AMELOBLASTIC CARCINOMA: A DIAGNOSTIC IMPASSE FOR BOTH PATHOLOGIST AND SURGEON

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Abstract

Ameloblastoma is a common and easily diagnosed odontogenic tumor. When present with histologic atypia is crucial because transformation to ameloblastic carcinoma is potentially life-threatening. Ameloblastic carcinoma, the malignant counterpart of the ameloblastoma, a rare entity, is characterized histologically by malignant epithelium in the primary, recurrent, or metastatic deposit. It has a predilection for mandible and commonly metastasizing to the regional lymph nodes or lung. Most ameloblastic carcinomas according to literature reviewed, arise de novo, with few cases of malignant transformation of an ameloblastoma. In this paper we present three cases of ameloblastoma, of which one was ameloblastic carcinoma when diagnosed finally. Our aim is to substantiate the diagnostic challenge of this rare entity for both surgeons and pathologists.

Key Words: Ameloblastoma, Ameloblastic Carcinoma, Histopathology, Diagnostic Parameters

Introduction

Primary carcinoma of jaw bones is a rare entity and the origins are different, including not only odontogenic origin, but also entrapped salivary gland epithelium. Ameloblastic carcinomas may arise de novo or in preexisting ameloblastoma or odontogenic cyst. Several definitions have been specified for ameloblastic carcinoma including a well-differentiated ameloblastoma with histo- logically malignant epithelial component[1]; a tumor with histologic evidence of malignancy and features of ameloblastoma and concomitant squamous cell carcinoma [2]; a tumor with combined features of an ameloblastoma with less differentiated areas [3]. The current concept accepted widely states that ameloblastomas in which there is histologic evidence of malignancy in the primary tumor or the recurrent tumor, regardless of whether it has metastasized can be termed ameloblastic carcinoma.[4,5]

In 1972, the WHO included the malignant ameloblastoma with odontogenic carcinomas in its classification. The classification system by the World Health Organization defines malignant amelob lastoma as an ameloblastoma, which has metastasized but exhibits the well-differentiated morphologic features of a typical ameloblastoma in both the primary and metastatic sites. Whereas, ameloblastic carcinoma is the pathologic designation describing an ameloblastoma with areas of obvious histologic malignancy.[6]

In 1982 Elzay[2], subclassified metastatic ameloblastomas under the heading of primary intraosseous carcinomas. Metastatic ameloblastomas that retained a well-differentiated appearance were designated as malignant ameloblastomas, and those tumors that demonstrated a poorly differentiated appearance were considered ameloblastic carcinomas.

Type 1: Arising from an odontogenic cyst
Type 2: Arising from an ameloblastoma
a. Well differentiated (malignant ameloblastoma)
b. Poorly differentiated (ameloblastic carcinoma)
Type 3: Arising *de novo*
a. Nonkeratinizing
b. Keratinizing.

In 1984, Slootweg and Muller [3], published the following modified classification system.

Type 1: Primary intraosseous carcinoma ex odontogenic cyst
Type 2:
a. Malignant ameloblastoma
b. Ameloblastic carcinoma, arising *de novo*, ex ameloblastoma or ex odontogenic cyst
Type 3: Primary intraosseous carcinoma arising de novo
a. Nonkeratinizing
b. Keratinizing.

In latest update of the WHO classification 2005 [7], Ameloblastic carcinoma is defined as a rare odontogenic malignancy that combines the histological features of ameloblastoma with cytological atypia, even in the absence of metastases. It may develop de novo(primary type) or by malignant transformation of an ameloblastoma (secondary type) with a distinction between carcinoma ex intraosseus ameloblastoma and carcinoma ex peripheral ameloblastoma.

In 2009, the most recent classification for Ameloblastic carcinoma was proposed by Kruse et al [8], where a primary ameloblastoma is followed by secondary metastasis with histopathological features of malignancy and without evidence of malignancy in the primary localization.

I. Malignant ameloblastoma
1a - Metastase with features of an ameloblastoma(well differentiated)
1b - Metastase with malignant features(poorly differentiated)
II. Ameloblastic carcinoma arising from an ameloblastoma
2a- Without metastase
2b -Metastase with features of an ameloblastoma(well differentiated)
2c -Metastase with malignant features(poorly differentiated)
III. Ameloblastic carcinoma with unknown origin histology
3a -Without metastase
3b -Metastase with features of an ameloblastoma(well differentiated)
3c -Metastase with malignant features(poorly differentiated)

Therefore, pertaining to the classifications, diagnosis of ameloblastic carcinoma is reserved for ameloblastomas that demonstrate a malignant morphologic appearance, regardless of whether metastasis is a proven fact at the time of discovery and treatment. We are reporting 3 cases initially diagnosed as ameloblastomas on incisional biopsy. Later one of them confirmed to be ameloblastic carcinoma on exisional biopsy. The aim of the present article is to highlight the diagnostic dilemma associated with it.

Material and Methods

The clinicopathologic features of all ameloblastomas in our department archives were reviewed. The study included 3 cases with both incisional and excisional reports available, which had evident clinical documentation, radiographs, and histological findings.

Case Reports:

The clinical, radiographic, and histological features of the 3 cases were tabulated and analyzed (Table 1).

CASE No.	AGE/ GENDER	SITE	RADIOGRAPHICAL FINDINGS	HISTOPATHOLOGICAL FINDINGS
1	29 M	Mandibular left posterior region	Multilocular radiolucency with scalloped margin in relation to34,35,36,37	Unencapsulated bony mass with multiple follicles lined by ameloblastic epithelium. Presence of squamous metaplasia occasionally. Sclerotic bony trabeculae evident at periphery.
2	60 M	Mandibular left posterior region	Scalloped border showing diffused radiolucency	Follicular arrangement with ameloblastic type of epithelium was observed along with focal nuclear atypia and mild increased mitotic activity.
3	55 M	Right labial cortical plate of mandible	Soap bubble appearance	Follicles of varying size lined by ameloblastic epithelium were seen. Mild increased mitotic activity noticed.

Tabular representation of clinical and pathological features of the 3 cases.

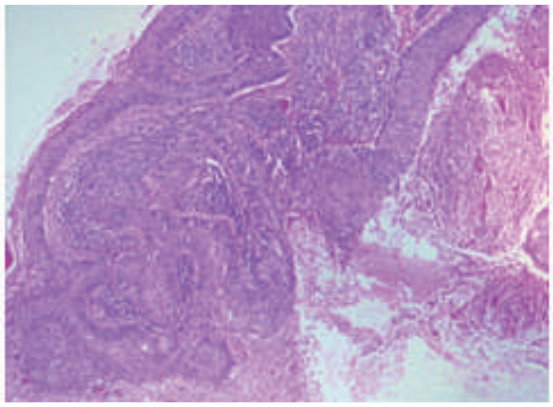

Fig1. Ulcerated mucosal surface with acute inflammation is seen along with pleomorphism of irregularly arranged epithelial cells in cords mostly.

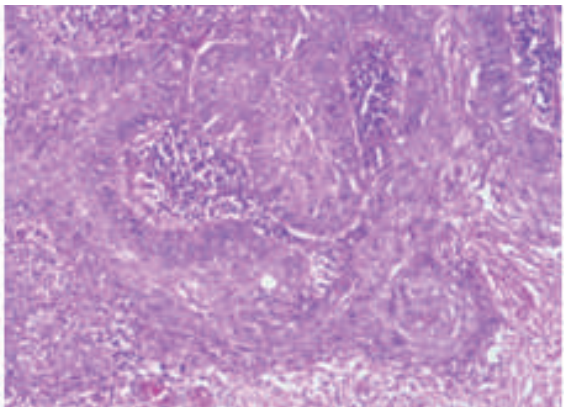

Fig 4. Ameloblastic differentiation with marked cellular atypia, showing loss of peripheral palisading or nuclear polarity and inflammatory component.

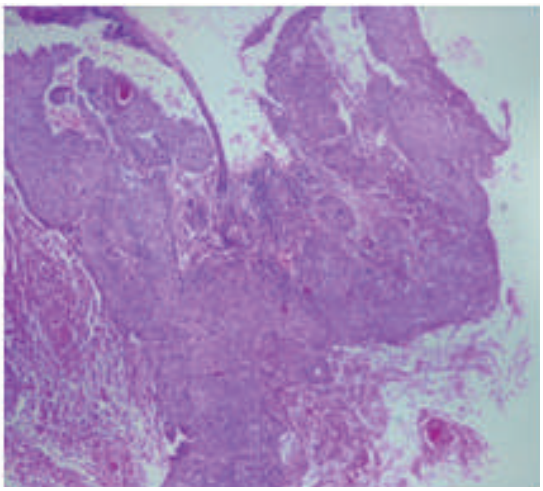

Fig 2. Ameloblastic differentiation seen along with pleomorphism of irregularly arranged epithelial cells in nests and cords.

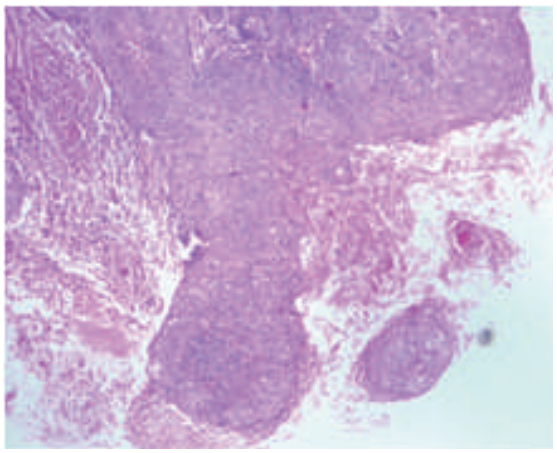

Fig 5.Islands of cells with high mitotic activity undergoing squamous metaplasia.

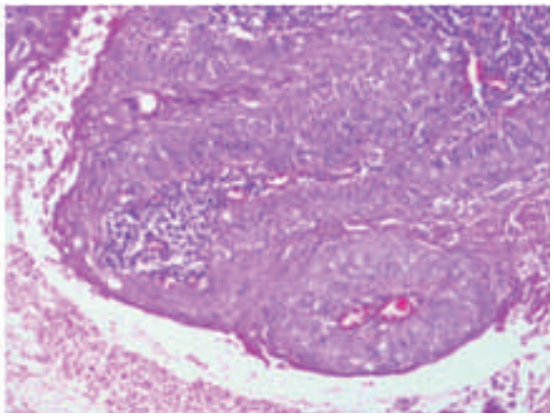

Fig 3.Ameloblastic differentiation with marked cellular atypia, showing loss of peripheral palisading or nuclear polarity and inflammatory component

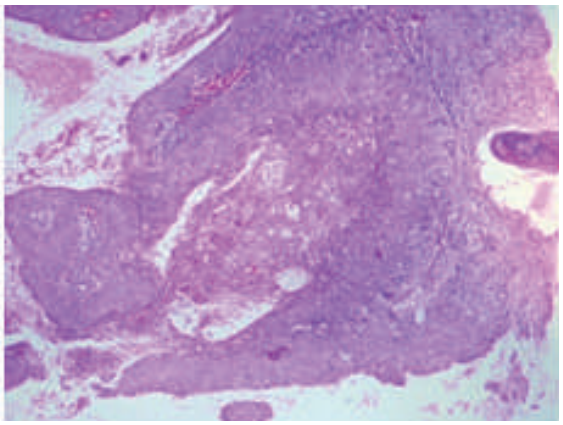

Fig 6. Areas showing keratin pearl formation surrounded by ameloblastic differentiated cells in cords.

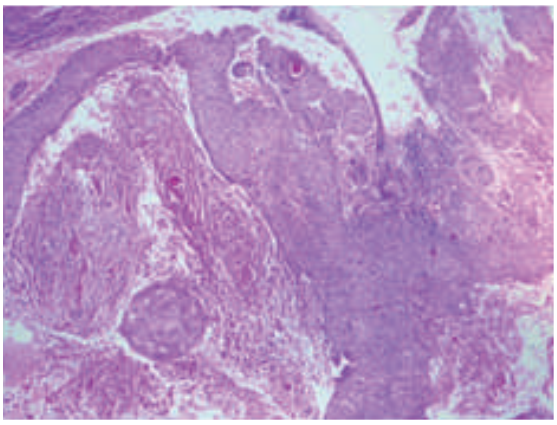

Fig 7. A satellite island of cells showing squamous metaplasia admist inflammatory cells and blood component mimicking squamous cell carcinoma

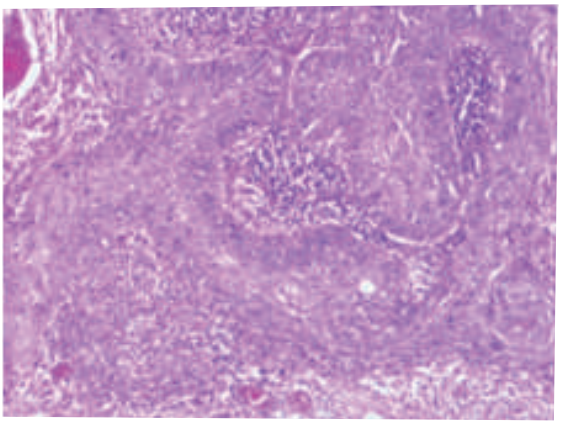

Fig 8. *Tall columnar cells demonstrating nuclear pleomorphism, and mitotic figures.*

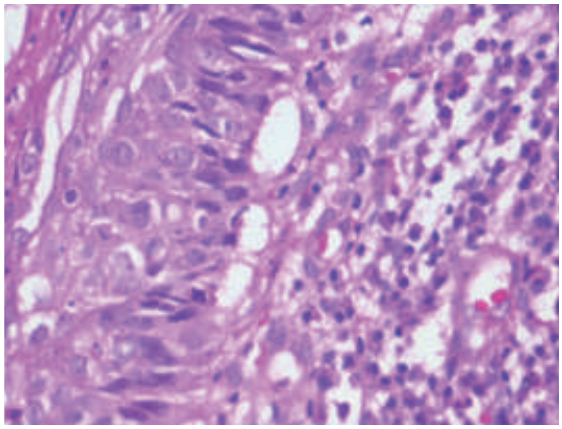

Fig 9. Tall columnar cells demonstrating nuclear pleomorphism, and mitotic figures in high power.

Discussion

Yoon et al,[9] after reviewing literature reported 98 cases between 1984 to 2008 cases and their own 6 cases along with it, making the total 104 cases. Later when we reviewed literature from 2009- 2011 ,we found evidence of 19 more cases reported in English literature suggestive of the scanty matter available to draw any conclusive parameters for diagnosis of this impasse.

Pilch[10],suggested that diagnosis of ameloblastic carcinoma is not difficult if its histopathological features are obviously suggestive of dysplasia, but however ameloblastomas also in some cases possess obvious mitotic activity. So, now the question in the current time is, what parameter should be mandatory as to distinguish how extensive a feature should be to diagnose a case as ameloblastic carcinoma. Benlyazid et al[11], reported the largest series of cases (66 cases) in recent years. On calculation the mean age was found to be 45.9 years in their case series with a higher rate of occurrence in males and in the mandible. However, Gnepp[12], concluded with a mean age of 33.5 years with similar observations on gender and site .He emphasized on cytopathological features along with ameloblastic differentiation to give a conclusive diagnosis.

According to Hall et al [13], four clinical criteria can be helpful for diagnosis of ameloblastic carcinoma such as rapid growth, propensity to perforate the cortex, pain, and paresthesia, that are distinct from their benign counterpart. They also specified the histopathological parameters such as the presence of sheets, islands, or trabeculae of epithelium, the absence of stellate reticulum–like structures, and round-to-spindled epithelial cells with little or no differentiation toward the columnar cell morphology of ameloblastoma suggest the possibility of malignant transformation. In addition to this, other authors also suggested histopathologic features like granular cell metaplasia and extensive clear cell component could be the predictors for metastasis and / or aggressive behavior.[4,14,15]

In our cases, the radiographic appearance of the lesion and histopathological features were consistent

with that of an ameloblastoma and pertained to same in incisional biopsy report too. Case 1 and Case 2 did retain the benignity on excisional biopsy, while Case 3 showed more of malignant features in certain areas suggestive of ameloblastic carcinoma. Among all the reviewed cases in literature till present time, 27% of Ameloblastic Carcinoma were misdiagnosed as benign counterpart at first hispathological diagnosis. In our Case 3, clinically a bony hard swelling was seen extending upto the left angle of mandible, which was tender in nature with no signs of parasthesia. Intraorally, there was presence of an ulcer of size 1cm X 3cm along with white slough and indurated border. Radiographically a diffuse radiolucency was seen, all above features suggestive of a benign aggressive lesion. Histopathological report of incisional biopsy also matched with clinical diagnosis.

On excisional biopsy, the patient's tissue sample showed;

- Ulcerated mucosal surface with acute inflammation is seen along with pleomorphism of irregularly arranged epithelial cells in cords and nests(Figures 1,2)
- Islands lined by tall columnar cells showing high pleomorphism with nuclear atypia and mitotic activity(Figures 3,4)
- Areas of squamous metaplasia with keratin pearl formation was also observed among the nests and cords of ameloblastic differentiated cells(Figures 5,6,7)
- High mitotic activity was seen under low and high power objective(Figure 8,9)

All the above features were suggestive of malignancy, correlative of ameloblastic carcinoma

In the differential diagnosis of ameloblastic carcinoma, the following points are consistently discussed;

1. Exclusion of metastasis or invasion of bone by tumor from adjacent soft tissue or paranasal sinus. Its also important to exclude metastases in the jaws from visceral neoplasms.[16]

2. Acanthomatous ameloblastoma (which exhibits varying degrees of squamous metaplasia and even keratinization of the stellate reticulum portion of the tumour islands; however, peripheral palisading is maintained and no cytologic features of malignancy are found) and kerato-ameloblastoma(rare variant of ameloblastoma that shows prominent keratinizing cysts) may cause some confusion and divert the pathologist from the otherwise ameloblastomatous feature.[4,17]

3. The squamous odontogenic tumor may also be mistaken for ameloblastic carcinoma. It is composed of islands of squamous epithelium that lack stellate reticulum like zones and peripheral palisading. [18]

4. Squamous cell carcinoma arising in the lining of an odontogenic cyst is also considered a differential diagnosis. Histologically, this tumor tends to more closely resemble oral squamous cell carcinoma rather than Ameloblastic carcinoma.[4,19]

5. Presence of clear cell component demands exclusion of all clear cell variant of odontogenic and nonodontogenic (primary or metastatic) neoplasm).[13]

6. Ameloblastic carcinomas arising de novo, maybe confused with primary intraosseous squamous cell carcinoma (PIOSCC), metastatic carcinoma to the jaw, central high-grade mucoepidermoid carcinoma, and bony invasion of carcinoma originating from the adjacent soft tissue. So, ameloblastic differentiation should be the basic criteria for diagnosis.[19]

7. Basaloid squamous carcinoma (BSC), may possess the diagnostic dilemma because of presence of solid nests and strands of tumor cells with peripheral palisading. To rule out Periodic acid–Schiff (PAS) positivity in microcystic spaces present in BSC was useful.

Conclusion

We would suggest for a pathologist, a more comprehensive review of every bit tissue specimen received (incisional and excisional) so as to avoid least possibility of evading a proper diagnosis. As suggested by Hall et al [13] significant populations of clear cells are indicative of malignancy, so may have prognostic importance. While reporting a specimen resembling ameloblastoma, if presence of signs malignancy or clear cells is obvious, then further investigations like immuno histochemistry(IHC) should be conducted without any prejudice to rule out ameloblastic carcinoma. IHC markers like Alpha-smooth muscle actin (a-SMA) , CK18, parenchymal MMP-2, stromal MMP-9, and Ki-67 can be useful in diagnosis of Ameloblastic carcinoma.[20,21,22]

Radiographic findings if includes a poorly defined radiolucency, sometimes with focal radiopacities which is a rare feature in ameloblastomas, indicating of something more. So, radiographic features should be studied very closely from a clinician point of view.For a surgeon, surgical resection with 10-15 mm margin free of tumour as recommended consistently, should be mandatory for every surgical procedure. Particularly in the maxilla, extent of the resection may be limited related to adjacent important anatomical structures.[23] Philip et al. suggested to apply adjuvant radiotherapy in patients with positive resection margins, multiple positive lymph nodes, extracapsular spread, perineural invasion, and in patients where salvage surgery would be inefficient.[24]Radiation therapy though proposed its efficacy depends on the lesion and considered critically as most of the ameloblastic carcinomas are intraosseous and chemotherapy regimens have been rarely reported. Regular follow- up and CT- or MRI controls should be significantly followed among clinicians due to their tendency to reccur. To prevent late recurrences, longtime follow up should be mandatory.

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