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RESEARCH ARTICLE

EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE, WITH CEREBRAL INVOLVEMENT: A CASE REPORT

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Abstract

Background: Extranodal NK/T-cell lymphoma, nasal type (ENKTL), is a rare and aggressive subtype of non Hodgkin lymphoma, characterized by a distinctive clinicopathological profile including angiocentric growth, vascular destruction and extensive necrosis. It is universally associated with Epstein-Barr virus (EBV) infection, which plays a central role in its pathogenesis through latent viral gene expression and modulation of the tumor microenvironment. Its clinical presentation often mimics inflammatory diseases, leading to diagnostic delay.
Case presentation: We report the case of a 33-year-old male presenting with progressive nasal obstruction and destructive centrofacial lesions. 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 a partial metabolic response.
Conclusion: ENKTL should be suspected in persistent necrotic midline lesions. CNS involvement is rare but indicates poor prognosis and requires aggressive multidisciplinary management. This case highlights the importance of repeated biopsies and advanced imaging in atypical presentations.

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.

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Case report: -

A 33-year-old male patient with no significant past medical history presented with a 6-month history of progressive nasal obstruction, crusted rhinorrhea and destructive centrofacial lesions. Clinical examination revealed extensive necrosis involving the nasal septum and bilateral inferior 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.

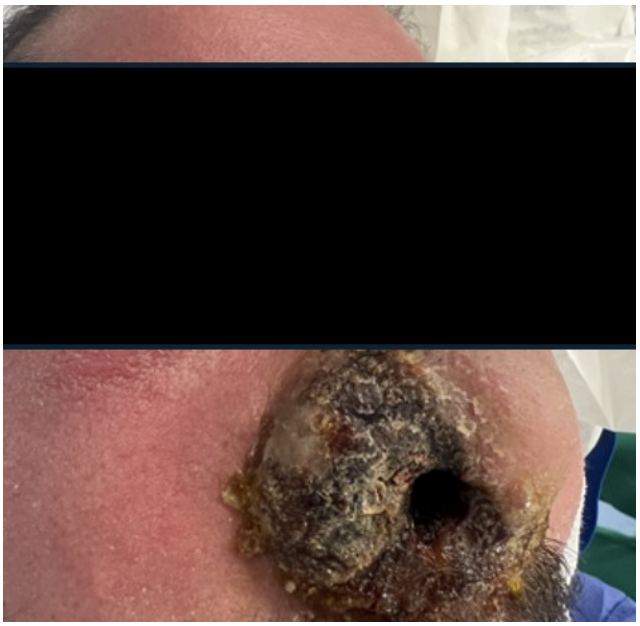

Figure 1: Initial clinical presentation showing a necrotic centrofacial lesion.

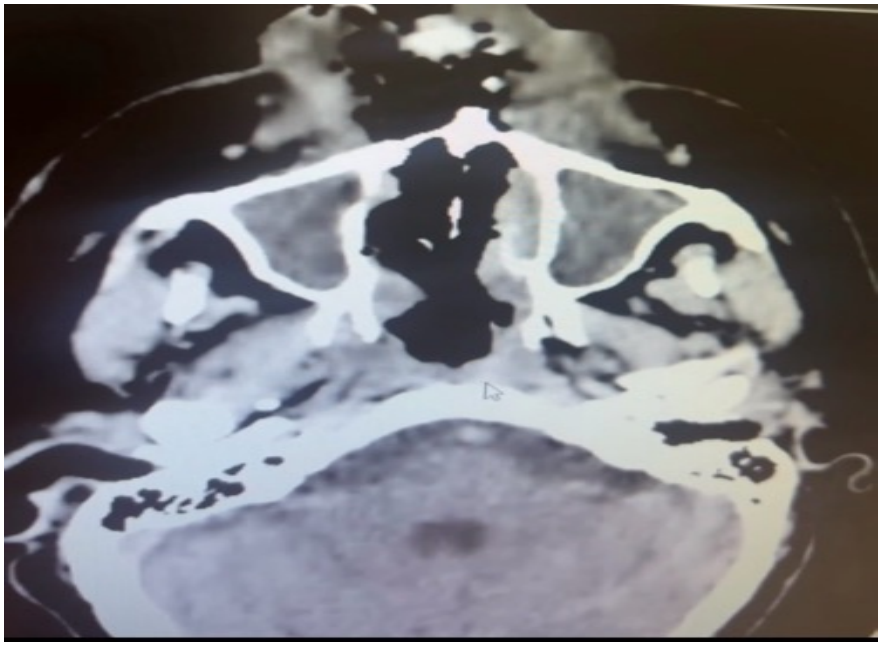

Figure 2: Axial computed tomography (CT) of the paranasal sinuses demonstrating destructive naso-sinus involvement.

Histopathological examination 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-cell lymphoma, nasal type. FDG PET-CT demonstrated an extensive hypermetabolic involvement of the nasal pyramid and paranasal sinuses, infiltration of the left maxillary sinus and ethmoidal cells, as well as a hypermetabolic lesion in the right frontal lobe (12 × 16 mm), consistent with cerebral involvement (Figure 3). The patient was therefore classified as stage IV according to Lugano staging system (Table 1).

The patient was treated with an asparaginase-based chemotherapy regimen (MOGAD protocol), including:
- Methotrexate: 3000 mg/m² IV (Day 1)
- Oxaliplatin: 130 mg/m² IV (Day 2)
- Gemcitabine: 1000 mg/m² IV (Day 1 + Day 8)
- L-asparaginase: 2000 IU/m^2 IV (Day 3 + Day 17)
- Dexamethasone: 40 mg/day orally from Day 1 to Day 4

Supportive care included hydration with saline and bicarbonates, as well as folinic acid rescue following methotrexate administration. Radiotherapy was not performed due to advanced-stage disease with systemic and central nervous system involvement, where systemic chemotherapy remains the mainstay of treatment. The patient underwent the sixth cycle and demonstrated a partial metabolic response on FDG PET-CT, with a Deauville score of 4 (Table 2).

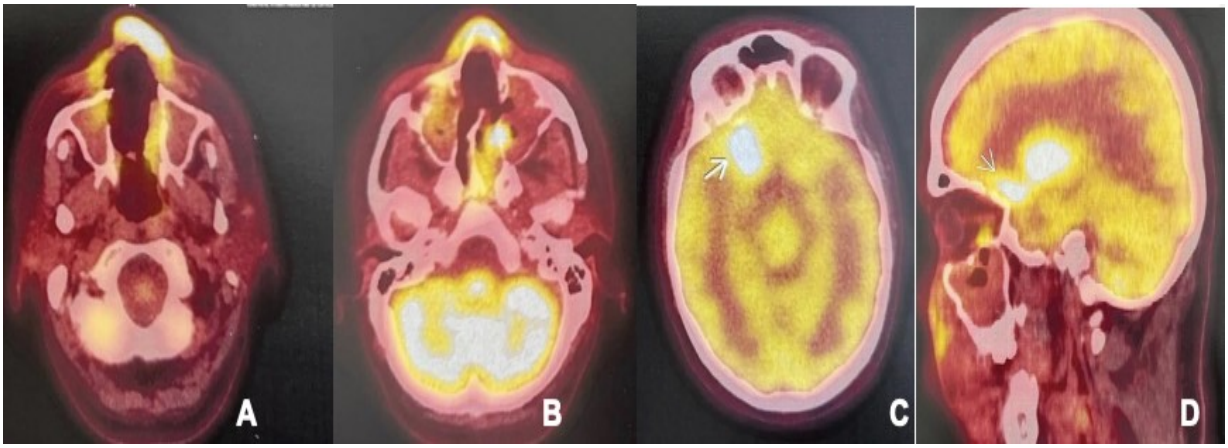

Figure 3: 18F-FDG PET-CT imaging demonstrating hypermetabolic activity in the nasosinusal region (A, B) and focal cerebral uptake in the right frontal lobe (C, D).

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

Stage	Definition
I	Involvement of a single lymph node region or a single extralymphatic site (IE)
II	Involvement of ≥2 lymph node regions on the same side of the diaphragm
II E	Stage II with contiguous involvement of a single extranodal site
III	Involvement of lymph node regions on both sides of the diaphragm, which may include the spleen
IV	Diffuse or disseminated involvement of one or more extralymphatic organs (e.g., bone marrow, liver, central nervous system), with or without nodal involvement

Staging is performed using FDG PET-CT for FDG-avid lymphomas. Stages I–II are generally considered limited disease, while stages III–IV represent advanced disease. Stage IV indicates non-contiguous extranodal dissemination [1].

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

Score	Definition
1	No residual uptake above background
2	Uptake ≤ mediastinal blood pool
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately increased compared with liver
5	Uptake markedly increased compared with liver and/or new lesions
X (optional)	New areas of uptake unlikely related to lymphoma

Scores 1–3 are consistent with complete metabolic response (CMR) in most clinical settings.
Scores 4–5 suggest residual or progressive metabolic disease, requiring clinical correlation [2].

Discussion: -

Extranodal NK/T-cell lymphoma, nasal type, represents a biologically aggressive lymphoma entity with unique epidemiological, virological, and pathological features. Its strong association with EBV infection is a defining hallmark, with viral-driven oncogenesis mediated through latent gene expression (LMP1, LMP2) promoting proliferation, immune escape, and resistance to apoptosis [3], [4], [5]. From an epidemiological perspective, ENKTL demonstrates marked geographic variation in its distribution. It is significantly more prevalent in East Asia and Latin America, where it accounts for approximately 5–10% of all non-Hodgkin lymphomas, compared to less than 1% in Western populations [4], [6]. This disparity is likely attributable to differences in EBV strain variants, host genetic

susceptibility, and environmental factors [5], [7]. The disease predominantly affects middle-aged males, although younger individuals may also be affected, particularly in endemic regions [4].

A major issue highlighted by our case is the diagnostic delay, which remains a well-recognized challenge in ENKTL. The initial clinical presentation often overlaps with benign inflammatory or autoimmune conditions, particularly granulomatosis with polyangiitis (GPA). Both entities may present with destructive midline lesions, sinus involvement, and nonspecific radiological findings. However, the absence of ANCA, the rapid progression, and the presence of extensive necrosis should prompt reconsideration of the diagnosis [8], [9]. In this context, our case illustrates a classical but critical diagnostic pitfall. Histopathological confirmation remains complex. The angioinvasive nature of ENKTL leads to ischemic necrosis, frequently resulting 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, early integration of immunohistochemistry and EBV detection (EBER) is essential to avoid misdiagnosis [4], [5]. From a radiological perspective, conventional CT imaging lacks specificity and may fail to differentiate ENKTL from infectious or inflammatory processes. In contrast, ^{18}F-FDG PET-CT has emerged as an essential tool, not only for staging but also for detecting occult systemic involvement and guiding biopsy sites [10], [11], [12]. This case is particularly noteworthy due to the rare association of sinonasal ENKTL with cerebral involvement at diagnosis. Such presentation remains uncommon and poses a significant diagnostic and therapeutic challenge.

CNS involvement in ENKTL is uncommon, with reported incidence ranging from 2% to 9%, but it carries a particularly poor prognosis [13], [14]. It is typically associated with advanced-stage disease, high EBV DNA load, and aggressive biological behavior [13], [14]. The mechanisms underlying CNS dissemination remain incompletely understood but may involve hematogenous spread facilitated by angioinvasion or direct extension from adjacent structures [13], [14], [15]. Histologically, ENKTL typically shows an angiocentric and angiodestructive lymphoid infiltrate associated with prominent coagulative necrosis and apoptosis. The neoplastic cells are usually medium sized, although cytologic variability is common, and they are characteristically accompanied by a marked inflammatory background. On immunohistochemistry, tumor cells typically express cytoplasmic CD3ε, CD56, and cytotoxic molecules such as granzyme B, TIA-1, and perforin, while surface CD3 is usually absent. Demonstration of EBV in tumor cells by EBER in situ hybridization is considered essential for diagnosis [4].

Therapeutically, ENKTL is characterized by intrinsic resistance to anthracycline-based chemotherapy due to P-glycoprotein-mediated drug efflux. This has led to the development of asparaginase-based regimens, such as SMILE (dexamethasone, Methotrexate, Ifosfamide, L-asparaginase, Etoposide) and MOGAD (Methotrexate, Oxaliplatin, Gemcitabine, Asparaginase, Dexamethasone), which exploit the metabolic vulnerability of NK/T lymphoma cells lacking asparagine synthetase [4],[13]. These protocols have significantly improved response rates, particularly in advanced or refractory disease [4],[13]. Management of ENKTL depends primarily on the disease stage and the risk profile. In localized early-stage nasal ENKTL, radiotherapy remains an essential component of curative therapy, and current practice generally combines it with non-anthracycline chemotherapy, delivered in sequential, concurrent, or sandwich schedules [4],[7]. Curative radiotherapy doses of approximately 50–54 Gy are commonly used in localized nasal disease to optimize locoregional control [4],[7]. On the other hand, advanced-stage or disseminated ENKTL requires systemic asparaginase-based chemotherapy as the main therapeutic backbone, since anthracycline-based regimens are associated with inferior outcomes [4],[6]. The role of CNS-directed therapy (intrathecal chemotherapy or high-dose methotrexate) remains controversial, with no standardized approach currently established. Similarly, consolidation with hematopoietic stem cell transplantation may be considered in selected high-risk patients, although evidence is limited and heterogeneous [13], [15].

Conclusion: -

ENKTL should be considered in any destructive midline lesion, especially in cases with negative initial biopsies. Early use of advanced imaging and repeated biopsies is essential to avoid diagnostic delay. Central nervous system involvement, although rare, significantly worsens prognosis and requires aggressive multidisciplinary management.

Ethical approval: -

This study was conducted in accordance with the Declaration of Helsinki.

Informed consent: -

Informed consent was obtained from the patient for publication of this case report and accompanying images.

Conflict of interest: -
The authors declare no conflict of interest.

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