CASE REPORT

Primary clear cell carcinoma of parotid gland: Case report and review of literature

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INTRODUCTION

Clear cell carcinoma (CCC) is a low grade malignant neoplasm representing approximately 1% of all salivary gland tumors. The differential diagnosis of clear cell salivary neoplasms encompasses a broad range of possibilities, including primary salivary clear cell tumors, such as CCC, epithelial-myoepithelial carcinoma (EMEC), and clear cell myoepithelial carcinoma (CCMEC), as well as clear cell variants of other salivary tumors, including acinic cell carcinoma, oncocytoma and mucoepidermoid carcinoma. Metastatic tumors such as renal cell carcinoma or balloon cell melanoma are also a consideration.

CASE REPORT

A female 88-year-old, presented with a gradual painless mass of 2 months duration in the right parotid region. There was no history of tumor elsewhere and her medical history was non-contributory. On palpation, a painful non-tender mass of about 3 cm was found. It was adherent to the skin and deep tissues. The facial nerve was not involved.

A fine-needle aspiration was performed. Cytology revealed evidence of malignancy, with ductal and acinic cells suggestive of CCC. The analysis showed hypercellularity with large cells having enlarged nucleus and also multinuclear cells with a prominent and large nucleolus.

Computed tomography (CT) scan showed a 2.8 × 1.7 cm solid poorly defined mass in the superficial lobe of the right parotid gland that hinted in the deep lobe [Figure 1a]. Moreover, the mass was intensely and homogeneously enhanced with contrast and the structural appearance was that of a solid lesion of parenchymatose consistency with colliquative necrosis in the central areas. The cervical CT also revealed the presence of one metastatic cervical node with deep soft tissue and skin extension.

On the suspicion of a CCC, a full body CT was performed to rule out a renal tumor or metastasis, but it failed to show pathological results [Figure 1b]. A diagnosis of primary CCC was thus made.

Histology disclosed a non-encapsulated well defined tumor, though it had some infiltrating areas [Figure 3a and b]. The mass was totally composed of cells with round central nucleus...
and abundant clear cytoplasm [Figure 3c]. Pleomorphism was limited. No mitoses were found. Areas without clear cells were not observed. Additionally, one of the 34 isolated neck nodes was positive.

Tumor cells were negative for glycogen and mucin [Figure 3d]. Immunohistochemical stains revealed that the tumor cells were positive for high-molecular-weight cytokeratins, carcinoembryonic antigen (CEA) [Figure 3e] and epithelial membrane antigen (EMA) and were negative for low-molecular-weight cytokeratins (CAM 5.2 and AE3), vimentin, S-100 protein, CK (cytokeratin) 7 and CK20. A posterior immunohistochemical study revealed that the tumor cells were positive for CD 10 (cluster of differentiation) [Figure 3f], which suggested the possibility of metastasis of renal clear cell adenocarcinoma.

The patient underwent postoperative radiotherapy and she was free from local or distant disease during 4 years of follow-up.
Unfortunately, in 2011, an abdominal CT disclosed metastatic disease in the right lung, however no additional treatment was performed due to old age and poor health. The patient died a few months after that finding.

DISCUSSION

CCC of salivary glands is a relatively rare tumor. This tumor has a female preponderance and a median age in the sixth and seventh decades of life. This low-grade malignant tumor of putative duct cell origin is composed exclusively of a monomorphic population of undifferentiated cells that have optically clear cytoplasm but lack features that would allocate them in any of the specific categories.

Malignant neoplasms account for 15-35% of all parotid gland tumors; 21-42% of those correspond to metastatic processes. Most metastatic tumors of the salivary glands proceed from lesions of the head and neck and consist of melanomas in 45% of cases and squamous cell carcinomas of the skin in 37%. Only a small percentage arises from distant sites such as the lung, breast, kidney, gastrointestinal tract, and prostate.

Tumors composed exclusively of or predominantly of clear cells are infrequent in the parotid gland, representing only 1-2% of all salivary gland tumors, originating also in other areas, including normal or aberrant gland tissue. Clear cells in these lesions most often result from artifacts of fixation, but in some instances, they may be a reflection of peculiar functional states of the tumor cells. A scarcity of organelles, glycogen storage, and accumulation of mucins, lipids, tonofilaments, and immature zymogen granules also may account for this appearance.

Primary salivary clear cell neoplasms can be divided into those that diagnostically require evidence of myoepithelial differentiation (i.e., CCMEC and EMEC) and those that do not (i.e., CCC). Most of these tumors have been reported as sporadic cases with the exception of a few well-documented series of either EMEC or CCC, and to our knowledge, myoepithelial differentiation has not been documented in CCC till date. CCC is a classic and distinct entity that represents the latter differentiation pathway. By definition, CCC contains a significant proportion of clear cells, but it does not fit into any other recognized neoplastic entities. Although non-lipid and non-mucin, but glycogen rich clear cell tumors in salivary glands have long been recognized, they were only recently included in the third WHO (World Health Organisation) classification as a distinct low-grade carcinoma. The WHO classification of salivary gland tumors does not define a specific category for clear cell tumors and only indicates that the presence of clear cells is a feature common to the various neoplastic formations originating in that site.

The natural course is an indolent, painless mass that occurs predominantly in the minor salivary glands. The biological behavior is not very aggressive and development, which is very slow, is usually asymptomatic and indeed, the tumor often reaches considerable dimensions before being diagnosed.

When clear cells predominate, a definitive diagnosis may be problematic because many of these tumors will share common histologic features. Indeed, the segregation of benign from malignant neoplasm may be obfuscatory. The histopathologic finding of a malignant clear cell tumor in a parotidectomy surgical specimen involves the necessity of differential diagnosis between clear cell primary parotid tumors and metastases. Carcinomas from the kidney, liver, large bowel, prostate and thyroid are known to have the potential for clear cell differentiation and all of them are able to metastasize to the maxillofacial area with renal cell carcinoma doing so most frequently.

Classically, the differential diagnoses of clear cell tumors in the parotid area includes mainly clear cell variants of primary tumors such as clear cell myoepithelial carcinoma, clear cell EMEC, clear cell acinic cell carcinoma, clear cell adenocarcinoma of salivary glands and hyalinizing CCC. Also clear cell mucoepidermoid carcinoma, clear cell oncocytoma and clear cell odontogenic tumors need to be ruled out. Immunohistochemical evaluation is essential in distinguishing these tumors, but its sensibility and specificity is occasionally not enough to confirm the diagnosis. Some authors consider that definite differentiation between CCC and metastatic renal clear cell adenocarcinoma in the salivary gland is often impossible by pathologic studies alone and requires clinical evaluation to rule out a primary renal tumor.

CCC of salivary glands usually expresses epithelial markers (cytokeratins, EMA, and CEA) but lacks expression of myoepithelial markers (S-100 protein, actin, vimentin, and glial fibrillary acid protein). Immunohistochemical staining in renal clear cell adenocarcinoma shows complete negativity for high-molecular-weight cytokeratin and weak and moderate patchy staining for low-molecular-weight cytokeratin (CAM 5.2) in more than 80% of the cases. It also stains strongly forEMA and vimentin and it is negative for actin, S-100, glial fibrillary acid protein, and CEA. Recently, CD10 immunoreactivity was observed in 90% to 94% of the cases of renal CCC, which permits more specificity in the histopathologic diagnosis. CD10 is a cell membrane associated neutral endopeptidase, also known as enkephalinase, CALLA, and EC3.3.24.11, that plays a physiological role in degrading biologically active peptides, including those implicated in autocrine growth stimulation of certain cancers.

Clear cell myoepithelial carcinoma shows sheets of clear cells sometimes admixed with spindle shaped and other myoepithelial cells. These cells are positive for cytokeratins, S-100 and actin (alpha smooth muscle actin). The tumor cells are also positive for glycogen. Clear-cell variants of acinic
Primary parotid clear cell carcinoma

Saldaña Rodriguez, et al. 104

Figure 4: Schematic guide to diagnosing salivary clear cell tumors. IHC: Immunohistochemistry, EM: Electron microscopy, LM: Light microscopy

Primary parotid clear cell carcinoma are usually never pure and cells with periodic acid Schiff positive and diastase resistant cytoplasmic zymogen granules are also present. Sebaceous neoplasms are positive for fat stains and clear cell mucoepidermoid carcinomas show positivity for mucin. Metastatic renal cell carcinomas are positive for both fat and glycogen and immunohistochemically positive for vimentin and CD10.

Because of the lack of awareness, CCC is often misdiagnosed as poorly differentiated carcinoma, squamous cell carcinoma, acinic cell carcinoma, mucoepidermoid carcinoma and EMEC.

Wide excision is the treatment of choice for most CCC,[10,17,18] although neck dissection and radiotherapy have been performed in some cases.[10,18] The decision to include node dissection or radiotherapy is generally based on the presence of positive margins, high-grade histology, invasion (vascular/neural) or positive neck nodes.[19] While these prognostic factors also apply to CCC, an additional factor correlated with nodal metastasis is the presence of mitotic activity.[10,18]

Adverse biologic behavior ranges from multiple recurrences to local nodal or distant disease.[5,10,11,18] Patients may develop multiple recurrences up to two decades after resection and tends to occur at intraoral sites (65%). The rate of recurrence is 17% and the metastatic rate is 21%. Close follow-up is therefore, important. No patient has died of CCC.[5]

CONCLUSION

It is generally considered that definite differentiation between clear cell primary tumors of parotid gland and metastatic clear cell renal adenocarcinoma in the same location is quite difficult. The importance of the correct diagnosis lies in the possibility of localizing the primary tumor and treating it adequately. Although CCCs in the parotid region are rare, when the histopathologic study demonstrates a clear cell epithelial tumor in this area, primary CCC should come to mind as one of the main possibilities, besides metastatic renal clear cell adenocarcinoma and a thorough clinical and radiological examination will help us to arrive at the right diagnosis.

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Primary parotid clear cell carcinoma

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