

# Giant cell-rich osteosarcoma – A rare case

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## Abstract

Giant cell-rich osteosarcoma (GCRO) is an exceedingly rare histological variant of conventional primary osteosarcoma. It constitutes about 1%–3% of all osteosarcomas, and is extremely uncommon in the maxillofacial region. The unusual histopathological appearance and the rarity of the lesion poses a great diagnostic challenge. This article aims to present a rare case of GCRO involving the mandible in a 52-year-old male patient.

**Keywords:** Giant cell, mandible, mitotic figures, osteoclast, osteoid, osteosarcoma, pleomorphism, spindle cells, storiform streaming pattern

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## INTRODUCTION

Osteosarcoma is the most common malignant bone tumor characterized by the formation of disorganized immature bone or osteoid tissue from mesenchymal tumor cells.<sup>[1]</sup> It most commonly occurs in the appendicular skeleton involving the metaphysis of long bones.<sup>[1,2]</sup> Jaw osteosarcoma (JOS) constitutes only about 6%–13% of all cases of osteosarcoma.<sup>[1,3]</sup> Common histologic variants of osteosarcoma include osteoblastic, chondroblastic and fibroblastic types depending on the cellular atypia and the type of the extracellular matrix, produced by the tumor cells.<sup>[4]</sup> Giant cell-rich osteosarcoma (GCRO) is an extremely rare histologic variant, accounting for only 1%–3% of conventional osteosarcoma.<sup>[1-3]</sup> GCRO is an undifferentiated high-grade sarcoma with numerous osteoclast-like giant cells and variable amount of tumor osteoid.<sup>[5]</sup> The radiological and histopathological differentiation of GCROs from other benign and malignant giant cell tumors (GCTs) is highly challenging.<sup>[5]</sup>

It is important to differentiate them from other aggressive GCTs as the prognosis and treatment differs between them.<sup>[3]</sup> Most cases of GCRO reported in the world literature involve the extremities and to the best of our knowledge, only five cases of GCRO involving the jaws have been reported so far [Table 1].<sup>[1-3,5,6]</sup> Here, we present a rare and probably the sixth case of GCRO involving the body and angle of the mandible in a 52-year-old male patient.

## CASE REPORT

A 52-year-old male patient reported to the Department of Oral and Maxillofacial Pathology, Guru Nanak Institute of Dental Sciences and Research, Kolkata, with the chief complaint of a progressively enlarging swelling associated with intermittent pain in the lower front tooth region for 1 year. The swelling started as a small growth in the lower anterior tooth region, which increased in size remarkably during the last 2 months, causing difficulty in chewing.

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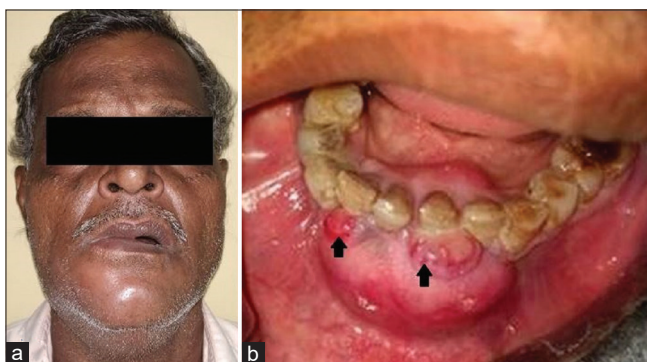
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Initially, the swelling was not associated with pain, but gradually over time, the patient experienced occasional pain in that region. Past dental history revealed a fracture of the right body of the mandible due to trauma several years ago, which was left untreated. The patient denied any habit of smoking or alcohol intake, but chewed khaini for the past 25 years. His medical and surgical histories were noncontributory.

Extraorally, a diffuse swelling was evident on the right lower third of the face with partial obliteration of the mentolabial fold. The mouth opening was normal with no jaw deviation [Figure 1a]. On palpation, a smooth surfaced, small diffuse swelling was noted above the chin, which was nontender, nonpulsatile and firm. The swelling was fixed to the underlying structures and the overlying skin appeared to be free. The lower border of the mandible in between the parasymphysis was irregular. No local rise in temperature or paresthesia was elicited. Regional cervical lymph nodes were not palpable.

Intraoral examination revealed poor oral hygiene with the presence of a large (4.0 cm × 2.0 cm), well-defined swelling extending from the left mandibular canine (33) to the right canine (43) region, causing obliteration of the vestibule, more on the labial side than on the lingual aspect. The overlying mucosa appeared reddish pink with two focal areas of ulcerated lobules labially in relation to the lower left incisors (31 and 32) and lower right lateral incisor (42) [Figure 1b]. On palpation, the swelling was firm, tender and nonpulsatile. The regional teeth from the lower left canine to right canine region (33, 32, 31, 41, 42 and 43) were tender on percussion and exhibited Grade 1 mobility.

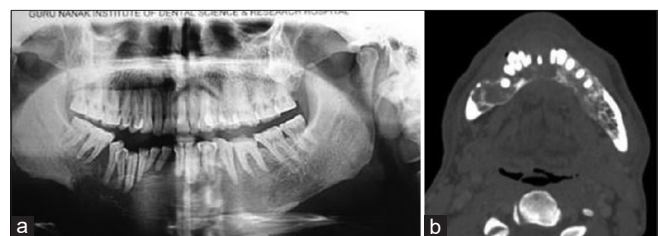


**Figure 1:** (a) Extraoral photograph of the patient reveals a diffuse swelling in the lower right third of the face with partial obliteration of the mentolabial fold. (b) Intraoral photograph reveals a well-defined swelling extending from the lower left canine to the right canine region, causing obliteration of the labial and lingual vestibule. The overlying mucosa is reddish pink with two focal areas of ulcerated lobules in relation to the lower left incisors and lower right lateral incisors. The arrow shows the two ulcerated lobules on the lesion

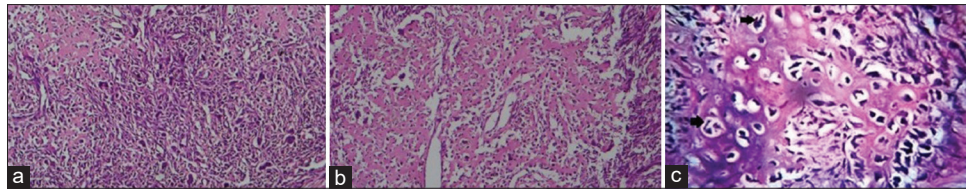
Considering the clinical extent of the lesion, a panoramic radiograph was advised, which revealed the presence of a large, irregular, destructive, radiolucent lesion extending from the lower left first premolar (34) to the lower right second molar (47) region with destruction of the lower border of the mandible [Figure 2a].

The noncontrast, multislice spiral computed tomography (CT) scan of the mandible revealed an expansile lesion which extended from the right angle of the mandible involving the body and up to the left angle of the mandible [Figure 2b]. CT scan was vital in visualizing the extent of the lesion on the left side of the mandible, which was not appreciated in the orthopantomogram (OPG). Based on the clinical and radiological features, a provisional diagnosis of intraosseous malignancy was made. Our differential diagnosis included osteoblastoma, aggressive ossifying fibroma, fibrosarcoma, chondrosarcoma, osteosarcoma and metastatic carcinoma. The patient was referred to the department of oral and maxillofacial surgery for incisional biopsy. Histopathological examination revealed the presence of abundant bizarre-shaped (fusiform or spindle) cells in the stroma arranged into solid sheets or a fascicular pattern with focal production of lace-like osteoid [Figure 3a and b]. The neoplastic osteoblasts revealed marked nuclear pleomorphism, hyperchromatism, prominent nucleoli and numerous atypical mitotic figures [Figure 3c]. The fibrovascular connective tissue stroma consisted of pleomorphic spindle cells arranged in a storiform and streaming pattern with hyperchromatic nuclei [Figure 4a and b]. Presence of multiple osteoclast-like giant cells amidst the tumor cells could also be noted [Figure 5]. The overall histopathological features were suggestive of “giant cell-rich variant of osteosarcoma.”

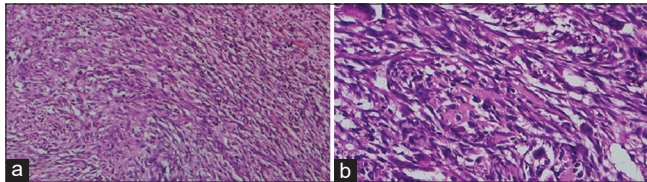
Hemi-mandibulectomy was done extending from the right angle to the left angle of the mandible [Figure 6a and b], and the patient was referred to a state general medical hospital for adjuvant radiotherapy and was advised for



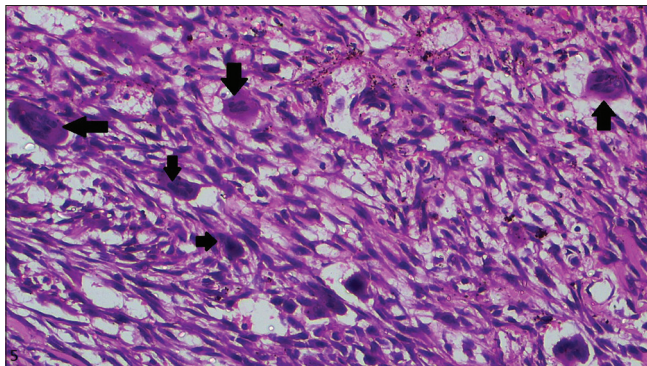
**Figure 2:** (a) Orthopantomogram reveals the presence of a large, irregular, destructive, radiolucent lesion involving the lower left premolar to the lower right second molar region. (b) Computed tomography image reveals an expansile lesion which extended from the left angle of the mandible involving the body and up to the right angle of the mandible



**Figure 3:** (a) Histopathological image shows abundant bizarre-shaped (fusiform or spindloid) cells arranged into solid sheets and fascicular pattern in the stroma along with the presence of osteoid in a lace-like pattern and numerous giant cells (H&E, ×100 for ×10 magnification). (b) Irregularly contoured eosinophilic tumor osteoid with neoplastic osteoblasts showing nuclear atypia (H&E, ×100 for ×10 magnification). (c) Tumor osteoid showing neoplastic osteoblasts with marked nuclear pleomorphism, hyperchromatism, prominent nucleoli and atypical mitotic figures (H&E, ×400 for ×40 magnification). The arrow shows the atypical mitotic figures



**Figure 4:** (a) Histopathological image reveals the arrangement of the spindloid cells with hyperchromatic nuclei in a "streaming" and "storiform" pattern in the fibrovascular connective tissue stroma (H&E, ×100 for ×10 magnification). (b) Presence of pleomorphic and hyperchromatic spindloid cells in the stroma (H&E, ×400 for ×40 magnification)



**Figure 5:** Histopathological image shows the presence of numerous osteoclast-like giant cells with multiple nuclei in the connective tissue stroma (H&E, ×400 for ×40). The arrow shows the multinucleated osteoclast-like giant cells

periodic follow-up. However, the patient did not comply with subsequent follow-up, post surgery.

## DISCUSSION

"Sarcoma" in Greek means "fleshy excrescence." The term "osteosarcoma" was introduced by Alexis Boyer in 1805.<sup>[7]</sup> Osteosarcoma is the most common, aggressive primary malignant tumor affecting the bone, in which the malignant mesenchymal cells produce tumor osteoid.<sup>[1]</sup> Osteosarcoma was histologically classified into central, intramedullary and surface variants with a number of subtypes by the World Health Organization. The central osteosarcoma is further subdivided into the conventional osteosarcoma, telangiectatic osteosarcoma,

small-cell osteosarcoma and low-grade osteosarcoma. The conventional osteosarcoma predominantly comprised of the osteoblastic, chondroblastic and fibroblastic variants depending on the cellular atypia and the type of extracellular matrix, produced by the tumor cells.<sup>[4,8]</sup> GCRO is an uncommon histologic variant of conventional osteosarcoma comprising about 1%–3% of primary osteosarcoma.<sup>[2,3]</sup> Bathurst first described this variant in 1986 under the term "osteoclast-rich osteosarcoma."<sup>[1-3,5]</sup> GCRO consists of an abnormally increased number of giant cells, almost swamping the sarcoma cells.<sup>[9]</sup>

Osteoclast-like giant cells which originate due to differentiation of mononuclear phagocytes have a tendency to cause bone resorption which plays a significant role in the pathogenesis of bone tumors. Histones are basic nuclear proteins responsible for the nucleosome structure of the chromosomal fiber in eukaryotes. The pathogenesis of GCT can be attributed to the mutations in the histone H3.3-protein encoding H3F3A gene. Specifically, GCRO may show a mutation of the H3K27me3 (the trimethylatedlysine residue at position 27 in the protein histone H3) mutation.<sup>[10]</sup> GCRO has also been reported to originate from previous low-grade osteosarcoma with amplification of the MDM2 and CDK4 genes.<sup>[6]</sup>

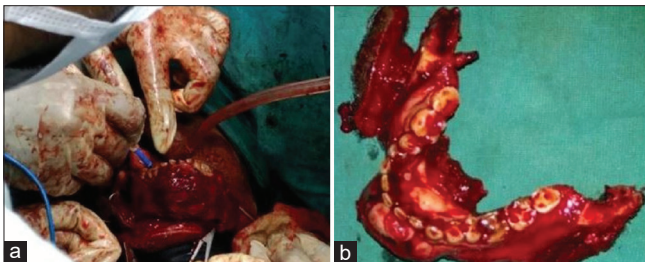
Osteosarcoma in the long bones may develop in preexisting conditions such as Pagets disease, fibrous dysplasia, retinoblastoma or in patients having a history of previous irradiation or trauma, whereas most cases of JOS do not have any suggestive history.<sup>[5,11]</sup> The patient under discussion had a history of a fracture involving the right body of the mandible due to trauma about 25 years back, which was left untreated.

The average age of the onset of JOS is usually 10–20 years later than that of its skeletal counterpart.<sup>[1]</sup> GCRO of the maxillofacial region commonly occurs in elderly individuals and shows slight male predilection.<sup>[1,2,5]</sup> In our case too, the patient was a 52-year-old male, which was in accordance with the previous literature.

**Table 1: Giant cell-rich osteosarcomas in the jaws**

Author	Age	Sex	Site	Histopathological features	Radiological features	Treatment
Fu HH <i>et al.</i> (2011)	67	Female	Mandible	Presence of tumor osteoid and sarcoma cells swamped by osteoclast-like giant cells	Osteolytic lesion	Segmental mandibulectomy with reconstruction by free fibula myocutaneous flap followed by radiotherapy and chemotherapy
Verma RK <i>et al.</i> (2011)	56	Female	Maxilla	Pleomorphic round-to-ovoid and spindle cells arranged in fascicles and sheets with numerous giant cells and areas of lace-like osteoid	Expansile, hyperdense, soft-tissue mass occupying the whole of the maxilla on CT scan, and areas of calcification were seen within the substance of tumor with sclerosis of adjacent bone	Total maxillectomy followed by radiotherapy (60 Gy) and five cycles of chemotherapy
Sun LM <i>et al.</i> (2015)	28	Female	Mandible	Sheets of atypical plump spindloid cells with scanty osteoid and numerous multinucleated giant cells	Lytic in appearance	Surgical excision, radiotherapy and chemotherapy
Hirose K <i>et al.</i> (2017)	64	Male	Maxilla	Atypical mononuclear cells with numerous osteoclast-like giant cells along with the presence of neoplastic bone	Maxillary bone expansion and destruction of cortical bone on CT	Segmental maxillectomy
Shetty SS <i>et al.</i> (2018)	16	Male	Mandible	Pleomorphic ovoid, round or spindle cells with numerous osteoclast-like giant cells and lace-like osteoid	Ill-defined mixed radiolucent- radiopaque lesion with loss of trabecular pattern on OPG	Access osteotomy with segmental mandibulectomy followed by reconstruction using stainless steel plate
Present case (2019)	52	Male	Mandible	Abundant bizarre-shaped spindloid cells arranged into solid sheets or fascicles with focal production of lace-like osteoid and multiple osteoclast-like giant cells	Large, irregular, destructive radiolucent lesion on OPG and an expansile lesion on CT	Hemi-mandibulectomy

OPG: Orthopantomogram, CT: Computed tomography



**Figure 6:** (a) Hemi-mandibulectomy extending from the right angle to the left angle. (b) Gross specimen of the resected part of the mandible

GCRO primarily arises in the medullary cavity of a growing long bone, specifically the distal femur, proximal tibia and proximal humerus, but it is exceedingly rare in the orofacial region.<sup>[1,2]</sup> In the head-and-neck region, mandible is more commonly involved than maxilla by GCRO where the most frequently involved sites are the posterior body, horizontal ramus and ascending ramus of the mandible. The maxillary lesions usually develop in the alveolar ridge and often involve the maxillary sinus and the orbital floor.<sup>[1,2,5]</sup> In our case, the lesion started in the anterior mandible as a small asymptomatic swelling which later extended on either sides to involve the body and the angle.

Osteosarcoma in the initial phase manifests as a nondescript swelling, only to become overly aggressive in the later phase of life.<sup>[12]</sup> This was seen in the present case as well, where a small swelling became significantly large within a short span of time. The average duration of symptoms before it is diagnosed is reported to be 3–4 months. GCRO is

nonspecific clinically and mainly characterized by swelling, pain and general discomfort.<sup>[5,9]</sup> The same holds true in our case where the patient reported to us when the subjective symptoms appeared while the lesion was present since 1-year duration.

JOS may radiologically manifest as an osteolytic or osteoblastic area with ill-defined margins. The involvement of the periosteum may result in “sunburst appearance.”<sup>[11]</sup> The “Codman’s triangle” occurs due to the triangular elevation of periosteum. Symmetric widening of periodontal ligament space due to tumor infiltration along the periodontal space is known as “Garrington sign.”<sup>[11]</sup> The radiological feature of GCRO is different from that of the conventional osteosarcoma.<sup>[3,5]</sup> According to Bathurst, “many of the classic radiological features of an osteosarcoma are absent in cases of GCRO and the radiological appearance involves an ill-defined margin surrounding a predominantly lytic lesion; a soft-tissue mass is usually not present.”<sup>[1,5]</sup> OPG in our case revealed a lytic destructive lesion with indistinct margins without sclerosis, while the CT findings demonstrated the extent of the lesion. The classic radiological features were missing in our case too.

GCRO is an undifferentiated sarcoma with paucity of osteoid. Osteoclast-like giant cells are usually present in 13%–25% of osteosarcoma cases, specifically involving the hemorrhagic and perivascular areas. In contrast to this,

the histological picture of GCRO consists of a diffuse infiltration of a larger population of giant cells almost covering up the tumor cells. Although the histological appearance of GCRO is dominated by numerous osteoclast-like giant cells, the key diagnostic feature is the presence of irregularly contoured eosinophilic osteoid usually surrounded by a rim of osteoblasts. The tumor also consists of sheets and fascicles of anaplastic stromal cells or atypical spindle cells with marked cellular pleomorphism, pale chromatin, conspicuous nucleoli and numerous mitotic figures. Clusters of giant cells admixed with fibroblastic cells appear with bundles of collagen-rich fibroblastic tissue. The osteoclast-like giant cells are characterized by large pleomorphic nuclei, irregular nuclear membrane and prominent nucleoli.<sup>[1-3,5]</sup> Our case showed the presence of numerous osteoclast-like giant cells present along with spindle cells arranged in a storiform and streaming pattern. Hence, initially, the tumor was thought to be a GCT, which could be either benign or malignant. However, on meticulous examination of the slides, the presence of irregular tumor osteoids in a lace-like pattern was noted, with pleomorphic osteoblasts showing pronounced nuclear hyperchromatism and pleomorphism, thereby ruling out the possibility of a GCT and corroborating to the findings of GCRO. Differentiation of GCRO from GCT is of prime importance due to the different treatment strategies and prognosis of the lesions.<sup>[5]</sup>

Osteoblastoma and aggressive ossifying fibroma which was included in the clinicoradiological differential diagnosis was ruled out on the basis of histopathological findings. The invasive nature of the neoplasm along with the presence of remarkable cellular and nuclear pleomorphism and atypical mitoses in the present case differentiated it from osteoblastoma, which has a characteristic pushing margin, bland osteoblasts and a prominent vascular stroma, but lacks invasion and atypical mitoses. The characteristic mixed radiolucent radiopaque appearance with a sclerotic border and the histological presence of cementum-like spherules with peripheral brush borders of aggressive ossifying fibroma were absent in the referred case, thereby excluding them.<sup>[13]</sup>

The most important histopathological differential diagnosis of GCRO includes fibroblastic variant of conventional osteosarcoma, telangiectatic osteosarcoma and undifferentiated pleomorphic sarcoma. GCRO lacks the characteristic blood-filled channels and has a much more uniform distribution of multinucleated giant cells, thus excluding telangiectatic osteosarcoma. The storiform arrangement of the spindle cells is common to both GCRO and the fibroblastic variant of osteosarcoma,

however the clustered appearance of the giant cells in GCRO helps in differentiation from the fibroblastic variant. Undifferentiated pleomorphic sarcoma is likely to have a similar picture as GCRO consisting of the streaming pattern of the tumor cells, but the presence of tumor osteoid in GCRO helps in its exclusion.

The treatment modality of GCRO is same as that of traditional osteosarcoma.<sup>[9]</sup> It consists of aggressive surgical resection followed by radiotherapy and chemotherapy. The survival rate is 80% with clear surgical margins. Radiotherapy is used as an adjunct treatment only in cases of positive surgical margins before the introduction of chemotherapy.<sup>[11]</sup> JOS exhibits a lower incidence of metastasis and a better prognosis with approximately 40% of 5-year survival rate as compared to 20% from its skeletal counterparts.<sup>[2,12]</sup> However, the survival rate of GCRO does not differ much from that of high-grade osteosarcoma.<sup>[14]</sup> The role of osteoclast-like giant cells in the prognosis of GCRO is still not well known.<sup>[2]</sup> The present case was treated with hemi-mandibulectomy and referred for radiotherapy.

## CONCLUSION

GCRO has no distinct clinical or radiological features that may aid in its recognition. It is a very rare clinical entity which poses a striking resemblance to that of a GCT. The unusual histological appearance and the exceptional rarity of the lesion poses a great diagnostic challenge; thus, the clinical, radiological and histopathological findings should be integrated for its early diagnosis and proper management.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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