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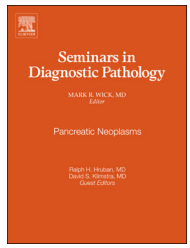

Cytologic evaluation of cervical lymph node metastases from cancers of unknown primary origin

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ABSTRACT

Fine-needle aspiration biopsy (FNAB) is often the first diagnostic procedure performed in patients with head and neck (HN) masses. Metastatic squamous cell carcinoma (SCC) to cervical lymph nodes is by far the most common malignancy aspirated in the HN, but in approximately 3–10% of patients, a primary tumor will not be found even after complete clinico-radiological workup. Several HN cancers are associated with oncogenic viruses, including HPV-associated SCC and EBV-associated nasopharyngeal carcinoma (NPC). While the primary tumor is sometimes small or undetectable, patients often present initially with cervical lymph node metastases. HPV-associated SCC and EBV-associated NPC are typically non-keratinizing carcinomas that can mimic several other poorly differentiated HN cancers by FNAB but have a significantly better prognosis. Therefore, the precise classification of the metastatic disease in the FNAB material is very useful since it can facilitate the subsequent location of the primary tumor, and it can provide prognostic and therapeutic information as well. In this review, we discuss the major entities that can present as a metastatic cancer of unknown primary in cervical lymph node other than supraclavicular, including their cytologic features and the role of ancillary studies.

Introduction

Fine-needle aspiration biopsy (FNAB) plays an important diagnostic role in patients presenting with cervical nodules including enlarged lymph nodes, allowing accurate triaging among reactive/inflammatory, infectious, and metastatic disease and helping to efficiently guide the clinical management.[1] FNAB, often in conjunction with ultrasound guidance, is currently the first-line ancillary method for the evaluation and diagnosis of palpable head and neck (HN) masses of all types.[1] As such, metastatic HN cancers are frequently initially diagnosed through FNAB. Metastatic squamous cell carcinoma (SCC) to cervical lymph nodes (CLN) is by far the most common malignancy aspirated in the HN (>90% of cases), followed by papillary thyroid carcinoma (PTC), melanoma, and nasopharyngeal carcinoma (NPC).[1] Patients with metastatic SCC in CLN often have a prior or concurrent history of HN-SCC at the time of the FNAB, but in a significant number of cases, the diagnosis of metastatic SCC by FNAB precedes identification of the primary tumor, which is typically

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identified during subsequent workup, including a thorough history and physical examination, nasopharyngolaryngoscopy, and imaging studies with CT scan, MRI, and/or PET/CT scan. However, in approximately 3–10% of patients, a primary site of origin will not be identified after a thorough clinical and radiologic workup, resulting in a metastatic carcinoma of unknown primary (CUP). HN-SCC of unknown primary is defined as the presence of SCC in ≥1 CLN that are not exclusively in the supraclavicular region, without an identifiable primary tumor. In the case of an isolated left supraclavicular CLN metastasis (Virchow's node), including SCC, the SCC primary almost always originates from the skin or from an organ below the clavicles.[2] This unique condition is associated with a different natural history and a worse prognosis than metastatic HN-SCC and will not be discussed further in this review. When the primary tumor site of HN-SCC remains unknown, wide-field irradiation including the entire pharyngeal and laryngeal tissues is more likely to be applied, resulting in increased morbidity. Therefore, it is useful to identify the primary tumor site of origin to provide for a more targeted therapy. The cytologist evaluating FNAB specimens from CLN can play an important role in this process. In addition, in patients with metastatic disease, with or without a known primary, cytological material may be the only tumor specimen available for diagnostic workup. Therefore, FNAB material is valuable not only for diagnostic but also for prognostic and therapeutic purposes. In this review, we discuss the major entities that can present as a metastatic cancer of unknown primary in CLN other than supraclavicular, including their cytologic features and the role of ancillary studies.

Head and neck carcinomas associated with oncogenic viruses

Several HN cancers are associated with oncogenic viruses, and they typically originate from specific anatomic sites such as Waldeyer's ring. They include HPV-associated SCC and EBV-associated NPC. Waldeyer's ring, encompassing specific subsites such as the oropharynx, nasopharynx, and pharynx, is a well-recognized replication site for several pathogenic viruses including HPV, EBV, adenoviruses, herpes, and HIV and may constitute a reservoir for the viruses following exposure.[3] Therefore, the detection of the oncogenic virus in the FNAB material of a metastatic carcinoma can be useful for the clinical management since it facilitates the subsequent location of the primary tumor and can often provide prognostic and therapeutic information as well.[4–13]

HPV-associated HN squamous cell carcinoma

Many of the primary tumors that are identified among patients with HN-SCC of unknown primary are located within the oropharynx, and up to 80–90% of oropharyngeal SCC are caused by oncogenic high-risk (HR) HPV.[14,15] HPV type 16 is the most common genotype, accounting for 90–95% of HPV-positive HN-SCC.[3,14,15] In contrast, only a small percentage of SCCs arising from non-oropharyngeal HN sites are positive for HR-HPV. Therefore, the detection of transcriptionally active HR-HPV in FNAB specimens from metastatic SCC strongly implicates the oropharynx as the site of origin.[4–9] In addition, the prognosis of patients with HPV-associated HN-SCC is overall significantly better than conventional HN-SCC (i.e., associated with tobacco and alcohol consumption), due in part to increased chemo- and radiosensitivity.[14,16] Conventional HN-SCC, which is often keratinizing, is associated with more genetic alterations and genetic instability than HPV-associated HN-SCC, which is predominantly non-keratinizing and associated with inactivation of selective tumor suppressor genes (e.g., *TP53* and *RB*) through the effects of the specific viral oncoproteins E6 and E7.[14,17] Accordingly, several clinical trials investigating less intensive treatment regimens (treatment de-escalation) with less morbidity or new tailored immunotherapies (therapeutic vaccines) in patients with HPV-associated HN-SCC are ongoing.[18] There are several other characteristic clinicopathological features of HPV-associated HN-SCC that make it truly a distinct variant of HN-SCC.[14,17] In contrast to patients with conventional HN-SCC, patients with sexually transmitted HR-HPV-associated SCC are younger, typically nonsmokers and nondrinkers, and of higher socioeconomic status.[14] They are also less likely to develop a second HN malignancy than patients with conventional HN-SCC, probably because of the absence of a field effect and of a recognized pre-neoplastic lesion.

HPV preferentially targets the highly specialized reticulated lymphoepithelium within crypts of the oropharyngeal mucosa.[3,14,19] The explanation for why this specialized epithelium appears to be particularly vulnerable to HPV infection is unclear.[14] HPV-associated HN-SCC arises most commonly in the lingual and palatine tonsils without any associated dysplasia of the adjacent surface squamous epithelium.[3] This may explain why certain screening methods, including both oral rinses and oral brushing specimens, have not been very successful at detecting squamous cell carcinoma precursor lesions.[20,21]

Histologically, the most common morphologic variant of HPV-associated HN-SCC is a non-keratinizing SCC that resembles the reticulated tonsillar lymphoepithelium. The tumor cells show a lobular pattern of growth often with frequent mitoses. The absence of keratinization and high nuclear–cytoplasmic ratio imparts a "basaloid" appearance. These features may reflect the intrinsic qualities of the tissues targeted by HPV (i.e., reticulated lymphoepithelium) rather than specific alterations of cell morphology and function.[3] Several other less common histologic patterns of HPV-associated HN carcinomas have been described. They include papillary SCC,[22] undifferentiated carcinoma,[23] adenosquamous carcinoma,[24] and small cell neuroendocrine carcinoma, which is associated with a poor clinical outcome.[25] On cytology, while metastatic conventional HN-SCC usually show variable degrees of keratinization and are easy to diagnose, HPV-associated HN-SCC can be more difficult to recognize as SCC because of their basaloid-appearing features, which can overlap with that of several other HN neoplasms (Fig. 1A and B; Table 1).[26]

Oropharyngeal HN-SCC including those that are HPV-associated commonly present with occult or small (T1/T2)