ORIGINAL ARTICLE

Cemento-ossifying fibroma of jaws—correlation of clinical and pathological findings

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Abstract Cemento-ossifying fibroma (COF) belongs to the group of bone-related lesions of the oral cavity. The aim of this study was refine its histologic features and to correlate histopathological picture and clinical behavior of the tumor. The quantity of bone spherules, their cellularity, the existence of hemorrhage, inflammation, and endochondral ossification in the stroma of the tumor were analyzed and correlated with patients main symptoms of ten patients with COF. All patients had swelling that lasted between 3 and

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Z. Tepavčević Institute of Pathology, Faculty of Stomatology, University of Belgrade, dr Subotića 1, Belgrade, Serbia 20 months (mean 10.4 months). Other clinical symptoms were facial asymmetry, eye bulb protrusion, and teeth displacement. The evolution of the tumor was longer in the mandible (12.3 months) than in maxilla (9.5 months). The main histomorphological diagnostic criterion for COF was psammoma-like structures. In lesions with longer case history, the number of "psammomatoid" bodies was greater. In lesions with shorter course of the disease, their number was lower and stromal hemorrhage and inflammation were presented. One patient had secondary superposition of aneurysmal bone cyst in the prime COF of mandible. Histological appearance of COF may be influenced by the tumor evolution. A significant correlation between the clinical course of the disease and histological parameters has been certified.

Keywords Fibro osseous lesions · Ossifying fibroma · Cementifying fibroma · Psammoma-like bodies

Introduction

Cemento-ossifying fibroma (COF) is a well-demarcated lesion composed of fibrocellular tissue and mineralized material of varying appearances. It is benign odontogenic tumor that belongs to a group of bone-related lesions. In addition to COF, this group of bone-related lesions comprises of fibrous dysplasia, osseous dysplasias, and central giant cell lesion (granuloma), cherubism, aneurismal bone cyst, simple bone cyst [1]. Cemento-ossifying fibroma was formerly classified as the one of the fibro-osseous lesions that contains cementum [2–5]. Numerous synonyms that were equally used (cementifying fibroma, ossifying fibroma, and cemento-ossifying fibroma) are used in the literature [1, 3, 6–8].

Clinical, radiological, and histopathologic picture of all fibro-osseous lesions may be very similar to COF, making their diagnosis more difficult. Swelling and pain accompanied by teeth displacement are the most frequently stated as the first symptom of COF. Large longstanding lesions may cause face asymmetry or even eye protrusion [2–4, 6–10]. The evolution of COF is long and is measured in months or years.

Cemento-ossifying fibroma can occur in both jaws, but more frequent occurrence of COF is in the mandible, in females [11]. This lesion is often presented in the literature as case reports [9, 10, 12]. The study with a largest sample so far (75) was described by Su et al. who showed no female predilection [7, 8]. According to findings of other studies, COF occurs in all ages with highest incidence between the age of 20 and 30 [2–4].

Radiologically, a well-defined radiolucency with or without sclerotic border is typically seen in COF. However, radiographic findings of COF depend on its maturity, i.e., the duration of the lesion. The early tumor often manifests as well-circumscribed radiolucent lesion, resembling ground glass, and it is almost impossible to be distinguished from fibrous dysplasia [13]. On panoramic radiographs, computed tomography (CT) and magnetic resonance, COF is usually presented as lytic lesion of the bone with well-defined sclerotic edge [7, 8, 12, 14]. With the maturing of the tumor, the more intensive forming of spherules resembling cementum in it is present, and radiological image shows calcification within the osteolytic lesion [13]. Old lesions can be purely radiopaque.

Histological features of COF are typical and they are different from other benign fibro-osseous lesions. The tumor consists of multiplied fibroblasts in storiform arrangement that produce collagen fibers. The presence of mitoses without signs of atypia and pleomorphism is also possible. The stroma of the tumor typically contains bone spherules-cementum granules that vary in number and size. However, it does not contain signs of haemorhagee, inflammatory cells, and signs of hyaline cartilage [15-18]. The more mature the lesion, the more emphasized is the described bone formation of "psammoma-like" bodies, thus becoming a predominant histomorphologic criterion in pathohistological diagnostication. The bone in COF is the newly formed, the so-called woven bone with peripheral lamellar maturing. On the surface of the bone spiculae, there are inactive osteoblasts focally [2-4, 7-9, 14, 18]. Having established the diagnosis based on the pathohistological finding, the treatment method is defined which is solely surgical. With regard to the absolutely benign nature of the lesion, simple curettage, enucleation, or excision are sufficient for a cure, and the recurrence of the disease are uncommon [13, 16, 17, 19]

Aim

The aim of the study was to show clinico-morphological features of COF and to correlate its histological image to clinical findings of the tumor.

Materials and methods

The study included ten cases of jaw COF from The Register of Institute of Pathology from 1991 to 2005. All surgical specimens sent, was fixed in 10% formalin, decalcified and molded in paraphin blocks. The material was cut into the 5-mm sections and stained by the following techniques: hematoxylin and eosin (HE), reticulin and Masson's Trichrome.

Following clinical parameters were noted: patients' sex and age, localization of the lesion, the type and duration of symptoms.

Histological parameters included: the quantity of spherules, the existence of hemorrhage, inflammation and hyaline cartilage in the stroma of the tumor.

Results

The study included five females and five males. The youngest patient was a 14-year-old male, and the oldest was a 54-year-old female (mean age 27.1 years). Maxilla was involved in six (60%) patients, mandible in three (30%) patients, and one patient had involvement of the cranial base with COF. The evolution of the tumor was longer in mandible (12.3 months), when comparing to maxilla (9.5 months). Mandible involvement and was accompanied by somewhat milder clinical picture than maxilla.

The basic symptom was swelling noted in all patients. Six patients (60%) suffered on pain, while teeth displacement and eye protrusion were noted as symptoms of the disease in three patients. The duration of the disease varied from 3 to 20 months (mean 10.4 months). Correlation of relevant clinical data with histologic parameters was shown in Table 1.

Radiographic findings of COF varied from radiolucent, mixed (radiolucent-radiopaque), to radiopaque. All the patients underwent CT scans in order to establish diagnose and the extent of the tumor. In one patient, two lesions on CT scan were diagnosed (Fig. 1). Both were biopsied and histological analyzed. A lesion in right frontal bone was confirmed as fibrous dysplasia (Fig. 2) and lesion in left maxilla as COF (Fig. 3).

In six (85%) of seven cases with dominant finding of bone spherules within the lesion, a longer case history was evident (8-16 months).

Psammoma-like body structure was the leading histomorphologic parameter in seven patients through histolog-

Table 1	Clinical	and	histol	ogic	characteristics	of	COF
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Patient Sex	Sex	Age (years)	COF localization	Symptoms	Duration; case	Histological findings			
					history (months)	Spherules	Hemorrhage	Inflammation	Cartilage
1	М	18	Skull base	Pain, swelling, eye protrusion	6	Rarely	Yes	No	No
2	F	40	Maxilla	Swelling, displacement of the teeth	15	Dominant	No	No	No
3	М	31	Maxilla	Swelling, displacement of the teeth	8	Dominant	No	Yes	No
4	F	15	Maxilla	Eye protrusion, pain	3	Rarely	Yes	No	No
5	F	20	Maxilla	Eye protrusion, pain	5	Dominant	No	No	No
6	F	54	Mandible	Pain, swelling	16	Dominant	No	No	No
7	М	33	Maxilla	Swelling, displacement of teeth	20	Rarely	No	No	No
8	М	19	Mandible	Pain, swelling	9	Dominant	Yes*	Yes	No
9	М	14	Maxilla	Swelling	10	Dominant	No	No	No
10	F	27	Mandible	Pain, swelling	12	Dominant	No	No	No

F female, M male, *ABC aneurismal bone cyst

ical analysis (Fig. 3 and 4). Three cases of COF have trabecular and anastomosing lattice as pathologic appearance. Special histochemical staining was applied (silver impregnation of tissues and Masson's Trichrome) which showed that the structure of spherules was anisotropic. The structures of the so-called psammoma-like bodies were made out of newly formed osteoid of different maturity and mineralization rate (Fig. 5). There was a more mature osteoid on their surface, which was calcified more intensely, while in the central parts a fresh, immature osteoid and connective tissue could be observed (Figs. 6 and 7). Psammoma bodies had very few cells or were without cells, rudely mineralized, with possible individual inactive osteoblasts on the surface. Numerous cells in bone spherules were described only in four cases (Fig. 5).



Fig. 1 CT scan showing lesion in left maxilla (cemento-ossifying fibroma) and right frontal bone (fibrous dysplasia)

Hemorrhage in stroma accompanied by rich vascularization was detected in three cases. The finding of secondary superpositioned aneurismal bone cyst (ABC) in the prime lesion of mandible in one case was interesting (Fig. 8). Rare inflammatory infiltrates in the stroma with perivascular localization were described in two cases. Hyaline cartilage was not detected in biopsies in the patients who were involved in our research.

Discussion

Cemento-ossifying fibroma is a benign fibro-ossseous lesion that occurs mostly in mandible [5, 13]. There is an affinity for the molar area in both of the jaws [7, 8].

With respect to the fact that this benign tumor is a rare intraosseal neoplasm, the literature mostly describes indi-



Fig. 2 Typical histological appearance of fibrous dysplasia was found in lesion from right frontal bone. (HE, $\times 10$)



Fig. 3 Histologic features of cementifying fibroma a typical tumor feature with rudely mineralized material resembling cementum in fibroblastic stroma (HE, $\times 10$)



Fig. 5 Numerous cells (osteoblasts) are on the surface and into the psammoma-like body structures (He, $\times 200)$

vidual cases. The research that included the greatest number of patients (75) was published by Su et al. who found no female predilection of COF except in the fourth decade of life [7, 8]. Valid conclusions cannot be drawn about the distribution of lesion by criterion of sex from the stated literature. While some authors emphasize its prevalence in females, the others state that this tumor is equally present in both sexes [7, 8, 11]. Our examination of ten patients showed the equal presence in both males and females.

The mean age of our patients with COF was 27.1 years; what is in concordance with the data from the literature that point to the fact that COF most frequently occurs in people in the third decade of life (between the age of 20 and 30) [8].

The analyzed clinical parameters—duration of the disease and symptoms (pain, swelling, teeth displacement,

eye protrusion)—in our study were similar to those stated in the literature [5, 11, 13]. The most common clinical finding of COF is expansion of the buccal and lingual cortices and in larger lesions may expand the inferior aspect of the mandible [13]. Neighboring mandibular teeth in are often displaced superiorly. Tumor evolution in our study was longer when the lesion is localized in the mandible (12.3 months) when compared to its evolution in maxilla (9.5 months). However, the localization of the lesion in mandible was accompanied by somewhat milder clinical picture (only pain and swelling). It is possible that composition of mandible, centrally located spongious bone surrounded with cortical plate, may influence slower expansion of the COF. Contrary to mandible, cancellous composition of maxilla may be cause of shorter course of



Fig. 4 The mesenchymal stroma surrounding the hypocellular bone spherules (HE, $\times 100$)



Fig. 6 Histochemical stains show irregular mineralization of bone spherules (reticulin, $\times 200$)



Fig. 7 Histochemical stains show irregular mineralization of bone spherules (Masson's Trichrome, $\times 200$)

COF. Although pain and paresthesia are rare in COF according to some authors [11], pain was evident in six (60%) of our patients with COF. Small lesions seldom cause any symptoms and are detected only on radiographic examination. In our study, clinical symptoms in maxilla were more prominent and besides the pain and swelling were manifested by teeth displacement. COF in maxilla often expand into the maxillary antrum and may cause eye protrusion. Displacement of maxillary teeth is typically inferiorly.

The most frequent radiographic feature in our study was mixed radiolucent-radiopaque, but varied from radiolucent to radiopaque. Typical radiographic finding of COF is usually radiolucent, or mixed radiolucent-radiopaque, while only minority of the COF are only radiopaque [7, 8]. Radiographic finding of well-defined lesion with mildly sclerotic edge resembling "ground glass" in our investiga-



Fig. 8 Secondary aneurismal bone cyst in combination with prime cemento ossifying fibroma (Masson's Trichrome, ×10)

tion indicated to a wide diagnostic palette which was absolute indication for biopsy.

Differential diagnosis of radiographically diagnosed similar "ground glass lesion" may include: fibrous dysplasia, hyperparathyroidism, osteitis deformans, and diffuse sclerosing osteomyelitis [13]. Fibrous dysplasia and COF represents diagnostic dilemma for both clinicians and pathologists because of their radiographic overlapping [20] and histological similarity. Toyosawa et al. demonstrated recently that fibrous dysplasia and ossifying fibromas could be distinguished one from one another on the basis of polymerase chain reaction analysis with peptide nucleic acid for GNAS mutations at the Arg²⁰¹ codon [21]. Although ossifying fibroma may occur in hyperparathyroidism [22] and present as a ground glass lesion on radiography, brown tumor could be differentiated on the basis of elevated blood calcium and parathyroid hormone levels. In osteitis deformans calcium and phosphorous may be normal, but alkaline phosphatase levels are highly elevated. Diffuse sclerosing osteomyelitis may have mixed radiolucent-radiopaque presentation, has no defined border on radiography, and is a low grade infection which requires precise anaerobic culture from a trephine bone biopsy specimen. Additionally, mineralized material of sclerosing osteomyelitis is reactive sclerotic bone lined with osteoblasts lying on seams of osteoid-no cementumlike calcifications are present.

Cemento-ossifying fibroma could be often confused with focal cemento osseous dysplasia because of similar mixed (radiolucent-radiopaque) radiographic image. Focal cemento osseous dysplasia is reactive lesion, not a neoplasm, and it occurs around roots of mandibular teeth and fails to expand bone. Contrary to this, COF are potentially aggressive lesions that cause cortical expansion and often cause divergence of teeth. Both lesions may show similar histological features with trabecular bone and cementifying areas. Older lesions of focal cemento osseous dysplasias may show dense corticated bone islands, a finding that is not present in COF [13].

On computed tomography, COF has predominant soft tissue consistency with variable amount of linear or irregular calcifications with areas of low CT density may be noted, due to cystic changes [23, 24]. Magnetic resonance imaging of COF is important in assessing the extent of the lesion, and appears as iso- or hypo-intense to muscles [23], but is poor in clearly defining bony component of the tumor [25]. Clinically and microscopically, COF is well demarcated and tends to expand the bone. On surgical exploration, this bone expansion is very important in distinguishing the lesion from cementoosseous or fibrous dysplasia [26].

For a long time it has been suggested that origin of COF is odontogenic - from periodontal ligament. However, finding of microscopically identical neoplasm in frontal, ethmoid, temporal, and sphenoid bones made this presumption questionable [11]. Two possible explanations for occurrence of cementifying fibromas outside the jaws exist. The first is that they develop from ectopic periodontal membrane, and the second is that periodontal membrane is a mesodermal germ layer. Other primitive mesenchymal cells may be able to differentiate in the same manner to produce a tumor [27].

Cemento-ossifying fibroma in the osteolytic stage is predominated by proliferating fibrous connective tissue with a homogeneous or moderate cellularity, rich vascularity, and hemorrhage. Corresponding radiographs during the osteolytic stage reveal well-defined radiolucencies. The late (osteosclerotic) stage is characterized by a presence of an irregular cementum-like mass. Radiographic findings in this late phase reveal irregular radiopacity with or without areas of mixed radiolucency [8]. Microscopically calcifications in COF resemble normal cementicles that are present in the periodontal ligament [13]. Although there were attempts to improve differentiation of cementum from bone on the basis of cetilpiridinium chloride and immunohistochemical detection of collagen I and III [28], such distinction nowadays is considered equivocal and out of clinical relevance [1]

It is most frequently emphasized that COF morphology is typical and that variations in histopathological appearance of lesions are very small [3, 15, 18, 19, 22, 29, 30]. Histological parameters analyzed in our sample showed that there was a significant morphological difference in lesions with different clinical manifestations. As stated in the literature, the dominant histological criterion is bone spherules [3, 6-9, 14, 19, 22, 29, 30]. The number and mineralisation of bone spherules in our study varied during tumor maturation. Our research confirmed that the number and appearance of psammoma-like bodies depended on the disease duration, i.e., on "maturity" of the tumor. The number of the so-called psammoma-like bodies was smaller in cases with short evolution of the disease, but the greater aggression of the lesion. Fast clinical course and short duration of the disease were present in the patients whose histological findings, together with typical COF manifestation, also showed the symptoms of atypical reactive inflammation in the stroma of the tumor (emphasized lymphoplasmacytic infiltrates) or in the area of intralesional hemorrhage [3, 7, 8, 22, 29-31].

Most of COF in our study with longer case history had greater bone spherules. It is very difficult to definitely prove claim that older lesions consist of more bone tissue, but sporadic cases of unduly operated lesions in the literature confirmed that older lesions contain more osseous tissue than the same younger lesion in the past [32]. Still, we histologically recognize two types of COF: juvenile trabecular ossifying fibroma (JTOF) and juvenile psammomatoid ossifying fibroma (JPOF) they have different clinical course. JTOF is lesion in younger patients, mean age range 8.5-12 years. Contrary, JPOF occur in patients about 20 years. It is well known that JTOF has trabecular and anastomosing lattice, while JPOF is characterized by a small ossicles resembling psammoma body [1]. According to these two facts, we can assume that that trabecular lattices become pssamomatoid during long clinical course.

Secondary superpositioned ABC was diagnosed in one patient with the prime COF of mandible. The occurrence of superpositioned ABC on benign fibro-osseous lesions is extremely rare and to our knowledge, there are just a few case of superposition of ABC on COF described in the literature [30, 31, 33].

Some authors indicates that psammomatous-ossifying fibroma have similar stroma like in COF, but innumerable round cement-like or psammoma-like particles, also called ossicles [34]. Contrary to COF, psammomatous-ossifying fibroma arises exclusively in the extragnathic craniofacial bones.

Although some authors state the histological existence of hyaline cartilage in the stroma of COF and other fibroosseous lesions, we have not noted such histological parameter in the patients that were involved in our research.

After establishing the final pathohistological diagnosis of COF, the treatment of choice was enucleation and in some cases radical surgical intervention. At surgical exploration, COF tends to be well demarcated from surrounding bone, allowing relatively easy separation of the tumor from its bony bed. The recommended therapy for ossifying fibroma is enucleation [5, 11, 13]. This is usually sufficient for successful treatment. Recurrences are possible; in which case, a wider resection is recommended. In such cases, bone grafting is often necessary.

With respect to completely benign nature of this lesion, there were no recurrences of the tumor for 4 years.

Conclusion

Clinical features of COF are unspecific and radiological diagnosing is difficult due to its variable radiographic presentation depending on tumor maturity. The only valid diagnostic method is pathohistological analysis of excised tumor. Specific histomorphologic appearance of COF facilitates the diagnostic differentiation from other fibro-osseous lesions. Histological parameters of COF are relatively clearly defined and do not show any major changes. Still, it has been noted that the appearance of COF changes, depending on the tumor evolution. We point out a notable correlation between the clinical course of the tumor and histological parameters, which asks for constant cooperation of clinicians and pathologists in the process of diagnosing and treatment of this lesion.

Conflict of interest The authors declare that they have no conflict of interest.

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