Management of Central Giant Cell Granuloma With Subcutaneous Denosumab Therapy

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Purpose: In recent years, the treatment of central giant cell granuloma (CGCG) has become focused on the inhibition of osteoclast differentiation and proliferation. Medications that were developed for the treatment of giant cell tumor of bone and bone resorption from metastatic skeletal disease have shown some success in the treatment of CGCG. The present report describes 2 cases of CGCG of the mandible that were treated effectively with subcutaneous denosumab.

Materials and Methods: Two cases of histologically diagnosed CGCG of the mandible were treated with monthly subcutaneous injections of denosumab 120 mg primarily or after intralesional corticosteroid therapy. Clinical and radiographic follow-ups were recorded over a period of 24 months (case 1) and 15 months (case 2).

Results: In the 2 cases, progressive radiodensity and osseous regeneration were noted 4 to 6 months after denosumab therapy was initiated. A decrease in lesion size and improvement in bone contour and facial symmetry were seen in the 2 cases.

Conclusion: The major radiographic, clinical, and histologic responses seen in these 2 cases suggest that denosumab may represent a viable alternative or adjunctive procedure to eliminate or decrease the extent of surgical intervention and morbidity in the treatment of CGCG. Future prospective studies with a larger sample would provide more comprehensive information about the long-term effects and possible adverse side effects of treating CGCG of the jaws with denosumab.

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Central giant cell granuloma (CGCG) of the jaws was first documented as "giant-cell reparative granuloma" by Jaffe[1] in 1953. Jaffe sought to differentiate these lesions from giant cell tumors that are seen mainly in the long bones of the skeleton. Giant cell tumors exhibit relatively aggressive clinical behavior, high rates of recurrence, and a potential for metastasis.[2,3] Although CGCGs of the jaws have no significant malignant potential, they can be locally aggressive, with a high recurrence rate, and produce cortical expansion, displacement of teeth, root resorption, and sensory alteration.[4,5] The term *giant-cell reparative granuloma* is seldom used because it remains questionable that it represents a reparative process.

Most cases of CGCG arise as a painless expansion of the alveolar bone and may be first recognized as

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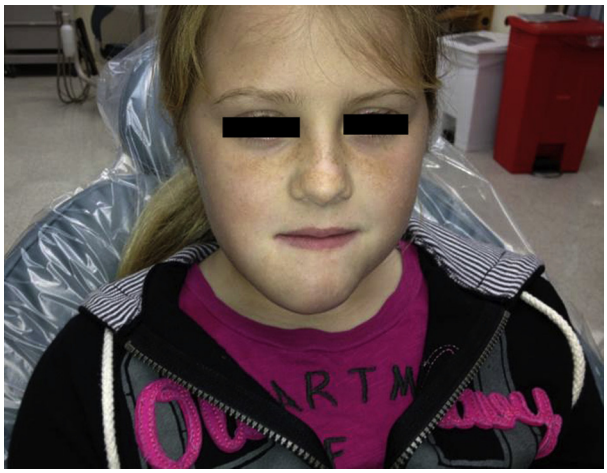

FIGURE 1. Case 1. Patient photograph at initial presentation. Frontal view shows facial asymmetry and chin displacement to the right side.

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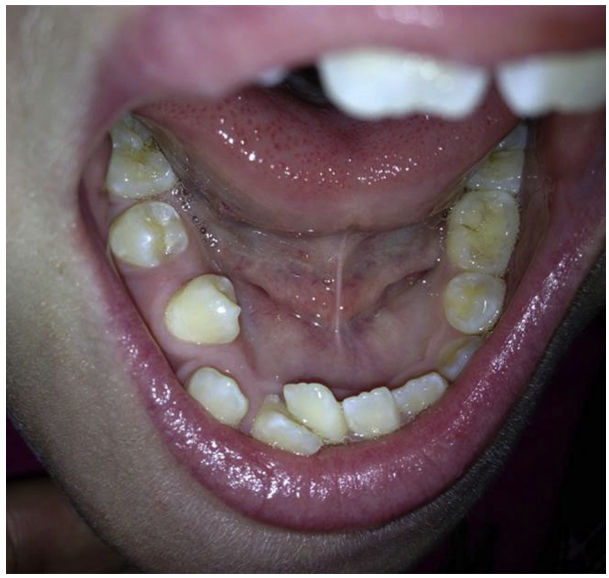

FIGURE 2. Case 1. Intraoral photograph showing labial and lingual expansion and displacement of the anterior mandibular teeth.

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radiolucencies found at routine radiographic examination. Occasionally, pain, paresthesia, or tooth displacement may be reported. Radiographically, CGCG can be unilocular or multilocular, with a potential to reach at least 10 cm, resorb adjacent tooth roots, and perforate cortical bone.[6] A classification of aggressive and nonaggressive giant cell lesions, based on clinical and radiographic parameters, characterizes aggressive lesions as larger than 5 cm, showing rapid growth, tooth displacement, root resorption, recurrence, and cortical perforation.[7,8] Histologically, CGCG may resemble the aforementioned giant cell tumor of bone, aneurysmal bone cyst, brown tumor of hyperparathyroidism, and giant cell lesions of cherubism, which contain multinucleated giant cells that are virtually identical to the multinucleated cells of CGCG. The multinucleated cells of giant cell tumor of bone contain antigenic properties and phenotypic markers that are similar to the mononuclear precursor cells that differentiate into osteoclasts.[9-11] Giant cell tumor of bone is thought to have 2 cell populations, including osteoclast-like giant cells and background stromal cells of osteoblastic origin.[12] The tumor cells in CGCG and other giant cell lesions express immunohistochemical markers for macrophages and osteoclasts, which suggests they arise from mononuclear precursor cells of the granulocyte and macrophage lineage.[13-15]

The most frequent treatment of CGCG is surgical curettage, which results in a recurrence rate of 11 to 49%.[16-19] Surgical resection with 0.5-cm margins is much more effective, resulting in a recurrence rate of 6% in 1 clinical study.[18] However, complete surgical resection may extensively compromise esthetics and function in some cases. The overall recurrence rate was found to be 26.3% in the largest review of CGCG in the literature.[5] The highest rates of recurrence are seen in tumors exhibiting aggressive clinical behavior, producing pain, paresthesia, and root resorption.[5]

Intralesional corticosteroid injections were introduced as a nonsurgical alternative treatment for CGCG in 1988.[20] Weekly corticosteroid injections resulted in complete resolution in 3 of 4 lesions over a period of 6 weeks in the first documented series of reported cases of CGCG treated in this manner.[21] Steroids inhibit bone resorption and induce apoptosis of osteoclasts.[22-24] Although some cases of CGCG respond well to corticosteroid therapy, the results are inconsistent and highly variable. Marx and Stern[25] reported that, in their experience, 65% of cases of CGCG treated with intralesional corticosteroids showed complete resolution, whereas 35% of cases did not respond at all or behaved more aggressively, requiring further curettage or resection. Recurrence most often was noted within 12 to 18 months after the initial treatment and was correlated with the size of the lesion.[25]

The multinucleated giant cells in CGCG and giant cell tumor of bone are known to express calcitonin receptors, which is the basis for calcitonin therapy of CGCG.[26,27] Calcitonin has been theorized to inhibit osteoclast function. Eight of 9 patients treated with subcutaneous calcitonin injections showed no decrease in lesion size after 6 months of therapy, but showed complete resolution after 18 months.[28] There appear to be a variable number of calcitonin receptors on the giant cells of CGCG, with only 56% of lesions