

Giant Cell Tumor of the Skull: Review of the Literature

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J Neurol Surg A 2016;77:239–246.

Abstract

Background Giant cell tumors (GCTs) are rare in the skull. The present report describes a case with a primary GCT located in the temporal bone and reviews the relevant literature. We also propose a treatment strategy for GCT of the skull.

Clinical Presentation A 41-year-old man presented with headache and auditory disturbance. Radiologic images showed a lytic expansive extradural lesion originating primarily from the right temporal bone and expanding into the middle cranial fossa and the infratemporal fossa. A biopsy specimen of the lesion was obtained from the external auditory meatus. Total removal was performed with temporal craniectomy, mandibular condylar process removal, tympanoplasty, and mastoidectomy.

Discussion The rate of recurrence of GCTs is related to complete resection and location of the GCT rather than to the degree of invasiveness. Some of the mononuclear cells and stromal cells in GCT express receptor activator of nuclear factor κ - β ligand (RANKL). Because inhibition of RANKL and bisphosphonate therapy might eliminate giant cells, this approach might be useful for recurrent or unresectable GCTs of the skull.

Conclusions Preoperative diagnosis by biopsy is important in determining the therapeutic strategy of GCTs. Complete resection is important to reduce the recurrence rate of GCTs in the skull.

Keywords

- ▶ giant cell tumor
- ▶ bisphosphonate
- ▶ RANKL
- ▶ denosumab
- ▶ temporal bone

Introduction

Giant cell tumors (GCTs) mainly originate in the metaphyseal region of the long bones, especially in the distal femur, proximal tibia, and distal radius. GCTs are rare primary bone neoplasms, representing only 5% of all bone tumors, and they are exceedingly rare in the skull.^{1–11} GCT in the skull was first reported by Echols in 1945,¹² and more than a dozen cases have since been described. GCTs of the skull occur most

frequently in the sphenoid and temporal bones and very rarely in the frontal, parietal, and occipital bones.^{4,6}

Although GCTs in the skull are characterized as benign, they can be locally aggressive and biologically unpredictable. Total surgical removal is frequently difficult, and the use of both adjuvant radiotherapy and chemotherapy remains controversial. Recent reports suggest that monoclonal antibody-based treatment and bisphosphonate may be useful for the treatment of GCTs of the long bones.^{13–17}

received

April 28, 2014

accepted after revision

March 10, 2015

published online

June 19, 2015

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Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0035-1554808>.
ISSN 2193-6315.

This report describes a case of primary GCT located in the temporal bone of the skull and reviews the relevant published literature in relation to diagnosis, treatment, and prognosis of this phenomenon. We conclude with suggestions concerning a treatment strategy for GCTs in the skull.

Case Presentation

A 41-year-old man presented with a 2-year history of headache and 1-year history of hypacusia. One week before, the headache in the temporal region and mandible became severe. He had a fever (38.8°C), stiff neck, and positive Kernig sign. His past medical history included cholelithiasis, and his family history was unremarkable.

Laboratory testing showed a C-reactive protein of 8.45 mg/dL and a white blood cell count of 9,300/ μ L. Cerebrospinal fluid (CSF) examination showed 71.5 cells/ μ L (mononuclear cell, 98%; polynuclear cell, 2%), a total protein of 98 mg/dL, and a glucose of 56 mg/dL. Xanthochromia was present. X-ray showed no neoplastic lesions on any of the epiphyses of the long bones. Head computed tomography (CT) showed a lytic expansive extradural lesion 5 cm in diameter originating primarily from the right temporal bone and expanding into

the middle cranial fossa and the infratemporal fossa. The mass lesion had an inhomogeneous low density and had calcification in the peripheral zone (**Fig. 1A**). This extradural lesion caused mass effect on the temporal cortex, and a low-density area was apparent in the temporal cortex. Contrast-enhanced CT revealed no areas of enhancement. Head magnetic resonance imaging (MRI) showed an extradural lesion that contained multilocular cysts. The periphery had a low intensity on T1-weighted imaging and in T2-weighted imaging and the center had a high intensity on T1-weighted imaging and T2-weighted imaging. Cysts of the tumor did not enhance, but the attached dura enhanced markedly (**Fig. 1B**). The low-density area in the temporal cortex on CT corresponded with an area of high density of T1-weighted MR imaging (**Fig. 1C**). Temporal bone target CT showed bony erosion of the middle cranial fossa and mandible and a mass lesion in the external auditory canal (**Fig. 1D**). Angiographic examination showed tumor stain from the right superficial temporal artery and the middle meningeal artery.

The patient was hospitalized, and meningitis was treated with a course of antibiotics. Biopsy of the lesion was obtained via the external auditory meatus under local anesthesia. Histologic examination showed findings consistent with

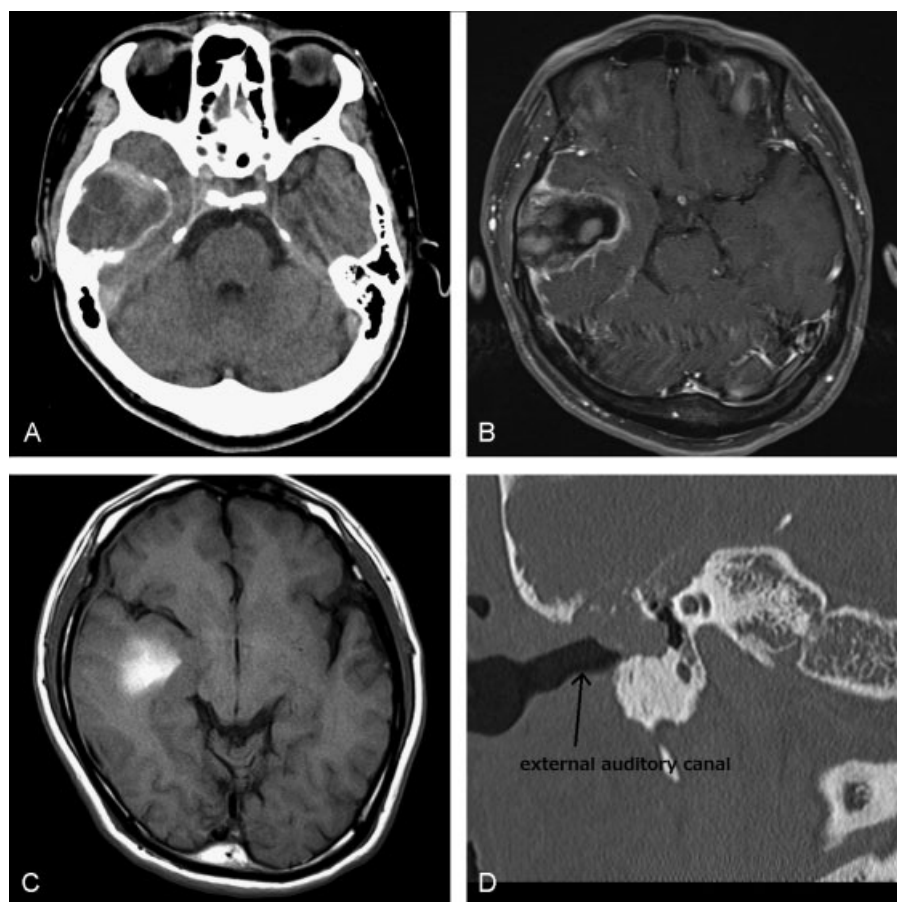


Fig. 1 (A) Axial plain computed tomography (CT) scan at the time of admission shows a lytic expansive extradural inhomogeneous mass 5 cm in diameter arising from the right temporal bone and compressing the temporal cortex. Calcification is present in the peripheral zone. (B) Axial enhanced magnetic resonance (MR) image shows an extradural lesion that contains multiple cysts without enhancement. The attached dura is well enhancing. (C) Axial plain T1-weighted MR image shows a high-intensity area in the right temporal cortex. (D) Target coronal CT scan of the right temporal bone shows an invaded base of the temporal fossa and a mass lesion extending toward the external auditory canal.

bone tumor including GCT of bone. Neuronavigation-guided tumor removal was performed with temporal craniectomy, tympanoplasty, mastoidectomy, and removal of the mandibular condylar process and zygomatic arch. The tumor had invaded into the squamous part of the temporal bone and temporal muscle, and it had some cysts with a soft membrane and a blood component. The contents of the tumor had the appearance of yellow powder, and the tumor was hypovascular. The dura and arachnoid were yellowish and thickened. The brain parenchyma had an appearance similar to that seen in a crush wound. The foramen rotundum was normal, but the foramen ovale and spinosum were destroyed. The Fallopian canal was not eroded and the chorda tympani was not invaded; the tympanic membrane and ossicles (malleus and incus) were eroded but the stapes was intact. The tumor was resected totally along with the eroded dura, then tympanoplasty (type III+ replacement cartilage with conductance), and mastoidectomy were performed. The defect in the dura was covered with periosteum, and the zygomatic arch and temporal convexity were reconstructed using a titanium mesh plate (►Fig. 3D).

Histologic examination showed that this tumor was composed of mononuclear cells and osteoclast-like multinucleated giant cells (►Fig. 2A), similar to the histologic findings of the biopsy specimen. The mononuclear cells resembled monocytes, and the nuclear atypia was mild to moderate. The nuclei of the multinucleated giant cells were similar to those of mononuclear cells. There was almost no mitotic figure. Areas of hemorrhage, hemosiderin deposition, necrosis, and fibrosis were seen, and multiple cystic changes were present. The cysts were filled with old blood and had a fibrous cyst wall without lining cells (►Fig. 2B). The tumor had expanded into the dura (►Fig. 2C). Staining for CD68 was positive on both multinucleated giant cells and mononuclear cells. The MIB-1 index was < 5%. Histopathologically, the tumor was diagnosed as GCT, and the cysts were considered to be secondary aneurysmal bone cysts.

Gross total resection of the tumor was achieved and confirmed by postoperative MRI (►Fig. 3A, B). The mass effect and the high-intensity lesion in the temporal cortex disappeared (►Fig. 3C). The low-density area on CT in the temporal cortex also disappeared. Three-dimensional CT showed a 57 × 28 mm skull defect (►Fig. 3D). The patient had no neurologic deficits after surgery. His chief complaint (headache) and his hearing loss resolved. At the 4-month follow-up, he has made satisfactory progress without recurrence.

Discussion

The present report described a case of GCT in the temporal bone and involving the zygomatic arch, temporal muscle, infratemporal fossa, ossicula auditus, and dura. GCT is a tumor that arises from connective tissue within bone marrow, and it usually involves the epiphysis of long bones. Although GCTs constitute 5% of all primary bone tumors, GCTs in the skull are very rare. Moreover, GCTs invading to the infratemporal fossa like our case was reported only in one case.¹⁸ We reviewed the published literature (►Table 1).

Symptoms

Symptoms of GCTs vary according to the location of the tumor and associated nerve invasion, although headache is a common symptom regardless of tumor location. GCTs of the temporal bone are usually associated with pain behind the ear, conductive hearing loss resulting from the tumor invading the infratemporal fossa and obstructing the eustachian tube, and facial weakness. GCTs involving the sphenoid bone are associated with headache, ophthalmoparesis, trigeminal hypesthesia, and visual disturbance. GCTs in the sellar region are associated with headache, visual field defect, blindness, diplopia, dysfunction of the second through eighth cranial nerves, neck pain, endocrinopathy, and mental status changes.²

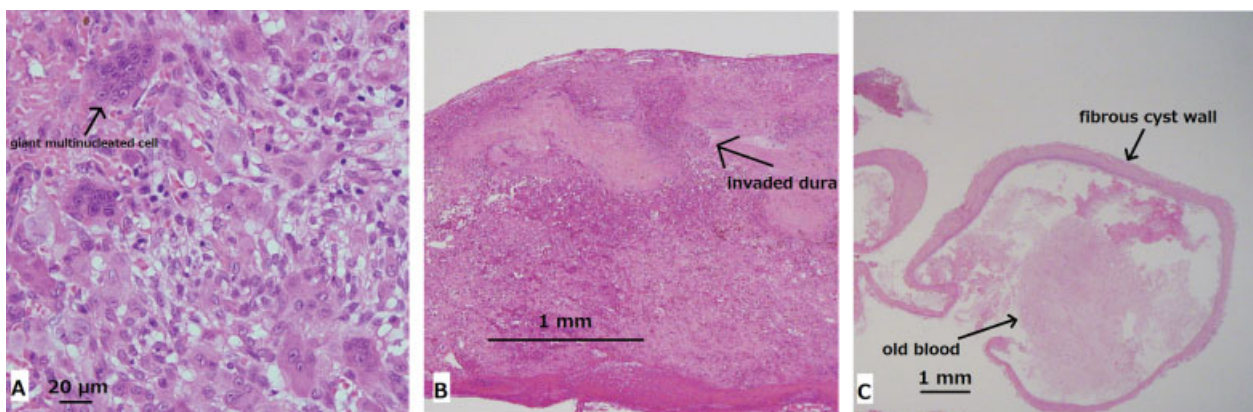


Fig. 2 (A) Photomicrograph showing a giant cell tumor section composed of mononuclear cells and scattered numerous giant multinucleated cells (hematoxylin and eosin [H&E] original magnification ×400; magnification bar: 20 μm). (B) Cross section of the vein with multinuclear giant cells in the dura (H&E original magnification ×40; magnification bar: 1 mm). (C) Cysts contain blood constituents; the cyst wall is fibroid and shows hyaline degeneration. The cysts do not adhere to solid tissue, mainly because tumor cells around the cysts underwent necrosis (H&E original magnification ×12.5; magnification bar: 1 mm).

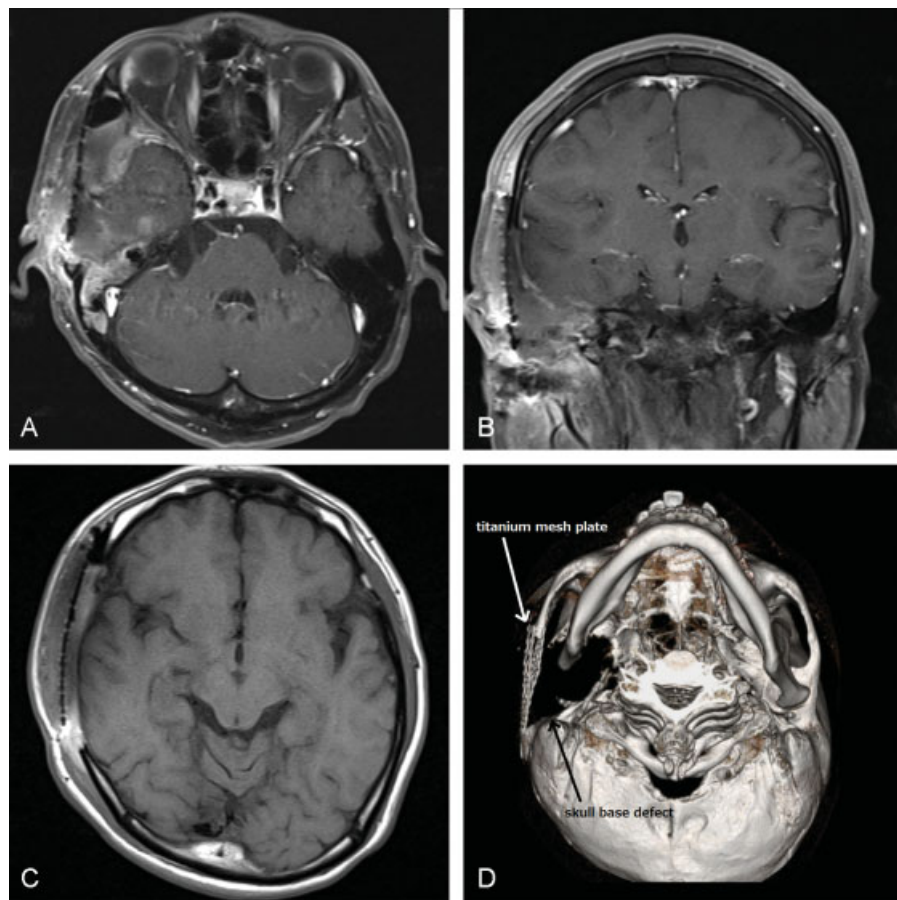


Fig. 3 (A) Axial enhanced T1-weighted magnetic resonance (MR) image after operation shows total removal of tumor and resolution of compression of the temporal cortex. (B) Coronal enhanced T1-weighted MR image after surgery shows the defect in the temporal skull base. (C) Axial plain T1-weighted MR image after operation shows disappearance of high-intensity area in the right temporal cortex. (D) Bone three-dimensional computed tomography scan shows a 57 × 28-mm temporal skull base defect and the removal of the processus condylaris. The temporal convexity and zygomatic arch are reconstructed using a titanium mesh plate.

In the present case, there was no apparent increases of polynucleate cells, but meningitis was suspected prior to surgery by the clinical appearance of stiff neck, headache, and fever. Chemical meningitis caused by the leak of the tumor component into the CSF is one possibility. A bacterial meningitis was considered to be unlikely, but if it would have been the case, a relation to the external auditory meatus or mastoid air cells could have been assumed.

There have been no reports of GCTs with meningitis in the published literature.

Histopathologic Data

GCTs of the temporal bone sometimes invade into the external auditory meatus. This allowed us to perform a preoperative biopsy using a fiberscope via the external auditory meatus. GCTs of the sphenoid bone are sometimes amenable to biopsy via the nasal cavity.

Osteoclast-like giant cells and their precursors express receptor activator of nuclear factor κ - β (RANK), and some mononuclear cells and stromal cells express RANK ligand (RANKL). RANKL has three isoforms and is usually produced as the membrane-bound type (RANKL 1). RANKL 2 has a shorter intracellular domain than the RANKL 1, and RANKL 3

lacks a transmembrane domain and is produced from RANKL 1 via cleavage by metalloprotease. RANKL 3 is thought to act as a soluble form of RANKL (sRANKL).^{19,20} It is said that the aggressive osteolytic activity of GCTs is related to RANKL 1 and 3. Thus RANKL 1 and 3 may represent therapeutic targets for the management of GCTs of the long bones.¹⁵

Differential Diagnosis

GCT is difficult to distinguish from giant cell reparative granuloma (GCRG) because these two lesions have a similar radiographic appearance. GCTs generally have larger giant cells and more nuclei when compared with GCRGs. Further, giant cells are found diffusely throughout the tissue in GCTs and tend to be localized in hemorrhagic sites in GCRGs. Bone cortex is destroyed in GCTs and maintained in GCRGs. GCTs tend to have a stronger degree of nuclear atypia and a greater number of mitosis when compared with GCRGs.

In the present patient, giant cells were seen diffusely throughout the tissue specimen (including the biopsy specimen obtained via the external auditory meatus) with a locally aggressive appearance. Also, the specimen had a mild degree of nuclear atypia and few mitoses. While the specimen showed necrosis, it was difficult to differentiate

Table 1 Summary of reported giant cell tumors^a

Study	Age, y sex	Duration of symptoms	Location	Cysts	Size, mm	DI	PI	Treatment	Outcome (duration)
Chan et al ³²	77, M	1 wk	sphe	-	NA	NA	NA	Biopsy	D (7 mo)
Chiarini et al ¹	70, M	NA	tem	-	25	-	-	Surg	NR (3 y), LM
Company and Ramos ³³	19, M	5 mo	sphe	-	NA	NA	NA	SR	RE (2 mo)
Elder et al ²	2, F	5 mo	tem	-	70	+	-	PR	NR (13 mo)
	7 wk	NA	tem	-	NA	-	-	TR	NR (11 mo)
Epstein et al ³⁴	25, M	3 y	tem	-	100	NA	NA	PR	NR
	48, M	4 y	unc	+	NA	-	-	SR + rad (76 Gy) + chemo (MTX)	NR
Findlay et al ³	23, M	7 mo	tem	-	60	+	-	PR + rad (50 Gy)	NR (8 mo)
Ohaegbulam et al ³⁵	25, M	8 mo	sphe	NA	NA	+	-	PR	NR
Gupta et al ²²	17, F	6 mo	cliv	+	76	-	-	Surg + rad (45 Gy)	NR (2 y)
Harris et al ⁴	24, F	NA	occip	-	NA	+	-	Surg	NR
He et al ³⁶	34, M	10 y	tem	-	NA	+	-	SR	NR
Iizuka et al ⁵	32, M	2 y	tem	-	30	+	-	TR	NR (4 y)
Isaacson and Berryhill ²¹	42, M	3 y	tem	-	40	+	+	TR	NR
	47, M	NA	tem	NA	NA	NA	NA	SR	RE (1 y)
Wolfe et al ¹⁰	25, F	9 mo	sphe	NA	NA	NA	NA	SR + rad	NR (14 y)
	16, F	7 wk	sphe	NA	NA	NA	NA	PR + rad	NR (8 y)
	19, F	2 y	sphe	NA	NA	NA	NA	SR + rad (60 Gy)	NR (10 y)
	20, M	2 mo	sphe	NA	NA	NA	NA	PR + rad	NR
	29, F	22 mo	sphe	NA	NA	NA	NA	TR + rad	RE (5 y)
	69, M	1 y	sphe	NA	NA	NA	NA	Surg	D (9 d)
	23, M	1 y	sphe	NA	35	NA	NA	Biopsy + rad	D (1 y)
	35, M	Several years	sphe	NA	NA	NA	NA	SR + rad	NR
	16, M	4 mo	sphe	NA	NA	NA	NA	SR + rad	NR
	19, M	8 mo	sphe	NA	NA	NA	NA	PR + rad	NR
Kamoshima et al ⁶	12, F	2 mo	fron	-	20	+	-	TR	NR (18 mo)
Kashiwagi et al ⁷	17, F	NA	tem	+	NA	NA	NA	Surg	NR
	20, M	NA	tem	+	NA	NA	NA	NA	NA
	31, M	NA	tem	-	NA	NA	NA	NA	NA

(Continued)

Table 1 (Continued)

Study	Age, y sex	Duration of symptoms	Location	Cysts	Size, mm	DI	PI	Treatment	Outcome (duration)
	12, F	NA	sphe	-	NA	NA	NA	NA	NA
	35, M	NA	sphe	+	NA	NA	NA	NA	NA
Watkins et al ³¹	23, F	7 wk	sphe	-	20	-	-	TR	NR
	27, F	5 mo	sphe	-	NA	-	-	Surg + rad	RE (3 mo)
Lee et al ³⁷	20, M	1 mo	tem	-	50	-	-	SR	NA
Matsushige et al ³⁸	77, F	Sudden onset	tem	+	NA	NA	NA	SR	NR
Motomochi et al ³⁹	38	3 mo	tem	+	120	-	-	SR + rad (45 Gy)	NR
	53	1 mo	occip	-	40	-	-	TR + rad (30 Gy)	NR
Pai et al ⁴⁰	26, M	2 y	tem	+	NA	-	-	TR	NR
Pitkethly and Kempe ⁴¹	13, F	3 y	sphe	NA	NA	-	-	Biopsy + rad (50 Gy)	NR (2 y)
	23, M	2 mo	sphe	NA	NA	+	-	PR + rad (49.5 Gy)	NR (6 mo)
Carmody et al ⁴⁶	16, M	6 wk	sphe	-	45	-	-	SR + rad (50 Gy)	NR (10 mo)
Reed et al ⁴²	3, M	4 mo	unc	+	30	-	-	TR	NR
Rock et al ³⁰	32, F	1 y	sphe	-	50	-	-	TR	NR (6 mo)
Sheikh et al ⁴³	14, M	8 mo	tem	-	NA	-	-	Surg	NR
Silvers et al ⁴⁷	55, F	1 y	tem	+	20	NA	NA	TR	NR
Spallone et al ⁴⁴	46, M	8 mo	tem	-	50	+	+	SR	NR (10 mo)
Tang et al ⁹	61, F	3 mo	tem	-	NA	-	-	PR + rad (54 Gy)	NR
Yamamoto et al ¹¹	31, F	8 wk	sphe	-	NA	NA	NA	PR + chemo (adri)	RE (5 mo)
	45, F	NA	sphe	-	NA	-	-	PR + rad + chemo (adri)	RE (2 y)
Zorlu et al ⁴⁵	14, F	2.5 mo	sphe	-	60	-	-	SR + rad (60 Gy)	RE (3 mo)

Abbreviations: adri, Adriamycin; chemo, chemotherapy; cliv, clivus; DI, dura invasion; D, dead; F, female; fron, frontal; LM, lung metastasis; M, male; MTX, methotrexate; NA, not available; NR, no recurrence; occip, occipital; PI, parenchyma invasion; PR, partial removal; rad, radiation; RE, recurrence; sphe, sphenoid; SR, subtotal removal; Surg, surgery; tem, temporal; TR, total removal; unc, unclassified.

^aThis article reviewed age, sex, duration of symptoms, location, cysts, size, dura invasion, parenchyma invasion, treatment, and outcome. The table shows that invasion to brain parenchyma is extremely rare. The effect of radiation and chemotherapy is controversial.

between primary necrosis due to tumor itself and secondary necrosis.

Paget disease of the bone is sometimes complicated by GCT. It usually shows a high level of alkaline phosphatase, increase in the density of the bone, formation of bone trabeculae, thickened cortical bone, and sclerosis that is said to have a cotton wool like appearance in X-ray. Histopathologically, Paget disease shows a mosaic pattern with mixed sclerosis and absorption. Basically, GCT caused by Paget disease originates in the metaphyseal region of long bones, skull, facial bone (especially bones of the jaw), and spine. If GCT is located in the bones of the jaw, Paget disease must be considered.²¹ The present case did not have these characteristics.

Aneurysmal bone cysts are benign lesion composed of large vascular spaces separated by trabeculae of connective tissue and bone. GCT is sometimes complicated by secondary aneurysmal bone cysts, so it is important to distinguish between GCT and primary aneurysmal bone cysts. Radiographically, GCT also involves the epiphysis, which is in contrast with aneurysmal bone cysts that usually originate in the diaphysis. Histopathologically, if tumor components are seen, it is not a primary aneurysmal bone cyst.²¹ In the present case secondary aneurysmal bone cysts were seen.

Treatment

Although GCTs in the skull are locally aggressive, a malignant phenotype exists in only 5 to 10% of cases. Patients who may benefit from chemotherapy are either those with GCTs that are incompletely resectable or those with GCTs that are not suitable for surgery. No standard chemotherapy protocol exists for the treatment of GCTs.¹¹ Patients have been treated with interferon- α and chemotherapeutic regimens consisting of methotrexate, cyclophosphamide, and doxorubicin with limited success. Some reports have described the use of radiation therapy alone or after surgery for patients with GCTs.^{3,9,11,22} However, radiation may cause a sarcomatous transformation in the residual tumor tissue. Other authors believe that GCTs are not radiosensitive.^{2,6,11} Recent reports suggest that RANKL 1 and 3 are targets of treatment for GCTs of the long bone.^{15,16} Denosumab is a fully human monoclonal antibody that specifically inhibits membrane-bound and soluble RANKL, thereby inhibiting osteoclast-like giant cell-mediated bone destruction. One article showed that denosumab was effective in 86% of the patients who had unresectable and recurrent GCTs of the long bones.¹⁵ The histopathologic characteristics of GCT in the skull are similar to GCT of the long bones. In the same way, we believe that denosumab might inhibit bone destruction and eliminate giant cells in the skull. However, denosumab is not currently approved for use in Japan.

In the present case, the concentration of sRANKL in the serum was 18.5 ng/mL (296 pmol/L), which is higher than that seen in control patients (62 ± 43 pg/mL).²³⁻²⁶ Possibly, sRANKL can be useful detecting recurrence at an early stage because some previous reports showed that the aggressive osteolytic activity of GCTs are related to RANKL 3.¹⁵ The level

of sRANKL can be easily monitored through sampling of peripheral blood.²⁷

Antiosteoclastic agents such as bisphosphonates have the same effect as denosumab. Bisphosphonates can be used to mitigate bone destruction and prevent local recurrence following surgery in patients with osteolytic neoplasms, such as GCTs of the long bones.^{13,15-17,28,29} One study suggested that postoperative treatment of patients with GCTs in the long bones with oral bisphosphonate produce symptomatic benefit and decrease recurrence rates, even though no change in tumor size was observed with preoperative treatment.¹⁶ So we utilized an oral bisphosphonate for our patient after discharge to prevent recurrence.

Prognosis

GCTs in the skull have a low potential for metastasis, but they are locally aggressive and accompanied by a high rate of recurrence (40–60%).^{27,30} Therefore they are not strictly clinically benign. In our review, the recurrence rate was 22%. Preoperative diagnosis by biopsy is thus very important to help guide whether complete resection should be performed or not because the risk of recurrence is related to the degree of resection rather than to the degree of invasiveness. The risk of relapse also varies according to the location of GCTs. For example, the GCTs of the sphenoid bone cannot be resected completely because the cavernous sinus is often involved. By contrast, GCTs of the temporal bone are relatively easy to resect.³¹

A few reports describe the relationship between the removal and recurrence rate. Only 1 of 11 patients with total removal had a recurrence, whereas 5 of 11 patients with subtotal removal experienced recurrence. In our review, the maximum time to recurrence was 60 months (average: 15 months). Close follow-up is necessary for at least a period of 60 months, especially during the first year after surgery.

Our review of the published literature showed that 3 of 50 patients died. One such case was related to sepsis and a cerebrovascular accident.³ The other cases of death were related to multifocal gastroduodenal ulceration and tumor growth.¹⁰

Conclusions

Preoperative diagnosis by biopsy is critical to help guiding the therapy. Complete resection of the tumor is important to reduce the risk of recurrence. It is often difficult to remove the tumor totally in some locations such as the sphenoid bone; therefore bisphosphonates may be useful in patients with recurrent or unresectable GCTs.

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