Case Report

Ameloblastic carcinoma: A case report and evaluation

Adesh S Manchanda[1], Ramandeep S Narang[1], Ravneet S Nagi[2]

Department of [1]Oral and Maxillofacial Pathology and Microbiology, [2]BDS, Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar, Punjab, India

Abstract

Malignant odontogenic neoplasms are extremely challenging to study due to their rarity and variable clinical presentations. Ameloblastic carcinoma (AC) is one such odontogenic tumor which has been the subject of controversy, in part because of its scarcity, complicated by confusion in terminology along with complexity in classification. Histologic features of AC resemble tumor cells of ameloblastoma but exhibit cellular atypia. Surgical resection for this kind of lesion, leaving at least a 2 cm free margin coupled with neoadjuvant radiotherapy, might prove fruitful results. The current paper reports a case of an extraosseous variant of AC which posed a diagnostic challenge due to variable presentations histopathologically, suggesting the need for evidence-based case studies and molecular workup for a better therapeutic and prognostic insight.

Keywords: Ameloblastic carcinoma, ameloblastoma, CK18, Ki-67

Address for correspondence: Dr. Ramandeep S Narang, Department of Oral and Maxillofacial Pathology and Microbiology, Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar, Punjab, India.
E-mail: narangraman@yahoo.com

Submitted: 18-Oct-2021, **Accepted:** 27-Jan-2022, **Published:** 28-Feb-2022

INTRODUCTION

The term ameloblastic carcinoma (AC) was first used by Shafer in 1983 to describe ameloblastoma (AB) exhibiting malignant transformation.[1] However, the term AC was first introduced by Elzay in the year 1982.[2] AC is a relatively rare type of tumor which according to the World Health Organization (WHO) is a carcinoma that can be classified as metastasizing (malignant) AB or AC.[3] AC is a tumor that develops in the jawbones from the epithelial cells that generate from tooth enamel showing signs of malignancy and dysplastic features which are absent in AB.[4] The biggest challenge faced while diagnosing an odontogenic tumor as AC is differentiating it from AB and malignant AB because of the overlapping clinical features, histological picture and difference in the management protocol.[5] According to the WHO 2017 Classification, this malignant odontogenic tumor exists in two forms: primary (ACpt) and secondary (ACst) form, the prime difference between both being that ACpt is not preceded by simple AB (*de novo* carcinoma) while the secondary type (ACst) is a result of malignant transformation of preexisting benign AB (carcinoma ex AB).[6] Furthermore, studies revealed the ACst was differentiated from ACpt by determining the presence of some benign ameloblastic cells in ACst.

AC, a rare entity among malignant odontogenic tumors, most commonly involves the mandible followed by maxillary involvement. Gender predilection weighs more toward males.[7] The age range of appearance of AC in various literatures is fifth to seventh decade with a mean age of 53.5 years but some cases defied the age range by being presented in the second decade.[7] The diagnosis of AC primarily begins with the interpretation of existing

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.jomfp_378_21

How to cite this article: Manchanda AS, Narang RS, Nagi RS. Ameloblastic carcinoma: A case report and evaluation. J Oral Maxillofac Pathol 2022;26:S63-7.

clinical signs and symptoms which according to existing literary sources are pain, facial swelling, ulceration, paresthesia, trismus and dysphonia. According to Hall *et al.,* four points in the clinical criteria prove to be helpful in diagnosing AC such as rapid growth, locally aggressive, proclivity to perforate the cortex, pain and paresthesia to distinguish them from their benign equivalent.[8] AC from radiographic standpoint can be viewed as an ill-defined unilocular or multilocular radiolucent lesion with ill-defined borders often coexisting with local radiopacities, mirroring dystrophic calcifications.[9] Radiologically features such as root resorption and loss of lamina dura can also be seen.

The gold standard for diagnosing AC lies in its microscopic features and further on using immunohistochemical markers in differentiating it from other odontogenic tumors which might masquerade it histopathologically. AC is notorious owing to its high recurrence rate having ability to recur locally 0.5–11 years after definitive therapy. It also possesses the potential to metastasize to distant parts most commonly lungs along with cervical lymph node infiltration which can be confirmed during palpation.[10] Hereby, we report a rare case of peripheral variant of AC (PAC), which posed a diagnostic challenge due to variable presentations histopathologically.

CASE REPORT

A 55-year old male patient reported with a complaint of gingival swelling and pain in left lower region of jaw for the last 7 months. Swelling was sudden in onset, started 7 months ago, and was progressive in nature. The patient gave a history of alcohol consumption once daily and smoking 5–6 bidis/day for the last 25 years. On extraoral examination, a minor swelling at the left lower border of the mandible was observed, which was mildly tender on palpation, but did not exhibit any change in color. A slight rise in surface temperature was encountered. The swelling extended anteroposteriorly just above the lower border of mandible from commissural area of the lip toward angle of mandible. Submental group of lymph nodes was found to be palpable. Intraoral examination disclosed a pale pinkish gingival swelling of size 3 cm × 1.5 cm, extending from left canine (#33) to mesial aspect of first molar (#36) buccally [Figure 1a], and as a nonmovable, sessile nodular swelling situated at the floor of the mouth, lingual to #33 extending distally as a whitish and reddish nonhomogeneous mass till #35 [Figure 1b]. The swelling was soft in consistency, tender on palpation, leading to mild obliteration of buccal vestibular space. Teeth pertaining to the third quadrant were not showing any grade of mobility, and no discharge was related to the swelling.

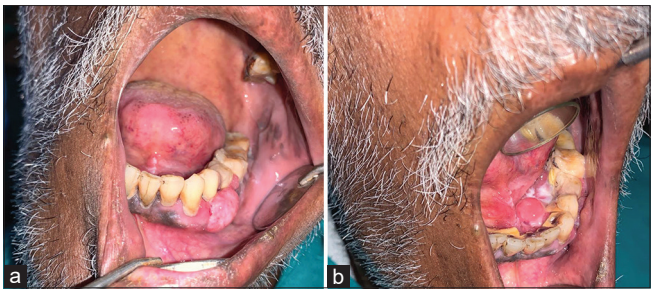

Figure 1: (a) Intraoral photograph showing a gingival swelling, extending from left canine (#33) to mesial aspect of first molar (#36) buccally. (b) Intraoral photograph showing a sessile nodular swelling situated at the floor of the mouth, lingual to #33 extending distally as a whitish reddish nonhomogeneous mass till #35

Radiographically, a well-defined radiolucent lesion was seen extending from mesial aspect of left central incisor (#31) to the furcation area of left first molar (#36) [Figure 2]. Generalized horizontal bone loss was seen in the maxilla and mandible with missing 11, 16, 25 and 26. The clinical and radiographic picture was suggestive of various differentials such as ossifying fibroma, giant cell granuloma and fibroma.

To reach a final diagnosis, a biopsy was conducted by resecting a specimen of size 1 cm × 8 mm from lower labial left gingival region and another bit of size 1 cm × 1 cm from the lingual nodular swelling. Microscopic examination showed islands and follicles of odontogenic cells with peripheral palisaded cells showing cuboidal to basaloid to columnar appearance and central cells showing stellate reticulum-like appearance. Few follicles showed squamous differentiation, microcystic changes and keratin formation centrally [Figure 3a-c]. Some follicles showed dysplastic features such as cellular atypia, nuclear hyperchromatism, mitotic figures and increased mitotic activity. One area showed sheets and islands of tumor epithelial cells with keratin pearl formation in an inflamed fibro cellular connective tissue stroma [Figure 3d-f]. Based on these findings, a diagnosis of Ameloblastic Carcinoma was considered. Differential diagnosis to these findings included lesions such as basaloid squamous cell carcinoma, ameloblastoma, squamous odontogenic tumor, acanthomatous AB and oral SCC. Special stains (PAS) and IHC markers (Ki-67 and CK18) were performed for a confirmatory diagnosis. PAS stain showed negative expression for mucin in the microcystic spaces [Figure 4a]. IHC showed a uniform immunoreactivity for Ki-67 labeling index to nearly 18% in areas highlighting an increased proliferative rate [Figure 4b]. The follicles mimicking a benign AB showed a Ki-67 LI of ~3%. IHC with CK18 helped in differentiating AB from AC with CK18 diffusely positive in all the layers in AC, and only in selective stellate

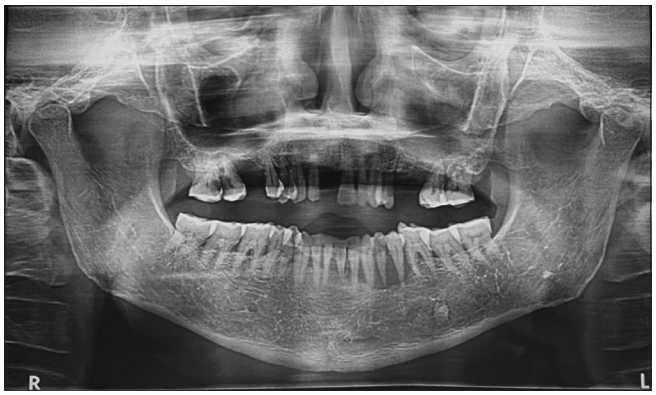

Figure 2: A well-defined radiolucent lesion extending from mesial aspect of left central incisor (#31) to the furcation area of left first molar (#36)

reticulum cells in AB follicles [Figure 4c and d]. Based on these, a definitive diagnosis of AC was arrived at. Following this, a wide surgical excision was done, and tumor-free margins were obtained in the resected section. The patient was followed up and had an uneventful postoperative course for 4 months.

DISCUSSION

Odontogenic malignancies are in rarity and account for only 1% of all the cysts and tumors of the jaw.[8] Owing to its rare frequency and the variable clinical presentations, odontogenic carcinoma has faced substantial transformations in its terms and WHO classification over the years. WHO recognized AC as a separate entity in 2005 as a tumor with ameloblastomatous differentiation showing cytologic features of malignancy with or without metastasis, further on subdividing it as primary and secondary type (intraosseous and peripherally differentiated).[11] At present, a single diagnostic term recognized universally for it is AC.[12]

In the present report, a PAC is seen which is described as an extraosseous AB with histological evidence of malignant transformation. PAC arises from the extraosseous remnants of dental lamina or basal cells of oral epithelium. It usually grows in the soft tissues overlying the posterior portion of mandible and presents clinically as a sessile or pedunculated mass of gingiva with smooth or irregular papillomatous surface, of approximately 1–2 centimeters in size. The clinical presentation of our case was in concordance to it.

The microscopic diagnosis of AC requires familiarity with histological features of AB. Despite the existence of areas or foci that resemble AB, AC shows changes in patterns and cytologic features. In our case, a varied morphological presentation was seen histopathologically with areas of

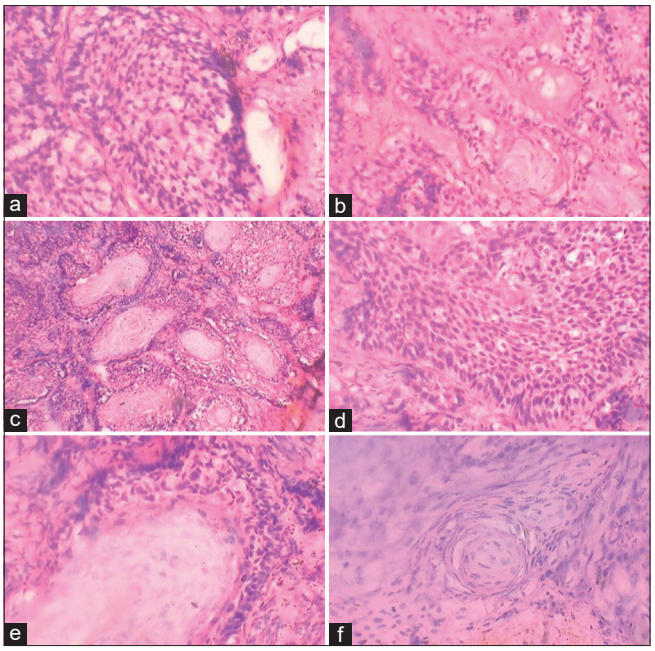

Figure 3: (a-c) Histopathological examination showing follicles and islands of odontogenic cells with squamous differentiation, microcystic changes and keratin formation centrally (a and b; H and E, ×400), (c; H and E, ×100). (d-f) Histopathological examination showing odontogenic follicles showed dysplastic features such as cellular atypia, nuclear hyperchromatism, mitotic figures and increased mitotic activity. One area showed sheets and islands of tumor epithelial cells with keratin pearl formation. (d-f; H and E, ×400)

follicular AB, islands showing squamous differentiation, microcystic changes, keratin formation and features of cytological atypia. A negative expression for PAS in the microcystic spaces ruled out a differential of basaloid SCC. Squamous odontogenic tumor was excluded from the list as they show benign squamous epithelium with microcystic changes and keratinization but lack the AB differentiation and cytologic atypia. The presence of cytological atypia, a 18% Ki-67 labeling index and a diffusely positive CK18 expression, in all layers of the follicles helped in negating AB and its variants and SCC. Other rare differentials which can be confused with AC include metastatic carcinoma to the jaws from the lungs, breast, gastrointestinal tract and salivary perineural infiltration or soft-tissue invasion.

Abnormal cell proliferation is an essential feature of tumorigenesis. Ki-67 is a 319-358 kDa protein, considered a reliable marker for the proportion of proliferating cells and to predict the lesion's behavior.[13] Ki-67 gene is located on human chromosome 10. Various studies indicated that the location and appearance of Ki-67 is dynamic throughout a cell's life; for instance, its expression is low during G1 and early S-phase of a cell cycle, whereas it markedly increases to reach a maximum during mitosis. Ki-67 has come about as a useful indicator

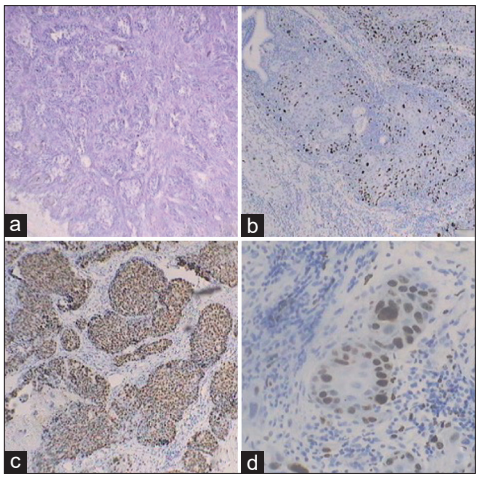

Figure 4: (a) PAS stain showing negative expression for mucin in microcystic spaces (PAS, ×100). (b) IHC showing uniform immunoreactivity of Ki-67 (Ki-67, ×100), (c) CK18 diffusely positive in all the layers in AC (CK18, ×100), (d) and only in selective stellate reticulum cells in AB follicles (CK18, ×400)

in tumor marking as it might be applied for different conditions of cell growth and tumor recurrences allied with cell growth. Birajdar *et al*.[14] in their study on expression of Ki-67 in OSCC found positivity at the periphery of the tumor nests than the center. The present case showed a uniform Ki-67 positivity rate in the tumor islands showing atypia. Bello *et al*., in 2009 found that Ki-67 labeling index in AC was three times that of AB.[15] Yanamoto *et al*. in their study found the Ki-67 LI levels in AC to be (12.2%) higher than that in AB (4.2%).[16] Jabbarzadeh *et al*. in their systematic review on Ki-67 expression as a diagnostic biomarker in odontogenic cysts and tumors found Ki-67 LI in AB to be 4.39 +/– 0.47 which was significantly lower to that in AC (17.59 ± 2.80%).[17] Yoon *et al*. in their study assessed the expression and usefulness of CKs, MMP's and Ki-67 between AB and AC and inferred that mean Ki-67 LI was 17.21%, which was significantly higher than that of AB (3.57%).[18] Sancheti *et al*. in their case report on AC found Ki-67 LI to be nearly 20% in the highest proliferating areas.[19] The Ki-67 LI of our report showed similar findings with a highest proliferative rate of 18%.

CK-18 gene is located on chromosome 12q13. It has been recognized for 30 years as a structural protein that is specific to epithelial cells and is consequently involved in both cell motility and cancer progression along with patient prognosis in variety of cancers. CK-18 has proven to be considerately useful in differentiating between AB and AC as it is seen to be diffusely positive in all tumor cells in AC and only weakly positive in stellate reticulum cells of AB. Similar findings have also been observed in studies conducted by Sancheti *et al*.[19] and Yoon *et al*.[18] Casaroto *et al*. in their case report and literature review concluded that there is a reduced or lack of CK18 expression in odontogenic cells.[20]

Recently, SOX2 has been put forward as a sensitive and specific IHC marker for AC. Matrix metalloproteinase 2 and 9 have also been deliberated as potential markers for differentiation between AB and AC where MMP-2 values came back comparatively higher for AC than in AB. MMP-9 was unable to yield satisfactory results.[14] Expression of p63 is markedly increased in cases of AC. CD-138 is strongly positive in AC, whereas weakly positive in AB. Nonetheless, superseding priority is given to Ki-67 as an IHC marker to confirm a diagnosis as AC as various sources have labeled it as efficient, specific and sensitive.

The prognosis of AC wholly depends on its nature of aggressiveness and ability to metastasize. Maxillary AC cases are identified to have a more unfavorable prognosis as compared to mandible. Higher mortality rate is observed in ACst than in the primary variant. Another problem encountered is the high recurrence rate of AC, to counter these two problems, the main aim should be to surgically resect the affected portion along with 2mm of normal adjacent bone (en bloc resection) along with chemotherapy and radiotherapy. However, the step which will determine the success of the treatment is follow-up of the patient to track recurrence and to reduce the number of fatal incidences.

Since the present case showed focal areas resembling AB, we postulated that AC arose from AB and is of ACst type. The rarity of peripheral variant of AC and its spectrum and the diversity in its histomorphological presentation postulates diagnostic dilemmas suggesting the need for evidence-based case studies and molecular workup for a better therapeutic and prognostic insight.

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 initial s 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.

REFERENCES

1. Moro A, Foresta E, Gasparini G, Pelo S, Forcione M, Cristallini EG, *et al*. Ameloblastic carcinoma of the maxilla: A case report and an updated view of the literature. Oncol Lett 2016;12:4339-50.
2. Elzay RP. Primary intraosseous carcinoma of the jaws. Review and update of odontogenic carcinomas. Oral Surg Oral Med Oral Pathol 1982;54:299-303.
3. Abiko Y, Nagayasu H, Takeshima M, Yamazaki M, Nishimura M, Kusano K, *et al*. Ameloblastic carcinoma ex ameloblastoma: Report of a case-possible involvement of CpG Island hypermethylation of the p16 gene in malignant transformation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:72-6.
4. Avon SL, McComb J, Clokie C. Ameloblastic carcinoma: case report and literature review. J Can Dent Assoc 2003;69:573-6.
5. Abir B, Abouchadi A, Tourabi K, Lakouichmi M. Ameloblastic carcinoma of the mandible: A case report and review of the literature. Med Buccale Chir Buccale 2017;23:95-8.
6. Soluk-Tekkeşin M, Wright JM. The world health organization classification of odontogenic lesions: A summary of the changes of the 2017 (4th) edition. Turk Patoloji Derg 2018;34:34-5.
7. Deng L, Wang R, Yang M, Li W, Zou L. Ameloblastic carcinoma: Clinicopathological analysis of 18 cases and a systematic review. Head Neck 2019;41:4191-8.
8. Hall JM, Weathers DR, Unni KK. Ameloblastic carcinoma: An analysis of 14 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:799-807.
9. Kishore M, Panat SR, Aggarwal A, Upadhyay N, Agarwal N. Ameloblastic Carcinoma: A case report. J Clin Diagn Res 2015;9:D27-8.
10. Roy Chowdhury SK, Ramen S, Chattopadhyay PK, Moorchung N, Rajkumar K. Ameloblastic carcinoma of the mandible. J Maxillofac Oral Surg 2010;9:198-201.
11. Slootweg PJ, Müller H. Malignant ameloblastoma or ameloblastic carcinoma. Oral Surg Oral Med Oral Pathol 1984;57:168-76.
12. Speight PM, Takata T. New tumour entities in the 4th edition of the world health organization classification of head and neck tumours: Odontogenic and maxillofacial bone tumours. Virchows Arch 2018;472:331-9.
13. Alsaegh MA, Altaie AM, Zhu S. p63 expression and its relation to epithelial cells proliferation in dentigerous cyst, Odontogenic keratocyst, and ameloblastoma. Pathol Oncol Res 2020;26:1175-82.
14. Birajdar SS, Radhika M, Paremala K, Sudhakara M, Soumya M, Gadivan M. Expression of Ki-67 in normal oral epithelium, leukoplakic oral epithelium and oral squamous cell carcinoma. J Oral Maxillofac Pathol 2014;18:169-76.
15. Bello IO, Alanen K, Slootweg PJ, Salo T. Alpha-smooth muscle actin within epithelial islands is predictive of ameloblastic carcinoma. Oral Oncol 2009;45:760-5.
16. Yanamoto S, Kawasaki G, Mizuno A. Expression of p21WAF1/CIP1, p53, and Ki-67 proteins in malignant ameloblastomas and amelobalstomas. Asian J Oral Maxillofac Surg 2002;14:155-60.
17. Jabbarzadeh M, Hamblin MR, Pournaghi-Azar F, Vakili Saatloo M, Kouhsoltani M, Vahed N. Ki-67 expression as a diagnostic biomarker in odontogenic cysts and tumors: A systematic review and meta-analysis. J Dent Res Dent Clin Dent Prospects 2021;15:66-75.
18. Yoon HJ, Jo BC, Shin WJ, Cho YA, Lee JI, Hong SP, *et al*. Comparative immunohistochemical study of ameloblastoma and ameloblastic carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:767-76.
19. Sancheti S, Somal PK, Sarkar S. Ameloblastic carcinoma: A diagnostic dilemma. Indian J Pathol Microbiol 2019;62:501-3.
20. Casaroto AR, Toledo GL, Filho JL, Soares CT, Capelari MM, Lara VS. Ameloblastic carcinoma, primary type: Case report, immunohistochemical analysis and literature review. Anticancer Res 2012;32:1515-25.