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Case Report

Odontogenic fibroma amyloid-variant: a typical case and brief considerations about mimickers

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Summary
The World Health Organization's (WHO) updated classification of head and neck tumors (2017) defined odontogenic fibroma as a rare neoplasm. In this report, we describe an unusual, typical and rare variant of a central odontogenic fibroma with diffuse amyloid-like protein stromal deposition, and discuss the differential diagnosis with other entities. Radiographically, this lesion presented as a well-defined radiolucency of the mandible, partially cystic. Histologically, the lesion showed a unique confluence of odontogenic epithelial rests in a moderately cellular connective tissue. Immunohistochemical staining highlighted a mixture of benign epithelial and Langerhans cells within connective tissue with diffuse amyloid-like stromal deposition. The importance of recognizing this variant of odontogenic fibroma is due to its benign prognosis and clinical course.

Key words: odontogenic fibroma amyloid-variant

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Conflict of interest
The Authors declare no conflict of interest.

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Introduction

The odontogenic tumours include a very heterogeneous spectrum of rare lesions ranging from inflammatory cysts, hamartomas and benign neoplasms to malignant neoplasms, with metastatic and/or disabling potential. From the earlier classification in 1952, many important revisions have been made over the past decades, mainly dividing odontogenic tumors in two categories based on biologic behaviour as malignat and benign (WHO 1st, 2nd and 3rd edition respectively in 1971, 1992 and in 2005) [1,2]. Like earlier editions, the updated classification of head and neck tumours (WHO 4th edition, 2017) [3] elaborated a simpler division also in light of genetic and molecular data, dividing them under the headings of epithelial, mesenchymal (ectomesenchymal) and mixed odontogenic tumours. This classification is still not free of criticisms and debate [1] and will probably require future improvements.
Odontogenic fibromas (OF) are defined as a rare neoplasm belonging to the benign mesenchymal lesions, made of mature fibrous connective tissue, with variable amounts of inactive-looking odontogenic epithelium, with or without evidence of calcification. Since 1992, these tumors have been classified into 2 types according to their histological features: epithelium-poor type and epithelium-rich type [4]. Furthermore, they are classified as central odontogenic fibroma (or intraosseous) and peripheral (extraosseous) odontogenic fibroma. Central odontogenic fibroma (COF) is a rare benign neoplasia of the jaws, accounting for less than 0.1% of all odontogenic tumors [5], with a wide patient age range and a slight female predilection. Peripheral odontogenic fibroma is more com-

mon than the central variant, occurring twice as frequently in females as in males, and it has an age peak in the second to fourth decades of life [6].
A neoplasm with similar histological and clinical features is the calcifying epithelial odontogenic tumour (CEOT) representing the main differential diagnosis of odontogenic fibroma. It belongs to a different group of neoplasms in the WHO classification, i.e. the benign epithelial odontogenic one, and is featured by overall recurrence rates much higher then odontogenic fibromas. This rare benign epithelial odontogenic tumour also secrets an amyloid protein that tends to calcify [7].
The mandible is affected twice as often as the maxilla, and the body is the more common site. Rare cases are extraosseous [8].
A correct recognition of this entity is mandatory because of its different prognosis, requiring a different clinical management.
In this report, we describe an unusual, typical and rare variant of a central odontogenic fibroma with diffuse amyloid-like protein stromal deposition. Differential diagnosis with other entities is discussed.

Materials and methods

A 26-year-old woman presented at our institution with a well-defined radiolucency of the mandible (dimension 1.0 cm), partially cystic. Expansion of the lingual cortical bone and partial interruption of the buccal cortical one was evident, without invasion of adjacent tissue. Divaricating with slight resorption of the root of teeth (#44) was seen, together with focal calcification (Figs. 1, 2).
An incisional biopsy was performed and sent for histopathologic examination. After diagnosis, an excisional biopsy followed with extensive bone and soft tissues sampling. No residual neoplasm was evident.
One-year follow-up after surgery showed no remarkable changes.
The surgical specimen was fixed in 10% buffered neutral formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin. Immunohistochemical staining was performed on paraffin sections of formalin-fixed tumor tissue according to standard laboratory procedures (Agilent 22C3 pharmDx on Dako Autostainer, Dako, Glostrup, Denmark).
Molecular analysis of the BRAF gene was performed using polymerase chain reaction to detect mutation of exon 15 using high resolution melt analysis and allele-specific PCR.
A review of the literature for reported cases of odontogenic tumor variants was conducted using PubMed and Metacrawler, including Mesh terms and manual searches.

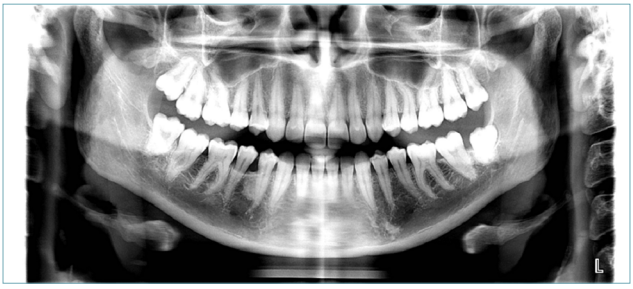

Figure 1. Increased radiopacity area projected of the right lower mandibular bone, next to the root of #44 (ADA - American Dentistry association/FDI - Federation Dentaire Internationale).

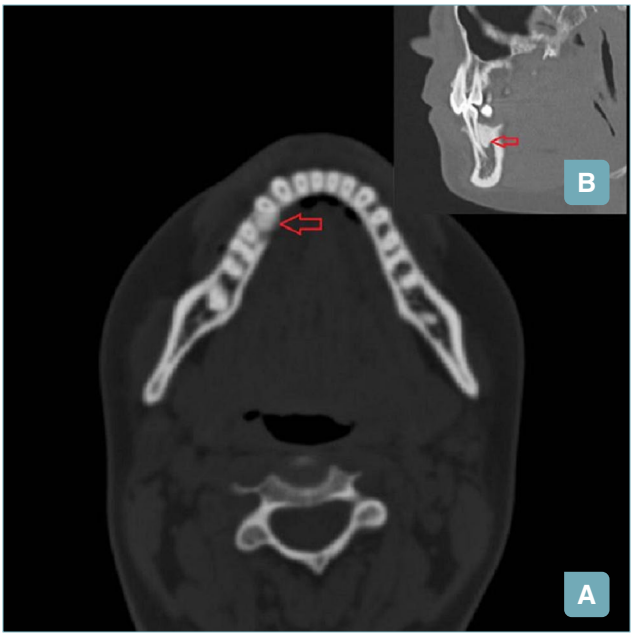

Figure 2. Axial (a) and Sagital (b) CT scan confirm sclerotic lesion in the left mandibular body around the root of #44 (ADA - American Dentistry association/FDI - Federation Dentaire Internationale).

Results

The specimen consisted of three whitish fragments (1.5 x 0.3 x 0.3 cm in dimension).
Histological examination revealed a biphasic neoplasm: an odontogenic epithelial component growing in strands, with focal calcifications and a moderately cellular connective stroma with homogeneous acidophilic areas and scattered fusocellular elements. (Figs. 3, 4). Necrosis and cellular atypia, either in the

epithelial or spindle cell component, were absent. Rare typical mitosis was present.
The epithelial component expressed diffuse membranous reaction for CK-AE1/AE3, CK19, CK14, Bcl2, CK8/18 and nuclear expression for p63 and p40, consistent with odontogenic epithelium; the epithelial aggregates exhibited a network of dendritic Langerhans cells, highlighted with S100 and CD1a antibodies. Immunoreaction for p53 and CD117 was limited to rare cells. All other markers tested (CK7, actin 1A4, TTF1 and CK20) were negative. Congo red staining revealed a massive amyloid deposit, and green birefringence was demonstrated with examination at polarized light. A faintly and doubtful cytoplasmic reactivity for BRAF V600E antibody prompted us to proceed with the molecular analysis of BRAF gene.
The molecular analysis of BRAF V600E mutation was negative.
A diagnosis of central odontogenic fibroma with diffuse amyloid-like protein stromal deposition was done.

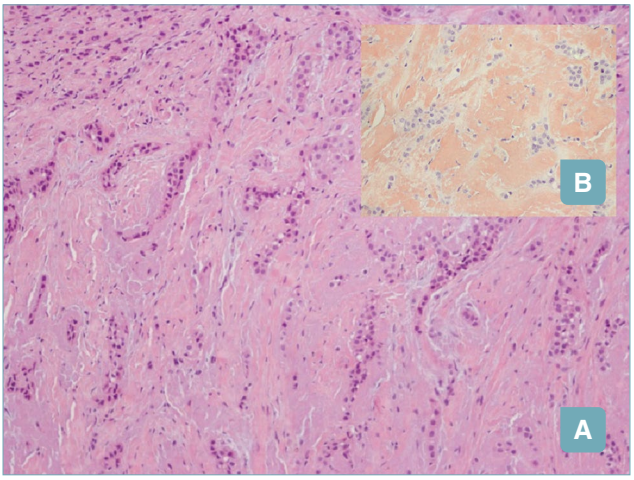

Figure 3. (a) Incisional biopsy: odontogenic epithelial nests, in a moderately cellular connective tissue (H&E, 100x); (b) Congo red staining revealed amyloid deposits as homogeneous eosinophilic globular masses. (Congo red stain, 200x).

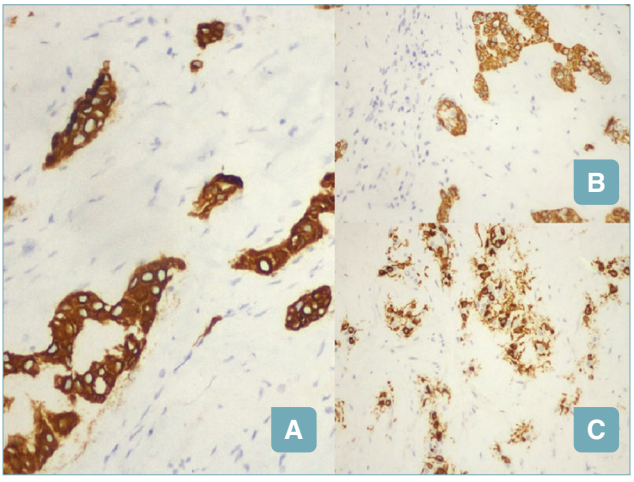

Figure 4. Keratin profile (immunohistochemistry, a - CK-AE1/AE3 and b- CK8/18, 200x); c: Langerhans cells (immunohistochemistry, CD1a, 200x).

Discussion

The amyloid rich variant of central odontogenic fibroma (COF) is perhaps the most challenging differential diagnosis for CEOT and this distinction remains still controversial [6]. The distinction between these two entities is clinically relevant, as COFs are generally expected to behave non-aggressively after treatment. Although controversy remains, several authors argue that these tumours are better classified as a variant of COF rather than a variant of CEOT classification, to avoid overtreatment [6,9,10].
A review of the literature shows that a neoplasm with morphological and immunohistochemical features similar to our case has been classified along the years as a non-calcifying Langerhans cell-rich variant of calcifying epithelial odontogenic tumor [11] or as central odontogenic fibroma and myxoma. Because of its features and rarity and due to the presence of few descriptions with an overlapping of clinical and pathological findings, this always created a sort of confusion among pathologists. Since 2011 [6], and endorsed by the last WHO blue book (2017), a rare variant of central odontogenic fibroma whith amyloid-like protein deposition is considered.
CEOTs are as rare as odontogenic fibromas. The mandible is affected twice as often as the maxilla, and the body is the most common site. Both sexes are equally affected. They occur in patients of any age, with predilection for individuals in their third to sixth decade of life (mean age about 40 years). The overall recurrence rate is about 15%. Almost 60% of CEOTs show a dentigerous relationship to an impacted tooth [11]. The non-calcifying Langerhans cell-rich variant of CEOT, also termed atypical-CEOT [12], has the following different clinical aspects when compared with the “classical” forms [13]: predilection for individuals of Asian ethnicity; usual onset at middle age; almost 2:1 female predominance; predilection for anterior maxilla; typically a unilocular radiolucency around the roots of teeth; no detectable radiopaque foci; characteristic depression of the palatal bone/mucosa; exten-

sive root resorption; widely scattered and very small epithelial islands in a hypocellular fibromyxoid background; numerous Langerhans cells within the epithelium; juxtaepithelial deposition of amyloid globules without calcification; rare occurrence of relapse.

Odontogenic fibroma occurs with equal frequency in the maxilla and the mandible, more commonly in the anterior-premolar region. Central odontogenic fibromas seldom occur around crowns of impacted teeth. Most fibromas reside in a peri- or interradicular location [14]. Root resorption is common in fibromas [13].

The most interesting reasons to recognize odontogenic fibromas in comparison to CEOTs are different prognosis and reccurence rates. CEOTS are not so biologically aggressive and the overall recurrence is about 15% [15]. Although odontogenic fibroma is usually treated by enucleation and curettage, which sometimes requires removal of adjacent teeth, the recurrence rate has been described as very low, about 4% [16].

An interesting morphologic signature of both neoplasms is the presence of amyloid-like material, which can be highlighted by morphology and histochemical stains (Congo red) [17]. Tumour epithelial cells produce a kind of amyloid-like protein, called odontogenic ameloblast-associated protein (ODAM) [18], which is produced physiologically by developing tooth germs and by odontogenic epithelial, as in the Pindborg tumor (calcifying epithelial odontogenic tumour - CEOT) and in the odontogenic fibroma (amyloid-variant).

Detailed immunohistochemical studies of CEOT are not plentiful in the literature [19,20], and the expression of CKs (especially CK14 and CK19) are very similar in both CEOTs and COFs [17], vanishing the usefulness of immunohistochemistry as a useful tool for differential diagnosis.

Currently, the decreasing cost and increased throughput capacities of next generation sequencing (NGS) have led to rapid advances in the understanding of molecular pathogenesis of tumours, including odontogenic neoplasms [21]. Various signalling pathways regulate the process of odontogenesis [10] and some gene mutations seems to be clearly implicated in the pathogenesis of odontogenic tumours and odontogenic cystic neoplasms. Investigations focusing on RAS and BRAF mutations have been summarized in many studies [22,23], although few studies focused specifically on rare lesions. These mutations are present only in the epithelial tumour tissue, but are absent in the surrounding stromal tissue [24]. As previously described [25] and as it was expected to be, our case of odontogenic fibroma resulted negative for BRAF V600E mutations.

Conclusions

Odontogenic tumors, as a whole, are rare, and the combination of their infrequency with their morphologic overlap makes the diagnosis challenging. Unfortunately, the contribution to diagnosis of immunohistochemistry, molecular and genetic analysis in odontogenic tumours is unrelevant. In most cases, clinical history, radiology and careful attention to morphology is often sufficient to establish a diagnosis. We agree that cases with these features have to be diagnosed as odontogenic fibroma, instead of CEOT, because of the benign prognosis of the lesion deserving a less strict follow-up.

Our patient received radical excision, with no recurrence after 1.5 years of follow-up.

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