Neuropathy in lymphoma: a relationship between the pattern of neuropathy, type of lymphoma and prognosis?

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ABSTRACT

Background: Neuropathies associated with lymphoma (NAL) are rare and present a great clinical heterogeneity, making them difficult to diagnose and worsening their prognosis.

Objectives: (1) To report the different patterns of NAL and discuss the mechanisms encountered; (2) to determine the relationship between a given type of lymphoma and a specific type of neuropathy; and (3) to assess the prognosis of NAL.

Methods: Among 150 patients with lymphoma and neuropathy, we selected 26 in whom the neuropathy was not related to drug induced or IgM-antimyelin associated glycoprotein neuropathies. The pattern of neuropathy was defined in terms of its clinical and electrophysiological features. Neurological improvement, haematological remission and occurrence of death were taken into account to determine the prognosis.

Results: 13 patients (50%) had a demyelinating polyneuropathy (PNP), seven (27%) had a radiculopathy linked to proximal root tumoral infiltration and six (23%) had an axonal multiple mononeuropathy (MM) related to distal lymphomatous infiltration or to paraneoplastic microvasculitis. Hodgkin's lymphoma was only associated with demyelinating PNP. High grade B cell lymphoma was strongly associated with radiculopathy. Neurological improvement was observed in 69% of patients with demyelinating PNP, 29% with radiculopathy and 50% with MM. Haematological remission was observed in 46% of patients with demyelinating PNP, 29% with radiculopathy and 83% with MM.

Conclusions: Demyelinating PNP, the most frequently observed neuropathy in this study, had the best neurological prognosis. Chemotherapy combined with immune mediated treatment was the most effective treatment in this group. Identifying the type and mechanism of NAL is crucial in order to define the therapeutic strategy and improve the prognosis.

Peripheral neurological complications of lymphomas are rare and much less frequent than central complications.[1] They have usually been reported in single cases or small series.[2–5] In addition to the common causes of peripheral nerve involvement, such as nerve compression by a lymphomatous mass, iatrogenic toxicity and herpes zoster virus infection,[6] there are mechanisms that are more specifically related to lymphomas, such as nerve tumoral infiltration, also called "neurolymphomatosis",[2 4 7 8] or immune complications induced by the lymphoma. These immune processes can result in various neuropathies, such as inflammatory demyelinating neuropathy[9–12] or neuropathies secondary to the secretion of a monoclonal immunoglobulin[3 13 14] and paraneoplastic neuropathies of uncertain origin.[15–17] All patterns of neuropathy have been described in the context of lymphoma.[1] Whether this great clinical heterogeneity is related to these different pathological processes or is linked to the type of lymphoma affecting the peripheral nerve is not well known. When the neuropathy occurs in patients with previously undiagnosed lymphoma, misdiagnosis or delayed diagnosis is frequent and can have an adverse effect on the outcome. The prognosis of neuropathy associated with lymphoma (NAL) has only been estimated in neurolymphomatosis, in which death may occur in 75% of patients.[2] Yet when neurolymphomatosis is properly diagnosed and treated, complete resolution of symptoms is observed in 47% of patients.[4] The aims of the present study were (1) to analyse the different patterns and mechanisms encountered in NAL; (2) to determine whether there is a relationship between a given type of lymphoma and a specific type of neuropathy; and (3) to assess the prognosis of these neuropathies.

METHODS

Patients

On the basis of the selection criterion "patients presenting with neuropathy and lymphoma", 150 patients were identified from the authors' files. Of these, 124 were excluded because they presented with drug induced (n = 68) or IgM-antimyelin associated glycoprotein neuropathies (n = 20) or other possible causes of neuropathy (n = 26), or because of a lack of data (n = 10). Finally, 26 patients were selected for the study: 16 were consecutive and were followed-up by KV between 2000 and 2005 and the remaining 10 were followed up by PB, TM or JML between 1995 and 2005. During the latter period, a total of 400 patients with lymphoma, with or without neuropathy, were followed-up at the Salpêtrière Hospital. All patients included in the study had undergone a neurological examination and an electrophysiological study. Patients were classified into different groups according to the pattern of neuropathy based on the initial clinical and electrophysiological data. A demyelinating polyneuropathy (PNP) was diagnosed on the basis of peripheral neuropathy, with weakness or sensory symptoms in at least two limbs, associated with demyelinating criteria on electrophysiological examination.[18] Onset was defined as "acute" if symptoms developed within

less than 4 weeks, subacute if they developed within 4–8 weeks and progressive if they developed over a period of more than 8 weeks. Acute demyelinating PNP was defined as an acute onset without relapse during the course and chronic demyelinating PNP as a progression of symptoms or relapses during the 6 months following the onset. Radiculopathy corresponded to a proximal and distal sensorimotor deficit (with loss of deep tendon reflex) localised in a root distribution, associated with a neurogenic pattern with a similar root distribution, without conduction abnormalities, suggesting demyelinating features. Axonal multiple mononeuropathy (MM) corresponded to an axonal distal asymmetrical motor or sensory neuropathy with a nerve trunk distribution. Axonal distal polyneuropathy was diagnosed on the basis of a symmetrical distal motor or sensory involvement without conduction abnormalities suggesting demyelinating features.

Electrophysiological study

The median, ulnar, tibial and peroneal nerves were examined on both sides in all patients. For each nerve, distal latency, conduction velocity, compound muscle action potential (CMAP) amplitude (baseline to negative peak), areas under negative phase and CMAP duration were measured. For each nerve segment, the reduction in CMAP amplitude or area on proximal versus distal stimulation was calculated. A conduction block was defined as a decrease in amplitude of 30% between proximal and distal sites of stimulation for any nerve, with the exception of stimulation at Erb's point, for which a 50% decrease in amplitude was used. F wave latency was recorded after distal supramaximal stimulation (at least 20 stimuli). Sensory nerve action potential amplitude (peak to peak) was measured in the median, ulnar, radial, tibial and superficial peroneal nerves on both sides, with surface recording and stimulating electrodes. A needle electromyographic examination was performed in all patients. For details of the electrophysiological study, see Viala and colleagues.[19]

Nerve biopsy studies

Eleven patients underwent a nerve biopsy. Morphological and immunostaining studies of peripheral nerves and molecular analysis of lymphoid clonality are detailed in the supplementary data file appendix 1 (available online).

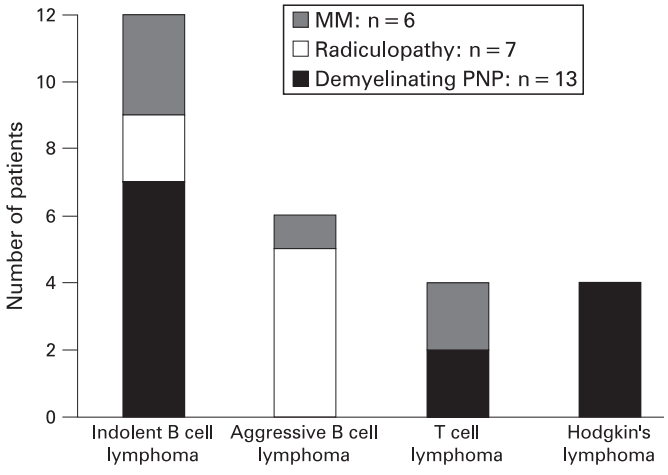

Figure 1 Lymphoma subtype in relation to the type of neuropathy. Demyelinating PNP, demyelinating polyneuropathy; MM, multiple mononeuropathy.

Evaluation procedures

Neurological recovery was defined as complete resolution of neurological signs and symptoms. Neurological improvement was defined as an improvement of at least two Medical Research Council grades in any muscle and by a decrease in pain and sensory symptoms. Patients were considered to have worsened if motor strength decreased by at least two Medical Research Council grades in any muscle or if weakness extended to other muscles, or if sensory and painful symptoms increased.

RESULTS

There were 13 men and 13 women, and mean age at onset of neuropathy was 56 years (range 24–80). Half of the patients (13 cases) had demyelinating PNP, 27% (seven cases) displayed features of radiculopathy and 23% (six cases) had MM. None of the patients had distal axonal polyneuropathy. The relationship between lymphoma subtype and pattern of neuropathy is shown in fig 1.

Demyelinating polyneuropathy group (n = 13)

The main characteristics of the demyelinating PNP group are summarised in the supplementary data file table 1 (available online).

Clinical, electrophysiological, biological and histopathological features

Mean age at onset of neuropathy was 57 years. Demyelinating PNP preceded the lymphoma in nine cases, with a mean time between the first symptoms of neuropathy and lymphoma diagnosis of 13 months. When demyelinating PNP was associated with previously diagnosed lymphoma, the mean delay between lymphoma diagnosis and onset of neuropathy was 48 months. The onset of demyelinating PNP was progressive in three patients and acute or subacute in 10 patients, but the course was chronic in all patients. Five patients had a predominantly sensory form with ataxic gait or distal paresthesia, and three patients presented with a predominantly motor form.

In the electrophysiological study, patients had various patterns of demyelination. Six patients also had secondary early axonal loss. Mean protein content was 80 mg/dl (range 40–156). None of the patients had cells on CSF examination. Distal nerve biopsy was performed in three patients and showed demyelinating features without cellular infiltrate.

For the nine patients presenting with inaugural neuropathy, the criteria for testing for malignant haemopathy were as follows: a severe and rapid course of demyelinating PNP with a poor response to the initial therapy (four cases), emergence of an abnormal inguinal lymph node during the course of the demyelinating PNP (one case), and the presence of monoclonal gammopathy (five cases) or hypogammaglobulinaemia (one case). Three patients met two of these criteria. Lymphoma diagnosis was based on lymph node biopsy findings in five patients and bone marrow biopsy findings in four patients.

Response to treatment and prognosis

Response to treatment and outcomes in this group are summarised in the supplementary data file table 2 (available online). Patients received several lines of treatment because prednisone and intravenous immunoglobulins (IVIg) were poorly effective as the firstline treatment. None of the patients (0/5) improved after corticotherapy and 1/6 patients improved after IVIg. Plasma exchange (PE) was effective as a last line of

treatment in 2/2 patients. The best efficacy was observed with a combination of chemotherapy and immune mediated treatments, such as IVIg or PE (improvement in 4/6 patients). By the end of the follow-up period (mean follow-up 28.25 months), four patients had made a complete neurological recovery, four experienced a neurological improvement, one was stabilised and four patients had worsened. Thus the overall neurological outcome was favourable in 69% of patients. Complete haematological remission was observed in 46% of patients. Three patients (23%) died, all from severe infections.

Radiculopathy group (n = 7)

The main characteristics of the radiculopathy group are summarised in the supplementary data file table 3 (available online).

Clinical, electrophysiological, biological and histopathological features

Mean age at onset of neuropathy was 59 years. Radiculopathy was inaugural in all cases. The time between the first symptoms of neuropathy and lymphoma diagnosis ranged from 1 to 52 months (mean delay 14). Radiculopathy was always asymmetrical with a sensory and motor deficit and was painful in most patients. A bifocal distribution affecting the lumbosacral (L4, L5, S1) and cervical (C8, D1) roots was observed in five patients, while the remaining patients presented isolated lumbosacral root involvement. Electromyography showed neurogenic features in the clinically affected root territory in all patients, with fibrillation in 5/7 patients. Electrophysiological studies found a reduction in CMAP with a radicular distribution in 5/7 patients. Distal sensory potentials were normal except in two patients. These two patients had a severe reduction of the distal sensory potentials in the territory of sensory deficit, suggesting that the radicular involvement included the dorsal root ganglion.

On the initial CSF examination, tumoral cells were only found in one patient. Elevated CSF protein content associated with pleiocytosis without tumoral cells was observed in three cases, and CSF was normal in the other patients. Nevertheless, CSF examinations were repeated during the course of the disease, a mean of three examinations per patient being required before lymphomatous cells were observed.

One patient had a monoclonal IgG kappa gammopathy in serum and another had hypogammaglobulinaemia. MRI was performed in all patients and showed nerve root gadolinium enhancement in three cases but at later stages of the disease.

A distal nerve biopsy performed on patients who had alteration of distal sensory potential on electrophysiological study showed axonal loss without signs of demyelination or cellular infiltrate.

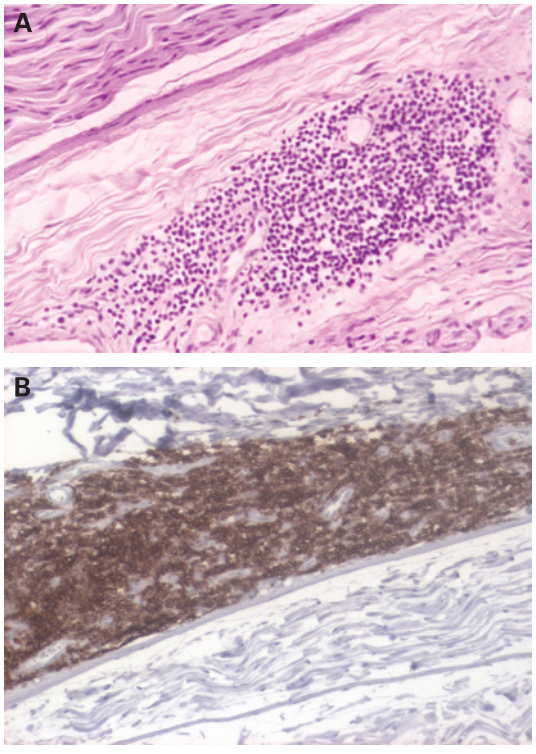

Figure 2 Case No 26: superficial peroneal nerve biopsy. Longitudinal section of paraffin embedded tissue seen under light microscopy. (A) Haematoxylin–eosin stain. Presence of a perivascular lymphocytic infiltrate, localised in the perineurium. Mononuclear cells did not invade the vessel wall (original magnification ×250). (B) Marked CD20 expression (B lymphocytes), which is very prominent in the mononuclear cells infiltrate (original magnification ×400). Molecular biology study confirmed that they consisted of tumoral B lymphocytes showing the clonal immunoglobulin heavy chain rearrangement.

Response to treatment and prognosis

Neurological worsening and death occurred in 5/7 patients within a mean delay of 38 months (range 9–96) from the onset of neurological symptoms, despite a transitory improvement after corticosteroid therapy in three cases. Two patients, who had a short diagnostic delay, had haematological and neurological remission (follow-up after the last treatment of 36 and 24 months).

Axonal multiple mononeuropathy group (n = 6)

The main characteristics of the MM group are summarised in the supplementary data file table 4 (available online).

Clinical, electrophysiological, biological and histopathological features

Mean age at onset of neuropathy was 48 years (range 32–70). MM was inaugural in all cases. The mean delay between the first symptoms of neuropathy and lymphoma diagnosis was 17 months. Initial presentation was a sensorimotor multiple mononeuropathy in three patients, a pure sensory multiple mononeuropathy in two and one had a mononeuropathy of the sciatic nerve.

Electrophysiological studies showed a marked alteration of CMAP and distal sensory potential amplitudes in the same nerve trunk distribution with side to side asymmetry in all patients but one, the latter having only an asymmetrical reduction of distal sensory potential amplitudes in multiple nerve trunk nerve territories. Asymmetrical active denervation was found in all cases but one.

Two patients had monoclonal gammopathy, of the IgG kappa and IgM kappa type, and one patient had hypogammaglobulinaemia. CSF protein content was normal or slightly elevated (mean of 56 mg/dl), and one patient had 4 cells/mm^3.

Distal nerve biopsy was performed in all six cases. No amyloid deposit was observed in any of the biopsies. Tumoral nerve infiltration was diagnosed in four patients, on cytological examination (one case) or on immunohistological and molecular biology studies (three cases), showing lymphocytic B cell infiltrates with the same clonal immunoglobulin heavy chain

rearrangement in nerve and in blood or bone marrow (fig 2A, B). Another patient had perivascular predominantly CD3+ cell infiltrate with several CD20+ cells without demonstrated clonal type on biological study and with moderate axonal loss. The remaining patient had loss of myelinated fibres without infiltrate in nerve but granulomatous lesions in muscle.

Response to treatment and prognosis

Haematological remission was observed in all cases but one (mean follow-up 40 months). In the latter patient, the neuropathy progressed in spite of chemotherapy and she died from a septic complication of autologous bone marrow transplantation. Neurological symptoms improved after chemotherapy in three patients. The progression of the neuropathy was stopped in two patients, but with the persistence of neurological impairment and pain.

DISCUSSION

NAL can reveal the haematological malignancy or occur in a patient with a known lymphoma. For the neurologist, diagnosing the neuropathy is challenging as it usually occurs in patients with previously undiagnosed lymphoma, with a widely varying clinical presentation and requires many differential diagnoses. For the haematologist, the problem is to identify the mechanism of the neuropathy so as to adapt the treatment, using drugs with good penetration into the nervous system in cases of lymphomatous nerve infiltration, performing immunomodulatory treatment in dysimmune neuropathy or modifying the chemotherapy in drug induced neuropathy. Both approaches require a good knowledge of this rare entity. In this study based on the analysis of 26 patients with NAL, half of the patients had demyelinating PNP, 25% had radiculopathy linked to proximal root tumoral infiltration and the remaining patients had axonal MM related to distal lymphomatous infiltration or to paraneoplastic microvasculitis. The neuropathy revealed the lymphoma in 85% of patients, and it is therefore important to note that the diagnostic keys for the lymphoma differ according to the type of neuropathy. In the event of demyelinating PNP, either a severe or rapid course, a poor response to therapy with an early axonal loss or the presence of systemic abnormalities should lead to an associated lymphoma being suspected. The presence of monoclonal gammopathy should also prompt diagnostic tests to rule out the possibility that a lymphoma is associated with the demyelinating PNP. In our study, 55% of patients with inaugural demyelinating PNP had a monoclonal gammopathy, whereas the prevalence of monoclonal gammopathy is 17% in B cell non-Hodgkin lymphomas[20] and 18% in idiopathic chronic inflammatory demyelinating polyneuropathy.[21] In radiculopathy, CSF examination remains the crucial diagnostic tool, but has to be repeated as in the majority of our patients three lumbar punctures were needed before tumoral cells could be evidenced. Radiculopathy can mimic demyelinating neuropathy with confusing proximal and distal weakness, but radiculopathy linked to tumoral infiltration is more painful and asymmetrical. A progressive course leading to bilateralisation of symptoms or a cauda equina syndrome is suggestive of the diagnosis. Motor conduction study abnormalities, when present, are only moderate and do not reach values indicative of demyelination. During the course, elevated CSF protein content is often associated with pleiocytosis above 20 cells/mm^3, which is rare in demyelinating neuropathy.[21] Radiculopathy might also be confused with mononeuropathy of the sciatic nerve. The reduced distal sensory potentials of sural and superficial peroneal nerves allowed nerve trunk involvement to be distinguished from radiculopathy. Nevertheless, in cases of involvement of the dorsal root ganglion, it may be very difficult to differentiate radiculopathy from plexopathy or sciatic nerve lesions. Imaging studies, however, can help to distinguish between them.[4]

In MM, the immunohistological and molecular biology study of the nerve biopsy is of prime importance in diagnosing the lymphoma, underlining the need to keep frozen nerve biopsy samples. In the context of known lymphoma, the occurrence of MM usually leads to the suspicion of tumoral infiltration, cryoglobulinaemia or paraneoplastic vasculitis,[22 23] or, more rarely, a neuropathy secondary to amyloidosis or immunoglobulin deposit.[24 25] Nevertheless, when MM occurs in unknown lymphoma, tumoral infiltration might be difficult to diagnose because of its "vasculitis-like" presentation. Thus demonstration of a clonal cell population in the perivascular infiltrate is needed to correct the diagnosis.

Another question raised by this study is the relationship between a given type of lymphoma and a specific type of neuropathy. Hodgkin's lymphoma was only associated with demyelinating PNP. Two particular presentations were observed: a predominantly sensory form and a severe predominantly motor form. Both were subacute. Sensory neuronopathy[16 17] and sensory inflammatory demyelinating polyneuropathy have previously been reported in Hodgkin's lymphoma.[26] Subacute motor neuronopathy has been described in Hodgkin's lymphoma but with a benign course,[27] contrasting with the severe course in our patients. Indolent B cell lymphomas were found in the three groups of neuropathy and represented 54% of demyelinating PNP, 50% of MM and 29% of radiculopathy. T cell lymphoma was revealed by MM and by demyelinating PNP. In contrast, a link seemed to exist between aggressive B cell lymphomas and the pattern of radiculopathy, as 71% of patients with radiculopathy had an aggressive B cell lymphoma, a fact that likely accounts for the radiculopathy group having the worst prognosis. Nevertheless, our study shows that the prognosis of NAL could also depend on the pattern of neuropathy, as demyelinating PNP and MM can have a favourable outcome even in the event of T cell lymphoma. Demyelinating PNP had a favourable neurological outcome in 69% of our patients, including four patients who recovered fully. Interestingly, the greatest efficacy was obtained with a combined treatment associating chemotherapy and immunomodulatory therapy (principally PE or IVIg). In the MM group, the haematological prognosis was good, with only 17% of deaths and more than 80% of patients having haematological remission. The neurological progression was stopped in the majority of treated patients but persistent neurological sequelae were more frequent than in the demyelinating PNP group. Nevertheless, these results must be interpreted cautiously given the small number of patients in our study and the heterogeneous nature of the treatments administered. In contrast with other studies,[6 15 28–30] we did not observe any patient with distal axonal symmetrical polyneuropathy or motor neuron disease. By excluding patients with drug induced neuropathy or other causes of neuropathy, we may have inadvertently excluded patients with concomitant NAL.

CONCLUSION

This study underlines the high occurrence of demyelinating PNP in lymphoma, and suggests that a combination of chemotherapy and immune mediated treatment can lead to a good prognosis. Proximal tumoral infiltration of the peripheral

nervous system is revealed by radiculopathy and is usually associated with aggressive B cell lymphoma. This entity appears to have the poorest prognosis. In contrast, distal nerve tumoral infiltration revealed by axonal MM seems to have a more favourable prognosis. Identifying these different mechanisms with appropriate investigations is crucial to reduce the diagnostic delay, define the therapeutic options and improve the prognosis.

Competing interests: None.

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