Human Pathology (2019) **93**, 1–5

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Human PATHOLOGY

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Original contribution

Mucoepidermoid carcinoma of the oropharynx: a tumor type with a propensity for regional metastasis unrelated to histologic grade☆,☆☆,★

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Received 2 July 2019; revised 9 August 2019; accepted 13 August 2019

Keywords:
Mucoepidermoid carcinoma;
Base of tongue;
Lymph node metastasis;
MAML2;
Oropharyngeal carcinoma

Summary The designation "mucoepidermoid tumor" is a historic one used in reference to a form of mucoepidermoid carcinoma (MEC) that was believed to be benign. This bygone notion was based on the observation that the vast majority of MECs arising from the intraoral minor salivary glands behave in a benign fashion, particularly when they do not exhibit high grade features. There has been a recent move to partition the oral vault into the oral cavity proper and the oropharynx based on awareness that these compartments are distinct, and that similar tumor types arising from these compartments may behave in dramatically different ways (e.g, oral cavity squamous cell carcinoma *vs* oropharyngeal squamous cell carcinoma). The pathology databases from 3 large academic medical centers were searched for cases of MECs arising in the oropharynx. Relevant clinical and pathological information was collected from the medical records. Twenty-five cases were identified. They were from 18 females (72%) and 7 males (28%), ranging in age from 31 to 88 years (median, 61). Twenty-two (88%) were classified as low (n = 12) or intermediate (n = 10) grade, and 3 (12%) as high grade. Most arose from the base of tongue (n = 24), but one arose from the lateral pharyngeal wall. The median tumor size was 2.0 cm. Nineteen patients underwent neck node dissections. Of these, 13 (68%) had histologically documented lymph node metastases. MECs that lacked high grade features were almost as likely to metastasize as those with high grade features (50% *vs* 66%, Fisher exact = 1). Of 3 metastases tested, 2 harbored the *MAML2* gene fusion. MECs arising from the base of tongue are associated with an alarmingly high rate of nodal metastases. This behavior cannot be predicted by histologic grading or *MAML2* status. The propensity to metastasize may to some degree reflect the unique microenvironment of the oropharynx.

1. Introduction

Mucoepidermoid carcinoma (MEC) is a tumor of salivary gland origin that is comprised of admixed mucinous, intermediate and squamoid cells. MECs of the oral vault are not

☆ Funding/Support: No funding or support is associated with this study.
☆☆ Competing interests: There are no conflicts of interests for any of the authors.
★ The study abstract was presented at the 2019 United States and Canadian Anatomic Pathology Conference (Washington, DC).
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https://doi.org/10.1016/j.humpath.2019.08.014
0046-8177/

common, and the evolving terminology over the years has reflected uncertainties regarding their origin and behavior. The term "adenosquamous carcinoma", for example, represented an early view that MECs of the upper respiratory tract arose from the mucosa and represented a histologic variant of squamous cell carcinoma [1]. Conversely, the term mucoepidermoid "tumor" was based on the notion that MECs of the oral cavity consistently behave in a benign fashion and therefore should not be embellished with a carcinoma designation [2,3]. This latter view was later to be rejected by observations of aggressive behavior in those oral MECs showing high grade histologic features [4]. Subsequent studies have focused on those histological features that might be useful to pathologists in distinguishing aggressive from non-aggressive forms of intra-oral MECs [5]. More recently, focus has shifted towards genetic alterations as a means to predict tumor behavior. Some have suggested, for example, that fusions involving the *MAML2* gene correlate with low histologic grade, less advanced clinical stage, and improved clinical outcome [6,7].

There has been a recent move to partition the oral-oropharyngeal chamber into the oral cavity proper (anterior two-thirds of tongue, buccal and labial mucosa, gingiva, hard palate, retromolar pad, floor of the mouth) and the oropharynx (posterior one-third of tongue, soft palate, palatine tonsils, lateral and posterior pharyngeal walls) based on the awareness that these compartments are anatomically and histologically distinct, and that similar tumor types arising from these compartments may behave in dramatically different ways. Most notably, squamous cell carcinomas of the oropharynx, in sharp contrast to their counterparts in the oral cavity, are much more likely to be caused by human papillomavirus (HPV), metastasize to regional lymph nodes, and favorably respond to therapy [8]. Although the distinct behavior of HPV-related oropharyngeal squamous cell carcinoma (HPV-OPSCC), such as the proclivity of even small cancers to metastasize to regional lymph nodes, is generally attributed to intrinsic biologic properties of HPV, it is possible that it could be related in part to the unique microenvironment from which these tumors arise [9]. Other tumor types including low grade salivary gland carcinomas tend to display increased metastatic potential when they take origin from the oropharynx [10,11]. The purpose of this study was to determine whether MECs of the oropharynx behave in a predictably benign fashion, or if location in the oropharynx infers enhanced metastatic potential.

2. Patients and methods

Approval for this study was obtained from the institutional review board. The surgical pathology databases from 3 large academic hospitals (Mount Sinai Hospital, New York, NY; Johns Hopkins Hospital, Baltimore, MD; and UT Southwestern Medical Center, Dallas, TX) were searched for cases of MECs arising in the oropharynx between 2002 and 2018. The surgical pathology reports were reviewed to determine tumor grade, patient demographics, and tumor staging. When available, slides were reviewed to confirm tumor classification, grade and regional lymph node status. The tumors were graded according to the AFIP scheme for grading MECs [5,12]. A small subset of the cases had previously undergone fluorescence in situ hybridization (FISH) using a commercially available *MAML2* dual color break apart probe (Z-2014-200, Zytovision, Germany) as previously described [13]. One of these cases has been previously published [14].

3. Results

Twenty-five MECs from the oropharynx (OP) were identified. The clinical features are summarized in the Table. Twenty-four (96%) arose from the base of tongue and one (4%) arose from lateral pharyngeal wall. Eighteen (72%) of the patients were women and 7 (28%) were men, ranging in age from 31 to 88 years (median, 61). The tumors ranged in size ranged from 0.3 cm to 4.1 cm (median, 2.0). Two of the patients presented with cervical lymph nodes metastasis, and their primary oropharyngeal MECs were discovered during the subsequent staging evaluation.

Twenty-two cases were available for slide review. Twenty-two (88%) of the MECs were low (n = 12) or intermediate (n = 10) grade, and 3 (12%) were high grade. Lymph node dissection was not performed in 6 patients. Of the 19 patients who underwent regional lymph node dissections, 13 (68%) had histologically confirmed lymph node metastasis (Figure). The metastases involved unilateral lymph nodes in eight cases and bilateral lymph nodes in 5 cases. The oropharyngeal primaries for the cases that metastasized were low grade in 4 cases (4 of 12, 33%), intermediate grade in 7 cases (7 of 10, 70%), and high grade in 2 cases (2 of 3, 66%). MECs that lacked high grade features were almost as likely to metastasize as those with high grade features (50% *vs* 66%, Fisher exact = 1).

Ten of the MECs had undergone testing for the *MAML2* gene fusion. 3 of the samples failed for technical reasons. Of the remaining 7 cases, 6 (86%) were *MAML2* gene fusion positive and 1 (14%) was negative. Of the 3 metastases tested, 2 harbored the *MAML2* gene fusion (Figure). Of these *MAML2* gene fusion positive cases, the primary oropharyngeal tumor was low grade in both cases.

4. Discussion

MEC of the oral vault has long been regarded as an indolent tumor with aggressive clinical behavior restricted to those rare tumors showing high grade histologic features. This study highlights a predilection for lymph node metastasis as a property of anatomic site rather than histologic grade. MECs of the base of the tongue were found to metastasize to regional lymph node often and sometimes early: 68% of the patients who had undergone lymph node dissections had metastatic spread, and 2 presented with nodal spread before the primary tumors were

Table Summary of clinical and pathologic features of oropharyngeal mucoepidermoid carcinomas

Case	Age (y)	Sex	Site	AFIP grade	Size (cm)	Lymph node dissection performed	Metastasis	*MAML2* translocation
1	51	F	BOT	Low	0.6	Yes	Yes	NA
2	71	M	BOT	Low	2.6	Yes	No	NA
3	58	M	BOT	Low	2.2	No	NA	NA
4	61	F	BOT	Intermediate	2.1	Yes	Yes	NA
5	65	F	BOT	Low	2.8	Yes	No	NA
6	49	F	BOT	Low	1.0	Yes	No	NA
7	80	F	BOT	High	Unknown	Yes	Yes	NA
8	36	F	BOT	Intermediate	Unknown	Yes	Yes	NA
9	31	M	BOT	Intermediate	Unknown	Yes	No	NA
10	75	F	BOT	Intermediate	1.3	Yes	Yes	NA
11	64	F	BOT	Intermediate	2.6	No	NA	NA
12	88	M	BOT	Low	2.8	Yes	Yes	NA
13	56	F	BOT	Intermediate	2.3	Yes	Yes	NA
14	42	F	BOT	Intermediate	1.0	Yes	Yes	NA
15	63	M	BOT	Intermediate	4.1	Yes	Yes	NA
16	44	F	BOT	High	2.7	No	NA	NA
17	62	F	BOT	Low	1.5	No	NA	NA
18	71	F	BOT	High	1.3	Yes	Yes	NA
19	64	M	BOT	Intermediate	3.0	Yes	No	Positive
20	41	F	BOT	Low	3.0	No	NA	Positive
21	61	F	BOT	Low	0.4	No	NA	Positive
22	77	F	LPW	Low	1.1	Yes	Yes	Positive
23	70	F	BOT	Intermediate	1.4	Yes	Yes	Negative
24	39	M	BOT	Low	2.0	Yes	No	Positive
25	47	F	BOT	Low	0.3	Yes	Yes	Positive

Abbreviations: BOT, base of tongue; LPW, lateral pharyngeal wall; NA, not applicable; ND, not done.

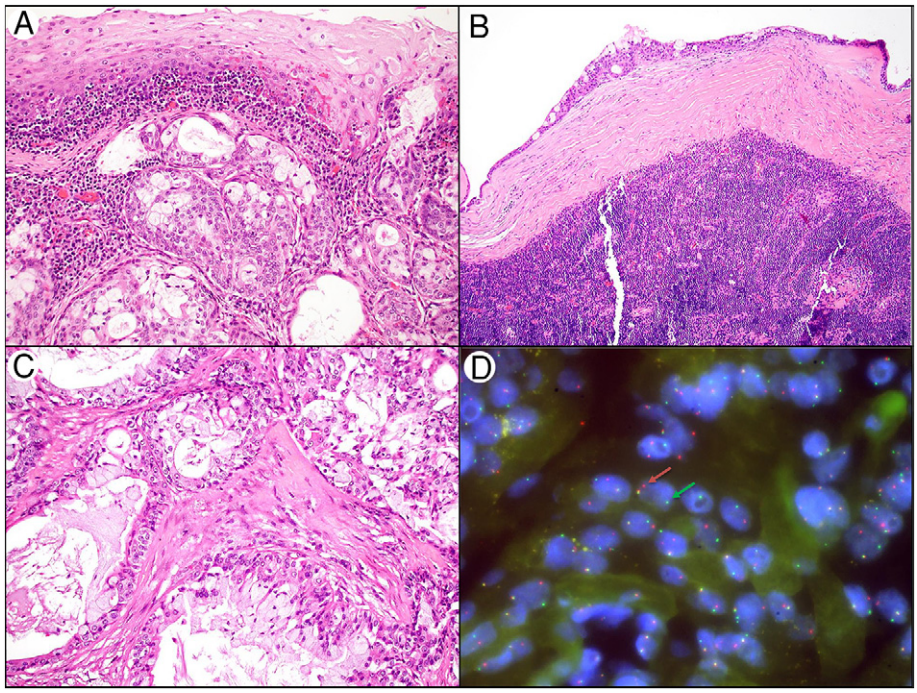

Figure Mucoepidermoid carcinoma arising in base of tongue. The tumor is comprised of mixed mucinous, clear and intermediate cells without evidence of high grade features (A). The lymph node metastasis exhibits cystic change (B) with the same bland cellular components (C). *MAML2* dual color break apart FISH demonstrates one intact gene (ie, green and red together) and one rearranged *MAML2* gene where the green probe (green arrow) and red probe (red arrow) are split (D).

even discovered. Unexpectedly, this propensity did not correlate with histologic grade. Those oropharyngeal MECs without high grade features were almost as likely to metastasize to regional lymph nodes as those with high grade features. The vulnerability of this particular anatomic site may have been overlooked in earlier studies prior to recent directives to partition the oral vault into the oral cavity proper and oropharynx [15]. In their review of MECs of the oral cavity, Olsen et al [16] identified the "tongue" as a disproportionate site of origin for lymph node metastasis, particularly for those tumors lacking high grade features. But most if not all of these metastasizing MECs arose from base of tongue (ie, oropharynx) rather than oral tongue (ie, oral cavity proper) based on a tumor mapping diagram provided in that publication [16].

In addition to and even independent of tumor grade, molecular classification of MECs based on *MAML2* gene fusion status has been advocated as a way to predict clinical behavior [17]. Some have found that MECs harboring *MAML2* fusions are associated with improved clinical outcomes including much lower rates of nodal metastasis [6,18]. We found that the *MAML2* fusion is not always protective of lymph node metastasis. In the 3 metastatic MECs tested, 2 were gene fusion positive. This finding supports the counter view that *MAML2* translocation status should not supersede other conventional parameters which might also now include tumor location [19-21].

The proclivity of oropharyngeal MECs to metastasize to regional lymph nodes may not necessarily reflect intrinsic biologic tumor properties. Instead, it may reflect the unique histologic, ultrastructual and immunologic terrain of the oropharynx. Take HPV-related tumorigenesis as one notable example: The immunosuppressive environment of Waldeyer's ring likely contributes to HPV infection and HPV-related tumorigenesis [22]; the discontinuity of the basement membrane lining the tonsillar crypts may expedite early penetration of tumor cells beyond the epithelium and into the stroma [23]; and the rich lymphatic network of the oropharynx may facilitate early spread to regional lymph nodes [24,25]. This capacity for oropharyngeal tumors to spread to regional lymph nodes may not be restricted to HPV-related squamous cell carcinoma. Cribriform adenocarcinoma is a minor salivary gland carcinoma that often occurs in the base of the tongue [10], while its twin - polymorphous adenocarcinoma - usually arises from the palate. Although these 2 tumors are similar in almost all respects and are currently classified as the same tumor type [26], cribriform adenocarcinoma is set apart by its striking propensity to metastasize to regional lymph nodes [11] – a difference that could be accounted for solely on the basis of tumor location. Our finding should draw attention to the oropharynx, and in particular the base of tongue, as a unique environment that is particularly conducive to nodal metastasis.

MECs of the oropharynx are not common. Although we were able to pool 26 cases from the experience of 3 large cancer referral centers over an extended period of time, this approach did not enable adequate patient follow-up and evaluation of survival as a function of nodal stage. In their recent analysis of the National Cancer Database, Ellis et al [4] found that nodal disease was strongly associated with decreased survival for patients with MEC of the oropharynx. They further noted that the risk of nodal metastasis correlated with a high histologic grade, but combined oral and oropharyngeal sites such that the significance of lymph node metastasis remains unknown for patients with low grade MECs of the oropharynx. Prophylactic neck dissection has been recommended for MECs of the oral cavity and oropharynx showing high grade histologic features [4]. Our observations suggest expanding this recommendation to include all MECs arising from the base of tongue irrespective of high grade histologic grade, a point punctuated by reports of tumor related deaths associated with base of tongue MECs lacking high grade features [16].

In summary, MECs of the base of the tongue have a propensity to metastasize to cervical lymph nodes even in the presence of histologic and molecular genetic features that would predict indolent behavior. The unique microenvironment of the oropharynx may serve to bridge this paradox between pathologic characteristics and clinical behavior. Further insight into this unique microenvironment may contribute to a better understanding not just of MECs but other tumor types as well.

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