Can Differences in Vascularity Serve as a Diagnostic Aid in Fibro-Osseous Lesions of the Jaws?

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Purpose: Different lesions in the fibro-osseous group share microscopic features; thus, establishing a definitive diagnosis based on microscopic features alone can be a challenge. There is a need for additional microscopic tools to aid in differentiating these lesions. This study compared parameters related to vascularity among 3 lesions in the fibro-osseous group: fibrous dysplasia (FD), central ossifying fibroma (COF), and cemento-osseous dysplasia (COD).

Materials and Methods: This study was a cross-sectional analysis of biopsied lesions retrieved from 3 medical centers over a 14-year period. The primary predictor variables were the vascularity parameters (number, perimeter, and area). The outcome variables were diagnoses of FD, COF, and COD. Diagnosis was based on clinical, microscopic, and radiologic correlations. From each histopathologic slide, 5 representative fields were captured with a computerized digital camera. The number of blood vessels was counted, and the surface area and vascular perimeter were measured by tracing the perimeter of each vessel. Data were statistically analyzed using analysis of variance with logarithmic transformation and a Tukey adjustment.

Results: Sixty-six cases were included in the study (26 in FD group, 26 in COF group, and 14 in COD group). The mean number of vessels showed only a tendency to be larger in the FD group compared with the COF and COD groups (5.4 ± 2.6, 3.7 ± 2.3, and 3.6 ± 1.7, respectively), but the results did not reach the threshold for significance. The mean vascular perimeter was 1,385.8 ± 859.2 pixels in the FD group and 742.6 ± 661.8 in COF group after logarithmic transformation (P = .012). The perimeter in the COD group was smaller (941.1 ± 502) compared with that in the FD group, but the difference did not reach the threshold for significance. The mean area was 25,061 ± 24.875.6 in the FD group and 11,773.8 ± 21,734.4 in the COF group after logarithmic transformation (P = .004). The perimeter in the COD group was smaller (13,011.1 ± 8,338.3) compared with the FD group, but the difference did not reach the threshold for significance.

Conclusion: The vascular content of the FD group was markedly higher than of the COF group. These vascular changes can aid in differentiating these lesions microscopically.

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Different lesions in the fibro-osseous group share microscopic features; thus, establishing a definitive diagnosis based on microscopic features alone can be a challenge. There is a need for additional microscopic tools to aid in differentiating these lesions.

Fibro-osseous lesions (FOLs) of the craniofacial bones are a diverse group of pathologic conditions that include developmental lesions, reactive or dysplastic diseases, and neoplasms.1–3 FOLs have been reclassified several times.2,4–6 In 2008, Eversole et al2 suggested the subclassification of FOLs to 5 categories based on pathogenic mechanisms: bone dysplasias such as fibrous dysplasia (FD), cemento-osseous dysplasia (COD), inflammatory or reactive processes, metabolic diseases, and neoplastic lesions such as ossifying fibroma (COF).

All FOLs show histologic similarities, namely replacement of mature bone by cellular fibrous tissue. This soft tissue contains a large variety (quantity and appearance) of mineralization foci. Therefore, it is widely accepted that a final diagnosis based on subclassification is challenging and is made based on a combination of clinical, radiographic, and histopathologic findings.1–3,7–12

Several publications have stated that FD has a tendency for considerable bleeding during surgical procedures and great precautions should be taken perioperatively to avoid such complications.13,14 Ippolito et al15 noted prominent histologic vascular tissue in FD and its tendency to bleed, but these observations are only descriptive and not quantitative. Such reports concerning COF or COD have not been found, leading to the assumption that FD could have a higher vascular predominance than the other 2 types.

The aim of this study was to investigate whether vascularity-related features could serve as an additional diagnostic aid in differentiating FOLs. The working hypothesis was that the vascular content as measured by histomorphometric analysis of the number, perimeter, and area of the vessels would be higher in FD based on observations in the literature regarding major bleeding during surgical procedures in patients with FD of the jaws.

Materials and Methods

STUDY DESIGN

The study was a cross-sectional analysis.

SAMPLES

The study population was composed of all patients whose biopsy examinations indicated a final diagnosis of FOL (FD, COF, or COD) in 3 institutions with an oral pathology service (Rabin Medical Center, Petach-

Tikva, Israel; Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; and the School of Dental Medicine at Tel-Aviv University, Tel-Aviv, Israel) from January 1, 2000 through December 31, 2014. To be included in the study, patients had to have a good-quality biopsy slide and clinical and radiographic information consistent with the final diagnosis of FD, COF, or COD according to criteria described by Eversole et al2 and El-Mofty.5 Patients were excluded if their records were missing vital epidemiologic or clinical information that could not be retrieved and did not allow a definitive diagnosis or if the quality of the histopathologic slide was severely compromised and could not be properly interpreted.

DATA RETRIEVAL

Information was retrieved from medical records, including radiographs and computed tomograms when available. Histopathologic slides stained with hematoxylin and eosin were retrieved from the pathology archives. The medical records were cross-linked with the histopathologic findings to validate the diagnosis.

STUDY VARIABLES

The primary predictor variables were the vascularity parameters (number, perimeter, and area). The outcome variables were the diagnoses of FD, COF, and COD according to criteria described by Eversole et al2 and El-Mofty.5

HISTOMORPHOMETRIC ANALYSIS

From each histopathologic slide, 5 representative fields were randomly chosen at x400 magnification and captured with a computerized digital camera attached to the microscope. This magnification was selected to allow identification and tracing of the vascular perimeter for analysis. Single endothelial cells were not identified or traced. In each field, the number of blood vessels was counted. In addition, the summed surface area (measured as pixels squared) and the vascular perimeter (measured as pixels) were measured by tracing the perimeter of each vessel in each field using a feature in Olympus CellSens 2.12 microscope imaging software (Olympus, Center Valley, PA).

The study was approved by the ethics committees.

DATA ANALYSIS

Data were statistically analyzed by a medical statistician using SPSS 17 (SPSS, Inc, Chicago, IL) and analysis of variance (ANOVA) with logarithmic transformation and a Tukey adjustment and χ² test. Because multiple groups were compared, the Bonferroni correction was used, with the P value set at .0016.
Results

In total 105 cases were retrieved (37 in FD group, 45 in COF group, and 23 in COD group). Thirty-one cases were excluded from the study because of the poor condition of the histologic slides and 8 because of partial medical records and imaging. Therefore, 66 cases were included in the analysis (26 in FD group, 26 cases in COF group, and 14 in COD group). In most cases, 5 fields were captured from each case (total, 130 fields in FD group, 130 fields in COF group, and 70 fields in COD group). Two fields in the FD group and 1 in the COF group were excluded because of poor quality. Subclassification of FD, COF, and COD according to age (by ANOVA) and gender (by \( \chi^2 \) test) is presented in Table 1. Table 2 presents the relevance of age and gender for vascular number, perimeter, and area per field using the Pearson correlation test and the \( t \) test, respectively. All results showed no statistical relevance.

Because of the high variance of the results, logarithmic transformation was performed to stabilize the distribution for area and perimeter. For ANOVA, a Tukey adjustment for differences between groups was performed.

The mean number of vessels was larger in the FD group compared with the COF and COD groups (5.4 ± 2.6, 3.7 ± 2.3, and 3.6 ± 1.7, respectively), but the results showed only a tendency to be higher for the FD group compared with the COF and COD groups.

The mean vascular perimeter per field was considerably larger in the FD group than in the COF group. The mean perimeter was 1,385.8 ± 859.2 pixels in the FD group and 742.6 ± 661.8 in the COF group after logarithmic transformation \((P = .012)\). The perimeter in the COD group was smaller (941.1 ± 502) than in the FD group, but the difference did not reach the threshold for significance \((P = .67)\).

The mean vascular area per field was considerably larger in the FD group than in the COF group. The mean area was 25,061 ± 24,875.6 in the FD group and 11,773.8 ± 21,734.4 in the COF group after logarithmic transformation \((P = .004)\). The perimeter in the COD group was smaller (13,011.1 ± 8,338.3) than in the FD group, but the difference did not reach the threshold for significance \((P = .38)\).

Results for the number of vessels, mean perimeter, and area for each of the 3 groups are presented in Table 3.

Using all 3 parameters (number, perimeter, and area) differentiated the COF from the other 2 lesion types with a sensitivity of 80.77% and specificity of 65%, but lower rates were calculated for FD and COD.

Discussion

FOLs are a diverse group of pathologic conditions that have different clinical and radiographic manifestations in some cases, but share similar histologic characteristics. Differentiating these lesions can present a pathologic diagnostic challenge because of the overlap in microscopic features and in some clinical and radiographic features. Figures 1 to 6 show typical histologic and radiographic appearances of FD, COF, and COD. There are no relevant stains that can be used as a diagnostic aid, except genetic analysis for the \( GNAS \) gene in FD.\(^1\)\(^3\) The objectives of the present study were to investigate parameters related to vascularity that might distinguish FD, COF, and COD as a possible aid for diagnosis. The working hypothesis was that the vascular content would be higher in FD based on several clinical reports of severe bleeding during surgical procedures performed on FD lesions, observations that were rarely described in the literature for COF or COD.\(^1\)\(^3\)\(^5\)

The area and perimeter of vessels were markedly higher in the FD group than in the COF group, indicative of a higher level of vascularization. It reflects the fact that vessels in the fibrous component of FD tend to be larger than in the other 2 types. Although the mean number of vessels, classically referred to as vascular density, did not reach the threshold for significance, it is less representative of the function of vascular density than the summed vascular area or perimeter per microscopic field, because in analysis of vascular density a large vessel has the same impact as the smallest capillary.

Because this is the first quantitative histomorphometric study of these lesions in the literature, there are no previous data for comparison.

In the present study, a comparative analysis of the vascularity associated with the lesions was performed. The methodology in the study (biopsied cases) could present a certain bias from an epidemiologic point of view, because a biopsy examination is not mandatory for diagnosis for all the lesions included, and surgical excision is only routinely performed in cases of COF. However, for the analysis of
microscopic features of vascularity, the bias could not be avoided. It should not influence the interpretation of the results regarding the microscopic parameters and is relevant only for the relative frequency of the groups. FD is known as a lesion that tends to “burn itself out”; in static cases, the vascular content is expected to be lower than in active cases; however, the common practice is for biopsy specimens to be taken only in active cases, with the intent of excluding other pathologies.2,3 In “burned out” cases, a biopsy specimen is not indicated. Within the limitation of this study, it is safe to assume that, in the cases included, biopsy specimens were obtained during the active stage.

From a demographic perspective, there were marked differences in age and gender among groups. The specimens in the COD group were exclusively from women compared with those in the COF (80%) and FD (57%) groups. This female predominance is in agreement with previous reports of COD.1,3 The mean age of patients with COD was 42 years compared with 29 years in the FD group and 34 years in the COF group. The mean age in the COD group in the present series also is in agreement with reports stating that COD is most common in the fourth to fifth decades compared with COF or FD, which are more common in younger adults.9,16,17

In this study, COD showed a tendency in all investigated parameters to have a lower vascular content than FD, but the results did not present statistically significant differences. A possible explanation might be that the COD group was smaller than the other 2 groups. This could reflect an ethnic difference, because compared with the US population, in which COD is found mostly in women of African descent, the Israeli population is mostly Caucasian, and the present results suggest that COD is a relatively rare

<p>| Table 2. SIGNIFICANCE OF VASCULAR NUMBER, PERIMETER, AND AREA PER FIELD ACCORDING TO AGE AND GENDER |
|----------------------------------|--------|--------|--------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Perimeter</th>
<th>Area</th>
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</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>4.6 ± 2.8</td>
<td>1,161.4 ± 1,009.9</td>
<td>25,539.7 ± 30,843.8</td>
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<tr>
<td><em>P value</em></td>
<td>.61</td>
<td>.95</td>
<td>.94</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>4.3 ± 2.4</td>
<td>998.7 ± 679.3</td>
<td>14,624.5 ± 17,546.3</td>
</tr>
<tr>
<td><em>P value</em></td>
<td>.61</td>
<td>.95</td>
<td>.94</td>
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<tr>
<td><strong>Age, <em>P value</em></strong></td>
<td>.2</td>
<td>.11</td>
<td>.09</td>
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Abbreviation: SD, standard deviation.


| Table 3. RESULTS FOR FD, COF, AND COD |
|--------------------------------------|--------|--------|--------|
|                                     | FD     | COF    | COD    |
| **Number**                         |        |        |        |
| Mean ± SD                          | 5.4 ± 2.6 | 3.7 ± 2.3 | 3.6 ± 1.7 |
| *P value*                          | .031, .061 | .031, .99 | .061, .99 |
| **Perimeter**                      |        |        |        |
| Mean ± SD                          | 1,385.8 ± 859.2 | 742.6 ± 661.8 | 941.1 ± 502 |
| *P value*                          | .0121, .67 | .0121, .24 | .671, .24 |
| **Area**                           |        |        |        |
| Mean ± SD                          | 25,061 ± 24,875.6 | 11,773.8 ± 21,734.4 | 13,011.1 ± 8,338.3 |
| *P value*                          | .0041, .38 | .0041, .29 | .381, .29 |

Abbreviations: COD, cemento-osseous dysplasia; COF, central ossifying fibroma; FD, fibrous dysplasia; SD, standard deviation.

* Mean number of vessels per field.
† Mean summed perimeter of vessels per field.
‡ Mean summed area of vessels per field.
§ FD versus COF.
∥ FD versus COD.
¶ COD versus COD.

FIGURE 1. Fibrous dysplasia. Small irregular bone trabeculae are seen in a loose connective tissue and large vascular spaces are visible (arrows) (hematoxylin and eosin stain; magnification, ×400).


FIGURE 2. Computed tomogram of fibrous dysplasia (shown in Fig 1) in the right body of the mandible. Notice the ground-glass appearance and the ill-defined borders of the lesion.

FIGURE 3. Central ossifying fibroma. Small irregular bone trabeculae and calcifications are visible in a cellular fibrous tissue, with some small blood vessels (arrow) (hematoxylin and eosin stain; magnification, ×400).


FIGURE 4. Axial computed tomographic view of central ossifying fibroma (shown in Fig 3) in the right maxilla. Note the mixed density and well-defined borders.

condition in Israel. In addition, the benign and often pathognomonic radiographic appearance of periapical cemental dysplasia results in avoidance of biopsy procedures in some cases; however, the frequency of non-biopsied lesions consistent with COD could not be evaluated in the setting of this retrospective study.3

At the diagnostic stage of FOLs, evaluation of intralesional vessel size can aid in differentiating FD from COF, in addition to other clinical radiographic and pathologic criteria. Further investigation is required for the clinical relevance of bleeding during surgery.


FIGURE 6. Panoramic radiographic image of cemento-osseous dysplasia (shown in Fig 5) periapical to the first molar. The lesion shows a well-defined and corticated radiolucency with a central radiopaque area, which is not confluent with the root. Shmuly et al. Vascularity of Fibro-Osseous Lesion of Jaw: J Oral Maxillofac Surg 2017.

References


