<table>
<thead>
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<th>Case 1</th>
<th>13 year old boy presented with a left tongue lesion, reported to “pop” after growing rapidly. It was 3.2 cm.</th>
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<td><strong>Diagnosis:</strong></td>
<td>Alveolar Soft Part Sarcoma</td>
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Malignant neoplasm showing pseudoalveolar growth of large, eosinophilic cells characterized by a specific fusion gene (*ASPSCR1-TFE3*)

**Clinical Issues**
- A rare malignant soft tissue neoplasm (0.5-0.9%)
- 5% of ASPS arising in the oral cavity
- In children: 25% of H&N ASPS involve tongue/oral cavity
- Age: Wide range; Strong predilection for adolescents
- Sex: Female > Male (~2:1)
- Site: Childhood tumors have a predilection for ENT sites
- Painless mass, occasionally bleeding
- Local recurrences common (44%), up to 9 yr after presentation
- Indolent with 80-85% 5-year survival (especially in children)

**Microscopic**
- Uninvolved surface with vascular invasion nearly always seen
- Multinodular growth of organoid, nested, compact cords to solid architecture, separated by variably thick septa of vascularized dense connective tissue
- Without intercellular cohesion, the neoplastic cells create a pseudo-alveolar pattern—slough into the alveolus
- Abundant, granular, eosinophilic cytoplasm, vesicular nuclei, prominent nucleoli

**Ancillary Tests**
- Positive: MYOD1 (cytoplasmic); NSE, Desmin, TFE3 (nuc)
- t(X;17)(p11.2;q25): *ASPSCR1/TFE3* fusion

**Differential Diagnoses**
- Granular cell tumor, rhabdomyoma (adult), rhabdomyosarcoma, oncocytoma, hibernoma, crystal storing histiocytosis

**References:**
- Pediatr Blood Cancer. 2018 Apr;65(4) (PMID: 29286582)
### Case 2
**Oral Cavity**

78 year old female presented with a mass in the palate identified during vocalization efforts. Imaging seems to show extension into the sinus.

**Diagnosis:**

Polymorphous adenocarcinoma: Cribriform carcinoma

(Cribriform adenocarcinoma of minor salivary glands (CAMSG) or Cribriform adenocarcinoma of tongue (CATS))

Minor salivary gland adenocarcinoma showing cribriform architecture, open nuclear chromatin, and paradoxical propensity for metastatic disease, considered spectrum of polymorphous adenocarcinoma, low grade (PLGA).

**Clinical Issues**

Range: 21-85 years (mean: 57 years)

Vast majority affect tongue (usually base)

30% have cervical lymph node metastases at time of diagnosis

Managed with wide excision, often accompanied by neck lymph node dissection

**Microscopic**

Invasive periphery (muscle, bone, vessels, nerves)

Solid, cribriform to microcribriform and papillary structures

Fibrous septa separate solid mass into irregularly shaped and variably sized nodules

Central comedonecrosis

Mucinous-spindle cell myofibroblastic stromal septa

Nuclei are ovoid to irregular, with pale, optically clear to ground-glass vesicular chromatin

Nucleoli are small and often peripherally located

**Ancillary Tests**

All neoplastic cells positive: AE1/AE3, CAM5.2, CK7, SOX10, S100 protein. Focal-negative: p40, p63, SMA

**PRKD** fusions or rearrangements

**Differential Diagnoses**

Pleomorphic adenoma, polymorphous adenocarcinoma, low grade, metastatic carcinoma, basal cell adenocarcinoma, adenoid cystic carcinoma

**References**

This rare odontogenic tumor was first described by Mosqueda-Taylor et al when he and his colleagues presented 6 cases in 2014; to-date, 16 cases have been reported. All 16 cases occurred in patients below age 20 with M:F of 9:7. The majority (88%) occurred in the posterior mandible and present as well-delineated radiolucencies, usually unilocular with most (71%) being larger than 3 cm, and ¾ being associated with the third molar. Grossly, they are multilobulated, glossy, discrete, solid tumors without cystic spaces. It comprises abundant fibromyxoid tissue that is delicately collagenous resembling the dental papillae, surrounded at the periphery by cuboidal-to-columnar cells resembling enamel epithelium, sometimes with stellate reticulum-like areas. The surface of the tumor often has a characteristic undulating character, often with deep invaginations. Sub-epithelial mesenchymal hypercellularity similar to a cambium layer is noted. The epithelium is positive for CD14 and CK19, amelogenin, ameloblastin and dentin sialophosphoprotein precursor, but other markers including vimentin are variably expressed. The subepithelial condensation is usually positive for CD34 and syndecan-1. Proliferative index is < 5%. In rare cases, there is an abundance of epithelium and abortive tooth-like structures as well as deposition of enameloid and even calcifications. The differential diagnoses include ameloblastic fibroma because of the presence of both epithelial and mesenchymal components but the distinctive peripheral layer of epithelium and the hypercellular cambium layer distinguish this tumor. The peripheral layer of epithelium which is not seen in any other odontogenic tumor also distinguishes POT from odontogenic myxoma. This case, unlike previously reported cases, presented with a massive recurrence requiring a mandibulectomy. It is also one of the few cases that contained many abortive tooth-like structures. As such, one may speculate that this epithelium-rich variant of the POT may behave more aggressively than the ones that do not display this feature.

References
Dr. Sook-Bin Woo
Case #4: KRAS-positive oral histiocytosis of uncertain etiology and biology, not further classified

This unusual condition is not further classifiable. In brief, this otherwise healthy patient in his third decade of life presented with a histiocytic disorder worsening over four years in spite of immunosuppressive therapy, that was positive for KRAS mutation, with complete resolution after local radiation therapy with 10 Gy. The histiocytes in this case were positive for CD163 while the PU.1 study for monocyte-macrophage transcription factor (SPI-1 gene) was diffusely positive within the nuclei. The lack of positivity for S100 protein, langerin, EBER, ALK, CD15, CD30, the usual markers for infectious agents and strong positivity for macrophages and histiocytes ruled out Langerhans cell histiocytosis, EBV-mucocutaneous ulcer and lymphomas. Interestingly, histiocytic disorders often show BRAF mutations and these include Langerhans cell histiocytosis, Erdheim-Chester disease, Rosai-Dorfman disease and some cases of cranial and intracranial xanthogranuloma. One unusual and interesting differential diagnosis is follicular dendritic cell sarcoma (FDCS) which exhibits large cells but with less cytoplasm, and nuclei with irregular outlines and coarse chromatin and that is positive for CD21, CD23 and CD35. Extranodal FDCS in the head neck occurs mostly in the oropharynx and especially in the tonsils, and because they are p16 positive, may be mistaken for p16+ squamous cell carcinoma, if there is no suspicion for FDCS.

References
Mucoepidermoid carcinoma (MEC) is the most common tumor of minor salivary glands [1, 2]. A large subset of these MECs harbor gene fusions involving MAML2 [3, 4]. Most MECs are easy to identify; uncommon variants may cause some diagnostic difficulty [5, 6].

Mucoepidermoid carcinoma, along with other salivary gland tumors, may involve the oropharynx [7, 2] with mucoepidermoid and adenoid cystic carcinomas being the most common [8, 9, 2, 1].

MEC of the oropharynx affects females more than males [7]; and the age of presentation ranges from 31 to 88 years, with a median of 61 [7]. Most arise in the base of tongue and are associated with a high rate of lymph node metastasis. Histologically, 88% are classified as low to intermediate grade and 12% as high-grade [7]; however, neither grading nor MAML-2 status predicts the risk of metastasis [7].

This case is a ciliated variant of MEC (CV-MEC) with a MAML2 fusion which has recently been described by Bishop et al [5]. CV-MECs show cystic spaces lined by a mixture of intermediate cells, epidermoid cells, mucocytes and ciliated columnar cells [5]. Conventional MEC, when present, represents a minor component [5]. Most cases are positive for the break-apart fluorescence in situ hybridization (FISH) for MAML2 [5]. Interestingly, this tumor also showed a focal spindle cell pattern. A case of MEC with a predominant spindle cell component has been described involving the palatine tonsil [10]. The spindle cell pattern showed bland spindled to fusiform cells arranged in organoid-like nests with scattered goblet cells [10]. FISH revealed the presence of a t(11;19) CRTC1-MAML2 gene fusion [10]. MAML2 rearrangement was identified in our case. This finding establishes a clear connection to the MEC group of tumors and is a valuable ancillary test in establishing the diagnosis [5].

The differential diagnosis includes polymorphous adenocarcinoma, epithelial-myoepithelial carcinoma, adenoid cystic carcinoma, secretory carcinoma, salivary duct carcinoma, basaloid squamous cell carcinoma and human papillomavirus (HPV)-related squamous cell carcinoma and HPV-related multiphenotypic carcinoma (HPV-MC).

Polymorphous adenocarcinoma (PAC), previously known as polymorphous low-grade adenocarcinoma (PLGA)[11], is rare in the oropharynx [12]. The cells of PAC are monomorphic (ductal cell type) [13], show ovoid, vesicular nuclei with inconspicuous and peripherally located nucleoli, and have scant to moderate, lightly eosinophilic cytoplasm [13]. There is a wide range of morphologic patterns (hence the term polymorphous) including tubular, fascicular, solid, cribriform and papillary [14-16]. PAC cells may be arranged in single files or narrow trabeculae forming concentric whorls (targetoid appearance) around nerves [16]. These tumors may be focally positive for p63 but are negative for p40 [16]; PAC does not show MAML-2 rearrangements.

Epithelial-myoepithelial carcinoma (EMC) is a biphasic tumor [17] which contain abluminal clear polygonal myoepithelial cells and luminal ductal cells with scant cytoplasm [18, 13, 17]. EMC may have ancient and Verocay-like changes [17]; sebaceous differentiation may be present [17, 19]. Variants such dedifferentiated, oncocytic, myoepithelial anaplasia and double-clear add to
the histologic diversity [20, 19]. Mucocytes and epidermoid cells are not present in these
tumors. p63, along with other standard myoepithelial markers, highlight the myoepithelial cells.

Adenoid cystic carcinoma (ACC) of the base of the tongue has been reported in the literature
[21, 22]. ACCs show myoepithelial cells with high nuclear to cytoplasmic ratios. These cells
have angulated hyperchromatic nuclei and may be associated with variable amounts of basal
lamina and stromal material, contributing to the morphologic diversity of these tumors. A
glandular component is also present. Altogether, these features yield the tubular, cribriform and
solid patterns characteristic of ACC. In challenging cases, testing for fusions of \(\text{MYB}, \text{MYBL1}\) or
\(\text{NFIB}\) can be helpful [23]. \(\text{MYB-NFIB}\) fusion positive ACCs are more likely to arise from minor
salivary glands [24]. ACCs lack mucocytes and epidermoid cells.

Secretory carcinoma (SC), previously known as mammary analogue secretory carcinoma [25]
has rarely been reported in the base of the tongue [26]; SCs are circumscribed and divided by
thin septa with a lobular-like architecture [25]. SCs may show microcystic, papillary-cystic,
“follicular” and solid patterns [27]. A cystic glandular pattern lined by cells with a cuboidal
appearance with “bubbly” secretions is common [25]. SCs may have focal areas of mucin-
containing cells that may stain with mucicarmine [27]. SCs are positive for mammaglobin and
\(\text{S100}\) protein and are negative for \(\text{p63}\) [27]; SC show rearrangement of the \(\text{ETV6}\) gene by
fluorescence in situ hybridization [27]. MEC is negative for \(\text{S100}\) protein.

A carcinoma ex-pleomorphic adenoma with invasive micropapillary SDC and ACC components
involving hard and soft palate has been reported [28]. SDCs are histologically similar to high-
grade invasive and in-situ ductal carcinoma of breast [29, 30]; SDCs show pleomorphic cuboidal
to polygonal cells arranged in clusters, sheets and invasive irregular glandular formations within
a desmoplastic stroma [30]. SDCs may show cribriform, solid or micropapillary patterns with
comedo necrosis [30]. This morphology is not seen in the current case. SDC lacks mucocytes
and \(\text{p63}\) positive epidermoid cells.

Most HPV-related carcinomas arise in the oropharynx and show a basaloid morphology [31-35].
The epithelium is arranged in sheets and ribbons of basaloid cells with high-nuclear to
cytoplasmic rations. In these tumors, focal definitive squamous differentiation is noted; these
tumors do not show cystic formations and lack mucocytes and cystic spaces. The cells stain
with \(\text{p63}\) [36], \(\text{p40}\) and cytokeratin 5/6 [37]. They are both positive for \(\text{p16}\) [38] and in situ
hybridization for high-risk types of HPV, either DNA ISH or RNA ISH [39, 40].

HPV-related multiphenotypic carcinoma (HPV-MC) are described in the nasal cavity; an
oropharyngeal primary has not be described in the literature [41]. Histologically, HPV-MC grow
in solid nests of basaloid cells and have apparent mitoses and necrosis [41]. HPV-MC cells
show histologic and immunohistochemical evidence of myoepithelial differentiation [41]. They
may also show squamous and sarcomatoid differentiation [41]. HPV-MC cases are positive for
\(\text{p16}\) by immunohistochemistry and HPV by DNA or RNA in situ hybridization [41]. HPV-MC are
negative for fusions involving \(\text{MYB}, \text{MYBL},\) and \(\text{NFIB}\) genes [41].

Basaloid squamous cell carcinoma (BSCC) is a rare variant of squamous cell carcinoma [42,
34, 43, 44]. HPV-related squamous cell carcinoma is frequently confused with this tumor [43];
however, BSCC is frequently associated with tobacco smoking and alcohol abuse [45, 46].
BSCCs arise frequently in the larynx, hypopharynx and oropharynx [34, 46]. BSCCs also have
nests of small crowded cells with scant cytoplasm, basaloid cells, with a “jigsaw” puzzle pattern.
The cells also form cords [45] and peripheral palisading may be seen [46]. The tumor stroma
shows varying amounts of basal lamina; this feature has been called “stromal pericellular
hyalinization” or “hyalinosis” [46]. Additionally, stromal material is produced in “cystic spaces” producing a cribriform-like pattern that may be confused with ACC [46, 45, 34]. Focal necrosis may be encountered [44, 46]. BSCCs show focal conventional squamous cell carcinoma or dysplasia [45, 44] and lack mucocytes and “true” cystic spaces.

Additionally, the differential diagnosis includes cystic lesions with cilia such as ciliated HPV-related carcinomas and ciliated adenosquamous carcinoma [47, 5].

Ciliated HPV-related carcinomas show nonkeratinizing squamous epithelium and cystic/microcystic formations lined by “pseudostratified/multilayered-appearing” ciliated columnar cells [48]; these squamous cells and ciliated cells are positive for high-risk HPV by in situ hybridization [48].

Ciliated HPV-related adenosquamous carcinoma (CHAC) involves the palatine tonsil and the base of tongue [47]. CHACs show microcystic formations or nonkeratinizing squamous nests with glandular elements, including cuboidal to columnar cells and mucous cells that resemble MEC [47] with ciliated cells being present in all cases [47]. CHACs may present as cystic lymph node metastasis similar to ciliated MEC [5]. Focal keratinization and atypia are usually seen [47]. These tumors are positive for p16 and are also positive for HPV in situ hybridization [47]. MAML2 rearrangements are not present [47]. MEC may be p16 positive, potentially creating confusion [5]; therefore, testing should include MAML2 and HPV testing [5].

Additionally, mucoepidermoid carcinoma “arising in a possible bronchogenic cyst” in the thymic region has been described [49]. The presence of ciliated cells in a lateral neck mass may therefore be interpreted as a benign lesion such as a branchial cleft cyst [5].

The treatment of MEC is individualized with surgery alone, radiation alone or a combination of surgery and radiation therapy [8, 9, 50, 1]; High-grade MECs may be treated with adjuvant radiation [1]. However, in a study of radiation therapy of minor salivary gland malignancies, sinonasal and oropharyngeal primaries seem to be associated with poorer local control [51].

The 5-year and 10-year predicted overall survival for tumors of minor salivary glands is 86% and 69%, respectively [1]. In the oropharynx, minor salivary gland carcinomas show 5-year and 10-year rates of disease-specific survival of 75.1% and 61.6%, respectively [2]. In this group, independent prognostic factors include tumor grade, T stage, N stage, and age of more than 70 years. Regarding survival, as the number of reported MEC variants is low, additional studies may be performed to further clarify this issue.

References


Dr. James Lewis, Case # 6: Adenosquamous Carcinoma

Adenosquamous carcinoma (AdSCC) is one of the more confusing of the variants of squamous cell carcinoma (SCC) when arising in the head and neck. In its most basic definition, it consists of a biphasic tumor composed of SCC with a component of gland forming tumor with “punched out” luminal spaces. In the head and neck, three peculiar characteristics should be noted. The WHO does not require the presence of mucin but, in this author’s experience, it is virtually always present. In addition, unlike some other organ systems such as the lung, there is no % cutoff for the amount of gland formation/adenocarcinoma so it can range from very focal to extensive. The third, and most interesting and controversial characteristic, is that the gland component may contain tumor cells with cilia.

Based on the largest descriptive studies, it constitutes ~1-2% of all head and neck SCC. It most commonly arises in the larynx and oral cavity, then is evenly distributed amongst all other mucosal sites. Patients have similar demographics to conventional SCC, with no obvious differences in the largest studies in the literature. Nodal metastases are similar in frequency to conventional CC as well. There is no grading system so a differentiation status should not be reported. As AdSCC is rare, no specific treatments have been defined and so it is managed largely in the same manner as conventional SCC. Prognosis is the most controversial feature and has been addressed by a few case matching studies in the literature. Although numbers are small, in a study controlling for HPV status for oropharyngeal cases, AdSCC had worse prognosis than conventional SCC\(^1\) with hazard ratios for disease free and disease specific survival of 2.21 and 1.49\(^3\). It is generally considered, across oncologic practice, as a “high risk” form of SCC. Where clinical treatment is unclear, should be managed more aggressively, akin to other “high risk” forms of head and neck SCC.

AdSCC morphologically consists of overt SCC with associated gland formation. The latter is usually in the deeper aspects of the tumors and typically is associated with cells with higher nuclear to cytoplasmic ratios and more rounded nuclei. The glands have smooth contours, rounded profiles and are distinct. Their lumina contain lightly basophilic mucin with eosinophilic globules in it and intracytoplasmic mucin globules are sometimes seen. The gland spaces characteristically have degenerating neutrophils and nuclear debris within them. True cilia, when present, are usually focal and must have clear, crisp morphology with terminal bars, rather than the “fuzzy” borders that mimic cilia.

The most important aspects for AdSCC involve the pathologic diagnosis and not misdiagnosing it as something else. One must consider conventional SCC invading in and around non-neoplastic salivary gland tissue, conventional SCC with “gland like” and adenoid nests or artifactual basophilic mimicking mucin, and finally mucoepidermoid carcinoma. Conventional SCC, particularly of the supraglottic larynx, but at an anatomic subsite, invades into the normal salivary gland tissue. When it degenerates, one tends to get ductal differentiation so that these are intimately admixed with the SCC. The key is noting the cytology around the glands/ducts as it is reactive, not neoplastic. Typically it lacks the same degree of atypia as the carcinoma. The nests of conventional SCC often degenerated where squamous cells fall apart from each other (acantholysis) so that irregular spaces form centrally. The key is that these spaces are highly variable and irregular in shape, not punched out with rounded shapes and very smooth borders of the cells with the lumen, as is seen with true gland formation. Mucin production in AdSCC is usually obvious. The key is basophilic material with intraluminal eosinophilic globules. Mucicarmine special staining can be very helpful but it not required for diagnosis.

Mucin like degenerative material in acantholytic squamous nests lacks the globules and is much more irregular and inconsistent. AdSCC is most often confused with mucoepidermoid carcinoma. That latter, almost by definition, should not have bonafide squamous differentiation, nor should it have surface involvement. There is usually cystic change that is absent in AdSCC as well. Nuclei in the solid, squamoid/epidermoid nests of MEC are typically round, and there is less pleomorphism than in AdSCC.

Key References:


Dr. James Lewis, Case 7: Basaloid Squamous Cell Carcinoma

Basaloid squamous cell carcinoma (BSCC) is perhaps the most confusing of all of the variants of SCC when arising in the head and neck, with what may be construed as a “Dr. Jekyll and Mr. Hyde” phenotype 1. First described by Wain et al. in 1986, it occurs across all head and neck mucosal anatomic subsites and has widely varied prognosis depending on HPV and/or EBV status in oropharyngeal and nasopharyngeal tumors.

BSCC has a predilection for the supraglottic larynx, oropharynx, and hypopharynx, but also occurs with regularity in the sinonasal tract and nasopharynx, and occasionally in the oral cavity. It has not been convincingly described in the major salivary glands. In its most basic definition, it is a basaloid carcinoma with squamous differentiation usually on H&E examination, but by immunohistochemistry alone if necessary. The basaloid component consists of tightly circumscribed nests of cells in lobules with prominent peripheral palisading and comedonecrosis. Small pseudocystic/pseudoglandular spaces containing basophilic material that mimics true mucin are common as is stromal hyalinization, either as small nodules in the nests or as thin lines of stroma around and between the nests. Architecturally, a jigsaw puzzle pattern where the nests mold to one another is characteristic. The tumor cells are round with variably prominent nucleoli with brisk mitotic activity and apoptosis. The tumors can be overtly biphasic with a clear squamous component mixed with them, either keratinizing or nonkeratinizing, depending on the location. Sometimes, there is only SCC or surface squamous dysplasia. Metastases can hold either component.

The differential diagnosis is extensive and one of the reasons BSCC is so difficult for pathologists. It includes solid adenoid cystic carcinoma, neuroendocrine carcinoma, and adenosquamous carcinoma. When arising in the oral cavity, BSCC can be difficult to distinguish from the rare (but well described) oral basal cell carcinoma. BSCC is immunophenotypically squamous, with expression of high molecular weight cytokeratins (34betaE12 and 5/6) and diffuse positive expression of p63 and p40, although occasional tumors are focally positive only (or completely lacking) for the latter two markers. The tumor cells never express neuroendocrine or myoepithelial markers. Solid adenoid cystic carcinoma either completely lacks p63/p40 or, if retained in the solid nests, stains only at the periphery in a patchy, linear distribution. Basal cell carcinoma is EMA negative and is positive for BerEP4. It also lacks the stromal hyalinization, high mitotic activity, and necrosis so frequent in true BSCC.

What is the clinical significance of BSCC? When first described, it was considered a very high risk type of SCC, occurring mostly in older male smokers. Over time, however, as HPV (and EBV) related head and neck carcinomas have become more frequent (and more frequently detected), it has become apparent that BSCC is a mixed variant that probably can (and should be) divided into those that are viral-associated versus those that are not. Outcome studies, even those where BSCC patients are matched case for case with conventional SCC patients, have shown mixed results with some showing worse prognosis for BSCC, some no difference, and even some where BSCC is prognostically favorable. HPV likely explains these confusing findings. Begum and Westra and Chernock et al. found that the majority of oropharyngeal BSCC are related to transcriptionally-active high risk HPV while virtually all non-oropharyngeal cases are not 2,3. These series had few or no nasopharyngeal or sinonasal cases. They suggest that the HPV-negative oropharyngeal BSCC and non-oropharyngeal BSCC are best considered as a group with very aggressive clinical behavior, worse than conventional SCC. Nasopharyngeal BSCC is rare. In the older versions of the WHO classification, it was not even listed as a numerical type, but in the 2017 blue book, it became a third type of nasopharyngeal carcinoma after keratinizing and nonkeratinizing (differentiated and undifferentiated). Constituting far less than 1% of all NPC, it has been shown that most nasopharyngeal BSCC are related to EBV, presumably with a prognosis similar to other EBV-positive nasopharyngeal carcinomas.

Key References: