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REVIEW

Update of newly-recognized salivary gland neoplasms: molecular and immunohistochemical findings and clinical importance

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Update of newly-recognized salivary gland neoplasms: molecular and immunohistochemical findings and clinical importance

With the advancement of molecular testing and the routine use of immunohistochemical stains, salivary gland tumours previously categorized as adenoma or adenocarcinoma, not otherwise specified, are being reclassified with distinct diagnoses. Newly recognized benign entities include: sclerosing polycystic adenoma, keratocystoma, intercalated duct hyperplasia and adenoma, and striated duct adenoma. Newly recognized malignant salivary gland tumours include: microsecretory adenocarcinoma, sclerosing microcytic adenocarcinoma, and mucinous adenocarcinoma. Additionally, rare subtypes of mucoepidermoid carcinoma have been described, including Warthin-like and oncocytic. Understanding of intraductal carcinoma continues to evolve. Correctly distinguishing these lesions from mimickers can be crucial for appropriate patient care and prognostication, as well as future conceptualization of salivary disease.

Keywords: intercalated duct hyperplasia and adenoma, intraductal carcinoma, keratocystoma, microsecretory adenocarcinoma, mucinous adenocarcinoma, mucoepidermoid carcinoma subtypes, sclerosing microcytic adenocarcinoma, sclerosing polycystic adenoma, striated duct adenoma

Introduction

Molecular testing for salivary gland neoplasms is becoming routine for accurate diagnosis and for clinical management. New molecular discoveries have provided a greater understanding for the pathogenesis of various benign and malignant salivary gland lesions and have led to the definition of new entities and the reclassification of nonneoplastic lesions to neoplasms. In the 5th edition of the World Health Organization (WHO), newly recognized benign neoplasms include: sclerosing polycystic adenoma, keratocystoma, intercalated duct hyperplasia and adenoma, and striated duct adenoma. An increasing number of low- to intermediate-grade salivary gland carcinomas have been determined to harbour tumour

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Abbreviations: ACA NOS, adenocarcinoma, not otherwise specified; BCA, basal cell adenoma; CA, canalicular adenoma; EMC, epithelial-myoepithelial carcinoma; IDA, intercalated duct adenoma; IDC, intraductal carcinoma; IDH, intercalated duct hyperplasia; IDL, intercalated duct lesion; MA, mucinous adenocarcinoma; MAC, microcystic adnexal carcinoma; MEC, mucoepidermoid carcinoma; MSA, microsecretory adenocarcinoma; OMEC, oncocytic mucoepidermoid carcinoma; SDA, striated duct adenoma; SG IPMN, salivary gland intraductal papillary mucinous neoplasm; SMA, sclerosing microcystic adenocarcinoma; SMCA, secretory myoepithelial carcinoma.; SPA, sclerosing polycystic adenoma; WHO, World Health Organization.

defining-gene fusions (Table 1). The newly introduced malignant entities include microsecretory adenocarcinoma, sclerosing microcytic adenocarcinoma, and mucinous adenocarcinoma.[1] New subtypes of mucoepidermoid carcinoma, such as the Warthin-like and oncocytic subtypes, have recently been recognized due to molecular sequencing. There has been reorganization of "low-grade cribriform cystadenocarcinoma" and "low-grade salivary duct carcinoma" into the diagnosis of intraductal carcinoma due to detection of specific tumour fusions. In addition, there are multiple emerging but not yet WHO-classified entities.

Due to increasing diagnostic precision, the number of salivary gland tumours that cannot be classified is decreasing. Adenocarcinoma not otherwise specified (ACA NOS) is a diagnosis of exclusion and is defined as a salivary gland carcinoma that forms glandular structures but cannot be otherwise categorized as a distinct entity. ACA NOS is generally considered an aggressive tumour type; however, there has been recent recategorization of novel low-grade tumours out of the ACA NOS category, such as microsecretory adenocarcinoma, sclerosing microcystic adenocarcinoma, and mucinous adenocarcinoma. This potential

Table 1. Genetic alterations in select salivary gland tumours

Tumour type	Region	Gene
Sclerosing polycystic adenoma	3q26.32	*PTEN* *PIK3R1* *PIK3CA* *HRAS* *AKT1* *TFG::PIK3CA*[12]
Keratocystoma		*IRF2BP2::RUNX2*[17]
Intercalated duct lesions		*CTNNB1* *HRAS* hotspot mutations[20]
Striated duct adenoma		*IDH2* p.R172S (4 cases – 50%) *IDH2* p.R172G (2 cases – 25%) *IDH2* p.R172T (1 case – 12.5%) *IDH2* p.R172M (1 case – 12.5%)[21]
Microsecretory adenocarcinoma	5q14.3	*MEF2C::SS18*[24]
Microcribriform adenocarcinoma	18q11.2	*SS18::ZBTB7A*[23]
Sclerosing microcystic adenocarcinoma	1p36.33	*CDK11B*[30]
Mucinous adenocarcinoma/Intraductal papillary mucinous neoplasm		*ATK1* p.E17K[31,32]
Mucoepidermoid carcinoma subtypes	t(11;19)(q21;p13) t(11;15)(q21;q26)	*CRTC1::MAML2* (40–90%) *CRTC3::MAML2* (6%)
Intraductal carcinoma		Intercalated duct[38]: *NCOA4::RET* (predominant) *STRN::ALK* (rare) *TUT1::ETV5* (rare) *KIAA1217::RET* (rare) Apocrine[46]: *TRIM27::RET* *HRAS*, *PIK3CA*, *TP53* mutations Mixed intercalated duct-apocrine[38]: *TRIM27::RET* (predominant) *NCOA4::RET* (rare) Oncocytic[40]: *TRIM33::RET* *BRAF* V600E mutations

Partially adapted from Skalova *et al.*[1]

grade heterogeneity illustrates the potential issues with prognosis based on the broad assumption of an ACA NOS diagnosis. Further subclassifying ACA NOS may facilitate more precise prognostication or provide access to targeted therapies.[2] Regardless of morphology, nomenclature, or genetics, it remains critical to appropriately grade salivary tumours based on histologic features, as grade is one of the most important determinants of clinical treatment (neck dissection, adjuvant therapy) and prognosis. Such high-grade features for which to evaluate in all tumours include: increased mitotic activity, necrosis, nuclear anaplasia/pleomorphism, and vascular invasion. In salivary tumours, even some low-grade carcinomas can have perineural invasion; therefore, this finding is interpreted with caution. All carcinomas generally regarded as low grade have the potential for high grade transformation (so-called dedifferentiation), and such features should be reported.

While immunohistochemistry and molecular findings will be discussed for the selected entities, readers are directed to additional exhaustive reviews of salivary immunohistochemistry and genetics.[3,4] Lastly, while molecular findings (point mutations, fusions, amplifications) often correlate with morphology and may be diagnostically specific, only few are targetable therapeutically.[5] The subsequent review aims to provide readers with concise introductions to novel and emerging entities in salivary pathology, rather than a global approach to diagnosis of all salivary neoplasms.

Sclerosing Polycystic Adenoma

The entity was initially described in 1996 as a pseudoneoplastic condition of fibrosis and epithelial proliferation comparable to fibrocystic disease of the breast.[6] The name sclerosing polycystic adenoma (SPA) was suggested following demonstration of clonality using the human androgen receptor (HUMARA) locus and additional clinicopathologic findings suggestive of a neoplastic lesion with a low malignant potential.[7] The additional findings included local recurrence (up to 30% of cases), intraductal epithelial dysplasia from mild to carcinoma *in situ*, and a case of invasive carcinoma arising in a relapsing SPA.[8–10]

CLINICAL FEATURES

SPA has been predominantly reported in the parotid gland with a male predilection. The typical clinical presentation is a slow-growing painless mass that is rarely multifocal.[11]

GROSS FEATURES

The gross features of SPA are nonspecific and include a well-circumscribed, firm, or rubbery nodule surrounded by normal salivary gland tissue.[10] The tumour size can range from 1 to 12 cm.[12]

MICROSCOPIC FEATURES

The microscopic features of SPA vary greatly and are reminiscent of fibrocystic changes of the breast and sclerosing adenosis. Typically, SPA presents as a well-circumscribed nodule that can be entirely or partially encapsulated, with lobular architecture in a variably sclerotic stroma with bands of hyalinized fibrosis. The lesion contains a proliferation of ducts lined with a flattened bilayered epithelium comprised of ductal cells that can have apocrine, vacuolated, and mucinous changes.[10] The ducts can range from small ductules to large cystic spaces containing luminal secretions and/or foamy macrophages.[12] Focal intraluminal epithelial proliferations are observed in all cases and can form solid, microcystic, and cribriform structures. The neoplastic acini can contain enlarged acinar cells with coarse hyper-eosinophilic PAS-positive, diastase-resistant granules or hyaline globules.[10] These globules may represent altered zymogen granules, and when observed is a hallmark feature of SPA. Typically, there is a proliferation of myoepithelial cells that can be found surrounding the ductal spaces. It is important to take into consideration that the microscopic features of SPA are variable and cases may present without a classic feature such as fibrosis or apocrine changes.[12]

IMMUNOHISTOCHEMICAL/MOLECULAR FEATURES

SPA is comprised of ductal, myoepithelial, and acinar elements. The immunophenotype reflects these constituents. The ducal cells and acinar cells are positive for SOX10 and keratin (AE1/3, CAM5.2). Ducts with intraluminal epithelial proliferations are surrounded by an intact myoepithelial layer positive for SMA, p63, and calponin. The acinar cells with coarse hyper-eosinophilic granules are positive for GCDFP-15. DOG-1 is weak or focal in the neoplastic acini.[10,12] Recently, next-generation sequencing has detected *PIK3CA* and *PIK3R1* genetic alterations and a novel *TFG::PIK3CA* fusion[13] (Table 1).

DIFFERENTIAL DIAGNOSIS / CLINICAL IMPORTANCE

The differential diagnoses range from benign to malignant and include pleomorphic adenoma, acinic cell carcinoma, and salivary duct carcinoma. Pleomorphic adenoma lacks acini, typically has at least focal chondromyxoid stoma, and can harbour fusions involving *PLAG* or *HMGA2*. While the proliferation of serous acini in SPA can resemble acinic cell carcinoma, the presence of myoepithelial cells excludes this diagnosis. Acinic cell carcinoma will also have *NR4A3* rearrangements. When an apocrine intraductal component is present in SPA, it may resemble a salivary duct carcinoma. GCDFP-15 will not assist in differentiating; however, the intraductal components of SPA will be surrounded by myoepithelial cells.[12] It is significant to note that intralesional sclerosis is common within SPA and should not be misinterpreted as invasive carcinoma.

Keratocystoma

Keratocystoma is a rare benign salivary gland tumour with less than 15 cases reported in the literature.[1] The lesion was first reported by Seifert *et al.*[14] in 1999 as an unusual choristoma of the parotid gland. Keratocystoma became the preferred name as it is recognized as a true cystic neoplasm with tumour cells arising from the salivary gland ductal epithelium via a metaplasia-like process.[15]

CLINICAL FEATURES

It occurs primarily in the parotid gland as a slow-growing painless lesion. It has been reported to arise in children and adults with a wide age range (8–38 years).[16]

GROSS FEATURES

Multilocular cystic lesions are filled with a keratin-like substance. The largest dimension has been reported to measure up to 4 cm.[15]

MICROSCOPIC FEATURES

The tumour is comprised of multiple cystic spaces with keratotic lamellae and focal epithelial nests. The cystic spaces are lined by stratified squamous epithelium with a parakeratotic or orthokeratotic surface; however, a granular cell layer is typically absent. Budding of the basal layer may be present. The nuclei are uniform and bland with abundant eosinophilic cytoplasm. Keratocystoma may present with solid squamous islands surrounded by collagenous islands that are not to be interpreted as invasive growth. A foreign body reaction to keratin in the form of granulomas with a dense lymphoid infiltrate may be focally present.[15,16]

IMMUNOHISTOCHEMICAL/MOLECULAR FEATURES

The tumour cells are positive for AE1/AE3 and CK5/6 and negative for CK8/18, S100, and calponin. There are no associated molecular genetic features reported at this time.[16] Recently, a *RUNX2* rearrangement was identified in seven cases; specifically, *IRF2BP2::RUNX2* in six of the seven cases (Table 1). *RUNX* rearrangements have not been described in other salivary gland tumours, potentially highlighting the uniqueness of keratocystoma as a neoplasm.[17]

DIFFERENTIAL DIAGNOSIS / CLINICAL IMPORTANCE

The differential diagnosis includes: squamous cell carcinoma, mucoepidermoid carcinoma (MEC), Warthin tumour (infarcted), and epidermoid or dermoid cysts. Squamous cell carcinoma is an overtly malignant epithelial tumour characterized by invasion, often perineural or intravascular invasion, and necrosis. Most squamous cell carcinomas in the parotid represent cutaneous metastases to intraparotid lymph nodes, which is far more common than keratocystoma. Keratocystoma is benign, lacks significant cytological atypia, and contains only scant mitoses confined to the basal layer. Keratocystoma will not have mucous cells that are found in MEC and will have significant keratinization. Squamous metaplasia and necrosis can be seen in an infarcted Warthin tumour; however; a Warthin tumour may focally contain bilayered oncocytic epithelium and lymphoid stroma with germinal centre formation not present in keratocystoma. As the differential diagnosis includes benign and malignant entities, it is crucial to exclude malignancy in order to avoid overtreatment and associated morbidities.[16]

Intercalated Duct Adenoma and Hyperplasia

Intercalated duct lesions (IDL) are a morphologic spectrum from intercalated duct hyperplasia (IDH) to intercalated duct adenoma (IDA). IDA is distinguished

from IDH based on architecture, with IDA being a discrete well-defined, partially or completely encapsulated tumour that does not respect the background salivary parenchyma.[1] There is an association between IDLs and other salivary gland lesions such as: basal cell adenoma (BCA), epithelial-myoepithelial carcinoma (EMC), basal cell adenocarcinoma, pleomorphic adenoma, MEC, Warthin tumour, and acinic cell carcinoma.[18] IDLs have also been reported in the setting of chronic parotitis.[19] It is postulated that IDL is a precursor lesion for other neoplasms.[18]

CLINICAL FEATURES

The majority of IDLs occur in the parotid, followed by the submandibular gland, with few found in the oral cavity. The reported age range for IDL is from 19 to 80 years with a mean of 53.8 years old and a female:male ratio of 1.7:1.[18] Smaller intercalated duct lesions are frequently identified incidentally on resection specimens, whereas intercalated duct adenomas can manifest clinically, as they can grow to larger sizes.[1]

GROSS FEATURES

The majority of cases reported are small, unifocal lesions typically measuring 1 to 8 mm. Diffuse or multifocal lesions are also reported.[18]

MICROSCOPIC FEATURES

IDLs histologically recapitulate normal intercalated ducts that architecturally range from hyperplasia to encapsulated adenoma with hybrid patterns (Figure 1). The first (hyperplastic) pattern of IDL is composed of a nonencapsulated proliferation of intercalated ducts with little intervening stroma, which is present amongst the acinic and mucous cells of the normal salivary gland parenchyma. The second (adenomatous) pattern is that in which the IDLs form discrete, rounded, well-defined, partial to fully encapsulated nodules separate from the normal salivary gland parenchyma. The fibrous capsule surrounding adenoma can vary in thickness. The third (hybrid) pattern includes mixed features of a partially encapsulated adenoma-like lesion admixed with irregular hyperplasia-like areas at one or more edges. It is postulated in these hybrid areas that the hyperplastic intercalated duct areas transition to discrete adenomatous areas. In each architectural pattern, the IDLs consist of proliferations of small ducts lined by eosinophilic to amphophilic ductal cells with small bland nuclei.[18]

IMMUNOHISTOCHEMICAL/MOLECULAR FEATURES

IDLs are diffusely positive for CK7 and S100 and focally positive for Estrogen Receptor (ER) and lysozyme. A myoepithelial layer surrounds all the ducts. Immunohistochemically, IDLs otherwise recapitulate the staining pattern of normal intercalated ducts, with the exception of S100 negativity in nonlesional ducts compared to S100 expression in lesional ducts.[18] A subset of IDLs have shown beta-catenin localization to the nucleus.[20] Molecular sequencing has identified pathogenic mutations, specifically *CTNNB1* in hyperplastic and hybrid IDL-type lesions. *CTNNB1* mutations are also found in the BCA (up to 80%). *HRAS* hotspot mutations have been reported in IDAs, which have also been found in EMC. These genetic findings suggest that IDLs are truly neoplastic and demonstrate molecular overlap with BCAs and EMCs (Table 1).

DIFFERENTIAL DIAGNOSIS / CLINICAL IMPORTANCE

IDLs may be present in association with other salivary gland neoplasms such as EMC and basal cell adenocarcinoma and has been proposed to represent a precursor lesion to other neoplasms.[1] This hypothesis is supported by reports of IDLs located next to a morphologically distinct tumour, a phenomenon often referred to as a hybrid tumour.[18,19]

Striated Duct Adenoma

Striated duct adenoma (SDA) is a rare salivary gland neoplasm composed of ducts lined by a single layer of luminal cells with minimal intervening stroma that recapitulates striated ducts. There was previous debate if SDA is a distinct entity from canalicular adenoma and if a malignant counterpart of SDA exists. Molecular sequencing has identified *IDH2* p.R172X mutations, confirming that it is a unique entity separate from canalicular adenoma.[21] In the literature, at least one tumour has been diagnosed as a low-grade salivary gland adenocarcinoma with striated duct differentiation; however, the criteria for this diagnosis remains unclear.[2]

CLINICAL FEATURES

SDA can occur in the major and minor salivary glands, with the majority of cases arising in the parotid gland. In all cases, the clinical presentation was a palpable mass. The size of the tumours ranged from 0.5 to 3.0 cm, with a mean of 1.5 cm. Of the patients available for follow-up, no evidence of

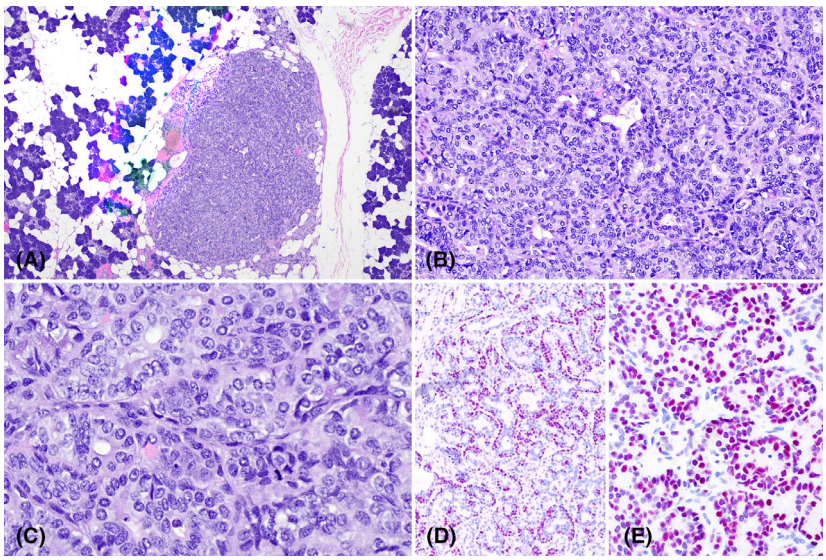

Figure 1. Intercalated duct lesion. (A) This small intercalated duct lesion is nodular, with scant peripheral infiltration into adjacent salivary and adipose tissue. (B) It is composed of back-to-back ducts/tubules. (C) The lesional tubules are lined by a bilayered epithelium with cuboidal luminal cells and flattened abluminal cells. (D) Immunostain for p40 is positive in abluminal cells. (E) SOX10 is diffusely positive, consistent with intercalated duct phenotype. Images courtesy of Vijayalakshmi Ananthanarayanan, MBBS, MD.

recurrence or distant metastasis had been noted, with the longest follow-up period of 42 months.[22]

MICROSCOPIC FEATURES

Architecturally, SDA presents as a circumscribed and encapsulated mass that arises within or adjacent to normal salivary gland tissue (Figure 2). It can present multifocally, in which all nodules are encapsulated.[22] SDA is a unilayered ductal tumour composed of a monophasic population of cuboidal to columnar eosinophilic cells that are arranged in compact tubules. The discrete tubules can vary from the size of normal striated ducts to cystically dilated with

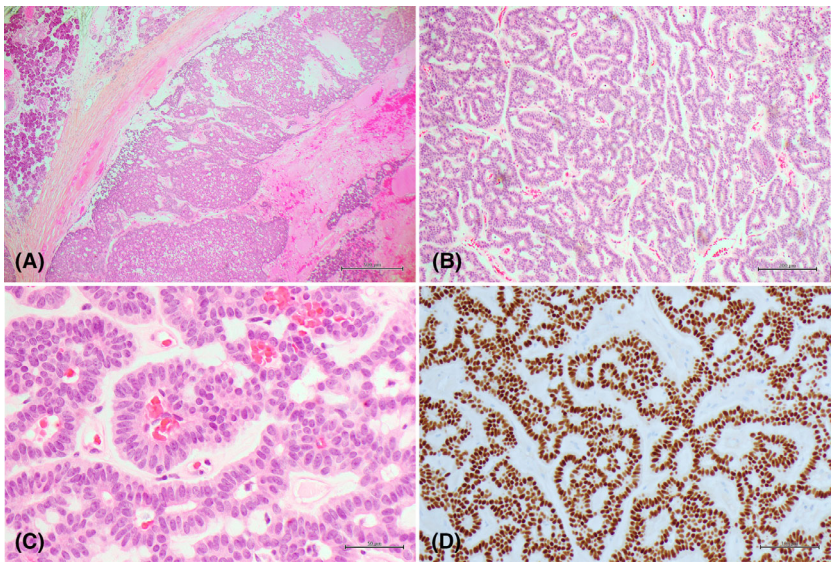

Figure 2. Striated duct adenoma. (A) The lesion is circumscribed and encapsulated, present adjacent to normal salivary gland tissue. (B) Cells are arranged in compact tubuloductal structures with background paucicellular vascular stroma. (C) Cells are cuboidal to columnar, with pale cytoplasm and oval nuclei with small nucleoli. (D) SOX10 is diffusely, strongly positive, as is S100 (not pictured). Images courtesy of Julie Guilmette, MD.

colloid-like eosinophilic serous secretion. The nuclei are monotonous and oval with occasional nuclear inclusions. The cytoplasm is homogenous and eosinophilic. The stroma is scant to edematous and can have dispersed haemorrhage and fat. There are no high-grade features, including nuclear pleomorphism, increased mitotic activity, or tumour necrosis.[21]

IMMUNOHISTOCHEMICAL/MOLECULAR FEATURES

SDAs are positive for S100 (strong and diffuse), CK7, and SOX10 (Figure 2); however, there has been variation in histologically and molecularly confirmed SDAs. In the majority of cases, SDAs are negative for smooth muscle actin, calponin, smooth muscle myosin, and DOG1. When SMA and p63 highlight focal isolated abluminal cells, caution should be taken to not interpret this finding as a true basal or myoepithelial layer.[22] SDA can histologically resemble normal striated ducts; however, normal striated ducts have a delimiting basal cell layer and are negative for S100 and SOX10, in contrast to SDAs. It has been found that the *IDH1/2* immunohistochemical stain demonstrates strong reactivity in a granular to globular cytoplasmic pattern that correlates with the molecular evidence of *IDH2* mutations (Table 1). Interestingly, *IDH1/2* has been shown to have a weak nonspecific blush in normal striated ducts.[21]

DIFFERENTIAL DIAGNOSIS / CLINICAL IMPORTANCE

The main differential diagnosis is canalicular adenoma. Canalicular adenomas (CA) demonstrate only luminal cell differentiation. They predominantly arise in the minor salivary glands, particularly the upper lip. Canalicular adenomas classically demonstrate beaded ribbons, cords, and interconnecting tubules composed of columnar cells in an abundant myxoid stroma. Canalicular adenomas have a similar staining pattern to SDA with positivity for CK7 and S100; however, they do not contain the molecular *IDH2* alterations.[21] Both lesions are benign and will have no impact on clinical management.

Microsecretory Adenocarcinoma

Microsecretory adenocarcinoma (MSA) is a recently-defined low-grade malignancy with an intercalated duct-like phenotype and a characteristic chromosomal rearrangement of the *MEF2C* gene (5q14.3) with *SS18* (18q11.2), with less than 30 reported cases.[1] There have been four reported cases with an alternate fusion *SS18::ZBTB7A*, which are thought to represent a unique tumour entity with the proposed name of microcribriform adenocarcinoma (MCA)[23] (Table 1). Based on a limited number of cases, these lesions appear to preferentially occur in nonoral sites and cytologically appear to be low grade, similar to MSA.[23]

CLINICAL FEATURES

MSA predominantly occurs in the oral cavity, with the most common location being the palate, followed by the buccal mucosa. MSA presents as a painless slow-growing mass. The reported mean age is 49.5 years old with a slight female predominance.[24]

MICROSCOPIC FEATURES

MSA has consistent histologic features that include: microcystic tubules, flattened intercalated duct-like tumour cells with attenuated to clear cytoplasm, monotonous oval hyperchromatic nuclei with indistinct nucleoli, abundant basophilic luminal secretions, fibromyxoid stroma, and circumscribed borders with subtle infiltration (Figure 3).[24]

IMMUNOHISTOCHEMICAL/MOLECULAR FEATURES

MSA has a consistent immunophenotype that is positive for S100, p63, and SOX10, and negative for p40 calponin and mammaglobin (Figure 3). There is variable expression for SMA.[24] As above, there are *SS18* gene fusions.

DIFFERENTIAL DIAGNOSIS / CLINICAL IMPORTANCE

The differential diagnosis includes secretory carcinoma, polymorphous adenocarcinoma, and adenoid cystic carcinoma. The intraluminal secretions of MSA can be reminiscent of secretory carcinoma; however, secretory carcinoma has more abundant eosinophilic cytoplasm and is positive for mammaglobin, negative for p63, and has a *ETV6::NTRK3* fusion. The bland cellular features, and permeative growth pattern of invasion with focal single filing and occasional cribriform growth, may resemble polymorphous adenocarcinoma, with both lesions having the same S100+/p63+/p40− immunophenotype. However, polymorphous adenocarcinoma displays greater architectural diversity and is more infiltrative, with the classical targetoid pattern of invasion around nerves and vessels. Additionally, polymorphous adenocarcinoma and its cribriform subtype will have point mutations

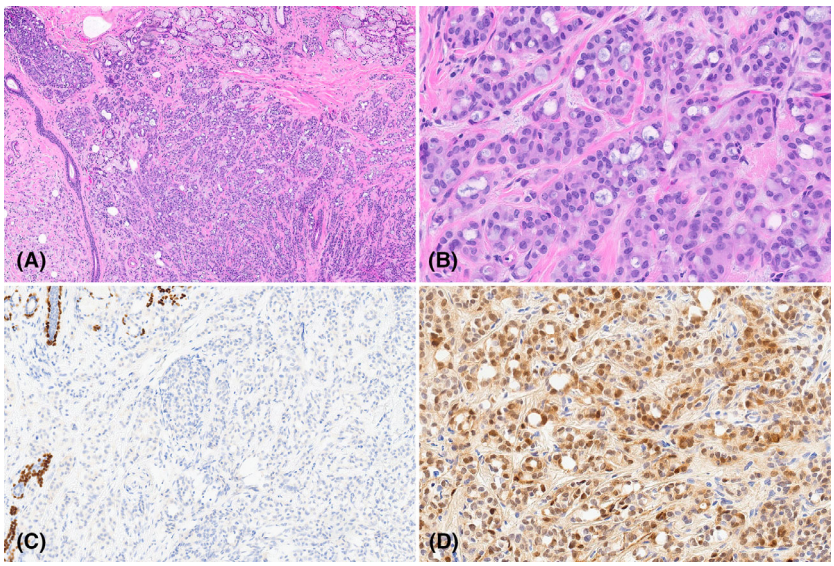

Figure 3. Microsecretory adenocarcinoma. (A) This carcinoma infiltrates between adjacent salivary acini and ducts. (B) It is composed of compressed nests and microcysts with intervening collagenous stroma. (C) Immunostain for p40 is negative in tumour cells but positive in abluminal cells of entrapped ducts and acini. (D) S100 protein is positive.

or rearrangements of *PRKD1*, *PRKD2*, or *PRKD3*. MSA may resemble the tubular form of adenoid cystic carcinoma, which can have a tubular and cribriform growth pattern with intraluminal secretions and fibrous stroma. Adenoid cystic carcinoma is more infiltrative and is comprised of both ductal and myoepithelial cells, whereas MSA lacks myoepithelial differentiation. Adenoid cystic carcinoma also harbours rearrangement of *MYB*, *MYB1*, and/or *NFIB*. It is important to distinguish MSA from adenoid cystic carcinoma, which is aggressive and high grade, while MSA generally behaves in an indolent manner.[24]

While MSA is classified as a low-grade malignancy, there has been one reported case of high-grade transformation with metastasis. This case of MSA had the chromosomal rearrangement of *MEF2C::SS18* and histologically had high-grade features including necrosis, apoptosis, mitotic figures (10/10 high-power fields), lymphovascular invasion, and perineural invasion.[25] This finding illustrates the key concept that all salivary glands tumours generally regarded as low grade have the potential for high-grade transformation. Applying generic histologic grading concepts (necrosis, mitoses, pleomorphism, vascular invasion) is essential for patient management.

Sclerosing Microcystic Adenocarcinoma

Sclerosing microcystic adenocarcinoma (SMA) is a rare salivary gland malignancy that has morphology reminiscent of cutaneous microcystic adnexal carcinoma (MAC). Historically, reports of such tumours in the oral cavity and other mucosal head and neck sites used inconsistent terminology, including: microcystic adnexal carcinoma occurring in extracutaneous sites, sclerosing sweat-duct-like carcinoma, and syringomatous carcinoma.[26,27] Due to the absence of adnexal structures attributed to the mucosal sites, a name change was proposed to "sclerosing microcystic adenocarcinoma".[28]

CLINICAL FEATURES

SMA has been reported exclusively in minor salivary gland sites, including the tongue, labial mucosa, floor of mouth, buccal mucosa, and one case in the nasopharynx. Unlike MAC, SMA has a good outcome, with no reported recurrences or distant metastases.[28]

MICROSCOPIC FEATURES

SMA has a distinct low-power microscopic appearance that is similar to MAC, with nests, strands, cords, and tubules of tumour cells embedded in a thick fibrous or desmoplastic stroma (Figure 4). The collagenous areas tend to predominate. Perineural invasion is commonly seen. SMA is a biphasic tumour with central cuboidal ductal cells that are surrounded by peripheral myoepithelial cells. The lumens formed by the ductal cells can contain dense,

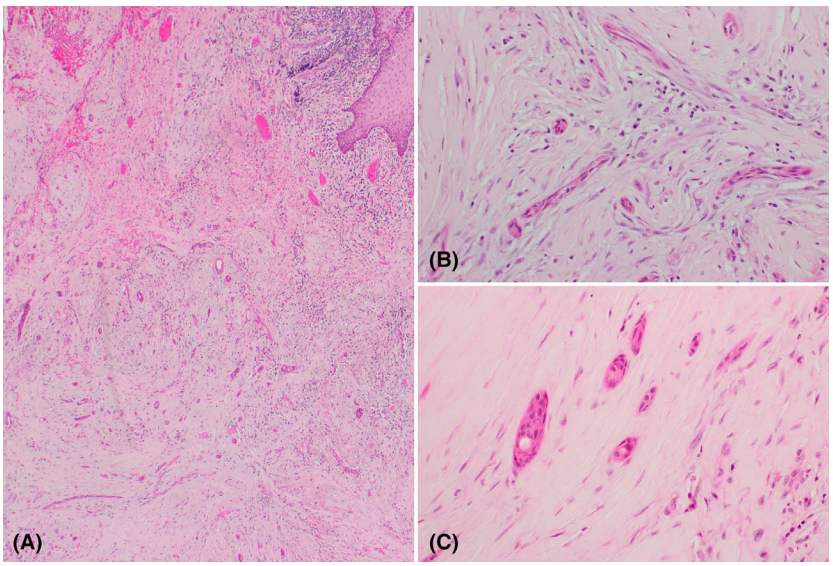

Figure 4. Sclerosing microcystic adenocarcinoma. (A) The submucosal stroma is diffusely effaced by a neoplasm composed of fibrocollagenous tissue with indistinct epithelial cords. (B) Neoplastic cells are compressed by the adjacent abundant stroma. (C). Individual tumour islands are actually bilayered tubules with occasional lumina and surrounded by abluminal basal cells. Images courtesy of Rong Hu, MD, PhD.

globular, eosinophilic secretory material. The nuclei are bland and round to oval, with evenly dispersed chromatin and occasional nucleoli. Mitotic figures are not conspicuous and high-grade features such as nuclear pleomorphism and necrosis are not present. However, perineural invasion is commonly identified.[29]

IMMUNOHISTOCHEMICAL/MOLECULAR FEATURES

Immunohistochemistry may be useful in distinguishing SMA from its differential diagnoses; however, it is of overall limited value for the specific diagnosis of SMA. The tumour is biphasic, with the luminal/ductal cells expressing pankeratin and CK7, while the abluminal myoepithelial cells express smooth muscle actin, S100, p63, and p40.[1,28] Currently, one case of SMA has undergone whole-exome sequencing, which revealed moderate tumour mutational burden and putative loss of function mutations in *CDK11B* (Table 1). Interestingly, there were no overlaps with the known MAC mutations involving *CDKN4/6*, *TP53*, and *JAK1* genes that are identified in ~20% of MAC cases. These findings suggest that SMA may be a distinct entity from cutaneous MAC and that the moderate tumour mutational burden may be associated with the immunosuppression frequently seen in SMA patients.[30]

DIFFERENTIAL DIAGNOSIS / CLINICAL IMPORTANCE

The differential diagnosis includes squamous cell carcinoma, hyalinizing clear-cell carcinoma, and adenoid cystic carcinoma. SMA can be differentiated from squamous cell carcinoma due to its lack of keratinization, low-grade cytology, and its biphasic epithelial and myoepithelial cell architecture.[1] While hyalinizing clear-cell carcinoma does have dense connective tissue stroma and trabecular architecture, it is not biphasic (being diffusely positive for high molecular weight keratins and p63/p40) and it lacks luminal secretions. Adenoid cystic carcinoma is biphasic and has a propensity for perineural invasion. The tubular subtype of adenoid cystic carcinoma can show deeply infiltrative growth with stromal sclerosis. Adenoid cystic carcinoma typically has a dominant myoepithelial component with hyperchromatic and angulated nuclei. There is usually more pronounced cytologic atypia and at least focal cribriform architecture in adenoid cystic carcinoma.[29] Molecular testing for the *MYB* gene rearrangement, present in adenoid cystic carcinoma, can assist in challenging cases. Adenoid cystic carcinoma is considered an aggressive salivary gland malignancy; therefore, differentiation from SMA (a low-grade tumour) is essential for patient treatment.

Mucinous Adenocarcinoma and Salivary Gland Intraductal Papillary Mucinous Neoplasm

Mucinous adenocarcinoma (MA) is defined as a primary salivary gland adenocarcinoma that displays prominent intracellular and/or extracellular mucin.[1] Historically, mucin-producing adenocarcinomas were divided based on their histologic pattern and diagnosed as: colloid carcinoma, papillary cystadenocarcinoma, and signet ring carcinoma.[31] Currently, MA is recognized as a histologically heterogenous entity that encompasses patterns of papillary, signet ring, colloid, and mixed subtypes with a common *ATK1* p.E17K mutation.[1] This mutation has also been reported in a minor salivary gland entity comprised of low-grade papillary cystic proliferations of mucinous columnar cells designated as salivary gland intraductal papillary mucinous neoplasm (SG IPMN) due to its resemblance to pancreatic duct mucinous lesions.[32] There is controversy whether MA and SG IPMN are discrete entities or part of a disease spectrum. IPMN is currently thought be a low-grade mucinous adenocarcinoma due to the histologic overlap and a clonal *ATK1* p.E17K mutation (Table 1). While previously regarded as intraductal, these minor salivary gland neoplasms often lack peripheral p63-positive basal cells, and therefore are best regarded as invasive (low-grade carcinoma).[32]

CLINICAL FEATURES

MA occurs predominantly in the intraoral minor salivary glands in locations such as the buccal mucosa, palate, tongue, labial mucosa, and floor of the mouth. They have a relatively equal sex distribution and have a peak incidence in the 8th decade of life.[31]

GROSS FEATURES

MA will have solid or cystic components with a gelatinous cut surface.

MICROSCOPIC FEATURES

In this histologically heterogenous group of tumours, overt mucin production rather than architectural pattern is the defining feature. The main architectural patterns include papillary, colloid, signet-ring, and mixed subtypes. The papillary pattern is often the predominant architecture, with complex or simple papillary fronds that project into cystic spaces (Figure 5). The second most common architectural feature is the colloid pattern, with tumour cells nests suspended in pools of mucin. The signet ring pattern is rarely seen.[31]

IMMUNOHISTOCHEMICAL/MOLECULAR FEATURES

All histologic patterns of MA have a CK7-positive and CK20-negative immunophenotype. Diffuse, strong expression of NKX3.1 (as seen in prostatic adenocarcinomas) has been observed in SG IPMN.[32] As above, there are *ATK1* p.E17K mutations.

DIFFERENTIAL DIAGNOSIS / CLINICAL IMPORTANCE

The differential diagnosis also includes other mucin-producing salivary gland carcinomas such as MEC, salivary duct carcinoma, and myoepithelial carcinoma. MEC can be mucin-rich; however, epidermoid/intermediate cells would express p63 and p40. A mucinous or rhabdoid subtype of salivary duct carcinoma will express the androgen receptor. The mucinous subtype of myoepithelial carcinoma will have nests/cords/trabeculae of neoplastic cells and will generally express S100, calponin, SMA, and CK14. It is necessary to rule out a metastasis from a prostatic, gastrointestinal, pancreaticobiliary, or lung primary. A combination of clinical history, imaging, immunohistochemical studies, and the presence of *AKT* p.E17K mutation will aid in differentiating a salivary gland primary versus a metastasis.[31] MA generally has a good prognosis, although there are limited patient data reported. Progressive disease has been documented in MA with colloid or signet ring patterns, whereas disease progression was not seen in purely papillary tumours. Therefore, identification of high-risk elements of colloid or signet ring patterns may be helpful for prognostication.[31]

Mucoepidermoid Carcinoma Subtypes

ONCOCYTIC MUCOEPIDERMOID CARCINOMA AND WARTHIN-LIKE MUCOEPIDERMOID CARCINOMA

Oncocytic mucoepidermoid carcinoma (OMEC) is a rare but diagnostically challenging type of MEC due to its histologic overlap with other benign and low-grade oncocytic salivary gland tumours.[33] This subtype is reported to occur more frequently in the parotid gland with a male predilection. OMEC is comprised predominantly of oncocytic cells with varying amounts of mucin production, cystic change, and/or associated lymphoid stroma (so-called Warthin-like)

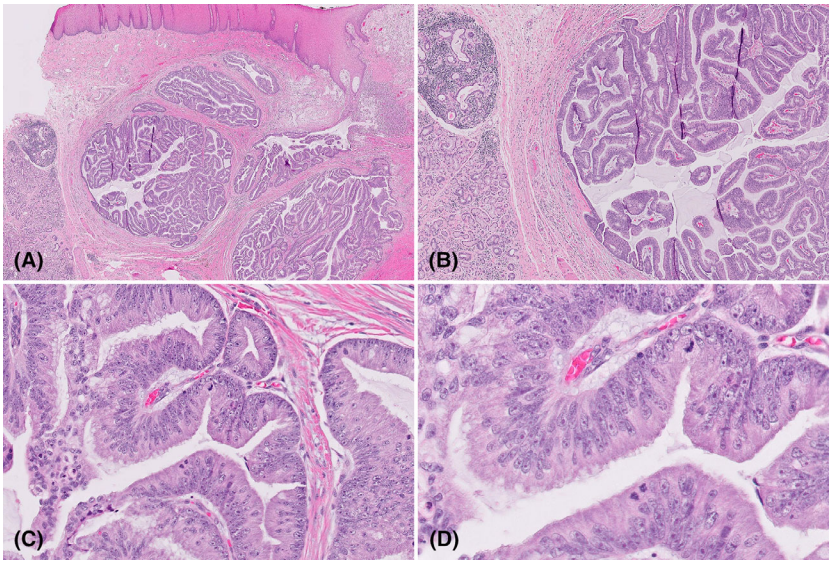

Figure 5. Mucinous adenocarcinoma/intraductal papillary mucinous neoplasm. (A) This neoplasm undermines oral mucosa adjacent to minor salivary glands. (B) The nests have rounded to focally infiltrative borders and contain well-developed papillae with some intraluminal pale mucinous material. (C) Cells are columnar and contain oval nuclei with prominent nucleoli. (D) Nuclei are basally located below amphiphilic, vacuolated cytoplasm. Scattered mitoses are present. This lesion lacked a basal cell layer, was positive for NKX3.1, and harboured an *AKT* p.E17K mutation.

(Figure 6).[34] When the traditional aspects of MEC (epidermoid, intermediate, and mucus producing cells) are limited, it can be difficult to differentiate from salivary oncocytoma, oncocytic cystadenoma, oncocytic myoepithelioma, pleomorphic adenoma, oncocytic carcinoma, acinic cell carcinoma, or salivary duct carcinoma. OMEC has diffuse nuclear expression of p63, which contrasts the peripheral staining pattern in oncocytomas and oncocytic carcinomas. Acinic cell carcinoma and salivary duct carcinoma are negative for p63. Oncocytic myoepitheliomas and pleomorphic adenomas will have positivity for other myoepithelial markers such as calponin and which will be negative in the p63-positive epidermoid cells of OMEC.[34] Approximately 80% of MECS, including the subtypes, harbour gene fusions involving *MAML2* (Table 1). Therefore, *MAML2* testing can be useful in diagnostically challenging cases when positive; however, a negative test result does not rule out OMEC.[33] The majority of reported lesions are low grade; however, cystic spaces are less prominent on OMEC and it is unclear how the grading schemes can be applied to these lesions.[34]

Warthin-like mucoepidermoid carcinoma can be regarded as a subtype of OMEC, with large cystic spaces and a lymphoid component. The epidemiology of the Warthin-like subtype differs from that of OMEC in that it has been reported to have a female predilection, while also preferentially located in the parotid. Histologically, the tumour is composed of cystic spaces lined by multilayered oncocytic to squamoid cells surrounded by a rim of lymphoid tissue with germinal centres. The Warthin-like areas may be abundant and the classic MEC architecture can be sparse. The main differential diagnosis for Warthin-like MEC is a Warthin tumour. The key distinguishing feature from Warthin tumour is that Warthin-like MEC lacks the classic, well-organized bilayered oncocytic epithelium that characterizes a true Warthin tumour (Figure 7). Additionally, p63 expression is also limited to the basal oncocytic layer in true Warthin tumour. The Warthin-like subtype, like all MEC subtypes, continues to have *MAML2* gene fusions; therefore, *MAML2* testing can be useful in challenging cases.[35]

Mucoacinar carcinoma is a rare subtype of mucoepidermoid carcinoma with serous acinar differentiation, reflecting a distal intercalated duct/acinar phenotype (designated as mucoacinar carcinomas). In 11 reported cases, MAML2 fluorescence *in situ* hybridization was positive in both the acinar and the mucoepidermoid components. Two cases tested by next-generation sequencing demonstrated *CRTC1::MAML2*.[36]

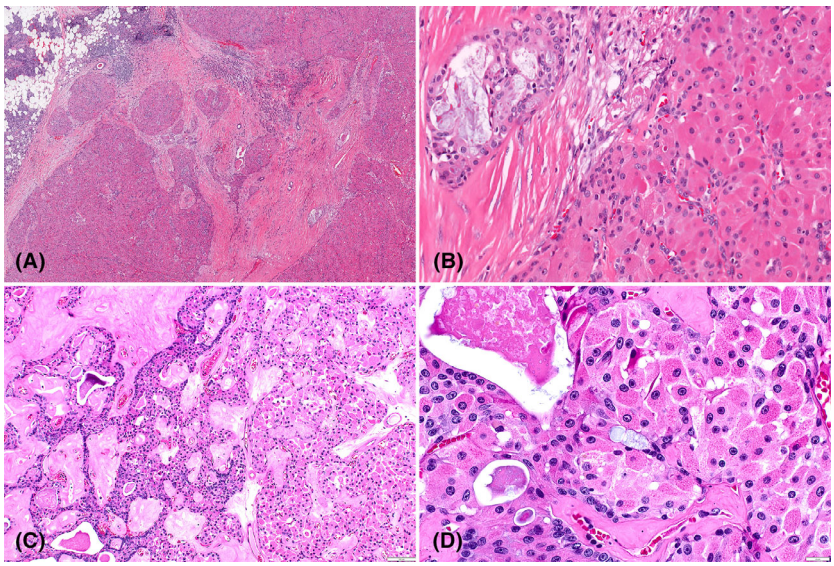

Figure 6. Oncocytic mucoepidermoid carcinoma. (A) This carcinoma shows peripheral infiltration into fibrous and inflammatory stroma. (B) Nests are predominantly solid and composed of oncocytic cells with occasional mucocytes. (C) A second example showing corded growth with hyalinized stroma, intermediate cells (left), and oncocytic cells (right). (D) On higher power, microcysts and mucinous cells are identified. Images A&B courtesy of Daniel Lubin, MD. Images C&D courtesy of Andrey Prilutskiy, MD and Madhu Roy, MD, PhD.

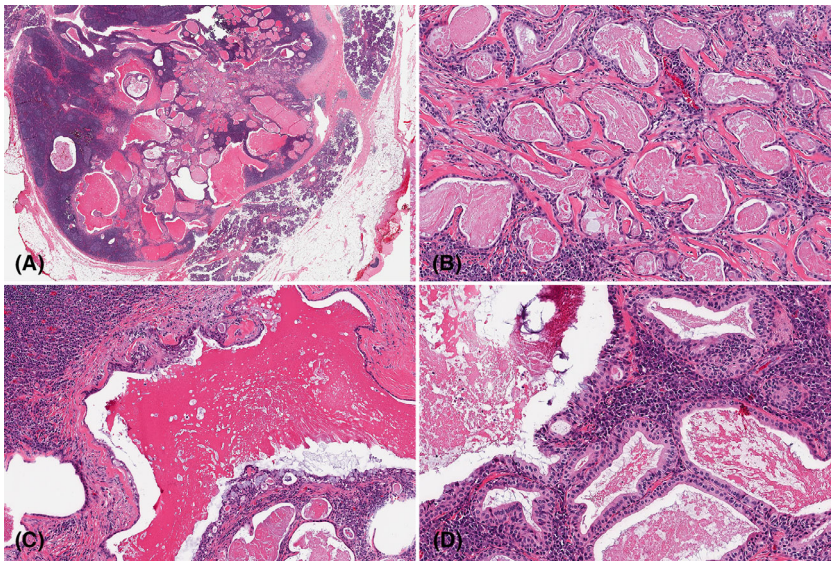

Figure 7. Warthin-like mucoepidermoid carcinoma. (A) On low power, this neoplasm demonstrates macro- and microcystic spaces with surrounding lymphoid stroma, reminiscent of Warthin tumour. (B) Microcysts are lined by plump to flattened epithelial cells. (C) In areas, large cystic spaces are lined by scattered mucocytes. (D) Cuboidal to columnar cells line these microcysts, resembling the oncocytic bilayer of Warthin tumour. Images courtesy of Daniel Lubin, MD.

Intraductal Carcinoma, Re-understood

"Intraductal carcinoma" was first introduced into the literature in 1983 by Chen.[37] Following this, multiple reports of the same tumour were published under various names, including "low-grade salivary duct carcinoma", and "low-grade cribriform cystadenocarcinoma". In the 2017 WHO, intraductal carcinoma (IDC) became the new designation for tumours previously described as "low-grade cribriform cystadenocarcinoma", and "low-grade salivary duct carcinoma". There has been controversy surrounding

IDC, primarily due to its disputed relationship with salivary duct carcinoma, variability in nomenclature, and emerging understanding of the neoplastic cell populations.[38]

Intraductal carcinoma is a rare, usually low-grade salivary malignancy that is histologically characterized by papillary, cribriform, and solid proliferations that are entirely or predominantly contained with a peripherally-located myoepithelial layer. These histologic features are reminiscent of atypical ductal hyperplasia or ductal carcinoma *in situ* of the breast. The three subtypes of IDC include: intercalated duct (Figure 8), apocrine (Figure 9), and oncocytic. Recently, subtype-specific genetic anomalies have been identified (Table 1). The intercalated duct type often has *NCOA4::RET* fusion, with the rare occurrence of *STRN::ALK*, *TUT1::ETV5*, or *KIAA1217::RET*.[39] The apocrine type predominantly harbours *PIK3CA*, *HRAS*, and *TP53* mutations or *TRIM27::RET* fusion.[18] Mixed intercalated/apocrine tumours usually harbour *TRIM27::RET* fusion, or rarely *NCOA4::RET*.[39] The oncocytic subtype characteristically has *TRIM33::RET* fusion or *BRAF* V600E mutation.[40] The *NCOA4::RET* and *TRIM27::RET* fusions were not identified in any tested salivary duct carcinomas (SDC).[38] Intercalated duct and oncocytic IDCs are positive for S100, SOX10, and mammaglobin, but they are negative for androgen receptor. Apocrine IDC has the opposite pattern. IDC is usually low-grade and noninvasive, but can demonstrate invasion (confirmed by at least the focal absence of a myoepithelial layer).[38] However, recent studies have suggested that the peripheral myoepithelial layer may also be neoplastic (as it harbours the tumour-defining gene fusion), raising the possibility that these tumours are already invasive.[41]

Emerging Entities

Adenocarcinoma, not otherwise specified (NOS), is a heterogenous group of salivary gland tumours that is slowly diminishing as more entities are being recognized either by molecular sequencing or by pooling cases with distinct characteristics. Palisading adenocarcinoma has been proposed as a morphologically unique biphasic salivary gland tumour with a neuroendocrine-like appearance and a predilection for the sublingual glands of women. Next-generation sequencing has not revealed any fusions or obvious driver mutations in fewer than 10 reported cases and the tumour appears to behave in an indolent manner.[42] Secretory myoepithelial carcinoma (SMCA) was the proposed name for signet ring cell (mucin-producing) adenocarcinoma, a rare low-grade salivary gland neoplasm.[43] Recently, NKX3.1 positivity was reported in four cases of SMCA, which has also been reported in SG IPMN (previously discussed). Additionally, alterations to the *PTEN/PI3K/AKT* pathway were

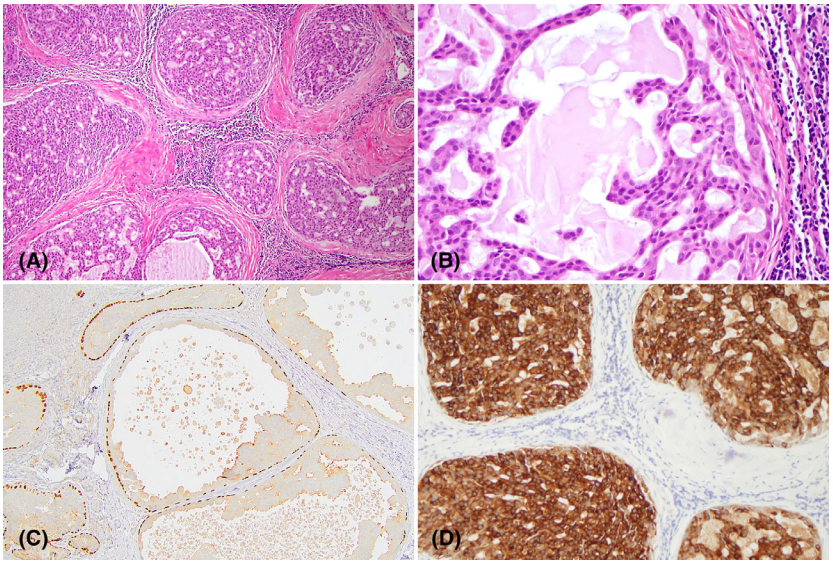

Figure 8. Intraductal carcinoma, intercalated duct type. (A) This neoplasm contains multiple nests composed of a cribriform and papillary proliferation surrounded by a flattened layer of myoepithelial cells. (B) The tumour cells are amphiphilic to eosinophilic with oval nuclei. (C) Immunostain for p63 highlights peripheral myoepithelial cells. (D) The luminal cells are strongly positive for mammaglobin. Images A,B,D courtesy of Julie Guilmette, MD.

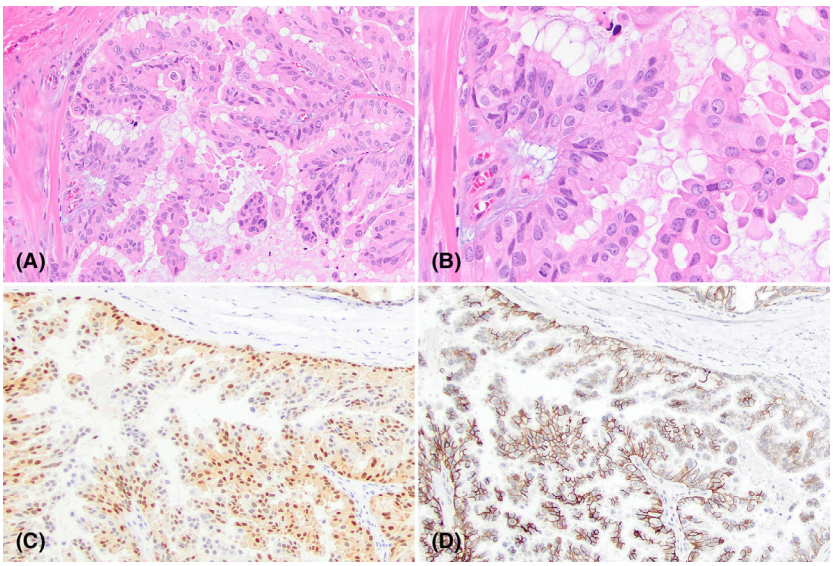

Figure 9. Intraductal carcinoma, apocrine type. (A) Tumour nests contain an intraluminal papillary and micropapillary proliferation. (B) The apocrine tumour cells have abundant eosinophilic cytoplasm with apical snouts and variable nucleoli. (C) Neoplastic cells are positive for androgen receptor. (D) Her2 can show strong membranous expression. Images courtesy of Adam Fisch, MD, PhD.

noted and one case had a *SEC16A::NOTCH1* fusion, the first extramammary tumour reported with this fusion.[44] By recognizing these entities, a better understanding of their characteristics will evolve as more cases or series are reported. Within established entities, novel subtypes have been described based on molecular and histologic findings. For instance, *HMGA2::WIF1* rearrangement characterizes a distinct subtype in the spectrum of pleomorphic adenoma, with prominent trabecular and canalicular adenoma-like morphology.[45] The question of organization remains: at which point subtypes should be separated as unique entities, a problem which this review will not solve.

Conclusion

Molecular genetic understanding of salivary gland neoplasms has significantly advanced in recent years. This knowledge has allowed for reclassification and reunderstanding of various salivary lesions. Entities included in the most recent 5th edition of the WHO include: sclerosing polycystic adenoma, keratocystoma, intercalated duct hyperplasia and adenoma, striated duct adenoma, microsecretory adenocarcinoma, sclerosing microcytic adenocarcinoma, and mucinous adenocarcinoma. Rare subtypes of mucoepidermoid carcinoma include Warthin-like and oncocytic. Understanding of intraductal carcinoma is burgeoning and continues to evolve. Pathogenic understanding, clinical treatment, and patient prognostication will improve with increasing knowledge of these diverse entities. Salivary lesions of the head and neck remain dynamic, and only with pooled understanding and collaborative research will the medical community make strides in these diseases.

Conflict of interest

The authors have no conflicts of interest and have permission to include histology images from contributors.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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