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# Juvenile Ossifying Fibroma: A Clinicopathologic Study of 8 Cases and Comparison with Craniofacial Fibro-osseous Lesions

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**Background :** Juvenile ossifying fibroma (JOF) is defined as a variant of the ossifying fibroma, and the latter includes juvenile trabecular ossifying fibroma (JTOF) and juvenile psammomatoid ossifying fibroma (JPOF). JOF can be distinguished from other craniofacial fibro-osseous lesions by its tendency to recur and its clinical mimicry of malignant bone tumors, but some clinical and histological features of JOF overlap with the other fibro-osseous lesions as well. We aimed to identify the clinicopathologic definition of JOF. **Methods :** Forty-two cases of fibro-osseous lesions were reviewed and they were classified into JOF, fibrous dysplasia (FD) and ossifying fibroma (OF). **Results :** JTOF had long, slender and anastomosing trabeculae of osteoid in a fibrocellular stroma, and JPOF had small ossicles resembling psammoma bodies with a thick collagenous rim in the fibrous stroma, which are features that differ from those of FD and OF. Radiologically, JOF and OF showed a well-defined lesion but FD exhibited an ill-defined lesion. Clinically, the average age of the JOF patients was the youngest, followed by OF and FD. For JOF, three cases had rapid growth and two others showed recurrences. JOF mainly occurred in the paranasal sinuses, OF in the mandible and FD in any craniofacial bone. **Conclusion :** We demonstrated the distinct characteristics of JOF and these features may be helpful for the diagnosis and management of this malady.

**Key Words :** Fibroma, Ossifying; Juvenile

Juvenile ossifying fibroma (JOF) is a benign bone-forming neoplasm, and it is defined as a variant of the ossifying fibroma in the craniofacial skeleton of young age patients.[1,2] It is known to have two distinct histological subtypes, that is, juvenile trabecular ossifying fibroma (JTOF) and juvenile psammomatoid ossifying fibroma (JPOF).[2,3] JOF has been considered as a distinct disease entity from conventional ossifying fibroma (OF) and the other fibro-osseous lesions because of its tendency to occur at a young age and its locally aggressive behavior.[1] Moreover, JOF may clinically manifest with rapid painless expansion of the affected bone as an aggressive lesion mimicking malignancy such as osteosarcoma.[4] So, it is important to accurately recognize JOF for making the diagnosis and managing this disease. Yet there also has been some controversy about the recognition of this entity because some features of JOF overlap, to some extent, with those of other fibro-osseous lesions.[1-3] In this paper, we define the specific, precise clinicopathologic features of JOF conducting a review of the fibro-osseous lesions of the craniofacial bone.

## MATERIALS AND METHODS

Forty-two surgically resected fibro-osseous lesions of the craniofacial bones were retrieved from the surgical pathology files of Asan Medical Center (AMC) from 1997 to 2007. The clinical histories and radiological findings were available for all the cases. The pathological materials were reviewed by two pathologists.

The histology of fibro-osseous lesions usually consisted of three parts, which were osseous components, fibrous components and the secondary changes. We analyzed our cases according to the former two components and we set the criteria for the classification as the following: fibrous dysplasia (FD), curvilinear bony trabeculae without osteoblastic rimming in fibrous stroma; ossifying fibroma (OF), irregular and short osteoid with osteoblastic rimming in a fibrous stroma; JPOF displays psammomatoid or spherical osteoid with or without osteoblastic rimming in a fibrous stroma, and JTOF displays long, slender anastomosing bony trabeculae with or without osteoblastic rimming in a fibrous stroma. The secondary changes included aneurysmal bone cyst (ABC)-like changes, myxoid changes and hemorrhage.

## RESULTS

Eight cases of JOF (two cases of JTOF and six cases of JPOF), seven cases of OF and 27 cases of FD could be classified after analysis of the histological findings.

Microscopically, for the osseous components, JTOF showed a mixture of cellular osteoids without osteoblastic rimming, and there were trabeculae of immature bone with osteoblastic rimming (Fig. 1A). OF also showed irregular trabeculae (Fig. 1B), similar to those of JTOF, but the trabeculae in JTOF were longer and slenderer, with an anastomosing pattern resembling paintbrush strokes. It was occasionally difficult to distinguish the cellular osteoid from the cellular fibrous stroma, and the latter was reminiscent of adamantinoma (Fig. 1A). FD also exhibited similar irregular immature bone trabeculae, but the FD cases had no or scant osteoblastic rimming and the trabeculae were curvilinear woven bones (Fig. 1C). JPOF exhibited spherical or ovoid ossicles that resembled psammoma bodies with or without osteoblastic rimming and some ossicles were calcified with a basophilic center and an eosinophilic fringe with lamellation. The ossicles of JPOF were surrounded by a thick irregular collagenous rim and the ossicles were occasionally fused together (Fig. 2A). OF sometimes partly showed cellular or acellular spherical ossicles of immature bone, but the ossicles of OF were more uniform with a thinner and less conspicuous collagenous rim (Fig. 2B) and they showed the transition with irregular bony trabeculae.

The fibrous components of JOF, OF and FD exhibited similar features. The stroma consisted of cohesive or loosely packed fibroblasts around the osseous components. In JOF, the cellularity of the fibrocellular stroma tended to be variable, ranging from a scanty fibroblastic stroma that was due to closely packed ossicles to a highly cellular stroma. The stroma of FD consistently showed relatively low cellularity.

Secondary changes were commonly encountered in JOF, including ABC-like changes such as multinucleated giant cell infiltration and hemorrhage in JTOF (Fig. 3A), and myxoid (Fig. 3B) and hemorrhagic cystic changes in JPOF (Fig. 3C). Such findings were uncommon in OF and FD.

When the radiological findings were compared after histo-

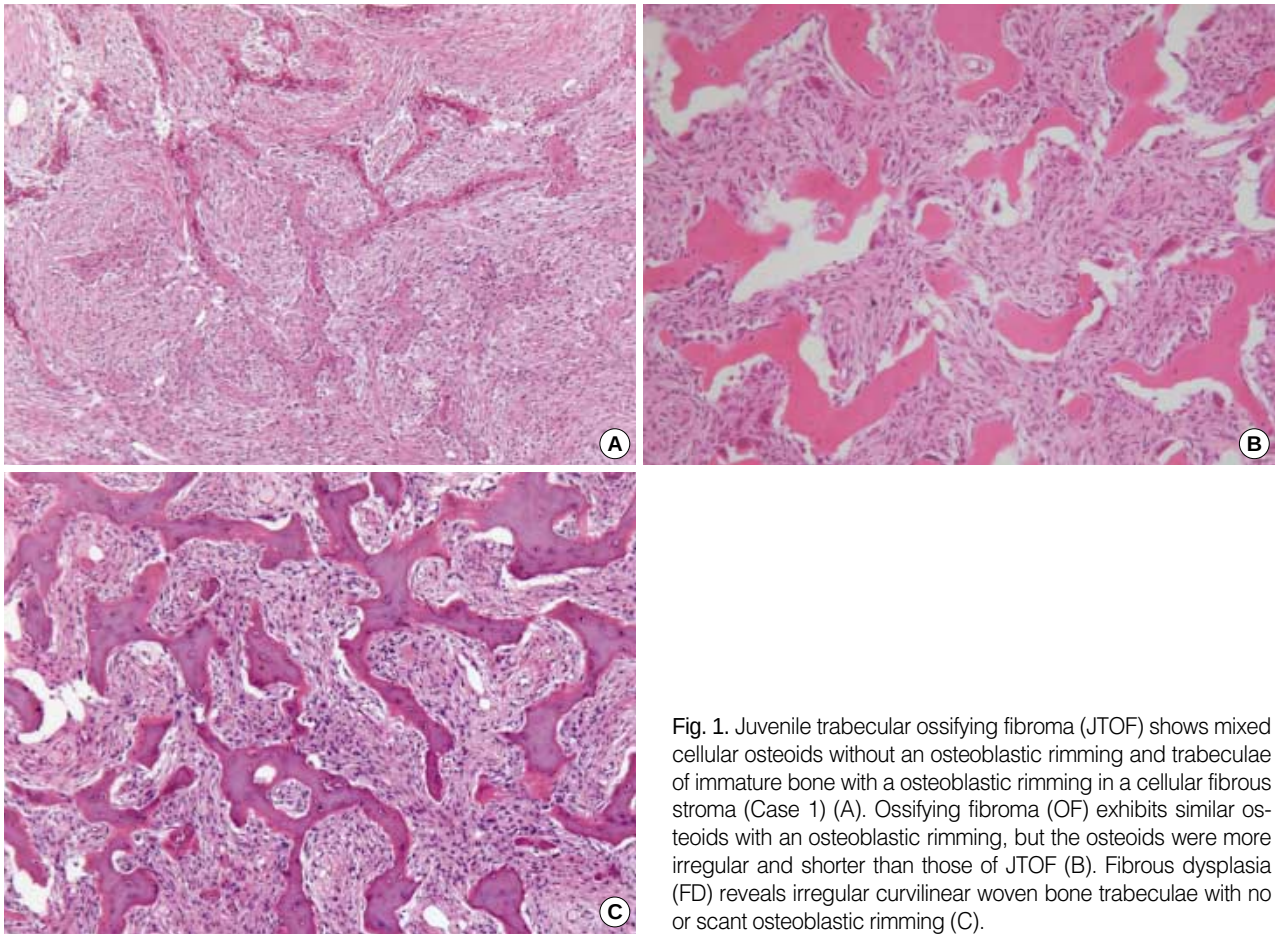


Fig. 1. Juvenile trabecular ossifying fibroma (JTOF) shows mixed cellular osteoids without an osteoblastic rimming and trabeculae of immature bone with a osteoblastic rimming in a cellular fibrous stroma (Case 1) (A). Ossifying fibroma (OF) exhibits similar osteoids with an osteoblastic rimming, but the osteoids were more irregular and shorter than those of JTOF (B). Fibrous dysplasia (FD) reveals irregular curvilinear woven bone trabeculae with no or scant osteoblastic rimming (C).

logical classification, JOF and OF showed similar well defined, radiolucent bone expansions with soft tissue density (Fig. 4A-C). JOF showed a more aggressive mass (Fig. 4B) than OF (Fig. 4C). In contrast to OF and JOF, FD exhibited a poorly defined lesion with a "ground-glass" appearance, with expansion of the involved bone throughout its length (Fig. 4D).

Clinically, some differences were found between the different patients. Although the patients with JTOF (7 and 26 years old) and JPOF (from 8 to 58 years old) were not always young, the patients with JOF had the youngest average age (20.5 years), followed by OF (25.1 years) and FD (29.6 years). A gender preponderance was absent for all the entities. JTOF occurred in the maxilla and skull bone, and the sites of JPOF were the paranasal sinuses, maxilla, and skull bone. The mandible and maxilla were favorable sites of OF. FD was found in any craniofacial bone, such as the maxilla, followed by the mandible, skull so on.

One patient with JTOF and two patients with JPOF had been admitted, complaining of the rapid growth of the lesions for three weeks to three months. The above JTOF patient with rapid growth experienced a recurrence 17 months after the surgery, and the patient received reoperation. The resected tumor showed the same features of JTOF without any evidence of malignancy. Another patient with JPOF manifested radiological changes that were suspicious for a local recurrence and further management is being planned. The remaining six patients with JOF have been well at 4 to 65 months of follow-up. There has been no recurrence in the patients with OF during follow-up. Two patients with FD received surgeries twice because of the incomplete initial surgery (Table 1).

## DISCUSSION

The fibro-osseous lesions are thought to be the result of diverse processes in which the normal bone architecture is replaced by fibroblasts and collagen fibers that contain various amounts of mineralized material, and these lesions include a broad group of several entities like OF, JOF, FD and so on.[5] Most of them have been considered as benign lesions, but JOF has been classified as a different disease because of its local aggressive behavior

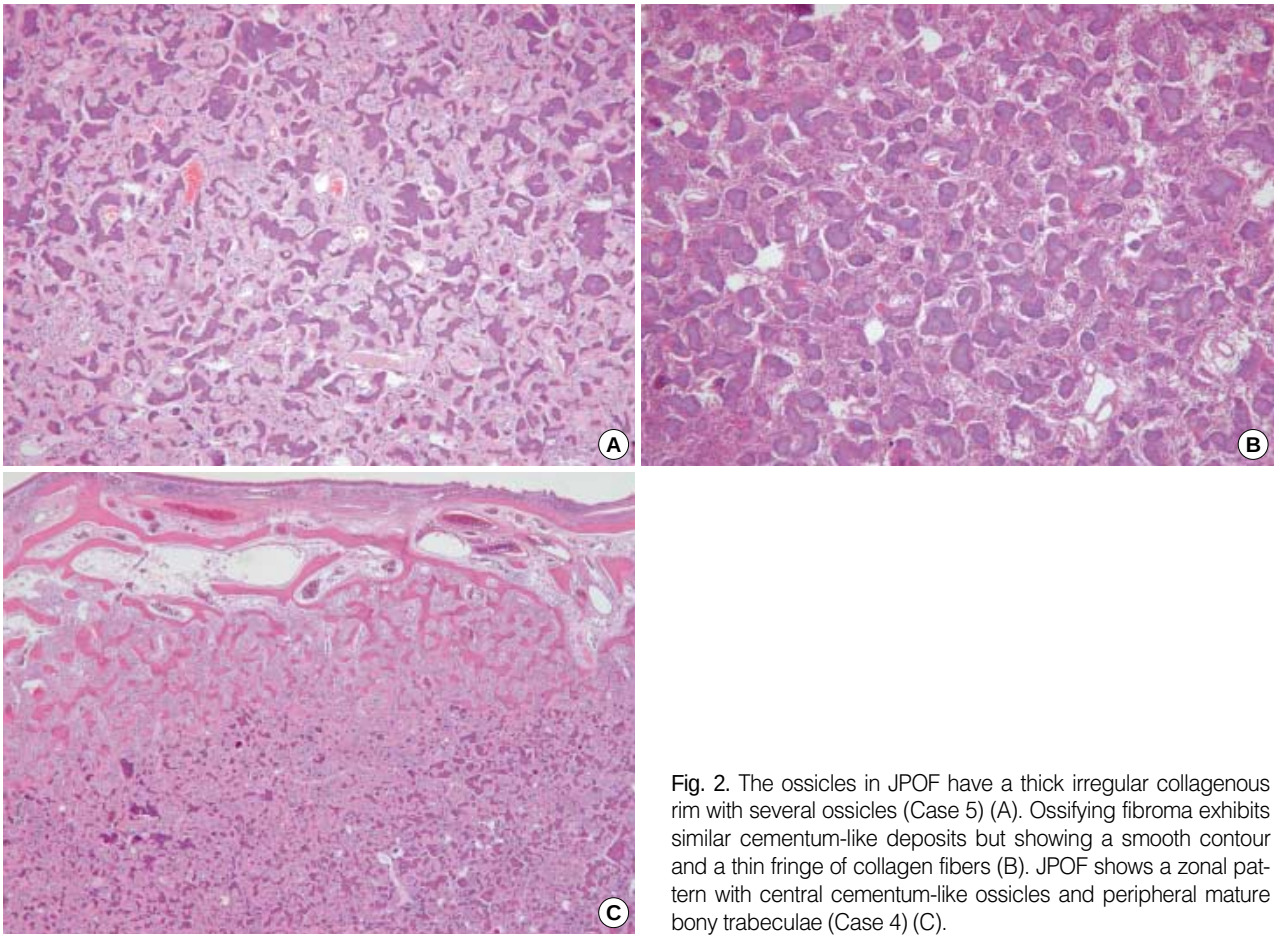


Fig. 2. The ossicles in JPOF have a thick irregular collagenous rim with several ossicles (Case 5) (A). Ossifying fibroma exhibits similar cementum-like deposits but showing a smooth contour and a thin fringe of collagen fibers (B). JPOF shows a zonal pattern with central cementum-like ossicles and peripheral mature bony trabeculae (Case 4) (C).

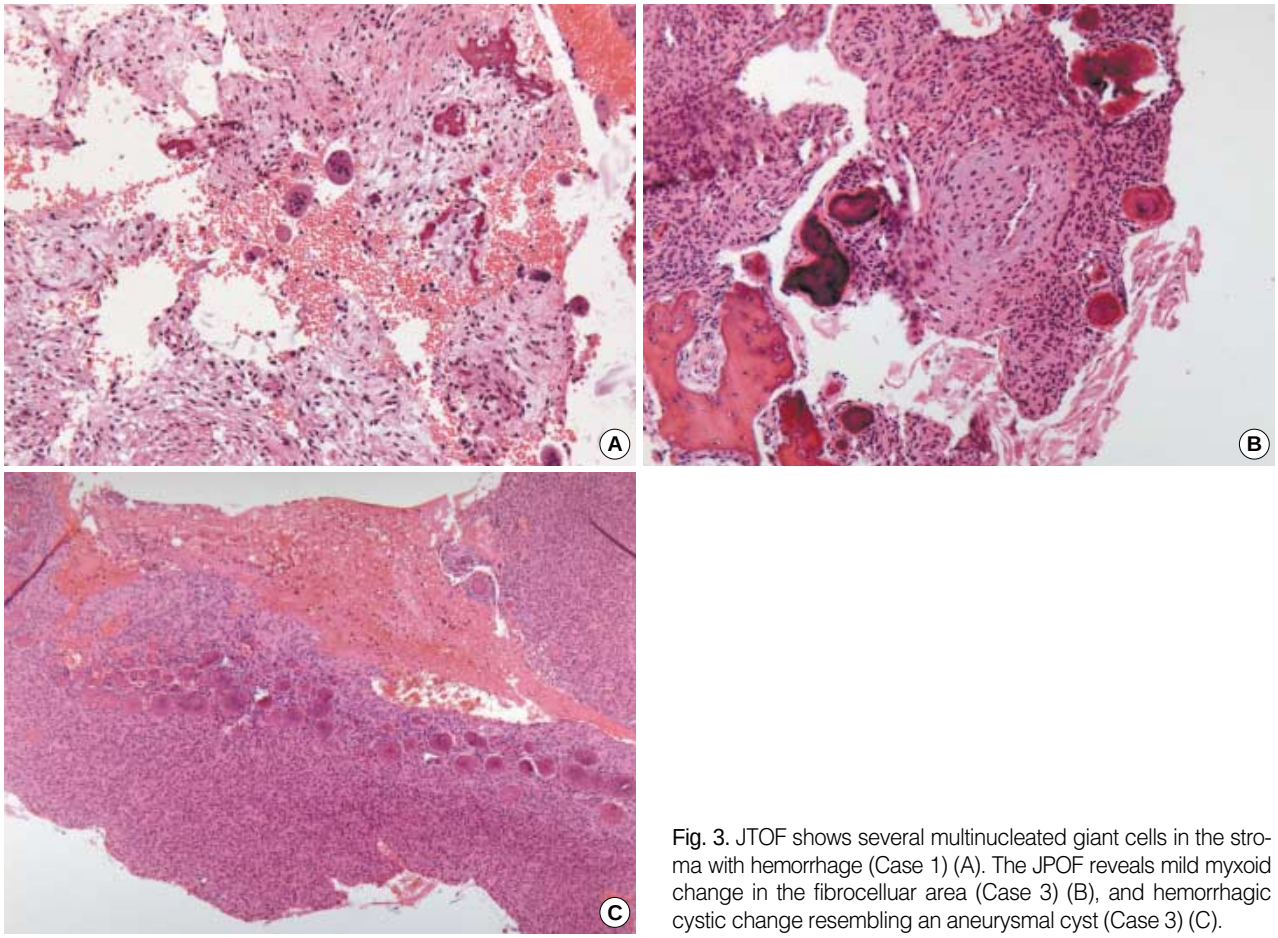


Fig. 3. JTOF shows several multinucleated giant cells in the stroma with hemorrhage (Case 1) (A). The JPOF reveals mild myxoid change in the fibrocelluar area (Case 3) (B), and hemorrhagic cystic change resembling an aneurysmal cyst (Case 3) (C).

and its tendency to predominantly occur in children and adolescents.[1,6,7] JOF needs to be distinguished from malignant bone tumors in that there is a similarity of clinical manifestations,[4,6-8] but JOF can be easily excluded from malignant bone tumors on the routine histological examination. Additionally, it may be difficult to distinguish JOF from other fibro-osseous lesions because of the overlapping features.[1,6,7] We analyzed 42 fibro-osseous lesions of the craniofacial bone based on the descriptions in the literature[1-6,9-20] and on our own experience.

According to the WHO classification, the cementum-like deposits seen in OF show a smooth contour with a radiating fringe of collagen fibers, but the ossicles in JPOF have a thick irregular collagenous rim.[2] This description was confirmed in our cases (Fig. 2A, B). Moreover, JOF may show a zonal pattern with central cementum-like ossicles and peripheral mature bony trabeculae (Fig. 2C), but OF seemed to show a mixed, random pattern. These features of osseous components were unique histological features and they could be clues for the diagnosis of JOF.[1-4,9] No or scant osteoblastic rimming in osseous components suggested FD.[1-4] Although the fibrous components were relatively similar between JOF, OF and FD, an extremely cellular fibrous stroma tended to be observed in JOF, which may be attributed to the aggressiveness of JOF according to other reports.[1,9,10] The secondary ABC-like changes that were present in some cases of JOF, and not in OF and FD may suggest JOF[1-3], but these features may not be very specific since many fast growing bone lesions may develop ABC-like changes.[1,11,12] Therefore, the characteristic osseous components of JOF that were described as above, and the highly cellular fibrous stroma with or without secondary changes are best recognizable as features of JOF.

Fibro-osseous lesions also have relatively distinct radiological features. JOF and OF both displayed well-demarcated, round or oval lesions. Additionally, JOF often revealed aggressive lesions with cortical destruction, which can be used to discriminate JOF from OF. FD manifested ill-defined contiguous lesions because of their blending with normal bone, with expanding of the involved bone throughout its overall length over several years, which demonstrates a slow growth pattern. The area of the involved bone adjacent to the lesion showed a transitional thickened area that histologically demonstrated a blending region

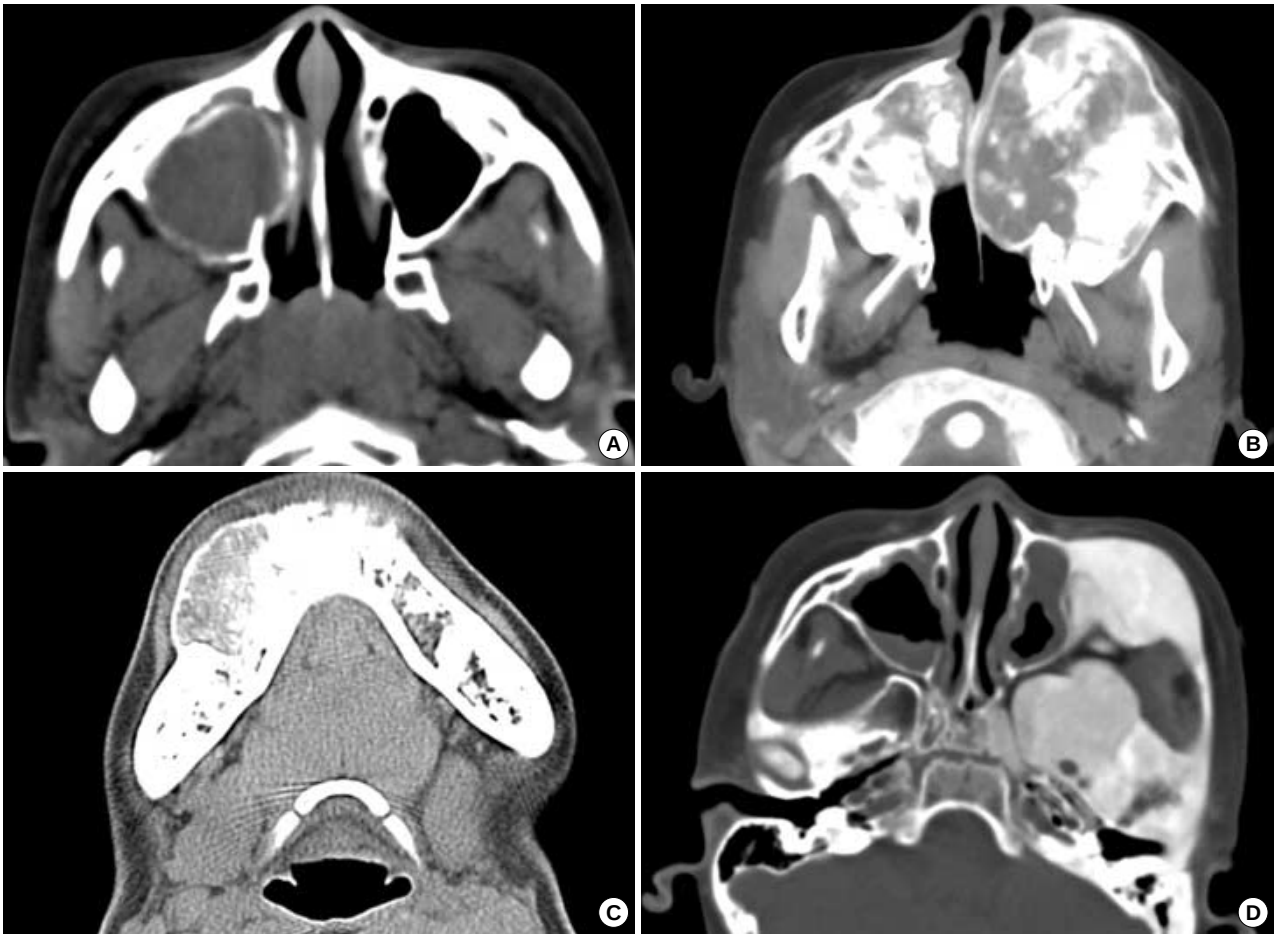


Fig. 4. On the computer tomography, JTOF shows a relatively well defined, radiolucent mass-like lesion with soft tissue density in the right maxilla (Case 1), (A). JPOF exhibits a relatively well defined, mixed radiolucent and radiodense mass-like lesion with an aggressive pattern in the left maxilla (Case 3), (B). Ossifying fibroma also shows a similar well demarcated lesion frequently affecting the mandible (C). Fibrous dysplasia shows a poorly defined, asymmetrical "ground-glass" lesion blending into the normal bone (D).

Table 1. Clinical findings of juvenile trabecular ossifying fibromas and juvenile psammomatoid ossifying fibromas

| Case | Age/Sex | Site | Dx. | Management | Follow-up period/ outcome |
|---|---|---|---|---|---|
| 1 | 7/F | Right maxilla | JTOF | Resections (x2) | 23Mo/Recurrence |
| 2 | 26/F | Skull | JTOF | Resection | 4Mo/NED |
| 3 | 10/F | Left maxilla | JPOF | Resection | 12Mo/Recurrence |
| 4 | 9/M | Left ethmoid sinus | JPOF | Resection | 10Mo/NED, F/U loss |
| 5 | 23/M | Right frontal sinus | JPOF | Resection | 11Mo |
| 6 | 8/M | Mandible | JPOF | Resection | 15Mo/NED |
| 7 | 23/F | Right zygomus | JPOF | Resection | F/U loss |
| 8 | 58/M | Inferior turbinate | JPOF | Resection | 65Mo/NED, F/U loss |

Dx, Diagnosis; JTOF, Juvenile trabecular ossifying fibroma; JPOF, Juvenile psammomatoid ossifying fibroma; Mo, Month; NED, no evidence of disease; F/U, Follow-up.

between the lesion and normal bone, and the boundary of the lesion was ill defined and not clear. In one case of JOF, it appeared as a relatively ill-defined confluent lesion that mimicked FD due to the extension of lesion to several adjacent bones. Yet the lesion still suggested JOF, because it partly showed a well-defined and localized mass-like area with a clinically rapid growth pattern, which was unusual for FD. Moreover, the area between the lesion and the normal adjacent bone was abrupt, in contrast to those

areas of FD. In addition, the lesion of FD showed a typical ground glass appearance but JOF or OF displayed focal or heterogeneous opacity in the lesion. These image findings could discriminate JOF from FD and OF, the same as in other reports.[1,2,13-17]

Regarding the clinical features, the lesion location and patient age may not be helpful as differential points due to the overlapped features of these diseases. Nevertheless, each entity had some distinct features. The sites of JOF in our cases were consistent with other reports[1,18-20] in that JTOF mainly occur in the maxilla, mandible, and fronto-ethmoid complex, and JPOF occurred in the paranasal sinus, calvarium, maxilla and mandible, as well as in the sites frequented by OF and FD. JOF mainly occurred at young ages (JPOF, mean age: 21.8 years; JTOF, mean age: 16.5 years), but the age range of JPOF has been described to be quite wider (3 months to 72 years old).[1,2,18-20] These features were similarly observed in our cases that the JTOF patients were 6 and 26 years old, and JPOF showed more variable ages that ranged from 8 to 58 years old.

The clinical behavior of JOF has been reported to be more aggressive than the other fibro-osseous lesions, and certain histological features, including hypercellular stroma, psammomatoid ossicles, garland-like strands of cellular osteoid and myxoid change, have been previously mentioned to be related with JOF aggressiveness.[1] These secondary changes were observed in our recurred cases of JOF and also in our other cases of JOF. Although some of our patients with JOF in our cases showed rapid growth and recurrences, we need more follow-up data to determine the clinical significance of JOF.

The genetic differences in cranial fibro-osseous lesions are not well established, but some genetic studies had been done. Nonrandom chromosome break points at Xq26 and 2q33, resulting in (X;2) translocation, were identified in some cases of JPOF.[21] For OF, alterations in the tumor suppressor gene HPRT2 were identified in two out of four cases.[22] In FD, an activating point mutation of the alpha subunit of the stimulatory G protein gene (GNAS) at the $Arg^{201}$ codon was identified in extragnathic FD, and this was recognized as a molecular maker, but this gene has not been examined for gnathic FD.[23-25] So far, the results of these early studies are not be helpful for practical diagnosis. Progressive molecular research in the future may make the definition of JOF clear and explain the biological behavior of JOF.

In summary, we reviewed 42 craniofacial fibro-osseous lesions and we could identify JOF as a distinct clinicopathologic entity. If a patient has the characteristics of JOF as mentioned above such as distinct histological features, occurrence sites and radiological features etc, then the possibility of JOF should be in mind and the informed clinicians should perform appropriate management and watchful follow-up.

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