A Recurrent Case of Ameloblastic Fibroma in 37-year Old Male

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ABSTRACT

Ameloblastic fibroma (AF) is a benign mixed epithelial and mesenchymal odontogenic tumor. This was previously grouped in odontogenic tumor showing odontogenic epithelium with odontogenic ectomesenchyme, with or without hard tissue formation. This report describes a case of ameloblastic fibroma in a 37-year-old male who came with the complain of swelling in the left side of lower jaw since one year. Enucleation of the mass followed by reconstruction was done six years back. However, after two years of initial treatment; radiographic findings suggested recurrence. Histopathological examination confirmed the diagnosis of ameloblastic fibroma. Patient had no clinical and radiographic evidence of recurrence in three and six months' follow-up. Because of the higher proliferative capacity and malignant degree of the mesenchymal component in the recurrent neoplasm, sarcomatous transformation may occur. Hence, a long term clinical and radiographical follow-up is essential due to its transformation into ameloblastic fibrosarcoma.

KEY WORDS

Ameloblastic, Benign, Recurrence, Fibroma, Tumors

INTRODUCTION

The World Health Organization (WHO), in 2017, classified ameloblastic fibroma (AF) as a benign mixed epithelial and mesenchymal odontogenic tumor and defined it as "rare, benign, true mixed tumor composed of odontogenic mesenchyme resembling dental papilla and epithelial tissue resembling odontogenic epithelium, in which no dental hard tissues are present".[1] This was previously grouped in odontogenic tumor showing odontogenic epithelium with odontogenic ectomesenchyme, with or without hard tissue formation.[2] It is not possible to distinguish between AF and early-stage odontomas before they differentiate and mature histopathologically.[1] This report describes a case of AF in 37 years male patient which recurred six years after the initial treatment.

CASE REPORT

A 37-year-old male reported to the dental department with the chief complain of swelling in the left side of lower jaw since one year. The swelling was gradual on onset, slow-growing, progressive in nature but not associated with pain or tenderness. There was no paresthesia as well. He was operated for lesion on the same site, six years back which was diagnosed as ameloblastic fibroma and treated by enucleation followed by reconstruction. Follow-up was done after two years of initial treatment where he had no symptomatic complains but Cone-beam computed tomography (CBCT) imaging suggested recurrence of the lesion. He was advised to undergo re-surgery, but he declined because he was not experiencing any clinical symptoms. He had no other relevant medical history.

On clinical examination, there was mild unilateral swelling in the left mandible extending below the submandibular region. Also, a visible scar was noted in the submandibular area suggestive of previous treatment. On palpation, the swelling was firm, non-fluctuant, non-tender with no visible discharge (Fig. 1). On intraoral examination, there was vestibular obliteration on buccal aspect extending from distal of left first premolar to distal of left first molar. The teeth on the same region 35, 36 and 37 were restored. The overlying epithelium was apparently normal.

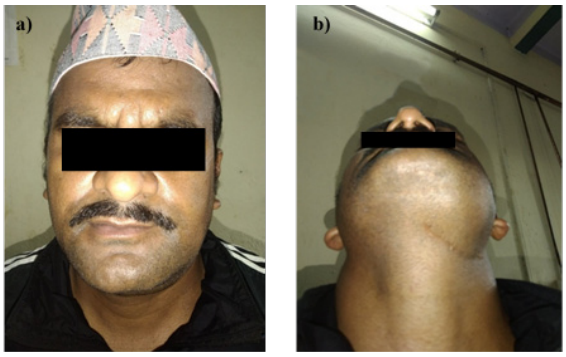

Figure 1. Extra oral photographs showing a) swelling in the left mandible extending below the submandibular region, b) visible scar on same side.

The panoramic radiograph revealed a well-defined multilocular radiolucent area involving the left body of mandible with evidence of root resorption with respect to 34 to 38. A reconstruction plate was also visible. CBCT showed an expansive lesion with 4.62 cm × 2.8 cm × 2.2 cm in extension with perforation of buccal and lingual cortical plates extending from apical region with respect to 33 to 38 (Fig. 2).

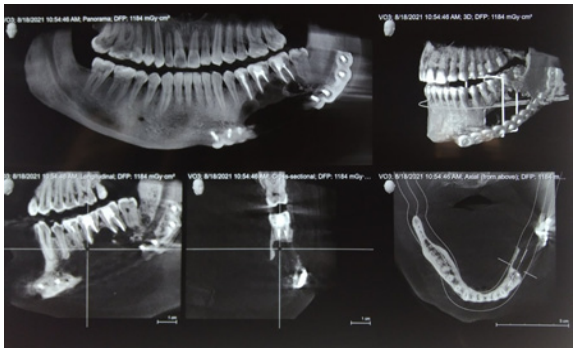

Figure 1. CBCT showed an expansive lesion with 4.62 cm × 2.8 cm × 2.2 cm in extension with perforation of buccal and lingual cortical plates extending from apical region with respect to 33 to 38.

Segmental resection of mandible extending from distal of 32 to distal of 48 was performed followed by reconstruction. The specimen was submitted for histopathological analysis.

The excised specimen consisted of mandibular body extending from 33 to 38 along with small bone like fragments, altogether measuring 7.6 cm x 5.3 cm x 2.8 cm in size. Growth segment from the medial aspect was removed which was whitish brown in color, firm in consistency measuring 5.2 cm x 2.5 cm in size. Representative specimens from the center and peripheral region were taken (Fig. 3).

Microscopically, the soft tissue section revealed tumor mass of odontogenic epithelium arranged in strands, cords, islands and follicles having peripheral ameloblast like cells with hyperchromatic nuclei and central stellate reticulum like cells. The cords and strands consisted of a double layer of cuboidal cells. The central cells showed cystic degeneration at few places. The connective tissue stroma consisted of loosely arranged collagen fibers resembling embryonic ectomesenchyme. Juxtaepithelial hyalinization

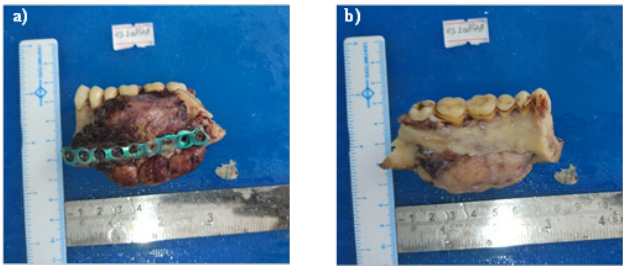

Figure 3. Excised specimen consisted of mandibular body extending from 33 to 38, a) lateral aspect, b) medial aspect.

was noted around few islands. Deeper connective tissue showed muscle fibers, few adipocytes and endothelial lined blood vessels with extravasated erythrocytes. Bony trabeculae with osteoblastic rimming and osteocytes within the lacunae and areas of hemorrhages could also be appreciated. There was no evidence of hard tissue formation on the section. The degree of cellularity varied in different areas of the lesion. Some areas were hypercellular, whereas others were sparsely cellular and myxoid. Atypia and mitotic activities were not evident (Fig. 4).

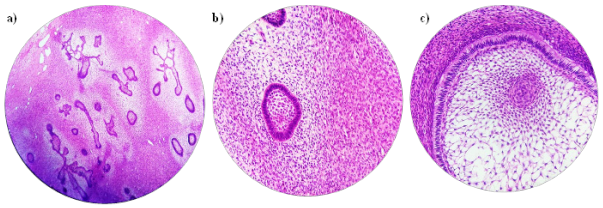

Figure 4. Histological picture of ameloblastic fibroma. a) 4x magnification, b) 10x magnification, c) 40x magnification.

Based on the clinicohistopathological findings, a final diagnosis of ameloblastic fibroma was made.

On subsequent follow-up of three and six months, patient had no clinical and radiographic evidence of recurrence (Fig. 5).

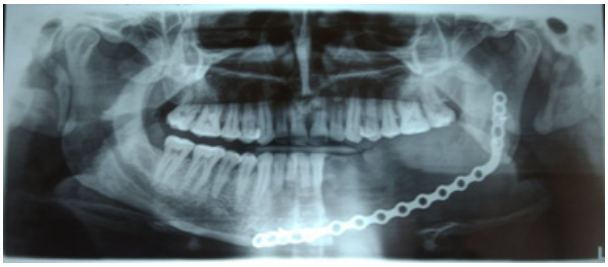

Figure 5. Radiographic after six months of follow-up.

DISCUSSION

Ameloblastic fibroma constitutes 1.5-6.5% of all the odontogenic tumors.[1] Kruse initially reported AF in 1891 as a cystic tumor of the mandible, which was later categorized as a benign neoplasia by Thoma and Goldman in 1946.[3,4] Our case involved a male patient of 37 years old with AF occurring in lower mandible. AF is common in young adults, especially in the first two decades of life with a slight male predilection.[1] The posterior mandible is the most common

site of occurrence especially in the first permanent molar and second primary molar area. About 3/4th of the cases is associated with an impacted or unerupted teeth. It mainly occurs as an intraosseous variant, and only few peripheral cases are reported.[5]

The pathogenesis of AF is controversial. It has been correlated with events of normal odontogenesis. The AF morphologically resembles the normal tooth primordium before hard tissue production begins.[1] Yamamoto et al. studied various immunohistochemical (IHC) markers of intracellular and extracellular proteins in AF.[6] Their study revealed cytokeratin positivity (CK 7, 13, 14) in the odontogenic epithelium, tenascin positivity in the mesenchymal tissue surrounding the dental lamina-like epithelium, isolated regions of immature dental papilla-like cells, and vimentin positivity in the basement membrane. These findings suggest that AF develops in similar pattern to the early stage of tooth formation.[6]

The ameloblast-like cells in AF are too primitive to induce ectomesenchyme cells, and their interactions are poorly understood. It is also unclear why odontoblastic differentiation is not induced in AF. Reichart et al. described two variants: a neoplastic type having no induction phenomena and a hamartomatous type with inductive capabilities.[7] There has been a long debate as to whether AF represents a hamartomous growth or is a true benign neoplasm. It is appropriately designated as a neoplasm as it has the potential for unlimited growth, recurrence, as well as malignant transformation. Also, AF can be seen in adults after the age of 20 years where odontogenesis is completed. Furthermore, the recurrent cases do not show further steps of differentiation into dental hard tissue forming odontogenic tumor of more advanced histodifferentiation.[8]

Cahn and Blum hypothesized that an AF could evolve into an odontoma, a type of hamartoma, if the lesion is allowed to persist.[7] As a result, AF, ameloblastic fibro-dentinoma (AFD), and ameloblastic fibro-odontoma (AFO) are all stages of the same lesion, which would be a developing odontoma in its early stages.[7] This represents the second variant of AF, a non-neoplastic, hamartomatous type with inductive capability. This maturational theory is supported by Trodahl and Carr et al. who pointed out that some recurrent lesions initially pointed out as AF showed maturation toward AFO or odontoma.[9,10] The fact that all of these tumors have a similar distribution in the jaws and occur in the same overall patient age range adds to the maturational hypothesis. However, occurrence of AF in older age group compared to AFO and differences in ultrastructural and IHC features contradict the continuum concept.[7]

Initial investigations on AF found BRAF V600E mutation and a low frequency of fractional allelic loss of tumor suppressor gene loci.[1] BRAF V600E mutations have been reported in other benign mixed odontogenic tumors (AFD, AFO) as well. This mutation is the strongest activator of the downstream RAS/RAF/MEK/ERK-MAPK signalling pathway. This pathway gets continuously activated, and the cell divides and proliferates unrestrictedly to form a tumor (Fig. 6).[1]

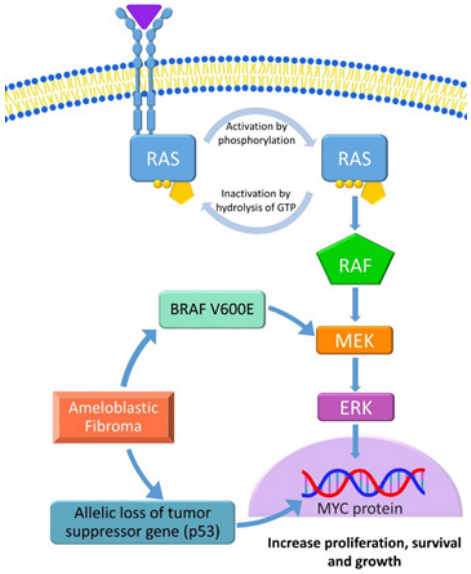

Figure 6. Pathogenesis of ameloblastic fibroma.

AF has no specific signs or symptoms; however, it can be seen on a routine radiograph in the form of cysts and other odontogenic tumors.[5] This neoplasm manifests as asymptomatic, slow-growing expansile lesion of the jaws.[1] It is commonly discovered as an unexpected finding during normal radiographic examinations.[8] Larger lesions may be associated with pain, ulceration or drainage or even cause facial asymmetry.[9]

Radiographically, the smaller lesions have unilocular radiolucency with a smooth, well-defined periphery while larger ones appear multilocular pattern. Associated features may include unerupted or displaced teeth, divergence of the adjacent teeth, root resorption and cortical perforation. These lesions may be confused with dentigerous cyst at the initial phase because they are often associated with impacted teeth.[7]

On gross pathology, the tumor mass is often solid, well-circumscribed, round or oval in shape and grayish-white in color. It consists of thin, transparent capsule-like border and has smooth outer surface.[1]

The histological features of AF comprise odontogenic epithelium arranged in strands, cords and islands. The strands demonstrate two or three layers of cuboidal or columnar cells. The islands are lined by tall ameloblast-like cells surrounding stellate reticulum like cells. Cyst formation is not usually seen but if present, remains small. The growth of odontogenic epithelium supported by a primitive mesenchymal connective tissue stroma. The cell-rich ectomesenchyme consists of plump fibroblasts with little collagen fibrils reminiscent of the dental papilla.

The degree of cellularity varies within the same tumor and between tumors.[8] Few cases present with diffuse juxtaepithelial hyalinization.[7]

There was no evidence of hard tissue formation in our case, ruling out AFD and AFO. In the present case, atypical features and mitotic activity were not observed, thus eliminating ameloblastic fibrosarcoma. Therefore, it is critical to collect sections from various locations of the lesion.

Based on histology, AF can be classified as granular cell type, in which granular cells predominate in the ectomesenchyme, papilliferous with significant epithelial growth, ameloblastoma in combination with AF, and cystic ameloblastoma.[7]

The cytology of AF consists of branching epithelial structures and a hypercellular stroma. The stromal portion is composed of plaques and streaming uniform cells with distinct cellular borders and hyperchromatic, slightly spindled or rounded nuclei. Cytological atypia, miotic activity and necrosis are not found.[7]

According to the IHC studies, the tumor cells were positive for CD 34, vimentin, Ki 67, and p53, but negative for smooth muscle actin, S 100, CD 68, and desmin.[11] Sano et al. assessed the growth potential of AF and related lesions by Mindbomb E3 Ubiquitin Protein Ligase 1 (MIB-1) immunohistochemistry.[12] They discovered a distinct difference between the AF ectomesenchyme and the neighboring connective tissue of mesodermal origin, and concluded that AF epithelial cells invade the nearby normal mesenchyme, likely causing de novo ectomesenchymal stroma development.

The ultrastructural observations include changes in the basal lamina region, which are consistent with an attempted inductive stimulation and have some resemblance to normal odontogenesis.[8] It is also possible to appreciate different degrees of granulofilamentous material thickening of the lamina densa.[7]

For minor lesions, enucleation and curettage is the preferred treatment. For severe lesions and recurrent occurrences, a comprehensive approach of marginal or segmental resection is indicated. Proper monitoring and a long follow-up are critical to avoid recurrence.[7] Trodahl and Zallen et al. reported a recurrence rate of 43.5% and 18%, respectively.[9,13]

In our case, a conservative surgical approach was followed initially. However, two years after the first surgery, the case reoccurred. A segmental excision of the mandible was performed followed by reconstruction for the second time. So, we advise a more aggressive treatment to prevent recurrence.

In this scenario, the tumors' recurrence may have been caused by the inadequacy of the surgical boundary. Thus, local management is highly reliant on the extent of the initial resection, and conservative surgery must be changed by wide surgical resection, particularly when the cortical plates have been perforated. The use of adjuvant postoperative radiation and chemotherapy is still debatable. Several examples utilizing chemotherapy drugs like cyclophosphamide and fluorouracil have yielded excellent results. Furthermore, radiotherapy (40-60 Gy) administered after surgery can produce positive benefits.[11]

Kobayashi et al. suggested that up to two thirds of ameloblastic fibrosarcoma (AFS) arise from transformation of an AF.[14] Howell et al. supported this theory that most of the lesions emerge from preexisting benign neoplasm as AF is frequently seen in younger individuals while AFS is seen in older patients.[15] Lai et al. found in their review of the literature that 51% of AFS had previously documented AF at the same site.[16]

AF shows high rate of recurrence with more than 45% turning to malignant AFS.[5] Malignant transformation of AF can occur many years after the original diagnosis, and has been reported to be 10, 12, or 14 years after the initial diagnosis.[17]

Also, a long term clinical and radiographical follow-up is essential due to its transformation into ameloblastic fibrosarcoma. Because of the higher proliferative capacity and malignant degree of the mesenchymal component in the recurrent neoplasm, sarcomatous transformation may occur.[11]

An overexpression of Ki-67, Proliferating cell nuclear antigen (PCNA), p53 labelling indices and Bcl-2 proteins, along with mitotic figures in the histology, may be useful markers to identify malignancy.[11] "Reappearance" may not represent true recurrence but rather residual tumor tissue, as the result of inadequate initial surgery. The aggressive biologic behavior of AF does not justify radical initial treatment, although large tumors, and those of the maxilla may have to be treated more radically.[17] Therefore, the tendency to "recur" does not always indicate aggressive behavior of the AF. While in contrast, recurrence rate and malignant transformation of this lesion is recorded as relatively low in case of older patients (> 22 years of age) where odontogenesis is completed.[8]

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