Ameloblastic carcinoma: A case report and evaluation

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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

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

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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 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.

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
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 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
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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 considerably 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 metastasise. 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 chemotheraphy 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.

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Conflicts of interest
There are no conflicts of interest.
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