

CASE REPORT

Natural Killer/T-cell Lymphoma of Nose—A Diagnostic Dilemma and Its Clinical Impact: A Case Report

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ABSTRACT

Aim: To study the clinical course, investigatory findings, and the need for timely diagnosis of extranodal natural killer/T-cell lymphoma, nasal type (ENKTL-NT) and to understand the diagnostic difficulties and treatment options.

Background: Extranodal natural killer/T-cell lymphoma, also known as “Stewart’s Granuloma,” is a rare non-Hodgkin’s lymphoma originating in the nasal cavity. It mostly arises from the malignant transformation of cytotoxic T cells. It is characterized by aggressive and rapidly progressing necrotic lesions involving the mid face, principally the nose and palate. It is a diagnosis made by the exclusion of other infective and granulomatous mid-facial lesions.

Case description: A 35-year-old male presented with bilateral nasal obstruction for 20 days, left cheek swelling for 2 days, associated with progressive left-eye swelling and nasal regurgitation of fluids. Local examination showed extensive nasal crusting, and septal and palatal perforation. No clinical improvement was seen with empirical antibiotics and antifungals. Immunohistochemistry (IHC) was positive for cluster of differentiation (CD) 3 and 56, which led to a diagnosis of ENKTL-NT, and chemotherapy was started. However, he succumbed to coronavirus disease-2019 (COVID-19) disease during the course of treatment.

Conclusion: Extranodal natural killer/T-cell lymphoma, nasal type is an aggressive form of non-Hodgkin’s lymphoma with a clinical picture masquerading as acute invasive fungal sinusitis, mid-face granulomatous lesions, etc. This leads to delayed diagnosis, which in turn affects morbidity and mortality. Therefore, a timely and precise diagnosis with aggressive treatment is a must.

Clinical significance: Extranodal natural killer/T-cell lymphoma, nasal type, is rare with rapid and aggressive local tissue necrosis and progression. Its refractory behavior to our initial treatment regimens raised suspicions. In the current challenging times, trying to decrease misdiagnosis is of paramount importance. Through this case report, we aim to alert fellow practitioners to keep this entity in the differential diagnosis of such an aggressive clinical picture with a short history.

Keywords: Case report, Lymphoma, Nasal midline swelling, Sinonasal malignancy.

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BACKGROUND

Extranodal natural killer/T-cell lymphoma, nasal type (ENKTL-NT), is a rare and aggressive mid-facial necrotizing lesion that is characterized by destructive, mucosal lesions of the upper aerodigestive tract. A strong association with Epstein–Barr virus (EBV) has been found in nearly all cases with expression of markers of NK cells and less frequently T cells.¹ Common presenting complaints include rhinorrhea, epistaxis, nasal stuffiness, and pain. Constitutional symptoms like fever and malaise are unusual and are seen in advanced cases. Here, we present a case of ENKTL-NT in a 35-year-old male with a short clinical history.

CASE DESCRIPTION

A 35-year-old male presented with bilateral nasal obstruction for 20 days, left cheek swelling with pain and headache for 2 days with a history of endoscopic sinus surgery, elsewhere, 2 weeks back. External examination showed a soft mildly tender swelling under the left eye and firm tender swelling of the left nasal vestibule, nasolabial fold, and upper lip was present (Fig. 1A). The vestibular swelling was covered with a black eschar. Nasal endoscopy showed extensive thick crusts in bilateral nasal cavities with large anterior septal perforation (Fig. 1B) leading us to make a provisional diagnosis of secondary atrophic rhinitis. Empirical antibiotics along with nasal douching with antioxaena solution were advised. There was progressive left ocular swelling rapidly progressing with

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inability to open the eye, associated with headache which was excruciating and continuous. There was a history of low-grade fever without chills or rigors associated with nasal regurgitation of fluids and discharge from the left upper tooth for 10 days. There was no history of epistaxis, vision disturbances, or nasal discharge. He was known hypertensive on irregular medication.

Repeat nasal endoscopy showed destruction of upper and lower lateral cartilages on the left with the nasal process of maxilla appearing naked. Oral examination revealed a small midline palatal perforation covered with slough. The ocular examination was normal.

All routine blood and urine investigations were within normal limits. Viral markers and screening for syphilis were negative. Reverse transcriptase polymerase chain reaction (RT-PCR) for coronavirus disease-2019 (COVID-19) and Mantoux test also tested negative. Skin smears from ear lobes showed no evidence of Hansen's disease. Antineutrophil cytoplasmic antibody (c-ANCA), a serological marker for Wegener's granulomatosis was also negative. Nasal endoscopic smears were positive for methicillin-resistant *Staphylococcus aureus* (MRSA) and fungal elements. Histopathological examination (HPE) revealed areas of necrosis with proliferating capillaries, neutrophil infiltration, and atypical lymphocytes with fungal hyphae. Periodic acid Schiff and Gomori's methanamine silver stain showed evidence of *Candida* spp. following which Liposomal Amphotericin B (5 mg/kg) was started assuming the cause to be invasive fungal sinusitis.

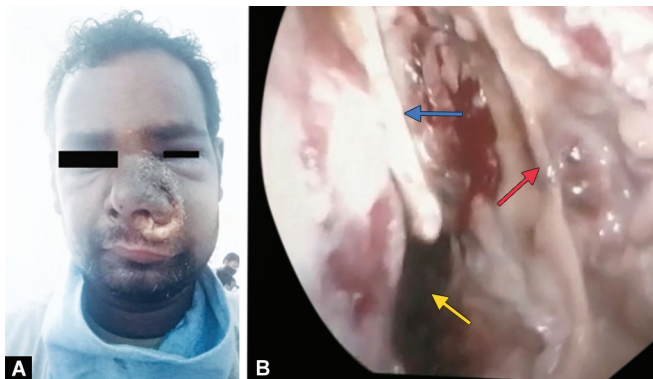
Computerized tomography of paranasal sinuses (CT-PNS) showed soft tissue swelling of the left vestibule (Fig. 2A), large anterior septal perforation, and bony defect of the hard palate on the right (Fig. 2B). Magnetic resonance imaging (MRI) brain and orbits with contrast was done to rule out intracranial or orbital extension and cavernous sinus thrombosis. Ultrasonography (USG) abdomen showed mild hepatosplenomegaly.

As there was no clinical improvement, deep biopsies were taken again and sent for HPE. Sections showed large irregular fragmented tissue lined by stratified squamous epithelium with focal ulceration, composed of necrotic tissue, foci of lymphoid cells, and hemorrhage with additional atypical cells and bare nuclei, suggestive of ENKTL-NT (Fig. 3). Immunohistochemistry (IHC) was positive for CD3 and CD56, and negative for CD20. Also, Ki67 was focally high. Flouro-deoxy glucose positron emission tomography with non-contrast computerized tomography (FDG-PET NCCT) of the whole body showed moderately increased FDG concentration in the ulceroproliferative growth of left premaxillary region and nasal cavity with nasal septal perforation without orbital or intracranial extension with standardized uptake value (SUV) of 6. It was, therefore, staged as T2 N0 M0 according to the TNM staging of ENKTL-NT.

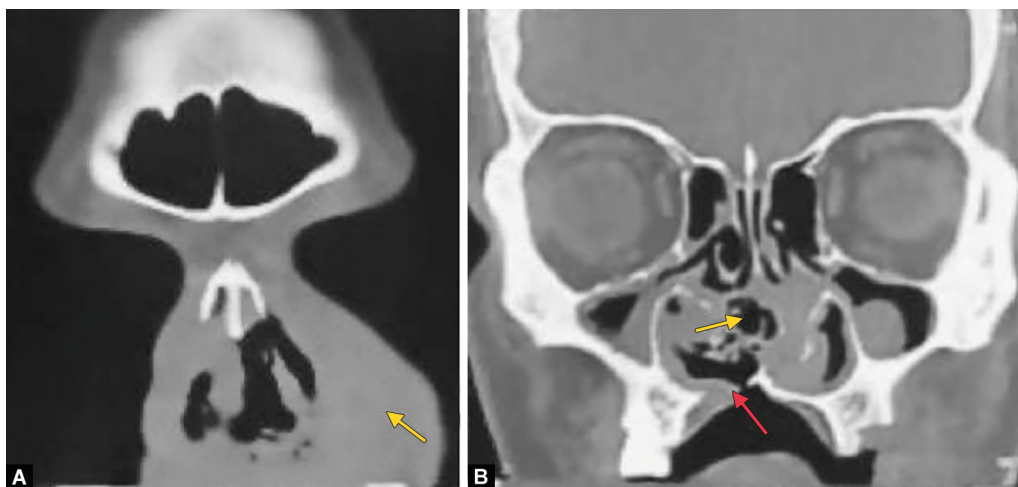
Following histopathological confirmation, the patient was referred to the department of medical oncology. A chemotherapy regimen including dexamethasone, ifosfamide, etoposide, carboplatin (DeVIC) was started. The patient had symptomatic improvement over 10 days of starting chemotherapy. However, we unfortunately lost the patient to COVID-19 infection.

DISCUSSION

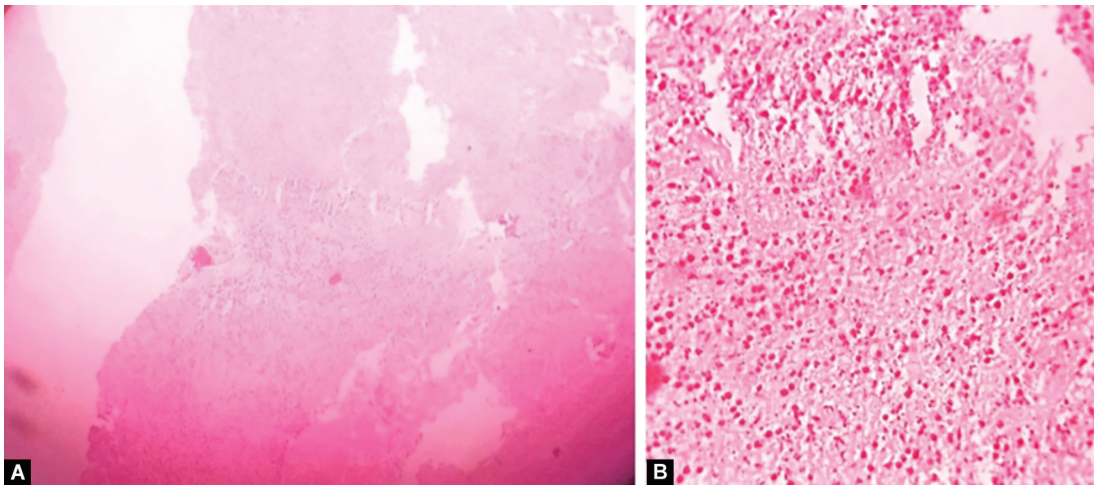
Extranodal natural killer/T-cell lymphoma, nasal type accounts for less than 10–15% of non-Hodgkin's lymphomas and is the second most common primary sinonasal malignancy. Amongst them the most common and well characterized are the nasal type.² The term "lethal midline granuloma" was first coined for this clinical picture by McBride in 1897.^{2,3} Later various other names were in use like angiocentric T-cell lymphoma, angiocentric immunoproliferative lymphoma and polymorphic reticulosis.⁴ Furthermore, ENKTL-NT was defined in 2008 World Health Organization (WHO) classification as a "predominantly extranodal lymphoma characterized by



Figs 1A and B: (A) Clinical picture showing left nasovestibular swelling covered with eschar and associated left ocular swelling with minimal eye opening; (B) Endoscopic picture showing anterior septal perforation (yellow arrow), naked nasal process of the maxilla (red arrow), and naked perpendicular plate of ethmoid (blue arrow)



Figs 2A and B: (A) Computerized tomography of paranasal sinuses (CT-PNS) coronal cuts showing left homogenous vestibular swelling (yellow arrow); (B) Coronal cuts showing anterior septal defect (yellow arrow) and left bony palatal defect (red arrow)



Figs 3A and B: (A) Low-power microscopic picture; (B) High-power microscopic picture showing diffuse lymphocyte infiltrate with focal areas of necrosis and atypical cells

vascular damage and destruction, prominent necrosis, cytotoxic phenotype and association with EBV.⁵ Representing a group of rare tumors of natural killer (NK) and NK/T cells, the WHO classified NK/T-cell lymphoma into three different types such as (A) extranodal NK/T-cell lymphoma, nasal and extranasal types, (B) NK cell leukemia, and (C) blastic variant (CD4 and CD56 positive).⁶ The disease most commonly occurs around the fourth and fifth decades with a male-to-female ratio of 8:1 to 2:1.⁷

Microscopically, the lesions usually look like necrotic granuloma with an angiocentric growth pattern and zonal necrosis.³ Also, NK cells along with T cells arise from a common progenitor in the bone marrow. Furthermore, NK cells are cytolytic and usually act against tumor cells and infected cells without prior sensitization and express the CD56 marker. However, due to common origin, NK cells also express T-cell markers (CD2 and CD20). Approximately 10–20% of these cases have skin involvement.^{3,8} Epstein–Barr virus RNA is present in 80–100% of cases of nasal NK/T cell lymphoma.⁹ Zhong et al. reported that most upper aerodigestive NK/T cell lymphomas were genotypically of NK cell origin and only a few belong to T-cell lineage.¹⁰

The most common presenting complaint is nasal obstruction with or without nasal discharge. Oral and nasal ulcer with perforation of the nasal septum and mutilation of surrounding tissues eventually occurs.¹¹ Nasal NK/T-cell lymphoma is an aggressive lesion with rapid evolution and high mortality if not treated timely. The high mortality is due to septicemia, invasion into blood vessels leading to intracranial complications.

There are several infective, inflammatory, and benign conditions, rather more common and less morbid but with a similar clinical spectrum. The non-specific nature of its presentation, its rarity, and lack of previous experience in encountering this entity by the treating practitioner can all contribute to misdiagnosis. Even with an early diagnosis and prompt treatment, the chances of survival are poor. In our case, owing to the history of prior nasal surgery elsewhere and extensive rusting led us to think of secondary atrophic rhinitis with superadded infection. Worsening symptoms with progressive external deformity and positive fungal elements on potassium hydroxide (KOH) mount caused us to think of acute invasive fungal sinusitis and start systemic antifungals. However, with persisting symptoms and fungal culture turning negative, we

Table 1: TNM classification for ENKTL-NT¹⁶

Stage	Features
T1	Confined to the nasal cavity
T2	Anterior ethmoidal sinus, maxillary sinus, and hard palate
T3	Posterior ethmoidal sinus, sphenoid sinus, frontal sinus, and oral cavity
T4	Alveolar process, infratemporal fossa, and intracranial fossa
N0-N1	With or without nodular compromise
M0-M1	Local or far metastases

evaluated the patient for other infective and inflammatory nasal conditions such as tuberculosis, leprosy, Wegener's granulomatosis, sarcoidosis, rhinoscleroma, and syphilis. All these conditions present with non-specific complaints like nasal obstruction, nasal discharge, epistaxis, crusting, mid face deformities etc. which are similar to that of ENKTL-NT. Hence, leading to dilemma in swift and precise diagnosis.

The estimated 5-year overall survival for ENKTL-NT is between 40 and 50%.¹² Survival is heavily dependent on stage at diagnosis. Long-term follow-up suggests a continued risk of relapse up to 10 years from diagnosis.^{13,14}

There was no standard staging system thus far for ENKTL owing to poor understanding of the disease in the past due to its rarity. The Ann Arbor (AA) staging system was originally designed for Hodgkin's lymphoma. However, this staging method has limited utility in defining the prognosis and management planning, as it is extranodal.¹⁵ To overcome these deficiencies, the TNM staging system was proposed (Table 1).¹⁶

Treatment of ENKTL-NT has evolved over the years. Early studies showed that anthracycline-based chemotherapy regimens, such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), are largely ineffective in ENKTL-NT.¹⁷ Due to this, radiotherapy at doses ranging from 45 to 60 Gy was adopted as the treatment of choice. Eventually, concurrent chemoradiation therapy (CCRT) was developed which included various regimens such as DeVIC; etoposide, methyl prednisone, cytarabine, and cisplatin (ESHAP); and etoposide, ifosfamide, cisplatin, and dexamethasone

(VIPD) in 4–5 cycles. Based on French studies in relapsed/refractory ENKTL-NT, L-asparaginase appeared effective even as a single agent. Consequently, L-asparaginase based regimens such as etoposide, cyclophosphamide, Mensa, dexamethasone, methotrexate, and asparaginase (SMILE) were introduced in the front-line treatment approach. High-dose chemotherapy with autologous hematopoietic stem cell transplantation (AH SCT) for aggressive relapse.¹⁸ A better prognosis is expected with early and accurate diagnosis along with aggressive treatment with CCRT. The role of a surgeon is limited to debridement and securing the airway when needed, after a prompt diagnosis.

CONCLUSION

Nasal NK/T-cell lymphoma is an aggressive disease with a rapid downhill course. When left untreated, it has a very high mortality rate due to septicemia and/or intracranial extension. Combined chemotherapy followed by involved field external irradiation is believed to improve survival rates. The confusing clinical picture poses as a diagnostic dilemma and calls for a high degree of suspicion for correct diagnosis to prolong patient survival.

Clinical Significance

Extranodal natural killer/T-cell lymphoma, nasal type, is rare with rapid and aggressive local tissue necrosis and progression. Its refractory behavior to our initial treatment regimens raised suspicion. Given its poor survival rate of 5 despite an accurate diagnosis, trying to decrease the misdiagnosis is of paramount importance. Through this case report, we aim to alert fellow practitioners to keep this entity in the differential diagnosis of such an aggressive clinical picture with a short history.

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