Seminars in Diagnostic Pathology 32 (2015) 264–274

Available online at www.sciencedirect.com

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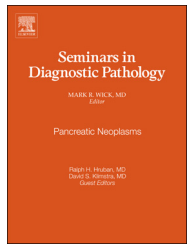

Update in salivary gland cytopathology: Recent molecular advances and diagnostic applications

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ARTICLE INFO

Keywords:
Salivary gland
Fine-needle aspiration
PLAG1
MYB
CRTC1
ETV6

ABSTRACT

Salivary gland tumors (SGT) are notorious for their extraordinary diversity and for the morphological overlap that exists between many of these entities. Fine-needle aspiration biopsy (FNAB) has a well-established role in the evaluation of patients with a salivary gland lesion, helping to guide clinical management. However, salivary gland FNAB has several limitations and does not allow for a specific diagnosis in some cases. For these reasons, salivary gland FNAB is considered one of the most challenging areas in cytopathology. Over the last decade, new salivary gland entities have been recognized, enlarging SGT diversity and complexity even more. In addition, a subset of SGT, including common entities such as pleomorphic adenoma and uncommon new entities such as mammary analog secretory carcinoma, have been characterized cytogenetically by the presence of specific translocations. The molecular consequences of these translocations and their potential prognostic and therapeutic values are not yet well characterized. However, these translocations and their resulting fusion oncogenes and oncoproteins can be used as diagnostic clues in salivary gland FNAB material in order to overcome the limitations of cytomorphological evaluation alone. In this review, we focus on SGTs currently known to harbor translocations and fusion genes, including uncommon and recently recognized entities, and discuss their potential application to salivary gland FNAB.

Introduction

Despite its limitations, fine-needle aspiration biopsy (FNAB) has a well-established role in the evaluation of salivary gland lesions and is reported to have a high sensitivity (86–100%) and specificity (90–100%).[1–10] Although the accuracy of FNAB is good for distinguishing benign from malignant salivary gland lesions (81–100%), it is more variable when used to specifically subtype a neoplasm (48–94%).[1–10] It is important to keep in mind that the main role of salivary gland FNAB is not necessarily to obtain a precise classification but rather to distinguish neoplastic from non-neoplastic lesions and, when neoplastic, benign and low-grade neoplasms from high-grade malignant tumors in order to guide the preoperative strategy and clinical management. Among malignant tumors, it is important to distinguish not only low-grade and high-grade malignancies but also primary and metastatic disease, because treatment options including the type and extent of surgery can differ significantly.

Salivary gland FNAB is one of the most challenging areas in cytopathology for several reasons including (a) the extraordinary

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http://dx.doi.org/10.1053/j.semdp.2014.12.008
0740-2570/

diversity of salivary gland tumors (SGTs) with 37 distinct epithelial neoplasms recognized by the latest WHO classification of head and neck tumors,[11] and certainly several more in the new upcoming edition, (b) the intratumoral heterogeneity of SGTs, and (c) the morphological overlap that exists between many SGTs. Therefore, cytomorphology alone, without the use of ancillary studies, has limitations. Descriptive diagnoses such as "basaloid neoplasm" or "oncocytic lesion," with a broad differential diagnosis including both benign [e.g., pleomorphic adenoma (PA)] and malignant tumors [e.g., adenoid cystic carcinoma (AdCC)], have been widely used, and may be all that is feasible in a subset of cases.[1] Ancillary diagnostic markers are needed in order to overcome these cytological limitations.

The characteristic cytomorphologic features of the common SGTs are very well described.[1,12,13] Therefore, in this review, we focus on recent molecular advances in SGTs, including uncommon and recently recognized entities, and their potential diagnostic applications in salivary gland FNAB.

Translocations and fusion oncogenes in salivary gland tumors

The recent discoveries of specific translocations and resulting fusion oncogenes in a subset of SGT has been a significant breakthrough that has led to changes in the way that SGTs are diagnosed in surgical resection specimens and also in FNAB samples.[14–17] Although the translocation t(3;8), which results in upregulation of *PLAG1* (pleomorphic adenoma gene 1) gene expression in PA, has been known for almost 2 decades,[18–21] the discovery of translocations in other SGTs, especially carcinomas, are more recent. These cytogenetic hallmarks involve common SGTs such as mucoepidermoid carcinoma (MEC) and AdCC, as well as uncommon SGT such as hyalinizing clear cell carcinoma (HCCC), mammary analog secretory carcinoma (MASC), and lately the controversial entity cribriform adenocarcinoma of minor salivary glands (CAMSG).[22,23] The major translocations and resulting fusion oncogenes found in SGTs are summarized in Table 1. It is likely that in the near future, additional SGTs will join this list. Many of these genetic alterations are not specific since they have been found in other tumor types from other organs that may or may not show morphological overlap with their SGT counterpart. For example, the translocation t(6;9) involving *MYB* and *NFIB* is characteristic of AdCC of the salivary gland but is also commonly found in AdCC of the breast as well as in benign dermal cylindromas, which look morphologically similar to AdCC but behave very differently.[24–26] In contrast, translocation t(12;22), generating the EWSR1–ATF1 fusion oncogene, which is characteristic of HCCC,[27–29] is also consistently found in at least 4 other neoplasms with diverse morphologies and behaviors, including angiomatoid fibrous histiocytoma, clear cell sarcoma of soft parts, clear cell sarcoma-like tumor of the gastrointestinal tract, and primary pulmonary myxoid sarcoma,[30] as well as clear cell odontogenic carcinoma, which is the intraosseous counterpart of HCCC.[28] However, within the limited spectrum of SGTs, these translocations appear to be specific and therefore can serve as ancillary diagnostic markers.

Although their precise role in the carcinogenesis of SGT is still unclear, these translocations and resulting fusion oncoproteins typically target transcription factors involved in

Table 1 – Benign and malignant salivary gland tumors associated with translocations.

Salivary gland tumor	Most common translocation	Genes involved	Prevalence	Other common translocations or abnormalities	Other genes involved	Main references
Benign						
Pleomorphic adenoma	t(3;8)(p21;q12)	*PLAG1*, *CTNNB1*, and *LIFR*	50–60%	*HMGA2* rearrangement, *HMGA2*, and *MDM2* amplification	*HMGA2*, *MDM2*, and *WIFI*	18–21,38,39
Malignant						
Mucoepidermoid carcinoma	t(11;19)(q21–22;p13)	*MAML2–CRTC1* gene fusion	60–75%	t(6;22)(p21;q12)	*EWSR1–POU5F1* gene fusion	42–46
Adenoid cystic carcinoma	t(6;9)(q22–23;p23–24)	*MYB–NFIB* gene fusion	64%	*MYB* rearrangement		24,25,63–68
Mammary analog secretory carcinoma	t(12;15)(p13;q25)	*ETV6–NTRK3* gene fusion	90–100%			70–72
Hyalinizing clear cell carcinoma	t(12;22)(q13;q12)	*EWSR1–ATF1* gene fusion	85%			27–29
Carcinoma-ex-pleomorphic adenoma	same as pleomorphic adenoma	same as pleomorphic adenoma		Same as pleomorphic adenoma + additional alterations including mutations of *TP53* and amplification of *HER2*		32,37,39
Cribriform adenocarcinoma of MSG	*PRKD* rearrangement	*PRKD1*, 2, 3. *ARID1A*	80%	Variant fusions		23

MSG: minor salivary glands.