Neurolymphomatosis[1]

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The term "neurolymphomatosis" (NL) has included infiltration of the peripheral nervous system by lymphoma and nontumor lymphocytes. We describe NL as a lymphoma entity that affects cranial and peripheral nerves and roots. We reviewed the medical records of patients at the Massachusetts General Hospital (MGH) who registered between 1972 and 2000, as well as cases published in the English-language literature. Inclusion criteria were (A) histopathologic demonstration of lymphoma within peripheral nerve, nerve root/plexus, or cranial nerve or (B) CT/MRI or intraoperative evidence of nerve enlargement and/or enhancement beyond the dural sleeve in the setting of prior or concurrent lymphoma in systemic or CNS sites. We identified 25 patients with NL in addition to 47 reported by others. Four clinical presentations were (1) painful involvement of nerves or roots, (2) cranial neuropathy with or without pain, (3) painless involvement of peripheral nerves, (4) painful or painless involvement of a single peripheral nerve. Twenty of our patients and 44 of those reported had histopathologic confirmation of lymphoma infiltrating root or nerve. In the remainder, diagnosis was based upon clinical presentation, nodular nerve enlargement or enhancement, and lymphoma cells in spinal fluid or extraneural sites. For antemortem diagnosis, imaging studies were of greatest utility, followed by biopsy. Thirty-three patients of the combined series were not correctly diagnosed until postmortem examination. Systemic chemotherapy was used to address the multiple potential sites of involvement. When properly treated, NL carries a prognosis similar to primary CNS lymphoma in the modern era. *Neuro-Oncology 5, 104–115, 2003 (Posted to Neuro-Oncology [serial online], Doc. 02-017, February 12, 2003. URL http://neuro-oncology.mc.duke.edu)*

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[3]Abbreviations used are as follows: CSF, cerebrospinal fluid; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; EMG, electromyogram; MGH, Massachusetts General Hospital; NCAM, neural cell adhesion molecule; NHL, non-Hodgkin's lymphoma; NL, neurolymphomatosis; PCNSL, primary central nervous system lymphoma; PNS, peripheral nervous system.

Infiltration of the peripheral nervous system (PNS)[3] by lymphoma was termed "neurolymphomatosis" (NL) prior to identification of the causative B lymphocyte (Lhermitte and Trelles, 1934). The least common clinical presentation of nervous system lymphoma (Dickenman and Chason, 1958; Griffin et al. 1971), malignant lymphocytic infiltrates of root, plexus, and nerve, is separable from nontumor disorders associated with lymphoma such as irradiation, chemotherapy, or paraneoplastic effects (Borit and Altrocchi, 1971; Kuroda et al., 1989; Schoenfeld et al., 1983; Trelles and Trelles, 1983; Trelles et al., 1976; Vallat et al., 1995).

In the last 25 years, we have seen 25 individuals with "neurolymphomatosis" amongst a population of 180 individuals with primary non-Hodgkins lymphoma (NHL) of the brain, and a like number with neuraxis complications of coincident systemic lymphoma. This population is supplemented by 47 patients reported in the literature. In this paper we identify NL as lymphoma of roots and nerves distinct from paraneoplastic or therapy-related disorders of root and nerve. We define the clinical features of NL, provide the basis for systemic and local therapy, and create hypotheses concerning the homing and trafficking of "nerve-seeking" malignant lymphocytes.

Patients and Methods

We reviewed the medical records of patients (1972 to 2000) whose malignant lymphoma infiltrated cranial nerve, peripheral nerve root, plexus, or nerve. These were identified from (A) the Massachusetts General Hospital (MGH) Brain Tumor Center database, (B) those seen in consultation by the Neuro-Oncology service, and (C) surgical pathology or autopsy cases identified through the SNOMED database of the MGH Pathology Department. Case ascertainment is not exhaustive. All patients had symptomatic examination findings referable to the cranial or spinal nerves. The diagnosis of NL reflected (A) histologic demonstration of malignant lymphocytes within peripheral nerve, nerve root/plexus, or cranial nerve or (B) CT/MRI or intraoperative evidence of nerve enhancement and/or enlargement beyond the dural sleeve in the setting of primary central nervous system lymphoma (PCNSL) or systemic NHL. We excluded patients with root or nerve infiltration by leukemia, those having NHL with leukemic transformation, or those with benign or malignant meningeal infiltrates without root invasion. No HIV or herpes virus-related lymphoma is represented, nor are examples of coexistent NHL and paraneoplastic root or nerve disorders. We reviewed the English-language literature utilizing a Medline search for case reports of lymphomatous involvement of the PNS or "neurolymphomatosis."

The time origin of interest in this study is the onset of symptoms. However, subjects entered this study only at diagnosis. Thus, our data are left-truncated; that is, we are missing from our population subjects with very long intervals from the onset of symptoms to diagnosis, as well as subjects who have experienced onset of symptoms but who die without a diagnosis. Left-truncated data require specialized statistical methods for estimation, all of which require an assumption of quasi-independence: independence between the time from onset of symptoms and diagnosis and the time from onset of symptoms and death, conditional on the second time exceeding the first time. We first tested for quasi-independence in both data sets using the Tsai test (Tsai, 1990). If the null hypothesis of independence was not rejected, we intended to use the Turnbull (1976) estimator to estimate the distribution of the time from onset of symptoms to diagnosis (this is right-truncated by time to death or last follow-up) and the distribution of the time from onset of symptoms to death (this is left-truncated by the time from onset of symptoms to diagnosis).

Results

Seventy-two patients were included in the study. Of 25 individuals seen at MGH, 11 were female and 14 male. Median age was 63 years (range, 18 to 84 years). Forty-seven previously published case reports described 22 female and 25 male patients with a median age of 56 years (range, 17 to 83 years).

Results of Statistical Analysis

The Tsai (1990) test rejected the null hypothesis of quasi-independence for both data sets ($P = 0.013$ for the MGH data set and $P = 0.002$ for the literature cases). Because of this apparent dependence, we are not justified in computing generalized Kaplan-Meier curves for the survival distributions of interest. Thus, we simply report the ranges of the time from onset of symptoms to diagnosis and the time from onset of symptoms to death or last follow-up.

Presentation

NL presentations fit 1 of 4 patterns:

1) painful involvement of nerves or roots
2) cranial neuropathy with or without pain
3) painless involvement of peripheral nerves
4) painful or painless involvement of a single peripheral nerve

The following case reports identify the patterns of presentation of NL.

Case Report 1: Painful Involvement of Nerves or Roots

A 61-year-old woman, over months, developed progressive left lower extremity weakness and painful paresthesias. The examination and electromyogram (EMG) findings were consistent with femoral neuropathy. After 3 months of gradual improvement, she developed, over weeks, pain and progressive weakness of both lower extremities. Disc resection at T12-L1 failed to improve symptoms. A right-sided Bell's palsy, 5 months after first symptoms, responded to therapy with steroids, as did residual leg weakness. When medications ceased, she noted severe radicular pain of the low back and legs and then became paraplegic. She retained urine and feces, and could not feel stimuli over both distal legs. She noted paresthesias from the right fourth and fifth digits to the ulnar condyle. In combination with constant, deep, burning pain were intermittent electrical sensations, obliging her to receive strong analgesics. MRI studies revealed enhancement of the right seventh cranial nerve and the conus, as well as marked thickening of the lumbosacral nerve roots (Fig. 1). Malignant B lymphocytes were present in samples of cerebrospinal fluid (CSF) obtained from lumbar and cervical puncture sites. Normal were CT of the chest, abdomen, and pelvis; HIV-1 antibody titers; and slit-lamp examination of the eye. A diagnosis of NL was made. After receipt of solely 7 biweekly cycles, then monthly cycles of parenteral methotrexate (8 g/m^2, then 3.5 g/m^2), she regained gait as well as bowel and bladder function, with residual right facial weakness. Spinal fluid studies were free of malignant cells. Twenty-seven months after establishment of complete response, having received 17 total cycles of methotrexate, she is without objective weakness and has only subjective numbness of the left foot. Sequential MRI studies reveal no enhancement of nerve roots, whose caliber is now normal.

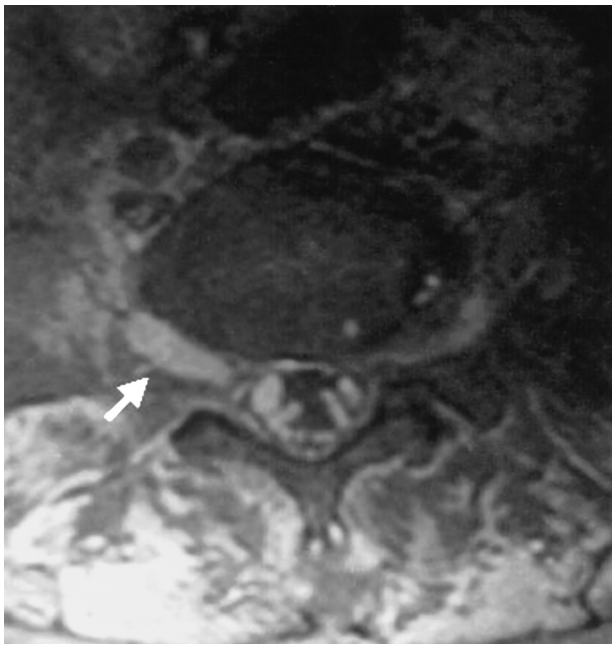

Fig. 1. T1-weighted spine MRI of the patient described in case report #1. Axial section through the extradural portion of the S1 nerve roots demonstrates marked thickening and homogeneous enhancement on the right side (arrow) and to a lesser degree of the cauda equina and the left S1 root.

Twenty-two patients of the combined series (10 of ours, 12 reported) presented with painful affliction of multiple nerves or nerve roots. In 8 of our patients and 7 of those reported elsewhere, symptoms localized to lumbosacral roots or nerves. Three of our patients and 2 reported patients developed a complete cauda equina syndrome with bowel, bladder, or sexual dysfunction. One of our patients had a lower cervical and upper thoracic radiculopathy, another, a T4 radiculopathy. Commonly, back and circumferential limb pain was soon followed by an ascending motor and sensory polyradiculopathy. The pain was severe, relentless, and dysesthetic, and migrated into widespread areas of the proximal extremities beyond the afflicted nerve root or its dermatome. It was unaffected by movement, position, or Valsalva's maneuver and mandated significant amounts of analgesics. Weakness often progressed, eventually resulting in symmetric paraparesis or quadriparesis with muscle atrophy. In some patients the asymmetry of symptoms was similar to mononeuropathy multiplex. Isolated plexopathies were infrequent (2 lumbosacral, 3 brachial plexopathies in the combined series). The syndromes evolved over weeks to months, with the exception of the rapidly progressive polyneuropathy described by Schoenfeld et al. (1983). The initial clinical diagnoses included degenerative joint disease, disc herniation, paraneoplastic or viral radiculoneuropathies, and inflammatory neuropathies, for which steroid therapy, laminectomy, intravenous immunoglobulin, or plasmapheresis were provided. The diagnoses were reconsidered when pain progressed in association with motor and/or sensory dysfunction beyond the territory of single nerve roots or nerves in spite of treatment.

Case Report #2: Cranial Neuropathy With or Without Pain

A 63-year-old man developed a left-sided Bell's palsy. He was provided with a 7-day course of prednisone and completely recovered. Thirty-six months later the left facial weakness recurred with hearing deficit, light-headedness, and nausea. Without resolution, over the following 4 months, he developed radiculopathic weakness and numbness of the lower extremities. A motor neuropathy was identified on EMG. Brain MRI revealed enhancement and thickening of the left seventh and eighth nerve complex, as well as a mass adjacent to the fourth ventricle (Fig. 2). Biopsy of the extra-axial tumor showed an immunoblastic B-cell lymphoma. The lumbar CSF contained atypical mixed T and B cells when examined by flow cytometry. Normal were slit-lamp examination of the eye, chest radiograph, and HIV-1 antibody titers. After the patient was treated with intravenous methotrexate (8 g/m^2) every 10 days for 3 months, there was resolution of weakness as well as cranial nerve enlargement. The CSF cytologic examination normalized. His residual symptoms were limited to bilateral auditory deficits and mild weakness of the lower left face. Seven months later, and 5 years after the first facial weakness, tumor recurrence was heralded by lethargy, hallucinations, headaches, and nausea. The brain MRI now showed enhancing masses in the third and both lateral ventricles, with infiltration of the corpus callosum, hypothalamus, and infundibular stalk.

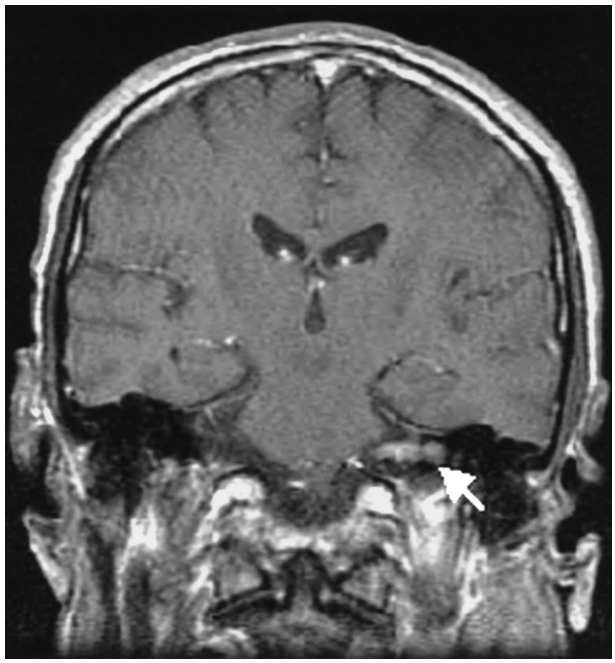

Fig. 2. T1-weighted brain MRI of the patient described in case report #2. Coronal section through the internal auditory canal shows homogeneous enhancement and thickening of the left facial nerve (arrow).

Six percent of the lumbar spinal fluid cells were monoclonal B cells. A second radiographic and clinical complete response was achieved after 4 months and an additional 12 cycles of intravenous methotrexate. The patient remains disease free on maintenance methotrexate (cycle 27) 4 years from initial diagnosis and 4 1/2 years after initial symptoms.

Fifteen patients of the combined series (7 of ours, 8 of the literature cases) presented with involvement of a single cranial nerve. Three patients experienced "Bell's palsy," of which 2 were bilateral and 1 was recurrent. Other manifestations were lateral rectus muscle palsies (n = 4), oculomotor neuropathy (n = 4), trigeminal neuropathy (n = 2), hearing loss (n = 1), and vocal cord paralysis (n = 1). Only in 4 patients (1 reported [Abdel-Aziz and van Loveren, 1999] and 3 of ours with preauricular or eye pain) was the cranial neuropathy painful. Initially, many of these patients were thought to harbor "cranial neuritis multiplex" or the Miller-Fisher variant of Guillain-Barré syndrome.

Case Report #3: Painless Involvement of Peripheral Nerves

A 43-year-old woman experienced numbness and paresthesias in her feet. Slowly ascending symptoms involved her hands and forearms and led within months to weak legs and then arms. The identification of intervertebral disc prolapses at C5/6 and C6/7 on MRI was followed by unsuccessful laminectomy and discectomy 3 months after symptom onset. She became restricted to a wheelchair 2 months later. A diagnosis of chronic inflammatory demyelinating polyneuropathy having been made, she had transient benefit from oral corticosteroids. Intravenous immunoglobulin infusion was without benefit. Eight months after symptom onset, the sudden appearance of right facial weakness was immediately followed by a left-sided Bell's palsy, which improved spontaneously. The left pupil became dilated, and vertical diplopia was present. The lumbar CSF contained lymphocytes identified as clonal B cells with light-chain expression restricted to lambda. Scans of systemic organs were normal, as was a right temporal meningeal biopsy. Methotrexate by vein was provided for "neurolymphomatosis" with leptomeningeal involvement. With the first cycle (8 g/m^2), strength improved in all extremities and paresthesias resolved. With delay in provision of further drug, she became confused and mute. There was facial diplegia and asymmetric quadriparesis with bilateral foot drop. Only strength and reflexes in the right arm were spared, but muscles were diffusely atrophic. Sensory deficits were consistent with a mixed small and large fiber neuropathy with mild foot allodynia. Within the pineal area was present a cystic mass on MRI study. The trigeminal nerve and ganglion and the oculomotor nerve on the left were thickened and enhanced with contrast. Similar changes were noted in the lumbosacral roots and plexus (Fig. 3). Chemotherapy was resumed and led to complete resolution of her cognitive symptoms. Strength improved remarkably. Symptomatic improvement noted after each cycle of methotrexate did not persist when therapy was delayed for more than 2 weeks by bouts of infection. She succumbed 16 months after symptom onset. Postmortem examination revealed thickening of all spinal nerve roots, brachial and lumbosacral plexus, and facial and trigeminal as well as peripheral nerves (Figs. 4 and 5). Aside from the PNS, lymphoma involved the pineal gland, the choroid plexus of the lateral ventricle, and retroperitoneal lymph nodes.

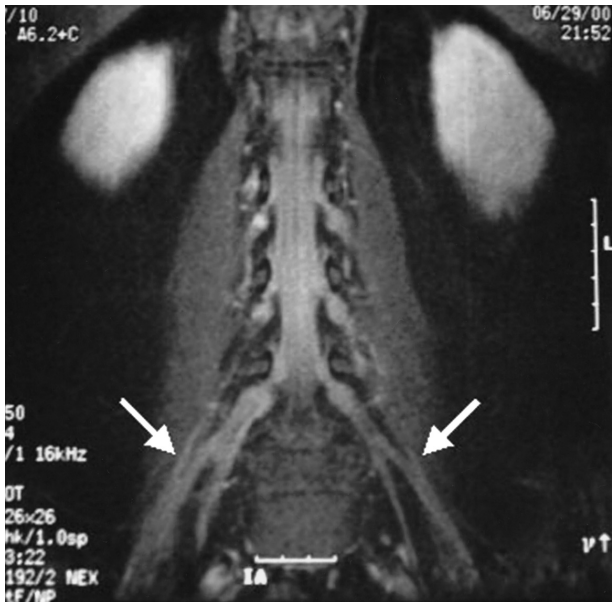

Fig. 3. Coronal MRI of the lumbosacral plexus and spine of case #3 reveals marked thickening and enhancement of all nerve roots and the visible portion of the plexus (arrows; T1-weighted image with gadolinium).

A painless peripheral neuropathy was the initial manifestation of NL in 20 patients of the combined series (4 of ours, 16 of the literature cases). Paresthesias, numb-

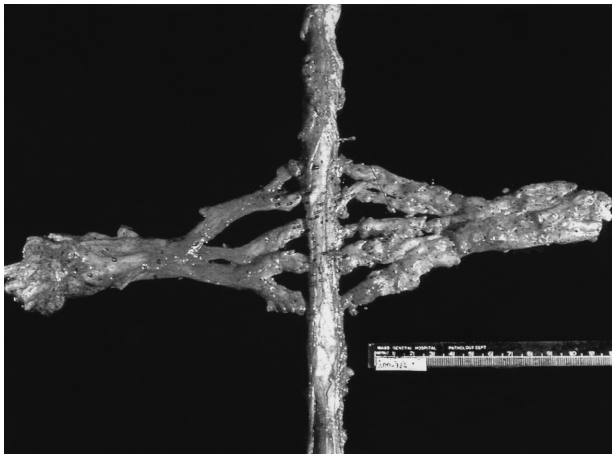

Fig. 4. Autopsy preparation of the lumbar spinal cord, cauda equina, and lumbosacral plexus of case #3. Of note is the nodular appearance of the cauda equina as well as the diffuse thickening of all lumbosacral nerve roots and the plexus.

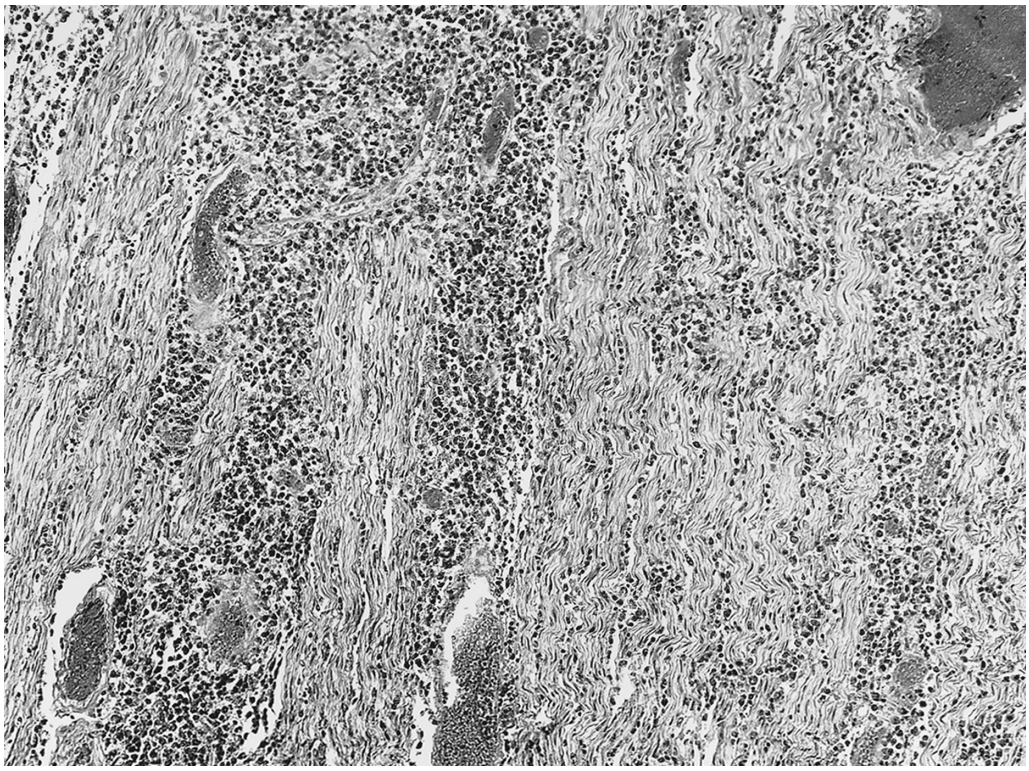

Fig. 5. Photomicrograph of the cauda equina of the patient described as case #3 shows an endoneural infiltrate of large atypical mononuclear cells consistent with diffuse large B-cell lymphoma [HE + myelin stain].

ness, and loss of deep tendon reflexes preceded weakness in the lower extremities. Rare were examples of asymmetric or patchy onset or early proximal limb weakness reflecting plexus invasion.

Case Report #4: Painful or Painless Involvement of a Single Peripheral Nerve

Over 8 months, a 49-year-old man developed progressive neuropathic pain that followed the pattern of the lower lumbar nerve roots on the right side. The foot became weaker, and a foot drop arose. The right gastrocnemius (2/5) and anterior tibialis muscles (0/5) were weak, and the right ankle jerk was absent. An EMG revealed absent motor responses in the right posterior tibial nerve. MRI showed a mass within the distal sciatic and posterior tibial nerve which was a Burkitt's-like B-cell lymphoma. Partial reduction of its size was achieved after 4 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, but left-sided neck and leg pain and right facial paresis appeared. The lumbar spinal fluid contained clonal B cells similar to those in the sciatic nerve. Deterioration occurred in spite of craniospinal irradiation and intrathecal cytosine-arabinoside chemotherapy. On postmortem examination, 6 months after symptom onset, he was found to have diffuse involvement of nerve roots, dorsal root ganglia, and peripheral nerves in the absence of extraneural lymphoma.

Both of our patients with mononeuropathy at onset have been reported (Misdraji et al., 2000; Quiñones-Hinojosa et al., 2000). Nine others had lymphoma within sciatic (Eusebi et al., 1990; Kanamori et al., 1995; Misdraji et al., 2000; Pillay et al., 1988; Purohit et al., 1986; Roncaroli et al., 1997), median (van den Bent et al., 1995), radial (vanBolden et al., 1987), and T2 spinal nerves (Misdraji et al., 2000). Motor and/or sensory deficits (n = 5), more common than pain syndromes (n = 4), preceded diagnosis of NHL by 5 months to 2 years. Whether nerve invasion heralds systemic disease is uncertain: Isolated mononeuropathy (n = 4) persisted more than 30 months after diagnosis (Kanamori, Misdraji [cases 1 and 4], Pillay), but our 2 patients, and 3 reported by others, developed more widespread lymphoma (Eusebi, Purohit, Roncaroli). Another 2 had prior systemic lymphoma (vanBolden, van den Bent). Delay in

Table 1. Nervous system structures and compartments affected at the time of autopsy or by the time the neurological syndrome had completely evolved (determined by biopsy, spinal fluid analysis, and/or imaging studies)

Structure	MGH n = 25	Literature n = 47
nerve root	18	29
peripheral nerve	13	33
cranial nerves	14	23
plexus	5	18
spinal fluid	13	20
epidural	4	0
brain parenchyma	10	9

Abbreviation: MGH, Massachusetts General Hospital.

Table 2. Diagnostic findings in 25 patients with NL seen at MGH and 47 patients reported in the literature, including the results of imaging studies, nerve biopsies and spinal fluid analysis as well as autopsy findings[a]

	Painful involvement of nerves or roots		Cranial neuropathy with or without pain		Painless involvement of peripheral nerves		Painful or painless involvement of a single peripheral nerve		Mixed syndromes	
Diagnostic data	MGH n = 10	Literature n = 12[b]	MGH n = 7	Literature n = 8[c]	MGH n = 4	Literature n = 16[d]	MGH n = 2	Literature n = 9[e]	MGH n = 2	Literature n = 2[f]
Premortem diagnostic data										
radiographic enlargement/ enhancement of nerve/ root beyond the dural sleeve	5	2	4	4	1	2	8	2	–	
intraoperative visualization of enlarged nerve	1	–	–	–	–	–	–	–	–	–
biopsy of peripheral or cranial nerve	1	3	2	3	–	5	2	7	1	–
spinal fluid cytopathology positive for malignant lymphocytes (at diagnosis)	2	2	–	4	1	4	–	–	–	2
automated cell sorting of spinal fluid positive for clonal lymphocytes	2	–	–	–	2	–	1	–	1	–
Biopsy/autopsy of systemic site (lymph node, extra-nodal site, bone marrow) or brain	7	9	6	6	4	12	1	5	1	2
Postmortem finding of nerve infiltration by lymphoma	5	8	5	4	4	11	1	1	–	2

Abbreviations: MGH, Massachusetts General Hospital; NHL, non-Hodkin's lymphoma; NL, neurolymphomatosis.

a. Most patients had more than one positive test. Sixty-four patients (20 of ours, 44 of those reported) had histopathologic confirmation of nerve infiltration by lymphoma (41 at autopsy [15, 26], 24 through nerve biopsy [6, 18]; one patient with positive nerve biopsy underwent postmortem examination). In the remaining 8 patients (5, 3), diagnosis was based upon clinical presentation, in addition to imaging findings and biopsy-proven systemic NHL (4 cases [2, 2]), imaging findings and spinal fluid cytopathology (1 patient [0, 1], spinal fluid cytopathology, flow cytometry and imaging findings (1 case [1, 0]), flow cytometry of spinal fluid and imaging findings (1 case [1, 0]), and biopsy-proven brain lymphoma with intra-operative visualization of nodular thickening of adjacent cranial nerves (1 case [1, 0]).

b. References: Barron et al., 1960; Carey et al., 2000; Gherardi et al., 1986; Ince et al., 1987; Jellinger et al., 1979; Kohut, 1946; Kuntzer et al., 2000; Lachance et al., 1991; Stack, 1991; Swarnkar et al., 1997; Valencia et al., 1999.

c. References: Abdel-Aziz and van Loveren, 1999; Galetta et al., 1992; Kajiya et al., 1995; Manon-Espaillat et al., 1990; Teoh et al., 1980; Wilkins and Samhouri, 1979; Young et al., 1945.

d. References: Allison and Gordon, 1955; Borit and Altrocchi, 1971; Diaz-Arrastia et al., 1992; Gerardi et al., 1986; Grisold et al., 1993; Guberman et al., 1978; Julien et al., 1991; Krendel et al., 1991; Mauney and Sciotto, 1983; Moore and Oda, 1962; Pattengale et al., 1979; Schoenfeld et al., 1983; Vallat et al., 1995; Zuer et al, 1988.

e. References: Eusebi et al., 1990; Kanamori et al, 1995; Misdraji et al., 2000; Pillay et al., 1988; Purohit et al, 1986; Roncaroli et al., 1997; vanBolden et al., 1987; van den Bent et al., 1995.

f. References: van den Bent et al., 1999; Walk et al., 1998.

diagnosis or ineffective therapy led to progressive nervous system involvement over weeks to several months following a relapsing-remitting or progressive pattern. Nervous system structures affected by the time the neurological syndrome had completely evolved or at autopsy are given in Table 1.

Diagnosis

Usually months passed from initial symptoms to diagnosis (range, 2 weeks to 4 years in our patients, a few days to 9 years in those reported) as a consequence of alternative diagnoses. In 33 cases of the combined series (11, 22) a clinical or histopathological diagnosis of neurolymphomatosis was not established until autopsy. Sixty-four patients of the combined series (20, 44) had histopathologic confirmation of nerve infiltration by lymphoma, 24 through biopsy, and 41 at autopsy (Table 2). One patient with positive nerve biopsy underwent postmortem examination. In 8 patients, diagnosis was based upon clinical presentation, nodular nerve enlargement or enhancement, and lymphoma cells in spinal fluid or extraneural sites. Premortem and postmortem diagnostic data are summarized in Table 2.

Histopathology

The vast majority of patients in whom an exact histopathological diagnosis was available were classified as large B-cell lymphomas at the time of diagnosis of NL. Two of our patients had experienced prior follicular lymphoma. Nine cases of the combined series were not classified at all,

3 only as "B-cell lymphomas." Four of the literature cases were diagnosed with peripheral T-cell neoplasms.

Systemic NHL and NL

Prior systemic NHL existed in 14 patients of the combined series (5 of ours, 9 of those reported). A coincident diagnosis of NHL and NL was found in 11 cases (4, 7), and 4 patients (1, 3) developed clinically recognized systemic dissemination of lymphoma after diagnosis of NL. Ultimately, spread to systemic sites and brain parenchyma occurred in 53 individuals (19, 34) determined by biopsy or autopsy (Table 2). Nineteen NL patients (10, 9) suffered from parenchymal CNS lymphoma, although this complication was recognized prior to autopsy in only 10 patients.

Treatment

Standardized criteria to measure response are not available for NL. In the majority of cases, complete response denoted the resolution of clinical symptoms and positive diagnostic findings (enlargement/enhancement of peripheral neural structures, malignant lymphocytes in spinal fluid). Treatment for NL has included resection of peripheral nerve masses (n = 0 in our cases, n = 5 in the literature), chemotherapy, and/or radiation therapy. Four patients in the combined series experienced transient spontaneous improvement. Twenty-seven patients (5, 22) received prednisone. The majority (17 patients) had initial benefit, but disease progression was the rule, in spite of continuation of therapy or upon tapering the steroids. Various chemotherapy regimens were used by us and others: CHOP, MCHOD (methotrexate, cyclophosphamide, doxorubicin, vincristine, dexamethasone), VAC (vincristine, doxorubicin, cyclophosphamide), ProMACE (procarbazine, methotrexate, doxorubicin, cyclophosphamide, etoposide)/Cytabom (cytarabine, bleomycin, vincristine, methotrexate), intrathecal chemotherapy (methotrexate, cytosine arabinoside), or myeloablative chemotherapy with autologous bone marrow transplantation. Five of our patients received intravenous high-dose methotrexate (8 g/m^2). Radiation therapy was given with curative intent (n = 1 of ours and 9 reported) and for palliation of whole brain, the craniospinal axis, and/or lumbosacral roots invaded by lymphoma. Of the 38 patients of the combined series who received treatment other than steroids only, "complete remission" was achieved in 18, "partial remission" in 13, and stable disease in 3. Fifty-two patients have passed away, within 2 weeks to 84 months after symptom onset in our patients and 1 week to 372 months in the literature cases (interval unknown in 7 patients). Five of our patients are in remission (2.4 to 70 months since onset of symptoms), as were 15 of the reported cases (range, 2 weeks to 9 years).

Discussion

Nerve-seeking lymphoma represents a unique subtype of extranodal lymphoma. NL denotes localized invasion of cranial or peripheral roots or their nerves. This process, commonly outside the arachnoid investment of nerves, is distinct from infiltration that may accompany subarachnoid seeding and separable from perineural tumor seen in epidural lymphoma (Epelbaum et al., 1986). The malignant lymphocytes of NL distinguish it from the benign infiltrates of paraneoplastic or inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy or paraproteinemias, and from the acellular neuropathic complications of drugs such as vinca alkaloids. Diagnostic criteria are available for meningeal lymphoma (Lachance et al., 1991). In these instances, the lymphocytes are clustered in the epineurium in comparison to perivascular sites in NL. However, NL has yet to be classified as a distinct entity, and thus its characteristic symptoms are often missed, and oncologists or neurologic consultants fail to obtain the appropriate spinal fluid and radiographic studies. Successful therapy is contingent upon the recognition that the disease exists outside the dural sleeve. When properly treated, NL carries a prognosis not unlike that associated with primary CNS lymphoma in the modern era.

That NL has eluded definition before reflects uncertainty regarding the role of meningeal lymphoma, the tendency to lump NL with benign radicular processes, and the insistence on histologic confirmation of NL. Vallat excluded all patients whose CSF lymphocyte count exceeded 3/μl (Vallat et al., 1995) and thus excluded the coincident meningeal invasion and NL that occur in up to 25% of cases. Diaz-Arrastia restricts the diagnosis by obligating the clinician to histopathologic confirmation (Diaz-Arrastia et al., 1992).

Eight cases of the combined series (5 of ours, 3 from the literature) fulfilled only criterion B (see Methods). As demonstrated by our case 1, all 8 had met our clinical definition of NL in the setting of histopathological proof of lymphoma involving systemic sites, brain, meninges, or spinal fluid. These patients were included since they provide unique clinical insights. Our 5 patients experienced painful polyradiculoneuropathy and root enlargement beyond the dural sleeve. This constellation is the most vexing for neuro-oncologists, as biopsy of the afflicted site carries risk. Similarly, the cases reported by Kajiya et al. (1995) and Manon-Espaillat et al. (1990) demonstrate the diagnostic dilemma of NL presenting as an isolated cranial neuropathy which cannot be biopsied. Van den Bent's case of NL of the median nerve shows that in the correct clinical setting nonneural tissue—in this case a lymph node adjacent to the enlarged median nerve—can be biopsied with essentially no morbidity (van den Bent et al., 1995). By not obligating the clinician to histopathological diagnosis of NL, our case series provides a more realistic view of the clinical spectrum of NL disease. This is especially telling, as in 45% of the combined series a clinical or histopathological diagnosis of NL was not established until autopsy, and thus chemotherapy was not provided or extradural disease was not addressed. Chemotherapy options may outweigh the lack of pathological confirmation of clinical difficulties, as these 8 cases had enlarged roots distinguishable from benign radiculopathies. Indeed, the literature lacks an

example of a lymphoma patient in whom paraneoplastic or infectious or Guillain-Barré–related thickening or enhancement of nerve, root, or plexus was present. Having said that, we strongly recommend tissue diagnosis of NL whenever feasible but also recognize the need to initiate treatment in patients in whom tissue diagnosis fails.

NL would appear to be the least common neurologic manifestation of lymphoma. Only 1 example of infiltration of the PNS and 1 with cranial nerve infiltration were found in 228 patients reviewed by Currie and Henson (1971). This figure is likely too low. Richmond et al. (1962) found lymphoma of peripheral nerves or trunks in 1% of their patients. In an autopsy series of NHL, which included 44% with leukemic conversion, peripheral nerve involvement was found in 40% of 145 patients dying of lymphoma (Jellinger, 1976). From our experience, we estimate that NL represents 10% of primary lymphoma of the nervous system (300 cases per year, or 0.2% of all NHLs). Between 8.5% and 29% of NHLs metastasize to the nervous system (6000 cases per year [Bunn et al., 1976; Hoerni-Simon et al., 1987; Law et al., 1975; Recht, 1991; Recht et al., 1988; Richmond et al., 1962; Young et al., 1979]), an estimated 10% of those to the PNS. Thus, NL occurrences likely account for 1000 cases in the United States each year.

The clinician should be aware of 4 broad clinical presentations, including painful polyneuropathy or polyradiculopathy, cranial neuropathy, painless polyneuropathy, and peripheral mononeuropathy. Painful polyradiculopathy or neuropathy occurred in 31% of the combined series, while painless affliction was seen in 28%, cranial neuropathy in 21%, and mononeuropathy in 15%. Whereas widespread involvement of the PNS characterizes the later stages of NL, 4 literature cases of lymphomatous mononeuropathies stand out by their lack of disease dissemination after up to almost 5 years of follow-up.

Unlike meningeal lymphoma, in which 97% of the cases have abnormal CSF cytology (Young et al. 1979), or parenchymal brain or epidural lymphoma, which can readily be identified with enhanced MRI, NL is difficult to diagnose. Clinically, it mimics nonneoplastic or paraneoplastic neuropathies. Only 55% of patients of the combined series were diagnosed antemortem. Clinical findings that suggest NL, as opposed to remote effect or inflammatory process, includes severe pain, particularly when it affects all four limbs, asymmetric distribution, and rapid evolution.

Imaging studies are of greatest utility (Table 2): Nerve or root MRI enlargement or enhancement was seen in 29 patients of the combined series. Peripheral lesions of the plexus were more difficult to detect. They were best seen on coronal MRI images, revealing characteristic diffuse thickening and enhancement of roots, trunks, or peripheral nerves (Fig. 3). Nerve root enhancement and nodular thickening are not specific for NL but can also be seen in acute or chronic inflammatory radiculoneuropathies and tumors of the peripheral nerve sheath (Byun et al., 1998). Interpretation of imaging studies in the context of clinical presentation and laboratory tests is necessary. The utility of MRI in the evaluation of peripheral nerve infiltration has been noted (Pillay et al., 1988; Purohit et al., 1986).

Less common is histologic confirmation. Of 30 patients from the combined series who underwent biopsy of nerve or root, NL was confirmed in 24 (Table 2). More limited still is the role of CSF cytologic evaluation and automated cell sorting. Of the 33 patients of the combined series who ultimately developed leptomeningeal spread of their disease, spinal fluid cytopathology was diagnostic in 21. At initial diagnosis, malignant cells were found in spinal fluid of only 15 patients (Table 2). Automated cell sorting of spinal fluid specimens revealed a clonal cell population in 6 patients.

PCR-based testing for monoclonal rearrangement of immunoglobulin heavy-chain genes in B-cell lymphomas can be applied to diagnose NL (Kuntzer et al., 2000; Kuroda et al., 1992).

In 48 patients of the combined series, nerve infiltration by lymphoma could not be demonstrated histopathologically during their lifetime, and in 8, not at all. The clinical diagnosis of NL requires integration of clinical information and imaging findings as well as morphological data obtained from neural tissue, nonneural tissue, and spinal fluid. In selected cases, only the response to empiric treatment may lead the clinician to the correct diagnosis.

As with PCNSL, most NL is due to diffuse large B-cell lymphomas when classified by the REAL or WHO systems (Harris et al., 2000). The causative cells stain for B-cell-associated surface antigens (CD19, CD20, CD22, CD79a) and have a high proliferative index when stained with MIB-1.

NL likely antecedes discovery of systemic disease. In our combined series, systemic lymphoma preceded 19% of NL cases. However, 73% of patients with NL were ultimately found to harbor systemic lymphoma diagnosed by biopsy or autopsy. Concomitant involvement of CNS structures was seen in 26% (Table 2).

The therapy must include knowledge of the extent of both symptomatic and asymptomatic root and nerve involvement as well as the coexistent invasion of brain parenchyma, CSF, and systemic extranodal sites. Staging should include slit-lamp examination of vitreous body; MRI-enhanced images of brain and lumbar nerve roots as well as symptomatic sites of cervical or thoracic involvement; and CT scans of chest, abdomen, and pelvis. The role of ^{18}FDG-PET imaging is not clear as of this writing. NL involves roots within, as well as beyond, the borders of the subarachnoid space. Thus, intrathecal drugs and traditional "cranio-spinal" radiation fields will not treat all involved roots and nerves. Indeed, one of our patients, having received intrathecal cytarabine, upon postmortem examination had no evidence of tumor involving intradural nerve roots but did reveal persistent involvement of extradural nerve roots, plexus, and peripheral nerves.

Spontaneous stabilization or improvement has been described but is the exception (4 patients of the combined series). Twenty-seven patients of the combined series were provided with steroids. These benefits were invari-

ably transient and never curative, which suggests that NL shares with PCNSL a response to corticosteroids that is short-lived and does little other than to obscure the diagnosis. Radiation therapy was provided either with curative intent or for palliation. The majority of patients at least stabilized their disease, if not achieving a complete or partial response. It remains unclear whether radiation therapy adds any benefit in the treatment of this highly chemosensitive tumor. Noteworthy in this regard are patients with localized disease (mononeuropathy) in whom excellent local control was achievable with systemic chemotherapy in combination with local irradiation. For the control of drug-refractory localized lymphomatous aggregates, radiation therapy is clearly indicated.

Chemotherapy is used to address the multiple potential sites of involvement. From our experience with intravenous methotrexate in the treatment of PCNSL (Batchelor et al., 2000; Cher et al., 1996; Gabbai et al., 1989; Glass et al., 1994), this drug is provided as first-line treatment. Methotrexate in doses to 8 g/m^2 provides therapeutic concentrations to brain, to spinal fluid (Glantz et al., 1998), and presumptively to lymphoma in intradural and extradural sites in root and nerve. Our most durable responders have received methotrexate as infusions of 8 g/m^2 every 2 weeks with limited toxicity (< grade 3, Common Toxicity Criteria of the National Cancer Institute) of neutropenia, thrombocytopenia, or azotemia. We have observed clinical improvement (functional recovery, reduction of pain), as well as at least partial radiographic resolution (improvement of nerve root enlargement and enhancement), within 6 cycles of the drug.

However, we can provide no guidance as to optimal therapy. Fifteen of our patients and 23 in the literature received chemotherapy. Fifteen of the combined series received intrathecal drugs, usually methotrexate or cytosine arabinoside. The response rate ("complete response" or "partial response") to combined treatment regimens was 82%. Overall survival calculated from symptom onset ranged from 1 week to 372 months in the combined series. Accurate survival data could not be calculated.

NL patients are overrepresented in the appearance of idiopathic diseases of possible autoimmune etiology. Clinical and pathologic links to Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy are evident. Borit's patient had 31 years of exacerbations from painless polyradiculoneuropathy involving his right leg, followed by episodes of rapidly developing quadriparesis (Borit and Altrocchi, 1971). The diagnosis of NL was made at autopsy. It is conceivable that lymphoma arose by malignant degeneration of an autoreactive B-cell clone targeting peripheral neural structures that was the basis for this patient's long-standing idiopathic polyradiculoneuropathy. A patient of ours had a 9-year history of episodes of idiopathic brachial plexopathy as painless arm weakness and then developed plexus involvement by NL. Patients with peripheral mononeuropathy often have symptoms for up to 2 years, which suggests the existence of a premalignant stage analogous to inflammatory pseudotumors of peripheral nerves (Weiland et al., 1996). Other patients of the combined series had recurrent chorioretinitis, celiac disease, hypothyroidism, Bell's palsy, Sjögren's syndrome, systemic lupus erythematodes, erythema nodosum, erythema multiforme, or allergic purpura in their medical history. However, epidemiological data supporting a pathogenetic link between autoimmune diseases and NL are unavailable.

Of greatest interest is the targeting of clonal B cells to PNS structures. Site-specificity of lymphoma likely reflects differences in its molecular biology. In this regard NL is analogous to other extranodal lymphomas such as mucosa-associated lymphoid tissue, body cavity, and intravascular subtypes (Mann, 1999), and may share with them target acquisition based on expression by tissue of a stimulating antigen. Putative antigens include autoantigens and bacterial (*Borrelia* sp.) or viral antigens (HTLV-1). Unproven is the suggestion that these cells are the sites of extranodal generation of lymphoma (Quiñones-Hinojosa et al., 2000), as related diseases, primary CNS lymphoma and angiotropic lymphoma involving brain or subarachnoid space, seem to originate from peripheral lymphocytes (Julien et al., 1999; Larocca et al., 1998; Montesinos-Rongen et al., 1999).

As in normal lymphoid cells, adhesion receptors seem to determine the tissue-specific dissemination patterns of certain lymphoma subtypes (Drillenburg and Pals, 2000; Shipp et al., 1997). Lymphocytes initially are subject to loose tethering, followed by stable adhesion and ultimately migration. These processes are mediated by selectins (tethering), whereas integrins and activation of integrins by cytokines are the basis for adhesion and migration (Carlos and Harlan, 1994; Lee and Benveniste, 1999; Pignatelli and Vessey, 1994; Springer, 1994; van den Berg et al., 1993). Several selectins, integrins, and chemokines have been implicated in the pathogenesis of CNS and systemic NHL. Within the group of selectins, neural cell adhesion molecule (NCAM) expression (CD56) is related to peripheral T-cell lymphoma targeting to CNS, muscle, gastrointestinal tract, and nasopharynx. This molecule, via homophilic interaction with other cells expressing CD56, may play a role in the process of lymphomatous spread (Kern et al., 1992). Yet Misdraji et al. (2000) were unable to confirm CD56 expression in their series of diffuse large B-cell lymphomas in peripheral nerves. L-selectin influences adherence of lymphocytes to central white matter tracts (Huang et al. 1991). We have shown that LFA1/ICAM-1 interaction on lymphoma cells and tumor blood vessel endothelial cells may play a role in homing to the CNS (Bashir et al., 1992). Potential mechanisms of the adhesion of cells to the nervous system also include the family of *N*-cadherins (Albelda, 1993) and the adhesion molecule CD44 (Aho et al. 1993, 1997; Matsumara and Tarin, 1992). Specific adhesion molecules as the basis for organ selectivity of NL remain to be identified.

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