



# Osteochondroma of the Tentorium Cerebelli: Report of the First Case and Review of Literature

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Indian J Neurosurg

## Abstract

Osteochondromas are tumors composed of both bony and cartilaginous elements. These slow-growing lesions commonly occur in the appendicular skeleton. Intracranial presentation is extremely rare with very isolated case reports in the literature. We present here the first case of an osteochondroma arising from the tentorium cerebelli with a nonsystematic review of all cases of intracranial osteochondromas reported in the English literature till now. A literature search was performed by two authors independently using PubMed and Google Scholar search engines. Osteochondromas in the intracranial compartment were included. Baseline parameters like age, sex, site, radiological findings, treatment outcomes, and complications were analyzed. Thirty-two cases were included in the review. The mean age of presentation was 33 years and males were affected more than females. The skull base was the most common site of origin followed by the convexity and falx cerebri. Gross total excision was achieved in all cases involving the supratentorial compartment ( $n = 14$ ). Skull base osteochondroma excision can lead to serious complications due to iatrogenic injury to critical neurovascular structures. Surgery is the primary modality of treatment and there is no role for radiotherapy and chemotherapy. Multiple sections of the tumor should be subjected to histopathological examination to avoid missing low-grade chondrosarcomas.

## Keywords

- ▶ intracranial osteochondroma
- ▶ calcified lesion
- ▶ tentorial osteochondroma
- ▶ skull base lesion

## Introduction

Osteochondroma or exostosis, the most common bone tumor, accounts for 10 to 15% and 20 to 50% of all and benign bone tumors, respectively.<sup>1,2</sup> Considered a developmental lesion by few authors, these benign tumors are composed of cortical and cancellous bone covered with a cartilaginous cap.<sup>3,4</sup> These tumors commonly arise from the metaphysis of long tubular bones like the femur, tibia, and humerus.<sup>5,6</sup> Intracranial osteochondromas are extremely rare and there are only

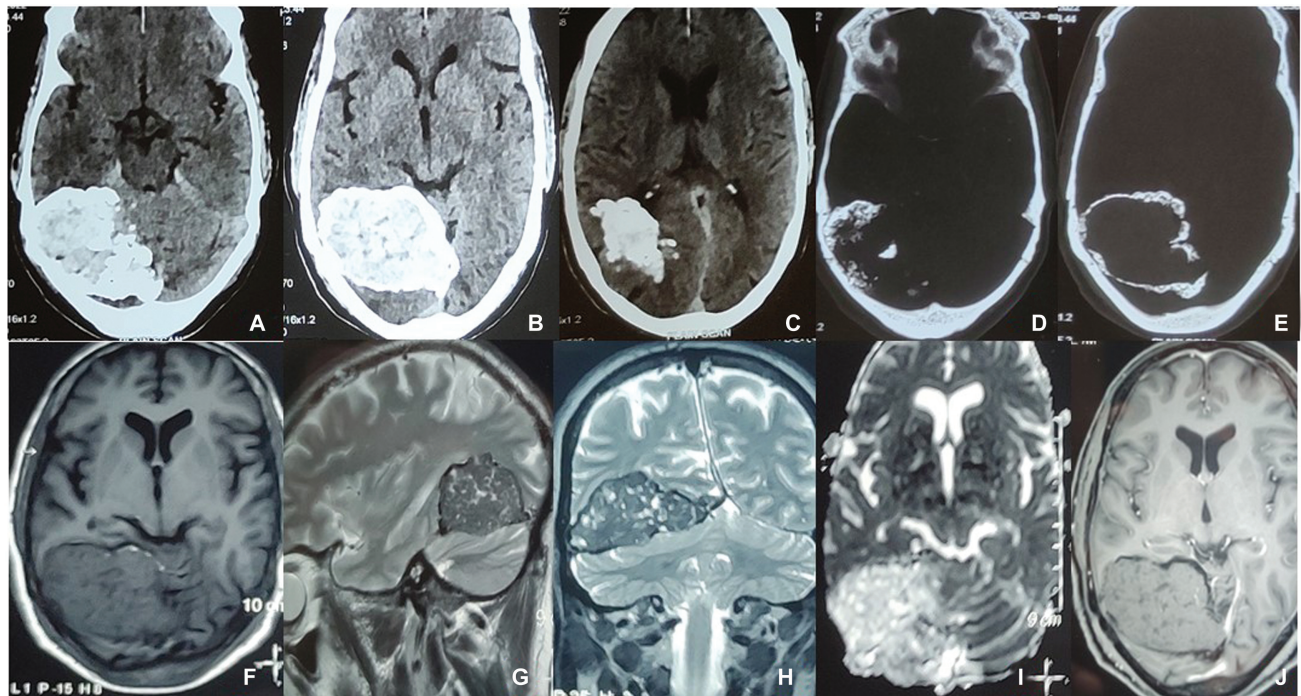
around 31 isolated cases reported in the literature in the past 100 years.<sup>7-10</sup> They usually arise from the skull base due to the presence of cartilage rests in multiple skull base synchondroses. Also, there are few reported cases arising from the convexity dura and falx cerebri. We hereby report the first case of osteochondroma arising from the tentorium cerebelli without any bony attachments. Also, we have comprehensively reviewed the English literature and present here the summary of all reported cases to decipher the challenges involved in managing these rare intracranial lesions.

DOI <https://doi.org/10.1055/s-0044-1789268>.  
ISSN 2277-954X.

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Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India



**Fig. 1** (A–C) Computed tomography (CT) of the head brain window shows a hyperdense lesion in the region of the tentorium cerebelli. (D, E) Peripheral rim of calcification can be seen on bone window. Magnetic resonance imaging (MRI) of the head shows a (F) T1 isointense, (G, H) T2 hypointense lesion with (I) diffusion restriction and (J) no enhancement.

## Illustrative Case

### Clinical History and Radiology

A 67-year-old man presented with complaints of continuous dull aching holocranial headache and on-off dizziness for 4 months. Clinical examination showed positive right cerebellar signs. Computed tomography (CT) scan of the head with bone windows showed a large well-defined hyperdense lesion in the right occipital region with an irregular peripheral rim of calcification (►Fig. 1A–E). Contrast-enhanced magnetic resonance imaging (CEMRI) of the brain showed a well-defined, nonenhancing extra-axial lesion in the right occipital region widely based on the superior surface of the right tentorium cerebelli displacing the inferior surface of the occipital lobe upward. There was peripheral rim of increased hypointensity suggestive of calcification. The lesion was T1 isointense and T2 hypointense, with restricted diffusion. Posteromedially the lesion was reaching up to the torcula, and there was no perilesional edema (►Fig. 1F–J).

### Intraoperative Findings

In the prone position, the patient's head was slightly rotated to the left side to keep the right occipital region at the highest point. An inverted U-shaped incision was made (►Fig. 2A). Right occipital craniotomy was done (►Fig. 2B) and the dura was opened based on the right transverse sinus (►Fig. 2C). The right occipital lobe was gently retracted to expose the bony hard lesion arising from the superior surface of the tentorium. The lesion was not suckable even at highest settings of the cavitron ultrasonic suction aspirator. Hence, tumor decompression was started using a long cutting drill and bleeding was controlled with temporary Gelfoam packing.

The bony hard tumor had a good plane with the occipital lobe superiorly, cerebellum below, and quadrigeminal cistern arachnoid anteriorly. While drilling at the depth, a cottonoid got struck in the drill and the superficial draining vein got damaged, and the bleeding was controlled with Gelfoam. Near total excision of the lesion was done (►Fig. 2D, E). Small portions of the lesion near the right transverse-sigmoid junction and torcula were left behind due to profuse venous bleed there. As the brain was full at the time of closure, expansile occipital duraplasty was done and occipital bone flap was not replaced (►Fig. 2F, G). Immediate post-op CT showed diffuse subarachnoid hemorrhage and tense posterior fossa (►Fig. 3A–C). Posterior fossa decompression and lax duraplasty were done. The patient was extubated 2 days after the second procedure and was discharged on the seventh postoperative day. The patient was asymptomatic at 3 months of follow-up and neuroimaging (►Fig. 3) showed two small discrete foci of residual tumor near the torcula and right transverse-sigmoid junction (►Fig. 3D–I).

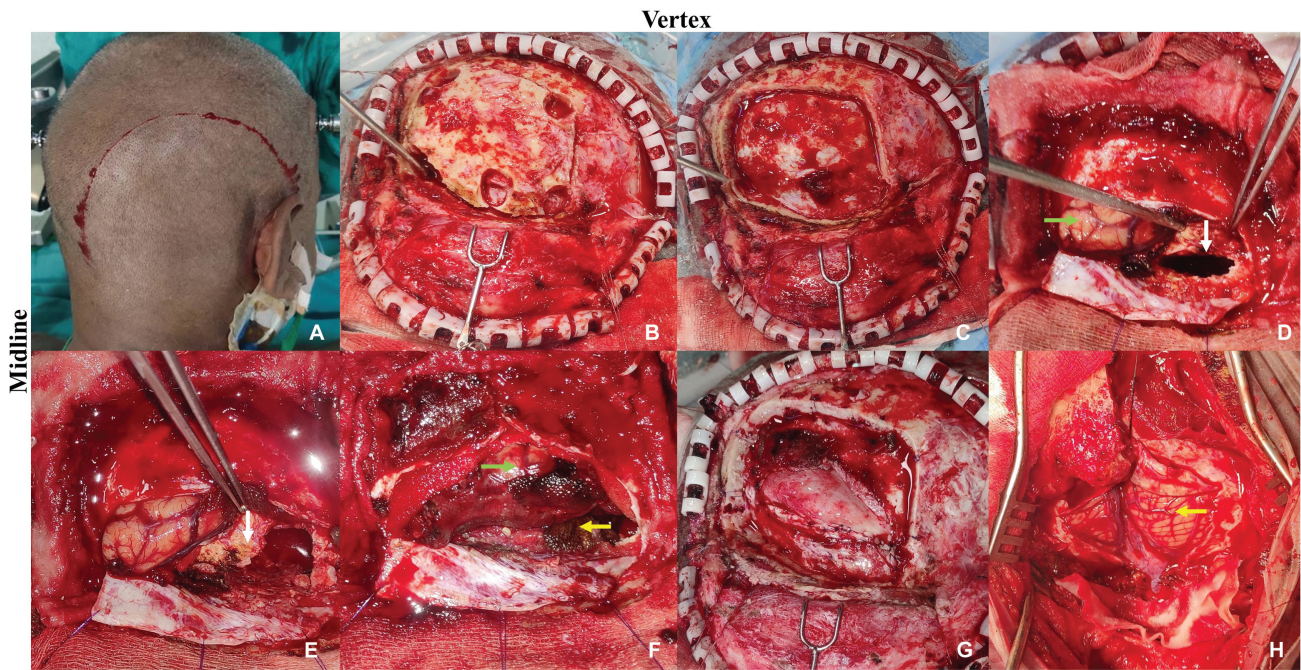
### Histopathology Findings

Histopathological examination showed a calcified lesion with multiple lobules of cartilaginous tissue. The cartilaginous area had an outer perichondrium and inner hyaline cartilage. A small portion of bone with fatty marrow was also noted. The overall features were suggestive of osteochondroma (►Fig. 3J).

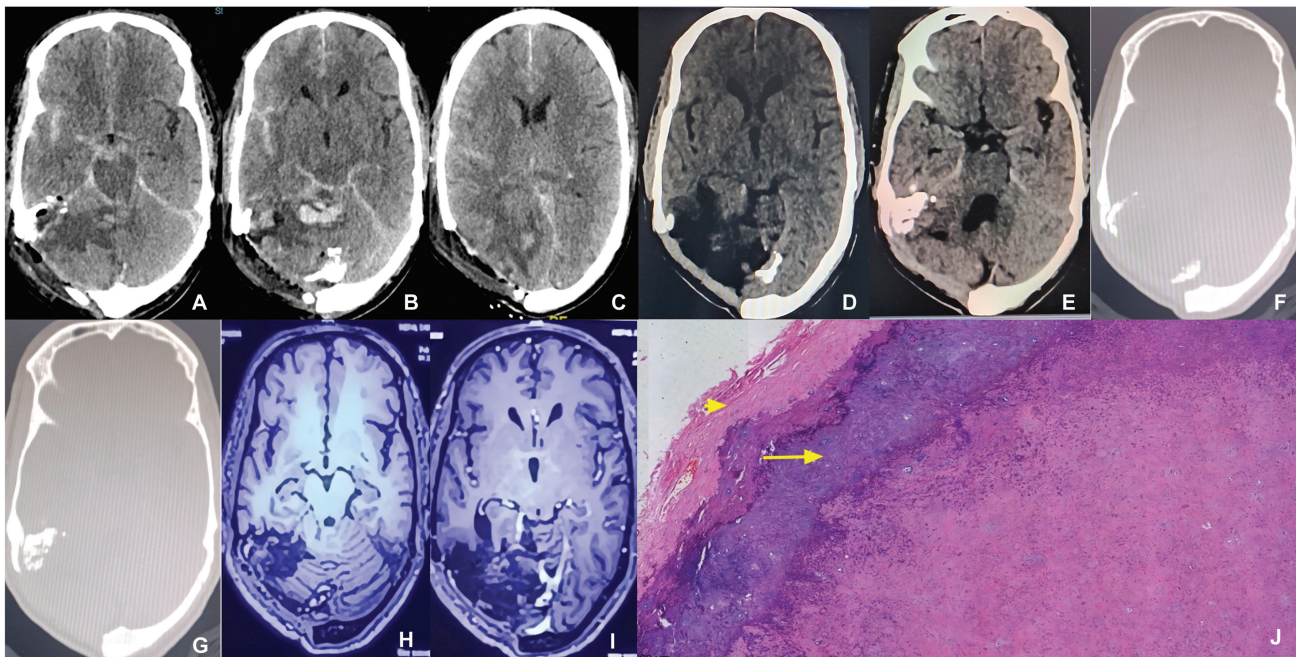
### Materials and Methods

As intracranial osteochondromas are extremely rare, we did a comprehensive nonsystematic review of literature and





**Fig. 2** Intraoperative images. (A) The patient is positioned in prone and the head stabilized in a three-pin holder and skin incision marked. (B) Craniotomy with burr holes. (C) Bone flap removed and dura exposed. (D, E) Tumor being decompressed. (F) Following tumor removal and hemostasis. (G) Duraplasty. (H) Second surgery: posterior fossa decompression. *Green arrow*: occipital lobe; *yellow arrow*: cerebellum; *white arrow*: tumor.



**Fig. 3** (A–C) Immediate post-op computed tomography (CT) showing evidence of near total excision and subarachnoid hemorrhage. (D–G) Follow-up CT done at 3 months and (H, I) magnetic resonance imaging (MRI) showing stable disease. (J) Histopathology image showing fibrous perichondrium and underlying hyaline cartilage marked with *arrowhead* and *arrow*, respectively.

analyzed all the published reports to study their clinico-radiological findings and treatment outcomes. We performed an internet search using PubMed and Google Scholar using the following keywords: intracranial, osteochondroma, tentorial, sellar, skull base, cerebral, and dural. All the cases with a lesion found in the intracranial compartment were included

in the review. Osteochondromas involving the mandible, atlas, and other facial bones were excluded. From each published article, we extracted the following information: age, sex, presenting complaints, location, radiological findings, surgical method and extent of resection, follow-up duration, final outcome, and complications.



## Results

Initial search identified 163 articles published over the past 100 years. After applying the inclusion and exclusion criteria, 31 articles were finalized for review (► **Table 1**). All the articles were isolated case reports. In 6 of 31 articles, only the abstract was available in the English language and hence only information available from the abstract was included. The present case was also included in the statistical calculation. The mean age at presentation was 33 years and the age range was between 15 and 73 years. Twenty-two patients (68.85%) were males and the remaining 10 (31.3%) were females. Seventeen of 32 cases (53.1%) were seen to arise from the base of skull (sellar, parasellar, petrous apex, posterior clinoid, and basiocciput). Fourteen cases (43.8%) were seen in the supratentorial region and were associated with either the falx or the convexity dura. The present case (3.1%) arose from the tentorium cerebelli. Initial reported cases had only X-ray and CT scans (9/32), and MRI findings were reported since 1989. Preoperative neuroimaging showed calcification in 96.8% (30/31) patients. In one case reported by Somerset et al,<sup>11</sup> calcification was wrongly identified as hemorrhage on preoperative scans. Information about the extent of tumor resection was available in 31 patients. In this, 17 patients (54.8%) underwent gross total excision and 14 patients (45.2%) underwent partial decompression or near total excision. Three patients (9.6%) died in the postoperative period. Two patients had hemorrhage in residual tumor and one patient died of pneumonia. The mean follow-up duration was 21 months. One patient developed hydrocephalus during follow-up and was managed with a ventriculoperitoneal shunt.

## Discussion

### Origin

Osteochondromas are benign tumors that have both cartilaginous and bony elements. This term should be used when there is a significant osteoid component seen in the tumor.<sup>12</sup> In long tubular bones, cartilage of the epiphysis herniating through a periosteal defect results in the development of osteochondroma.<sup>5</sup> Intracranial osteochondromas arise from the cartilaginous rests between suture lines, and this explains their predilection to occur in the skull base, which is developed by cartilaginous ossification.<sup>13</sup> Fibroblast cells in the meninges can undergo metaplastic changes resulting in the development of osteochondroma.<sup>8</sup> This mechanism explains the origin of these lesions in the supratentorial region. Other described sources are the mesenchymal cells in the perivascular zone and in the craniovertebral junction.<sup>13</sup> The present case arising from the tentorium is the first of its kind, and metaplasia rather than growth from the cartilaginous rest is the possible mechanism of its origin.

### Age and Sex Distribution

In the tubular bones, these lesions are common in first three decades of life as the epiphysis closes after this age.<sup>3</sup> In our

review, the mean age of incidence was 33 years. However, the age at presentation of the case (tumor from the basiocciput) described by Lotfinia et al<sup>14</sup> was 73 years. Also, in our case the age of the patient was 67 years. An extremely slow growth rate and late onset metaplasia are the probable explanations for this finding. In long bones, osteochondromas occur more commonly in males than in females with a male-to-female ratio of 3:1.<sup>15</sup> In our review of intracranial osteochondromas, the male-to-female ratio was 2:1.

### Clinical Features

Osteochondromas are slow-growing tumors, and hence in most cases they cause symptoms due to mechanical compression or irritation of adjacent neural structures.<sup>16</sup> Unilateral or bilateral progressive vision loss, bitemporal hemianopia, and hypopituitarism are the symptoms of sellar tumors.<sup>10,13,16–19</sup> Ptosis, dilated nonreactive pupil, corneal sensory loss, diplopia, and complete ophthalmoplegia indicate a parasellar involvement or extension.<sup>7,20–23</sup> Spastic weakness, lower cranial nerve involvement, and occipitocervical pain are seen in tumors involving the basiocciput.<sup>2,14</sup> Headache, seizures, contralateral limb and facial weakness, sensory loss, and lobar signs are seen in tumors in the supratentorial compartment.<sup>1,3,5,6,8,9,11,24–30</sup> In one patient, there was sudden onset headache with vision loss due to probable intratumoral hemorrhage.<sup>31</sup> Osteochondromas can sometimes occur as multiple lesions where it is usually associated with the hereditary multiple exostosis syndrome.<sup>3</sup> It can also occur along with other mesenchymal syndromes like Maffucci's syndrome (soft-tissue hemangiomas with multiple enchondromatosis) and Ollier's disease (polysystemic enchondromatosis).<sup>6,14</sup> In the case reported by Bakdash et al,<sup>20</sup> the patient had associated Ollier's disease.

### Radiology

Most of the earlier reported cases were diagnosed using X-ray and CT scans. Osteochondromas appeared as a hyperdense, lobulated calcified mass lesion.<sup>23,25,28</sup> MRI findings of this lesion was first described by Beck and Dyste.<sup>1</sup> Most osteochondromas show hypointense signal in both T1 and T2 sequences as a result of high calcium content. However, certain lesions can have a hypointense rim with associated hyperintense core. This hyperintensity indicates increased fat content or myxoid degeneration within the lesion.<sup>9,12</sup> Contrast enhancement is absent in most osteochondromas and in few cases minimal peripheral heterogeneous enhancement can be seen. This finding helps differentiate them from its closest differential diagnosis, the meningiomas, which show homogenous contrast enhancement and dural tailing.<sup>6,8</sup> In fact, authors who reported cases in the pre-MRI era have performed angiography to differentiate these tumors from vascular meningiomas.<sup>20,28</sup> Another characteristic feature of osteochondroma is the presence of hyperostosis and absence of edema in the surrounding brain parenchyma.<sup>29</sup> Dermoid cysts can also have an appearance similar to

**Table 1** Summary of cases of intracranial osteochondroma reported in English literature

Sl. no.	Study	Age, sex	Complaints	Location	Radiology	Surgery	Follow-up (mo)	Outcome
1	Levitt <sup>23</sup>	20, F	Unilateral complete ophthalmoplegia, proptosis and headache, and bilateral corneal sensory loss	Sellar region	X-ray: calcific lesion in the sella turcica; no evidence suggestive of raised intracranial pressure	Frontoparietal craniotomy and tumor decompression	6	Partial resolution of ophthalmoplegia Residual lesion on skull X-ray
2	Alpers <sup>25</sup>	49, M	Seizures and hemiparesis × 3 y	Parietal	X-ray: calcified lesion in the left parietal region	Craniotomy and total excision	108	Recurrence after 4 y: operated and biopsy was chondrosarcoma. The patient underwent irradiation, was operated again for recurrence, and died
3	Richards and Thompson <sup>13</sup>	49, M	Bilateral progressive vision loss × 1.5 y. Bitemporal hemianopia and features of hypopituitarism	Sellar region	X-ray: irregular calcified mass in the sella extending upward	Transnasal transsphenoidal approach and decompression and placement of the polyethylene tube in cyst space	24	Vision improved. No change in residual lesion size on follow up X-rays
4	Bakdash et al <sup>20</sup>	25, F	Unilateral ptosis, diplopia × 1 y. Dilated nonreactive pupil present	Tip of right petrous bone	X-ray: irregular calcification near the posterior clinoid process	Right temporal craniotomy and complete removal of tumor	6	Complete resolution of ptosis and diplopia, and pupils became reactive
5	Ito et al <sup>19</sup>	24, M	Diplopia and hypopituitarism × 1 mo	Posterior clinoid process	X-ray: cauliflower-shaped calcified mass	Partial tumor removal		Patient died on the second postoperative day due to bleeding in residual tumor
6	Himuro et al <sup>18</sup>	52, F	Unilateral vision loss × 7 y	Parasellar region	X-ray: hyperdense lesion with calcification	Right frontotemporal craniotomy + partial removal		
7	Ikedo et al <sup>22</sup>	41, M	Diplopia × 5 y Exophthalmos and right abducent nerve palsy	Middle fossa	X-ray: lesion with mottled calcification	Right frontotemporal craniotomy + subtotal excision		
8	Matz et al <sup>28</sup>	20, M	Headache, vomiting, blurring of vision, impaired memory and concentration × 8 mo	Frontoparietal parasagittal region	X-ray: partially calcified mass in the frontoparietal region with extension toward the anterior cranial fossa CT: hyperdense mass with peripheral rim of calcification	Left frontotemporoparietal craniotomy and total excision	2	Hydrocephalus on follow-up treated with ventriculoperitoneal shunt
9	Yamaguchi et al <sup>32</sup>	24, M		Middle fossa		Multiple operations	45	Died due to intracranial hemorrhage
10	Beck and Dyste <sup>1</sup>	48, M	Bifrontal headache × 1 y. Gait disturbances × 6 mo. Left hand tactile anomia, mild alexia, and agraphia	Inferior portion of the falx	X-ray: large calcified mass CT and MRI: calcified nonenhancing mass in the region of the posterior part of the corpus callosum	Left frontoparietal craniotomy and gross total excision	3	Improvement in gait, anomia, and agraphia noted
11	Hatayama et al <sup>21</sup>	15, M	Left abducent nerve palsy and trigeminal neuralgia	Parasellar region	CT and MRI: calcified lesion in the parasellar region	Craniotomy and subtotal excision		
12	Agildere et al <sup>24</sup>	26, F	Headache	Parasellar region	CT and MRI: calcified, lobulated lesion in the right parasellar region			

(Continued)

**Table 1 (Continued)**

Sl. no.	Study	Age, sex	Complaints	Location	Radiology	Surgery	Follow-up (mo)	Outcome
13	Mashiyama et al <sup>27</sup>	28, F	Psychomotor epilepsy	Frontal parasagittal region	CT and MR: calcified lesion in the frontal parasagittal region	Total removal		
14	Sato et al <sup>33</sup>	38, M	Seizures and diplopia	Parasellar region	CT and MRI: lobular, heterogeneous enhancing calcified mass	Craniotomy and partial excision		
15	Altinörs et al <sup>17</sup>	43, M	Headache, vision loss, and ptosis	Sellar region	CT and MRI: calcified mass in the sellar-suprasellar region with heterogeneous enhancement	Craniotomy and partial excision		
16	Haddad et al <sup>12</sup>	25, M	Fall at ground level followed by seizure	Parietal region	X-ray, CT, and MRI: calcified nonenhancing mass in the parietal region Marginal portion of the lesion was hypointense	Parietal craniotomy and gross total excision	12	No evidence of recurrence
17	Nagai et al <sup>9</sup>	45, F	Headache	Posterior frontal region	X-ray, CT, and MRI: calcified mass lesion in the right posterior frontal region. Marginal portion of the lesion was hypointense and attached to the convexity dura	Craniotomy and total excision		
18	Lin et al <sup>8</sup>	15, M	Headache and generalized seizure for 1 y Episode of apnea	Bifrontal region	X-ray and CT: calcified hyperdense lesion in the frontal region based on falk MRI: peripheral enhancement of the lesion was seen on contrast images	Bifrontal craniotomy and gross total excision	36	No evidence of recurrence
19	Bonde et al <sup>2</sup>	20, M	Stiffness, weakness, and tingling sensation on the right half of the body, hoarseness of voice × 8 mo	Basiocciput	Large bony lesion in the anterior basiocciput causing brainstem compression	Retromastoid approach and partial excision		Died on the 12th postoperative day due to pneumonia
20	Inoue et al <sup>31</sup>	29, M	Sudden onset headache with unilateral vision loss	Sellar region	CT and MRI: heterogeneously enhancing suprasellar mass with destruction and calcification of sella	Partial excision		Vision improved
21	Somers et al <sup>11</sup>	33, F	Headache, weakness, and muscles spasms on one side of the body × 4 y	Parietal region	MRI: large dural-based mixed-intensity lesion	Parietal craniotomy + total excision		
22	Venkata et al <sup>6</sup>	24, M	Seizures × 3 mo Headache × 2 mo	Frontal region	CT and MRI: mixed density mass with calcification	Total excision		No evidence of recurrence
23	Lotfinia et al <sup>14</sup>	73, M	Spastic quadriparesis, gait disturbances, and dull aching occipitocervical pain	Basiocciput	MRI: bony lesion causing brainstem compression	Medial suboccipital craniotomy + total excision	18	Most of the symptoms resolved
24	Majumdar et al <sup>3</sup>	35, F	Headache and hemiparesis, and 3 episodes of complex partial seizures × 1 y	Frontal	CT and MRI: broad dural-based calcified extra-axial lesion	Frontoparietal craniotomy + gross total excision		

Table 1 (Continued)

Sl. no.	Study	Age, sex	Complaints	Location	Radiology	Surgery	Follow-up (mo)	Outcome
25	Amita et al <sup>5</sup>	17, M	Progressive facial palsy × 5 mo; 2 episodes of generalized tonic-clonic seizures	Frontal	CT and MRI: extra-axial lobulated calcified lesion	Frontoparietal craniotomy + total excision	3	No new deficits
26	Hongo et al <sup>7</sup>	43, M	Diplopia × 3 y	Posterior clinoid process	CT: calcified lesion in the posterior clinoid causing destruction of the petrous apex MRI: Noncalcified regions showed enhancement	Orbitozygomatic approach and subtotal excision	12	Diplopia improved
27	Hori et al <sup>26</sup>	40, M	Decreased sensation in upper extremity	Frontal	CT: calcific lesion with a cyst MRI: calcified weakly enhancing lesion	Total excision		
28	Sekiguchi et al <sup>10</sup>	39, F	Unilateral progressive vision loss × 3 mo	Sella	CT and MRI: irregular calcified mass in the sellar-suprasellar region with parasellar extension	Endoscopic transsphenoidal approach and partial excision		Visual acuity improved
29	Zanotti et al <sup>16</sup>	16, F	Progressive headache and vision loss × 2 mo	Suprasellar region	CT and MRI: irregular calcified mass lesion in the suprasellar region compressing optic chiasm	Supraorbital approach and total excision		Visual acuity improved. Panhypopituitarism in the postoperative period and required hormone supplements
30	Ozyoruk et al <sup>29</sup>	25, M	Headache and speech disturbances × 3 mo	Parietal	CT and MRI: calcified extra-axial mass lesion in the left parietal region	Craniotomy and gross total excision		
31	Sarkinaite et al <sup>30</sup>	25, M	Weakness and paresthesias in right extremity × 1 y	Frontal	CT and MRI: calcified lesion in the frontal region	Craniotomy and gross total excision		Symptoms improved
32	Present study	67, M	Headache and gait ataxia	Tentorium	CT and MRI: calcified, hypointense nonenhancing mass lesion in the tentorium cerebelli	Craniotomy and near total excision	6	No evidence of recurrence

osteochondromas in MRI by showing heterogenous signal intensity and lack of contrast enhancement.<sup>30</sup>

### Histopathology

Osteochondromas are composed of mature cartilaginous and osteoid elements.<sup>2,11</sup> Somerset et al<sup>11</sup> demonstrated multiple lobules of mature hyaline cartilage throughout the lesion. This was interspersed by mature bone tissue with adipose tissue and hematopoietic stem cells in certain areas. They also found that the fibroblastic dura continued with the cartilaginous areas of the tumor. This in turn confirms the metaplasia theory. In our patient, we were able to distinctly identify cartilage, mature bone, and hematopoietic stem cells. The main pathological differential diagnosis is low-grade chondrosarcoma.<sup>5</sup> Hence, histopathological examination of multiple sections is extremely important to rule out this condition. Absence of hemorrhage, necrosis, high cellularity and mitotic rate, pleomorphic cells, and nuclear atypia helps in differentiating osteochondroma from low-grade chondrosarcoma.<sup>6,11</sup>

### Treatment and Outcome

Osteochondromas are resistant to chemotherapy and radiotherapy as they are benign slow-growing tumors, making surgical removal the only available treatment option.<sup>2,13</sup> However, removal of these lesions can be technically challenging. As compared with meningiomas, osteochondromas are relatively less vascular with preserved arachnoid and do not have pial blood supply.<sup>11</sup> But osteochondromas are extremely hard in consistency, and removal can become difficult particularly in difficult locations like the skull base where they sit very close to critical neurovascular structures. Bonde et al<sup>2</sup> noted that the tumor was extremely firm in comparison with normal bone and required continuous drilling and piecemeal removal. The proximity to the jugular bulb further complicated the procedure. In our case, the tumor was seen completely within the tentorial leaflets and posteriorly abutting the torcular. Anteriorly the tumor was just behind the quadrigeminal cistern although the arachnoid plane was well maintained here. We removed the tumor using a high-speed cutting pneumatic drill and took utmost care to safeguard the transverse sinus and torcula superficially and the great cerebral veins at the depth of exposure.

In the present review, we found that 17 (54.8%) patients underwent gross total excision of the lesion. A closer look at the data showed that all the 14 patients (100%) with a tumor in the supratentorial compartment underwent gross total excision. On the other hand, only 3 of 16 patients (18.8%) who had a tumor near the skull base underwent total tumor excision. We have excluded our case here as the tumor was found arising from the tentorium. Among patients who underwent gross total excision, only one patient with osteochondroma from the parietal region had recurrent disease and biopsy from the second surgery turned out to be a chondrosarcoma. The patient underwent a repeat surgery and radiotherapy but expired 9 years after the first surgery.<sup>25</sup> Apart from this, three more patients (9.6%) died in postoperative period and all these patients had a tumor in the skull base region.<sup>2,19,32</sup> Thus, it can be concluded that these

tumors have a very low recurrence rate and less chance of malignant transformation. At the same time, surgical mortality is high, particularly with tumors involving the skull base due to the proximity to critical structures. Hence, gross total excision in supratentorial osteochondromas and maximal safe resection with serial follow-up of skull base osteochondromas will be a safe strategy.

### Conclusion

The presence of calcified mass with minimal or no enhancement and without surrounding edema on radiology should raise suspicion of osteochondromas preoperatively. Surgery is the treatment modality of choice with good long-term outcome. Preservation of the adjacent critical neurovascular structures from iatrogenic trauma while removing this bony hard lesion is an important factor affecting postoperative morbidity and/or mortality.

### Authors' Contribution

R.S. developed the concept and design of the study, edited the manuscript, and is the guarantor. S.D. and M.C.S performed the literature search, data acquisition, data analysis, and statistical analysis. S.D. prepared the manuscript. R.S. and M.C.S. reviewed the manuscript.

### Conflict of Interest

None declared.

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