Bilateral central ossifying fibroma affecting the mandible:
report of an uncommon case and critical review of the
literature

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Ossifying fibroma (OF) is a well demarcated benign neoplasm primarily found in the jaw and composed of fibrocellular tissue and mineralized material. Occurrence of multiple OFs (synchronous) is rare in the jaws, and only 10 cases have been documented. The aim of this report was to present an additional case of bilateral central OF in the mandible of a patient not affected by the hyperparathyroidism–jaw tumors syndrome (HPT-JT), emphasizing the features that distinguish this lesion from HPT-JT and performing a critical review of the current literature and concepts.

Benign fibro-osseous lesions (FOLs) are a poorly defined and to some extent controversial group of lesions affecting the jaws and craniofacial bones. FOL refers to a group of pathologic processes in which normal bone is replaced by fibroblasts and collagen fibers containing variable amounts of mineralized material.1-3 This group encompasses fibrous dysplasia, benign fibro-osseous neoplasms (central ossifying fibroma), and a heterogeneous group of reactive lesions (osseous dysplasias). Because of the histopathologic similarities among these lesions, the definitive diagnosis requires a precise correlation of the clinical, histopathologic, and imaging findings.1,2

The World Health Organization currently defines ossifying fibroma (OF) as a benign neoplasm which often presents well demarcated borders and is composed histologically of fibrocellular stroma and variable amounts of mineralized material showing different morphologic appearance.4 These tumors are typically found as solitary lesions in patients lacking relevant medical history or occurrence of similar lesions in the past.5 The occurrence of multiple or recurrent OF in the jaws is considered to be rare and has been associated with hormonal abnormalities, such as hypercalcemia associated with hyperparathyroidism.2,5-7

The aim of the present report was to present an unusual case of bilateral central OF affecting the mandible of a patient not affected by the hyperparathyroidism–jaw tumors syndrome (HPT-JT) and to review the current knowledge regarding the occurrence of multiple ossifying fibromas in the jaws.

CASE REPORT

A 35-year-old female patient was referred for evaluation of facial asymmetry. The patient’s chief complaint was an asymptomatic slowly progressive growth in the left mandible. Clinically, her face showed moderate asymmetry at the left mandible area (Fig. 1, A). Intraoral examination revealed a hard swelling in the left mandible involving intact alveolar mucosa and extending from the second premolar region to the retromolar area; it measured ~3 cm in greatest diameter (Fig. 1, B).

A panoramic radiograph showed a large well demarcated radiolucency surrounded by a sclerotic border in the left body and extending into the angle of the mandible. The radiograph did not detect any evidence of calcification within the lesion. Incidentally, a contralateral well circumscribed radiolucency with variable degrees of calcification was found, involving the region of the second and third molars (Fig. 2). Computed tomography revealed an extensive unilocular and hypodense image associated with the clinical expansion of the left mandible. The other lesion located on the right mandible also showed a hypodense area with internal dense opacities mimicking snowflakes (Fig. 3).
Incisional biopsies were performed in each reported lesion, and both specimens showed a similar histomorphologic pattern. Hematoxylin and eosin–stained sections showed well demarcated lesions that were separated from the surrounding bone by a thin zone of fibrous tissue. The lesions were mainly composed of cellular fibrous tissue rich in fibroblasts, with occasional areas showing a storiform pattern (Fig. 4). The lesion located on the left mandible showed scarce areas of small spherical calcifications (cementum-like); in contrast, the right mandible specimen exhibited a larger amount of such calcified structures (Fig. 4).

Based on the clinical, imaging, and histopathologic features, a diagnosis of bilateral central OFs was rendered, and levels of serum calcium, phosphorus, and parathyroid hormone (PTH) were determined to rule out a possible correlation between the jaw lesions and hyperparathyroidism. Serum tests showed calcium values at 9.73 mg/dL (normal range 8.4-11 mg/dL), phosphorus 4.2 mg/dL (normal range 2.5-5 mg/dL) and PTH 56.34 pg/mL (normal range 15-65 pg/mL). Results of blood tests (white blood cell count, red blood cell, hemoglobin, and hematocrit) were all within normal limits. Therefore, surgical enucleation of these lesions was performed in 2 different surgical interventions. During surgical removal, the lesions showed delimitation and separation from the surrounding bone and were entirely enucleated. The microscopic findings of both lesions showed features identical to those described in the 2 previous incisional biopsies. The patient is still under periodic clinical and radiographic follow-up. After 3 years, she showed no signs or evidence of recurrence and was in good health.
Ossifying fibroma is mainly diagnosed between the second and fourth decades of life, with women being affected more frequently than men.1-3 To the best of our knowledge, multiple synchronous central OFs are rare events, with only 10 previously reported cases.8-17 The main features of these cases are summarized in Table I.

Based on the previously published cases of multiple OFs, 7 patients (70%) were female and 3 (30%) male. The mean age was 33.8 years (ranging from 6 to 55 years old). Clinically, 5 cases (50%) presented as painless slow-growing lesions and 4 cases (40%) were associated with pain. All cases were associated with facial enlargement. The present case showed clinical features similar to the previously reported cases: The present patient was a 35-year-old woman at the time of the diagnosis, presenting with an asymptomatic growth on her left mandibular region, causing moderate facial asymmetry.

The imaging features were similar among the 10 cases reviewed and were characterized by well circumscribed mainly radiolucent lesions, with intralosomal calcification in 6 cases (60%). Conservative surgery was the treatment in 8 patients (80%), and en bloc resection was performed in 3 lesions (30%). The mean follow-up time was 1 year (ranging from 6 to 48 months); therefore, conclusive results regarding recurrence could not be reliably assessed. Recurrences were documented in 2 cases (20%). Similarly, the present case showed radiolucent and well circumscribed lesions with only 1 of them showing focal radiopacities (right side). The treatment performed in both lesions was surgical enucleation, and after 3 years of follow-up no recurrence had been detected.

Multiple or recurrent OFs of the jaws had been previously reported in association with HPT-JT. Jackson et al. (1990)6 were the first authors to described families with multiple cases of primary hyperparathyroidism and jaw tumors affecting 3 generations of the same family.

HPT-JT is an inherited autosomal dominant disorder characterized by the occurrence of parathyroid adenomas or carcinomas, fibro-osseous lesions of the mandible and maxilla, Wilms tumor, renal cysts, renal hamartomas, renal cortical adenomas, papillary renal cell carcinoma, pancreatic adenocarcinoma, and testicular tumors.5,18 Inactivation of the HRPT2 gene is associated with the pathogenesis of hereditary HPT-JT.2,5,7

The association between alterations in the serum values of PTH and the presence of OFs in the jaws is highly suggestive of HPT-JT.5 Approximately 35% of the patients presenting the syndrome have OFs, which may appear at as early as 13 years of age.19 The recommended treatment in these cases is surgical removal, but there is the possibility of recurrent jaw tumors after surgery in patients with HPT-JT.7

In the present case, serum calcium, phosphorus, and PTH levels were determined to exclude a possible association with HPT-JT. It is important to highlight that among the similar cases reported, only Yih et al. (1989)11 and Khanna and Andrade (1992)12 mentioned that serum levels of calcium and alkaline phosphatase were determined.

In the case reported by Yih et al. (1989)11 (Table I), serum levels of alkaline phosphatase increased through the time of the patient’s follow-up. Interestingly, they found that the patient’s mother also had an OF in the left mandible and another in the maxilla. Unfortunately, the authors did not investigate the serum levels of PTH, which could represent a misdiagnosis of the reported
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<th>Case</th>
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<th>Gender/age (y)</th>
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| 1    | Bradley and Leake, 1968 | F/6 | Lesion 1: right maxilla  
Lesion 2: right angle of the mandible | Painless expanding mass showing marked asymmetry in the right face | RE: multicystic lesions | NR | Right maxilla: surgical enucleation and curettage  
Right mandible: scheduled for removal | NR |
| 2    | Takeda and Fujioka, 1987 | M/55 | Lesion 1: left maxilla  
Lesion 2: right maxilla | Spontaneous pain and swelling of maxillary region | RE: well circumscribed lesions showed radiolucent areas intermingled with radiopaque areas | NR | Right maxillary sinus: surgical enucleation  
Left maxillary sinus: partial hemimaxillectomy | NR |
| 3    | Hauser et al., 1989 | M/35 | Lesion 1: right maxillary sinus  
Lesion 2: left maxillary sinus | Swelling associated with bilateral proptosis, zygomatic enlargement, infraorbital nerve paresthesia, partial nasal obstruction | RE: well circumscribed mixed radiolucent/radiopaque lesions. No evidence of root resorption was noted.  
CT: well circumscribed lesion with calcified masses | NR | Right maxillary sinus: surgical enucleation  
Left maxillary sinus: partial hemimaxillectomy | NR |
| 4    | Yih et al., 1989 | F/31 | Lesion 1: left mandibular body  
Lesion 2: right maxilla  
Lesion 3: left mandible (2 y later) | Pain in the left of the face associated with the first molar | RE: well circumscribed unilocular radiolucency | Alkaline phosphatase: 218 IU/L  
Serum calcium: normal limits  
Phosphate: normal limits | Left mandibular body and right maxilla: surgical enucleation | Residual radiolucency 2 y later no recurrence after 4 y |
| 5    | Khanna and Andrade, 1992 | M/33 | Lesion 1: right maxilla  
Lesion 2: left body of mandible | Swelling large, hard, and painless | RE: large lesions contained diffuse calcifications | Alkaline phosphatase: normal limits  
Serum calcium: normal limits | Right maxilla and left body of the mandible: surgical enucleation | 1 y after the treatment, the patient did not return for follow-up |
| 6    | Hwang et al., 2001 | F/25 | Lesion 1: right mandibular body  
Lesion 2: left maxillary tuberosity  
Lesion 3: left mandibular body  
Lesion 4: left maxillary  
Lesion 5: right maxilla | Marked swelling, hard and painless, with no signs of inflammation | RE: large calcified mass surrounded by a radiolucent halo zone with corticated margin | Blood tests all within normal limits | Right mandibular body: partial hemimandibulectomy  
Right maxilla: hemimaxillectomy | Initially the patient refused treatment; 3 y later, surgical remission of the lesions was undertaken |
| 7    | Bertolini et al., 2002 | F/37 | Lesion 1: left maxilla and hard palate  
Lesion 2: right body of the mandible  
Lesion 3: left body of the mandible | Large, hard, and painless slow-growing mass in the right and left body of the mandible and the left maxilla | RE: large radiolucency in the left maxilla and right body of the mandible. There was also a smaller lesion in the left body of the mandible.  
CT: revealed fibrous calcified masses that involved the left maxilla and the right and left mandibular body | NR | Right mandible: partial mandibulectomy  
Left mandible: curettage  
Left maxilla: intraoral surgical removal | Mandible: no recurrence after 2 y  
Maxilla: no recurrence after 1 y |
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<tr>
<td>8</td>
<td>Barberi et al., 2003</td>
<td>F/53</td>
<td>Lesion 1: left infraorbital region&lt;br&gt;Lesion 2: right hard palate</td>
<td>Slowly progressive growth without pain or tenderness</td>
<td>RE: showed partial opacification of left maxillary sinus&lt;br&gt;CT: well demarcated soft tissue mass of high density, inhomogeneous for context: several areas of low density and scattered calcifications</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>9</td>
<td>Stergiou et al., 2007</td>
<td>F/36</td>
<td>Lesion 1: left mandible&lt;br&gt;Lesion 2: right mandible&lt;br&gt;Lesion 3: left maxilla</td>
<td>Pain and hard swelling of mandible</td>
<td>RE: well circumscribed unilocular radiolucency containing diffuse calcifications&lt;br&gt;CT: well demarcated lesions showing areas of low density and scattered calcifications</td>
<td>NR</td>
<td>Left mandible, right mandible, and left maxilla: surgical enucleation and curettage</td>
<td>No recurrence after 6 mo</td>
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<td>10</td>
<td>Chindia et al., 2008</td>
<td>F/27</td>
<td>Lesion 1: right angle and body of the mandible&lt;br&gt;Lesion 2: left maxilla</td>
<td>Painful and hard swelling of the mandible and expansion of the left maxilla</td>
<td>RE: mandibular lesion was corticated and maxillary lesion was less well defined with almost complete obliteration of the maxillary sinus</td>
<td>NR</td>
<td>Mandible: surgical enucleation&lt;br&gt;Left maxilla: surgical enucleation</td>
<td>Recurrence after 6 mo (mandible)</td>
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<td>11</td>
<td>Present case</td>
<td>F/35</td>
<td>Lesion 1: left mandible&lt;br&gt;Lesion 2: right mandible</td>
<td>Hard swelling of the left mandible associated with moderate facial asymmetry</td>
<td>RE: large radiolucency surrounded by a radiopaque halo in the left and right body of the mandible&lt;br&gt;CT: unilocular and hypodense image</td>
<td>Serum calcium: 9.73 mg/dL&lt;br&gt;phosphorus: 4.2 mg/dL&lt;br&gt;PTH: 56.34 pg/mL</td>
<td>Left mandible: surgical enucleation&lt;br&gt;Right mandible: surgical enucleation</td>
<td>No recurrence after 3 y</td>
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RE, Radiographic examination; NR, not reported; CT, computerized tomography.
case, given the family background, which is highly suggestive of HPT-JT. In our opinion, this is the most important diagnostic criteria for patient screening, and it was not performed, and the possibility of their relationship with HPT-JT was not adequately ruled out. In the present case, the serum calcium, phosphorus, and PTH levels were normal, allowing us to exclude the association. In addition, in 7/10 previous reported cases, the mean follow-up period was not mentioned or was considered to be too short to completely rule out the possibility of the late systemic manifestation related to endocrine alterations.

The etiology and pathogenesis for both clinical forms of OFs (solitary and multiple) remain unknown. Interestingly, these different forms of OFs present very similar clinical, radiologic, and histopathologic features, showing that they are different clinical presentations of the same pathology. Most significantly, it is important to bear in mind that, in general, OFs are solitary lesions and multiple occurrence is rare. Multiple or solitary OFs are often detected incidentally through radiographic examination of the jaws. Additionally, clinicians should be aware of the possibility of HPT-JT in young patients, because this disease is usually associated with recurrent or multiples OFs of the jaws.

In conclusion, the literature regarding the clinical features and origin of multiple OFs is very scarce and controversial. The relevance of this issue relies on the possibility of associations of multiple OFs with HPT-JT, which in turn is associated with additional abnormalities in others organs, including malignant tumors and systemic findings.

REFERENCES


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