

# Alpha Smooth Muscle Actin Expression in a Case of Ameloblastic Carcinoma: a Case Report

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## ABSTRACT

**Background:** The aim of the present article is to report a case of ameloblastic carcinoma and use a marker alpha smooth muscle actin as a tool to differentiate cases of ameloblastic carcinoma from that of ameloblastoma.

**Methods:** Case study reporting a case of ameloblastic carcinoma (AC) with expression of alpha smooth muscle actin (alpha-SMA) as a marker for emergence of stromal myofibroblasts. The expression of myofibroblasts was also compared with that of ameloblastoma.

**Results:** Difference between the two lesions in the pattern of expression of alpha smooth muscle actin was also observed. There was increase in the number of myofibroblasts in the stroma of AC while in ameloblastoma, it was comparatively less. Secondly, few areas of the carcinomatous ameloblastic island also exhibited a mild positivity towards alpha smooth muscle actin.

**Conclusions:** Increase in number of stromal myofibroblast may be taken as a predictor for carcinomatous transformation. Further studies with greater sample size can validate the use of alpha-SMA as a marker to differentiate ameloblastic carcinoma from ameloblastoma.

**Keywords:** carcinoma; ameloblastoma; myofibroblasts; alpha-smooth muscle actin, human.

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## INTRODUCTION

Shafer in 1983 [1] introduced the term ameloblastic carcinoma (AC) to describe ameloblastomas in which there had been histological malignant transformation.

It is currently defined as a rare odontogenic malignancy that combines the histological features of ameloblastoma with cytological atypia, even in the absence of metastases. Although this lesion represents a separate entity, differentiating it from ameloblastoma has been often challenging to pathologists [2]. Recent study targets the different expression pattern of immunohistochemical markers in order to differentiate a case of AC from ameloblastoma.

A wide range of epithelial-associated factors are implicated in the relative aggressive biological behaviour of the odontogenic epithelium while only a few studies have investigated non-epithelial factors [3]. Tissue integrity is maintained by the stroma in physiology. In cancer however, tissue invasion takes place with the help of stroma. Myofibroblasts and cancer-associated fibroblasts are important components of the tumour stroma [4]. In fact the presence of stromal myofibroblasts has been linked to the biological behaviour of both benign and malignant tumours [5].

In a recent case study, we attempted to differentiate AC from ameloblastoma on the basis of difference in expression pattern of alpha smooth muscle actin (alpha-SMA).

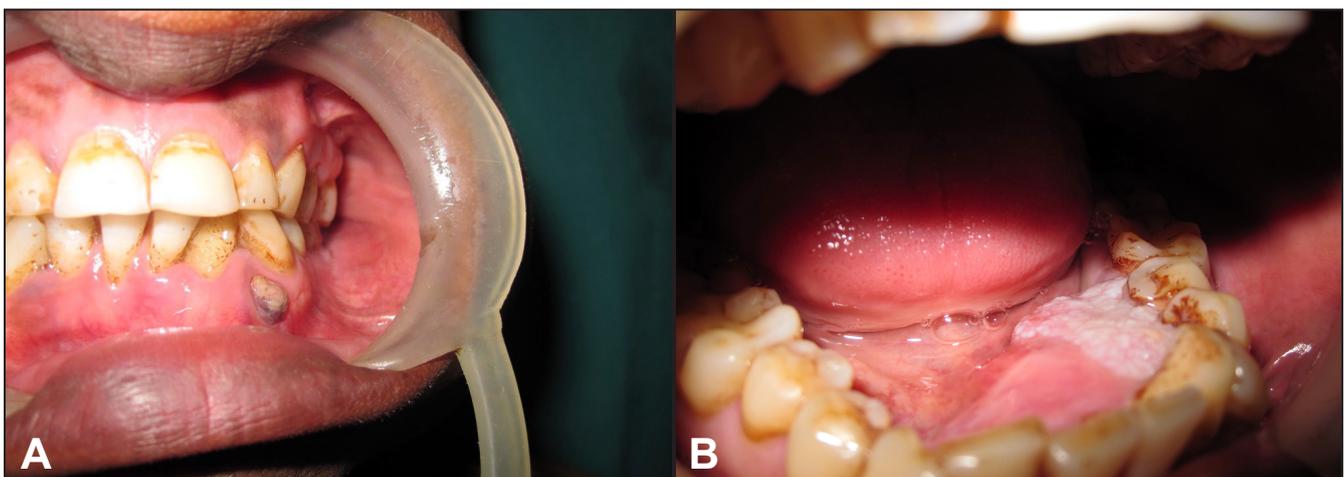
## CASE DESCRIPTION AND RESULTS

A 27 year old male patient presented to the department of oral and maxillofacial surgery with a chief complaint of the pain and swelling over the left lower back side of the face since last 4 months. The swelling was insidious

in onset and was associated with moderate degree of pain. The skin over the swelling was normal in colour but there was slight increase in temperature. Intraoral examination revealed expansion of the lingual cortical plate in the anterior aspect and buccal cortical plate in the posterior region. Two ulcers were seen with respect to the swelling, one on the anterior lingual aspect measuring about 12 x 8 mm and second one measuring about 5 x 4 mm (Figure 1A, B).

Computed tomographic image of the mandible showed an ill-defined radiolucent mass with respect to the left ramus/body area of size about 2 x 3 cm (Figure 2). The radiograph clearly reveals the perforation of the buccal cortical plate. The differential diagnosis included aggressive odontogenic tumour, intraosseous squamous cell carcinoma, and metastatic carcinoma. Incisional biopsy was performed and the findings were suggestive of AC. As the patient did not give any history of previous surgery, so the primary variant of ameloblastic carcinoma was considered. Patient underwent hemimandibulectomy along with excision of the tumour mass under general anaesthesia, following which he was suggested radiation therapy (Figure 3).

The excisional specimen underwent routine tissue processing and samples were used for haematoxylin and eosin staining and immunohistochemical (IHC) staining for alpha-SMA. Sections of 3  $\mu$  thicknesses were cut and mounted on organo-silane coated slides (Biogenex). After dewaxing in xylene, sections were dehydrated in ethanol, rinsed in distilled water, placed in 3% H<sub>2</sub>O<sub>2</sub> for 10 min and rinsed in distilled water for 15 min. For antigen retrieval procedure, slides were placed in citrate buffer solution, pH = 6, in a microwave at 92 °C for 10 min. After cooling at room temperature for 20 min, slides were exposed to primary alpha-SMA mouse anti-human antibody (Biogenex), dilution 1:100, for 60 min at room temperature. Slides were rinsed in PBS for 10 min. For antibody detection, universal



**Figure 1.** Intraoral view showing buccal (A) and lingual (B) cortical expansion and overlying mucosal ulceration.



**Figure 2.** Computed tomography image showing mandibular cortical plate expansion and erosion of the bony plates.



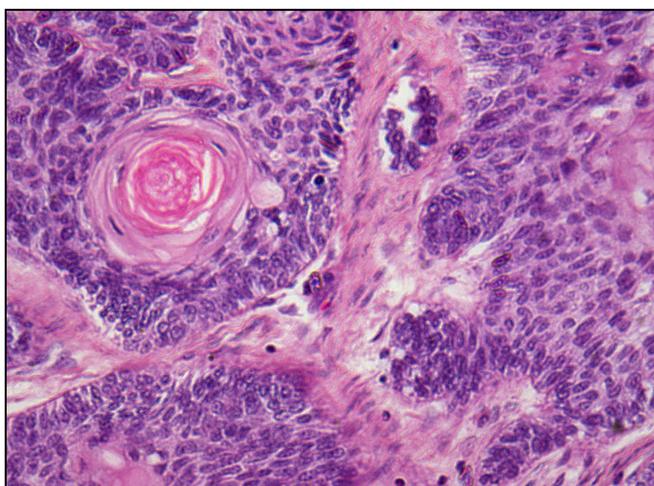
**Figure 3.** The surgically excised mandibular specimen showing the extent of the lesion.

immune peroxidase polymer anti-mouse rabbit kit was used. Sections were rinsed in PBS for 10 min, reacted with AEC substrate-chromagen kit, rinsed in PBS for 2 min, counterstained in Harris hematoxylin (Nice chemicals), and covered with DPX mounting medium. Tissue sections of a specimen of follicular variant of solid multicystic ameloblastoma were also examined for alpha-SMA to determine whether these diagnostic tests could be used to differentiate AC (primary) from ameloblastoma.

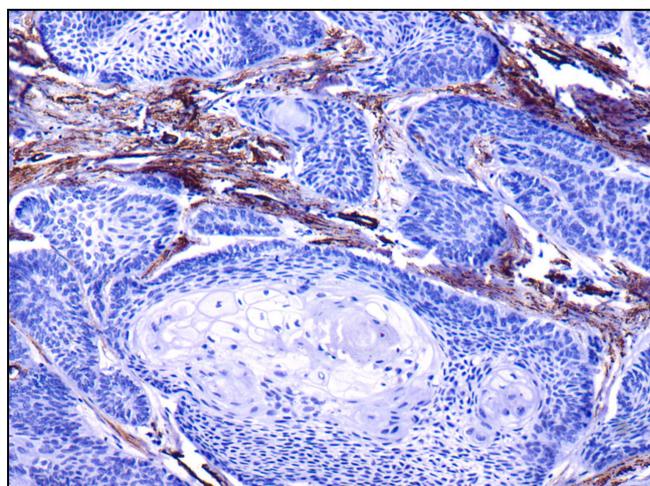
The hematoxylin and eosin stained sections of AC showed odontogenic epithelial islands of highly irregular shape spread in a scanty fibrous connective tissue stroma. The periphery of epithelial islands was lined by columnar ameloblast-like cells. The central portion showed cells of both stellate shape and squamous cells. The odontogenic epithelial islands exhibited pleomorphism and showed abnormal

mitotic figures. The central cells in few areas showed pleomorphism with an attempt of malignant keratin pearl formation. Basilar hyperplasia was observed in few islands. The stroma was well vascularized. Necrosis, vascular and neural invasion were not observed (Figure 4). Based on the findings of cellular pleomorphism, presence of mitotic figure and irregular shaped islands of odontogenic epithelial cells, a diagnosis of AC was made.

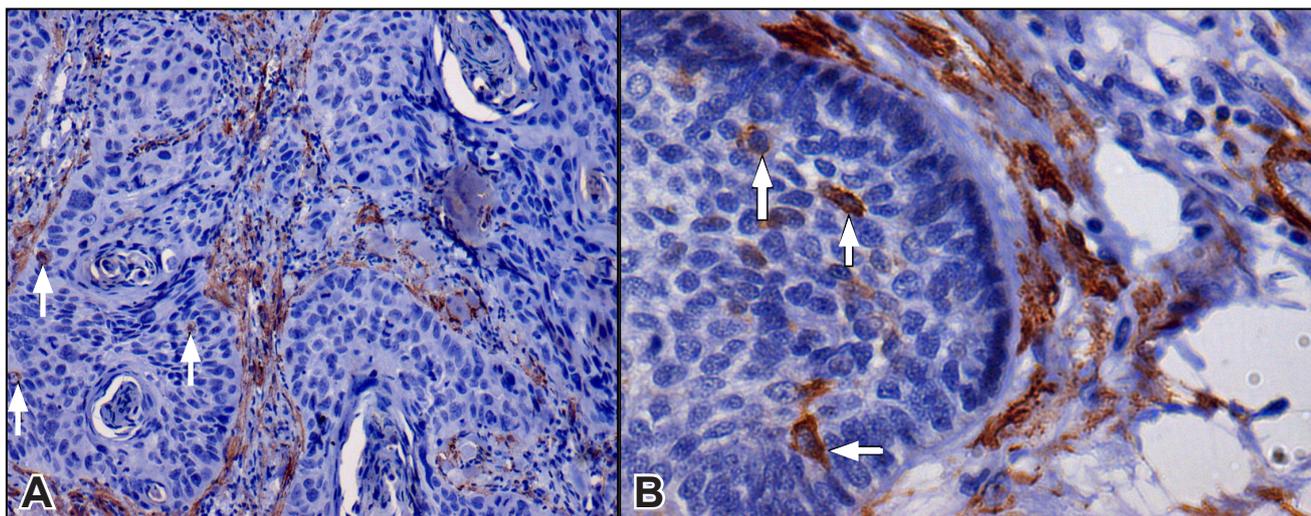
IHC stained slide of AC showed strong immunoreactivity to alpha-SMA in the stroma surrounding the tumour islands (Figure 5). Additional finding was that few cells within the tumour island also exhibited faint positivity towards alpha-SMA (Figure 6A, B). While in case of follicular ameloblastoma, alpha-SMA positive cells were seen only in the stroma and that too in reduced number. Positive cells in the wall of endothelial vessels were taken as internal positive control (Figure 7).



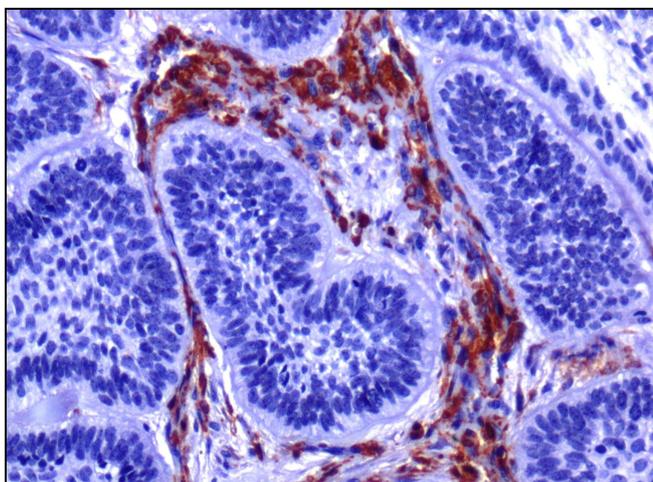
**Figure 4.** Haematoxylin and eosin stained section of ameloblastic carcinoma showing cellular atypia (original magnification x400).



**Figure 5.** Increased expression of alpha smooth muscle actin in ameloblastic carcinoma (original magnification x100).



**Figure 6.** Expression of alpha smooth muscle actin (indicated by arrows) in the epithelial islands of ameloblastic carcinoma: A = original magnification x200; B = original magnification x400.



**Figure 7.** Expression of alpha smooth muscle actin in the stroma of follicular ameloblastoma (original magnification x200).

## DISCUSSION

Carcinomas derived from ameloblastoma have been given the name ameloblastic carcinoma. These may arise *de novo*, ex ameloblastoma, or ex odontogenic cyst [6].

Two types of typical ameloblastoma must also be considered in the differential diagnosis of AC. First being the 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. The other being kerato-ameloblastoma, which is a rare variant of ameloblastoma that contains prominent keratinizing cysts that may cause some alarm and distract the pathologist from the otherwise ameloblastomatous features. An additional consideration in the differential

diagnosis of ameloblastic carcinoma is squamous cell carcinoma arising in the lining of odontogenic cyst. Histologically, this lesion tends to more closely resemble oral squamous cell carcinoma than what we have described for AC. However, it is of interest that AC can apparently arise from a cystic lining [7].

AC occurs in a wide range of age groups with no apparent sex predilection. Posterior portion of the mandible is the most common site of involve with maxillary involvement being less frequent. The lesion most commonly presents with swelling with or without associated pain, rapid growth, trismus and dysphonia [1].

Tissue stroma is essential for the maintenance of the epithelial tissues. Both, the epithelium and the stroma, makes up an ecosystem in which there is a continuous molecular cross-talk between the participating cells. The appearance of myofibroblasts in the adjoining stroma is secondary to the neoplastic changes in the adjacent epithelium. TGF $\beta$ 1 and PDGF released by neoplastic cells, even at a pro-invasive state, are responsible for emergence of myofibroblast [3].

Tumour progression occurs within a microecosystem, where cancer cells and myofibroblasts exchange proteinases and cytokines that promote growth directly through stimulation of proliferation and survival, as well as invasion through local proteolysis of the extracellular matrix and stimulation of motility. Studies on oral squamous cell carcinoma demonstrated the increased stromal myofibroblasts as assessed by alpha-SMA immunoreactivity is associated with poor prognosis [2]. In the present study we investigated the expression of alpha-SMA in AC and compared the findings to that of a case of follicular ameloblastoma. Increased expression of alpha-SMA positive cells was seen in the stroma of AC (Figure 5 and Figure 6A, B). The expression of

alpha-SMA in the epithelial islands of AC was minimal. Similar study was done by Kamath et al. [2] and Bello et al. [8], and they also reported increased expression of alpha-SMA in the stroma of AC and few areas of epithelial islands were also positive for alpha-SMA. They suggested the use of alpha-SMA in differentiating AC from ameloblastoma and expression of alpha-SMA within the epithelial islands is highly predictive of AC. The role of myofibroblast in tumour progression is an important area of current research and has emerged as a potential target for therapeutic intervention. These cells are recruited by the tumour cells and infiltrate the tumour microenvironment to support tumour growth and progression by the secretion of growth factors, extracellular matrix proteins, and by stimulating angiogenesis [9]. Recent reviews have emphasized the advantages of therapeutic targeting of the tumour-associated stroma as the stromal cells is presumably critical for the growth of nearby neoplastic cells and these are stable genetically in contrast to carcinoma cells, which accumulate adaptive mutations during the course of therapy in order to acquire drug resistance [10]. At present, there are relatively few studies in support of the expression of alpha-SMA in odontogenic

carcinomas to correlate it with the diagnosis and prognosis of these lesions. Study involving larger sample size and survival analysis is needed to validate this conclusion.

## CONCLUSIONS

Ameloblastic carcinoma is a relatively aggressive lesion. Early diagnosis and treatment may help in decreasing patient morbidity. Pathologist still find it difficult to differentiate a case of ameloblastoma from ameloblastic carcinoma. Immunohistochemical expression of alpha smooth muscle actin may help in establishing an early diagnosis and chemotherapeutic agents against stromal myofibroblasts can be used as an adjunct to the surgery in planning the treatment for these locally aggressive and infiltrating lesions.

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The authors report no conflicts of interest related to this study.

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