Giant cell tumors of the clivus: Case report and literature review

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INTRODUCTION

Giant cell tumors (GCTs) are generally benign, locally aggressive lesions that are typically located in the metaphysis of long bones. GCTs of the skull are rare and constitute <1% of all reported bone GCTs. These tumors preferentially involve the sphenoid and temporal bones.[11] Clival GCTs are rare with only eight cases reported to date. Furthermore, malignant clival GCT is quite rare and difficult to treat because of its location, high vascularity, and resistance to treatment.[10] Herein, we report an uncontrolled clival GCT despite repeated surgery and radiation, and review the literature, focusing on their treatment. Moreover, we first showed a high MIB-1 index, which implied malignant transformation of GCT.

CASE DESCRIPTION

A 25-year-old man experienced double vision for 1 month. He had no history of trauma or surgery. Physical examination revealed overall good health. Neurological examinations revealed right abducens nerve palsy. Motor and sensory examinations including cerebellar tests were normal with full cooperation and orientation. Results from laboratory tests conducted on admission, which included blood biochemical analysis, complete blood count, pituitary function, and tumor markers, were normal.

Computed tomography (CT) demonstrated a homogeneously enhanced mass (5.1 cm × 3.1 cm × 4.9 cm) in the clivus [Figure 1a and b]. The mass was isointense...
and hypointense on T1- and T2-weighted magnetic resonance imaging (MRI), respectively [Figure 1c and d]. Gadolinium-enhanced MRI revealed a homogeneously enhanced tumor extending into the brainstem [Figure 1e]. Three-dimensional (3D) CT angiography showed feeder arteries arising from the bilateral meningo-hypophyseal trunks (MHTs) [Figure 1f]. Preoperative embolization was not conducted owing to the risk of internal carotid artery (ICA) migration of embolic materials. A neuronavigation-guided operation was performed via the endonasal endoscopic transsphenoidal approach (EEA). The tumor was yellowish gray and bled profusely [Figure 2a and b]. Partial resection was performed because of massive intraoperative bleeding from the feeding artery (850 mL; [Figure 2b]). Histopathological analysis revealed a cellular tumor comprised of osteoclastic giant cells and stromal cells [Figure 2c]. Postoperative MRI showed partial resection [Figure 2d]. The MIB-1 index was 4.2%. One month after the operation, the patient received 3D conformal radiotherapy at a dose of 50 Gy delivered in 25 fractions. Two months after the initial surgery, MRI confirmed gradual postradiation tumor regrowth [Figure 2e]. The tumor gradually increased in size and eventually invaded the brainstem, leading to brainstem edema [Figure 2f]. Therefore, a second operation was planned; however, because of massive intraoperative bleeding during the previous operation, preoperative angiography was performed before surgery. Angiography revealed weak tumor staining, which may have been caused by radiotherapy [Figure 3a and b]. Seven months after the first surgery, we used the EEA for the epidural lesion. The tumor was fibrotic and there was slight intraoperative bleeding [Figure 3c]. Thereafter, 1 month after the second surgery, we performed the anterior transpetrosal approach (ATPA) for the subdural lesion [Figure 3d]. Although blood control was good owing to MHT interruption by this approach, the tumor was tightly adhered to the brainstem, and we performed a partial resection [Figure 3e]. Histopathological analysis revealed mitotic spindle cell proliferation [Figure 3f]. The MIB-1 index was 26.3%. Postoperatively, the patient had right hemiparesis and died 19 months after the second operation because of respiratory dysfunction due to tumor regrowth.

Informed consent was obtained from this patient.

DISCUSSION

Only 3–7% of all primary bone neoplasms manifest as GCTs, which are relatively rare.[3] They commonly originate in the epiphysis of long bones such as the distal femur, proximal tibia, and distal radius; they are rare in the cranium.[4] Cranial GCTs tend to occur in the skull, and tumors found at the skull base frequently involve the sphenoid bone.[5,13] Moreover, clival GCTs are extremely rare. Wolfe et al. first described a surgically treated clival GCT in 1983; only eight cases have been
reported since. We summarize 9 clival GCTs including our case [Tables 1 and 2]. The patients’ age at diagnosis ranged from 9 to 62 years, with 5 male and 4 female patients. Major symptoms included headaches owing to high intracranial pressure and diplopia caused by abducent nerve palsy. The symptoms lasted for 1–6 months. The tumor size (maximum diameter) ranged from 30 to 76 mm leading to elevated intracranial pressure. In most cases, including ours, clival erosion, and a homogeneously enhanced tumor were observed on CT and Gadolinium-enhanced MRI, respectively. Although feeding arteries were not described in previous reports, we observed that the MHT arteries supplied the tumor.

Some papers reported that total resection could enable a reduction in GCT recurrence. However, because of...
extensive intraoperative bleeding during the clival GCT surgeries, complete resection was considered difficult (complete resection 22.2%, 2/9). Moreover, in our case, radical resection was hindered by massive bleeding from the feeding artery, which originated from the ICA. Many surgical approaches, including the EEA, frontal craniotomy, and transmaxillary approach, have been utilized for treating clival GCTs. We performed the EEA during the first and second surgeries and the ATPA for the third surgery. Partial resection was achieved via EEA, subtotal (transsphenoidal approach) (57.6 CGE/32 Fr) during the first and second surgeries and the ATPA for the third surgery. Partial resection was achieved via EEA, subtotal (transsphenoidal approach) (57.6 CGE/32 Fr) during the first and second surgeries and the ATPA for the third surgery. Partial resection was achieved via EEA, subtotal (transsphenoidal approach) (57.6 CGE/32 Fr) during the first and second surgeries and the ATPA for the third surgery. Partial resection was achieved via EEA, subtotal (transsphenoidal approach) (57.6 CGE/32 Fr) during the first and second surgeries and the ATPA for the third surgery. Partial resection was achieved via EEA, subtotal (transsphenoidal approach) (57.6 CGE/32 Fr) during the first and second surgeries and the ATPA for the third surgery. Partial resection was achieved via EEA, subtotal (transsphenoidal approach) (57.6 CGE/32 Fr) during the first and second surgeries and the ATPA for the third surgery. Partial resection was achieved via EEA, subtotal (transsphenoidal approach) (57.6 CGE/32 Fr) during the first and second surgeries and the ATPA for the third surgery. Partial resection was achieved via EEA, subtotal (transsphenoidal approach) (57.6 CGE/32 Fr) during the first and second surgeries and the ATPA for the third surgery. Partial resection was achieved via EEA, subtotal (transsphenoidal approach) (57.6 CGE/32 Fr) during the first and second surgeries and the ATPA for the third surgery. Partial resection was achieved via EEA, subtotal (transsphenoidal approach) (57.6 CGE/32 Fr) during the first and second surgeries and the ATPA for the third surgery.

### Table 1: Clinical characteristics and outcome of clival giant cell tumor cases reported in English literature

| Author, year | Age (years), sex | Location | Symptoms | Duration | Neurology | Size (cm) | CT | MRI | BSA | Angiography |
|--------------|-----------------|----------|----------|----------|-----------|-----------|-----|-----|-----|-------------|
| Wolfe et al., 1983 | 16, female | Clivus | Headache, diplopia, visual disturbance | 4-7 weeks | NA | NA | NA | NA | NA | NA |
| Kattner et al., 1998 | 9, female | Clivus | Headache, diplopia | 1 month | CN VI palsy | NA | Bone erosion | Enhanced | – | NA |
| Zorlu et al., 2006 | 14, female | Clivus | Headache, diplopia | 2.5 months | None | 6×4×3.5 | NA | Enhanced | – | NA |
| Gupta et al., 2008 | 17, female | Clivus | Headache, diplopia, amenorrhea, visual disturbance | 6 months | CN II atrophy, CN VI palsy, CN V disturbance | 7.6×5.4 | Bone erosion | Enhanced | – | NA |
| Sasagawa et al., 2012 | 26, male | Clivus | Headache, diplopia | NA | CN VI palsy | 3×3 | Bone erosion | Enhanced, cystic | + | ICA dislocated |
| Iacoangeli et al., 2013 | 31, male | Clivus | Headache, diplopia | NA | CN VI palsy | NA | Bone erosion | Enhanced | – | NA |
| Roy et al., 2013 | 19, male | Clivus | Headache, facial hypesthesia | 6 months | CN V disturbance | 5.6×3.6×3.5 | Bone erosion | NA | – | NA |
| Agrawal et al., 2014 | 62, male | Clivus | Headache, diplopia | 3 months | CN VI palsy | NA | NA | Enhanced | – | NA |
| Present case | 25, male | Clivus | Diplopia | 1 month | CN VI palsy | 5.1×3.1×4.9 | Bone erosion | Enhanced | + | Feeding artery (MHT) |

*Progressive. CT: Computed tomography, MRI: Magnetic resonance imaging, BSA: Brainstem adhesion, CN: Cranial nerve, NA: Not available, ICA: Internal carotid artery, MHT: Meningohypophyseal trunk.

### Table 2: Surgical outcomes of clival giant cell tumor cases reported in English literature

| Author, year | Treatment (approach) | Intraoperative finding | Recurrence | Outcome | Follow-up (months) | MIB1 |
|--------------|----------------------|------------------------|------------|---------|--------------------|------|
| Wolfe et al., 1983 | Partial (transseptal biopsy and decompression) → postoperative radiation | NA | – | Alive with tumor | 96 | NA |
| Kattner et al., 1998 | Biopsy (transsphenoidal approach) → subtotal (transsphenoidal approach) → postoperative radiation (57.6 CGE/32 Fr) | NA | – | Alive with tumor | 12 | NA |
| Zorlu et al., 2006 | Subtotal (transsphenoidal approach) → recurrence (3 months) → EBRT (60 Gy/30 Fr) → nasal bleeding → removal of intranasal tumor | NA | + | Alive with tumor | 24 | NA |
| Gupta et al., 2008 | Subtotal (Le Fort I) → postoperative radiation (45 Gy/25 Fr) → EBRT (60 Gy/30 Fr) → nasal bleeding → removal of intranasal tumor | Moderate vascularity | – |Alive with tumor | 24 | NA |
| Sasagawa et al., 2012 | Subtotal (transsphenoidal approach) → postoperative radiation (50 Gy/25 Fr) → recurrence → subtotal (osteosarcoma) → intranasal tumor → embolization → lung metastasis | High vascularity | + | Death | 9 | 10% |
| Iacoangeli et al., 2013 | Total (EEA) | ICA rupture | – | Alive without tumor | 72 | NA |
| Roy et al., 2013 | Total (Le Fort I) → radiotherapy (45 Gy) | High vascularity | – | Alive without tumor | 18 | NA |
| Agrawal et al., 2014 | Subtotal (bifrontal approach) | NA | NA | NA | NA | NA |
| Present case | Subtotal (EEA) → postoperative radiation → regrowth → subtotal (EEA, ATPA) | High vascularity, brainstem invasion | + | Death | 31 | 4.2% → 26.3% |

ATPA: Anterior transpetrosal approach, CDDP: Cisplatin, EBRT: External beam radiotherapy, EEA: Endonasal endoscopic transsphenoidal approach, ICA: Internal carotid artery, NA: Not available, MHT: Meningohypophyseal trunk.
because of massive intraoperative bleeding; therefore, postoperative radiation therapy was performed. During the ATPA, we could ligate the feeding artery from the MHT and control intraoperative bleeding. Based on this fact, we believe that bleeding control could have been more effective by performing the ATPA before the EEA. Although we were able to observe the prepontine cistern via the ATPA, the tumor was tightly adhered to the brainstem and could only be resected partially. Only two cases, including ours, have shown brainstem adhesion.

Radiation therapy has been performed for seven residual tumors. In most cases, the tumor was stable for >1 year. However, two cases including ours showed malignant transformation, leading to resistance to radiation therapy. Sasagawa et al. reported a secondary malignant clival GCT with an MIB-1 index of 10%. In our case, the MIB-1 index increased from 4.2% to 26.3% at recurrence. Although other reports have not analyzed the MIB-1 index, it might be an indicator for malignant transformation. This would be natural history, not induced by radiation because of its short duration of 7 months in our case. Whereas <2% of extracranial GCTs become malignant, the malignant transformation of intracranial GCTs is exceptionally rare.

Chemotherapy has not been performed for clival GCTs and has rarely been evaluated in other skull base GCTs. Yamamoto et al. reported two cases of cranial base GCTs that responded well to chemotherapy and showed regression on periodic CT scans. Denosumab, a fully human monoclonal antibody against RANKL, was effective for treating extracranial GCTs. Such chemotherapeutic agents should be considered for the treatment of malignant clival tumors, where radical resection is complicated.

**CONCLUSIONS**

It is challenging to treat clival tumors because of their location, vascularity, and potential malignant transformation. Angiographic assessment is important in order to control intraoperative bleeding. Pathological assessments such as the MIB-1 index are required for further investigation of the biological properties of clival GCTs.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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