

CASO CLÍNICO

Acinic Cell Carcinoma of Parotid Gland: Report of Three Cases and Literature Review

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Abstract: Primary Acinic Cell Carcinoma (ACC) is an uncommon salivary gland (SG) tumor, making up 1% of all SG neoplasms. The parotid is the most common topography, and the ACCs are more frequently diagnosed in the fourth to sixth decades of life. In this study, along with a brief review of the literature, we discussed the clinical, histopathological, and prognostic features of these SG tumors through three reported cases. All of the tumors occurred in left parotid of non-smoking and non-drinking white patients, aging 80, 51, and 56 years. The lesions were painless and presented as slow-growing, large, firm, and movable solitary masses in the left mandible angle. The patients were initially submitted to a clinical, radiographic and computed tomography exam, followed by fine-needle aspiration and an excisional biopsy to confirm the diagnosis. All of the patients were treated with surgery followed by radiotherapy. Two of the patients had a local recurrence, one of which had cervical lymph node involvement, but both are still alive. The other patient did not have a local recurrence or lymph node involvement, but developed distant pulmonary metastases and died. The follow-up times were 18, 102 e 22 (with death) months. Upon histopathological analysis, ACC typically shows a solid pattern of growth, with cells exhibiting serous acinar cell differentiation and cytoplasmic basophilic granules. Complete surgical resection is the usual therapeutic choice. The literature describes ACC as a tumor with low malignant potential, but several recurrences and metastasis have been reported, as verified in the present study.

Resumo: O Carcinoma de Células Acinares (CCA) é um tumor incomum das glândulas salivares (GS), perfazendo 1% de todas as neoplasias de GS. A parótida é a localização mais comum, e os CCAs são mais frequentemente diagnosticados entre a quarta e sexta décadas. No presente estudo, junto com uma breve revisão da literatura, foram discutidas as características clínicas, histopatológicas e prognósticas destes tumores através do relato de três casos. Todos os tumores ocorreram na glândula parótida esquerda de pacientes leucodermas, não fumadores e sem hábitos de bebida, com idades de 80, 51 e 56 anos. As lesões eram assintomáticas e apresentaram-se como uma grande massa única de crescimento lento, endurecida e móvel, no ângulo mandibular esquerdo. Os pacientes foram inicialmente submetidos aos exames clínico, radiográfico e tomográfico, seguidos de aspiração por agulha fina e biópsia excisional para confirmação do diagnóstico. Todos os pacientes foram tratados com cirurgia seguida de radioterapia. Dois pacientes tiveram recidivas, um deles com envolvimento de linfonodos cervicais, porém ambos ainda estão vivos. O outro paciente não apresentou recidiva ou envolvimento linfonodal, mas desenvolveu metástases pulmonares e foi a óbito. Os tempos de acompanhamento foram de 18, 102 e 22 (com óbito) meses. Ao exame histopatológico, os CCAs demonstraram um típico padrão de crescimento sólido, com células exibindo diferenciação acinar serosa e grânulos basofílicos no citoplasma. A ressecção cirúrgica completa é a opção terapêutica usual. A literatura descreve o CCA como um tumor de baixo potencial de malignidade, porém, diversas recorrências e metástases tem sido relatadas, como verificado no presente estudo.

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INTRODUCTION

Salivary gland (SG) tumors represent 3% of all neoplasms of the head and neck. Primary acinic cell carcinoma (ACC) of the SG is a clinically low-grade malignancy that comprises 1% of all SG neoplasms, 5 to 11% of malignant SG tumors, and approximately 12.5% of parotid gland carcinomas^[1-3].

In SG topography, up to 81 to 98% of ACC cases occur in the parotid gland. ACC rarely originates in the submandibular gland and only a few cases were reported in the minor SG of the oral cavity^[4,5]. ACC typically presents as slow growing masses in middle-aged patients (5th and 6th decades of life). It is slightly more common in women than men^[2,3,6,7].

Due to its indolent behavior, ACC was thought to be a benign neoplasm until 1953, when it was finally considered to be malignant^[8,9]. In 1972, the World Health Organization (WHO) proposed the categorization of the acinic cell neoplasms in the WHO's International Classification of Diseases for Oncology (ICD-O) as "acinic cell tumors", separate from undoubtedly benign or malignant neoplasms. Currently, the more recent ICD-O (ICD-10) confirms these neoplasms as true adenocarcinomas^[10].

Considering that ACC is an uncommon malignant neoplasm, there are still limited data concerning its clinical, histopathological, and prognostic features. Along with a brief review of the literature, this study aims to broaden our understanding of primary ACCs of the parotid glands through the description of three cases.

CASE REPORT

Patient 1

An 80-year-old non-smoking and non-drinking white female arrived at the General Hospital of Ribeirão Preto School of Medicine (GHRPSM) complaining of a painless swelling at the left mandible angle, in the parotid gland topography. The initial swelling had been observed six months earlier, but grew quite quickly in the past three weeks. On clinical examination, the tumoral lesion presented as a large, firm, and freely movable mass in the left mandible angle, which was 3 cm in diameter. No pain or facial palsy was associated. The patient was initially submitted to a clinical, radiographic, and computed tomography (CT) exam (Figure 1), and a fine-needle aspiration biopsy (FNAB) was performed with inconclusive cytological findings. As the lesion was localized in the superficial parotid lobe, it was excised by a

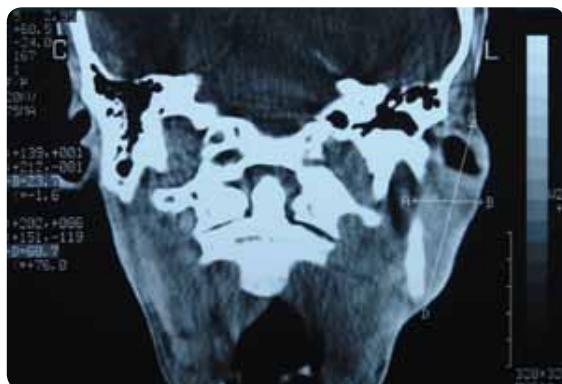


Figure 1 - Preoperative anteroposterior tomographic exam demonstrating a large mass in the left face.

superficial parotidectomy that spared the facial nerve, followed by postoperative radiotherapy. The histopathological exam confirmed the diagnosis of ACC. The slides stained by hematoxylin and eosin showed a solid-cystic neoplasm with serous acinar differentiation intermingled with a lymphoid infiltrate, composed by some enlarged rounded cells with hyperchromatic and eccentric nuclei and a basophilic granular cytoplasm (Figure 2). In addition, some scattered clear, vacuolated, and intercalated duct cells also were present. The cytoplasmic granules were PAS positive, and diastase resistant. There was a local recurrence 10 months after the initial diagnosis, but there was no local or distant metastasis. The patient is still alive 18 months after the diagnosis.

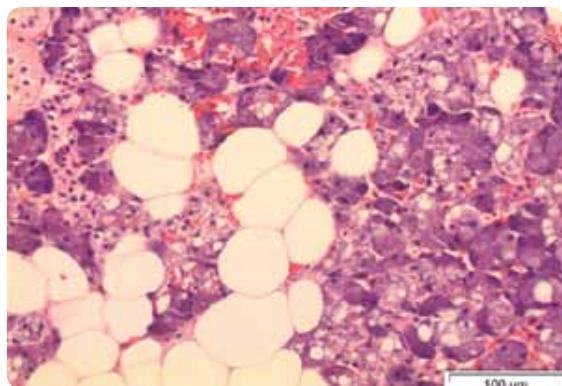


Figure 2 - Microscopic features of the tumor. Tumor showing serous acinar differentiation characterized by small glands composed of polygonal cells with round and eccentric nuclei, and a basophilic granular cytoplasm (hematoxylin-eosin, x200).

Patient 2

A 51-year-old non-smoking and non-drinking white male arrived at GHRPSM with a three month history of a slow growing painless lump on the left side of his face. On palpation, a firm, painless, irregular, and freely movable nodule, that was 15 cm in diameter, was detected in the parotid,

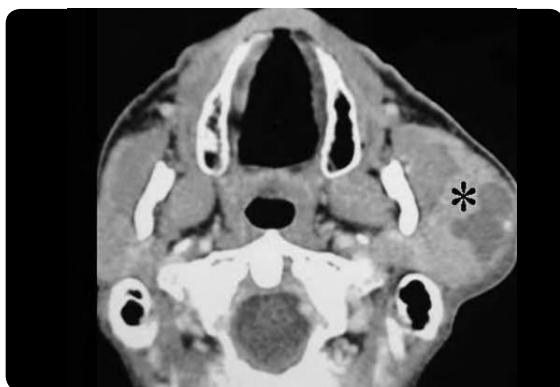


Figure 3 - Preoperative axial computed tomography image showing a well-circumscribed mass in left parotid gland (asterisk).

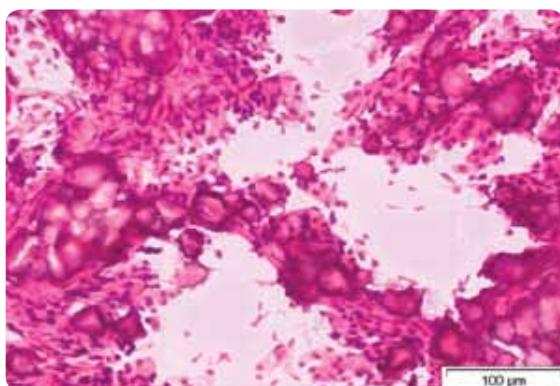


Figure 4 - Fine-needle aspiration biopsy smears disclosing numerous psammoma bodies (Papanicolaou, x200).

beside a cervical nodule that was 1 cm in diameter. He had a previous history of a resected ACC in the left parotid gland. After a clinical exam, the patient underwent radiographic and CT exams (Figure 3), and then a FNAB was performed to confirm the hypothesis of ACC. The cytological analysis showed highly cellular smears composed by grouped structures or isolated cells. The cells showed a round or oval nuclei, few nucleoli, and a granular basophilic cytoplasm. There were abundant psammoma bodies (PBs) with concentric lamination (Figure 4). Total parotidectomy with left cervical emptying and coadjuvant radiotherapy was performed. The histopathological exam disclosed a tumor with cells surrounded by a prominent desmoplastic stromal reaction. It also confirmed the lymph nodal involvement. The patient had a local recurrence 58 months after the initial histopathological diagnosis, but he had no additional lymph node involvement or distant metastasis in an overall follow-up of 102 months. He is still alive.

Patient 3

A 56-year-old non-smoking and non-drinking white woman arrived at GHRPSM complaining of a progressive



Figure 5 - Radiographic exam showing pulmonary metastases presented as irregular nodules with diffuse margins and scattered distribution. They are predominantly localized in the lower region of the lungs.

swelling in the left preauricular region. She had first noted this swelling three months earlier. Clinical examination showed a firm, mobile, painless, and well-defined nodule in the left parotid topography measuring 5 cm in diameter. Clinical, radiographic, CT, and FNAB exams were preformed. All of them were indicative of malignancy. Since the lesion was localized in the deep lobe of the parotid gland, it was surgically removed through a total parotidectomy. The diagnosis of ACC was confirmed by the histopathological exam, and then the patient underwent postoperative radiotherapy. Within the first year of follow-up, no local recurrence or cervical lymph node involvement was noted, but immediately after this period, she developed distant pulmonary metastases diagnosed by a chest radiographic exam. The pulmonary metastases presented as several irregular nodules with diffuse margins localized predominantly in the lower region (Figure 5). After that, the patient died of respiratory failure, 22 months after the initial diagnosis.

DISCUSSION

ACC is considered to be the least aggressive cancer of SGs^[3,11]; however, the WHO recognizes its potential to behave in an aggressive manner^[10]. In head and neck topography, ACC is usually found in the parotid gland and appears as a slow growing tumor, with no classical clinical features distinguishing it from other SG lesions^[12].

Despite being considered a low-grade neoplasm with an indolent clinical course,¹³ secondary tumors can appear within five years of the diagnosis in 82% of the cases^[5]. The recurrence rate for these tumors ranges from 30% to 50%^[6], and when the deep lobe of the parotid gland is reached, local

recurrences are higher than in superficial tumors (72% and 18%, respectively)^[14]. Additionally, the cervical metastases rate ranges from 3.8-16%^[3,5], distant metastases have been reported between 7%-29%^[15], and the death rate due ACC varies from 1.3% to 26%^[3,5,16].

Most investigations have noticed that women are affected more frequently than men, and that ACC happens at an earlier age than other SG tumors^[4,15]. Most cases are unilateral^[15]; however, there was a single report of bilateral parotid involvement^[8].

In ACCs, clinicopathologic characteristics can be very important to predict the patients outcome, especially tumor size^[6,14,16,17], compromised surgical margins^[5,14,17,18], and involvement of the deep lobe of the parotid gland^[5,16]. Age, histological grade, and the presence of metastatic disease have also been considered significant prognostic factors^[3]. As a consensus, regional and distant metastases are given a poor prognosis, while the lungs and bones are the most preferable sites for ACC dissemination^[13,14,15].

Some authors initially believed that ACC could originate from the acini^[19]. However, it has been suggested that the multiple morphological growth patterns of ACC are possibly due its origin from stem or reserve epithelial cells found at the intercalated ducts and terminal tubules, which could be precursor cells for both acini and duct cells of the mature SG tissue^[20]. The main histopathological feature for ACC diagnosis is the identification of neoplastic acinar cells forming solid or microcystic areas, which are the most common growth patterns^[2,21]. Sometimes it is possible to discern some other neoplastic acinar cells, such as oncocytic and vacuolated cells^[12].

The term "acinic" denotes similarity of the tumor cells with acinar gland cells. In a microscopic point of view, ACC can show acinar differentiation and is composed of neoplastic acini and duct-like cells, often ordered in a solid pattern, and generally with a dense lymphoid stroma^[22,23]. The tumor cells are polygonal and have a fine granular cytoplasm with a basophilic or amphophilic aspect, and these cytoplasmic granules are characteristically PAS positive and diastase-resistant^[7]. Moreover, primary ACC can demonstrate distinct histopathological patterns and frequently exhibit combinations of them: solid, follicular, microcystic, and papillary-cystic^[5].

There is no specific immunohistochemical profile specifically associated with these tumors. In that way, immunohistochemistry is not very useful to distinguish ACCs from other SG tumors. This technique normally is not required for diagnosis^[2,7,15]. Some studies postulated that electron microscopy could be helpful in certain cases^[4]. The ultrastructural characteristic of cells with acinar differentiation, the

existence of a rough endoplasmic reticulum, and round to ovoid electron-dense granules in cytoplasm analogous to the zymogen granules of normal serous cells can be considered as diagnostic evidence^[4,24].

The cytologic interpretation of an FNAB exam can be a difficult task due to the heterogeneity of the SG tumors, and, among the SG, one of the highest false negative rates occurs in ACCs^[25]. Because of the heterogeneous cytological presentation of ACC, the smears were conclusive in only one of our three cases (Patient 2). However, the FNAB exam was useful to distinguish between a benign or malignant neoplasm in the other case (Patient 3). In all cases, it was the histopathological exam that provided the confirmation of the ACC diagnosis.

The abundant PBs found in the ACC smears of Patient 2 have rarely been described. The PBs are concentric lamellated calcified structures presented as basophilic concretions. They have been associated with dystrophic calcification of dead or dying tissue, but their physiopathology remains poorly understood^[26]. Since the first description by Bottles and Löwhagen in 1985^[27], only a few cases of PBs in FNAB specimens of ACCs have been described in the English literature^[28,29,30]. Notwithstanding, PBs were reported in several others SG neoplasms, such as adenoid cystic carcinoma^[31], oncocytic adenocarcinoma^[32], salivary duct carcinoma^[33], and some other benign and malignant mixed tumors^[34,35]. Recently, Das^[26] suggested that PBs can represent an active biologic process associated with retardation of the tumor growth mechanism, also capable of serving as a barrier against the neoplasm dissemination.

The association between tumor grade and biologic behavior remains controversial. ACC can be classified as both low- or high-grade tumors. Low-grade ACCs are generally interpreted as corresponding to the architecture of normal salivary acini. They are encapsulated and measure less than 3 cm. On the other hand, high-grade ACC resembles the early phases of acini embryonic development and are poorly differentiated^[20]. Several studies indicate that high histopathological grade is a key feature for the identification of a subset of ACCs with aggressive behavior^[2,3,6,36]. However, there are reports contradicting this association^[4,15,37,38]. In addition to low- or high-grade tumors, a few cases of dedifferentiated ACCs have been reported^[18,39,40,41]. These dedifferentiated tumors typically present as a recurrent disease^[41]. Albeit a single histopathological pattern usually prevails, mixed grades may occur within a single tumor^[18].

The pulmonary metastases of Patient 3, detected one year after initial diagnosis of ACC, could be concomitant with the primary tumor. However, scarce cases are docu-

mented in the literature of primary ACCs concurrently with lung metastases^[13,42-44] Hynes *et al*^[44] reported a rare case of a primary ACC in the submandibular gland simultaneous to pleural involvement.

Distant metastases in ACCs tend to occur five to 30 years after primary diagnosis^[13,15]. However, lower intervals have been found, as in case reported by Vidyadhara *et al*^[5] where the metastases in both lungs and thoracic vertebra were found after only four months of an incomplete primary surgical tumor resection. Cohn *et al*^[45] report a case of an ACC with a distant metastasis to the bone, lung, and skin after only two years from the initial diagnosis. Moreover, Tavora *et al*^[13] reported an unusual case of lung metastases one year before to the diagnosis of an occult primary ACC in the parotid gland. Although recurrences and metastases tend to occur after prolonged latency intervals^[15], two of our patients had a recurrence and metastasis in a short period of time (Patient 1 and Patient 3, respectively), and the other already presented with lymph nodal involvement in the first clinical referral. These data reinforce that some cases of ACC are potentially aggressive neoplasms.

Management of ACC is supported on some reports of small numbers of cases accumulated over several decades. According to Oliveira *et al*^[38], the high recurrence rate seems to be predominantly determined by the surgical approach. Excision of cervical lymph nodes is indicated for those patients who have lymphadenopathy^[46]. Postoperative radiotherapy has been recommended in patients with advanced clinical

stage, high-grade tumors, or positive surgical margins^[20], and for some other factors such as verified in Patient 2 (recurrent tumor and deep lobe involvement)^[15,17]. Since ACC carries a significant morbidity with high recurrence and metastasis rates, some studies warn that this tumor, in contrast to most other SG malignant tumors, may not respond to postoperative radiotherapy^[3,6,47].

The 5-year overall survival (OS) has been estimated to be about 83% in ACCs^[3]. However, due to differences in populations, staging, therapies, and follow-up extension, this estimate can vary widely. Federspil *et al*^[36] found a 5-year OS of 73% and Laskawi *et al*^[6] found 64%. According to Miki *et al*^[48], due to the slow growth pattern of ACC, survival analyses should be interpreted with a long follow-up period (10 to 20 years) to identify the true influence of ACC on extended survival.

In summary, we report three cases of ACC primary of the parotid gland. In one of them numerous psammoma bodies were found in cytological smears, which is a very rare finding. In another case, rapid pulmonary commitment from the primary ACC was verified. The literature describes ACC as a tumor with low malignant potential, but several recurrences and metastasis have been reported, as verified in the present study. Our reports suggest that ACCs can be aggressive neoplasms.

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