Jornal Brasileiro de Patologia e Medicina Laboratorial
ISSN: 1676-2444
ISSN: 1678-4774
Sociedade Brasileira de Patologia Clínica; Sociedade Brasileira de Patologia; Sociedade Brasileira de Citopatologia

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Jornal Brasileiro de Patologia e Medicina Laboratorial,
vol. 55, no. 5, 2019, September-October, pp. 488-497
Sociedade Brasileira de Patologia Clínica; Sociedade Brasileira de Patologia; Sociedade Brasileira de Citopatologia

DOI: 10.5935/1676-2444.20190044

J Bras Patol Med Lab. 2019; 55(5): 488-497.

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Adenoid cystic carcinoma: immunohistochemistry and differential diagnosis, a case report

Carcinoma adenoide cístico: imuno-histoquímica e diagnóstico diferencial, um relato de caso

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ABSTRACT

A 52-year-old male patient complained of loss of sensitivity and pain in the maxilla. After examination, root canal treatment of tooth 12 was requested. Subsequently, there was a purplish increased volume of softened consistency in the area of vestibular attached gingiva of tooth 12. The anterior upper dental segment presented mobility. Incisional biopsy revealed malignant neoplasm of glandular epithelial origin, suggestive of solid adenoid cystic carcinoma (ACC). An immunohistochemical panel was performed, which confirmed the histopathological suspicion. Solid ACC may lead to diagnostic difficulties, since this lesion exhibits morphological features similar to other malignancies.

Key words: head and neck neoplasms; adenoid cystic carcinoma; differential diagnosis; immunohistochemistry.

RESUMO

Paciente do sexo masculino, 52 anos de idade, queixou-se de perda de sensibilidade e dor na maxila. Após investigação, foi solicitado o tratamento endodôntico do elemento dentário 12. Posteriormente, observou-se aumento de volume arroxeado e consistência amolecida na porção vestibular da gengiva inserida do elemento 12. O segmento dentário superior anterior apresentava mobilidade. A biópsia incisional evidenciou neoplasia maligna de origem epitelial glandular, sugestiva de carcinoma adenoide cístico (CAC) sólido. Um painel imuno-histoquímico foi realizado, o qual confirmou a suspeita histopatológica. O CAC sólido pode gerar dificuldades de diagnóstico, pois essa lesão exibe aspectos morfológicos similares aos de outras neoplasias malignas.

Unitermos: *neoplasias de cabeça e pescoço; carcinoma adenoide cístico; diagnóstico diferencial; imuno-histoquímica.*

RESUMEN

Paciente masculino, 52 años de edad, quejase de pérdida de sensibilidad y dolor en la maxila. Después de la consulta, se indicó el tratamiento endodóntico del elemento dental 12. Luego, se observó aumento de volumen amoratado y consistencia ablandada en la superficie vestibular de la encía insertada del elemento 12. El segmento dental superior anterior presentaba movilidad. La biopsia incisional demostró neoplasia maligna sugestiva de carcinoma adenoide quístico (CAQ) sólido. Se realizó un panel de pruebas inmunohistoquímico que confirmó la sospecha histopatológica. El CAQ sólido puede causar dificultades de diagnóstico, pues esa lesión muestra aspectos morfológicos semejantes a otras neoplasias malignas.

Palabras clave: *neoplasias de cabeza y cuello; carcinoma adenoide quístico; diagnóstico diferencial; inmunohistoquímica.*

First submission on 01/18/19; last submission on 04/03/19; accepted for publication on 04/03/19; published on 10/20/19

INTRODUCTION

Adenoid cystic carcinoma (ACC) in the oral cavity, commonly arises from the minor salivary glands of the hard palate, usually affecting patients after the fourth decade of life and showing a predilection for the female gender[1, 2].

ACC usually exhibits a slow-growing increased volume, sometimes ulcerated, and bone destruction may occur at more-advanced stages[3, 4]. The patient may present pain, loss of facial nerve function or paralysis, due to possibile perineural invasion of such neoplasia[1].

Microscopically, ACC are composed of myoepithelial cells and ductal cells exhibiting angular, hyperchromatic nuclei and clear cytoplasm, arranged in a stroma of dense fibrous connective tissue. Three histopathological patterns are recognized: cribriform, tubular and solid, which can coexist in different proportions[1, 2, 4, 5]. The solid ACC pattern presents small, cuboidal, basophilic cells with little cytoplasm and is related to a worse prognosis, due to the high rate of tumor invasion, high ability for distant metastasis, that usually occurs in the lungs, and high potential for relapse[1, 5]. The solid ACC pattern is similar to other epithelial neoplasms[2, 6-9]. Thus, immunohistochemistry can assist the pathologist at the diagnosis.

In this context, the present study aims to report a case of ACC with solid pattern in an adult patient, focusing on the immunohistochemical profile and differential diagnosis of this neoplasm.

CASE REPORT

A 52-year-old white male patient sought dental care at a private clinic in the city of Natal, Rio Grande do Norte, Brazil, complaining of loss of sensitivity and pain in the right maxillary region. At the initial clinical and radiographic examinations, no alterations were found to justify the patient's initial complaint. Thus, the dental surgeon (DS) referred the patient to an otorhinolaryngology-head and neck surgeon evaluation. The medical examination did not notice anything unusual, and the patient was referred back to the DS, who decided, due to his complaints, to perform root canal treatment on tooth 12.

One month after the endodontic treatment the patient returned complaining about the emergence of purplish spots on the gingiva. An intraoral clinical examination revealed an increased hard, asymptomatic, non-bleeding, volume purplish-colored, located on the vestibular surface of the attached gingiva near tooth 12 (**Figure 1**). Mobility was also observed throughout the anterior superior dental segment. In view of these findings, the DS requested a computed tomography (CT) scan resulting in a report suggestive of malignant neoplasia.

Incisional biopsy was performed under local anesthesia. The material was sent for microscopic analysis. Histopathological findings revealed a malignant neoplasm of glandular epithelial origin characterized by the proliferation of cuboidal epithelial cells and pale nucleus, arranged in infiltrative nests and sheets; areas of comedo necrosis, and perineural (**Figure 2A**), muscle (**Figure 2B**) and bone (**Figure 2C**) invasion were observed. Such characteristics were consistent with the solid variant of adenoid cystic carcinoma.

In order to rule out other lesions with histopathological characteristics similar to ACC, an immunohistochemical panel was performed using the ENVISION detection system (EnVisionTM G|2 Doublestain System, Dako North America Inc., Carpinteria, CA, USA), described in **Table**. After the diagnosis, the patient decided to carry out the treatment in another State, so information about the clinical outcome of the case was not available.

DISCUSSION

Malignant neoplasms affecting salivary glands are relatively rare, accounting for less than 7% of head and neck cancers. From these, only 10% are diagnosed as adenoid cystic carcinoma[4].

ACC can develop at a variety of anatomical sites, including the major and minor salivary glands, lacrimal glands and glands of the nasal cavity[1, 2]. Perineural involvement occurs between 29.4% and 62.5% of cases, and is considered a possible route for dissemination of neoplastic cells[1].

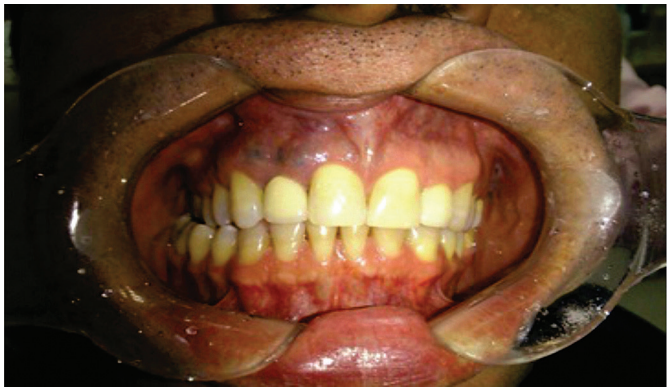

FIGURE 1 – *Clinical aspect*

Intraoral aspect of the patient, evidencing a purplish increased volume, located in the gingival region of the maxilla, in the area adjacent to the apex of the element 12.

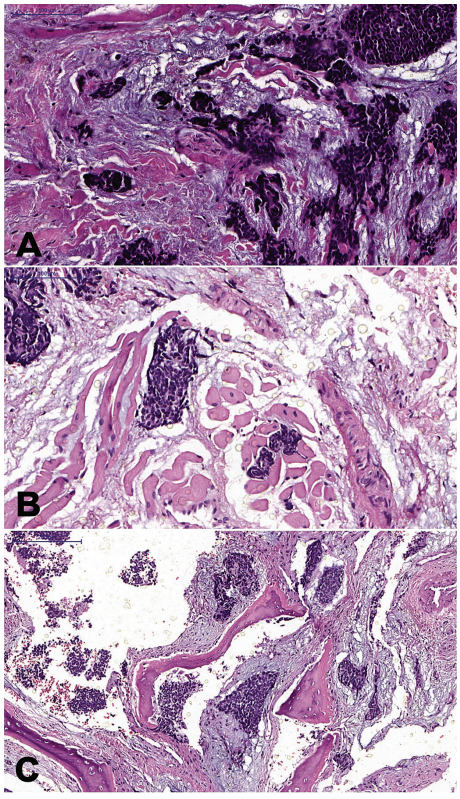

FIGURE 2 – *Microscopy*

Tumor cells in the form of nests and islands spreading (A) perineural, (B) muscle and (C) bone invasion (100 µm, HE).

HE: hematoxylin and eosin.

TABLE – Primary antibody, manufacturer, clone and immunoexpression (Envision Flex System)

Primary antibody	Clone	Immunoexpression
Anti-AE1/AE3	AE1/AE3	Positive
Anti-calponin	CALP	Negative
Anti-CD10	56C6	Negative
Anti-CD56	123C3	Rare positive cells
Anti-chromogranin A	Polyclonal	Negative
Anti-CK19	RCK 108	Negative
Anti-CK20	Ks20.8	Negative
Anti-CK5/6	D5/16 B4	Negative
Anti-CK7	OV-TL 12/30	Positive
Anti-CK8/18	B22.1+B231	Positive/focal
Anti-C-kit	Y145	Positive/focal
Anti-GFAP	Polyclonal	Rare positive cells
Anti-human cytokeratin, high molecular weight (34βE12)	34βE12	Positive/focal
Anti-Ki-67	MIB-1	Positive (20%)
Anti-p63	DAK-p63	Negative
Anti-S100	Polyclonal	Positive
Anti-Synaptophysin	DAK-SINAP	Negative
Anti-α-SMA	1A4	Positive/focal

CK: cytokeratin; GFAP: glial fibrillary acid protein; α-SMA: smooth muscle actin.

The present study reports a case of ACC with intraosseous maxillary invasion, an unusual location when compared to other reports in the literature[1, 2, 4]. Painful symptomatology is an infrequent clinical finding, especially in the early stages; loss of facial nerve function or paralysis may subsequently occur, due to the high perineural and neural invasion ability of this neoplasm[1]. In the case presented in this study, the patient reported both symptoms, compatible with the perineural invasion evidenced in the histopathological examination.

The diagnosis of ACC, as well as of the majority of salivary gland tumors, is based on the histopathological characteristics of the lesion[10]. ACC exhibits three architectural patterns: tubular, cribriform and solid[1, 2, 4, 5]. The solid pattern is the most aggressive, due to the proliferation of small tumor cells arranged in nests, islands, and sheets of invasive basaloid cells, similar to the morphological characteristics found in the present case[5].

In some situations, especially in cases of incisional biopsies, the diagnosis of ACC may be difficult, since the lesion fragment may not be representative for the diagnosis. Thus, when necessary, immunohistochemistry may assist in establishing a definitive diagnosis.

When the ACC predominantly exhibits the solid variant, with scarcity or absence of cribriform and/or tubular variants, the diagnosis may be difficult, since it presents morphological characteristics similar to tumors with basaloid cell features, such as basal cell adenocarcinoma (BCA), squamous basaloid carcinoma (SBC), sinonasal undifferentiated carcinoma (SNUC) and central neurocytoma (CN)[2].

BCA is a rare tumor accounting for 2.9% of malignant salivary gland neoplasms[6]. The solid pattern of ACC is the most frequent and when presented in the isolated form, associated with necrosis, it leads to the differential diagnosis for solid ACC[2]. Its immunohistochemical staining for labeling is variable: basal cells are positively labeled for S100, vimentin and, partially, for a variety of cytokeratins [(CK) 5, 6, 8, and 17] while ductal cells express strong CK staining, and partial labeling with S100. Neoplastic cells are negative for alpha smooth muscle actin (α-SMA)[6]. In the present case, there was a diffuse expression for α-SMA, discarding this hypothesis.

Another lesion presenting as an important differential diagnosis is squamous basaloid carcinoma[2]. SBC is an uncommon and quite aggressive subtype of squamous cell carcinoma, occurring more frequently in the upper aerodigestive tract, having as primary sites the oral cavity, pharynx, larynx, and

trachea[7]. Neoplastic cells presented immunostaining for high molecular weight cytokeratins and carcinoembryonic antigen (CEA), confirming the epithelial histogenesis of the lesion[7]. In the present case, there was positive high-molecular-weight cytokeratin (34βE12) membrane focal expression, positive for CK7, evidencing the labeling of luminal cells, and positive for S100, strongly marking the population of non-luminal cells.

SNUC is a rare and aggressive malignant neoplasm of uncertain histogenesis that occurs in the paranasal sinuses; the affected individuals present facial pain, nasal obstruction, and epistaxis as first symptoms[2, 8]. Most undifferentiated nasal carcinomas react with cytokeratins and are focal positive for epithelial membrane antigen (EMA), while neuron-specific enolase, synaptophysin, and chromogranin may show irregular immunoreactivity[8]. Regarding the present case, negative marking for CK19, synaptophysin, and chromogranin was observed, thus excluding this hypothesis.

CN is usually located into the ventricular system, affecting young adults in the second or third decade of life. They are immunopositive for neural markers, such as synaptophysin and neuron-specific enolase, as well as negative for the glial fibrillary acid protein (GFAP) and neurofilament protein, allowing diagnosis[9]. The present case was negative for synaptophysin and presented focal positive expression of GFAP in rare cells, discarding central neurocytoma.

Salha *et al*. (2016)[2] reported a case of solid intraosseous ACC originating in the paranasal sinuses with expansion into the oral cavity. In the immunohistochemical evaluation, positive and diffuse labeling for AE1/AE3, CK7 and CD117, focal expression for CK5/6, 34βE12, CAM5.2 and S100 proteins were observed in this study. In addition, the tumor also had strong nuclear expression for p16 and negative immunoblotting for p63, p40, neuron-specific enolase, CD56, CEA, CD99, thyroid transcription factor 1 (TTF-1), androgen/estrogen receptor (A/ER), and progesterone receptor (PGR), ruling out possible lesions from a neural origin[2].

The immunohistochemical results found in the present case are similar to those reported by Salha *et al*., in which positive and diffuse immunoblotting was observed for AE1/AE3 and CK7. The intense labeling of CK7 indicates the increased presence of luminal cells (**Figure 3A**). Likewise, positive labeling for S100 in non-luminal cells was observed. Immunoblotting for CK8/18 was focal and compatible with immunostaining for carcinoma of salivary glandular origin. Alpha-SMA is usually absent or focal in solid ACC; however, it displayed diffuse expression, evidencing some cells with myoepithelial differentiation (**Figure 3B**).

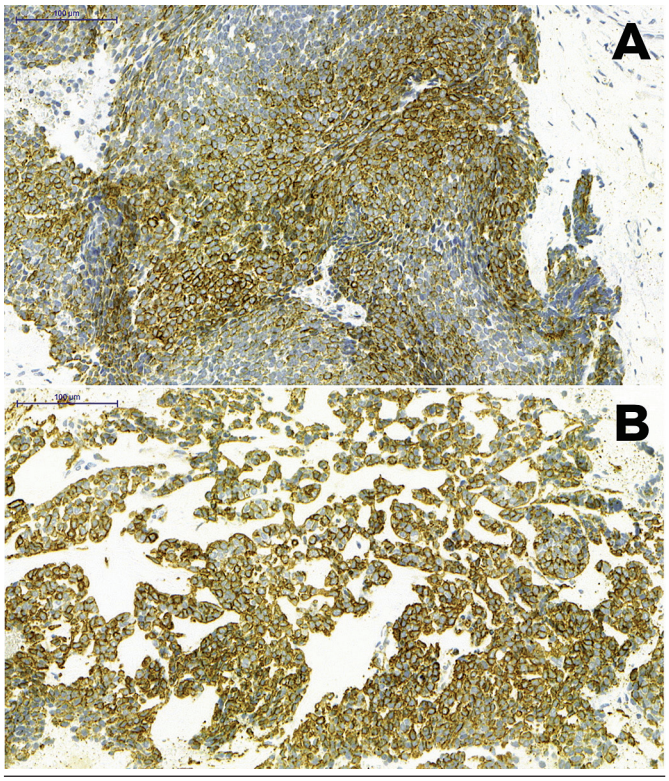

FIGURE 3 – *Immunohistochemistry*

Immunoexpression of solid ACC, in which tumor showed diffuse expression for (A) CK7 and (B) α-SMA (100 µm).

ACC: adenoid cystic carcinoma; CK: cytokeratin; α-SMA: alpha-smooth muscle actin.

CONCLUSION

Neoplasms of intraosseous salivary glands are rare, but should be considered at the time of diagnosis, since some cases may delay to correct diagnosis of the lesion and impair the clinical evolution of patients. ACC, when present in its solid variant, provides diagnostic difficulties, since this lesion exhibits similar morphology to other neoplasms. Thus, the need for recognizing ACC in its solid form, to discuss its differential diagnosis, and to emphasize the requirements to establish a correct diagnosis for clinical management and appropriate treatment is highlighted.

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