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Primary Neurolymphomatosis: A Literature Review

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ABSTRACT

Background: Primary neurolymphomatosis (PNL) is a rare clinical entity resulting from direct lymphomatous infiltration into the peripheral nervous system. Its diagnosis is challenging as the hematological condition is unknown at the onset of neurological symptoms.

Methods: We report two of our own cases and the first extensive review of published cases of PNL to delineate its clinical features, paraclinical investigation results, progression, and treatment response more precisely. We extracted demographic data, clinical presentation, results of the investigations performed, type and number of treatments, overall survival, and progression-free survival.

Results: We describe 301 cases of PNL in patients with a mean age of 57.9 years, 61% of whom were men. The most common clinical presentation was an often painless asymmetric neuropathy. Other presentations included multifocal neuropathy preferentially affecting the sciatic and peroneal nerves, radiculopathy, brachial plexus lesions, cauda equina syndrome, and cranial nerve palsy. Systemic signs and deterioration of clinical status were uncommon.

Diagnosis was established after a median of 8 months, based on histological results (76%) or a cluster of elements in cases of positive PET findings.

A B-cell lymphoma was diagnosed in 73% of cases. Systemic chemotherapy (90%) and rituximab (60%) were the most common treatments, with a response rate of 45%. Relapse occurred in 24% of patients, and 55% ultimately died from PNL. Overall survival was 28 months. Type of treatment was not associated with survival.

Conclusions: This literature review provides an overview of the available data concerning PNL presentation and progression.

1 | Introduction

Neurolymphomatosis is a rare clinical entity defined as a direct infiltration of hematologic malignancies, such as non-Hodgkin lymphoma (NHL), into the peripheral nervous system (PNS) at the root, peripheral nerve, or cranial nerve level [1]. Neurolymphomatosis can be distinguished from direct nerve or root compression by the presence of lymphomatous masses or adjacent lymphadenopathy, leptomeningeal lymphomatosis, paraneoplastic neuropathies, and chemotherapy- or radiation-induced neuropathies. In primary neurolymphomatosis (PNL), nerve involvement occurs as the sole inaugural manifestation of the hematologic malignancy or concomitantly with nodal or other extranodal systemic involvement [2].

Various presentations of PNL have been reported, including painful peripheral neuropathy or radiculopathy, cranial neuropathy, painless polyneuropathy, and mononeuropathy or mononeuropathy multiplex [2]. As the lymphoma remains undetected at the time of neurological symptom onset, the diagnosis of PNL is often challenging and delayed. It requires extensive diagnostic testing both to rule out differential diagnoses and to obtain sufficient evidence for the establishment of the diagnosis. It often includes comprehensive blood testing, imaging, and histological (e.g., bone marrow, nerve structures) studies. The usefulness of new imaging techniques, such as ^{18}F-fluoro2-deoxy-D-glucose (FDG) positron emission tomography (PET), has been highlighted over the years, and such techniques are thought to facilitate earlier diagnosis and treatment, potentially improving the outcome of this debilitating neurological entity [3].

Only a limited amount of information is available for this disease, due to its rarity. Several case reports and series have been published in recent years [3, 4]. However, publications to date either included only a small number of cases or focused on specific characteristics of the disease, such as topographical involvement [5], or on diagnostic tools [6]. There has been no comprehensive report covering all single cases of PNL to date, despite the publication of several reviews [7, 8].

We therefore performed a systematic review of all published cases of PNL to obtain a more precise description of the clinical presentation, progression, prognosis, and response to treatment of this rare entity.

2 | Case Reports

We first report two new cases from our institutions.

2.1 | Case 1

A 72-year-old man with no relevant prior medical history initially presented in February 2021 with relapsing steroid-sensitive right arm pain and shoulder weakness of subacute onset, suggestive of Parsonage-Turner syndrome. Electroneuromyography and plexus MRI suggested an inflammatory demyelinating neuropathy with conduction blocks affecting the right upper limb. Etiologic diagnostic examinations were negative (lumbar puncture (LP) with cytokine determinations and immunophenotyping, accessory salivary gland biopsy and myelogram all gave normal results). Distal neuromuscular biopsy and C5 right dorsal root ganglion biopsies gave inconclusive results. FDG-PET scan revealed moderate isolated right brachial plexus hypermetabolism. The patient refused plexus biopsy. The Karnofsky performance status (KPF) was 60, and the ECOG performance status was 2. Despite treatment intensification with probabilistic immunochemotherapy (cyclophosphamide, rituximab and bendamustine), central nervous system symptoms emerged (ataxia and pyramidal signs). In September 2022, a surgical cervical spinal column biopsy confirmed the presence of a diffuse large B-cell lymphoma. A new immunochemotherapy regimen combining rituximab, methotrexate, and aracytine was administered. After 18 months of treatment, the symptoms have subsided, but moderate gait abnormality and right hand ataxia persist. The patient is considered in remission of his hematological disease.

2.2 | Case 2

In September 2020, a 50-year-old man experienced sudden painless paresthesia of the right hand, accompanied, in the following month, by pain and motor deficit. An initial suspicion of ulnar nerve compression led to neurolysis, but subsequent edema, paresthesia throughout the right arm, pain exacerbation, and a progression of right lower limb weakness led to the resumption of investigations, including an inconclusive full-body CT scan and plexus MRI examinations. LP revealed only high levels of protein (0.75 g/L). Nerve conduction studies suggested demyelinating neuropathy with proximal conduction blocks in the upper limbs associated with prominent axonal loss. Intravenous immunoglobulin (IVIg) therapy was initiated, but the patient was switched onto corticosteroids due to a continual worsening of his condition. The emergence of severe radicular pain and swallowing difficulties led to a new set of investigations. The cerebrospinal fluid displayed a lymphocytic meningeal reaction with 60 lymphocytes, together with high IL10 and normal IL6 levels. Distal radial nerve biopsy revealed severe axonal neuropathy associated with small B-lymphocyte infiltrates. Plexus MRI revealed a thickening and enhancement of all cervical roots, and PET showed intense hypermetabolism in the right lumbosacral roots compatible with neurolymphomatosis. The Karnofsky performance status (KPF) was 60, and the ECOG performance status was 2. Despite the absence of histological evidence, treatment for diffuse large B-cell lymphoma was initiated in July 2021, together with high-dose corticosteroid therapy. The patient initially responded to this treatment and was considered to be in remission. Two years after the completion of treatment, the patient experienced a relapse presenting as meningeal infiltration and is currently undergoing treatment.

3 | Systematic Review

3.1 | Methodology

Our study is a systematic literature review which followed PRISMA reporting guidelines. Informed consent was obtained from the two patients of our institution. In March 2024, we searched PubMed for human studies published in English (at least the abstract) with the keywords “neurolymphomatosis”, “primary neurolymphomatosis”, and each of these terms in combination with any of the following: “cranial nerves”, “plexus”, “cauda equina syndrome”, “neuropathy”, “mononeuritis”, and “mononeuritis multiplex”. The reference lists of the articles identified were then examined to identify additional relevant articles. Very few of the studies identified were reported only as abstracts from which it was not possible to extract data; these studies were not included [9, 10]. We took care not to include patients with lymphomatous compressive masses of nerve structures and intravascular lymphomatosis without evidence of nerve infiltration.

We extracted the following information from each article: year of publication, number of cases of PNL, lymphoma type according to the international consensus classification [11], patient sex, median age at diagnosis, disease course (acute: < 3 months, subacute: 3–6 months, chronic: > 6 months), the time, in months, between symptom onset and diagnosis, the presence of motor and/or sensory and/or cranial nerve deficit, symmetry of signs, involvement of the upper and/or lower limbs, presence of pain, systemic signs, type and number of treatments classified into five treatment groups (systemic chemotherapy, immunotherapy [rituximab], steroids, intrathecal chemotherapy, and other [radiotherapy, surgery, etc.]), occurrence of relapses and clinical status (dead or alive), and time from diagnosis to last follow-up visit. We also recorded the results of each investigation performed during diagnostic examinations, including LP, blood tests, nerve conduction studies (NCS; axonal or demyelinating features), MRI (organomegaly, nerve hyperintensity, hypertrophy or gadolinium enhancement), positron emission tomography-computed tomography (PET-CT), histology (bone marrow, nerve structures, etc.) and autopsy. On nerve structure biopsy, neurolymphomatosis was diagnosed if lymphoid cell infiltration into the nerve was observed in the epineurium, perineurium, or endoneurium, in association with various degrees of mononuclear cell infiltration. We also noted whether the diagnosis was made after the first set of investigations or later, and the tests on which the final diagnosis was based.

Clinical presentation at diagnosis was defined as reported by the authors of the articles concerned or was otherwise established on the basis of the patient's symptoms and/or signs, classified into six groups, as follows:

- Radiculopathy: Involvement of one or more nerve roots.
- Multifocal neuropathy (mononeuritis, mononeuritis multiplex): sensory and motor deficits in the distribution of specific peripheral nerves.
- Neuropathy: peripheral nerve disorder, either symmetric (length-dependent) or asymmetric, affecting two or more limbs with no evidence of specific trunk involvement suggestive of mononeuritis multiplex.
- Cauda equina syndrome: involvement of lower-limb peripheral nerves with sphincter disturbances.
- Brachial plexus lesion: sensorimotor deficit of one upper limb without truncal or radicular topography.
- Cranial neuropathy: involvement restricted to the cranial nerves.

Individual patients could be assigned to several of these groups, as several different conditions, such as cranial and nerve involvement, for example, could be concomitant.

Due to the retrospective nature of our study, each result is reported for the number of patients for which the corresponding information is available.

Overall survival (OS) was defined as the time from diagnosis (of lymphoma) to death or last clinical follow-up; progression-free survival (PFS) was defined as the time from the diagnosis of lymphoma to whichever of the following occurred first: relapse, progression, death, or last imaging and/or clinical follow-up visit.

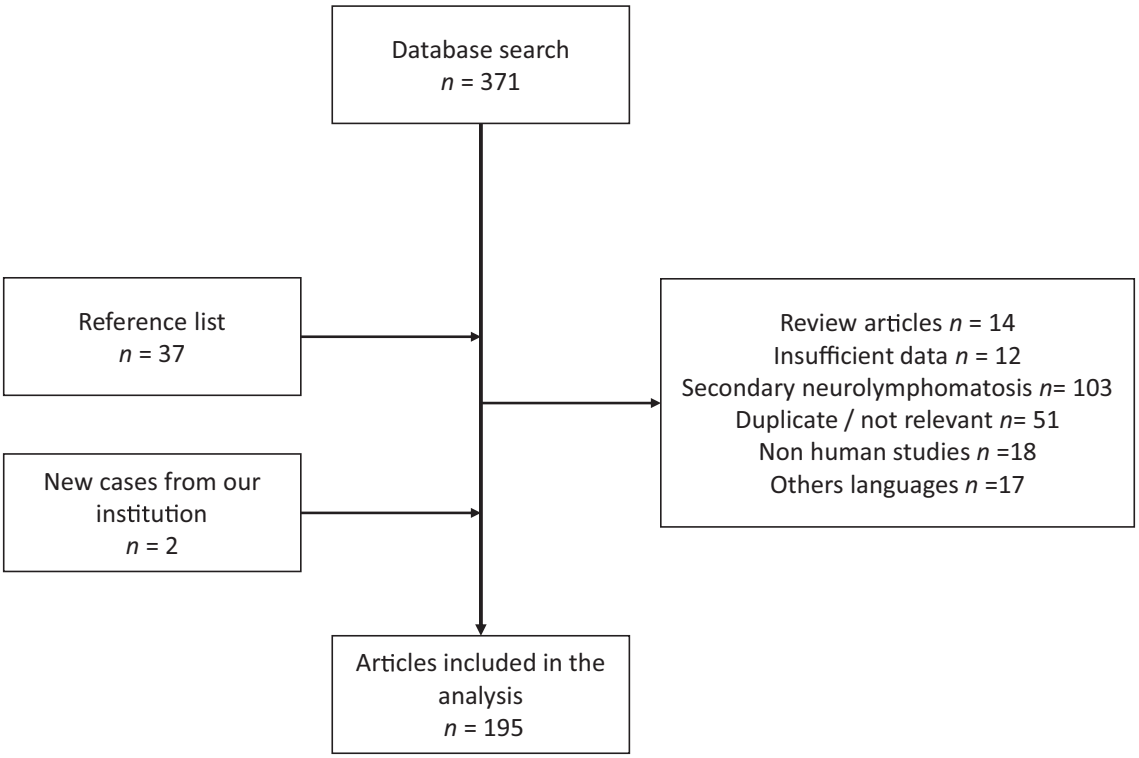

FIGURE 1 | Flow chart.

TABLE 1 | Baseline characteristics of the patients.

	Total $n = 301$
Age, median [IQR], years	60 [49–68.5]
Sex, male, *n* (%)	184 (61)
Type of lymphoma, *n* (%)	
B-cell lymphoma	221 (73)
NK/T-cell lymphoma	27 (9)
Other lymphoma	39 (13)
Unclassified lymphoma	14 (5)
Course, *n* (%)	
Acute	37/216 (17)
Subacute	83/216 (38)
Chronic	96/216 (44)
Neurological symptoms, *n* (%)	
Asymmetric	238 (79)
Motor	192 (64)
Sensory	226 (75)
Sensorimotor	173 (62)
Upper limbs	104 (35)
Lower limbs	178 (59)
Pain	131 (44)
Peripheral nerve presentation, *n* (%)	
Radiculopathy	44 (15)
MN/MNM	72 (24)
Neuropathy	109 (36)
Brachial plexus	34 (11)
Cauna equida syndrome	29 (9)
Isolated cranial neuropathy	33 (11)
Other sites of involvement, *n* (%)	
Central nervous system	9 (3)
Systemic	52 (22)
First-line treatment	
Systemic chemotherapy	210/247 (90)
HD-MTX	46/210 (22)
CHOP	62/210 (30)
Rituximab	102/247 (41)
Steroids	139/247 (60)
Intrathecal chemotherapy	53/247 (21)
Other treatment	78/247 (32)
Surgery	14/78 (18)
Radiotherapy	46/78 (59)
IVIg	5/78 (6)
ASCT	7/78 (9)

Abbreviations: ASCT, autologous stem-cell transplantation; CHOP, chemotherapy regimen based on cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone administered alone or together with rituximab; HD-MTX, high-dose methotrexate; IVIg, intravenous immunoglobulin; MN/MNM, mononeuritis/mononeuropathy multiplex.

3.2 | Statistical Analysis

Data are expressed as numbers and percentages for categorical variables and as median and interquartile range for continuous variables. We used two-tailed Kruskal–Wallis tests to compare means between groups and Fisher's exact test assess differences for categorical variables. Bonferroni correction was applied for multiple comparisons. Survival analysis and multivariate analysis were performed in R version 3.6.3 with the packages 'survival', 'survminer' and 'dplyr'. Data are right-censored for patients lost to follow-up. $p < 0.05$ were considered significant.

4 | Results

We identified 195 articles (Figure 1, Table S1) corresponding to 299 cases of PNL, to which we added our two patients to obtain a total of 301 cases of primary neurolymphomatosis.

The demographic, clinical, and paraclinical characteristics of the cohort are presented in Table 1.

4.1 | Clinical Presentation

The signs and symptoms of the patients varied considerably according to the sites involved. At diagnosis, the most common features of the peripheral nerve disorder were sensorimotor (62%), asymmetric (79%), affecting the lower limbs (59%), and with a chronic course (44%). Cranial neuropathy was seen in 29% of patients (80/277), in association with peripheral nerve involvement in 47/277 (17%). The symptoms were mostly painless (146/277; 56%).

The clinical presentation was suggestive of neuropathy in 36%, multifocal neuropathy in 24% (the nerves most frequently affected were the sciatic ($n = 20$) and peroneal ($n = 13$) nerves in the lower limbs and the ulnar ($n = 8$) and median ($n = 7$) nerves in the upper limbs), radiculopathy in 15%, brachial plexus lesions in 11%, cauda equina syndrome in 10%, and cranial neuropathy in 11% (Figure 2). Clinical presentation is presented by diagnostic group in Table 2.

A deterioration of general condition (e.g., poor appetite or weight loss) was reported in 27 cases (11%) and systemic signs (such as adenopathy $n = 18$, fever $n = 13$, localized mass $n = 10$, erythema $n = 6$) were found in 52 (22%) cases.

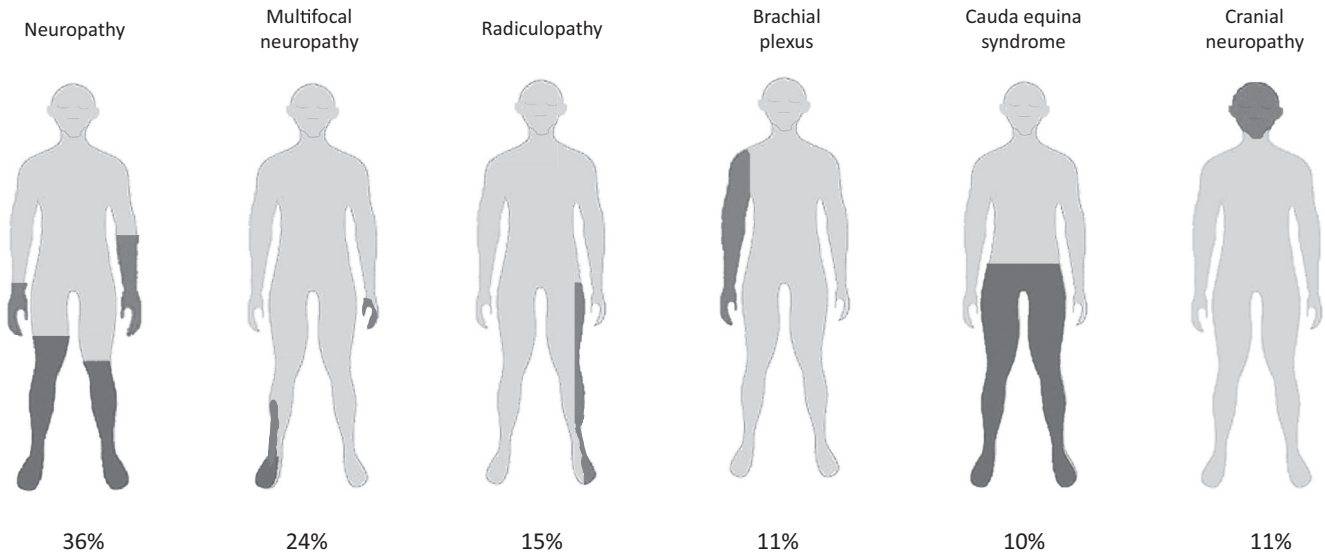

FIGURE 2 | Proportion of patients in each clinical presentation group.

4.2 | Diagnostic Investigation

The diagnostic investigations included comprehensive blood tests, CSF examination ($n = 200$), NCS ($n = 147$), MRI ($n = 194$), PET ($n = 104$), osteomedullary biopsy ($n = 79$) and nerve structure biopsy ($n = 171$) (Table 3). Since 2015, 56% of patients have undergone nerve MRI (90/161) and 60% (101/161) have undergone PET scans.

CSF abnormalities were detected in 144/200 patients (72%). Albuminocytologic dissociation was observed in 28 patients (20%) and 50 patients (35%) had meningitis (≥ 10 cells/mm^3). CSF protein levels were abnormal (> 0.45 g/dL) in 77 patients (39%): median 1.1 g/dL (IQR 0.7–2.1 g/dL) and the median number of cells was 47/mm^3 (IQR 21–112/mm^3). Atypical or abnormal cells were found in 59 patients (30%).

Nerve conduction studies gave abnormal results for 142/147 patients (97%). In most cases, the axons were affected. Forty-three patients (29%) had features of demyelination including, when specified, conduction blocks in 15, reduced motor conduction velocities in 10, prolonged distal latency in 8, prolonged or absent F waves in four, and reduced sensory conduction velocities in two patients.

An MRI description was reported for 200 patients (66%), including peripheral nerve MRI for 141 (71%), with abnormal results in 133 cases (94%). Nerve structure biopsies were reported for 171 patients (57%), including distal nerve biopsies, but also proximal nerve, root, or plexus biopsies (45%). In 20 cases (13%) features of demyelination were encountered.

PET scan results were available for 132 patients (44%) and demonstrated abnormal uptake by nerve structures in 118 cases (82%).

Fifty-five patients underwent explorations by MRI, PET, and peripheral nerve structure biopsy. An abnormal result compatible with PNL (PET and MRI) or sufficient for the diagnosis of PNL (nerve histology) was obtained with similar frequencies for PET ($n = 50$) and MRI ($n = 43$), but significantly less frequently for nerve histology ($n = 31$) than for PET ($p = 0.11$).

4.3 | Diagnosis

The median time from symptom onset to PNL diagnosis was 8 months (IQR 3–14.9 months) [1.5 (IQR 1–3.25), 5 (IQR 3–6) and 12 months (IQR 8.25–23.5) for patients with acute, subacute and chronic courses of disease, respectively]. Patients diagnosed more rapidly than the median diagnostic delay after symptom onset were similar in terms of demographic and clinical data to the patients diagnosed at the median diagnostic delay or later (Fisher's exact tests, *p*-adjusted values).

PNL was diagnosed after the first set of investigations in 85/301 (28%) patients. An initial erroneous diagnosis was reported for 102/216 (47%) patients. These erroneous diagnoses included spinal degenerative disease (19%), chronic inflammatory demyelinating polyneuropathy (CIDP) (18%), inflammatory neuropathies such as lumbosacral radiculoplexus neuropathy, vasculitis, and sarcoidosis (15%), brachial neuritis (17%) and various other diagnoses (Guillain–Barre syndrome, meningoradiculitis, nerve entrapment, etc., 30%) and were not specified for the remaining 12 patients (4%).

On multivariate analysis, patients with an initial erroneous diagnosis were more likely to present peripheral nerve involvement of the brachial plexus ($p = 0.04$), more frequently had features of demyelination in nerve conduction studies ($p = 0.02$) and inconclusive diagnostic results for distal peripheral nerve biopsies ($p = 0.03$) than patients for whom the diagnosis was reached after the first set of investigations.

The final diagnosis was based on histological results ($n = 228$; 76%) from 87 (27%) distal peripheral nerve biopsies and 31 (10%) proximal nerve structure biopsies, CSF analysis ($n = 20$; 7%), autopsy results ($n = 18$; 6%) or osteomedullary biopsy ($n = 14$; 5%),

TABLE 2 | Clinical presentation by diagnostic group.

	Neuropathy ($N=107$)	Multifocal ($N=74$)	Radiculopathy ($N=45$)	BP ($N=35$)	CES ($N=29$)	Cranial ($N=33$)	p
Age, years, median (IQR)	60 (49.5–70.8)	63 (53.5–71)	60 (49–69)	62 (59–64.5)	61 (49–68.8)	50 (45.5–62.2)	0.19
Sex, male, number (%)	64 (60)	42 (57)	27 (60)	22 (63)	18 (62)	15 (45)	0.71
Course $n=213$							
Acute	10 (13)	5 (8)	4 (13)	4 (20)	9 (36)*	5 (26)	0.03
Subacute	29 (39)	19 (32)	18 (58)	10 (50)	10 (40)	8 (42)	0.26
Chronic	38 (51)	36 (61)	9 (29)	6 (30)	6 (24)*	6 (32)	<0.01
Clinical symptoms							
Asymmetric	76 (71)	68 (92)	42 (93)	34 (97)	16 (55)*	NA	<0.01
Motor	83 (78)	46 (62)	29 (64)	24 (69)	21 (72)	NA	0.21
Sensory	92 (86)	56 (76)	35 (78)	25 (71)	24 (83)	NA	0.27
Pain	41 (38)	41 (55)***	27 (60)***	16 (46)	11 (38)	8 (24)	<0.01
Upper limbs	40 (37)**	29 (39)**	12 (27)**	35 (100)	7 (24)**	NA	<0.01
Lower Limbs	78 (73)**	49 (66)**	32 (71)**	10 (29)	25 (86)**	NA	<0.01
Cranial nerves	18 (17)***	10 (14)***	7 (16)***	11 (31)***	7 (24)***	33 (100)	
Ataxia	4 (4)	4 (5)	2 (4)	0	0	NA	0.55
Paraplegia	10 (9)**	2 (3)**	4 (9)**	1 (3)**	12 (41)	NA	<0.01
Central nervous system signs	1 (1)	3 (4)	2 (4)	2 (6)	0	2 (6)	0.43
Other signs							
Poor general status	17 (16)	6 (8)	2 (4)	3 (9)	1 (3)	1 (3)	0.09
Systemic signs	24 (22)	13 (18)	4 (9)	5 (14)	1 (3)	8 (24)	0.09

Note: It was possible for patients to belong to several categories. Unless otherwise indicated, the numbers in brackets are percentages.
Abbreviations: BP, brachial plexus group; CES cauda equina syndrome group; IQR, interquartile range; NA, not applicable.
*Significantly different from multifocal group (adjusted $p<0.05$).
**Significantly different from brachial plexus group (adjusted $p<0.05$).
***Significantly different from cranial nerve group (adjusted $p<0.05$).

or was based exclusively on the results of a suggestive PET scan in 21 patients (7%).

A B-cell lymphoma was diagnosed in 220 cases (73%), 150 (68%) of which were classified as diffuse large B-cell lymphomas (DLBCL), a T-cell lymphoma was diagnosed in 9%, an NK/T-cell lymphoma in 3% and another type of lymphoma, such as follicular, mantle cell, or marginal zone lymphoma in 32 cases (11%). In 5% of cases, the lymphoma was not classified.

4.4 | Treatment

The first-line treatment was reported for 247 patients (82%). Systemic chemotherapy was administered to 210 patients (90%). High-dose methotrexate was used in 46 cases (19%), methotrexate in 58 (23%) and CHOP in 100 (46%); 102 (41%) patients received rituximab, 139 (60%) steroids, and 53 (21%) received intrathecal chemotherapy. Seventy-eight patients (32%) underwent another type of treatment, such as surgery ($n=14$), radiotherapy ($n=46$), intravenous immunoglobulin treatment ($n=5$), or autologous stem-cell transplantation ($n=7$). Patients received a median of two types of treatment [IQR 1–3].

4.5 | Progression

Clinical progression was reported in 283 (94%) of patients. The median follow-up was 14 months [IQR 6–31.5 months]. After the first-line treatment, 134 patients (45%) displayed a stabilization

TABLE 3 | Paraclinical investigations by clinical presentation.

	Neuropathy (*N* = 107)	Multifocal (*N* = 74)	Radiculopathy (*N* = 45)	BP (*N* = 35)	CES (*N* = 29)	Cranial (*N* = 33)	*p*
CSF analysis	78 (73)	42 (57)	31 (69)	23 (66)	22 (76)	23 (70)	0.28
Meningitis	3 (4)	1 (2)	0	1 (4)	0	1 (4)	0.80
Albuminocytologic dissociation	13 (17)	7 (17)	1 (3)	3 (13)	1 (5)	3 (13)	0.35
Positive cytology results	20 (26)	11 (26)	12 (39)	4 (17)	13 (59)*	9 (39)	0.02
Nerve conduction studies	69 (64)	45 (61)	19 (42)	20 (57)	9 (31)*,**	2 (6)*,**,***,****	< 0.01
Axonal	42 (61)	22 (49)	15 (79)	10 (50)	5 (56)	1 (50)	0.33
Demyelinating	21 (30)	13 (29)	4 (21)	8 (40)	2 (22)	1 (50)	0.80
Nerve structure MRI	36 (34)	33 (45)	25 (56)	18 (51)	20 (69)*	19 (58)	< 0.01
Hyperintensity	34 (94)	31 (94)	25 (100)	15 (83)	20 (100)	17 (89)	0.20
Hypertrophy	16 (44)	18 (55)	20 (80)	11 (61)	12 (60)	10 (53)	0.15
Gd+							
PET	53 (53)	27 (36)	23 (51)	20 (57)	9 (31)	13 (39)	0.13
Nerve uptake	47 (89)	22 (81)	21 (91)	18 (90)	9 (100)	13 (100)	0.47
Systemic uptake	16 (30)	8 (30)	7 (30)	4 (20)	4 (44)	4 (31)	0.87
Nerve structure biopsy	66 (62)	59 (80)	29 (64)	20 (57)	15 (52)	7 (21)*,**,***,****	< 0.01
Peripheral nerve	49 (74)	39 (66)	5 (17)*,**	11 (55)	3 (20)*,**	6 (86)***	< 0.01
Proximal nerve	7 (11)	10 (17)	13 (45)*	1 (5)***	2 (13)	1 (14)	< 0.01
Root or plexus	10 (15)	10 (17)	11 (38)*	8 (40)*	1 (7)	0	< 0.01

Note: The numbers in brackets are percentages.
Abbreviations: BP, brachial plexus group; CES, cauda equina syndrome group; IQR, interquartile range.
*Significantly different from neuropathy group (adjusted $p < 0.05$).
**Significantly different from multifocal group (adjusted $p < 0.05$).
***Significantly different from radiculopathy group (adjusted $p < 0.05$).
****Significantly different from brachial plexus group (adjusted $p < 0.05$).

or improvement of their disease, whereas 149 (55%) continued to deteriorate.

Relapses occurred in 71 patients (24%) after a median of 5 months (IQR 0.1–120 months). When reported, the sites of tumor recurrence were: a peripheral nerve ($n = 22$; 31%), the central nervous system ($n = 16$; 23%), a cranial nerve ($n = 12$; 17%) or systemic ($n = 21$; 30%).

By the time of the last follow-up visit, 122/220 patients had died (55%). The survival curves calculated for subjects for whom we had follow-up information are presented in Figure 3. Survival did not differ between diagnostic groups ($p = 0.88$). Overall survival at 1 year was 73% and median overall survival was 28 months. The multivariate analysis identified B-cell lymphoma as the only factor independently associated with survival (HR = 0.63, 95% CI: 0.42–0.94). Survival was similar in patients with an erroneous initial diagnosis and in those correctly diagnosed straight away ($p = 0.37$).

5 | Discussion

We performed the first extensive literature review of all published cases of PNL for which individual data are available. Our analysis of 301 patients with primary neurolymphomatosis is much larger than the largest cohort study to date (18 subjects) [4] and the largest previous literature reviews (92 and 197 patients) [7, 8] on this topic.

The first reported case of neurolymphomatosis was published in the early 20th century [12] but PNL remains a rare entity. It affects 3 in 100 patients with intermediate/high-grade non-Hodgkin B-cell lymphoma annually [13], but peripheral nerve infiltration with lymphomatous cells appears to be relatively common in autopsy studies [14], suggesting that the disease may be under recognized.

The clinical presentation of PNL varies considerably between patients. One third of cases are due to an often painless asymmetric sensorimotor neuropathy with a chronic course,

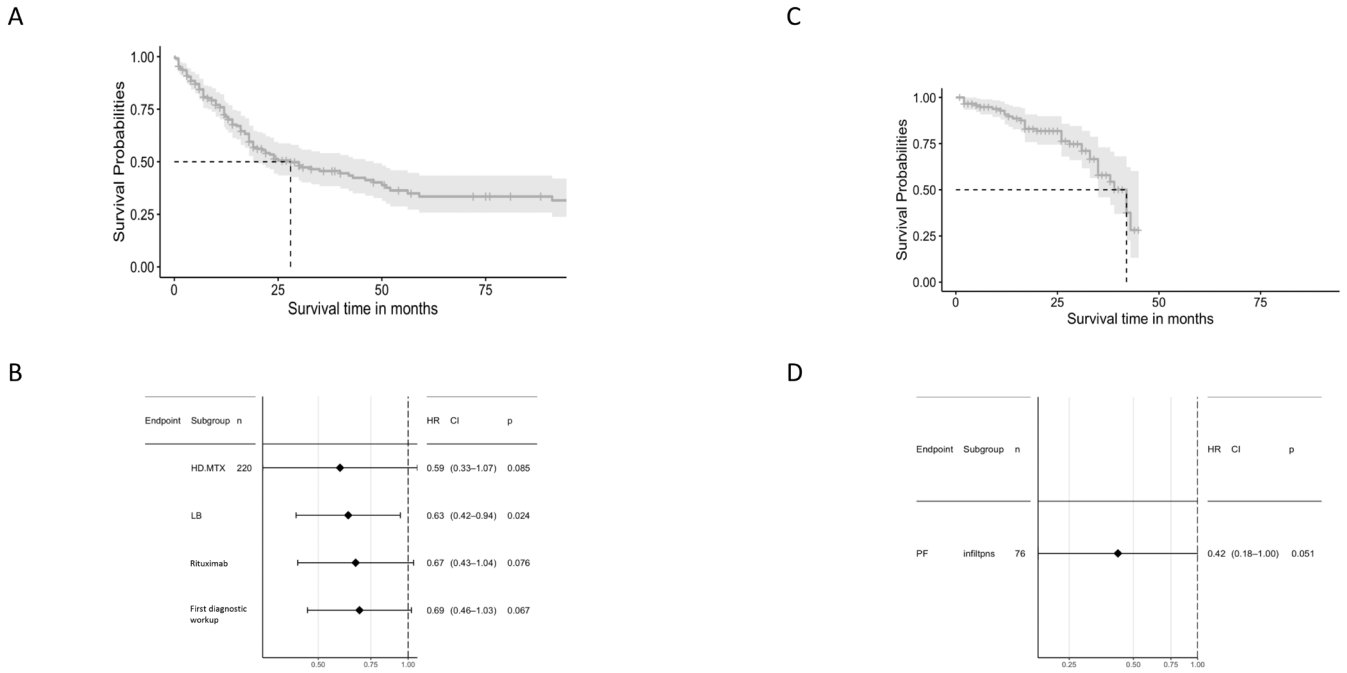

FIGURE 3 | Survival analysis. (A) Overall survival. (B) Multivariate analysis of factors associated with overall survival. (C) Progression-free survival. (D) Multivariate analysis of factors associated with progression-free survival.

predominantly affecting the lower limbs. Despite this high frequency, this presentation is all but absent from some studies conducted at single center [4]. Another third of the patients have a painful multifocal neuropathy or radiculopathy with a subacute or chronic course, the most commonly reported forms so far [2, 4, 15]. The last third of the patients mostly have acute or subacute brachial plexus, cauda equina, or cranial nerve lesions. Despite the presence of symptoms suggestive of the diagnosis (e.g., asymmetric distribution, pain, progressive disease), no particular sign has been identified as independently associated with a shorter time to diagnosis, highlighting the challenge posed by the diagnosis of this condition. Indeed, only one third of patients were correctly diagnosed after the first series of tests. Spinal degenerative disease was the most common erroneous diagnosis, followed by chronic inflammatory demyelinating neuropathy. Indeed, as previously highlighted [15], 29% of patients presented misleading features suggestive of demyelination in nerve conduction studies. Systemic symptoms/signs remain uncommon (found in one in five patients) and simultaneous involvement of the central nervous system is rare.

Histological evidence of the infiltration of lymphomatous cells, mostly of the B-cell type, into the nerve is usually required for diagnosis. Evidence of such infiltration was obtained for two thirds of the patients, but more invasive proximal nerve structure biopsy was required in almost half the cases. CSF or osteomedullary infiltration can be used for diagnosis in patients with asymmetric neuropathies for whom other etiologies have been ruled out and nerve histology is inconclusive. It has recently been suggested that imaging studies based on nerve MRI and PET can accelerate diagnosis [3]. PET has been described as the most sensitive non-invasive diagnostic investigation for this purpose [2]. In our cohort, abnormalities were more frequently found on nerve MRI than on PET scans. Furthermore, if the analysis was restricted to patients explored by MRI, PET, and nerve histology, none of these investigations was found to outperform the others. However, we acknowledge that nerve structure tracer uptake on PET is more suggestive of an infiltrative process than gadolinium enhancement on MRI. Nevertheless, our findings suggest that the diagnostic investigations should be extensive as diagnosis is based on a combination of various clinical and laboratory investigations.

Median survival for this population exceeded 2 years regardless of the diagnostic group, which is longer than previously reported [7]. Having a B-cell lymphoma appears to be the only factor associated with a favorable outcome. Furthermore, a multivariate analysis of our findings did not support the previous report of an additional survival benefit for patients on rituximab treatment [4]. This result may reflect the lack of exhaustive data available for all patients. More than half the patients continue to deteriorate on treatment. Recurrences occurred early, after a median of 5 months, and involved the peripheral and central nervous systems in almost equal proportions. Eventually, 55% of the patients died from the disease. Diagnosis on autopsy is now rare.

Our study has several limitations essentially inherent to its retrospective nature, such as selective reporting and a lack of comparison groups. These limitations are aggravated by the diversity of specialties of the doctors/journals reporting these cases, which also resulted in high rates of missing data. The precision of the data for survival curve calculation is linked to the precision of the data available.

Improvements in our understanding of the characteristics of PNL are important to accelerate diagnosis, which could improve outcomes.

Author Contributions

Sahar Chakroun: writing – original draft. **Alice Faucher:** writing – original draft. **Antoine Gueguen:** writing – review and editing. **Jehane Fadlallah:** writing – review and editing. **Emilie Corvilain:** writing – review and editing. **Nathalie Kubis:** writing – review and editing. **Pierre Lozeron:** conceptualization, investigation, writing – review and editing, supervision.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.