Nasopharyngeal carcinoma

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The most common type of nasopharyngeal tumor is a carcinoma. The etiology of nasopharyngeal carcinoma (NPC) is multifactorial; race, genetics, Epstein-Barr virus (EBV) infection, and the environment all play a role. NPC is rare in white populations, but it is one of the most common cancers among Chinese. EBV is almost always present in NPC, indicating that this virus plays an oncogenic role. The viral titer can be used to monitor therapy or possibly as a diagnostic tool in the evaluation of patients who present with a metastasis from an unknown primary. Exposure to environmental carcinogens, especially high levels of volatile nitrosamines (specifically, those in Cantonese-style salted fish), has been implicated in this complicated disorder; carcinogens related to smoking, formaldehyde exposure, and radiation have also been implicated.

NPC primarily affects adults, as its peak incidence occurs in patients between the ages of 40 and 60 years. The male-to-female ratio is approximately 3:1 irrespective of geographic location. Most patients present with an asymptomatic cervical mass (typically in the apex of the posterior cervical triangle or in the superior jugular chain of nodes), serous otitis media, epistaxis, and/or nasal obstruction. The standard of care for patients with a high suspicion of NPC is endoscopic evaluation of the upper aerodigestive tract with gross lesion biopsy and random biopsies of the lateral, superior, and posterior walls of the nasopharynx; the lateral wall is the most common site of tumor development, particularly the fossa of Rosenmüller.

The World Health Organization defines NPC as a carcinoma arising in the nasopharyngeal mucosa that exhibits light-microscopic or ultrastructural evidence of squamous differentiation. It encompasses squamous cell carcinoma and nonkeratinizing carcinoma. Most tumors are exophytic (~75%). The features of keratinizing squamous cell carcinoma are well known, but it is the more common, nonkeratinizing or "classic" NPC that is discussed here. Nonkeratinizing NPC can be classified as either *undifferentiated* or *differentiated*. The undifferentiated type is made up of solid sheets of syncytial-appearing large tumor cells arranged in irregular islands and trabeculae of carcinoma intimately associated with and intermingled with inflammatory elements (figure 1). The nuclear chromatin is cleared or vesicular, accentuating the prominent nucleoli. There is a high nucleus-to-cytoplasm ratio with amphophilic cytoplasm (figure 2). Keratin is strongly and diffusely immunoreactive, which helps confirm the diagnosis of carcinoma. An in situ hybridization or polymerase chain reaction assay for "EBV-encoded early RNA" is the most sensitive and specific analysis available at present.

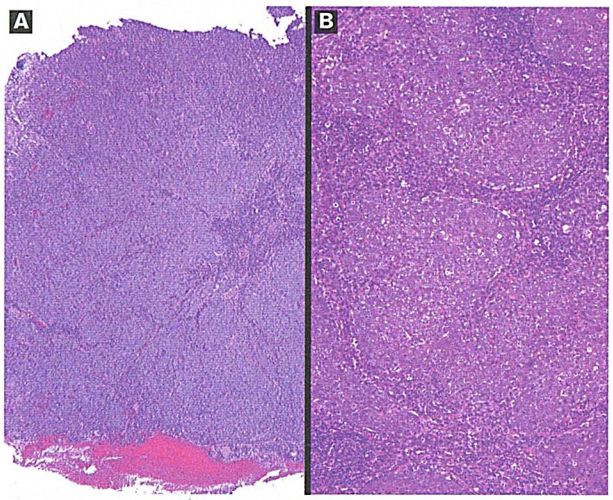

*Figure 1. The epithelial neoplastic proliferation can be polypoid (**A**) and made up of syncytial nests of epithelial cells (blue cells here) separated by lymphoid elements (**B**).*

The classification of a nonkeratinizing NPC as either undifferentiated or differentiated can be arbitrary, difficult to achieve, and of no clinical or prognostic significance. However, there is a broad histologic differential diagnosis, which includes melanoma, rhabdomyosarcoma, lymphoma, olfactory neuroblastoma, Ewing's sarcoma, and primitive neuroectodermal tumors. In fact, even floridly reactive germinal centers sometimes contain large vesicular nuclei and lack a well-defined mantle zone. The differential considerations can often be confirmed by a pertinent immunohistochemistry panel.

In view of the strategic location of the nasopharynx and the tendency of NPC to invade surrounding tissues, the

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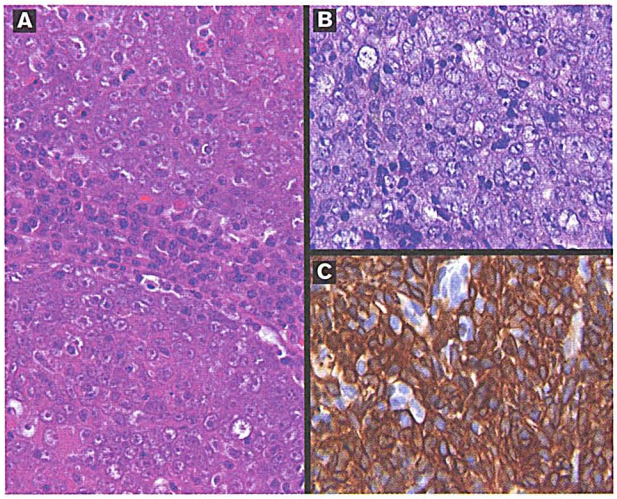

*Figure 2. Well-formed syncytial nests of cells are separated by lymphoid cells. The nuclei are large and vesicular with prominent nucleoli (**A**). Nuclear pleomorphism and overlap can be profound (**B**). The epithelial nature of the neoplasm is confirmed with keratin immunohistochemistry (**C**).*

first line of therapy is irradiation. Surgery, if performed at all, is reserved for radioresistant and/or locally recurrent tumors. NPCs are highly malignant with extensive and early lymphatic spread (as a result of a rich lymphatic plexus) and a high incidence of hematogenous spread. Direct extension into the base of the skull and surrounding paranasal sinuses, orbit, and basal foramina is common. Approximately 50% of patients have lymph node metastasis at presentation. Chemotherapy is usually reserved for disseminated disease.

Overall 5-year survival in the United States ranges from 40 to 80% (dependent on endemic versus sporadic disease). The survival rate associated with squamous cell carcinoma is lower (20 to 40%) than that of undifferentiated NPC (65%). Young patients (<40 yr) and women have a better prognosis. Poor prognostic indicators include advanced clinical stage, cranial nerve involvement, keratinizing histology, and an absence of EBV.

Suggested reading

Franchi A, Moroni M, Massi D, et al. Sinonasal undifferentiated carcinoma, nasopharyngeal-type undifferentiated carcinoma, and keratinizing and nonkeratinizing squamous cell carcinoma express different cytokeratin patterns. Am J Surg Pathol 2002;26:1597-1604.

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