Abstract
Giant cell tumors (GCTs) are rare, usually affecting the epiphyses in long bones of the extremities. GCTs may be locally aggressive with a high rate of local recurrence and exhibit the potential for distant metastasis. They seldom occur in the skull, where they preferentially affect the sphenoid and temporal bones. Several case reports with follow-up describe gross total resection of skull-base GCT to be curative. Radiation therapy, although controversial, is reserved for lesions that cannot be completely resected. Here, we describe the case of an 18-year-old female with GCT of sphenoid bone who underwent subtotal resection followed by adjuvant radiotherapy, although whose radiotherapy could not be completed because of her demise due to erythema multiforme associated with phenytoin and cranial radiation therapy syndrome.

Keywords: Erythema multiforme associated with phenytoin and cranial radiation therapy syndrome, giant cell tumor, radiotherapy, sphenoid bone

Introduction
Giant cell tumors (GCTs) are considered to be locally aggressive benign tumors, also known as osteoclastoma, which typically occurs in the epiphyses of long bones, particularly the distal femur, proximal tibia, distal radius, and proximal humerus. GCT rarely manifests in the skull, accounting for <1% of all GCTs of the bone, primarily involving the sphenoid and temporal bones in the middle of the cranial fossa.[1‑3] It has a tendency toward local recurrence and late malignant change with metastases, especially to the lung.[4,5] Due to the small number of skull GCTs reported in the literature, standard treatments remain unclear, and the efficacy of surgery as well as adjuvant therapies remains undefined. Due to the rarity of the presentation of GCT of the sphenoid bone, we report this case, who was treated with subtotal resection followed by adjuvant radiotherapy, but unfortunately, radiotherapy could not be completed as the patient died due to erythema multiforme associated with phenytoin and cranial radiation therapy (EMPACT) syndrome.[6]

Case Report
An 18-year-old female presented with headache and numbness above her right eye for 2 months refractory to all medical management. Examination of the cranial nerves revealed facial paresthesia along the distribution of ophthalmic (V1) division of the right trigeminal nerve (CN V). Ophthalmological and rest of the neurological examinations were normal, there was no evidence of any endocrine disorder, and the medical history was noncontributory. Contrast enhanced computed tomography scan revealed an ill-defined enhancing lesion in infrasellar region with extension to sella and suprasellar region displacing pituitary gland. The mass involved superficial part of clivus and also encased cavernous sinuses and internal carotid arteries (ICA) bilaterally. It also involved ethmoidal air cells anteriorly and extended up to preoptic cistern posteriorly [Figure 1]. Gadolinium-enhanced magnetic resonance imaging (MRI) scan reconfirmed the presence of a large tumor mass involving sellar region. The tumor revealed low signal intensity on T1 and T2-weighted images (WIs) with moderate heterogeneous
Biswas and Halder: Giant cell tumor of the sphenoid bone

enhancement [Figure 2]. She underwent frontotemporal craniotomy with zygomatic-osteotomy with subtotal resection of tumor extracranially. Portions of the tumor encasing ICA and sinus could not be removed. Histopathological examination was compatible with GCT of bone, grade-2; base of the skull [Figure 3]. She was planned to receive three-dimensional conformal radiotherapy to deliver a total dose of 45 Gy in 25 fractions over 5 weeks. However, after 2 weeks of treatment, she developed seizures for which injection phenytoin was administered subsequent to which she developed erythema multiforme majus (EMM)-like lesions which started within the radiation portals initially with subsequent development of toxic epidermal necrolysis (TEN). The patient succumbed to death thereafter.

Discussion

GCTs are generally considered histologically benign; however, they may exhibit locally aggressive behavior with a high rate of local recurrence of up to 60% if treated purely by intralesional curettage. In addition, GCTs exhibit the potential for distant metastasis, most commonly to the lung, which occurs in 4% of patients with GCT.[7] The incidence of GCT is low, accounting for only ~4%–5% of primary tumors of the skeleton; and it occurs more frequently in females than in males, between the second and fourth decades of life following skeletal maturation.[8] GCTs most frequently occur in the metaphyses of long bones, but rarely in the skull, accounting for <1% of bone GCTs, where it is usually located in sphenoid and temporal bone. In the present case, the tumor primarily arose from infrasellar region. Skull-base GCTs generally present with headache, decreased vision, visual field defect, diplopia, ophthalmoplegia, deafness, endocrinopathy and dysfunction of cranial nerves, most commonly the sixth followed by the third cranial nerve.[9] However, our patient developed a headache and facial numbness which indicated the involvement of the fifth cranial nerves. X-ray and Computed tomography scan of skull GCTs frequently demonstrate expansive and occasional lytic bone lesions usually without the classical “soap bubble” appearance. On MRI, GCTs are usually hypointense or isointense on T1-WIs and T2-WI with contrast enhancement.[10,11] A similar pattern was observed in the present case. The major radiological differential diagnoses include chordoma, giant-cell reparative granuloma, aneurysmal bone cyst, fibrous dysplasia, “brown tumor” of hyperparathyroidism, eosinophilic granuloma, and plasmacytoma. Imaging examination alone is insufficient to differentiate these lesions, and thus the final diagnosis is dependent on histopathology. Histologically, GCTs are primarily composed of mononuclear stromal cells and giant cells. Cellular morphology is sufficient for the diagnosis of GCT and immunochemistry is not essential.

The clinical behavior of GCT is unpredictable, and thus treatment remains controversial. Radical surgical extirpation is the treatment of choice for cranial GCT, which requires complete removal of the diseased bone. However, this may not be possible due to anatomical location or the involvement of vital structures, as observed in the present case. Therefore, the recurrence rate is very high, and the use of adjuvant therapy is invaluable.[12,13] GCTs were previously considered to be radioresistant with a potential for sarcomatous transformation following radiotherapy. However, along

Figure 1: Contrast enhanced computed tomography scan revealing an ill-defined enhancing lesion in infrasellar region involving ethmoidal air cells

Figure 2: Gadolinium-enhanced magnetic resonance imaging (a) coronal view, (b) axial view showing tumor extensions

Figure 3: Histopathology revealing giant cell tumor
with the development of modern megavoltage irradiation and precise image-guided system, the tumor control rate has significantly improved, and the frequency of malignant transformation has reduced. Therefore, radiotherapy is recommended as a postoperative adjunctive therapy particularly for incomplete resection in skull base, with a dose of 45–50 Gy to gain a recurrence-free survival.\[14\] In our case, adjuvant radiotherapy was started but stopped midway as the patient developed phenytoin-induced EMM-like lesions within radiation portal which progressed to TEN. EMM, Stevens-Johnson syndrome (SJS), or TEN represent a spectrum of hypersensitivity reactions associated with the use of antiepileptic drugs including phenytoin, phenobarbital, carbamazepine, valproate, and lamotrigine, the incidence with phenytoin being as high as 15% for SJS and 2.4% for TEN, especially in the first 8 weeks of use.\[15,16\] Concurrent use of radiation therapy has rarely been seen to produce intensification of these reactions in the radiotherapy treatment portals. The authors suggested the acronym “EMPACT” to describe this disorder.\[6\] There is increasing anecdotal support in the literature for a synergistic effect between phenytoin therapy and cranial radiotherapy that can result in the life-threatening SJS.\[17\] The immunological mechanisms underlying EMPACT are still unclear and subject to speculations. In 1988, Delattre et al. already speculated about an immunological mechanism underlying a phenomenon similar, if not identical, to that described as EMPACT nowadays.\[18\]

Systemic chemotherapy may be considered if local control fails following radiotherapy or distal metastases are identified. Studies have indicated that topical or systemic use of bisphosphonates may present a novel adjuvant therapy for GCT by inducing apoptosis of stromal tumor cells and stimulating osteogenic differentiation of the remaining tumor stromal cells following surgery.\[19,20\] In one case report by Goto et al., Denosumab, a monoclonal antibody functioning as an RANKL inhibitor was tried in a postoperative setting which resulted in marked shrinkage of tumor.\[21\] Radiographical and histological grading systems do not predict clinical outcome; however, the extent of surgical resection has been shown to affect prognosis. The majority of recurrences occur within the first 2 years following treatment, although late recurrences have also been reported and thus long-term surveillance is recommended.\[22\]

**Conclusion**

GCTs are generally benign, locally aggressive lesions with a potential to metastasize. Surgical extirpation is the standard treatment for skull-based GCT, and adjuvant radiation must be applied in all cases due to the high rate of local recurrence and since complete resection cannot be achieved. Bisphosphonate administration is also recommended.

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**Conflicts of interest**

There are no conflicts of interest.

**References**