Recurrent Giant Cell Reparative Granuloma of the Skull Base and the Paranasal Sinuses Presenting with Acute One-Sided Blindness

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ABSTRACT

The etiology, pathogenesis, histopathologic diagnosis, prognosis, and treatment of giant cell reparative granulomas of the skull are controversial. We report a 14-year-old girl with an advanced recurrent giant cell reparative granuloma of the skull base and paranasal sinuses whose only clinical manifestation was a loss of vision. After undergoing endovascular catheter embolization, the patient underwent repeated surgical resections of the mass via a combined frontobasal and modified infratemporal approach followed by radiation therapy. Histopathologic examination confirmed the diagnosis of giant cell reparative granuloma. A traumatic event in the patient's history—a fossa canina abscess followed by tooth extraction 14 months before admission—supports the theory of a reactive reparative process as a pathogenetic mechanism for this disease. Histopathologic criteria and clinical aggressiveness must be considered to achieve adequate treatment of giant cell lesions of the skull.

KEYWORDS: Giant cell reparative granulomas, giant cell tumor, skull base

Skull Base, volume 12, number 1, 2002. Address for correspondence and reprint requests: Prof. Dr. med. Peter K. Plinkert, D/o ORL:HNS, University of Saarland, Kirrberger Str., D-66421 Homburg/Saar, Germany. E-mail: hnoppli@med-rz.uni-saarland.de Departments of ¹Otorhinolaryngology: Head and Neck Surgery, ²Neurosurgery, ³Neuroradiology/Interventional Radiology, University of Tübingen, Tübingen, Germany; ⁴Department of Pathology, Reference Center of Bone Diseases, University of Freiburg, Freiburg, Germany; ⁵Department of Otorhinolaryngology: Head and Neck Surgery, University of Saarland, Homburg/Saar, Germany. Copyright © 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662. 1531-5010,p;2002,12,01,009,018,ftx,en;sbs00247x.

Giant cell reparative granulomas (GCRGs) are rare and classified among tumor-like lesions.¹ Their etiology, histopathologic diagnosis, and treatment are controversial.² With the exception of the maxilla, GCRGs are unusual in the skull. They usually are regarded as benign lesions. Patients may be clinically asymptomatic or may manifest aggressive symptoms, depending on the location of the GCRG. Histologically, it is difficult to differentiate GCRGs from other osseous lesions like true giant cell tumors of bone (GCT) or the "brown tumors" of hyperparathyroidism (resorptive giant cell granulomas), but identification is important for treatment and for determining prognostic factors, such as rate of recurrence and metastases. Treatment options include curettage, complete surgical excision, and radiation therapy, but outcomes appear to depend on the biological behavior of the individual lesion.

The following case emphasizes the potential biological aggressiveness of these primarily benign lesions and supports the hypothesis that a reactive reparative process may be the pathogenetic mechanism underlying this disease.

CASE REPORT

A 14-year-old girl reported almost complete loss of vision in her left eye to her family doctor. She was referred to our department for further evaluation of an extensive left-sided mass of the skull base and paranasal sinuses detected on magnetic resonance imaging (MRI) and computed tomography (CT). Physical examination showed mild hyposensitivity in the area of the mandibular branch of the left trigeminal nerve and a left epipharyngeal mass. An ophthalmologic examination revealed a central scotoma with severely decreased visual acuity (1/20) in the left eye. Extraocular movements were intact, and no diplopia was present. Fourteen months before admission, the patient had an abscess in the left

Figure 1 The coronal, contrast-enhanced T2-weighted magnetic resonance image shows an extensive mass with homogeneous contrast enhancement invading the left middle cranial fossa, the entire sellar region, the left cavernous sinus, the clivus, and the pharyngeal wall. The tumor fills the sphenoid sinus and the left masticatory space.

canine fossa and tooth 26 was extracted. Otherwise, her medical and surgical history was unremarkable.

The CT and MRI scans revealed an extensive left-sided mass measuring about $6 \times 6 \times 5$ cm involving the middle cranial fossa, sphenoid wing, sellar region, clivus, orbital apex, cavernous sinus, sphenoid sinus, nasopharynx, and parapharyngeal space (Fig. 1). The left optic nerve was displaced superiorly (Fig. 2). The infiltrating tumor had caused osteolytic destruction at the skull base and walls of the left paranasal sinuses. The floor of the maxillary sinus was lowered in the area where the patient's tooth had been extracted to treat the canine fossa abscess (Fig. 3).

An endoscopically controlled biopsy sample from the sphenoid sinus showed histopathologic features consistent with GCRP (Fig. 4). A large

Figure 2 Left paramedian sagittal T1-weighted magnetic resonance image shows infiltration of the left orbital apex and displacement of the optic nerve superiorly. Circular swelling of the mucosa and irregular signal inhomogeneities are visible in the floor of the left maxillary sinus.

Figure 3 Coronal computed tomographic scan (bone window) shows osteolytic destruction of the sphenoid bone and lateral wall of the left maxillary sinus. The floor of the maxillary sinus in the area of the patient's earlier canine fossa abscess (tooth 26) is lowered.

number of proliferating fibroblasts embedded in the loose vascularized stroma (Fig. 4A) had slender, drawn-out, fully isomorphic nuclei. A few nuclei appeared somewhat hyperchromatic (Fig. 4B). Mitosis was rarely encountered. Within the granulation tissue, many multinucleated giant cells were unevenly distributed and often clumped in areas of hemorrhage. Cystic degeneration and focal osteoid deposition or even bone formation was observed (Fig. 4C). Clinical examination and endocrinologic testing excluded an underlying endocrinologic disorder such as hyperparathyroidism.

The patient underwent almost complete endovascular catheter embolization of the pterygopalatine branches of the left maxillary artery, which provided more than 90% of the tumor's blood supply (Fig. 5). Then the tumor was almost completely resected through a combined frontobasal and modified infratemporal approach. The cavity was

closed with abdominal fat (Fig. 6). Histopathologic examination of the resected mass confirmed the diagnosis of GCRG with no histomorphologic signs of malignancy.

Four months after surgery, follow-up imaging revealed a marked recurrence or progression of the residual tumor (Fig. 7). Angiography showed that the highly vascularized tumor received its blood supply from the left internal maxillary artery, the paracavernous branches of the internal carotid artery (ICA), and branches of the ascending pharyngeal artery. After embolization of the tumor, the patient underwent a surgical revision. Because of the tumor's extension and its separation into several compartments, the anterior portions were resected through a transfrontal approach with extradural and intradural exploration. The tumor tissue was capsulated and contained thin, bony, shell-like structures. The pituitary gland was displaced

Figure 4 (A) Reparative giant cell granuloma showing a loose vascularized spindle cell stroma with a large number of fully isomorphic proliferating fibroblasts and many multinuclear giant cells. Mitosis was rarely encountered [hematoxylin and eosin (H & E) stain, $\times 64$]. (B) Under higher magnification, the spindle cells include mostly roundish or elongated nuclei. Some appear slightly hyperchromatic. Several multinuclear giant cells are unevenly distributed within the granulation tissue and often clumped in areas of hemorrhage (H & E stain, $\times 100$). (C) Next to the multinuclear giant cells are focal deposits of osteoid (van Gieson's stain, $\times 64$).

anteriorly by the mass, but no intracranial extension of tumor was found. The residual tumor was approached through a combined transmaxillary and infratemporal approach, but the portions that enclosed the ICAs and that infiltrated the clivus could not be resected (Fig. 8). Therefore, the patient underwent postoperative radiation therapy (6 MV photons, 54 Gy). After treatment, the patient suffered from anosmia and a persistent severe decrease in visual acuity. Otherwise, her cranial nerve functions were intact. Clinical and radiologic fol-

low-up revealed no signs of recurrent disease 18 months after she completed radiotherapy (Fig. 9).

DISCUSSION

In 1953, Jaffe first used the term *giant cell reparative granuloma* to differentiate lesions of the maxilla and mandible from true GCTs, aneurysmal bone cysts, and fibrous dysplasia.³ GCRGs are rare,

Figure 5 (A) Initial lateral angiogram of the left external carotid artery (ECA) shows intensive tumor stain fed by branches of the maxillary artery. (B) Postembolization angiogram of the distal ECA after devascularization of the tumor with polyvinyl alcohol particles.

Figure 6 Axial computed tomography scan after primary resection of the tumor shows fat filling most of the tumor bed. Residual tumor tissue is present at the lateral orbital wall, in the dorsal region of the sphenoid sinus, and in the middle cranial fossa. Some granuloma tissue remained in the left sellar region and middle cranial fossa (not shown).

accounting for fewer than 7% of all benign tumors of the maxilla and the mandible.^{4,5} Outside these preferred sites of occurrence, GCRGs occur even less frequently. They have been reported, however, in the temporal bone,⁶⁻⁸ paranasal sinus,^{9,10} skull base,¹¹ and orbit.¹² Reports of GCRGs in other parts of the body are sporadic.¹³⁻¹⁵ A review of the literature on GCRGs is complicated by the inconsistent use of the terms *giant cell reparative granuloma* and *giant cell tumor*. Confusion about the histopathology and clinical behavior of these giant cell lesions has led to frequent retrospective reinterpretations of cases and revised diagnoses.^{6,9,13}

The pathogenesis of GCRGs and their therapeutic consequences are major points of discussion. Electron microscopic and histochemical studies have suggested that histiocytes are the histiogenetic progenitors of the giant cells in GCRG.¹⁶ The ongoing debate especially involves controversies about the term *reparative* and its etiologic implications. Initially, a hyperplastic reparative reaction to intraosseous hemorrhage after trauma was suggested as the cause.³ Hirschl and Katz also described hemorrhage, possibly linked to trauma, as the etiologic

Figure 5. Preoperative MRI in Case 2, revealing an enhanced mass lesion in the left petroclival region.

Case 2

This case was a 69-year-old woman who had a petroclival meningioma on the left side (Fig. 5). Her ocular movements were intact preoperatively. She underwent excision of the tumor via a combined presigmoid transpetrosal approach. The electrical stimulation-induced EOG responses obtained in this case were useful for detecting a segment of the oculomotor nerve displaced by the tumor mass before such a segment was exposed within the operative field. Electrical stimulation of the oculomotor nerve provoked a clear negative monophasic wave in traces from the pair of electrodes in a horizontal orientation (Fig. 6). A segment of the abducent nerve located beneath the tumor mass was also identified from EOG responses observed before this nerve was exposed in the operative field. A similar EOG

Figure 6. In the left eyeball, when the oculomotor nerve was stimulated intracranially, an ocular movement towards the right side was induced. It yielded a clear monophasic positive wave with a high reproducibility. The electrode placements were the same as in Fig. 1.

Figure 7. Ocular movements recorded an intermittent multiple spiky waves when the surgeon manipulated the abducent nerves mechanically in Case 2.

response to those obtained in case 1 was noted when the abducent nerve was stimulated. EOG responses were also elicited by surgical manipulation performed during mechanical dissection of the abducent nerves from the tumor tissue (Fig. 7). The postoperative ocular movement was full, and MRI demonstrated total removal of the tumor except for immediately adjacent to the abducent nerve (Fig. 8). The findings in this case suggested that monitoring of mechanically induced EOG responses may be useful for avoiding damage to the ocular motor nerves.

DISCUSSION

Techniques for intraoperative electrical stimulation of cranial nerves have been reported by several investigators.^{9,10} Broadly speaking, these techniques can be separated into two groups: monopolar and bipolar stim-

Figure 8. Postoperative MRI in Case 2.

factor in reparative granuloma of the bone.¹³ Yet no study has shown a strong correlation between these lesions and trauma.^{2,13} The trauma, however, could occur many years before the granulomatous lesion.¹³ Wiatrak et al. implicated inflammation as the etiologic agent of GCRG in the paranasal sinuses, especially if there is no history of trauma.¹⁰ Batsakis proposed that "injury imposed upon the periodontal membrane, the odontogenic mesenchyma, the dental sac or its ancestral cells is probably the initiating insult."¹⁷ In summary, most authors believe that a granulomatous reaction to intraosseous hemorrhage caused by trauma or inflammation is the primary cause of GCRG.^{6,9,10} The canine fossa abscess and subsequent tooth extraction in our patient appear to fulfill Jaffe's definition of a trauma that would predispose the patient to develop a GCRG.

The clinical symptoms associated with giant cell lesions of the skull are mixed and depend on the site of the lesion. Headaches and cranial nerve lesions are for the most frequently encountered symptoms.^{2,11,18} Six criteria (i.e., pain, rate of growth, swelling, tooth root resorption, cortical perforation, and recurrences) have been used to evaluate the clinical behavior of GCRG of the maxilla, which ranges from asymptomatic to aggressive.¹⁹ Our patient's only symptom was the severe decrease in visual acuity in the left eye and mild hyposensitivity in the area of the third branch of the trigeminal nerve on the same side. Given the aggressive course of her disease, we agree with Hoopes et al.¹² that it appears inappropriate to consider this destructive, locally invasive and enlarging lesion as a benign reparative process, even though it is not a neoplasm by definition and in contrast to the true GCTs of bone.^{1,12}

Giant cell reparative granulomas have no pathognomonic radiographic appearance, and they may mimic other osseous lesions. A combination of CT and MRI is best for assessing giant cell lesions of bone, including the skull base.²⁰ CT tends to be most useful for assessing bony destruction and thus for following bony involvement. On T2-weighted MRIs, these tumors usually have high signal intensity and low to medium intensities on T1-weighted MRIs. MRI tends to be more suitable for evaluat-

ing the soft-tissue structures surrounding and compromised by the tumor.^{8,20} Because the radiologic and clinical findings of GCRG are nonspecific, the diagnosis is established primarily by histologic evaluation of the specimen.

Several giant cell lesions must be included into differential diagnosis. First, a resorptive giant cell granuloma associated with hyperparathyroidism (so-called brown tumor) must be considered. Both lesions have almost identical radiologic and histologic features. In such cases, hyperparathyroidism must be excluded by clinical investigation.²¹ Because of the osteoid deposition associated with GCRGs, the diagnosis of osteosarcoma also must be excluded. In the jaws, however, most osteosarcomas are chondroblastic. When multinucleated giant cells dominate the pattern of GCRG, an osteoclastoma (GCT) must be excluded. Despite discussion in the literature,¹² this primary bone tumor with malignant potency has never been reported to have developed in the jaw bones.²¹ Some investigators believe that these lesions represent a continuum of the same disease process.^{22,23} Others, however, suggest that the two entities can be distinguished by certain clinical criteria. GCRGs usually appear between the ages of 10 and 25 years, whereas GCTs manifest in the third and fourth decades of life and are rarely seen in patients younger than 20.²⁹ Unlike GCTs, which show a predilection for long bones, GCRGs are rarely found outside the skull.¹³⁻¹⁵ Although histopathologic features of GCRGs and GCTs overlap considerably, accounting for the controversy about their classification, the histologic pattern of GCRGs differs somewhat from that of GCTs (Table 1).

The treatment modalities are curettage, surgical excision, and radiation therapy. Surgery predominates over radiation as the treatment of choice.^{2,11} Complete surgical excision is favored because recurrence rates are high with incomplete removal.^{14,19,22} One study reported a 50% incidence of recurrence after curettage compared with 10% after complete surgical excision.²² Complete surgical excision, however, can be difficult or even impossible in certain locations. In general, the skull base represents a surgical challenge because of its density of

Table 1 Histopathological Features of Giant Cell Reparative Granuloma and Giant Cell Tumors

Giant Cell Reparative Granuloma	Giant Cell Tumors
Fewer multinucleated cells with fewer nuclei, increased cytoplasm and irregular shapes, clusters in uneven patches or foci ^{7,8,11,22,24}	More evenly distributed, more uniform appearance ^{2,7,8,22,24}
Spindle cell proliferation between clusters ²	Greater incidence of mitotic figures ^{7,8,22}
Increased incidence of osteoid (new bone formation), hemorrhage, and hemosiderin ^{11,22}	Mononuclear cells more oval than spindle shaped ²

vital structures. When incomplete resection leads to recurrence, a complex approach to treatment (e.g., surgery followed by radiation therapy) may be necessary.^{10,11,24} Otherwise, the main concern is sarcomatous transformation of the lesion. Surgical debulking followed by radiation therapy has failed to prevent tumor from recurring.¹⁰

CONCLUSION

To our knowledge, this is the only reported case of an advanced GCRG of the skull base and paranasal sinuses associated with severe ipsilateral loss of vision as the only presenting symptom. Because borderline cases between GCRG and GCT show various degrees of aggressiveness and recurrence, GCRGs should be followed closely with CT and MRI after surgery. Treatment should be tailored to the individual patient. The potential clinical aggressiveness of this primarily benign lesion may require extensive surgery and postoperative radiotherapy.

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Commentary

This is a well-written article about a single case of giant cell reparative granuloma. This disease process is relatively rare, and its history is variable. The authors have done an excellent job of reviewing the natural history of the disease and of discussing patient management.

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Commentary

The authors present an unusual case of recurrent giant cell reparative granuloma (GCRG) of the skull base that manifested as acute monocular blindness. GCRG, a rare, benign fibro-osseous lesion, typically presents as an expansile mass in the region of the mandible and maxilla. As this case demonstrates, GCRG can involve the skull base and enlarge to massive proportions, making surgical treatment challenging. The authors initially resected the lesion through a combined frontobasal and modified infratemporal approach, which provided wide access laterally but more limited access in the deep midline. Interestingly, the lesion recurred where the initial surgical exposure was most limited. The recurrence argues for the need for an extensive surgical exposure as was achieved in the reoperation through a combined transfrontal-transmaxillary-infratemporal approach. It is natural to try to limit the extent of the surgical approach for what typically is a benign-behaving lesion like GCRG. This case, however, demonstrates the importance of a wide surgical exposure to achieve radical resection.

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