Histologic and immunohistochemical identification of cribriform adenocarcinoma

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Objective. To assess whether tumors originally classified as adenocarcinoma not otherwise specified (Adca-NOS), adenoid cystic carcinoma (ACC), and polymorphous low-grade adenocarcinoma (PLGA) could be reclassified as cribriform adenocarcinoma of the tongue and minor salivary gland (CATMSG).

Study Design. Tumors diagnosed between 1992 and 2014 at Oral Pathology Laboratory, Inc. (New York Presbyterian Hospital) were selected. Each tumor was reviewed by 3 oral pathologists to confirm the diagnosis of CATMSG. After review, 11 of 70 Adca-NOS, 5 of 38 ACCs, and 5 of 23 PLGAs met the histologic criteria for CATMSG. One case diagnosed as CATMSG in 2014 was used as a control, and the following stains were completed: epithelial membrane antigen, Hector battifora mesothelial-1, p16, and CAM 5.2. Eleven Adca-NOS, 2 ACCs (tissue was available for only 2 of the 5 adenoid cystic carcinoma cases), and 5 PLGAs underwent immunohistochemical (IHC) staining. Positive HMBE-1, p16, and CAM 5.2 staining along with negative staining for epithelial membrane antigen were considered supportive of a diagnosis of CATMSG.

Results. Based on histologic features and IHC results, we were able to reclassify 10 tumors (8 Adca-NOS and 2 PLGA) as CATMSG.

Conclusion. CATMSG should be distinguished from other salivary gland tumors with similar histologic features. The diagnosis of CATMSG can be made on hematoxylin and eosin staining alone, but IHC analysis can be useful for confirmation. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;124:45-51)

Cribriform adenocarcinoma of the tongue and minor salivary gland (CATMSG) is a relatively new salivary gland neoplasm. It was originally described by in 1999 by Michal et al.[1] All 8 cases in the original study were found within the substance of the tongue, presented with metastasis to the cervical lymph nodes, and had a characteristic histomorphology. The tumor demonstrates solid islands and microcystic areas showing both cribriform and tubular growth patterns divided by fibrous septa. Portions of the tumor also exhibit a papillary configuration.[1]

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The histologic appearance of CATMSG is similar to that of papillary thyroid carcinoma (PTC). The similarity initially raised questions as to whether these tumors represented metastatic papillary thyroid carcinoma or arose from the lingual thyroglossal duct anlage.[1] Both CATMSG and PTC have solid tumor islands, some of which contain papillary structures. The individual tumor cells are crowded, often overlapping one another, and contain nuclei that appear vesicular to optically clear.[2] Immunohistochemical (IHC) studies can be used to distinguish between CATMSG and PTC. PTC shows positive staining with thyroid transcription factor-1 (TTF-1) and thyroglobulin, whereas CATMSG does not.[3] CATMSG also shows positive staining with myoepithelial markers (p63, calponin, CK14, SMA, and CK5/6), cytokeratins (AE1/3, CAM5.2, CK7, CK8, and CK18), vimentin, c-kit, and S-100. CATMSG exhibits variable positive staining with p16, galectin-3, Hector battifora mesothelial-1 (HBME-1), cyclin D1, and p53.[1-3] HBME-1 is monoclonal directed against mesothelial cells and has shown highly sensitive and specific

Statement of Clinical Relevance

Cribriform adenocarcinoma of the minor salivary gland is a tumor that can be confused with polymorphous low-grade adenocarcinoma, adenoid cystic carcinoma, adenocarcinoma not otherwise specified, or metastatic papillary thyroid carcinoma. Despite its tendency to metastasize to cervical lymph nodes, this low-grade tumor has a favorable prognosis.

immunohistochemically staining in follicular and papillary carcinomas of the thryroid.[4] The following stains are negative in CATMSG: Epithelial Membrane Antigen (EMA), Estrogen Receptor (ER), Progesterone Receptor (PR), Epidermal growth factor receptor (EGFR), HER-2 (Human epidermal growth factor receptor-2).[3]

In the 2005 edition of the World Health Organization Classification of Tumors: Pathology and Genetics of Head and Neck Tumors, CATMSG was recognized as a variant of polymorphous low-grade adenocarcinoma (PLGA).[5] In 2011, Skalova et al. published a paper suggesting that CATMSG be described as a distinct entity rather than as a variant of PLGA.[6] Subsequently, histologically identical tumors found in other minor salivary glands throughout the oral cavity and the lips prompted a change in the name from cribriform adenocarcinoma of the tongue to cribriform adenocarcinoma of the tongue and minor salivary gland.[1,3,6] Although PLGA and other salivary gland tumors, such as adenoid cystic carcinoma (ACC), can present with cribriform and tubular areas, it is important to make the histologic distinction between these tumors.

The aim of this study was to assess whether tumors previously classified as adenocarcinoma not otherwise specified (Adca-NOS), ACC, and PLGA could be reclassified as CATMSG on the basis of the identification of specific histologic features and IHC makers.

STUDY DESIGN

We reviewed all cases (n = 131) from the Oral Pathology Laboratory, Inc., archives at the New York Hospital of Queens diagnosed as Adca-NOS (n = 70), ACC (n = 38), and PLGA (n = 23) between the years 1992 and 2014. A total of 21 cases revealed histologic criteria suggestive of CATMSG. These cases included 11 of 70 Adca-NOS, 5 of 38 ACC, and 5 of 23 PLGA. Paraffin blocks were not available for 3 of the 5 ACC cases. Sufficient tissue was available for additional recuts and immunohistochemistry for all other cases (n = 18). A case diagnosed in 2014 as CATMSG was used as a control (Figure 1) to compare the histology and IHC staining properties (Figure 2).

IHC staining was performed on formalin-fixed, paraffin-embedded tissue sections. The IHC panel performed on the 18 cases included EMA, CAM 5.2, p16, and HBME-1. Lesions that stained positive for CAM 5.2, p16, HBME-1, and negative for EMA were reclassified as CATMSG. The following IHC stains were chosen for the panel because they were found not to be positive in the salivary gland differential diagnosis (p16 and HBME-1), to be positive in ACC and PLGA but not CATMSG (EMA), and to exhibit diffuse staining in CATMSG (CAM5.2).

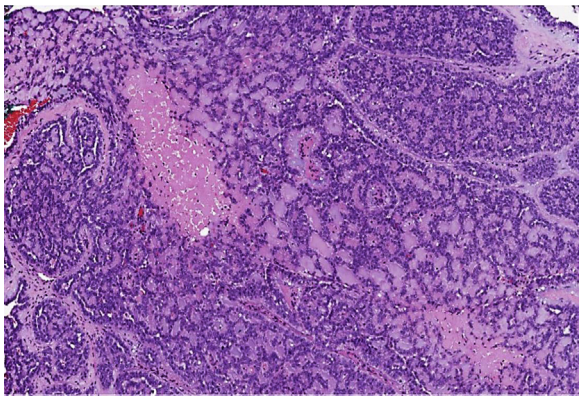

Fig. 1. Control case exhibits portions of the tumor exhibiting cribriform and papillary areas. The characteristic artifactual cleft between adjacent and basal cell layer is also seen (hematoxylin-eosin, original magnification ×4). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM03606.*

RESULTS

Of the 18 available cases, 10 cases had histologic features as well as IHC profile consistent with CATMSG. The mean age of the patients from the reclassified 10 cases in this study was 61.4 years with an age range of 32 to 83 years. These cases included 4 male and 6 female patients. The most common sites for lesions diagnosed as CATMSG was the palate (n = 4) and the buccal mucosa (n = 3). There were 2 cases from the retromolar pad and 1 from the upper lip. All cases diagnosed as CATMSG were positive for CAM 5.2, p16, and HBME-1 and negative for EMA. Clinical data and IHC staining results are presented in Table I.

DISCUSSION

Clinical and histology

CATMSG is a rare low-grade salivary gland malignant neoplasm that occurs in the minor salivary glands of the oral cavity. Over 40 cases have been documented.[7] The tumor was initially described in the tongue but was later discovered in other minor salivary gland tissues.[1] In 2015, a similar tumor was described within the minor salivary glands of the epiglottis.[8] CATMSG presents with a characteristic morphology that has features that mimic the histology of other salivary gland tumors, such as ACC and PLGA. PLGA and ACC have different clinical implications and treatment protocols, making distinction of the tumors imperative. Equally as important is distinguishing CATMSG from metastatic papillary thyroid carcinoma.

In previous studies, most patients diagnosed with CATMSG are in their fifth to sixth decades of life; however, patients from a wide age range have been affected (25-85 years; Table II). Men and women are