Clinical Pathologic Conference Case 4: Hylanizing Clear Cell Carcinoma

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Clinical Presentation

A 40-year-old female, in relatively good health, presented to her primary care physician for a cold. During an exam of her oropharynx, the physician inquired about a 1.5×1.5 cm lump on the posterior aspect of her tongue. The patient reported not knowing of its presence. The patient then inquired of her dentist if he had ever noticed this lesion, which he had not. Her general dentist then referred the patient to the University of California San Francisco Department of Oral and Maxillofacial Surgery for evaluation. Upon examination by an oral and maxillofacial surgeon, the patient had an exophytic, circumscribed, smooth surfaced, somewhat reddened mass posterior to the left circumvallate papillae (Fig. 1). There was no sub-mandibular or cervical LAD. The patient was completely asymptomatic and did not report dysphagia or dysphonia. Magnetic resonance images showed an infiltrative, homogenous lesion of approximately 1.5×1.5 cm in diameter in the left posterior portion of the tongue that was mostly exophytic but extended into the skeletal muscle (Fig. 2). Cervical lymph nodes were also not evident by imaging.

Clinically, a lingual thyroid nodule was strongly suspected and the patient was referred to the department of radiology for a technetium thyroid scan to confirm the

presence of ectopic thyroid tissue on the lingual dorsum, the most common site of ectopic thyroid tissue. However, this scan only identified thyroid tissue in the anterior neck, representing the normal location of the thyroid gland. No labeling of thyroid tissue was noted in the posterior tongue (Fig. 3), so this diagnosis was unlikely. The patient was then taken to the operating room for an incisional biopsy.

Differential Diagnosis

The clinical differential diagnosis of a well-circumscribed asymptomatic soft tissue nodule of unknown duration located on the posterior dorsal tongue is extensive. According to the history provided, the lesion was first identified by the patient's physician after an upper respiratory tract infection and had not been previously noted by her dentist. This could indicate that either the lesion had been present for a long time and recently increased in size or that it had just recently developed.

The location, clinical appearance, and lack of symptoms produced by this lesion favored a developmental lesion. Lingual thyroid occurs most frequently in the midline posterior dorsal tongue or slightly lateral to the midline. The incidence of lingual thyroid is reported to be 1:100,000 and it can remain undetected for years. Typically, it becomes symptomatic in women around puberty, menopause, or pregnancy [1]. Another developmental lesion in the differential is a thyroglossal duct cyst. Although 60 to 80% occur more commonly below the hyoid bone, they can occur on the midline posterior tongue, where 10 to 24% present lateral to the midline, usually on the left side. Histologically, they can be lined with respiratory epithelium, especially in the lingual location, and therefore could enlarge after an upper respiratory tract infection [2]. Other

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Fig. 1 Gross photograph of the 1.5 × 1.5 cm exophytic, non-ulcerated nodule on the posterior dorsum of the tongue just left of midline

developmental entities to consider include the enteric duplication cyst and the bronchogenic cyst, respectively. They are both rare and usually present during infancy as asymptomatic swellings, but have also been reported in adults. Intraoral choristomas are rare, but when they occur the most common location is the tongue. These can be cartilaginous, osseous, sebaceous, glial, odontogenic, or epidermoid. Of these, the cartilaginous choristoma is the most common [3].

Benign soft tissue neoplasms can be included in the differential diagnosis due to the clinical appearance of this lesion. Benign neural tumors such as neurofibroma, schwannoma, and nerve sheath myxoma occur frequently on the tongue and usually have a slow growth. The nerve sheath myxomas, specifically, have a female predilection. Granular cell tumor is a common tongue lesion with a female predilection, but usually presents as a sessile

Fig. 3 Image of technetium labeled thyroid scan shows uptake in the central neck, but not in the lingual area

ill-defined nodule and occasionally appears yellow. Lymphangiomas are also common in the tongue but most have a pebbly irregular surface appearance because they tend to be superficial. Lymphangiomas located deeper in the connective tissue can have a smoother surface and clinically appear as a mass. Ectomesenchymal chondromyxoid tumor has been reported exclusively on the tongue as a well-defined nodule. Although they occur more commonly on the anterior dorsal surface of the tongue there is one reported case occurring on the posterior dorsal tongue [4]. Myoepithelioma can occur outside of the salivary gland and present in the tongue as a slow growing mass. Myopericytomas and solitary fibrous tumors are also benign soft tissue neoplasms that have been reported to occur on the tongue. Adult rhabdomyomas can appear on the tongue as well demarcated masses, although they are more common in males. Leiomyoma and lipoma, including variants such as chondrolipoma and osteolipoma are other benign soft tissue tumors that can present as a tongue mass.

Fig. 2 **a** T1 weighted axial MRI shows an infiltrative lesion of the left posterior dorsum of tongue (*yellow arrow*). **b** T2 weighted coronal MRI identifies a well-circumscribed, unencapsulated lesion on the left dorsum of the tongue (*yellow arrow*)

Salivary gland neoplasms can also be included in the differential diagnosis. In general, they are reported to be more common in women and the most common intraoral benign salivary gland neoplasm is pleomorphic adenoma. Pleomorphic adenoma occurs more frequently in the hard palate, but it has been reported in the tongue. In the minor salivary glands, malignant neoplasms are more prevalent. Mucoepidermoid carcinoma, adenoid cystic carcinoma, and hyalinizing clear cell carcinoma can occur as slow growing masses in the tongue.

A malignant soft tissue neoplasm like alveolar soft part sarcoma can also be included in the differential diagnosis. These lesions tend to occur more frequently in the tongue in younger females [5]. Additionally, the tongue is also a frequent site for soft tissue metastases, especially breast cancer and renal cell carcinoma. Lymphomas, both Hodgkin and Non-Hodgkin, can occur in the tongue, although intraorally the most common site is the palate. Hodgkin lymphoma of Waldeyer's ring has been reported to appear as a posterior dorsal tongue mass.

The most common reactive lesion occurring on the tongue is an irritation fibroma and it could present as a large nodule. Infectious etiologies also enter the differential. In fact, the tongue is a common location for tuberculosis, which usually presents as a mass with surface ulceration. Cysticercosis, can occur on the tongue and it appears clinically as a well-defined nodule. Actinomycosis, usually secondary to trauma, has been reported in the tongue but it is very uncommon. Lastly, amyloid deposits are common in the tongue and can appear as single or multiple smooth surfaced nodules.

Diagnosis and Discussion

The incisional biopsy showed an infiltrating tumor composed of cytologically monotonous epithelioid cells, with predominantly clear cytoplasm, forming variably-sized cords and sheets with alternating areas of hyalinized stroma (Fig. 4). Tumor was seen invading the lamina propria, submucosa, and superficial skeletal muscle. No definitive

squamous differentiation was seen and the overlying squamous epithelium was unremarkable.

The differential diagnosis of clear cell neoplasms of the head and neck is finite and includes: clear cell variant of squamous cell carcinoma; metastatic renal cell carcinoma; clear cell odontogenic carcinoma; clear cell variants of salivary gland tumors, including mucoepidermoid carcinoma, acinic cell carcinoma, and oncocytoma; and primary clear cell neoplasms of salivary gland origin, including epithelial-myoepithelial carcinoma, myoepithelial carcinoma, and hyalinizing clear cell carcinoma.

As this case had no obvious connection to the surface epithelium, a clear cell variant of squamous cell carcinoma was ruled out. Furthermore, the patient had no history of renal cell carcinoma, and the histomorphologic features seen did not favor this as an occult metastasis. Finally, given the lack of radiographic evidence of a jaw lesion and the location on the posterior tongue, clear cell odontogenic carcinoma was not considered and the differential diagnosis was reduced to salivary gland tumors with clear cell features. The infiltrative nature of the lesion was most consistent with a malignant neoplasm, and therefore, the benign salivary gland tumors with clear cell features, namely, clear cell oncocytoma and clear cell myoepithelioma, were also ruled out. Epithelial-myoepithelial carcinoma was ruled out by the lack of characteristic biphasic duct-like structures with central cuboidal cells and outer clear cells. The remaining differential diagnosis included myoepithelial carcinoma, clear cell mucoepidermoid carcinoma, and hyalinizing clear cell carcinoma (HCCC).

A histochemical stain for mucicarmine was negative, thus making mucoepidermoid carcinoma unlikely. Immunohistochemical stains were also performed, including cytokeratin AE1/AE3 and p63, which showed strong and diffuse cytoplasmic and nuclear expression, respectively. Smooth muscle actin and calponin, commonly used myoepithelial markers, were both negative (Fig. 5). These findings effectively ruled out mucoepidermoid and myoepithelial carcinoma. The most appropriate diagnosis therefore was HCCC of salivary gland. The location of this tumor and histomorphologic features, including alternating

Fig. 4 **a** Cords and islands of an infiltrative epithelial neoplasm are seen beneath mucosal epithelium in the lamina propria. Hyalinized areas are seen alternating between the epithelial cords and islands (40×). **b** Higher magnification shows cords and islands of monotonous epithelioid cells with a prominent clear cell component (200×)

Fig. 5 **a** Mucicarmine stain was negative throughout the lesional cells (200×). **b** Smooth muscle actin immunohistochemical staining was also negative (200×). **c** CK AE1/AE3 showed diffuse cytoplasmic staining of tumor cells (200×). **d** Combined immunohistochemical staining for high molecular weight cytokeratin and p63 showed diffuse and strong cytoplasmic and nuclear staining, respectively (200×)

bands of hyalinized connective tissue with cords and strands of clear cells, combined with immunohistochemical results, best supported the diagnosis of HCCC of salivary gland.

The patient was taken to the operating room for complete excision of this central tongue lesion. The resected surgical specimen measured $3.2 \times 2.2 \times 2.2$ cm and the tumor measured 1.2 cm in greatest diameter and 0.6 cm in maximal thickness. All surgical margins were clear of tumor and there was no evidence of invasion into adjacent structures. The tumor did not cross the midline. Necrosis and perineural and lymphovascular invasion were not identified. Lymph nodes were not submitted. Therefore, the patient was staged, according to the American Joint Committee on Cancer staging for head and neck cancers, as pT1Nx, and as such did not receive adjuvant treatment. The patient is 18 months post treatment and is free of recurrence or metastasis and has no persistent symptoms as a result of surgical excision.

In 1994, Milchgrub et al. [6] were the first to describe the HCCC of salivary gland origin in 11 cases, mostly of adult women, with 82% arising from minor salivary glands of the oral cavity. The lesion they described was that of an infiltrating neoplasm composed of islands, trabeculae, and nests of monomorphic clear cells that were glycogen rich, mucin negative and surrounded by hyalinized bands with minimal cellular pleomorphism and a very low mitotic index. They demonstrated epithelial, without myoepithelial differentiation, by immunohistochemistry (cytokeratin and epithelial membrane antigen positive; S-100 and smooth

muscle actin negative) and ultrastructural demonstration of tonofilaments, desmosomes and interdigitating microvilli without actin filaments or dense bodies. Two of eleven cases had ipsilateral lymph node metastases at presentation. Eight of ten patients had surgery; 3 of those had either pre- or postoperative radiation therapy. All eight of these were alive at a mean follow-up period of 3.6 years (6 months to 11 years). One patient died from surgery, one died of unrelated causes, and one was lost to follow-up.

When evaluating primary clear cell neoplasms of salivary origin, Wang et al. [7] propose distinguishing those that have clear cell variants (mucoepidermoid carcinoma, oncocytoma, acinic cell carcinoma) from primary salivary clear cell neoplasms, which can be subdivided into those that require myoepithelial differentiation (epithelial-myoepithelial carcinoma; clear cell myoepithelial carcinoma [CCMEC]) and those that do not (HCCC). To aid in this latter differentiation, they proposed the use of the monoclonal antibody to calponin as a novel and sensitive marker of smooth muscle phenotype as it is a 34-kd smooth muscle-specific cytoplasmic protein regulator of contraction without analogues in non-muscle cells. They also distinguished CCMEC from HCCC by its bulky nodular cellular component with varying populations of spindled and plasmacytoid cells, while the latter lack these cytologic features and infiltrate in cords, islands, and sheets. They also demonstrated that HCCC lacked ultrastructural features of myoepithelial differentiation but contained features of glandular cells, particularly desmosomes and luminal microvilli. They did a meta-analysis of reported cases in

the literature and showed 67% of cases of HCCC were of intraoral minor salivary gland origin while 72% of CCMEC were of parotid origin. They found that both had a female preponderance and a median age at presentation in the 6th and 7th decades of life.

In a review of HCCC in 2009, including eight additional cases, Solar et al. reported that HCCC accounts for less than 1% of all salivary gland tumors. There was a female predilection (71%) and 80.7% of cases were in the oral cavity, with the two most common sites being the tongue (28%) and palate (21%) [8]. All were slow-growing and painless swellings and were treated with wide local excision; adjuvantly, three patients received radiation and one chemotherapy. They found that 25% of patients had metastatic disease at presentation, but posited that this may be a result of case selection publication bias. Because of this, though, they suggest that careful assessment of regional lymph nodes is necessary. Although perineural invasion was reported in fifteen cases and necrosis in one case, they found no correlation between morphologic features and tumor behavior. All cases were S-100 and/or SMA and/or MSA negative, indicating lack of myoepithelial differentiation. They found that the presence of clusters of clear cells associated with hyalinization of stroma is the most important finding that should raise suspicion of HCCC.

In their report of eight additional cases and review of the literature, O'Sullivan-Mejia et al. [9] also found a strong female and oral cavity predominance (72.7 and 81.8%, respectively). Although they found mitoses in 32.7% of cases, they did not find that this feature, nor necrosis, correlated with recurrence, aggressive behavior, or metastasis. They also report that p63 immunohistochemical staining, in the absence of staining with other markers of myoepithelial differentiation, distinguishes HCCC from tumors with myoepithelial differentiation.

In their review of the histogenesis and classification of clear cell carcinoma as a squamous lesion, Dardick and Leong reported in 2009 that squamous differentiation underlies this entity as it exhibits ultrastructural features such as tonofilaments, desmosomes, filopodia and organization, which are also features characteristic of squamous cells [10]. From this they drew two conclusions: (1) HCCC can be considered a well-characterized neoplasm with squamous differentiation; and (2) that it may have a close

histomorphogenic relationship with mucoepidermoid carcinoma, but that it was not a monomorphic variant of EMEC and does not have evidence for neoplastic myoepithelial differentiation.

This case illustrates that the differential diagnosis of non-ulcerated masses of the dorsal tongue is quite extensive. Clinical presentation, symptoms, radiologic features, and most importantly, an incisional biopsy, are all important in the clinical work up of these cases. This case also illustrates nicely the more limited differential diagnosis of clear cell lesions of the head and neck while describing the histochemical and immunohistochemical studies necessary to distinguish these lesions.

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