CASE REPORT

Acute demyelinating neuropathy in a patient with neurolymphomatosis

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SUMMARY

Peripheral neurological complications of lymphomas are rare and much less frequent than central complications. Nonetheless, on occasion, systemic non-Hodgkin's lymphoma may directly infiltrate the peripheral nervous system at various levels. This report describes a man with non-Hodgkin's lymphoma and leptomeningeal disease who developed progressive areflexic quadraparesis. Initial electromyography (EMG) was consistent with a polyradiculopathy and a repeat EMG performed 1 month later for worsening symptoms showed evidence of demyelination. The patient expired due to systemic complications of his illness. Autopsy of the sural nerve showed moderately severe distal sensory axonal loss, direct infiltration of the brachial plexus by malignant lymphocytes and demyelination in brachial and lumbar plexus, most prominent in areas of neoplastic infiltration. Based on this patient's course and pathology, we suggest that widespread demyelination may accompany neurolymphomatosis and the clinical presentation may be indistinguishable from an acute demyelinating neuropathy.

BACKGROUND

Peripheral neurological complications of lymphomas are rare and much less frequent than central complications. Nonetheless, on occasion, systemic non-Hodgkin's lymphoma may directly infiltrate the peripheral nervous system at various levels. This report describes a man with non-Hodgkin's lymphoma and leptomeningeal disease who developed progressive areflexic quadraparesis. Careful study of the clinical and laboratory features of the patient's presentation highlight the importance of consideration of neurolymphomatosis in patients with lymphoma who develop generalised weakness as well as the importance of the spinal fluid examination in patients presenting with an acute inflammatory polyneuropathy (AIDP, also known as Guillain-Barre syndrome) phenotype. Furthermore, the similarities among this case and cases of patients with AIDP, highlight the potential role of systemic inflammatory response in the development of the pathology of neurolymphomatosis.¹

CASE PRESENTATION

A man with medical history of ulcerative colitis and progressive sclerosing cholangitis, for which liver transplantation was performed 2 years prior to his presentation, was admitted for fever, back pain and thrombocytopenia. On admission, the

patient was being treated with cyclosporine and prednisone. Earlier, the patient had also been treated with azathioprine. Workup showed diffuse marrow replacement of his spine without cord compression, a left hepatic lesion, splenomegaly and widespread adenopathy. Bone marrow flow cytometry showed large, phenotypically abnormal, clonal B cells consistent with aggressive lymphoma. He received high-dose cyclophosphamide and then was admitted again for neutropenic fever, myalgias, arthralgia and back spasms. On resolution of the neutropenia, his first cycle of ProMACE-CytaBOM (procarbazine, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine and methotrexate) was administered. Approximately 2 weeks later, he was readmitted with headache, fever, chills, intractable nausea and vomiting. Approximately 1 week after admission, he began to develop progressive weakness of all four limbs evolving over about a week to a point where he was non-ambulatory. MRI of the brain was normal. Neurological examination showed bifacial weakness, diffuse 3/5 proximal and distal weakness and areflexia. Nerve conduction studies were performed and showed profoundly decreased motor amplitudes but intact sensory responses (table 1). A lumbar puncture showed elevated cerebrospinal fluid (CSF) protein (134) and 65 white cells with malignant lymphocytes on cytological examination. He was initiated on a 5-day course of intravenous immunoglobulin for possible acute inflammatory demyelinating neuropathy and intraomaya chemotherapy with cytarabine.

The patient stabilised by day 3 of intravenous immunoglobulin treatment and continued to improve to the point of being able to ambulate. Ommaya reservoir taps were negative but a lumbar tap revealed persistent lymphomatous cells. He was treated with a second cycle of ProMACE-CytaBOM.

Five weeks after admission, he developed abrupt worsening over 3 days with severe generalised back pain, paraesthesia in the arms, ptosis, diplopia and paresis. Neurological examination was similar to prior but more asymmetric with a right third cranial nerve palsy, L>R arm and R>L leg weakness, absent deep tendon reflexes and markedly decreased proprioception in both feet. There were no swallowing problems. His forced vital capacity remained stable ranging from 2.3 to 3.3 which was not significantly different from his baseline when measured at his pretransplant evaluation.

Nerve conduction studies at that time (table 1) showed marked deterioration with loss of motor

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Table 1 Summary of nerve conduction findings

		First exam			Second exam		
		Latency (m/s)	AMP (mV)	CV (m/s)	Latency (m/s)	AMP (mV)	CV (m/s)
Sensory							
Median	R	2.3	0.052	13.92	NR		
Ulnar	R	1.9	0.052	10.99	NR		
Radial	R	ND			0.006		50
Sural	L	3.1	0.006	ND	NR		
Motor							
Median wrist	R	2.3	1.17		3	0.89	
Elbow		7.8	1.16	48.2	10.6	0.14	33.6
Axilla		10.3	0.88	54			
Ulnar wrist	R	2.4	1.59		3	0.13	
Below elbow		5.4	1.26	69.4	9	0.03	30.3
Above elbow		8.3	1.06	43.1	9.6	0.03	31.9
Tibial					4	0.26	
					21.5	0.15	25.7
Peroneal ankle	L	4.3	1.02		ND		
Fibular head		13	0.7	36.8			
Polpитеal fossa		16	0.71	38.3			
Peroneal ankle	R	4	0.25		NR		
Fibular head		12.5	0.19	38.8			
Polpитеal fossa							

AMP, amplitude; CV, conduction velocity; L, left; ND, not done; NR, no response; R, right.

and sensory amplitudes, conduction block and slowing and lack of denervation potentials in two severely weak, proximal muscles. The study was interpreted as consistent with a demyelinating motor-sensory polyneuropathy.

MRI of the spine with gadolinium did not show evidence of nerve root involvement.

The patient continued to worsen and became too ill to allow for continued treatment of the underlying malignancy.

INVESTIGATIONS

OUTCOME AND FOLLOW-UP

The patient died shortly thereafter of systemic complications of his illness. An autopsy of the left sural nerve ([figure 1A](#)) was performed and showed moderately severe and uniform decrease in the density of large myelinated fibres, myelin ovoids and scattered demyelinating fibres. An increase in the number of endoneurial macrophages was seen on immune-staining for macrophages ([figure 1B](#)) but no amyloid was seen in the congo red stained sections (not shown). Autopsy of the left proximal lower lumbar plexus ([figure 1C](#)) showed many demyelinating fibres scattered throughout the biopsy and a few myelin ovoids. Autopsy of the left proximal lower brachial plexus ([figure 1D](#)) showed large areas of active demyelination which was most prominent in areas with large numbers of infiltrating neoplastic mononuclear cells.

DISCUSSION

There are many causes of peripheral neuropathy in patients with lymphoma.² These may include: (1) causes directly related to lymphoma such as tumorous nerve infiltration (neurolymphomatosis)^{3,4} or direct nerve compression by lymphomatous mass; (2) immune complications induced by the lymphoma resulting in inflammatory demyelinating neuropathy or other paraneoplastic neuropathies⁵; (3) those directly related to a paraprotein such

Figure 1 (A) Toluidine blue stained 1 µm thick cross-sections of the patient's sural nerve obtained at autopsy. There is a significant reduction in the density of large myelinated fibres. Occasional myelin ovoids (not shown) were seen. (B) CD68 stained frozen section of the patient's sural nerve showed increased numbers of endoneurial macrophages (in red). (C) Toluidine blue stained 1 µm thick cross-sections of the patient's proximal lumbar plexus obtained at autopsy. There is a reduction in the density of large myelinated fibres. Myelin ovoids (asterisk) were rare, and many thinly myelinated (arrow) and demyelinated large fibres (arrowheads) were seen. (D) Toluidine blue stained 1 µm thick cross-sections of the patient's proximal lower brachial plexus obtained at autopsy. Myelin ovoids (not shown) were rare, and a numerous acutely demyelinating fibres and demyelinated fibres (arrowheads in inset) were seen. The demyelination is much more prominent in areas with high levels of endoneurial infiltration of lymphoma cells (above and to the right of the dotted line). There is a reduction in the density of large myelinated fibres. Scale bars: A and C: 20 µm; B: 250 µm; D: 40 µm, inset 15 µm.

as hyperviscosity, anti-myelin-associated glycoprotein syndrome or secondary amyloidosis⁶ and (4) those related to treatment or the generalised disease state of the patient including chemotherapy, radiation therapy, stem cell transplantation, malnutrition or infection.⁶ In a study of 26 patients with lymphoma with neuropathy unrelated to drug treatment or IgM anti-myelin-associated glycoprotein antibodies, the most common finding was demyelinating neuropathy in half, with the balance having root involvement from lymphoma (27%) or multiple axonal neuropathies from tumour infiltration or paraneoplastic microvasculitis.⁵

The patient's chemotherapeutic agents included cyclophosphamide and ProMACE-CytaBOM. Vincristine is the chemotherapeutic agent in this regimen most commonly associated with neuropathy,⁷ and it is associated with a length-dependent sensory motor axonal peripheral neuropathy. However, in our case, there was evidence of demyelinating neuropathy with relatively preserved sensory potentials on nerve conduction studies. Etoposide may cause a pure sensory neuropathy.⁷ Cytarabine very rarely causes peripheral neuropathy, generally only at much high doses⁷ than those administered to this patient.

Neurolymphomatosis (NL) is defined as invasion of cranial nerves and peripheral nerve roots, plexus or nerves by non-Hodgkin's lymphoma. Rarely, it is the first manifestation of non-Hodgkin's lymphoma. More commonly, it disseminates into the peripheral nervous system from systemic sites or due to lymphomatous infiltration of the meninges or the central neuraxis.⁸

The diagnosis of NL requires integration of clinical information, imaging findings and morphological data obtained from neural tissue, non-neural tissue and CSF. The diagnosis is often delayed in the absence of systemic lymphoma. Historically, in almost half of the reported cases, a clinical or histopathological diagnosis of NL was not established until autopsy.^{3 4} However, recent advances in the use of both imaging techniques⁹ and fascicular biopsy of involved nerves including the brachial plexus¹⁰ will likely increase the antemortem diagnosis of this condition.

Patients with NL may present with radiculopathy, primarily in the lumbosacral region. Neuropathic pain radiating into the lower limbs is followed by an ascending sensorimotor polyradiculoneuropathy, eventually resulting in symmetric paraparesis or quadriparesis. Disease course in some patients resembles mononeuropathy multiplex and isolated plexopathies. Mononeuropathy, most commonly of the sciatic nerve, may be secondary to lymphomatous infiltration. In addition, median, radial and intercostal nerve involvement has been reported.⁸ The mononeuropathy can remain isolated for years, but the majority of patients develop more widespread lymphoma or have a history of prior systemic lymphoma.³ In about 20% of patients with NL, the early disease course is characterised by isolated cranial neuropathy. 'Bell palsy' (cranial nerve VII), sometimes bilateral or recurrent; abducens, oculomotor and trigeminal neuropathy; hearing loss and vocal cord paralysis have been described.⁸

While AIDP itself is firmly associated with both Hodgkin and non-Hodgkin's lymphomas,² reports of patients presenting with an acute classical Guillain-Barre like syndrome (ie, maximal weakness before 28 days¹¹) attributable to neurolymphomatosis are extremely rare. Shoenfeld and coauthors¹² describe a case of a 32-year-old woman with histiocytic lymphoma who, after receiving radiation treatment and two cycles of chemotherapy, experienced onset of progressive tetraparesis. She died 10 days after onset of symptoms. Autopsy showed widespread infiltration of peripheral nerves by histiocytic cells and loss of myelin staining with Luxol fast blue. Interestingly, CSF was acellular at the time of onset of weakness and no evidence of systemic lymphoma was found at autopsy. Phan *et al*¹³ described a case of a patient with Burkitt's lymphoma and tetraparesis. CSF showed numerous malignant lymphocytes. Nerve conduction studies showing mild slowing of velocities, loss of F-waves, and drop in motor amplitudes at 14 days were interpreted as consistent with Guillain-Barre syndrome. However, the findings could have represented progressive radiculopathy superimposed on the effects of neurotoxic chemotherapy. The patient was treated with both systemic and intrathecal chemotherapy and plasma exchange. He improved temporarily, with partial normalisation of the CSF but relapsed and died. No autopsy was performed.

Previous case reports have described the presence of pathological demyelination in NL. Tomita *et al*¹⁴ found demyelination unrelated to macrophages at the site of lymphomatous cell invasion and axonal degeneration distal from the site of the lymphomatous cell invasion.

Overall the prognosis in NL is poor. Some authors have estimated that death may occur in 75% of patients.¹⁵ Nonetheless when neurolymphomatosis is properly diagnosed and treated, at least temporary complete resolution of symptoms is observed in 47% of patients.^{3 4} A recent report of 19 patients, all diagnosed with fluorodeoxyglucose positron emission tomography CT suggested that prognosis has not significantly improved, with 11 of 19 patients dying within 1 year of diagnosis and maximum survival among the other eight being less than 8 years.¹⁶

This is striking case of a patient with acute weakness in a patient with leptomeningeal lymphoma and autopsy proven neurolymphomatosis. Several features of this case suggest that the possibility that lymphomatous infiltration of the nerve may have been accompanied by a more generalised demyelinating neuropathy. First the patient responded rapidly to the combination of treatment with intravenous immunoglobulin and intrathecal chemotherapy without clearance of lymphomatous cells from the subarachnoid space. While this response could be attributed to the cytarabine alone, it is likely that the intravenous immunoglobulin had a significant effect. Second, the autopsy specimens of the lumbar plexus showed demyelination without evidence of infiltrating lymphoma. Third, the relatively rapid initial generalised motor decline and the subsequent acute relapse of generalised weakness are much more typical of immune mediated demyelination than of NL. Based on this patient's clinical presentation and pathology, we hypothesise that in patients with neurolymphomatosis, demyelination may either be a local result of lymphomatous infiltration or a more distant, likely immunological effect and that these two patterns may coexist in the same individual.

Learning points

- ▶ Neurolymphomatosis (NL) may mimic (or possibly coexist with) acute inflammatory demyelinating neuropathy (Guillain-Barre Syndrome). While further study is needed, patients with acute onset of diffuse weakness who are at risk for neurolymphomatosis may benefit from evaluation (and treatment as indicated) for both disorders.
- ▶ Evaluation of spinal fluid should be routinely performed in suspected cases of acute inflammatory polyneuropathy. The presence of a significant pleocytosis should prompt a search for an alternative diagnosis.
- ▶ Neurolymphomatosis is difficult to definitively diagnose by peripheral biopsy; if suspected, other modalities such as fluorodeoxyglucose positron emission tomography and proximal biopsy will have higher yields.
- ▶ Neurolymphomatosis may trigger a localised or more generalised attack on the peripheral nervous system. This could be due to the exposure of immunogenic epitopes in regions of direct tumour invasion. Further study should be undertaken to determine whether this is a significant contributor to the morbidity in NL.

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