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CASE REPORT

Primary Intraosseous Adenoid Cystic Carcinoma of the Mandible: Histopathological and Immunohistochemical Analysis

Román Carlos-Bregni · Elisa C. Vidaurre · Ana Carolina Netto · Jorge E. León · Oslei P. Almeida

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Abstract Primary intraosseous salivary gland tumors of the mandible are rare, with mucopidermoid carcinoma being the most frequent, followed by adenoid cystic carcinoma (ACC). We present a case of a central ACC involving the mandible of a 46-year-old man. He presented an indurated swelling on the vestibular aspect of the left mandibular body and ipsilateral paraesthesia of the lower lip. A panoramic radiography revealed a large radiolucent area, with irregular margins, involving the body and ramus of the left mandible, and CT scan confirmed that the lesion was confined within the mandibular bone. The histopathological features were of an ACC. CT scan also revealed multiple nodular lesions in both lungs suggestive of metastases. The patient was surgically treated by hemimandibulectomy. The patient is well with no evidences of recurrences in the mandible. The present case shows that the clinical and immunohistochemical profile of primary intraosseous ACC is similar to what is found in ACC involving the salivary glands.

Keywords Adenoid cystic carcinoma · Intraosseous · Mandible · Immunohistochemistry

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R. Carlos-Bregni · E. C. Vidaurre · A. Carolina Netto
Centro Clínico de Cabeza y Cuello,
6 ave. 7-39 zona 10, ed. Las Brisas of. 501,
Ciudad de Guatemala 01010, Guatemala

J. E. León (✉) · O. P. Almeida
Department of Oral Pathology, Oral Diagnosis Department,
Dental School, Piracicaba-UNICAMP, University of Campinas,
Av. Limeira 901, Caixa Postal 52,
CEP: 13414-903 Piracicaba-SP, Brazil
e-mail: jorgeesquiche@yahoo.com.br

Introduction

Primary central salivary gland carcinomas of the mandible are uncommon, and its origin is still controversial. Most cases are well differentiated mucoepidermoid carcinomas, followed by adenoid cystic carcinoma (ACC) and other rare types. To our knowledge, only about 26 cases of central ACC arising in the mandible were reported [1–8]. Pathogenesis of central salivary gland tumors is unknown, but it is considered they originate from epithelial linings of cysts, particularly dentigerous cysts, or more probably from ectopic salivary gland tissue [2]. Recently, Mahomed et al. [8], reported a case of central ACC of the mandible with areas that showed morphologic features of odontogenic differentiation. Clinically and radiographically they may mimic odontogenic cysts and tumors, and a final diagnosis can be obtained only after histological examination [4]. The aim of this study is to report the clinicopathological and, for the first time, the immunohistochemical (IHC) features using a large panel of antibodies, of a case of central ACC occurring in the mandible of an adult man.

Case Report

A 46-year-old male presented with persistent pain in the left posterior mandibular region, and progressive ipsilateral paraesthesia of the lower lip. Clinical examination displayed a non-ulcerated swelling on the vestibular aspect of the left mandibular body. A panoramic radiography and computed tomography (CT) scan revealed a large radiolucent lesion with irregular margins involving the body and ramus of the left mandible (Fig. 1). The lesion was confined within the mandible with focal erosion of the vestibular cortical bone. A clinical diagnosis of malignant mesenchy-

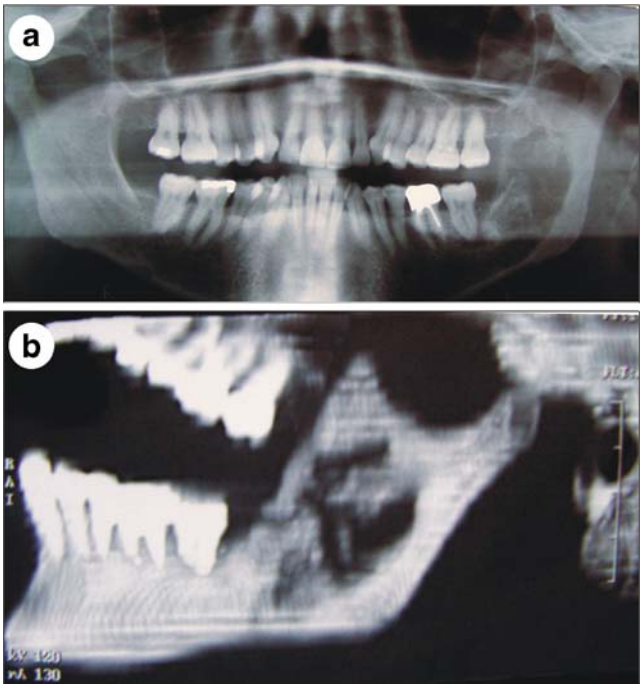

Fig. 1 Panorex radiograph (**a**) and sagital CT scan (**b**) of central ACC showing a lytic lesion with irregular margins involving the left body and ramus of the mandible

mal or odontogenic neoplasia was considered. Under local anesthesia, an incisional biopsy was performed. Microscopical examination showed prominent cribriform and focal tubular glandular patterns of growth, with numerous non-luminal cells with myoepithelial characteristics and scarce true luminal cells. The cribriform areas showed pseudocysts and hyalinized material suggestive of proteoglycans and basement membrane. The histopathological features were similar to typical ACC of the salivary glands (Fig. 2).

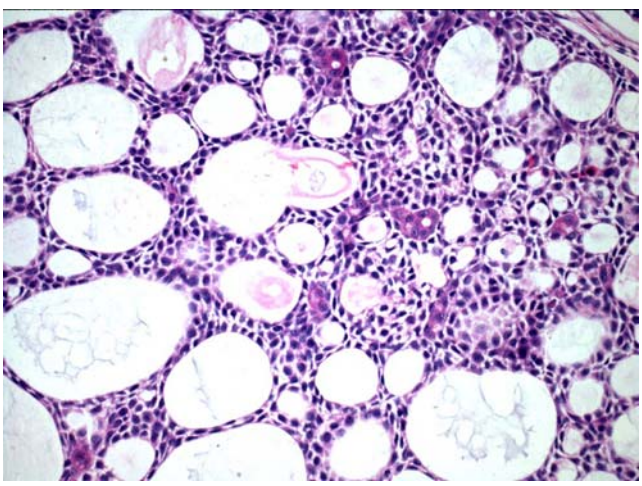

Fig. 2 Microscopical aspect of central ACC showing prominent cribriform pattern, characteristic myoepithelium component and scarce true luminal cells (H&E, × 200)

Possibility of metastases was considered and extensive clinico-radiological investigations were performed, including clinical and CT scan evaluation of the head and neck area, along with chest radiograms and CT scan. The latter revealed multiple nodular lesions in both lungs suggestive of metastases (Fig. 3), but the lymph nodes of the neck were negative.

Surgical treatment consisted of hemi-mandibulectomy, followed by mandibular reconstruction using titanium plates and free fibular flap**.** Histopathological analysis of the resected specimen showed similar features of the incisional biopsy, and the assessment of the surgical margins did not show evidences of residual tumor. The patient is still being monitorated, and after 24 months of follow-up he is alive with no evidences of local recurrence.

A large panel of antibodies was used for IHC evaluation (Table 1). True luminal cells were more intensely marked than myoepithelial-like cells with vimentin, cytokeratins (CKs) (AE1/AE3, 34βE12, CK5 and CK14), β-catenin, and E-cadherin (Fig. 4a and b). Bcl-2 stained homogenously both true luminal cells and myoepithelial-like cells. CK7 and CK19 stained strongly true luminal cells and scarce myoepithelial-like cells (Fig. 4c), while CK8 marked weakly and focally the true luminal cells only. The exuberant myoepithelial component was deep stained with p63, alpha-smooth muscle actin (SMA) and epithelial membrane antigen (EMA), and less intensely and focally for muscle-specific actin (MSA). Scarce positivity for CD43 in a membranous and/or cytoplasmic pattern affecting mainly the myoepithelial-like cells was detected. Nuclear and cytoplasmic positivity for S100 was found in true luminal cells and scarce myoepithelial-like cells (Fig. 4d). The labeling index with MCM-2 and MCM-5 (minichromosome maintenance protein) and Ki-67 was 7%, 6%, and 3%, respectively, which was calculated after analyzing

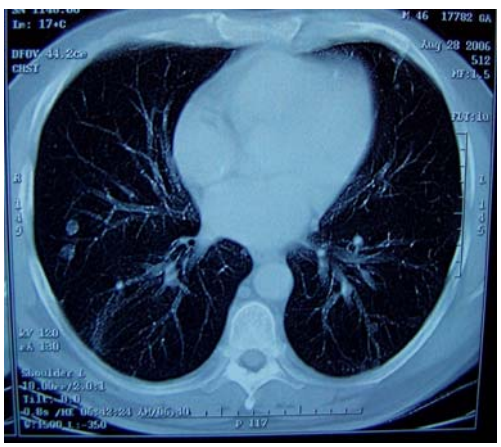

Fig. 3 Chest axial CT showing multiple and bilateral nodular lesions, consistent with metastases

Table 1 Antibodies used for immunohistochemical evaluation of primary adenoid cystic carcinoma of the mandible

Antibody	Source/Clone	Dilution	Immunohistochemical findings	
			True luminal cells	Myoepithelial-like cells
CK-cocktail	Dako®[a], AE1/AE3	1:500	++	+
CK-HMW	Dako®[a], 34βE12	1:200	++	+
CK1	Novocastra®[b], 34βB4	1:200	neg	neg
CK4	Novocastra®[b], 6B10	1:200	neg	neg
CK5	Novocastra®[b], XM26	1:400	++	+
CK6	Novocastra®[b], LHK6B	1:200	neg	neg
CK7	Dako®[a], OV-TL12/30	1:400	++	scarce cells +
CK8	Dako®[a], 35βH11	1:200	+/−	neg
CK10	Dako®[a], DE-K-10	1:200	neg	neg
CK13	Novocastra®[b], KS-1^{A}3	1:400	neg	neg
CK14	Novocastra®[b],NCL-L-LL002	1:200	++	+
CK16	Novocastra®[b], LL025	1:200	neg	neg
CK18	Dako®[a], DC10	1:400	neg	neg
CK19	Dako®[a], RCK 108	1:200	++	scarce cells +
EMA	Dako®[a], E29	1:400	neg	+
β-catenin	Novocastra®[b], 17C2	1:100	++	+
E-cadherin	Dako®[a], NCH-38[4]	1:200	++	+
CEA	Dako®[a], II-7	1:500	neg	neg
C-erbB-2	Dako®[a], polyclonal	1:200	neg	neg
Vimentin	Dako®[a], Vim 3B4	1:400	++	+
CD56	Novocastra®[b], 1B6	1:50	neg	neg
S100	Dako®[a], polyclonal	1:12000	+	scarce cells +
SMA	Dako®[a], 1A4	1:400	neg	++
MSA	Dako®[a], HHF-35	1:800	neg	+/−
CD117	Dako®[a], polyclonal	1:200	neg	neg
CD43	Dako®[a], DF-T1	1:1000	neg	scarce cells +
D2-40	Dako®[a], D2-40[1]	1:100	neg	neg
GFAP	Dako®[a], 6S2	1:400	neg	neg
p63	Dako®[a], 4A4	1:600	neg	+
p53	Dako®[a], DO-7	1:200	neg	neg
bcl-2	Dako®[a], 124	1:50	+	+
MCM-2	Novocastra®[b], CRCT2.1	1:20	7%	
MCM-5	Novocastra®[b], CRCT5.1	1:15	6%	
Ki-67	Dako®[a], MIB-1	1:200	3%	

CK cytokeratin; *HMW* high molecular weight; *EMA* epithelial membrane antigen; *CEA* carcinoembryonic antigen; *SMA* alfa-smooth muscle actin; *MSA* muscle-specific actin; *GFAP* glial fibrillary acidic protein; *MCM* minichromosome maintenance protein

++, strong positive; +, positive; +/−, weak and focal positive

[a] Dako A/S, Glostrup, Denmark

[b] Novocastra Laboratories Ltda, Newcastle, England

about 1,000 cells in five high-power fields. The tumor was negative for all other markers used.

Discussion

ACC is the first or second most common salivary gland tumor of the mouth, involving mainly the palate and it is rarely intraosseous. At long term, most if not all patients with ACC develop distant metastases, mainly to the lungs and bone, despite local control of the tumor. The occurrence of bone metastases usually corresponds to rapid tumor dissemination and death of the patient, whereas lung metastases demonstrate a less aggressive clinical course [6].

Martinez-Madrigal et al. [4] and Li et al. [9] reported a total of 29 cases of primary central salivary gland tumors of the mandible, most involving the posterior area. Mucoepidermoid carcinoma corresponded to almost half of cases, followed by ACC, but there were cases of rare tumors as adenocarcinoma not otherwise specified (NOS), acinic-cell carcinoma and myoepithelial carcinoma. It is also interesting to consider that an extensive review of the literature also revealed 12 reported cases of benign salivary gland tumors involving the jaws, mainly pleomorphic adenoma [2, 10].

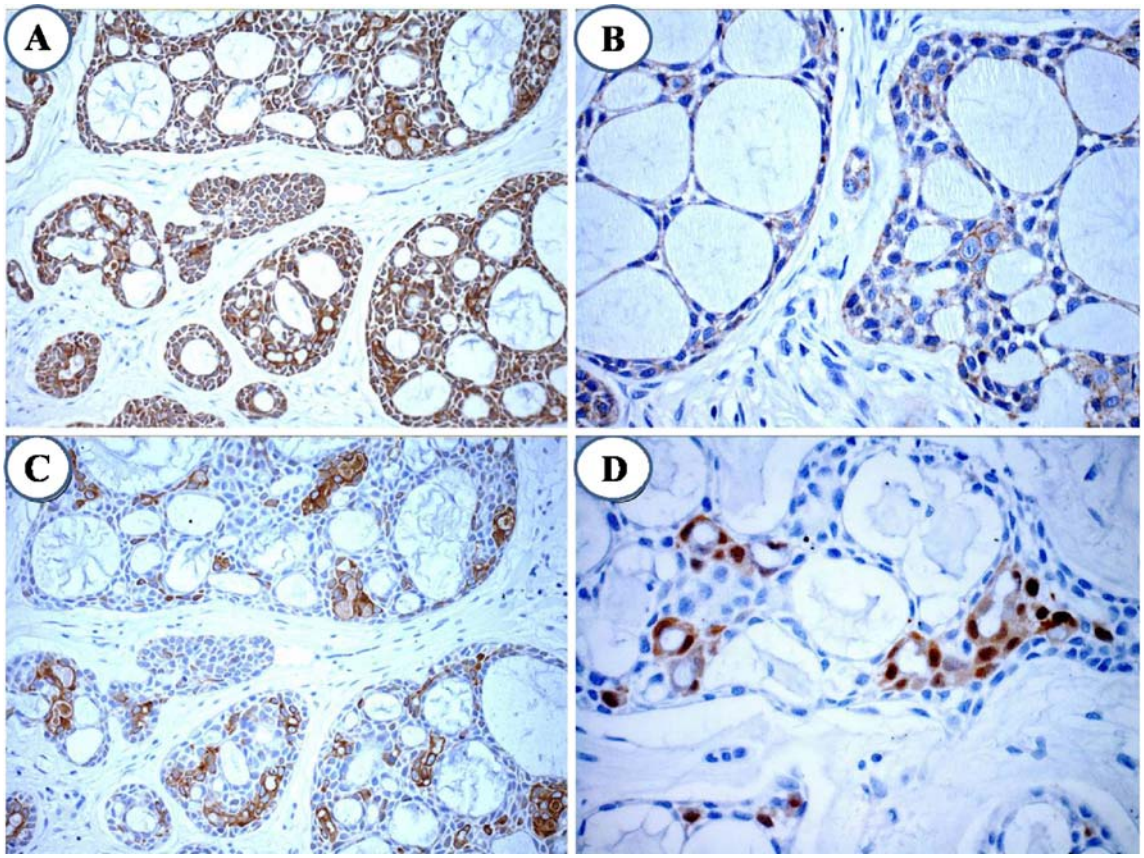

Fig. 4 Immunohistochemical findings of the central ACC of the mandible. **a** Stronger positivity for CK5 in true luminal cells than in the myoepithelial component (× 200). **b** β-catenin highlighted more the true luminal cells than the myoepithelial-like cells (× 400). **c** True luminal cells strongly marked for CK7. Note faint expression in scarce myoepithelial-like cells (× 200). **d** Strong nuclear and cytoplasmic positivity for S100 in the true luminal cells (× 400)

We found a total of 26 cases of primary ACC of the mandible reported in the literature. The age of the patients ranged from 24 to 82 years, with a slight male predilection, and the most common site was the posterior body or angle of the mandible. Pain and swelling were the most frequent symptoms. Surgical resection was the treatment of choice, but radiotherapy also was commonly used. Pulmonary metastases were detected in one third of the patients during the follow-up of 1 to 14-years [1–8]. The current case is within these characteristics, including the presence of multiple nodular lesions in both lungs suggestive of metastases, and negative neck for regional metastases. Presence of distant but not regional metastases confirms that the biological characteristics of central ACC is similar to those reported in patients with ACC arising in the major or minor salivary glands.

Strict diagnostic criteria have been established to confirm the central origin of salivary gland tumors involving the mandible: 1. radiographic evidence of osteolysis; 2. presence of intact cortical plates; 3. absence of primary lesions within the salivary glands; and 4. histological confirmation [4, 6]. All these diagnostic criteria were satisfied in the case here reported, except by a focal erosive area of the vestibular cortical bone, which very probably represents the initial extraosseous extension of the tumor. The present patient underwent wide surgical excision of the tumor, he is alive and well, however with evidences of multiple nodular lesions in both lungs suggestive of metastases that were not treated.

Most central salivary gland tumors of the jaws involve the mandible, and this occurs with 65% of intraosseous ACC. Theories proposed for the pathogenesis of central salivary gland tumors, include neoplastic transformation of the epithelial linings of odontogenic cysts, metaplasia of the epithelial rests of Malassez or presence of ectopic salivary gland tissue [2, 4]. Recently, Mahomed et al. [8] reported a case of central ACC of the mandible, which showed areas of cribriform and tubular growth patterns merged with cystic spaces. Some of the latter were lined by epithelium that resembled the reduced enamel epithelium or showed corrugated luminal surface reminiscent of odontogenic keratocyst, besides the formation of aberrant dental hard tissue. In the present case, it was not possible to relate the tumor with either remanescent of salivary gland or odonto-

genic tissues. Nevertheless, the location in the posterior body of the mandible, involving non-tooth bearing areas, and the IHC results indicate the origin probably from sequestered salivary gland tissues. In fact, as suggested by Mahomed et al. [8] epithelial rests derived from the oral ectoderm within the jaws possibly have the capacity to differentiate along both odontogenic and salivary tissues.

There are many IHC data about ACC arising either in major and minor salivary glands. In summary, carcinoembryonic antigen (CEA), EMA, CK, and S100 strongly stain cells lining true lumina. All remaining cells are of myoepithelial phenotype expressing CK, vimentin, SMA, p63, and S100 [11–13]. Similar results were found in the present as well as in the Mahomed et al. [8] case, and also in five cases of ACC of the external auditory canal [14], one case of primary cutaneous ACC [15], and 16 cases of primary ACC of the lungs [16]. In the current case, an interesting finding in the myoepithelial component was the homogeneous positivity for EMA, which is mainly found in true luminal cells. Luo et al. [17] showed preferential expression of S100 and glial fibrillary acidic protein (GFAP) in ACC of the salivary glands, indicating that Schwann cell diferentiation in modified myoepithelial cells correlates with perineural invasion in salivary malignancy. In the present case, the scarce positivity for S100 and the negativity for GFAP indicate the variable expression of these markers in the myoepithelial-like cells. ACC of the salivary glands express β-catenin, E-cadherin, and C-kit [18, 19], but in the current case, only the two formers were expressed in membranous pattern. High expression of p53 and bcl-2, and low Ki-67 index is usually found in ACC of the salivary glands [20, 21]. In the present case, bcl-2 was positive while p53 was negative. As expected, and similar to findings of Vargas et al. [21], MCM-2 expression was slightly higher than Ki-67. MCM-5 expression has not been reported in ACC, but this proliferative marker was expressed similarly to MCM-2. It was demonstrated that CD43 is expressed in ACC, and D2-40 in normal and malignant myoepithelial cells, but the latter was not studied in ACC [22, 23]. The current case expressed only CD43 in scarce myoepithelial-like cells and it was negative for D2-40. In summary, although the expression of some proteins varies slightly from case to case of ACC, the main results of the present case are similar to those described in ACC of the salivary glands.

In conclusion, the clinical and immunohistochemistry characteristics of the present case reinforces that ACC of the jaws are similar to those involving the salivary glands, and therefore probably originate from entrapped remanescents of salivary gland tissue or oral ectoderm with potential salivary tissue differentiation.

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