Extranodal NK/T-celllymphoma nasal type withcerebralinvolvement: a case report

Abstract :

Background:
Extranodal NK/T-celllymphoma, nasal type (ENKTL), is a rare and aggressivesubtype of non-Hodgkin lymphoma,characterized by a distinctive clinicopathological profileincludingangiocentricgrowth, vascular destructionand extensive necrosis.
It isuniversallyassociatedwith Epstein-Barr virus (EBV) infection, whichplays a central role in itspathogenesisthrough latent viral gene expression and modulation of the tumormicroenvironment.
Its clinical presentation often mimicsinflammatorydiseases, leading to diagnostic delay.
Case presentation:
We report the case of a 33-year-old male presenting with progressive nasal obstruction and destructive centrofaciallesions. Initial biopsies were non-diagnostic. Imaging suggested granulomatosis with polyangiitis. Repeated biopsies confirmed ENKTL. FDG PET-CT revealed locoregional extension with cerebral involvement. The patient was treated with an asparaginase-based regimen (MOGAD protocol) resulting in an incompletemetabolicresponse.
Conclusion:
ENKTL shouldbesuspected in persistent necrotic midline lesions. CNS involvement is rare but indicates poorprognosis and requiresaggressivemultidisciplinary management. This case highlights the importance of repeated biopsies and advancedimaging in atypicalpresentations.

Keywords : Extranodal NK/T-celllymphoma, nasal type lymphoma, Epstein–Barr virus, central nervous system involvement, sinonasaltumor, asparginasd-basedchemotherapy

Introduction :

Extranodal NK/T-cell lymphoma, nasal type, is a rare and aggressive subtype of non-Hodgkin lymphoma characterized by angiocentric growth, vascular destruction, and extensive necrosis. It is strongly associated with latent Epstein-Barr virus infection.

Clinically, it predominantly involves the upper aerodigestive tract, particularly the nasal cavity and paranasal sinuses. Its presentation often mimics chronic inflammatory or granulomatous diseases such as granulomatosis with polyangiitis, frequently resulting in delayed diagnosis.

Central nervous system involvement is uncommon but represents a severe and poor prognostic feature.

We report a case of nasal NK/T-cell lymphoma with cerebral involvement in a young patient, emphasizing diagnostic traps and therapeutic challenges.

Case report:

A 33-year-old male patient with no significant past medical conditions, who presented with a 6-month history of progressive nasal obstruction, crustedrhinorrhea and destructive centrofaciallesions.Clinical examination revealed extensive necrosis involving the nasal septum and bilateralinferior and middle turbinates**(Figure 1).**Initial radiological findings suggested an extensive, locally invasive, ulcerated and nodular nasal and paranasal mass responsible for a perforation of the nasal septum and pansinusitis, initially raising the suspicion of granulomatosis with polyangiitis **(Figure 2).**Two initial nasal biopsies were non-contributory, and ANCA testing was negative.Due to worsening symptoms, deep mucocutaneous biopsies were performed.

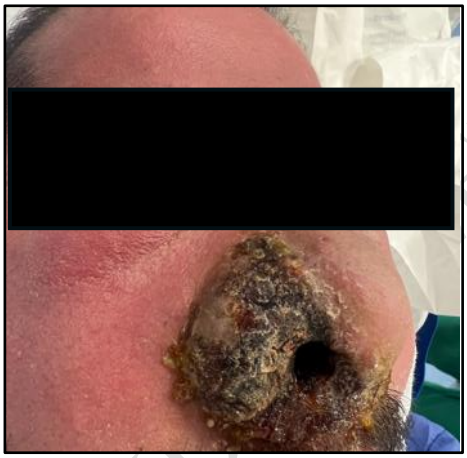

Figure 1: Initial clinical presentation showing a necrotic centrofacial lesion.

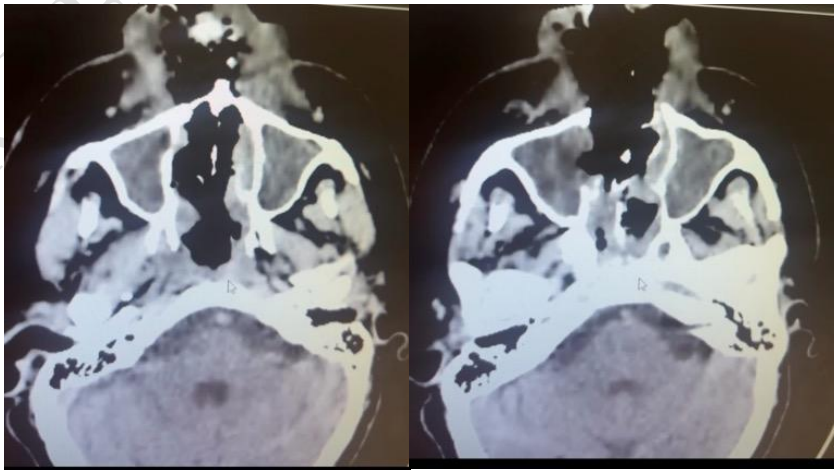

Figure 2: Axial computed tomography (CT) of the paranasal sinuses demonstrating destructive naso-sinus involvement.

Histopathologicalexamination of the nasal biopsy revealed a diffuse lymphomatous proliferation infiltrating the nasal mucosa, composed of medium-sized atypical cells with pleomorphic hyperchromatic nuclei and frequent mitotic figures. The tumor cells were associated with numerous histiocytes and a prominent vascular network, with evidence of angioinvasion and focal necrosis. Immunohistochemical analysis demonstrated diffuse positivity of the neoplastic cells for CD3, along with expression of CD56 and Granzyme B. The proliferation index (Ki-67) was high, estimated at approximately 80%. Tumor cells showed heterogeneous positivity for LMP1, while CD20 and CD5 were negative. Overall, the

morphological and immunophenotypic features are consistent with a diagnosis of extranodal NK/T-celllymphoma, nasal type.

FDG PET-CT demonstrated: an extensive hypermetabolic involvement of the nasal pyramid and paranasal sinuses, an infiltration of the left maxillary sinus and ethmoidal cells and it also showed a hypermetabolic lesion in the right frontal lobe (12 × 16 mm), consistent withcerebralinvolvement**(Figure 3).**

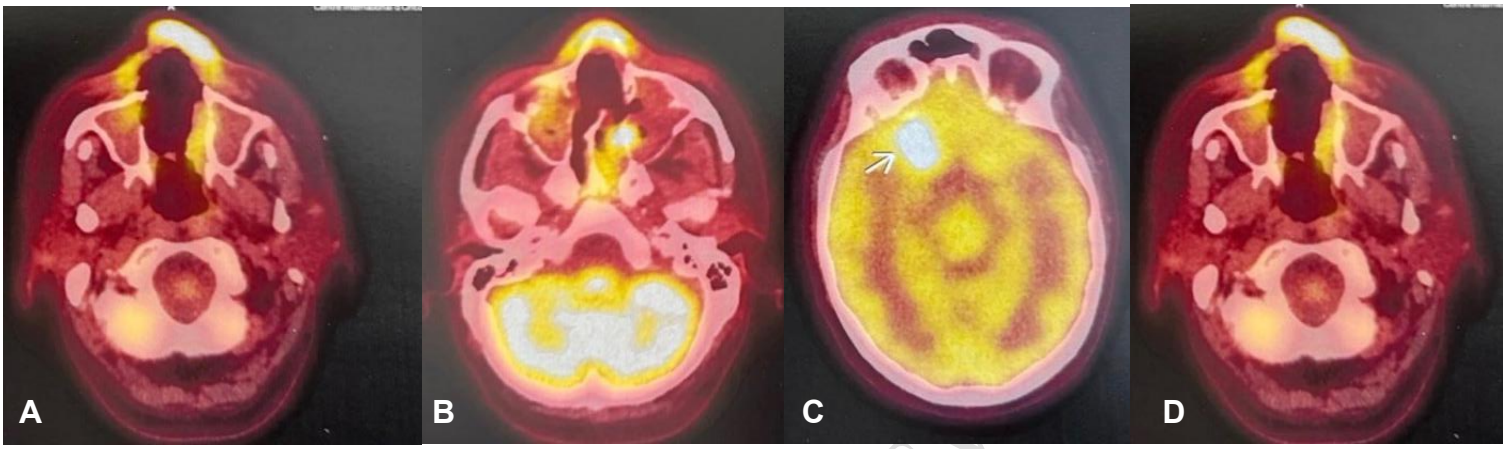

Figure 3: ^{18} F-FDG PET-CT imaging demonstrating hypermetabolic activity in the nasosinusalregion (A, B) and focal cerebral uptake in the right frontal lobe (C, D)

The patient wasthereforeclassified as stage VI according to Lugano staging system**(Table 1)**

Table 1. Lugano Classification Staging System for Lymphoma (2014)

Stage	Definition
I	Involvement of a single lymphnoderegion or a single extralymphatic site (IE)

Stage	Definition
II	Involvement of ≥2 lymphnoderegions on the sameside of the diaphragm
IIE	Stage II withcontiguousinvolvement of a single extranodal site
III	Involvement of lymphnoderegions on bothsides of the diaphragm, whichmayinclude the spleen
IV	Diffuse or disseminatedinvolvement of one or more extralymphaticorgans (e.g., bonemarrow, liver, central nervous system), with or without nodal involvement

Stagingisperformedusing FDG PET-CT for FDG-avidlymphomas. Stages I–II are generallyconsideredlimiteddisease, while stages III–IV representadvanceddisease. Stage IV indicates non-contiguousextranodaldissemination[1].

Chemotherapy based on the MOGAD protocol (an asparaginase-containing regimen) was initiated. Radiotherapy was not recommended in this case given the stage of systemic disseminated NK/T-cell lymphoma.The patient is currently undergoing the fifth cycle and demonstrates a partial metabolic response on FDG PET-CT, with a Deauville score of 4 **(Table 2).**

Table 2. Deauville 5-Point Scale for FDGPET-CT Response Assessment

Score	Definition
1	No residualuptakeabove background
2	Uptake ≤ mediastinalblood pool
3	Uptake>mediastinum but ≤ liver
4	Uptakemoderatelyincreasedcomparedwithliver
5	Uptakemarkedlyincreasedcomparedwithliver and/or new lesions
X*(optional)*	New areas of uptakeunlikelyrelated to lymphoma

Scores 1–3 are consistent withcompletemetabolicresponse (CMR) in mostclinical settings. Scores 4–5 suggestresidual or progressive metabolicdisease, requiringclinicalcorrelation[2].

Discussion :

Extranodal NK/T-celllymphoma, nasal type, represents a biologicallyaggressivelymphomaentitywith unique epidemiological, virological, and pathologicalfeatures. Itsstrong association with EBV infection is a defininghallmark, with viral-drivenoncogenesismediatedthrough latent gene expression (LMP1, LMP2) promotingproliferation, immune escape, and resistance to apoptosis[3], [4], [5].

From an epidemiological perspective, ENKTL demonstratesmarkedgeographic variation in its distribution. It issignificantly more prevalent in East Asia and Latin America, whereitaccounts for approximately 5–10% of all non-Hodgkin lymphomas, compared to lessthan 1% in Western populations [4], [6]. This disparityislikelyattributable to differences in EBV strain variants, host geneticsusceptibility, and environmentalfactors[5], [7]. The diseasepredominantly affects middle-aged males, althoughyoungerindividualsmayalsobeaffected, particularly in endemicregions[4].

A major issue highlighted by our case is the diagnostic delay, whichremains a well-recognized challenge in ENKTL. The initial clinicalpresentationoftenoverlapswithbenigninflammatory or autoimmune conditions, particularlygranulomatosiswithpolyangiitis (GPA). Bothentitiesmaypresentwith destructive midlinelesions, sinus involvement, and nonspecificradiologicalfindings. However, the absence of ANCA, the rapid progression, and the presence of extensive necrosisshould prompt reconsideration of the diagnosis[8], [9]. In thiscontext, our case illustrates a classical but critical diagnostic pitfall.

Histopathological confirmation remainscomplex. The angioinvasive nature of ENKTL leads to ischemicnecrosis, frequentlyresulting in false-negative biopsies, as seen in our patient. This underscores the importance of performing multiple, deep, and image-guided biopsies targeting viable tissue areas, as recommended in the literature[9], [8]. Furthermore, earlyintegration of immunohistochemistry and EBV detection (EBER) is essential to avoidmisdiagnosis[4], [5].

From a radiological perspective, conventional CT imaginglacksspecificity and may fail to differentiate ENKTL frominfectious or inflammatoryprocesses. In contrast, ^{18}F-FDG PET-CT has emerged as an essential tool, not only for staging but also for detectingoccultsystemicinvolvement and guidingbiopsy sites[10], [11], [12]. In our case, PET-CT played a crucial role in identifyingcerebralinvolvement, significantlyimpactingbothstaging and prognosticevaluation.

CNS involvement in ENKTL isuncommon, withreported incidence rangingfrom 2% to 9%, but it carries a particularlypoorprognosis[13], [14]. It istypicallyassociatedwithadvanced-stage disease, high EBV DNA load, and aggressivebiologicalbehavior[13], [14]. The mechanismsunderlying CNS disseminationremainincompletelyunderstood but mayinvolvehematogenous spread facilitated by angioinvasion or direct extension from adjacent structures[13], [14], [15].

Histologically, ENKTL typically shows an angiocentric and angiodestructivelymphoidinfiltrateassociatedwithprominentcoagulativenecrosis and apoptosis. The neoplasticcellsare usually medium sized, althoughcytologicvariabilityiscommon, and they are characteristicallyaccompanied by a markedinflammatory background. On

immunohistochemistry, tumorcellstypically express cytoplasmic CD3ε, CD56, and cytotoxicmoleculessuch as granzyme B, TIA-1, and perforin, while surface CD3 isusually absent. Demonstration of EBV in tumorcells by EBER in situ hybridizationisconsidered essential for diagnosis[4].

Therapeutically, ENKTL ischaracterized by intrinsicresistance to anthracycline-basedchemotherapy due to P-glycoprotein-mediateddrug efflux. This has led to the development of asparaginase-basedregimens, such as **SMILE**(dexamethasone, Methotrexate, Ifosfamide, L-asparaginase, Etoposide) and **MOGAD** (Methotrexate, Oxaliplatin, Gemcitabine, Asparaginase, Dexamethasone), which exploit the metabolicvulnerability of NK/T lymphomacellslacking asparagine synthetase[4],[13]. Theseprotocols have significantlyimprovedresponse rates, particularly in advanced or refractorydisease[4],[13].

Management of ENKTL dependsprimarily on the disease stage and therisk profile. In localizedearly-stage nasal ENKTL, radiotherapyremains an essential component of curative therapy, and current practice generallycombinesitwith non-anthracycline chemotherapy, delivered in sequential, concurrent, or sandwich schedules[4],[7].Curative radiotherapy doses of approximately 50–54 Gy are commonlyused in localized nasal disease to optimizelocoregional control[4],[7].On the other hand, advanced-stage or disseminated ENKTL requiressystemic asparaginase-basedchemotherapy as the main therapeutic backbone, since anthracycline-basedregimens are associatedwithinferioroutcomes[4],[6].

The role of CNS-directedtherapy (intrathecalchemotherapy or high-dose methotrexate) remainscontroversial, with no standardizedapproachcurrentlyestablished. Similarly, consolidation withhematopoietic stem cell transplantation maybeconsidered in selected high-risk patients, althoughevidenceislimited and heterogeneous[13], [15].

Conclusion :

ENKTL shouldbeconsidered in any destructive midlinelesionregardless of geographiccontext. Initial negative biopsies do not rule out the diagnosis and requirefurther investigation when suspicion remains high. FDG PET-CT is essential for accuratestaging and detection of occultdisease. The presence of central nervous system involvementsignificantlyworsensprognosis and requiresadapted management.

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