Salivary gland lesions: recent advances and evolving concepts

Ruta Gupta, MD, FRCPA,[a,b] Deepak Balasubramanian, MS, DNB, MCh,[c,d] and Jonathan R. Clark, M.Biostat FRACS[b,c,d]

Recently, there have been significant developments in our understanding of salivary gland pathology, and new entities, such as mammary analogue secretory carcinoma, have been described. Attempts are being made to identify effective therapeutic agents for salivary duct carcinomas by using molecular diagnostic techniques. Concepts such as high-grade transformation have been described, which not only influence macroscopic and microscopic evaluation of a specimen but, given the high incidence of metastases and morbidity, also carry significant treatment implications. Specific chromosomal translocations, which can be detected by fluorescent in situ hybridization, can augment diagnostic accuracy and carry prognostic implications.

The landscape of benign salivary gland lesions is changing with better understanding of chronic sclerosing sialadenitis related to IgG4. This multiorgan inflammatory condition may primarily present as a salivary gland lesion and clinically and radiologically mimic a salivary gland malignancy. Histology and immunohistochemistry play a critical role in its accurate diagnosis.

The purpose of this article is to review these changes, with an emphasis on their effect on patient management. Given their diagnostic, prognostic, and therapeutic implications, it is critical that surgeons, oncologists, pathologists, and those involved in caring for patients with salivary gland tumors are aware of these changes while considering management options.
(Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119:661-674)

The classification of salivary gland tumors is rapidly evolving with description of new entities, such as mammary analogue secretory carcinoma (MASC).[1] Other entities, such as salivary duct carcinoma, are being increasingly recognized with improved understanding of their molecular characteristics.[2,3] The concept of high-grade transformation has been described in adenoid cystic carcinoma, acinic cell carcinoma, and other salivary gland tumors.[4,5] Furthermore, specific chromosomal translocations, which can be easily detected by fluorescent in situ hybridization (FISH), have been described in adenoid cystic carcinoma, mucoepidermoid carcinoma, MASC, and in the rare hyalinizing clear cell carcinoma.[6-9] These chromosomal translocations may improve diagnostic accuracy and carry prognostic implications.[6-10] Most of these changes are being fueled by increased use of ancillary diagnostic techniques and genetic sequencing. However, considering their diagnostic, prognostic, and therapeutic implications, it is critical that surgeons and those involved in caring for patients with salivary gland tumors are aware of these changes while considering management options.

Here, we review the changes in our understanding of salivary gland lesions, with an emphasis on their effect on patient management. We also look at the recently described disease in the salivary gland associated with immunoglobulin G4 (IgG4). Table I briefly summarizes both the conventionally recognized salivary gland tumors and the current evolution in salivary gland pathology.

NEW ENTITIES

Mammary analogue secretory carcinoma

MASC, a low-grade malignant neoplasm of the salivary gland, was described by Skalova et al. in 2010.[1] Skalova et al. studied 16 examples of morphologically similar salivary gland tumors, which had been designated as zymogen granule–poor acinic cell

[a]Department of Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Missenden Road, Camperdown NSW 2050, Australia.
[b]Central Clinical School, University of Sydney, NSW 2006, Australia.
[c]Sydney Head and Neck Cancer Institute, The Chris O'Brien Lifehouse, Missenden Road, Camperdown NSW 2050, Australia.
[d]Department of Head and Neck Surgery, Royal Prince Alfred Hospital, Missenden Road, Camperdown NSW 2050, Australia.
Received for publication Jul 6, 2014; returned for revision Feb 7, 2015; accepted for publication Feb 20, 2015.

2212-4403/$ - see front matter
http://dx.doi.org/10.1016/j.oooo.2015.02.481

Statement of Clinical Relevance

This article reviews the changes in salivary gland pathology, with an emphasis on their effect on diagnosis, prognosis, and patient management, and provides relevant information for surgeons, oncologists, and pathologists involved in caring for patients with salivary gland tumors.

Table I. Current evolution in salivary gland pathology

New entities	*Old entities: new concepts*	*New ancillary diagnostic/prognostic/ predictive tests*
a. Mammary analog secretory carcinoma b. Hyalinizing clear cell carcinoma c. IgG4-related chronic sclerosing sialadenitis	a. Salivary duct carcinoma: Genetic alterations amenable to targeted therapy: -Her2 amplification in salivary duct carcinoma -BRAF mutations in salivary duct carcinoma b. Epithelial−myoepithelial carcinoma: improved recognition of a wide morphologic spectrum. c. High-grade transformation in: -Acinic cell carcinoma -Adenoid cystic carcinoma -Epithelial−myoepithelial carcinoma -Myoepithelial carcinoma -Mammary analog secretory carcinoma -Mucoepidermoid carcinoma	Chromosomal translocations of diagnostic or prognostic utility detectable by fluorescent in situ hybridization: -Mucoepidermoid carcinoma -Adenoid cystic carcinoma -Hyalinizing clear cell carcinoma -Mammary analog secretory carcinoma

IgG4, immunoglobulin G4.

carcinomas in the past, and identified a specific, novel chromosomal translocation (ETV6-NRTK3 fusion gene; (12; 15) (p13; q25)).[1] This rearrangement results in fusion of transcription regulator ETV6 with membrane receptor kinase NTRK3.[1] MASCs show morphologic and molecular features similar to the secretory carcinomas of the breast, leading to the proposal of the nomenclature *mammary analog secretory carcinoma*.[1,11,12] MASCs occur in men and women in both major and minor salivary glands.

Previous diagnosis. These tumors were largely categorized as zymogen granule−poor acinic cell carcinoma or rarely as mucoepidermoid carcinoma in the past.[1,13]

Histology, special stains, and immunohistochemistry. Macroscopically, MASCs are relatively well-defined, lobulated neoplasms with a cystic component (Figure 1A).[1,14] These tumors show a solid, tubular or microcystic pattern (Figure 1B). The tubular and microcystic spaces contain thin eosinophilic, bubbly secretions. The lining polygonal cells show eosinophilic, granular, or vacuolated cytoplasm and a uniform central round nucleus with a single distinctive nucleolus[1,4,14] (Figure 1C). Invasion into periglandular tissue has been described.[1,14] Lymphovascular and perineural involvement, although rare, have been described.[14]

Special stains, such as periodic acid Schiff's reagent following diastase digestion (DiPAS) (Figure 1D) and mucicarmine highlight the secretions. Immunohistochemically, the tumor cells show strong and diffuse positivity with S100 (Figure 1E), MUC4, and mammoglobin and lack immunoreactivity with squamous and myoepithelial markers, such as p63, calponin, and SMA.[1]

Diagnosis. PREOPERATIVE FINE-NEEDLE ASPIRATION. A definitive preoperative diagnosis is difficult, although there are case reports describing the cytologic features of MASC in fine-needle aspiration (FNA) specimens. MASCs show several overlapping cytologic features with other low-grade salivary gland neoplasms, such as acinic cell carcinoma, low-grade mucoepidermoid carcinoma, and myoepithelial neoplasms.[15,16]

A cellblock with high cellular yield may facilitate special stains and discriminatory immunohistochemical panel.

POSTOPERATIVE FINAL HISTOLOGIC DIAGNOSIS. Histologic diagnosis is relatively easily made in a resection specimen based on the morphologic features in conjunction with special stains and immunoreactivity for S100, MUC4, and mammoglobin.[1,13,14,17] FISH studies for (*ETV6-NRTK3* fusion gene; (12; 15) (p13; q25)) (Figure 1F) are also available, if needed.

The main differential diagnosis is acinic cell carcinoma. Distinction of acinic cell carcinoma from MASC is based on recognizing the presence of intracytoplasmic zymogenic granules in acinic cell carcinoma and their absence in MASC.[18] Acinic cell carcinomas also lack immunoreactivity with S100 and MUC4.

Lack of stromal matrix, spindle-shaped or clear cells, targetoid perineural invasion at the periphery, and a discriminatory immunohistochemical panel, as described above, comprising of S100, MUC4, p63, CK5/6, and calponin can help in distinguishing this entity from other low-grade myoepithelial neoplasms, mucoepidermoid carcinoma, and polymorphous low-grade carcinoma, respectively.[1,13,14]

Management and prognosis. Prognostic information for MASC is still evolving. Historically, MASC has