Osteosarcoma of the cranial vault and skull base in pediatric patients

Report of 3 cases

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Cranial osteosarcoma is very rare in children, rendering the development of optimal treatment algorithms challenging. The authors present 3 cases of pediatric cranial osteosarcoma: a primary calvarial tumor, a cranial metastasis, and a primary osteosarcoma of the cranial base. A review of the literature demonstrates significant variation in the management of cranial osteosarcomas and the outcome for patients with these tumors. This series and literature review is presented to improve the understanding of pediatric cranial osteosarcoma and to reinforce the importance of maximal resection in optimizing outcome.

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Key Words • osteosarcoma • calvaria • pediatric • skull base • metastasis • craniofacial • oncology

OSTEOSARCOMA is an aggressive malignancy of primitive mesenchymal cell origin.29,57 Although it is the most common primary bone tumor in people of all ages, osteosarcoma accounts for only 3%–5% of all childhood malignancies.41,47 Pediatric osteosarcomas most commonly arise in the appendicular skeleton, with 85% occurring in the metaphyses of long bones, particularly the distal femur and proximal tibia. In the axial skeleton, the pelvis is the most common site. Ninety percent of all metastases occur in the lungs.29,48 Craniofacial osteosarcomas are rare. They typically present in the 3rd or 4th decade of life, account for fewer than 5% of osteosarcomas in children, and comprise only 1% of all pediatric head and neck malignancies.22,31,41,46 The most common craniofacial sites are the mandible and maxilla, followed by the calvaria and then the skull base.3,5,35,38

Approximately half of all osteosarcomas occur in the context of Paget disease, fibrous dysplasia, or prior therapeutic irradiation, which may account for the rarity of pediatric cases.7,33,42 Independent of radiation exposure, a history of retinoblastoma is also associated with an increased risk of craniofacial osteosarcoma.38 Tumors arising secondary to a pathological process are typically more aggressive and have higher recurrence rates than those arising de novo.54,59 Malignancy resulting from these predisposing factors is also more likely to appear at a more advanced age,32 contributing to the low incidence of cranial osteosarcoma in the pediatric population.32,33,59

Traumatic injury has also been implicated in the development of osteosarcoma.41 We report our experience treating cranial osteosarcoma in three 14-year-old boys and review the available literature regarding the management of these rare, aggressive tumors.

Case Reports

Case 1

A 14-year-old boy presented to the emergency center with a painful swelling over the left temporal region after minor trauma. He denied constitutional symptoms and was neurologically intact on examination. The patient reported a history of trauma 5 years earlier when he was hit in the head with a baseball bat in the same location. A CT scan of the head performed at the time of the initial injury showed no abnormality. At this presentation, CT revealed a 4.9-cm expansile mass of the anterior inferior left parietal bone

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

Abbreviation used in this paper: PEEK = polyetheretherketone.
Cranial osteosarcoma in children

Fig. 1. A: Preoperative coronal head CT scan demonstrating a large mass arising from the inferior left parietal bone and extending into the epidural and subgaleal spaces. B: Preoperative coronal T1-weighted MR image obtained after contrast agent administration, demonstrating a large cystic mass with epidural and subgaleal extension. C: Intraoperative photograph showing a large encapsulated scalp mass arising from the inferior parietal bone.

(Fig. 1A). The mass protruded into the intracranial and subgaleal spaces. Enhancement of the underlying dura mater was noted on MR images obtained after administration of a contrast agent (Fig. 1B). No metastases were identified by chest CT or bone scan. The mass demonstrated rapid growth in the short interval between diagnosis and resection.

A left craniectomy was performed with en bloc excision of the mass and a 1-cm rim of normal-appearing bone circumferentially (Fig. 1C). Intraoperatively, the tumor was encapsulated without visible invasion of the underlying dura or overlying scalp. Postoperatively, the patient was clinically stable. Pathological evaluation of the surgical specimen revealed osteoblastic osteosarcoma.

After completion of standard 3-drug adjuvant chemotherapy with methotrexate, doxorubicin, and cisplatin,19 CT, MRI, and nuclear bone scans revealed no evidence of disease recurrence or metastatic foci; however, persistent dural enhancement was noted. Reconstructive cranioplasty with a custom polyetheretherketone (PEEK) implant, resection of underlying dura, and duraplasty was performed 9 months after the initial surgery. Histopathological examination of the resected dura did not show any evidence of malignancy. At last follow-up, 16 months after diagnosis, the patient was well without neurological deficit or evidence of disease.

Case 2

A 14-year-old boy presented with a pathological fracture of the right femur and was diagnosed with osteoblastic osteosarcoma by bone biopsy. No metastatic lesions were identified by chest CT or bone scan at the time of the initial diagnosis. The patient received neoadjuvant chemotherapy and then underwent limb salvage surgery consisting of distal femur resection and implantation of a femoral prosthesis. Histopathological analysis demonstrated more than 95% tumor necrosis. Surgery was followed by completion of a standard regimen of adjuvant chemotherapy with methotrexate, doxorubicin, and cisplatin.

Three months after completion of the chemotherapy regimen, a surveillance bone scan showed increased tracer uptake in the skull. A CT scan of the head showed a lytic lesion in the left parietal calvaria, without evidence of intracranial disease. The patient was asymptomatic. The lesion was resected en bloc, including a 1-cm margin of normal-appearing bone circumferentially. The dura and scalp appeared normal. Pathological analysis confirmed metastatic osteoblastic osteosarcoma. The patient completed 6 courses of postoperative salvage chemotherapy with high-dose ifosfamide and etoposide.

Eleven months after resection of the skull lesion and 3 months after completion of salvage salvage chemotherapy, the patient returned with pulmonary metastases and recurrent disease in the skull, showing rapid growth on serial CT (Fig. 2A). Craniectomy and wide resection of the calvarial lesion were performed. Intraoperatively, extensive epidural extension was noted with focal erosion through the dura indenting the brain parenchyma, but not invading the arachnoid mater (Fig. 2B). In addition, extensive invasion of the superior sagittal sinus was noted (Fig. 2C). The infiltrated dura was widely resected up to the sinus, and the outer leaflet of the sinus was coagulated with bipolar cautery. A titanium mesh cranioplasty was performed over the calvarial defect.

The pathological findings were consistent with osteoblastic osteosarcoma with tumor infiltrating the dura. Postoperatively, the patient was neurologically intact and clinically stable. Because of the extensive metastasis, the patient was enrolled in a Phase I trial for salvage chemotherapy. Despite treatment, further progression of both the residual skull and pulmonary lesions was observed. At last follow-up, 27 months after diagnosis, the patient was alive, had progressive disease, and was no longer receiving treatment.

Case 3

A 14-year-old-boy presented to an outside hospital with left eye pain, periorbital swelling, blurred vision, and significant epistaxis. On examination, he had diminished peripheral vision in a proptotic left eye, but was otherwise without neurological deficit. He was taken to the operating room for control of epistaxis. Endonasal biopsy revealed chondroblastic osteosarcoma. Further workup demonstrated a large calcified eroding mass of the skull base, extending into the nasopharynx, left maxillary sinus, ethmoidal sinuses, and sphenoid sinus and along the midline of the anterior skull base to involve the sella turcica and clivus (Fig. 3). He was transferred to our facility for further treatment. A bone scan did not show any evidence of metastatic disease; CT of the chest showed possible small nodules. The patient was started on standard neoadjuvant chemotherapy.

After 2 cycles of chemotherapy, the patient underwent open transnasal resection of the lesion, which was per-
formed in conjunction with the otolaryngology service. The tumor was resected from the left maxillary sinus and nasopharynx, debulked, and stripped from the roof of the nasal cavity, the medial wall of the orbit, the sphenoid sinus including the anterior wall of the sella turcica, and the clivus. The tumor had not invaded the dura mater. Gross-total resection was achieved, but negative margins were not possible as the tumor abutted the dura surrounding the pituitary gland and internal carotid artery. Facial reconstruction was performed by otolaryngologists.

After surgery, the patient’s vision was stable and he had no new neurological deficit. Pathological analysis confirmed chondroblastic osteosarcoma with less than 1% tumor necrosis, reflecting a poor response to chemotherapy, which was therefore discontinued: adjuvant consolidation radiation therapy was administered. After radiotherapy, the patient developed a suspicious lesion in the maxillary sinus; this was resected, and pathological evaluation revealed a mucocele without evidence of tumor. Because of interval enlargement of a lung nodule that was present at diagnosis, it was resected as well. Pathological analysis revealed pleural and parenchymal sclerosis with no evidence of tumor. At last follow-up, 12 months after diagnosis and 3 months after completing therapy, the patient was alive without evidence of residual or recurrent disease. He had persistent visual loss in the left eye and anosmia, but no evidence of pituitary insufficiency or progressive neurological deficit.

Discussion

Primary osteosarcoma of the skull and cranial base is rare, with fewer than 150 cases reported since 1945, when osteosarcoma of the posterior skull was first characterized by Garland. Few reports of calvarial osteosarcoma in the pediatric population exist in the literature and even fewer describe osteosarcoma metastasis to the skull.

Clinical Presentation

The presenting symptoms of cranial osteosarcoma vary based on the anatomical site of the lesion. Like osteosarcoma of the long bones, craniofacial osteosarcomas often present as slow-growing masses. Unlike long bone lesions, however, craniofacial tumors are frequently painless or only mildly tender. Common presenting symptoms include headache, cranial nerve palsies, exophthalmos, and visual impairment. Elevation of the serum alkaline phosphatase level is common, although not uniformly observed. Imaging with MRI and CT may reveal bone growth with lytic regions and periosteal remodeling, as seen in osteosarcomas of other areas. The most common skull masses in children are dermoid cysts and Langerhans cell histiocytosis, which may be difficult to distinguish from malignant tumors such as osteosarcoma or Ewing sarcoma. Although the lytic and sclerotic radiological pattern is highly suggestive of osteosarcoma, the differential diagnosis of this finding in children includes Ewing sarcoma, aneurysmal bone cyst, osteomyelitis, and chondrosarcoma. It should be noted that in Case 1 the imaging appearance was thought to be most consistent with an aneurysmal bone cyst, underscoring the need for definitive diagnosis by histopathological analysis of tissue.

Metastasis of craniofacial osteosarcoma is uncommon relative to primary osteosarcoma originating in other anatomical locations and most often occurs in the lungs.
Cranial osteosarcoma in children

or brain. Metastatic spread to the brain is uncommon, but when it does occur it is usually a late event, often after multiple recurrences, and is associated with poor survival. Metastasis to the skull from a distant primary tumor is also uncommon and presents a unique treatment consideration. The current survival rate for children with localized osteosarcoma is approximately 65%, compared with 25% for patients with metastatic disease.

Histopathology

Osteosarcomas are characterized by spindle cell morphology and excessive production of irregular, immature bone (osteoid). Osteosarcomas are grouped into subtypes based on histological appearance. The majority (90%) are grouped as “conventional” high-grade, inamedullary osteosarcomas consisting of osteoblastic, chondroblastic, and fibroblastic histological subtypes, with osteoblastic being the most common. Other less common histological subtypes include telangiectatic, parosteal, periosteal, and small cell osteosarcomas. Improved survival has been reported for chondroblastic osteosarcoma of the mandible, but no prognostic implications for histological tumor type have been identified for cranial tumors.

Treatment

Data to guide the optimal management strategy for primary osteosarcoma of the calvaria and skull base are sparse, and there is even less information regarding metastasis to the skull. This has resulted in wide variation in treatment; however, the most important prognostic factors are metastatic disease status, the ability to completely resect all sites of tumor, and histological response to chemotherapy.

High-grade osteosarcomas are treated with high-dose, multiagent chemotherapy (doxorubicin, cisplatin, methotrexate, ifosfamide) in conjunction with complete resection. Chemotherapy may improve outcomes by shrinking the tumor to improve resection or managing residual tumor when gross total resection is not achievable. Neoadjuvant chemotherapy was initially implemented in osteosarcoma therapy to give surgeons time to plan limb salvage and prosthetic reconstruction, in addition to the aim of reducing tumor burden to improve the extent of resection. Although neoadjuvant therapy has become standard practice because of the predictive value of the histological response to therapy, Goorin et al. found no improvement in event-free survival in patients who received presurgical chemotherapy compared with those who were treated with immediate resection. In patients who present with aggressive disease that poses an immediate threat to vital structures or those whose disease progresses during neoadjuvant therapy, immediate resection may be more appropriate.

Preoperative chemotherapy should be considered on a case-by-case basis, depending on the precise location of the cranial tumor and feasibility of obtaining a complete resection in the event that the tumor does not respond to initial chemotherapy.

The extent of resection is widely reported to be the best predictor of long-term survival. In a meta-analysis of 163 cases of osteosarcoma involving patients of any age, Kassir et al. found significantly better survival in patients with osteosarcoma of the mandible and maxilla than in those with cranial tumors. This difference may reflect the relative difficulty of achieving gross-total resection of tumors in the calvaria and cranial base compared with the mandible and maxilla. Patient age was not reported or analyzed with respect to survival differences. Although the paucity of cases makes standardization of care difficult, it appears that when gross-total resection cannot be achieved, extensive resection coupled with adjuvant chemotherapy or radiation optimizes long-term survival.

Resection of involved dura is an important component of achieving maximal resection. Contrast enhancement on MRI may not be a definitive indicator of dural involvement. Dura adjacent to a neoplastic process may enhance because of thickening resulting from reactive processes. In a study of 32 patients with primary calvarial lesions of varying etiologies, 16 patients had dural enhancement, but dural invasion was identified in only 6 of these patients; the remaining 10 had inflammatory or hypervascular changes or no changes in the dural architecture. Because enhancement may represent tumor invasion, dural resection is prudent if it can be achieved with a low risk of significant morbidity.

The need for follow-up imaging to assess tumor recurrence or progression of residual disease makes selection of materials used in closure of the cranial defect after craniotomy a key element of operative planning. Titanium implants produce minimal metallic artifact on MRI and CT. PEEK also produces minimal artifact on MRI, making it an excellent option for cranial reconstruction when autologous bone is unavailable or not suitable.

Radiation has largely been reserved for the management of unresectable disease and metastasis. Guadagnolo et al. published a retrospective study of 119 patients with craniofacial osteosarcoma who underwent macroscopic total resection at MD Anderson Cancer Center between 1960 and 2007. This study found that radiation therapy significantly improved local control, diseasespecific survival, and overall survival in patients with positive or uncertain resection margins after surgery. Conversely, for patients with negative resection margins, radiotherapy did not improve survival.

Two groups have reported on the development and clinical use of intraoperative brachytherapy administered via custom applicators in patients with cranial or spinal tumors adjacent to the dura. This may be a useful option in the future in children with osteosarcoma where dural resection is not possible, such as Case 2, or where effective external beam radiation doses may carry a significant risk of neurotoxicity, such as epidural tumors of the spine.

Previously Reported Pediatric Cases of Cranial Osteosarcoma

A search of the English language literature revealed 35 cranial osteosarcomas previously reported in children (Table 1). Twenty-three cases were de novo cranial osteosarcomas: 14 calvarial tumors and 9 tumors of the skull base. Nine cases of cranial osteosarcoma secondary to prior therapeutic radiation have been reported in children, 2 involving tumors...
TABLE 1: Summary of previously reported cases of calvarial and skull base osteosarcomas in pediatric patients*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age at Dx (yrs), Sex</th>
<th>Location</th>
<th>Primary/ Metastasis†</th>
<th>Risk Factors</th>
<th>EOR</th>
<th>Adjuvant Tx</th>
<th>Follow-Up (mos)</th>
<th>Outcome</th>
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</table>

(continued)
Cranial osteosarcoma in children

of the skull base and 7 involving tumors of the calvaria. Four cases of metastatic cranial osteosarcoma have been reported: 3 cases of metastatic cranial osteosarcoma from primary long bone tumors (2 involving the calvaria and 1 involving the cranial base) and 1 case of metastatic osteosarcoma to the cranial base with a history of radiotherapy, in the context of multifocal disease.

The mean age of the pediatric patients with cranial osteosarcoma was 12.2 years and was similar in patients with calvarial and skull base tumors (12.6 and 11.6 years, respectively). Of those cases in which extent of resection was reported, gross-total resection was achieved in 4 (33%) of 12 calvarial tumors compared with only 1 (13%) of 8 skull base tumors. Of the 23 calvarial tumors reported in children, 7 (30%) occurred after therapeutic radiation, whereas 2 (17%) of 12 primary skull base tumors arose after radiotherapy. Among all reported cases, the average duration of follow-up was 30.2 months. In children whose survival was reported, 63% of patients with calvarial tumors (10 of 16) and 44% of children with skull base tumors (4 or 9) were alive at the end of the follow-up period.

In most reported cases of primary cranial osteosarcoma, the patients were treated with extensive resection and neoadjuvant or adjuvant chemotherapy. Patients in some of the earlier cases were treated without resection or with resection with or without radiation. When outcomes are reported, these patients had poor survival compared with more recent cases, suggesting that adjuvant chemotherapy and extensive resection improves outcome. Early studies report a 5-year survival of 9% in patients of all ages, but more recent reports suggest that 5-year survival may be as high as 31%. The wide variation in the management and outcomes of pediatric cases of cranial osteosarcoma is likely due to difficulty in identifying ideal therapy because of the small number of cases.

Trauma has been implicated in the development of osteosarcoma of the extremities, but has rarely been identified in the bones of the skull. Our Case 1 is only the third reported case of posttraumatic pediatric osteosarcoma of the skull, and the first report of calvarial osteosarcoma occurring years after a traumatic injury. The first case reported in the literature was an 8-year-old boy who presented 10 weeks after striking his head during a fall; an occipital mass grew steadily after his injury. The second reported case involved a 16-year-old boy who presented with a mass 5 months after falling, and pathological analysis revealed osteosarcoma. Our patient presented 5 years after an initial trauma with a parietal mass. Although remote trauma seems unlikely to play a significant role in the development of a rapidly growing, high-grade malignancy, it cannot be entirely excluded given the reported role of trauma in osteosarcoma pathogenesis.

Two reports of pediatric patients with metastatic lesions to the calvaria have been described previously. Kornreich et al. reported on a patient who was found to have osteoblastic osteosarcoma of the distal femur and a calvarial metastasis. The tumor invaded the dura and could not be separated from it. The metastatic tu-

<p>| TABLE 1: Summary of previously reported cases of calvarial and skull base osteosarcomas in pediatric patients* (continued) |</p>
<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age at Dx (yrs), Sex</th>
<th>Metastasis†</th>
<th>Risk Factors</th>
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</tr>
</tbody>
</table>

* ant = anterior; chemo = chemotherapy; Dx = diagnosis; EOR = extent of resection; GTR = gross-total resection; NR = not reported; prog = progressive; RT = radiation therapy; STR = subtotal resection; Tx = therapy.
† Refers to skull lesion.
mor in our series also demonstrated extensive dural invasion, whereas both primary tumors did not. A second metastatic cranial osteosarcoma, reported by Kim and colleagues, was also from a primary tumor of the distal femur and also demonstrated pulmonary metastases, both features described in the second case in our series. Neither of the previous reports provides treatment details or outcomes for these patients, making ours the first report of a therapeutic approach to the cranial metastasis of osteosarcoma in a pediatric patient.

Nine cases of osteosarcoma of the skull base in pediatric patients have been reported. Several papers describe unresectable tumors or subtotal resection of skull base osteosarcoma, due to the difficult anatomy. Our third case is the first report describing an open transnasal approach to resection of osteosarcoma of the skull base in a pediatric patient. Gross-total resection was achieved followed by radiation therapy, and there has been no evidence of recurrence. Given the importance of complete resection for long-term survival, surgical approaches that facilitate safe resection of tumors surrounding critical skull base structures are important to improving outcomes in these rare tumors.

Conclusions

We report 3 unique cases of cranial osteosarcoma in pediatric patients and a review of the literature. While review of reported cases reveals variability in surgical management of pediatric patients, those cases and our own reinforce the importance of maximal surgical resection in optimizing long-term outcome.

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Disclosure

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

Author contributions to the study and manuscript preparation include the following: Conception and design: Bollo. Acquisition of data: Hadley. Analysis and interpretation of data: Gressot. Drafting the article: Hadley. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Bollo. Study supervision: Bollo.

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