Evolving concepts and new entities in the 2017 WHO classification of salivary gland tumors☆

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Abstract

For the past decades, many new salivary gland entities have been described which are somewhat related to the discovery of unique molecular alterations in these tumors. The 4th edition of World Health Organization (WHO) classification of head and neck tumors has included several new entities, e.g. secretory carcinoma, sclerosing polycystic adenosis and intercalated duct lesions and modified several carcinomas, e.g. clear cell carcinoma, intraductal carcinoma and polymorphous adenocarcinoma. In addition, in the 4th edition, the concept of high grade transformation has been introduced. In this review, we aimed to illustrate the major changes in the WHO classification, focusing on the rationale behind these changes, the morphologic features of the new described entities and the ancillary diagnostic tools that may help with the differential diagnoses of salivary gland neoplasms.

Keywords clear cell carcinoma; high grade transformation; intercalated duct lesion; intraductal carcinoma; polymorphous adenocarcinoma; sclerosing polycystic adenosis

Introduction

With the publication of the 4th edition of World Health Organization (WHO) classification of head and neck tumors in 2017,[1] several significant changes have taken place in the classification of salivary gland neoplasms which impact the daily pathology practice. In this article, we review these changes, summarizing them in three sections: 1) the introduction of the concept of high grade transformation (HGT); 2) the modification of several carcinomas including polymorphous adenocarcinoma (PAC), clear cell carcinoma (CCC) and intraductal carcinoma (IC); and 3) the inclusion of new entities, e.g. secretory carcinoma (SC), sclerosing polycystic adenosis (SPA) and intercalated duct lesion (IDL).

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High grade transformation in salivary gland carcinoma

The concept of high grade transformation (a.k.a. dedifferentiation) was first introduced in salivary gland carcinoma by Stanley et al. in 1988.[2] The authors described six cases of acinic cell carcinoma (AciCC) which were associated with high grade adenocarcinoma or undifferentiated carcinoma. Among these six patients, two developed distant metastases and two eventually died of their disease. Since then, high grade transformation have been reported in over 100 patients with an expanding list of different types of salivary gland carcinoma, including AciCC,[2–6] adenoid cystic carcinoma (ACC),[7–9] epithelial-myoepithelial carcinoma (EMC),[10–12] SC,[13,14] PAC,[15–17] CCC,[18,19] myoepithelial carcinoma,[20] and mucoepidermoid carcinoma (MEC).[21,22] Table 1 provides a brief summary of the literature on the histologic features and clinical outcomes of salivary gland carcinomas with HGT. In general, HGT can be defined as progression of a carcinoma (typically low grade) with classical histologic features into a pleomorphic high grade carcinoma (Figure 1). The high grade component is characterized by marked nuclear pleomorphism and cytologic atypia, prominent tumor necrosis and high mitotic index (typically 10 or more mitotic figures per 10 high power fields). Compared to the conventional types of salivary gland carcinoma, tumors with HGT have been reported to have more aggressive clinical behaviors, including advanced clinical stage at presentation, frequent recurrences, high rate of lymph node or distant metastases and increased risk of disease-related death (Table 1). Therefore, it is important to recognize and report the presence of HGT in a salivary gland carcinoma. Relatively new to the prior edition, the 4th edition of the World Health Organization (WHO) classification of head and neck tumors has incorporated the concept of HGT into salivary gland carcinoma.[1]

Practice points

- HGT is typically characterized as a carcinoma with marked nuclear atypia, frequent mitotic activity and comedo necrosis juxtaposed to a (low grade) salivary gland carcinoma with typical conventional histology.
- HGT should be documented as it has been reported to be associated with adverse clinical behaviors.

The evolving concepts in salivary gland neoplasms

PAC and cribriform adenocarcinoma of salivary gland (CASG)

PAC was first proposed by Evans and Batsakis in 1984 as a distinct type of salivary gland carcinoma under the nomenclature of polymorphous low grade adenocarcinoma (PLGA).[23] In the 4th edition of the WHO classification of head and neck tumors, the term has been shortened to polymorphous adenocarcinoma.[1] The majority of PAC occurs in the minor salivary glands, in particular the palate. In general, PAC is considered to be an indolent tumor with approximately 15% risk of regional nodal metastasis, less than 5% risk of distant metastases and negligible risk of disease-related death.[23–25] Histologically, PAC is characterized by architectural diversity and cytologic uniformity with vesicular oval nuclei and chromatin clearing. Various architectural patterns have been described in PAC, such as single file arranged in a targetoid concentric fashion around

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Histologic features and clinical outcomes of salivary gland carcinoma with high grade transformation (HGT)

Carcinoma (reference)	N (largest series/ total cases)	Histologic features of HGT described in the literature	Clinical manifestation
Acinic cell carcinoma[2–6]	22/73	Acinic differentiation in all cases Pleomorphism, nuclear anaplasia, prominent nucleoli High mitotic rate Tumor necrosis	Primary tumor site: parotid (100%) Stage IV: 52% DOD: 62%
Adenoid cystic carcinoma[7–9]	16/60	Pleomorphic large vesicular nuclei and conspicuous nucleoli High mitotic rate Comedo-type necrosis Other: desmoplastic stroma, tumor calcification, squamous metaplasia, micropapillary growth pattern	Primary tumor site: parotid (13%), submandibular (23%), minor salivary gland (64%) Nodal metastasis: 39% Distant metastasis: 44% Morality: 24%
Epithelial-myoepithelial carcinoma[10–12]	12/31	HGT can occur in myoepithelial or ductal component Myoepithelial anaplasia High mitotic rate Tumor necrosis	Primary tumor site: parotid (74%), submandibular (16%), minor salivary gland (11%) DOD: 6% Nodal metastasis: 33% Distant metastasis: 17%
Secretory carcinoma[13,14]	3/7	Anaplasia, nuclear pleomorphism, prominent nucleoli Solid growth Geographic comedo-type necrosis	Primary tumor site: parotid (50%), minor salivary gland (50%) DOD: 43% Distant metastasis: 43% Recurrence: 57%
Polymorphous adenocarcinoma[15–17]	2/6	Severe cytologic atypia Marked increased mitotic activity Necrosis	Primary tumor site: palate (83%), nasal cavity (17%) Distant metastasis: 0% DOD: 0%
Clear cell carcinoma[18,19]	1/2	Large bizarre nuclei Focal necrosis Atypical mitosis	Primary tumor site: base of tongue: 100% Recurrence: 100% Distant metastasis: 50% DOD: 50%

DOD: dead of disease, N: number of cases.

Table 1

vessels or nerves, cords, trabecular, anastomosing reticular, tubular, solid, cribriform and papillary patterns (Figure 2a). Among these patterns, papillary and cribriform may bear some prognostic significance. For example, Evans et al. have reported that "more than focal" papillary growth pattern is associated with an increased risk of lymph node metastases,[26] while Xu et al. have recently reported that at least 10% papillary or at least 30% of cribriform growth is an independent predictor for shorter disease free survival.[24] Therefore, it is prognostically relevant to document the presence of papillary and cribriform growth patterns in PAC.

In 1999, Michal et al. described cribriform adenocarcinoma of salivary gland, a group of carcinoma with overtly optic nuclear clearing and predominant cribriform and solid growth in association with peripheral palisading, artificial clefts and glomeruloid appearance (Figure 2b).[27] These tumors have a predilection to base of tongue, but may occur in minor salivary glands of upper aerodigestive tract and even in major salivary glands.[24,28,29] Compared with classical PAC, CASG has been reported to have a higher risk (up to 65%) of nodal metastases[28,29]; however, no differences in survival have yet been reported. Since its first report, ongoing debate has existed regarding whether CASG and PAC are two separate entities or a continuous spectrum (or variant) of the same tumor with overlapping histologic features.[24,26]

Recently, several molecular alterations have been reported in PAC and CASG.[30–32] Fusions involving *Protein Kinase D1* (*PRKD1*), *PRKD2* or *PRKD3* loci were detected in 80% of CASG, less than 10% of classical PAC, and 45% of indeterminate tumors with mixed features between PAC and CASG.[31] On the other hand, *PRKD1* p.Glu710Asp hotspot somatic mutation was reported in more than 73% of classical PAC.[24,30,31] In addition to the morphologic overlapping between PAC and CASG, the facts that both tumors have molecular alterations affecting the same gene locus but through different mechanisms adds more fuel to the ongoing debate. Clearly, additional studies correlating

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