Epithelial-myoepithelial carcinoma in the floor of mouth: Case report and review of the literature

Carcinoma epitelial-mioepitelial no assoalho bucal: relato de caso e revisão da literatura

Abstract

Purpose: to document the clinical, histopathological and immunohistochemical findings of an epithelial-myoepithelial carcinoma (EMC) in the floor of mouth and submandibular region. Furthermore, we intend to discuss the current literature about this tumor.

Case description: the biphasic pattern of neoplastic cells could be confirmed by immunohistochemical analysis, which showed positivity for cytokeratin (CK7) in luminal cells and for α-smooth muscle actin (α-SMA) in those non-luminal. All of the features were consistent with the diagnostic criteria required for EMC and the patient was referred for specialized treatment.

Conclusion: EMC is a rare type of malignant tumor, accounting for about 1% of all salivary gland tumors. Arising most frequently in the parotid gland (75%), approximately 10% of the tumors have their origin in the submandibular gland, and rarely affect the minor salivary glands. The diagnosis should be based on conventional light microscopy and confirmed by immunohistochemical analysis.

Key words: Adenocarcinoma; immunohistochemistry; submandibular gland

Case Report

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Introduction

The epithelial-myoepithelial carcinoma (EMC) is a rare low-grade malignant salivary gland neoplasm comprising approximately 1% to 2% of all primary salivary gland tumors (1). It was first described by Donath et al. in 1972 and recognized as a distinct entity by the World Health Organization (WHO) in 1991 (2-4).

Approximately 60% of the patients with EMC are female (4) and the majority of them are in the seventh and eighth decades of life. It affects the parotid gland in about 80% of cases (5-7), however, lesions arising in minor salivary glands and extraoral areas have also been reported (19% to 31%) (3,6). Soft palate seems to be the site of predilection of minor salivary gland EMCs (3,4).

Histologically, the tumor is characterized by a biphasic cytomorphology comprised of an inner layer of duct lining cells and an outer layer of clear myoepithelial cells (1,5,6). It can also show a multinodular growth pattern with tumor islands separated by a basement membrane and dense fibrous connective tissue bands. In many cases, the clear myoepithelial cell components are more predominant than the typical biphasic character (8). Based on the primary histological characteristics, the EMC can be classified in four categories: solid, tubular, pappilary and cribriform (5).

We present a case of EMC involving the floor of mouth and submandibular region. Furthermore, we discuss the current publications, with a survey of cases reported in English literature in the last 10 years (Table 1).

Case Description

An 84-year-old woman was referred to the Stomatology clinic on September 2011, complaining of a “swelling in the tongue”, that she had noticed for about 3 months. During the interview, the patient reported having smoked for 20 years and his family history revealed two brothers previously diagnosed with cancer. The physical examination revealed a rubbery mobile mass in the right submandibular region (Fig. 1A). On oral evaluation, a firm, oval, lobulated mass measuring approximately 5 cm in diameter was found involving the mouth floor and submandibular region. The tumor surface was uneven and reddish. Occlusal radiograph showed no resorption of the alveolar bone adjacent to the tumor. There was neither neuro-paralysis nor cervical lymphadenopathy, but the patient had trismus and great difficulty in mouth opening. Clinical finds directed to the following suspicions: pleomorphic adenoma, adenoid cystic carcinoma and mucoepidermoid carcinoma.

Table 1. List of EMC cases reported in the English literature over the past 10 years (2002-2012).

<table>
<thead>
<tr>
<th>Author(s) (Year)</th>
<th>Patient’s gender/age</th>
<th>Location</th>
<th>Treatment</th>
<th>Recurrence (Time)</th>
<th>Metastasis (Location)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patra, Panda, Saikia (2012)</td>
<td>50</td>
<td>Maxillary sinus</td>
<td>Surgical excision</td>
<td>No</td>
<td>Yes (regional nodal)</td>
</tr>
<tr>
<td>Hussaini et al. (2012)</td>
<td>M/83</td>
<td>Subauricular region</td>
<td>Further surgery with a wider excision margin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Yang, Chen (2012)</td>
<td>F/60</td>
<td>Submandibular gland</td>
<td>Total excision of the submandibular gland</td>
<td>No</td>
<td>Yes (lungs)</td>
</tr>
<tr>
<td>Cherian, Kulkarni, Bhat (2010)</td>
<td>M/70</td>
<td>Hard palate</td>
<td>Surgical excision</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Matos et al. (2010)</td>
<td>F/48</td>
<td>Tongue (ventral surface)</td>
<td>Surgical excision</td>
<td>Yes (4 years)</td>
<td>No</td>
</tr>
<tr>
<td>Peters et al. (2010)</td>
<td>F/60</td>
<td>Tongue (base)</td>
<td>Schemo-radiotherapy and surgery</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Voss et al. (2009)</td>
<td>M/53</td>
<td>Skull base (parotid gland)</td>
<td>Surgical resection</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kainuma et al. (2010)</td>
<td>M/74</td>
<td>Parotid gland</td>
<td>Surgical resection</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Teppo, Paronen (2008)</td>
<td>M/53</td>
<td>Hard palate</td>
<td>Surgical excision and postoperative irradiation</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Yamada et al. (2007)</td>
<td>M/72</td>
<td>Submandibular gland</td>
<td>Upper neck dissection</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Jain, Thomas, Singh (2006)</td>
<td>F/25</td>
<td>Mandible, thyroid cartilage and masseter muscle</td>
<td>Surgical excision</td>
<td>No</td>
<td>Yes (Cervical lymph-node)</td>
</tr>
<tr>
<td>Kumai, Ogata, Yumoto (2006)</td>
<td>M/76</td>
<td>Tongue (base)</td>
<td>Subtotal glossectomy, bilateral neck dissection</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kleist et al. (2003)</td>
<td>F/78</td>
<td>Parotid gland</td>
<td>Parotidectomy</td>
<td>No</td>
<td>Yes (Cervical lymph-node)</td>
</tr>
<tr>
<td>Manuel et al. (2002)</td>
<td>F/68</td>
<td>Parotid gland</td>
<td>Parotidectomy and radiotherapy</td>
<td>Yes (7 months)</td>
<td>Yes (Cervical lymph-node and Chest wall)</td>
</tr>
<tr>
<td>Senis Segarra et al. (2002)</td>
<td>F/60</td>
<td>Cheek</td>
<td>Tracheotomy, exeresis</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

F, Female; M, Male
An incisional biopsy was carried out beneath local anesthesia with removal of two fragments from different locations. Examination of the hematoxylin-eosin (HE) stained sections (Fig. 1B) revealed a salivary gland neoplasm characterized by proliferation of non-luminal cells with polygonal morphology, clear and ample cytoplasm and large nuclei. These cells were arranged in solid nests and strands permeated by dense fibrous connective tissue. In some nests it was possible to identify the differentiation of luminal cells with eosinophilic cuboidal morphology describing ductiform structures. This biphasic pattern of neoplastic cells could be confirmed by positivity for cytokeratin (CK7) in luminal cells (Fig. 2A) and for α-smooth muscle actin (α-SMA) in that non-luminal (Fig. 2B). The CK7 and the α-SMA were used with dilution of 1:50 and source LSAB. The incubation of the CK7 was over night, while the α-SMA was 60 minutes. All of the features were consistent with the diagnostic criteria for EMC. Laboratorial tests showed absence of metastasis and the patient was referred to treatment with specialized medical team.

**Discussion**

EMC usually arises as a separate entity and usually develops in the parotid gland of women. It occurs more frequently in the seventh and eighth decades (4,7,8), Nonetheless, other sites have been reported, such as the submandibular gland (4,9). In rare instances this tumor can involve the tongue (1). It is commonly called a low-grade malignant neoplasm which usually have a good prognosis (8,10), but minor salivary gland EMC is an extremely rare and potentially aggressive tumor (3).

In some cases, the local rate of recurrence is high, ranging from 31.3% to 43%, and most recurrences manifest within 5 years (6,11). This may be partly because EMC often appears histologically benign, and this can result in its incomplete excision (12). Metastasis to regional...
Epithelial-myoepithelial carcinoma

have been proposed for their identification in tumors (12). markers such as cytokeratin 14, P63, CD10 and D2-40
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differentiation (2). These generally benign features account
of clear cells in solid arrangements consistent with the type
that most reported cases are not correctly diagnosed. Some authors divide EMC into 2 subtypes: 1) a tubular
cribriform type characterized by a double-layered tubule
ductal structure and 2) a solid type dominated by clear
cells (1). In the present case, the tumor showed prevalence
of clear cells in solid arrangements consistent with the type
2. In particular, previous studies directed their attention to
the solid variant of EMC, because it is found to be associated
with a more aggressive behavior compared with the other
histological types (5).

Other microscopic features of EMC include periodic
acid-Schiff (PAS) positivity of the clear cells, with
corresponding negativity on diastase digestion; markedly
PAS-positive basement membrane, with minimal cellular
atypia; infrequent mitoses and a tendency to exhibit ductal
differentiation (2). These generally benign features account
for why this tumor had been previously regarded as an
adenoma. However, there is often evidence of nerve and
blood vessel invasion (10), and this tendency together with
the recurrences and metastasis already reported give us the
possibility to consider it an aggressive lesion.

The diagnosis of EMC is difficult, partly because of
the rarity of the tumor, partly because of the complicated
histopathological characteristics and it has been speculated
that most reported cases are not correctly diagnosed. Some authors divide EMC into 2 subtypes: 1) a tubular
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It is important to apply appropriate immunohistochemical
methods to characterize the nature of the tumor different
cell components. The myoepithelial cells are recognized
immunohistochemically by the positivity of myo-
filaments (13). Besides the myogenic proteins, many other
markers such as cytokeratin 14, P63, CD10 and D2-40
have been proposed for their identification in tumors (12).
In our case, immunohistochemistry showed positivity for
cytokeratin (CK7) in the epithelial cells and positivity for
α-smooth muscle actin (α-SMA) in the myoepithelial
component of the tumor. This combination of pathological
findings, together with the typical biphasic (epithelial
and myoepithelial components) histological morphology,
compose the basis of EMC diagnosis (11).

EMC has also been investigated by molecular genetics
methods, but the published data do mainly not reflect the
specific biphasic cellular arrangement or different growth
patterns of EMC (5). However, a diagnostic approach to
the variable appearances of EMC could be prognostically
important, since tumors predominantly composed of clear
cells in a solid arrangement, as the present case, are considered
to be associated with a more aggressive behavior (10).
The differential diagnosis of EMC includes clear cell
dominated tumors such as myoepitheliomas, acinic cell
carcinomas, mucoepidermoid carcinomas, and metastatic
clear cell tumors (7,8,13). Because adenoid cystic carcinoma
(ACC) can also show a double-layered, duct-like structure, it
can be mistaken for EMC (2), but different immunostaining
characteristics are useful for distinguishing between EMC
and ACC. The identification of S-100 protein can help in this
differentiation. The inner ductal cell layer in ACC will stain
positive, whereas only the outer ductal cell layer in EMC is
positive for this protein (4). In the present case, the clinical
hypotheses were pleomorphic adenoma, adenoid cystic
carcinoma and mucoepidermoid carcinoma, but the final
diagnosis was well established after careful examination
on the clinic, histopathologic and immunostaining
characteristics.

For Yamada et al. (4) the value of image examination
such as computed tomography (CT), magnetic resonance
imaging (MRI), and positron emission tomography (PET) for
the pathologic diagnosis of EMC has yet to be established.
Also, EMC image interpretation by PET, a new promising
imaging system for cancer, has not been reported. According
to these authors, although a preoperative specific diagnosis
of EMC cannot be established, the malignant nature of the
tumor is detectable by the combination of PET, CT, and
MRI (4). In our patient, the occlusal radiograph was obtained,
but it brought no little light to diagnosis.

Given the above, we emphasize the importance of
considering clinical, histopathological and immuno-
histochemical findings in the diagnosis of benign and
malignant lesions in salivary glands as the different tumors
present many similarities, and this fact can confuse the
professionals in the correct diagnosis leading to wrong
treatments, with possible unsatisfactory outcomes.

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