Neurol Sci (2000) 21:241-245

CASE REPORT

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Brachial plexus neuropathy as unusual onset of diffuse neurolymphomatosis

Received: 21 June 2000 / Accepted in revised form: 31 August 2000

Abstract We present a patient with a large B cell gastric lymphoma in total remission who, after 4 months, developed a fatal progressive peripheral neuropathy with an unusual early involvement of the right brachial plexus. No evidence of lymphoma was found at whole body computed tomography, magnetic resonance imaging of the head, cervical spine and right brachial plexus, bone marrow biopsy or repeated lumbar punctures. The diagnosis of neurolymphomatosis was made only at postmortem examination.

Key words Non-Hodgkin's lymphoma · Neurolymphomatosis · Paraneoplastic neuropathy · Guillain-Barré syndrome

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Introduction

Neurolymphomatosis is a rare complication of non-Hodgkin's lymphoma (NHL) with signs of painful subacute or chronic sensorimotor polyneuropathy. The systemic lymphoma may be clinically silent and in most cases is associated with leptomeningeal involvement. A more progressive neuropathy is also described, mimicking the Guillain-Barré syndrome. Cranial nerve involvement is frequent. The diagnosis is often difficult to make in life and, in approximately half of the patients, is not made until the time of autopsy.

The pathogenesis of this neuropathy is unknown. Postmortem examinations generally reveal extensive infiltration of lymphoma cells into the cranial and peripheral nerves and into the nerve roots [1-7].

Case report

The patient was a 64-year-old man diagnosed with a stage IIE2 diffuse large cell gastric lymphoma (Working Formulation Group F) in January 1998. Immunohistochemical analysis demonstrated that the tumor cells belonged to the B cell lineage and were CD20-positive and CD3- and CD5-negative. After four courses of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy, the patient achieved complete pathological remission comfirmed by gastric sample. During the fourth course, he complained of myalgia in his right arm with progressive weakness and muscle wasting of his arm, forearm and intrinsic hand muscles. Nerve conduction velocity studies showed prolonged latencies with low amplitude responses of musculocutaneous, axillary and median nerves of the right side, suggesting involvement of the brachial plexus (Table 1).

A whole body computed tomography scan and magnetic resonance imaging of the head, cervical spine and right brachial plexus showed no evidence of lymphoma. A lum-

Table 1 Results from neurophysiological studies

Nerve	At admission			Week 2			Week 3		
	Latency (ms)	NCV (m/s)	Amplitude (μV)	Latency (ms)	NCV (m/s)	Amplitude (μV)	Latency (ms)	NCV (m/s)	Amplitude (μV)
Right musculocutaneous	12.0	NP	500	Absent	NP	NP	Absent	NP	NP
Right axillary	7.9	NP	300	Absent	NP	NP	Absent	NP	NP
Right median	5.0	48	500	4.9	41.0	200	Absent	NP	NP
Right peroneal	5.2	40	300	5.3	38.0	300	5.4	37.0	100
Left sensory median	2.9	NP	3.8	2.8	NP	3.7	2.7	NP	2.5
Left sensory sural	NP	45	10	NP	44.1	5.9	NP	44.1	1.8

NP, not performed; *NCV*, nerve conduction velocity

bar puncture at admission showed 83.1 mg/dl and 110 mg/dl protein and glucose, respectively, in the cerebrospinal fluid (CSF) in the absence of white cells and with a normal cytological profile (Table 2). LDH and β_2-microglobulin levels were elevated. High-dose corticosteroid therapy was initiated without improvement of the clinical picture.

Electrophysiological studies performed one week later showed reduced nerve conduction velocities in the median (41 m/s) and peroneal (38 m/s) nerves with low amplitude responses. Latencies of musculocutaneous and axillary nerves were impossible to detect. A second lumbar puncture revealed rare lymphocytes, 68 mg/dl protein, 100 mg/dl glucose, 239 U/l LDH (serum, 423 U/l) and 5060 μg/l β_2-microglobulin (serum, 1550 μg/l). The neurophysiological findings suggested the diagnosis of atypical Guillain-Barré syndrome or polyneuropathy associated with lymphoma.

Immunoglobulin therapy (0.4 mg/kg on days 1-5) was initiated, leading to a marked improvement of myalgia and weakness of the right arm. Tests for serum antibodies against myelin-associated glycoprotein (anti-MAG), GM1 gangliosides (anti-GM1), Purkinje cells (anti-YO) and type 1 anti-neuronal nuclear autoantibodiies (anti-HU) were all negative.

The patient was discharged but readmitted to the hospital one week later for mild somnolence and impaired mental status. CSF analysis by lumbar puncture revealed rare typical lymphocytes, 209.1 mg/dl protein, 64 mg/dl glucose, 290 U/l LDH (serum, 547 U/l), and 8700 μg/l β_2-microglobulin (serum, 2060 μg/l). Bone marrow biopsy was negative, as were serological tests for toxoplasma, cytomegalovirus, Epstein Barr virus (EBV), or human herpes viruses (HHV) 1 and 2. A third electromyographic examination documented a further slowing of the motor nerve conduction velocities and a lowering of both the sensory and motor action potential voltages. Examination of a right sural nerve specimen showed normal findings.

In the subsequent days, the patient became progressively more confused, had increasing weakness of all the limbs, amyotrophy of the right arm, left facial palsy, diplopia and increasing difficulty in swallowing. A whole body computed tomography scan and brain magnetic resonance imaging revealed a moderate increase of the ventricular space volume. Another lumbar puncture was performed. Examination

Table 2 Cerebrospinal fluid and serum analyses

	At admission	Week 2	Week 3	Week 4
Cerebrospinal fluid				
White cells (cells/mm^3)	0	1	0	40
Cytological profile	Normal	Rare lymphocytes	Rare typical lymphocytes Common leukocytes	Granulocytes
Glucose (mg/dl)	110	100	64	57
Protein (mg/dl)	83.1	68.0	209.1	69.9
Chloride (mg/dl)	114	110	113	113
β_2-microglobulin (μg/l)	2170	5060	8700	>6000
LDH (U/l)	92	239	290	594
Serum				
β_2-microglobulin (μg/l)	2000	1550	2060	1860
LDH (U/l)	662	423	547	808

LDH, lactate dehydrogenase

of the CSF showed: 40 white cells/ml (granulocytes), 69.9 mg/dl protein, 57 mg/dl glucose, 594 U/l LDH (serum, 808 U/l), and >6,000 μg/l β_2-microglobulin (serum, 1860 μg/l). A presumptive diagnosis of leptomeningeal involvement of lymphoma was made and intrathecal methotrexate (10 mg) and corticosteroids (methylprednisolone, 40 mg) were administered.

This treatment led to a mild improvement of the patient's mental status. However, 24 h after methotrexate administration, respiratory failure with pulmonary edema developed and the patient died, despite aggressive supportive care.

Autopsy findings

Examination of multiple sections revealed scanty perivascular infiltrates in the cerebral hemispheres, including some large atypical forms. Most of the cells stained for B cell markers. The most striking changes were observed in sections of the brachial plexus where the nerve trunks appeared expanded by heavy interfascicular lymphoid infiltrates (Fig. 1). The endoneurium of individual nerve fascicles was diffusely infiltrated by a monomorphous population of large atypical lymphoid cells with scattered mitotic figures (Fig. 2).

Immunohistochemical staining performed on paraffin-embedded sections showed that the majority of these lymphoid elements were positive for the CD20 B cell antigen and negative for the CD3 and CD5 T cell markers as already found in the primary gastric lymphoma. In addition, the lymphocytes were positive for monotypic but not for the κ Ig light chains. No neoplastic cells were histologically detected in any of the previously known sites of disease.

To assay the presence of EBV and HHV-8 DNA, the polymerase chain reaction (PCR) for the BZLF1 and for the major capside protein genes was performed, respectively, on deparaffinized specimens of the brachial plexus. Both tests were negative, as was the analysis by PCR followed by hybridization for the gag-pol-env genomic regions of HTLV-1.

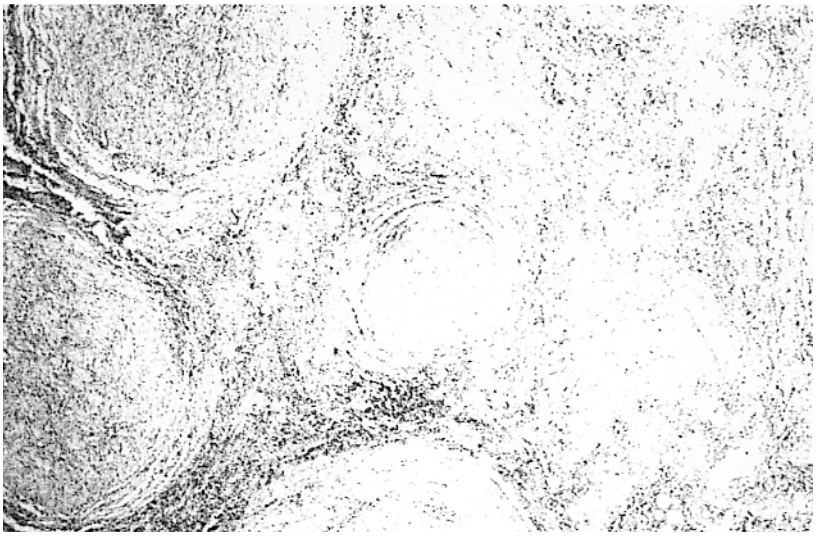

Fig. 1 Section of the brachial plexus where the nerve trunks appear dilated by interfascicular lymphoid infiltrates

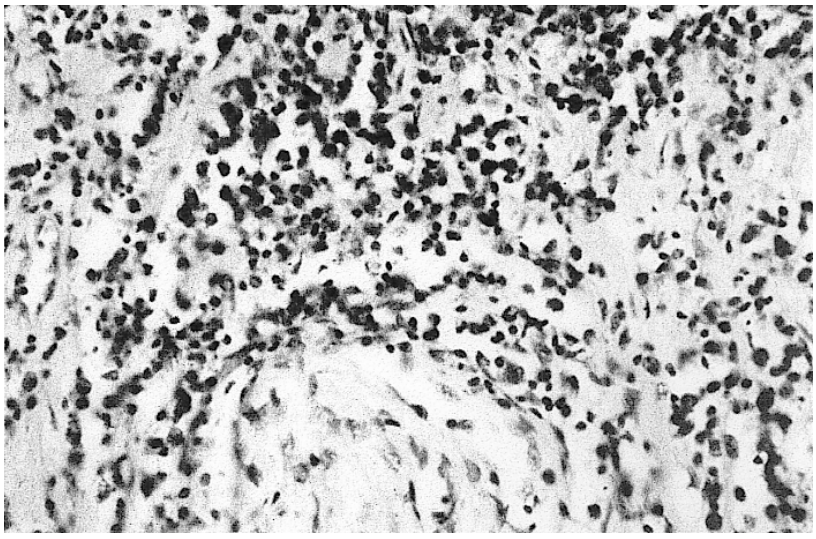

Fig. 2 Widespread infiltration of the endoneurium by monomorphous neoplastic lymphoid cells

Discussion

Since 1934, after the definition of this syndrome by Lhermitte and Trelles [8], approximately 50 cases of neurolymphomatosis have been described. In 1992, Diaz-Arrastia et al. reviewed 39 cases from the literature [1]. Most of these were correlated to NHL with evidence of widespread systemic disease [1-7]. The real incidence of neurolymphomatosis in NHL is unknown owing to the lack of specific criteria for clinical diagnosis and to the inconsistency of the autopsy series [1].

In the vast majority of cases, patients present subacute progressive neuropathy, while our patient developed an acute and rapidly progressive sensory-motor peripheral neuropathy, mimicking the Guillain-Barré syndrome with unusual clinical features.

In some of the reported cases [9-10], the clinical course was similar to our case and a clinical diagnosis of Guillain-Barré syndrome was made in 5 of 6 patients. In our patient, there was in increase in CSF protein content in the absence of white cells but with increased levels of LDH and β_2-microglobulin, suggesting a diagnosis of a relapsing lymphoma involving the nervous system.

The pathogenic mechanisms of peripheral nerve involvement in lymphoma are heterogeneous. This disease may be part of a continuum of nervous system involvement by systemic lymphoma [7], ranging from leptomeningeal diseases to relatively pure forms of peripheral nerve neurolymphomatosis. A paraneoplastic mechanism may be considered [11, 12] although, in the case presented, antibodies against nerve components could not be detected.

On the other hand, the neuropathy and the lymphoma could have a common origin due to a retrovirus or other neurotropic and oncogenic virus [13]. In humans, herpesvirus and HTLV-1 are the most strongly suspected. In the case reported by Kuroda et al. [14], the patient was seropositive for HTLV-1. Retrovirus-like particles and HTLV-1-specific DNA sequences were demonstrated in lymphomatous T cells in one patient described by Vital et al. [2]. In the case presented herein, the lack of DNA sequences specific for EBV, HHV-8 and HTLV-1 makes a viral mechanism unlikely.

The mild polyneuropathy associated with low-grade NHL is considered to be different from the clinicopathological entity of neurolymphomatosis. Alternative pathogenetic mechanisms, such as antibody-mediated nerve damage, may also be implicated in this case [15, 16].

Our patient suffered from a fatal progressive sensory-motor peripheral neuropathy mimicking the Guillain-Barré syndrome but with histopathological evidence of lymphomatous nerve infiltration showing the same cellular phenotype of the primary gastric lymphoma. The syndrome developed after a complete response to chemotherapy, suggesting a selection of chemoresistant clones with specific neurotropism. Alternatively, peripheral nerves may constitute a sanctuary site for chemotherapy due to the blood-nerve barrier.

In conclusion, peripheral nerve infiltration may occur in NHL and should not be confused with an inflammatory process. Neurolymphomatosis should be considered in the diagnostic evaluation of polyneuropathy developing during the course of lymphoproliferative disorders.

Sommario *Viene descritto il caso di un uomo di 64 anni con linfoma gastrico in totale remissione che, dopo 4 mesi, ha sviluppato una grave plessopatia brachiale destra seguita da neuropatia periferica progressiva. Gli esami strumentali (tomografia assiale computerizzata (TAC) di tutto il corpo, risonanza magnetica (RM) dell'encefalo, del midollo cervicale e del plesso brachiale destro, biopsia midollare e studio seriato del liquido cefalo-rachidiano) non hanno mai evidenziato segni di recidiva di linfoma. Solo l'esame autoptico e lo studio immunoistochimico su sezioni del plesso brachiale destro hanno consentito la diagnosi di neurolinfomatosi.*

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