Cytology of the Salivary Glands

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KEYWORDS

• Salivary gland • Cytology • Immunohistochemistry • Molecular

ABSTRACT

Common usage of fine-needle aspirate (FNA) for salivary gland lesions is the preoperative determination of whether a lesion is neoplastic, its lineage, and if neoplastic, whether it is low grade/benign, or high grade. Immunohistochemical stains can be performed on cell blocks to determine lineage and help refine diagnosis, although their performance is not always equivalent to that seen in surgical specimens. Several characteristic translocations have been described in various entities in these categories, and these can be evaluated using fluorescence in situ hybridization. In the future, high-throughput next-generation sequencing panels may further refine cytologic diagnosis in salivary tumors.

INTRODUCTION

The main objective of fine-needle aspirate biopsy (FNAB) in salivary gland lesions is to provide an assessment of a salivary gland nodule that can influence the decision for surgical intervention, as well as extent of surgery. Here, priorities for the cytopathologist can be summarized as follows: (1) distinction between neoplastic and non-neoplastic lesions, (2) lineage determination for neoplasms (ie, epithelial, hematolymphoid, melanocytic, and mesenchymal tumor categories), and (3) separation of benign/low-grade tumors from high-grade tumors. For high-grade malignancies, separation of primary tumors from metastases is often a priority as well.[1–10] Specific diagnosis is actually not necessary for an informative FNAB, and may be challenging if not impossible in many cases, given the considerable cytologic overlap between various entities.[3,11,12]

The performance of FNAB in obtaining the objectives outlined previously relies mainly on a strong foundation in traditional morphologic assessment. But even in experienced hands, there are several pitfalls and deficiencies in cytologic evaluation. Thus, akin to surgical pathology, a role for immunohistochemical and even molecular studies on aspirate material has emerged to refine diagnosis. This article focuses mainly on the application of immunohistochemical and molecular testing as applied to the salivary epithelial neoplasms.

DIFFERENTIAL DIAGNOSIS

Salivary gland tumors are arguably the most diverse group of neoplasms per unit of total body volume.[13] This diversity, as well as morphologic overlap between several tumor types, make FNAB diagnosis very challenging. Proper diagnosis on surgical specimens requires adequate sampling and an algorithmic approach; the aforementioned diversity makes "wallpaper matching" potentially treacherous. FNAB diagnosis also benefits from an algorithmic approach, but without a unifying architectural configuration or "border" as seen on paraffin sections of a tumor resection, aspirates are paradoxically a more complex amalgamation of parameters.[1–10]

FNAB, as alluded to previously, also relies heavily on cellularity and stromal/extracellular characteristics. Because non-neoplastic considerations have not been preselected away from the differential diagnosis (surgical resections are more likely to be performed for tumors), these still

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Surgical Pathology 7 (2014) 61–75
http://dx.doi.org/10.1016/j.path.2013.10.006
1875-9181/14/$ – see front matter

come into play and background inflammatory cell milieu thus becomes important. Furthermore, tinctorial qualities for a given tumor may vary on FNA smears in comparison with tissue sections, given the difference in stain preparation. For instance, as clear cell change is often composed of a combination of glycogenation, fixation, and staining, tumors that have clear-cell morphology on tissue sections may have a more oncocytoid appearance on aspirate material. Additionally, on FNA smears, cytoplasmic characteristics for myoepithelial and occasionally acinar cells may be stripped and absent altogether, imparting a basaloid appearance to a tumor that would be clear cell or oncocytic on histologic sections. Similar to histologic sections, cell constituents in a tumor are important on FNA, and here cell shape and size become even important for this determination.[1–10]

A detailed differential diagnostic approach is beyond the scope of this article. However, key FNAB categories that are encountered include the cellular/basaloid aspirate, the oncocytic or oncocytoid aspirate, cystic aspirate, and the lymphoid background rich aspirate. For this discussion, only epithelial neoplasms will be considered.

The cellular or basaloid aspirate commonly includes cellular pleomorphic adenoma, myoepithelioma, basal cell adenoma/adenocarcinoma, and adenoid cystic carcinoma (**Table 1**). Of these, adenoid cystic carcinoma is considerably more aggressive and is thus useful to recognize. All tumors in this category contain a mixture of ductal and myoepithelial cells, but certain characteristics, although often subtle, may be useful in separating these groups. Even cellular pleomorphic adenomas have areas containing the characteristic feathery myxoid matrix that appears metachromatic magenta on a Romanowsky-type stain (**Fig. 1**A, B). In contrast to the other categories, pleomorphic adenomas tend to have more cell heterogeneity, often containing plasmacytoid myoepithelial cells, ductal cells, and spindled stromal cells. Tumor cells that are embedded within the stroma may have a stellate or spindled appearance.[14,15] Myoepithelioma is not usually distinguishable from pleomorphic adenoma based on FNA alone given the considerable overlap, but the presence of ductal elements, if identified, would exclude this diagnosis.[16,17] Basal cell adenomas and basal cell adenocarcinomas are more uniform cytomorphologically (hence, the historic term monomorphic adenoma) and have a more collagenized stroma, although they still often have interdigitating tumor cells interspersed within (**Fig. 2**).[18–21] In contrast, adenoid cystic carcinoma is exceptionally monomorphic and contains angulated hyperchromatic nuclei with exceptionally scant cytoplasm with characteristic cylinders of matrix around which tumor cells are arranged, sharply demarcated rather than intermingling like the other categories (**Fig. 3**). One exception is the membranous variant of basal cell adenoma/adenocarcinoma, which has stroma that is very similar to that of adenoid cystic carcinoma.[18,22] But the nuclei of adenoid cystic carcinoma have coarser heterochromatin and a more irregularly shaped nucleolus than the other entities (see **Fig. 3**, inset).[23]

The oncocytic or oncocytoid aspirate has a broad differential diagnosis, but main considerations include oncocytoma, oncocytic cystadenoma, Warthin tumor, mucoepidermoid carcinoma, acinic cell carcinoma, mammary

Table 1
Key differential diagnostic considerations for the cellular basaloid aspirate

Diagnosis	Cytonuclear Features	Stromal/Background Characteristics
Pleomorphic adenoma	Diverse: bland ductal cells, plasmacytoid, epithelioid, and spindled cells	Myxoid with interspersed spindled to stellate cells Metachromatic on Romanowsky stain
Myoepithelioma	Bland plasmacytoid, epithelioid, and spindled cells, no ductal component	Myxoid to hyaline, less prominent than in pleomorphic adenoma
Basal cell adenoma/ Adenocarcinoma	Monomorphic ovoid cells with scant cytoplasm, can have ductal or squamous metaplasia, occasional peripheral palisading	Collagenized stroma with interdigitating tumor cells[a]
Adenoid cystic carcinoma	Monomorphic angulated hyperchromatic cells with angulated irregular nucleoli	Cylinders of hyaline stroma with a peripheral arrangement tumor cells

[a] Membranous variant may have adenoid cystic like stroma.