Use of Oral Cyclophosphamide for Antiangiogenic Therapy in Recurrent Aggressive Giant Cell Lesion of the Mandible

Mandibulanın Rekürrent Agresiv Dev Hücreli Lezyonun Antianjiogenik Tedavisinde Oral Siklofosfamit Kullanımı

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ABSTRACT

Giant cell lesions account for approximately 7% of all benign lesion of jaw. The management of giant cell lesion of bone remains a difficult and frustrating problem for oral and maxillofacial surgeons, orthopedic surgeons, and oncologists. Although these tumors rarely metastasize, they are locally aggressive and destructive, and they have a high recurrence rate.

In this report, we present a case of aggressive giant cell lesion of the mandible. The lesion recurred 15 months following surgery. Treatment was further accomplished with curettage and antiangiogenic therapy using cyclophosphamide resulting in a dramatic reduction of lesion size. The lesion recurred 6 months later, necessitating radical surgery. However, reduced size of the lesion due to antiangiogenic therapy enabled a more conservative surgical approach.
INTRODUCTION

Giant cell lesions account for approximately 7% of all benign lesion of jaw\(^1\). Giant cell lesions may be encountered in patient ranging from 2 to 80 years of age, although more than 60% of all cases present before 30. About 70% of cases occur in the mandible. Lesions are more common in anterior portion of the jaws, and mandibular lesions frequently cross the midline\(^2\).

On the basis of the clinical and radiologic features, several investigators have suggested that central giant cell lesions of the jaws be categorized as non-aggressive lesions and aggressive lesions\(^1\). Non-aggressive lesions of the jaw respond favorably to simple curettage. Aggressive lesions have been reported to recur as high as 70% after enucleation of curettage\(^3,4\).

Giant cell lesions of jaw appear as radiologically well-defined unilocular or multilocular radiolucencies that can cross the midline\(^1\). The radiographic findings are not specifically diagnostic. Small unilocular lesions may be misdiagnosed for periapical granuloma or cysts. Multilocular giant cell lesions can not be distinguished from ameloblastoma or other multilocular lesions\(^2\).

The management of giant cell lesion of bone remains a difficult and frustrating problem for oral and maxillofacial surgeons, orthopedic surgeons, and oncologists. Although these tumors rarely metastasize, they are locally aggressive and destructive, and they have a high recurrence rate. Furthermore, there are no available biologic markers to predict the clinical behavior, and routine histologic techniques do not help the clinician determine prognosis\(^3,5\).

Kaban et. al. have hypothesized that giant cell lesions are proliferative vascular lesions and therefore would be expected to respond to antiangiogenic therapy\(^6\).

In this report, we present a case of aggressive giant cell lesion of mandible treated with curettage and antiangiogenic therapy using cyclophosphamide, after second recurrence.

CASE REPORT

In May 2001, a 23 year-old male patient referred to our clinic with a painless swelling on the right side of his face. Intraoral examination revealed a small, painless, non-ulcerative expansion of the right mandible behind the permanent first molar. Clinically, the patient was otherwise healthy. A panoramic radiograph showed a unilocular radiolucency at the angulus of the mandible with well-defined margins (Figure 1). The patient reported that the swelling had been present for two months without causing any discomfort. The patient was scheduled for surgery. Under local anesthesia, enucleation of the tumoral structure and curettage was performed, preserving teeth and nerves. The histological report revealed a giant cell lesion. The patient attended regular visits for a year without any signs of recurrence.

Recurrence was observed approximately 15 months after the surgery. The clinical findings were identical with those of the first visit. Incisional biopsy was taken under local anesthesia. Again, the histological report confirmed a giant cell lesion. In July 2002, the patient underwent extended surgery under general anesthesia. The final histological report described a vascular intrasosseous malformation and a giant cell lesion. Second recurrence of the lesion was detected in
December 2002. Computed tomography of the cranium with 3-dimensional bony reconstruction was obtained, which revealed an expansive bone lesion with lytic areas in the angulus of the right mandible (Figure 2).

Because the final histological findings included a vascular intraosseous lesion besides a giant cell lesion, an angiography was planned. Preoperative carotid arteriogram was performed, demonstrating the hypervascularity of the tumor (Figure 3). The tumor was mainly fed by the right facial artery, and it was embolized with 250-350µm polyvinyl alcohol particles. Postembolization angiogram showed total devascularization (Figure 4).

After angiography and embolization, final surgery including curettage was performed under general anesthesia. The histological report was identical. The patient received peroral cyclophosphamide (50 mg/day) during the postoperative 3 months. Computed tomography of the cranium with 3-dimensional bony reconstruction was repeated 3 months later, showing a small residual expansile bone lesion without any sign of recurrence (Figure 5).

Six months after antiangiogenic therapy, the progressive decrease in the size of the bone cavity stopped and a painful swelling began to grow. The patient was scheduled for radical surgery comprising segmental resection of the mandible.

DISCUSSION

The most common therapy of central giant cell lesion is surgery, ranging from simple curettage to resection. Neovascularization is a prerequisite for progressive growth of solid tumors and their metastases. This process is tightly regulated by a large number of proangiogenic and antiangiogenic factors such as Vascular Endothelial Growth Factor (VEGF), basic Fibroblast Growth factor (bFGF) and matrix-metalloproteinases. The inhibition of angiogenesis is an innovative therapeutic approach and could represent a powerful adjunct to traditional therapy of tumors.
Kaban et al. have hypothesized that giant cell lesions are proliferative vascular lesions and therefore would be expected to respond to antiangiogenic therapy. Dose-response effect of cyclophosphamide on VEGF 165/164-mediated angiogenesis using the rat mesenteric-window angiogenesis assay has been reported to suppress overall angiogenic response significantly. Giant cell lesions are also known to be richly vascular and, as a result, transcatheter endovascular embolization has been used alone and in combination with chemotherapy in the treatment of these lesions.

Aggressive giant cell lesions have been reported to have recurrence rates as high as 70% after enucleation of curetage. These tumors also have a proliferative vascular network as we shown in our case. Angiogenesis is essential for the growth, invasion, and metastasis of solid tumors. The inhibition of this process, or antiangiogenesis, is a promising therapeutic anti-cancer strategy. Several antiangiogenic compounds including interferon alpha, thalidomide, paclitaxel, etoposide, and cyclophosphamide are currently in preclinical or clinical development for the treatment of neoplasms. Antiangiogenic therapy using interferon alpha in combination with curettage results in a high rate of tumor control in aggressive giant cell tumors.

Recent preclinical studies have shown that frequent administration of low doses of chemotherapeutic drugs ("metronomic" dosing) can affect tumor endothelium and inhibit tumor angiogenesis, reducing significant side effects (e.g., myelosuppression) involving other tissues, even after chronic treatment. Studies have shown that continuous low-dose therapy with various chemotherapeutic drugs including cyclophosphamide may have a highly selective effect against cycling vascular endothelial cells, and may be relevant to the use of continuous or frequent administration of low doses of certain types of drugs as an optimal way of delivering antiangiogenic therapy.

Although human studies are rare for powerful anti-angiogenic therapies, preliminary results
with different anti-angiogenic agents in different cancers are promising, especially when antiangiogenesis is used in combination with current cancer treatment modalities including curettage, as performed in our case.\textsuperscript{17,18}

In selected cases, antiangiogenic therapy should be considered for treatment of aggressive recurrent giant cell tumors, in combination with curettage. Combined treatment may successfully control growth of the tumor. This is especially important in the viewpoint of reduced tumor size, facilitating conservative radical surgery and reduced morbidity. Oral cyclophosphamide as an antiangiogenic agent may be alternative to interferon alpha in this setting. Oral cyclophosphamide may also be an alternative regimen in patients who can not tolerate or are resistant to interferon alpha treatment. Further prospective studies in patients with aggressive giant cell tumors are needed to evaluate effectiveness of oral cyclophosphamide.

REFERENCES


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