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CASE REPORT PEER REVIEWED | OPEN ACCESS

Chondroblastic osteosarcoma of the calvarium in a 74-year-old male: Diagnostic pitfalls and molecular insights

Shailaja Raj, Micheal McCormack

ABSTRACT

Introduction: Chondroblastic osteosarcoma (COS) of the craniofacial skeleton is a rare mesenchymal malignancy that often mimics chondrosarcoma histologically, due to chondroid matrix admixed with osteoid matrix and hyaline cartilage. These tumors are difficult to diagnose and their optimal diagnostic approach and management remain poorly defined.

Case Report: This is a 74-year-old male who presented with a right frontal-parietal skull mass. Magnetic resonance imaging (MRI) brain revealed an expansile calvarium lesion with possible dural involvement. Biopsy confirmed COS. He received neoadjuvant doxorubicin and cisplatin, followed by surgical resection. Final pathological analysis revealed no treatment response. Two years later, he developed a locoregional recurrence, for which he received stereotactic radiosurgery. Recurrence biopsy and next-generation sequencing identified deletions in cyclin-dependent kinase inhibitor 2A (CDKN2A), cyclin-dependent kinase inhibitor 2B (CDKN2B), and methylthioadenosine phosphorylase (MTAP). A trial of regorafenib was unsuccessful. The patient died from neurological complications shortly thereafter.

Conclusion: This case highlights the clinical and management challenges of craniofacial COS.

Keywords: Chondroblastic osteosarcoma, Craniofacial skeleton, Expansile calvarium lesion, Metaphyseal region, Neoadjuvant doxorubicin, Neurological complication

Shailaja Raj[1], Micheal McCormack[1]

Affiliations: [1]Assistant Professor, Department of Hematology and Oncology, Atrium Wake Forest Baptist University Hospital, Winston-Salem, North Carolina, USA.

Corresponding Author: Shailaja Raj, Atrium Wake Forest Baptist University Hospital, Winston-Salem, North Carolina, USA; Email: Shailaja.raj@advocatehealth.org

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INTRODUCTION

Osteosarcoma is a high-grade primary bone malignancy that arises from primitive mesenchymal cells producing malignant osteoid. It most commonly affects adolescents and young adults and typically involve the metaphyseal regions of long bones. Less frequently [1] osteosarcoma occurs in the craniofacial skeleton particularly the mandible, maxilla, and skull where it presents unique diagnostic and therapeutic challenges [2]. Osteosarcoma of central nervous system accounts for less than 10% of all osteosarcomas and differs from appendicular osteosarcoma in its age distribution, histologic subtypes, and biological behavior [3]. The chondroblastic subtype defined by a predominance of cartilaginous matrix with focal osteoid matrix poses a specific diagnostic challenge due to its resemblance to conventional chondrosarcoma, especially in small or poorly representative biopsy samples. Distinguishing between these entities is clinically crucial: osteosarcoma typically responds to multimodal therapy, including chemotherapy, whereas chondrosarcoma is relatively chemo resistant and treated primarily with surgery [4, 5]. This case highlights the diagnostic complexity of cranial COS in an elderly patient and underscores the absence of therapeutic decision-making.

CASE REPORT

A 74-year-old Caucasian male presented with a progressively enlarging, painless mass on the right side of

his skull. Neurological examination was normal. Magnetic resonance imaging (MRI) of the brain demonstrated an expansile, enhancing mass centered within the right frontal and parietal bones, with associated mass effect on the underlying right frontal lobe and subjacent dural thickening and enhancement, suggesting possible dural involvement by neoplasm (Figures 1 and 2).

Histologic examination demonstrated a cellular proliferation of spindled to ovoid cells involving the medullary cavity of the bone characterized by permeative growth. Areas of cartilaginous matrix with associated increased peripheral and cellular spindling was observed. Admixed foci of osteoid matrix production were seen. These atypical cells were characterized by moderate nuclear pleomorphism encompassing irregular nuclear contours, variably hyperchromatic to vesicular chromatin, and scattered admixed mitotic figures (Figure 3). These morphologic findings were consistent with a conventional osteosarcoma, chondroblastic type.

The patient was treated with neoadjuvant doxorubicin and cisplatin. He underwent surgical resection of his cranial lesion with negative margins. Pathology demonstrated extensive viable tumor, with no treatment response suggestive of a chemotherapy resistant tumor. He was placed on surveillance following surgery. After 24 months (Figure 4), MRI identified a new enhancing lesion in the right parietal calvarium with nodular thickening of adjacent dura, consistent with locoregional recurrence. This was treated with Gamma Knife stereotactic radiosurgery.

Next-generation sequencing (NGS) of the tumor tissue revealed homozygous deletions of CDKN2A and CDKN2B, along with MTAP loss, all of which are associated with high-grade, treatment-refractory disease. Further progression (Figure 5) caused dizziness and multiple falls. The patient declined systemic chemotherapy. Regorafenib, a multi-kinase inhibitor approved for the treatment of refractory sarcomas, was initiated for palliative disease control. During treatment, he developed seizures, impaired balance, and an inability to ambulate.

Given his progressive clinical deterioration, the patient elected to transition to comfort-focused care and hospice. He died several weeks later.

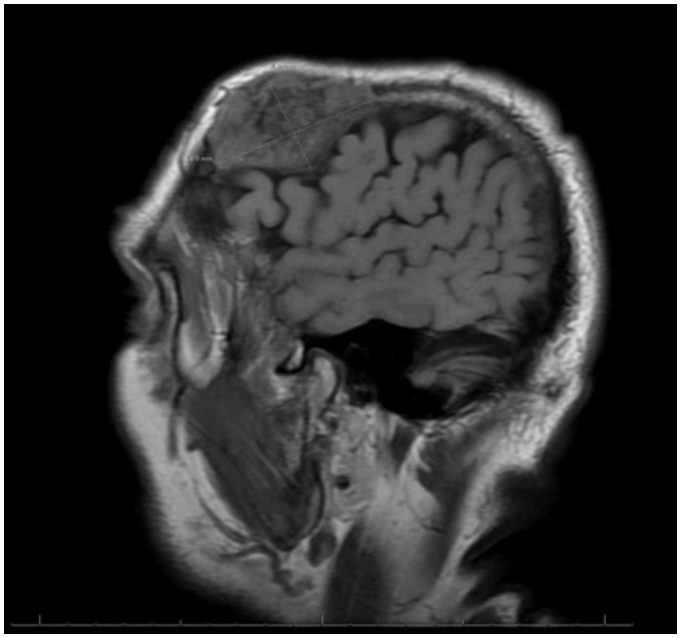


Figure 1: Chondroblastic osteosarcoma presentation with axial view showing tumor proven by biopsy, A 6.1 × 3.9 × 3.9 cm (AP × CC × TR) heterogeneous low T1 signal with peripheral restricted diffusion (suggesting a high cellular content) mass lesion centered within the right frontoparietal calvarium. Further this is an expansile enhancing mass centered within the right frontal and parietal bones with associated local mass effect on the right frontal lobe with subjacent dural thickening and enhancement suggesting possible dural involvement by neoplasm versus reactive inflammation.

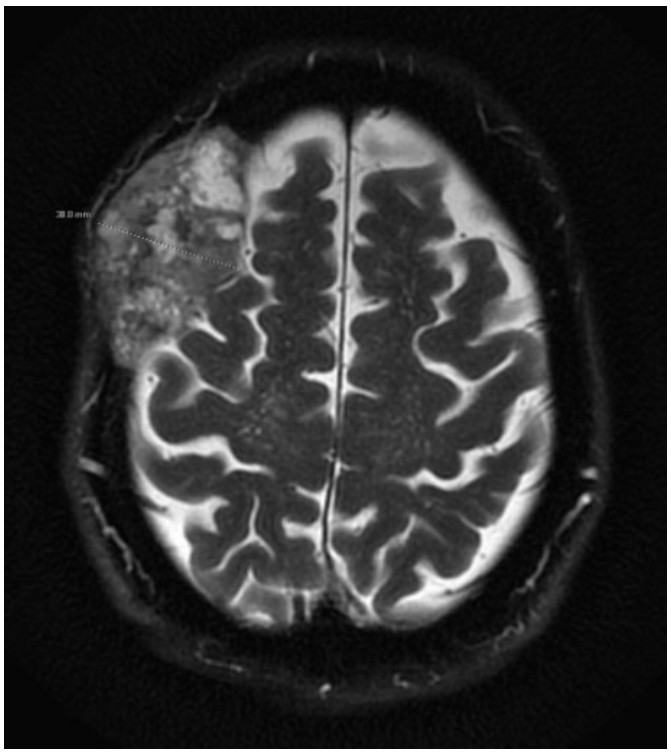


Figure 2: MRI showing tumor compression of the parietal region causing unsteadiness and headaches. This is a 6.1 × 3.9 × 3.9 cm (AP × CC × TR) heterogeneous mass lesion centered within the right frontoparietal calvarium. There is susceptibility artifact associated with this lesion secondary to calcifications/destroyed bone. There is heterogeneously high T2 signal within the lesion. There is associated subjacent mild mass effect on the right frontal lobe with minimal effacement of the sulci. There is no associated vasogenic edema within the brain parenchyma. There is subjacent dural thickening and enhancement. No additional osseous lesions are identified.

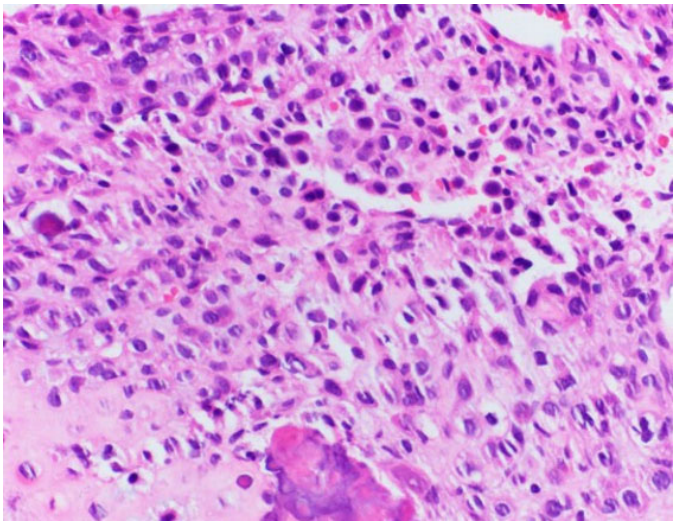


Figure 3: Histologic examination demonstrated a cellular proliferation of spindled to ovoid cells involving the medullary cavity of the bone characterized by permeative growth. Areas of cartilaginous matrix with associated increased peripheral and cellular spindling was observed. Admixed foci of osteoid matrix production were seen. These atypical cells were characterized by moderate nuclear pleomorphism encompassing irregular nuclear contours, variably hyperchromatic to vesicular chromatin, and scattered admixed mitotic figures.

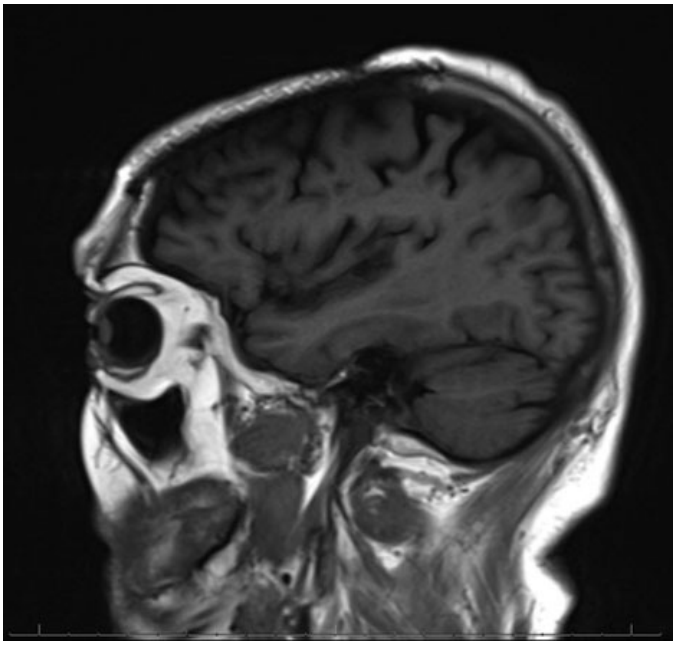


Figure 4: MRI shows postsurgical changes of right frontal craniectomy for osteosarcoma resection. There is smooth enhancement at the craniectomy site and subadjacent dura without evidence of nodular or mass like enhancement to suggest tumor progression. No focal marrow replacing lesion suggestive of neoplasm. No focal mass in orbits. Complete opacification of the right frontal sinus. Periventricular and deep cerebral white matter T2/FLAIR hyperintense signal most likely the sequela of chronic ischemic microvascular disease. No evidence of acute infarct. No mass effect, acute hemorrhage, or hydrocephalus. No abnormal enhancement to suggest neoplasm, abscess, or mass lesion. Grossly normal flow-related signal in the major intracranial arteries and dural sinuses.

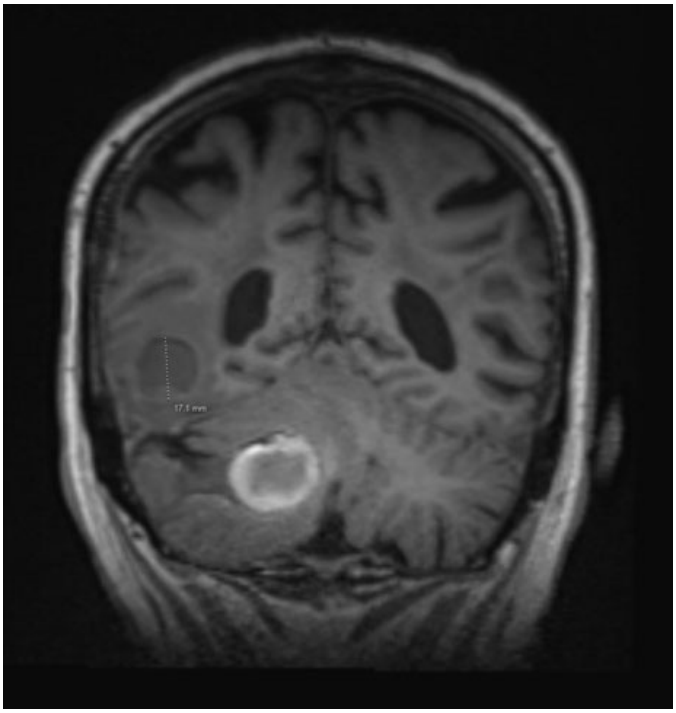


Figure 5: Recurrence of tumor with multiple enhancing calvarial lesions. New small acute/early subacute ischemic infarct in right peri-atrial white matter. New parenchymal hematoma in the posterior right temporal lobe measuring up to 2 cm, which could relate to the adjacent tentorial neoplasm or could represent a hemorrhagic infarct related to right-sided dural venous sinus thrombosis. Corresponding edema and local mass effect without supratentorial midline shift. There is no evidence for obstructive hydrocephalus or cerebellar tonsillar herniation at this time.

DISCUSSION

Chondroblastic osteosarcoma (COS) is a histopathologic subtype of osteosarcoma characterized by abundant malignant cartilage with variable osteoid production. Although the diagnosis in our patient was established by histopathologic examination, distinguishing COS from conventional chondrosarcoma can be challenging, particularly in limited biopsy specimens where osteoid may be sparse or absent [6]. The presence of malignant osteoid remains the defining diagnostic feature. Immunohistochemistry may assist in the differential diagnosis, with COS typically expressing vimentin, S100, and epithelial membrane antigen, and only rarely cytokeratin, whereas chondrosarcoma is generally positive for vimentin and S100 but lacks osteoid production [7]. In diagnostically challenging cases, molecular testing may provide additional support, as isocitrate dehydrogenase 1/2 (IDH1/2) mutations are frequently detected in chondrosarcoma but are typically absent in osteosarcoma [8].

Chondroblastic osteosarcoma accounts for approximately 10% of all osteosarcomas and less than 1% of malignant head and neck tumors, with the jaws representing the most common site of involvement. In contrast to

extracranial osteosarcoma, which predominantly affects adolescents and young adults, craniofacial COS typically presents during the third and fourth decades of life [9]. Furthermore, it exhibits distinct biological behavior, with a substantially lower rate of distant metastasis, particularly to the lungs, but a higher propensity for local recurrence. This high recurrence rate is largely attributable to the technical difficulty of achieving complete (R0) surgical resection in the anatomically complex craniofacial region while preserving function and aesthetics [10].

Current evidence consistently identifies complete surgical excision with negative margins as the most important prognostic factor for long-term survival. In addition, the histological response to neoadjuvant chemotherapy has been recognized as an important prognostic indicator in conventional osteosarcoma [11]. Patients with ≥90% tumor necrosis had significantly improved 5- and 10-year overall survival (OS) and disease-free survival (DFS) compared with those with <90% tumor necrosis. These findings are consistent with previous studies [12]. However, when analyzed according to histological subtype, the prognostic value of tumor necrosis differed. Patients with osteoblastic osteosarcoma and ≥90% tumor necrosis demonstrated significantly better 5- and 10-year OS and DFS than those with <90% tumor necrosis, whereas in COS, only a trend toward improved OS and DFS was observed. However, there remains no consensus regarding the optimal width of negative surgical margins, and studies have reported conflicting results concerning the impact of margin distance on survival [13].

Although current European Society for Medical Oncology (ESMO) guidelines recommend treating high-grade craniofacial osteosarcoma similarly to extracranial osteosarcoma with neoadjuvant chemotherapy, surgery, and adjuvant chemotherapy, several retrospective series have failed to demonstrate a survival benefit from either neoadjuvant or adjuvant chemotherapy in craniofacial COS [14]. Given its relatively low metastatic potential and limited response to systemic therapy, some investigators have questioned the routine application of multimodal treatment protocols derived from extracranial osteosarcoma and have suggested that complete surgical resection alone may provide the best outcomes for many patients. Radiotherapy is generally reserved for unresectable tumors, positive margins, recurrent disease, or situations in which surgery would result in unacceptable morbidity [15].

Collectively, these observations highlight the important biological differences between craniofacial and extracranial osteosarcomas and support an individualized treatment approach that prioritizes complete surgical resection whenever feasible [16–21].

CONCLUSION

Chondroblastic osteosarcoma of the calvarium is an exceedingly rare and aggressive malignancy, particularly in older adults. This tumor requires accurate diagnosis, molecular profiling, and careful choice of treatment to obtain good treatment response. IDH1/2 mutations are specifically seen in chondrosarcomas and may help differentiate them from COS. Vascular endothelial growth factor (VEGF) pathway influenced by differentially expressed in chondrocytes 2 (DEC2) is another mutation that is specific to COS.

From a therapeutic perspective, MTAP loss and CDKN2A/B deletions have been associated with resistance to standard therapeutic approaches. This points to the need for individual multimodal targeted treatments in order to optimize outcomes. Further research to better define the molecular microenvironment of chondroblastic osteosarcoma is needed in order to identify effective therapies.

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Author Contributions

Shailaja Raj – Conception of the work, Design of the work, Acquisition of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Micheal McCormack – Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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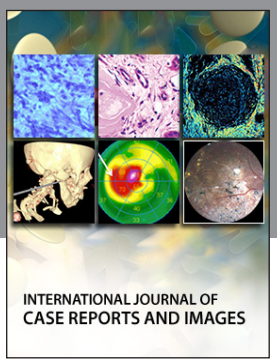
Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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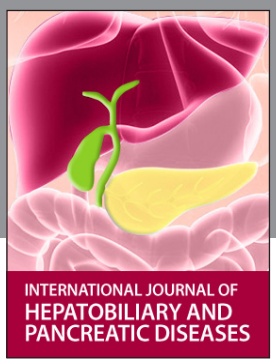
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