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Aggressive ameloblastic fibrosarcoma in maxilla: case report and new perspectives based on the current literature

Fibrossarcoma ameloblástico agressivo em maxila: relato de caso e novas perspectivas com base na literatura atual

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ABSTRACT

Ameloblastic fibrosarcoma (AFS) is a rare malignant tumor characterized by benign epithelial component within a malignant fibrous stroma. It occurs as a *de novo* lesion or from a previous ameloblastic fibroma. The aim of this paper is to report an aggressive and recurrent case of AFS in the maxilla of a 38-year-old patient. Histopathological diagnosis can be challenging, especially when it is based on incisional biopsy specimens. Hence, this report highlights not only the importance of the histological features for diagnosis but also the clinical behavior of AFS based on current literature evidence.

Key words: neoplasms; maxilla; diagnosis.

INTRODUCTION

Ameloblastic fibrosarcoma (AFS) is an extremely rare malignant odontogenic neoplasm. To date, about 85 cases have been published in the English literature. AFS is defined by the World Health Organization (WHO) as a neoplasm structurally similar to ameloblastic fibroma (AF), but with its ectomesenchymal component showing sarcomatous appearance[1, 2]. It can arise from a pre-existing AF or as a *de novo* lesion[3]. In addition, it mainly affects males during the third decade of life. The mandible is the most common region and its main clinical features include swelling and pain[1]. In this report, we describe a case of an aggressive AFS in the maxilla. New data on this uncommon neoplasm is also provided in order to guide future studies.

CASE REPORT

A 38-year-old male patient was referred to the Head and Neck Surgery Service with a large firm swelling on the left side of maxilla. The patient mentioned that the swelling had shown fast growth over a period of one month. Pain and tenderness were not reported. Extra-oral examination showed facial asymmetry characterized by enlargement of the malar and lateral region of the nose. No palpable lymph nodes were present. Initial intra-oral examination showed an extensive lesion with tumoral aspect in the region of teeth 23 to 27. Preoperative hematological exams, radiographs, and computed tomography (CT) were requested, and an incisional biopsy suggested the diagnosis of "atypical ameloblastoma". Two weeks after biopsy, the lesion had doubled in size. It showed an exophytic growth pattern and ulcerated appearance, with necrosis and formation of pseudomembrane (**Figures 1** and **2**). The patient had difficulties in eating, reduced mouth opening and altered phonation. Marked weight loss in the latest few days was also reported. Based on the clinical conditions, a medial maxillectomy with safety margins was performed. The histopathological analysis revealed benign epithelial islands similar to those of follicular ameloblastoma. The islands were composed of peripheral columnar or cuboidal cells arranged in a palisading pattern. Polyhedral cells resembling the stellate reticulum were found in the center of the islands. The epithelial components were widely separated by a malignant ectomesenchymal

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stroma. This consisted of hypercellular connective tissue with plump polygonal to fusiform stromal cells, which showed mild to moderate cytological atypia. Mitotic cells were dispersed throughout the lesion. A final diagnosis of AFS was performed (**Figures 3-5**). Evaluation after 15 days of surgery showed no intercurrences. Four months after the treatment, the patient showed good extra-oral healing (**Figure 6**). However, a new lesion indicating recurrence was detected at the treated area (**Figure 7**). New surgical removal associated to adjuvant radiotherapy was planned. Unfortunately, the patient refused to undergo further interventions and died four months later.

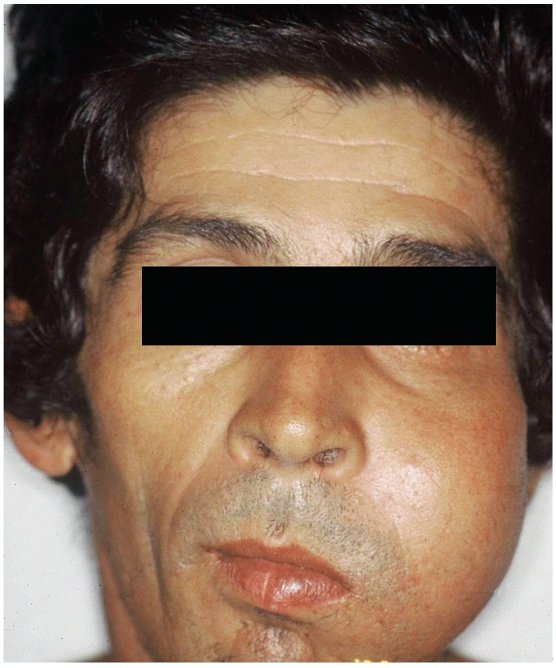

FIGURE 1 – *Extraoral asymmetry involving the left side of maxilla*

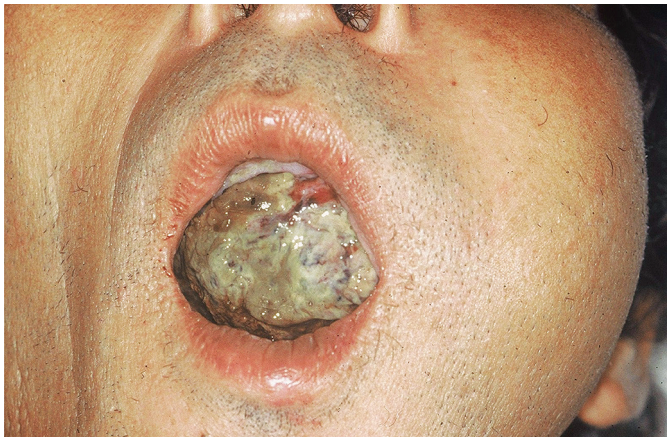

FIGURE 2 – *Intraoral view of the primary lesion showing an exophytic and ulcerated appearance*

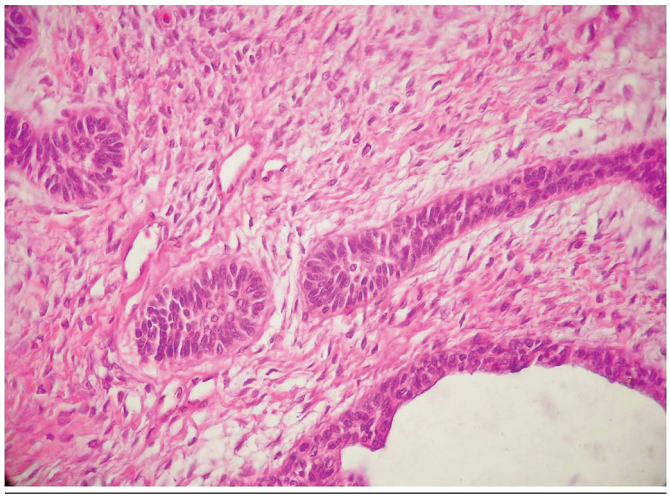

FIGURE 3 – *Mixed epithelial and mesenchymal components (HE, 200×)*

HE: hematoxylin and eosin.

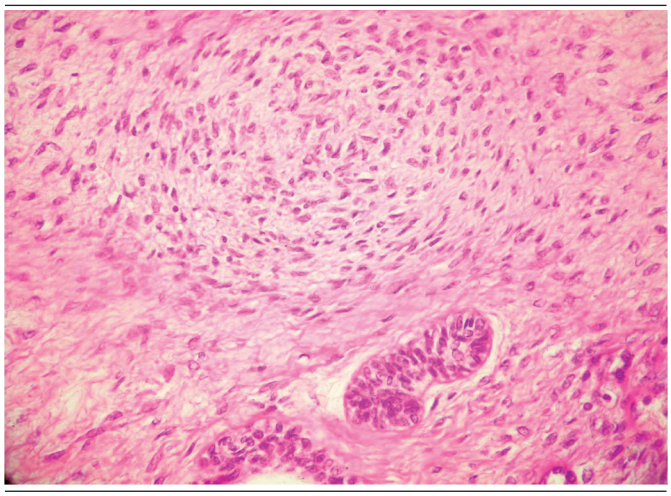

FIGURE 4 – *High cellularity with mild cellular pleomorphism (HE, 200×)*

HE: hematoxylin and eosin.

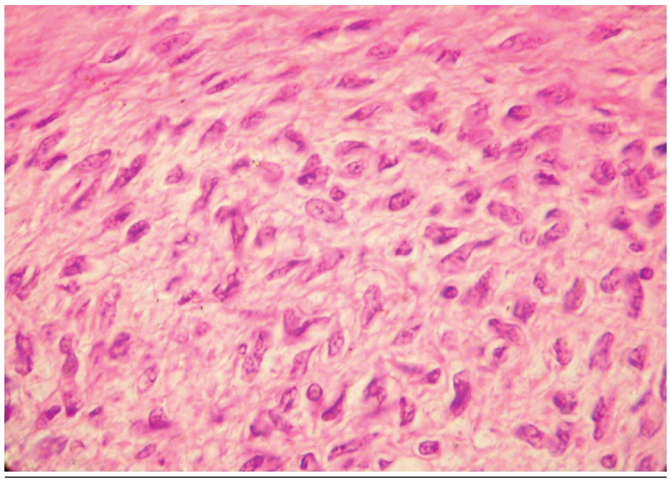

FIGURE 5 – *Mild pleomorphism and presence of numerous malignant cells (HE, 400×)*

HE: hematoxylin and eosin.

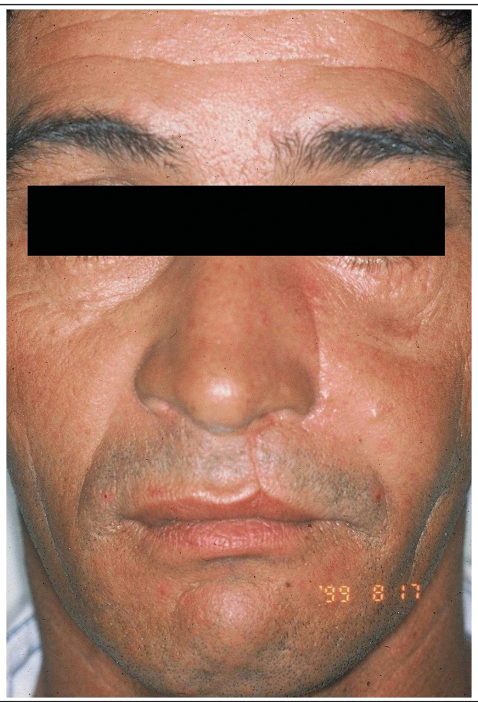

FIGURE 6 – *Extraoral view during follow-up*

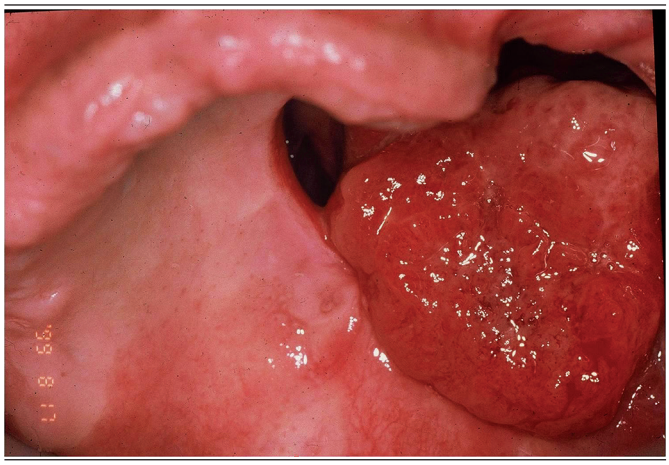

FIGURE 7 – *Recurrence after treatment*

DISCUSSION

Malignant odontogenic tumors (MOTs) correspond to just a small percentage of the odontogenic neoplasms, with an incidence ranging from 0% to 6.1%. Among MOTs, odontogenic sarcomas are much less frequent than carcinomas[3]. AFS is considered to be the malignant counterpart of AF, consisting of benign odontogenic epithelium with malignant mesenchyme[4].

In the present case, the tumor affected the posterior region of the maxilla of a 38-year-old male patient. According to a literature review, AFS is really more common in males[4-7]. On the other hand, only 84 cases of AFS have been reported in the literature since its first description, with 63 involving the mandible and only 21 the maxilla, as search in the literature up to June 2016 demonstrated.

The history of the present case suggests that the tumor was probably a *de novo* lesion, since the patient had no history of previous surgery or diseases involving the mandibular region. Carlos-Bregni *et al*. (2003)[1] observed that approximately one-third of all AFS derived from a previous AF. There is heterogeneity of signs and symptoms in AFS, with pain and swelling being the most common features[3]. The male-to-female ratio is 1.6:1[1]. The size of the tumor also varies and is related to the time spent for a final diagnosis. We observed that the tumor had grown rapidly from the initial clinical exam until the time of surgery. This fast growth resulted in serious functional consequences for the patient and weight loss.

The initial diagnosis suggestive of ameloblastoma in our case was made on the basis of an incisional biopsy. Establishment of a correct diagnosis of AFS may be challenging because well-differentiated malignant areas may resemble other benign odontogenic tumors, such as ameloblastomas and AF[5]. Thus, careful histopathological examination is critical. The degree of malignancy is determined based on some parameters, such as cellularity, palisade pattern, number of mitosis and atypia[5]. In our case, some areas showed hypercellularity, pleomorphism and mild mitosis activity in the mesenchymal component, findings that are indicative of AFS. Unfortunately, there are no helpful immunohistochemical (IHC) markers that could improve final diagnosis. Therefore, the diagnosis of AFS using hematoxylin and eosin staining remains the gold pattern. An IHC panel composed of epithelium markers may be useful in identifying epithelial nests in cases whose epithelial component is rather bland, and thus, excluding the pure sarcomas. In our case, considerable epithelium nests were detected. Hence, IHC evaluation was not necessary to support the diagnosis, because the histopathological aspects described in our case are typical of AFS[1,6].

Recurrence is common in AFS, with 37% of the reported cases having at least one episode[1]. In contrast, metastasis is not a major characteristic[4]. Fatal cases have usually been associated with uncontrolled local infiltration and numerous recurrences[5,6]. Among the 84 cases published until now (including the present), 15 patients (20%) died as a direct result of the AFS, and all had recurrent tumor. Data related to fatal cases are shown in the **Table**.

Some studies have found predictors of survival rate in oral squamous cell carcinoma, such as vascular endothelial growth factor A (VEGF-A) genetic polymorphisms, micro ribonucleic

TABLE – Features of the fatal AFS cases in the current English literature

Author	Year of publication	Age (years)	Sex		Localization		Recurrence	Metastasis	AF	Follow-up (months)
Pindborg[8]	1960	17	M			Maxilla	y	n	n	26
Cina *et al*.[9]	1962	32		F	Mandible		y	n	y	30
Muroya and Shigematsu[10]	1962	43	M		Mandible		y	n	NA	33
Peychl and Sazana[11]	1971	17		F		Maxilla	y	n	n	54
Mori *et al*.[12]	1972	3.5		F	Mandible		y	n	n	60
	1972	40		F	Mandible		y	n	y	228
Hatzifotiadis and Economou[13]	1973	15	M			Maxilla	y	n	n	24
	1983	27	M		Mandible		y	y	y	120
Takeda *et al*.[14]	1984	19	M			Maxilla	y	n	y	114
	1984	18		F	Mandible		y	n	n	12
Park *et al*.[15]	1995	17	M		Mandible		y	n	n	3
Tajima *et al*.[16]	1997	14	M			Maxilla	y	n	n	6
Yamagushi *et al*.[17]	2004	31	M		Mandible		y	n	NA	NA
Kousar *et al*.[18]	2009	20		F	Mandible		y	y	y	15
Amorim *et al*.[this study]	2016	38	M			Maxilla	y	n	n	8
		Mean 23.4	60%	40%	60%	40%	100%	13.3%	30.5%	Mean 52

AFS: ameloblastic fibrosarcoma; AF: ameloblastic fibroma; M: male; F: female; NA: not available.

acid (RNA) 99a and others[7, 19]. These new markers should also be studied in AFS in order verify if it is possible to detect the most aggressive cases. A case report by Williams *et al*. (2007)[4] showed alterations of the p53 and c-KIT genes restricted to the sarcomatous component. Diffuse nuclear reactivity for p53 and Ki-67 in the atypical mesenchymal cells and diffuse cytoplasmic reactivity for Bcl-2 protein, alpha-smooth muscle actin (α-SMA) and vimentin were detected in another case of AFS[5].

In ameloblastomas, a significant relation between stromal CD10 and Ki-67 expression in cases of recurrent cases compared to non-recurrent has been described[20]. Masloub *et al*. (2011)[21] concluded that higher expression of CD10 and osteopontin might be a useful tool to identify areas with locally invasive behavior and high risk of recurrence in ameloblastomas. Thus, such markers should be considered in the study of AFS and should be also analyzed in AF, since this lesion is a possible precursor of AFS. In our case, the surgical specimen showed features for diagnosis of AFS, and in some areas, hypercellular connective tissue with plump polygonal to fusiform stromal cells, which showed mild to moderate cytological atypia, and some mitotic cells dispersed throughout the lesion were identified. So, for diagnosis and management of the case, it was not necessary to perform immunohistochemical study.

In the case reported by Bertoni *et al*. (2016)[22], a low-level Ki-67 expression was observed in AFS. The authors also reported that c-KIT gene (CD117) expression is associated with sarcomatous components of AFS, but not those of AF. Loss of heterozygosis (LOH) in the short arms of chromosomes 3 and 9, at the 3p24.3, 9p22-p21, and 9p22 loci, was also evident in AFS. The allelic loss fraction was reported to be 74.6 compared with that of AF, and these findings suggest that genetic changes allow malignant transformation of AF.

Pourdanesb *et al*. (2015)[23] reported that clinicopathologic diagnosis at the first presentation is very important to distinguish AF from AFS, what can have a tremendous impact on prognosis and management. These authors reported the case of a 34-year-old woman with a recurrent, rapidly growing, debilitating lesion. The lesion had been previously misdiagnosed as ameloblastoma.

In conclusion, the report of new cases of AFS is crucial to add further information, in relation to treatment, diagnosis and management. Based on current knowledge, it is possible to suggest the use of p53, Ki-67, Bcl-2, α-SMA marker, VEGF-A, genetic polymorphisms and microRNA 99a in order to evaluate the clinical behavior of AFS.

RESUMO

O fibrossarcoma ameloblástico (FSA) é um tumor maligno raro caracterizado pela presença de componente epitelial benigno em um tecido conjuntivo fibroso maligno. Pode desenvolver-se a partir de um fibroma ameloblástico ou como uma lesão nova. O objetivo deste estudo é relatar um caso de um FSA agressivo e recorrente em maxila em um paciente de 38 anos. O diagnóstico histopatológico desse tumor pode ser difícil, principalmente a partir de biópsias incisionais. Este trabalho também discute fatores em relação aos aspectos histopatológicos para o seu diagnóstico, assim como seu comportamento clínico, com base em revisão atual da literatura.

Unitermos: *neoplasias; maxila; diagnóstico diferencial.*

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