Review Article

Recent advances in salivary gland cytopathology

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Abstract

Salivary gland tumors (SGTs) are noted for their exceptional heterogeneity and diversity and for the common morphological overlap taking place between the different entities. Fine needle aspiration cytology (FNAC) is a valuable tool in the primary diagnosis and management of SGTs. These lesions are generally not subjected to incisional or core needle biopsy because of possible risk of causing a fistula or disruption of the capsule with seeding of tumor cells and subsequent recurrence. FNAC has not been associated with these complications, emphasizing its critical role in the diagnosis of SG lesions. In addition, FNAC is a suitable sampling method for new molecular testing. Recent advances in molecular techniques and the availability of molecular markers have allowed the analysis of submicroscopic alterations in the tissues of these tumors. Moreover, new neoplastic entities have been recognized that contain oncogenic translocations. In this review, we will discuss the recent advances in SG neoplasia and new molecular findings in the SGTs will also be addressed.

KEY WORDS: Salivary cytopathology, recent molecular advances, salivary gland tumors

Introduction

Head and neck pathology is a diverse subspecialty because of the proximity of tissues of various types and the wide range of primary and metastatic neoplasms that frequently occur in this site. Salivary gland tumors (SGTs) are noted for their exceptional heterogeneity and diversity and for the frequent morphological overlap taking between the different entities. There is perhaps no tissue anywhere in the body that is subject to such a diverse range of tumors and tumor-like conditions. Fine needle aspiration cytology (FNAC) has a well-established critical role in the evaluation of salivary gland (SG) lesions.[1–5] These lesions are generally not subjected to incisional or core needle biopsy because of the possible risk of causing a fistula or disruption of the capsule with seeding of tumor cells and subsequent recurrence. FNAC has not been associated with these complications, emphasizing its critical role in the diagnosis of SG lesions. FNAC of the SGs is virtually risk-free and offers enough information to plan appropriate patient management.

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Some studies demonstrated the sensitivity, specificity, and accuracy of tumor typing of FNAC for SGTs range from 81% to 100%, 94% to 100% and 61%–80%, respectively.[1–5] The diagnostic precision can be substantially developed by procuring a complete clinical history, obtaining an adequate cellular specimen, and having knowledge of the variety and frequencies of possible diagnostic entities presenting as a SG mass. However, a precise diagnosis by FNAC may seem an impossible task. Hence, FNAC is an effective modality for SG lesion evaluation, providing rapid and valuable initial triage information, such as salivary vs. nonsalivary origin of the lesion, neoplastic vs. nonneoplastic, and low-grade benign vs. high-grade malignant.

In addition, FNAC is a suitable sampling method for new molecular testing. Recent advances in molecular techniques and the availability of molecular markers have allowed the analysis of submicroscopic alterations in the tissues of these tumors. These studies, although preliminary, have set the stage for an in-depth analysis of target chromosomes to identify putative genes associated with these tumors.[6–9] More detailed analysis may therefore identify specific oncogenes and tumor suppressor genes possibly associated with development and progression of these tumors. Over the last decade, new SG entities have been recognized and, in addition, new molecular profiles have been described for some tumors.

This review attempts to highlight the recent advances in the field of SG cytopathology, with an emphasis on lesions that are currently known to harbor recurrent genetic alterations.

Translocation–Associated Salivary Gland Tumors

Translocations are believed to be occurring in 20% of all cancers. Traditionally, translocations have been thought to be rare in epithelial tumors. But the latest discoveries of specific translocations and their resultant fusion oncogene products in a subset of SGTs have shed new light upon the knowledge of the molecular evolution of these rare neoplasms. Although *PLAG1* rearrangements in pleomorphic adenomas (PAs) have been known for some time now, it has other SGTs, especially carcinomas have been found to have translocations as well. These include commons SGTs such as mucoepidermoid carcinomas (MEC), adenoid cystic carcinoma (AdCC), and the newly described entity mammary analog secretory carcinoma (MASC). This list is likely to grow with controversial newer additions such as cribriform adenocarcinomas of the minor salivary glands (CAMSG), thanks to the rapid advancements of next generation sequencing and genomic and expression profiling methods, happening in the arena of molecular diagnostics.

It is to be noted that many of these genetic alterations may not be specific as they are known to occur in other tumor types from other organs as well. But, within the limited spectrum of SGTs, these fusions and their downstream targets are new important potential biomarkers for clinical and molecular diagnosis of SGTs.

Pleomorphic Adenoma (PA)

PA is the commonest SGT, accounting for 60%–70% of all parotid gland, submandibular gland, or accessory gland tumors, while sublingual sites are extremely rare.[10] It is a slowly growing, painless, and movable mass, observed in patients of 40–45 years with a female predominance. PAs may also occur in young children, and its incidence is found to be less than 1%. Two components are required to reliably make a diagnosis of PA: myoepithelial cells and chondromyxoid stroma. Myoepithelial cells, either ovoid, plasmacytoid, or spindle-shaped with abundant well-defined cytoplasm and bland finely granular nuclear chromatin and smooth nuclear membrane are seen embedded in fragments of chondromyxoid matrix.[11] The cytological diagnosis of PA is not difficult in typical cases [Figure 1]. However, if the stromal component is scanty or missing, and smears are highly cellular, the distinction from basaloid neoplasms and myoepithelial adenoma can be difficult or even impossible. Moreover, cytological atypia, background mucus, metaplastic epithelial cells (squamous, oncocytic, mucinous, or sebaceous) may mimic low-grade MEC and hyaline stromal globules or a beaded hyaline stroma may give rise to suspicion of well-differentiated AdCC.[12] In difficult cases, positive immunostaining for intermediate filaments such as GFAP and negative staining of majority of cells for cytokeratin can be helpful.[13]

Extensive cytogenetic studies of PAs have shown that approximately 70% of the tumors are karyotypically abnormal.[10] Four main cytogenetic subgroups have been described:

i. Tumors with rearrangements involving 8q12 (39%): commonest translocations are t(3;8)(p21;q12);[10] [Figure 2]
ii. tumors with rearrangements of 12q13-15 (8%): commonest translocations are t(9;12)(p24;q-15);
iii. tumors with sporadic changes not involving either of the above; and
iv. tumors with an apparently normal karyotype (30%).[10]

The target gene in PAs with 8q12 abnormalities is *PLAG1*, and the translocations lead to activation of *PLAG1* expression. The most common fusion partner of *PLAG1* is *CTNNB1*, the gene encoding β-catenin.[14] The target gene in PAs with rearrangements of 12q13-15 is the *HMGA2* gene, resulting in its amplification. The *PLAG1*- and *HMGA2*- containing fusions may be detected by reverse transcriptase-polymerase chain reaction (RT-PCR) or fluorescence in-situ hybridization (FISH). *PLAG1* upregulation can also be assessed by immunohistochemistry; most PAs (94%) are strongly immunoreactive for *PLAG1*,[15] whereas *PLAG1* is negative in most SG carcinomas, including AdCC, MEC, and acinic cell carcinoma (ACC).

Conflicting reports of specificities of the *PLAG1* and *HMGA2* alterations with respect to PAs exist. Some authors claim that the five *PLAG1*- and *HMGA2*- containing fusion genes so far identified are all tumor-specific and, therefore, may be used as diagnostic markers for PAs.[10] But others mention the characteristic translocations involving these genes have also been found in other benign mesenchymal tumors.[16]

Moreover, the prognostic significance of these alterations has been debated upon. In one study, high level expression of *HMGA2* has been suggested to be of importance for malignant transformation of PAs, whereas others say that there is currently no known prognostic significance for these molecular abnormalities in terms of PA behavior.[16]

Cytologically, cellular PAs may be difficult to distinguish from other similar looking neoplasms, and, in such settings, immunocytochemistry and/or FISH for *PLAG1* can prove useful.

Mucoepidermoid Carcinoma (MEC)

MEC is the most general primary SG malignancy, in both adults and children.[10] They occur with equal frequency in major and minor SGs, with 45% predominating in the parotid. MECs are composed of three cell types: epidermoid, intermediate, and mucinous cells [Figure 3]. They include a wide range of spectrum from non-aggressive low-grade cancers to highly aggressive forms, and it is important to distinguish between low-grade and high-grade MECs as the treatment and prognosis depend on the grade: low-grade tumors can treated by local excision with the 5-year survival rate being 98%, whereas the high-grade MECs need radical therapy with possible lymph node dissection with the 5-year survival rate dropping to about 56%.[17]

MECs can sometimes be extremely challenging to diagnose by FNAC alone, especially the low-grade forms. Hence, when feasible, a cell block preparation is valuable because it may provide diagnostic elements and/or material for ancillary techniques such as FISH.[18] Molecular studies of these tumors are few and limited in number of cases. They had shown infrequent alterations in oncogenes such as *H-RAS* (<20%).[19] Recently, it has been discovered that MECs, irrespective of histological grade, are characterized by a recurrent chromosomal translocation t(11;19)(q21;p12) resulting in *CRTC-MAML2* fusion in 40%–70% cases[20] [Figure 4]. The fusion transcript was found to disrupt the Notch signaling pathway. Further studies by Behboudi et al.[21] highlighted the prognostic importance of this fusion.

Although *CRTC-MAML2* polyclonal antibodies have been developed commercially, further studies are needed to evaluate their diagnostic utility for MEC.[18] The *CRTC –MAML2* translocation can be identified using FISH or RT-PCR-based assays. Fusion-positive cases that have been found in younger patients, are smaller, tend to be low-grade, and show lesser incidence of recurrence, metastases, and tumor-related mortality than fusion-negative cases.[21] The fusion has been found to occur in MECs at other sites as well, including, lung, thyroid and cervix, whereas it has not been found in any other SG carcinoma. It is therefore specific to MECs and can also be used as a diagnostic tool to differentiate MECs from other high-grade SG carcinomas.[22]

Some studies have shown this fusion product to be positive in Warthin's tumor (WT) as well, whereas other authors have not found this association.[22,23] Moreover, the presence of high-grade aggressive tumors in some translocation positive cases highlighted by recent studies has put the credibility of *MAML2* FISH as a true prognostic marker to test.[22] But, for now, *MAML2* FISH is considered potentially prognostic, although its clinical utility has yet to be proven sufficiently.[16]

Adenoid Cystic Carcinoma (AdCC)

AdCC is the second most common SG malignancy, comprising 10% of all SG cancers.[10] It is the most common malignancy in the minor SGs with the highest frequency in the palate, followed by the tongue, buccal mucosa, lip, and floor of the mouth. Histologically, it is a basaloid tumor, consisting of ductal epithelial and myoepithelial cells in different configurations, namely, tubular, cribriform, and solid patterns, each of them usually forming a part of a composite tumor. Perineural invasion is a common and frequently conspicuous feature of AdCC. In addition, it may also extensively invade the underlying bone. FNAC smears show basaloid cells and metachromatic hyaline material in the form of hyaline spherical globules [Figure 5].

AdCC is important because it is relentless clinical course and usually a fatal outcome. The local recurrence rate ranges up to 85% in several series of these tumors, the recurrence being a serious sign of incurability. Hence, a correct diagnosis is very useful in managing these aggressive cancers. A subset

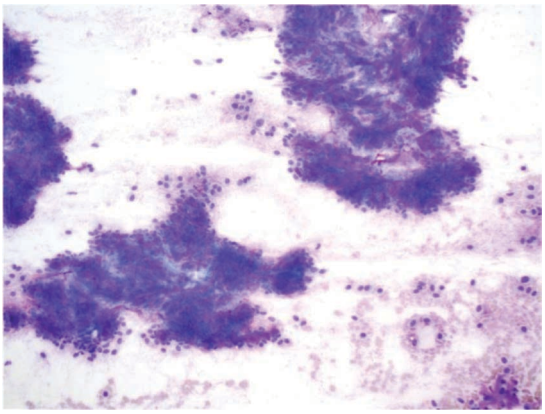

Figure 1: Pleomorphic adenoma showing benign epithelial cells entrapped in typical fibrillar fibromyxoid stroma (Papanicoloau stained, × 100).

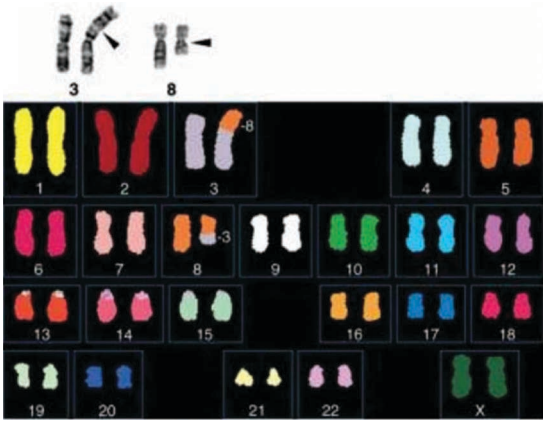

Figure 2: Karyotype of a pleomorphic adenoma showing the most common abnormality t(3;8)(p21;q12) translocation.[10]

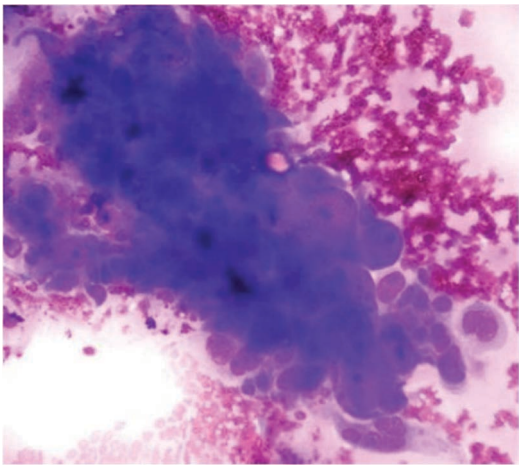

Figure 3: Mucoepidermoid carcinoma—high grade with pleomorphic, clearly malignant cells with squamoid differentiation. Areas with mucoid background were also present in the same slide. (Papanicoloau, × 100).

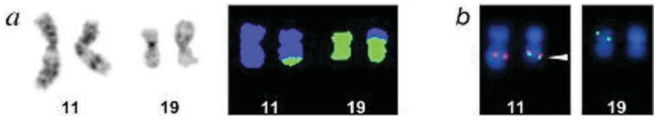

Figure 4: Mucoepidermoid carcinoma showing translocation t(11;19) (q21;p12) resulting in *CRTC-MAML2* fusion.[31]

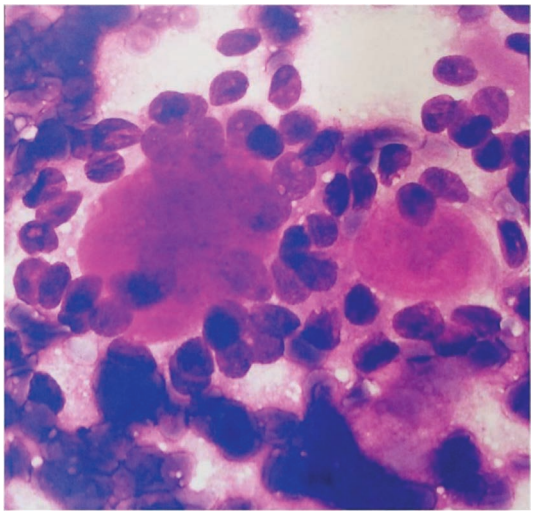

Figure 5: Adenoid cystic carcinoma showing uniform hyperchromatic epithelial cells adherent to large hyaline stromal globule (May-Grunwald Giemsa, × 100).

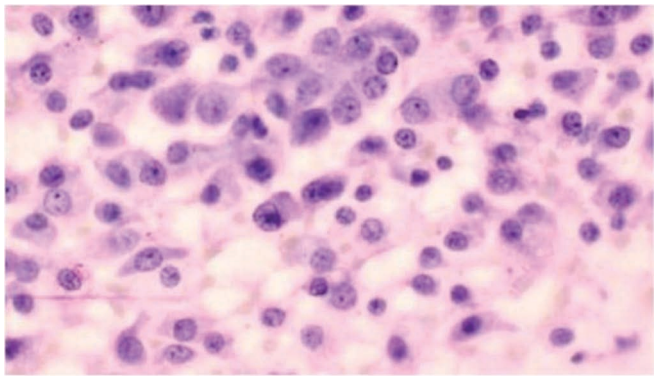

Figure 6: Mammary analog secretory carcinoma showing loosely cohesive populations of low-grade appearing cells with round to oval nuclei, fine granular chromatin, and moderate amount of vacuolated cytoplasm in a background of pale-staining eosinophilic homogenous seromucinous material (Papanicoloau, × 100).[28]

of AdCCs, especially the solid subtype can be difficult to distinguish from other tumors with hyaline stromal globules, such as PA, epithelial-myoepithelial carcinoma, and polymorphous low-grade adenocarcinoma (PLGA). Immunocytochemical stain CD117 (c-Kit) is strong positive for the tumor cells, but it is not specific.[24] Multiple studies have found no evidence of c-KIT mutations in AdCC and trials using imatinib (which targets c-KIT) have shown that it appears to have low

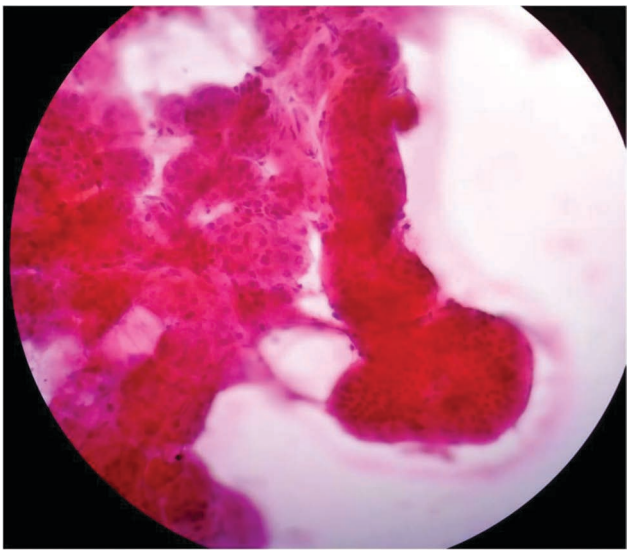

Figure 7: Acinic cell carcinoma showing epithelial cells in clusters and microacinar groups with scant inconspicuous fibrovascular stroma. Individual cells have medium-sized, rounded nuclei and bland chromatin with abundant fine cytoplasm. (Papanicoloau, × 100).

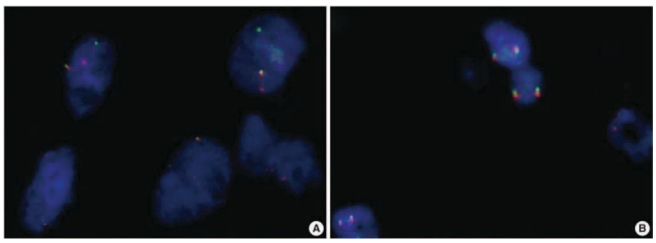

Figure 8: ETV6 in a case of mammary analog secretory carcinoma showing one fused (yellow) and one split (red and green) signal indicating a translocation.[31]

efficacy.[25] Several studies have also demonstrated isolated genomic losses at individual loci such as loss of heterozygosity 12q, 1p, and 9p. These may be helpful in future investigations of these tumors.[10] Alterations of p53 and Rb genes have also been reported in AdCCs.

The t(6;9)(q21-24;p13-123) has been reported in several tumors and is considered to be a primary event in at least a subset of these tumors.[10] This translocation causes the fusion of *MYB* oncogene with the *NFIB* transcription factor gene and was seen in 100% of the cases tested by Persson et al.[26] with the resultant overexpression of *MYB*. This fusion has not been observed in any other SGT except rare cases of PLGA and cylindromas of skin, indicating that it may be a hallmark of AdCC. Furthermore, the resulting *MYB* overexpression occurs in almost 90% of AdCCs including those without the *MYB-NFIB* fusion, suggesting that other molecular mechanisms may be involved.[18] Further studies are needed to evaluate whether these tumors with alternate underlying mechanisms show different biological behavior and, hence, different clinical consequences as well. Immunoreactivity for *MYB* has been

found to be positive in AdCCs, more in alcohol-fixed FNAC smears and frozen tissue samples than in paraffin-embedded tissue sections taken from resected specimens, the probable reason being the different fixation methods affecting the fusion positivity rates. The fusion product can also be detected by FISH as reported by Hudson and Collins,[27] FISH being as specific as immuno-studies but less sensitive for distinguishing AdCC from PA.[18] At this point, nothing conclusive can be said about the definitive role of this translocation in AdCC as a diagnostic marker, a prognostic marker, or therapeutic target.

Mammary Analog Secretory Carcinoma (MASC)

MASC of SG origin is an entity recently described by Skalova et al.[28] Cytologically, it is characterized by loosely cohesive populations of low-grade appearing cells with round to oval nuclei, fine granular chromatin, and moderate amount of vacuolated cytoplasm in a background of pale-staining eosinophilic homogenous seromucinous material [Figure 6]. This tumor resembles secretory carcinoma of the breast, histologically and immunohistochemically, hence the name. It also mimics ACC, sharing the granular cytoplasm, microvacuoles, and microcystic growth pattern of ACC but lacking the cytoplasmic basophilia characteristic of ACC owing to the presence of zymogen granules [Figure 7]. Moreover, it has been found to have a completely different immunohistochemical profile of CK7, vimentin, S100, gross cystic disease fluid protein (GCDFP)-15, all of which are absent in ACC. In addition, and most importantly, it harbors a t(12;15)(p13;q25) translocation, resulting in *ETV6-NTRK3* fusion product. MASC is the only known primary SGT harboring this translocation, and it has been detected in almost 100% of cases reported in the recent literature. Earlier MASC was classified under ACC or adenocarcinomas—NOS. But, as Bishop et al.[29] have reported, recent molecular studies have indicated that most nonparotid ACCs probably represent MASC, on the basis of *ETV* translocation. It is to be noted that these fusions have also been observed in other neoplasms such as acute myeloid leukemia, congenital mesoblastic nephroma, and fibrosarcoma,[30] suggesting that the fusion protein has transforming activity in cells of different lineages.

The cytological picture of MASC can be confused with that of other oncocytic SGTs such as PA, MEC, ACC, and WT. The most definitive marker, *ETV6-NTRK3* fusion product can be detected using an RT-PCR assay or a FISH-based approach [Figure 7]. Alternatively, some authors have proposed that next-generation sequencing (NGS) can also be used, its advantage being that NGS can be performed on FNAC material with only nanograms of DNA.[18] This tumor, similar to its mammary counterpart, behaves like an indolent tumor with an overall favorable outcome, but certain reports of high-grade transformation with aggressive clinical course have also come forward.[28]

In terms of SG mimics, there is less of an impact to the diagnosis of MASC, because both result in essentially similar clinical outcomes. However, *ETV6* FISH is useful to make the diagnosis in difficult cases and to rule out the benign SGTs. In addition, the *ETV6-NTRK3* translocation may represent a therapeutic target for MASC in the future, thus also enhancing its potential diagnostic role.

Conclusion

SGTs are notorious for their extraordinary heterogeneity and diversity in the morphological picture. Despite its limitations, FNAC plays a well-established role in the evaluation of SGTs. Although cytomorphology and histomorphology still remain the mainstays of the initial management of SGTs, there is a need for new diagnostic, prognostic, and therapeutic biomarkers based on molecular studies so as to improve the classification and, thereby our understanding of SGTs. FNAC specimens, especially cell blocks are feasible for most molecular genetic studies as they can provide adequate material for these ancillary studies. The abnormal oncoproteins resulting from the translocations seen in a subset of SGTs can be detected by using immunocytochemistry or on FISH. Newer modalities such as NGS will greatly facilitate further research for the development of improved therapeutic options for patients of SGT.

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