

PHARMACOLOGICAL AND SURGICAL INTERVENTIONS FOR THE TREATMENT OF GIANT CELL TUMOR OF THE MANDIBLE; REPORT OF A CASE AFTER 5-YEAR FOLLOW-UP

MANDIBULA'NIN DEV HÜCRELİ TÜMÖRÜ TEDAVİSİNDE FARMAKOLOJİK VE CERRAHI TEDAVİ YAKLAŞIMLARI; 5 YILLIK TAKIP İÇEREN VAKA RAPORU

Yrd. Doç. Dr. Özgür ERDOĞAN*

Prof. Dr. Emin ESEN*

Prof. Dr. Metin YAVUZ**

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ABSTRACT

Giant cell lesions are uncommon tumors of the maxillofacial bones. The tumor may show aggressive or non-aggressive clinical behavior. Surgery is the main treatment approach. Pharmacological treatment options include calcitonin therapy, intralesional corticosteroid injection and interferon alpha therapy. In this article, we present 5 year follow up findings of a 30-year-old female patient with a giant tumor in her mandible, which was treated with a combination of intralesional corticosteroid injection and nasal calcitonin inhalation.

Key words: Giant cell tumor; Mandible; Case report.

ÖZET

Dev hücreli lezyonlar çene-yüz kemiklerinin nadir görülen tümörleridir. Tümör, agresif veya agresif olmayan klinik seyir gösterebilir. Cerrahi, temel tedavi yaklaşımıdır. Farmakolojik tedavi seçenekleri kalsitonin tedavisi, lezyon içi kortikosteroid enjeksiyonu ve interferon alfa tedavisini kapsar. Bu makalede, alt çenesinde dev hücreli tümör mevcut 30 yaşındaki bayan hastaya uygulanan lezyon içi kortikosteroid ve nasal kalsitonin inhalasyonu uygulamalarının 5 yıllık takip bulguları sunulacaktır.

Anahtar kelimeler: Dev hücreli tümör; Mandibula; Vaka raporu

Giant cell tumor is a mesenchymal neoplasm, which is mainly seen in long bones¹. Maxillofacial bones are rarely involved. Its relationship to central giant cell granuloma is controversial and some authors claim that these two lesions represent two different stages of the same process². Surgery is the main treatment for giant cell tumor and type of the surgery ranges from simple curettage to segmental resection based on the biological behavior of the lesion³. Pharmacological treatment options are calcitonin therapy, intralesional corticosteroid injection and interferon alpha therapy⁴⁻⁸. Radiotherapy has also been used for its treatment⁹.

Calcitonin therapy and intralesional corticosteroid injection have variable success rates for the treatment of the giant cell lesions of the jaws. In this case report, we present a 30-year-old female patient with a giant tumor in her mandible, which was

treated with a combination of intralesional corticosteroid injection and nasal calcitonin inhalation. The treatment approaches and the literature findings are presented in this report.

CASE REPORT

A 30-year-old female patient was referred to the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Çukurova University in June 2001. The patient had 6 previous operations due to recurrent masses in the maxilla and the mandible over an 8-year period. The initial mass had developed in the anterior maxillary region in 1993. The lesion had been curetted and was histopathologically diagnosed as "reparative giant cell granuloma". The subsequent masses had developed in the left maxillary molar, right maxillary anterior, right mandibular premolar, left mandibular molar and right maxillary molar regions

*Çukurova Üniversitesi, Dişhekimliği Fakültesi, Ağız-Diş-Çene Cerrahisi AD.

**Çukurova Üniversitesi, Tıp Fakültesi Plastik, Rekonstruktif ve Estetik Cerrahi AD.



respectively. All lesions had been curetted and the histological appearances were similar. The patient was otherwise healthy.

Clinical examination revealed a 2x3 cm expansile mass in the right mandibular premolar/canine region (Figure 1). The lesion was localized on the mandibular alveolar bone and was non-tender to palpation. The patient had significant parasthesia in both sides of the lower lip. A panoramic radiograph showed an irregular bone defect in the right mental area and another radiolucent lesion with regular borders in the left mental area (figure 2). Under local anesthesia, an incisional biopsy was performed from the lesions. Histologic appearances were similar for both lesions. The biopsy material was consistent with a neoplasm and was composed of lymphocytes, histocytes and young osteoid tissue in a vascular fibroblastic stroma. The lesions were diagnosed as giant cell tumor. The patient was evaluated for hyperparathyroidism and found free of the disease.

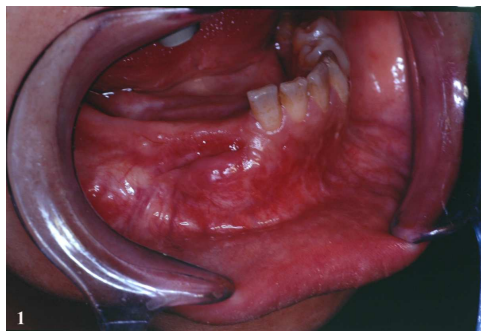


Figure 1: Initial intraoral photograph showing expansile mass at the right mandibular premolar/molar region

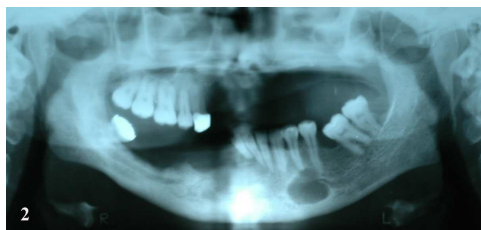


Figure 2: Initial panoramic radiographs showing radiolucent lesions in the right and the left mandibular premolar regions

Intranasal calcitonin therapy was selected as the treatment of choice. An inhalation dose of 200 units/day of salmon calcitonin was started. The therapy continued for 10 months. At the end of the

tenth month, neither clinical nor radiographical signs of any regression of the lesions were apparent. Additional intralesional corticosteroid injection was started. A mixture of 1 cc triamcinolone acetonide 4% (Kenacort-A, Bristol-Myers Squibb İlaçları Inc., Turkey) and 1 cc bupivacaine 0.5% (Marcaine, AstraZeneca, Turkey) was injected in each lesion one time per week. Access to the left-sided lesion was performed via the root canal of the first premolar tooth while the injection to the right-sided lesion was conducted transmucosally. After each injection, the canal was obstructed with sterile cotton, and zinc-eugenol cement.

The combined therapy/applications of corticosteroid and calcitonin were continued for 10 weeks. A purulent infection developed in the left-sided lesion at the tenth week, which was characterized with local swelling, pain and pus drainage. The corticosteroid injection was stopped and the patient was treated with oral antibiotic (amoxicillin 500 mg 3x1). The infection resolved after one week. The tumor in the right side enlarged approximately 1 centimeter in diameter during 1 year and it caused increased mobility in the mandibular incisor teeth (Figure 3).

Intranasal calcitonin therapy and additional intralesional corticosteroid injection were not found beneficial for the patient and surgery was planned. Under general anesthesia with nasotracheal intubation, the mandible was resected from the right third molar to the left first molar region by means of submandibular incision. The continuity defect was reconstructed with vascular, osseo-musculo-cutaneous fibula flap (figure 4). The patient was hospitalized for 3 weeks and discharged uneventfully. The patient was treated with a partial removable denture. The patient has been followed up for 5 years. During the follow-up period, there was no evidence of a recurrence.



Figure 3: Clinical photograph at the 11th month of the combined therapy of intranasal calcitonin and intralesional corticosteroid injection

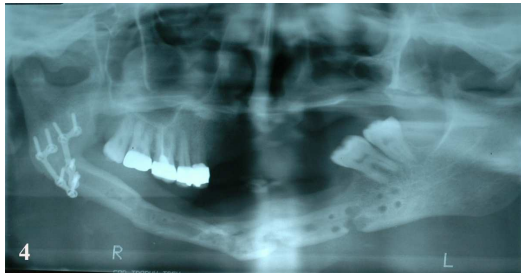


Figure 4: Postoperative panoramic radiograph

DISCUSSION

Although the giant cell tumor represents the characteristics of a true neoplasm, many authors agree that these lesions are the aggressive variants of central giant cell granuloma¹. Kratochvil et al² showed that giant cell tumor of the long bones and central giant cell granuloma of the jaws contain similar osteoclastic giant cells and both lesions response to different immunohistochemical agents in similar ways. They also concluded that both lesions represent the same disease process. Some authors use the term "giant cell lesion", since the non-aggressive variants are identical to those of central giant cell granulomas^{3,4,10}.

Giant cell tumor, central giant cell granuloma and giant cell lesions of the hyperparathyroidism have similar clinical and microscopic findings. A patient in this category should be initially evaluated to rule out the hyperparathyroidism. Non-surgical alternative treatments for giant cell lesions in a patient who is free of hyperparathyroidism include systemic calcitonin, intralesional corticosteroids, interferon alpha therapy and radiotherapy^{4,9}.

Controversial success rates of intralesional corticosteroid injection have been reported^{4,11,12,13,14}. The mechanism of action is not clear. It has been thought that giant cell tumor destructs bone by osteoclast or osteoclast-like multinucleated giant cells existing in its neoplastic stroma¹⁴. These cells produce lysosomal proteases such as cathepsin B, cathepsin L, β glucuronidase, lysozyme, and tartrateresistant acid phosphatase that cause bone resorption. Carlos and Sedeno¹¹ hypothesized that intralesional injection of steroids leads to inhibition of extracellular production of lysosomal proteases and cause steroidal apoptotic action on osteoclast-like cells thus producing a regression in the tumor size. They applied intralesional injection of triamcinilone acetonide to four patients

and found improvement and eventual resolution of the lesions. Kurtz et al⁴ reported a successful treatment with intralesional corticosteroid injection. Their patient was a 10-year old girl with a central giant cell lesion, which had been previously enucleated and recurred four months later in the anterior mandibular region. They applied a course of intralesional triamcinilone weekly of a total of 6 injections. After repeating the same procedure for 18 months, they reported complete resolution of the lesion.

The literature comprises of mainly successful results of intralesional corticosteroid administration^{4,11-13}. However, contrary results have also been reported. Pogrel et al⁷ stated that administration of intralesional corticosteroid to an 11-year old girl with biopsy-proved central giant cell granuloma caused more rapid increase in the tumor size. The authors terminated the therapy and treated the patient with systemic calcitonin. A report by Goldman et al.¹⁵ failed to show any effect of steroid injection for the treatment of giant cell lesion located at maxillary bone in a 16-year old girl.

We applied intralesional corticosteroid injections in accordance with the procedure described by Terry and Jacoway⁵. According to this protocol, an equal mixture by volume of triamcinilone acetonide and a local anesthetic is injected weekly lasting at least 6 weeks. The suggested dosage is 2 ml of mixture of the drugs for a lesion with 2-centimeter radiolucency. We prepared a 2 ml solution consisting of 1 ml triamcinilone acetonide and 1 ml bupivacaine for each lesion and repeated the injections for ten weeks. At the tenth week of the therapy, a purulent infection developed in the left-sided lesion. Since the injections were performed via the root canal of the first premolar, the bacterial plaque of the root canal, which had been probably pushed into the lesion, could be the cause of infection. After termination of the injections and a course of one-week antibiotic therapy, the infection ceased.

Calcitonin is produced by the C cells of the thyroid gland. It lowers the serum calcium level and has osteoblastic activity. Its mechanism of action on giant cell lesions is not well understood. It has been shown that giant cells of the lesion have calcitonin receptors⁷. Calcitonin may act directly on these receptors or its antiosteoclastic activity may lead to tumor's regression¹⁵. The first report concerning systemic calcitonin application in the treatment of

giant cell lesions of the jaw was by Harris⁶ in 1993. He treated 4 patients with calcitonin for 12 to 34 months and reported complete resolution in 3 of 4 patients. After this study, a number of successful reports have been published^{7,16,17,18}. Pogrel¹⁶ administered systemic calcitonin to 10 patients between the ages of 7-29 years. Eight of 10 patients were reported to be tumor free in 26-50 months of the follow-up period. One patient had recurrence after 26 months of the therapy, thus underwent an additional calcitonin therapy and subsequent curettage. The other patient, who had a poor compliance to the therapy, did not favorably respond to calcitonin treatment for 4 months and treated surgically.

Our patient preferred to receive calcitonin by nasal route. Its absorption by nasal route is proposed to be erratic and the absorption rate can vary between 30% and 100%.¹⁶ After 12 months, no clinical or radiographic improvement was evident in neither of the lesions. The right-sided lesion had buccolingual and mesiodistal growth and the mobility of the anterior mandibular teeth increased. It has been reported that subcutaneous injection of calcitonin is more effective than intranasal application⁷. This might be the reason of failure of calcitonin treatment in our patient. Our patient was also relatively older than previously reported patients were.

Our patient did not show any favorable response to the non-surgical treatment during 12 months. Because of potential risks of aggressive infiltration to the proximal tissues, distant metastasis and previous recurrences of the lesion, we choose to perform a radical surgery. The lesion was treated by a segmental mandibular resection with continuity defect. The defect was reconstructed with free fibula flap in the same session.

A relatively new treatment for giant cell lesions of the jaw is interferon alpha therapy. Kaban et al⁸ firstly applied this therapy to a 5-year old girl who had a rapidly growing giant cell tumor in her mandible. The patient was treated with interferon 2-alpha for 12 months. After 12 months, the tumor was reported to be completely resolved and at the third year of the follow-up, no evidence of a recurrence was apparent. Their hypothesis was that giant cell tumors are proliferative vascular lesions and therefore supposed to respond well to antiangiogenic therapy. In 2002, Kaban et al³ reported a series of 8 patients treated

with interferon alpha. All patients had aggressive type of giant cell tumor in their jaws. According to treatment protocol, the lesions were enucleated with preservation of teeth and nerves initially. At postoperative 48-72nd hours the patients were started to receive daily subcutaneous injection of interferon 2-alpha or 2-beta during an average period of 7.3 months. Seven of 8 patients completed the treatment to date of the report. All of the patients were reported to tolerate the treatment well with minor complications and were found tumor free in 0.5-6.7 years of follow-up period. This therapy was administered with moderate to good success rate by other studies as well.^{15, 19} Despite the promising results of this therapy, interferon alpha is associated with significant side effects and it should be considered if other therapeutic options failed.^{15, 20}

CONCLUSIONS

Treatment of giant cell lesions of the jaws still presents a clinical dilemma. Its relationship to hyperparathyroidism is not well known. It is hypothesized that even in the hyperparathyroidism-free patients, there is a circulating parathormon-like hormone inducing these lesions¹⁶. The success of currently applied pharmacological treatment including intralesional corticosteroid injection, systemic calcitonin therapy and interferon alpha therapy is obscure. Other potential promising, non-surgical treatment options are anti-VEGF (vascular, endothelial growth factor), osteoprogenitor, and Imatinip, a tyrosine kinase inhibitor used to treat chronic myeloid leukemia.²⁰⁻²² In this report, we described a patient with histological-proven mandibular giant cell tumor, who did not respond to nonsurgical treatments. Further studies are needed in order to find the optimal treatment regimen.

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- Yazışma Adresi**
Yrd. Doç. Dr. Özgür Erdoğan
Çukurova Üniversitesi, Dişhekimliği Fakültesi,
Ağız-Diş-Çene Cerrahisi AD.
Balcalı, ADANA
Tel: 322-3387330
Faks: 322-3387331
Email: ozgerdogan@yahoo.com

