Neurolymphomatosis:
an International Primary CNS Lymphoma Collaborative Group report

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**Scientific Category:** Clinical trials and observations
Abstract:

Neurolymphomatosis (NL) is a rare clinical entity characterized by infiltration of peripheral nerves, nerve roots, plexus, or cranial nerves by malignant lymphocytes. The International Primary CNS Lymphoma Collaborative Group retrospectively analyzed 50 patients assembled from 12 centers in 5 countries over a 16 year period. NL was related to NHL in 90% and to acute leukemia in 10%. It occurred as the initial manifestation of malignancy in 26% of cases. The affected neural structures included peripheral nerves (60%), spinal nerve roots (48%), cranial nerves (46%) and plexus (40%) with multiple site involvement in 58%. Imaging studies often suggested the diagnosis with 77% positive MRI, and 84% (16/19) positive CT-PET studies. CSF cytology was positive in 40% and nerve biopsy confirmed the diagnosis in 23/26 (88%). Treatment in 47 patients included systemic chemotherapy (70%), intra-CSF chemotherapy (49%) and radiotherapy (34%). Response to treatment was observed in 46%. The Median overall survival was 10 months with 12 and 36 months survival proportions of 46% and 24% respectively. NL is a challenging diagnosis but contemporary imaging techniques frequently detect the relevant neural invasion. An aggressive multimodality therapy can prevent neurological deterioration and is associated with a prolonged survival in a subset of patients.
Introduction:

The term neurolymphomatosis (NL) encompasses nerve infiltration by neotrophic neoplastic cells in the setting of an unknown or a known hematologic malignancy. It is a rare neurologic manifestation of non-Hodgkin lymphoma (NHL) and leukemia with a poorly defined incidence. The most comprehensive review identified 72 cases of NL caused by NHL that were reported during a 28 year period. The majority of patients with NL described in the literature suffered from NHL and in that setting, NL appears to represent a unique subtype of extranodal disease. However, nerve infiltrating disease may occur rarely in leukemia and therefore, the present study assessed this clinical entity in patients with either NHL or leukemia.

The typical manifestations of NL are of a neuropathy that may affect peripheral nerves, nerve roots, plexus, or cranial nerves. The most common presentations include painful peripheral neuropathy or radiculopathy, cranial neuropathy, painless polyneuropathy and peripheral mononeuropathy or a mononeuropathy multiplex.

Successful therapy is contingent upon the recognition of this unique neurological complication, yet the diagnosis is difficult and often elusive. Because NL is rare, there is limited information available on mode of presentation, clinical course, the yield of diagnostic procedures and response to therapy. As well, the survival following diagnosis and treatment is poorly characterized as it has never been reported in a systematic study.

The International Primary Central Nervous System Lymphoma Collaborative Group (IPCG) is a multidisciplinary group established in 2002 under the sponsorship of the International Extranodal Lymphoma Study Group. Given the rarity of NL this neurologic complication of lymphoma and leukemia was identified as an area for which collaborative work could further our understanding of the disease. We report a retrospective analysis of 50 cases of NL that were assembled by 9 IPCG investigators from 12 centers in 5 countries. Because malignant infiltration of
peripheral nerves occurs in both NHL and leukemia, the current study investigated both conditions under the common term of NL.

**Methods:**

A retrospective chart review was conducted by the IPCG investigators to collect information on HIV seronegative adult patients whose final diagnosis was compatible with the definition of clinical neuropathy characterized by infiltration of malignant lymphocytes. As this study is retrospective inclusion of patients was based on final diagnosis of NL that often required the full perspective of the course of neurologic manifestations and the related diagnostic workup. Eligible were patients with neoplasms categorized as either lymphoma or leukemia. Other hematologic malignancies were excluded. Eligibility criteria included patients whose clinical manifestation was consistent with either a primary NL, defined as NL that is the first manifestation of the hematologic malignancy, or patients with secondary NL, in which NL is a site of relapse or progression of a previously diagnosed lymphoma or leukemia. In principle, NL was defined as neuropathy which is characterized by infiltration of malignant cells. Yet, manifestation of either cranial neuropathy or cauda equina involvement in the presence of positive cytology was not considered as NL unless evidence existed for intradural as well as extradural infiltration of the affected nerves or alternatively, additional data indicated that malignant infiltration of either peripheral nerves and/or neural plexi has also developed. Malignant infiltration of nerve structures that occurred in the set-up of a bulky disease that entrapped and infiltrated the neural elements was excluded. In primary NL infiltration of the affected neural structure had to be proved by a biopsy or at autopsy. In secondary NL the diagnosis required exclusion of other causes of neuropathy, presence of positive imaging findings that detected specific neural involvement and evidence for disease progression. If diagnosis remained in doubt a biopsy of the affected structure was required or otherwise autopsy findings indicated the final diagnosis.
A data collection form was sent to investigators and each one received ethics committee approval from all participating institutions for the release of case information that was rendered anonymous. Requested information included patient demographics, details of clinical history and presentation, prognostic parameters such as Eastern Cooperative Oncology Group Performance Status (ECOG-PS), serum lactate dehydrogenase (LDH) level, disease stage, extranodal site(s) involved at the diagnosis of lymphoma, International Prognostic Index (IPI) score, cell type or karyotype and total white blood cell count at diagnosis. Information was requested on neurologic status (muscle weakness, sensory deficit, autonomic abnormalities) as well as on the neurologic function at the diagnosis of NL. The neurologic function was assessed according to the following scale: 0= No neurologic symptoms; fully active at home/work without assistance. 1= Minor neurologic symptoms; fully active at home/work without assistance. 2= Moderate neurologic symptoms; fully active at home/work but requires assistance. 3= Moderate neurologic symptoms; less than fully active at home/work and requires assistance. 4= severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution, unable to do work. Data was collected on diagnostic measures conducted for evaluation of the neuropathy including imaging studies, cerebrospinal fluid (CSF) evaluation, and biopsy and DNA analysis of body fluids or tissues. In addition, the form requested information on types of treatment given for NL, response to treatment which was evaluated by post treatment ECOG-PS, neurologic function score, neurologic status and post treatment imaging studies. Data on disease progression, site(s) of involvement and survival were reported.

Descriptive summaries included proportions for categorical variables and medians, minimums, and maximums for numeric variables. Overall survival was calculated from the date of diagnosis of NL to the date of death. Surviving patients were censored at the date of last follow-up. Survival curves were estimated using the
Kaplan-Meier product-limit methods and comparisons between primary and secondary NL were examined by the log-rank test.

**Results:**

Information on a total of 50 patients was assembled. Patients with NL were diagnosed from January 1993 to November 2008. During this 16-year period only 15 (30%) patients were diagnosed during the first 8 years (until December 2000) and 35 patients were diagnosed afterward with 50% of all cases identified after January 2004. Of the 11 cases diagnosed up to 1998, in four the final diagnosis was established only at autopsy while in all the rest diagnosis was arrived ante mortem. The increased rate of detection of NL during the last 5 years raised the issue whether the presumably earlier or facilitated diagnosis is associated with changes in clinical features and treatment outcome compared to those described previously. Therefore, we present the main features of our series in parallel to those enumerated in the English literature (tables 1 and 2). The literature search was conducted for reports of adult patients with high grade lymphoma or acute leukemia presenting with cranial, spinal or peripheral nerve infiltration by malignant cells of these hematologic malignancies.

**Clinical features and diagnostic modalities:**

Patient characteristics are summarized in table 1. The median age of the current IPCG series was 55.5 year (range 18–80 years) and 30 (60%) were males. The underlying malignancy was NHL in 45 (90%) patients and 5 suffered from acute lymphoblastic leukemia. Of the 45 patients with NHL, 11 (24%) had initial diagnosis of primary CNS lymphoma (PCNSL). The predominant malignant cell type was B-cell and of the 5 patients with T-cell disease, 3 suffered from acute leukemia. The most common subtype of lymphoma was diffuse large B-cell (34/45; 75.5%). Four patients had follicular lymphoma (9%), 2 peripheral T-cell lymphoma (4%), and one mantel...
cell lymphoma (2%) and, in 4 cases (9%) information on the subtype of the disease was not available.

NL occurred as the first manifestation of malignancy (primary NL) in 14 (28%) cases (including 11 patients with systemic NHL, 2 with PCNSL and one with leukemia) and as a relapse or progression of a previously treated disease in the remaining 36 (23 patients with systemic NHL, 9 with PCNSL and 4 with leukemia). The two patients with primary NL that initially were diagnosed as PCNSL presented with cranial neuropathy as the initial manifestation of their disease. Cranial nerve infiltration by malignant lymphocytes was proved by biopsy. Both were then defined as PCNSL but at disease progression they continued to manifest features compatible with NL that included extension of neural involvement beyond the dura matter. One patient also developed parenchymal brain involvement during disease progression.

Secondary NL was diagnosed within a median interval of 10 months (range: 4-120 months) following initial diagnosis of the hematologic malignancy. The median ECOG-PS at the diagnosis of NL was 2. The IPI was reported in 32 of 34 (94%) patients with systemic NHL, and 26 (81%) of them had intermediate to high IPI (presence of 2 or more prognostic factors) at diagnosis.

NL affected more than one anatomic structure in 29 (58%) patients (table 1, figure 1A-C). Peripheral nerves were the most frequently involved site while spinal, cranial nerve involvement and neural plexus infiltration occurred at a similar rate. The manifestation of painful neuropathy was recorded in 38 (76%) patients with sensorimotor neuropathy being the most common type (36 cases). Notwithstanding, the infiltrative nature of NL, pure motor neuropathy was described in 20% of the patients and pure sensory neuropathy was noted in a single patient.

The diagnostic modalities included CSF analysis (in 45 patients), imaging studies that were reported for all patients, and nerve biopsy that was obtained in 26 (52%) of the patients (table 2). CSF analysis was remarkable for elevated protein in 61%, low glucose level in 11% and, elevated cell count (>5 cells/mm³) in 44%. Malignant cells
were detected in the CSF in 18 (40%) of the studies and suspicious cytology was reported in another 6 (13%). Of the 20 patients with elevated cell count 12 had positive cytology and 4 suspicious cytology. Thus, 8 patients had positive or suspicious cytology in face of normal CSF cell count. Of patients with abnormal CSF cell count in 6 (30%) cases no cranial or spinal root involvement was evident. All the rest manifested a combined affliction of cranial and/or spinal roots together with plexus and/or peripheral nerves involvement. The CSF evaluation also included PCR-based gene rearrangement analysis of either the immunoglobulin heavy-chain or of the T-cell receptor in 12 cases (24%) and was positive in 4 (33%).

All patients were evaluated by imaging and 23 (46%) were assessed by more than one modality. MRI was done in 47 (94%) cases while 18F-fluoro-2-deoxy-D-glucose (FDG) PET-CT was performed in 19 (38%) patients, the majority [16 (84%)] attained in patients diagnosed after 2004. The diagnostic yield of MRI and FDG-PET was high (table 2), with abnormal findings found in 77% and 84% respectively. MRI findings were detailed in 41/47 (87%) patients and included abnormal enhancement of the affected neural structure in 31 (76%) cases. The affected nerves were most commonly characterized as thickened (22/41; 53%), in 7 (17%) the involvement was diffuse, and in 12 (30%) it was nodular. Despite the high yield of imaging evaluation the findings were often not definitive and consequently nerve biopsy was performed in 26 (52%) patients. The biopsy demonstrated NL in 23 (88%) patients. Biopsy was performed from cranial nerves (2 cases), L2 spinal nerve root (1), brachial plexus (1), and peripheral nerves (15) including sciatic, peroneal, sural, femoral, and median nerves. Of the five sural nerve biopsies three were negative while all other biopsies demonstrated neural infiltration by malignant cells. For 7 patients the site of biopsy was not specified.

**Therapeutic management and outcome:**

Treatment was administered to 47 (90%) patients with NL (table 2). Treatment varied, with systemic chemotherapy given to 33 (70%), intra-CSF chemotherapy to 23 (49%),
and radiotherapy in 16 (34%). Both intravenous and intra-CSF treatment was administered to 19 (40%) patients, 4 (8.5%) received only intra-CSF therapy and 10 patients were managed by radiotherapy alone.

Systemic chemotherapy included high-dose methotrexate (MTX) in 23 patients (given as monotherapy to 10 patients), high-dose cytarabine in 18 patients (given as monotherapy to 5 patients), and other combination chemotherapy in 5 cases (including 4 rituximab-CHOP combination). Intra-CSF chemotherapy was administered by lumbar puncture or through an intraventricular Ommaya device. This treatment was given to 13 patients who manifested cranial and/or spinal root involvement and to 11 patients who had high CSF cell count. Of the 23 patients who received intra-CSF chemotherapy, 11 (48%) were treated with more than one agent. Intra-CSF chemotherapy included cytarabine given to 17 patients, MTX in 14, and 3 patients were treated with rituximab.

Radiotherapy was delivered to symptomatic sites of NL however 3 patients received a craniospinal field. Due to the retrospective nature of this case series data related to treatment toxicity was inadequately reported.

The response to treatment was assessed by comparing the pre- and post treatment score of ECOG-PS, neurologic function score, report of neurologic status, and objective response as detected by imaging. Of the 47 treated patients pre- and post treatment evaluations were available as follows: ECOG-PS and neurologic function in 35 patients, detailed neurologic status in 28 cases, and imaging in 25 patients.

Response to treatment based on 35 pre- and post treatment evaluations was noted in 16 (46%) patients who presented with a complete or partial resolution of their symptoms and signs. An additional 9 (26%) patients stabilized on treatment and the remaining 10 patients progressed despite treatment. The median ECOG-PS changed from 2 (pre-treatment) to 1.5 (post-treatment) and median neurologic function score from 2 to 1. These changes were not statistically significant (paired t-test). Post treatment imaging demonstrated complete resolution of the previously documented
abnormalities related to NL in 14 (56%) of 25 patients (figure 1D-G), partial response in another 3 (12%) cases, one patient showed no change and 7 (28%) worsened. Objective response as demonstrated by imaging corresponded to clinical and neurological improvement in all 17 patients.

The overall median survival calculated from the diagnosis of NL was 10 month (figure 2A) with 12-month and 36-month survival proportions of 46% and 24% respectively. When survival of patients with primary NL was compared to survival of secondary NL no statistically significant difference was observed (p=0.129) although the median survival of the 13 patients with primary NL was 20 months and that of secondary NL was 8 months (figure 2B).

**Discussion:**

Diagnosis of NL requires integration of clinical presentation (symptoms/signs), imaging findings and pathological data obtained from neural, extraneural tissue and the CSF. A high index of suspicion and familiarity with the clinical manifestations of NL is necessary. As it is a rare manifestation of hematologic malignancies, diagnosis is often delayed and its incidence remains unknown.

The current series is the largest detailed series ever collected. It describes the presentation, treatment and outcome of 50 NL cases that were diagnosed over a 16 year period (group C, table 1 and 2). A previous literature review covered a 28 year period and identified 47 cases which were reported together with 25 cases identified retrospectively by the authors¹ (group A table 1 and 2). Following this publication we found an additional 44 cases whose report was published during an 8 year period (group B table 1 and 2).

The majority (>50%) of patients in the present report were diagnosed in the last 5 years. This might be a product of an innate bias linked with the retrospective nature of our series as more recent cases are probably easier to identify and their records may be more accessible for review. Alternatively, it may be related to an increased awareness of this rare manifestation of lymphoma and leukemia or simply reflect a
facilitated diagnosis associated with the use of contemporary imaging techniques. Lastly, it may signify a trend in the biological behavior of hematologic malignancies related to a selection of specific neurotropic clones associated with either more aggressive treatment or longer survival. In order to clarify whether any of the above might have had an impact on our findings we have tried to compare the current series to previous publications (groups A and B). Group B corresponds to the period of diagnosis of the greater fraction of our patients (group C).

**Diagnostic modalities:**

Clinically, NL mimics nonneoplastic and paraneoplastic neuropathies. Clinical findings that suggest NL, as opposed to remote effects or inflammatory processes, include severe pain, asymmetric distribution, and rapid evolution. Painful neuropathy predominated in our series and was common in previously published cases (table 1). Regardless, the diagnosis is elusive and in 46% of group-A patients (identified early in the time period studied), the precise diagnosis was established only at autopsy. In the present case series and in group B from the literature (table 2) NL was more often detected ante mortem with diagnosis at autopsy reported in only 8 and 5% of cases respectively. This phenomenon of a decrease in the rate of post mortem diagnosis is likely related to the improved resolution of current imaging techniques that can detect affected neural structures with increased precision.

Of all diagnostic tools, imaging studies are of greatest clinical utility. All our patients were evaluated by one or more imaging techniques, the majority (94%) by MRI. MRI reveals nerve or root enlargement with or without contrast enhancement and oftentimes involvement of neural plexus (brachial or lumbar) that is more difficult to detect\(^1\,\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!}\)
affected patients (table 2) and facilitates the diagnosis particularly when a history of hematologic malignancy is known. PET-CT appears to be a highly sensitive diagnostic method facilitating identification of NL based on our experience and that reported in the literature (group-B in table 2, figure 1A, 1B, 1F). Altogether, the reported experience is of 40 NL patients evaluated by PET-CT amongst which 87.5% were positive studies. Although the total number of reported cases diagnosed by PET-CT is still small, positive findings are highly suggestive of the diagnosis of NL particularly in patients with a known history of hematologic malignancy. Together with MRI findings, PET-CT may define the best target for a biopsy, if one is indicated, especially in the instance of primary NL. Although the majority of our patients were evaluated by multiple diagnostic modalities (table 2), biopsy of an affected nerve was indicated for pathological confirmation in 52% of the patients. The diagnostic yield of the biopsy was high (88%) (table 2) and was similar to the rate previously described in the literature (table 2, group A and B). Therefore, if imaging and CSF findings are non-conclusive a nerve biopsy presents a reasonable approach if the risk does not outweigh the expected benefit.

**Treatment and outcome:**

There is no known standard treatment for NL and therefore, optimal management is ill defined. Treatment of NL consists of either chemotherapy alone or combined with radiotherapy. In order to select the appropriate therapy knowledge of the extent of systemic and nervous system involvement is essential. NL involves roots within, as well as beyond, the borders of the subarachnoid space and thus intra-CSF chemotherapy and standard craniospinal radiation fields will not treat all of the involved areas. Systemic chemotherapy is critical to address the multiple sites of involvement.

In the current series, 90% of the patients were treated, a rate that appears higher than that reported in the literature (groups A and B in table 2). This is probably related to the fact that our retrospective chart review specifically requested
information on therapeutic management. The information collected from the literature contains inadequate information on clinical management as some of the case reports addressed only the unusual neuroimaging findings.\(^8,11,14-21\).

In the current series, the majority of patients (70\%) were managed by systemic chemotherapy. The most effective regimen is unknown and the selection is often based on protocols used to treat CNS involvement by malignant lymphoma. Many centers employed intravenous high-dose methotrexate, either alone or in combination with other drugs and particularly with high-dose cytarabine. Methotrexate is effective against lymphoma affecting the nervous system and when given in high doses can penetrate the blood-brain and blood-nerve barrier. Any other choice of chemotherapy must also meet those criteria. However, in our series approximately 30\% of treated patients did not receive systemic chemotherapy due to the fact that NL represented relapse of a chemoresistant disease.

Radiotherapy has a limited role in the treatment of NL due to involvement of multiple sites, affecting both the CNS and the peripheral nervous system. Extensive radiation fields are poorly tolerated in most patients but limited-field radiotherapy can be very effective in relieving unremitting neuropathic pain attributed to a particular nerve, plexus or nerve root. Clinical improvement (functional recovery, reduction of pain), as well as radiographic resolution (improvement of nerve root enlargement and enhancement or normalization of FDG-PET uptake) has been observed in 50 to 70\% of treated patients (table 2) (figure 1D-E, 1F-G). Standardized criteria to measure response are not available and therefore no recommendations can be made from regarding treatment response.

There is no previous information on overall survival of patients with NL. The median survival from diagnosis of NL in our series was 10 months with 36-month survival proportion of 24\%. These data indicate that an aggressive multimodality therapeutic
approach can achieve long term survival in some patients. The trend toward longer median survival observed in primary NL likely reflects the fact that NL was the presenting manifestation of the malignant disease unlike in secondary NL. Nonetheless, long term survival was observed in secondary NL with one in four of all patients alive at 3 years.

In conclusion, it appears that NL is more frequently diagnosed in recent years. It is likely related to increased awareness of the disease and an enhanced rate of diagnosis due to the extensive use of contemporary imaging techniques that accurately localize abnormal process affecting neural structures. Early recognition and treatment of this rare neurological manifestation of lymphoma and leukemia may improve outcome.

**Acknowledgment:**

We thank Joachim M. Baehring M.D. from the department of Neurology, Medicine and Neurosurgery, Yale University School of Medicine, New Haven, Connecticut, USA for providing information and clarifying data related to his series of patients (group A) which is included in tables 1 and 2 of this manuscript. We thank Marc C. Chamberlain M.D. who is a co-author of this manuscript for providing imaging studies for figure 1A, 1B and 1C of this manuscript.

**Authorship Contributions:**

S.G. and B.A. contributed equally to the research design, data collection, and data analysis and reviewed the manuscript; T.T.B., M.J.B., F.B., D.S., O.K., M.C.C., P.R., A.N., E.S., and D.B-Y collected data and reviewed the manuscript; T.S. designed research, collected data, analyzed data, and wrote the manuscript.
Conflict-of-interest disclosure: The authors declare no competing financial interests.

References:


Table 1: Patient characteristics and clinical features of neurolymphomatosis

<table>
<thead>
<tr>
<th></th>
<th>Group A*</th>
<th>Group B **</th>
<th>Group C ***</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Literature review with MGH case-series</td>
<td>Literature review Case reports</td>
<td>Current IPCG case series</td>
</tr>
<tr>
<td>Number of patients</td>
<td>72</td>
<td>44</td>
<td>50</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (54%)</td>
<td>26 (59%)</td>
<td>30 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>33 (46%)</td>
<td>16 (36%)</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>2 (4.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age (years)</td>
<td>63 (18-84)</td>
<td>56 (16-71)</td>
<td>55.5 (18-80)</td>
</tr>
<tr>
<td>NL as an extranodal site of systemic lymphoma</td>
<td>29 (40%)</td>
<td>27 (61%)</td>
<td>33 (66%)</td>
</tr>
<tr>
<td>NL as the presentation of malignancy</td>
<td>NA</td>
<td>13 (29.5%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Malignant cell type:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cells</td>
<td>59 (82%)</td>
<td>29 (66%)</td>
<td>41 (82%)</td>
</tr>
<tr>
<td>T-cells</td>
<td>4 (5%)</td>
<td>11 (25%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>NK cells</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not classified</td>
<td>9 (13%)</td>
<td>3 (6.8%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Parenchymal brain involvement</td>
<td>19 (26%)</td>
<td>NA</td>
<td>11 (22%)-PCNSL</td>
</tr>
<tr>
<td>Affected neural structures*:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Peripheral nerves</td>
<td>46 (64%)</td>
<td>9 (20%)</td>
<td>30 (60%)</td>
</tr>
<tr>
<td>Spinal nerves</td>
<td>47 (65%)</td>
<td>14 (32%)</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>Neural plexus</td>
<td>23 (32%)</td>
<td>15 (34%)</td>
<td>20 (40%)</td>
</tr>
<tr>
<td>Cranial nerves</td>
<td>37 (51%)</td>
<td>15 (34%)</td>
<td>23 (46%)</td>
</tr>
<tr>
<td>Painful neuropathy</td>
<td>34 (47%)</td>
<td>25 (57%)</td>
<td>38 (76%)</td>
</tr>
<tr>
<td>Type of neuropathy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure motor</td>
<td>NA</td>
<td>7 (16%)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Pure sensory</td>
<td>NA</td>
<td>8 (18%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>NA</td>
<td>23 (52%)</td>
<td>36 (72%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>6 (14%)</td>
<td></td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>
*Group A consists of a retrospective case series of 25 patients diagnosed in Massachusetts General Hospital (MGH) and literature review of additional 47 cases that were published together \(^1\).

**Group B is based on literature review \(^4,7-41\)

***Group C is the current case series

NA= not available; NL=neurolymphomatosis; PCNSL = primary central nervous system lymphoma.
Table 2: Diagnostic modalities and response to treatment of neurolymphomatosis

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>No. positive/No. of tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>NA</td>
<td>3/11 (27%)</td>
<td>7/11 (64%)</td>
</tr>
<tr>
<td>MRI</td>
<td>28/40 (70%)</td>
<td>28/35 (80%)</td>
<td>36/47 (77%)</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>NA</td>
<td>19/21 (90%)</td>
<td>16/19 (84%)</td>
</tr>
<tr>
<td>CSF cytology</td>
<td>21/52 (40%)</td>
<td>10/24 (42%)</td>
<td>18/45 (40%)</td>
</tr>
<tr>
<td>CSF PCR gene rearrangement</td>
<td>NA</td>
<td>2/2 (100%)</td>
<td>3/11 (27%)</td>
</tr>
<tr>
<td>Biopsy of affected nerve</td>
<td>24/30 (80%)</td>
<td>19/21 (90%)</td>
<td>23/26 (88%)</td>
</tr>
<tr>
<td>Diagnosis established only by autopsy</td>
<td>33 (46%)</td>
<td>2 (5%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>No. pts treated for NL#</td>
<td>43 (60%)</td>
<td>34 (77%)</td>
<td>47 (94%)</td>
</tr>
<tr>
<td>IV HD-MTX</td>
<td>5/43 (12%)</td>
<td>8/34 (23.5%)</td>
<td>23/47 (49%)</td>
</tr>
<tr>
<td>Intra CSF chemoTx.</td>
<td>15/43 (35%)</td>
<td>14/34 (41%)</td>
<td>23/47 (49%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>10/43 (23%)</td>
<td>17/34 (50%)</td>
<td>16/47 (34%)</td>
</tr>
<tr>
<td>Response rate##</td>
<td>31/43 (72%)</td>
<td>20/34 (58%)</td>
<td>16/35 (46%)</td>
</tr>
</tbody>
</table>

*Group A consists of a retrospective case series of 25 patients diagnosed in Massachusetts General Hospital (MGH) and literature review of additional 47 cases that were published together 1.

**Group B is based on literature review (for references see table 1)
***Group C is the current case series

# Some patients were treated by chemotherapy other than high dose methotrexate.

## Includes complete and partial response by clinical improvement or by post treatment imaging.

ChemoTx.=chemotherapy; CSF=cerebrospinal fluid; HD-MTX=high dose methotrexate; IV=intravenous; NA= not available; NL=neurolymphomatosis:

No.=number; PCR=polymerase chain reaction; pts=patients.
Figure Legends:

**Figure 1:** Imaging studies in Neurolymphomatosis

Figure 1A, and 1B are FDG-PET imaging of a patient with neurolymphomatosis (NL).

Figure 1A demonstrates multiple sites involvement including the brachial and lumbosacral plexi (arrows). Figure 1B and 1C shows that there is a bilateral involvement of the brachial plexus in the same patient clearly detected by both FDG-PET (1B) and by MRI (1C) T2 STIR imaging.

Figure 1D and 1E are enhanced MRI imaging (T1-weighted with gadolinium) of a patient with NL that affected multiple cranial nerves. Figure 1D shows bilateral abnormal enhancement of the oculomotor nerves that corresponded to the clinical presentation of bilateral ophthalmoplegia. Figure 1E shows complete resolution of abnormal enhancement following 2 cycles of treatment with intravenous high dose methotrexate and intra-CSF treatment with cytarabine. These imaging findings matched the marked neurological improvement observed under treatment.

Figure 1F and 1G are FDG-PET imaging of a patient with NL who presented with severe painful sensorimotor neuropathy and bilateral brachial plexus involvement.

Figure 1F demonstrates FDG-PET findings at diagnosis of NL compatible with bilateral brachial plexus involvement by lymphoma. Figure 1G shows complete resolution of abnormal tracer uptake following two courses of treatment with systemic high-doses of methotrexate and cytarabine. The treatments lead to clear neurological improvement and good control of the painful neuropathy.

**Figure 2:** Survival of patients with neurolymphomatosis.

Figure 2A shows the overall survival of the 50 patients from date of diagnosis of neurolymphomatosis (median: 10 months). Vertical lines indicate censored observations.
Figure 2B demonstrates the survival of patients with either primary neurolymphomatosis (median 20 months; 13 patients) or with secondary NL (median 8 months; 37 patients). Vertical lines indicate censored observations.
Neurolymphomatosis: an International Primary CNS Lymphoma Collaborative Group report

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