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Educational Case: Extranodal NK/T-Cell Lymphoma, Nasal Type

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Keywords
pathology competencies, organ system pathology, hematopathology—white cell disorders, classification of leukemia and lymphoma, T cells, natural killer cells, lymphoma, nasal type

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Primary Objective

Objective HWC3.1: Morphology of Acute Leukemia and Lymphoma. Describe the morphologic features that characterize typical cases of acute leukemia and lymphoma.

Competency 2: Organ System Pathology; Topic HWC: Hematopathology—White Cell Disorders; Learning Goal 3: Classification of Leukemia and Lymphoma.

Patient Presentation

A 57-year-old man from Mexico presented to the emergency department for recurrent epistaxis. The nose was packed with Merocel nasal tampons bilaterally. Four weeks later, he was admitted to interventional radiology for embolization of the distal internal maxillary arteries, bilaterally. One week later (5 weeks post-presentation), he underwent debridement of the oropharynx, the nasopharynx, and drainage of lacrimal duct due to palatal and nasal/nasopharyngeal mucosal necrosis. Computed tomography (CT) imaging of the head was performed immediately before the procedure of debridement. No personal or family history of cancer was elicited. Physical examination was unremarkable other than the above-described mucosal necrosis. There was no palpable lymphadenopathy or organomegaly on physical examination.

Diagnostic Findings, Part 1

Imaging studies (magnetic resonance imaging and CT) reveal (1) diffuse swelling of the uvula and soft palate with a heterogeneous appearance suggesting underlying inflammatory/infectious process and soft palate necrosis; (2) left medial canthus soft tissue abscess without evidence of retro-orbital extension; (3) nasopharyngeal soft tissue thickening causing obstruction of the torus tubarius bilaterally with resultant fluid opacification of middle ear cavities and right mastoid; an underlying mass could not be excluded; (4) pansinusitis with apparent extension of infection into the left pterygopalatine fossa (Figures 1 and 2).

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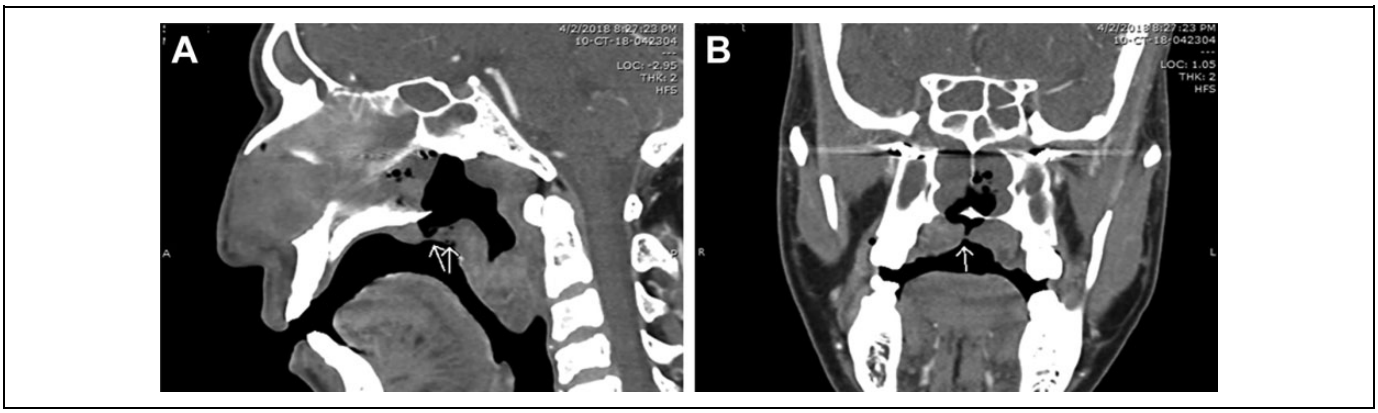

Figure 1. Computed tomography scan shows swelling of the uvula and soft palate with a heterogeneous appearance. The white arrows point to the soft tissue lesion in both sagittal (A) and coronal (B) planes.

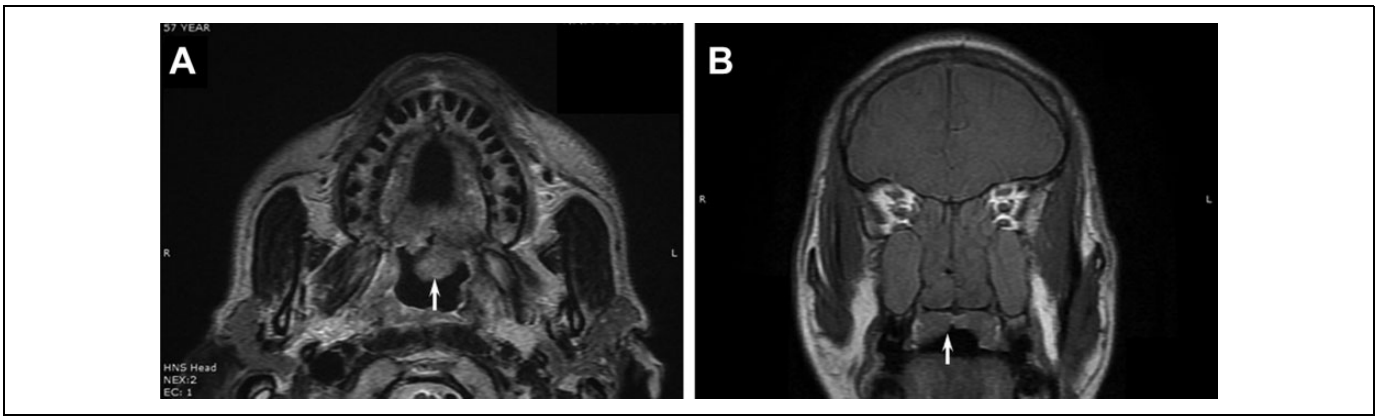

Figure 2. Magnetic resonance imaging with the white arrows pointing to the thickened soft palate area in both transverse (A) and coronal (B) planes.

Questions/Discussion Points, Part 1

What Is the Differential Diagnosis for a Nasopharynx Necrosis/Mass?

The nasopharynx (which consists in part of the soft palate) is the upper part of the throat behind the nose. It is a part of the pharynx comprised of 3 separate segments: the nasopharynx, the oropharynx, and the hypopharynx. The primary causes for tissue necrosis in the nasopharynx are infection, inflammation, or tumor. Tissue necrosis can lead to hemorrhage as evidenced in our case, which presented with recurrent epistaxis.

Nasopharyngeal infection may be caused by viruses, bacteria (including Klebsiella rhinoscleromatis causing rhinoscleroma), and fungal organisms. Sarcoidosis, Rosai-Dorfman disease, and Wegener granulomatosis are uncommon inflammatory diseases that can cause mass lesions and/or necrosis in the nasopharynx. If the nasopharyngeal infection does not respond to the treatment and atypical cells instead of microorganisms are identified (as in the present case), then the diagnosis of malignancy should be considered.

Tumors of the nasopharyngeal area are rare and represent less than 1% of all head and neck neoplasms. Benign tumors of nasopharynx are extremely rare, seen predominantly in children and young adults. The relatively common benign nasopharyngeal tumors include angiofibroma, hemangioma, papilloma, hamartoma, and benign salivary gland neoplasms. Malignant tumors, such as carcinoma, sarcoma, and lymphoma, arise from their corresponding normal tissue structures of the nasopharyngeal region.

What Would Be the Next Step in the Diagnostic Evaluation?

In order to clarify the cause of the patient's symptoms, an important next step is to biopsy the lesion and the adjacent tissue for pathologic assessment. Given that imaging studies cannot rule out an underlying mass, nasopharyngeal tumors must be considered. A biopsy is also useful in determining reactive inflammation due to infection and evaluating for granulomatous disease.

Diagnostic Findings, Part 2

Histologic evaluation of the biopsies reveals multiple fragments of largely ulcerated tissue, focally lined by squamous

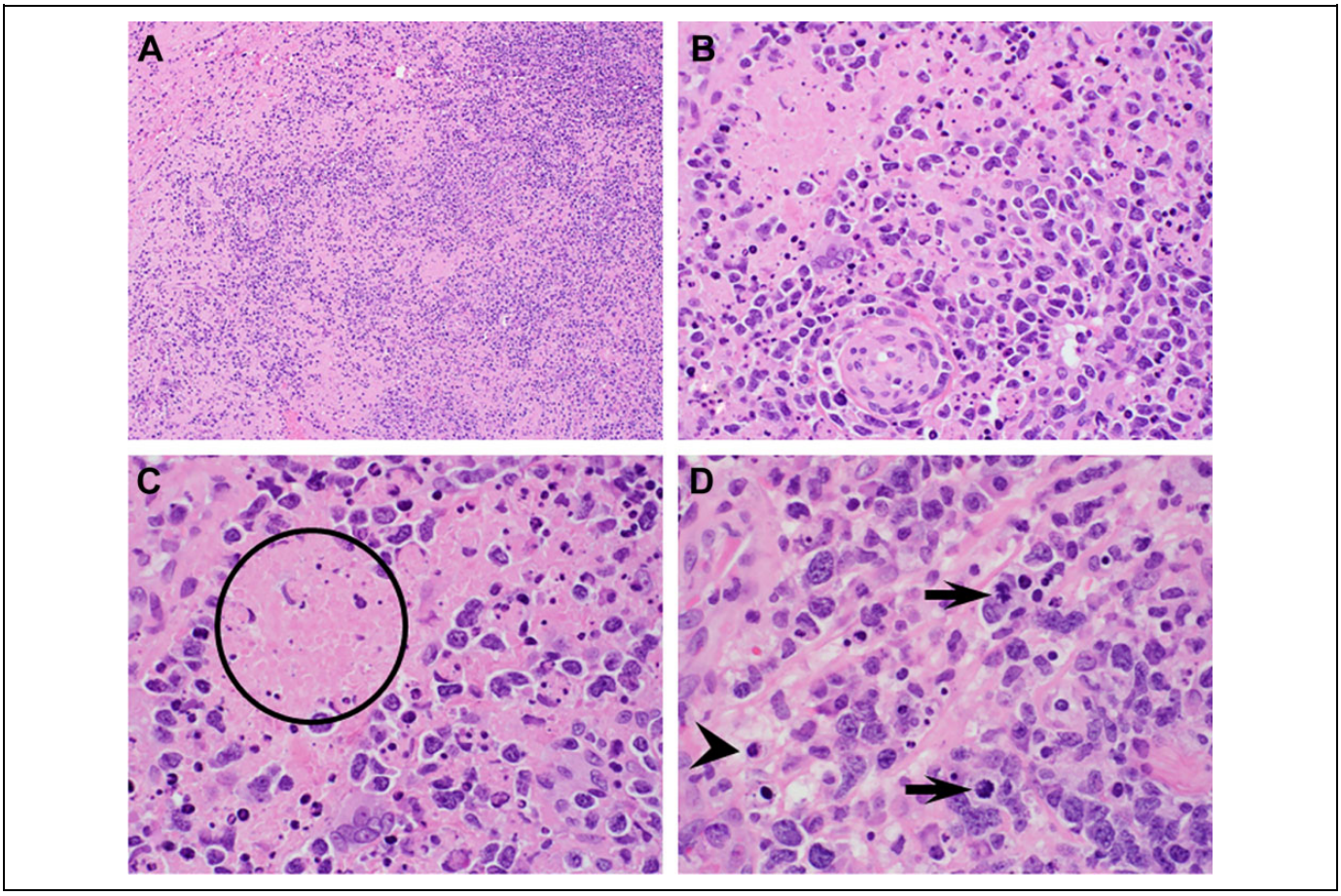

Figure 3. Photomicrograph of the biopsies of the lesion. A, There is a diffuse infiltrate of discohesive cells with extensive necrosis. B, The infiltrate is composed of mixed small, medium-sized, and large lymphoid-looking cells. C, A necrotic area (black circle) with nuclear dusts is shown. D, The cells often have irregularly folded nuclei, granular chromatin, and small visible nucleoli. Mitosis (black arrows) and apoptotic bodies (black arrowhead) are seen (D; H&E stain; original magnification, ×100 [A], ×400 [B], and ×600 [C and D]).

or respiratory epithelium. Extensive necrosis is noted. In the better preserved areas, there is a diffuse infiltrate of discohesive cells. An angiocentric and angiodestructive growth pattern is present. The infiltrate is composed of mixed small, medium-sized, and large lymphoid-looking cells. The cells often have irregularly folded nuclei, granular chromatin, and small visible nucleoli. Mitosis and apoptotic bodies are seen (Figure 3).

Questions/Discussion Points, Part 2

What Is the Differential Diagnosis Now? What Would Be the Next Step in the Diagnostic Evaluation?

The morphologic features of the lesion (cellular atypia, extensive necrosis, and increased mitotic activity) suggest a malignant process. The common malignant neoplasms in the nasopharyngeal area include carcinoma, sarcoma, melanoma, and hematolymphoid tumors. The histologic and cytologic characteristics of the biopsies are most consistent with lymphoma, particularly extranodal NK/T-cell lymphoma, nasal type (ENKTL-NT). However, other non-Hodgkin lymphomas, such as diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), and other T-cell lymphomas, undifferentiated nasopharyngeal carcinoma (NPC), and soft tissue sarcoma must be excluded by immunohistochemistry/in situ hybridization (ISH).

Extranodal NK/T-cell lymphoma, nasal type, is an Epstein-Barr virus (EBV)-associated lymphoma of NK cells or T cells, predominantly involving extranodal tissue, most commonly involving the upper aerodigestive tract including nasal cavity, nasopharynx, paranasal sinuses, and palate. Other affected sites reported in the United States and Europe include the skin/soft tissue, gastrointestinal tract, testis, and even breast and central nervous system (CNS).[2] Patients with nasal involvement of ENKTL-NT usually present with symptoms of nasal obstruction and epistaxis, sometimes with extensive destructive midfacial lesion previously known as "lethal midline granuloma." Histologically, it is characterized by angiocentricity and angiodestruction, leading to vascular obstruction and the consequent ischemic, coagulative necrosis. Tumor cells typically have a broad cytological spectrum, ranging from bland-looking small lymphocytes to large pleomorphic cells. Variable amounts of

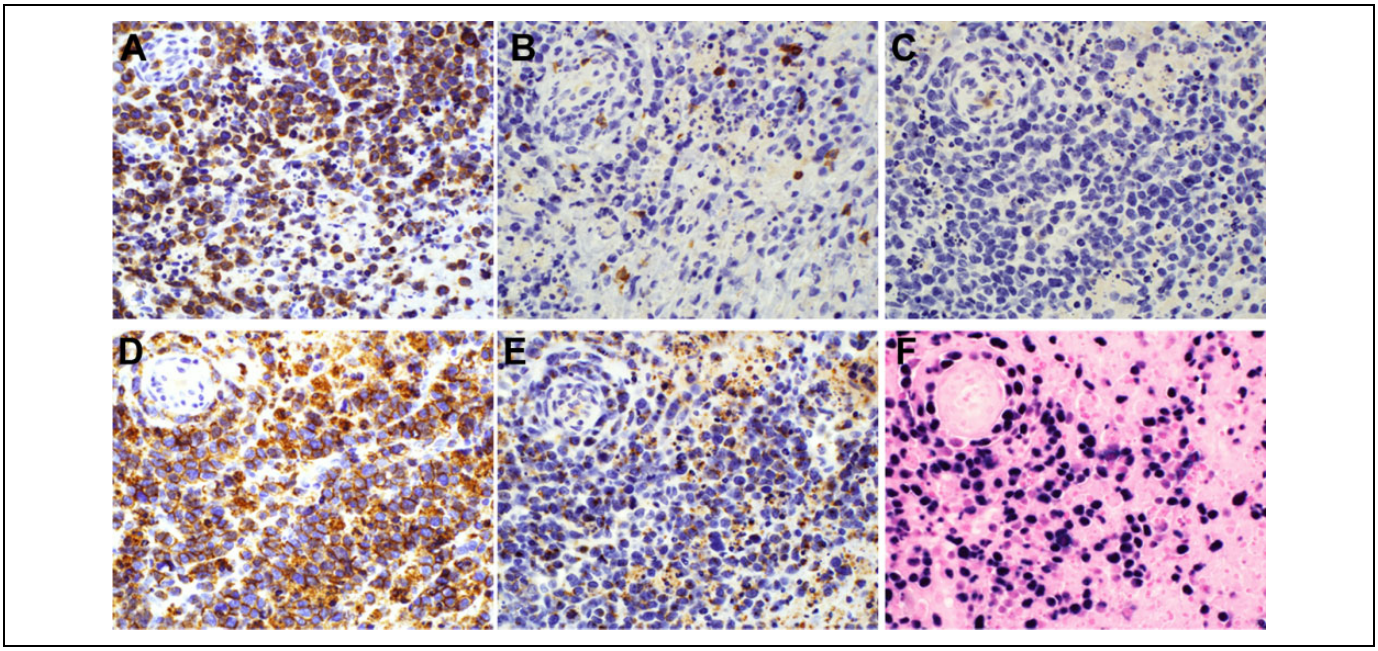

Figure 4. Immunohistochemical stains show the tumor cells are positive for CD3 (A), CD56 (D) and TIA-1 (E), and negative for CD5 (B) and CD20 (C). A-E, Immunoperoxidase staining; original magnification, ×400. F, Epstein-Barr virus–encoded RNA in situ hybridization show tumor cells are diffusely positive (original magnification, ×400).

reactive inflammatory cells are admixed with tumor cells, sometimes mimicking an inflammatory process.[3]

While the histopathologic features are well described, diagnosis can be challenging owing to the presence of extensive coagulative necrosis, so that repeated biopsies may sometimes be necessary for correct diagnosis. Suspicion of ENKTL-NT is crucial for timely diagnosis to avoid diagnostic delay, especially when only highly necrotic biopsy samples are available.[4] In addition to the medical history, clinical manifestations, and morphologic features, immunohistochemistry, ISH, and/or flow cytometric studies confirm the diagnosis.

Diagnostic Findings, Part 3

Immunohistochemistry stains show that the tumor cells are positive for CD3 (T cells), CD56 (natural killer cells), and T-cell intracellular antigen-1 (TIA-1, which marks cytotoxic T cells) and negative for CD5 (T cells, also marker for some B-cell neoplasms including chronic lymphocytic leukemia/small lymphocytic lymphoma and mantle cell lymphoma) and CD20 (B cells; Figure 4). Epstein-Barr virus–encoded RNA (EBER) ISH is positive (Figure 4).

Questions/Discussion Points, Part 3

How Do We Narrow the Differential Diagnosis and Make the Correct Pathologic Diagnosis?

The most common immunophenotype of ENKTL-NT is that the tumor cells are positive for CD2, CD3ϵ, CD56, and cytotoxic molecules (granzyme B, perforin, and TIA-1) but lack surface CD3, CD4, CD5, and CD8. Extranodal NK/T-cell lymphoma, nasal type tumor cells often express CD25, FS-7-associated surface antigen (FAS, also known as CD95), FAS ligand (FASL), and human leukocyte antigen-DR isotype (HLA-DR). CD30 expression is identified in about 30% to 40% of cases.[5] Epstein-Barr virus infection should be confirmed in virtually all cases to render a diagnosis of ENKTL-NT. Therefore, when $CD3^+$ nasal lymphomas do not show EBER positivity, other types of T-cell lymphoma should be considered. In the present case, EBER ISH is diffusely positive in tumor cells (Figure 4). The immunohistochemistry and ISH results confirm the diagnosis of ENKTL-NT.

Differential Diagnosis

Nasopharyngeal carcinoma is a rare malignancy with geographically varied incidence. A markedly high rate of NPC is seen in certain well-defined populations, including natives of southern China, Southeast Asia, the Arctic, and the Middle East/North Africa.[6,7] A biopsy sample is essential for a definitive diagnosis of NPC. Histologically, undifferentiated NPC may be confused with lymphoma. In addition, both undifferentiated NPC and ENKTL-NT are associated with EBV and thus EBER ISH positive. However, NPC cells express various epithelial markers, such as cytokeratins, p63, and epithelial membrane antigen (EMA). The presence of lymphoid markers and/or lack of epithelial markers can rule out NPC.

Diffuse large B-cell lymphoma and BL are high-grade non-Hodgkin B-cell lymphomas. Diffuse large B-cell lymphoma is an aggressive neoplasm composed of intermediate or large lymphoid cells whose nuclei are the same size as, or larger

than, those of normal macrophages or more than twice the size of those of normal small lymphocytes, with a diffuse growth pattern. Diffuse large B-cell lymphoma, not otherwise specified (NOS), is the most common type of non-Hodgkin lymphoma in the world. Burkitt lymphoma is a highly aggressive but curable lymphoma characterized by sheets of monomorphic medium-sized B cells with round nuclei, multiple small nucleoli, and numerous mitotic figures. The cytoplasm is deeply basophilic, often containing lipid vacuoles, best observed in air-dried touch imprints. Many scattered tingible body macrophages are usually present, due to a high rate of apoptosis, and form a so-called starry sky appearance. *MYC* gene translocation to an immunoglobulin locus can be demonstrated in more than 90% of cases. Both DLBCL and BL tumor cells are positive for CD20, CD79a, PAX-5, and other B-cell markers. Positivity for CD10 and BCL6, negativity for BCL2, Ki67 > 95%, and presence of an MYC break point but absence of BCL2 and BCL6 break points may help with the BL diagnosis.[8] Both DLBCL and BL are excluded by negative CD20 and positive T-cell markers (CD3, TIA-1) in this case. It is important to mention that the 3 major types of B-cell lymphoma that are related to EBV are BL, classic Hodgkin lymphoma, and DLBCL.

Mesenchymal malignancies in the nasopharyngeal area include lesions such as rhabdomyosarcoma, fibrosarcoma, and angiosarcoma. Embryonal type of rhabdomyosarcoma consists round to spindled primitive mesenchymal cells with hyperchromatic nuclei, while alveolar type shows fibrous septa separating loosely cohesive rhabdomyoblasts into alveolar spaces and multinucleated giant cells. By immunohistochemistry, rhabdomyosarcoma cells are positive for desmin, myoglobin, myogenin, and other skeletal muscle markers. Soft tissue sarcomas are excluded by positive T-cell markers in this case.

Epidemiology of ENKTL-NT

All ENKTL-NT studies demonstrate a male predominance. The median patient age at diagnosis is about 53 years based on the data from most Asian cohorts and Western ENKTL-NT studies including US Surveillance, Epidemiology, and End Results (SEER) study.[2]

Which Virus Is Etiologically Associated With ENKTL-NT?

Epstein-Barr virus is etiologically associated with several malignant neoplasms, including quite a few lymphoproliferative disorders, such as ENKTL-NT; aggressive NK cell leukemia; EBV-positive DLBCL, not otherwise specified; BL; plasmablastic lymphoma; lymphomatoid granulomatosis; posttransplant lymphoproliferative disorders; and mucocutaneous ulcer; and nonlymphoproliferative disorders, such as NPC.[5] Patients with chronic active EBV infection often progress to overt lymphoma or leukemia over a long-term clinical course.[9,10]

The universal association of ENKTL-NT with EBV across all ethnic groups suggests a pathogenic role of the virus in the disease. In the United States and Europe, given the low level of suspicion for this neoplasm, diagnosis is often delayed because the biopsy specimen is necrotic or because bacterial and fungal stains are incorrectly interpreted as evidence that the primary process is an invasive bacterial or fungal sinusitis, rather than lymphoma, leading to repeated, but unsuccessful, courses of antimicrobial therapy. In these situations, elevated cell free plasma EBV-DNA would be highly predictive of $EBER^{+}$ tumors and could be very helpful in the workup and diagnosis of patients with suspected ENKTL-NT.[2]

What Are Possible Treatments of ENKTL-NT?

Given its rarity, there is no standard therapy for ENKTL-NT due to the lack of randomized controlled trials. Historically, anthracycline-based chemotherapy was used but resulted in poor outcomes. The combined approach of non-anthracycline-based chemotherapy with radiotherapy is currently recommended as a first-line treatment for ENKTL-NT.[5,11] One meta-analysis summarized that in 7 retrospective cohort studies with 1593 patients included, compared with induction chemotherapy followed by radiotherapy, upfront radiotherapy significantly improved overall survival of patients with limited stage ENTKL.[12,13]

With further understanding of the specific protein expression within ENKTL-NT, new drugs targeting CD38 (daratumumab, naked anti-CD38 antibody), CD30 (brentuximabvedotin, anti-CD30 antibody conjugated with auristatin E), programmed death-ligand 1 (PD-L1), and programmed death 1 (PD-1) show promising future. More specific to ENKTL-NT may be the use of EBV-antigen-targeted cytotoxic T lymphocytes that seem effective by themselves or as maintenance therapy for this disease. The overall goal would be to produce a deep response and move those relapsed/refractory patients onto an allogeneic bone marrow transplant protocol. Future clinical trials with these novel immunotherapies are needed to determine efficacy and timing setting.[14]

Prognosis and Predictive Factors

The prognosis of ENKTL-NT depends on the primary localization of the lymphoma. Extranasal ENKTL is very aggressive in general, except for rare cases of primary cutaneous ENKTL which may have a protracted clinical course. However, patients with nasal type ENKTL have variable prognosis, from well responding to treatment to dying of disseminated disease despite aggressive therapy.[3] Unfavorable prognostic factors include advanced age of the patient (age $\geq$60), late-stage disease (stage III/IV),[15] unfavorable International Prognostic Index, high level of circulating EBV DNA, bone marrow involvement, and a high proliferation rate by Ki-67.[3] Unfortunately for the present patient, his positron emission tomography (PET)-CT demonstrated possible recurrence of disease in his left nasal cavity with metastasis to lungs, cecum, and vertebra. The patient has the option of whether he wants hospice/palliative care or additional chemotherapy to try to treat his disease.

Interestingly, recent multivariate survival analysis showed that the expression levels of PDGFRA and PD-L1 were independent factors in the prognosis of patients with ENKTCL.[16] Kim et al demonstrated that high quantity of tumor-infiltrating $FOXP3^+$ regulatory T cells or PD-L1 expression on tumor cells independently predicted better prognosis.[5]

Teaching Points

- Extranodal NK/T-cell lymphoma, nasal type, is an EBV-positive, aggressive lymphoma characterized by prominent necrosis, vascular damage, and cytotoxic phenotype. It appears to be derived from NK cells or rarely, cytotoxic T cells.
- Extranodal NK/T-cell lymphoma, nasal type almost always has an extranodal presentation, most commonly involving the upper aerodigestive tract including the nasal cavity, nasopharynx, paranasal sinuses, and palate. Other affected sites include the skin/soft tissue, gastrointestinal tract, testis, breast and CNS.
- Patients with nasal involvement present initially with nonspecific localized symptoms including nasal obstruction, purulent nasal discharge, and epistaxis. But the disease can extend to adjacent tissues causing extensive necrotic lesions in the midline facial area and even widely disseminate in late stage.
- Histological features of this disease are diffuse infiltration of atypical lymphoid cells with angiocentricity and angiodestruction, frequent coagulative necrosis, broad cytological spectrum, and variable amounts of inflammatory cells.
- Epstein-Barr virus infection should be confirmed in virtually all cases to establish the diagnosis.
- The combined approach of non-anthracycline-based chemotherapy with radiotherapy is currently recommended as a first-line treatment for ENKTL-NT. Novel immunotherapy drugs are under study.
- Extranasal ENKTL is highly aggressive, except for rare cases of primary cutaneous ENKTL which may have a protracted clinical course. The prognosis of nasal ENKTL-NT is variable.

Declaration of Conflicting Interests

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