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SINE QUA NON RADIOLOGY-PATHOLOGY

Adenoid Cystic Carcinoma of the Oral Cavity: Radiology–Pathology Correlation

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Abstract Adenoid cystic carcinoma in the oral cavity is an uncommon salivary gland malignancy that has a propensity for perineural spread. A high-grade variant is evidenced by an abundance of pleomorphic cells, loss of the classic biphasic epithelial-myoepithelial growth pattern, and comedonecrosis, as well as elevated Ki-67. CT and MRI can both be useful for demonstrating the extent of invasion in oral cavity-associated adenoid cystic carcinoma, which can attain the inferior alveolar nerve for perineural spread by direct invasion through the mandible. Reflecting the aggressive nature of this high-grade malignancy, [18]FDG-PET can demonstrate hypermetabolism and can be useful for staging. These features are exemplified in this sine qua non radiology–pathology correlation article.

Keywords Adenoid cystic carcinoma · Pathology · Radiology

History

A 59-year-old male with a 25 pack-year smoking history presented with a lump under the left tongue, dysphagia, and left chin numbness. The patient had undergone recent dental extractions, and it was initially believed by his dentist to be an abscess. The patient was subsequently referred to otolaryngology at our institution when the lesion started bleeding

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3 months later, during which time the patient experienced 30 pounds of weight loss. The patient did not have additional significant past medical history.

Radiological Features

CT with contrast was performed, which showed an infiltrative mass centered in the left sublingual space (arrow) with invasion into the left mandibular body (Fig. 1). The degree of mandibular bone marrow invasion was more conspicuous on MRI, which was obtained shortly after the CT (Fig. 2). Furthermore, the mass was markedly hypermetabolic on [18]FDG-PET/CT, which otherwise did not demonstrate metastases. The differential considerations based on the imaging include salivary gland malignancy, squamous cell carcinoma, and sarcoma.

Diagnosis and Treatment

The patient underwent left hemi-mandibulectomy, hemi-glossectomy, and floor of mouth resection with bilateral neck dissection. The gross resection specimen showed an unencapsulated, ill-defined, firm, tan-white mass measuring 5.7 cm in greatest dimension, centered in the floor of mouth with infiltration into adjacent mandible, lingual skeletal muscle, and fibroadipose tissue (Fig. 3). There was also direct extension of the tumor into an adjacent lymph node.

Hematoxylin and eosin-stained sections revealed two distinct areas in the tumor: an area of nested, duct-like growth containing cells with high nuclear:cytoplasmic ratios, oval to angulated nuclei with coarse chromatin, and variably prominent nucleoli; and an adjacent area of solid sheet-like growth with pleomorphic nuclei and increased mitoses (Fig. 4). In
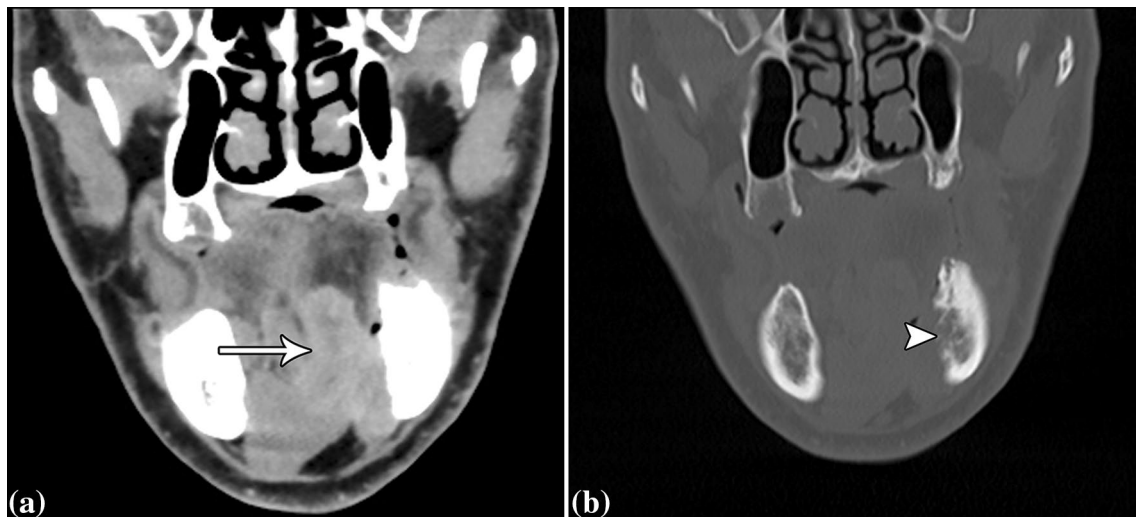
Fig. 1 Coronal soft tissue (**a**) and bone (**b**) window post-contrast CT images show an infiltrative mass centered in the left sublingual space (*arrow*) with direct invasion into the left mandibular body (*arrow-head*), with obliteration of the inferior alveolar canal, which attests to the aggressive behavior of a malignant neoplasm

Fig. 2 Coronal T1-weighted MRI shows an infiltrative mass (*arrow*) in the left oral cavity with invasion of the surrounding musculature and extension into the left mandibular bone marrow, where it envelops the left inferior alveolar nerve, which is consequently inseparable from the tumor. By comparison, the intact right inferior alveolar nerve is visible in cross-section (*arrowhead*)

Fig. 3 The gross specimen reveals an ill-defined, firm, tan-white mass centered on the floor of mouth with invasion of lingual skeletal muscle and the mandible (*asterisk*), without distinguishable residual normal sublingual gland
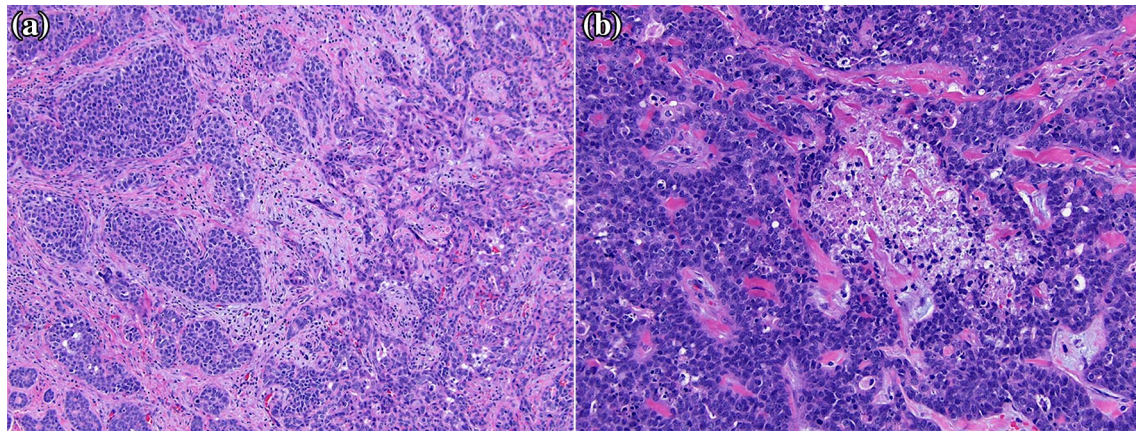
Fig. 4 Hematoxylin and eosin-stained sections show two distinct areas: a relatively well-differentiated carcinoma with nested, duct-like growth containing cells with high nuclear:cytoplasmic ratios, oval nuclei with coarse chromatin, and variably prominent nucleoli (**a**, *left* side); and a more poorly-differentiated carcinoma with solid, sheet-like growth with pleomorphic nuclei and increased mitoses (**a**, *right* side). Occasional tumor necrosis was present in areas of solid-to-nested growth (**b**)
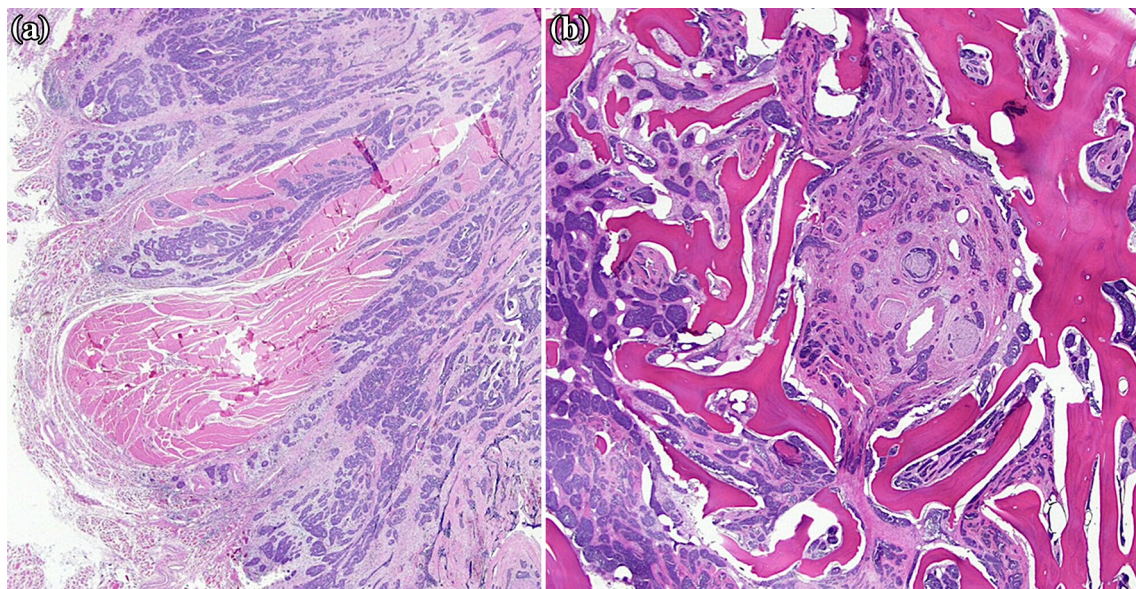

Fig. 5 Low power hematoxylin and eosin-stained sections show variably-sized cords and nests of cells that infiltrate into skeletal muscle (**a**) and bone with perineural invasion of the inferior alveolar nerve (**b**)

addition, variably-sized cords and nests of cells infiltrated into skeletal muscle and bone with perineural invasion (Fig. 5). Immunostains demonstrated p40, p63, and CK5/6 positive myoepithelial cells at the periphery of the nests and c-kit (CD117) positive epithelial cells at the center of the nests. Overall, these features were consistent with a high-grade variant of adenoid cystic carcinoma.

The patient received seven cycles of TFHX (paclitaxel, infusional 5-fluorouracil, hydroxyurea, and twice-daily radiation therapy administered every other week) with no evidence of recurrence at 6 months after resection.

Discussion

Adenoid cystic carcinoma is a malignant neoplasm that predominantly originates from the submandibular, sublingual, and minor salivary glands and is comprised of epithelial and myoepithelial cells organized in tubular, cribriform, solid, or combined architectural forms [1]. It is a relatively uncommon neoplasm, representing about 1% of all malignant tumors in the head and neck region and is the fourth most common malignant salivary gland tumor accounting for 10% of all such tumors [2, 3]. Adenoid cystic carcinoma is slightly more prevalent in females than males and occurs

most commonly during the fifth and sixth decades of life [4, 5].

Salivary gland tumors are usually best depicted on MRI. In particular, involvement of cranial nerves and tumoral infiltration around the nerves and osseous structures is optimally assessed via non-contrast T1-weighted and contrast-enhanced, fat-suppressed T1-weighted MR sequences [6]. Perineural spread typically appears as enlargement and abnormal enhancement of the affected nerve and widening or obliteration of the nerve canal. Since adenoid cystic carcinoma of the oral cavity can attain, engulf, and infiltrate the inferior alveolar nerve by first eroding through the mandibular cortex and infiltrating through the bone marrow, CT can be complementary to MRI, as demonstrated in this case.

In general, ^{18}FDG-PET is considered complementary and sometimes superior to anatomical imaging modalities for staging and restaging of salivary gland malignancies and PET often has a positive impact on clinical management for such cases [7]. High-grade salivary gland malignancies tend to be more hypermetabolic than low- and intermediate-grade malignancies, as exemplified in this case of adenoid cystic carcinoma [8]. However, adenoid cystic carcinomas often do not have significant activity on ^{18}FDG-PET, perhaps due to their slow growth [9]. The aggressive nature of the adenoid cystic carcinoma in this case may account for the hypermetabolism on ^{18}FDG-PET.

Grossly, the adenoid cystic carcinoma tends to be poorly circumscribed, unencapsulated, and firm with a white to gray-white cut surface and significant variability in size [5]. Hemorrhage and necrosis are not common gross features, but if observed, should raise concern for a high-grade variant [5]. Histologically, the tumor is heterogeneous with varying combinations of the three distinct architectural patterns [1, 5]. The tumor cells are usually quite uniform in appearance with scant clear to slightly eosinophilic cytoplasm and bland, oval to sharply angulated basophilic nuclei with coarse chromatin. The tubular pattern is the least common type and lowest grade with small nests of ductal cells surrounded completely by a second myoepithelial cell layer in a background of eosinophilic hyalinized stroma [5]. The cribriform pattern is most common and is comprised of invasive islands of basaloid cells with many cystlike spaces, referred to as pseudocysts, forming a "Swiss-cheese" or "sieve-like" pattern [1, 2, 5]. The solid pattern demonstrates large islands and cords of carcinoma with areas of necrosis, increased mitotic activity, and perineural spread [5]. A high-grade variant must be identified in the setting of conventional adenoid cystic carcinoma and is evidenced by increasingly pleomorphic cells, loss of the classic biphasic epithelial-myoepithelial growth pattern, and comedonecrosis [5].

Immunohistochemical stains for smooth muscle actin, S100, p40, p63 demonstrate positivity in myoepithelial cells of adenoid cystic carcinoma [5, 10]. Adenoid cystic carcinoma also demonstrates strong positive staining for c-kit (CD117) in tumor cells regardless of pattern or grade [10–12]. Increased cellular proliferation as assessed by Ki-67 has also been described in high-grade solid-type adenoid cystic carcinoma and been shown to correlate with a worse prognosis [13]. The histologic differential diagnosis includes polymorphous adenocarcinoma, carcinoma ex pleomorphic adenoma, and basal cell adenocarcinoma.

Many adenoid cystic carcinomas are characterized by recently described recurrent chromosomal rearrangements, including t(6;9) [14, 15]. Persson et al. revealed that this translocation resulted in the fusion of two transcription factors, MYB-NFIB, which subsequently spurred studies on the role of MYB (myeloblastosis) overexpression in the pathogenesis of ACC [14, 16]. While a significant proportion of adenoid cystic carcinomas do not harbor this specific chromosomal aberration, the identification of the MYBL1-NFIB fusion product resulting from t(8;9) translocations suggested that overexpression of transcription factors from the family of MYB genes may play a key role in adenoid cystic carcinoma tumorigenesis [17, 18]. The exact biological sequence of events that drives the growth of adenoid cystic carcinoma still remains unclear. However, the emerging model suggests transformation of a low-grade neoplasm resulting from altered regulation of the MYB locus leads to subsequent growth and acquisition of additional genetic hits [15]. Novel therapies targeting the MYB protein may show more promise as our understanding of this sequence improves.

The likelihood of lymph node metastases increases by 5–10 fold in patients with high-grade variants of adenoid cystic carcinoma, occurring in 43–57% of patients with tumors showing these histologic features [19]. Thus, standard neck dissection is considered mandatory in patients with such tumors.

Compliance with Ethical Standards

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