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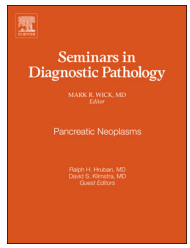

Cytologic mimics of non-Hodgkin lymphoma in the head and neck

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ABSTRACT

Non-lymphoid small round blue cell tumors of the head and neck are particularly difficult to diagnose when metastatic to a lymph node. The cytopathologist or surgical pathologist evaluating these lesions has to be aware of the various non-hematopoetic neoplasms that present in the head and neck area that can mimic non-Hodgkin lymphoma. Presented here are the various lesions commonly seen which needs to be entertained depending on where in the head and neck the lesion is located. More recently, a plethora of HPV related head and neck tumors has been described and these lesions add to the mix in this challenging milieu of cases.

Introduction

A myriad of non-lymphoid small "rounded-cell" malignancies can present as apparent non-Hodgkin lymphoma (NHL) in head/neck fine-needle aspiration (FNA) biopsy specimens. Included in this category are HPV-related neoplasms that may mimic NHL, particularly when they metastasize to the lymph nodes. Due to the nondescript cytomorphology of these malignant small "rounded" cells, ancillary testing, particularly immunohistochemical (IHC) staining, of a cell-block is often critical for a specific diagnosis.

Olfactory neuroblastoma (ONB)

Olfactory neuroblastoma (ONB) is the accepted diagnostic term for a malignant neuroectodermal neoplasm with multiple historical synonyms. It arises from the olfactory epithelium of the upper one-third of the nasal cavity in association with the cribriform plate.[1] Because of this location, cytopathology of the primary neoplasm is rarely encountered unless touch imprints of fresh tissue are examined. FNA smears are typically from metastatic deposits, regional nodes, or soft tissue. Cytologically, a diagnosis of low- or high-grade NHL may be entertained along with that of other malignant small cell neoplasms because smears are highly cellular and composed of rounded cells with minimal cytoplasm.[2] In some cases, fibrillar neuropil and poorly formed rosettes may be encountered.[3] Dispersed cytoplasmic fragments may emulate the lymphoglandular bodies so common to NHL smears, creating a possible pitfall in interpretation. ONB is positive for neuroendocrine markers such as synaptophysin and CD56, as well as calretinin, a newly described useful marker.[4] S-100 stain shows a sustentacular pattern of staining but only in low-grade forms of ONB (Fig. 1). The Hyam's system used in grading tissue specimens cannot be applied to aspirate smears.

Sinonasal undifferentiated carcinoma (SNUC)

This highly aggressive neoplasm of the upper sinonasal tract is of uncertain histogenesis and contains round to polygonal cells with abundant necrosis. It must be differentiated from ONB, the Ewing family of tumors (EWS), and other poorly differentiated carcinomas that may arise in this region. It is reasonable to hypothesize that it arises from progenitor Schneiderian and

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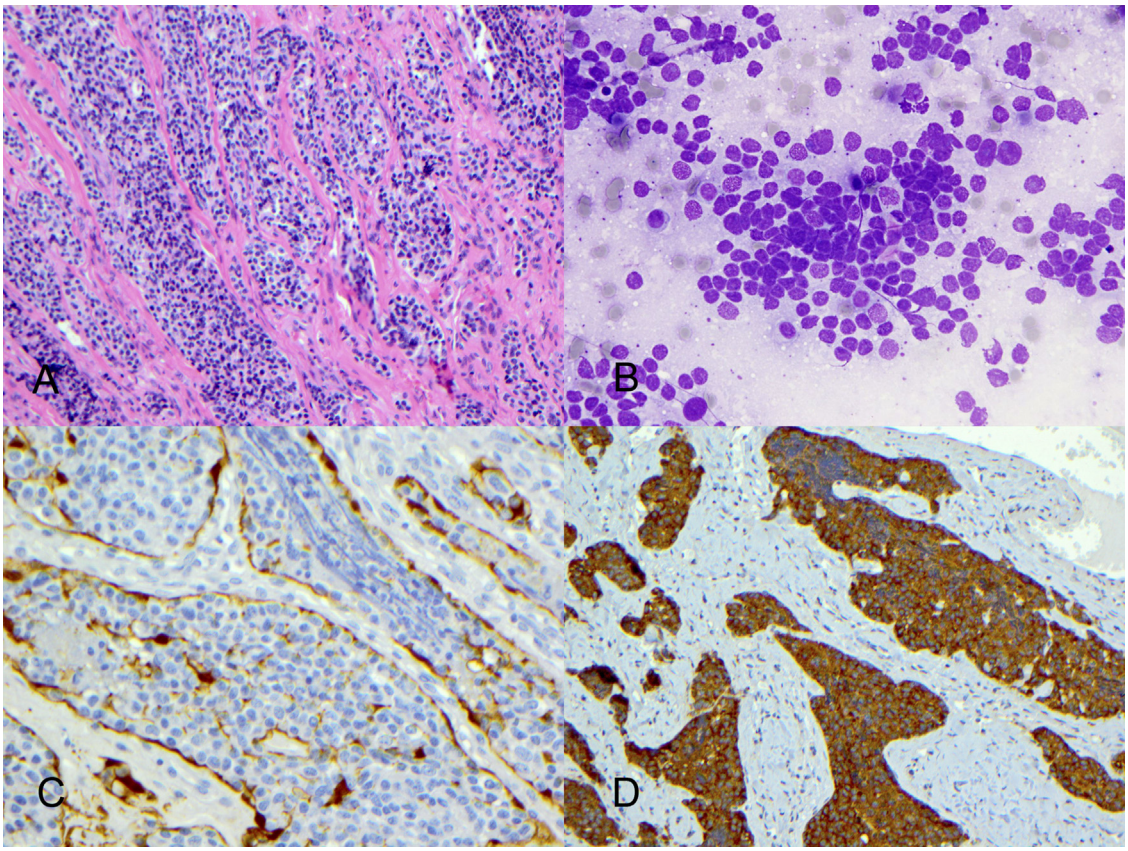

Fig. 1 – Olfactory neuroblastoma. (A) Trabecular cords of cells exhibit uniformly rounded small oval nuclei without mitoses, necrosis, or nuclear pleomorphism (H&E stain). (B) Uniformly sized cells in this FNA smear are arranged in loose clusters with rounded nuclei and minimal cytoplasm (Romanowsky stain). (C) S-100 shows a sustentacular pattern of staining. (D) Synaptophysin stain is strong and diffuse.

olfactory epithelium. In a period of several weeks to months, it can spread to involve the nasal cavity, orbit, skull base, and brain with bone destruction. There are no proven causative agents. More recently, it has been associated with the HPV virus that shows an improved disease-free and overall survival in affected cases.[5,6] Cytologic specimens are usually encountered in aspirates of metastatic disease. Smears contain single cells and cell aggregates often dispersed in a necrotic background. Polygonal cells have round to oval nuclei, usually possess a discrete macronucleolus, and sparse cytoplasm. Histologically, the tumor is arranged in solid or lobular sheets and trabeculae, often with abundant necrosis and a high Ki-67 index (Fig. 2). IHC staining is positive for pan-keratin stains and rarely focal for neuroendocrine markers. Although high-grade large cell NHL is part of the differential diagnosis of SNUC aspirates, the presence of cell aggregates and the absence of lymphoglandular bodies are usually sufficient to eliminate NHL from consideration.

Ewing sarcoma/primitive neuroectodermal tumor (EWS/PNET)

This "family" of tumors usually arises in the bone but may appear as a soft tissue tumor. Within the head and neck, EWS/PNET is commonly seen in the skull and jaws, and less often in the sinonasal tract, palate, and orbit.[7] These tumors are defined by a characteristic translocation of the *EWSR1* gene on chromosome 22q12 to the *FLI-1* gene on chromosome 11q24 in approximately 85% of cases. In the other 15%, *EWSR1* gene is fused to other members of the ETS transcription factor family. The resulting oncoproteins serve as molecular signatures for the disease. EWS/PNET occurs in children and young adults (up to 40 years) but has been reported rarely in the elderly also. Bulky polypoid masses with pushing borders are composed of a diffuse sheet-like proliferation of small uniformly sized cells with fine granular chromatin without nucleoli (Fig. 3). In smears, these cells closely simulate NHL, but cells are about 2–3 times the diameter of mature lymphocytes. Cytoplasmic vacuoles or blebs are often but not invariably present. In a logistic regression analysis study of small round cell neoplasms, cytoplasmic vacuolization and scant cytoplasm were most helpful in the identification of Ewing sarcoma.[8] A lacy smear background may be seen in cases where cells have abundant cytoplasmic glycogen. Immunohistochemical markers CD99 and FLI-1 are positive but not specific for this lesion. Reverse transcription polymerase chain reaction (RT-PCR) or FISH to detect the cytogenetic alterations in EWS/PNET are currently most specific diagnostically.

Merkel cell carcinoma (MCC)

MCC, a cutaneous malignancy of the elderly, has a marked predilection for the head and neck, particularly the periocular