

Neurolymphomatosis Caused by Nasal-type Extranodal Natural Killer/T-cell Lymphoma

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To the Editor: Neurolymphomatosis (NL) is a clinical disorder that presents with peripheral neuropathy due to lymphomatous infiltration of the nerves. NL is generally associated with B-cell lymphomas, and T-cell lymphoma is extremely rare. Nasal type extranodal natural killer (NK)/T-cell lymphoma (ENKL) is a rare lymphoma associated with Epstein-Barr virus (EBV), which is more common in East Asia than in the West.^[1] Central nervous system (CNS) lesions are occasionally observed as sites of ENKL involvement, and extranodal involvement often leads to an unfavorable prognosis.^[2,3] Here, a rare case of NL associated with ENKL that mainly presented as progressive multiplex painful mononeuropathy with multiple white matter lesions is reported.

A 26-year-old woman referred to our hospital after presenting asymmetrical numbness, pain, and weakness of bilateral legs with an intermittent fever for 3 months. The patient had experienced significant weight loss, but her prior medical history was not significant.

Physical examination revealed patchy erythema with blisters on her distal arms. Neurological examination revealed paralgnesia in the left planta, distal arm, outer calf, and inside of the right calf. The left Achilles tendon reflexes decreased. The left upper limb muscle strength was 2/6 distally and 3/6 proximally. Positive Babinski's sign was observed on the left side. The patient was considered to have possible CNS involvement, multiplex mononeuropathy, and skin lesions.

The laboratory findings included slight anemia (hemoglobin 108 g/L; normal: 115–150 g/L), thrombocytopenia (platelet [PLT]: $100 \times 10^9/L$; normal: $125\text{--}350 \times 10^9/L$), an elevated lactate dehydrogenase level (lactate dehydrogenase: 276 U/L; normal: 125–225 U/L), and an extremely elevated ferritin level ($>572 \mu\text{g/L}$; normal: 10–140 $\mu\text{g/L}$). The cerebrospinal fluid was not remarkable. Electromyography revealed diminished or no compound muscle action potential and sensory nerve action potential amplitude in the left median and ulnar nerves and the right tibialis anterior nerves, indicating multiplex mononeuropathy with axonal damage.

Two courses of high-dose dexamethasone therapy resulted in transient improvement of the patient's temperature and neurological symptoms, while the thrombocytopenia worsened (PLT: $51 \times 10^9/L$).

Bone marrow puncture revealed some atypical lymphocytes, but flow cytometry was negative. Magnetic resonance imaging of the brain revealed multiple white matter lesions with no enhancement [Figure 1a and 1b]. An ¹⁸F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) scan demonstrated extensive involvement of the left brachial plexus nerve, right tibial nerve, left median nerve, left ulnar nerve, CNS, muscle, nasopharynx, and skin [Figure 1c]. Finally, skin biopsy on the left arm showed infiltration of lymphomatous cells [Figure 1d–1h]. The lymphoma cells were positive for EBV-encoded RNA upon *in situ* hybridization [Figure 1i]. Biopsy indicated a pathological diagnosis of ENKL.

The patient had no response to subsequent salvage therapy because of continuous worsening of symptoms and she ultimately died 5 months after onset.

NL is an uncommon manifestation of lymphoma characterized by infiltration of the peripheral nerves by malignant cells. However, neuropathy can be the first manifestation, as observed in the present case. Diagnosing NL is clinically challenging. FDG-PET appears to be a high-sensitive diagnostic method for identifying NL, with a positivity rate as high as 87.5–91.0%.^[4,5] Intense FDG uptake in the involved nerve, as observed in this case, is a typical sign of NL, as indicated in a previous report.^[5]

Approximately 80% of the reported NL cases originate from B-cells.^[4] However, NK cell lymphoma is very rare, and the present case was finally diagnosed as ENKL pathologically. ENKL is an aggressive lymphoma preferentially occurring at unusual sites, including the CNS, skin, nasopharynx, and similar areas. It deteriorates rapidly despite active treatment.

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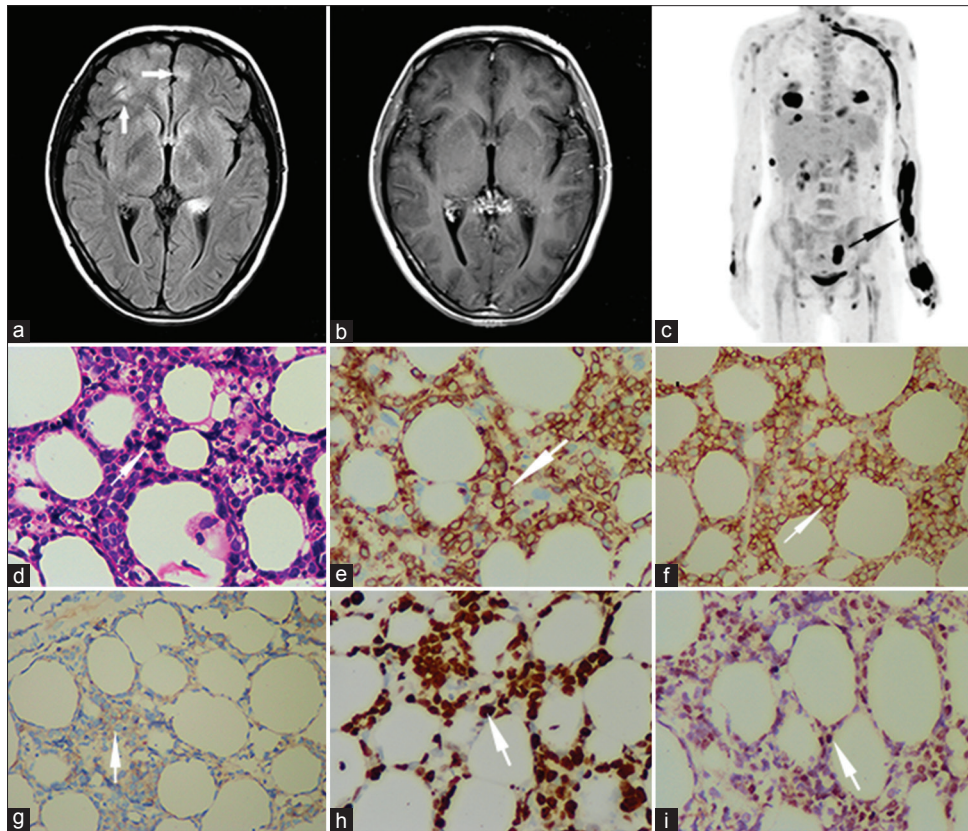


Figure 1: Images and pathology of the patient (a: Fluid attenuated inversion recovery and b: Postcontrast T1 weighted). Magnetic resonance imaging of the brain revealed multiple white matter lesions without enhancement. (c) ^{18}F -fluoro-2-deoxyglucose positron emission tomography neurolymphomatosis located in multiple sites. (d) Invasion of lymphomatous cells was primarily observed in the skin biopsy through hematoxylin and eosin staining (original magnification $\times 400$). (e) Immunohistochemical staining was positive for cluster of difference 3 (original magnification $\times 400$), (f) cluster of difference 8 (original magnification $\times 400$), (g) cluster of difference 56 (original magnification $\times 200$), (h) Ki-68 (original magnification $\times 400$), and (i) Epstein-Barr virus-encoded RNA-*in situ* hybridization (original magnification $\times 400$).

In conclusion, NL is a possible cause of progressive multiplex painful mononeuropathy. The present case suggests that NL can occur with ENKL.

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Conflicts of interest

There are no conflicts of interest.

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