Case Report

Giant cell reparative granuloma of the sphenoid: Case report and review of the literature

Osama A. Jamil1, Mirna Lechpammer2, Sashank Prasad3, Zachary Litvack1, Ian F. Dunn1

Departments of 1Neurosurgery, 2Pathology, 3Neurology, Brigham and Women’s Hospital, Harvard Medical School, Boston

E-mail: *Osama A. Jamil - osama.jamil@childrens.harvard.edu; Mirna Lechpammer - mirna_lechpammer@dfci.harvard.edu; Sashank Prasad - sprasad2@partners.org; Zachary Litvack - litvackz@gmail.com; Ian Dunn - idunn@partners.org

*Corresponding Author

Received: 10 April 12 Accepted: 27 September 12 Published: 27 November 12

Abstract

Background: Giant cell reparative granulomas (GCRGs) are rare lesions in the cranial bones. We present a case of this rare lesion emanating from the clivus and replacing the sphenoid sinus, a highly unusual location for this entity.

Case Description: The case and clinical course of a 29-year-old female who presented with a large sphenoid mass are described here. The patient presented with symptoms of severe headache and diplopia; imaging demonstrated a large sphenoid mass which was completely resected via an endoscopic endonasal approach. It was based on the clivus and was shown to be a GCRG.

Conclusion: GCRGs are benign granulomatous lesions which should be considered in the differential in the setting of a sphenoid mass.

Key Words: Clivus, diplopia, giant cell reparative granuloma, giant cell tumor, neurofibromatosis-1

INTRODUCTION

Giant cell reparative granulomas (GCRGs) are benign osteolytic non-neoplastic granulomatous lesions of bone which occur most commonly in the maxilla and mandible in children and young adults.[1,2,13] Lesions occurring outside the jaw have a second peak between the fifth and seventh decades of life.[1,28] Involvement of the cranial bone, however, is relatively rare. The skull base is the most common cranial site of occurrence of GCRG in patients aged 20-40 years.[1,13]

This entity has to be pathologically distinguished from a giant cell tumor (GCT) which is a true neoplasm. Other bone lesions to be considered in the cranial and facial bones include aneurysmal bone cyst (ABC), fibrous dysplasia, chondroblastoma, osteosarcoma, cherubism, and brown tumor of hyperthyroidism. Management options in the literature have included gross total resection, curettage, radiation, and calcitonin therapy.[1-27]

We present a very unusual case of a 29-year-old female presenting with severe headache and diplopia found to have GCRG based on the clivus and involving the entire sphenoid sinus.

CASE REPORT

A previously healthy 29-year-old female developed two months of progressively worsening headaches. She had been treated with amitriptyline and sumatriptan, and with antibiotics for presumed sinusitis. Ten days before presentation, she developed horizontal binocular diplopia, initially occurring at the end of the day, and then
becoming more persistent. She did not describe visual loss in either eye. She was evaluated in our emergency room.

Her neurologic examination was notable for her eye examination. On examination, the visual acuity without correction was 20/20. Color vision and confrontation visual fields were normal. The pupils reacted normally without anisocoria or an afferent pupillary defect. There were slight bilateral abduction deficits, greater on the left. Alternate cover testing revealed a 6 prism diopter esophoria in primary gaze which increased to 8 prism diopeters in right gaze and 10 prism diopeters in left gaze. The abducting saccades were slowed bilaterally, greater on the left. There was no nystagmus. Examination of the fundus revealed normal optic nerves without pallor or swelling. In summary, the patient had partial bilateral sixth nerve palsies causing binocular horizontal diplopia.

Her laboratory panel was normal, showing no abnormalities of calcium metabolism or pituitary hormones.

Imaging revealed a large mass occupying the sella turcica, sphenoid sinus and encroached upon the prepontine cistern in displacing the clival dura posteriorly. Computed tomography (CT) revealed a heterogeneous lesion causing bony erosion of the dorsum sella and clivus. The infundibulum was minimally deviated to the right and normal pituitary appeared elevated and was seen underneath the optic chiasm. On magnetic resonance imaging (MRI), the lesion was $T_1$ isointense with moderate contrast enhancement [Figures 1-4]. The diagnoses considered based on imaging included pituitary macroadenoma, primary sinus abnormality, plasmocytoma, metastasis, lymphoma, or chordoma.

**Procedure**

She underwent an endoscopic endonasal transsphenoidal resection of this lesion so that a diagnosis could be established, and symptomatic relief was provided by complete resection. A mass emerging from the right sphenoid ostium was immediately appreciated during the sphenoidotomy. Similar findings were observed in the left sphenoid ostium, though the face of the sphenoid had not been eroded. The mass, however, filled the entire sinus. A frozen section suggested a reactive and non-neoplastic process. Therefore, it was felt that surgical resection should be undertaken in this young patient for immediate symptomatic improvement and removal of the offending process. It was highly vascular and was dissected from the roof, walls, and floor of the sphenoid sinus. The sellar floor, superior clivus, and posterior clinoids had been partially eroded and the mass was highly adherent to the clival dura; the tumor did not appear to be emanating from the pituitary as the sellar dura was intact. The mass ultimately was entirely extradural, with no dural violation and no intradural cerebrospinal fluid (CSF) leak. It was most adherent to the clival dura. Macroscopically, a gross total resection was achieved as the tumor was resected off the dura. The MRI showed gross total resection [Figures 5 and 6].

Postoperatively, she recovered well and her headaches and diplopia resolved within a month after surgery.

**Pathology**

Histopathological examination demonstrated a large number of osteoclast-like, multinucleated giant cells within a background of mononuclear stromal cells and spindle-shaped fibroblasts associated with areas of hemorrhage. The final histopathological diagnosis was consistent with GCRG [Figure 7]. The pathologic differential diagnosis includes (but it is not limited to) GCT, solid areas of ABC, and brown tumor of hyperparathyroidism. GCRG is distinctly different from GCT of bone, both histologically and clinically. Hemorrhagic foci and osteoid production, an unusual feature in GCT, is commonly seen in GCRG. Cystic degeneration and components of ABC are uncommon. The histologic appearance of GCRG is similar to brown tumor of hyperparathyroidism, and this diagnosis should be excluded with laboratory analysis.

**Follow-up**

Her symptoms resolved soon after surgery. She was lost to follow-up in the short term, but we were able to

---

**Figure 1:** (a) Sagital, (b) axial, and (c) coronal noncontrast images show sellar/suprasellar mass
see her again at six months. Although the patient was asymptomatic, we performed a routine surveillance MRI six months after surgery, given the rarity of the lesion, which showed a recurrence of the mass [Figure 6a]. We performed repeat endoscopic resection of the lesion [Figure 6b], and follow-up imaging six months after surgery shows no further recurrence.

**DISCUSSION**

GCRG is a benign granulomatous lesion of the bone. It is a locally aggressive lesion. This entity occurs most commonly in children or in young adults aged 10-30, with an increased preponderance for females. It was initially described by Jaffe in 1954 [1,3,10,20,21,24,25]. GCRG for cranial bones were first described by Hirschl and Kratz in 1974 [3]. Other sites described in the literature include hand and feet, axial skeletons and long bone, facial bone, sphenoid, ethmoid bone, orbit, nose, and cranial vault [1-3,6,7,16-18,27]. GCRG of the temporal bone may be associated with squamous cell carcinoma [9]. It may also be associated with genetic conditions like neurofibromatosis-1 (NF-1) and Noonan syndrome [5].

The etiology of GCRG is unclear. Jaffe, who initially described the lesion, believed that this lesion was caused by trauma [8] as trauma can result in a hyperplastic and reparative reaction of bone [3]. Other proposed etiologies include developmental anomalies, hormonal influences, and infection [3].

Symptoms depend on the location. GCRG in the cranial bones presents symptomatically as hearing loss, tinnitus, facial weakness, and dysphagia. The temporal bone is the most common cranial site for GCRG; lesions here may present with headache, a palpable mass, tinnitus, vertigo, localized pain, or hoarseness, dysphagia, and conductive hearing impairment. Sphenoid bone lesions present with diplopia, vision changes, and headache [4,14,23]. The sixth nerve exits the brainstem from the inferior aspect of the pons and then ascends within the Dorello’s canal to enter the cavernous sinus. The soft tissue mass involving the sphenoid sinus and clivus in this case likely leads to dysfunction of the sixth nerves at this site.

Radiological findings are nonspecific and it is difficult to distinguish between GCT and GCRG; CT scan will reveal lytic areas. MRI reveals an area of low intensity on both $T_1$- and $T_2$-weighted images which indicate fibrosis or hemosiderin [22]. These tumors do enhance; however, the degree of enhancement varies [1,3,11,14,19].

The management of GCRG is usually surgical. The rate of recurrence after gross total resection is about 10-20% [26,28]. Nonsurgical options include radiation and calcitonin therapies [14,26,28] though the rarity of these lesions has prevented uniform paradigms of treatment. Calcitonin receptors can be identified in tissue samples.
Figure 5: Coronal (a) and sagittal (b) magnetic resonance imaging (MRI) noncontrast showing transsphenoid resection of the majority of the large sellar/suprasellar mass.

Figure 6: Sagittal contrast enhanced magnetic resonance imaging (MRI) shows resection of the majority of the sellar/suprasellar mass with thickening and nodular enhancement along the clivus. (a) Recurrence of the mass. After repeat endoscopic resection of the lesion (b).

Figure 7: Histological features of giant cell reparative granuloma; a: Multinucleated giant cells dispersed within fibroblastic matrix, hematoxylin and eosin (H and E)-stained section; original magnification ×100; b and C Osteoclast-like giant cells, H and E-stained section and smear; original magnification ×200; bar = 200 μm (panels B and C).
obtained in patients with GCRG. Calcitonin inhibits osteoclastogenesis, reducing abnormal bone turnover to normal levels and this together with the fact that giant cells express calcitonin receptors make it a reasonable choice for therapy. Anti-inflammatory drugs may be useful because of the infectious/inflammatory etiology of the disease.[14,26] Radiation is a tool but sarcomatous degeneration is a theoretical concern.

The diagnosis of GCRG is a pathologic one; other lesions in its differential diagnosis include true GCT, brown tumor of hyperparathyroidism, ABC, chondroblastoma, fibrous dysplasia, osteosarcoma, and cherubism.[1,13,27] It is particularly important to exclude GCT. GCTs are benign locally aggressive tumors. They have an incidence of 3-7%. Only 2% involve the skull.[6] Sphenoid and ethmoid bones are sites for GCTs. These occur in the third or fourth decade of life. Symptoms depend on the location. Headache, diplopia, changes in vision, and trigeminal and facial nerve signs are symptoms when these lesions involve the sphenoid bone. Temporal bone lesions cause conductive hearing impairment, retroauricular pain, facial nerve weakness/paralysis, and blockage of the Eustachian tubes.[14] GCT has a higher rate of recurrence—45 to 62%—and 1-6% of these tumors metastasize to the lungs.[1,28] These tumors can also undergo malignant transformation. The origin of GCRG and GCT are different. GCRG originates from the periosteal connective tissue, whereas GCT arises from the connective tissue of the bone marrow.[1] Both of these lesions are composed of multinucleated giant cells and small oval or spindle-shaped fibroblasts. GCRG is distinguished from GCT by the patchy distribution of multinucleated giant cells, increased spindle-shaped fibroblasts, greater hemorrhage and hemosiderin formation, increased inflammatory component, and increased osteoid formation.[1,3,6,14] In contrast, increased mitotic activity is a feature of GCT.[3,13,14] Giant cells in cranial and extracranial GCT and CCRG are immunohistochemically positive for CD68.[6,29] This is important as it suggests histiocytic differentiation.[29] Giant cells and stromal cells are negative for the S100 protein as well as Mac-387.[6] Brown cell tumor of hyperparathyroidism usually occurs in life and is characterized by multiple lesions. Parathyroid hormone, serum and urinary levels of calcium, phosphate, and bone or serum alkaline phosphatase are used in the diagnosis of brown cell tumors.[14] Moreover in the differential, ABCs are non-neoplastic lesions of the bone containing giant cells. X-ray shows cystic cavity in bone. MR imaging reveals a heterogeneous high signal intensity lesion. Histologically, they are characterized by thin-walled blood-filled sinuses lined by fibroblasts and giant cells.[1,14] Chondroblastoma of the temporal bone is a locally aggressive tumor.[14] Histologically, it is characterized by hemosiderin pigment, chondroid differentiation, scattered giant cells, and calcification. It appears as a high-density mass on CT scan.[3] Chondroblastoma can be ruled out by negative S100.[6] Negative S100 and CD1a also exclude Langerhans cell histiocytosis.[17]

**CONCLUSION**

GCRG is a benign non-neoplastic granulomatous lytic lesion of the bone. Its etiology is clearly unknown but maybe traumatic with some role for infection or inflammatory processes. Differential diagnosis includes GCT, ABC, chondroblastoma, and brown cell tumor of the bone. Management includes surgical (either as gross total resection or curettage) or nonsurgical (radiation, calcitonin, and anti-inflammatory drugs) modalities. Nonsurgical modalities should be considered for lesions that cannot be completely resected. Although the recurrence rate after total resection is modest (10-20%), close follow-up is warranted. To our knowledge, this is the first known case of GCRG based in the elivus.

**REFERENCES**

1. Aralasmak A, Aygun N, Westra WH, Yousem DM. Giant cell reparative granuloma of the sphenoid bone. AJNR Am J Neuroradiol 2006;27:1675-7.
2. Bayar MA, Erdem Y, Golcek C, Kolteker E, Kilic C, Yusufi U, et al. Giant cell reparative granuloma of the axis. Turk Neurosurg 2009;19:432-7.
3. Boedeker CC, Kayser G, Ridger GJ, Maier W, Schipper J. Giant-cell reparative granuloma of the temporal bone: A case report and review of the literature. Ear Nose Throat J 2003;82:926-9, 933-4, 936-7.
4. Ciappetta P, Salvati M, Bernardi C, Raco A, Di Lorenzo N. Giant cell reparative granuloma of the skull base mimicking an intracranial tumor. Case report and review of the literature. Surg Neurol 1990;33:52-6.
5. de Lange J, Rosenberg AJ, van den Akker HP, Koole R, Wirds J, van den Berg H. Treatment of central giant cell granuloma of the jaw with calcitonin. Int J Oral Maxillofac Surg 1999;28:372-6.
6. Elder JB, Berry C, Gonzalez-Gomez I, Kreger MD, McComb JG. Giant cell tumor of the skull in pediatric patients. Report of two cases. J Neurosurg 2007;107:69-74.
7. Fechner RE, Fitz-Hugh GS, Pope TL Jr. Extraordinary growth of giant cell reparative granuloma during pregnancy. Arch Otolaryngol 1984;110:16-9.
8. Garza-Mercado R, Cavazos E, Hernandez-Batres F. Giant cell reparative granuloma of the cranial vault: Exceptional bone lesion. Neurosurgery 1984;15:228-32.
9. Hirshk S, Katz A. Giant cell reparative granuloma outside the jaw bone: Diagnostic criteria and review of the literature with the first case described in the temporal bone. Hum Pathol 1974;5:171-81.
10. Kattner KA, Stroink A, Gupta K, Fukushima T, Li C. Giant cell tumor of the sphenoid bone. Skull Base Surg 1998;8:93-7.
11. Kim HJ, Lee HK, Suh DC, Choi CG, Kim JK, Lee JH, et al. Giant cell reparative granuloma of the temporal bone: MR findings with pathologic correlation. AJNR Am J Neuroradiol 2003;24:1136-8.
12. Larcher-enosub N, Pongtippan A, Tuntiyatorn L, Cheewaruangroj W, Bhummichitra K, Sirikulchayanonta V. Giant cell reparative granuloma concurrent with squamous cell carcinoma of the temporal bone: A case report and review of the literature. J Med Assoc Thai 2007;90:369-75.
13. Lee MY, Lee EJ. Giant cell tumor of the petrous temporal bone with direct invasion into the middle ear. J Craniofac Surg 2006;17:797-800.
14. Liu J, Zhong DR, Liu LF, Han DY, Yang WT, Jiang SC. Giant cell reparative granuloma of the temporal bone. Acta Otolaryngol 2001;121:523-8.
granuloma of the petrous bone: Demonstration of the proliferative component. Surg Neurol 1997;48:64-8.

16. Mercado GV, Shields CL, Gunduz K, Shields JA, Eagle RC Jr. Giant cell reparative granuloma of the orbit. Am. J. Ophthalmol 1999;127:485-7.

17. Moser A, Hoffmann KM, Walch C, Sovinz P, Lackner H, Schwinger W, et al. Intracranial reparative giant cell granuloma secondary to cholesteatoma in a 15-year-old girl. J Pediatr Hematol Oncol 2008;30:935-7.

18. Murphey MD, Nomikos GC, Flemming DJ, Gannon FH, Temple HT, Kranzdorf MJ. From the archives of AFIP. Imaging of giant cell tumor and giant cell reparative granuloma of bone: Radiologic-pathologic correlation. Radiographics 2001;21:1283-309.

19. Nackos JS, Wiggins RH 3rd, Harnsberger HR. CT and MR imaging of giant cell granuloma of the craniofacial bones. AJNR Am J Neuroradiol 2006;27:1651-3.

20. Oda Y, Tsuneyoshi M, Shinohara N. “Solid” variant of aneurysmal bone cyst (extragnathic giant cell reparative granuloma) in the axial skeleton and long bones: A study of its morphologic spectrum and distinction from allied giant cell lesions. Cancer 1992;70:2642-9.

21. Orto R, Bovo R, Ciorba A, Ceruti S, Martini A. Giant cell granuloma of the temporal bone: A case report. B-ENT 2008;4:45-8.

22. Reis C, Lopes JM, Carneiro E, Villainho A, Portugal R, Duarte F, et al. Temporal giant cell reparative granuloma: A reappraisal of pathology and imaging features. AJNR Am J Neuroradiol 2006;27:1660-2.

23. Rogers LF, Mikhail M, Christ M, Wolff A. Case report 276. Giant cell (reparative) granuloma of the sphenoid bone. Skeletal Radiol 1984;12:48-53.

24. Santos-Briz A, Lobato RD, Ramos A, Millán JM, Ricoy JR, Martínez-Tello Fj. Giant cell reparative granuloma of the occipital bone. Skeletal Radiol 2003;32:151-5.

25. Saw S, Thomas N, Gleson MJ, Bödi I, Connor S, Hortobágyi T. Giant cell tumour and central giant cell reparative granuloma of the skull: Do these represent ends of a spectrum? A case report and literature review. Pathol Oncol Res 2009;15:291-5.

26. Souter MA, Bird PA, Worthington JP. Giant cell reparative granuloma of the temporal bone treated with calcitonin. Otol Neurotol 2006;27:999-1002.

27. Whitehead RE, Melhem ER, Kasznica J, Eustase C, Telangiectatic osteosarcoma of the skull base. AJNR Am J Neuroradiol 1998;19:754-7.

28. Williams JC, Thorell WE, Treves JS, Fidler ME, Moore GF, Leibrock LG. Giant cell reparative granuloma of the petrous temporal bone: A case report and literature review. Skull Base Surg 2000;10:89-93.

29. Yamaguchi T, Dorfman HD. Giant cell reparative granuloma: A comparative clinicopathologic study of lesions in gnathic and extragnathic sites. Int J Surg Pathol 2001;9:189-200.