Innovative Management of Ossifying Fibroma of the Facial Bones Using Denosumab

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Ossifying fibroma (OF) of the jaws presents as a slow-growing, benign, fibro-osseous lesion that poses a risk for significant local destruction. Effective treatment of OF usually requires wide resection, which may lead to substantial morbidity. There are no alternative treatment options reported to date. Osteoclasts, a type of multinucleate giant cell that expresses receptor activator of nuclear factor-kappa B ligand (RANKL), play a major role in OF pathogenesis as well as in central giant cell granuloma (CGCG). CGCG is currently treated with denosumab, a human monoclonal antibody that inhibits bone lysis by binding to RANKL.

OF is a tumor composed of proliferating fibroblasts and osseous products, primarily affecting the mandible's molar region (in 70–90% of cases) in individuals aged 20–40 years of age. Diagnosis involves histological, clinical, and radiological examination; however, the lesions are often asymptomatic and found incidentally. This challenge contributes to delayed or a complete lack of treatment, which may lead to significant facial deformity due to extensive tumor growth [1].

Histologically, OF frequently consists of osteoclast-like giant cells that express receptor activators of nuclear factor kappa-B (RANK). The recruitment of osteoclast-like giant cells into the tumor is thought to be linked to RANKL expression, contributing to the tumor's aggressive osteolytic activity.

Managing OF poses challenges due to its variable clinical behavior. Surgical options range from curettage to resection, potentially causing significant facial deformity. Recurrence rates vary from 26.3% to 50%, where long-term follow-up with periodic examinations and radiographs is essential. Denosumab, a human monoclonal antibody (IgG2) that inhibits bone lysis by binding to RANKL, has shown promise in reducing and eliminating giant cells. This report presents, to the best of our knowledge, the first case ever of aggressive craniofacial OF successfully treated with denosumab.

PATIENT DESCRIPTION

A 37-year-old male was referred to the oral and maxillofacial unit with a complaint of painless swelling over the left side of his face for the past 6 months. The patient's medical history did not include any noteworthy incidents. The patient had no prior medical consultations or treatments related to this condition. An extraoral examination revealed a diffuse, firm, non-tender swelling on the left side of the midface, accompanied by paresthesia of the infraorbital nerve.

An intraoral examination revealed widespread swelling that extended posteriorly to the maxillary tuberosity above the left buccal vestibule. On fiberoptic laryngoscopy, a protrusion of the lateral wall of the nose on the left side, lined with normal mucosa, was seen. Computed tomography images revealed an extensive hypodense and hyperdense lesion affecting the left maxilla, maxillary sinus, orbital floor, and nasal cavity. The lesion broke through the walls of the maxillary sinus and the orbital floor, pushing the eye globe coronally. An open biopsy under general anesthesia revealed a mineralized matrix composed of woven and lamellar bone deposits with a deficiency of osteoclasts, along with a hypercellular stroma rich in fibroblasts. A diagnosis of OF was established. Due to the tumor's substantial size and the consequent aesthetic results on removal, it was decided to attempt denosumab treatment. The patient received nine 120 mg subcutaneous injection doses (Xgeva®, Amgen Inc., Thousand Oaks, CA, USA) following the standard treatment protocol for central giant cell lesions. Injections were administered

on days 1, 8, 15, and 29 of the treatment periods, with the remaining doses given monthly for 6 months. Prior to and throughout the treatment period, blood tests for C-terminal telopeptide, calcium, phosphate, vitamin D, alkaline phosphatase (ALP), and parathyroid hormone (PTH) levels were performed, with all values staying within normal limits. Throughout the treatment period, the patient was monitored with cone-beam computed tomography (CBCT) scans. Following the treatment conclusion, the patient was treated with alendronate orally for 6 months to eliminate the rebound side effects of denosumab discontinuation. Radiographically, the lesion's preliminary calcification was still visible after 2 months of treatment [Figure 1].

Twelve months after treatment completion, reshaping of the lesion was performed to address the remaining facial asymmetry, and a repeat biopsy was taken. Histopathological examination confirmed residual signs of OF with a significant presence of mineralized material and new bone formation. At the 24-month follow-up, the patient's condition remained stable, with no clinical changes in the residual lesion. Radiographically, the lesion appeared increasingly hyperdense, indicating continued new bone formation.

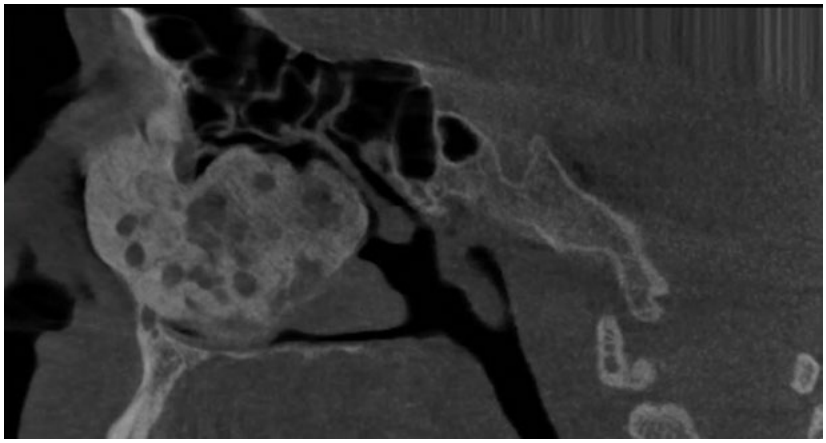
COMMENT

This report is the first case ever in which denosumab was used to treat OF. The study introduces a novel therapeutic approach to manage this challenging lesion. OF typically consists of a hypercellular fibrous stroma with mineralized bone or cementum-like material and is believed to originate from the pluripotent mesenchymal cells of the periodontal ligament [2]. It most commonly affects the posterior jaws in women aged 20–40 years [2,3], although our case involved a 37-year-old male.

Clinically, OF varies from asymptomatic swelling to symptoms like nasal obstruction, paresthesia, or sinusitis, depending on lesion size and location. Large lesions exhibit aggressive behavior, producing significant osseous destruction. In our case, the patient's main complaint was swelling. Pain was not reported; however, the patient did experience infraorbital paresthesia. Radiographically, lesions show mixed radiolucent-radiopaque patterns correlating with maturation. In this case, significant bony destruction and orbital involvement were noted.

Surgery remains the standard treatment, but recurrence and morbidity are major concerns [1]. To minimize morbidity, we applied denosumab, a monoclonal antibody targeting RANKL, inhibiting osteoclast activity. Denosumab has shown promise in other fibro-osseous or giant cell-rich lesions like CGCG [4]. Although not approved for OF, its off-label use was justified based on shared cellular mechanisms. This administration necessitates careful ethical consideration, including thorough patient counseling regarding the experimental nature of the treatment, potential risks, and the absence of long-term efficacy data. Given the mesenchymal cell similarities observed among other giant cells linked to fibro-osseous lesions, we applied the standard treatment protocol used for CGCG to our patient. The patient responded well, with radiographic evidence of new bone formation and no recurrence after 24 months. Alendronate was prescribed for 6 months post-treatment to prevent rebound bone turnover, based on DAPS study findings [5]. Importantly, no side effects or medication-related osteonecrosis of the jaw were observed during or after treatment. The clinical endpoint was defined by the stability of the lesion, absence of symptoms, and facial symmetry, while the radiologic endpoint was defined by progressive calcification and radiodensity consistent with new bone formation. These endpoints were reached and remained stable at the 24-month follow-up. An additional consideration

Figure 1. Cone-beam computed tomography imaging 24 months after therapy completion showing the calcification of the lesion



is the cost-effectiveness and accessibility of denosumab. While this drug offers a less invasive alternative to potentially disfiguring surgery, its high cost and limited availability in some healthcare systems may restrict widespread use, especially in resource-limited settings. A cost-benefit analysis may be warranted in the future to guide treatment decisions.

CONCLUSIONS

OF poses significant diagnostic and therapeutic challenges due to its variable clinical behavior and potential for recurrence. While traditional surgical treatments are effective, they are frequently accompanied by high morbidity and recurrence rates. This case report highlights the successful use of denosumab in treating an aggressive craniofacial OF, marking a significant step forward in managing these complex lesions. While further studies and long-term data are needed to evaluate the safety, cost-effectiveness, and role of denosumab in routine clinical practice, this case report provides promising evidence for its potential use.

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Capsule

Albumin orchestrates a natural host defense mechanism against mucormycosis

Pikoulas and co-authors uncovered a master regulatory role of albumin in host defense against Mucorales through the modulation of fungal pathogenicity. Initial studies identified severe hypoalb uminaemia as a prominent metabolic abnormality and an independent biomarker of poor mucormycosis outcome across three distinct cohorts of patients with mucormycosis. Notably, purified albumin selectively inhibits Mucorales growth among a range of pathogens, and albumin-deficient mice display susceptibility specifically to mucormycosis. The antifungal activity of albumin is mediated by the release of bound free fatty acids (FFAs). Albumin prevents FFA oxidation, which otherwise abolishes their antifungal properties, and sera from patients with mucormycosis display high levels of oxidized FFAs. Physiologically, albumin-bound FFAs suppress the expression of key virulence factors by inhibiting protein synthesis, the reby rendering Mucorales avirulent in vivo.

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Capsule

Long COVID involves activation of proinflammatory and immune exhaustion pathways

Long COVID (LC) involves a spectrum of chronic symptoms after severe acute respiratory syndrome coronavirus 2 infection. Current hypotheses for the pathogenesis of LC include persistent virus, tissue damage, autoimmunity, endocrine insufficiency, immune dysfunction, and complement activation. **Aid** et al. performed immunological, virological, transcriptomic and proteomic analyses from a cohort of 142 individuals between 2020 and 2021, including uninfected controls (n=35), acutely infected individuals (n=54), convalescent controls (n=24), and patients with LC (n=28). The LC group was characterized by persistent immune activation and proinflammatory responses for more than 180 days after initial infection compared with convalescent controls, including upregulation of JAK-STAT, interleukin-6, complement, metabolism and T cell exhaustion pathways. Similar findings were observed in a second cohort enrolled between 2023 and 2024, including convalescent controls (n=20) and patients with LC (n=18). These data suggest that LC is characterized by persistent activation of chronic inflammatory pathways, suggesting new therapeutic targets and potential biomarkers of disease.

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