Extranodal NK/T-Cell Lymphoma, Nasal-Type: Case Report and Review of the Literature

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Abstract:
Extranodal NK/T-Cell Lymphoma is a rare and deadly malignancy that develops from natural killer or cytotoxic T cells. It is strongly associated with Epstein-Barr virus infection, and failure to detect these DNA fragments raises concerns about the adequate diagnosis. While it commonly presents in the nasal or upper aerodigestive tract, it has also been reported in extranasal sites. Asparaginase-containing regimens remain effective in treating extranodal NK/T-cell lymphoma, and their adoption has improved the overall survival rate in patients. We present an uncommon case of extranodal NK/T-cell lymphoma, nasal-type, in an 84-year-old male and provide a brief review of the literature.

Keywords: Extranodal NK/T-Cell Lymphoma, Non-Hodgkin Lymphoma, Nasal

Introduction:
Mature T-cell and natural killer (NK)-cell lymphomas (NKTL) compose a heterogeneous group of non-Hodgkin lymphomas. One of the most aggressive subtypes of this group is Extranodal NK/T-cell lymphoma, nasal type (ENKTL-NT). Extralymphatic NK/T-Cell Lymphoma (ENKTL) has a predilection for Asian and Latin American populations and accounts for 10% of all NHL and 30% of all extranodal lymphomas in these regions. However, it only accounts for roughly <1.5% of lymphomas in the United States. It appears to affect more males than females and commonly presents between the 4th and 6th decades of life. It is widely known for its association with Epstein-Barr virus (EBV) infections.

In part due to its rarity in US and Europe, lesions are often mistaken for invasive bacterial or fungal infections, delaying diagnosis and treatment. It manifests as necrotic and ulcerative lesions with notable vascular damage in the upper aerodigestive tract (e.g., nasal cavity, nasopharynx, paranasal sinuses, and palate). Less commonly, its presence has been documented in extranasal sites such as the skin, gastrointestinal tract, and testes. ENKTL appears most frequently in patients over the Age of 60 years, although studies have shown that it can be found in both geriatric and pediatric patients. The mortality rate is higher than in other lymphomas and has poorer response rates to radiation and Chemotherapy. Survival rates for this cancer are devastatingly low, with the average individual diagnosed at a late stage living only 20 months after diagnosis. Patients whose malignancy was identified in the early stages of the disease lived an average of 7 years post-diagnosis; survival for those with the end-stage illness at the time of diagnosis was less than seven months.

Case Presentation:
An 84-year-old man complained for six months of intermittent nasal obstruction, followed by two months of painless soft palate ulceration. The process eventually reached the hard palate, resulting in a fistula. Antibiotics and anti-inflammatory drugs failed to treat the condition. The patient’s foul-smelling discharge, halitosis, nasal bridge distortion, night sweats, weight loss, and central face swelling led the patient’s family to seek medical attention. The patient had controlled type II diabetes, hypertension, and a localized prostatic carcinoma that had been treated with surgery and radiation. On physical examination, a 4.5-3.5 cm irregular lesion with discharge and necrotic debris was observed on the hard palate, along with mild nasal crusting.

The nasal cavity was filled with a destructive midfacial mass on CT imaging. The nasal septum had been destroyed, revealing an irregular soft tissue mass measuring approximately 4.5 x 3.4 cm in the left and right lateral walls. There was no regional lymphadenopathy. The nasopharynx, palate, upper airways, and subcutaneous tissues were involved. On MRI, the lesion showed heterogeneous signal intensity, internal necrosis, and a significant enhancement of solid components. Tissue confirmation was recommended due to the tumor’s radiological suspicion of Extranodal NK/T-Cell Lymphoma, Nasal-Type.

Due to the necrotic nature of the obtained tissue, a non-diagnostic endoscopic incisional biopsy was non-diagnostic. A second tissue biopsy revealed stratified squamous mucosa with small- to medium-sized, highly
atypical lymphoid cells infiltrating the surrounding soft tissue. A bone marrow biopsy demonstrated the same type of cells seen in the nasal biopsy (Figure 1A,B,C). Tumor cells were positive for CD2, CD3 (cytoplasmic), CD30, CD43, and CD56, while negative for surface CD3, CD5, CD10, CD20, CD21, CD23, Cyclin-D1, CD4, CD8, CD7, CD57, cytokeratin and S100 (Figure 2A,B,C). The tumor was positive for Epstein-Barr virus (EBV). The diagnosis of Extranasal NK/T-Cell Lymphoma, Nasal-Type, was confirmed by histomorphology and immunohistochemistry. 60% nuclear staining with Ki-67 revealed a high proliferation rate of the tumor cells. Mutation in the p53 gene was observed. The treatment with radiation was started, but there was no response. The patient's CHOP chemotherapy was started, but it was not finished because the patient passed away five months after the initial diagnosis.

Discussion:

A distinct problem in diagnosing uncommon types of malignant lymphoma is the resemblance to many inflammatory or other neoplastic conditions. In addition, even pathologic differentiation can be troublesome since they mimic undifferentiated metastatic carcinomas by sharing diffuse growth patterns and cytologic atypia characteristics. 7 One of these uncommon lymphomas is NKTCL, a non-Hodgkin lymphoma, mostly extranasal, frequently of NK and (rare) T-cell origin, closely related to the Epstein-Barr virus (EBV). The World Health Organization (WHO) classifies NKTCL into nodal, extranodal (sometimes referred to as non-nasal)-cutaneous and other extranodal types, and disseminated (leukemic). 8 NK/T-cell lymphomas are almost always found in extranasal tissue of the nose, nasopharynx, or oropharynx, which are referred to clinically as nasal NK/T-cell lymphoma. 9 ENKTL frequently involves the nasal cavity and nasopharynx and occasionally occurs primarily in non-nasal areas, including the skin, gastrointestinal tract, lung, liver, salivary gland, and testis. The median age of ENKTL patients at diagnosis is around 50-55 years old. 10

The classic presentation often involves aerodigestive tract complications, such as nasal obstruction, epistaxis, and palatal perforation/ulceration. 1,5 Less commonly, they have been identified in the skin, gastrointestinal tracts, testis, and salivary glands. Cases of disseminated disease involving the liver, spleen, and bone marrow are rare and referred to as aggressive NK/T-cell leukemia/lymphoma. 6 Presentation includes facial and neck symptoms: Facial pain, diplopia, visual impairment, eyeball protrusion, eyelid ptosis, pupil anomalies, nasal obstruction, refractory sinusitis, Velo-palatal motor disturbances, cranial nerve neuropathies, intra-orbital, and intrasinus masses. Other associations include respiratory failure and liver and spleen enlargement. 11 NKTCL is rarely found in Caucasians or the Western population, having a prevalence estimated at around 0.17-1.15% of all non-Hodgkin lymphomas, with 45% of these having NKTCL origin. 12 ENKTL shows high prevalence in East Asia and South America but is rare in the Western World. According to the data from US Surveillance Epidemiology and End Results, the incidence of ENKTL in the United States has grown in recent years. The United States has increased in the past years with an estimated relative change of up to 10% per year. In US populations, ENKTL is also more prevalent among Asian Pacific descent and Hispanics than whites. 4

The CT and MR appearances of nasal NK/T-cell lymphoma are nonspecific, and the diagnosis requires histologic confirmation. However, the differential diagnosis of nasal NK/T-cell lymphoma should be included if the images present soft tissue of the nasal cavity with bony erosion or destruction; involvement of the orbital cavity, nasopharynx, and infratemporal fossa; and subcutaneous or nasolabial fold soft tissue infiltration, especially in Asian populations. 13 Given ENKTL's aerodigestive presence, separating it from other upper airway disorders (e.g., invasive fungal infections, Wegener's granulomatosis, and other malignancies) can be challenging. 1 Therefore, nasal endoscopy with direct visualization and biopsy, in addition to computed tomography (CT) or magnetic resonance imaging (MRI) of the head, is essential in the initial work-up ENKTL. 9,14 In our case, an initial biopsy was not diagnostic due to the excessive necrosis and degeneration of the obtained material, and a repeat biopsy was carried out with positive results. These tumors have a broad spectrum of cytology and can present with varying sizes of anaplastic cells, causing a diagnostic challenge. 2 Additionally, the histology and cell lineage alone are only sometimes discriminating. Therefore, the pathologist's role in diagnosing these lymphomas is critical, given their ability to understand and differentiate hematolymphoid cells and immunoprofiling. 4,6

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The universal association of ENKTL-NT with Epstein-Barr virus (EBV) across all ethnic groups suggests a common pathogenesis. Although the pathogenesis of Epstein-Barr virus-associated T/natural killer-cell lymphoproliferative diseases (EBV-T/NK-LPDs) is unclear, some evidence indicates that EBV infects T/NK cells during the primary infection. As it has been proposed in diffuse large B cell lymphoma, the integration of genomic structural alterations in ENKTL has identified three molecular subgroups related to the cell of origin of ENTCL (NK vs. T cell), pathogenic alterations, EBV sequences, and clinical outcome. EBV infection is the earliest event, leading to the susceptibility of NK and T cells to genomic alterations that together will result in the pathogenesis of ENKTCL. The model suggests that EBV infection is the earliest event, leading to the susceptibility of NK and T cells to genomic alterations that together will result in the pathogenesis of ENTCL. Consequently, these alterations influence the prognosis and therapy response. A previous study of cytological and cytogenetic features of malignant and nonmalignant EBV-positive natural killer (NK) cells suggested that EBV infection alone does not cause malignant transformation and that additional genetic abnormalities may be involved. The most established marker for disease monitoring in ENKTL is the EBV-DNA load in the peripheral blood detected by quantitative polymerase chain reaction (PCR) assay. Suzuki and colleagues reported that a high pretreatment plasma EBV-DNA level (>1000 copies/mL) was associated with a significantly lower OS in 32 ENKTL patients. In Liang Wang et al. study, their findings indicated that post-treatment EBV-DNA positivity can predict early relapse and poor prognosis for patients with early-stage NKTL in the era of asparaginase and may be used as an indicator of minimal residual disease.

While bone marrow involvement is rare, when present, it may present as a single malignant cell or as an aggregation of lymphocytes. Therefore, identifying EBV-encoded RNA can help identify malignant cells. In addition to histological interpretation, peripheral blood EBV polymerase chain reaction (PCR) may also be utilized. Although staging is essential when planning radiation therapy, it fails to consider the prognostic impact or treatment response rate. The Ann Arbor staging system is used to diagnose NKTL, but extranasal sites such as the aerodigestive tract, local invasion, and regional lymph node involvement are not considered. TNM staging is also used for planning anthracycline therapy in patients with nasal NKTL and is not intended for diagnosis at extra-nasal sites but does consider lymph node invasion. In a study by Gehong Dong and his group, they examined the genetic profiles of ENTKCLs from Asian and Hispanic ethnic groups, which showed close similarity, indicating shared pathogenetic mechanism and tumor evolution. They discovered a novel functional link between the loss of the TSG PRDM1 and activating STAT3 mutations to promote NK cell growth and survival. They reported that their study provides a genetic roadmap for further analysis and facilitates the investigation of actionable therapeutic opportunities in this aggressive Lymphoma.

Histopathologically, the lymphoma cells are polymorphous and show an angiocentric growth pattern, which induces vascular obstruction and prominent necrosis. Tumor cells are usually NK cells (surface CD3−, cytoplasmic CD3ε+, CD2+, CD5−, and CD56+) in most cases, but in rare cases can also be T cells. The lymphoma cells of ENKT are invariably infected with the Epstein-Barr virus (EBV). The extranodal involvement pattern seems connected with the CD56 marker, the neural cell adhesion molecule (NCAM) possessing hemophilic connection properties. The neoplastic cells are thus redistributed to other sites and evolve as new malignancy sites. The skin is the most common site for NKTL dissemination. However, CD56 is not always present in cases of ENKT. In a study by Jing Yang et al., they retrospectively studied the complete data of 288 patients with early-stage upper aerodigestive tract ENKTL. CD56-negative ENKTL was found in sixty patients (20.8%). This group of patients with negative CD56 had significantly inferior survival outcomes, indicating that CD56-negative ENKTL should be regarded as a distinct phenotype. Therefore, this entity needs further evaluation of optimal treatment strategies. In another study by Jing Yang et al., they retrospectively studied 443 patients with newly diagnosed ENKTL. CD56 was expressed in 337 patients (76.1%). They concluded that CD56 negative NKTL differs from CD56 positive NKTL in both the tumor microenvironment and survival outcomes, and asparaginase-based treatment may overcome the poor prognosis brought by CD56 negativity. Although our patient’s tumor was positive for CD56, it was diagnosed late, which explains the poor prognosis leading to his demise.
The pathologic process within the malignant lymphoma cells often shows angio-centricity and angio-destruction, resulting in zonal necrosis that is CD2-, surface CD3-, cytoplasmic CD3e+, CD56+, and cytotoxic molecules+ (TIA-1, granzyme B, and perforin). These markers are unique to NK cells, and CD56 or cytotoxic molecules are required for diagnosis. While EBV almost always infects these lymphoma cells, the detectable EBV DNA fragments in circulation reflect residual disease and foreshadow an unfavorable prognosis. The role of CD30 in the pathologic process within malignant lymphoma was studied. Yanfen Feng et al. studied the frequent expression of CD30 and its clinical significance in a subset of 91 patients with ENKTL. CD30 expression was detected in 43 (47.3%) patients. They concluded that no clinicopathologic features were associated with CD30 expression, and CD30 positivity showed no prognostic significance in patients with ENKTL. The tumor cells of our patient in this report were positive for CD30.

Extranodal nasal-type NKTCLs are rare malignancies for which standardized therapy has not yet been established. Furthermore, no randomized clinical trials can determine such a scheme. Therefore, it is recommended that these patients enroll in clinical trials and receive treatment in highly specialized clinics, especially when diagnosed at a late stage. Concerning nasal-type NKTCLs, one can use radiotherapy at a dose of at least 50 Gy as a single therapy, but this is associated with a high rate of local and distant recurrence. Combined therapy is recommended using the CHOP treatment scheme (cyclophosphamide, doxorubicin, vincristine, and prednisone).

Radiation therapy or Chemotherapy alone is insufficient for treating stage I/II NK/T-cell lymphomas. Instead, a combination of both is recommended for treatment. Early treatment regimens that revolved around anthracycline-containing agents (cyclophosphamide, Adriamycin, vincristine, prednisolone, or "CHOP" therapy) were later deemed ineffective. New SMILE regimens (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide) and radiation therapy have achieved survival rates at two years, reaching 60%. Modifying SMILE therapy with peg-asparaginase, the pegylated derivative of L-asparaginase has also been suggested as it reduces the toxic profile and extends the half-life allowing it to be given at lower rates of infusion. Chemotherapy alone is the standard for stages III/IV of the disease. Hematopoietic stem cell transplant (HSCT) has also been assessed for effectiveness in the setting of treatment for this disease. Unfortunately, it has remained unclear if HSCT has been successful, especially in relapse cases or those refractory to Chemotherapy due to autologous HSCT dependence upon chemotherapy sensitivity. Definitive conclusions cannot be drawn concerning this therapeutic alternative.

Su YJ, Wang PN, et al. retrospectively reviewed 101 ENKTL patients diagnosed between February 1998 and October 2015 to define the clinical features, outcome, and prognostic factors for extranodal NK/T-cell lymphoma (ENKTL) patients in Taiwan. They concluded that Age≥ 60 and stage III/IV are independent poor prognostic factors for progression-free survival (PFS) and overall survival (OS). They also concluded that early-stage ENKTL patients had an excellent response to combined chemoradiotherapy with an anthracycline-containing regimen but with a high relapse rate and short disease-free survival. However, anthracycline-containing regimens in the advanced stage had poor responses and dismal outcomes. While adding L-asparaginase has improved complete response rates, advanced-stage ENKTL-NT shows poor long-term survival. Strategies directed at targeting latent EBV in tumor cells are being explored. Novel approaches, such as adoptive cellular therapy with EBV-CTLs, are promising and exciting options that need further investigation. Our patient received radiation therapy upon diagnosis, but there was no response. The patient’s CHOP chemotherapy was started, but it was not finished because the patient passed away five months after the initial diagnosis.

Despite the aggressive nature and relapse of ENKTL, new studies have shown promising activity of potential therapeutic agents such as checkpoint inhibitors. Avoiding anthracyclines has also demonstrated an improved prognosis in patients with ENKTL. EBV-infected lymphoid cells express EBV-associated antigens making them a potential target for immunotherapy. Positive outcomes in clinical trials suggest that targeted gene therapy will become a mainstay in the future. In a study of 20 patients with ENKTL in Hungarian experiences reported by Annamária Bakos et al., they reported that ENKTL treatment is more effective with non-anthracycline-containing regimens. They also concluded that L-asparaginase containing Chemotherapy and concurrent or sequential chemoradiotherapy improves survival and CR rates. These different reports indicate that there must be agreement regarding the most effective consolidative therapy, and continuous investigations are encouraged. Autologous HSCT as a consolidation therapy for ENKTL at first complete remission (CR) was examined in a retrospective study of 62 patients (advanced stage, N = 31). With a median follow-up of 43.3 months, the 3-year overall survival (OS) and progression-free survival (PFS) were 67.6% and 64.5% in early-stage patients and 52.3% and 40.1% for
advanced-stage patients. There were no differences in survival compared to patients receiving Chemotherapy and radiation therapy.  

**Figures:**

Figure 1: Microscopic examination of nasal biopsy

1A: Low power view showing diffuse infiltration by lymphoid cells (H&E stain X 20 magnification)
1B: Intermediate power showing coagulative necrosis and ulceration of the surrounding tissues (H&E stain X 40 magnification)
1C: Medium to large atypical tumor lymphoid cells with abundant karyorrhectic debris in the background (H&E stain X 40 magnification)

Figure 2: Ancillary studies of the nasal biopsy

2A: Angiocentric growth leads to vessel wall invasion and destruction. Ulnación and coagulative necrosis of the surrounding tissues (H&E stain X 40 magnification)
2B: In-situ hybridization of the early RNA of the Epstein-Barr virus (EBER). Most lymphoma cells have strong nuclear labeling
2C: Tumor cells with strong membranous positivity with CD56.

**Acknowledgements:**

Special thanks to Mohab Idriss, Braegen Amaya-Turnbull, and Eman Indimi, MD candidates at the American University of the Caribbean, for their assistance in preparing manuscript images and reviewing the final manuscript.

**References:**

11. Aozasa K, Zaki MA. Epidemiology and