A rare case of a metastatic giant cell–rich osteosarcoma of the mandible: Update and differential diagnostic considerations

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A metastatic giant cell–rich osteosarcoma (GCRO) to the jaws is an exceedingly rare neoplasm. To date, fewer than 10 cases have been reported in the English language literature. In this article, we describe an additional case of a metastatic GCRO that presented the diagnostic challenge of a painless mass in the posterior mandible of a 19-year-old girl who exhibited rapid and aggressive local growth. The lesion was confirmed radiologically as an ill-defined expansive osteolytic mass showing cortical perforation. Microscopically, the presence of osteoclast-like giant cells permeated with atypical oval and rounded mesenchymal cells in a fibrovascular stroma, cellular atypia, and scarce osteoid formation were observed. Immunohistochemistry revealed the Ki-67 proliferative index in 50% of positive cells, positivity for vimentin and CD68, as well as scarce positivity for CDK4. The patient's medical history involved a GCRO in the proximal ulna. This report highlights the aggressive behavior of GCRO and its high capacity for metastasis to different parts of the body. Clinicians, pathologists, and surgeons should be aware of the giant cell–rich variant of osteosarcoma of the jaws, an imminent "wolf in a sheep's skin", because its indolent but unrelenting growth and dissemination, with radiographic and histologic characteristics that may represent a diagnostic pitfall regarding aggressive central giant cell lesions of the jaws. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:e163–e169)

Osteosarcoma of the jaws (OSJ) is defined as an invasive and highly metastatic bone-forming tumor characterized by the production of osteoid, chondroid, and fibrous connective tissue by malignant mesenchymal cells.[1,2] According to the relative amount of osteoid, cartilage, or collagen produced by the tumor, the lesion is histopathologically subclassified into the following types: osteoblastic, chondroblastic, fibroblastic, and, less frequently, telangiectatic, epithelioid, osteoblastoma-like, chondroblastoma-like, small cell, giant cell–rich, and low-grade central.[1,2] The most common clinical feature of OSJ is swelling, whereas bone pain during activity is characteristic of long bone osteosarcoma.[3] In gnathic bones, the mandible is involved in 54% of cases, mainly in the posterior region.[4] A slight predilection to women has also been reported. The mean age of affected patients is 41.3 years.[3] Although OSJ is the most frequent primary malignant bone tumor affecting children and adolescents,[5] it is not very common. In a large Brazilian multicenter study in which biopsy record information was provided about the occurrence of malignant oral and maxillofacial lesions in children and adolescents, OSJ represented 0.009% of the specimens submitted to histopathological analysis and 13.8% of cases among all pediatric oral and maxillofacial malignant lesions.[5]

In 1986, Bathurst et al. described a series of 9 cases of osteosarcomas of the long bones.[6] The lesions exhibited scanty or no tumor osteoid tissue, with sarcoma cells swamped by multinucleated giant cells. This histologic variant, namely, giant cell–rich osteosarcoma (GCRO), accounts for only 3% of all osteosarcomas.[7] It is exceedingly rare in the jaws[8-14] and has a more aggressive behavior compared with other osteosarcomas that affect the head and neck region.[9] However, due to its histologic aspects, it is capable of mimicking giant cell–rich lesions, such as giant cell bone tumors, which makes its diagnosis a great challenge.[7]

Statement of Clinical Relevance

Giant cell–rich osteosarcoma (GCRO) is exceedingly rare in the jaws. A challenging example of metastatic GCRO affecting the mandible of an adolescent woman with locally aggressive growth and metastasis to the lung, forearm, and femur leading to death is reported.

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Because the pathogenesis of OSJ is unknown, it is not clear whether the lesions represent independent primary tumors or metastatic disease.[15] Nevertheless, metastases from osteosarcomas of the long bones in the oral and maxillofacial region are extremely rare, with few cases published.[16] Thus, well-documented reports of additional cases will be useful. In the present article, we report a metastatic GCRO in the mandible of a 19-year-old girl that showed locally rapid and aggressive growth and metastasis to the lung, forearm, and femur, leading to death. In addition, the demographic, clinical, and radiographic characteristics; differential diagnosis; and treatment of GCRO of the jaws are summarized in order to assist the diagnosis.

CASE REPORT

A 19-year-old woman was referred by her general dentist to the Oral Medicine Service of the Federal University of Sergipe in Aracaju, Brazil. Her chief complaint was a painless tumor in the region of the mandible of 2 months' duration. Noncontributory socioeconomic status or family history was declared, but the medical history of the patient involved amputation of the proximal ulna due to osteosarcoma at the age of 16 years. Ulnar resection material was assessed, and histopathological findings were consistent with those of a GCRO (Figure 1).

Extraoral examination revealed facial asymmetry with swelling present on the right lower third of the patient's face. Intraoral examination revealed a large and ulcerated lesion measuring approximately 3.0 cm, with areas of necrosis, a sessile base, and irregular borders, located in the region of the right mandibular molars (Figure 2). Computed tomography disclosed an ill-defined, expansive osteolytic lesion in the right posterior mandible. Cortical perforation and soft tissue extension were also observed. The largest diameter of the lesion size was 4.0 cm (Figure 3). Serum bone-specific alkaline phosphatase was increased but within the normal range for her age. The clinical, radiologic, and biochemical findings allowed us to consider a possible metastatic GCRO.

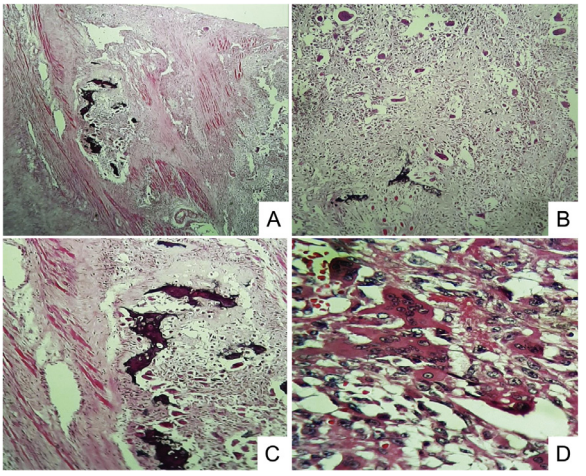

Fig. 1. Histopathologic features of a giant cell–rich osteosarcoma of the ulna. **(A)** A moderately cellularized lesion containing osteoid matrix deposition and dense fibrous stroma is observed (hematoxylin and eosin, × 40). **(B)** Proliferation of oval mononuclear cells depositing immature osteoid matrix surrounded by malignant multinucleated giant cells (hematoxylin and eosin, × 100). **(C)** Foci of osteoid matrix in different stages of maturation (hematoxylin and eosin, × 200). **(D)** A histologic section demonstrates moderate pleomorphism of mononuclear cells and multinucleated giant cells (hematoxylin and eosin, × 400).

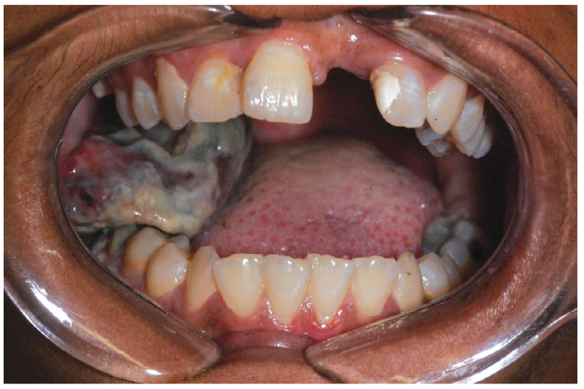

Fig. 2. Clinical aspects of a giant cell–rich osteosarcoma of the mandible. Intraoral view showing an extensive sessile swelling with necrotic ulcerated areas on the right side of the posterior mandible.

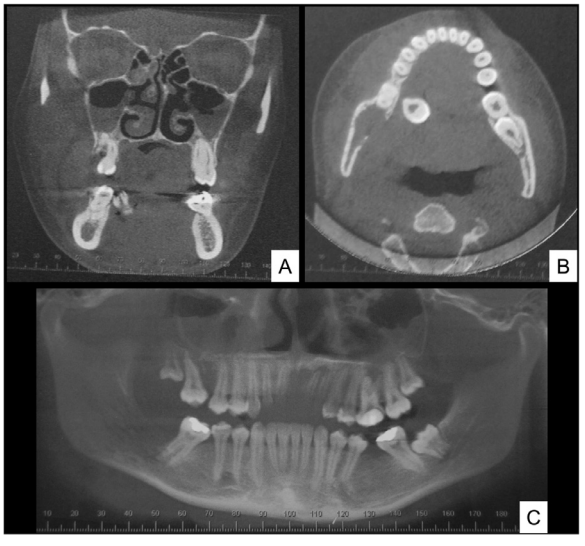

Fig. 3. Computed tomography features of a giant cell–rich osteosarcoma of the mandible. **(A)** Coronal section showing a mass in the right posterior mandible with soft tissue extensions. **(B)** Axial section showing expansion and bony destruction of the lingual cortical plate, as well as displacement of an adjacent dental unit. **(C)** Panoramic view exhibiting an osteolytic lesion on the right side of the apex of the second molar and in the region of the third molar.

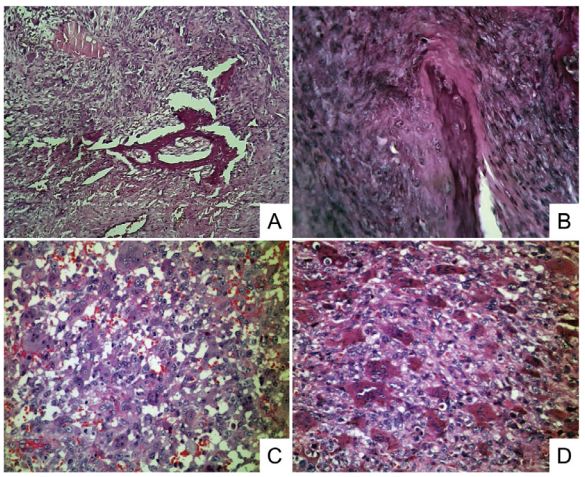

Fig. 4. Histopathologic features of a giant cell−rich osteosarcoma of the mandible. **(A)** The histopathologic findings reveal a cellularized lesion containing multinucleated giant cells, fibrovascular stroma, and focal osteoid deposition (hematoxylin and eosin, × 100, × 200). **(B)** Abundant proliferation of oval or spindle mononuclear cells depositing osteoid matrix (hematoxylin and eosin, × 400). (C, D) A histologic section demonstrates moderate nuclear pleomorphism of mononuclear cells, prominent nuclei, and vesicular chromatin, surrounded by multinucleated giant cells (hematoxylin and eosin, × 400).

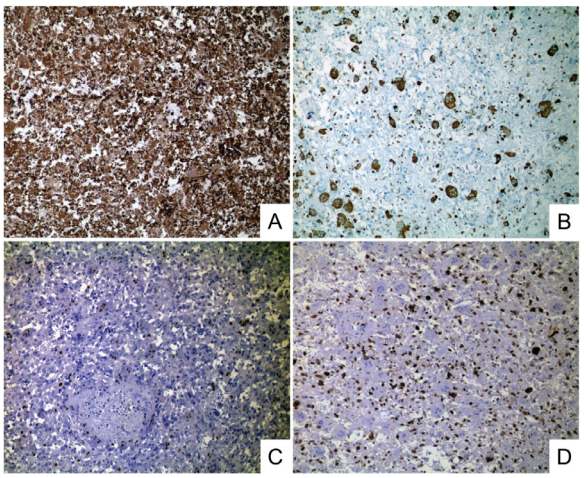

Fig. 5. Immunohistochemical features of a giant cell−rich osteosarcoma. **(A)** Tumor cells showing strong and diffuse positivity for vimentin (immunohistochemical, × 200). **(B)** CD68 expression in multinucleated giant cells (immunohistochemical, × 200). **(C)** Focal and scattered positive reactions of some mononuclear cells and multinucleated giant cells to CDK4 (immunohistochemical, × 200). **(D)** Strong and diffuse Ki67 staining of mononuclear cells (labeling index: ~50%; immunohistochemical, × 200).

An incisional biopsy was performed under local anesthesia. Microscopic examination revealed a tissue fragment with the presence of multiple osteoclast-like giant cells permeated with abundant proliferation of atypical oval and rounded mesenchymal cells in a fibrovascular stroma. The presence of cellular and nuclear pleomorphism, mitotic figures, scarce osteoid formation, and hemorrhage was also noticed (Figure 4). The histopathologic features were consistent with those of a GCRO. Immunohistochemistry studies were carried out. Table I depicts the antibodies used. Tumor cells were positive for vimentin, and oval cells and osteoclast-like giant cells were positive for CD68, also showing scarce positivity for CDK4. The Ki-67 cell proliferation index was ~50% (the mean number of positive cell nuclei in 5 consecutive high-power fields was counted; Figure 5).

The patient was referred to the oncology service. Within a short period of hospitalization, the patient had diffuse tumors in the forearm and femur, in addition to multiple nodules and masses spread through the lung parenchyma (Figure 6), suggestive of metastatic involvement. It is important to note that metastases to other parts of the body may have occurred a priori or simultaneously in the mandible. The patient was palliatively managed with vincristine-cisplatin combination chemotherapy; however, she died within a period of 5 weeks.

Table I. Antibodies used for the immunohistochemical analysis of the reported case

Antibodies	*Clone*	*Sources*	*Nature of antibodies*	*Dilution*
CD68	PG-M1	Dako	Monoclonal (mouse)	FLEX
CDK4	EP180	Epitomics	Monoclonal (rabbit)	1:100
Vimentin	V9	Dako	Monoclonal (mouse)	FLEX
Ki-67	SP6	Spring	Monoclonal (rabbit)	1:200

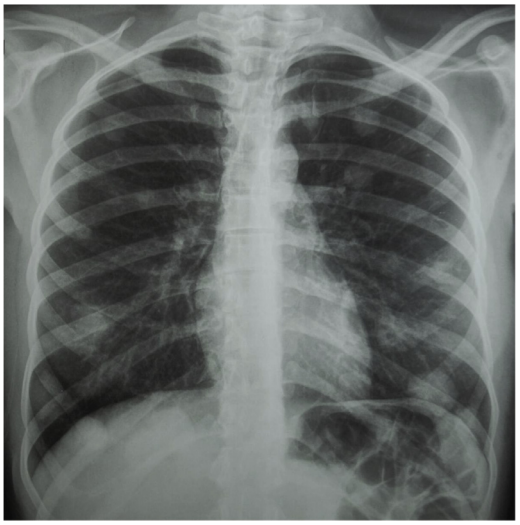

Fig. 6. Chest x-ray showing multiple nodules and diffuse masses in the lung parenchyma suggestive of metastatic involvement.

DISCUSSION

We report here a rare case of metastatic GCRO in an adolescent patient who had other metastatic lesions in different parts of the body, causing death within a short time after the initial diagnosis. Although about 15% of individuals with osteosarcoma were found to have bone or lung metastasis at diagnosis, metastasis of the oral cavity was the first sign of metastatic disease diagnosed 3 years after treatment of the primary tumor.[17] This case also highlights the pitfalls involved in the histopathologic aspects of the lesion in view of some of the characteristics of GCRO, such as the presence of numerous giant cells similar to osteoclasts, atypical cells, and the scant formation of osteoids.[6,7,18] In addition, the current case showed exuberance of multinucleated giant cells, as previously reported by Bathurst et al.[6] However, because there are a variety of malignant lesions containing giant cells[19,20] and GCRO of the oral cavity is seldom addressed, with 7 single cases reported worldwide thus far,[8-14] the diagnosis is a great challenge.

Noteworthy, all cases of GCRO of the oral cavity have been reported from Asia and South America, including India,[8,10,13] China,[9,11] Japan,[12] and Brazil.[14] The mean age of patients with GCRO of the oral cavity published in the literature was 47.6 years (range 16-67 years), but individuals in the second and third decades of life, as well as in the sixth and seventh decades, were also affected. In a large American study in which information on epidemiology and prognostic factors associated with OSJ was presented, the mean age of 541 individuals was 41.3 years.[3] According to Kirschnick et al.,[21] oral metastatic tumors are more frequently diagnosed in the fifth to seventh decades of life and only 10.3% were patients under 40 years of age. However, because giant cell−rich bone tumors encompass various benign or malignant lesions, some authors have highlighted the age of the affected patients.[22,23] Giant cell lesions of the jaws, odontogenic carcinomas, and odontogenic sarcomas seem reasonable possibilities. Although other conditions, such as aneurysmal bone cyst, chondroblastoma, and cherubism, may appear in the mandible, with osteoclasts-like giant cells being a characteristic or defining feature, we ruled them out because the clinical, radiologic, and biological findings were very different.[23] Interestingly, as observed in GCRO of long bones, with a male-to-female ratio of 1.28,[7] there is a male-to-female ratio of 1.3:1 for individuals affected with oral metastasis.[21]

Osteosarcoma metastases to oral and maxillofacial regions are considered uncommon and may originate from different primary tumor sites.[16,21,24] Irani[16] found that only 5 of 412 cases of oral metastases were from an osteosarcoma located in the fibula, femur, and tibia. Almost all cases affected the mandible, as in the present case. Painless or painful, ulcerated, exophytic masses or rapidly progressing bony swelling associated with numbness may occur.[21,24] Carnelio et al.[25] reported a case of osteosarcoma metastasis to the palate in an 18-year-old male who was affected by rapidly progressing painful swelling, infiltrated the surrounding tissue, and caused difficulty in chewing. Alves et al.[26] reported the example of an exophytic tumoral mass in the posterior mandible of a 15-year-old girl resulting from a metastatic telangiectatic osteosarcoma. Likewise, Mariano et al.[14] published a case of a metastatic GCRO in a 55-year-old male with a necrotic and ulcerated lesion on the lower labial mucosa. Another report by Choo et al.[27] reported GCRO metastasis to the skin and other sites, including the lungs and the mandible, in a 43-year-old male patient. Furthermore, it is pertinent to note that the lesions, including the one affecting our case, were of considerable size, and most patients had multiple metastatic lesions in different parts of the body. On this basis, osteosarcoma metastasis can be detected as late-stage and widespread metastatic disease, resulting in a generally poor patient prognosis, as seen in the present case.[14,26,27]

With respect to the radiographic aspects of GCRO of the jaws, ill-defined lesions with osteolytic areas, bone expansion, and destruction of cortical bone image have been documented,[8,12] as also observed in the present case. However, a radiolucent lesion with a destructive and irregular pattern has also been reported.[10] In contrast, Chow[7] reported that plain radiography of a long bone GCRO revealed a multiloculated lesion with osteolytic and expansive cortical erosion. Therefore, because the scarcity of cases and because most of the reported cases have described aspects similar to those of benign or malignant odontogenic lesions, nonodontogenic tumor, and metastases, it is difficult to define a typical radiographic characteristic that distinguishes GCRO from other osteolytic lesions of the jaws.

GCRO displays lesions of uncertain histogenesis and complex karyotype.[1] Most cases show changes in loss or gain of function of multiples genes, including those related to terminal osteoblast differentiation or cell cycle control, such as the CDK4, MDM2, and RUNX2 genes.[1,12] The microscopic appearance of GCRO signals an undifferentiated form compared with other conventional osteosarcomas, especially because the scanty formation of osteoid.[28] In fact, the infiltration of multinucleated giant cells may represent a reactive component or be the main neoplastic component of the tumor.[29] In the first case, monocyte recruitment and differentiation in multinucleated giant cells take place by activating the receptor of nuclear factor κB (RANK) and its ligand (RANKL).[29]

Benign and malignant lesions of the bone that also carry multinucleated giant cells in their tumor component should be considered in the setting of differential

diagnosis. The histopathologic characteristics of giant cell lesions and chondroblastomas, such as the presence of multinucleated giant cells in the background of mononuclear cells, reactive bone, or fibrochondroid material, may be a cause of confusion when considered separately.[1] Regarding the presence of cellular and nuclear pleomorphism, atypical mitoses, invasive tumor pattern, and osteoid matrix produced directly by neoplastic cells are more indicative of a diagnosis of GCRO than, for example, a diagnosis of giant cell tumor of bone or chondroblastoma.[30] In malignant neoplasms, in addition to the multinucleated giant cell component, the malignant cells, arrangement, and atypical fibrochondroid material help to delimit the particularities of these lesions.[1,19] The biphasic appearance of malignancy in giant cell tumors of bone and in giant cell–rich dedifferentiated chondrosarcomas, for instance, is a precise criterion for differentiation from GCRO.[1,19,31-33] Table II depicts the histopathologic differential diagnosis of GCRO of the jaws.[31-34] Notably, the area of neoplastic bone produced by malignant tumor cells is the main factor contributing to the diagnosis of GCRO.[1,7]

Cytogenetic and molecular analyses are also used to differentiate GCRO from other giant cell–rich lesions, although there is no exclusive immunoprofile for GCRO.[1] Because a variety of epithelial and mesenchymal lesions may have a component of multinucleated giant cells, vimentin immunostaining helps to clarify the mesenchymal origin of the lesion. The immunopositivity of multinucleated giant cells to CD68 confirms the osteoclast phenotype, indicating that these cells may be reactive cells.[9] Although Chow[7] did not detect amplification of the CDK4 and MDM2 genes in a series of seven GCROs examined, our case showed CDK4 immunostaining. On the other hand, Hirose et al.[12] detected amplification of MDM2 and CDK4 in a case of GCRO of the maxilla, a phenotype frequently observed in low-grade osteosarcomas or high-grade osteosarcomas progressed from low-grade osteosarcomas.[35] The mean labeling of the Ki67 proliferative index has already been observed in about 30% of positive osteosarcoma cells.[36] In the present case, we observed a 50% rate of positive cells, which was related to the aggressive potential of this neoplasm and represented a distinguishing feature compared with benign giant cell lesions.[7]

The treatment of primary or metastatic GCRO involves a multimodal approach, including surgical resection and chemotherapy. In metastatic disease, a palliative setting is also considered in some cases and can be extremely helpful to lengthen survival and control symptoms.[37,38] GCRO metastases to the oral and maxillofacial region were discovered by Mariano et al.[14] and Choo et al.[27] during the first year after

Table II. Histopathologic differential diagnosis of a giant cell–rich osteosarcoma of the jaws

Lesions	*Microscopic findings*
Central giant cell lesion[1,31]	Sheets and storiform areas Multinuclear giant cells scattered among ovoid/round or spindle mononuclear cells Vascular background, hemorrhage, and hemosiderin deposition Linear and fibrillar collagen Reactive bone formation at the border of the tumor surrounded by mature osteoblasts
Giant cell–rich chondroblastoma[1,31]	Sheet areas Admixture of mononuclear chondroblastic cells and multinucleated giant cells Chondroblasts with an ovoid/round nucleus with well-defined basophilic cytoplasm and longitudinal grooves Focal cytologic atypia Eosinophilic to amphophilic fibrochondroid material Pericellular calcifications (chicken wire)
Malignant giant cell tumor of bone[1,19]	High-grade sarcoma coexisting with a histologically benign giant cell tumor of bone components Storiform areas Multinuclear giant cells sparsely spread in the ovoid/round or spindle mononuclear cells Cytologic and nuclear atypia and typical mitotic figures Linear and fibrillar collagen Vascular background and hemorrhage Reactive bone formation at the border of the tumor surrounded by mature osteoblasts
Giant cell–rich dedifferentiated chondrosarcoma[1,32,33]	Chondroid and nonchondroid areas (biphasic appearance) Moderate to low cellularity and atypia of chondrocytes and atypical mitotic figures Eosinophilic to amphophilic fibrochondroid material Nonchondroid tumor component with multinucleated giant cells and stromal mononuclear cells mimicking a giant cell tumor of bone Invasion of surrounding tissues
Giant cell–rich malignant fibrous histiocytoma[1,34]	Fascicles, storiform, and myxomatous areas Atypical fibroblasts and pleomorphic undifferentiated cells with abundant cytoplasm Atypical mitotic figures Inflammatory infiltration of lymphocytes, histiocytes, and multinucleated giant cells Richly vascularized areas Reactive bone formation at the border of the tumor

diagnosis of the primary tumor, whereas they were diagnosed after 3 years in the present case. Of note, a study has emphasized that the 5-year risk of metastasis was 45% among patients with osteosarcomas, especially to the lungs and to the bone.[39] However, regardless of the period for the development of metastatic disease, metastases impact the overall survival of patient with osteosarcoma.[39] In addition, a positive surgical margin, histologic subtype, adjuvant chemotherapy, development of local recurrence, and use of amputation instead of limb salvage/wide resection are considered to be important predictive factors in survival rate.[37,39,40] For GCRO metastases involving the oral cavity, follow-up from 3 to 9 months has been reported.[14,27] In our case, these variables were preponderant factors shortening the life of the patient, who showed an aggressive osteosarcoma with multiple metastatic lesions.

CONCLUSIONS

Metastasis of GCRO to the oral and maxillofacial region is exceedingly rare and has seldom been reported. Because these lesions may mimic other giant cell lesions histologically and sometimes clinically, the clinician and pathologist should be cognizant of GCRO.

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