sinusitis

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Case Report

Nasal-Type Natural Killer/T-Cell Extranodal Lymphoma

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Abstract

Nasal-type extranodal natural killer/T-cell lymphoma (ENKTL) is a rare, aggressive non-Hodgkin lymphoma associated with the Epstein–Barr virus (EBV). It predominantly affects middle-aged men and is most common in East Asia and Latin America. Due to its nonspecific symptoms, including nasal obstruction and discharge, ENKTL is frequently misdiagnosed as chronic rhinosinusitis or fungal infection, leading to delays in diagnosis and treatment. This case report presents a 46-year-old Algerian male with persistent nasal obstruction, foul-smelling nasal discharge, and progressive midfacial destruction. Multiple biopsies initially suggested chronic rhinosinusitis with fungal infection, delaying the definitive diagnosis. Subsequent deep biopsies confirmed ENKTL through histopathological and immunohistochemical analysis. ENKTL is characterized by its locally invasive nature, leading to necrotizing lesions and midfacial destruction. Histopathological confirmation through multiple well-targeted biopsies is crucial to prevent misdiagnosis. However, the prognosis remains poor, with a 5-year survival rate ranging from 20% to 65%.

Keywords: extranodal NK/T-cell lymphoma; nasal type lymphoma; Epstein–Barr virus; lymphoma

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1. Introduction

Lymphomas constitute a complex and diverse group of malignant tumors of the reticuloendothelial and lymphatic systems. They primarily affect the lymph nodes, spleen, and other extranodal tissues. They represent 3–5% of all malignant tumors, with non-Hodgkin lymphomas accounting for 60% of all lymphoma cases [1,2]. Nasal lymphomas are extremely rare; they represent only 0.2% to 2% of all lymphomas [2]. Additionally, they generally carry a poor prognosis [2,3], as these lesions are often detected late due to their variable morphological characteristics and inconsistent localization in the body, making timely treatment challenging [2].

Nasal-type extranodal natural killer/T-cell lymphoma (ENKTL) is a highly invasive form of non-Hodgkin lymphoma that primarily involves the upper aerodigestive tract and has a predilection for the nasal cavities, nasopharynx, and paranasal sinuses [2,3]. It frequently affects middle-aged men and is strongly associated with the Epstein–Barr virus (EBV). Its incidence is higher in East Asia and Latin America, where EBV infection in young children is widespread [4]. The role of EBV in ENKTL's pathogenesis is well established; EBV-encoded RNA is consistently detected in neoplastic cells by in situ hybridization and is considered a diagnostic criterion [4,5].

Clinically, nasal-type ENKTL presents a diagnostic challenge due to its non-specific and often misleading symptomatology. The initial manifestations may mimic benign

conditions such as chronic rhinosinusitis or nasal polyposis, with symptoms including nasal obstruction, rhinorrhea, epistaxis, facial pain, or swelling. As the disease progresses, patients may develop ulceration, tissue necrosis, and the perforation of the nasal septum or hard palate. These features are due to the angiodestructive nature of the lymphoma, which leads to ischemic necrosis and superimposed infections [4,5].

Imaging studies, particularly MRI and PET-CT studies, play an important role in identifying tissue infiltration, local extension, and systemic involvement, but definitive diagnosis requires the histopathological examination of biopsy samples; repeated or multiple biopsies may be necessary due to the often necrotic nature of the initial specimens [5,6].

The management of ENKTL has evolved significantly over the past two decades. Despite therapeutic advances, the prognosis of ENKTL remains poor, especially in disseminated or refractory cases [5].

We report a case of nasal-type T/NK-cell extranodal lymphoma diagnosed after multiple biopsies at a stage of extensive locoregional destruction.

2. Case Report

The patient, B.A., is a 46-year-old male from Bejaia, Algeria. He is married and has three healthy children. He has been working as an office clerk since 2013 and as a livestock farmer (cattle and goats) since 2015. His medical history includes substance abuse. He was admitted for the management of crusty rhinitis.

The illness began six months earlier, marked by persistent bilateral nasal obstruction, foul-smelling nasal discharge, brown nasal crusts, diffuse headaches, facial pain, and dysosmia characterized by cacosmia. These symptoms prompted the patient to seek medical consultation, where symptomatic treatment was initiated.

Due to the lack of improvement, a facial CT scan was performed, revealing the bilateral polypoid filling of the maxillary sinuses, associated with the mucosal thickening of the middle and inferior turbinates (Figure 1).

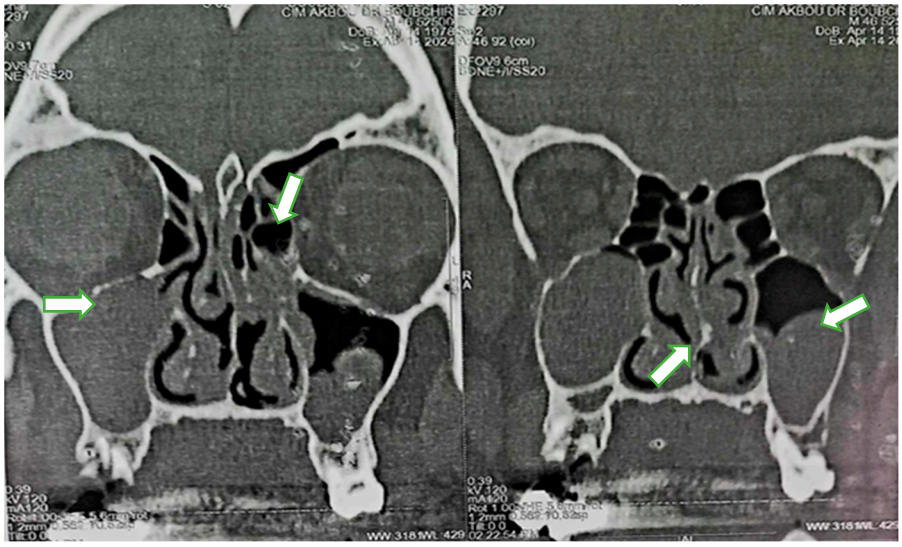

Figure 1. A CT scan was performed, revealing the bilateral polypoid filling of the maxillary sinuses, associated with the mucosal thickening of the middle and inferior turbinates (white arrows).

The patient underwent bilateral middle meatal antrostomy with the removal of crusts and multiple biopsies of the nasal mucosa in 31 August 2024. Histopathological examination revealed chronic rhinosinusitis with polyps and fungal superinfection, with no evidence of malignancy.

Worsening symptoms marked the patient's post-operative recovery. These included the development of a palatal ulcer that resulted in a buccal–nasal communication measuring approximately 1 cm in length and 0.5 cm in width, with the slight swelling of the nasal pyramid. General symptoms such as night sweats, weight loss, and a paroxysmal high fever appeared. Despite prolonged antibiotic and antifungal therapy, the treatment did not lead to improvement.

After 10 days of treatment and persistent symptoms, a bacterial culture was performed, revealing positivity for *E. coli* and *Pseudomonas* sp.

The patient presented with mild centro-facial swelling, the collapse of the nasal pyramid, and significant osteo-cartilaginous destruction involving the septum, turbinates, and nasal floor, along with greenish, foul-smelling crusts. The buccal–nasal communication had widened to approximately 4 cm in the anteroposterior axis and 2 cm in width, covered by whitish exudate, with the appearance of ulcerative lesions extending to the soft palate, uvula, and the left postero-lateral pharyngeal wall (Figure 2).

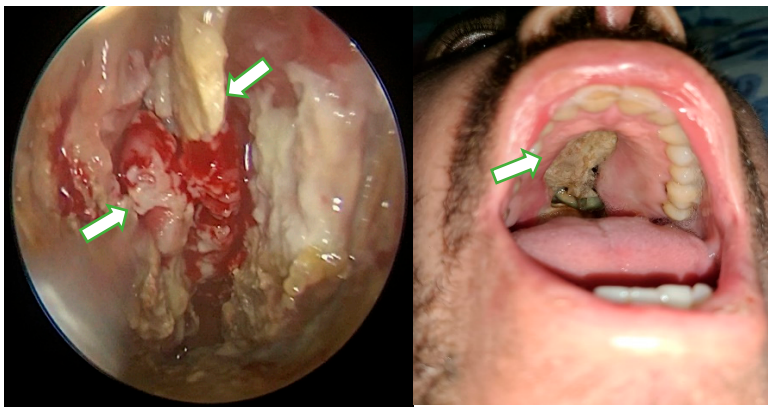

Figure 2. Inflammatory lesions with extensive endonasal and palatal destruction (white arrows).

Laboratory tests showed an inflammatory syndrome with CRP at 26 mg/L, candidiasis on mycological examination, and negative serologies for HIV, HBV, HCV, syphilis, and brucellosis, as well as a negative tuberculin skin test.

A second CT scan indicated chronic rhinosinusitis with extensive septal, turbinate, and bony palate destruction (Figure 3). Another nasal biopsy under general anesthesia with the cleaning and debridement of adherent crusts was performed on 2 October 2024. The histopathological findings indicated necro-inflammatory changes.

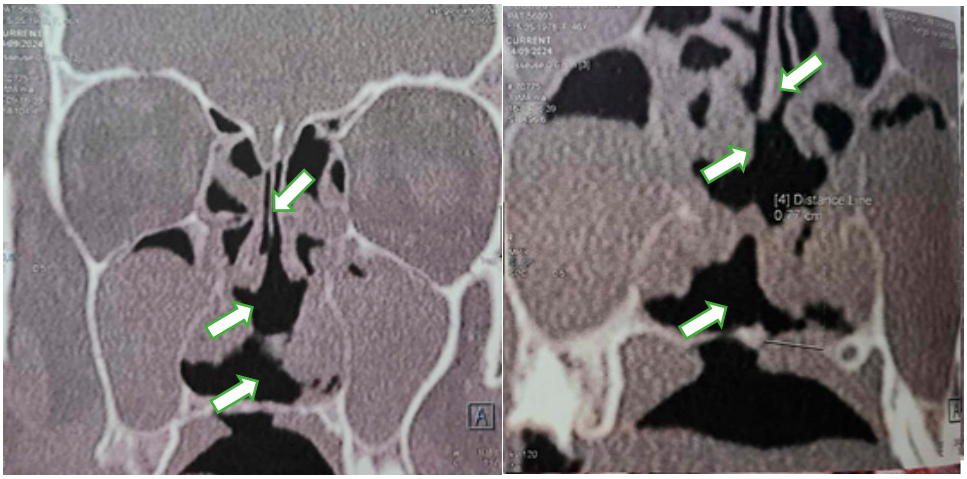

Figure 3. CT scan indicated chronic rhinosinusitis with extensive septal, turbinate, and bony palate destruction (white arrows).

Given the lack of improvement and worsening locoregional lesions despite antibiotic, antifungal, and anti-inflammatory treatments, another surgery was performed under general anesthesia on 23 November 2024 for deep and broad biopsies, including of healthy-looking adjacent tissues. The patient underwent endonasal endoscopic surgery with multiple deep biopsies, particularly at the edges of the necrotic lesions and passing through the peripheral healthy tissue to avoid biopsies of the necrotic tissue, which could distort the results. Histopathological examination confirmed nasal-type T/NK-cell lymphoma, further corroborated by immunohistochemical studies, which revealed the expression of CD56 and granzyme B on all tumor cells and EBV on the majority of cells and the presence of Ki67 at 70%.

The patient was referred to hematology for chemotherapy. In hematology, he benefited from a computed tomography (CT) scan of his neck, chest, abdomen, and pelvis (with iodinated intravenous contrast), as well as head and neck magnetic resonance imaging (MRI) and a fluorodeoxyglucose positron emission tomography–computed tomography (Pet scan), which found a high index of ENT and pulmonary tumor proliferation classified as stage IV according to the Ann Arbor classification.

A chemotherapy treatment was initiated based on the MOGAD protocol, combining high-dose methotrexate (HD-MTX), Ondansetron, Gemcitabine, Asparaginase, and Dexamethasone.

Unfortunately, the patient passed away after this chemotherapy.

3. Discussion

Nasal-type extranodal NK/T-cell lymphoma (ENKTL) is a non-Hodgkin malignant lymphoma (NHL) typically found in the upper airways [5]. The WHO [6] has classified it under the "nasal-type lymphoma" category.

ENKTL is associated with the Epstein–Barr Virus (EBV), likely due to the introduction of oncogenic proteins that induce the malignant transformation of T/NK cells [7,8]. It is endemic in East Asia and South America, where it accounts for 7–10% of all NHL cases. It is much less common in North America and Europe, representing less than 10% of NHL cases [9]. Geographic variations in EBV strains may explain this distribution [10].

Sinonasal ENKTL primarily affects middle-aged men, typically in their sixth decade [9,11]. It develops in the sinonasal cavities in 70% of cases, while 20–30% of cases occur at other sites such as the skin, salivary glands, liver, lymph nodes, gastrointestinal tract, lungs, and testicles [12].

Nasal obstruction and discharge are the most common initial symptoms [13]. Due to its locally aggressive potential, ENKTL often causes the perforation of the hard palate, the destruction of midfacial structures (e.g., sinonasal cavities and the nasopharynx), and damage to the cartilaginous and bony structures of the nose, leading to significant local deformation and the potential involvement of cranial nerves and meninges [14].

In our patient, the initial presentation mimicked chronic rhinosinusitis, confirmed by the histological analysis of surgical biopsy samples. Later, the possibility of sinonasal fungal infection further delayed diagnosis.

Literature reports have indicated that the average delay between the symptom onset and histopathological confirmation ranges from 2 to 12 months (Miyake et al.) [15] and can be up to 21.5 months (Sands et al.) [16]. Progressive tissue necrosis, ulceration, and crusting often result in secondary bacterial and fungal infections, leading to misdiagnosis and extended antibiotic and antifungal treatments, thereby further delaying diagnosis [17].

A persistent or recurrent fever of unknown origin, weight loss, or night sweats should always prompt the consideration of lymphoma [17]. Soon et al. [18] suggested that lym-

phoma should be suspected in patients with sinonasal symptoms and a persistent or recurrent fever unresponsive to treatment.

Diagnosis requires the histopathological analysis of multiple biopsies, including samples from healthy-appearing tissue at the periphery of necrotic areas to avoid false negatives. Biopsy specimens must be of a good quality and promptly sent for fresh-tissue analysis by an experienced pathologist [17,19].

In our case, multiple nasal, sinus, and palatal biopsies from more extensive lesions were necessary to achieve a conclusive result.

In the management of nasal cavity tumors, particularly when these lesions are isolated, the clinician must bear in mind that a lymphoma of this type may present as simple chronic rhinosinusitis or even of fungal origin. However, the unfavorable evolution of this type of tumor, despite well-managed treatment with antibiotics, antifungals, and anti-inflammatory agents, should draw the clinician's attention and motivate him not to hesitate to perform multiple biopsies passing through the surrounding tissues all around the central necrosis, to repeat them as often as necessary, and, above all, to direct the pathologist towards this type of tumor [4,20].

In this context, the use of advanced diagnostic tools is essential. MRI provides better visualization of tumor infiltration and locoregional extension. 18F-fluorodeoxyglucose positron emission tomography–computed tomography (18F-FDG PET-CT) is also valuable for staging, identifying secondary lesions, and monitoring the therapeutic response. Histological and immunohistochemical analyses (positivity for CD3, CD56, and granzyme B) remain indispensable to confirm the T/NK phenotype. The role of the Epstein–Barr virus (EBV), commonly associated with this lymphoma subtype, justifies the use of specific molecular markers such as circulating EBV-DNA, detectable via PCR [11,17].

Chemo-radiotherapy is the standard treatment for T/NK-cell lymphomas. Currently, several therapeutic protocols are available, with indications closely linked to the stage of the disease. In refractory or relapsed cases, autologous (auto-HCT) or allogeneic (allo-HCT) hematopoietic stem cell transplantation may be considered. Immunotherapy is an option for patients with relapses or chemotherapy resistance [21–23].

Despite initiating chemotherapy, our patient passed away after the third session.

The prognosis of ENKTL depends on the primary site of lymphoma. While the extranodal type is generally very aggressive, the nasal type has variable outcomes, ranging from a good treatment response to death from disseminated disease despite aggressive treatment [24]. The median survival of ENKTL patients is 13–42 months, with a 5-year survival rate of 20–65% [25,26].

4. Conclusions

Nasal-type extranodal NK/T-cell lymphoma (ENKTL) is an aggressive non-Hodgkin lymphoma characterized by necrotizing, locally destructive lesions. A diagnosis is often ambiguous and difficult to establish through clinical examination, imaging, and even the histopathological analysis of biopsy specimens. Thus, it is crucial to perform multiple broad biopsies from areas distant from necrotic tissues to ensure the collection of adequate diagnostic material.

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Informed Consent Statement: Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding authors.

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Abbreviations

The following abbreviations are used in this manuscript:

Auto-HCT	Autologous hematopoietic stem cell transplantation
Allo-HCT	Allogeneic hematopoietic stem cell transplantation
CRP	C-reactive protein
DNA	Deoxyribonucleic Acid
EBV	Epstein–Barr virus
ENKTL	Nasal-type extranodal NK/T-cell lymphoma
ENT	Ear, Nose, and Throat
18F-FDG PET-CT	18F-fluorodeoxyglucose positron emission tomography–computed tomography
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
MRI	Magnetic resonance imaging
NHL	Non-Hodgkin malignant lymphoma
PCR	Polymerase Chain Reaction
T/NK	T-lymphocyte/natural killer
WHO	World Health Organization

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