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MAML2 Rearrangements in Variant Forms of Mucoepidermoid Carcinoma: Ancillary Diagnostic Testing for the Ciliated and Warthin-Like Variants

Justin A. Bishop[1,2,3,*], **Morgan L. Cowan**[1], **Chung H. Shum**[4], and **William H. Westra**[1,2,3]

[1]Departments of Pathology, The Johns Hopkins University, Baltimore, MD

[2]Departments of Oncology, The Johns Hopkins University, Baltimore, MD

[3]Departments of Otolaryngology-Head and Neck Surgery, The Johns Hopkins University, Baltimore, MD

[4]Dahl-Chase Pathology Associates, Bangor, ME

Abstract

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy. Recent studies have shown that most MECs harbor gene fusions involving *MAML2* – an alteration that appears to be specific for MEC, a finding that could be diagnostically useful. While most cases of MEC are histologically straightforward, uncommon variants can cause considerable diagnostic difficulty. We present two variants of MEC for which *MAML2* studies were crucial in establishing a diagnosis: a previously undescribed ciliated variant, and the recently described Warthin-like variant.

All cases of ciliated and Warthin-like MEC were retrieved from the archives of The Johns Hopkins Hospital. Break-apart fluorescence in situ hybridization for *MAML2* was performed on all cases.

One ciliated MEC and 6 Warthin-like MECs were identified. The ciliated MEC presented as a 4.6 cm cystic lymph node metastasis originating from the tongue base in a 47-year-old woman. The Warthin-like MECs presented as parotid masses ranging in size from 1.2 to 3.3 (mean, 2.7 cm) in 4 women and 2 men. The ciliated MEC consisted of macrocystic spaces punctuated by a tubulopapillary proliferation of squamoid cells and ciliated columnar cells. The Warthin-like MECs were comprised of cystic spaces lined by multilayered oncocytic to squamoid cells surrounded by a circumscribed cuff of lymphoid tissue with germinal centers. In these cases, the Warthin-like areas dominated the histologic picture. Conventional MEC, when present, represented a minor tumor component. *MAML2* rearrangements were identified in all cases.

Warthin-like MEC, and now a ciliated form of MEC, are newly described variants of a common salivary gland carcinoma. Unfamiliarity with these novel forms, unanticipated cellular features (e.g. cilia), and morphologic overlap with mundane benign processes (e.g. developmental ciliated cysts, Warthin tumor) or other carcinomas (e.g. ciliated HPV-related carcinoma) may render these variants susceptible to misdiagnosis. These unusual variants appear to consistently harbor

[*]Address correspondence to: Justin A. Bishop, M.D., The Johns Hopkins University School of Medicine, 401 N. Broadway, Weinberg 2249, Baltimore, MD 21231, Telephone (410) 955-8116, Facsimile (410) 955-0115, jbishop@jhmi.edu.

MAML2 fusions - a finding that establishes a clear link to conventional MEC and provides a valuable adjunct in establishing the diagnosis.

Keywords

Mucoepidermoid carcinoma; MAML2; cilia; Warthin tumor; Warthin-like

Introduction

Mucoepidermoid carcinoma (MEC) is the most common type of salivary gland carcinoma. Recent evidence has shown that up to 75-80% of MECs harbor gene fusions involving *MAML2*, with the highest occurrence in low to intermediate grade tumors.(1-6) Even though the *MAML2* alteration is specific for MEC, *MAML2* testing is generally regarded as unnecessary. First, *MAML2* status is no longer believed to be a useful prognostic factor for patients with well documented MECs.(2, 3, 7-9) Second, the diagnosis of MEC is generally straightforward on histologic grounds alone such that ancillary diagnostic testing is not needed. The role of *MAML2* testing as a diagnostic adjunct is reserved for those tumors that deviate from the conventional appearance of MEC and more closely resemble some other tumor type. In those MECs where the histologic picture is dominated by oncocytic cells (i.e. oncocytic variant of MEC), for example, the finding of a *MAML2* rearrangement is extremely useful in distinguishing the oncocytic variant of MEC from other oncocyte-rich neoplasms including oncocytoma and oncocytic carcinoma.(4)

Recently a novel variant of MEC has been described that mimics Warthin tumor and is therefore regarded as “Warthin-like” MEC.(4, 10) MEC is characterized by a mixture of cell types including mucinous cells, clear cells, intermediate cells and epidermoid cells; but a ciliated cell component has not been previously described. Rather, the presence of ciliated cells is likely to be taken as evidence of a benign developmental cyst or, at the other end of the spectrum, the recently reported ciliated HPV-related squamous cell carcinoma.(11, 12) In this study, we highlight the usefulness of *MAML2* analysis in the identification of two diagnostically challenging variants of MEC: the newly described Warthin-like variant, and a previously undescribed ciliated variant.

Methods

Cases

The study was approved by The Johns Hopkins Institutional Review Board (CR00014867). Cases of ciliated MEC and Warthin-like MEC were identified in the surgical pathology archives of The Johns Hopkins Hospital. Three cases were internal cases, and 4 were external cases sent in consultation. Six of the cases were resection specimens, and one was a biopsy. The cases were reviewed by two study pathologists (JAB, WHW) and the histologic features were recorded. Clinical information for the internal cases was obtained from electronic medical records.

High-Risk Human Papillomavirus Studies

As HPV-related carcinomas of the oropharynx can occasionally be ciliated and even spread to the neck as ciliated cystic metastases, HPV studies were performed on the ciliated MEC to exclude a ciliated HPV-related carcinoma.(11, 12) Five-micrometer thick sections prepared from formalin-fixed and paraffin embedded tissue blocks. HPV testing consisted of p16 immunohistochemistry (clone INK4a; MTM Laboratories, Heidelberg, Germany) and HPV RNA in situ hybridization using the RNAscope HPV-HR18 Probe (Advanced Cell Diagnostics, Hayward, CA) which recognizes 18 high-risk HPV genotypes (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) as previously detailed.(13) P16 staining in the nucleus and cytoplasm of 70% or more of the tumor cells was regarded as a positive stain. For p16 immunohistochemistry and RNA in situ hybridization, a known HPV-related oropharyngeal carcinoma served as a positive control.

Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) was performed on formalin fixed paraffin embedded (FFPE) section using a commercially available *MAML2* dual color break apart probe (Z-2014-200, Zytovision, Germany), as previously described.(14) Under fluorescence microscopy, cells with two fusion signals of one orange and one green fluorochrome were scored as normal while cells with rearrangements for *MAML2* gene had one normal fusion signal and one orange and one green signal at a distance from each other. A mucoepidermoid carcinoma known to harbor the *MAML2* rearrangement served as a positive control, while normal salivary tissue served as a negative control.

Results

The clinical and pathologic findings of the cases are summarized in Table 1.

Ciliated Mucoepidermoid Carcinoma

One case of ciliated MEC was identified. The patient was a 47-year-old woman first noted in 2013 to have a right-sided neck mass deep to the right sternocleidomastoid muscle. Over a 4-year period, the mass had enlarged from 1.2 cm to 4.2 cm. At the time of surgical removal, the neck mass was submitted for frozen section evaluation. The results of metastatic carcinoma were communicated with a recommendation to inspect the oropharynx for a primary tumor. Upon examination, a firm 0.5 to 1 cm mass in the left base of tongue was noted and an excisional biopsy was performed.

The neck mass consisted of a large multiloculated cyst filled with pink proteinaceous material and lined by predominantly papillary epithelium (Figure 1). The cyst was surrounded by a rim of lymphoid tissue with a capsule and subcapsular space, consistent with a lymph node. Extranodal extension was absent. The epithelium lining the cyst was comprised of a mixed population of intermediate cells with clear cytoplasm, squamoid cells, mucinous cells, and eosinophilic columnar cells with numerous well-formed cilia (Figure 1). The tumor nuclei were small, round and monotonous with inconspicuous nucleoli. Mitotic figures were rare. The biopsy of the base of tongue revealed a 0.3 cm cystic tumor that was histologically identical to the cystic metastasis including the presence of cilia.

The tumor was p16 positive by immunohistochemistry (Figure 2A), but it was negative for high-risk HPV by RNA in situ hybridization (Figure 2B). Break apart FISH was positive for the *MAML2* rearrangement (Figure 2C).

The patient was treated with re-excision of the base of tongue which revealed no residual tumor. She is currently alive with no evidence of disease 6 months after treatment.

Warthin like Mucoepidermoid Carcinomas

Six cases of Warthin-like MEC were identified. Each case arose in the parotid gland. Four patients were women and 2 were men. The size of the 5 resected tumors ranged from 1.2 to 3.3 cm (mean, 2.7 cm. For the 4 consult cases, the submitted preliminary diagnoses were Warthin tumor (n=3) and lymphoepithelial cyst (n=1).

Histologically the tumors consisted of multiloculated cystic epithelial proliferations surrounded by a well-circumscribed cuff of prominent lymphoid stroma with germinal centers (Figure 3A). The cysts were filled with proteinaceous material, and most tumors exhibited scarring with or without cholesterol clefts in the lymphoid stroma. The cystic spaces were lined by multilayered oncocytic cells with scattered mucinous cells. In some areas the tumors exhibited a multilayered epithelial lining, but they lacked the classic, well-organized bilayered oncocytic epithelium that characterizes true Warthin tumor (Figure 3B). In 5 of 6 cases, there was one or more microscopic foci of conventional MEC either in the epithelium lining the large cysts or as nests scattered between the Warthin-like cysts (Figure 3C), comprising 5 to 20% of the tumor volume (mean, 10%). The epithelial components were cytologically bland throughout. There was no perineural or lymphovascular invasion, and the margins were negative for tumor. Break apart FISH was positive for the *MAML2* rearrangement in the Warthin-like and conventional areas (Figure 3D).

Treatment and follow up information was available for the 2 internal cases. Both were treated with resection only, and both patients are alive with no evidence of disease, 7 and 20 months post-treatment.

Discussion

Until relatively recently, chromosomal rearrangements in human neoplasms were believed to be limited to hematologic malignancies and sarcomas. Over the past few years, however, a growing list of epithelial malignancies has been found to harbor translocations as well. Many salivary gland tumors, in particular, are now known to harbor defining gene fusions including mucoepidermoid carcinoma (*CRTC1-MAML2* or *CRTC3-MAML2*),(1, 3) adenoid cystic carcinoma (*MYB-NFIB* or *MYBL1-NFIB*),(15, 16) secretory carcinoma (*ETV6-NTRK3*),(17) clear cell carcinoma (*EWSR1-ATF1*)(18), and polymorphous adenocarcinoma (*PRKD1-3* partnered with various genes).(19) In the case of secretory carcinoma, the discovery led to the recognition of an entirely new tumor type, but in most cases the finding of a recurring translocation has given pathologists a diagnostic “gold standard,” allowing them to truly appreciate the complete histologic spectrum of a given salivary gland neoplasm. In effect, the detection of a tumor-specific gene fusion facilitates

accurate tumor classification even in those peculiar variants that phenotypically deviate from its more conventional form.

The histologic spectrum of mucoepidermoid carcinoma (MEC) now includes a variant with cilia. Because they are restricted to the fully differentiated glandular cell, the microscopic detection of cilia has historically been taken as compelling evidence of a benign process, particularly in cytologic material.(20, 21) There are only rare reported cases of ciliated carcinomas, mostly in the gynecologic and gastrointestinal tracts.(22-25) Until this report, the presence of cilia in MEC has been restricted to those rare cases arising in the thyroid gland.(26, 27) More than simply a histologic curiosity, the finding of cilia in MEC may pose significant diagnostic difficulties. First, the presence of ciliated cells, especially when presenting as a lateral neck mass, raises the possibility of a benign branchial cleft cyst. This distinction is made more difficult by the bland cytomorphology that is typically seen in low-grade cystic examples of MEC. Even more problematic, ciliated MEC could be confused with the newly-described ciliated variant of HPV-related oropharyngeal carcinoma.(11, 12) Like our case of ciliated MEC, ciliated HPV-related carcinoma often presents as a cystic lymph node metastasis in the lateral neck from an oropharyngeal primary site. Confusion with ciliated HPV-related carcinoma is heightened by the observation that most MECs are p16 positive - a surrogate marker of HPV infection for those tumors arising in the oropharynx or presenting as a cervical lymph node metastasis.(28, 29) For ciliated carcinomas of the oropharynx and lateral neck where MEC and ciliated HPV-related carcinoma are considered in the differential diagnosis, the diagnostic workup should include *MAML2* testing and direct HPV testing (e.g. in situ hybridization) and not p16 immunostaining alone.(14) Moreover, at the histologic level, while HPV-related oropharyngeal carcinomas may exhibit foci of cilia and attenuated, bland cystic epithelium, they also demonstrate foci of overtly malignant non-keratinizing squamous cell carcinoma morphology, a feature that is absent in MEC.(11,12)

The association between Warthin tumor and MEC has been a matter of debate. It has long been reported that MEC was one carcinoma that could arise from Warthin tumors.(30-38) It is also well recognized that Warthin tumors frequently undergo squamous and/or mucinous metaplasia of the lining epithelium, and that these changes can sometimes resemble MEC. The relationship of MEC to Warthin tumor was not initially clear based on molecular genetic findings. Some early studies reported that benign Warthin tumors sometimes harbor the same *MAML2* translocations noted in MECs, a finding used to support the notion of Warthin tumor as a precursor lesion to MEC.(39-42) Others rejected this notion based on their inability to detect *MAML2* translocations in any Warthin tumor, even those with metaplastic changes.(43, 44) Much of this confusion has been clarified by Garcia, et al. and Ishibashi, et al. in their descriptions of a “Warthin-like” variant of MEC.(4, 10) *MAML2* fusions were consistently present in the purported “metaplastic Warthin tumors” that lacked a bilayered oncocytic epithelium and sometimes contained foci of conventional mucoepidermoid carcinoma, but were not present in conventional Warthin tumors that demonstrated a bilayered oncocytic epithelium. They concluded that the entire *MAML2*-rearranged tumor represents a low-grade form of MEC mimicking Warthin tumor.(4, 10)

The 6 cases presented here provide additional support to the existence of the newly-introduced “Warthin-like” variant of MEC. All 6 cases mimicked Warthin tumor at a superficial level, with a proliferation of cystically dilated glands and a prominent lymphoid stroma. The 4 consult cases were all sent with benign preliminary diagnoses, including the diagnosis of Warthin tumor in 3 of the 4 cases. Even though the lining epithelium was often multilayered and eosinophilic as is commonly encountered as a metaplastic alteration in Warthin tumor, all lacked the classic bilayered oncocytic lining epithelium that defines true Warthin tumor (Figure 4). In all 6 cases, *MAML2* FISH analysis confirmed the diagnosis of Warthin-like MEC. While 5 of 6 cases had small foci of conventional MEC, the *MAML2* rearrangement was found to be distributed throughout in all epithelial components (i.e. conventional and Warthin-like). This uniform distribution supports the position that these are truly phenotypic variants of MEC and not transformed Warthin tumors (i.e. MEC ex-Warthin tumor).

In conclusion, *MAML2* molecular analysis is now allowing the full histologic spectrum of MEC to come into focus. This spectrum now includes a ciliated variant and a Warthin-like variant. *MAML2* testing not only helps establish these tumors as histologic variants, but has practical diagnostic implications as well. The detection of a *MAML2* rearrangement in a ciliated cyst of the lateral neck can help avoid confusion with a developmental cyst at one extreme, and metastatic ciliated HPV-related carcinoma on the other. For Warthin-like MECs, detection of a MAML2 rearrangement can help avoid confusion with a true Warthin tumor showing mucinous and squamous metaplasia.

Acknowledgments

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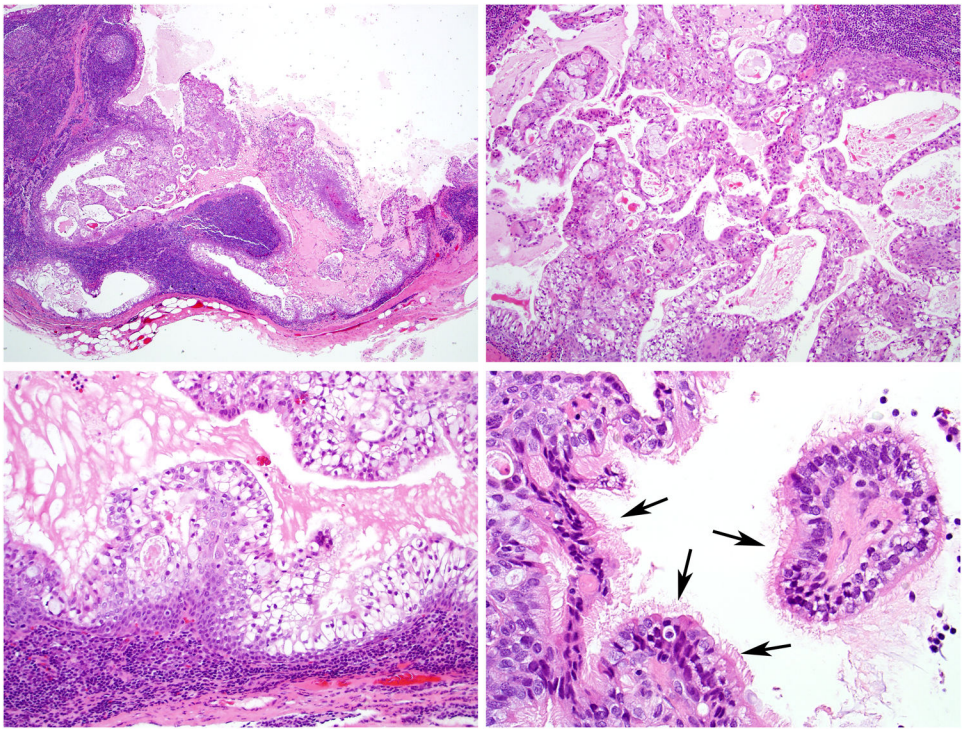

Figure 1.

This ciliated mucoepidermoid carcinoma presented as a cystic metastasis to a lateral cervical lymph node (A). The cystic lining was comprised of variably proliferative papillae and glandular spaces (B). The tumor cells were predominantly intermediate cells with clear cytoplasm, admixed with squamoid and mucinous cells. The nuclei were very bland (C). Many of the tumor cells exhibited cilia (arrows) (D).

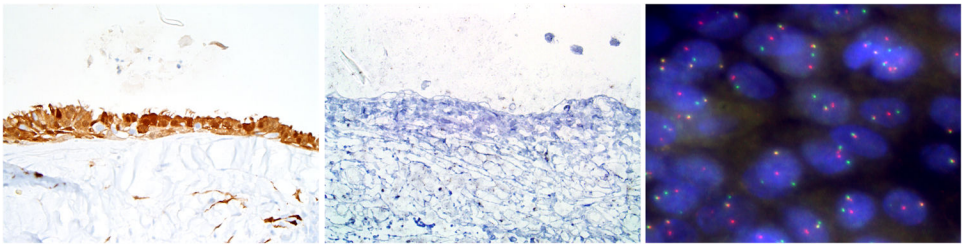

Figure 2.

The ciliated mucoepidermoid carcinoma was positive for p16 by immunohistochemistry (A) but negative for high-risk HPV by RNA in situ hybridization (B). Break apart FISH for *MAML2* was positive, with one intact gene and one rearranged.

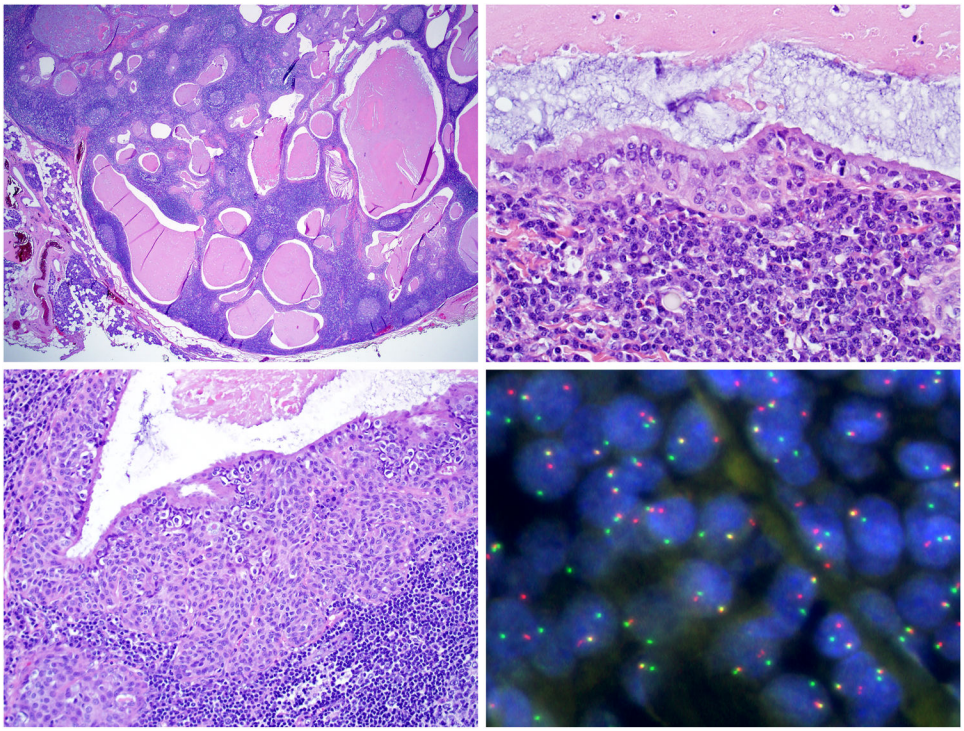

Figure 3.

The Warthin-like mucoepidermoid carcinomas closely resemble Warthin tumor at low power. There are composed of cystically dilated glands and surrounded by a well-circumscribed cuff of chronic inflammation with germinal centers (A). The squamoid epithelial lining may be multilayered and eosinophilic, resembling that of Warthin tumor (B). Most cases had at least rare foci of more proliferative epithelium recognizable as conventional mucoepidermoid carcinoma (C). Break apart FISH for MAML2 was positive throughout the tumor (D).

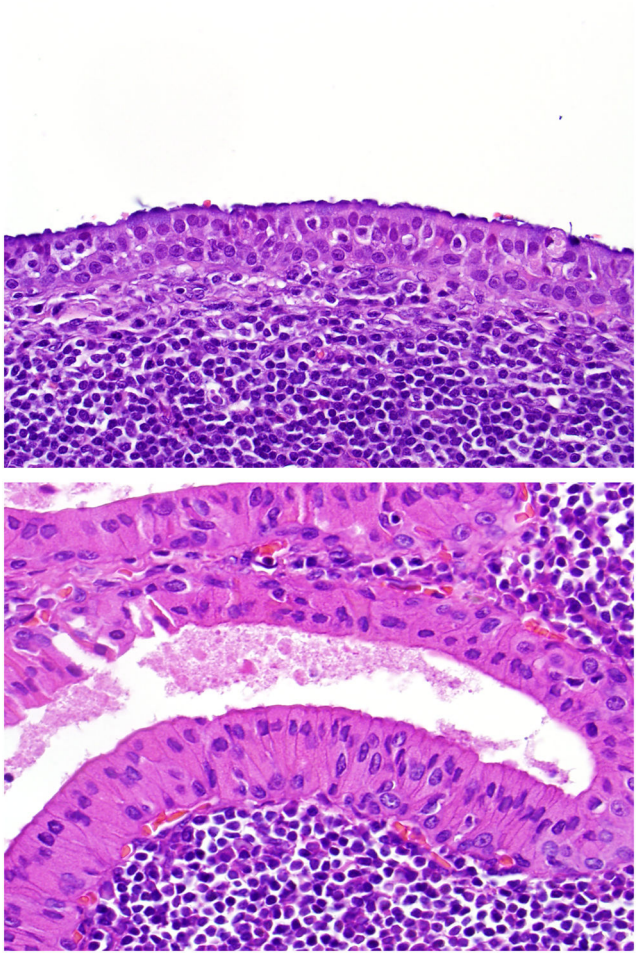

Figure 4.
Comparison of the epithelial linings of Warthin-like mucoepidermoid carcinoma (A) and true Warthin tumor (B). The lining of Warthin-like mucoepidermoid carcinoma is more disorganized and less overtly oncocytic.

Table 1

Clinical and pathologic characteristics of ciliated and Warthin-like variants of mucoepidermoid carcinoma.

Case	Variant	Age	Sex	Presentation	Primary tumor	Tumor Size (cm)	Submitted Preliminary Diagnosis	*MAML2* FISH
1	Ciliated	47	F	Cystic neck mass	Base of tongue	0.3	N/A	+
2	Warthin-like	42	M	Parotid mass	Parotid gland	3.1	Lymphoepithelial cyst	+
3	Warthin-like	33	F	Parotid mass	Parotid gland	3.2	Warthin tumor	+
4	Warthin-like	53	F	Parotid mass	Parotid gland	3.3	N/A	+
5	Warthin-like	51	M	Parotid mass	Parotid gland	NR	Warthin tumor	+
6	Warthin-like	51	F	Parotid mass	Parotid gland	1.2	N/A	+
7	Warthin-like	53	F	Parotid mass	Parotid gland	2.5	Warthin tumor	+

F=female; M=male; NR=not reported; N/A=not applicable.