determined) . Patient 3 presented with a mononeuropathy, and patients 4-9 asymmetrical multiple mononeuropathies.

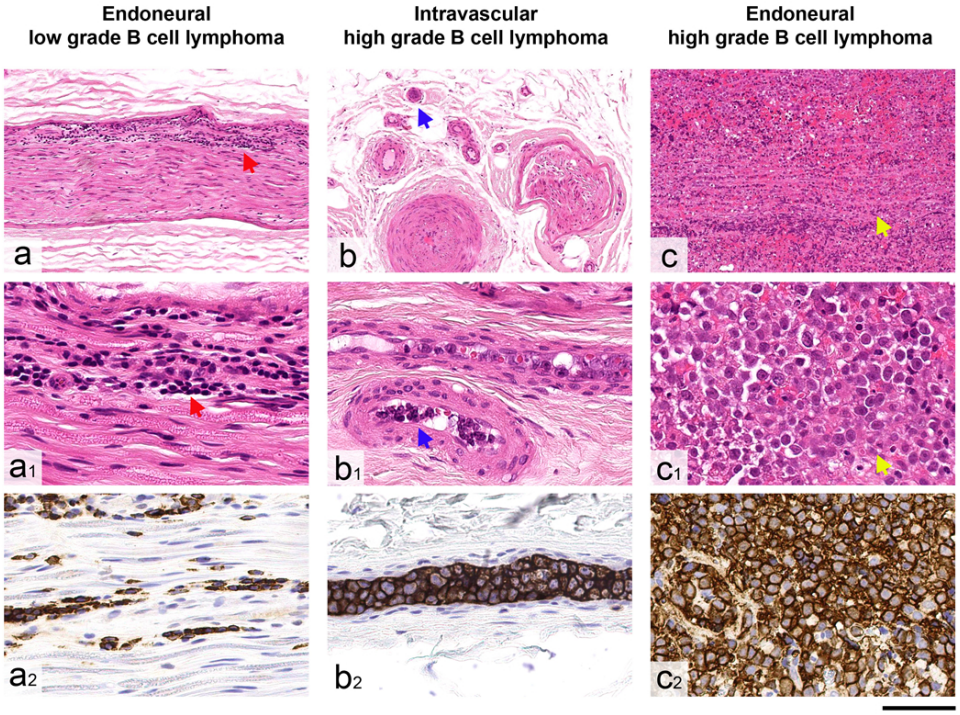

Figure 2: Histopathological nerve biopsy findings of B cell neurolymphomatosisPatient 1 (a, a1 and b2): Lymphoplasmacytic lymphoma. Haematoxylin and eosin (H&E) stained section (a and a1) demonstrates widespread subperineural and endoneural infiltration of small lymphocytes (red arrows). Immunostaining for CD20 confirms that the small endoneural lymphocytes are B cells. Patient 2 (b, b1, and b2): Intravascular large B cell lymphoma. H&E stained section (b and b1) shows large atypical lymphoid cells (blue arrows) in some of the epineural blood vessels. CD20 immunohistochemistry (b2) highlights dense epineural intravascular infiltrates of large atypical B lymphocytes. Patient 6 (c, c1 and c2): Diffuse large B cell lymphoma. H&E section (c and c1) shows a nerve fascicle completely overrun by large atypical lymphoid cells (yellow arrows), all of which show diffuse immunolabelling for B cell marker CD20 (c2). Scale bar: 200μm in a-c and 600μm in a1-c1 and a2-c2.