Central giant cell granuloma of the mandible: presentation of a rare case with prominent osteoblastic differentiation mimicking osteosarcoma

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Abstract: Central giant cell granuloma (CGCG) is a non-neoplastic proliferative lesion of unknown etiology. A wide variety of conditions could be misdiagnosed with CGCG, both histopathologically and radiographically. We report a rare case involving a 40-year-old female with CGCG of the mandible and prominent osteoblastic differentiation unlike that of conventional CGCG common to osteosarcoma. The patient presented with a painless swelling in the area between the lower left canine to the lower first molar. The lesion was surgically removed under general anesthesia, and the surgical specimen was investigated histopathologically and immunohistochemically. In this lesion, multinucleated giant cells were dispersed among a highly cellular stroma consisting of mononuclear round and spindle-shaped cells. Mononuclear cells demonstrated cellular pleomorphism and high proliferative activity, as evidenced by Ki-67 immunostaining. Immature osteoid was seen throughout the lesion, and most mononuclear cells exhibited Runx2 positivity. Despite these histopathological features in common with those of osteosarcoma, the lesion was shown radiographically to be well-defined and without infiltration of the surrounding bone, and a 3-year follow-up of the patient has thus far been uneventful. The lesion was diagnosed as a rare CGCG with prominent osteoblastic differentiation mimicking osteosarcoma.


Key words: central giant cell granuloma, jaw, osteoblast, osteosarcoma, Runx2

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Introduction

Central giant cell granuloma (CGCG) is a benign giant cell-rich lesion which typically manifests as an osteolytic lesion of the jaw bones (1). The lesion occurs more frequently in females than in males, is more often located in the anterior mandible than in the maxilla, and mainly affects patients between 10-25 years of age (2). CGCG must be distinguished from other lesions such as cherubism (3), hyperparathyroidism, and giant cell tumor of bone (4); all of these lesions are mixtures of osteoclast type giant cells and fibro-vascular stroma, and they all show similar histopathological findings. Herein, we report a case of CGCG showing prominent osteoblastic differentiation of mononuclear cells and mimicking the characteristics of osteosarcoma. The distinction between these two lesions has not received much attention.

Case report

A 40-year-old female patient noticed a painless swelling on the left side of her lower jaw. Two months later, she experienced tenderness in the same area and visited a nearby dental clinic. X-ray examination revealed an area of radiolucency, and the patient was referred to Hiroshima University Hospital. Additional radiographic images showed an area of comparatively well-defined multilocular radiolucency from the lower left canine to the first molar with expansion, thinning, and partial perforation of the buccal cortical bone (Figs. 1a & 1b). However, there was neither
resorption of related tooth roots nor calcification in the lesion, suggesting a clinical diagnosis of mandibular tumor.

An incisional biopsy from the surface of the lesion was performed. Histological examination revealed that multinucleated giant cells were dispersed in a highly-cellular stroma comprising both round and spindle-shaped cells, and that the giant cells were distributed randomly throughout the lesion (Fig. 2). Hemorrhage and osteoid formation in small parts were noted, and a histopathological diagnosis of CGCG was made.

The patient was admitted to the inpatient clinic, and the lesion was surgically removed under general anesthesia. The lesion was a relatively well-defined, solid and multilocular 2 × 5 cm mass. It was dark red in color and elastic hard in consistency. Histopathologically, the lesional tissue was not circumscribed, and it contained a large amount of newly-formed osteoid, which transformed into cortical lamellar bone surrounding the lesion at the periphery (Fig. 3). Areas of hemorrhage were frequently observed throughout the lesion. The lesion was composed of CD68 (clone KP1, diluted at 1:100, Dako, Glostrup, Denmark) positive, osteoclast-like multinucleated giant cells and CD68 negative mononuclear stromal cells with prominent vascular structures highlighted by CD34 (NCL-END, 1:100, Novocastra Laboratories Ltd., Newcastle upon Tyne, UK) immunostaining (Figs. 3, 4a & 4b). These histopathological findings were consistent with CGCG. There were, however, unusual features, such as immature osteoid deposits throughout the lesion (Figs. 3 & 5a). In addition, the mononuclear cells were mainly round or oval and widely positive for Runx2 (8G5, 1:300, MBL Co, Ltd., Nagoya, Japan) (Figs. 5b & 5c). Furthermore, mononuclear cells had large nuclei and showed cellular pleomorphism (Fig. 5b) and high mitotic activity, as evidenced by frequent Ki-67 (MIB-1, 1:100, Dako) expression (Fig. 5d). Although these findings are common to osteosarcoma, the present lesion was relatively well-defined and did not infiltrate into the surrounding bone on radiographic examination. Cellular and nuclear atypia were not evident in mononuclear cells, and abnormal mitoses were not found. In addition, a 3-year follow-up of the patient revealed no recurrence or serious complications after surgical removal of the lesion. After all of the findings were taken into consideration, a final diagnosis of CGCG with prominent osteoblastic differentiation was established.

**Discussion**

CGCG of the jaw bones, a benign proliferative lesion of unknown etiology, is characterized by variable clinical behavior that ranges from painless swelling to painful aggressive lesions (5). The radiological appearance of CGCG of the jaw usually presents as a well-defined solitary
radiolucent expansion in most cases and as a multilocular radiolucency in others. Some lesions are more destructive, with a marked tendency to recur (2). There have been several reports about the distinction between CGCG and other lesions that show similar histopathological findings: cherubism, aneurysmal bone cyst, hyperparathyroidism, and giant cell tumor of bone (3-4, 6). Recently, a novel mutation in exon 11 of the SH3BP2 gene in one sporadic case of CGCG was described, and another mutation in exon 4 of the same gene was demonstrated in one patient with cherubism, prompting investigation into the possible relationship between the pathogenesis of cherubism and that of CGCG (7). In addition, there are many unresolved questions regarding CGCG. For instance, does it represent a reactive or a neoplastic process? Do non-aggressive and aggressive CGCG represent a continuum of the same disease process, or should they be considered as two distinct entities? Also, what is the relationship between the aggressive form of CGCG and giant cell tumor of bone? (6, 8)

Herein, we presented a rare case of CGCG with prominent osteoblastic differentiation that bears histologic features similar to those of osteosarcoma of the jaw bones. These histopathological similarities between our case and osteosarcoma resulted in diagnostic difficulty for this particular case. Additionally, sarcoma cells show hypercellularity and high mitotic activity (9), and these histologic findings were also encountered in our case, as shown by the Ki-67 expression of mononuclear cells, which indicated a high proliferative activity of these cells. Most importantly, osteoid production by the neoplastic cells in osteosarcoma is considered a hallmark in the diagnosis of such lesions (10), and immature osteoid deposits were noted in our case: they were seen within the lesion and they contained mononuclear cells in a pattern resembling that of osteosarcoma, with a small number of scattered osteoclast-like giant cells. This finding was further evidenced by Runx2 expression, a key transcription factor associated with osteoblast differentiation, which revealed wide immunoreactivity in the mononuclear cells, and indicated osteoblastic differentiation identical to the pattern seen in cases of osteosarcoma, an unusual finding in CGCG. In a recent report, Runx2 expression by stromal cells was also noted in GCT of bone and was found to play an essential role in MMP-13 upregulation in GCT stromal cells through kinase pathways (11). This similarity in Runx2

![Fig. 4. Immunohistochemical findings of CGCG of the mandible. Immunoperoxidase stains for CD68 (a) and CD34 (b), hematoxylin counterstain, (a) × 200, (b) × 100. Osteoclast-like multinucleated giant cells were positive for CD68, while the mononuclear cells were not positive (a). Prominent vascular channels were demonstrated by CD34 immunostaining, indicating the highly vascular nature of the lesion (b).](image-url)

![Fig. 5. Histological finding and immunoreactivity for Runx2 and Ki-67 of mononuclear stromal cells. HE stain (a, b) and immunoperoxidase stains for Runx2 (c) and Ki-67 (d), hematoxylin counterstain, (a, d) × 100, (b) × 400, (c) × 200. Immature osteoid deposits containing mononuclear stromal cells were seen throughout the lesion (a). Mononuclear stromal cells were round- or oval-shaped and had large atypical nuclei. Note the cellular pleomorphism and mitotic figures (b, arrows). Mononuclear cells exhibited osteoblastic differentiation, as demonstrated by strong immunoreactivity for Runx2 (c). Ki-67 expression was noted in the mononuclear osteoblastic cells, indicating the high proliferative activity of these cells (d).](image-url)
expression in GCT of bone and in our case may help explain the aggressive behavior of the present case and also indicates that this case may represent a neoplastic rather than a reactive process. It should be noted that most of the mononuclear cells in this case were not spindle shaped and they resembled to some degree the osteoblasts cells surrounding and within osteoid in osteosarcoma.

Although these histopathological features are similar to those of osteosarcoma, the present case was relatively well-defined. On the other hand, cases of osteosarcoma do show infiltration into surrounding bone and are usually not well-circumscribed (10). Moreover, our case showed well-demarcated multilocular radiolucency in the radiographic evaluation. Conversely, this feature is not prominent in osteosarcoma cases in which ill-defined radiolucency with infiltration into the surrounding bone is characteristic (12). Furthermore, cellular and nuclear atypism of mononuclear cells and abnormal mitotic figures, which could be helpful in distinguishing these two lesions, were not prominent in the present case. In addition, a number of conditions that histologically are indistinguishable from CGCG, including cherubism, hyperparathyroidism and GCT of bone, must be excluded. However, the characteristic bilateral expansion of the jaw and the clinical appearance within the first few years of life favor a diagnosis of cherubism (13). Moreover, the correct diagnosis of hyperparathyroidism can be made on the basis of laboratory findings of hypercalcemia and hypophosphatemia in primary hyperparathyroidism and hyperphosphatemia in secondary hyperparathyroidism (14). It is unusual for GCT of bone to occur in the oral cavity and in contrast to CGCG, GCT is considered truly neoplastic with malignancy of the bone in 1.8% of the reported cases (4). Considering these findings altogether, the final diagnosis of CGCG was established.

In summary, we believe our case represents a rare example of CGCG showing prominent osteoblastic differentiation of mononuclear cells that resemble the characteristics of osteosarcoma. In such cases, clinicopathologic and radiologic correlation, along with careful inspection of histological and cytological findings, are mandatory to establish an accurate and final diagnosis.

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References