

# Desmoplastic Ameloblastoma: A Diagnostic Dilemma

<sup>1</sup>Narendra T Chaudhari, <sup>2</sup>Jagdish V Tupkari, <sup>3</sup>Manisha S Ahire, <sup>4</sup>Tabita Joy

## ABSTRACT

**Introduction:** Desmoplastic ameloblastoma (DA) is a rare variant of ameloblastoma that shows unique features, behavior, and presentation. Earlier it was believed to be less aggressive but this tumor has gained importance, as recent reports suggest increased incidence of destruction and recurrence. It is most commonly confused with fibro-osseous lesions and only histopathological examination helps to establish the final diagnosis. Due to varied clinical and radiographic appearance this lesion can be misdiagnosed, hence its adequate knowledge is imperative for dental health professionals to ensure appropriate management.

**Case report:** Herewith, we present a case of DA affecting the maxilla. Based on clinical, radiographic, computed tomography (CT) scan, magnetic resonance imaging (MRI), fine needle aspiration biopsy (FNAB) findings along with histopathological evaluation using special and immunohistochemistry (IHC) stains, the present case was diagnosed as DA.

**Management:** The tumor was treated by partial maxillectomy along with removal of the involved teeth and two bone plates were used to reconstruct the left maxillary anterior region and these plates were attached to the bone with monocortical screws. The postoperative healing phase was without any complications.

**Conclusion:** Some researchers suggest that DA might be less biologically aggressive than conventional ameloblastoma as the desmoplasia in DA might act as a limiting barrier for local spread of the DA tumor cells. But recently, few cases showed that DA tends to exhibit rapid growth and progressive behavior, with incidence of recurrence the same as conventional ameloblastomas. The radiological and histological findings of ill-defined borders and poor encapsulation require a long-term follow-up.

**Keywords:** Ameloblastoma, Desmoplastic, Dilemma, Maxilla, Recurrence.

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<sup>1</sup>Dental Surgeon and Consulting Oral Pathologist, <sup>2</sup>Professor and Head, <sup>3</sup>Assistant Professor, <sup>4</sup>Associate Professor

<sup>1</sup>Dental Surgeon and Consulting Oral Pathologist at Shri Sai Dental Multispeciality Clinic, Mumbai, Maharashtra, India

<sup>2-4</sup>Department of Oral Pathology and Microbiology, Government Dental College & Hospital, Mumbai, Maharashtra, India

**Corresponding Author:** Narendra T Chaudhari, Nirman Park Phase 3, A-6, Room no 4, Santoshimata road, Kalyan West 421301, Mumbai, Maharashtra, India, Phone: +919969529473 e-mail: naren.njoi@gmail.com

## INTRODUCTION

Ameloblastoma is the second most common benign odontogenic tumor<sup>1</sup> that locally manifests as an invasive, destructive,<sup>2</sup> and aggressive lesion.<sup>3</sup> Apart from malignant ameloblastoma and ameloblastic carcinoma, many researchers believe the conventional ameloblastoma to be a low-grade malignant tumor.<sup>4</sup>

Solid or multicystic, unicystic, and extraosseous are the clinical types of ameloblastoma, while the radiographic presentation is usually in the form of a unilocular or multilocular radiolucency.<sup>1</sup> The term "ameloblastoma" encompasses several histological patterns,<sup>5</sup> of which follicular and plexiform are the most common varieties, followed by the acanthomatous and granular cell types. Uncommon variants include desmoplastic, basal cell, clear cell, keratoameloblastoma, and papilliferous keratoameloblastoma.<sup>2</sup>

Desmoplastic ameloblastoma shows marked variations in its anatomical location, morphology and radiographic appearance as compared with the other forms of ameloblastoma, hence there was a need to classify it as a separate clinicopathologic type.<sup>1</sup> Subsequently, DA was included as a distinct variant of ameloblastoma in the World Health Organization classification of odontogenic tumors in 2005.<sup>4,6</sup>

The worldwide incidence of DA is about 0.9 to 12.1% of total ameloblastoma. In general, there are two histologic variants of DA, simple DA (88.0%) and DA with osteoplasia (12.0%).<sup>7</sup> The radiographic picture of DA is not specific<sup>1</sup> and can be confused with fibro-osseous lesions or malignant tumors.<sup>4</sup> The DA can resemble odontogenic fibroma, squamous odontogenic tumor, ameloblastic fibroma, and squamous cell carcinoma in its histopathological presentation.<sup>1</sup>

Desmoplastic ameloblastoma shows a more aggressive behavior than other types of ameloblastoma, which may be due to its potential to grow to a large size, peculiar anatomic location in anterior maxilla leading to an early invasion of adjoining structures and bone.<sup>8</sup> We report here a case of DA affecting the anterior maxilla, in a bid to assist the dental health professionals in better understanding of this unusual odontogenic tumor.

## CASE REPORT

A 16-year-old male patient visited our outpatient department with a chief complaint of asymptomatic, slowly

enlarging swelling in his left maxilla since 1 year. There was no history of trauma and his past medical history was unremarkable.

Extraoral examination showed a diffuse swelling in the left maxillary region extending from the ala of nose till zygomatic region anteroposteriorly and superoinferiorly from ala–tragus line to the occlusal plane (Fig. 1). The ala and floor of the nose appeared to be raised on the affected side. The swelling was oval and had a smooth surface. The skin over the swelling appeared to be normal. There was no tenderness on palpation. Intraorally, a firm to hard swelling was seen in the left maxillary region extending from 21 to 25 buccally and superoinferiorly from the vestibular mucosa to the marginal gingiva of the teeth on the buccal side. Expansion of only the buccal cortex was noted in the affected area. The swelling was approximately  $4 \times 2 \times 2$  cm in size, diffuse, oval in shape, and had a smooth surface (Fig. 2). The mucosa over the swelling appeared normal. On palpation, the swelling was nontender, and the inspection findings were confirmed. The swelling was

bony hard in consistency and was neither fluctuant nor compressible. It was nonpulsatile and was not fixed to the overlying mucosa and appeared to arise from within the bone.

The teeth in the affected area were not sensitive to percussion and no mobility could be demonstrated except slight displacement was noticed in 21, 22, and 23. Electric pulp vitality testing revealed that all the teeth in the vicinity were vital.

Orthopantomograph (OPG) revealed an ill-defined radiolucent lesion with wispy striae-like septae in the left maxillary region. The lesion was approximately  $2.5 \times 2$  cm in size. It caused displacement of 21, 22, 23, and 24. There was no displacement of floor of the maxillary sinus (Fig. 3). The MRI of maxilla showed a well-defined expansile mass with abnormal marrow intensity in left maxillary alveolar process and adjacent anterior wall of maxillary sinus. The lesion was hypointense on T1-weighted (T1W) and T2-weighted (T2W) images with thin internal septae (Fig. 4). A mild heterogeneous postcontrast enhancement



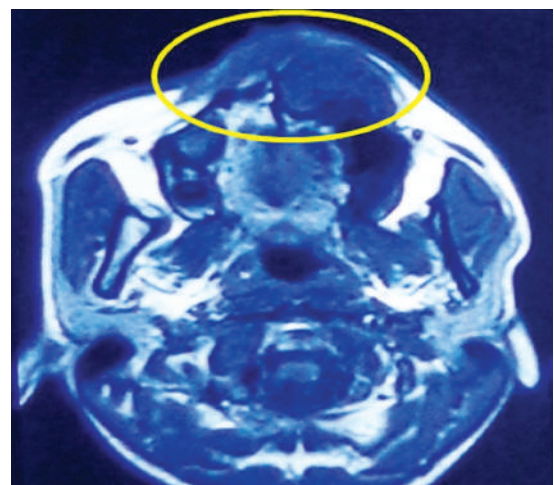
**Fig. 1:** Extraoral view showing diffuse swelling in left anterior maxilla



**Fig. 2:** Intraoral view showing expansion of buccal cortex with slight teeth displacement

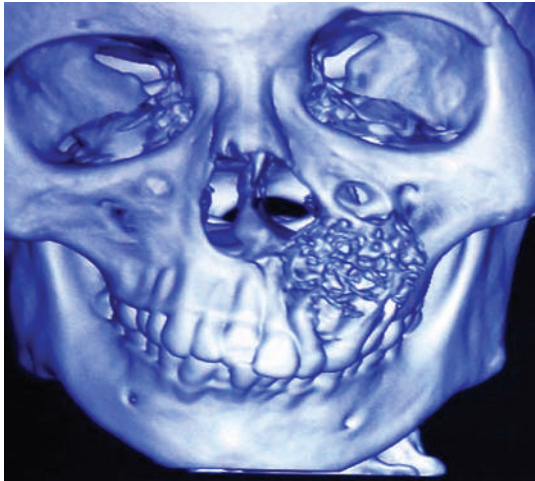


**Fig. 3:** Orthopantomograph view: an ill-defined radiolucent lesion with wispy striae-like septae in the left maxillary anterior region

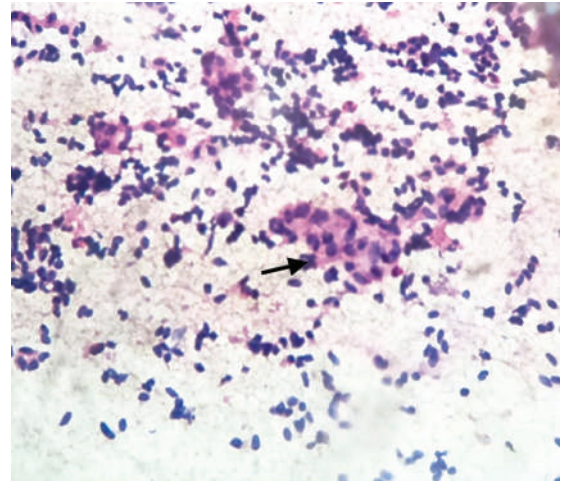


**Fig. 4:** The MRI showing a well-defined expansile mass which was hypointense on T1W and T2W images with thin internal septae

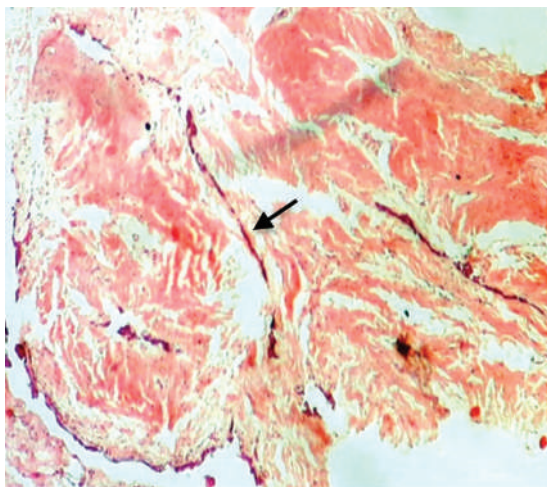




**Fig. 5:** Three-dimensional CT scan showing a moderately expansile lesion causing destruction of bone with few, irregular internal trabeculae



**Fig. 6:** Fine needle aspiration biopsy showing spindle- and oval-shaped odontogenic epithelial cells (10×)



**Fig. 7:** Incisional biopsy showing thin, long, and compressed strands of odontogenic cells surrounded by dense collagen fiber bundles (hematoxylin and eosin, 10×)



**Fig. 8:** Postoperative 3D CT showing maxillary reconstruction using two bone plates and monocortical screws

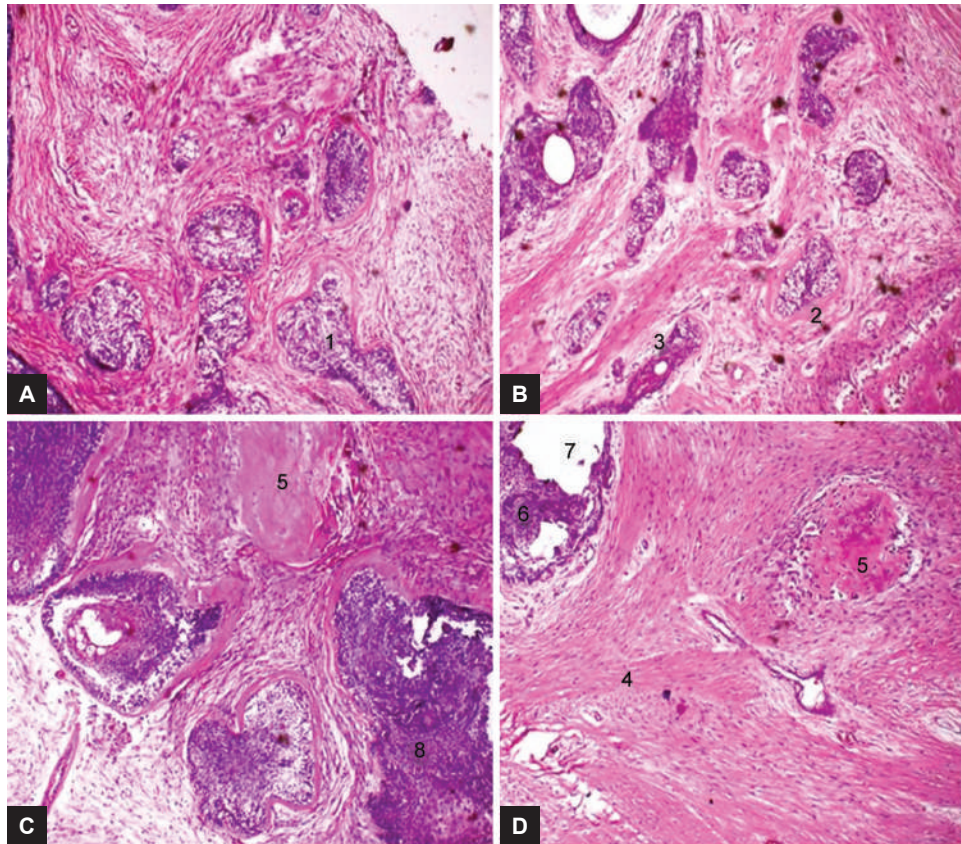
measuring  $3 \times 2.3 \times 2.7$  cm extended along the roots of adjacent teeth and caused splaying of the lateral incisor, canine, and 1st premolar. Three-dimensional (3D) CT scan view showed a moderately expansile lesion causing destruction of bone in left anterior aspect of maxillary alveolus. Thinning of overlying cortical bone with few, irregular internal trabeculae and no obvious extension into the sinus was also noted (Fig. 5). Based on clinical and radiological findings, a diagnosis of fibro-osseous lesion was made.

Fine needle aspiration biopsy displayed spindle- and oval-shaped odontogenic epithelial cells (Fig. 6) suggestive of “benign epithelial odontogenic tumor.” The complete hemogram showed values within the normal range. Incisional biopsy was performed to establish a definitive diagnosis which showed histopathological features like thin, long, and compressed strands of odontogenic cells surrounded by dense collagen fiber bundles and areas of homogenization with presence of peripheral bony trabeculae consistent with those of DA (Fig. 7).

The tumor was treated by partial maxillectomy along with removal of the involved teeth and two bone plates were used to reconstruct the left maxillary anterior region and these plates were attached to the bone with monocortical screws (Fig. 8). The postoperative healing phase was without any complications.

The surgical specimen consisted of a portion of the maxilla along with multiple teeth, extending from left central incisor to left maxillary second premolar. The specimen was subjected to histopathological examination. Microscopic examination revealed numerous irregular islands and cords of odontogenic epithelium with peripheral tall columnar ameloblast-like cells showing reverse polarity. These islands enclosed stellate reticulum-like cells consisting of few areas of squamous metaplasia, which were present in a dense collagenous stroma comprised of compactly arranged numerous collagen fiber bundles and plump to spindle-shaped fibroblasts. A few compressed strands of odontogenic cells were also noted.





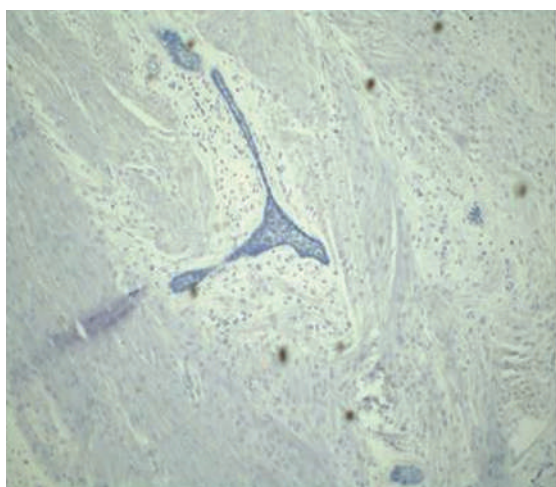
**Figs 9A to D:** Excisional biopsy (hematoxylin and eosin, 10×). 1. Odontogenic follicles, 2. eosinophilic condensation around follicles, 3. compressed odontogenic follicles, 4. desmoplasia, 5. osteoplasia, 6. squamous metaplasia, 7. cystic degeneration, 8. animal-like configurations

Narrow zones of eosinophilic condensation were present adjacent to the epithelial islands, along with evidence of osteoplasia in a few areas (Fig. 9). Immunohistochemical stains like desmin were negative (Fig. 10), whereas collagen VI was strongly positive in connective tissue stroma (Fig. 11). Special stains like Masson's trichrome (Fig. 12) and Van Gieson (Fig. 13) were used to demonstrate excessive collagen condensation and bone formation. These features were suggestive of DA.

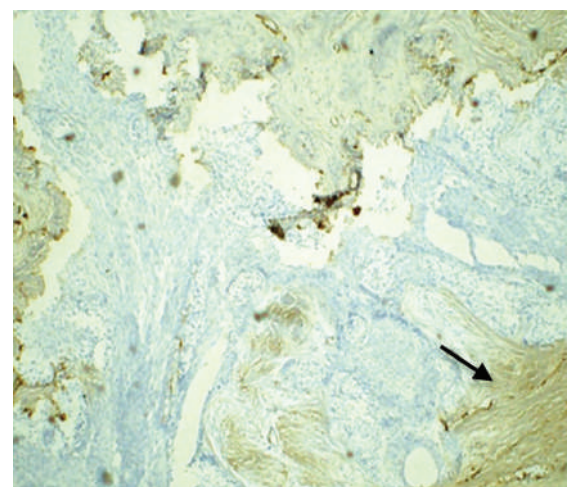
The postoperative follow-up of the patient after 1 year showed no evidence of recurrence of the lesion (Fig. 14).

## DISCUSSION

Desmoplasia is defined as the response of host cells to inductive stimuli exerted by tumor cells. The "desmoplastic reaction" is initiated by stromal cells which produce collagen and extracellular matrix proteins and

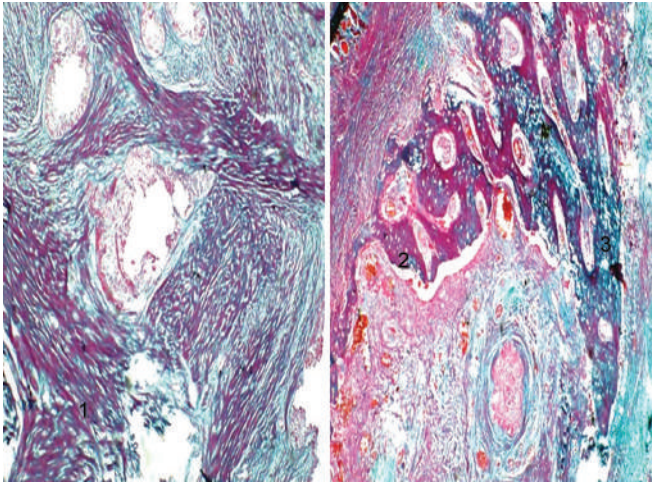


**Fig. 10:** Desmoplastic ameloblastoma tumor cells were negative for desmin (10×)

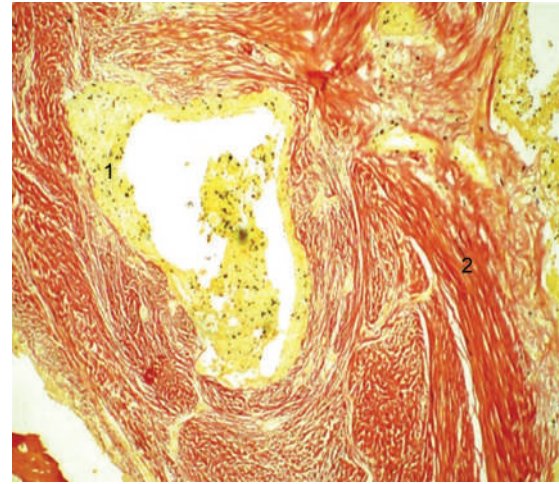


**Fig. 11:** Collagen VI is strongly positive in connective tissue stroma (10×)





**Fig. 12:** Masson's trichrome stain (10×). 1. Collagen fibers (mature and immature), 2. trabecular bone, 3. fibrous bone



**Fig. 13:** Van Gieson's stain (10×). 1. Odontogenic follicle, 2. collagen fibers



**Fig. 14:** Postoperative follow-up after 1 year

may facilitate the invasion process in cancer.<sup>9</sup> The DA is a rare unusual variant of ameloblastoma, which has a low incidence rate<sup>3</sup> and shows significant stromal desmoplasia histologically.<sup>2</sup> It was first described by Eversole et al, who labeled it as an “ameloblastoma with pronounced desmoplasia or DA.”<sup>8,10</sup> Till date, about 150 cases are reported in the literature.<sup>8</sup> Desmoplastic ameloblastoma was initially defined as a central lesion but recently, two cases of peripheral DA (PDA) were reported.<sup>11</sup> The PDA is believed to be arising as hamartomatous or neoplastic proliferations of the dental lamina, odontogenic remnants, or pluripotent cells in the basal cell layer of the mucosa. The peripheral variant exhibits the same histopathologic features as intraosseous DA. However, the peripheral variant being less aggressive, requires a conservative approach for treatment as compared with the intraosseous variant.<sup>12</sup>

“Hybrid” lesion is an extremely unusual variant and was first described in detail by Waldron and El-Mofty.<sup>13</sup>

It is a tumor in which histologically, areas of follicular or plexiform ameloblastoma coexist with characteristic areas of DA.<sup>14</sup>

### Clinical Features

The DA is predominantly seen in the 2nd to 5th decade of life and most commonly occurs in Japanese and Chinese populations. Usually there is equal gender distribution but some reports suggest male preponderance.<sup>3,8</sup> The DA tends to affect the anterior premolar region of the jaws,<sup>6</sup> with similar frequency in maxilla and mandible.<sup>15</sup> This is in contrast to the location of the classic types of ameloblastoma, which usually are found in the posterior area of the mandible.<sup>4</sup> In our case, the patient was male, belonging to second decade, and the lesion involved the left anterior region of maxilla.

In DA, the patient's first complaint is usually an asymptomatic swelling with cortical plate expansion<sup>16</sup> mainly in the alveolar region and usually occupying the tooth-bearing area.<sup>17</sup> Teeth displacement (92% of the cases) and root resorption (33% of cases) are routinely noted in DA.<sup>15</sup> In case of maxillary sinus involvement, nasal and pharyngeal obstruction does occur.<sup>5</sup> Maxillary lesions are more dangerous, due to the vicinity of vital structures and the maxillary sinus. They are associated with rapid spread due to very thin cortical bone.<sup>1</sup> The growth of DA is very fast when it involves the maxillary sinus<sup>18</sup> and also the treatment is complicated due to penetrating nature of DA in the surrounding bone.<sup>8</sup> Slowly enlarging, painless bony swelling with buccal cortex expansion and teeth displacement were the clinical findings in our case.

### Radiological Features

The most common radiographic presentation of DA is a mixed radiolucent/radiopaque lesion due to osseous

metaplasia within the dense fibrous septa resembling a benign fibro-osseous lesion. Also the borders of the lesion are poorly demarcated without capsule, suggestive of an infiltrative process<sup>1</sup> affecting the prognosis.<sup>3</sup> These features are not specific and can resemble other mixed radiolucent lesions.<sup>1</sup> The DA has a tendency for *de novo* synthesis of extracellular fibrous protein which could serve as nidus for calcification seen in the DA with osteoplasia.<sup>7</sup> The disappearance of the lamina dura and the periodontal ligament space can be seen in the early stages of tumor development.<sup>19</sup> Our case showed tooth displacement and ill-defined radiolucency on OPG, whereas CT and MRI scan revealed the extent and pattern of bone destruction along with internal architecture of the lesion.

This radiographic appearance may indicate that DA is more aggressive than other variants of ameloblastoma and warrants a radical approach to treatment.<sup>5</sup> The CT and MRI can be used to distinguish DA from other fibro-osseous lesions by the detection of thick, bony trabeculae situated peripherally between the tumor elements.<sup>15</sup> The differential diagnosis of a mixed radiodense-radiolucent lesion with diffuse borders includes fibro-osseous lesions (cemento-ossifying fibroma, cementoblastoma, and fibrous dysplasia), calcifying odontogenic cyst, and chronic sclerosing osteomyelitis. A definitive diagnosis prior to surgery requires histopathology to aid proper management.<sup>1,2</sup>

### Histological Features

The classical histopathological features of DA include extreme stromal desmoplasia in the form of moderately cellular, fibrous connective tissue with abundant collagen,<sup>1</sup> which squeezes or compresses the odontogenic islands and cords resulting in pointed, stellate, or "kite-like" appearance. The epithelial cells at the periphery of the islands are cuboidal, although columnar cells showing reversed nuclear polarity with hyperchromatic nuclei are seldom seen. The center of the islands may contain spindle-shaped or squamoid epithelial cells.<sup>16</sup>

Prominent osteoplasia in the form of metaplastic woven or mature bony trabeculae containing osteocytes and lined by plump active osteoblasts is also described, which can be attributed to stimulation of osteoblasts by tumor cell for formation of new bone. Granular cell transformation; follicular, plexiform, acanthomatous, and basaloid changes; and cystic degeneration within the tumor have also been reported.<sup>16</sup> Microcysts that contain eosinophilic amorphous deposits or appear empty may occur centrally.<sup>17</sup> A rare phenomenon of mucous cell differentiation is also reported.<sup>13</sup> In our case, some areas showed odontogenic follicles containing peripheral ameloblast-like cells, central area resembling stellate

reticulum-like cells, squamous metaplasia, and cystic degeneration, whereas other areas consisted of compressed odontogenic islands with peripheral cuboidal cells which contained indistinct cells in the central region. Irregular odontogenic islands which were pointed, stellate, bizarre animal-like configuration were also seen in many places.<sup>10</sup> Marked stromal desmoplasia along with eosinophilic condensation around follicles and osteoplasia in the form of woven as well as mature trabeculae was suggestive of DA.

Histopathology of DA is characterized by its infiltration into bone marrow spaces without a fibrous connective tissue capsule.<sup>19</sup> The precise diagnosis of DA depends on the identification of the typical ameloblastic areas, which may require examination of more tissue or a repeated biopsy.<sup>1</sup>

### Immunohistochemistry/Special Stains

In the past few IHC stains have been used to study tumor microenvironment. The stroma in DA shows positive stain for laminin V and type IV collagen, suggesting an inductive effect of the epithelium over the fibrous stroma, resulting in a duplicated basal lamina. This is manifested in the form of deposits of an acellular eosinophilic matrix associated with epithelial islands.<sup>11</sup> Expression of type III collagen indicates an ectomesenchymal origin for the stromal cells of the DA. Also strong immunolocalization of bone morphogenetic proteins 2, 3, 4, and 7 in the mesenchymal tissues explains the formation of hard tissues in this neoplasm.<sup>20</sup>

Type VI collagen staining adjacent to tumor islands in DA indicates an active synthesis of extracellular matrix proteins leading to newly produced connective tissue and not a scar tissue. Transforming growth factor (TGF)- $\beta$ , which is a potent local factor for modulating extracellular matrix formation and its marked immunoreexpression, suggests that TGF- $\beta$  produced by DA tumor cells plays a part in desmoplastic matrix formation.<sup>13</sup>

The immunoreexpression of S-100 and desmin is variable, while keratin immunoreactivity is irregularly seen in tumor cells showing squamous differentiation. Vimentin is not expressed by either squamoid or spindle-shaped cells. This may be due to different factors, such as dedifferentiation or the rate of proliferation of the neoplastic cells, inherent cellular potentials, or extracellular mediators.<sup>21</sup> In our case, the tumor stroma showed strong positivity for collagen VI, but desmin was negative. We preferred collagen VI over TGF- $\beta$  as TGF- $\beta$  regulates only extracellular matrix formation, whereas collagen VI demonstrates recently formed connective tissue, indicating active matrix synthesis leading to excessive stromal desmoplasia.



The studies related to special stains are scarce in DA. Special stains like Van Gieson to study desmoplasia<sup>4</sup> and Masson's trichrome to differentiate between fibrous/mature bone have only been used in the past.<sup>16</sup> We used Van Gieson and Masson's trichrome stains in the present case. Staining with Van Gieson showed abundant, dense red-colored collagen fiber bundles throughout the stroma and around the odontogenic follicles. The cells in the follicle showed black nucleus and the cytoplasm was yellow. Bone-stained red and numerous fine yellow-colored fibers were seen interspersed between the collagen fibers, suggestive of reticular or elastic fibers. Reticular fibers are fine, delicate fibers that provide support to coarse collagen network. Elastic fibers have microfibrillar structure and consist of three types—oxytalan, elaunin, and elastic fibers.<sup>22</sup> The presence of oxytalan fibers in the stromal tissue points the origin of DA from the epithelial rests of Malassez in the periodontal membrane.<sup>7</sup>

Masson's trichrome stains are used for selective demonstration of muscle, collagen fibers, fibrin, and erythrocytes. It is based on the principle that smaller dye molecule will penetrate and stain a tissue element, but whenever a larger dye molecule penetrates the same element it will then replace the smaller molecule.<sup>22</sup> In the present case, this stain demonstrated numerous bluish-green-colored collagen fiber bundles intermixed with reddish-pink-colored fibers. This differential staining could be attributed to difference in pore size between mature and immature fibers as diameter of fibril in collagen is up to 0.4  $\mu\text{m}$ , whereas microfibril has diameter about 40 nm.<sup>23</sup> Collagen VI is a type of collagenous protein referred to as "high molecular weight aggregate" and "short chain collagen"<sup>24</sup> having less pore volume. This indicates excessive new collagen formation leading to desmoplasia. Mature bone appeared reddish-pink in color, whereas fibrous bone was bluish-green in color, indicating active osteoplasia within the stroma.

### Management and Recurrence

The interface between the lesion and normal bone is usually difficult to locate, also DA tends to infiltrate between bony trabeculae; hence, curettage/enucleation often results in recurrence. Therefore, block excision is the most widely accepted form of treatment.<sup>2,5</sup> Ill-defined borders suggest an infiltration process and an aggressive biological behavior, so it requires an extensive treatment.<sup>6</sup>

Some researchers suggest that DA might be less biologically aggressive than conventional ameloblastoma as the desmoplasia in DA might act as a limiting barrier for local spread of the DA tumor cells.<sup>7</sup> But recently, few cases showed that DA tends to exhibit rapid growth and

progressive behavior, with incidence of recurrence same as conventional ameloblastomas.<sup>19</sup> The radiological and histological findings of ill-defined borders and poor encapsulation require a long-term follow-up.

The panoramic radiography cannot help to distinguish DA from fibro-osseous lesions due to superimposition; hence, cone beam CT scans are recommended as they provide more accurate visualization of the internal structure and expansion of maxilla-mandible tumors.<sup>25</sup>

### CONCLUSION

We report a case of DA in a male patient affecting the anterior maxilla. A brief review of DA is discussed and findings of various investigations like clinical, radiographic (MRI and CT scan), and histological examination (IHC and special stains) were helpful for diagnosis and confirmation of DA.

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