



# Neurolymphomatosis as primary presentation of extra-nodal NK/T-cell lymphoma, nasal type

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## Abstract

Neurolymphomatosis (NL) describes an infiltration of cranial and peripheral nerves by lymphoma cells, most frequently in non-Hodgkin B-cell lymphoma. This clinical entity is rare and poses a challenging diagnosis. We describe a case of a 64-year-old female patient with NL associated with extra-nodal NK/T-cell lymphoma (ENKTL), nasal type, presenting as a painful progressive mononeuropathy multiplex with an oral cavity lesion. ENKTL is usually associated with Epstein-Barr virus (EBV) infection and rarely affects the central and peripheral nervous system. Lumbar puncture, magnetic resonance imaging (MRI), nerve biopsy, and <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (FDG-PET) help to establish the diagnosis. Thereby, NL should be considered in the differential diagnosis of painful progressive multiple neuropathies, even in patients without previous history of cancer.

**Keywords** Neurolymphomatosis · Extra-nodal NK/T-cell lymphoma · FDG-PET · Mononeuropathy multiplex

## Introduction

NL is characterized by the infiltration of cranial or peripheral nerve roots by lymphomatous cells, most often B-cell non-Hodgkin lymphoma, and rarely by other lymphomas. ENKTL is a rare NK/T-cell non-Hodgkin lymphoma, associated with EBV infection, having a higher incidence in patients from East Asia and in indigenous individuals from Latin America [1].

NL most frequently involves peripheral nerves, spinal nerve roots, cranial nerves, and, to a lesser extent, neural plexus [2], which are frequently associated with intense pain and focal neurological deficit, namely peripheral and cranial neuropathy, muscular weakness, or sensory impairment. NL associated with ENKTL preferably infiltrates unusual sites, such as skin, soft tissues, gastrointestinal tract, testes, and central nervous system (CNS) [1].

In this article, we present the case of a progressive painful mononeuropathy multiplex and several other neurological findings throughout the clinical course.

## Case presentation

In August 2021, a previously healthy 64-year-old woman presented in an emergency department (ED) with a 5-month history of progressive right lower limb sensory complaints, describing persistent numbness and pain, with partial response to analgesic medication. Three months after initial admission, the patient returned to the ED, presenting right lower limb weakness, ipsilateral foot drop, and bilateral rotulian and aquilian areflexia. A lumbar spine MRI without gadolinium was conducted revealing an L4/L5 intravertebral herniated disc. A radiculopathy was admitted, and surgical treatment was sought that later proved to be ineffective.

One month later, the patient returned to the ED with a new onset of cranial polyneuropathy, presenting as diplopia and facial palsy that rapidly evolved to dysarthria, dysphonia, and dysphagia during admission. On the neurological examination, it was evident a right III and VI cranial nerve palsies, horizontal binocular diplopia, mydriasis of the right pupil, and right peripheral facial palsy. Ear, nose, and throat

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(ENT) examination revealed an exuberant ulcerative gingival mass which is observed in Fig. 1. No history of fever, fatigue, or weight loss was reported.

The patient also displayed an asymmetrical paraparesis (right knee flexion MRC grade 4/5, right ankle dorsiflexion 3/5, left lower limb global strength 4/5), bilateral areflexia, and lower limb patchy sensory loss, involving all sensory modalities.

She was admitted to the Neurology ward, where progressive muscle weakness was noted (with left hand dorsiflexion weakness MRC 3/5). At that time, a lumbar puncture was performed, with a cerebrospinal fluid (CSF) exam showing an elevated protein count of 301 mg/dL and pleocytosis with 208 cells/ $\mu$ L, showing a monocyte predominance and some lymphocytes, and a low glucose level (10 mg/dL). The cytology examination revealed no evidence of malignant cells, although flow cytometry was not performed at that time.

A detailed laboratory work-up with head computed tomography (CT) scan and brain MRI with gadolinium were unrevealing. Peripheral blood smear and immunophenotyping, autoimmune, paraneoplastic, and infectious studies were also unremarkable.

Electrophysiological studies demonstrated a pattern of mononeuropathy multiplex with asymmetric sensory and motor axonal loss, with no electrophysiological evidence of demyelination. Motor nerve conduction studies (NCS) showed an axonal neuropathy of the right peroneal nerve, left tibial nerve, and right ulnar nerve. In the sensitive NCS, the sensory response of the left peroneal was absent and the sural responses were asymmetric, abnormal on the right but intact on the left side. Median motor and sensory conduction studies are completely normal and symmetric. On EMG, motor unit action potentials (MUAPs) were normal; however, MUAP recruitment was reduced in the



Fig. 1 Gingival mass

peroneal and tibial innervated muscles. There was clear evidence of active denervation, both in peroneal and tibial innervated muscles.

Contrast-enhanced CT of the neck, chest, abdomen, and pelvis showed a bilateral adrenal mass and nasopharyngeal edema, prompting adrenal biopsy. Fine needle aspiration cytology of the adrenal mass was compatible with T-cell non-Hodgkin's lymphoma, probably NK type. A  $^{18}$ F-FDG PET scan revealed intense uptake in the right lower eyelid, right nasal cavity, nasopharynx, palatine tonsils, gingiva, left lobe of thyroid, breasts, mediastinal, right atrium, and both adrenal glands. There was also an intense uptake of inner surface of the right temporal lobe (eventually corresponding to the external ocular motor nerve), cervical, dorsal, and sacral nerve roots (C7-D1, D7-D8, L4-L5, L5-S1, S1-S2), and an uptake in the distal portion of the greater sciatic nerve, tibial, peroneal, and medial plantar nerve (Fig. 2).

The patient's clinical status declined, progressing to intense pain (predominantly in the morning), worsened to total right eye paresis, left III nerve palsy, and asymmetrical tetraparesis (right ankle dorsiflexion MRC grade 0/5, right knee flexion grade 2/5, left lower limb global strength grade 3/5, left hand dorsiflexion grade 3/5).

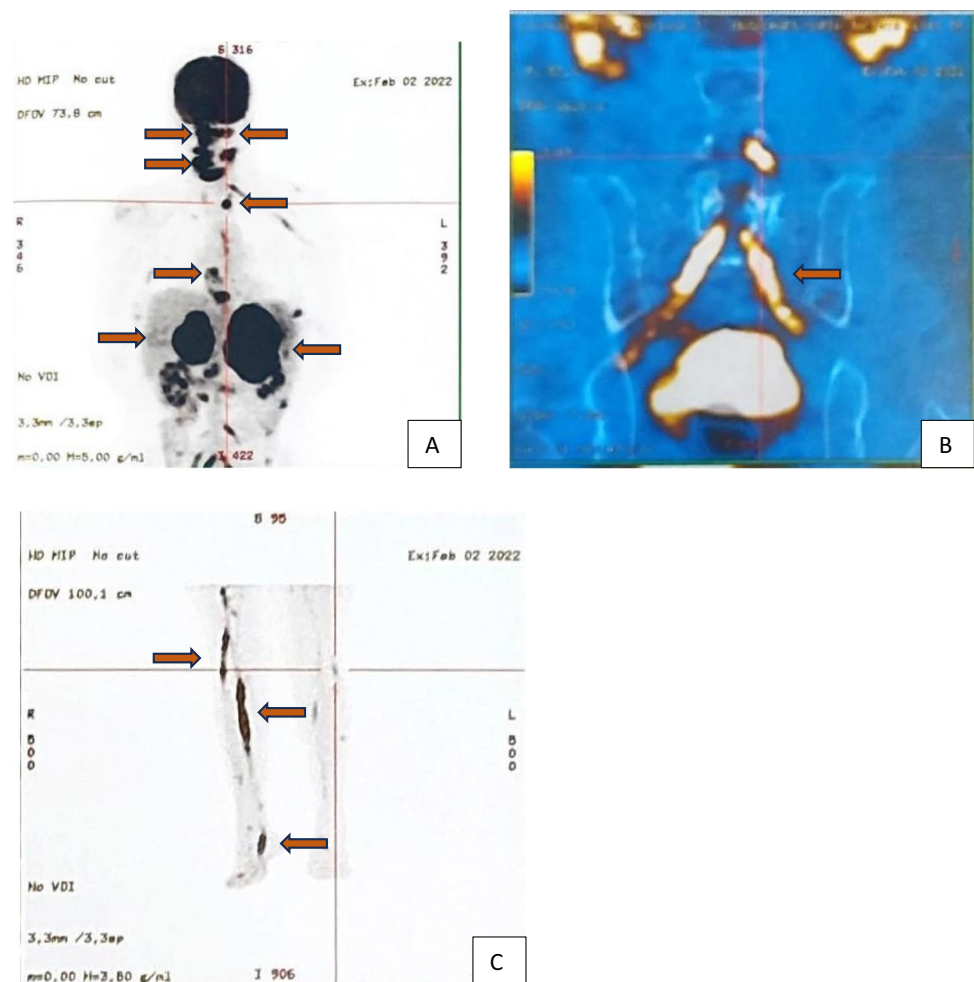
At this point, both clinical presentation and imaging studies pointed to the diagnosis of Neurolymphomatosis (NL), and a nerve biopsy was considered non-essential due to clinical worsening and the need of urgent therapy, and thus was not performed.

A hematology consult was required and the patient was started on dexamethasone. Subsequently, she was transferred to the hematology department to initiate appropriate treatment. Adrenal biopsy samples were re-examined, revealing small cells, with irregular and elongated nuclei, heterogeneous being CD20 $-$ , cCD3 $+$  (cytoplasmatic  $\epsilon$  chain of CD3), CD5 $-$ , CD2 $+$ , CD7 $-$ , CD4 $-$ , CD8 $+$ , CD30 $-$ , TiA-1 $+$ , granzymeB $+$ , BCL2 $+$ , EBER $+$ , and Ki67 expression was 100%, confirming the diagnosis of ENKTL. At this point, a diagnosis of ENKTL, nasal type, with systemic (nasopharynx, tonsils, gingival, and adrenal) and central nervous system involvement had been established.

A new lumbar puncture was performed with an increase of CSF protein level (977 mg/dL), abundant lymphocytosis (76 cells/ $\mu$ L), and high EBV viral load (43,825 IU/mL). CSF immunophenotyping was compatible with leptomeningeal involvement of NK/T cell lymphoma with CD2 $+$ , CD56 $+$ , weak CD8, sCD3 $-$ , CD4 $-$ , CD7 $-$ , and CD5 $-$  phenotype. Serum EBV viral load was also high at 17,154 IU/mL.

The patient was promptly started on chemotherapy with the modified SMILE regimen (high dose methotrexate, PEG-asparaginase, ifosfamide, etoposide, and dexamethasone), which resulted in a slight improvement of global muscle strength, right-side facial palsy and ophthalmoparesis, and reduction of the gingival mass.

**Fig. 2**  $^{18}\text{F}$ -FDG-PET findings, showing uptake in **A** right lower eyelid, right nasal cavity, nasopharynx, palatine tonsils, gingiva, left lobe of thyroid, mediastinal, right atrium, and an intense uptake of both adrenal glands. **B** Sacral nerve roots. **C** Greater sciatic nerve, tibial, medial plantar nerve



On the 6th day of chemotherapy, due to clinical deterioration with obtundation, an electroencephalography was suggestive of encephalopathy. Therapy with levetiracetam was initiated, given the clinical suspicion of epileptic seizures. Despite partial clinical recovery, the patient's global and neurological status continued to progress negatively, developing hyperactive delirium, probably related to a high-dose scheme of corticosteroids. On the 9th day of chemotherapy, the patient developed febrile neutropenia. Empiric antibiotic therapy was instituted, and blood cultures isolated an ESBL-producing *Klebsiella pneumoniae*. No abnormalities were detected on blood tests and head CT scan.

There was a progressive worsening of the neurologic status with worsening Glasgow Coma Scale (GCS) from 12 to 9. The workout revealed an EEG with a pattern compatible with non-convulsive status epilepticus. Therapy with lacosamide was added, without clinical or neurophysiological improvement, leading to the introduction of sodium valproate as a third anti-seizure drug. Given unfavorable clinical progression, a third lumbar puncture was performed on the 20th day of chemotherapy, documenting a reduction in CFS cells (21 cells/ $\mu\text{L}$ ) with a predominance of T/NK

lymphoma cells, a decrement in proteins (333 mg/dL) and low glucose (25 mg/dL) levels. However, EBV viral load continued to increase to 46,845 IU/mL. After the introduction of the third antiseizure drug, the patient achieved neurophysiological improvement, without criteria for non-convulsive status epilepticus. However, clinical neurological improvement was not registered, with progressive worsening of consciousness to GCS 6 and death on the 22nd day of chemotherapy.

## Discussion and conclusion

This complex case illustrates an association of two rare entities, NL and ENKTL. This type of lymphoma is usually associated with naso-oro-pharyngeal infiltration, as seen in our patient's ENT examination. Ophthalmoparesis was interpreted as a sign of nerve invasion and meningeal spread, since the PET-CT scan showed a linear uptake that can correspond to the external oculomotor nerve location and the CSF pleocytosis was compatible with T/NK-cell lymphoma infiltration. When a patient with an underlying lymphoid

malignancy develops neuropathy, NL should be suspected. However, when NL is the presenting clinical finding, the diagnosis is increasingly challenging [3]. The patient's prior history of radiculopathy may have acted as a confounding factor and delayed the final diagnosis, since NL manifestations presented first during the clinical course.

The differential diagnosis between NL and inflammatory neuropathy may be difficult, nonetheless NL is more often associated with mononeuropathy multiplex (which tends to be asymmetrical), severe pain, and a rapid clinical progression [4], while the classic acute inflammatory demyelinating neuropathy (AIDN) is often symmetrical. In our report, the asymmetric presentation and high CSF cell count eliminated the clinical suspicion for AIDN.

The diagnostic yield of CSF in NL is low and MRI findings suggestive of NL include enlarged and thickened peripheral and/or cranial nerves. In this case, head MRI findings were not suggestive of NL, and a lumbar MRI was deferred in favor of FDG-PET (which is associated with earlier detection than with MRI [5]). FDG-PET is the most sensitive and specific imaging method for identifying NL, holding an important role in differentiating NL from neuropathies, such as paraneoplastic. The nerve biopsy remains the gold-standard for diagnosing NL; however, due to its risk of complications and significant rate of false negative results, it is often omitted. In our report, the diagnosis was strongly supported by clinical presentation and suggestive results in FDG-PET, CSF cytology, flow cytometry, and non-neural tissue (adrenal glands) biopsy, the reason for which the nerve biopsy was considered non-essential. EBV is associated with several types of lymphomas, including ENKTL, some Burkitt lymphomas, Hodgkin Lymphoma, and diffuse large B cell lymphoma [2]. The variation of EBV viral load in relation to clinical response after treatment was also an important finding in this case (seriated CSF EBV-DNA of 43,825 UI/mL and 46,845 IU/mL). The EBV viral load is an important factor in assessing the clinical response and prognosis, which is included in the prognostic PINK-E score [6].

The mainstay of ENKTL treatment includes systemic chemotherapy, intrathecal chemotherapy, and/or radiotherapy [2]. The SMILE chemotherapy regimen, which includes methotrexate and asparaginase, is associated with better outcomes compared with other alternative regimens [7]. In the current case, the patient had a high-risk disease (over 60 years old, stage IV disease, extranasal disease, and positive EBV viral load) according to PINK-E score. Unfortunately, the prognosis for NL-associated lymphoma is poor, with an overall survival of months [8].

This patient illustrates a case of NL related to nasal type NK/T-cell lymphoma, which is rarely associated with NL. As suggested in the scarce literature on this topic, FDG-PET

and tissue biopsy are crucial in establishing the diagnosis [1–3, 5, 9]. The gingival hypertrophy was an important diagnostic clue, emphasizing the importance of semiology and clinical history in the diagnostic investigation.

## Declarations

**Ethical approval and informed consent.** The authors have obtained written informed consent from the patient for the publication of this paper.

**Competing interests** The authors declare no competing interests.

## References

1. Ghosh S et al (2022) Primary extranodal NK/T-cell lymphoma presenting as neurolymphomatosis involving multiple cranial nerves: a case report. *Acta Haematol* 145(1):97–105. <https://doi.org/10.1159/000518797>
2. Pan Q, Luo Y (2020) Recurrence of nasal type NK/T cell lymphoma presenting as neurolymphomatosis on 18F-FDG PET/CT: a case report and literature review. *Med (United States)* 99(1):1–5. <https://doi.org/10.1097/MD.00000000000018640>
3. Shimizu I et al (2014) Neurolymphomatosis in a patient with extranodal NK/T-cell lymphoma, nasal-type: a case report and literature review. *Intern Med* 53(5):471–475. <https://doi.org/10.2169/internalmedicine.53.0262>
4. Shree R et al (2016) The diagnostic dilemma of neurolymphomatosis. *J Clin Neurol* 12(3):274–281. <https://doi.org/10.3988/jcn.2016.12.3.274>
5. Aboueldahab N, Shafik MA, Megahed A, Vesselle H (2021) Neurolymphomatosis; a case report. *Clin Imaging* 80(July):329–333. <https://doi.org/10.1016/j.clinimag.2021.08.016>
6. Kim SJ et al (2016) A prognostic index for natural killer cell lymphoma after non-anthracycline-based treatment: a multicentre, retrospective analysis. *Lancet Oncol* 17(3):389–400. [https://doi.org/10.1016/S1470-2045\(15\)00533-1](https://doi.org/10.1016/S1470-2045(15)00533-1)
7. Alazawi S et al (2021) Neurolymphomatosis of the median nerve, optic nerve, L4 spinal nerve root and cauda equina in patients with B-cell malignancies: a case series. *J Med Case Rep* 15(1):1–11. <https://doi.org/10.1186/s13256-021-02714-8>
8. Li V, Jaunmuktane Z, Cwynarski K, Carr A (2019) Diagnostic delay in a case of T-cell neurolymphomatosis. *BMJ Case Rep* 12(12):1–8. <https://doi.org/10.1136/bcr-2019-232538>
9. Yi FF, Luo SS, Zhu WH, Zhao CB (2017) Neurolymphomatosis caused by nasal-type extranodal natural killer/T-cell Lymphoma. *Chin Med J (Engl)* 130(5):625–626. <https://doi.org/10.4103/0366-6999.200547>

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