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CASE REPORT

Malignant Transformation of a Desmoplastic Ameloblastoma to Squamous Cell Carcinoma: A Case Report

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Abstract
Ameloblastomas are the most common odontogenic tumors, excluding odontomas. Several morphologic variants have been described including follicular, plexiform, acanthomatous, granular cell, basaloid and desmoplastic. Desmoplastic ameloblastoma differs from other conventional ameloblastomas microscopically, clinically, and radiographically. Ameloblastic carcinoma, the malignant counterpart of ameloblastoma is characterized by cytologic features of malignancy combined within the overall histologic features of conventional ameloblastoma. Malignant transformation of ameloblastoma to squamous cell carcinoma is a controversial subject. Here we report a case of a desmoplastic ameloblastoma with malignant transformation to squamous cell carcinoma in a 49 year old African American man. The patient underwent tumor resection and radiation therapy with no evidence of disease recurrence or progression 16 months post operatively. To our knowledge malignant transformation of a desmoplastic ameloblastoma to squamous cell carcinoma has not so far been reported. This observation may lend some support to the argument that desmoplastic ameloblastoma is phenotypically and biologically distinct entity.

Keywords Malignant transformation · Desmoplastic ameloblastoma · Squamous cell carcinoma

Introduction

Ameloblastomas are the most common odontogenic tumors excluding odontomas. They usually occur in the 3rd to 4th decades of life with no significant sex predilection. Roughly, 80% of these lesions occur in the mandible with 2/3 in the posterior mandible. Several morphologic variants have been recognized including follicular, plexiform, acanthomatous, granular, basaloid and desmoplastic [1]. The desmoplastic ameloblastoma (DA) was initially recognized by Eversole et al. [2] and was referred to as ameloblastoma with pronounced stromal desmoplasia [2]. This entity was further defined by Waldron and El-Mofty 3 and was termed desmoplastic ameloblastoma (DA) [3]. In 2005, the term desmoplastic ameloblastoma was formally adopted by the World Health Organization [4]. DA is distinguished from other morphologic variants of ameloblastoma not only microscopically but also clinically and radiographically [1–8]. Unlike conventional ameloblastoma the lesions of DA occur more frequently in the anterior parts of the jaws especially the maxilla. Radiographically the desmoplastic lesions show a mixed radiolucent and radiopaque appearance, more suggestive of fibro-osseous lesions and lacking the multilocular radiolucency characteristic of conventional ameloblastoma. Microscopically, DA is distinguished not only by its predominant desmoplastic collagenous stroma but also by its characteristic epithelial component. The tumor epithelium consists of ovoid or follicle shaped island and narrow cords. The epithelial cells about the periphery of the islands and strands are mostly cuboidal. Typical columnar cells demonstrating reversed polarity which are commonly found in conventional ameloblastoma are rarely conspicuous. The central epithelial areas are composed of polygonal cells with occasional squamous metaplasia and rare foci of keratinization. Classic stellate reticulum of conventional ameloblastoma is laking. Bone formation within the desmoplastic stroma is occasionally seen.

Ameloblastic carcinoma, the malignant counterpart of ameloblastoma is characterized by atypical cytologic features of malignancy combined within the histologic features of conventional ameloblastoma. Malignant transformation of ameloblastoma to squamous cell carcinoma is a controversial subject [9, 10]. To our knowledge malignant transformation

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of a desmoplastic ameloblastoma to squamous cell carcinoma has not so far been reported. Here we report a case of a desmoplastic ameloblastoma in which squamous cell carcinoma developed.

Case Report

The patient is a 49-year-old, African American male with a history of paranoid schizophrenia but otherwise in good physical health. He presented with right nasal airway obstruction for several months. The patient also complained of occasional epistaxis. A maxillofacial CT scan showed an expansive radiolucent/radiopaque lesion, with lytic changes, in the alveolar process of the right maxilla extending superiorly into the right maxillary sinus and right nasal cavity. A displaced tooth was also noted along the anterolateral margin of the lesion (Fig. 1). An intraoperative frozen section biopsy specimen was reported as squamous cell carcinoma (Fig. 2). The patient underwent right total maxillectomy with free flap reconstruction and titanium plate orbital reconstruction. He completed a course of postoperative radiation therapy to 66GY without concurrent systemic therapy. He tolerated the treatment well without complications and there was no evidence of disease recurrence or progression 16 months post operatively.

Microscopic Examination

Sections of the resected tumor showed a biphasic neoplasm with both benign and malignant epithelial components in an extensive desmoplastic collagenous stroma. Destruction of the maxillary bone as well as reactive new bone formation was evident. The benign epithelial component showed typical morphologic features of DA (Fig. 3). It consisted of ovoid or follicle shaped island and narrow cords. The epithelial cells about the periphery of the islands and strands were mostly cuboidal. Typical columnar cells that demonstrate reversed polarity which are typically found in conventional ameloblastoma were rarely conspicuous. The central epithelial areas were composed of polygonal cells with occasional squamous metaplasia and rare foci of keratinization. Typical stellate reticulum of conventional ameloblastoma was laking. The malignant epithelial component was composed of infiltrating islands and small nests of well to moderately differentiated squamous cell carcinoma. Overlapping of the two component was focally evident. In these areas the benign odontogenic epithelium showed evidence of progression to squamous cell carcinoma (Fig. 4). Ki-67 and p53 immunohistochemical stains were performed to better characterize and classify the lesion. A distinct difference between the proliferation indices of the benign and malignant epithelial components was illustrated by Ki-67 (Fig. 5). p53 stain showed a higher nuclear expression within the squamous cell carcinoma component compared to that of DA (Fig. 6). Additional BRAF-V600E immunohistochemical stain was performed and was negative in both the benign and malignant component (Fig. 7).

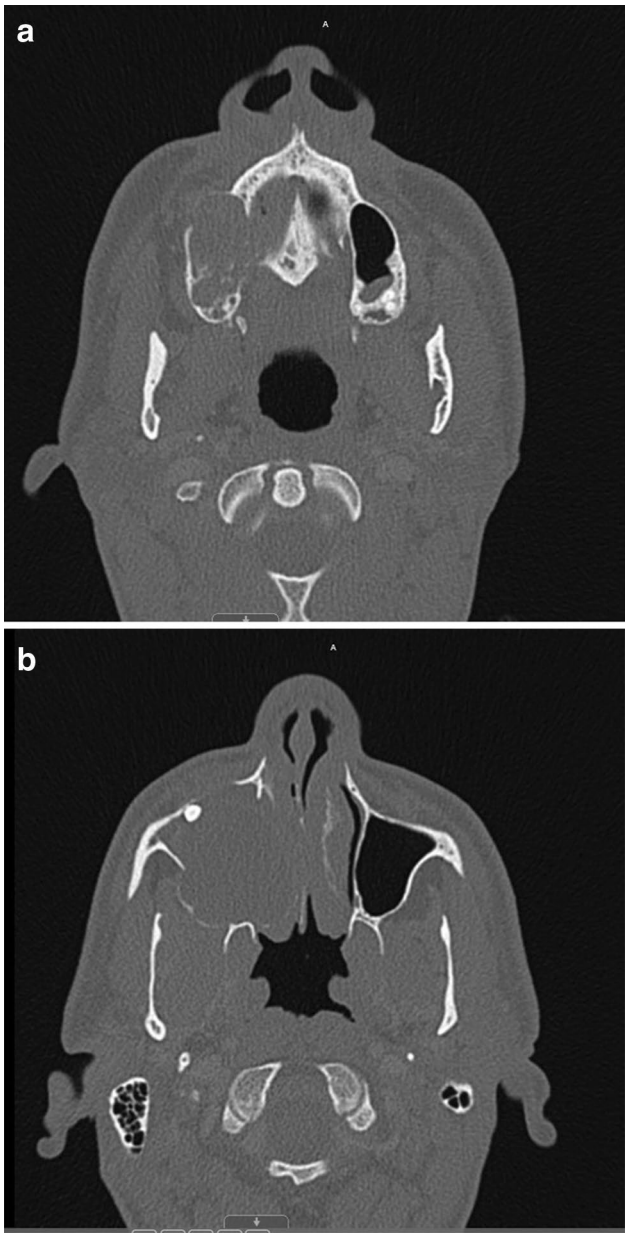

Fig. 1 Maxillofacial CT scans showing an expansive radiolucent/radiopaque lesion, with lytic changes, in the alveolar process of the right maxilla extending superiorly into the right maxillary sinus and nasal cavity (**a, b**). A displaced tooth was also noted along the anterolateral margin of the lesion (**b**)

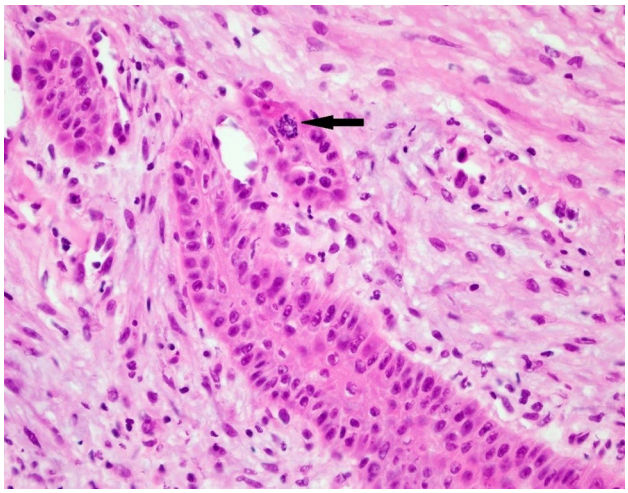

Fig. 2 Intra-operative frozen section showing dysplastic squamous epithelium, and nests of invasive squamous cell carcinoma. Atypical mitotic figure is seen (arrow)

Discussion

The Desmoplastic ameloblastoma consists of 0.9–12.1% of all ameloblastomas. The average age at presentation is approximately 42.3 years (range 17–70 years) with age and gender predisposition being similar to that of other ameloblastomas [11]. These lesions can be seen in various populations, most commonly encountered in Malaysians, Japanese, Afro-Caribbean's and Asians of Chinese decent residing in Malaysia and Hong Kong [12]. The histogenesis of DA is still not clear although some believe that desmoplastic ameloblastoma may originate from epithelial rests of Malassez in the periodontal membrane [11]. Sun et al. reviewed 35 papers consisting of 115 cases of desmoplastic ameloblastomas and reported a recurrence rate of 21.1% after enucleation whereas *en-block* resection decreased this rate to 3.1% [7]. In the case of conventional ameloblastoma, conservative surgery yields a recurrence rate of 60–80% [1] while marginal resection has a recurrence rate of up to 15% [13].

Because of differences in morphologic, clinical, radiographic and epidemiologic characteristics of DA as compared to the conventional variety, it is tempting to speculate that DA is indeed a separate type of odontogenic tumor and not a true ameloblastoma. The present case report may lend some support to this concept. The malignant counterpart of conventional ameloblastoma, whether de-novo or from an antecedent ameloblastoma, is ameloblastic carcinoma while in the current case malignant progression of DA lead to squamous cell carcinoma. The carcinoma component in the current case had higher Ki-67 proliferation index and p53 expression as compared to the DA areas of the lesion. To our knowledge there is no convincing evidence in published literature of a squamous cell carcinoma arising from a conventional ameloblastoma in contrast to commonly recognized cases of squamous cell carcinoma developing in a preexisting odontogenic cysts [1, 14, 15].

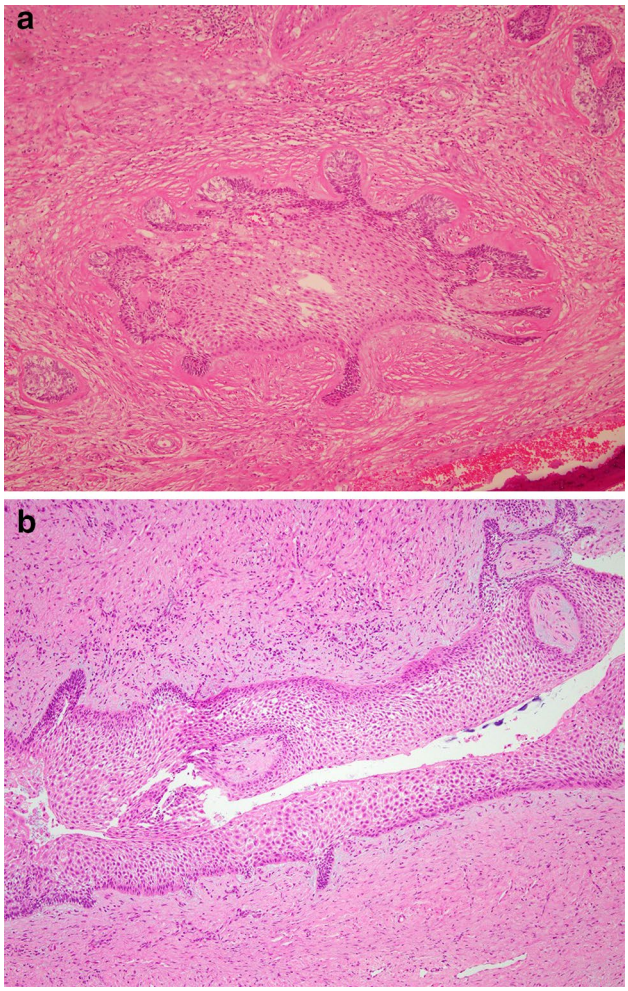

Fig. 3 Benign component of the lesion showing characteristic morphologic features of desmoplastic ameloblastoma of both of the epithelial component and the desmoplastic stroma (**a**). **b** Higher magnification of **a** showing epithelial component of desmoplastic ameloblastoma. The peripheral cells are cuboidal and lack the nuclear reversed polarity seen in conventional ameloblastoma. Stellate reticulum is also lacking in the central cells

The desmoplastic ameloblastoma is in itself a rare entity, its progression to squamous cell carcinoma is exceedingly rare and to our knowledge has not been previously reported. In the current case the patient had no prior history of squamous cell carcinoma at any other site or any other time and thus metastatic origin can be ruled out. Three cases of primary intra osseous carcinoma (PIOC) have been reported in literature [9, 15, 16], they affected both the mandible and maxilla and were thought to be arising from ameloblastoma. However the authors did not identify or describe the characteristic morphologic

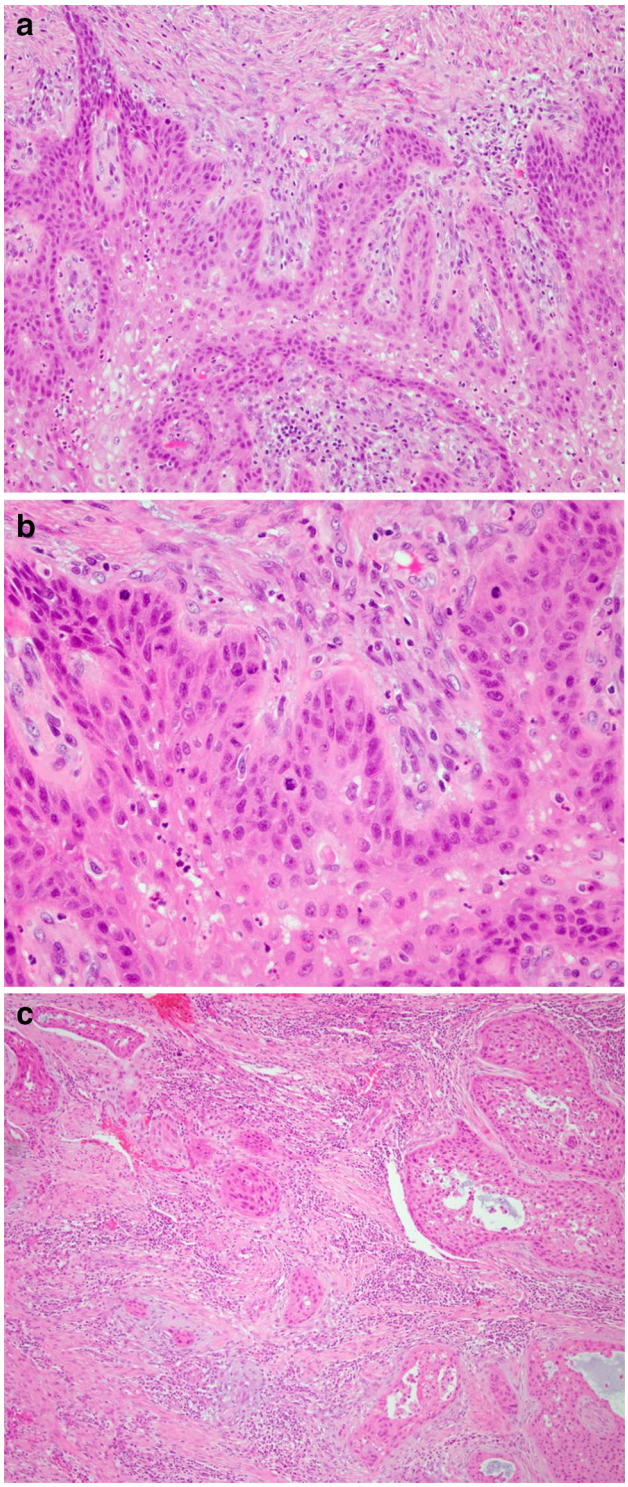

Fig. 4 The malignant epithelial component was composed of severely dysplastic squamous epithelium (**a, b**) and infiltrating islands and small nests of well to moderately differentiated squamous cell carcinoma (**c**). Overlapping of the two component was focally evident (**a**–**c**). In these areas the benign odontogenic epithelium showed evidence of progression to severe dysplasia and invasive squamous cell carcinoma

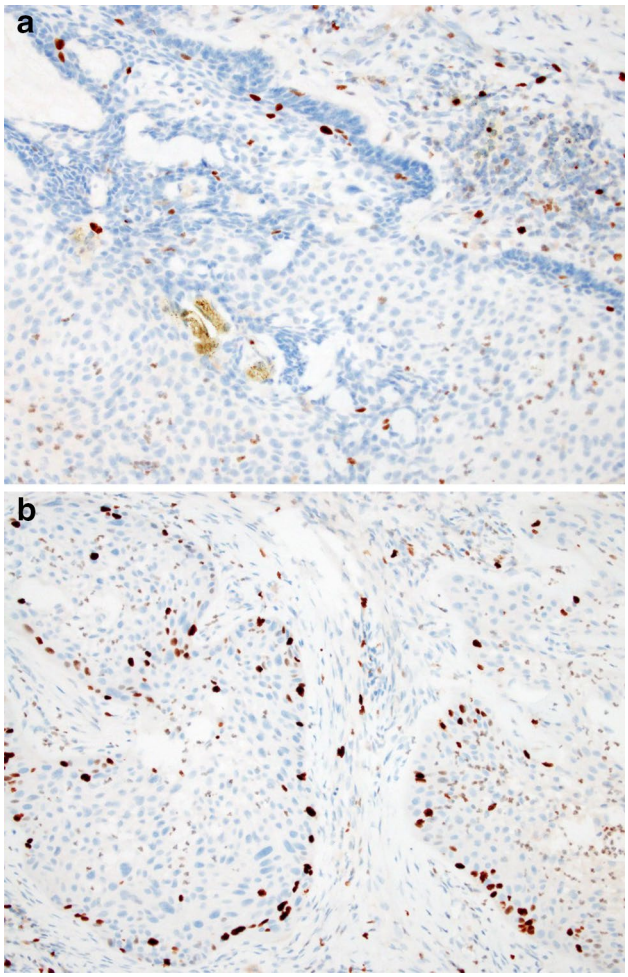

Fig. 5 Ki-67 immunohistochemical stain showing differences between the proliferation indices of the benign (**a**) and malignant (**b**) epithelial components

features of ameloblastoma in these lesions. Ueta et al. [16] reported a case of primary intra osseous squamous cell carcinoma (PIOSCC) that occurred at a surgical margin of a recurrent ameloblastoma at the mandibular ramus. However, the ameloblastoma and the SCC were seen separately, and there was no evidence of overlapping features or progression from ameloblastoma to squamous cell carcinoma as seen in the current case. Hamakawa et al. [10] reported coexistent PIOSCC with mandibular ameloblastoma. However, they were not able to conclude that the SCC arose from the ameloblastoma. They suggested that both tumors had occurred concurrently. Unlike reported cases of squamous cell carcinoma associated with conventional ameloblastoma, in the current case, the evidence of progression of benign DA to squamous cell carcinoma is clearly evident. This feature combined with morphologic, radiographic and clinical differences between DA and conventional ameloblastoma argues for the concept that

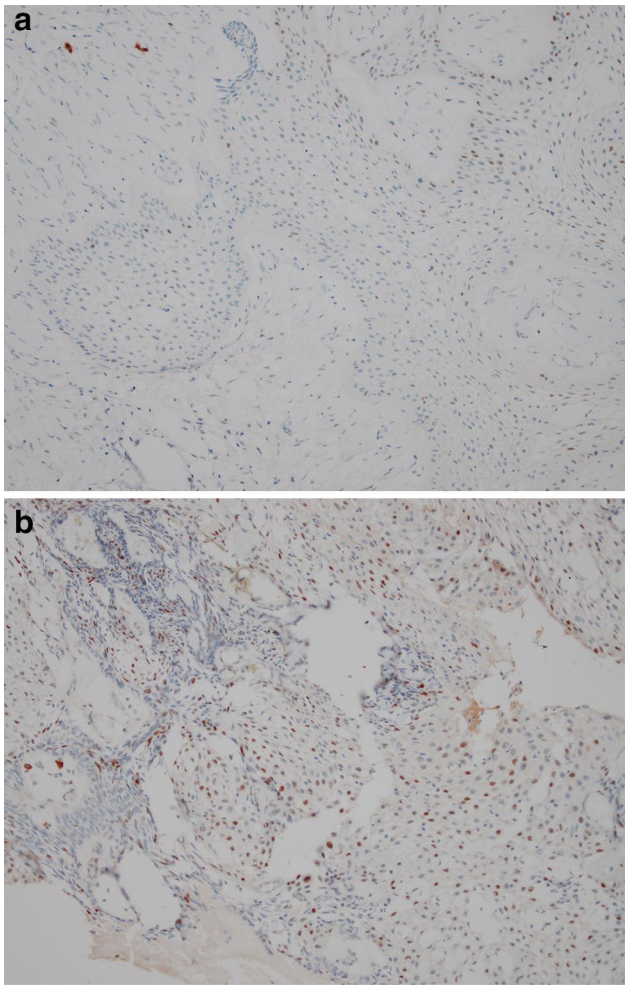

Fig. 6 p53 immunohistochemical stain showing lower nuclear expression in the benign ameloblastic component (**a**) and higher nuclear expression in the malignant squamous cell carcinoma component (**b**)

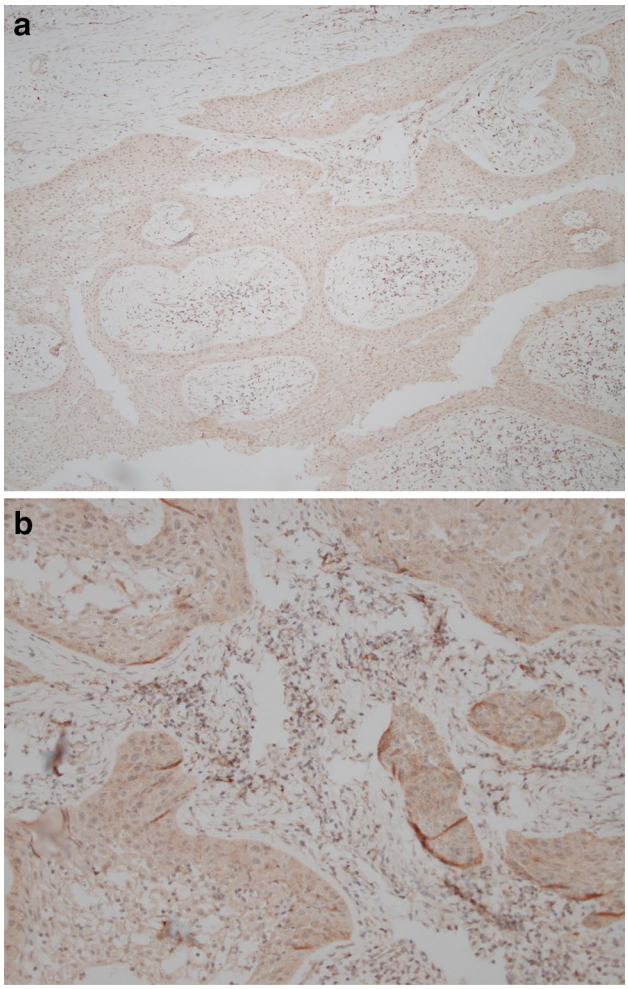

Fig. 7 BRAF V600E immunohistochemical stain is negative both in the benign (**a**) and the malignant component (**b**) with only weak background staining

desmoplastic ameloblastoma is phenotypically, clinically and biologically a distinct entity. We propose the term desmoplastic odontogenic tumor for this entity.

It has been shown that gene mutations in the MAPK pathway are present in almost 90% of ameloblastoma, with BRAF V600E being the most common [1, 17]. However in our case there is no significant BRAF staining within the benign DA or malignant component, suggesting further that the desmoplastic variety of ameloblastoma indeed differs even at a molecular level. Reports also suggest that it is uncommon for head and neck squamous cell carcinomas to harbor BRAF mutations [18], also evident from our case. It would be interesting to look at additional case series of DA for better understanding of the clinical and molecular biology of this unique entity.

The exact molecular mechanism involved in the malignant transformation in this case is not clear. However, the observed p53 overexpression in the squamous cell carcinoma component suggests that p53 mutation may have played a role.

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