INVITED REVIEW

ABSTRACT: Lymphoma occasionally affects the peripheral nervous system. When it does, the diagnosis can be elusive since many patients present without known lymphoma. Most peripheral nerve complications are due to non-Hodgkin's lymphoma (NHL), which infiltrates nerves causing axonal damage. This disorder can affect nerve roots and cranial nerves, often associated with lymphomatous meningitis. NHL may also infiltrate peripheral nerves and cause plexopathy, mononeuropathy, or generalized neuropathy. These neuropathies may resemble an asymmetric mononeuropathy multiplex or a generalized disorder such as chronic inflammatory demyelinating polyradiculoneuropathy. When NHL infiltrates diffusely, the term neurolymphomatosis is used. Hodgkin's lymphoma (HL), by contrast, rarely infiltrates nerves. More often, HL causes immunological disorders of the peripheral nervous system such as inflammatory plexopathy or Guillain–Barré syndrome. Other rare lymphomas such as intravascular lymphoma and Waldenström's macroglobulinemia can also affect peripheral nerves in specific ways. In addition, other malignant and nonmalignant lymphoproliferative disorders enter into the differential diagnosis of lymphomatous neuropathy. This review discusses the multiple peripheral nerve presentations of lymphoma from the clinician's point of view and provides a guide to the evaluation and diagnosis of these uncommon, challenging disorders.

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LYMPHOMA AND PERIPHERAL NEUROPATHY: A CLINICAL REVIEW

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Lymphomas can cause peripheral neuropathies.[2,17,18,22,36,52,55,56,89,133,143,146] These syndromes occur most frequently by direct infiltration of nerves but may also occur by paraneoplastic mechanisms, by metabolic and infectious processes, and as side effects of treatment.[24,89] Some are commonplace and may not suggest an underlying tumor, such as the distal sensory-motor axonal peripheral neuropathy that occurs in many patients with advanced cancer. Others are highly unusual, such as a rapidly infiltrating lymphoma with a presentation similar to Guillain–Barré syndrome (GBS) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). All can cause diagnostic confusion and lymphoma deserves consideration in the presence of any obscure neuropathy, despite its infrequency.

This review will focus on the peripheral nerve manifestations of lymphoma from the clinician's standpoint. Other reviews have discussed other manifestations of lymphoma, including spinal and central nervous system effects.[18,19,52,56,100,146] Since these syndromes may present in patients with known lymphoma or in patients in whom lymphoma is not suspected, these disorders are presented from both points of view.

A review of this scope has to have limitations. Treatment or the side effects of treatment are not discussed in detail except as they affect the diagnosis of lymphomatous neuropathy. Since few neurologists are called on to treat these patients, a detailed discussion of treatment is properly the concern of hematologists, radiotherapists, and oncologists. The pathological, immunological, and

Abbreviations: CD, cluster of differentiation; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CT, computed tomography; EBV, Epstein–Barr virus; EMG, electromyography and nerve conduction studies; GBS, Guillain–Barré syndrome; HIV, human immunodeficiency virus; HL, Hodgkin's lymphoma; HTLV-1, human T-cell leukemia virus 1; IVL, intravascular lymphoma; MRI, magnetic resonance imaging; NHL, non-Hodgkin's lymphoma; NL, neurolymphomatosis; PET, positron emission tomography; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; VZV, herpes zoster virus

Key words: chronic lymphocytic leukemia; Hodgkin's lymphoma; intravascular lymphoma; lymphoma; lymphomatoid granulomatosis; motor neuron disease; neuropathy; non-Hodgkin's lymphoma

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biochemical aspects of these diseases are also not discussed.

CLASSIFICATION OF LYMPHOMA

Lymphomas are hematopoietic neoplasms originating from immunocompetent cells, the lymphocytes, that spread to other lymphoid and nonlymphoid tissues either by direct infiltration or hematogenous dissemination. They are divided into two main groups: non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). The annual incidence of NHL in the U.S. is estimated at 3.5 per 100,000 and accounts for about 8% of new cancers and 10.3% of cancer deaths.[86] NHL is classified as B-cell or T-cell type, with B-cell types being more common. Diagnosis of the different B-cell and T-cell types may be done in many cases using standard microscopic examination; however, immunophenotyping, either by immunohistochemical stains or flow cytometry, or by molecular DNA/RNA studies may be necessary to confirm the diagnosis. Although the cause is unknown, evidence suggests that prior viral infections with Epstein–Barr virus (EBV) or human T-cell leukemia virus 1 (HTLV-1) are associated with subtypes of NHL.[86] Immunosuppression and human immunodeficiency virus (HIV) infection are also risk factors for NHL.[86] Several classification systems have been proposed, such as the National Cancer Institute's International Working Formulation; Revised European–American Lymphoma Formulation; and the World Health Organization (WHO) classification.[86,100] These systems classify tumors by cell type, growth patterns, and grade. In general, more advanced tumors with higher stages have a poorer prognosis and are more likely to spread to the nervous system.

HL is a lymphoma with Reed–Sternberg cells which occurs particularly in younger patients usually without a history of immunosuppression. HL is much less likely than NHL to cause disease outside of the lymphoreticular system. It originates most commonly in an age range of 16–34 years, with another subgroup presenting later in life.[86] The annual incidence of HL is estimated at 3.0 per 100,000 in the U.S.[86] Prior viral infections, especially with EBV and HIV, which is associated with a particularly virulent form, may also play a role in the etiology of subtypes of HL.[40,86] HL also has several classifications (Rye, WHO).[86,100] These systems classify HL by cell type, number of malignant cells (Reed–Sternberg cell variants) and growth pattern. Along with staging systems, these are helpful from a prognostic and treatment planning standpoint. HL has a much better prognosis than NHL, with approximately 80% of patients cured by modern treatment.[86] Staging of HL is much more predictive of prognosis than staging of NHL.

HL and NHL both infrequently cause peripheral and central nervous system complications, with NHL a much more common cause. One investigator found only 10 cases with nervous system involvement in 7,000 consecutive autopsies on lymphoma patients.[154] Despite the infrequent clinical presentation of neurological complications, these neoplasms seem to have a biological effect on the peripheral nervous system in many more patients. For example, Walsh found that although only 8% of a mixed population of lymphoma patients had clinical evidence of neuropathy, 35% had electrophysiological or pathological evidence of peripheral neuropathy.[143] Dickenman and Chason also found a much higher rate of abnormality of dorsal root ganglia cells than suspected by clinical evaluation in an autopsy series of lymphoma patients.[25] Most of the neurological complications occur in NHL. In two series, 98% of lymphoma patients with peripheral nerve[24] and central nervous system[53] complications had NHL. With higher grades, the rate of nervous system involvement increases, ranging from 6.5 to 17.5% in NHL. Most are B-cell NHL, with T-cell NHL accounting for only about 10%.[100] Neurological complications are much rarer in HL. O'Neill reported only 82 cases of all neurological types in a recent Medline review over 34 years, and most of these were indirect complications.[100] No good statistics exist for peripheral nerve disorders, which are much less frequent. Most reports describe single patients or small series of cases.

Other variants of lymphoma and lymphoproliferative disorders can also cause neuropathy.[24] Examples of variants of lymphoma are neurolymphomatosis (NL) and intravascular lymphoma (IVL). Examples of lymphoproliferative disorders are lymphomatoid granulomatosis and Castleman's disease. These latter two are usually included in this discussion because they mimic lymphomas.

PATHOGENESIS OF LYMPHOMATOUS NEUROPATHY

NHL can cause neuropathy by directly compressing or infiltrating nerves or by remote effects.[89,95,138] The mechanisms of nerve damage are often unknown, but several have been proposed.

First, in central nervous system disease, lymphoma cells can gain direct access to nerves by infiltration of cranial nerves or nerve roots. In peripheral nerve disease, lymphocytes can infiltrate adjacent

nerves from lymph nodes.[61,100] This may be facilitated at the spinal or dorsal root ganglion level where the blood–brain barrier is deficient.[90] Malignant lymphocytes may adhere to neural cell adhesion molecules.[4] These molecules, found on neurons and meninges, allow passage of certain classes of lymphocytes across the blood–brain or blood–nerve barrier.[69,70] Pathological samples typically show lymphoma cells surrounding vessels in the eipineurium,[138] suggesting hematogenous spread.[24] These infiltrates should not be mistaken for vasculitis since they do not infiltrate the vessel wall in most cases or cause fibrinoid necrosis.[138] Lymphoma also frequently invades the endoneurium, which is uncommon in carcinoma.[106,138] Endoneurial infiltrates are associated with a mix of segmental demyelination and axonal degeneration by mechanisms that are unclear.[89,106,138] The pathology may, in some cases, resemble Marek's disease in chickens, which is a well studied T-cell lymphoma affecting only peripheral nerves, caused by avian cytomegalovirus infection.[80,87] However, most infiltrative neuropathies in humans are due to B-cell lymphoma.[5,24]

Second, inflammatory, dysimmune neuropathies such as GBS[83,136,155] or CIDP[132,141] can occur in lymphoma due to the accompanying or preexisting immune perturbation. These disorders are more commonly reported with HL than NHL.[82,140] Since infiltrative lymphoma can mimic dysimmune neuropathies,[1,32] however, nerve biopsy with immunotyping is essential to diagnosis in most cases.[74,140] In some cases, antibodies likely derived from molecular mimicry of antigens in lymphoma cells or accompanying viral infections may attack similar antigens in nerve cells.[2] Examples include anti-Hu neuropathy,[20,21,85] multifocal motor neuropathy,[96] neuromyotonia,[78] and perhaps GBS and CIDP.

Third, hematogenous metastases can occlude vessels by local intravascular proliferation or direct pressure, resulting in nerve infarcts.[140] In addition, tumor emboli can infarct nerves (and brain) especially in the setting of IVL, also known as malignant angioendotheliomа or angiotrophic lymphoma.[41,137,147] These patients present with a vasculitic-like mononeuropathy multiplex syndrome often associated with stroke.[137,140]

Fourth, patients with HIV and lymphoma may develop neuropathy associated with tumor infiltration of the nerves.[42,140] HIV infections can be associated with an increased incidence of lymphoma and increased virulence.[40]

Rarer causes of mononeuropathy and asymmetric neuropathy syndrome in lymphoma are vasculitis[16,98] and cryoglobulinemia,[37] the latter often associated with monoclonal antibodies (types I–II cryoglobulinemia).[37] Also, in the setting of a monoclonal paraprotein, amyloidosis may cause neuropathy.[68,99]

Lymphoma cells can affect peripheral nerves remotely, causing generalized neuropathies.[57,58,96,132] Examples include NHL, chronic lymphocytic leukemia, Waldenström's macroglobulinemia, and osteosclerotic myeloma.[67] These may be due to circulating anti-nerve monoclonal antibodies secreted by the tumor cells or other factors as yet unknown, as in the case of osteosclerotic myeloma. In some cases, the monoclonal anti-nerve antibodies, usually immunoglobulin-M paraproteins, are directed at specific antigens such as myelin-associated glycoprotein and the ganglioside GM1.[57,58,66,76,96]

Nonmalignant lymphopoliferative disorders, such as Castleman's disease (angiofollicular lymph node hyperplasia), may cause neuropathy,[26,140] sometimes associated with Crow–Fukase syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; POEMS syndrome).[66,91] Although not a focus of this review, they often feature in the differential diagnosis of lymphomatous neuropathies. These disorders may be associated with a monoclonal gammopathy, which is likely not the cause of nerve damage but can be a diagnostic clue.

Frequently, neuropathies occur in lymphoma without clear explanation, as in all malignancies. They are usually mild, mostly sensory and axonal in type. The cause is not known but metabolic and toxic mechanisms are generally suspected, some undoubtedly related to treatment.[140]

Known viral infections such as herpes zoster virus (VZV) can directly affect nerves and nerve roots.[2,55] In addition, it is possible that EBV or other viruses may lead to a lymphoproliferative state similar to Marek's disease[80,87] or focal inflammatory disorders such as lymphomatoid granulomatosis.[81]

NEUROLOGICAL SYNDROMES IN INDIVIDUAL LYMPHOMAS

Lymphoma-associated neurological syndromes may present in patients with known lymphoma. Thus, a discussion of these syndromes in individuals where the diagnosis of lymphoma is established can be helpful to the clinician.

Non-Hodgkin's lymphoma. NHL is by far the most common cause of lymphomatous neuropathy syndromes (Table 1).[3,24,64,100] Some of these are associated with HIV infections or other disorders that depress the immune system.[42,114,150] These neoplasms can infiltrate cranial nerves,[38,45,97] roots,[100] plexuses,[62,71,123] and peripheral nerves, often ex-

Table 1. Peripheral nerve syndromes in lymphoma.

Syndrome	NHL	HL	NL	LG	IVL
Radiculopathy	+++	—	+	+	+
Plexopathy	+++	+ (autoimmune)	+	+	+
Mononeuropathy	++	—	++	+++	+++
Peripheral neuropathy	+++	++ (autoimmune)	+++	++ (asymmetric)	++ (asymmetric)
Motor neuropathy	++	+	—	—	—
GBS/CIDP	+	++	++ (infiltrative, non-autoimmune)	—	—
Sensory neuronopathy	—	+	—	—	—

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; GBS, Guillain–Barré syndrome. HL, Hodgkin's lymphoma; IVL, intravascular LG, lymphomatoid granulomatosis; NHL, non-Hodgkin's lymphoma; NL, neurolymphomatosis.

tending from regional foci of disease or by hematogenous dissemination.[100,119] They can also infiltrate peripheral nerves and cause a mononeuropathy or regional, asymmetric pattern suggesting vasculitic neuropathy.[24,62] With more diffuse infiltration, a GBS- or CIDP-like syndrome may occur, with some findings on electromyography and nerve conduction studies (EMG) suggesting demyelination.[1,16,101,141] Due to immunological disturbances, some of these patients may develop a true autoimmune neuropathy syndrome such as CIDP or other disorders associated with specific antinerve antibodies.[12,82,85,155] NHL can also cause a distal, predominantly axonal neuropathy during the late stages of advanced disease.[105,140]

Neurolymphomatosis. NHL and, rarely, HL can also present as neurolymphomatosis (NL). This disorder is generally defined as clinical neuropathy with associated malignant, lymphomatous infiltration of peripheral nerves proven by biopsy or autopsy.[5,8,23,24,44,46–48,75,89,107,127,128,139] Baehring and colleagues, in their extensive review, added a surrogate criterion for pathological evidence by allowing computed tomography (CT), magnetic resonance imagine (MRI), or intraoperative evidence of nerve infiltration beyond the dural sleeve in the setting of known central nervous system or systemic lymphoma.[5] Focal or diffuse enlargement of nerves or roots or contrast enhancement in the setting of known systemic or central nervous system lymphoma suggests neoplastic infiltration in the proper clinical setting. This criterion takes advantage of the advances in neuroimaging in these disorders and allows a presumptive diagnosis without need to resort to pathological proof, which in some cases may be difficult to obtain without added morbidity. In earlier studies, prior to immunolabeling and immunophenotypic analysis, it was sometimes difficult or impossible to determine whether the infiltration was malignant or inflammatory unless the cells looked neoplastic.

A major advance in the evaluation of these syndromes has been the introduction of immunolabeling or immunophenotypic analysis of cell markers. This can be accomplished by flow cytometry and immunohistochemistry. Flow cytometry is useful only in NHL, whereas immunohistochemistry is used in both NHL and HL. Cell types (B or T lymphocytes) are determined by demonstration of either B-cell or T-cell antigens on the surface or in the cytoplasm of the neoplastic lymphocytes. These antigens are often identified by cluster of differentiation (CD) numbers, as part of the standard nomenclature system for leukocyte differentiation antigens established by the World Health Organization through a series of international workshops. Diagnosis of subtypes of NHL can be accomplished by determination of patterns of expression of a number of lymphocyte antigens, which are generally a recapitulation of antigen expression at specific stages of lymphocyte maturation (Fig. 1). In addition, the pattern of immunoglobulin light chain expression by B-lymphocytes can be used to determine patterns of immunolabeling and can suggest monoclonal origin of B-lymphocytes and thus malignancy.[16,74,119,132,137] Distinction of subtypes of HL from certain variants of NHL can be aided by immunohistochemical staining of tissue sections.

In the past, diagnosis was more frequently made at autopsy than biopsy where unknown systemic or central nervous system malignancy is also often found.[5,24] This is likely to change with the use of modern imaging using the criteria of Baehring and colleagues.[5] Greater than 90% of these cases are B-cell with only about 10% T-cell NHL. HL is an extremely rare cause.[5,24] Patients may present with mononeuropathy, asymmetrical regional neuropathies in the leg or arm, polyradiculopathies, or a

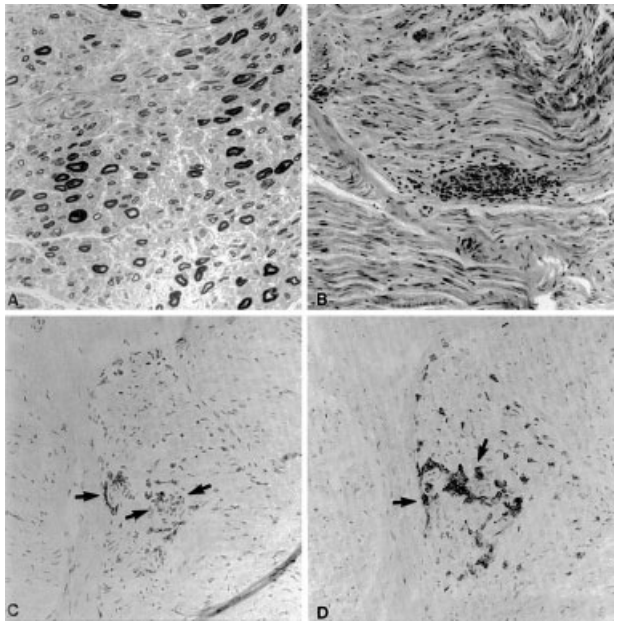

FIGURE 1. Sural nerve biopsy from a patient with chronic lymphocytic leukemia/small lymphocytic lymphoma and chronic neuropathy with intraneural neoplastic lymphocytes displaying the same immunophenotype ($CD22^+$ and $CD5^+$) as the peripheral blood and lymph node neoplastic lymphocytes, thereby establishing the infiltrate as the lymphomatous counterpart of the patient's B-cell chronic lymphocytic leukemia. **(A)** Semithin section of sural nerve showing moderate loss of myelinated fibers and clusters of thinly myelinated fibers. **(B)** Hematoxylin and eosin–stained paraffin section of sural nerve showing monomorphic lymphoid cell infiltrate. **(C)** Cryosection of sural nerve stained by immunohistochemical method showing $CD22^+$ cells in the endoneurium (arrows). **(D)** Cryosection of sural nerve stained by immunohistochemical method showing $CD5^+$ cells in the endoneurium (arrows). **(A),** × 300; **(B,C,D),** × 120. (Reprinted from Thomas FP et al.[124] with permission of Springer-Verlag.)

cauda equina syndrome.[6,23] Less commonly, they may present with a diffuse, progressive, and subacute or chronic peripheral neuropathy resembling GBS or CIDP.[9,117]

Hodgkin's Lymphoma. HL is less likely than NHL to infiltrate peripheral nerves, or present as a mass lesion, and more likely to cause autoimmune disorders due to the underlying immune system disturbance.[24,55,78,88,100] There are case reports of Guillain–Barré syndrome,[82,136,155] CIDP,[132,141] and presumed autoimmune sensory neuronopathy syndrome,[12,85,104] sometimes associated with anti-Hu antibodies.[85] These autoimmune paraneoplastic disorders can occur in early stages of HL. In addition, HL rarely infiltrates central or peripheral nervous system nerves but is commonly associated with VZV infection, with painful truncal, or occasionally limb, radiculopathy.[55]

Miscellaneous Syndromes. *Intravascular large B-cell lymphoma,* also known as angiotrophic lymphoma or malignant angioendotheliomatosis, may cause neuropathy.[137] These patients have lymphoma confined to the blood-vessel lumen.[131,137] Intravascular lymphoma presents neurologically most commonly as a stroke, due to intracranial vessel occlusion or embolic infarct.[137] However, patients can present with a cauda equina syndrome or a mononeuropathy. Diagnosis is made by biopsy or, more commonly, by autopsy.

Lymphomatoid granulomatosis is not considered a malignant lymphoma but is an angiocentric and angiodestructive lymphoproliferative disorder due to EBV infection.[7,27,35,39,49,54,60,63,81,93,103,108,112,148] Patients usually present with pulmonary and brain lesions but other sites may be involved. Pathological examination shows pulmonary angiitis, which has some characteristics in common with Wegener's granulomatosis and rare subtypes of lymphoma. Neurological symptoms can occur in up to 30% of the patients, but neuropathy is rare.[54] Involved peripheral nerves show demyelination and axonal degeneration in areas of lymphoid infiltration. Treatment with corticosteroids and cytotoxic agents may help. Diagnosis is made by biopsy of lung, brain, or peripheral nerve lesions.[81]

Chronic lymphocytic leukemia and *Waldenström's macroglobulinemia* may cause polyneuropathy by nerve infiltration or autoimmunity. Waldenström's macroglobulinemia can cause amyloid neuropathy[68] and neuropathy with antibodies directed at myelin-associated glycoproteins.[65,66] In addition to these disorders, osteosclerotic myeloma and Castleman's disease (angiofollicular lymph node hyperplasia), a nonmalignant lymphoproliferative syndrome, can also cause neuropathies. They are often accompanied by monoclonal gammopathies that can aid recognition but likely do not cause the disorder.[57] Castleman's disease and osteosclerotic myeloma may have multiorgan involvement characteristic of Crow–Fukase or POEMS syndrome.[67,91]

CLINICAL PRESENTATIONS

Patients most often present without known lymphoma, so a discussion of individual clinical presentations and approaches to their diagnosis can be helpful.

Cranial Nerve Disease. NHL can affect cranial nerves by infiltrating the dura and adjacent nerves. Greenberg et al. described five distinct dural syndromes: orbital, parasellar, middle fossa, jugular fo-

ramen, and occipital condyle.[45] The orbital and parasellar syndromes present with combinations of frontal headache, diplopia with extraocular nerve palsies, and sensory loss in the trigeminal first division. Proptosis occurs in the orbital syndrome. Facial pain and trigeminal sensory loss, sometimes with facial nerve palsy, characterize the middle fossa syndrome. The jugular foramen syndrome manifests with hoarseness and dysphagia due to lesions of the 9th to 11th cranial nerves. The condylar syndrome displays localized pain and ipsilateral tongue weakness and atrophy. Another ominous cranial nerve lesion has been termed the "numb chin syndrome"[83,100,118] referring to sensory loss in the mental nerve distribution caused by tumor invasion of the bone adjacent to the mental foramen. Although more common in solid malignancies such as prostate and breast, this syndrome can also occur in lymphoma.

Electrophysiological, neuroophthalmological, and neurovestibular examinations help to localize these disorders. In all of these cranial nerve syndromes, however, imaging and cerebrospinal fluid examination are crucial for diagnosis. Magnetic resonance imaging (MRI) in particular, with and without contrast, can detect local deposits and meningeal enhancement, indicative of meningeal infiltration that usually accompanies these syndromes.[100] Fusion positron emission tomography/computed tomography (PET/CT) imaging is a new technique for detection of masses and appears promising.[129] Cerebrospinal fluid cytological examinations, to look for evidence of meningeal infiltration, are abnormal in up to 80% of patients if at least three examinations are performed.[145] In addition, cerebrospinal fluid lactic dehydrogenase and beta$_2$ microglobulin levels can suggest lymphoma infiltration of leptomeninges.[100,145] If cerebrospinal fluid findings remain negative despite multiple studies, meningeal biopsy should be considered.[14,100] Other tests that can be useful in individual cases include CT scans for bony erosion, gallium scans for tumor masses, bone scans for infiltration, and PET scans to detect tumor deposits.[100]

Spinal Nerve Roots. Radicular involvement in lymphoma patients is most commonly due to herpes zoster (VZV) infections, usually in a truncal distribution.[2,55] Approximately 3–10% of lymphoma patients develop such infections.[18] In up to 5% of VZV infections, extremity nerve roots are affected, producing weakness with atrophy, variable sensory loss, and reflex changes (called segmental zoster paresis).[126] In these cases, VZV infection must be distinguished from mass effect of tumor or infiltration of roots. Diagnosis is usually easy when the typical rash appears but, rarely, the rash may be absent ("zoster sine herpete"[92]). EMG is helpful in detecting evidence of intraspinal disease but the peripheral nerves can be affected beyond the dorsal root ganglia as well, as evidenced by abnormal sensory nerve action potentials in some patients.

Almost all spinal and root syndromes are due to NHL and only rarely HL[100] (Table 1). The medical history and examination may not suggest the presence of malignancy, however, as these syndromes are often the initial manifestation of an underlying malignancy.[115] Patients present with radiculopathy or polyradiculopathy at a localized spinal level[61,100,115] or with a cauda equina syndrome.[13,24,115] Radicular involvement is manifest by typical root symptoms of distal pain, dysesthesias, paresthesias, and sensorimotor deficits in the distribution of the affected root.[6,100,123] Cauda equina lesions present with progressive, typically asymmetric involvement of the lower roots, initially manifesting with distal dysesthesias and sensory loss but less classic root pain.[24] Bladder and bowel function tend to be spared until late. EMG usually shows localized radicular involvement with sparing of distal sensory nerve action potentials in the distribution of clinical involvement and evidence of acute denervation in the paraspinal muscles. However, due to extraspinal involvement of the proximal plexus in some patients, distal digital or forearm sensory potentials may be affected, suggesting extraspinal disease as well.[30] The differential diagnosis in these patients, therefore, may span the multiple causes of root disease and plexopathy.

Diagnosis rests on needle biopsy of tumor masses or, less commonly, on open biopsy with or without decompression.[115] Positive cytology on cerebrospinal fluid examination can be helpful, especially in those without mass lesions and epidural enhancement on contrast CT[144] or MRI.[145] Due to the high frequency of meningeal involvement, cerebrospinal fluid examination should be performed even if spinal MRI is negative in atypical cases of radiculopathy or polyradiculopathy where lymphoma is considered a possibility.

These patients may have discrete epidural masses that compress the spinal cord, causing long tract signs, or they may infiltrate and compress exiting nerve roots causing the symptoms of pure radiculopathy.[100,115] EMG should be done early to localize the pathological process. In some cases, stimulation at Erb's point and of the nerve root can show the presence of a conduction block, indicating root disease or plexopathy.[30] Reduced distal sensory nerve action potentials indicate extraspinal involvement but often require unconventional studies of forearm

nerves that are rarely performed in many laboratories. Evidence by EMG of focal acute denervation in paraspinal muscles is strong evidence for intraspinal involvement. MRI and cerebrospinal fluid examination are needed to further stage the disease, along with other hematological tests.

Plexopathy. Plexopathies can be caused by infiltration of lymphoma, inflammation due to autoimmune inflammatory conditions associated with NHL or HL or the effects of radiation therapy.[10,59,71,72,102] Although several large series of malignant plexopathies have included patients with lymphoma, they were not analyzed separately and therefore only general statements can be made. In the brachial plexus, malignant plexopathies are more likely to present with pain and lower plexus involvement, sometimes associated with an ipsilateral Horner's syndrome.[72] However, Harper and colleagues did not find evidence for preferential involvement of the lower plexus in their series.[51] In lymphoma, the proximal plexus is often affected just distal to the root entry zone, with frequent spread to the meninges as evidenced by meningeal enhancement, epidural masses on MRI[100] or myelography, and abnormal cerebrospinal fluid cytology.[59,72] In localized lymphoma, MRI may show adenopathy or a high T2 signal mass that may enhance with contrast.[11,122] With NL, there is thickening of the nerve trunks and cords due to diffuse infiltration with increased T2 signal and some enhancement but no mass.[51,122] This picture can be mistaken for trauma or inflammatory plexopathy.[122]

In general, radiation plexopathy is much less painful than malignant plexopathy. There is typically a latency of 6 months or more from the time of radiation, and affected patients usually have experienced higher doses of radiation.[30,51,71,125] Initial symptoms are usually dysesthesias and paresthesias, and progression is slow over months to years with eventual development of weakness and reflex loss. Kori and colleagues[71,72] found that the upper plexus is more likely to be involved in radiation damage, presumably due to less protection from overlying tissue, although this was not the experience of Harper and colleagues.[51] Patients frequently have lymphedema.[72] Imaging studies show loss of tissue planes without mass lesions or enhancement.[10,51,123] Plexus imaging (MRI neurography) may be needed for optimal visualization.[122] Neurography requires special techniques using surface coils and is not available at many MRI centers. EMG can be helpful in differentiating these conditions. EMG usually shows myokymic discharges, which are relatively specific for radiation damage to nerves[51,79] and are not usually seen in neoplastic or inflammatory plexopathies. These discharges are characterized by high-frequency (5–150 Hz) firing of single motor units in repetitive bursts as doublets, triplets, or multiplets.[50] They are widespread and easily recognized in most cases of radiation plexopathy.[51]

Inflammatory plexopathies, caused by presumed autoimmune mechanisms, can be a presenting feature of HL or NHL, or can present in patients with established lymphoma.[77] These resemble typical cases of idiopathic brachial plexus neuropathy (Parsonage–Turner syndrome) with the acute onset of severe pain in the shoulder region followed rapidly by weakness of the proximal arm.[130] EMG shows no denervation of the paraspinal muscles in most cases.[33] Sensory nerve action potentials in the arm may be affected, establishing an extraspinal origin, but digital sensory potentials are often spared.[30,33]

Mononeuropathies. Mononeuropathies are rare and generally occur in the setting of NHL[29,89,133] and rarely in lymphomatoid granulomatosis[112] and intravascular lymphoma.[137] Mechanisms include neurolymphomatosis,[24] nerve infiltration by adjacent lymphoma,[97] infection with herpes zoster,[55] cryglobulinemia,[37] infarcts with intravascular lymphoma,[137] and vasculitis.[16,149] Mononeuropathies can occasionally be confused with plexopathy or radiculopathy, especially if they coalesce and present as a regional, multiple mononeuropathy syndrome. Electrodiagnostic testing can usually clarify the clinical disorder. The typical electrophysiological and pathological findings of nerve infiltration are of a mixed axonal and demyelinating process, which may be more heavily weighted towards one than the other.[138] There is often evidence of axonal damage distally, with reduced motor and sensory potential amplitudes and evidence of denervation.[24,89,143] In advanced cases, the patient may appear to have a generalized neuropathy, but asymmetries are often noted on clinical examination and electrodiagnostic testing. If imaging studies do not show adjacent adenopathy and clear evidence of nerve root infiltration with thickening of the nerves and contrast enhancement, then nerve biopsy is essential to establish the diagnosis.[89] Biopsy of an affected nerve is important, however, since unaffected nerves, even in the general area of involvement, may reveal no abnormality.[134] MRI and EMG can help to choose nerves suitable for biopsy.

Vasculitic disorders can occur in the setting of NHL as a presumed autoimmune complication or due to cryoglobulinemia, types 1 and 2.[37] These

patients typically have a primarily axonal process as determined by EMG. The nerves are affected in either a mononeuropathy or an asymmetrical regional pattern. Distal motor and sensory responses are diminished, and there is usually abundant evidence of acute and chronic denervation in the distribution of distal nerves.[16,37] Biopsy of an affected nerve, with immunolabeling to detect malignant lymphoma infiltration if present, is essential to accurate diagnosis in these syndromes.[132]

Polyneuropathy. Polyneuropathy can be caused by diffuse nerve infiltration[120] by NHL or NL which may mimic CIDP,[117] autoimmune neuropathies such a CIDP or GBS,[121] vasculitis, or cryoglobulinemia.[132]

The history helps to determine whether the process had an asymmetrical onset which suggests either nerve infiltration or a vasculitis.[17,24] Elevated serum lactic dehydrogenase levels in serum suggests a lymphoproliferative disease.[100,145] EMG may show a combination of axonal and demyelinating features, which can be confused with CIDP. MRI neurography using surface coils may help to detect suspected nerve infiltration. Demonstration of nerve thickening, nodule formation, and enhancement can strongly suggest an infiltrative process.[100] Cerebrospinal fluid examination is useful in demonstrating a lymphocytic pleocytosis and positive cytology in some cases, which may require additional treatment. In addition, peripheral nerve and central nervous system infiltration can occur while the lymphoma is in remission, presumably due to the sanctuary effect from chemotherapy drugs created by the blood–nerve barrier.[28,117,142]

Unless MRI neurography is unequivocal, nerve biopsy should be performed with immunolabeling studies.[73,121,124,132,137] Despite this, many patients are diagnosed at autopsy,[5] suggesting that clinicians should adopt a more aggressive approach to these patients. Multiple biopsies, directed by imaging techniques and EMG, should be performed in suspected cases.

Patients sometimes present, more commonly in HL,[82] with an autoimmune neuropathy that resembles CIDP or GBS.[121,132] The diagnosis of GBS is usual relatively straightforward using conventional techniques and criteria. Treatment is similar to that of uncomplicated GBS or CIDP. In addition, there have been reports of neuromyotonia occurring in the setting of NHL, presumably due to potassium channel antibodies.[78] Neuromyotonia is a distinct, high-frequency discharge distinguishable from myokymia.[50] Stiff-person syndrome and autonomic neuropathy have also been reported in HL,[31] presumably due to autoimmune mechanisms.[135]

Paraneoplastic vasculitis generally occurs with a presentation similar to conventional idiopathic vasculitis, with a sudden, painful, asymmetric onset. EMG is helpful in verifying isolated nerve involvement. Nerve biopsy is generally necessary to establish the diagnosis and to exclude an infiltrative process.[16] Cryoglobulinemia, types 1 and 2, should also be considered in cases of mononeuropathy or regional neuropathies.[37]

Motor Neuron Disease and Motor Neuropathy. Despite an epidemiological study that showed no increase of malignancy in motor neuron disease,[15] there have been scattered reports over the years of patients with motor neuron disease or motor neuropathy associated with lymphoma and other malignancies.[34,43,84,109–111,113,151–153] In addition to typical cases of amyotrophic lateral sclerosis, patients with subacute and chronic motor nerve disease have been described.[151–153] There have also been reports of multifocal motor neuropathy with antibodies directed at nerve gangliosides in patients with lymphoma,[96] and autopsy-proven amyotrophic lateral sclerosis with Waldenström's macroglobulinemia and antibodies to sulfated glucuronic acid paraglycoside.[110]

Among patients with HL or NHL and either classic amyotrophic lateral sclerosis or progressive spinal muscular atrophy,[94,111,151-153] some have paraproteinemia and abnormally increased cerebrospinal fluid protein levels with oligoclonal bands. Asymptomatic lymphoma was found in 2 of a series of 37 patients with amyotrophic lateral sclerosis undergoing routine bone marrow examination.[111] A monoclonal protein was found in one of these two patients. Only rare improvement occurs with immunosuppressive treatment.[43,94] Based on these studies, it has been suggested that patients with motor neuron disease and cerebrospinal fluid protein levels greater than 75 mg/dl, oligoclonal bands, or monoclonal serum proteins should undergo evaluation for lymphoproliferative disease.[153] Most amyotrophic lateral sclerosis centers have not reported a similar experience in patients with amyotrophic lateral sclerosis and these may be chance associations. However, since these cases are quite rare, they would be difficult to recognize in the population of otherwise typical patients with amyotrophic lateral sclerosis. A controlled, multicenter study would be needed to answer this question.

Motor neuron disease associated with anti-Hu (ANNA 1) antibodies seems to be a true paraneo-

plastic disorder[34] Anti-Hu antibodies can occur rarely in lymphoma patients.[21,85] These patients usually present with widespread abnormalities including encephalomyelitis and sensory neuronopathy. Up to 20% have signs of lower motor neuron disease.[34] They differ considerably from, and generally would not be confused with, typical amyotrophic lateral sclerosis.

Subacute motor neuropathy can occur in HL or NHL, with a course independent of the underlying malignancy.[116,151] These patients present with a subacute, asymmetrical, patchy, painless neuropathy mainly affecting the legs.[116] Sensory loss is minimal or absent. This neuropathy has a relatively benign, self-limited course. Most patients eventually stabilize or improve without treatment after months to years, with some recovering completely.[116] Pathology in those dying of the malignancy showed a combination of anterior horn cell neuronal degeneration, patchy segmental demyelination of the roots and proximal nerves, and inflammatory infiltrates.[116] The etiology is unclear but authors have opined that viral infection, previous radiotherapy, or immune paraneoplastic mechanisms may play a role.[116,151] Such associations may be by chance alone. A multicentered, controlled study would be needed to determine whether a true association exists with motor neuron disease.

CONCLUSIONS

Patients with known HL and NHL rarely develop peripheral nerve complications. These are much more common in B-cell derived NHL, especially in advanced stages. Patients may present with peripheral nerve complications or develop them during the course of the disease, even when in remission. This is presumably because lymphocytes may be sequestered inside the blood–nerve or blood–brain barrier where they are shielded from systemic chemotherapy. Tumor deposits or infiltration in the region of the spine and skull may cause radiculopathy or cranial neuropathy. The brachial or lumbar plexus may be affected by direct infiltration or secondary effects of lymphoma. In addition, individual nerves or adjacent groups of nerves may be affected by infiltration or associated complications or patients may develop diffuse infiltrative neuropathies in the setting of systemic lymphoma or neurolymphomatosis. Mononeuropathies may be caused by nerve infiltration, neurolymphomatosis, lymphomatoid granulomatosis, or intravascular lymphoma. Often, these conditions are mistaken for other more common causes, such as CIDP or inflammatory vasculitis. In addition, patients with both non-Hodgkin's and Hodgkin's lymphoma can develop conventional inflammatory, autoimmune conditions such as brachial plexopathy, Guillain–Barré syndrome, CIDP, or vasculitis of peripheral nerves. These need to be differentiated from lymphoma and other malignancies by imaging EMG, cerebrospinal fluid examination, and biopsy with lymphoma cell immunolabeling techniques. In addition, complications of treatment such as herpes zoster sometimes associated with segmental zoster paresis, radiation effects such as radiation plexopathy, and the effects of chemotherapy on peripheral nerves need to be considered.

In the future, patients with defined syndromes need to be more clearly described to facilitate their recognition. The role of new laboratory tests such as MRI neurography and PET scanning needs to be established. The biomechanisms of lymphoma cell spread to peripheral nerves requires study. If the involved cellular mechanisms can be identified, it may be possible to block infiltration with molecular antagonists.

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