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Oral cavity neuroendocrine carcinoma: a comparison study with cutaneous Merkel cell carcinoma and other mucosal head and neck neuroendocrine carcinomas

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Objectives. Published cases of oral high-grade neuroendocrine carcinoma (HGNEC) variably call the tumors Merkel cell carcinoma (MCC) or small-cell/high-grade neuroendocrine carcinoma. We studied cases of cutaneous MCC and mucosal HGNEC to better distinguish them and to better define oral cases.
Study design. Twelve cutaneous MCC and 14 mucosal HGNEC cases were identified. We reviewed the hematoxylin-eosin (H&E) morphology and performed immunohistochemistry for cytokeratin 20 (CK20), thyroid transcription factor 1 (TTF-1), p63, neurofilament (NF), and achaete-scute homolog 1 (MASH-1). We also performed polymerase chain reaction (PCR) for the Merkel cell polyomavirus (MCPyV).
Results. By morphology and immunohistochemistry, MCC and HGNEC showed many differences. CK20, NF, and TTF-1 stains were the most discriminatory. MASH-1 was expressed by both MCC and HGNEC. MCPyV was present in MCC and absent in all HGNEC. The 2 oral cavity mucosal carcinomas segregated into MCC and HGNEC types, the former having the H&E nuclear morphology and classic dot-like perinuclear CK20 staining typically associated with MCC.
Conclusions. Oral cavity neuroendocrine carcinoma can be segregated into MCC and small-cell/HGNEC types by morphology and CK20 immunohistochemistry. MCPyV was present by PCR in cutaneous MCC but was not found in mucosal HGNEC. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:209-217)**

Merkel cell carcinoma (MCC) is an uncommon aggressive neoplasm of neural crest origin usually arising in sun-exposed skin of the head and neck. It has some characteristic features. In many cases, the nuclei are round to oval with fine, almost blast-like, chromatin (so called intermediate type). Others, which have been termed small-cell type, have more angulated nuclei with molding.[1] Cytokeratin-20 (CK20) expression is characteristic, particularly with a dot-like pattern,[2-4] and neurofilament (NF) expression is also common and a useful feature.[1,5] More recently, investigators have found a strong association with the human Merkel cell polyomavirus (MCPyV) that is found in up to 80% of cases.[6-8] These tumors are classically regarded as primary cutaneous neuroendocrine carcinomas, and much literature exists on distinguishing them from metastatic high-grade neuroendocrine carcinomas (HGNEC) of other sites.[9,10] Although MCC is a relatively aggressive neoplasm, recently reported System for Electronic Evaluation and Retrieval data on almost 4,000 patients showed a 10-year relative survival rate of 57.3%. Certainly, compared with other neuroendocrine carcinomas, this is relatively favorable.[11]

High-grade neuroendocrine carcinoma of the upper aerodigestive tract is another uncommon aggressive neoplasm, with a similar morphology to MCC. The hematoxylin-eosin (H&E) morphology is almost

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always that of small-cell carcinoma, consisting of tightly packed cells with little cytoplasm, angulated hyperchromatic nuclei with "salt and pepper" chromatin, inconspicuous nucleoli, and nuclear molding. The nuclei are irregularly shaped, and there is brisk mitotic activity and frequently necrosis. Whereas sun exposure to the skin causes MCC, carcinogen exposure to mucosal surfaces from smoking and/or drinking leads to HGNEC. Such tumors can arise from any site in the upper aerodigestive tract, but there is a distinct predilection for the supraglottic larynx, with occasional cases in the oropharynx, oral cavity, and nasal cavity.[2,12,13] Outcomes are quite poor. Most patients with HGNEC present with nodal metastases and a large number develop distant metastases whereas MCC has a tendency for local recurrence.[12] Barker reported 2- and 5-year overall survival rates of 53% and 33%, respectively, for HGNEC.[14]

MCC and mucosal HGNEC are both high-grade neuroendocrine neoplasms that are morphologically, clinically, and immunophenotypically distinct. However, what does one do when confronted with a neuroendocrine carcinoma of the oral cavity? Because the oral cavity develops from ectoderm and is known to have normal Merkel/Toker cells,[15] the presumed sources for (or rather, line of differentiation of) MCC, it is certainly feasible that such tumors could develop there. There is no sunlight/ultraviolet exposure to induce MCC formation, however. It is also the case that smoking– and alcohol consumption–induced HGNEC/small-cell carcinomas do occur in the oral cavity and oropharynx, albeit relatively uncommonly. A handful of authors report cases of oral cavity neuroendocrine carcinoma (not including the lips) as MCC, whereas others describe oral cavity neuroendocrine carcinomas as HGNEC/small-cell carcinoma. To our knowledge, no one has attempted to robustly distinguish the 2 neoplasms at this anatomic site.[16-18] Yom et al.[19] reported 3 cases of tongue MCC and attempted to distinguish them from other possible tumor types, suggesting, as others have, that CK20 staining is the distinguishing feature between MCC and HGNEC. Most other case reports have simply made no mention of the issue, terming the tumors MCC or HGNEC without any attempt at differential diagnosis. Perhaps it is as suggested more recently, in a review article on oral neuroendocrine lesions by Mahomed,[20] that high-grade oral cavity neuroendocrine carcinomas may, just as in the parotid gland, consist of Merkel-type and pulmonary-type HGNECs, rather than the tumors being thought of as distinctly MCC or HGNEC/small-cell carcinoma. However, a clear framework to distinguish the different phenotypes is important, and as more and more cases are recognized, the clinical behavior of these differing tumors may be more clearly recognized such that the distinction may be important.

Also, a new development in skin MCC has been the detection of a polyomavirus (Merkel cell polyomavirus [MCPyV]) in a substantial number of such tumors.[21,22] As many as 80% of skin MCCs have been found to harbor viral DNA.[6-8] This novel polyomavirus has a high degree of homology with the African green monkey lymphotropic polyomavirus and is clonally integrated into tumor cell DNA with reproducible deletions in its replicative machinery. The virus has been found to be quite specific for MCC, not being found in any of a very large number of high-grade neuroendocrine carcinomas of other sites.[7]

Herein we studied 2 groups of neuroendocrine carcinomas: those arising from the mucosa of the upper aerodigestive tract (including several from the oral cavity) and those arising from the skin of the head and neck. To more clearly define them, we compared the tumors by morphology, immunohistochemistry (IHC) for a number of different markers, and MCPyV polymerase chain reaction (PCR).

METHODS

Approval was obtained for this study from the Human Research Protection Office of Washington University. A search of the files of the Barnes Jewish Hospital pathology laboratory identified 12 primary cutaneous head and neck MCC and 14 mucosal HGNEC cases. The diagnosis of mucosal HGNEC was corroborated at the time of diagnosis in all cases with positive neuroendocrine marker immunohistochemistry for synaptophysin, chromogranin-A, or both. All cases were clinically primary lesions (MCC to the skin and HGNEC to their respective anatomic mucosal subsite) without history or evidence of lung or other HGNEC. Two study pathologists (P.K. and J.L.) reviewed the H&E morphology, characterizing them according to 2 types. In type 1, the cells were hyperchromatic with angulated nuclei, prominent nuclear molding, and areas with spindled or ovoid nuclei (small-cell carcinoma features). In type 2, the nuclei were round and quite regular in size and shape, with crowded nuclei which were partially overlapping rather than molded to each other and which had very fine, pale chromatin (Merkel cell carcinoma features; Fig. 1).

IHC

Immunohistochemistry was performed on representative 4-μm sections cut from formalin-fixed paraffin-embedded tissue blocks for CK20, thyroid transcription factor 1 (TTF-1), p63, NF, and 2 different clones of the mammalian achaete-scute homolog 1 (MASH-1*1 and MASH-1*2; Table I). The CK20