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Extranodal hematopoietic neoplasms and mimics in the head and neck: an update ☆

Beenu Thakral MD [a,*], Jane Zhou MD [b], L. Jeffrey Medeiros MD [a]

[a] *Department of Hematopathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA*
[b] *Tufts Medical Center/Tufts University Medical School, 800 Washington Street, Box 802, Boston, MA 02111*

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Summary The head and neck region is a common site for extranodal lymphomas, second only to the gastrointestinal tract; and 12% to 15% of all head and neck tumors are lymphomas. Non-Hodgkin lymphomas are most common, and Hodgkin lymphoma occurs rarely at extranodal sites in the head and neck. Most non-Hodgkin lymphomas of the head and neck region are of B-cell lineage, and the Waldeyer ring is the most common site. Head and neck lymphomas have distinctive epidemiological and clinicopathologic features, including an association with immunosuppression, infectious organisms, or autoimmune disorders; site-specific differences (eg, thyroid gland versus ocular adnexa) for common lymphomas, such as extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; and genetic differences that provide insights into etiology. Furthermore, the diagnosis of non-Hodgkin lymphomas at extranodal sites implies differences in prognosis and therapeutic implications with lymphomas at nodal sites. In this review, we discuss various types of non-Hodgkin lymphomas and Hodgkin lymphoma, focusing on unique aspects related to the head and neck region. We also discuss a number of newer entities that are clinically indolent as well as mimics of lymphoma that can occur in the head and neck region, including infectious mononucleosis, Kikuchi-Fujimoto disease, Kimura disease, Castleman disease, and immunoglobulin G4–related disease.

1. Introduction

The head and neck region is a common site for nodal and extranodal lymphomas. Nodal lymphomas involving the head and neck region are similar to systemic lymphomas in general and are not further discussed here. Extranodal lymphomas and mimics of lymphoma in the head and neck region, in contrast, have some unique features and are the focus of this review.

Following the gastrointestinal tract, the head and neck region is the second most common region for extranodal lymphomas. Approximately one-third of all extranodal lymphomas occur in the head and neck, and extranodal lymphomas represent 12% to 15% of all head and neck malignant tumors [1]. The head and neck region provides a number of gateways for antigenic stimuli; and as a result, reactive and inflammatory processes are common in this region. Because of the complex anatomy of the head and neck, both unique and common neoplasms of all lineages can

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* Corresponding author. Department of Hematopathology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 72, Houston, TX, 77030. Tel.: +1 713 794 5446.
E-mail address: beenuthakral@gmail.com (B. Thakral).

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occur; therefore, the differential diagnosis of hematopoietic lesions in this region can be highly challenging.

2. Sinonasal tract

The sinonasal tract includes the nasal cavity and paranasal sinuses. Lymphomas of the sinonasal tract are uncommon worldwide and represent less than 5% of extranodal lymphomas [1]. However, lymphomas are the second most common malignancy after squamous cell carcinoma to arise in this area. Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma in Western countries, whereas extranodal NK/T-cell lymphoma of nasal type is more common in Asia and parts of Latin America [1,2].

Patients with DLBCL of the sinonasal tract usually present with nonspecific symptoms mimicking allergic rhinitis and upper respiratory infection. The maxillary sinus is the most common site, 37%; followed by the nasal cavity, 34%; accessory sinus, 10%; and the ethmoid sinus, 8.7% [3]. The mean age at diagnosis is the seventh decade; men are affected slightly more than women. The disease seems to affect white people more often than other ethnic groups in the United States [3]. The overall disease-specific survival (DSS) rates at 1 and 5 years were 85% and 68%, respectively. Involvement of multiple sites in the sinonasal tract is a poor prognostic factor [3].

Nasal-type extranodal NK/T-cell lymphoma is a neoplasm of NK cells and, less often, T cells (up to one-third) associated with Epstein-Barr virus (EBV) infection. Extranodal NK/T-cell lymphoma is more common in Asia and Latin America than in Western countries, indicating that genetic and environmental factors may play a role in pathogenesis. Virtually all cases of extranodal NK/T-cell lymphoma of nasal type are associated with EBV infection; and a defect in immune surveillance has been suggested, possibly due to common 30–base pair deletions of the *LMP1* gene. In Asia, the most common EBV variant seen in nasal-type nasopharyngeal NK/T-cell lymphoma is del-LMP1 (Gly335), which is different from EBV-positive nasopharyngeal carcinoma that carries del-LMP1 (Asp335) [4].

Additionally, a low frequency of HLA-A*0201 has been reported in EBV-infected Asian patients with nasal-type NK/T-cell lymphoma [5]. Extranodal NK/T-cell lymphoma affects adults across a broad age range (median, 40 years); children are also occasionally affected. The male-to-female ratio is 2:1. Rarely, extranodal NK/T-cell lymphomas of nasal type may present as a posttransplant lymphoproliferative disorder. Patients usually present with pain, bleeding, or nasal obstruction. The lymphoma may locally invade the facial skin, orbit, or nasopharynx. Lymphadenopathy is seen in 10% to 20% of patients, although a biopsy is not often performed. Most patients present with localized disease (stage I); 10% to 20% of patients present with advanced-stage disease, and bone marrow involvement occurs in about 10% of patients.

Histologically, extranodal NK/T-cell lymphomas of nasal type are commonly associated with coagulative necrosis and ulcer; therefore, these tumors can mimic an inflammatory process, particularly in small biopsy specimens. These tumors are well known to show an angiocentric and angiodestructive growth pattern, but this pattern can be absent in about one-third of cases [6,7]. The neoplastic cells can show a spectrum of sizes, from small to large. Mitotic figures are more numerous in lesions composed of large cells. Bone marrow involvement can be interstitial and subtle.

Immunophenotypic analysis by either flow cytometry or immunohistochemistry can be performed. The lymphoma cells most often are $CD2^+$, $sCD3^-$, cytoplasmic $CD3^+$ (epsilon chain), $CD5^-$, $CD4^-$, $CD8^-$, $CD43^+$, and $CD56^+$, consistent with NK cell lineage (Fig. 1). Tumors of T-cell lineage may express surface CD3, CD5, or CD8. The lymphoma cells in all cases have a cytotoxic immunophenotypecontributing to extensive necrosis and are positive for granzyme B, perforin, and T-cell intracellular antigen (TIA1). Tumors composed of large cells can express CD30. Detection of EBV by in situ hybridization for EBV-encoded small nuclear RNA (EBER) is required for the diagnosis. *MYC* and high Ki-67 expression are reported to correlate with large cell morphology and poorer prognosis [8].

The most common cytogenetic aberration in nasal-type extranodal NK/T-cell lymphoma is deletion of 6q21. A candidate gene at this locus is the tumor suppressor *HACE1* [9]. Genes involved in angiogenesis as well as the Notch and Wnt signaling pathways have also been implicated in pathogenesis [9]. Mutations in *TP53* (~80% of cases) and *β-catenin* (~20% of cases) have been reported in a subset of cases.

The prognosis of patients with extranodal NK/T-cell lymphoma depends greatly on disease stage, type, performance status, number of extranodal sites involved, and serum EBV DNA levels [9]. Localized disease is amenable to radiation therapy, whereas patients with widespread disease have poor prognosis, with a 5-year survival rate of approximately 50% [7]. Patients who present with nonnasal disease more often have tumors of T-cell lineage and have a prognosis poorer than that of patients with nasal disease [10,11]. An aggressive chemotherapy regimen composed of steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide has been shown to be somewhat effective in patients with extranodal NK/T-cell lymphoma of nasal type [12].

The differential diagnosis of nasal extranodal NK/T-cell lymphoma includes infectious processes (fungal/mycobacterial infections), chronic inflammation, and autoimmune etiologies, such as Wegener granulomatosis. Wegener granulomatosis can histologically simulate nasal-type NK/T-cell lymphoma in the form of mixed cellular infiltrate, vascular damage, and necrosis; but it can be distinguished from nasal-type extranodal NK/T-cell lymphoma by the absence of EBV-positive lymphoid cells. In addition,