LETTER TO THE EDITOR
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Primary Extra Nodal Natural Killer/T-cell Lymphoma (ENKTCL) of the CNS – A Rare Case Report with Diagnostic and Management Challenges

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Dear Editor,

Primary CNS lymphoma is a rare, aggressive malignancy that originates in the brain, spinal cord, cerebrospinal fluid, meninges, or eyes without systemic involvement, constituting ~3% of CNS tumors and <1% of non-Hodgkin's lymphomas. Among these, NK/T-cell variants are exceptionally rare and difficult to diagnose due to their nonspecific presentation and tendency to mimic other conditions. These lymphomas arise from natural killer or cytotoxic T-cells, frequently involving the meninges, and are typically associated with Epstein-Barr virus (EBV) [(1)]. WHO classifies three NK/T-cell neoplasms: aggressive NK leukemia, chronic NK lymphoproliferative disorder, and extranodal NK/T-cell lymphoma (nasal type) [(2)]. CNS involvement in these is extremely infrequent, representing roughly 2% of extranodal lymphomas and posing significant diagnostic and therapeutic challenges [(3)]. Given the lack of established protocols and limited documentation, such case reports are critical to advancing knowledge, refining diagnostic approaches, and improving treatment strategies for this rare and aggressive lymphoma.

We present the rare case of a 67-year-old woman—who developed bilateral hearing loss, progressive ataxia, anorexia, and 12-kg weight loss over two months. Brain MRI revealed neurodegenerative process. Neurological exam revealed bilateral gaze-evoked nystagmus and marked truncal ataxia without motor or sensory deficits. Given the above findings, an urgent CSF tap was done which revealed a total leucocyte count of 524/ul including 95% atypical lymphocytes having irregular nuclear, membrane, coarse chromatin and fine cytoplasmic projections which raised suspicion of atypical/reactive lymphoid proliferation and high protein (200.5 mg/dL). (Figure 1). Flowcytometric immunophenotyping on the CSF was advised but could not be performed due to inadequate sample. Meanwhile the patient was thoroughly investigated to look for any auto-immune or reactive/inflammatory conditions. Routine labs were largely unremarkable, aside from mild anemia and thrombocytopenia. Gram stain, TB Xpert, Biofire panel, culture, VDRL all were negative. Repeat MRI showed extensive white matter and brainstem involvement with diffusion restriction. PET-CT identified intensely FDG-avid basal ganglia hypermetabolism, and diffuse marrow activation. No nasal lesion was noted (Figure 2). Thus, a repeat CSF tapping was performed for flow cytometry which revealed 90.5% homogenously bright CD56 positive NK-cell proliferation along with moderate to bright homogenous expression of CD94, CD2, CD38 and HLA-DR with negative CD16 and CD57 suggestive of NK/T cell lymphoma over reactive proliferation of NK/T cells (Figure 3). Next-generation sequencing performed on CSF also identified a pathogenic somatic variant in *STAT5B* (p.N642H: c.1924A>C) with Variant allele frequency (VAF) of 31.28%, critical domain for STAT activation in JAK-STAT pathway, found to be associated with NK/T cell lymphoma. Additional mutations in *ARID1A* (p.Q1334del: c.3999_4001delGCA) (VAF:5.03%) and *TET2* (p.L1721W: c5162T>G) (VAF:45.62%) were found, and a variant of unknown significance in *GNA13* (VAF:63.65%: c.-3A>GGCA), potentially relevant for lymphoid biology which was further complemented with markedly

elevated EBV copy number in the CSF (4.7 million copies/mL) and moderate in blood (≈59,000 copies/mL). The patient was diagnosed with Primary CNS NK/T cell lymphoma. Bone marrow aspirate and biopsy were normocellular, unremarkable and the CBC revealed mild anemia with hemoglobin of 11g/dl; total leucocyte count: 6,200/ul and platelet count: 2,10,000/ul. Due to the poor performance status (ECOG 4; Eastern Cooperative Oncology Group), the management included modified DHAP: dexamethasone, cisplatin, cytarabine chemotherapy (excluding cisplatin), intrathecal methotrexate/cytarabine/hydrocortisone, and nivolumab. The treatment cycles resulted in clinical improvement and reduced EBV load (Table 1). She continues follow-up at her local centre.

ENKTCL, primary infiltration of the central nervous system's leptomeninges by NK/T-cell lymphoma remains an exceptionally rare clinical presentation and increasing awareness has contributed to more frequent identification (1). Li et al.[4] reported a 4.59% CNS involvement rate among 414 ENKTCL patients, with primary CNS disease accounting for less than 0.5%. The differential considerations included: **Reactive/viral lymphocytosis**, particularly due to EBV infection, given the markedly elevated EBV DNA levels in CSF and blood. However, reactive lymphocytes typically do not exhibit clonal markers or aberrant expression patterns as mentioned above. **Primary CNS lymphoma (PCNSL)**, often of diffuse large B-cell type (DLBCL), would generally express CD19/CD20 and light chains, which were absent here. **T-cell lymphoproliferative disorders**, such as T-cell leukemias or peripheral T-cell lymphomas, which may show CD3 expression and other lineage-restricted markers [5,6,7]. Without flow cytometry, the diagnostic ambiguity between atypical reactive changes and neoplastic lymphoproliferation would have persisted, delaying therapy. The emergence of next-generation sequencing has significantly enhanced the understanding of the mutational profile in NK/T-cell lymphoma. Initial exome sequencing studies identified *JAK3* mutations in roughly 35% of cases, implicating persistent activation of the JAK/STAT signalling axis as evidenced by activating mutations in *STAT3* and *STAT5B* [8]. There is no standard treatment after discovery of CNS disease. While conventional regimens like high dose methotrexate and intrathecal chemotherapy form the backbone, emerging data suggest anti-PD-1 antibodies and histone deacetylase (HDAC) inhibitors (chidamide) may significantly improve outcomes. Cai et al [9] observed complete remission in 11 out of 14 CNS-involved patients, with two achieving prolonged remission on anti-PD-1 maintenance. However, Nevel et al [10] cautioned that CNS ENKTCL often has a grim prognosis with a median overall survival of 3.8 months. Dynamic monitoring of EBV DNA levels also emerged as a robust biomarker of disease activity in several studies. Our patient showed clinical improvement following modified therapy with nivolumab and is undergoing continued chemotherapy and immunotherapy with regular follow-up. This case adds to the growing literature advocating integrated clinical, diagnostic and molecular approaches in CNS NK/T-cell lymphoma and underscores the importance of flow cytometric immunophenotyping which was not just confirmatory—but was transformative, shifting the diagnostic paradigm from neuroinflammatory to oncologic and guiding precision-based management involving chemotherapy, intrathecal therapy, and immunotherapy.

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Table 1: Epstein Barr Virus load at diagnosis and during therapy by Q-RTPCR for EBV.

EBV Q-RTPCR (copies/ml)	**31/5/2025**	**2/6/2025**	**9/6/2025**	**18/6/2025**	**1/7/2025**
Blood (copies/ml)	59,490		17,100	2,06,100	10,783
CSF (copies/ml)		46,89,000