Slow-Growing Palatal Mass:  
A Challenging Differential Diagnosis

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Case Presentation

A 41-year-old Brazilian man was referred to the Oral Medicine Center of Goiás State, School of Dentistry, Federal University of Goiás (Goiânia, Brazil) for evaluation of a painless swelling of 3 years’ duration on the hard palate (Fig 1). The patient had previously undergone 2 incisional biopsies without conclusive diagnosis and was otherwise healthy. No significant medical history and no other symptoms were reported. Family history was likewise unremarkable. Intraoral examination revealed a submucosal mass on the right side of the hard palate, extending from the premolar to the tuberosity region (Fig 1). On palpation, the mass was asymptomatic and resilient. Conventional radiographs showed an osteolytic lesion in the premolar area extending to the tuberosity and tooth resorption in the right second molar. Computed tomography and magnetic resonance (MR) imaging showed a neoplasm extending from the premolars to the tuberosity region on the right side of the maxilla and the resorption of the ipsilateral maxillary sinus floor (Fig 2). This mass was fairly well circumscribed, except at its medial margin with the soft palate. It appeared as a well-defined low signal mass on T1-weighted image, as high contrast enhancement on T1-weighted postcontrast image, and heterogeneous high signal on T2-weighted image (Fig 2). There was no significant lymphadenopathy according to imaging features and clinical examination.

Differential Diagnosis

Palatal masses are not uncommonly encountered in clinical practice and possible diagnoses, considering the posterior hard palate location in the present case, could include 1) an odontogenic or periodontal infection, 2) benign or malignant neoplasm from the salivary gland, or 3) soft tissue tumor.

1. Although the lesion was osteolytic, as shown by conventional radiographic screening, the reportedly painless, 3-year, slow-growing mass associated with a positive tooth vitality test, no fistula, and resilience to palpation eliminated the possibility of the lesion as an infectious source.

2. Salivary gland tumors became the main possible diagnosis, because the most frequent neoplasms in the palate are mixed tumors (pleomorphic adenoma) of the salivary gland and second in frequency is mucoepidermoid carcinoma.1-3

3. The term soft tissue tumor encompasses a diverse group of neoplastic and reactive proliferations arising from the nonskeletal supporting tissues of the body: fibrous tissue, fat, muscle,
nerves, and vessels. This group includes a tremendous variety of lesions, ranging from fibromas to alveolar soft part sarcoma. The possibility of a sarcomatous lesion was ruled out because of the evolution of the present case.

4. Another possibility, malignant lymphoma, although rare, was also considered because it occurs at any site in the human body, but it was ruled out because of the evolution of the reported case lesion.

After ruling out some clinical diagnoses, salivary gland neoplasm was the main hypothesis, and the next step consisted of complementary imaging examinations. Imaging helps to define the extent of the lesion, its growth into deep and adjacent tissues, and metastatic spread to lymph nodes. This information is important for establishing differential diagnoses, staging and treatment planning, and assessing recurrence. Computed tomography and MR imaging are the techniques of choice. MR imaging is generally accepted as a useful modality to show the extent,
margins, and morphology of salivary gland lesions. In general, low-grade lesions of the palate tend to be well demarcated and uniform and demonstrate T1 hypointensity and T2 hyperintensity. An ill-defined and infiltrative margin is regarded the most important finding of malignant growth. In addition, high-grade minor salivary gland tumors tend to demonstrate low-to-intermediate signal intensity on T2-weighted images related to their high cellularity. The present case demonstrated a well-circumscribed, diffusely enhancing, T2 hyperintense mass at the hard and soft palate (Fig 2). These imaging characteristics are nonspecific and may be seen in other salivary gland lesions as a pleomorphic adenoma and a malignant salivary gland neoplasm.

The incisional biopsy should be performed as quickly as possible in this type of lesion because, despite the relatively benign appearance of the lesion, a malignant tumor arising from the palate can mimic a benign tumor, but it may require aggressive therapy (radical surgery and/or radiation). Once the histologic diagnosis is obtained, early surgical intervention can be instituted, if necessary.

**Subsequent Course**

After incisional biopsy of a representative portion of the lesion, the specimens were fixed in 10% neutral buffered formalin and embedded in paraffin, and 5-μm sections were cut and stained with hematoxylin and eosin. Microscopic examination showed a monomorphous population of polygonal and round cells with abundant and clear cytoplasm, arranged in sheets, nests, and cords. The nuclei were usually located centrally or slightly eccentrically (Fig 3A). Few mitotic figures and nuclear pleomorphism were found.

Because there is a group of distinct tumors that histologically present clear cells in the parenchyma, an immunohistochemical panel was considered for differential diagnosis (Table 1). The samples were also stained with mucicarmine solution and periodic acid–Schiff. Serial sections were evaluated immunohistochemically for their affinity for various antibodies, using the labeled streptavidin-biotin-immunoperoxidase detection system (LSAB kit; K0492, DAKO, Carpinteria, CA). Appropriate positive controls were prepared for each antibody, and negative controls consisted of slides that were not treated with the primary antibodies. Clear cells were negative for mucicarmine and periodic acid–Schiff (Fig 3B). The identification of specific proteins revealed that the clear cells were positive for cytokeratin (CK) 8 and CK7 and the cells with eosinophilic cytoplasm were immunoreactive for CK14, pancytokeratin, and high-molecular-weight CK. Tumor cells were negative for vimentin, S100 protein, and smooth muscle actin. A low proliferative index, which can be measured by staining neoplastic cells with Ki-67 antibodies, was observed in this present case. Considering together the microscopic, histochemical, and immunostaining features, the pathologic diagnosis was clear cell carcinoma, not otherwise specified (CCC-NOS).

The patient underwent hemimaxillectomy and adjuvant radiotherapy. Microscopic diagnosis of the surgical specimen confirmed the CCC-NOS diagnosis. Locoregional recurrences and distant metastases remained undetected during the 12-month follow-up period (Fig 4). Provisional prosthetic rehabilitation was performed to provide more comfort to the patient.

**Discussion**

Tumors arising from minor salivary glands of the palate may exhibit an overlap of clinical and biologic features that may produce diagnostic and therapeutic dilemmas. Morphologic diversity is the hallmark of pleomorphic adenoma, and considerable morphologic variation is often present within a tumor. Carcinoma arising in pleomorphic adenoma is a pleomorphic adenoma in which a second malignant neoplasm develops in the epithelial component (carcinoma epithelial myoepithelial).

CCC-NOS is an uncommon salivary gland tumor of ductal origin without myoepithelial cell participation.
<table>
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<tr>
<th>Salivary Gland Neoplasm</th>
<th>Most Prevalent Age (Decade)/Site</th>
<th>Main Features of Tumoral Parenchyma</th>
<th>Histochemical and Immunohistochemical Panels</th>
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<tr>
<td>Clear cell carcinoma, not otherwise specified</td>
<td>Decades 4*-8*/minor glands—tongue and palate</td>
<td>Monomorphous population of polygonal to round cells with clear cytoplasm without ductal lumina and myoepithelial differentiation</td>
<td>CK7 and 8/18, CK19, CK5/6, CK14, CK17(^5,11)</td>
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<td>Epithelial myoepithelial carcinoma</td>
<td>Decade 7*/major glands—parotid</td>
<td>Bilayered ductal structures composed by clear myoepithelial cells that surround epithelial-lined ducts resembling intercalated ducts</td>
<td>Luminal cells: CK7, CK8, CK14, CK18/19(^12,13); nonluminal cells: CK14, vimentin, GFAP, S100, myosin, calponin</td>
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<tr>
<td>Myoepithelial carcinoma</td>
<td>Decade 6*/Major glands—parotid</td>
<td>Clear cells with myoepithelial differentiation</td>
<td>S100; vimentin; CD10, CK8/18, SMA, GFAP, calponin(^1,14)</td>
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<td>Mucoepidermoid carcinoma</td>
<td>Decades 3*-7*/major glands—parotid</td>
<td>Varying proportions of mucous and epidermoid cells</td>
<td>Mucicarmine; PAS after diastase digestion; mucous cells: CK7, CK8, CK19; epidermoid cells: CK7, CK8, CK13, CK14, CK19; intermediate cells: CK7, CK8, CK14(^1,12)</td>
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<td>Acinic cell carcinomas</td>
<td>Decades 3*-7*/major glands—parotid</td>
<td>Some neoplastic cells demonstrate serous acinar cell differentiation with cytoplasmic granules and clear cells may be occasionally numerous, but rarely predominate</td>
<td>PAS; mucicarmine; CK7, CK8(^12)</td>
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<td>Oncocytoma, clear cell variant</td>
<td>Decades 6*-8*/major glands—parotid</td>
<td>Composed of large epithelial oncocytic cells that may show predominant clear cell component</td>
<td>CK7, CK14, CK20, EMA, MSA, SMA, GFAP, calponin, S-100, vimentin: weakly positive(^1,15)</td>
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<tr>
<td>Malignant sebaceous tumors</td>
<td>Decades 7*-8*/major glands—parotid</td>
<td>Clear cells with lipid cytoplasm</td>
<td>Fat stain (Sudan III), androgen receptor(^1,16)</td>
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Abbreviations: CK, cytokeratin; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; MSA, muscle-specific actin; PAS, periodic acid–Schiff; SMA, smooth muscle actin.

*Variable results.

composed of a monomorphous population of cells with clear cytoplasm. CCC-NOS was previously considered a variant of epithelial myoepithelial carcinoma with absent ductal differentiation and has been referred to as monomorphic clear cell carcinoma. The term CCC-NOS was officially introduced, as a distinct low-grade carcinoma, in edition 3 of the World Health Organization classification of salivary tumors in 2005. However, this entity has been described by a variety of names, such as clear cell adenocarcinoma and hyalinizing clear cell carcinoma, all considered synonyms by the World Health Organization.

The diagnosis of CCC-NOS requires exclusion of other specific salivary gland neoplasms that commonly or consistently have a component of clear cells; such neoplasms encompass a broad range of possibilities. Thus, the differential diagnosis should particularly rule out epithelial myoepithelial carcinoma, myoepithelial carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, oncocytoma clear cell variant, sebaceous tumors, and metastasis from renal carcinoma. The establishment of the diagnosis depends on imaging, histopathologic, and immunohistochemical features; CCC-NOS should be considered the final diagnosis only after other specific tumor types with predominantly clear cell morphologies are excluded.

When evaluating palate lesions with MR imaging or computed tomographic features that include cortical resorption, a well-defined low signal mass on T1-weighted image, with high contrast enhancement on T1-weighted postcontrast image and a heterogeneous high signal on T2-weighted image, CCC should be considered in the differential diagnosis. Most publications have described this lesion on the tongue, whereas the imaging characteristics of CCC of the palate have not been previously described.

The role of static MR imaging in the differentiation of benign from malignant salivary gland tumors appears to be controversial due to significant, overlapping imaging findings. The dynamic MR imaging technique was developed to improve the differential diagnosis of salivary gland tumors. Evaluation of parameters, such as enhanced peak time and washout ratio in postcontrast images, and their correlation with histopathologic tumor features such as microvessel count and cellularity-stromal grade have been useful for differentiating benign from malignant salivary gland tumors.

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Microscopically, CCC-NOS are composed of a monomorphous population of polygonal to round cells with clear cytoplasm. Nuclei are eccentric and round and frequently contain small nucleoli. The tumor cells are arranged in sheets, nests, or cords without ductal structures. Mitotic figures are rare, but some tumors have a moderate degree of nuclear pleomorphism. In the hyaloid type, the stroma has thick bands of hyalinized collagen, but in other tumors it consists of interconnecting, thin fibrous septa that may be cellular or loosely collagenous. CCC-NOS are noncapsulated and infiltrative.

Periodic acid–Schiff staining with and without prior diastase digestion of the tissue demonstrates cyttoplasmic glycogen that varies from marked to not evident. Intracytoplasmic mucins are usually absent in mucicarmine stain in CCC, but are frequently positive in acinic cell carcinoma, mucoepidermoid carcinoma, and clear cell variant oncocytoma (Table 1). Ultrastructural investigations of CCC-NOS have found features of ductal but not myoepithelial differentiation. In many tumors, small areas containing cells with eosinophilic cytoplasm and foci of squamous differentiation can be present occasionally, as in the case reported. The true ductal lumina, as evidenced in epithelial myoepithelial carcinomas, was not observed. Thus, because main neoplasms present clear cells (Table 1), the presence of ductal structures is typically seen in epithelial myoepithelial carcinomas and not in CCC-NOS.

In addition to the histopathologic features seen in the present study, clear cells were immunoreactive to CK7 and CK8 (cytokeratin mainly expressed by epithelial cells from ductal origin) and negative for vimentin, S100, smooth muscle actin, and mucicarmine. This excludes the possibility of a tumor with...
myoepithelial differentiation (mucous or myogenic), usually observed in acinic cell carcinomas, mucoepidermoid carcinomas, and oncocytomas. When the clear cell component is predominant, metastasis of renal cells should be considered in the differential diagnosis. Renal cell carcinoma is the most common type of metastasis found in oral mucosa, with the gingiva, tongue, palate, and lip as the favored sites.\textsuperscript{18} This carcinoma may be excluded by abdominal computed tomography and immunostaining.\textsuperscript{4,5,18} In addition, vimentin protein shows strong positivity in most renal cell metastases, but it is not expressed in CCC-NOS\textsuperscript{4,5,20,23} Furthermore, renal cell metastases are strongly positive for epithelial membrane antigen and CD10, variably positive for CK7, and weakly positive for CK20.\textsuperscript{15,24}

The determination of CCC-NOS and the distinction of this tumor from other clear cell neoplasms are crucial in establishing the appropriate diagnosis and therapeutic approach. Typically, treatment of CCC-NOS involves wide surgical resection with or without lymph node dissection. Radiation therapy is more frequently reserved for patients with close resection margins, recurrent lesions, or lymph node metastases.\textsuperscript{3,11}

References