



Mucoepidermoid Carcinomas of the Larynx

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Introduction

Of the salivary gland tumors, mucoepidermoid carcinomas (MEC) account for 5% and are the most like to be malignant [1]. Due to their rarity, medical literature describing the management and outcomes of all grades of laryngeal MEC is even more limited to institutional case reports [2, 3]. In the absence of large case series, there is no universally accepted protocol for the treatment of laryngeal MECs or understanding of its etiology. Based on management paradigms for MEC in the oral cavity, it is generally accepted that primary treatment of laryngeal MEC is surgical, with extent of surgery dependent on tumor location and subsites involved [4-6]. For intermediate and high-grade subtypes, there may be a role for elective neck dissection and adjuvant radiotherapy with positive surgical margins [7-9].

We present a series of three laryngeal MEC treated at our institution with a variety of clinical findings and management. Our goal is to describe the utility of video laryngostroboscopy with laryngeal MEC diagnosis in patients who do not present with typical mucosal lesion symptoms. Moreover, we discuss the critical importance of histologic subtyping, which can be easily missed by surgeons and pathologists in patients presenting with hoarseness. Overall, we believe that the discovery of these laryngeal MECs were delayed mainly due to their rarity, but also due to the limited awareness of their presentation and diagnostic workup.

Case 1

A 45-year-old male with no smoking history presented with gradual, worsening dysphonia for one year. He had been treated with proton pump inhibitor for his hoarseness with gradual worsening. Laryngostroboscopy and MRI were initially performed. Direct laryngoscopy confirmed the presence infiltrating, diffuse submucosal mass throughout the bilateral supraglottis to both arytenoids and into the left greater than right paraglottic space. Directed submucosal biopsies of bilateral false vocal folds demonstrated invasive carcinoma involving the submucosa, most consistent with MEC. Immunohistochemical staining was performed. PET demonstrated fluorodeoxyglucose (FDG) uptake within the laryngeal lesion, but no evidence of metastatic spread. Extensive submucosal spread of the tumor involving both arytenoid cartilages and the interarytenoid space precluded organ-preservation surgery. A total laryngectomy with primary pharyngeal closure and bilateral modified radical neck dissection was performed. Postoperative course was uneventful. Final pathology showed a T3N0MX intermediate-to-high grade MEC with focal keratinization, arising from background low-grade MEC. Tumor was predominantly supraglottic, with infiltration of the thyroid cartilage at the base of the epiglottis, tumor abutting the hyoid bone, and extension into the subglottis. Perineural and angiolymphatic involvement were present. All 42 lymph nodes were pathologically negative and the mucosal and soft tissue margins of resection were free of disease. Radiation therapy was offered, but was declined. Two months later, he underwent secondary tracheoesophageal fistula creation with tracheoesophageal puncture prosthesis placement. He is now 14 months without evidence of persistent disease. He is phonating well with his voice prosthesis and is tolerating a full oral diet.

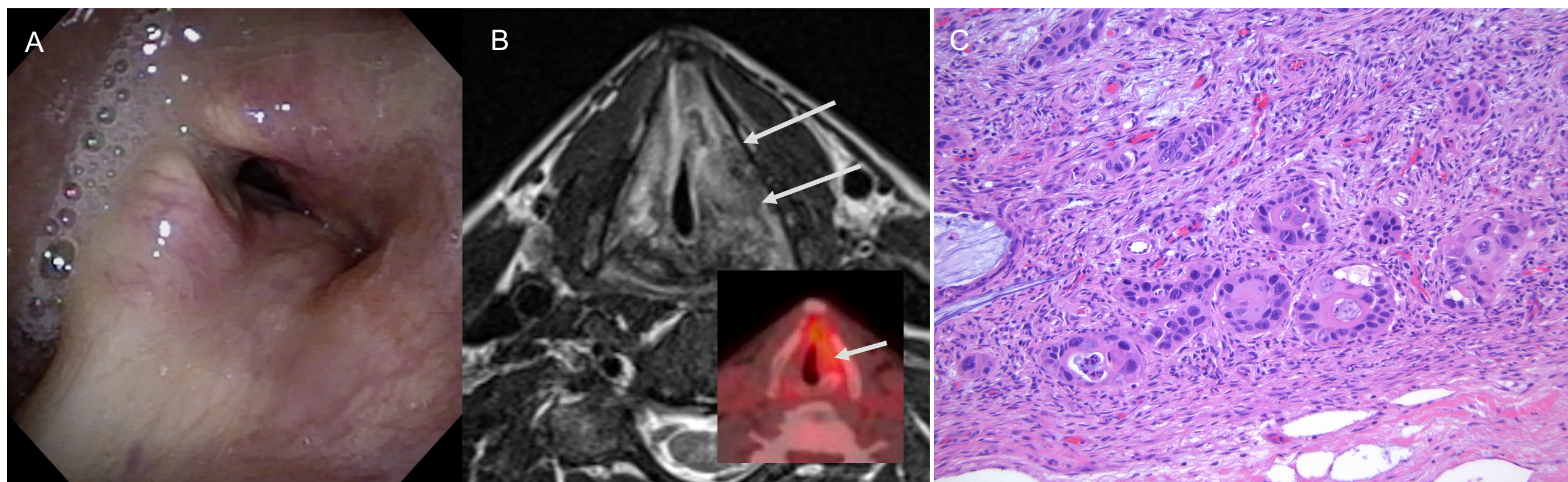


Figure A. Laryngostroboscopy demonstrated a diffusely full and plethoric appearance of the supraglottic larynx-- most notable in the right false vocal fold-- but no mucosal lesion was noted. The left true vocal fold was fixed and the right vocal fold demonstrated reduced abduction. Mucosal wave was nearly absent bilaterally and there was a small glottic gap with moderate compensatory laryngeal hyperfunction.

Figure B. Axial T2 MR shows heterogeneous tumor bulk involving the lower false vocal fold (arrows). PET CT (inset) shows corresponding mild uptake (arrow), lower than would be expected for squamous cell carcinoma or lymphoma.

Figure C. MEC infiltrating mucosa 200x. Positive for p63 and CK5/6. Special stains for mucicarmine and PAS highlighted rare mucocytes, which supported the diagnosis.

References

1. Mokhtari, S. and S. Mokhtari, Clinical features and differential diagnoses in laryngeal mucoepidermoid carcinoma. Clin Med Insights Pathol, 2012. 5: p. 1-6.
2. Karatayli-Ozgenay, S., et al., Malignant salivary gland tumours of the larynx: a single institution review. Acta Otorhinolaryngol Ital, 2016. 36(4): p. 289-294.
3. Mahstedt, K., J. Ussmüller, and K. Donath, Malignant sialogenic tumours of the larynx. J Laryngol Otol, 2002. 116(2): p. 119-22.
4. Veivers, D., et al., Supracricoid partial laryngectomy for non-squamous cell carcinoma of the larynx. J Laryngol Otol, 2001. 115(5): p. 388-92.
5. Tan, E., M.D. Mody, and N.F. Sabra, Systemic therapy in non-conventional cancers of the larynx. Oral Oncol, 2016. 82: p. 61-66.
6. Vander Ploegh, V., et al., Recent trends in the management of minor salivary gland carcinoma. Head Neck, 2014. 36(3): p. 444-55.
7. Rapisarda, A.D., et al., Mucoepidermoid carcinoma of the salivary glands: Review of the literature and clinicopathological analysis of 18 patients. Oral Oncol, 2007. 43(2): p. 130-6.
8. Mendelsohn, W.M., et al., Radiotherapy alone or combined with surgery for salivary gland carcinoma. Cancer, 2005. 103(12): p. 2544-50.
9. Holtzman, A., et al., Outcomes after primary or adjuvant radiotherapy for salivary gland carcinoma. Acta Oncol, 2017. 56(3): p. 484-489.
10. King, W., S. Ko, and D. Miller, Recurrent High-Grade Invasive Mucoepidermoid Carcinoma of Larynx: A Case Report and Review of the Literature. Rare Tumors, 2016. 8(2): p. 6204.
11. Yilmaz, M., et al., Mucoepidermoid carcinoma of the larynx. J Craniofac Surg, 2013. 24(5): p. 1862-3.
12. Nielsen, T.K., et al., Salivary gland carcinomas of the larynx: a national study in Denmark. Auris Nasus Larynx, 2012. 39(6): p. 611-4.
13. Alimoglu, Y., M. Mamanov, and A. Kaymaz, High-grade mucoepidermoid carcinoma of the larynx. J Craniofac Surg, 2011. 22(6): p. e62-4.
14. Jiang, L., et al., 18F-FDG PET/CT Imaging of Tracheal Mucoepidermoid Carcinoma. Clin Nucl Med, 2017. 42(11): p. 874-875.
15. Gold, D.R. and D.J. Amadio, Jr., Management of the neck in salivary gland carcinomas. Otolaryngol Clin North Am, 2005. 38(1): p. 99-105; ix.
16. Bell, R.B., et al., Management and outcome of patients with malignant salivary gland tumors. J Oral Maxillofac Surg, 2005. 63(7): p. 917-28.

Case 2

A 76 year-old male with a 58 pack-year history of smoking and COPD presented with 2 months of dysphagia for solid food, globus sensation, and unexplained weight loss of 18 lbs. in the preceding 6 months. Laryngostroboscopy and CT imaging were performed. Direct laryngoscopy confirmed the extent of the tumor noted by imaging and biopsy revealed a high-grade MEC. Immunohistochemistry was performed. PET-CT confirmed an FDG avid lesion centered in the left supraglottis without evidence of local or regional metastases. Due to the submucosal extension of tumor into the piriform sinus and the patient's severe COPD, he was not felt to be a good candidate for organ preservation surgery. A total laryngectomy with primary pharyngeal closure and bilateral modified radical neck dissection was performed. Final pathology confirmed a T3N0M0 high-grade MEC with focal necrosis and anaplasia, greater than 50 mitoses in 10 high-power fields. The carcinoma was predominantly in the left supraglottic region, extending deeply into the glottis and across the midline to involve the right aryepiglottic fold. The laryngeal aspect of the epiglottis with focal extension into the pre-epiglottic space was also involved by carcinoma. Resection specimen edges, soft tissue margins and all 52 lymph nodes were negative for carcinoma. He completed adjuvant radiotherapy of 60 Gray to the primary site 3 months after operation. 13 months postoperatively he has no evidence of persistent disease.

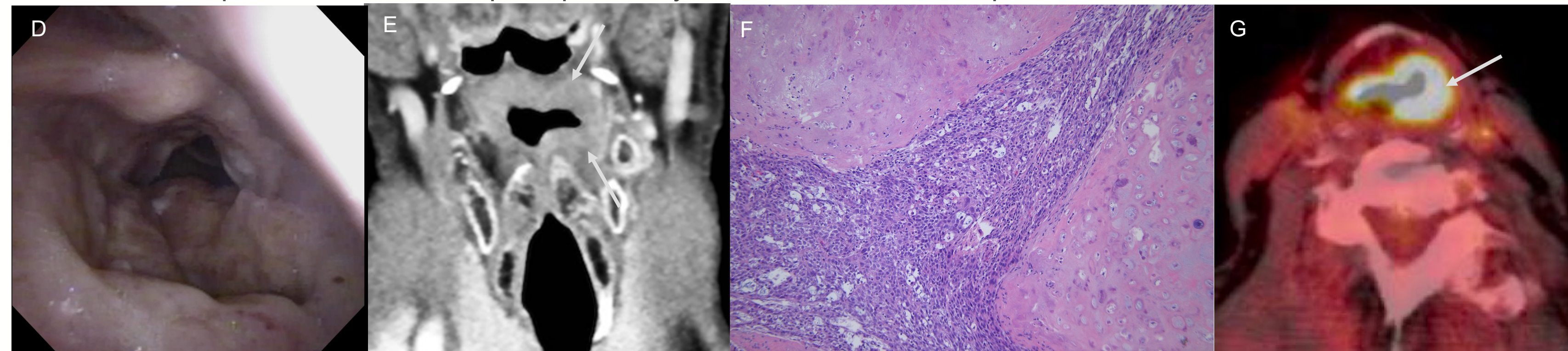


Figure D. Laryngostroboscopy demonstrated an erythematous mass involving the laryngeal surface of the epiglottis on the left extending down the aryepiglottic fold to the arytenoid, false vocal fold and true vocal fold with absence of mucosal waveform.

Figure E. Sagittal multiplanar CT reformat shows tumor along the laryngeal surface of epiglottis (arrows). There is no extension to the glottic level; note upper border of cricoid cartilage (yellow arrow).

Figure F. High Grade MEC eroding epiglottic cartilage 100x . Positive for p63 and negative for CK7 and CK20 tumor cells. Mucicarmine staining demonstrated rare mucocytes.

Figure G. Axial PET CT shows corresponding avid tumor uptake (arrow).

Discussion

From our research of minor salivary carcinoma literature, MEC are typically initially managed with resection and neck dissection followed by adjuvant radiation if intermediate and high-grade pathology [1, 2, 5, 10-13]. Therefore, we paralleled our treatments of laryngeal MECs from traditional submandibular MEC treatment of surgery followed by radiation based on histologic grade as well as regional metastases. Since our laryngeal MECs were FDG avid, PET CT identified our patients' primary laryngeal tumors as well as did not suggest metastatic spread of them, which we found none post-operatively [14]. It appeared that our lower grade MEC lesion was less FDG avid than similar staged squamous cell carcinomas of the larynx, which suggested the MEC phenotype. With such variation in radiographic imaging in previous reports, our diagnoses of MECs relied on histological evaluation, especially with MEC laryngeal cases having a history of being misdiagnosed [1]. In salivary MEC, the most common nodes involved are cervical and have been noted to be involved up to 40% on clinical presentation; laryngeal MEC nodal involvement has not currently been studied [15]. High-grade mucoepidermoid carcinomas have a greater risk for occult spread in comparison to their low-grade counterparts with a 13.7 increased hazard ratio [15, 16]. This literature is difficult to extrapolate to laryngeal MEC as there are limited inclusion of these rare tumors in these studies.

Case 3

A 62 year-old female with no smoking history presented with poor vocal quality and increasing difficulty phonating for several years. Laryngostroboscopy and CT with contrast were performed. Direct laryngoscopy failed to demonstrate any surface ulceration, but there was subtle cystic change on left true vocal fold with diffuse erythema. Palpation of the left paraglottic space demonstrated a deep, firm mass without evidence of subglottic extension or cricoarytenoid joint involvement. Superficial biopsy was unremarkable, but deeper submucosal biopsy within the paraglottic space revealed carcinoma most consistent with low-grade MEC. Immunohistochemistry was positive for p63 and pancytokeratin while negative for CK7, CK20, p53, and CD117 tumor cells. Mucicarmine staining demonstrated no mucin production. A PET-CT showed also performed with no evidence of metastasis. Given the proximity of the lesion to the thyroid cartilage and left arytenoid, a supracricoid partial laryngectomy was performed with ipsilateral modified radical neck dissection. Final pathology confirmed a T3N0M0 intermediate-grade MEC with diffuse, single cell infiltrative pattern. The tumor involved paraglottic space and extensive skeletal muscle, approaching but not invading thyroid cartilage. Soft tissue margins and 40 lymph nodes failed to demonstrate malignancy. Postoperatively, her course was uneventful. She is now 7 months from her initial surgery tolerating an unrestricted diet without tracheotomy. There is no evidence of persistent disease at this time.



Figure H. Laryngostroboscopy demonstrated no mucosal lesions, but there was markedly diminished mucosa wave formation on the left.

Figure I. Axial contrast-enhanced CT suggested the presence of a mass within the left paraglottic space.

Figure J. PET-CT demonstrate a small enhancing mass with mild FDG uptake (arrows). No invasive features are noted. The low SUV max of 3.8 (compared to 2.8 on the contralateral uninvolved side) was likely due to the lower histologic grade of this tumor.

Conclusions

- **Mucoepidermoid tumors of the larynx are difficult to diagnose**
- **Surgeons should consider a video laryngostroboscopy to identify submucosal pathology.**
- **MRI may have added utility over CT at identifying the extent of submucosal lesions in these unusual tumors with higher resolution of soft tissue.**
- **PET-CT scan may have value in distinguishing the extent of the laryngeal MEC since these tumors are FDG-avid.**
- **These methods may help identify a lesion early and allow for organ preservation surgery to be performed.**
- **Overall, MEC should be considered in the diagnosis of mass lesions of the larynx.**