**Unresectable Clival Giant Cell Tumor, Tumor Control With Denosumab After Relapse: A Case Report and Systematic Review of the Literature**

**Maria Grazia Pionelli, MD,* Sebastian D. Asafet, MD,* Elisa Tirtei, MD,* Anna Campello, MD,* Gianpaolo Di Rosa, MD† and Franca Fagioli, MD***

**Summary:** Giant cell tumors (GCTs) of the skull base are rare entities. Although considered histologically benign, GCTs are locally aggressive with a high rate of local recurrence. The present case describes a 14-year-old girl with a clival GCT who underwent long-term therapy with denosumab after local relapse. To our knowledge, it is the second case described with a follow-up term > 2 years from the start of denosumab and who did not receive any other adjuvant treatment besides denosumab. The patient achieved a local control of the disease. According to the few available data, radical excision with adjuvant therapy helps in long-term control in uncommon sites, such as the skull. However, the definitive treatment is still controversial because of their rarity and few follow-up data. The present case highlights the benefit of denosumab and its safety as long-term therapy and contributes to the existing literature with analysis and evaluation of the management strategies and prognosis.

**Key Words:** GCT, clival bone, skull base, pediatric oncology

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**BACKGROUND**

Giant cell tumor (GCT) is a histologically benign but locally aggressive bone tumor that occurs mainly in young adults with a peak incidence in the third and fourth decades of life.1,2 It most commonly affects the metaphysis of the long bones and rarely manifests in other anatomic sites, such as the pelvis, spine, or skull. Among GCTs of the skull, primary GCTs involving the clivus3 are extremely rare with only a few cases reported to date. Clival GCTs typically manifest with symptoms because of the compression of the cranial nerves. Because of their rarity and challenging location, there are no standard treatments for clival GCTs. A complete surgical resection is not always feasible with a high risk of local recurrence; therefore, the establishment of adjuvant treatments and strategies is essential to enhance local control and quality of life.4 Denosumab, a human monoclonal antibody to receptor activator of nuclear factor kappa B ligand (RANKL), known to be overexpressed in GCT, has gained a firm position in the systemic treatment of unresectable GCTs.5,6 Herein we report a juvenile case of GCT of the clivus where the patient demonstrated long-term tumor control with denosumab. We refer to the existing literature on GCTs with a review of the clinical characteristics, natural history, and treatment options.

**CASE PRESENTATION**

A 14-year-old girl presented to the hospital reporting a gradual loss in the clarity of her vision that had started out with blurred vision followed by ptosis and diplopia and had got progressively worse over a 2-week period. She also complained of an intermittent headache over the past 4 months. Her medical history was unremarkable, except for adenotonsillectomy surgery performed three months earlier. The neuroradiological examination assessed a severe reduction in visual acuity and a visual field defect in her left eye, partial left oculomotor nerve (CN III) palsy presenting as ptosis and anisocoria with afferent pupillary defect, partial trochlear nerve (CN IV) palsy and complete abducens (CN VI) nerve palsy. A computed tomography scan (CT) at the base of her skull showed a large hyperdense lesion within the sella turcica extending into the suprasellar region with bone erosion of the clivus and sphenoid bone, rare cystic elements, and some calcifications. Magnetic resonance imaging (MRI) of the brain revealed a lesion of 3.5×5.5×5.3 cm extensively occupying the clivus and invading the sella with displacement of the pituitary gland to the right (Fig. 1A). Her laboratory examinations were normal, including pituitary function tests. As a consequence of these clinical and radiologic conditions, the patient underwent endoscopic endonasal surgery with a subtotal resection to confirm the pathologic diagnosis and obtain volume reduction. Postoperative CT scan and MRI showed a minimal residual tumor most notable in the superior portion of the clivus and toward the left suprasellar cistern. The histologic examination revealed that the tumor comprised spindle-shaped mononuclear stromal cells with moderate mitotic activity (8 to 10 mitoses per 10 high-power fields) and irregularly distributed multinucleated osteoclast-like giant cells (containing up to 15 to 20 nuclei). Immunohistochemistry demonstrated a strong nuclear expression of H3F3A protein (Ab anti histon H3.3G34W) within GCT, confirming it as GCT of the bone. Postoperatively, the patient’s clinical course improved. Despite no evidence of hypocorticism, a replacement steroid therapy was recommended. The patient was then referred to our institution for further evaluation and treatment. A lung CT scan was negative for metastases and a dental assessment was revealed as normal. An ophthalmological evaluation demonstrated an improvement in her vision but persistence of left accommodation deficiency and partial left abducens nerve palsy. The patient was then referred for molecular-target therapy with denosumab and subsequent re-evaluation. She received 120 mg of subcutaneous denosumab every 4 weeks, with additional doses administered on Days 8 and 15 during the first month of therapy. She also took daily calcium and vitamin D supplements and her serum calcium level was checked regularly. The patient had a further MRI after 2 months of denosumab therapy with initial response. Taking the radiologic data into consideration, after a multidisciplinary evaluation, it was decided to continue treatment with denosumab. An MRI at 6 months of denosumab therapy showed marked reduction in size and enhancement of the clival lesion (Fig. 1B). Given the good
response to the treatment, a second surgery was planned with the aim of achieving a complete resection. The patient underwent endoscopic endonasal surgery again with the assistance of image-guided navigation. Intraoperative findings showed a hard, osteo-thickening tissue scarcely recognizable from healthy bone tissue. The residual tumor was removed out of the sella; the osteo-thickening component at clival level was removed using a drill and sent for histologic examination. The portion located inferiorly in the clivus appeared soft in consistency and was progressively resected. Only a portion firmly adhering to the internal carotid artery (ICA) was left in site. The following post-operative histologic analysis was compatible with the persistence of minimal residual disease of GCT of the bone with histologic signs of response to therapy. At that time, it was decided to conservatively monitor the patient closely at clinical and radiologic follow-up and discontinue denosumab therapy. The evaluation of pituitary function did not reveal hormonal deficits. MRI performed postoperatively at 1 month mostly showed residual signs of inflammation and a small amount of residual tumor in the right lateral portion of the clivus, so it was decided to have the patient return for another MRI in 3 months' time. Nevertheless, she returned to have diplopia in her left eye on lateral gaze 2 months after the second surgery. Now an MRI scan demonstrated a marked tumor regrowth, compared with the previous one, involving the left cavernous sinus with compression of the carotid artery (Fig. 1C). The patient's case was evaluated at a multidisciplinary tumor board recommending the restart of denosumab therapy and to consider radiotherapy in the case of further disease progression. No metastasis was identified at chest CT on reevaluation. MRI imaging performed at 1 month after restarting denosumab and then every 4 months showed a good response to denosumab with reduction of the mass in size and enhancement. Last follow-up imaging at 17 months from the resumption of denosumab therapy confirmed the disease as stable (Fig. 1D). As of the time of writing, the patient is asymptomatic with only a persisting reactive left mydriasis. Molecular-target therapy is being continued with doses administrated every 4 weeks, without any side effects.

REVIEW OF THE LITERATURE

This is a systematic review, with meta-analysis if necessary. Almost all the data and information are extracted from the published articles and studies, so it does not require ethical approval. This analysis will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement.7 The data and information will be retrieved from the databases PubMed and Web of Science. The keywords searched were sex, age, tumor localization, Campanacci system, follow-up time, primary or recurrent tumor, disease course, treatment of primary, and recurrent tumors.

Primary GCTs of the clivus are extremely rare lesions. Since Wolfe's8 first description in 1983, 24 cases of primary GCT involving the clivus have been published in PubMed and the listed journals and are reported in Table 1.

We summarized the available data, including our own case as described above. The patients' ages at diagnosis ranged from 9 to 62 years (mean 24.4 y); 42% 0 to 18 years, 50% 19 to 50 years, and 8% 50 years or above. Thirteen were males and 12 were females, with a higher mean age at diagnosis for the former (27 vs. 21.7 y). Almost all patients presented with headache, owing to high intracranial pressure, and with diplopia, caused by abducens nerve palsy which was the most common nerve involved. Less frequent symptoms were hearing loss, facial paresis or numbness, difficulty in swallowing or speech, and nasal twang, subtiling the involvement of the other cranial nerves. In most cases, the duration of symptoms before diagnosis did not exceed 6 months; only in 2 cases patients had a shorter pathologic history of 1 and 2 weeks, respectively, and in another case, it was 1-year long. From a radiologic point of...
| Patient, References | Sex, Age at Onset (y) | Clinical Presentation at Onset | Duration of Symptoms | Disease Site, Tumor Size (cm) | Imaging | Surgery | Recurrence/Malignant Transformation (Time From Surgery, Treatment) | Denosumab Therapy (Yes/No)/Duration | Outcome, Follow-Up (Time From Diagnosis) |
|---------------------|----------------------|--------------------------------|----------------------|------------------------------|---------|---------|---------------------------------------------------------------|-----------------------------------|---------------------------------|
| Wolfe et al⁸        | Female, 16           | Headache, diplopia, visual disturbance | 4-7 wk               | Sphenoid and clivus, NA     | Large midline mass involving sella, sphenoid and clivus | Endoscopic transseptal biopsy f/b STR | Yes                           | Alive with residual tumor, 8 y |
| Kattner et al⁹      | Female, 9            | Headache, diplopia (left CN6 palsy) | 1 mo                 | Sphenoid and clivus, NA     | Space-enhancing lesion, extending into the left cavernous sinus | Endoscopic transseptal biopsy f/b STR | Yes                           | Alive with residual tumor, 1 y |
| Sharma et al¹⁰      | Female, 18           | Headache, progressive hearing loss, facial paralysis, difficulty swallowing, nasal regurgitation (CN7-12 palsies), left cerebellar signs and pyramidal signs in the lower limbs | 6 mo                 | Petroclival, NA             | Space-enhancing lesion, mixed intensity | NTR—left retromastoid retrosigmoid approaches | Yes                           | Alive with no significant residual mass but persisting hearing loss, 1 y |
| Sharma et al¹⁰      | Female, 12           | Headache, right hearing loss, facial paresis, nasal regurgitation, nasal twang (CN7-12 palsies with tongue atrophy on the right side) | 3 mo                 | Petroclival, NA             | Space-enhancing lesion, mixed intensity | GTR—right retromastoid retrosigmoid approaches | No                            | Alive with no evidence of disease but persisting CN12 palsy, 1 y |
| Zorlu et al¹¹       | Female, 14           | Frontal headache, diplopia (minimal left CN5 palsies) | 2.5 mo               | Sphenoid and clivus, 6x4x3.5 | Space-enhancing lesion, lytic expansive mass | NTR—transsphenoidal sinus surgery | Yes                           | 1st recurrence, 2 mo, RT-EBRT |
| Gupta et al¹²       | Female, 17           | Diplopia, decreased vision, holocranial headache, amennorhea (minimal CN6 palsy, partial CN5 palsy), grade 1 optic atrophy | 6 mo                 | Clivus, 7.6×5.4 | Space-enhancing lesion, lobulated mass, eroding the sphenoid bone | STR—LeFort osteotomy | Yes                           | Alive with residual tumor, 2 y |
| Patient, References | Sex, Age at Onset (y) | Clinical Presentation at Onset | Duration of Symptoms | Disease Site, Tumor Size (cm) | Imaging | Surgery | Recurrence/Malignant Transformation (Time From Surgery, Treatment) | Denosumab Therapy (Yes/No)/Duration | Outcome, Follow-Up (Time From Diagnosis) |
|---------------------|-----------------------|-------------------------------|----------------------|-----------------------------|---------|---------|---------------------------------------------------------------|----------------------------------|----------------------------------------|
| 7. Sasagawa et al13  | Female, 26            | Headache, diplopia (right CN6 palsy) | NA                  | Clivus, 3×3                | STR—transsphenoidal sinus surgery | Yes     | Malignant transformation in osteosarcoma with lung metastasis, 10 y, CT (gem-doxo) | Malignant transformation in osteosarcoma with lung metastasis, 10 y, CT (gem-doxo) | Death, 10 y, 9 mo                     |
| 8. Iacoangeli et al14 | Male, 31              | Headache, diplopia (right CN6 palsy) | NA                  | Clivus, NA                | GTR—extended endoscopic endonasal approach | No      | Alive with no evidence of disease, 6 y                      | Alive with no evidence of disease, 6 y | Alive with no evidence of disease, 6 y |
| 9. Roy et al2       | Male, 19              | Headache, forehead and cheek numbness (right CN5 palsy), restricted field of vision | 6 mo                 | Clivus, 5.6×3,6×3.5        | T2 hyper-intense, NTR—right transmaxillary approach | Yes     | Alive with residual tumor, 1.5 y                            | Alive with residual tumor, 1.5 y | Alive with residual tumor, 1.5 y     |
| 10. Mahale et al15  | Male, 20              | Headache, diplopia, retro-orbital pain, recurrent transient epistaxis (right CN6 palsy), restricted field of vision | 2.5 mo               | Clivus, 6.6x3x3            | Uniform, moderate, space-enhancing lesion, T1 T2 and in FLAIR isointense to hypointense, large, lobulated mass, compressing optic ICAs | No      | NA, NA                                                      | NA, NA                           | NA, NA                                 |
| 11. Agrawal et al16  | Male, 62              | Headache, diplopia (bilateral CN6 palsy) | 3 mo                 | Clivus, NA                | Hyper-intense space-enhancing lesion | No      | NA, NA                                                      | NA, NA                           | NA, NA                                 |
| 12. Zhao et al3     | Male, 22              | Headache, diplopia, right facial numbness (left CN6 palsy, partial CN5 palsy) | 6 mo                 | Clivus, 4×4.68×3.7         | Moderate homogeneous space-enhancing lesion, T1 T2 isointense, compressing the optic chiasm and the cavernous sinuses on both sides | Yes + 3 courses of monthly intravenous bisphosphonate | Alive with no evidence of disease, 2 y | Alive with no evidence of disease, 2 y | Alive with no evidence of disease, 2 y |
| 13. Yildirim et al | Female, 27 | Headache, diplopia (left CN6 palsy) | 1 y | Sphenoid and clivus, 3.2×4.4×5.1 | Heterogeneously space-enhancing lesion, extending into both cavernous sinus, clival erosion | GTR—extended endoscopic endonasal approach | Yes | Alive with residual tumor and persisting left sixth nerve palsy, 6 mo |
|-------------------|-------------|----------------------------------|-----|---------------------------------|-----------------------------------------------|-----------------------------------------------|-----|---------------------------------------------------|
| 14. Le et al | Male, 49 | Headache, blurred vision in the right eye | 2 wk | Clivus, 4.9×3.2 | Large clival mass, eroding clival bone and compressing the optic chiasm, 3.2×4.4×5.1 | Transphenoidal endoscopic biopsy followed by tumor resection through LeFort osteotomy and medial maxillectomy | Yes | Alive with no evidence of disease, 1 y |
| 15. Shibao et al | Male, 25 | Diplopia (right CN6 palsy) | 1 mo | Clivus, 5.1×3.1×4.9 | Homogeneous space-enhancing lesion, T1 isointense T2 hypointense | STR—endoscopic endonasal transphenoidal surgery | Yes | Recurrence with increased MIB-1 index (malignant transformation?), 2 mo, surgery |
| 16. Inoue et al | Male, 16 | Headache, right ptosis, diplopia (right CN3 palsy) | 3 mo | Clivus, 3.6 | Homogeneous space-enhancing lesion, T1 isointense T2 slightly hypointense, bony erosion and invading left ICA | STR—endoscopic endonasal transphenoidal surgery | No | Recurrence, 2 wk, Denosumab |
| 17. Goto et al | Male, 34 | Diplopia (left CN6 palsy) | 1 wk | Sphenoid and clivus, NA | Heterogeneous space-enhancing lesion, T1 isointense T2 slightly hypointense, bony erosion and invading right cavernous sinus | NTR—endoscopic endonasal approach | No | Recurrence, immediately postoperative, Denosumab |
| 18. Patibandla et al | Male, 20 | Left hemi cranial headache, vomiting, left ptosis (left partial CN6 palsy) | 6 wk | Sphenoid and clivus, NA | Space-enhancing lesion, T1 T2 isointense, bony erosion | STR—bilateral transnasal transphenoidal endoscopic endonasal approach surgery | Yes | Alive with residual tumor, 3 mo |
| 19. de la Peña et al | Male, 34 | Right hearing loss, dizziness, tinnitus and right facial palsy (right peripheral CN7 palsy and CN8 deficit) | 3 mo | Petrous bone, sphenoid, and clivus, NA | Hyper-intensive lesion | STR—temporal craniotomy and endoscopic transnasal transphenoidal surgery | Yes | Alive with residual tumor and persisting right hearing loss, 4 y |
| 20. Huh et al | Female, 18 | Headache, diplopia (partial CN3 palsy) | 2 mo | Clivus, NA | Heterogeneous space-enhancing lesion, hyperintense, invading right cavernous sinus | NTR—extended endoscopic endonasal approach therapy | Yes | Recurrence, 6 mo, Denosumab and proton therapy |

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Unresectable Clival Giant Cell Tumor

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|---------------------|-----------------------|-------------------------------|----------------------|-----------------------------|---------|---------|-------------------------------------------------|-----------------------------|---------------------------------|
| 21. Satapathy et al24 | Male, 24              | Headache, diplopia, decreased vision (bilateral CN6 palsy), primary optic atrophy | 4 mo                 | Clivus, NA                  | Space-enhancing lesion, lobulated mass, bone erosion | GTR—extended bifrontal craniotomy | Yes                             | Alive, 8 mo                      |                                  |
| 22. Scotto di Carlo et al25 | Female, 55          | Holocranial headache, vomiting, tongue numbness, swallowing and speech difficulty | NA                   | Clivus, 5×2.8×3.8          | Space-enhancing lesion, lobulated mass | Resection through suboccipital approach | Yes                             | Recurrence, 1 mo, surgery and RT (tomotherapy) 2 degrees recurrence, 2 y after second treatment, planned for resurgery | Alive with evidence of tumor regrowth and persisting symptoms, 3 y |
| 23. Singh et al26    | Female, 35            | Headache, diplopia, blurred and decreased vision (left CN6 palsy) | 6 mo                 | Clivus, 4×2.5×0.5          | Homogenous space-enhancing lesion | STR—endoscopic endonasal transsphenoidal surgery | Yes                             | Alive with residual tumor, 6 mo |                                  |
| 24. Tanikawa et al27  | Male, 15              | Diplopia                       | 2 mo                 | Sphenoid and clivus, NA    | Space-enhancing lesion in the sphenoid sinus, with bone erosion | STR—endoscopic endonasal surgery | No                              | Recurrence, 3 mo, Denosumab        | Yes, monthly for 2 years, Alive with residual tumor, 5 y |
| 25. This study       | Female, 14            | Headache, decreased vision, diplopia, left ptosis (left partial CN3 and CN4, left CN6 palsy) | 2 wk                 | Sphenoid and clivus, 3.5×5.5×3 | Heterogeneous space-enhancing lesion, T1 isohypointense, involving posterior ethmoidal cells, left optic nerve and optic chiasm, left ICA and ipsilateral cavernous sinus | STR—endoscopic endonasal approach | No                              | Recurrence, 3 mo (after second surgery), Denosumab | Yes, monthly for a total of 23 mo to date, still in therapy | Alive with residual tumor and fixed a reactive mydriasis, 2.5 y |

CN indicates cranial nerve; CT, computed tomography; EBRT, external beam radiotherapy; f/b, followed by; GRT, gross total resection; ICA, internal carotid artery; NA, not available; NRT, near-total resection; RT, radiotherapy; STR, subtotal resection.
view, given the localization of the tumor, the maximum size reported was 76 mm in the largest dimension. In most cases, the tumor appeared as an expansile or lytic lesion and the clival erosion in question was observed on a CT scan. MRI mostly showed contrast enhancing with signal isointensity on T1-weighted images and variable intensity on T2-weighted images. The tumor showed a moderate to high vascularity in the majority of cases and in 3 cases a massive bleeding from the ICA was observed as a consequence of tumor resection. Histologically, tumor was described as composed from numerous multinucleated osteoclast-like giant cells scattered throughout the mass and ovoid or spindle mononuclear stromal cells with variable cellularity, while rare necrosis and insignificant cellular atypia. Osteoclast-like giant cells showed a variable number of nuclei (range: 10 to 40) and they were bigger in 1 case, with 50 to 70 nuclei. Conspicuous proliferative activity in the stromal tumor cell population was reported only in 1 patient, based on a Ki67 labeling index of 70%. An analysis of H3F3A histone mutation was done in 3 of the patients, including our case, and revealed as positive in all 3. Regarding treatment, data were available for all but 2 patients whose information about adjuvant treatment and follow-up were lacking. Overall, 29 tumor resections were performed: all the patients underwent surgery as initial treatment and 4 needed a further resection. The surgical approaches used were endoscopid endonasal approach, frontal or temporal craniotomy, transmaxillary, and retromastoid with endoscopic endonasal approach, the most commonly used (68%, 17/25 patients). The majority of patients were treated with subtotal or near-total resection. The gross total resection (GTR) was usually considered difficult and was achieved only in 4 cases. Postsurgery residual tumor reports were not available in 4 of the cases.

Fourteen patients were given adjuvant therapy after surgery. In 4 cases, a complete resection was achieved without residual disease; for these patients, surgery was the only treatment performed except for one who also underwent radiotherapy. All the remaining patients underwent subtotal or partial resections; these patients received further treatment as adjuvant therapy or to treat a relapse or progression of the disease. Radiotherapy was the most commonly treatment used (13/25, 52%) as an adjuvant therapy, except in our case where a systemic treatment with denosumab was started following surgery. In addition to radiation, 2 patients (Table 1: cases 12 and 19) were administered intravenous zoledronate (4 mg, once a month) and denosumab, respectively.

Overall, recurrence occurred in 9 cases after their first treatment, with an average time of 5.3 months (range: 2 wk to 24 mo). Most of them (6/9 cases, 67%) only underwent surgery with a partial resection on diagnosis. None of the patients who underwent GTR had a recurrence. The treatment of recurrence, however, according to the case in question: 1 patient was treated with RT (external beam radiotherapy), 1 patient had a second surgery and tomotherapy; the remaining 5 patients were prescribed denosumab treatment, and proton therapy was also given in just 1 case. Two patients experienced a second recurrence (Table 1: cases 5 and 22): in patient 5, the tumor regrew 1 year after radiotherapy and a second limited resection was performed; patient 22 had a recurrence 2 years later and a further surgery was planned at the time of the reported case. A malignant transformation was reported in 2 cases (Table 1: cases 7 and 15). In case 7, the tumor relapsed 10 years after surgery pathologic evidence of transformation to malignant osteosarcoma. In case 15, the tumor gradually regrew from 2 months’ postradiation, with an increased pathologic MIB-1 index up to 26.3% that was considered a malignant transformation by the authors.

Overall, 6 patients received denosumab treatment for a mean therapy time ranging from 5 months to 5 years. The doses consisted of monthly administrations with additional doses on day 8 and 15 only in the first month of therapy. Monthly denosumab therapy was continued for 5, 7, and 10 months in 3 patients, respectively. Therapy was performed for longer periods in 2 patients by gradually extending the intervals between doses: 1 patient received monthly denosumab doses for the first year, every 3 months for the second year and every 6 months for the third and fourth year; the second patient received monthly denosumab doses for 2 years, followed by 4 monthly doses for the next year and 6 monthly doses for the following 2 years. In our case, denosumab therapy was started after surgery as an adjuvant treatment with administrations every 4 weeks for 5 months; after tumor relapse, denosumab was resumed with doses every 4 weeks. No toxicity from denosumab was reported, except for mild hypocalcemia in 1 case.

After a mean follow-up period of 26.5 months from diagnosis (range: 3 to 129 mo), the majority of patients (15/25, 60%) were alive with a residual tumor. Five patients presented persisting mild symptoms or clinical signs at their last follow-up examination. One patient showed evidence of tumor regrowth and was prepared for a resurgery. Four patients were described with no evidence of disease in their last follow-up images. Two patients died: in 1 case death occurred as a result of pneumonia and sepsis 9 months after the diagnosis of secondary malignant GCT; the second patient died because of tumor regrowth 19 months after their second surgery.

**DISCUSSION**

GCTs are relatively uncommon bone tumors accounting for ~5% of all primary osseous bone tumors. They usually originate in the epiphyses of the long bones, such as the distal femur, proximal tibia, distal radius, and proximal humerus. Less than 1% of GCTs occur in the skull and among those, primary GCTs involving the clivus are extremely rare. Because of their expansive nature and proximity to the cavernous sinus, clival GCTs typically present with headache, diplopia, and cranial nerve palsies, of which the sixth is the most common involved followed by the third. In addition, a fifth cranial nerve palsy has been reported, as shown in the present review.

Although GCTs are generally considered histologically benign, these tumors may turn locally aggressive with a high rate of local recurrence but low potential for distant metastases. Furthermore, the clinical behavior of such tumors is unpredictable, and they should be regarded as potentially malignant. Complete surgical resection is the most appropriate treatment to prevent local recurrence, but this is difficult for GCTs located in anatomically complicated sites like the base of the skull and in close proximity to critical neurovascular structures, such as the ICA, pituitary gland, optic nerve, and cavernous sinus. Because of this very sensitive localization, surgery carries specific risks such as postoperative pituitary potential dysfunction, cranial nerve damage or intraoperative bleed for ICA injury. The limitations of surgical rea are evident in the current review since only 3 of 25 patients underwent GTR and 2 cases were further complicated by massive bleeding from the ICA during...
endonasal surgery. Therefore, these tumors are usually treated with subtotal or partial resection and adjuvant treatments.

It has been observed that disease progression often occurs rapidly within just 2 years. These recurrences have depended on the extent of tumor removal and the adjuvant therapy used with the risk of recurrence after partial resection being 47%. In cases managed purely with an intralesional surgical approach,12 the recurrence rate was 85%, highlighting the high risk of relapse in cases managed with no adjuvant treatment. Radical surgical extirpation, along with adjuvant therapy for GCTs, appears to provide the best result.

Radiotherapy was used in a total of sixteen patients as an adjuvant therapy or to treat recurrence. In 12/16 cases (75%) no tumor regrowth was noted after a median follow-up of 12 months but 3 patients had a recurrence respectively at 2 months, 1 year, and 2 years after irradiation. In particular, 1 patient developed a malignant transformation into osteosarcoma at 10 years after radiation.13 Hence, the local benefit of radiotherapy is still debatable and its risk of determining secondary malignancy cannot be excluded.28 Possibly radiotherapy could be considered in elderly patients.

For GCTs treatment in the selected cases, denosumab is dosed at 120 mg, administered subcutaneously every 28 days with loading doses on days 8 and 15 (in the first month of therapy) as neoadjuvant therapy.29 Definitive surgery is recommended to be done early, on average after 3 to 4 months of denosumab therapy. The reason for this choice is that preventing too thick a rim of bone from forming may make complete removal much more feasible. The use of denosumab in adjuvant therapy to reduce the risk of local relapse or as maintenance in the case of inoperable relapse has been described in case reports without, however, having a consensus for a clear indication, supported by the literature in an unequivocal way.30,31

Denosumab therapy, however, resulted in a good response in all patients. Two patients were given denosumab for 4 and 5 years, respectively, by gradually extending the dosing intervals and without any serious side effects reported.4,28 Furthermore, in our case, denosumab was used to treat relapse thus obtaining a long-term local benefit with radiologic and clinical stabilization at 2-year follow-up. The treatment continues to be maintained at this dosing interval for a total of 24 months from drug resumption. A gradual extension of the dosing intervals has currently been established with 4 monthly doses for the next 2 years, followed by lifelong monthly doses with hematological and radiologic assessments according to the timing of denosumab dosing. Although this treatment appears effective, potential side effects are widely reported including hypocalcaemia (5%), hypophosphatemia (3%), osteonecrosis of the jaw (1%), serious infection (2%), and new primary malignancy (1%).32 The use of denosumab should be considered, paying careful attention to the renal function of the patient, because renal dysfunction increases the risk of hypocalcaemia. Further reports on side effects of denosumab after discontinuation show risk of hypercalcemia 5 months after stopping denosumab, demanding the need to monitor electrolytes for months after completion of denosumab treatment.33

CONCLUSIONS

Because of their challenging location, it is often not possible to completely resect clival GCTs, highlighting the need for adjuvant treatment options. Although radiotherapy has been used as an adjuvant therapy over the past decades, its potential risks and effectiveness are still uncertain.6,11,27 Denosumab, however, is increasingly used in the chemotherapeutic treatment of residual GCTs.29,32 The results obtained from the studies in the literature demonstrate that this antibody has a clinically beneficial effect in terms of both radiologic response and the improvement of clinical symptoms. A gradual extension appears to be recommended, for the adjustment of the dosing interval, as in 2 cases previously reported.4,28 Moreover, our case contributes to the limited follow-up data of denosumab therapy, thereby contributing as an example of its effectiveness in treating relapses and long-term tumor control.

In conclusion, further experience with denosumab and longer patient follow-ups are still needed to reveal the maximum benefit in the use of denosumab therapy, and the most appropriate treatment protocol in the management of the atypically located GCTs. In addition, long-term effects of denosumab on the normal bone of the patients are not clear. In future, these questions will have to be clarified to use the drug more effectively and safely.

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