Hybrid lesions comprising central giant cell granuloma and fibrous dysplasia: A diagnostic challenge for pathologist

Manveen Kaur Jawanda, Ravi Narula, Madhu Shankari, Shruti Gupta
Department of Oral and Maxillofacial Pathology and Microbiology, Luxmi Bai Institute of Dental Sciences and Hospital, Patiala, India. 1Department of Oral and Maxillofacial Surgery, Guru Nanak Dev Dental College and Research Institute, Sunam, Punjab, India. 2Department of Oral and Maxillofacial Pathology, College of Dental Sciences and Hospital, Davangere, Karnataka, India

ABSTRACT
Hybrid lesions are the lesions consisting of association of features from different pathologies. We present a rare case of hybrid lesion with features of central giant cell granuloma (CGCG) and fibrous dysplasia (FD) involving mandible in a 33-year-old male. Hybrid lesions consisting of features of both benign fibro-osseous lesions and CGCG are very rare. Thus, the purpose of this paper is not only to present a rare case of hybrid lesion with features of CGCG and FD but also to emphasize on the need of careful clinical, radiological and histopathological examination of each and every tissue. There is an important need to report similar and other such cases, which will lead us to understand the interrelationship between these hybrid lesions in a better way and will further clarify their biologic behavior. This will decrease the incidence of misdiagnosis for such cases and will help in preventing recurrences.

Key words: Central giant cell granuloma, fibrous dysplasia, hybrid lesion

INTRODUCTION
The benign fibro-osseous lesions (BFOLS) of the jaws comprise a diverse, interesting and challenging group of conditions that pose difficulties in classification and treatment. Common to all is the replacement of normal bone by a tissue composed of collagen fibers and fibroblasts that contain varying amount of mineralized substances which may be bony or cementum like in appearance. BFOLS of the jaws have fibro-osseous component in common with central giant cell granuloma (CGCG). Lesions with features from various pathologies have been reported in the literature. These are called “hybrid lesions.”[1]

BFOLS such as fibrous dysplasia is a bone developmental anomaly characterized by hamartomatous proliferation of fibrous tissue within the medullary bone, with secondary bony metaplasia, producing immature, newly formed and weakly calcified bone, without osteoblastic rimming. FD occurs unilaterally, diagnosed in the second decade of life and is relatively common in maxilla. Females are less affected than males, with variable radiographic appearances and the lesion never cross the midline.[2]

CGCG is considered widely to be nonneoplastic lesion. A majority of giant cell granulomas are noted in females and approximately 70% arise in the mandible. Lesions are more common in the anterior portion of the jaw, and mandibular lesions frequently cross the midline.[2]

Hybrid lesions comprising CGCG with fibro-osseous component are very rare, with only nine cases reported in the literature so far.[1,3-8] These lesions may sometimes led to a confusion in their diagnosis as many pathologists report them taking into consideration one of the prominent histopathologic feature. These confusions may be because of the small number
of cases reported in the literature with uncertain clinical, radiographic and histopathologic features of these lesions. The purpose of this paper is to report a case of FD associated with CGCG and discuss the clinical, imaging and histopathological features of this hybrid lesion.

CASE REPORT

A 33-year-old male presented with painless enlargement of left side mandible since 5 years. Extra-oral examination revealed a swelling on the left posterior region of the mandible. It was hard and nontender, with overlying normal skin. Intraoral examination revealed swelling extending from 33 to 37 regions and 4.0 cm × 2.5 cm in diameter with slight obliteration of the buccal vestibule. The overlying mucosa was stretched out but intact.

The orthopantomograph showed a poorly defined lesion extending from 33 region to the ramus of the mandible with varying degree of opacifications having ground glass appearance at few sites. The lower border of the mandible was intact [Figure 1].

Routine blood investigations along with serum examination for alkaline phosphatase activity and calcium profile were performed and the values were within normal limits. Patient gave the history of surgical recontouring of the lesion 2 years back with a histopathological diagnosis of fibro-osseous lesion. The growth recurred again and attained the present size. Repeat surgical contouring and debulking of the lesion was done. Specimen was submitted for histopathological examination with a clinical diagnosis of fibro-osseous lesion. The healing was uneventful.

Gross examination of the specimen consisted of multiple fragments of brownish friable tissue measuring 3.0 cm × 2.5 cm in aggregate [Figure 2]. Histopathologically, the lesion consisted of areas of fibrovascular connective tissue made up of ovoid to spindle shaped fibroblasts and small blood vessels with scattered multinucleated giant cells consistent with the diagnosis of CGCG [Figure 3]. Other areas revealed irregularly shaped bony trabeculae lacking osteoblastic border in a cellular, loosely arranged fibrous stroma. The bony trabeculae are not connected to each other and assumed curvilinear shapes (Chinese script writing) [Figure 4]. Picrosirius red stain was used with polarizing microscope for distinguishing mature from immature collagen. Mature bone showed bright red birefringence whereas the immature woven bone showed greenish birefringence [Figure 5]. The histopathological, radiographic and clinical presentation suggests a hybrid lesion with features of both CGCG and FD.

DISCUSSION

The term BFOLS, in and of itself, is not meant to be a specific diagnosis. Fibro-osseous lesions are a heterogeneous group of entities consisting of a variably cellular, fibrovascular stroma along with varying amounts of mineralized material
consistent with either bone or cementum. Differential diagnosis [Table 1][2,10] among fibro-osseous lesions can be difficult, as these lesions don’t present a well-defined behavior. Diagnosis based on histological appearance alone has considerable limitations, and often, the pathologist can be no more specific than a diagnosis of “BFOLS.” However, with adequate clinical and radiological information and an adequate biopsy of surgical specimens, most fibro-osseous lesions of jaws can be assigned with reasonable certainty.[11] Our case has two kinds of different lesions, one is FD and another one is CGCG.

Till now only nine cases of hybrid lesion comprising CGCG with fibro-osseous component have been reported in the literature [Table 2].[1,3‑8] A search of the literature has failed to reveal the simultaneous occurrence of CGCG and FD except two case reports that have the same lesions as our case but with different appearance to our case.[5,8]

The age range of these hybrid lesions was 5–68 years with an average of 31.9 years. These lesions have got a more female predilection, but three cases in the previously reported literature show that it can also be present in the male patient, as it is in our case. The radiographic presentation of these lesions can also vary in terms of radiolucencies or radiopacities, unilocular or multilocular, or combination of any of these.[7] In our case, it presented as a poorly defined lesion with varying degree of opacifications having ground glass appearance at few sites.

FD is a genetic disorder originating from basal bone exhibiting predominantly metaplastic woven bone which is weakly calcified bone, without osteoblastic rimming. Ossifying fibroma (OF), on the other hand, is considered to be a highly cellular neoplasm exhibiting cimenticles, woven and lamellar bone components. This lesion is thought to originate in the alveolar bone and thought to have a periodontal origin. Differentiation between tumors of periodontal membrane origin and tumors of medullary bone origin is important because the latter tumors usually behave in a more aggressive fashion, even though they are benign.[12] The principle of picrosirius red-stained polarization is based on the strong reaction of acidic dyes such as Sirius red with collagen molecules that are rich in basic amino acids. Mature bone presents with parallel arranged, thick, strongly birefringent yellow-orange collagen fibers. On the other hand, immature types of calcification display a weak birefringence of greenish color.[13,14] In a study conducted by Kulkarni et al.[15] FD was mainly composed of mature trabeculae of bone along with small amount of woven bone and OF showed presence of cimenticles with predominantly immature green birefringence. Present case also showed predominantly red birefringence indicating mature trabecular bone with few areas of green birefringence.

Farzaneh and Pardis[5] and Penfold et al.[3] argue that the occurrence of giant cells in association with fibro-osseous conditions may represent a reaction that stimulates modification in the stroma of the original tumor. Theoretically, osteoblasts may activate osteoclast-type giant cells through paracrine mechanism. The present case may also be related to such a phenomenon.

Histologically, FD may present giant cells, which represent osteoclasts associated with eventual mineralized material. In hybrid lesions, however, giant cells appear scattered in fibrovascular tissue.[6] These features could be observed in our case. Hybrid lesions comprised of both giant cell and fibro-osseous components are rare, may be due to negligence of the pathologists in diagnosing the cases by considering only one prominent histopathological feature. Hence even surgeons may end up treating the lesions inadequately or patients may need to undergo multiple surgeries.
## Table 1: Differential diagnosis among various fibro-osseous lesions

|                        | Central giant cell granuloma | Hyperparathyroidism/ brown’s tumor | Aneurysmal bone cyst | Ossifying fibroma | Fibrous dysplasia | Paget’s disease | Chronic sclerosing osteomyelitis | Our case |
|------------------------|-----------------------------|-----------------------------------|---------------------|------------------|------------------|----------------|--------------------------------|----------|
| **Age/sex**            | Before end of third decade/more in females | Females older than 50 years      | 20 years/no sex predilection | Third–fourth decade/more in females | Second decade/no sex predilection | Older than 40 years/more in males | Adults/no sex predilection | 33-year-old male |
| **Clinical features**  | More in mandible, asymptomatic painless expansion of involved bone | Disturbance in ion metabolism, depletion of bone minerals, kidney stones, gastrointestinal disorders and muscle weakness | Expand painful lesion involving the mandible | Painless swelling in mandible | Painless osseous expansion with facial asymmetry involving maxilla | More in maxilla. Jaw expansion along with deep bone pain | A severely and constantly painful expansile lesion commonly involving mandible | Expand painless lesion involving posterior mandible |
| **Radiographic features** | An expansile unilocular or multilocular radiolucency with well-delineated and noncorticated margins | In jaw bones, the normal trabecular pattern may be lost and in severe disease distinctness of lamina dura is lost. Occasionally, a large destructive radiolucency may be present, indicative of a giant cell tumor - “brown tumor” | Unilocular or multilocular radiolucency with cortical expansion and thinning | Completely radiolucent or more often varying degrees of radiopaque, spherical to egg shaped, heterogeneous lesion with well demarcated margin from normal bone. Ossifying fibromas expand cortices equally and will displace adjacent structures | Ground glass appearance, will be fusiform, will expand bone but will remodel the cortex to make it distinct, with margins gradually blending into normal bone and will form around adjacent structures rather than displacing them | Mottled mixture of radiopacities and radiolucent- Cotton wool appearance because it is characterized by a fluffed, radiodense, cloud-like aggregation | Resembles fibrous dysplasia in its diffuse and poorly demarcated radiopaque appearance | Poorly defined lesion extending from 33 region to the ramus of the mandible with varying degree of opacifications Dysplastic bone formed around the mental nerve rather than displacing it |
| **Laboratory findings** | Hypercalcemia, hypophosphatemia Increased PTH and normal alkaline phosphatase | Hyperparathyroidia, hypophosphatemia Increased PTH and normal alkaline phosphatase | Hyperparathyroidia, hypophosphatemia Increased PTH and normal alkaline phosphatase | Hyperparathyroidia, hypophosphatemia Increased PTH and normal alkaline phosphatase | Hyperparathyroidia, hypophosphatemia Increased PTH and normal alkaline phosphatase | Hyperparathyroidia, hypophosphatemia Increased PTH and normal alkaline phosphatase | Hyperparathyroidia, hypophosphatemia Increased PTH and normal alkaline phosphatase | Hyperparathyroidia, hypophosphatemia Increased PTH and normal alkaline phosphatase |
| **Histopathological features** | Multinucleated giant cells in a background of oval to spindle shaped stromal cells. Osteoid may be deposited, particularly at the periphery of the lesion | Wide zones of osteoid rimmed with activated osteoblasts. Thin trabeculae of bone associated with numerous osteoclasts | Wide zones of osteoid rimmed with activated osteoblasts. Thin trabeculae of bone associated with numerous osteoclasts | Wide zones of osteoid rimmed with activated osteoblasts. Thin trabeculae of bone associated with numerous osteoclasts | Wide zones of osteoid rimmed with activated osteoblasts. Thin trabeculae of bone associated with numerous osteoclasts | Wide zones of osteoid rimmed with activated osteoblasts. Thin trabeculae of bone associated with numerous osteoclasts | Wide zones of osteoid rimmed with activated osteoblasts. Thin trabeculae of bone associated with numerous osteoclasts | Wide zones of osteoid rimmed with activated osteoblasts. Thin trabeculae of bone associated with numerous osteoclasts |

Cellular fibrous tissue composed of haphazardly arranged, variably shaped trabeculae of woven bone, which typically lack osteoblastic rimming. Mature lesions show parallel arrangement of trabeculae of lamellar bone

Osteosclerotic trabeculae with prominent reversal lines in a highly vascular fibrous connective tissue stroma

Sclerotic bone showing alternating areas of apposition and resorption. Between the trabeculae lies fibrous connective tissue infiltrated by chronic inflammatory cells

Delicate curvilinear bony trabeculae lacking osteoblastic rimming, surrounded by bland mesenchymal stroma. Multinucleated giant cells seen against a cell-rich stroma

**PTH:** Parathyroid hormone
Table 2: Reported hybrid lesions of central giant cell granulomas and fibro-osseous lesions in the literature

| Author          | Gender | Age | Site          | Radiographic features              | Histopathological diagnosis                        |
|-----------------|--------|-----|---------------|------------------------------------|-----------------------------------------------------|
| Penfold et al.  | Male   | 41  | Left maxilla  | Radiopaque expansion               | CGCG, ossifying fibroma                              |
| Shetty et al.   | Female | 39  | Left mandible | Mixed, multilocular expansion      | CGCG, cement-osseous dysplasia                       |
| Farzaneh and Pardis | Female | 20  | Right mandible| Radiopaque expansion               | CGCG, fibrous dysplasia                              |
| Kaplan et al.   | Female | 5   | Mandible      | Mixed, unilocular expansion        | CGCG, ossifying fibroma                              |
| Kaplan et al.   | Male   | 68  | Maxilla       | Unilocular expansion               | CGCG, ossifying fibroma                              |
| Kaplan et al.   | Female | 12  | Mandible      | Radiolucent, unilocular expansion  | CGCG, ossifying fibroma                              |
| Cruçoé-Rebello et al. | Female | 38  | Left mandible | Mixed, unilocular expansion        | CGCG, ossifying fibroma                              |
| Geetha et al.   | Male   | 9   | Left mandible | Mixed, unilocular expansion        | CGCG, ossifying fibroma                              |
| Kurra et al.    | Female | 18  | Right mandible| Radiolucent, multilocular expansion| CGCG, fibrous dysplasia                              |
| Jawanda et al.  | Male   | 33  | Left mandible | Poorly defined lesion with varying degree of opacifications | CGCG, fibrous dysplasia                              |

CGCG: Central giant cell granuloma

CONCLUSION

Because of the small number of these hybrid lesions, the enigmatic association of a FD with a CGCG is obscure. The relationship between FD and OF is well established,[16] but the association of FD with CGCG is still a dilemma. Given that the number of reported cases till date is so small that we are unable to speculate whether the presence of giant cells in both FD and CGCG is a result of reactive process or a feature of separate lesions or may actually represent distinct phases of a single benign morphological process. Hence, whether FD had developed more centrally and induced an adjacent giant cell reaction or whether two lesions simply originated independently, is open for debate. There is an important need to report similar and other such cases, as we feel that many cases are surgically managed but unfortunately not reported. All such cases should be reported, so that we can increase the literature bank that will lead us to understand the interrelationship between them in a better way and will farther clarify their biologic behavior.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Crusoé-Rebello I, Torres MG, Burgos V, Oliveira C, Santos JN, Azevedo RA, et al. Hybrid lesion: Central giant cell granuloma and benign fibro-osseous lesion. Dentomaxillofac Radiol 2009;38:421-5.
2. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. 2nd ed. Philadelphia, PA: WB Saunders Company; 2003.
3. Penfold CN, McCullagh P, Eveson JW, Ramsay A. Giant cell lesions complicating fibro-osseous conditions of the jaws. Int J Oral Maxillofac Surg 1993;22:158-62.
4. Shetty K, Giannini P, Leigh J. A hybrid giant cell granuloma and fibro-osseous lesion of the mandible. Oral Oncol Extra 2004;40:81-4.
5. Farzaneh AH, Pardis PM. Central giant cell granuloma and fibrous dysplasia occurring in the same jaw. Med Oral Patol Oral Cir Bucal 2005;10:E130-2.
6. Kaplan I, Manor I, Yahalom R, Hirshberg A. Central giant cell granuloma associated with central ossifying fibroma of the jaws: A clinicopathologic study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:e35-41.
7. Geetha NT, Pattathan RK, Shivakumar HR, Upasi AP. Fibro-osseous lesions vs. central giant cell granuloma: A hybrid lesion. Ann Maxillofac Surg 2011;1;70-3.
8. Kurra S, Reddy DS, Gunupati SKS, Reddy MS. Fibrous dysplasia and central giant cell granuloma: A report of hybrid lesion with its review and hypotheticated pathogenesis. J Clin Diagn Res 2013;7:954-8.
9. Waldron CA, Giansanti JS. Benign fibro-osseous lesions of the jaws: A clinical-radiologic-histologic review of sixty-five cases. Oral Surg Oral Med Oral Pathol 1973;35:190-201.
10. Singer SR, Mupparapu M, Rinaggio J. Clinical and radiographic features of chronic monostotic fibrous dysplasia of the mandible. J Can Dent Assoc 2004;70:548-52.
11. Waldron CA, Giansanti JS. Benign fibro-osseous lesions of the jaws: A clinical-radiologic-histologic review of sixty-five cases. II. Benign fibro-osseous lesions of periodontal ligament origin. Oral Surg Oral Med Oral Pathol 1973;35:340-50.
12. Fuller HM, Sheetz JH, Narkates AJ. Oxytalan connective tissue fibers: A review. J Oral Pathol 1974;3:291-316.
13. Rich L, Whittaker P. Collagen and picrosirius red staining: A polarized light assessment of fibrillar hue and spatial distribution. Braz J Morphol Sci 2005;22:97-104.
14. Montes GS. Structural biology of the fibres of the collagenous and elastic systems. Cell Biol Int 1996;20:15-27.
15. Kulkarni RR, Sarvade SD, Boaz K, Srikanth N, Nandita KP, Lewis AJ. Polarizing and Light Microscopic Analysis of mineralized components and stromal elements in Fibrous Ossifying lesions. J Clin Diagn Res 2014;8(6):42-45.
16. Lustmann J, Soskolne WA, Lewin E. Central Giant Cell Granuloma and periapical fibrous dysplasia occurring in the same jaw. Int J Oral Surg 1978;7:11-5.