



The Diagnostic Dilemma of Neurolymphomatosis

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Neurolymphomatosis (NL) defined as infiltration of the central nervous system or the peripheral nervous system (PNS) by malignant lymphoma cells is a rare clinical entity. However, the increasing use of fluorodeoxyglucose positron-emission tomography (FDG-PET) and magnetic resonance imaging in evaluating PNS disorders is resulting in; this condition being recognized more frequently. Here; we report five NL patients and review the current literature. We report five patients with non-Hodgkin's lymphoma (NHL) and NL, all of whom were men aged 47–69 years. The clinical presentation varied from symmetrical peripheral neuropathy to mononeuropathy. Peripheral neuropathy was the presenting manifestation of a systemic lymphoma in two patients (40%). Neuroimaging as well as whole-body FDG-PET helped in determining the correct diagnosis in all of the patients. NL is an unusual presentation of NHL resulting from infiltration of the PNS by malignant lymphomatous cells. While evaluating peripheral neuropathy, a high degree of suspicion of NL is required since the presenting symptoms vary, conventional radiology has only modest sensitivity, and a pathological diagnosis is often difficult. FDG-PET helps in the early diagnosis and treatment of this condition.

Key Words neurolymphomatosis, diffuse large-B-cell lymphoma, mononeuropathy, fluorodeoxyglucose positron-emission tomography.

INTRODUCTION

Neurolymphomatosis (NL), defined as invasion of the peripheral nervous system (PNS) (cranial nerves, peripheral nerves, roots, and plexus) by lymphoma cells, is a rare clinical entity;¹ being the least common way in which lymphoma can involve the PNS. It is important to differentiate NL, the common mode of PNS involvement in lymphoma, from other causes of PNS involvement in lymphoma (e.g., paraneoplastic PNS involvement, and radiation- and chemotherapy-induced damage to the PNS), since their treatment modalities differ.² The increasing use of positron emission tomography (PET) and magnetic resonance imaging (MRI) in evaluating PNS disorders is resulting in increasing numbers of NL cases being recognized.

Here we report five NL patients and review the current literature regarding the diagnosis and management of this rare condition.

PATIENT 1

Mr. A, a 69-year-old male, presented to us with a two month history of shooting pains in the bilateral gluteal regions and the back of the thigh, followed 1 month later by pin prick paresthesias in both upper limbs and the right half of the face, along with asymmetrical quadriparesis affecting the legs more than the arms, low-grade fever, dry cough, orthop-

Received January 29, 2016
Revised February 22, 2016
Accepted February 25, 2016

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noea, anorexia and loss of weight. He was diagnosed as a case of chronic inflammatory demyelinating radiculoneuropathy (CIDP) at another center and given intravenous immunoglobulin in a dose of 2 g/kg. However, his condition continued to worsen, and he was referred to our tertiary-care center. An examination revealed paradoxical breathing, wasting and hypotonia in all four limbs, asymmetrical quadriparesis (both proximal and distal, left upper limb more than right upper limb, and right lower limb more than left lower limb), areflexia, and patchy sensory loss involving all modalities in all four limbs and on the right side of the face. He was diagnosed as a case of multiple mononeuropathy and evaluated accordingly. A detailed laboratory work-up including hemogram, liver, kidney and thyroid function tests, and serum electrolytes including calcium produced normal findings. A vasculitic work-up (e.g., antinuclear antibody, anti-neutrophil cytoplasmic antibody and serum cryoglobulins) produced negative results. Nerve conduction studies (NCSs) and electromyography revealed motor-sensory axonal and demyelinating polyneuropathy. Analysis of the cerebrospinal fluid (CSF) showed 60 cells (all lymphocytes) per high power field (HPF), elevated protein (79 mg/dL), and a normal sugar level (88 mg/dL) (Table 1). There was no contributory malignant cytology. Contrast-enhanced computed tomography (CECT) of the chest and abdomen showed bilateral adrenal masses, and fluorodeoxyglucose positron-emission tomography (FDG-PET) showed intense uptake in both adrenal glands and in the abdominal lymph nodes, sacral nerve roots, and brachial plexus. Fine-needle aspiration cytology of an adrenal mass revealed diffuse large-B-cell non-Hodgkin's lymphoma (NHL). The differential diagnosis considered was NL or multiple mononeuropathy as a paraneoplastic manifestation of NHL. NL was considered much more likely based on the PET findings. During the hospital stay he developed respiratory failure requiring mechanical ventilation followed by sepsis, and succumbed to his illness at 4-weeks after admission. An autopsy revealed evidence of lymphomatous infiltration of the brachial and lumbosacral plexus (Fig. 1A and B) confirming the diagnosis of NL. This case has also been reported on elsewhere.¹

PATIENT 2

Mr. B, a 68-year-old male diagnosed as primary B-cell lymphoma 15 years previously and with two previous relapses and complete remission for 5 months, presented with 15-days history of right foot drop along with paresthesias and numbness along the lateral aspect of the right leg, dorsum, and sole of the right foot. A general examination revealed a single palpable lymph node in the left supraclavicular region. He had been diagnosed as L5-S1-radiculopathy at another

center based on MRI findings and was referred to our center for surgery. On examination, he had severe weakness of ankle dorsiflexion (MRC grade 1/5), ankle plantar flexion (2/5), ankle inversion, ankle eversion (2/5), and knee flexion (3/5). The right ankle jerk was absent. All sensory modalities were impaired below the right knee with sparing of the medial aspect of the leg. This clinical picture was more suggestive of sciatic nerve involvement, which was evaluated further. Routine blood investigations produced normal findings except for thrombocytopenia. An electrophysiological work-up was consistent with a diagnosis of sciatic neuropathy. Gadolinium-enhanced MRI revealed localized longitudinal thickening of the right sciatic nerve with contrast enhancement in the mid-thigh region (Fig. 1C) while FDG-PET showed intense FDG uptake in the right sciatic nerve in the same region with involvement of bone marrow (Fig. 1D). A lymph-node biopsy in the left supraclavicular region confirmed high-grade diffuse large-B-cell lymphoma. He was started on chemotherapy (bendamustine and rituximab), after which the power of his right leg improved.

PATIENT 3

Mr. C, a 56-year-old male, diagnosed as pre-B-cell lymphoma presented with painless distal lower motor neuron (LMN) quadriparesis while on chemotherapy (cyclophosphamide, vincristine, and prednisolone). Due to a possibility of vincristine-induced neuropathy, he was evaluated in an outpatient department. A hemogram, kidney and liver function tests, serum electrolytes and calcium and phosphorus levels were normal. NCSs showed demyelinating neuropathy with conduction blocks, while the CSF was negative for malignant cells. A possibility of paraneoplastic CIDP was considered, and a sural nerve biopsy revealed infiltration by malignant B cells suggestive of relapse. This patient was lost to follow-up.

PATIENT 4

Mr. D, 62-year-old male presented with an 8-month history of paresthesias and pain in both hands and feet and 1-month history of numbness of the right side of the face as well as weakness in both upper limbs. He had no systemic complaints. On examination he had weakness of the small muscles in both hands and bilateral hip flexors. The pain and touch sensations on the right side of the face were decreased by 40%. NCSs revealed sensorimotor axonal neuropathy in all four limbs with evidence of a conduction block in the right ulnar nerve. A possibility of vasculitic mononeuritis multiplex was evaluated in detail. Detailed hemogram and biochemistry investigations produced normal findings.

Table 1. Clinical and investigational profile of the cases

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	69	68	56	62	47
Sex	Male	Male	Male	Male	Male
Referral diagnosis at time of presentation	CIDP	DLBC-NHL with prolapsed intervertebral disc and radiculopathy	Pre B-cell lymphoma with chemotherapy-induced neuropathy	CIDP	Undifferentiated sarcoma
In remission	-	Yes	No; on chemotherapy	-	No
Clinical features	Fever, weight loss, cough, asymmetrical quadriparesis, paresthesias	Right foot drop	LMN-type quadriparesis	Mononeuritis multiplex without systemic symptoms	Fever, weight loss, headache, paraparesis, diplopia
CSF	Clear, 88 mg/dL sugar; 79 mg/dL protein; 60 cells (all lymphocytes), no malignant cells	Not analyzed	Not analyzed	Clear, 55 mg/dL sugar; 104 mg/dL protein; 10 cells (all lymphocytes) no malignant cells; lymphomatous cells when repeated after 3 months	Hemorrhagic, 560 mg/dL protein, 11 mg/dL sugar; no malignant cells
Radiological investigations	CECT revealed: bilateral adrenal masses	Gadolinium-enhanced MRI revealed: thickening of the right sciatic nerve with enhancement	Not done	Not done	Gadolinium enhanced MRI the spine and brain revealed: intense dural enhancement in the lumbosacral spine, leptomeningeal enhancement in the brain, thickening and enhancement of bilateral 5th and 3rd cranial nerves
FDG-PET findings	Intense uptake in both adrenal glands, abdominal lymph nodes, sacral nerve roots, and brachial plexus	Intense uptake in the right sciatic nerve with involvement of bone marrow (bilateral femur and tibia)	Not done	Intense uptake in palatine tonsils, left breast, mediastinal, axillary and hilar lymph nodes, bilateral humerus, and left testis	Intense uptake in the cerebellum, spinal cord, psoas muscle, lumbar plexus, sternum, and liver
NCSs	Motor-sensory axonal and demyelinating polyneuropathy	Axonal degeneration of right tibial and common peroneal nerves	Demyelinating neuropathy with conduction blocks	Sensorimotor axonal neuropathy in all four limbs with evidence of conduction block in the right ulnar nerve	Not done
Biopsy/FNAC	FNAC of adrenal mass revealed: DLBC-NHL	Lymph-node biopsy of the left supraclavicular region confirmed DLBC-NHL	Sural nerve biopsy revealed: infiltration of the nerve by malignant B cells	Axillary lymph node biopsy revealed: DLBC; sural nerve biopsy revealed: infiltration of the nerve by lymphomatous cells	Biopsy revealed high-grade lymphoma

CECT: contrast-enhanced computed tomography, CIDP: chronic inflammatory demyelinating polyradiculoneuropathy, CSF: cerebrospinal fluid, DLBC: diffuse large B-cell, FDG-PET: fluorodeoxyglucose positron-emission tomography, FNAC: fine-needle aspiration cytology, MRI: magnetic resonance imaging, NCSs: nerve conduction studies, NHL: non-Hodgkin's lymphoma, LMN: lower motor neuron.

FDG-PET revealed intense uptake in the palatine tonsils, left breast, mediastinal, axillary and hilar lymph nodes, bilateral humerus and left testis (Fig. 2A). A CSF examination showed 10 cells/HPF, protein at 59 mg/dL, and sugar at 104 mg/dL. A axillary lymph node biopsy revealed diffuse large-B-cell lymphoma, and a sural-nerve biopsy revealed infiltration by lymphomatous cells (Fig. 3). He was started on chemotherapy with rituximab, cyclophosphamide, vincristine, Adriamycin and prednisone (the R-CHOP regimen). He improved initially but returned after 3 months with difficulty walking, at which time he was found to have cerebellar ataxia. Gadolinium-enhanced MRI of the brain produced normal findings. The CSF contained lymphomatous cells suggestive of

central nervous system (CNS) involvement by lymphoma cells. He was further treated with whole-body radiation and chemotherapy, but succumbed to his illness. An autopsy was not performed since his relatives did not give consent.

PATIENT 5

Mr. E, a 47-year-old male, was apparently normal until September 2014, when he started experiencing low-grade fever, anorexia, weight loss and headache. He was evaluated at another center and diagnosed as undifferentiated sarcoma based on a biopsy of liver lesions. He received six cycles of paclitaxel, cyclophosphamide and Adriamycin from January

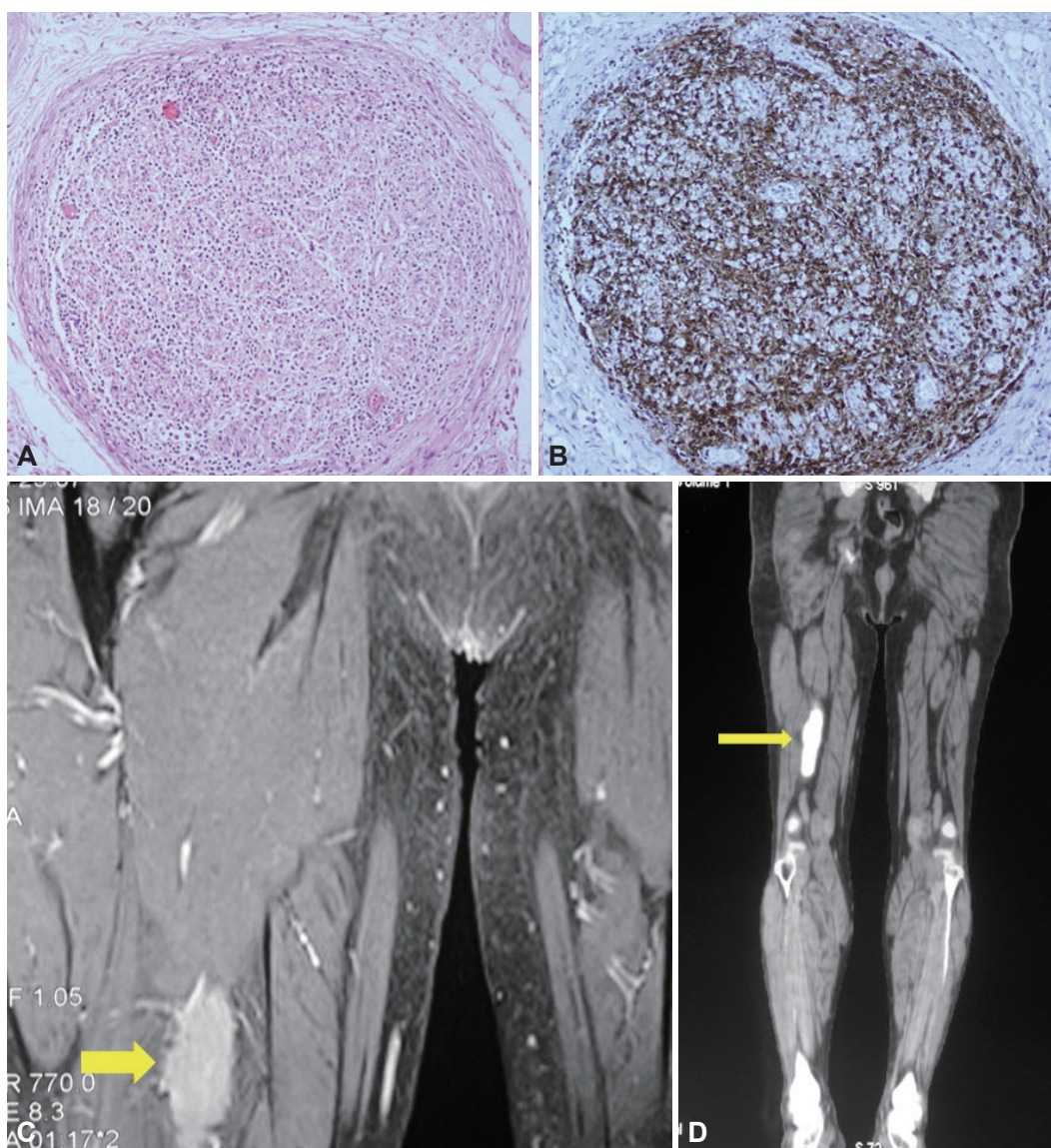


Fig. 1. Nerve bundle infiltration (patient 1), FDG-PET and MRI of right sciatic nerve (patient 2). A: A nerve bundle with infiltration by lymphoma cells (patient 1). B: CD 20 stain highlights diffuse infiltration by diffuse large B cells (patient 1). C: PET CT showing intense FDG uptake in right sciatic nerve (yellow arrow) (patient 2). D: intense enhancement of right sciatic nerve (arrow) on T1 weighted contrast MRI (patient 2).

to April 2015 which did not provide relief. His headaches became much more intense and holocranial. He subsequently developed severe low-back ache, paraparesis, and diplopia, and was referred to our hospital. On examination he had bilateral involvement of the 5th, 6th, 7th, 9th, and 10th cranial nerves, (LMN) weakness in both lower limbs with sensation at the T11 spinal level, and the LMN type of sphincteric involvement. He was evaluated for the possibility of neurosarcomatosis. Gadolinium-enhanced MRI of the brain and whole spine revealed intense dural enhancement in the lum-

bosacral spine, leptomeningeal enhancement over the cerebral convexities, and enhancement along multiple cranial nerves with thickening and enhancement of the bilateral trigeminal nerves (Fig. 2B and C). FDG-PET revealed intense uptake in the cerebellum, spinal cord (cervical, T1 to T3 and T11 to S1 segments) (Fig. 4), psoas muscles, lumbar plexus, sternum and liver. An independent review of the biopsy specimens produced findings consistent with a diagnosis of high grade lymphoma (the exact classification was not possible for technical reasons). The CSF was characterized by ele-

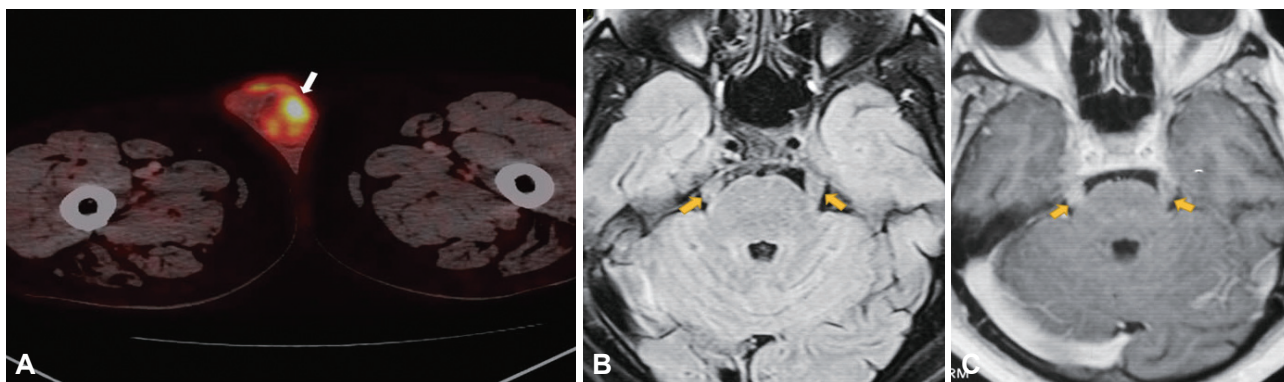


Fig. 2. FDG-PET images (patient 4) and MRI Brain images (patient 5). A: FDG-PET showing intense uptake (white arrow) in the left testis (patient 4). B and C: Thickened and enhancing trigeminal nerves (yellow arrows) on fluid-attenuated inversion recovery and T1-weighted MRI, respectively (patient 5). FDG-PET: fluorodeoxyglucose positron tomography, MRI: magnetic resonance imaging.

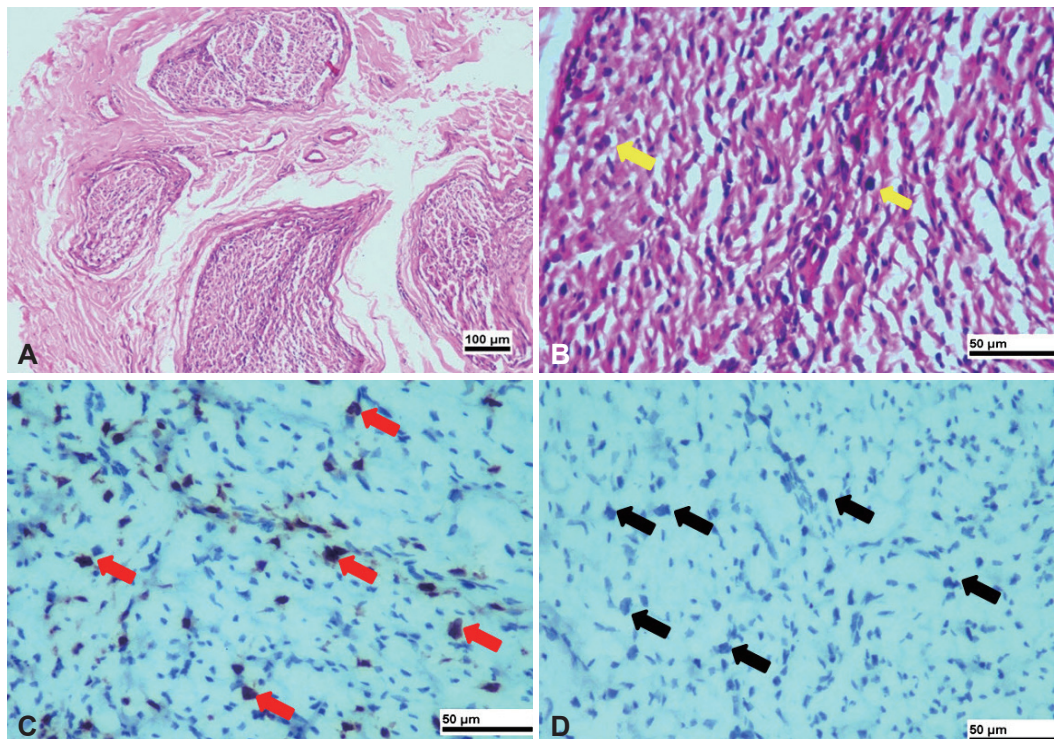


Fig. 3. Nerve Biopsy staining (patient 4). A: Hematoxylin and eosin-stained nerve biopsy sample that appears relatively normal at low magnification. B: High-power view of the same sample showing a few large atypical lymphoid cells (yellow arrows) amidst Schwann cells. C: CD20 immunostaining highlights these lymphoma cells (red arrows). D: The same cells were negative for CD3 immunostain (black arrows) (patient 4).

vated protein (560 mg/dL) and a low sugar level (11 mg/dL). CSF cytology could not be done because it was hemorrhagic. The patient had a seizure and developed aspiration pneumonia during his hospital stay. He was advised to receive further treatment, but his relatives took him home against medical advice where he succumbed to his illness. A final diagnosis of NL with lymphomatous invasion of the lumbar plexus and cranial nerves was made based on PET and MRI findings.

DISCUSSION

The mechanisms of PNS involvement in lymphoma are multifactorial and include paraneoplastic PNS involvement, PNS involvement secondary to chemotherapy and/or radiotherapy and NL.³⁻⁸ NL denotes infiltration of cranial or peripheral roots or nerves by malignant lymphomatous cells.⁹ It is seen most commonly with B cell lymphoma but can also occur with T-cell and NK-cell lymphomas or leukemias. This process, which commonly occurs outside the arachnoid invest-

ment of nerves, is distinct from the PNS infiltration that may accompany subarachnoid seeding and is separable from a perineural tumor seen in epidural lymphoma.⁹

NL is thought to occur only rarely. However in one autopsy series,¹⁰ peripheral nerve involvement was seen in 40% of patients dying of NHL. In another series,⁹ NL was estimated to account for approximately 10% of primary lymphomas of the nervous system. Although we cannot draw definite conclusions about the incidence of NL based on our small series, it is unlikely to be very rare given that we saw five affected patients over a period of approximately 18 months period.

NL in the PNS is distinct from paraneoplastic or inflammatory neuropathies as well as drug induced neuropathies, in terms of the clinical presentation, the response to treatment, and the prognosis. Conventionally, NL is thought to present as multiple mononeuropathy, while inflammatory and drug-induced neuropathies are considered to be more symmetrical. NCSs reveal axonal sensorimotor neuropathy in NL and paraneoplastic vasculitis and demyelinating sen-

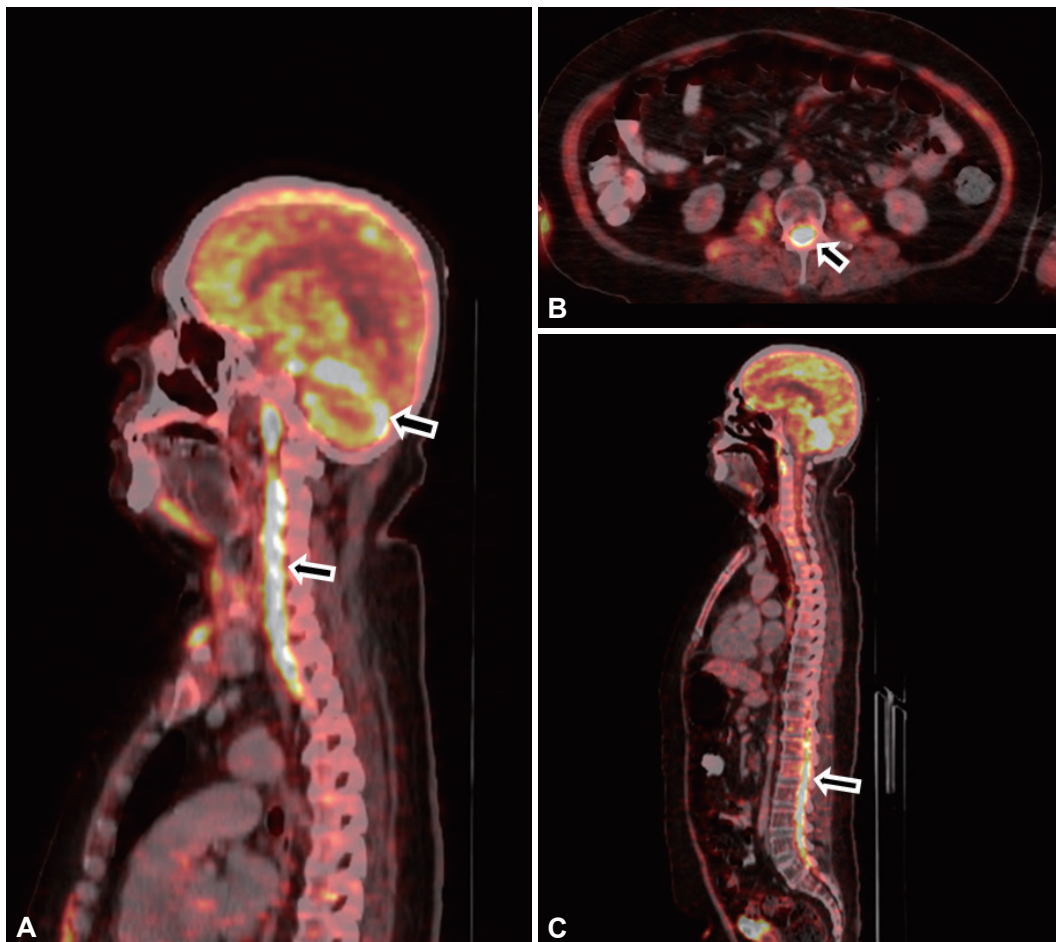


Fig. 4. FDG-PET images (patient 5). A: Intense diffuse FDG uptake (white arrows) in the periphery of both cerebellar hemispheres and the cervical cord. B and C: Intense diffuse FDG uptake (white arrows) in the thickened spinal cord in axial and saggittal sections, respectively (maximum standard uptake value of 25.9) (patient 5). FDG-PET: fluorodeoxyglucose positron tomography.

sorimotor neuropathy in paraneoplastic neuropathy that arise due to humoral factors.⁴ However our series suggests that NL can present as a symmetrical neuropathy (patient 3) as well as pure demyelinating (patient 3) or a mixed axonal and demyelinating neuropathy (patients 1 and 2). One large series⁹ found four main patterns of PNS involvement in NL: painful polyradiculopathy or neuropathy (31%), painless neuropathy (28%), cranial neuropathy (21%), and mononeuropathy (15%); the corresponding prevalence rates in our series were 40%, 20%, 20%, and 20%, respectively. Our findings are consistent with the above study⁹ and broadly similar to those of Tomita et al.¹¹ The clinical findings that suggest that NL to be a cause of multiple mononeuropathy include severe pain, particularly when it affects all four limbs and has an asymmetric distribution, and rapid evolution.⁹

NL is frequently misdiagnosed. All of the patients in the current series had been diagnosed with other conditions before a detailed evaluation was performed in our center. This was mainly due to the need for a biopsy to confirm the diagnosis, which is often difficult to perform since not all of the nerves are accessible in a biopsy procedure and there is a possibility of a permanent large deficit. Sural nerve biopsies were performed in two patients (patients 3 and 4), and the diagnostic yield was 100%. Furthermore, the diagnostic yield of CSF in NL is low [20% in the current series (only-patient 4) and 29.1% (21 of 72 patients) in a large series⁹], in contrast to meningeal lymphoma in which the yield is typically >95%.¹² Imaging studies (MRI and FDG-PET) often help in making the correct diagnosis. MRI findings that are suggestive of NL include enlargement or enhancement of nerves or nerve roots beyond the root sleeve. Since such findings can also occur with inflammatory neuropathies, they need to be interpreted in the context of clinical data and other investigations, MRI showed enlarged and thickened peripheral and/or cranial nerves in 40% (2 of 5) of the patients in the current study. Our results are similar to another series,⁹ in which nerve or root enlargement or enhancement on MRI was seen in 29 of 72 (40.3%) patients.

FDG-PET is currently the most sensitive and specific imaging technique for lymphoma. In the present study FDG-PET helped in making the diagnosis in three out of the four patients in which NL was diagnosed. FDG-PET exhibited 100% (4 of 4) sensitivity for the identification of lymphoma and its utility in the diagnosis of NL is also suggested by several case reports.¹³⁻¹⁷ However, FDG-PET may also provide negative findings even in patients with proven NL. One study,¹⁰ found that whole-body FDG-PET was negative in a patient who was eventually diagnosed as NL. Also, its specificity in the diagnosis of NL compared to CIDP is unclear.¹⁰ The current diagnostic yield of PET and CECT is estimated

to be 84%.⁸ Since the prognosis of NL has improved with modern treatments, the diagnostic criteria for diagnosing NL need to be relaxed. In one series,⁹ 45% of patients were diagnosed as NL only after autopsy. There have been no case reports of nerve thickening due to inflammatory or infectious disease processes in patients with lymphoma. Thus, although biopsy continues to be the gold standard for the diagnosis of NL, this can be diagnosed even in the absence of a histopathological confirmation and chemotherapy can be started empirically. In the absence of histological confirmation, the diagnosis of NL requires the appropriate integration of clinical and investigation data with histopathological data obtained from non-neural tissue and the CSF. Occasionally, only a good clinical response to empirical chemotherapy may lead the clinician to the correct diagnosis.⁹

Most cases of NL involve large B cell lymphoma (100% in our series with the grading of NHL possible in all of them). Though NL may antedate systemic lymphoma, it was previously found that eventually 73% of patients showed evidence of systemic disease.⁹ The evaluations performed at the time of presentation showed systemic disease in all of the cases in the current series which may be related to the relatively late presentation of the patients in our series.

TREATMENT

The treatment of NL is similar to that of primary CNS lymphoma. Before starting treatment it is essential to accurately estimate the extent of disease, and we suggest that staging should include examination of the vitreous, contrast-enhanced MRI images of the whole neuraxis, and whole-body FDG-PET. Since NL involves roots beyond the borders of the subarachnoid space,⁹ intrathecal drugs and traditional “cranio-spinal” radiation fields might not be effective. Thus, the mainstay of treatment includes systemic chemotherapy with or without intrathecal chemotherapy or radiotherapy. The response rate to combined treatment regimens in one series was 82%.⁹ It is difficult to comment on the exact treatment or prognosis based on our small series. The poor prognosis seen in our cases may be related to their late presentation, advanced stage as well as the diagnosis of diffuse large-B-cell lymphomas in all of the cases. The most effective regimen is unknown, and regimen selection is often based on protocols used to treat malignant CNS lymphoma. High dose methotrexate or; rituximab alone or as part of the R-CHOP regimen have been used. In one series; the best results were obtained with methotrexate.⁹

CONCLUSION

To conclude, NL should be considered in the differential diagnosis of any neuropathy especially one that is painful and rapidly evolving. Future studies of NL may help in establishing clear diagnostic and therapeutic protocols for this rare condition.

Conflicts of Interest

The authors have no financial conflicts of interest.

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