Newly described salivary gland tumors

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This review concentrates on three salivary gland tumors that have been accepted in the recent literature as new neoplastic entities: mammary analog secretory carcinoma (MASC), sclerosing polycystic adenoma (SPA) and cribriform adenocarcinoma of tongue and other minor salivary glands (CAMSGs). MASC is a distinctive low-grade malignant salivary cancer that harbors a characteristic chromosomal translocation, t(12;15) (p13;q25) resulting in an *ETV6–NTRK3* fusion. SPA is a rare lesion often mistaken histologically for low-grade salivary carcinoma. Previously thought to be a reactive fibroinflammatory process, but recent evidence of clonality, recurrences in up 30%, and dysplastic foci suggest it may be truly neoplastic. CAMSG is a distinct tumor entity that differs from polymorphous low-grade adenocarcinoma (PLGA) by location (ie, most often arising on the tongue), by prominent nuclear clearing, alterations of the *PRKD* gene family and clinical behavior with frequent metastases at the time of presentation of the primary tumor. Early metastatic disease seen in most cases of CAMSG associated with indolent behavior makes it a unique neoplasm among all low-grade salivary gland tumors. Salivary glands may give rise to a wide spectrum of different tumors. They are often diagnostically challenging as morphological features often overlap between different entities. Although conventional morphology in combination with immunohistochemical findings still provide the most important clues for diagnosis, recent advances in molecular pathology offer new diagnostic tools in investigating the differential diagnosis, as well as providing potentially valuable prognostic indicators. In the last two decades, several new salivary gland tumor entities have been described, namely MASC, SPA and CAMSGs.

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Mammary analog secretory carcinoma

Introduction

Mammary analog secretory carcinoma (MASC) of salivary gland origin is a recently described tumor that harbors a characteristic balanced chromosomal translocation,^{1–5} t(12;15) (p13;q25) resulting in an *ETV6–NTRK3* fusion,⁶ identical to that in secretory carcinoma of the breast.⁷ Secretory carcinoma (SC), also known as juvenile breast cancer, is a very rare and distinctive variant of mammary ductal carcinoma, initially described by McDivitt and Stewart in patients ranging from 3 to 15 years.⁸ Although most cases occur in children or young adults, a significant percentage of SCs arises in elderly patients of both sexes.⁹ Tognon *et al* demonstrated that SC of the breast harbors a recurrent balanced chromosomal translocation t(12;15) (p13;q25) *ETV6–NTRK3*, which leads to a fusion gene, comprising the *ETV6* gene on chromosome 12 and the *NTRK3* gene on

chromosome 15.⁷ The fusion gene *ETV6–NTRK3* encodes for chimeric tyrosine kinase that has been shown to have transformation activity in epithelial and myoepithelial cells of the mouse mammary gland.¹⁰

For many years, we began to identify a distinctive hitherto unrecognized neoplasm arising in the salivary glands characterized by morphological and immunohistochemical features strongly reminiscent of those of SC of the breast. These tumors were composed of microcystic and solid areas with abundant vacuolated colloid-like periodic acid–Schiff (PAS)-positive secretory material within the microcystic spaces; and had previously been categorized as either unusual variants of salivary acinic cell carcinoma (AciCC) or cystadenocarcinoma not otherwise specified (NOS).

We initially recognized MASC as an entity different from AciCC on the basis of three major findings.⁶ First, MASC showed no basophilia in the cytoplasm in any of the constituent cells, this being the hallmark of the serous acinar cells of AciCC resulting from the presence of cytoplasmic zymogen granules. Second, these neoplasms had a completely different immunohistochemical profile, almost always expressing S100 protein, mammaglobin, vimentin, STAT5 and MUC4, all of which were rare

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in AciCC. Finally, unlike AciCC, most cases of this carcinoma were found to harbor an *ETV6-NTRK3* fusion gene because of a t(12;15) (p13,q25), a finding identical to SC of the breast.⁷ As a result of the morphological similarity and identical fusion transcript *ETV6-NTRK3*, we therefore proposed the designation 'mammary analog secretory carcinoma (MASC) of salivary gland'.⁶

The near 100% rate of *ETV6* gene rearrangement in MASC has been subsequently confirmed by many other studies.^{11–14} Detection of *ETV6* by fluorescence *in situ* hybridization (FISH) is technically relatively straightforward and >250 cases of MASC have been published in the last 6 years since its original description in 2010.⁶

Histological Features

Grossly, MASC is usually a firm rubbery mass, with a white-tan to gray cut surface. Occasionally, on cut surface cystic spaces may be seen, containing yellow-whitish fluid. The borders of the tumors are usually circumscribed but not encapsulated and broad-front invasion within the salivary gland is often present (Figure 1a). Perineural invasion and extension to extraglandular tissues can sometimes occur, but lymphovascular invasion is not usual; similarly, necrosis is not typical.

Microscopically, most cases of MASC consist of a circumscribed mass divided by thin fibrous septa (Figure 1b) into lobules composed of microcystic, tubular and solid structures. Less commonly, a prominent fibrosclerotic stroma with isolated tumor cells in small islands or trabeculae are seen mostly in the central part of the tumor (Figure 1c). Abundant bubbly secretion is present within microcystic and tubular spaces (Figure 1d). This secretory material stains positively with mucicarmine, PAS before and after diastase digestion and with Alcian blue. Occasionally, MASC can be dominated by a single large cyst with multilayered apocrine-like or hobnail epithelial lining, and then only a minor part of the tumor displays the characteristic tubular, follicular, macro- and microcystic or papillary architecture, with typical secretions (Figures 1e and f).

The tumor cells have low-grade vesicular round-to-oval nuclei, each with finely granular chromatin and a distinctive centrally located small nucleolus (Figure 1a, inset). The cytoplasm may be pale pink to clear with a granular, vacuolated or foamy appearance. Cellular atypia is generally mild, and mitotic figures mostly rare. Thus, MASC may histologically resemble zymogen granule-poor AciCC, low-grade cribriform cystadenocarcinoma, and adenocarcinoma NOS. In contrast to AciCC, serous acinar differentiation is always absent. High-grade (HG) MASC is characterized by focal proliferation of distinct population of anaplastic cells arranged in solid and trabecular pattern with common perineural invasion (Figure 2a) and comedo-like necrosis

(Figure 2b). In contrast to the low-grade MASC, the tumor cells of the HG one display apparent nuclear polymorphism, distinctive nucleoli and they fail to reveal any secretory activity. Invasion of the skin was observed in all three cases.

Cytopathologic Features

On fine-needle aspiration, the smears are usually very cellular with sheets and clusters of bland polygonal epithelial cells admixed with bright pink filamentous matrix.^{15–17} The majority of cases demonstrate clusters of cells ranging from tight, small acinar-like structures to larger, papillary arborizing and tubuloglandular patterns. The cells have abundant vacuolated cytoplasm, with most having multiple small cytoplasmic vacuoles;^{15–19} some of these vacuoles contain mucin. The cytoplasm of other cells is finely granular and strongly eosinophilic. Nuclei are small, round and uniform, with eccentrically located small regular distinctive nucleoli. Extracellular material usually consists of mucin that in some cases is abundant.¹⁷ Overall, the fine-needle aspiration features are not specific, and original cytology diagnoses can include low-grade mucoepidermoid carcinoma,¹⁶ low-grade epithelial neoplasm NOS, salivary papillary neoplasm and even benign salivary epithelium.¹⁷

Immunohistochemical Findings

MASC is consistently positive for pan-cytokeratin (AE1-AE3 and CAM5.2), CK7, CK8, CK18, CK19, epithelial membrane antigen (EMA), S100 protein and vimentin, typically in a strong and diffuse pattern^{6,13,20–23} (Figure 3a). The tumor cells also show strong positive expression of STAT5a (signal transducer and activator of transcription 5a)⁶ and mammaglobin (secretory material is also positive)^{21,23} (Figure 3b). In addition, in most cases there is significant positivity for gross cystic disease fluid protein 15 (GCDFP-15) (particularly the secretory material), SOX10 and GATA-3 (Figure 3c). Basal cell/myoepithelial cell markers, such as p63, calponin, CK14, smooth muscle actin and CK5/6 are virtually negative as described in our original report.⁶ Since then, we have observed that although p63 protein is typically absent in the cells of MASC, it may occasionally reveal areas of peripheral staining suggestive of an intraductal MASC component.^{13,24} Another important finding is that the DOG1 staining profile in MASC is different from AciCC (Figure 3d). Most cases of MASC are DOG1 negative, whereas most AciCCs demonstrate intense apical membranous staining around lumina and variable cytoplasmic positivity.²⁵ Therefore, mammaglobin and S100 protein are useful markers for MASC^{6,13,23} and the findings are consistent in many reports.^{14,21–22,26–31} Nevertheless, co-expression of mammaglobin and S100 protein is not specific to MASC, and can be

observed also in polymorphous low-grade adenocarcinoma (PLGA), adenoid cystic carcinoma^{22,29} and low-grade salivary duct carcinoma (SDC).³² Salivary

carbonic anhydrase VI (CA6) has been recently introduced as a novel marker of AciCC with sensitivity and specificity equal to that of DOG1 in

Figure 1 Mammary analog secretory carcinoma of salivary glands (MASCs). (a) MASC are usually circumscribed but not encapsulated, and broad-front invasion within the salivary gland is often present. (b) The tumors consist of a circumscribed mass divided by thin fibrous septa into lobules composed of microcystic, tubular and solid structures. (c) Less commonly, a prominent fibrosclerotic stroma with isolated tumor cells in small islands or trabeculae are seen mostly in the central part of the tumor. (d) Abundant bubbly secretion is present within microcystic and tubular spaces. (e, f) Occasionally, MASC can be dominated by a single large cyst (e) with multilayered apocrine-like or hobnail epithelial lining (f).

Figure 2 Mammary analog secretory carcinoma of salivary glands with high-grade transformation (HG-MASC). (a, b) HG-MASC is characterized by focal proliferation of distinct population of anaplastic cells arranged in solid and trabecular pattern with common perineural invasion (a) and comedo-like necrosis (b).

Figure 3 Mammary analog secretory carcinoma of salivary glands (MASCs): immunoprofile. (a) MASC is consistently positive S100 in a strong and diffuse pattern. (b) Mammaglobin stains the cells and secretory material. (c) SOX10 is positive within the nuclei in most cells of MASC. (d) MASC is devoid of DOG1 expression in contrast to distinct membranous positivity in acinar cells of normal parotid gland (lower right corner).

discriminating it from MASC.³³ Some have postulated that morphology together with supporting S100 protein/mammaglobin immunoreactivity is sufficient to diagnose MASC and molecular confirmation of *ETV6* gene rearrangement is not required;³¹ this may be true for typical cases, but FISH still remains the gold standard for confirming the diagnosis of MASC in carcinomas with unusual morphology, particularly MASC with HG transformation^{34–36} and/or cases with morphology departing from usual appearances.^{37–38}

Molecular Findings

MASC of salivary glands, similar to SC of the breast, harbors a recurrent balanced chromosomal translocation t(12;15) (p13;q25), which leads to a fusion gene between the *ETV6* gene on chromosome 12 and the *NTRK3* gene on chromosome 15. The biological consequence of the translocation is the fusion of the transcriptional regulator (*ETV6*) with membrane receptor kinase (*NTRK3*) that activates kinase through ligand independent dimerization and thus promote cell proliferation and survival. The presence of the *ETV6-NTRK3* fusion gene has not been demonstrated in any other salivary gland tumor so far.⁶ Interestingly, the same translocation, *ETV6-NTRK3*, can be seen not only in SC of breast,⁷ but also in infantile fibrosarcoma,^{39,40} congenital mesoblastic nephroma,^{41,42} some hematopoietic malignancies,⁴³ ALK-negative inflammatory myofibroblastic tumors⁴⁴ and in radiation-induced papillary thyroid carcinoma.⁴⁵

For several years, we have been aware of a number of MASC cases positive for the *ETV6* gene split as visualized by FISH, but in which the classical *ETV6-NTRK3* fusion transcript (exon 5–exon 15 junction) was not detected by standard reverse-transcriptase polymerase chain reaction (RT-PCR).³⁸ Recent studies indicated that *ETV6* may fuse with genes other than *NTRK3*, or a subset of MASC cases may display atypical exon junctions *ETV6-NTRK3*.^{37–38} Interestingly, these atypical molecular features may be associated with more infiltrative histological features of MASC, and less favorable clinical outcomes in patients.^{37–38} In addition, MASCs with *ETV6-X* gene fusion and other atypical fusion transcripts often demonstrate abundant fibrosclerotic stroma and particularly prominent thick hyalinized fibrous septa. The neoplastic cells may be embedded in a completely hyalinized central part of the tumor (Figure 1c).

Currently, molecular confirmation is considered the gold standard for the diagnosis of MASC.

Clinical Features and Prognosis

MASC is usually encountered in adults (mean, 47 years; range, 14–78 years), with a slight male predominance.^{6,11,13,20,26–29} Most published cases

involved the parotid gland, followed by the oral cavity (23%), submandibular gland (8%), with two cases in the accessory parotid gland (2%). Interestingly, primary MASCs of thyroid gland have been recently reported in patients with no history of radiation exposure.^{46,47} More importantly, two of these thyroid MASCs showed a minor component of well-differentiated thyroid papillary carcinoma component. FISH was performed revealing *ETV6* rearrangement in both components, hence supporting common follicular cell origin of primary thyroid MASC.⁴⁶

MASC usually behaves indolently, but like other low-grade salivary gland carcinomas, there is some capacity for aggressive behavior including locoregional recurrence and distant metastasis. Particularly important is the rare occurrence of HG transformation that may result in tumor-related death.^{34–36}

The treatment of MASC has been variable, ranging from simple excision to radical resections, neck dissections, adjuvant radiotherapy and/or adjuvant systemic chemotherapy.^{6,28–30} Recognizing MASC and testing for *ETV6* rearrangement may be of potential value in patient treatment, because the presence of the *ETV6-NTRK3* translocation may represent a therapeutic target. Recent studies suggested that the inhibition of *ETV6-NTRK3* activation could serve as a target for the treatment of patients with this fusion at other sites^{48,49} and MASC as well.⁵⁰

Differential Diagnosis

The major differential diagnostic consideration is AciCC. The neoplastic cells of MASC resemble intercalated duct cells, and they have low-grade nuclei with distinctive nuclear membranes and centrally located nucleoli. The architectural patterns of MASC (ie, microcystic, papillary-cystic, follicular and solid) overlap with those of AciCC. However, the large serous acinar cells with cytoplasmic PAS-positive zymogen-like granules typical of AciCC are completely absent in MASC.⁶ In difficult cases, immunohistochemistry can aid in the distinction. MASC is consistently positive for S100 and mammaglobin, whereas AciCC is not.^{6,13–14,21–22,28} In contrast, AciCC is typically positive for DOG1 whereas MASC is usually negative.²⁵

Low-grade SDC (intraductal carcinoma) is characterized by a prominent cystic tumor component associated with proliferation of bland eosinophilic ductal cells, frequent intraluminal secretions, and S100 protein and mammaglobin immunoreactivity, the features that overlap with MASC.^{21,28,32} In contrast to MASC, however, the epithelial structures of low-grade SDC are characteristically surrounded by an intact layer of p63-positive myoepithelial cells. Rarely, this pattern may be mimicked by MASC displaying a focal intraductal (*in situ*) component,

but with only a very limited number of abluminal p63-positive cells.

Low-grade mucoepidermoid carcinoma is another potential consideration in the differential diagnosis of MASC because both tumors can have a prominent cystic component with cytologically bland cells that can be eosinophilic, clear or vacuolated. Focal mucicarmine staining in a MASC can cause confusion.¹³ In contrast to MASC, mucoepidermoid carcinoma is consistently positive for p63 in the epidermoid foci and is usually negative for S100 and mammaglobin. Finally, most cases of low-grade mucoepidermoid carcinoma harbor a different chromosomal translocation, t(11;19), resulting in *CRTC1-MAML2* fusion.^{51,52}

Other diagnostic considerations could include occasional cases of PLGA, low-grade adenocarcinoma or cystadenocarcinoma NOS, and cystadenoma NOS.⁵³ PLGA could be a consideration primarily because of its bland cytologic features and the fact that it is S100 positive and sometimes mammaglobin positive, but the differences are usually obvious morphologically.^{21,22}

Summary

MASC is a recently described salivary gland neoplasm defined by its close resemblance to secretory breast carcinoma, particularly at the genetic level where both tumors characteristically harbor the balanced translocation t(12;15) (p13;q25) resulting in the *ETV6-NTRK3* fusion gene. It is likely that MASC is more common and more variable in morphology and clinical behavior than originally considered. Recognizing MASC and testing for *ETV6* rearrangement is not only useful differential diagnostic tool but may be of potential value in patient treatment, because the presence of the *ETV6-NTRK3* fusion transcript may represent a therapeutic target in MASC.

Sclerosing polycystic adenoma

Introduction

Sclerosing polycystic adenoma (SPA) is a rare sclerosing tumor of salivary glands with a characteristic combination of histological features, somewhat reminiscent of fibrocystic changes, sclerosing adenosis and adenosis tumor of the breast. Both have cystic components with a prominent multilobular arrangement, often with small, proliferating, closely packed ductal structures, surrounded by a peripheral myoepithelial layer and stromal fibrosis with focal inflammatory infiltrates. SPA was first described by Smith *et al*⁵⁴ under the designation 'sclerosing polycystic adenosis', in a series of nine cases. Since this seminal paper, several small series and case reports have been published^{55–78} with the largest series of 16 cases published by Gnepp *et al*.⁵⁹

Overall, fewer than 100 cases of SPA have been reported so far.

This rare salivary gland lesion was initially believed to be reactive/inflammatory in nature,^{54,56} but later we have shown, using HUMARA-based analysis, that SPA is a clonal process.⁶⁰ Moreover, SPA frequently harbors intraductal epithelial dysplastic proliferations ranging from mild dysplasia to severe dysplasia/carcinoma *in situ*.^{56,58–60,63,67,69} In addition, cases with extensive *in situ* component giving impression of intralesional invasive adenocarcinoma⁷⁰ and frankly malignant invasive carcinoma ex SPA⁷⁹ were recently reported. Therefore, based on all these newly recognized findings, we suggest to coin the name 'sclerosing polycystic adenoma' (SPA).

Epidemiology and Clinical Findings

Patients range in age from 9 to 84 years with a slight female predominance; the mean age at presentation is around 40 years.⁸⁰ Most tumors involve the major salivary glands, in particular the parotid gland and less commonly, the submandibular gland.⁷⁶ Only rare definite cases have been reported in the minor salivary glands of the oral cavity,^{59,64,65,68} sinonasal tract⁷⁵ and in the lacrimal gland.⁷⁷ Other authors have also reported SPA arising from minor salivary glands, but based on the description and microphotographs, some of them may well not represent examples of genuine SPA.^{65,81,82} SPA is most commonly seen as a single lesion, but rare cases with multifocality have been documented.^{59,70,78} A unique report of two cases of SPA in a familial setting in two sisters aged 7 and 33 has been reported recently.⁷⁸ The younger patient suffered multiple recurrences.⁷⁸ Symptoms of SPA are nonspecific, the patients typically present with a slow growing painless mass with occasional mild pain or tenderness.

Cytopathologic Features

Very few cases of SPA have undergone fine-needle cytology; three cases in the Gnepp *et al*⁵⁹ multi-institutional series, plus one case each described by Imamura *et al*,⁵⁸ Kloppenborg *et al*,⁶¹ Etit *et al*⁶² and Gupta *et al*.⁶⁶ All the reports dealing with cytopathological features of SPA described the presence of syncytial epithelial duct cells with apocrine changes, foamy histiocytes, oncocytes and a cystic-type background with proteinaceous material.^{58,61–62,67} Fulciniti *et al*⁶⁷ have emphasized the combination of different cell types in a single sheet, including small ductal, apocrine and sebaceous-like cells with finely vacuolated cytoplasm as key cytological diagnostic features of SPA. In addition, less common cytological features were represented by sparse lymphoid elements and acinar epithelial cells with coarse cytoplasmic eosinophilic granules;⁶⁷ these cells had

Figure 4 Sclerosing polycystic adenoma (SPA). (a) SPAs are well-circumscribed tumors with multiple, densely sclerotic, irregularly defined lobules composed of abundant hyalinized collagen surrounding variably sized collections of ducts with varying degrees of cystic change. (b) The hallmark of SPA are acinar cells with coarse cytoplasmic eosinophilic granules. The ductal cells show variable cytomorphological characteristics, including foamy, vacuolated (c), apocrine, mucous, clear, squamous, columnar and oncocyte-like cells (d).

round to oval nuclei with even chromatin and indistinct nucleoli. Other reported findings include flat sheets of cells having a 'squamoid' appearance, cells forming glandular structures, markedly vacuolated cells 'reminiscent of sebaceous differentiation', and cells featuring apical cytoplasmic snouts.⁸⁰

Histological Features

SPAs are well-circumscribed tumors with multiple, densely sclerotic, irregularly defined lobules composed of abundant hyalinized collagen surrounding variably sized collections of ducts with varying degrees of cystic change (Figure 4a). The lesions are frequently unencapsulated, but may have a more or less complete pseudocapsule. The key histological features of SPA include lobular proliferation of ductal and acinar cells, the latter often containing large eosinophilic cytoplasmic zymogen-like granules (PAS-positive, diastase resistant). Not uncommonly, these granules may reach such a size so as to appear as intracytoplasmic globules (Figure 4b). The ductal cells show variable cytomorphological characteristics, including foamy, vacuolated, apocrine, mucous, clear, squamous, columnar and oncocyte-like cells

(Figures 4c and d). In addition, the focal presence of true acini composed of distinctly serous cells, juxtaposed to the more commonly occurring and characteristic eosinophilic, granulated acinar cells can be occasionally observed. In most cases, a variably prominent, cystic component is present. The cysts may be lined by flattened, apocrine or vacuolated cells (Figure 5a). Partly, the epithelial cells lining the cysts may be denuded and replaced by foamy macrophages (Figure 5b). Most commonly, the cellular components in SPA are embedded in a sharply delineated, dense, sclerotic collagenous stroma. The stroma may on occasion form hyalinized hypocellular nodules/plaque-like structures that may or may not contain residual epithelial cellular remnants and/or vacuolated foam cell-type macrophages. In addition, the stroma may also display a distinctly myxoid or even myxochondroid quality (Figure 5c). Commonly, the stroma harbors a variably intense, frequently nodular chronic inflammatory infiltrate. The acinar component may or may not show preservation of the lobular architecture. In the latter case, a sclerosing adenosis-like histopathological pattern is encountered and when this is associated with a stroma-induced distortion of the acini/ductules, the process may acquire an infiltrative

Figure 5 Sclerosing polycystic adenoma (SPA). (a-c) The cysts may be lined by flattened, apocrine or vacuolated cells (a). Partly, the epithelial cells lining the cysts may be denuded and replaced by foamy macrophages (b). In addition, the stroma may also display a distinctly myxoid or even myxochondroid quality (c).

appearance. Moreover, as described in a few cases by Gnepp *et al*,⁵⁹ stromal distortion may lead to the formation of radial scar-like structures. In addition, cases of SPA with dysplastic epithelial changes have been reported, and this may be severe enough to resemble low-grade ductal carcinoma *in situ* (DCIS) of the breast^{56,57,59,67,70} (Figures 6a-c).

Immunohistochemical Findings

Immunohistochemistry demonstrates preservation of the lobular architecture with staining of intact peripheral myoepithelial cell layer surrounding the ductal and acinar structures, including those with dysplastic and *in situ* ductal lesions (Figures 7a-c). The proliferative activity is low with MIB1 index 1–2% in both ductal and acinar structures, but is substantially increased in dysplastic intraductal epithelium and in DCIS lesions.⁷⁰

Immunohistochemistry shows that the ductal and acinar cells are positive for cytokeratin (AE1/AE3 and CAM5.2), variably positive for EMA, S100 protein, antimitochondrial antibody, but negative for CEA, p53 and HER-2/neu. The acinar cells with coarse granules react with GCDFP-15. Androgen, progesterone and estrogen receptors may be detected in 20%, 10% and 5% of ductal cells, respectively (Figure 7d). Ducts filled with hyperplastic and dysplastic epithelium are surrounded by an intact myoepithelial layer, positive for smooth muscle actin, p63 and calponin.

Molecular Findings

PCR-based analysis of patterns of X-chromosome inactivation was performed using a HUMARA in six cases of SPA with focal dysplastic epithelial structures. We were able to establish clonality

Figure 6 Sclerosing polycystic adenoma (SPA). (a-c) The tumor is composed of proliferating solid and tubular ductal structures separated by abundant fibrous stroma (a). Area with mild to moderate dysplastic epithelial changes with cribriform growth pattern consistent with ductal carcinoma *in situ* (b). More cellular foci with solid and tubular growth pattern within hyalinized sclerotic stroma are seen (c).

(non-random pattern of inactivation of X-chromosome) in all analyzable (female) cases.⁶⁰

Differential Diagnosis

SPA is a very rare tumor of salivary glands and most histopathologists are not familiar with this lesion, and thus it can be mistaken for other benign and even malignant entities, most often tumors such as pleomorphic adenoma, mucoepidermoid and AcicCs and, cystadenocarcinoma. Nevertheless, the histological features of SPA are very characteristic and awareness of these allows for a diagnosis of this lesion based on hematoxylin and eosin-stained sections alone. Other differential diagnostic considerations include polycystic (dysgenetic) disease and sclerotic sialadenitis, as well as SDC, (including the so-called low-grade variant) and adenocarcinoma, NOS. Major microscopic clues to a correct diagnosis include maintenance of the lobular architecture, ductal ectasia, scar-like hyalinised fibrous sclerosis,

and a spectrum of foam, apocrine, granular and mucous cells, in addition to the presence of tubuloacinar structures composed of large acinar cells with prominent brightly eosinophilic granules. In contrast, intraductal hyperplasia, particularly if associated with dysplasia, may lead one to suspect a neoplastic process, but clues to the benign nature of SPA are that it is well-circumscribed, lacks an invasive growth pattern, and that mitotic/proliferative activity is low.

The characteristic lobular growth pattern and large Paneth cell-like acinar cells of SPA are not seen in pleomorphic adenoma, whereas SPA lacks a prominent myoepithelial cell component and chondromyxoid stroma typical of PA. Chronic sclerosing sialadenitis lacks a nodular pattern and typical structural heterogeneity of SPA, although both lesions share prominent fibrosis. Moreover, large acinar cells with coarse PAS-positive zymogen-like cytoplasmic granules are not seen in chronic sclerosing sialadenitis.

Figure 7 Sclerosing polycystic adenoma (SPA): immunoprofile. (a-d) Immunohistochemistry demonstrates preservation of the lobular architecture with staining of intact peripheral myoepithelial cell layer surrounding the ductal and acinar structures, including those with dysplastic and *in situ* ductal lesions (a), calponin (b) and GFAP (c). Dysplastic ductal epithelium often demonstrates androgen receptors (d).

Both AciCC and mucoepidermoid carcinomas can be well circumscribed, and cells with small PASD-positive cytoplasmic granules are characteristic of the former. However, in our experience, the granules of AciCC are never as large as those seen in SPA, and furthermore AciCC never has the varied architecture and cell population of SPA. Mucous cells are largely absent from SPA, whereas they are almost always numerous in mucoepidermoid carcinoma, particularly the low-grade well-circumscribed examples. Furthermore, the myoepithelial cell mantle surrounding the cysts, ducts and acini of SPA is not seen in AciCC or mucoepidermoid carcinoma.

Summary

SPA is a rare sclerosing tumor of salivary glands characterized by combination of cystic ductal structures with variable cell lining including vacuolated, apocrine, mucinous, squamous and foamy cells, by prominent large acinar cells with coarse eosinophilic cytoplasmic zymogen-like granules, and closely packed ductal structures, surrounded by a peripheral myoepithelial layer and stromal fibrosis with focal inflammatory infiltrates. SPA frequently harbors intraductal epithelial dysplastic proliferations

ranging from mild dysplasia to severe dysplasia/carcinoma *in situ*. Moreover, SPA has been proven to be clonal process by HUMARA assay and is associated with considerable rate of recurrences. Therefore, based on all these newly recognized findings, we believe that SPA is likely a neoplasm, and we suggest to coin the name 'sclerosing polycystic adenoma'.

Cribriform adenocarcinoma of minor salivary glands

Introduction

Cribriform adenocarcinoma of minor salivary glands (CAMSGs) is a tumor originally described in 1999 by Michal *et al*⁸³ under the name cribriform adenocarcinoma of the tongue. In the original series, all eight neoplasms were located in the tongue; and their morphology was similar to papillary carcinoma of the thyroid gland resulting in the presumption that cribriform adenocarcinoma may have an origin in the lingual thyroglossal duct anlage.⁸³ After the original paper was published, we started to receive identical tumors located outside the tongue, including the soft palate, retromolar buccal mucosa and the

Figure 8 Cribriform adenocarcinoma of minor salivary glands (CAMSGs). CAMSG is composed predominantly of cribriform, solid and glomeruloid structures. The tumor is covered by intact mucosal epithelium (a) and lymphovascular invasion is often observed (b). The histological structure of CAMSG is quite characteristic with cribriform, tubular, glomeruloid or solid areas separated by fibrous tissue (c). In solid areas, the tumor nests are frequently detached from the surrounding fibrous stroma by clefts and often contains central necrosis (d). Characteristic feature seen in more than one-third of CAMSGs is presence of mucinous stroma composed of mucinous matrix and rare spindle cell myofibroblasts (e). Overlapping clear 'Orphan Annie eye-like nuclei' of CAMSG are remarkably similar to those of papillary thyroid carcinoma (f).

lip, which seriously questioned the theory of the origin in the lingual thyroglossal duct anlage. These new findings were summarized in a recent paper published by our group, and cribriform adenocarcinoma of the tongue was renamed as CAMSGs.⁸⁴

According to the last WHO Classification of Tumours of the Head and Neck of 2005, CAMSG is a provisional entity without a clear statement whether it represents a genuine entity or is merely a variant of PLGA.⁸⁵ Nevertheless, we believe, as well as some other authors,^{86–92} that CAMSG is a distinct neoplasm that should be classified separately from PLGA.

Histopathological Features

Grossly, the tumors are unencapsulated, white to gray in color, and hard in consistency, usually with no areas of necroses and hemorrhages, covered by nonulcerated intact epithelium (Figure 8a).

Histologically, the tumors have invasive margins and in most cases they infiltrate the muscular layer of the tongue and/or adjacent tissues. Lymphovascular invasion is observed in a third of cases (Figure 8b). The tumors are composed predominantly of cribriform (Figure 8c) to microcribriform and solid structures (Figure 8d) in variable

Figure 9 Cribriform adenocarcinoma of minor salivary glands (CAMSGs): immunoprofile. (a) SOX10 is usually diffusely positive. (b) Smooth muscle actin reacts often in a patchy manner.

proportions. Rare tumors may have an overtly cystic configuration. In most instances, the tumor architecture consists mainly of a solid mass divided by fibrous septa into irregularly shaped and sized nodules composed of centrally necrotic areas. In the solid areas, the tumor nests are frequently detached from the surrounding fibrous stroma by clefts (Figure 8d). The peripheral layer of such solid tumor nests often displays hyperchromatic nuclei in a somewhat palisaded pattern. In rare cases, psammoma bodies are found. Another characteristic feature seen in most cases is presence of mucinous spindle cell myofibroblastic stromal septa, composed of mucinous matrix and rare spindle cell myofibroblasts, seen mostly in early infiltrative foci (Figure 8e). The most prominent feature of the tumors, however, is the appearance of the nuclei. These often overlap one with another, and are pale, optically clear and vesicular with a ground glass appearance. Rarely, there are solid areas composed of these cells with optically clear nuclei. Cellular atypia is mild, and mitotic figures are in most cases rare. Generally, there are one to three small inconspicuous nucleoli. The cytoplasm is clear to eosinophilic. Cytologically, all tumors are composed of one cell type. The overall morphology of the tumor, particularly with focal papillary growth and with overlapping clear 'Orphan Annie eye-like nuclei', is remarkably similar to various variants of papillary thyroid carcinoma (Figure 8f). The cervical lymph node metastases have usually identical appearances to the primary tumors.

Clinical Findings

Two-thirds of tumors, published in the literature so far, were located in the tongue (usually the base of the tongue), and the rests of the tumors were in the soft palate, retromolar buccal mucosa, lingual tonsils, upper lip, floor of the mouth and epiglottis.^{84–89,93–96} One tumor located in the tongue was described to have a pedunculated configuration.⁸⁶ Women and men are approximately equally affected. The neck lymph node metastases are often present in the lateral neck at the time of

diagnosis, less commonly the cervical lymph node metastases are bilateral. The tumors were treated by surgical excision often accompanied by neck lymph node dissection. Approximately half of the patients received radiotherapy. All patients with available follow-up were alive and without signs of metastases.^{84,86–89,93–95}

Immunohistochemical Findings

CAMSGs react strongly with antibodies to AE1-3, CAM5.2, CK7, CK8, CK18, S100 protein, SOX10 (Figure 9a), calponin and vimentin. Smooth muscle actin reacts often in a patchy manner (Figure 9b). In addition, a significant positivity for c-kit (CD117) in 10–80% cells with a strong cytoplasmic and membranous expression has been reported.⁸⁴ Immunostaining for cyclin D1 and p53 protein demonstrate variable percentages of positive nuclei ranging between 0–35% (mean 15%) and 0–10% (mean 2.6%), respectively.⁸⁴ Basal and myoepithelial cell markers, such as p63, calponin, CK14 and CK5/6, are positive in all tumors with variable proportions up to 60% often at the periphery of the tumor nodules, especially marking the palisaded cells surrounding the glomeruloid structures. Expression of CK19 was variable with mild to moderate staining of membranes and cytoplasm in 12 out of 17 cases in two studies.^{84,89} EMA, EGFR, HER-2/neu, ER and PR are usually negative. More importantly, all the tumors are invariably completely devoid of any staining for TTF-1 and thyroglobulin. The Ki-67 proliferation index is < 25%.^{84,89}

Ultrastructure

Ultrastructurally, all the cells of the tumor are uniform and are thus of one cell type. They have irregularly clefted nuclei with nucleoli. The cytoplasm contains few organelles, including small numbers of mitochondria, lysosomes and Golgi apparatus. Rare cells contain stacks of confronting cisternae of rough endoplasmic reticulum. The cells are attached one to each other by well-formed desmosomes. Interestingly, at the ultrastructural

Figure 10 Cribriform adenocarcinoma of minor salivary glands (CAMSGs): ultrastructure. Tumor cells of CAMSG have features of hybrid myoepithelial-secretory cells, displaying the apical microvilli and containing groups of microfilaments in the cytoplasm within the same cells (arrowheads).

level, even the areas with a solid appearance at the light microscopical level reveal a microcribriform arrangement. The secretory spaces are composed of well-formed microvilli on the apical borders of the cells. A further unusual feature is that many of the secretory cells displaying the apical microvilli also contain groups of microfilaments in the cytoplasm. These cells thus had features of hybrid myoepithelial-secretory cells, and had thus all aspects of 'secretory myoepithelia'. Many cells, especially those in areas, which showed spindling of neoplastic cells, are found to contain numerous bundles of cytoplasmic tonofilaments (Figure 10). Presence of secretory myoepithelial cells in CAMSG seems to be almost unique^{83,84} with exception of very rare mucinous myoepithelial tumors that may contain abundant intracellular mucin.⁹²

Molecular Findings

No somatic mutations of *BRAF*, *K-RAS*, *H-RAS*, *N-RAS*, *c-kit* and *PDGFRα* genes were found in any of the analyzable cases in two papers.^{82,87} However, in RET proto-oncogene, heterozygous polymorphism Gly691Ser in exon 11 (one case), heterozygous polymorphism p.Leu769Leu in exon 13 (one case), heterozygous polymorphism Ser904Ser in exon 15 (one case) and intronic variant p.IVS14-24 G/A of exon 14 (two cases) were found in one study.⁸⁹ Weinreb *et al*⁹⁷ recently identified a novel and recurrent gene rearrangement in *PRKD1-3* in CAMSG, suggesting possible pathogenetic dichotomy from PLGA.

Differential Diagnosis

The most important differential diagnosis of CAMSG is PLGA. In several recent studies, the authors have argued that there is a significant proportion (about 35%) of the tumors on the PLGA spectrum exhibiting mixed morphology between PLGA and CAMSG.^{97–99}

Although CAMSG and PLGA may show morphologic overlap, and both tumor entities have molecular alterations affecting the same gene locus *PRKD1/2/3*, there are significant differences. Although mutations in *PRKD* genes¹⁰⁰ including novel *PRDK1* hotspot somatic mutation encoding p.Glu710Asp were reported in classic PLGA,¹⁰¹ most cases of CAMSGs harbor *PRKD1/2/3* translocations.⁹⁷ Moreover, there are significant differences between CAMSG and PLGA both in morphology and clinical behavior.

PLGA typically has a wide range of architectural appearances, including tubule and fascicle formation, as well as solid, cribriform and sometimes small papillary structures. A particularly characteristic feature of PLGA is the occurrence of streaming columns of single file or narrow trabeculae of cells forming concentric whorls, thereby creating a target-like appearance.⁸⁵ Perineural invasion is often seen, but does not indicate more aggressive behavior. At the cellular level, PLGA quite often contains clear cells and less frequently, mucous cells. In 3–5% of cases of PLGA, crystals resembling the tyrosine-rich crystals of some pleomorphic adenomas can be found.^{102,103} None of these features were ever described in CAMSG.

Myxoid stromal areas represented by mucinous spindle cell myofibroblastic stromal septa seen in a third of the cases of CAMSG may resemble stroma in the pleomorphic adenomas.¹⁰⁴ These myxoid myofibroblastic stromal septa in CAMSG, however, never produce true cartilage and its typical glassy appearance and its association with epithelial component at the advancing edges of the tumors is different from mesenchymal-like differentiation in pleomorphic adenomas.

The most striking feature of CAMSG is a nuclear similarity to papillary carcinoma of the thyroid gland, and this is not seen to any great extent in PLGA. Further, PLGA only rarely metastasizes, and it is our view that a good proportion of the putative examples of metastasizing PLGA could probably represent CAMSG, which had been included in some published series of PLGA. The literature records several possible examples of CAMSG published as PLGA or under other names. Perez-Ordóñez *et al*¹⁰⁵ described 17 PLGAs among which there were two examples of 'PLGA' of the tongue. In this series, there was a much higher metastatic rate than is usual for PLGA, as 5 of the 17 cases had secondaries in the neck lymph nodes. Two of these five cases had a papillary appearance, and Figures 4a and b of this paper show a tumor with an appearance identical to that of CAMSG.¹⁰⁵ Another possible candidate of CAMSG was reported by Colmenero *et al*.¹⁰⁶ In a series of 14 PLGAs, one tumor involved the base of the tongue and metastasized to the neck lymph nodes. Their Figure 2 (and possibly also Figure 3) shows a tumor very similar to CAMSG. Two other possible candidates for CAMSG were published under different names, and both carcinomas metastasized to the cervical lymph nodes.^{107,108}

Yajima *et al.* reported a tumor of the tongue in a 59-year-old man, which was called 'tubular adenocarcinoma',¹⁰⁸ and Crocker *et al.* described a 5-year-old boy with an adenocarcinoma, which the authors designated 'papillary adenocarcinoma of minor salivary gland'.¹⁰⁹ Particularly reminiscent are the pallor and ground glass quality of the nuclei as seen in both tumors, the solid and cribriform arrangement in the first tumor¹⁰⁸ and the papillary appearance resulting from tumor cell detachment from the stroma as seen in the other report.¹⁰⁹ As a consequence, therefore, we strongly suspect that if cases of CAMSG were excluded, then the metastatic rate of true PLGA would be exceptional. In contrast, the patients with CAMSG had lymph node metastases in 19/31 cases already at the time of the presentation of the primary tumor in the published series.⁸⁴

Another important differential diagnosis, especially in cases where the primary tumor is occult and excision of a metastatic focus in lateral neck lymph node is the first biopsy obtained from a patient, is a metastasis of a papillary carcinoma of thyroid gland. One illustrative case was described by Laco *et al.*⁸⁹ In their case 4, the original CAMSG located in the mouth floor was misdiagnosed as 'proliferating pleomorphic adenoma' and no further treatment was judged necessary. The lymph node lesion, which developed 37 months after removal of the primary tumor was misdiagnosed as a metastasis of papillary thyroid carcinoma. Total thyroidectomy was performed but no tumor was found. Subsequently, the lymph node was sent for second opinion, and diagnosis of metastasizing CAMSG was established. All the tissue samples resected from the nasopharynx, base of tongue and palatine tonsils were negative. Therefore, the original tumor in the mouth floor was sent for second opinion and diagnosed as CAMSG. Thus, the correct diagnosis of the primary tumor took 45 months and misdiagnosis of CAMSG as a metastatic thyroid papillary carcinoma led to unnecessary thyroidectomy.⁸⁹ CAMSG usually reveals a solid growth devoid of colloid and eosinophilic material present in follicular areas is rather pale in contrast to metastatic foci seen papillary thyroid carcinoma showing typical deeply eosinophilic colloid with 'moth-eaten peripheries' and frequent cystic configuration. In addition, giant multinucleated cells are not observed in CAMSG and psammoma bodies are found only exceptionally. Unlike papillary thyroid carcinoma, the CAMSG is composed of hybrid secretory myoepithelial cells. Most importantly, CAMSG is consistently negative with both thyroglobulin and TTF-1.^{83,89,89} However, one must be alerted to the fact that both CAMSG and papillary thyroid carcinoma may show variable expression of galectin-3, CK19 and HBME-1.⁸⁹

Summary

In conclusion, we are convinced that CAMSG is a distinct tumor entity that differs from PLGA by location (ie, most often arising on the tongue), nuclear features, histological structure, molecular alterations, and clinical behavior with frequent metastases at the time of presentation of the primary tumor. Early metastatic disease seen in most cases of CAMSG associated with indolent behavior makes it a unique neoplasm among all low-grade salivary gland tumors.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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