

Primary Extranodal Natural Killer/T-Cell Lymphoma of the Central Nervous System: A Rare Case Report with Diagnostic and Management Challenges

Santral Sinir Sisteminin Primer Ekstranodal Doğal Öldürücü/T-Hücreli Lenfoması: Tanı ve Yönetim Zorlukları İçeren Nadir Bir Olgu Sunumu

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To the Editor,

Primary central nervous system (CNS) lymphoma is a rare, aggressive malignancy that originates in the brain, spinal cord, cerebrospinal fluid (CSF), meninges, or eyes without systemic involvement, constituting approximately 3% of CNS tumors and <1% of non-Hodgkin lymphomas. Among these, natural killer (NK)/T-cell variants are exceptionally rare and difficult to diagnose due to their non-specific presentation and tendency to mimic other conditions. These lymphomas arise from NK or cytotoxic T-cells, frequently involving the meninges, and are typically associated with Epstein-Barr virus (EBV) [1]. The World Health Organization classifies NK/T-cell neoplasms into three categories: aggressive NK leukemia, chronic NK lymphoproliferative disorder, and extranodal NK/T-cell lymphoma (nasal type) [2]. CNS involvement is extremely infrequent in these cases, representing roughly 2% of extranodal lymphomas and posing significant diagnostic and therapeutic challenges [3]. Given the lack of established protocols and limited documentation, case reports are critical for advancing knowledge, refining diagnostic approaches, and improving treatment strategies for this rare and aggressive type of 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 the course of 2 months. Brain magnetic resonance imaging (MRI) revealed a neurodegenerative process. Neurological examination revealed bilateral gaze-evoked nystagmus and marked truncal ataxia without motor or sensory deficits. Given these findings, an urgent CSF tap was performed, which revealed a total leukocyte count of 524/ μ L, including 95% atypical lymphocytes having irregular nuclear membrane, coarse chromatin, and fine cytoplasmic projections, which

raised suspicion of atypical/reactive lymphoid proliferation. High protein (200.5 mg/dL) was also observed (Figure 1A). Flowcytometric immunophenotyping of the CSF sample was advised but could not be performed due to inadequate sample volume. Meanwhile, the patient was thoroughly examined for any autoimmune or reactive/inflammatory conditions. Routine laboratory tests were largely unremarkable, aside from mild anemia and thrombocytopenia. Gram staining, TB Xpert, BioFire panel, culturing, and VDRL results were all negative. Repeat MRI showed extensive white matter and brainstem involvement with diffusion restriction. Positron emission tomography-computed tomography identified intensely fluorodeoxyglucose-avid basal ganglia hypermetabolism and diffuse marrow activation. No nasal lesion was noted (Figure 1B, C). Thus, another CSF tap was performed for flow cytometry, which revealed 90.5% homogeneously bright CD56-positive NK-cell proliferation along with moderate to bright homogeneous expression of CD94, CD2, CD38, and HLA-DR with negativity for CD16 and CD57, suggestive of NK/T-cell lymphoma with overreactive proliferation of NK/T cells (Figure 2). Next-generation sequencing performed on the CSF sample also identified a pathogenic somatic variant in *STAT5B* (p.N642H: c.1924A>C), with variant allele frequency (VAF) of 31.28%, in the critical domain for STAT activation in the 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: c.5162T>G) (VAF: 45.62%) were also found, and a variant of unknown significance was observed in *GNA13* (c.-3A>GGCA) (VAF: 63.65%), potentially relevant for lymphoid biology. These findings were accompanied by a markedly elevated EBV copy number in the CSF (4.7 million copies/mL) and a moderate number in the blood (approximately 59,000 copies/mL). The

patient was diagnosed with primary CNS NK/T-cell lymphoma. The bone marrow aspirate and biopsy were normocellular and unremarkable and the complete blood count revealed mild anemia with hemoglobin of 11 g/dL, total leukocyte count of 6200/ μ L, and platelet count of 210.000/ μ L. Due to the patient's poor performance status as reflected by an Eastern Cooperative Oncology Group score of 4, the case management included modified DHAP chemotherapy (dexamethasone, cisplatin, and cytarabine, 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 center.

Extranodal NK/T-cell lymphoma (ENKTCL) with primary infiltration of the leptomeninges of the CNS by NK/T-cell lymphoma remains an exceptionally rare clinical presentation, but 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% of the cases. The differential considerations for our case included reactive/

viral lymphocytosis, particularly due to EBV infection, given the markedly elevated EBV DNA levels in the CSF and blood. However, reactive lymphocytes typically do not exhibit clonal markers or aberrant expression patterns, as mentioned above. Primary CNS lymphoma, often of the diffuse large B-cell type, 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, may also 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 signaling 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 of treatment,

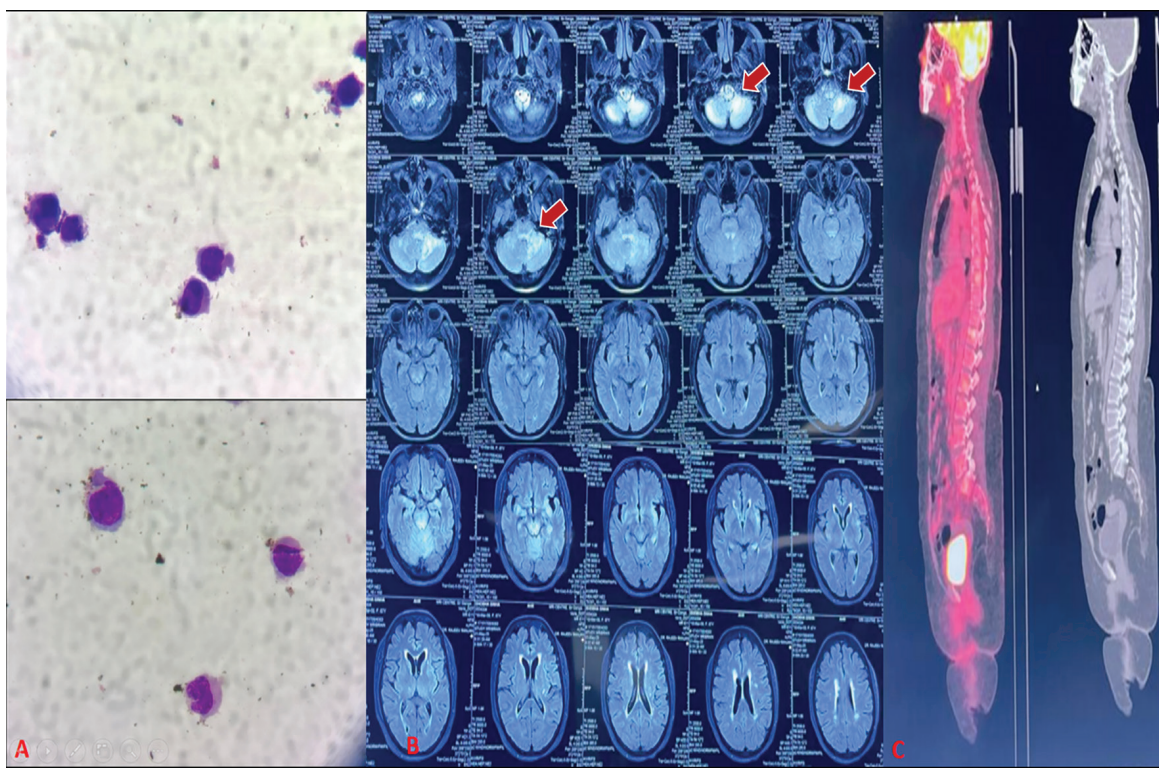


Figure 1. A) Representative images of CSF fluid cytology showing several abnormal lymphoid cells with small to intermediate size, irregular nuclear membrane, coarse chromatin, inconspicuous nucleoli and scant agranular basophilic cytoplasm with fine projections (1000 \times , Wright Giemsa stain). B) MRI brain- T2 and FLAIR hyperintensities are seen in the periventricular white matter, corona radiata and centrum semiovale region in bilateral frontoparietal white matter regions, bilateral cerebellar hemispheres with altered signal intensity areas in the left insular cortex and left hippocampus. Possibility of encephalitis? C) PET/CT showing inhomogeneous mild FDG uptake in the spinal cord in the cervical-dorsal spine along with inhomogeneous FDG uptake in the axial and appendicular skeleton, likely RES activation.

CSF: Cerebrospinal fluid; MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery; PET/CT: positron emission tomography/computed tomography; FDG: fluorodeoxyglucose; RES: reticuloendothelial system.

Table 1. Epstein-Barr virus load at diagnosis and during therapy as measured by quantitative reverse transcription polymerase chain reaction.

EBV load (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			

EBV: Epstein-Barr virus; CSF: cerebrospinal fluid.

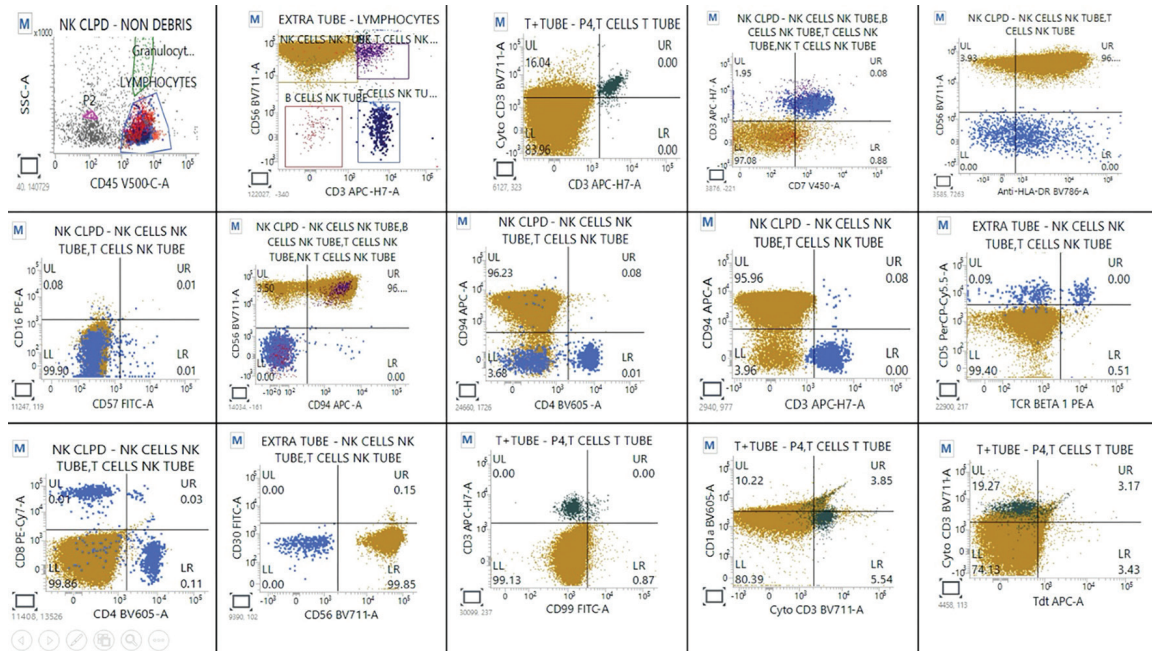


Figure 2. Flow cytometry plots performed on the CSF sample shows ~96% events in the lymphoid gate of which ~96.5% events corresponded to the NK cells showing bright CD56, HLA-DR and moderately bright CD94, CD2 and CD38. These cells were negative for CD4, CD8, CD30, CD99, Tdt, CD117, CD1a, CD13, CD33, TCR Beta 1, CD16, CD57 and rest of the lineage, T-lineage and myeloid cell markers suggestive of NK/T cell lymphoma over reactive proliferation of NK/T cells. BD FACSLytic™ flow cytometer. Protocol Used – Bulk Lysis-Stain-Wash method.

CSF: Cerebrospinal fluid; NK: natural killer.

emerging data suggest that anti-PD-1 antibodies and histone deacetylase inhibitors such as chidamide may significantly improve outcomes. Cai et al. [9] observed complete remission in 11 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 median overall survival of 3.8 months. Dynamic monitoring of EBV DNA levels also emerged as a robust biomarker of disease activity in these previous 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 treating CNS NK/T-cell lymphoma and underscores the importance of flow cytometric immunophenotyping, which was transformative, not just confirmatory, shifting the diagnostic paradigm from neuroinflammatory to oncological and guiding precision-based

management involving chemotherapy, intrathecal therapy, and immunotherapy.

Keywords: Extra nodal NK-T cell lymphoma, Primary CNS lymphoma, Flow cytometry NK-T cell lymphoma, *STAT3/5* mutation

Anahtar Sözcükler: Ekstranodal NK-T hücreli lenfoma, Primer SSS lenfoması, Akım sitometrisi NK-T hücreli lenfoma, *STAT3/5* mutasyonu

Ethics

Informed Consent: A written informed consent was obtained from the participant of the study/case.

Footnotes

Authorship Contributions

Concept: S.D.; Design: S.D., S.L., A.S.; Data Collection and Processing: S.D., A.S., R.R., V.A., J.K.; Analysis or Interpretation:

S.D., S.L., A.S., V.A., R.R., J.K.; Literature Search: S.D., A.S., V.A., J.K.; Writing: S.D., S.L., A.S., V.A., R.R., J.K.

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