Effects of lymphoma on the peripheral nervous system

R A C Hughes MD FRCP **T Britton** MB MRCP **M Richards** MD FRCP[1]
Departments of Neurology and Clinical Oncology[1], UMDS, Guy's Hospital, London SE1 9RT, UK

Keywords: lymphoma; peripheral neuropathy; herpes zoster; chemotherapy

Summary
Peripheral nervous system abnormalities occur in 5% of patients with lymphoma and have a wide differential diagnosis. Herpes zoster is the commonest cause. Vinca alkaloids are the only drugs used in lymphoma which commonly cause neuropathy. Compression or infiltration of nerve roots by lymphoma is a rare presenting feature but becomes more common with advanced disease. Radiation plexopathy does not usually develop until at least 6 months after irradiation and can be difficult to distinguish from neoplastic infiltration. Either multifocal infiltration of nerves or lymphoma-associated vasculitis may present as a peripheral neuropathy. The incidence of Guillain-Barré (GBS) syndrome, and possibly chronic idiopathic demyelinating polyradiculoneuropathy, appears to be increased in association with lymphoma, especially Hodgkin's disease. Subacute sensory neuronopathy and subacute lower motor neuronopathy have both been reported as paraneoplastic syndromes associated with Hodgkin's disease. Treatment of the underlying lymphoma is only rarely followed by recovery of the associated neuropathy.

Epidemiology
The annual incidence of lymphoma is about 11/100 000 persons of which about a quarter have Hodgkin's disease (HD) and the remainder non-Hodgkin's lymphoma (NHL). Neurological complications are not common in either. In a series of 438 cases examined neurologically at the London Hospital between 1962 and 1968 the commonest complication was herpes zoster and other neurological syndromes occurred in 5% or less of cases (Table 1)[1,2]. In a series of patients studied in Buenos Aires between 1984 and 1987 6% of 426 patients with HD and 3% of 563 patients with NHL developed herpes zoster[3]. In the same series 6% with HD and 4% with NHL had cord or nerve root involvement. Peripheral neuropathy is an important potential complication of chemotherapy and the following are less common but interesting causes of peripheral nervous system involvement by lymphoma:

Table 1. Percentage of patients with lymphoma having neurological involvement. From Currie *et al.* (Ref 1)

	HD (n=*210*)	NHL (n=*228*)
Intracranial	1.5	5
Orbital	0.5	3
Cauda/cord	5.5	4
Herpes zoster	10	5
Peripheral neuropathy	1.5	0.4

Infection: herpes zoster
Drug
Radiation
Root, plexus or nerve compression
Vasculitis
Paraproteinaemia: antibody mediated
Root, plexus or nerve/diffuse infiltration
Autoimmune: GBS
Paraneoplastic neuropathy

Herpes zoster
Herpes zoster occurred in between 3% and 10% of cases of lymphoma in the two large series already quoted, which is almost certainly higher than its frequency in the general population[1,3]. It is more likely to occur in patients with advanced disease and with iatrogenic immunosuppression from systemic chemotherapy, splenectomy and irradiation[3]. It is much more likely to be complicated by spread of infection from the dorsal root ganglia to cause motor neuropathy, myelitis and encephalitis, such complications being recorded in 7-26% of lymphomatous cases compared with only 2% of cases of herpes zoster in the general population[3]. Accordingly, prompt treatment of cutaneous herpes zoster with oral acyclovir is recommended for patients with lymphoma, even after successful chemotherapy.

Drugs
Chemotherapy especially with vinca alkaloids is probably the commonest cause of peripheral neuropathy in patients with lymphoma. All currently proven combination chemotherapeutic regimes for advanced lymphoma use at least one of the vinca alkaloids which makes it difficult to detect whether the other drugs are also neurotoxic. The evidence incriminating vinca alkaloids with peripheral neuropathy relates mostly to vincristine, but vindesine and vinblastine almost certainly produce similar neurotoxicity: vindesine and vinblastine are reported to be less neurotoxic but they are also less therapeutically active. The vinca alkaloids block spindle microtubular function in dividing cells and bind to and break down neurotubules in nerves[4]. Vincristine produces a peripheral neuropathy in an approximately dose dependent manner[5]. The first symptoms are generally of distal paraesthesiae affecting the hands before the feet and some patients develop mild sensory loss. Weakness may appear rapidly over about 2 weeks. In the legs, weakness is usually most marked distally and may prevent walking. In the upper limbs, the extensor muscles of the wrists and fingers are typically most severely affected. Constipation and occasional urinary frequency may be due to autonomic

Correspondence to: Professor R A C Hughes

Table 2. Drugs used in chemotherapeutic regimes for advanced HD or NHL

	Drugs	Clinically significant neuropathy in man
Natural products		
Vinca alkaloids[4-6]	Vincristine	Yes
	Vindesine	Yes
	Vinblastine	Yes
Epipodophyllotoxins[7]	Etoposide (VP-16)	Possibly
	Teniposide (VM-26)	?
Alkylating agents		
Nitrogen mustards[49]	Mechlorethamine	No
	Cyclophosphamide	No
	Infosamide	No
	Chlorambucil[13]	?
Triazenes	Dacarbazine[49]	Possibly
Anti-metabolites		
Folate antagonists	Methotrexate	No
Pyrimidine analogues	Fluorouracil	No
	Cytarabine[8-10]	Possibly
Antibiotics	Doxorubicin	No
	Mitoxantrone	No
	Bleomycin	No
Miscellaneous	Procarbazine[12]	Possibly
Steroids	Prednisolone	No
	Dexamethasone	No

neuropathy. Electrophysiological examination reveals evidence of denervation with fibrillation in distal muscles[6]. Sensory nerve action potentials are reduced in amplitude[5,6] but motor and sensory nerve conduction velocities are usually well preserved. Sural nerve biopsy reveals predominant axonal degeneration[6]. After the drug has been stopped, distal limb weakness generally improves but ankle jerks do not reappear. It is our practice to maintain the drug if paraesthesiae are only mild but stop it if sensory or motor deficits become severe enough to affect function.

Much of the evidence implicating other chemotherapeutic agents is less firm and often purely anecdotal (Table 2). Etoposide and teniposide are both semi-synthetic analogues of podophyllotoxin, which is an extract of the mandrake plant. Both etoposide and teniposide bind to tubulin at a site distinct from that where the vinca alkaloids act. Their anti-mitotic effect does not seem to arise from their effect on microtubular function. Nevertheless, both drugs may produce a mild sensorimotor peripheral neuropathy[7].

The pyrimidine analogue cytarabine has been associated with neuropathies, particularly when used in high dose. Two cases of pure sensory peripheral neuropathy occurred with conventional doses of cytarabine but no electrophysiological or histopathological studies were performed[8]. A severe sensorimotor neuropathy has been reported with high-dose cytarabine[9] but the patient had also received vincristine. Sural nerve biopsy revealed demyelination as well as axonal degeneration. A fatal neuropathy occurred in another patient given a total dose of 47 g cytarabine[10]. Sural nerve biopsy revealed loss of myelinated fibres and active axonal degeneration, but this patient had also received etoposide and daunorubicin.

Doxorubicin has not caused peripheral neuropathy in man but does produce experimental neuropathy in animals[11]. Procarbazine produces paraesthesiae in approximately 15% of patients. Decreased tendon reflexes have also been reported but the neuropathy is generally mild and is not a dose-limiting factor[12]. Chlorambucil does not usually cause neuropathy, although a case of possibly coincidental GBS has been reported in a patient treated with the drug for chronic lymphocytic leukaemia[13].

Radiation plexopathy

In patients who have been treated for lymphoma by radiotherapy, the appearance of neurological deficit may be due to irradiation and not the underlying disease itself. Knowledge of the likely patterns of radiation-induced peripheral nerve damage, which have recently been reviewed[14], is helpful in this differential diagnosis (Table 3). The brachial and lumbosacral plexuses are most at risk from the commonly used irradiation fields. Radiation damage is only likely when the dose has exceeded a threshold whose magnitude depends on the length of nerve irradiated and is less if the duration of treatment is shorter. For the brachial plexus the focal dose necessary to induce irradiation damage is said to be 4500 rad in 4 weeks, but there is some inter-individual variation in susceptibility. Radiation induced damage does not usually occur until after a latent period of 6 months and the interval may be much longer, sometimes many years. The symptoms of radiation induced damage develop insidiously, and rapidly developing neurological deficit usually has a neoplastic cause. Radiation induced damage characteristically causes myokymia which may be evident clinically as well as on an electromyograph. Horner's syndrome and anhidrosis suggest neoplastic involvement of the brachial plexus and not radiation damage. Pain is prominent with brachial plexopathy secondary to irradiation or neoplasm but with lumbosacral plexopathy pain usually indicates neoplastic infiltration. Irradiation of the paraaortic nodes may cause a flaccid paresis involving the myotomes from L4 to S1 which is probably due to affection of the lumbosacral plexus. Sensory and autonomic fibres are spared and pain is not prominent.

Although most cases have insidiously progressive and ultimately permanent deficit, occasional cases have earlier deficit (4 months or so after irradiation) which is transient and eventually recovers.

Table 3. Distinction between radiation and neoplastic plexopathy (after Thomas and Holdorff 1993, Ref 14)

	Radiation	Neoplastic infiltration
Clinical, CT or MRI mass	0	+
Interval less than 6 months	0*	+
Pain present		
brachial plexus	+	+
lumbo-sacral plexus	0	+
Horner's syndrome		
brachial plexus	0	+
Myokymia	+	0

*Rarely earlier and then reversible

Spinal cord and root compression

Root or cord compression by lymphomatous deposits in the vertebrae and extradural space are the commonest direct neurological complications of both HD and NHL. The lymphoma may spread into the vertebral canal via the intervertebral foramina from extravertebral deposits or infiltrate the bone itself and cause vertebral collapse[15]. Although nervous system involvement does not usually occur in the absence of widespread dissemination of the disease, epidural lymphoma was the presenting feature of 0.5% of cases of HD and 1% of cases of NHL in the Buenos Aires series[3]. The onset of weakness or other neurological deficit is preceded by pain in 50% of cases and the pain has usually been present for 1 week to several weeks. Lytic bone lesions are present on plain radiographs in only half of cases and so myelography or preferably magnetic resonance imaging are necessary to portray the lesion and its extent. Among the 21 CSF samples collected in the Buenos Aires series 43% were normal and neoplastic cells were only found in 24%.

The choice of treatment must depend on assessment of the individual case. In the patient with previously undiagnosed disease, biopsy and decompression are usually appropriate in the first instance. For other patients local radiotherapy usually combined with systemic and possibly intrathecal chemotherapy are often preferred. Even the authors of the recent large series from Buenos Aires were unable to draw conclusions about the best form of therapy[3].

Vasculitis

The occurrence of vasculitis is recognized in association with malignant disease, including lymphoma, but the mechanism and frequency of this association are not known. It is uncommon as a manifestation of lymphoma just as vasculitic neuropathy rarely has lymphoma as a substrate. Vincent *et al.*[16] discovered 50 examples of microvasculitis (consisting of vessel infiltration without fibrinoid necrosis or leucocytoclasis) in a series of 1076 nerve and muscle biopsies: seven of these 50 cases were associated with malignancy including one example of HD and one example of immunoblastic lymphadenopathy. In our own series of 180 nerve biopsies we have encountered 21 cases of vasculitis of which two were associated with malignancy. One was a man with low grade NHL who developed a sensory multiple mononeuropathy in the lower limbs which was cured by steroids. The other was a man with progressive lumbosacral plexopathy which developed 7 years after radiotherapy for stage I inguinal HD and which showed a partial response to steroids.

Paraproteinaemia

The plasma cell dyscrasias are not usually classified with the lymphomas and their complications will not be reviewed in detail. However, it is important to remember that there is a strong relationship between paraproteinaemia and neuropathy[17]. In a series of 279 cases of neuropathy of undiagnosed cause referred to the Mayo clinic 10% had a serum paraprotein[18]. Waldenström's macroglobulinaemia, multiple myeloma, osteosclerotic myeloma and monoclonal gammopathy of undetermined significance (MGUS) may each be associated with neuropathy. There is a now well-defined syndrome in which a benign IgM (usually κ) paraprotein is associated with a slowly progressive demyelinating neuropathy with predominant sensory impairment and postural tremor. The paraprotein usually has antibody activity against carbohydrate epitopes shared by the peripheral nerve myelin glycolipid sulphated glucuronyl paraglobosides and the central nervous system and peripheral nerve glycoprotein myelin-associated glycoprotein. Injection of these antibodies into the nerve of an experimental animal which shares the same epitope will induce demyelination[19], and plasma exchange and other forms of immunosuppression have been reported beneficial in treatment[20].

However, B cell lymphomas presenting as masses outside the bone marrow may be associated with neuropathy. A patient of ours presented with a B cell lymphoma in the right frontal lobe, and an IgM paraprotein. Three months after frontal lobectomy and total brain radiotherapy he developed a severe acute axonal predominantly sensory neuropathy. There was no evidence of tumour in the bone marrow or outside the nervous system and he made a slow but eventually complete recovery following treatment with chemotherapy. In a published case of B cell lymphomas occlusive microangiopathy due to deposition of IgM paraprotein caused a peripheral neuropathy[21].

Nerve infiltration

Infiltration of nerves to cause a peripheral neuropathy is uncommon and was not documented in the two large hospital-based surveys already quoted. When it does occur it may be the presenting feature and particularly difficult to diagnose. A patient was randomized in a trial of steroids as having GBS but died and was only found at post mortem examination to have diffuse infiltration of the peripheral nerves by NHL[22]. In many of the older cases in the literature the appropriate tests were carried out to distinguish T from B cell lymphomas. Some of these descriptions were very remarkable, particularly a patient with a recurrent polyneuropathy evolving over 30 years and associated at autopsy with diffuse lymphomatous infiltration of the peripheral nerves and leptomeninges[23].

Nerve infiltration has been reported with both T cell and B cell NHL but not with HD. Patients with cutaneous T cell lymphoma have developed painful neuropathy due to infiltration of the epineurium and endoneurium by neoplastic T cells[24]. Lymphomatous infiltration of peripheral nerves by non-cutaneous T cell lymphoma has also been reported in three cases and shown to be associated with infiltration of epineurial and to a lesser extent endoneurial vessel walls by lymphoma cells, presumably due to haematogenous spread[25,26]. Painful sensory and motor neuropathy was the presenting feature of a case of HTLV1 (human T-cell leukaemia virus) associated T cell leukaemia in which the nerves were shown post mortem to be diffusely infiltrated by leukaemic cells[27].

The occurrence of B cell lymphoma causing focal or diffuse peripheral nerve infiltration has been described by Vital *et al.* in a review of 10 cases[24]. One of their own three patients presented with an asymmetrical painful polyradiculoneuropathy which was proved at autopsy to be due to B cell lymphoma confined to the spinal roots. Another patient presented with a peripheral neuropathy and the diagnosis of lymphoma was made by identifying lymphomatous infiltration in a sural nerve biopsy[28]. Diagnosis was accomplished in about half the cases by finding

lymphoma cells in the cerebrospinal fluid but paraproteins were not found in the serum in any of the cases. One rare presentation of B cell lymphoma is with a progressive stroke-like disorder which has been called malignant angioendotheliosis: Vital *et al.* describe a unique case in which this condition presented with a painful common peroneal mononeuropathy[24]. Lymphomas associated with AIDS are usually of B cell type and have been reported as causing peripheral neuropathy[29]. A patient who had undergone liver transplant developed multiple cranial nerve palsies and weakness of the upper limbs which defied diagnosis until a sural nerve biopsy revealed Burkitt's lymphoma[30].

Marek's disease

Lymphomatous infiltration of nerves is a prominent feature of an interesting demyelinating neuropathy in turkeys and chickens, called Marek's disease, which is caused by a herpes virus. There is progressive infiltration of peripheral nerves by lymphoid cells, probably transformed T cells which have been activated by the causative virus, followed by macrophage-associated demyelination which resembles that in experimental allergic neuritis and GBS[31].

Guillain-Barré syndrome

There have been at least 10 case reports of acute sensory and motor neuropathy fulfilling the usual diagnostic criteria for GBS in association with HD[28,32-36]. Although there are also reports of GBS in association with other forms of cancer, and also with chronic lymphocytic leukaemia[1,37] the reports of an association with HD are more numerous and may represent a real, albeit rare association. There is also one report of GBS associated with NHL[38], and another with both HD and Castleman's disease[39]. The association with HD might be produced by a disturbance of normal immune suppressor mechanisms leading to the escape of an autoimmune disease, to more frequent infection with herpes viruses which are known precipitants of GBS, or to some other undiscovered mechanism. There is also a single report of acute dysautonomia occurring in association with HD[40].

Chronic idiopathic demyelinating polyradiculoneuropathy (CIDP)

Several cases of subacute or chronic demyelinating neuropathy have been reported in association with both HD and NHL, mostly as single case reports and mostly so long ago that appropriate investigations were not undertaken to discover the mechanism[41]. In some well studied cases diffuse lymphomatous infiltration of the peripheral nervous system has been discovered at autopsy[23]. In others, relapsing CIDP was found in association with systemic NHL but without nerve infiltration even on full post mortem examination[42]. Such cases raise the possibility of an association between CIDP as well as GBS and lymphoma, which is scarcely surprising since GBS and CIDP may be regarded as a spectrum.

Paraneoplastic neuropathy

Paraneoplastic neuropathy is a rare complication of certain carcinomas such as small cell lung carcinoma and carcinoma of the ovary and an even rarer complication of lymphoma. Several cases of acute sensory neuropathy associated with HD from the older literature have been referenced in a recent review[41]. Since that review, a particularly well-documented clinicopathological case has illustrated the inflammatory changes which occur in the dorsal root ganglia in this condition: a case of stage II Hodgkin's disease complicated 6 weeks after its presentation by an acute sensory neuronopathy which proved fatal within 5 days[39]. There were moderate T cell infiltrates in dorsal root ganglia. A search for antineuronal antibodies such as those seen in the paraneoplastic sensory neuronopathy associated with small cell lung carcinoma was not reported. In a similar case which came to autopsy 6 years after onset there was marked loss of dorsal root ganglion cells but no inflammation[43]. There are several reports of a paraneoplastic cerebellar degeneration associated with HD, and in a series of 21 such patients two had a mild sensory neuropathy (but both had vinca alkaloids)[44].

There is a small number of reports of subacute lower motor neuronopathy as a 'paraneoplastic' complication of lymphoma mostly in association with HD. Some of these patients have died and been found at post mortem examination to have severe loss of anterior horn cells[45]. In other patients, the disease process has continued to progress or left the patient with a plateau of persistent deficit which would be compatible with a neuronopathy [cases 3, 5, 6, and 8 of Schold *et al.*[45]]. In patients who have progressed and then improved [cases 2, 4, 7, 9 and 10 of Schold *et al.*[45]] it is difficult to understand how the improvement, sometimes amounting to complete recovery, could have occurred if the underlying pathology was a true neuronopathy. These cases were reported before the syndrome of multifocal motor neuropathy with conduction block was described: it is possible that the main pathology was an inflammatory demyelinating polyradiculoneuropathy or even a vasculitic disorder which was not revealed by the neurophysiological tests and limited biopsy tissue available.

One variant of B cell lymphoma called angiofollicular lymph node hyperplasia (Castleman's disease) has been associated with a progressive rather severe predominantly motor neuropathy due to a mixture of demyelination and axonal degeneration[46]. Patients with this condition may show an improvement in their neuropathy in response to steroids and chemotherapy[46]. Some patients with this condition have a paraprotein and other features of the POEMS syndrome [polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes (hyperpigmentation)]. The usual pathological substrate of this rare syndrome is osteosclerotic myeloma often associated with an IgA (less often IgG but not IgM) paraprotein[47].

The hope that removal of an underlying lymphoma will have a beneficial effect on an associated neuropathy is sometimes realized. A woman aged 75 became bedridden with a severe chronic, apparently axonal, sensory and motor neuropathy but recovered substantially within 3 months when a gastric B cell lymphoma was identified and removed[48]. Unfortunately, most patients with paraneoplastic syndromes fail to experience any improvement in their neurological condition when the underlying tumour is removed.

References

1 Currie S, Henson RA, Morgan HG, Poole AJ. The incidence of non-metastatic neurological syndromes of obscure origin in the reticuloses. *Brain* 1970;93:629-41

2 Currie S, Henson RA. Neurological syndromes in the reticuloses. *Brain* 1971;**94**:307-17
3 Correale J, Monteverde DA, Bueri JA, Reich EG. Peripheral nervous system and spinal cord involvement in lymphoma. *Acta Neurol Scand* 1991;**83**:45-51
4 Le Quesne PM. Neuropathy due to drugs. In: Dyck PJ, Thomas PK, eds. *Peripheral Neuropathy*. Philadelphia: WB Saunders, 1993:1571-81
5 Casey EB, Jellife A, Le Quesne PM, Millett YL. Vincristine neuropathy. Clinical and electrophysiological observations. *Brain* 1973;**96**:69-86
6 McLeod JG, Penny R. Vincristine neuropathy: an electrophysiological and histological study. *J Neurol Neurosurg Psychiatry* 1969;**32**:297-304
7 O'Dwyer PJ, Leyland-Jones B, Alonso MT, Marsoni S, Wittes RE. Drug Therapy. Etoposide (VP-16-213) Current Status of an Active Anticancer Drug. *N Engl J Med* 1985;**312**:692
8 Russel JA, Powles RL. Neuropathy due to cytosine arabinoside. *BMJ* 1974;**i**:652-3
9 Borgeat A, de Muralt B, Stalder M. Peripheral neuropathy associated with high-dose Ara-C therapy. *Cancer* 1986;**58**:852-4
10 Paul M. Peripheral neuropathy associated with axonal degeneration after cytosine arabinoside in acute leukaemia. *Br J Haematol* 1991;**79**:521-3
11 England JD, Asbury AK, Rhee E, Sumner AJ. Lethal retrograde axoplasmic transport of doxorubicin (adriamycin) to motor neurons. *Brain* 1988;**111**:915-26
12 Weiss HD, Walker MD, Wiernik PH. Neurotoxicity of commonly used antineoplastic agents (first of two parts). *N Engl J Med* 1974;**291**:75-133
13 Sandler RM, Gonsalkorale M. Chronic lymphatic leukaemic, chlorambucil, and sensorimotor peripheral neuropathy. *BMJ* 1977;**2**:1265-6
14 Thomas PK, Holdorff B. Neuropathy due to physical agents. In: Dyck PJ, Thomas PK, eds. *Peripheral Neuropathy*. Philadelphia: WB Saunders, 1993:990-1013
15 Davies-Jones GAB, Preston FE, Timperley WR. Lymphomas. In: *Neurological Complications in Clinical Haematology*. Oxford, London, Edinburgh, Boston, Melbourne: Blackwell Scientific Publications, 1980: 96-118
16 Vincent D, Dubas F, Hauw JJ, Hermith F, Buge A, Castaigne P. Nerve and muscle microvasculitis in peripheral neuropathy: a remote effect of cancer? *J Neurol Neurosurg Psychiatry* 1986;**49**:1007
17 Kyle RA, Dyck PJ. Neuropathy associated with the monoclonal gammopathies. In: Dyck PJ, Thomas PK, eds. *Peripheral Neuropathy*. Philadelphia: WB Saunders, 1993:1275-87
18 Kelly JJ, Kyle RA, O'Brien PC, Dyck PJ. The prevalence of monoclonal gammopathy in peripheral neuropathy. *Neurology* 1981;**31**:1480-3
19 Willison HJ, Trapp BD, Bacher JD, Dalakas MC, Griffin JW, Quarles RH. Demyelination induced by intraneural injection of human anti MAG antibodies. *Muscle Nerve* 1988;**11**:1169-76
20 Haas DC, Tatum AH. Plasmapheresis alleviates neuropathy accompanying IgM anti-MAG paraproteinaemia. *Ann Neurol* 1988;**23**:394-6
21 Prior R, Schober R, Scharffetter K, Wechsler W. Occlusive microangiography by immunoglobulin (IgM-kappa) precipitation: pathogenetic relevance in paraneoplastic cryoglobulinemic neuropathy. *Acta Neuropathol* 1992; **83**:423-6
22 Guillain-Barré Syndrome Steroid Trial Group. Double-blind trial of intravenous methylprednisolone in Guillain-Barré syndrome. *Lancet* 1993;**341**:586-90
23 Borit A, Altrocchi PH. Recurrent polyneuropathy and neurolymphomatosis. *Arch Neurol* 1971;**24**:40-7
24 Vital C, Vital A, Julien J, de Mascarel A, Vergier B, Henry P, *et al.* Peripheral neuropathies and lymphoma without monoclonal gammopathy: a new classification. *J Neurol* 1990;**237**:177-85
25 Gherardi R, Gaulard P, Prost C, Rocha D, Imbert M, Andre C. T-cell lymphoma revealed by a peripheral neuropathy. A report of two cases with an immunohistologic study on lymph node and nerve biopsies. *Cancer* 1986; **58**:2710-16
26 Zuber M, Gherardi R, Imbert M, Gaulard P, Kuentz M, Poirier J. Peripheral neuropathy with distal nerve infiltration revealing a diffuse pleiomorphic malignant lymphoma. *J Neurol* 1987;**235**:61-2
27 Kuroda Y, Nakata H, Kakigi R, Oda K, Shibasaki H, Nakashito H. Human neurolymphomatosis by adult T-cell leukaemia. *Neurology* 1989;**39**:144-6
28 Ince PJ, Shaw PJ, Fawcett PRW, Bates D. Demyelinating neuropathy due to primary IgM kappa B cell lymphoma of peripheral nerve. *Neurology* 1987;**37**:1231-4
29 Gold JE, Jimenez E, Zalusky R. Human immunodeficiency virus-related lymphoreticular malignancies and peripheral neurologic disease. A report of four cases. *Cancer* 1988;**61**:2318-24
30 Newman NJ. Multiple cranial neuropathies: presenting signs of systemic lymphoma. *Surv Ophthalmol* 1992; **37**:125-9
31 Hughes RAC. Animal models of Guillain-Barré syndrome. In: *Guillain-Barré Syndrome*. Heidelberg: Springer Verlag, 1990:249-60
32 Asbury AK, Arnason BG, Adams RD. The inflammatory lesion in idiopathic polyneuritis. Its role in pathogenesis. *Medicine* 1969;**48**:173-215
33 Julien J, Vital CL, Aupy G, Laugueny A, Darriet D, Brechenmacher C. Guillain-Barré syndrome and Hodgkin's disease - ultrastructural study of a peripheral nerve. *J Neurol Sci* 1980;**45**:23-7
34 Cuttner J, Meyer R. Guillain-Barré syndrome in a patient with Hodgkin's disease. *Mt Sinai J Med (NY)* 1978; **45**:415-17
35 Lisak RP, Mitchell M, Zwieman B, Orrechio E, Asbury AK. Guillain-Barré syndrome and Hodgkin's disease: three cases with immunological studies. *Ann Neurol* 1977;**1**:72-8
36 Sagar HJ, Read DJ. Subacute sensory neuropathy with remission: an association with lymphoma. *J Neurol Neurosurg Psychiatry* 1982;**45**:83-5
37 Powles RL, Malpas JS. Guillain-Barré syndrome associated with chronic lymphatic leukaemia. *BMJ* 1967;**3**:286-7
38 Sahadevan MG, Raman PT, Hoon RS. Landry-Guillain-Barré syndrome complicating lymphosarcoma: a case report. *J Assoc Physicians India* 1969;**17**:215-16
39 Case Records of the Massachusetts General Hospital. Case 39-1990. Presentation of case. *N Engl J Med* 1990; **323**:895-908
40 van Lieshout JJ, Wieling W, van Montfrans GA, Seffels JJ, Speelman JD, Endert E. Acute dysautonomia associated with Hodgkin's Disease. *J Neurol Neurosurg Psychiatry* 1986;**49**:830-1
41 McLeod JG. Peripheral neuropathy associated with lymphomas, leukemias, and polycythemia vera. In: Dyck PJ, Thomas PK, eds. *Peripheral Neuropathy*. Philadelphia: WB Saunders, 1993:1591-8
42 Sumi SM, Farrell DF, Knauss TA. Lymphoma and leukemia manifested by steroid-responsive polyneuropathy. *Arch Neurol* 1983;**40**:577-82
43 Horwich MS, Cho L, Porro RS, Posner JB. Subacute sensory neuropathy: a remote effect of carcinoma. *Ann Neurol* 1977;**19**:2-7
44 Hammack J, Kotanides H, Rosenblum MK, Posner JB. Paraneoplastic cerebellar degeneration. II. Clinical and immunologic findings in 21 patients with Hodgkin's disease. *Neurology* 1992;**42**:1938-43
45 Schold SC, Cho ES, Somasunderam M, Posner JB. Subacute motor neuropathy: a remote effect of lymphoma. *Ann Neurol* 1979;**5**:271-5
46 Donaghy M, Hall P, Gawler J, Gregson NA, Leibowitz S, Jitpimolard S, *et al.* Peripheral neuropathy associated with Castleman's disease. *J Neurol Sci* 1989;**89**:253-67
47 Miralles GD, O'Fallon JR, Talley NJ. Plasma-cell dyscrasia with polyneuropathy - The spectrum of POEMS syndrome. *N Engl J Med* 1992;**327**:1919-23
48 Enevoldson TP, Ball JA, McGregor JM. Resolution of a severe sensorimotor neuropathy following resection of an associated asymptomatic gastric lymphoma. *J Neurol Neurosurg Psychiatry* 1990;**53**:267-8
49 Calabresi P, Chabner BA. Antineoplastic agents. In: Gilman AG, Rall TW, Nies AS, Taylor P, eds. *Goodman and Gilman's Pharmacological Basis of Therapeutics*. New York: Pergamon Press, 1990:1209-63

Based on a paper read to Section of Neurology, 6 May 1993

(Accepted 25 January 1994)