Denosumab Treatment for a Residual Giant Cell Tumor of the Clivus: A Case Report and Review of the Literature

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ABSTRACT:

OBJECT Giant cell tumors are a locally aggressive primary bone neoplasm of osteoclast-like cells. These lesions largely occur in the epiphyses of long bones, but there have been rare reports of occurrence in the pelvis, spine, or skull. Of those located in the skull, involvement of the clivus has been rarely reported.

METHODS We present a case of an 18-year-old presenting with a third nerve palsy, found to have a lytic lesion of the upper clivus that was primarily treated with endoscopic endonasal resection. Her third nerve palsy resolved post-operatively, and subsequent histopathologic analysis revealed a giant cell tumor (GCT). 6 month post-operative MRI revealed progression of residual disease for which she was treated with adjuvant Denosumab. This treatment resulted in a significant decrease in the tumor size. She subsequently underwent proton beam radiation.

RESULTS At 1 year post surgery, the patient's MRI remained stable after completing Denosumab and proton therapy. She was neurologically intact and had no issues from her treatment.

CONCLUSIONS Denosumab has demonstrated anti-GCT efficacy. In combination with proton therapy, it has the potential to spare a young, vulnerable population from adverse long-term effects of traditional adjuvant radiation therapy. To the best of our knowledge, this is the first report of the use of Denosumab in the treatment of GCT of the clivus in the United States.

INTRODUCTION:

Giant cell tumors (GCT) are primary bone neoplasms that mainly affect young adults. These tumors are relatively rare and represent about 4.0-9.5% of all bone tumors[1]. While classically, GCTs are benign, they can be locally aggressive and rarely undergo malignant transformation[2,3]. Most GCTs present within the long bones of the extremities, such as the distal femur, proximal tibia, or distal radius; however, there have been rare reported cases involving the pelvis, spine, or skull[1].

The low incidence of skull base GCTs not only makes the definitive diagnosis more difficult, but also presents challenges as far as recommended treatments. There are no defined guidelines for the treatment of these lesions, but the mainstay of treatment has been gross total surgical resection and drilling of surrounding healthy bone[2]. Due to the challenging location of these tumors, however, complete resection is often not possible, which can result in residual or recurrent tumor. This dilemma highlights the importance of adjuvant therapy for GCTs[1]. Radiotherapy, with a dose of 45-60 Gy, has historically been used as adjuvant therapy in the treatment of GCTs. [1,3-6]. Because these tumors typically present in young adults, the long-term side effects of radiation become more problematic in this patient population.

Recent studies on GCTs of bone have shown that the secretion of receptor activator of nuclear factor kappa-B ligand (RANK-L) by osteoblast-like stromal cells stimulates the production of osteoclast-like giant cells. This up-regulation of osteoclast-like giant cells promote osteolysis[1]. Denosumab is a recently introduced monoclonal antibody that targets RANK-L to inhibit the osteolytic activation of these osteoclast-like cells, and has shown benefit for the treatment of

GCTs of the long bones[1]. Additionally, there have been two reports of its use in the treatment of skull base GCTs[1,7]. We describe a case of adjuvant Denosumab therapy in combination with proton therapy for the treatment of a residual clival GCT.

METHODS:

An otherwise healthy 18-year-old female presented to our hospital with a 1-month history of diplopia and headaches. Physical examination revealed a partial right oculomotor nerve palsy presenting as ptosis, anisocoria without afferent pupillary defect, and lateral deviation of the pupil. There were no symptoms of pituitary abnormality and pituitary hormone labs were within normal limits. Computed tomography (CT) of the skull base showed a lytic lesion of the dorsum sella and the upper clivus, with an exophytic component into the sphenoid sinus (Fig 1A). Magnetic resonance imaging (MRI) showed a heterogeneously enhancing, hyperintense lesion in the upper clivus that displaced the sellar contents anteriorly and superiorly, extending toward the right cavernous sinus (Fig 1B and C).

Due to concern that this represented a primary skull base tumor, resection was recommended via an expanded endonasal endoscopic approach. A routine endonasal approach to the sella and upper clivus was performed. The tumor was curetted out of the bone until all observable soft tissue had been removed. The portion of the tumor in the sphenoid sinus was also removed and sent for frozen sectioning. The dura mater of the sella turcica and posterior fossa were identified and appeared grossly intact. Tumor was progressively resected until the dorsum sella was completely removed, which was confirmed with a 30 degree angled endoscope. The only remaining bony margin was located inferiorly and this was subsequently removed using a 360 degree bone cutting tip on a Sonopet ultrasonic aspirator until solid, normal-appearing bone was identified. Following the completion of maximal resection, final inspection revealed no signs of cerebrospinal fluid leak. Histopathologic analysis confirmed the diagnosis of Giant Cell Tumor. Post-operatively, the patient did well. She was monitored in the ICU the night after surgery, and her head CT the following morning showed no acute findings. She was discharged home on post-operative day 1.

At 2 month post-operative follow-up, her diplopia, ptosis and headaches had resolved. Her right pupil remained 2mm larger than the left, but still briskly reactive. She had no other neurologic deficits. Follow-up MRI at 3 months post-operatively revealed a small amount of residual tumor in her right cavernous sinus, as well as possible small progression posterior to this remnant (Fig 1D and E). At this time, it was decided to conservatively watch the patient and have her return for another MRI in 3 months. At 6 months, post-operatively, her MRI showed further progression of her residual tumor (Figure 2A and B). This was most notable with posterior growth towards the pons. As this residual tumor was determined to be unresectable, she was referred for adjuvant treatment with Denosumab. The patient underwent 24 cycles of Denosumab over the course of 5 months. She tolerated her treatment well without any serious side effects.

MRI at 2 months after initiating Desonumab, showed a significant decrease in the sellar lesion with improvement in the compression of her pons (Figure 2C and D). Because she had shown signs of tumor growth prior to starting Desonumab, she was referred for proton beam radiation. The patient underwent 28 treatments at a dose of 50.51 D_{RBE} over the course of 37 days, and

then had 5 boost doses at 9.08 D_{RBE} over a 5 day period. Repeat MRI 1 year out from her initial surgery showed a stable size in the lesion when compared to after she initiated Desonumab (Figure 2E and F). She continued to feel well and was neurologically intact 1 year after surgery.

DISCUSSION:

Giant cell tumors of bone are rare primary osseous neoplasms that usually affect the epiphyses of the long bones of the extremities, but can rarely affect areas of the axial skeleton such as the spine and skull[1,8]. Overall, this lesion is more common in females, and usually occurs in the young adults. While generally considered a benign tumor, metastasis to the lungs can be seen in up to 5% of cases, and transformation to malignant sarcoma has been described[1-3]. The most common presenting symptoms for GCTs of the clivus are headache, diplopia, and cranial nerve palsies with normal endocrinologic function[1]. Our patient experienced a similar presentation.

Recent studies on the pathophysiology of giant cell tumors of the bone have revealed that RANK-L secretion by osteoblast-like stromal cells is involved in the induction of osteoclast-like cell production, as well as stimulation of osteolytic activity [9]. Gori et al. showed that undifferentiated marrow stromal cells with high levels of RANK-L support osteoclastogenesis [10]. Because GCT's are osteolytic tumors, inhibiting RANK activation with a RANK-L antibody, could prevent progression of disease. Denosumab, a new monoclonal antibody that targets RANK-L, has emerged as an effective chemotherapeutic treatment for residual skull base GCTs. This therapy has been approved in many countries and recent data suggests that it may even be able to serve as an alternative therapy in residual GCT's[1]. As this is a novel therapy, optimal length of treatment has not been determined. However, it has been concluded that therapy administration should not exceed 2 years as long-term use of Denosumab appears to increase the risk of osteonecrosis of the jaw, bone fractures, and severe hypocalcemia in those with renal dysfunction[1,7]. In the case of our patient, 24 cycles over the course of 5 months proved to be an effective treatment protocol as it decreased the size of her recurrent tumor.

Currently, there are no definitive treatment recommendations for skull-base GCTs, but the mainstay is function-preserving surgery[2]. The ideal treatment for GCTs is complete resection with wide surgical margins; however, the location of skull-base GCTs can make this difficult[7]. Often, such tumors are treated with subtotal or partial resection with adjuvant therapy, which historically has been standard radiotherapy with a dose of 45-60 Gy[1,3-6]. Although radiotherapy has been used as adjuvant therapy in many cases, its potential risk and effectiveness are still areas of debate. Prior research has shown malignant transformation of GCT's treated with standard radiation in up to 11% of cases [11,12]. Due to the small number of these cases, the overall effectiveness of standard radiation is still unclear [1,3]. Additionally, standard radiation in young individuals has many associated risks, including secondary malignancies, lymphedema, muscle atrophy and decreased joint motion[13]. Because of these risks, proton therapy offers an alternative radiation option with lower systemic risks. Proton radiotherapy continues to show safety and effectiveness in treating tumors of the skull base, especially in younger patients [14-16]. In the case of our patient, proton therapy was used due to her young age and with the hope of avoiding long-term complications.

Complete resection of tumor with wide margins is the optimal treatment for GCTs of the clivus. Unfortunately, this is not possible in most cases due to their challenging location. The difficulty of complete resection and the high rate of recurrence, especially from incomplete resection, highlight the importance of adjuvant therapy in the treatment of these tumors. Although previously approved for post-menopausal osteoporosis, Denosumab received FDA approval in 2013 to treat unresectable GCTs. The most recent data on the use of this adjuvant monoclonal antibody therapy is showing promise, but further investigating is necessary to show definitive benefit.

CONCLUSION:

Due to their challenging location, clival GCT's are often unable to be completely resected, highlighting the need for adjuvant treatment options. Denosumab is an emerging chemotherapeutic treatment for residual Giant Cell Tumors. Further studies are needed to show the maximum benefit and appropriate treatment protocol for Denosumab in the treatment of GCTs of the clivus.

Figure 1: Initial Head CT showing lytic lesion of the dorsum sella and upper clivus (A). Preoperative axial and sagittal MRI brain with contrast showing a heterogeneously enhancing, hyperintense lesion in the upper clivus (B and C). 3 month post-operative axial and sagittal MRI brain with contrast showing a small amount of residual tumor in her right cavernous sinus, as well as possible small progression posterior to this remnant (D and E).

Figure 2: 6 month post-operative axial and sagittal brain MRI with contrast showing further progression of her residual tumor (A and B). Axial and sagittal brain MRI with contrast 2 months after initiating Denosumab therapy, which showed a significant decrease in the size of her residual tumor (C and D). 1 year post-operative brain MRI with contrast showing stable size of tumor since completing Denosumab therapy.

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