

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,

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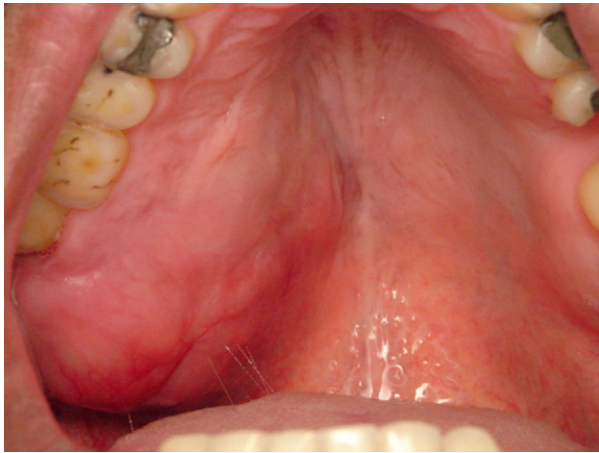


FIGURE 1. Intraoral aspect of the neoplasm in the hard palate, measuring 5.0 × 3.5 cm.

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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.^{4,5} Computed tomography and MR imaging are the techniques of choice. MR imaging is generally accepted as a useful modality to show the extent,

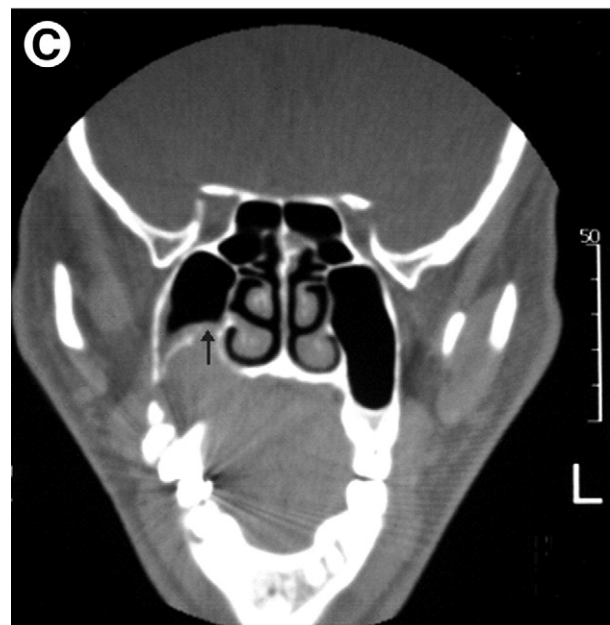


FIGURE 2. A, The diffusely enhanced mass extends to the soft palate (SP), which can be seen in the axial postcontrast spin echo T1-weighted MR image. B, The mass presents a heterogeneous hyperintense signal on spin echo T2-weighted MR image that presaturates the upper maxillary sinus (MS) floor. C, Coronal computed tomogram shows the maxillary sinus floor resorption (arrow) diffusely enhancing the pedunculated mass at the base of the tongue with extension into the bilateral valleculae. This mass is fairly well circumscribed, except at its medial margin with the soft palate. Differential diagnostic considerations at the time of imaging included lymphoma, squamous cell carcinoma, and granular cell tumor. There was no significant lymphadenopathy by size criteria.

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margins, and morphology of salivary gland lesions.⁶⁻⁸ 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.^{7,9} 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.⁶ The present case demonstrated a well-circumscribed, diffusely enhancing, T2 hyperintense mass at the hard and soft palate (Fig 2). These imaging characteristics are non-specific and may be seen in other salivary gland lesions as a pleomorphic adenoma and a malignant salivary gland neoplasm.¹⁰

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- μ m 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).^{1,2,4,5,11-16} 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 speci-

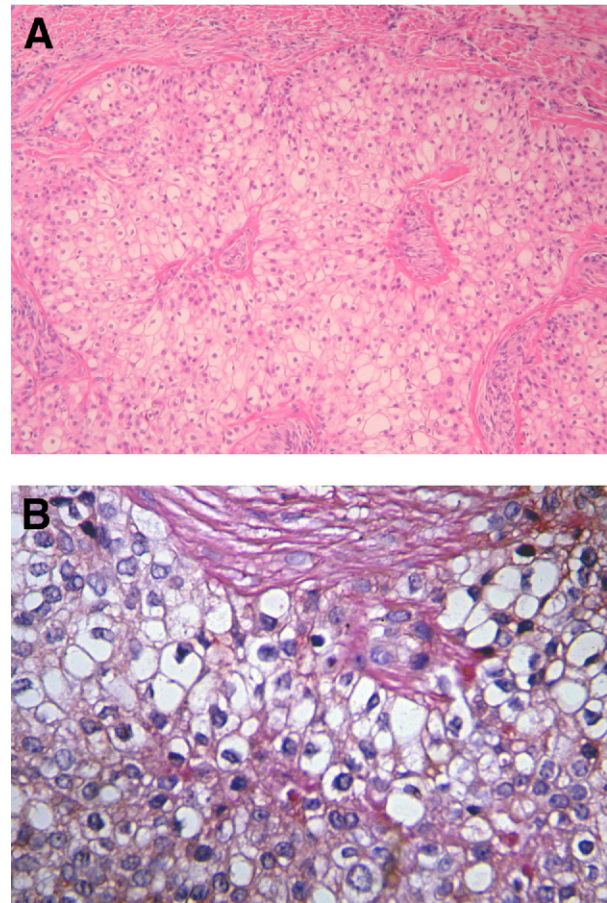


FIGURE 3. A, Neoplastic proliferation showing a predominance of a monomorphous cell population with abundant clear cytoplasm (hematoxylin and eosin stain, original magnification $\times 40$). B, Clear cells showing negativity for periodic acid-Schiff (original magnification $\times 40$).

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men 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).⁴

CCC-NOS is an uncommon salivary gland tumor of ductal origin without myoepithelial cell participation

Table 1. HISTOLOGIC FEATURES OF NEOPLASMS THAT COMMONLY HAVE A COMPONENT OF CLEAR CELLS

Salivary Gland Neoplasm ¹	Most Prevalent Age (Decade)/Site ^{1,2}	Main Features of Tumoral Parenchyma ^{1,2}	Histochemical and Immunohistochemical Panels	
			Positive	Negative
Clear cell carcinoma, not otherwise specified	Decades 4*-8*/minor glands—tongue and palate	Monomorphous population of polygonal to round cells with clear cytoplasm without ductal lumina and myoepithelial differentiation	CK7 and 8/18, CK19, CK5/6, CK14, CK17 ^{5,11}	Vimentin*, S100*, GFAP*, SMA*, mucicarmine, PAS, CK10/13 ⁵
Epithelial myoepithelial carcinoma	Decade 7*/major glands—parotid	Bilayered ductal structures composed by clear myoepithelial cells that surround epithelial-lined ducts resembling intercalated ducts	Luminal cells: CK7, CK8, CK14, CK18/19 ^{12,13} ; nonluminal cells: CK14, vimentin, GFAP, S100, myosin, calponin	Luminal cells negative for vimentin and MSA; nonluminal cells negative for CK7, CK8, CK13, CK19 ¹²
Myoepithelial carcinoma	Decade 6*/Major glands—parotid	Clear cells with myoepithelial differentiation	S100; vimentin; CD10, CK8/18, SMA, GFAP, calponin ^{1,14}	Carcinoembryonic antigen ¹⁴
Mucoepidermoid carcinoma	Decades 3*-7*/major glands—parotid	Varying proportions of mucous and epidermoid cells	Mucicarmine; PAS after diastase digestion; mucous cells: CK7, CK8, CK19; epidermoid cells: CK7, CK8, CK13, CK14, CK19; intermediate cells: CK7, CK8, CK14 ^{1,12}	Vimentin; MSA ¹²
Acinic cell carcinomas	Decades 3*-7*/major glands—parotid	Some neoplastic cells demonstrate serous acinar cell differentiation with cytoplasmic granules and clear cells may be occasionally numerous, but rarely predominate	PAS; mucicarmine; CK7, CK8 ¹²	CK13, CK14, CK19; vimentin; MSA ¹²
Oncocytoma, clear cell variant	Decades 6*-8*/major glands—parotid	Composed of large epithelial oncocytic cells that may show predominant clear cell component	CK7, CK14, CK20, EMA, MSA, SMA, GFAP, calponin, S-100, vimentin: weakly positive ^{1,15}	Clear cells negative for SMA, ¹ CD10 ¹⁵
Malignant sebaceous tumors	Decades 7*-8*/major glands—parotid	Clear cells with lipid cytoplasm	Fat stain (Sudan III), androgen receptor ^{1,16}	

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.

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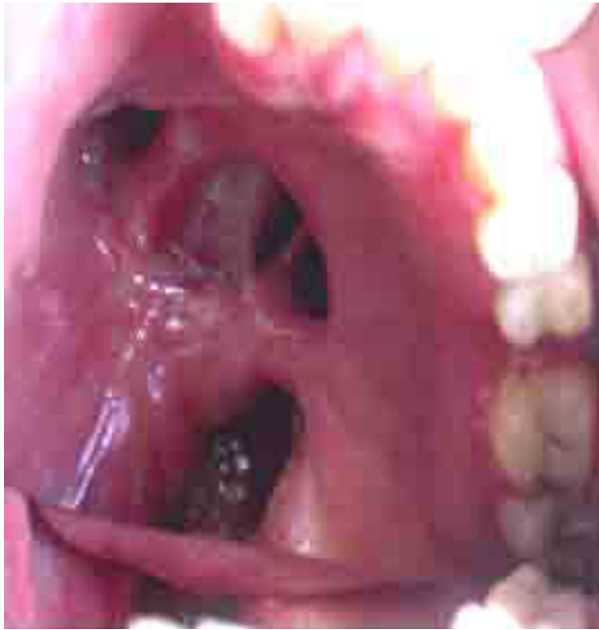


FIGURE 4. Twelve-month follow-up period without clinical evidence of recurrence.

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composed of a monomorphous population of cells with clear cytoplasm.¹⁻³ CCC-NOS was previously considered a variant of epithelial myoepithelial carcinoma with absent ductal differentiation and has been referred to as *monomorphous clear cell carcinoma*.¹⁷ 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 2005.¹ 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.¹

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.^{1,2,4,5,18} 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.^{1,2,4,5,19,20} 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.^{1,2,4,5,20}

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,²¹ 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.^{10,22}

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.^{1,2,5,11,17,18,20} CCC-NOS are noncapsulated and infiltrative.^{1,2,5,11,20} Periodic acid-Schiff staining with and without prior diastase digestion of the tissue demonstrates cytoplasmic glycogen that varies from marked to not evident.¹ Intracytoplasmic mucins are usually absent in mucicarmine stain in CCC,^{5,11} but are frequently positive in acinic cell carcinoma, mucoepidermoid carcinoma, and clear cell variant oncocytoma (Table 1).^{1,2,19} 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,⁵ as in the case reported. The true ductal lumina, as evidenced in epithelial myoepithelial carcinomas, was not observed.^{1,2,5,11,20} 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.^{1,2,4,5,11,20}

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.¹⁸ This carcinoma may be excluded by abdominal computed tomography and immunostaining.^{4,5,18} In addition, vimentin protein shows strong positivity in most renal cell metastases, but it is not expressed in CCC-NOS.^{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.^{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.^{5,11}

References

- Barnes L, Eveson JW, Reichart P, Sindransky D: World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumors (ed 1). Lyon, IARC Press, 2005, p 209
- Ellis GL, Auclair PL, Gnepp DR: Surgical Pathology of the Salivary Glands (ed 1). Philadelphia, WB Saunders, 1991
- Pires FR, Pringle GA, de Almeida OP, Chen SY: Intra-oral minor salivary gland tumors: A clinicopathological study of 546 cases. *Oral Oncol* 43:463, 2007
- Li C-Y, Shirasuna K, Ishibashi H, et al: Epithelial-myoepithelial carcinoma arising in pleomorphic adenoma of the palate. *Oral Surg Oral Med Oral Pathol* 90:460, 2000
- Suzuki H, Yamauchi G, Hashimoto K: Clear cell carcinoma of the mandibular gingiva "minor salivary gland": A case report with immunohistochemical study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 103:e36, 2007
- Mukherji SJ: Upper aerodigestive tract: Pharynx, *in* Som PM, Curtin HD (eds): *Head and Neck Imaging* (ed 4). St Louis, MO, Mosby, 2002, p 1465
- Suenaga S, Indo H, Noikura T: Diagnostic value of dynamic magnetic resonance imaging for salivary gland diseases: A preliminary study. *Dentomaxillofac Radiol* 30:314, 2001
- Kaneda T, Minami M, Ozawa K, et al: Imaging tumors of the minor salivary glands. *Oral Surg Oral Med Oral Pathol* 78:385, 1994
- Shah GV: MR imaging of salivary glands. *Magn Reson Imaging Clin North Am* 10:631, 2002
- Ueda F, Suzuki M, Matsui O, et al: MR findings of nine cases of palatal tumor. *Magn Reson Med Sci* 4:61, 2005
- Yang S, Zhang J, Chen X, et al: Clear cell carcinoma, not otherwise specified, of salivary glands: A clinicopathologic study of 4 cases and review of literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 106:712, 2008
- de Araújo VC, de Sousa SO, Carvalho YR, et al: Application of immunohistochemistry to the diagnosis of salivary gland tumors. *Appl Immunohistochem Mol Morphol* 8:195, 2000
- Kusafuka K, Takizawa Y, Ueno T, et al: Dedifferentiated epithelial-myoepithelial carcinoma of the parotid gland: A rare case report of immunohistochemical analysis and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 106:85, 2008
- Savera AT, Sloman A, Huvos AG, et al: Myoepithelial carcinoma of the salivary glands: A clinicopathologic study of 25 patients. *Am J Surg Pathol* 24:761, 2000
- Ozolek JA, Bastacky SI, Myers EN, et al: Immunophenotypic comparison of salivary gland oncocytoma and metastatic renal cell carcinoma. *Laryngoscope* 115:1097, 2005
- Gomes CC, Lacerda JC, Pimenta FJ, et al: Intraoral sebaceous carcinoma. *Eur Arch Otorhinolaryngol* 264:829, 2007
- Milchgrub S, Gnepp DR, Vuitch F, et al: Hyalinizing clear cell carcinoma of salivary gland. *Am J Surg Pathol* 18:74, 1994
- Ponniah I, SureshKumar P, Karunakaran K: Clear cell carcinoma of minor salivary gland—case report. *Ann Acad Med Singapore* 36:857, 2007
- Ogawa I, Nikai H, Takata T, et al: Clear-cell variant of mucoepidermoid carcinoma: Report of a case with immunohistochemical and ultrastructural observations. *J Oral Maxillofac Surg* 50:906, 1992
- Wang B, Brandwein M, Gordon R, et al: Primary salivary clear cell tumors—A diagnostic approach: A clinicopathologic and immunohistochemical study of 20 patients with clear cell carcinoma, clear cell myoepithelial carcinoma and epithelial-myoeplithelial carcinoma. *Arch Pathol Lab Med* 126:676, 2002
- Uzochukwu NO, Shrier DA, Lapoint RJ: Clear cell carcinoma of the base of the tongue: MR imaging findings. *AJNR Am J Neuroradiol* 28:127, 2007
- Yabuuchi H, Fukuya F, Tajima T, et al: Salivary gland tumors: Diagnostic value of gadolinium-enhanced dynamic MR imaging with histopathologic correlation. *Radiology* 226:345, 2003
- Aguirre A, Rinaggio J, Diaz-Ordaz E: Lingual metastasis of renal cell carcinoma. *J Oral Maxillofac Surg* 54:344, 1996
- Meer S, Altini M: CK7+/CK20—Immunoexpression profile is typical of salivary gland neoplasia. *Histopathology* 51:26, 2007