Case Report

Ameloblastic carcinoma of the mandible: A case report

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Abstract

Ameloblastic carcinoma (AC) is a rare, primary epithelial odontogenic malignant neoplasm. It is the malignant counterpart of ameloblastoma. It comprises 1% of all cysts and tumours occurring in the jaws, arising from tissues associated with odontogenic epithelium. The objective of the present study was to describe a clinical case of a 63-year-old male with an enlargement in the mandible on the left side. Panoramic radiography revealed a radiolucent area with poorly defined borders, and an incisional biopsy was performed for the histopathological study using immunomarkers such as SOX2 and Ki-67. Ki-67 is considered a marker of cell proliferation, and SOX2 reportedly participates in the development of the ameloblastic epithelium lineage and is associated with a more aggressive clinical course. A final histopathological diagnosis of AC was given. Unfortunately, the patient died one week before surgical resection (the surgical treatment of choice for AC).

Keywords: Ameloblastic carcinoma, ameloblastoma, case report, Ki-67, SOX2

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Submitted: 11-Aug-2022, **Revised:** 24-Oct-2022, **Accepted:** 16-Dec-2022, **Published:** 21-Mar-2023

INTRODUCTION

Ameloblastic carcinoma (AC), the malignant counterpart of ameloblastoma (AB), is a rare, primary epithelial odontogenic malignant neoplasm.[1] Approximately 1% of all cysts and tumours occurring in the jaws arise from tissues associated with the odontogenic epithelium.[2] Men are at a slightly higher risk than women.[1] Patients vary in age from 4 to 90 years old, with an average age of 44 years.[3] The term "ameloblastic carcinoma" was introduced by Elzay in the year 1982.[4] In 1984, Slootweg and Miller proposed a modification in Elzay's classification related to the origin of the tumour. Accordingly, it is categorised as a malignant odontogenic tumour, according to the 2017 World Health Organization (WHO) classification.[5] AC is an ameloblastoma with metastatic histological features and malignant cytological characteristics.[6] It may arise *de novo* or originate from a pre-existing ameloblastoma or an odontogenic cyst.[7] The primary type (*de novo* carcinoma) is not preceded by simple AB, whereas the secondary type (carcinoma ex AB) is a malignant transformation of a pre-existing benign AB.[8] The common clinical signs of AC are rapid swelling, rapid growth, and cortical bone expansion with erosion.[3,5] AC tends to be aggressive and results in local bone destruction, occasionally with focal radiopacities, which is extremely unusual for AB.[7] A wide local excision is the treatment of choice.[8] The purpose of this report was to present a case of AC and investigate its clinicopathological correlations.

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.jomfp_339_22

How to cite this article: Nancy PC, Selenne RSR, J. Valente FA. Ameloblastic carcinoma of the mandible: A case report. J Oral Maxillofac Pathol 2023;27:233-7.

CASE HISTORY

A 63-year-old male visited the maxillofacial surgery department in Guanajuato, Mexico, due to facial asymmetry and diffuse swelling in the buccal, nasogenian, and submandibular regions on the right side of his face. The patient used to smoke two to four packs of cigarettes daily from 16 years of age. He began to notice a significant increase in the size of the posterior mandible after two years of development. He underwent multiple medical and dental consultations that included the administration of antibiotics and antifungals, and his teeth were extracted without noticing improvement. Over time, he began to lose more teeth in the lesion area. The tumour continued to increase in size, causing facial asymmetry, and the patient presented to maxillofacial surgery service for a re-evaluation.

Extraoral examination revealed diffuse swelling in the buccal, nasogenian, and submandibular regions on the right side, soft consistency, and a colour similar to the adjacent skin. Submandibular lymph node group IB and upper jugular lymph node group IIB, both on the right side, were positive [Figure 1a].

Intraoral examination revealed a tumour-like lesion located in the middle and posterior third of the edentulous alveolar ridge and involving the buccal and lingual region of the right side of the mandible, which extended to the retromolar area of the same side, irregular shape and surface, erythematous colour with yellowish areas, diffuse borders, and soft consistency [Figure 1b]. Radiographic examination with orthopantomography revealed a radiolucent lesion in the body and ramus of the mandible on the right side with an irregular shape, and poorly defined borders. It measured approximately 6.5 × 3.5 cm, with the destruction of the alveolar and basal bone and without the association of the teeth. Incisional biopsy was performed and analysed by the oral and maxillofacial pathology service [Figure 2].

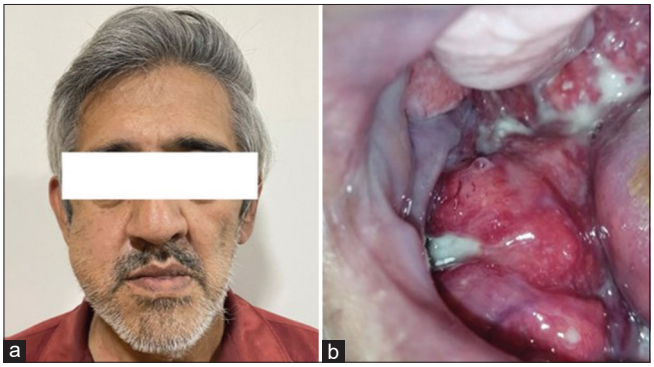

Figure 1: (a) Extraoral photograph showing diffuse swelling in the buccal, nasogenian, and submandibular region on the right side. (b) Intraoral photograph showing a tumour-like lesion located in the middle and posterior third of the edentulous alveolar ridge and involving the buccal and lingual regions of the right side of the mandible

Histopathology examination by haematoxylin and eosin (H&E) staining revealed a neoplasm formed by sheets, nests, follicles, and trabeculae spanning the epithelium. The follicles had a central area of comedonecrosis and some star-shaped cells. Peripheral cells had hyperchromatic nuclei with focal reverse polarity. Cellular pleomorphism, increased nuclear–cytoplasm ratio, nuclear hyperchromatism, and abnormal mitosis could be seen. In the dense fibrous connective tissue stroma, some areas close to the neoplastic cells exhibited hypercellularity, and spindle cells formed a streaming pattern. The rest of the stroma was loose, dense fibrous connective tissue with diffuse severe chronic inflammatory infiltrate, covered by stratified squamous parakeratinised epithelium with areas of acanthosis, cellular and nuclear pleomorphism, and pyknotic nuclei [Figure 3a–d].

To complement the histopathological analysis, we performed immunohistochemistry and staining for SOX2 and Ki-67; Ki-67 showed moderate positivity, and SOX2 was highly positive [Figure 4a and b].

Therefore, a definitive diagnosis of ameloblastic carcinoma was made. The patient was referred to the oncology department for treatment, but died due to respiratory failure secondary to SARS-CoV-2 infection a week before the procedure could be carried out.

DISCUSSION

The purpose of this report was to present a case, performing clinical-pathological correlations of a 63-year-old male patient, with the final diagnosis of ameloblastic

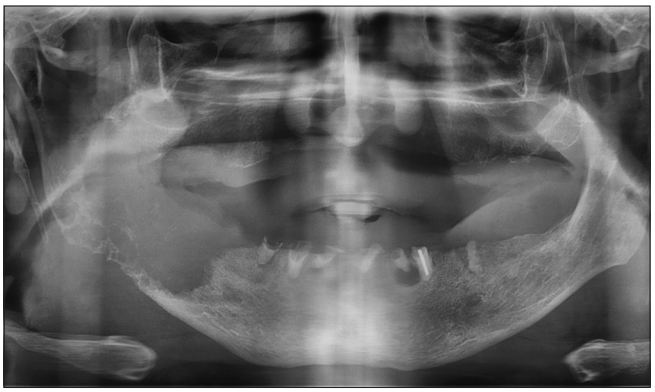

Figure 2: An orthopantomography showing a radiolucent lesion with poorly defined borders located in the body and ramus of the mandible on the right side

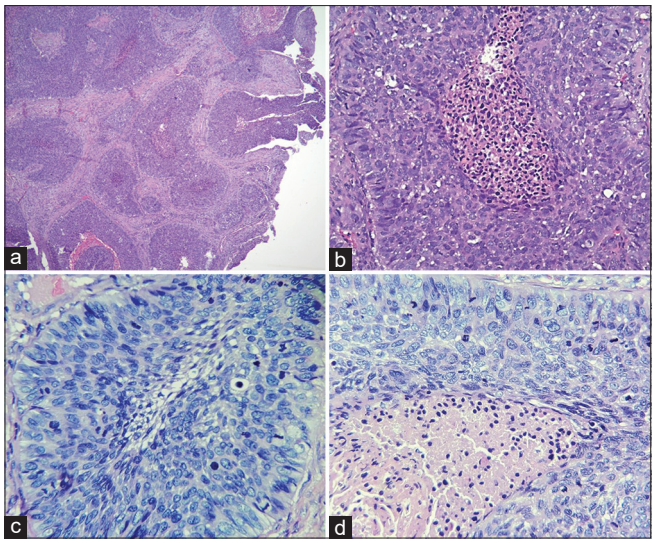

Figure 3: (a) Haematoxylin and eosin (H&E) histopathological examination (4×) showing a neoplasm formed by sheets, nests, follicles, and trabeculae spanning the epithelium. (b) H&E histopathological examination (40×) showing follicles with a central area of comedonecrosis and some star-shaped cells. Peripheral cells have hyperchromatic nuclei with focal reverse polarity. (c and d) H&E histopathological examination (40×) showed the presence of cellular pleomorphism, increased nuclear–cytoplasm ratio, nuclear hyperchromatism, and abnormal mitosis. In the dense fibrous connective tissue stroma, some areas close to the neoplastic cells exhibited hypercellularity and spindle cells formed a streaming pattern

carcinoma (AC). However, we cannot rule out a pre-existing ameloblastoma due to the time of evolution and the history of multiple previous dental extractions. In the literature, it is mentioned that it may arise *de novo* or originate from a pre-existing ameloblastoma or odontogenic cyst.[7] In the 5th edition of the WHO classification of head and neck tumours, AC is considered a primary odontogenic carcinoma histologically resembling ameloblastoma.[9] The primary type (*de novo* carcinoma) is not preceded by simple AB, while the secondary type (carcinoma ex AB) is a malignant transformation of a pre-existing benign AB.[10]

The most common site of AC is the posterior mandible. Painful swelling, numbness of lower lip, rapid growth, cortical bone expansion with erosion, perineural invasion, and mucosal ulceration are the typical clinical manifestations of AC.[10] The clinical symptoms of AC are more aggressive than that of ameloblastoma. Distinct features from ameloblastoma are swelling with rapid growth, perforation of the cortex, pain, tooth mobility, a non-healing extraction site, ulcer or fistula, facial asymmetry, trismus, and paresthesia.[4] The clinical presentation of our patient was similar to that described in the literature.

Radiographically, it can show either unilocular or multilocular radiolucency with tooth-root resorption and

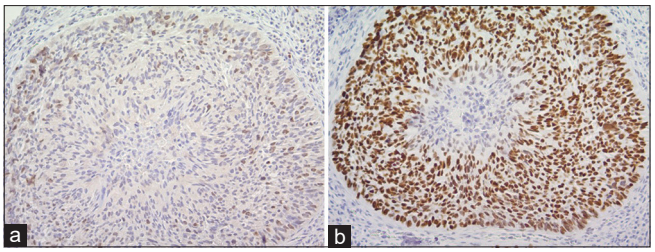

Figure 4: Immunohistochemistry: (a) showing moderately positive staining for Ki-67 (Ki-67, 40×); (b) showing highly positive staining for SOX2 (SOX2, 40×)

tooth displacement. Ameloblastic carcinoma may have either an ill-defined or a well-defined border.[7] Loss of lamina dura and root resorption is evident. In case of AC, there is often the presence of focal radiopacity, reflecting dystrophic calcifications.[4] In our case, the patient showed unilocular radiolucency with poorly defined borders, which is a common radiographic feature in patients with AC.

Histopathological evaluation shows ameloblastic differentiation, palisading of basaloid cells, and stellate reticulum pattern in the follicles and features of malignancy such as cellular atypia, mitotic figures, and nuclear hyperchromatism.[5] Atypical cells form nest and broad ribbons, which may branch and anastomose with focal areas of subtle necrosis to more obvious central, comedonecrosis-like areas.[11] The pathogenesis of malignant transformation of ameloblastoma may occur either spontaneously or because of induction following chemotherapy or post-surgical radiation. Aggressive behaviour and metastatic potential associated with ameloblastoma has been noted in two of its variants: one is the granular cell type and the other is the clear cell type.[12] Deng *et al*.[13] reported in their study that clear cells can be found in some cases, and tumours with clear cells have greater invasiveness, higher recurrence, and mortality.

The histopathologic differential diagnoses in our case include ameloblastoma. On the other hand, AC has certain features of benign ameloblastoma such as reverse polarisation, peripheral palisading, and stellate reticulum-like cells. It has features of malignancy such as high nuclear-to-cytoplasmic ratio, increased mitoses with atypical forms, cytological atypia, and necrosis.[14] Basaloid squamous cell carcinoma has features that distinguish AC from squamous cell carcinoma including the jigsaw puzzle-type nesting of the tumour cells, the presence of stellate reticulum, and the distinctive cystic degeneration of the nests.[15] Primary intraosseous carcinoma lacks the peripheral palisading and stellate reticulum when compared to the present case of AC.[8]

Clear cell odontogenic carcinoma (CCOC) is identified by the proliferation of neoplastic epithelial cells with clear cytoplasm arranged in islands and strands. According to some authors, AC and CCOC may represent different clinicopathological manifestations of a malignant ameloblastic neoplasia associated with clear cell metaplasia. While EWSR1 rearrangements is identified in clear cell odontogenic carcinoma, BRAF V600E point mutation is instead identified in ameloblastic carcinoma.[16] Furthermore, the spindle cell variant of AC should be differentiated from odontogenic sarcoma: spindle cell areas are negative for vimentin and positive for cytokeratin.[8] The squamous odontogenic tumour may also be mistaken for AC. It is composed of islands of squamous epithelium that lack stellate reticulum-like zones and peripheral palisading.[8]

Cell proliferation is an essential process in all living organisms because of its roles in cell growth and the maintenance of tissue homeostasis. The control of proliferation is completely dysregulated in neoplasms. For this reason, the assessment of cell proliferation activity by immunohistochemistry analysis has become an important tool to provide useful information about the behaviours of several tumours.[17] Some immunohistochemical markers used to differentiate AC from AB include SOX2, CK18, parenchymal MMP-2, stromal MMP-9, Ki-67, and p53.[6] A study published by Farshbaf *et al*.[18] indicated an overexpression of SOX2 and PITX2 (TF in Wnt pathway) and high levels of Ki-67 protein. Also, an increased POLR2J, CDKN2C, and decreased EIF3S5 expression was seen. The Ki-67 antigen is preferentially expressed during the late G1 phase of the cell cycle, whereas quiescent cells (G0 phase) lack Ki-67 expression.[17]

Ki-67 is considered a reliable marker for the proportion of proliferating cells and to predict the lesion's behaviour; it has come about as a useful indicator in tumour marking as it might be applied for different conditions of cell growth and tumour recurrences allied with cell growth.[19] The gene of sex-determining region Y-box 2 (SOX2) is located on chromosome 3p26.3-q27 and plays a pivotal role in maintenance of the stem cell phenotype of embryonic stem cells (ESCs) during embryogenesis. SOX2 amplification or overexpression was found in at least 25 different human cancers, and forced SOX2 expression promotes neoplastic progression by accelerating cancer cell proliferation, migration, invasion, and metastasis. Moreover, elevated SOX2 expression is positively correlated with poor survival of cancer patients.[20] Lei *et al*.[21] found SOX2 as a specific and sensitive marker for AC—also expressed in dental lamina—and has been linked to a more aggressive clinical course. There are approximately 60% of mutations in BRAAF-V600E, a gene that plays an important role in tumour cell proliferation, differentiation, and apoptosis.[22] In our case, two immunomarkers were performed, of which we obtained a moderate positive for Ki-67 and a highly positive for SOX2, indicating a high aggressiveness of the tumour.

Resection is the first choice of treatment, with bloc removal and 1–2 cm of normal bone as a margin.[23] And neck dissection should be considered only when local metastasis is suspected.[22] Radiation therapy is not effective against the lesion in bone, and this may be acceptable in patients with poor general conditions or in cases where complete resection is not possible.[11] Distant metastasis of the tumour is one of the causes of death, and whether metastasis will occur or not cannot be predicted based on histology. The most common metastatic site is the lungs,[13] although it can metastasize to bones and brain.[24]

Five-year survival rates noted in literature range from 68% to 79%, with a slightly decreased 10-year survival rate of 57%, despite the reported recurrence rate of 28%.[25] Survival rate depends upon local recurrence, and regional or distant metastasis.[12] Maxillary AC cases are identified to have a more unfavourable prognosis compared to the mandible. Higher mortality rate is observed in ACs than in the primary variant.[19]

CONCLUSION

Although ameloblastic carcinoma has rarely been reported in the literature, it is vital for clinicians to perform detailed oral examinations and pay attention to the clinical signs of the patient—such as rapid growth, asymmetry, and non-healing areas—and consider AC as a probable diagnosis to avoid delays in the adequate diagnosis of potentially malignant neoplasms. Tools such as imaging studies and histopathology can be used to identify AC. Immunomarkers, such as Ki-67 and SOX2, may be useful for diagnosis in cases of suspected AC to enable timely treatment and provide the most favourable prognosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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