



## Case Report

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# Ameloblastoma in the Oral Cavity: Two Cases Study Long Evolution

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## Abstract

This work presents two variants of ameloblastoma: Ameloblastic carcinoma and malignant ameloblastoma. The first one occurred in a 71-year-old man with a history of odontogenic cyst resection at 61 years of age. The second presented in a 20-year-old man. Both cases showed 3 recurrences before resorting to hemi-mandibulotomy. The ameloblastic carcinoma started slowly in the patient with a 17-year evolution ending with a poor prognosis for life. The malignant ameloblastoma after hemi-mandibulotomy did not show tumor activity and presented a better prognosis for life. The ameloblastic carcinoma after surgery, chemotherapy and radiotherapy showed partial response with local and nodal recurrence. The evolution of both cases was contrary to expectations, with the ameloblastic carcinoma being more malignant and aggressive. Despite recent advances, the life expectancy of these patients is poor, so it is important to understand the origin and factors that initiate these tumor cells to improve treatment.

## Keywords

Ameloblastic carcinoma, Oral cavity, Surgery face, Ameloblastoma malignant

## Introduction

Robinson described ameloblastic carcinoma for the first time [1], while in 1983 Shafer added the term odontogenic tumor with malignant histological transformation [2]. Ameloblastic carcinoma and malignant ameloblastoma are two malignant variants of ameloblastoma. They constitute only < 1% of odontogenic tumors. The etiology of ameloblastic carcinoma corresponds to a locally aggressive neoplasia of the odontogenic epithelium, diverse histology depending on the stage of odontogenesis, with ameloblast cell types and stellate reticulum [3], occurring in the dental lamina, the dental follicle of the teeth unerupted or the remains of molasses, gingival surface epithelium or in the line of dental cysts. The tumor was identified on biopsy as an aggressive, unicystic, extraosseous/peripheral odontogenic tumor (it may or may not present metastasis). The developed enamel organ shows three cell types, ameloblasts, stellate reticulum and stratum intermedium, the first being in ameloblastoma [3,4].

Initially, ameloblastoma considered in the subtypes: Solid/multicystic, extraosseous/peripheral, desmoplastic and unicystic [5], a complex classification lacking behavioural and biological importance that was modified and only the solid/multicystic type was identified as ameloblastoma. Variants of ameloblastoma have been demonstrated due to follicular, plexiform, and acanthomatous cells that are histologically distinctive and with diagnostic entity. While peripheral

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ameloblastoma and unicystic ameloblastoma behave differently [4] and remain specific subtypes.

## Epidemiology

The global incidence of ameloblastic carcinoma is 1% of odontogenic tumors [6,7], the registration in 2020 of new cases were: Lip and oral cavity cancer 377,713, distributed in Asia 65.8%, Europe 17.3%, North America 27.3%, Latin America and the Caribbean 4.7%, Africa 3.8%; and in Mexico 1500 new cases [8]. Metastases in ameloblastic carcinoma are rare (15%), and when they occur, they are in regional lymph nodes or the lung [9].

## Pathophysiology

Ameloblastic carcinoma defined as a malignant extraosseous due to cellular transformation that reaches the dental lamina and the basal cells of the oral epithelium. Its growth reaches the soft tissue of the posterior mandibular line. Clinically, it is a gingival peduncle mass with an irregular papillomatous surface (1 and 2 cm). Both the centre and the periphery shown high-growth cells, areas of necrosis, neural and vascular invasion that reaches the keratin of the tissues [10]. The pathogenesis of ameloblastic carcinoma is controversial due to the multiple genes involved that contribute to its malignancy [11], with high methylation in p16 and high mitochondrial apoptosis as an inducing factor in cell transformation [9].

## Histopathology

The histopathological analysis indicates that in 18 cases, 75% had a follicular pattern and one with a cribriform pattern. Another report [3] indicates 25% of cases with plexiform cells. Twenty-five cases showed peripheral palisade cells and high mitosis; the fifteen cases not specified. Likewise, seven cases (46.6%) showed reverse polarity. 87% of ameloblastic carcinomas had made up of stellate reticulum-type cells with necrosis in 86%. Acanthomatous metaplasia identified in 61.5%, and only three cases presented clear cells, spindle cells in five cases and one showed ghost cells. This indicates a range of cells with a high mitotic index transforming into malignant cells [3].

## Clinical Presentation

Even with a low frequency of ameloblastic carcinoma, its presentation by sex is 4:1 men:woman, with an average age of 56 years in a wide range between 15 to 84 years, with mandibular location (92%). Clinically the symptoms are swollen jaw, pain, perforation of the cortex, limitation in mouth opening, paresthesia, extended mandibular resection, recurrence of 50%, local invasion of 15%, and incidence of 2%. The 100% cure rate occurs in patients with primary tumor treated with chemotherapy plus radiotherapy [12]. The symptoms that occur in the jaw are due to an obstruction that causes discharge or nasal congestion in 47% of cases, the lump on the jaw (35%), leads to dental pain (12%), loss of teeth (6%), gingival ulcer (6%), orbital involvement (47%), decreased vision (24%), hypoesthesia in the ophthalmic and maxillary branches of the trigeminal nerve (18%), diplopia (18%), limitation in ocular mobility (6%) [13].

## Diagnosis

Initial cases and a prompt diagnosis show in the incisional biopsy cords of basal epithelial cells with limited reverse polarity, little connective tissue, minimal presence of stellate reticulum, few mitoses and absence of necrosis. These findings identified as basaloid ameloblastoma, however, the atypia of the neoplastic epithelial cells, the increase in the nucleus:cytoplasm ratio and the high percentage of the cell proliferation marker by Ki-67 identifies it as ameloblastic carcinoma, recognizing it as nonspecific and variable [14].

The use of immunohistochemical markers to differentiate ameloblastic carcinoma from conventional ameloblast and non-odontogenic carcinomas are Ki-67, p53 and cytokeratin CK-14, 18 and 19, Ki-67 positivity > 18% in a range between 12% and 54% identifies ameloblastic carcinoma contrasted with ameloblastoma with positivity of only 2%. The AE1/AE3 cytokeratin present homogeneous labelling with the neoplastic epithelium and complemented by cytokeratin CK14 and nineteen, while the C-SMA marker in ameloblastic carcinoma exists a notable variation in the presence of neoplastic cells in the stellate reticulum-type zone [14,15].

Radiographically, the lesion defined as a perforation of the cortical bone with extension to the soft tissues. The tumor mass is expansive, hard, and surrounded by a normal-looking mucosa.

## Treatment

Surgery with wide margins (2 to 3 cm) is the treatment of choice, with dissection of regional lymph nodes and close postoperative follow-up. Depending on whether lymph nodes are positive or not, radiotherapy and chemotherapy recommended. However, there is no established proposal in the literature due to the absence of prospective randomized studies [10]. Experts argue that these therapies are not applicable in ameloblastomas; however, other works suggest adjuvant radiotherapy in ameloblastic carcinoma [16] with satisfactory results.

Ameloblastic carcinoma is a tumor of rare presentation; this paper reviewed the cases of oral cancer in a period from 2016 to 2023, finding only two variants of ameloblastic carcinoma and described as cases.

## Case One

71-year-old male, positive for smoking for 10 years, tonsillectomy at the age of eighteen, with chronic degenerative diseases. The condition tumor began at the age of sixty-one as an odontogenic tumor in the left jaw. Management of the odontogenic tumor given after 10 years it showed accelerated growth. Orthopantomography showed a mandibular mass in the left anterior thirds, with maximum diameters of 85 × 52 × 53 mm. The incisional biopsy performed, and the pathology report indicated an ameloblastic odontogenic carcinoma, without metastatic nodes, without invasion to adjacent tissues, free surgical edges, but second primary in lane of the cheek. The patient was assessed for RT and 70 Greys was applied in 35 fractions for 7 weeks. The patient at the end of RT showed dry epithelitis,odynophagia and grade I

mucositis, and increased volume in the lower left hemi face due to tumor activity, the result of a partial response.

Physical examination of the male in the oncology service revealed an apparent age consistent with that referred to and the rest of the examination was in normal condition.

**Surgical Management and Follow-up**

03/16/2017. Left hemi-mandibulectomy (70%) with reconstruction, with free graft, microvascularized fibula, and mandibular titanium plate

06/07/2017. Exploration and closure with flaps, viable graft

09/28/2017. Graft removal

03/12/2018. Removal of osteosynthesis material

01/16/2019. At the site where the left mandibular angle was located, a solid hemispherical nodule with a diameter of

18 × 18 × 25- mm observed, suggestive of tumor activity

01/08/2019. CT scan showed a 45 × 25 mm tumor in the parapharyngeal space, with external chemotherapy management.

09/12/2019. Radicalization of cheek injury (negative)

03/17/2020. Chemotherapy of 7 cycles Docetaxel/ Carboplatin. Partial answer

08/16/2020. CT showed tumor activity in the infratemporal fossa and left masticatory space with 80% calcification in response to chemotherapy. Involvement of the medial and lateral pterygoid muscles, as well as the masseter, extended caudally to the ipsilateral submandibular space, displacing adjacent structures, including the parotid and hypopharynx. Respecting mucosal pharyngeal and parapharyngeal spaces

10.11.2020. Radiotherapy with conventional fractionation 70 Greys/35 Fractions/7 weeks. It showed dry Glepithelitis, GI mucositis, increased volume in the lower left hemi face, associated with tumor activity due to ameloblastoma. Every week he reviewed in his hygiene stockings, use of oral pilocarpine, chlorhexidine and polyvinylpilporridone mouthwashes for grade 3 mucositis

05/26/2021. PET-CT negative for right cervical lymphadenopathy at levels IB, IIa, IIB up to 9 mm short axis SUVmax 2.7. Expansive left maxillary condyle lesion, without evidence of metabolic activity, lymph nodes and esophagus with an inflammatory appearance. PET-CT Negative to activity

06/10/2021. Resection of Eccrine Angiomatous Hamartoma (EAH) soft tissues

07/04/2022. PET-CT showed right cervical hyper metabolic nodes at level I and IIA of up to 7 mm short axis SUVmax 3.5 associated with loss of the fatty hilum, apparent decrease in size.

12/22/2022 PET-CT Right cervical hypermetabolic lymph nodes observed at levels I and IIA of up to 7 mm short axis SUVmax 3.5, previous pet-CT May 2021: Right cervical lymphadenopathy of levels IB, IIA and IIB up to 9 mm axis short SUVmax 2.7.

01/27/2023. The patient had 7 years of evolution as ameloblastic carcinoma with different tumor surgeries in the jaw, follow-up reconstructions, CT, and RT treatment with partial response to treatments, and tumor activity in ganglia, with poor prognosis in the medium term for life (Table 1).

**Case Two**

It corresponded to a 20-year-old male, with tumor activity in the right mandible, and 3 recurrences and application

**Table 1:** Malignant variants of odontogenic ameloblastoma behavior and evolution.

|                                                              | Case 1                                                                           | Case 2                                                |
|--------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------|
| Location                                                     | Left mandible                                                                    | Right mandible                                        |
| Ameloblastoma type                                           | Recurrences carcinoma                                                            | Recurrences malign                                    |
| Tumor onset age (years)                                      | 61                                                                               | 20                                                    |
| Age at end of follow-up                                      | 77                                                                               | 43                                                    |
| Orthopantomography (mm)                                      | 85 × 52 × 53                                                                     | 33 × 30                                               |
| Dissected tumor size (mm)                                    | 60 × 40                                                                          | 31 × 28                                               |
| Hemimandibulectomy surgery (%)                               | 70                                                                               | 65                                                    |
| Histopathology                                               | Osteoclast-like giant cells, cortical destruction, nodular hemorrhage            | Granular tissue, dermal invasion, perineural invasion |
| Recalls and surgeries                                        | 3                                                                                | 4                                                     |
| Time of evolution since onset of tumor manifestation (years) | 17                                                                               | 23                                                    |
| Complementary treatments                                     | Chemotherapy 7 cycles (docetaxel/cisplatin)<br>Radiotherapy 70 Grey/35 Fractions | NA                                                    |
| Recurrences and Tumor Activity “AT” (months)                 | With TA 31                                                                       | Without TA                                            |
| Prognosis                                                    | Reserved for life with tumor activity                                            | Good evolution without tumor activity                 |

The third level hospital with 16 years as an institution, has only registered two cases of ameloblastic carcinoma.

**Table 2:** Comparison of tumor entities in the specific oral cavity of the jaws in a period from 2016 to 2022 in a tertiary hospital.

| Tumors entity                                                                                                                    | Age at diagnosis (years) | Age at end of treatment (years) | Men:Woman Ratio | Treatment surgical. CT; RT |
|----------------------------------------------------------------------------------------------------------------------------------|--------------------------|---------------------------------|-----------------|----------------------------|
| Ameloblastic carcinoma (n = 2)                                                                                                   | 43.5 [20-71]             | 49.0 [26-79]                    | 3:1             | 4:1:3                      |
| Squamous cell carcinoma (n = 17)                                                                                                 | 50.7 [26-83]             | 64.9 [42-83]                    | 11:5            | 12:13:13                   |
| Others: mucinous carcinoma, exadenoma, chordoma, neuroectodermal, plasma cell granuloma, neuroblastoma, and osteosarcoma (n = 9) | 39.2 [10-78]             | 41.0 [11-84]                    | 5:3             | 7:4:2                      |

Registry of cases of tumors in the oral cavity with importance in the jaws for the period 2016-2022 from a tertiary hospital in the Mexican Bajío. CT/RT = Chemotherapy/Radiotherapy.

of surgery, in the first there was resection and placement of thoracic graft, the second resection and placement of titanium plate, and the third was hemi-mandibulotomy with reconstruction with microvascularised peroneal tissue. Histopathology data described as granular tissue, with invasion to dermis, per neural invasion, characterized as recurrent malignant ameloblastoma, under surveillance for 7 years the patient showed good health conditions and functional prosthesis, asymptomatic and without data of local or lymph node metastasis. The service discharged him at the age of 43 years. The comparative data presented in Table 2.

Discussion

The variants of ameloblastoma carcinoma and malignant ameloblastoma are two variants that present a different evolution in patients, this work describes both variants, which, in their evolution although both are recurrent ameloblastic carcinoma has an evolution towards metastasis, while malignant ameloblastoma does not present them. The ratio of ameloblastic carcinoma with respect to oral neoplasms treated in the study hospital was 0.069%, with a higher incidence in men compared to women, like what has reported globally. The treatment of these neoplasms with surgery in ameloblastic carcinomas was 100%; for squamous cell carcinoma it was 53% and the rest of the other types were 86%. The case studies ameloblastic carcinoma and malignant ameloblastoma recurrences involved bone cortical destroying cells identified on biopsy and hemimaxillotomy being of higher aggressiveness in ameloblastic carcinoma, cells that prevailed in the patient even after CT and RT treatments. Depending on the stage and cellular invasion, the application of chemotherapy and radiotherapy in most cases applies as seen in Table 2. However, this indicates that these tumor types located in the oral cavity have a partial response in most cases.

Case one was characterized by the presence of carcinogenic antigen CA-19.9 positive with a high concentration (reference < 3 U/mL) of 15.2 U/mL, indicating a continuous tumor activity that was present in both the second and third biopsy with cortical destruction reported by histopathology. In Table 2, the minimum age of presentation of ameloblast and squamous cell carcinoma ranges above 20 years, where the average age is between 43 and 51 years. It has suggested that the beginning of tumor growth corresponds to latent

cells of the dentition, which manifest as cysts, as observed in ameloblast carcinoma. The carcinoma amyloplastic are extremely aggressive locally and at a distance, with metastases to the lung and liver are reported more than 60%, having a higher prevalence in men than in women.

The ameloblastic carcinoma (case 1) presented a partial response to the treatments since a tumor occurred, in the parapharyngeal space that when treated with chemotherapy and radiotherapy with response partial, adding tumor activity in the infratemporal fossa and left masticatory space. The tumor activity between ameloblastic carcinoma and malignant ameloblastoma even with its recurrences, age could be the factor that influences the response to treatment, the first case started in old age compared to the malignant carcinoma that started at age 20 and had a better response. The ameloblastic carcinoma clinically and histologically, were malignant with local invasion with bone destruction, perineural invasion and vascular permeation, so the diagnosis was poor. Finally, an average 17 years of follow-up in treatment in ameloblastic carcinoma contrasts with 23 years in ameloblastoma malign with poor prognosis for life.

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Conflict of Interest Statement (Mandatory)

The authors declare that we have no potential conflict of interest in the information, data, or opinions expressed in this document.

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