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Case Report

Clinical and Histological Diversity of Ossifying Fibroma: A Series of 4 Cases Showing Aggressive Behavior

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Abstract

Aim: Juvenile Ossifying Fibroma (JOF) is a variant of ossifying fibroma. It occurs in young age group 5-18 years old causing sever malocclusion, encroaching vital anatomical areas. Commonly presented with rapid alarming growth. Two histopathological patterns are linked to the aggressive biological behavior namely juvenile trabecular ossifying fibroma (JTOF) and psammomatoid ossifying fibroma (POF). JTOF mostly affects children and adolescents with equal gender and site distribution between the mandible and maxilla. While POF occurs chiefly in extra-gnathic sites, especially in paranasal sinuses, periorbital bones and skull base. Surgery with wide excision is the optimal treatment. **Subjects & methods:** This article presents detailed review concerning clinical radiographic and histopathological examination of four cases. The age range of the patients studied was between 7 and 22 years with reflection to treatment protocol and prognosis. **Results:** The conditions observed in these cases primarily affected the maxilla, extending towards the floor of the orbit and, in some instances, the nasal septum. In other cases, the conditions were in the mandible. **Conclusion:** OF is a benign tumor having aggressive subtypes with high recurrence rates. For accurate diagnosis, it is crucial to examine the clinical, radiographic, and histopathological aspects of the lesions because they share similar characteristics with other aggressive bone abnormalities. Early detection and an appropriate treatment strategy involving enucleation with curettage or resection of the tumour according to the size of the lesion, followed by long-term follow-up, are essential for optimal outcomes.

Keywords: ossifying fibroma; bone neoplasms; treatment.

Introduction

Ossifying fibroma (OF) is a fibro-osseous neoplasm characterized by active growth and the presence of a cell-rich fibrous stroma, bands of osteoid tissue and trabeculae of woven bone. Symptoms vary depending on the location and can include pain, paraesthesia, malocclusion, sinusitis and proptosis.[1] This paper demonstrates four cases of the aggressive entities, JTOF and POF, in the maxilla and mandible of children and young adults that were managed by surgical excision

Case Series

Case 1

A 7-year-old male presented to the Oral and Maxillofacial Surgery department, Cairo University complaining of a painless swelling related to the right side of the mandible with a duration of three months. The patient had good oral hygiene and was medically free.

The patient's clinical history revealed that a similar lesion was surgically excised three months earlier and was then diagnosed as a cemento-ossifying fibroma.

Intraoral examination revealed a hard bony swelling covered by intact normal colored mucosa, extending from the lower left central incisor to the lower right first primary molar, measuring 1 x 2cm **(Fig. 1).**

Cone-beam computed tomography (CBCT) was performed. The CBCT showed an expansile well-defined radiolucent lesion affecting the lower right posterior region, extending from the distal surface of the lower left lateral incisor to the mesial surface of lower right first permanent molar **(Fig. 2)**

A differential diagnosis of juvenile trabecular ossifying fibroma, psammomatoid ossifying fibroma, odontogenic myxoma and ameloblastic fibroma were suggested. An excisional biopsy was performed under general anaesthesia and was sent to the Oral and Maxillofacial Pathology department, Cairo university for histopathological analysis. Grossly, the specimen was whitish in color with a solid cut section and firm consistency.

Histopathological examination revealed hypercellular fibrous collagenous stroma composed of plump spindle to stellate fibroblasts with round ossified ossicles **(Fig. 3).** The histopathological diagnosis of POF was made. The lesion was treated by wide surgical excision with follow-up for 2 years with no evidence of recurrence.

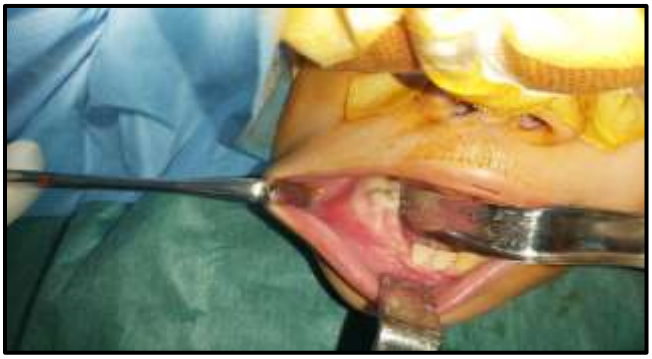

Figure 1. Intraoral examination showing firm swelling with expansion of buccal bone of lower right mandible.

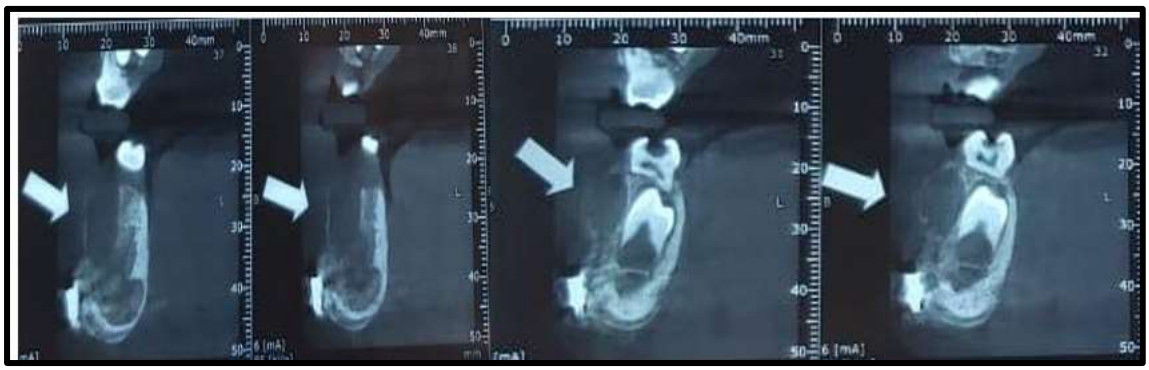

Figure 2. CBCT scan serial cuts showing radiolucency with well-defined borders in the tooth-bearing area. Note the residual thin rim of cortex around the lesion (arrows).

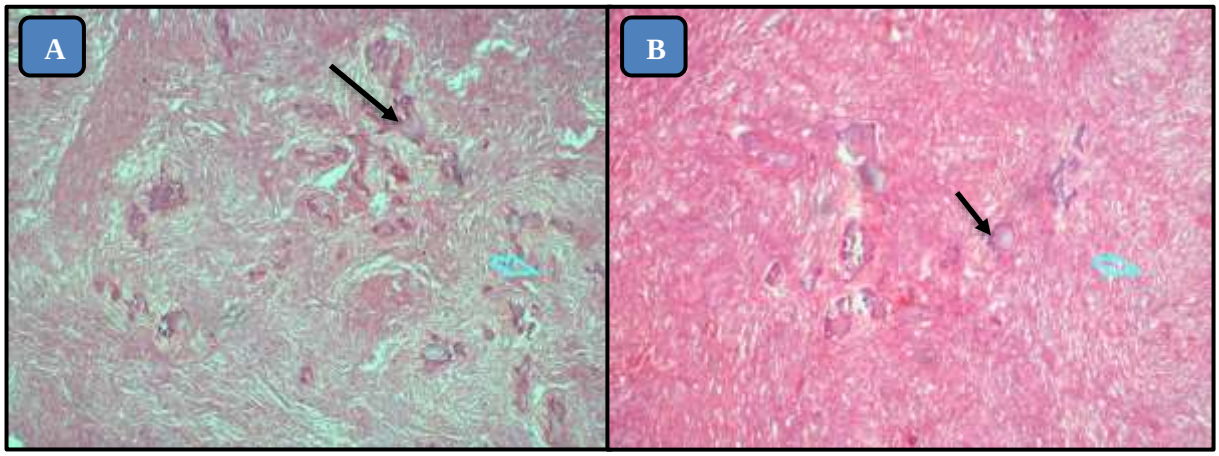

Figure 3. Psammomatoid ossifying fibroma (A) Cellular proliferation (green arrow) with many globular bony ossicles. (B) Round and ovoid calcified ossicles with benign spindle cells (black arrows).

Case 2

A 14-year-old male presented to the Oral and Maxillofacial Surgery department, Cairo University complaining of a mild painful swelling in the upper right posterior area with a duration of two months. There was no prior occurrence of the lesion. The patient had good oral hygiene and was medically free.

Intraoral examination revealed a hard bony swelling covered by intact normal colored oral mucosa, extending from the upper right first premolar till the upper right second molar, measuring 5 x 5 x 2cm **(Fig. 4).**

Cone-beam computed tomography (CBCT) was performed. The CBCT showed an expansile well-defined mixed radiolucent-radiopaque lesion affecting the upper right posterior region, extending from the upper right first premolar till the upper right second molar **(Fig. 4).**

A differential diagnosis of odontogenic myxoma, juvenile trabecular ossifying fibroma, psammomatoid ossifying fibroma and osteosarcoma were suggested.

An incisional biopsy was performed under local anesthesia and was sent to the Oral and Maxillofacial Pathology department, Cairo University for histopathological analysis. The incisional biopsy was accessed buccally and grossly the lesion was reddish white in color and firm consistency. The cut section was solid.

Histopathological examination revealed hypercellular stroma formed of plump spindle and stellate cells with few bands of osteoid tissue together with immature bone trabeculae, without osteoblastic rimming **(Fig. 5).** Immunostaining with osteopontin was performed and confirmed the osteoblastic lineage of the stromal cells **(Fig. 6).** Lack of dysplastic features in stromal cells excluded osteosarcoma. So, the case was diagnosed as juvenile trabecular ossifying fibroma. The lesion was treated by wide surgical excision, follow-up for 2 years showed no evidence of recurrence

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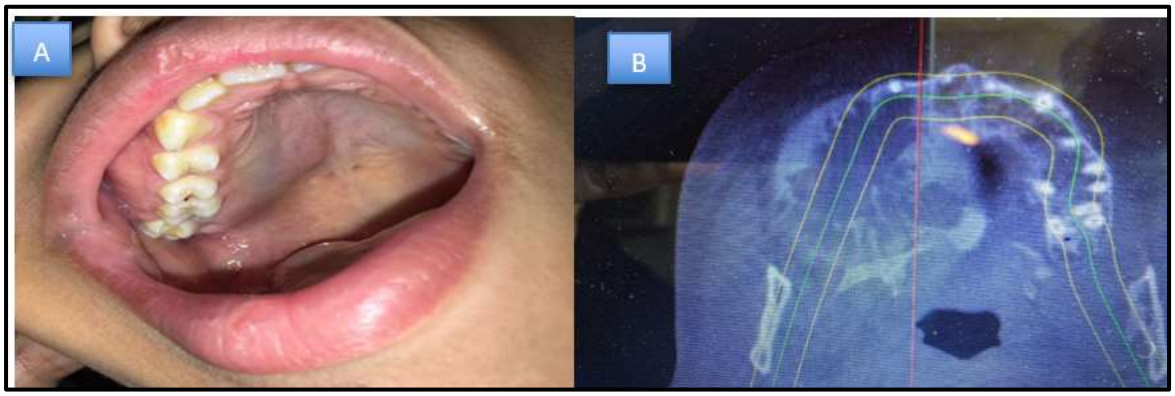

Figure 4. (A) Intraoral examination showing firm swelling with expansion of buccal & palatal premolar-molar area of upper right maxillary region. (B) ACT scan showing unilateral radiolucency with irregular well demarcated borders causing bone expansion upper right maxillary area.

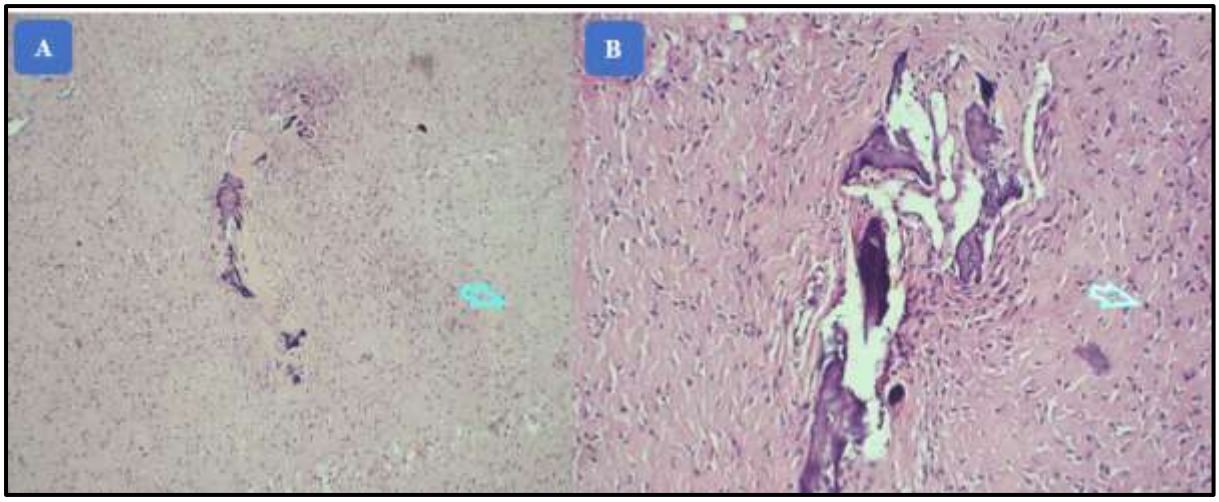

Figure 5. (A) Cellular proliferation of spindle cells (green arrow) with immature bone trabeculae. (B) Plump spindle and stellate cells (green arrow) surrounding immature bone trabeculae.

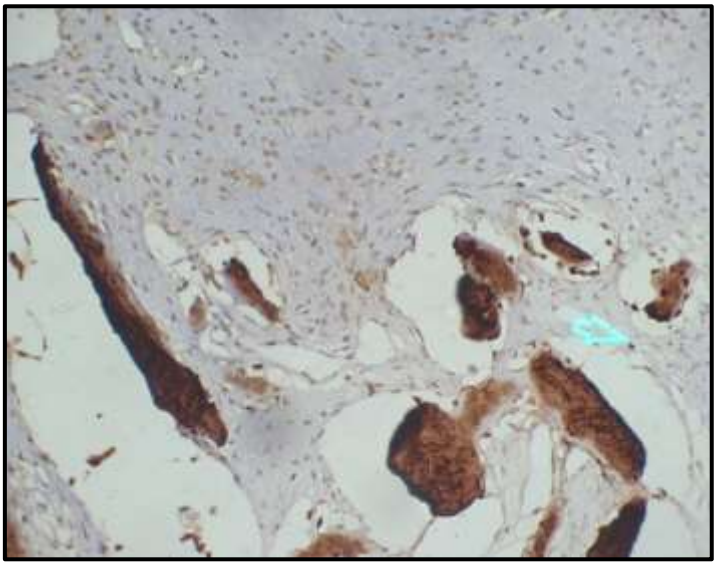

Figure 6. Positive immunostaining with osteopontin.

Case 3

An 8-year-old female presented to the Oral and Maxillofacial Surgery department, Cairo University complaining of a painless swelling on the left side of the face with a duration of three months causing breathing difficulties. The patient had poor oral hygiene and was otherwise medically free.

The patient's clinical history revealed a similar lesion was removed five years ago and was then diagnosed as odontogenic myxoma. The lesion later recurred, and an incisional biopsy was performed. It was diagnosed as a juvenile ossifying fibroma.

Cone-beam computed tomography (CBCT) was performed. The CBCT showed an expansile well-defined mixed radiolucent-radiopaque lesion extending from the floor of

the orbit to the alveolar bone involving the upper left lateral incisor to the upper left second premolar. It also the nasal septum and extended posteriorly to the soft palate.

Wide surgical excision was performed under general anaesthesia and the specimen was sent to the Oral and Maxillofacial Pathology department, Cairo University for histopathological analysis.

Histopathological examination revealed multiple small uniform basophilic ossicles embedded in a hypercellular stroma formed of plump spindle and stellate shaped cells **(Fig. 7),** reactive bone was also observed at the periphery **(Fig. 8).**

The final diagnosis of the resected lesion confirmed the previous diagnosis of psammomatoid ossifying fibroma. 18 months follow up revealed no recurrence. The patient was recommended to continue the follow up every 12 month for 5 years.

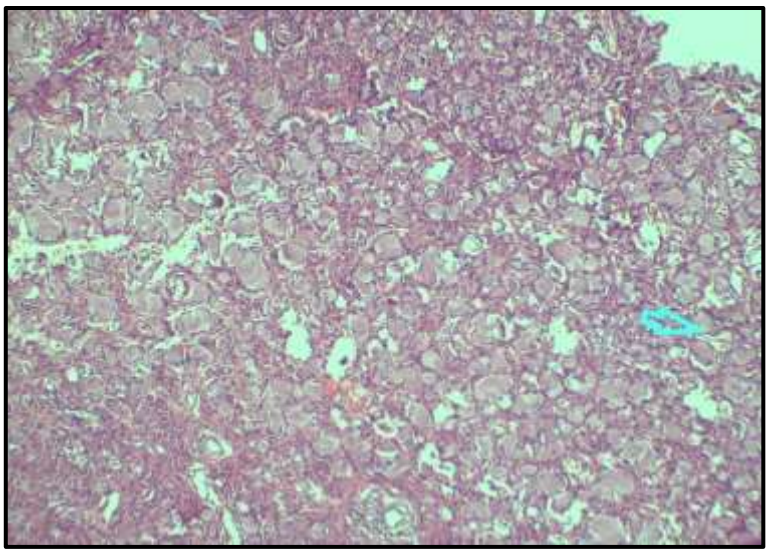

Figure 7. Hypercellular stroma containing numerous spherical ossicles (green arrow).

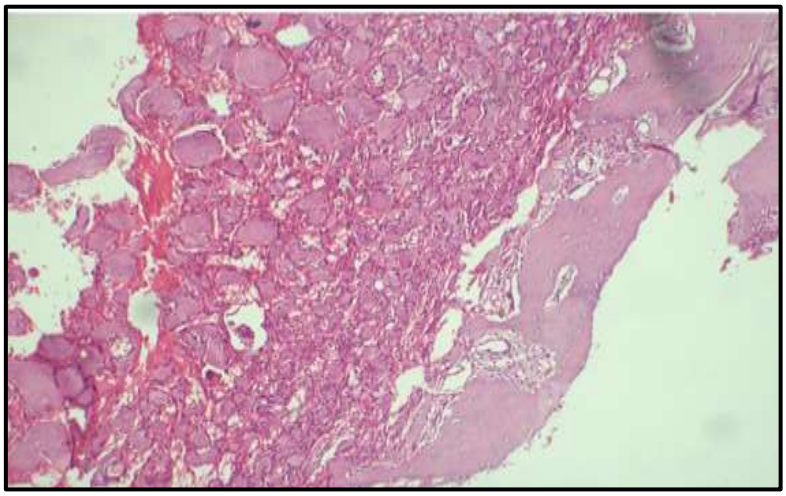

Figure 8. Hypercellular stroma containing numerous spherical ossicles with peripheral reactive bone.

Case 4

A 22-year-old female presented to the Oral and Maxillofacial Surgery department, Cairo University complaining of a painless swelling on the lower left posterior area with a duration of 1.5 years. The patient had good oral hygiene and was medically free.

Intraoral examination revealed a hard bony swelling covered by intact normal colored oral mucosa affecting the lower left posterior area. Lymph node examination revealed non-palpable cervical lymph nodes.

A panoramic radiograph showed an expansile multilocular radiolucency extending from the lower left second molar to the condyle **(Fig.9 .**

An incisional biopsy was performed under local anesthesia and sent to the Oral and Maxillofacial Pathology department, Cairo university for histopathological analysis. A superficial incisional biopsy was taken from the buccal aspect of the lesion.

Grossly, the specimen was reddish white in color having irregular surface texture and rubbery consistency. The cut section was cystic.

Histopathology revealed cellular fibrous stroma composed of proliferating plump spindle and stellate cells with osteoid deposition without osteoblastic rimming. Areas of bone trabeculae surrounded by osteoblasts were also noted **(Fig.10)** Large vascular spaces devoid of epithelial lining engorged with red blood cells were evident and surrounded by multinucleated giant cells **(Fig. 10).** Ultimately, a diagnosis of juvenile trabecular ossifying fibroma with aneurysmal changes was made. One year follow up revealed no recurrence. The patient was recommended to continue the follow up every six month for 5 years.

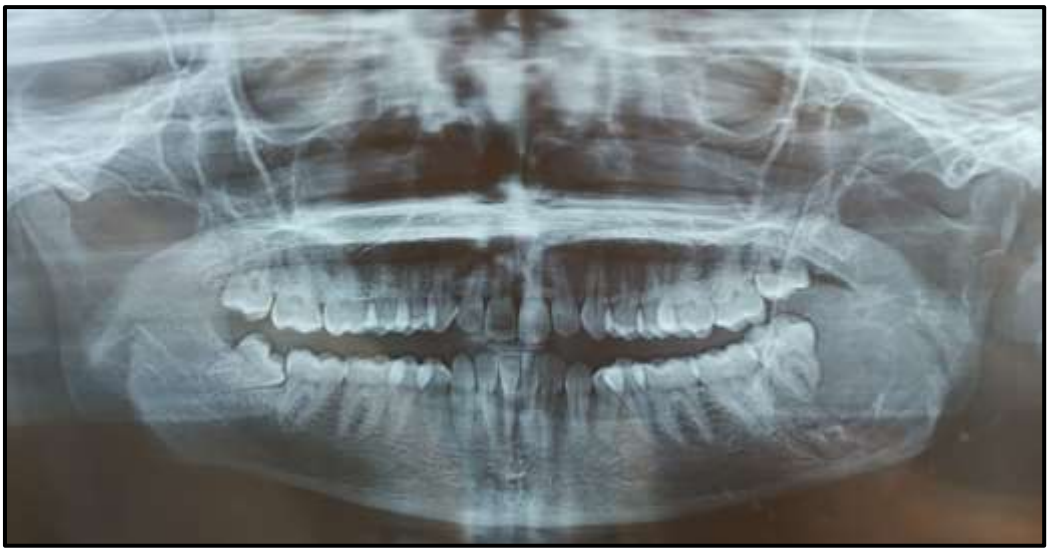

Figure 9. Panoramic radiograph showing an expansile multilocular radiolucency extending from the lower left second molar to the condyle.

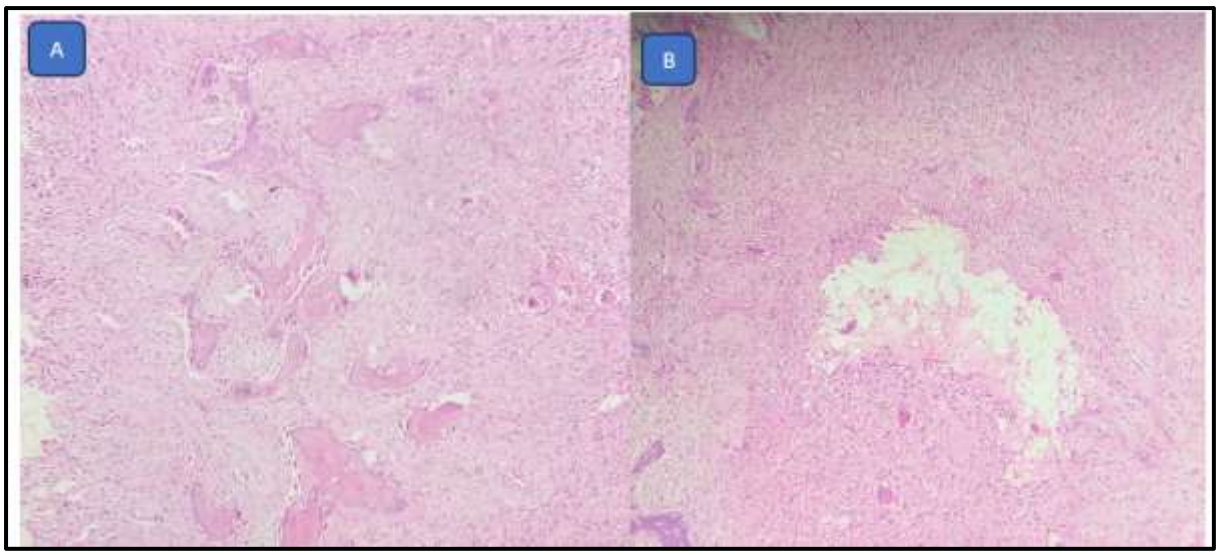

Figure 10. (A) Fibrous stroma composed of proliferating plump spindle and stellate cells with immature bony trabeculae surrounded by osteoblasts. (B) A large vascular space devoid of epithelial lining, engorged with red blood cells and surrounded with multinucleated giant cells.

Discussion

Ossifying fibroma (OF) is a rare benign fibro-osseous neoplasm having aggressive entities, which arises in the craniofacial complex of children and young adults. They occur more commonly in the maxilla and very rarely in the mandible (2).

Origin and Genetic Background

OF is a fibro-osseous neoplasm showing active growth style consisting of a cell-rich fibrous stroma, containing bands of osteoid tissue without osteoblastic lining, together with trabeculae of more typical woven bone. It has been proposed that OF arises as a result of differentiation of multipotential precursor cells of mesenchymal progenitors of cranio-facial complex as well as undifferentiated cells of the periodontal apparatus to form cementum, osteoid or fibrous tissue combination (2).

The WHO defines the aggressive entities of as "an actively growing lesion mainly affecting individuals below the age of 15 years, which is composed of a cell-rich fibrous tissue containing bands of cellular osteoid without osteoblastic rimming together with trabeculae of more typical woven bone. Usually, no fibrous capsule can be demonstrated, but the lesion is well demarcated from the surrounding bone". The tumor grows asymptomatically achieving a large size giving suspicion of malignancy. Histopathologically, two types have been identified: the psammomatoid and trabecular types (3).

The genetic molecular events that may drive JTOF tumorigenesis have not been extensively exposed but reports about *CTNNB1* mutations needs further investigations (4). Other studies revealed chromosome 12 long arm rearrangement covering MDM2 and RASAL1. MDM2 amplification in up to 70% without immunohistochemical MDM2 overexpression. In addition, HPRT2 mutations have been found in OF (25 - 50%) associated with hyperparathyroidism-jaw tumor syndrome (5).

Prevalence

Both JTOF and POF are rare with the POF being recorded more often than the JTOF (6). JTOF arises predominantly in children and adolescents (mean 11.3 years), with <20% of cases affecting individuals older than 15 years. There is no sex predilection (4).

The peak incidence of POF is in the second to fourth decades with a broad range and M:F ratio approximately 1.4:1. POF shows a striking affinity for the paranasal sinuses and orbital bones, while JTOF usually affect the jaws, with almost equal distribution between the maxilla and mandible (6).

Clinical Behaviour

JTOF and POF are types of that present as aggressive and expanding lesions. JTOF has gnathic predilection with equal site distribution between the mandible and maxilla. It often displays aggressive expansion with disruption of cortical bone and involvement of nearby anatomical structures. Symptoms may vary depending on the location and may include pain, paresthesia, malocclusion, sinusitis and proptosis. POF is frequently observed in individuals who are between the ages of 16 and 33, and it tends to affect males more often than females. It typically affects the paranasal sinuses, orbit and fronto-ethmoidal complex (7).

JTOF is commonly observed in young people with an average age of 8 to 12 years. The condition has no sex predilection. JTOF's rapid growth, demographics and histopathological features can often cause confusion with osteosarcoma and fibrous dysplasia (8).

Generally, OFs can affect individuals across a broad age range. The cases documented in this paper had an age distribution, ranging from 7 to 14 years old, which is consistent with the published literature (8).

Although some studies reported variable sex predilection for OFs, Wang K *et al.,* (9) suggested male predominance for POF, which came in line with the cases in our study. In the present study, JTOF were present in the upper alveolus region of the maxilla and mandible, while POF cases developed within the sinonasal bones. This finding is consistent with the commonly reported occurrence sites of these conditions in other case series (10).

Radiographic Profile and Clinical Differential Diagnosis

Commonly, radiographic examination shows well-demarcated lesion with areas of radiolucency intermixed with radiopacity, depending on the amount of calcified tissue produced. Radiographs can show root displacement and resorption, though rarely (2). JTOF appears predominantly radiolucent and shows a well-defined border with varying degrees of radiopacity. While, POF usually appears as a well-circumscribed expansile lesion, varying from lucent to ground glass to more discrete calcifications (10).

Histopathological Diversity

The aggressive variants of are characterized by zones of fibrous tissue proliferation intermixed with bone trabeculae and calcified ossicles (11). Histopathological examination of shows diverse stromal tissue arrangements. It reveals areas of ample cellular mesenchymal lineage which can alternate with myxomatous areas. Variable bone trabeculae or ossicles together with giant cells might be present (3).

In the current study, the histopathological presentation demonstrated both aggressive variants. Some cases showed a stromal background formed of dominating numerous plump spindle and stellate cells with few bands of osteoid tissue together with immature bone trabeculae, without osteoblastic rimming. Other cases revealed numerous multiple small uniform basophilic ossicles embedded in a hypercellular stroma. All cases shared the plump appearance of the stromal cells, lacking any dysplastic features. This enabled us to rule out the possibility of osteosarcoma in rapidly growing radiographic lesions.

JTOF consists of a more cellular proliferation of plump bipolar to stellate cells that grow more loosely with a stroma containing scant collagen. Osteoid appears to form directly from the stroma as elongated, curved or branching trabeculae without osteoblastic rimming. The trabeculae may become ossified into immature

woven bone. Osteoclast-type giant cells are relatively common and secondary cystic change has been reported particularly around the new bone (12, 13).

POF contains a moderately to highly cellular, compact proliferation of spindled of stellate cells with scant stroma and small rounded deposits of woven bone with central calcification resembling psammoma bodies or cementum. Osteoblastic rimming is not observed. Larger deposits of bone may coalesce to form angulated or linear trabeculae. Secondary cystic change is relatively common (14).

Histological Differential Diagnosis

There are some overlapping histopathological features with other fibro-osseous lesions of the maxillofacial area. Therefore, diagnostic work up must include all clinical, radiographic and histopathological data to reach the definitive diagnosis (15).

To start with, differential diagnosis with conventional OF, can occur. Given that it is more common. They may share similar radiographic appearance despite the frequent multilocular appearance of the aggressive entities, the conventional OF on the other hand is typically unilocular and well circumscribed, with high mandibular site of occurrence (16).

Fibrous dysplasia's radiographic characteristic "ground glass" appearance distinguish it from JTOF and POF. Besides, histopathologically, the immature woven bone typically seen as "Chinese letters" stands as an important diagnostic clue. Also, bony trabeculae usually have no osteoblastic rimming. Fibrous dysplasia tends to blend with surrounding bone and this continuity of normal and pathologic bone is not a typical feature of OF. On the molecular level, fibrous dysplasia is associated with GNAS mutations (17).

Cementoblastoma is a neoplasm of cementum intimately involved with tooth root. It appears in the radiograph as a radiopaque mass with a narrow radiolucent rim. Histopathologically, it consists of dense cementum-like tissue with multiple reversal lines and fibroblastic stroma and commonly arise in the mandible. Pain is a common symptom, due to the involvement of vital tooth structure (18).

Cemento-osseous dysplasia can share some histopathologic similarities with OF, having variably cellular fibrous stroma with mineralizing tissues. However, regardless of the subtype, cemento-osseous dysplasia seldom shows any bony expansion, unlike OF, and is mostly asymptomatic, limited to teeth bearing area. Cemento-osseous dysplasia is diagnosed by clinical and radiographic correlation and biopsy is performed only in limited number of cases to avoid complications limited to poor vascularity (19).

In addition to fibro-osseous lesions, histopathological overlap with other intra-bony aggressive lesions such as osteosarcoma, especially fibroblastic osteosarcoma as well as low grade osteosarcoma can occur. The key point for differential diagnosis is the presence of cytologic atypia in the malignant stromal cells (20).

Moreover, another aggressive lesion that may resemble OF is osteoblastoma with similar alarming rapid growth behaviour. However, the presence of well-formed bone trabeculae lined by prominent plump osteoblasts often shifts the diagnosis to osteoblastoma. Osteoblastoma has a rich fibrovascular stroma with occasional presence of giant cells.

Central giant cell lesions should be considered if numerous giant cells were histopathologically encountered. Besides, parathyroid hormone profile might help in hormonal imbalance cases. In general, the slight atypical plump stromal spindle cells with ossicles formation might help in the differential diagnosis favouring POF (16).

Extra cranial (extradural) meningioma, psamommatous meningioma variant can create confusion due to presence of calcified psammoma bodies and immature bone formation. The definitive diagnosis can be

concluded by Somatostatin receptor subtype 2A (SSTR2A), EMA and variable PR positivity of meningioma (21).

Immunostaining

Stromal cells will show positivity for RUNX2, a major transcription factor for the osteogenic lineage. Generally, immunohistochemistry may not be helpful in differential diagnosis since other like fibrous dysplasia, are also RUNX2 positive. Interesting study by Kaur H et al, 2022, demonstrated total negative immune expression of MDM2 in the studied cases of ossifying fibroma and fibrous dysplasia while osteosarcoma revealed high immunostaining intensity for MDM2 with conclusion that MDM2 shows high specificity to differentiate osteosarcoma from benign mimics like ossifying fibroma (20).

Treatment Modalities

The anatomical location and the histopathological variant play a minimal role in the recurrence rate following a successful surgical approach. While simple enucleation of JTOF and POF usually ends with an expected recurrence, enucleation followed by curettage reduces the recurrence rate, only to an extent. Enucleation with peripheral osteotomy proved a better outcome over the curettage option. In order, to further eliminate the recurrence of JTOF and POF, resection is the treatment of choice. However, in 2020, Chrcanovic, B.R. and Gomez, R.S. stated that enucleation followed by peripheral osteotomy or curettage should be always the first line of treatment to avoid the lifetime disfigurement for these young patients that can result from surgical resection (4).

In 2021, Titinchi, F. mentioned that enucleation can be kept for small lesions, while enucleation with curettage is the treatment of choice for well-defined lesions, whether unilocular or multilocular in the radiograph. For extensive and recurrent lesions, resection might be the only life-saving approach. Otherwise, resection is avoided to reduce morbidity after these kinds of surgeries (15).

Prognosis and Recurrence

The preferred treatment for both subtypes is complete surgical excision rather than conservative curettage, as incomplete resection increases the likelihood of recurrence and the recurrent tumor tends to be more aggressive than the primary one. Long-term follow-up is necessary, as recurrence may occur within 6 months to 19 years following surgery (22).

Depending on the extent of disease and the involvement of the surrounding structures, an open surgical approach may be required for complete resection. Radiotherapy is not recommended due to the tumor's radio-resistance and high risk of malignant transformation, as well as the harmful effects of radiotherapy on children. Given the high recurrence rate (30–50%) and aggressive behaviour of the lesion, JTOF and POF should be treated as locally aggressive neoplasms (11).

Conclusion

JTOF and POF are rare benign fibro-osseous lesions with a rather high risk of recurrence. A careful examination and correlation of the clinical, radiological and histopathological components of these lesions is mandatory for accurate diagnosis due to the overlapping histopathologic findings with other intra-bony aggressive lesions. Early diagnosis and an adequate treatment plan consisting of complete surgical excision followed by long-term follow-up of the patient is paramount.

Conflict of interests
The authors declare no conflict of interest.

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Ethics
This study protocol was approved by the ethical committee of the faculty of dentistry, Cairo university on 31 January 2023, number: 29-1-23

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