Atypical ameloblastoma – an enigma in diagnosis: review of literature and report of a case

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Received: 25/06/2010
Accepted: 06/08/2010

Abstract
Ameloblastoma, a benign neoplasm of jaw bones is the most common of all odontogenic tumors. Its pathology is generally well understood and is easy to diagnose. This article presents a rare case of an ameloblastoma with atypical features depicting an example of the diagnostic difficulty posed by some ameloblastomas and briefly reviews the classification and literature of odontogenic malignancies. This case is unusual in the fact that although the clinical presentation was suggestive of a malignancy, the histological features were not sufficient to warrant the lesion as malignant. Albeit, the features of epithelial dedifferentiation were evident at post operative histopathological evaluation but no proof was available to authenticate frank metastasis or carcinoma. The case was diagnosed as an atypical ameloblastoma and frequent follow up was recommended. This article discusses about ameloblastic carcinoma, other odontogenic malignancies and emphasizes the need for standardization and quantification of the fundamental concepts of odontogenic malignancies for more reliable and early diagnosis for better treatment and prognosis.

Key words: Atypical ameloblastoma, proliferative ameloblastoma, ameloblastic carcinoma.
Introduction
Of all the odontogenic tumors, the pathology of ameloblastoma – being the most common is generally well understood. However the concept of odontogenic malignancies has been a subject of considerable discussion and controversy for many years. The term ameloblastic carcinoma is used to designate a lesion with histological evidence of malignancy in primary tumor, regardless of whether it has metastasized (1). The malignant epithelial proliferation may initially be present with a resemblance to an ameloblastoma (de novo ameloblastic carcinoma) or sometimes an ameloblastoma may show features of epithelial dedifferentiation overtime (ameloblastic carcinoma ex-ameloblastoma) (2). If the anaplastic features are not sufficient to justify an ameloblastoma as malignant, it can be called as atypical ameloblastoma (3). Ameloblastic carcinoma is a rare odontogenic malignancy that challenges the diagnostic acumen of the pathologists as the understanding of the identifying histological features of the tumor is some what vague and not standardized/quantified. We herein report a rare case of ameloblastoma which had an aggressive behavior and histologically had areas of cytological atypia which warrant a more aggressive surgical approach and follow up. The purpose of this article is to emphasize the need for standardization and quantification of the fundamental concepts of odontogenic malignancies for more reliable and early diagnosis because this has a direct bearing on the treatment plan and prognosis.

Case Report
A 58 years old male patient reported to the out patient department of Manipal college of dental sciences, Mangalore in February 2007 with the chief complaint of a non tender swelling of 2 years duration on the left side of his face. The swelling had started as a small peanut size bulge and had gradually increased to the present size. The patient gave no history of fever, malaise, associated pain or paresthesia or dysphagia. The past medical history revealed an unhealed extraction socket in relation to 37. The malignant proliferation may initially be present with a resemblance to an ameloblastoma (de novo ameloblastic carcinoma) or sometimes an ameloblastoma may show features of epithelial dedifferentiation overtime (ameloblastic carcinoma ex-ameloblastoma) (2). If the anaplastic features are not sufficient to justify an ameloblastoma as malignant, it can be called as atypical ameloblastoma (3). Ameloblastic carcinoma is a rare odontogenic malignancy that challenges the diagnostic acumen of the pathologists as the understanding of the identifying histological features of the tumor is some what vague and not standardized/quantified. We herein report a rare case of ameloblastoma which had an aggressive behavior and histologically had areas of cytological atypia which warrant a more aggressive surgical approach and follow up. The purpose of this article is to emphasize the need for standardization and quantification of the fundamental concepts of odontogenic malignancies for more reliable and early diagnosis because this has a direct bearing on the treatment plan and prognosis.

Microscopically, the tissue sections from the buccal aspect showed a characteristic lining suggestive of a unicystic ameloblastoma consisting of a basal layer of tall columnar ameloblast like cells exhibiting reversal of polarity. The superficial layers consist of several rows of stellate reticulum like cells. Focal areas of lining epithelium showed flattened basal cells. Proliferations of the lining epithelium into the lumen as well as underlying connective tissue were also observed. The mural as well as the luminal proliferations showed plexiform ameloblastoma with areas of microcyst formation arising as a result of stromal degeneration. The stromal blood vessels showed degenerative changes appearing only as ghostly outlines surrounding few inflammatory cells.

The sections from the unhealed socket area revealed ulcerated parakeratinised stratified squamous epithelium.
with epithelial proliferation noted at the margin of ulcer. Deeper in the connective tissue the epithelial proliferation from the margin of ulcer merged with the plexiform ameloblastoma. The sections taken from the lingual aspect revealed a follicular ameloblastoma showing numerous small and large sized ameloblastomatous follicules with a central core of stellate reticulum like cells and areas of cystic degeneration. Sheets of odontogenic epithelial cells within the connective tissue demonstrated extensive cellular pleomorphism with cells varying from ovoid to spindle in shape (Fig. 2). Occasional mitosis (typical and atypical) was evident within the sheets of odontogenic epithelium along with other features like increased nuclear cytoplasmic ratio, prominent nucleoli (Fig. 2).

However, the epithelial dedifferentiation as seen in the present case, is not enough to warrant the ameloblastoma as malignant. Such tumors can be called as atypical ameloblastoma (3).

Ameloblastic carcinoma is a malignant odontogenic tumor, the diagnosis of which is as enigmatic, as was its position in the classification of odontogenic malignancies. The term Ameloblastic carcinoma was acknowledged by the World Health Organization (WHO) (2) as late as in 2002. The classification of odontogenic malignancies and the concept of malignancy in ameloblastoma is a controversial topic which has been discussed for long. Various classifications have been developed to categorize ameloblastic carcinomas (2-5).

The WHO published its classification for malignant neoplasms and other tumors related to the odontogenic apparatus in 1972 and recognized the following subtypes:

**Odontogenic carcinoma**
A. Malignant ameloblastoma
B. Primary intraosseous carcinoma (PIOC)
C. Other carcinoma arising from odontogenic epithelium including those arising from odontogenic cyst

In this initial attempt to classify odontogenic carcinomas, the WHO failed to specifically delineate ameloblastic carcinomas. This WHO classification system recognized and distinguished PIOC from malignant ameloblastoma but it did not consider the possibility that a squamous cell carcinoma could arise in a pre-existing ameloblastoma and had no sub-division under which such entities could be placed.

Initially, the term ameloblastic carcinoma was introduced to describe ameloblastomas in which there had been histological malignant transformation in association with less differentiated evidence of metastatic growths. Such tumors showed features of ameloblastoma intermingled with those of carcinoma.

Elzay (4) in 1982 suggested that the WHO classification...
be modified to permit the separation and recognition of closely related entities. So he classified all intraosseous carcinoma under the heading of PIOC and then those tumors were subclassified and subtyped according to histological evidence of origin. The proposed classification was as follows:

**Primary Intraosseous Carcinoma**

*Type 1* – Arising ex odontogenic cyst

*Type 2* – Arising ex ameloblastoma
   a) Well differentiated - Malignant ameloblastoma
   b) Poorly differentiated - Ameloblastic carcinoma

*Type 3* – Arising de novo
   a) Non-keratinizing
   b) Keratinizing

Accordingly, the PIOC type II recognized the potential for malignification of ameloblastoma with varying degree of differentiation. Hence II A was reserved for tumors which histologically demonstrated proper ameloblastoma in the jaw and in any metastatic lesion. In essence, such tumors would be well differentiated where as the type II B sub classification was reserved for less differentiated tumors having histological features of ameloblastoma and squamous cell carcinoma concomitantly.

Two years later, in 1984, Slootweg and Müller (5) published a paper reviewing 42 cases of malignant ameloblastoma (according to WHO) and adding 2 more to the list. They pointed out that some cases of PIOC may have areas that are morphologically similar to malignant ameloblastoma. Thus there is a possibility that a PIOC would have been classified as a malignant ameloblastoma if metastasis had occurred or as a PIOC if metastasis had not occurred. They also pointed out that matters had been further complicated because of no distinction between malignant ameloblastoma and ameloblastic carcinoma. They pointed out that the WHO classification of odontogenic carcinoma should be revised in some aspects. They advocated the modification proposed by Elzay (4) and proposed a slight modification taking in account the various possible origins of PIOC. So the classification they proposed was:

**Primary Intraosseous Carcinoma**

*Type 1* – Primary intraosseous carcinoma ex odontogenic cyst

*Type 2* – Primary intraosseous carcinoma arising ex ameloblastoma
   a) Malignant ameloblastoma
   b) Ameloblastic carcinoma, arising de novo, ex ameloblastoma or odontogenic cyst

*Type 3* – Primary intraosseous carcinoma arising de novo
   a) Non-keratinizing
   b) Keratinizing

So, they accepted that malignant ameloblastoma and ameloblastic carcinoma be included under the encompassing term “PIOC ex ameloblastoma” as proposed by Elzay (4). And they proposed that for giving a correct diagnosis, the taxonomic problem can be avoided by assuming that ameloblastic carcinomas can arise not only de novo or from a well differentiated ameloblastoma but also from other sources of odontogenic epithelium eg. odontogenic cyst. Thus, the main difference between Elzay’s (4), and Slootweg and Müller’s (5) schemes relates to the minor point of histogenesis.

In 1992, a modified WHO classification system for the odontogenic carcinomas was published (7), including the following categories:

**Odontogenic carcinoma**

A. Malignant ameloblastoma
B. Primary intraosseous carcinoma
   *(de novo, ex ameloblastoma, ex odontogenic cyst)*
C. Malignant variants of other odontogenic epithelial tumors
D. Malignant changes in odontogenic cyst

Inspite of all the proposals made, it failed to recognize ameloblastic carcinoma as a separate entity. Since the WHO classification did not recognize the existence of ameloblastic carcinoma, all such lesions had to be classified either as PIOC or as malignant ameloblastoma. Because of this overlapping of terminologies, the potential of the histological diagnosis to distinguish the biologic behavior, prognosis and treatment plan of the ameloblastic carcinoma and closely related tumors was hindered. This taxonomic problem continued for a decade and finally ended in 2002 when ameloblastic carcinoma was recognized by the WHO in its revised version by Philipsen and Reichart (2).

The categories identified in the WHO’s revised version 2002 (2) were:

**Odontogenic carcinoma**

A. Metastasizing ameloblastoma
B. Ameloblastic carcinoma
   * Primary (=de novo)
   * Carcinoma ex ameloblastoma (=dedifferentiated)
   * Peripheral
C. Primary intraosseous carcinoma
   * Solid
   * Cystogenic
D. Ghost cell odontogenic carcinoma
E. Clear cell odontogenic carcinoma

Thus, the term “ameloblastic carcinoma” was used by Shafer, Elzay(4), Slootweg and Müller’s (5), primarily to convey the presence of cytologic features of malignancy in an ameloblastoma came into being and got recognized.

Ameloblastic carcinoma is considered to be a rare odontogenic malignancy. Akrish et al. (6) analyzed all the published cases in English language literature between the years 1984 and 2004 to find only 37 cases reported in addition to the case presented in the paper (making a
total of 38 cases). It might be that, because of the pro-
longed controversy around ameloblastic carcinoma it
was either wrongly categorized or less reported. Unfor-
unately, as a consequence of this, the understanding of
the identifying clinical and histological features of the
tumor is still some what vague and not standardized/
quantified.
Although Corio et al. (1) had reported the mean age of
occurrence to be 30.1 years with no gender predilec-
tion, recently Akrish et al. (6) reported the mean age of
occurrence to be 52 years and the male to female ratio
being 1.5 to 1. The posterior mandible was the most fa-
vored site in both the reports. Radiographically the tu-
mor resembles ameloblastoma and mostly appears as a
multilocular radiolucency. Clinically the patients mostly
complain of expansion, a hard mass, rapid growth, fac-
cial asymmetry, a nonhealing extraction site, an ulcer,
a fistula or perforation of the cortex. These clinical fea-
tures though suggestive of a malignancy, are again not
pathognomonic. In the present case also the patient had
most of these features.
Histologically ameloblastic carcinoma demonstrates
more cytologic atypia and mitotic activity than ame-
loblastoma. It includes the features of epithelial dedi-
fferentiation. There is lack of evidence of reverse po-
larization, sheets of disordered mitotically active small
basaloid cells with dark nuclei; larger squamoid or po-
olygonal cells with vesicular nuclei; or elongated spind-
dled epithelial cells (6). The histological diagnosis is not
an easy one and a pathologist must rule out a lexicon of
differential diagnosis which includes the typical amelo-
blastoma, metastatic carcinoma to the jaw, intra bony ex-
tension of a surface mucosal carcinoma, central salivary
gland tumor, PIOC, acanthomatous ameloblastoma, ke-
ratoameloblastoma, squamous odontogenic tumor, and
calciifying epithelial odontogenic tumor. In the present
case also all these differential diagnoses were ruled out
as elaborated by Coiro et al. (1)
Until 2004, the terms aggressive or proliferative ame-
loblastoma, ameloblastic carcinoma and atypical amelo-
blastoma were used synonymously by some in-
vestigators (7). In 2004 Slater (3) suggested that ame-
oblastomas which exhibit basilar hyperplasia and an in-
creased mitotic index should be designated as “atypical
ameloblastomas” or “proliferative ameloblastomas” be-
cause these findings are probably insufficient to permit
a diagnosis of ameloblastic carcinoma in the absence of
nuclear pleomorphism, perineural invasion or other his-
tologic evidence of malignancies (3). The picture is fur-
ther complicated by the fact that although the presence
of abundant mitotic figures is one of the most important
diagnostic criteria, the prognostic significance of this is
not known (8).
The enigma about the diagnosis of ameloblastic carcino-
ma is further aggravated because the diagnostic criteria
to distinguish between ameloblastoma, atypical amelo-
blastoma and ameloblastic carcinoma are not standar-
dized/ quantified. Many important questions/concepts
remain unanswered e.g. Is the diagnosis of atypical amelo-
blastoma of any relevance for treatment options?
What features are necessary to differentiate between the-
se closely related lesions? Which histologic feature is
a sine qua non for diagnosing a particular odontogenic
malignancy? If two lesions have an overlapping features
e.g. Presence of mitotic figures or a high proliferative in-
dex, how many mitoses per high power field or what per-
cent of cells showing high index should distinguish two
closely related lesions? We hereby strongly propose that
the fundamental concepts of odontogenic malignancies
should be standardized and quantified for more reliable
and early diagnosis because this has a direct bearing on
the treatment plan and prognosis.
To conclude, the present case is an example of the diag-
nostic difficulty posed by some ameloblastomas. This
case is unusual in the fact that although the age, rapidity
of growth and clinical presentation were suggestive of a
malignancy, the histological features were not sufficient
to warrant the lesion as malignant. Albeit, the features of
epithelial dedifferentiation were evident at post operative
histopathological evaluation but no proof was available
to authenticate frank metastasis or carcinoma. Hence in
the light of current concepts the tumor was categorized
as an ameloblastoma with atypical features and frequent
follow up was recommended.

Atypical ameloblastoma.
References