Malignant giant cell tumor in the posterior fossa of a neonate

Case report

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Giant cell tumors (GCTs) of the bone are rare, usually benign but locally aggressive neoplasms that primarily occur in the epiphyses of long bones. They seldom develop in the cranium; when they do, they involve principally the sphenoid and temporal bones. These tumors usually affect young adults, and few reports in children have been published. Primary malignant GCTs of the skull are even more uncommon. The 3 published cases all involved adults over 40 years of age. Herein, the authors present a case of a highly aggressive primary malignant GCT of the posterior fossa in a 5-week old preterm infant. One month after the gross-total resection of the tumor found in the bone, the infant’s condition rapidly deteriorated and she died. Magnetic resonance imaging and postmortem examination revealed a tumor larger than it had been before the operation, with expansion toward the brain. To the best of the authors’ knowledge, this is the youngest patient reported with a primary malignant GCT of the skull, and actually the first case in a pediatric patient. In addition, the extremely high growth rate of the tumor in the postoperative period renders this case the most aggressive primary malignant GCT of the cranium described so far.

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Key Words • giant cell tumor • malignant tumor • posterior fossa

Giant cell tumors of the bone (osteoclastomas) are rare primary bone neoplasms, representing approximately 5% of tumors of the skeleton. They usually affect young adults in their 3rd or 4th decade of life; occurrences before puberty are exceptions. The epiphyses of long bones, especially the distal femur, proximal tibia, and distal radius account for 75–90% of GCTs, although several cases of unusual localization have been documented. The cranium is involved infrequently, and when it is, the tumors show a predilection for the sphenoid and temporal bones. Giant cell tumors of the bone are generally regarded as benign lesions, even though a tendency toward local recurrence and late malignant change with metastasis has been reported. Malignancy diagnosed at initial presentation is extremely rare.

In this report, we present a case of a primary malignant GCT of the posterior fossa in a 5-week old preterm infant, who died 1 month after gross-total resection of the tumor. We discuss both diagnostic and therapeutic considerations based on a review of the pertinent literature.

Case Report

This female infant was born to an Asian mother and a Caucasian father at 27 gestational weeks. At birth, she weighed 1.1 kg. She was initially administered 1 dose of surfactant and then was extubated 2 hours after birth and treated with nasal CPAP with room air. The results of repeated cerebral ultrasound examinations were normal. At the age of 3 weeks (30 gestational weeks), a fluctuating left-sided facial paresis was suspected. Two weeks later (32 gestational weeks, weight 1.6 kg) she developed acute hydrocephalus, bradycardia, and hypotension.

Imaging Findings. Magnetic resonance imaging revealed a large (35 mm diameter), low T2 signal intensity, high T1 signal intensity, homogenously enhancing posterior fossa tumor, originating from the bones of the skull base—the right temporal bone and the right margin of the clivus (Figs. 1 and 2). This large tumor was causing severe compression of the brainstem, cerebellum, and
fourth ventricle. A high-signal intensity rim indicative of edema was seen in the pons adjacent to the tumor, but no obvious infiltration of the brain was detected.

**Operations.** A ventriculostomy was performed as an emergency procedure, and the extraaxial tumor (lacking an intraaxial component) involving the posterior fossa was microsurgically resected with the infant in a prone position 1 day later.

**Postoperative Course.** The infant was extubated and showed temporary relief of signs and symptoms. The ventricular catheter was removed, and subsequent ultrasound examination showed that the size of the ventricles remained stable. An MR imaging study performed on the 3rd postoperative day showed gross-total resection of the tumor in the posterior fossa but residual tumor at the temporal bone and clivus and more widespread edema in the brainstem (Fig. 3). Four weeks later (36 gestational weeks) the infant’s condition rapidly deteriorated, and additional MR imaging showed hydrocephalus and an even larger tumor in the posterior fossa than had been originally seen, with signal intensities and contrast enhancement pattern of the tumor identical to the original findings. The infant died the next day.

**Histopathological and Autopsy Findings.** Histopathological assessment of the surgical samples displayed numerous osteoclast-like giant cells surrounded by a dense population of quite homogeneous mononuclear cells that showed a high tendency toward both proliferation and apoptosis. No osteoid-like material was seen in the surgical specimen. A sarcomatous spindle cell component was detected focally but it was very limited (< 10%). Immunohistochemical staining with antibodies directed to α-fetoprotein, human gonadotrophin, placental antibody, glial fibrillary acidic protein, microtubule-associated protein 2, neurofilament, and synaptophysin were all negative. Giant cells were immunohistochemically labeled with a histiocyte marker such as CD68 but were negative for labeling with markers such as S100 protein and CD1a. Based on these findings, the tumor was classified as being a malignant GCT of the bone (Fig. 4). At autopsy, tumor growth was seen in the posterior fossa. The cerebellum was macroscopically altered (Fig. 5a), and in cross-sectioning of the brainstem and cerebellum some quite well demarcated nodules of tumor were seen (Fig. 5b and c). The histological assessment of the postmortem material revealed a GCT, consistent with previous findings in the surgical specimen (4 weeks earlier). It is noteworthy that the sarcomatous

![Fig. 1. Preoperative MR images. a: Axial T2-weighted image. b and c: Axial T1-weighted images before (b) and after (c) Gd administration. The tumor is relatively homogeneous and shows a very low T2 signal intensity and high T1 signal intensity (compared with brain) and enhances homogeneously. Note also the wide temporal horns indicative of obstructive hydrocephalus.](image1)

![Fig. 2. Preoperative MR images showing infiltration (arrows) into the right temporal and occipital bones. a: Axial T2-weighted image. b and c: Coronal T1-weighted images before (b) and after (c) Gd administration.](image2)
component was still inconspicuous, seen only focally. The tumor was pressing toward the brain parenchyma with a demarcated margin, and reactive gliosis was noted in the brain parenchyma itself.

**Discussion**

Malignancy develops in only 5–10% of GCT cases, and most of the cases of GCTs of the cranium reported in the literature are benign. Primary malignant GCTs presenting with aggressive and malignant behavior from the onset are extremely uncommon, even in the long bones of the appendicular skeleton. To the best of our knowledge, only 3 cases of primary malignant GCT of the skull have been reported previously. The first case concerned a 41-year-old man with a malignant GCT of the sphenoid bone, who received radiation therapy. No recurrence of the tumor was found 15 months after the diagnosis (last follow-up). Another case of primary malignant GCT of the parietal bone was reported in an 81-year-old woman. Surgical resection was performed, and histological examination of the lesion demonstrated Paget disease with a malignant GCT. The patient experienced local recurrence of the malignant GCT and eventually died 18 months after the initial presentation, having developed pulmonary metastases. Finally, the third well-documented case was a primary malignant GCT of the skull arising from the sphenoid bone in a 77-year-old man. The patient and his family refused any treatment after the biopsy of the tumor, and he died 7 months later from sepsis and stroke—unrelated to the tumor, although the tumor was still present—without evidence of disseminated disease.

There has been some deliberation in the literature about what constitutes a malignant GCT of the bone, and a variety of criteria have been used to establish the diagnosis. The original classification of malignant GCTs by Jaffe et al. separated these lesions into 3 categories, representing a continuum from benign (Grade I) to intermediate (Grade II) and malignant (Grade III). Recent WHO recommendations regarding malignancy in GCT use the terms primary and secondary malignant GCT, as originally defined by Hutter et al. The secondary malignant GCT is a high-grade spindle cell sarcoma lacking residual GCT that develops at the site of a benign GCT treated surgically or with radiation therapy. In the primary malignant GCT, in contrast, areas of conventional GCT are present with abrupt transition to a sarcomatous spindle cell component. Histologically, in the current case the dominant feature was the clearly malignant-appearing homomorphous stroma cells intermingled with benign osteoclast-type giant cells associated with abnormal mitotic figures and combined with foci that were indistinguishable from benign GCT. In addition, conspicuous areas of the sarcomatous component were seen, and thus the diagnosis of malignant primary GCT was justified. A tumor that might be difficult to differentiate histologically from a malignant GCT, especially in patients with Paget disease, is

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**Fig. 3.** Midsagittal and axial T1-weighted Gd-enhanced MR images obtained before surgery (a and b), 3 days after resection (c and d), and 1 day before death (e and f). The majority of the tumor was successively resected, but a narrow layer of enhancing tumor remained on the posterior margin of the clivus and inside the right temporal bone (not shown). Postoperative edema, some traces of blood, small bubbles of air and some enhancement on the surface of the brainstem can be detected as postoperative changes in c and d. The images from the last study (e and f) show the large recurrence of the enhancing tumor with hydrocephalus.
the giant cell–rich osteosarcoma. This tumor may contain fields of benign-appearing osteoclast-type giant cells, and the features of anaplasia might be minimal. For the diagnosis of giant cell–rich osteosarcoma in the midst of the neoplastic cells, osteoid (that is, tumor bone produced by the atypical stromal cells) is seen.

Radiographic features of GCTs typically include a radiolucent, osteolytic lesion causing bone erosion, with-

Fig. 4. Histological and immunohistochemical features of a malignant GCT. a: Staining with H & E showing giant cells. b: Staining for Ki 67 showing very high proliferative activity in tumor. c: Staining for CD68 immunoreactivity showing giant cell activity. d: Results of CD1a staining showing lack of labeling of tumor cells. Original magnifications × 10 (inset × 40).

Fig. 5. Gross view of the brain (weight 400 g). The large hemispheres were unaffected except that the ventricles were somewhat enlarged. The infratentorial structures were largely altered. a: Note the large tumor (dotted line) at the base deforming the cerebellum and brainstem, measuring up to 4 cm in diameter. The identifiable cerebellar hemisphere is marked with open stars. b: Cross-section through the cerebellum and brainstem approximately at the level of the medulla. The tumor components are marked with dotted lines, the vermis with open stars. c: Cross-section at the level of the caudal parts of the pons. The base of the pons is marked with a black star and the vermis with an open star. Note the nodular growth pattern of the tumor.
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out a sclerotic rim, but with sharp margins on CT.4 The plain film characteristics of GCTs in adults are indistinguishable from those of other radiolucent lesions of the skull. Magnetic resonance imaging demonstrates a well-circumscribed lesion that is isointense on T1-weighted images and hypointense on both T2-weighted and diffusion-weighted images. The mass typically enhances heterogeneously. The major radiological differential diagnosis includes giant cell reparative granuloma and brown tumors of hyperparathyroidism.5,28 A CT study alone is not sufficient for the differentiation of GCTs from these lesions. However, giant cell granulomas are often preceded by a history of tooth extraction or trauma, while brown tumors are usually multiple and demonstrate other imaging and laboratory evidence of hyperparathyroidism. The MR imaging characteristics of the tumor in our neonatal case showed a characteristically hypointense pattern on T2-weighted images, but the other characteristics were less typical; on the T1-weighted images the signal was hyperintense, and the enhancement pattern was homogeneous rather than heterogeneous as reported previously. Although the tumor origin from the bone was correctly depicted, and the aggressive malignant behavior was obvious on the basis of the previous normal ultrasound examinations, the accurate histopathological diagnosis could not be predicted from the MR images.

The definitive treatment for GCTs of the bone is surgical extirpation. The value of radiation therapy is debated because GCTs were initially thought to be radioresistant and malignant transformation following radiation treatment has occurred.29 However, advances in radiation therapy have led to recent reports of its safety and efficacy in the management of GCTs,18,32 especially when either the lesions are anatomically inaccessible or surgical excision is judged to be incomplete.2 In addition, chemotherapy using adriamycin has proved to be effective in controlling local disease in surgically inaccessible and radioresistant tumors, as well as in remnant or recurrent tumors.33 As diagnosed in our patient, primary malignant GCTs are extremely rare.3,29,31 The prognosis for a patient with such a tumor is poor, and most of the patients die rapidly, usually within a few months to 1 year.9,13,15 To the best of our knowledge, we present the most aggressive GCT of the skull ever reported, since our patient died 1 month after surgery with a tumor larger than it was before the operation. Because of the rarity of malignant GCTs of the skull, no consensus on treatment or prognosis can be proposed. However, complete surgical excision to forestall local recurrence should be the goal, with radiation therapy and/or chemotherapy reserved for unresectable or incompletely extirpated tumors. Unfortunately, in the case we present here, the progress of the tumor in the postoperative period was so extremely rapid that there was no time for additional interventions.

Conclusions

Primary malignant GCTs of the skull are extremely rare and only 3 cases have been reported to date, all of which were in patients over the age of 40 years. This report contributes another case of a primary malignant GCT of the skull to the literature. It is noteworthy that the case described here was highly malignant, being the most aggressive malignant GCT of the skull ever reported. Histologically the tumor displayed a conspicuous sarcomatous component whereas the conventional GCT pattern with brisk mitotic activity dominated. More importantly, our case represents the youngest patient harboring such a tumor. The rapid progression to death due to recurrence of the tumor just 1 month after surgery was quite unexpected.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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