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Posterior Fossa Ependymoma in a Child with Extensive Chondro-Osseous Metaplasia Occurring at Cerebellopontine Angle and Masquerading as a Vestibular Schwannoma: An Exceptionally Rare Clinicopathological Manifestation with Review of Literature

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Abstract

Ependymoma occurring at the cerebellopontine (CP) angle is an extremely uncommon sight and poses diagnostic and management dilemmas to neurosurgeons, radiologists, and neuropathologists alike. Moreover, the presence of extensive chondro-osseous metaplastic elements in ependymomas is an exceptionally infrequent histopathological manifestation. However, due to the seldom-seen nature of this histomorphological feature, there is no definite consensus regarding its etiopathogenesis and clinical consequences, and there is an extreme scarcity of literature elucidating its clinicopathological spectrum and prognostic significance. Herein, we illustrate an intriguing clinical tale of a 7-year-old male child with posterior fossa ependymoma, central nervous system (CNS) World Health Organization (WHO) grade 3, arising at the right CP angle and masquerading as a vestibular schwannoma, which in itself is a rare presentation, and additionally, exhibiting extensive chondro-osseous metaplasia, which is a very uncommon histomorphological observation. To the best of the authors' knowledge and after a comprehensive literature search, the coexistence of these two rare observations has merely been described once in international literature. This case sheds light on and highlights the importance of keeping ependymoma as a possible differential while coming across CP angle space-occupying lesions. They should be diligently distinguished from schwannomas and other masqueraders that typically occur at this site, as they have diverse management and follow-up protocols, with varying prognostic outcomes for the patients. Moreover, this case also unravels and details the clinicopathological characteristics of a scarcely described feature of chondro-osseous metaplasia in ependymomas.

Keywords

- ependymoma
- cerebellopontine angle
- chondro-osseous metaplasia
- posterior fossa
- vestibular schwannoma

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Introduction

Ependymomas are rare neuroepithelial neoplasms that are driven by oncogenetic events in tumor cells that result in ependymal differentiation and comprise a mere 1.6 to 1.8% of all primary central nervous system (CNS) tumors. They are relatively well-circumscribed neoplasms composed of ependymal differentiated tumor cells that usually arise in close vicinity of the ventricular system of the brain, commonly in the fourth ventricle (i.e., in the posterior fossa [PF]), supratentorial region, and in the spinal cord, where they are frequently related to the conus or filum terminale.[1]

Ependymomas show a bimodal pattern of age distribution, the first peak occurring in childhood with the mean age of presentation being 4 years where they preferentially occur intracranially with the majority of the neoplasms occurring in the PF (ependymal-lined ventricular system) followed by a supratentorial location. The second peak is observed in adults, usually presenting between 20 and 40 years of age, where they typically arise as intramedullary spinal tumors. However, an ependymoma occurring at the cerebellopontine (CP) angle is an extremely uncommon sight, which poses diagnostic and management dilemmas to neurosurgeons, radiologists, and neuropathologists alike.

The most recent Fifth Edition of World Health Organization (WHO) Classification of Central Nervous System Tumors 2021 recognizes myxopapillary ependymoma and subependymoma as distinct histopathological subtypes, which are well described in the literature.[2] However, the occurrence of extensive chondro-osseous metaplasia in ependymoma is an exceptionally rare pathological finding and there is an extreme scarcity of literature elucidating its clinicopathological spectrum and prognostic significance.

Herein, we illustrate an intriguing clinical tale of a 7-year-old male child with PF ependymoma, not otherwise specified (NOS), CNS WHO grade 3, arising at the right CP angle and masquerading as a vestibular schwannoma, which in itself is a rare presentation and additionally exhibiting extensive chondro-osseous metaplastic elements, which is an extremely infrequent histopathological manifestation. To the best of the authors' knowledge and after a comprehensive literature search, the coexistence of these two rare observations has merely been described once in international literature.

Case Presentation

A 7-year-old boy presented to the pediatric emergency department of a tertiary hospital with chief complaints of projectile vomiting, headache, lethargy, and inability to feed for the last 2 days following a trivial fall while playing outside. There was no history of associated fever, drowsiness, altered sensorium, blurring of vision, seizures, or behavioral change. Also, there was no long-standing history of any chronic ailments or medications. On examination, the child was hemodynamically stable with only mild dehydration present and there were no signs of any neurological deficits. The evaluated Glasgow Coma Scale (GCS) score was 15 (eye-opening: 4; best verbal response: 5; best motor response: 6). There were no signs of papilledema and the rest of the systemic examination was unremarkable as well.

He was advised a noncontrast computed tomography scan, which revealed the presence of a well-defined soft-tissue lesion in the right CP angle with multiple foci of calcification within the space-occupying lesion (SOL). It was seen causing compression over the pons and the fourth ventricle and upstream minimal dilation of the third and bilateral lateral ventricles. There was no evidence of bony hyperostosis. He subsequently underwent a gadolinium contrast-enhanced magnetic resonance imaging (MRI) scan, which showed a well-defined mass lesion of size 57 × 30 mm in the right CP angle cistern appearing as hypointense on T1-weighted (T1W) and hyperintense on T2W and fluid-attenuated inversion recovery (FLAIR) sequence with moderate heterogeneous enhancement on the postcontrast study (as shown in ►**Fig. 1**). The lesion was abutting the basilar artery, encasing the right vertebral artery, and compressing upon underlying pons, medulla oblongata, and fourth ventricle resulting in upstream obstructive hydrocephalus with mild periventricular ooze. Radiological

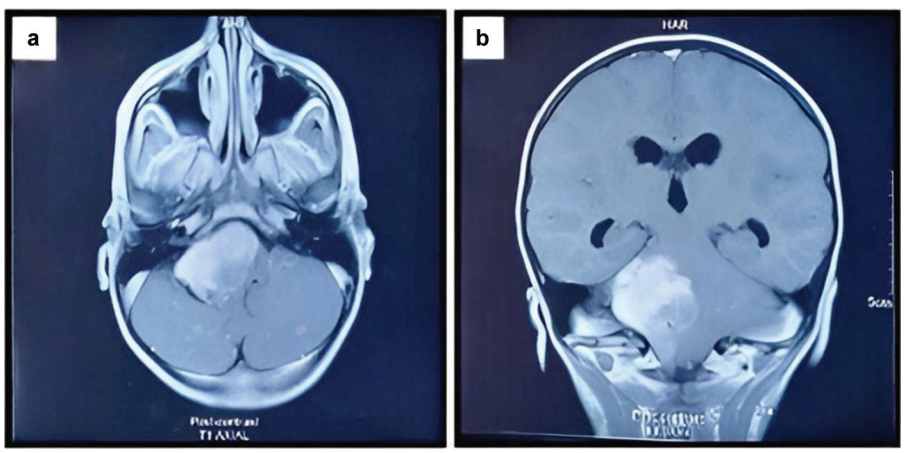

Fig. 1 Radiological findings. Magnetic resonance imaging (MRI) scan showing a well-defined mass lesion of size 57 × 30 mm in the right cerebellopontine (CP) angle cistern with moderate heterogeneous enhancement on the postcontrast study. (**a**) T1 axial and (**b**) coronal views.

features were indicative of a right CP angle SOL, likely to be a vestibular schwannoma.

The child underwent right retromastoid-suboccipital (RMSO) craniotomy under general anesthesia and gross total resection of the tumor was done. Intraoperatively, it was a reddish-brown tumor, and soft to firm in consistency. The excised tumor was entirely submitted for histopathological examination and confirmatory diagnosis.

The excised tumor mass was received in the histopathology department in 10% neutral buffered formalin and was entirely processed. Five-micron thick, hematoxylin and eosin–stained sections were prepared from formalin-fixed and paraffin-embedded tissue. Multiple sections examined from the tumor tissue exhibited the presence of a cellular, well-circumscribed tumor composed of uniform and monotonous round to oval small cells with indistinct cellular outlines embedded in a fibrillary matrix. They had round nuclei with speckled chromatin and inconspicuous nucleoli. The tumor was heterogeneous in composition with the presence of nodules with a higher cellular density as compared with surrounding syncytial areas. Characteristic perivascular pseudorosettes were present with tumor cells arranged in a radial fashion surrounding the vascular lumina creating an intervening anucleate zone. Numerous true ependymal rosettes were also appreciated comprising cuboidal to columnar cells surrounding a central lumen. A striking histopathological feature observed was the presence of extensive areas of mature cartilage and bony trabeculae with mineralization, as metaplastic elements within the tumor proper. Large areas of tumor necrosis were present along with dense acute inflammatory infiltrate and atypical mitoses were frequently observed with mitotic count of 8 to 10 per high-power field. Hyalinization of blood vessels was seen as well. However, no areas of nuclear pleomorphism or areas of cystic or myxoid degeneration were seen (as shown in ►**Fig. 2**).

Immunohistochemistry (IHC) was performed on 2-µm thick sections taken on poly-L-lysine coated slides. An extensive panel of immunohistochemical antibodies was applied to clinch an accurate diagnosis. On IHC, the tumor cells showed diffuse immunoreactivity for glial fibrillary acidic protein (GFAP), perinuclear dotlike and ringlike immunostaining for epithelial membrane antigen (EMA), strong nuclear and cytoplasmic positivity for S100, focal positivity with pancytokeratin (AE1/AE3), and membranous immunostaining with CD 99. Ki-67 proliferation index was around 75%. The tumor cells were negative for synaptophysin, chromogranin, IDH1, OLIG2, and neurofilament (as shown in ►**Fig. 3**).

Based on the corroborative radiological, histopathological, and immunohistochemical findings, a final impression

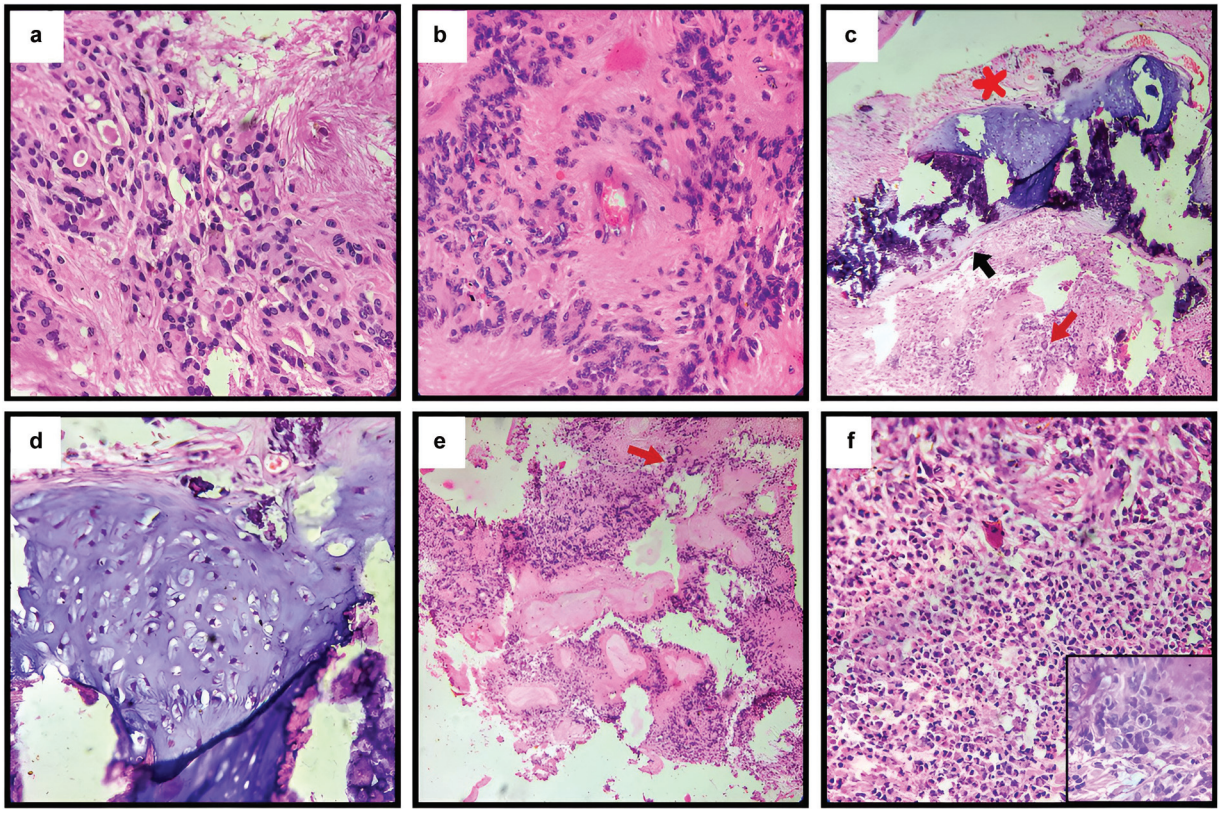

Fig. 2 Histopathological findings. (**a**) Numerous true ependymal rosettes comprising cuboidal to columnar cells surrounding a central lumen, hematoxylin and eosin ×400. (**b**) Characteristic perivascular pseudorosettes with tumor cells arranged in a radial fashion surrounding the vascular lumina creating an intervening anucleate zone, hematoxylin and eosin ×400. (**c**) Section showing the presence of large areas of mature cartilage (*red asterisk*), bony trabeculae with mineralization (*black arrow*), and true ependymal rosettes (*red arrow*), hematoxylin and eosin ×100. (**d**) Extensive areas of mature cartilage within tumor proper, hematoxylin and eosin ×400. (**e**) Extensive areas of formation of bony trabeculae within tumor proper along with true ependymal rosettes (*red arrow*), hematoxylin and eosin ×100. (**f**) Large areas of necrosis within the tumor along with dense acute inflammatory infiltrate and presence of atypical mitotic figures (*inset*), hematoxylin and eosin ×400.

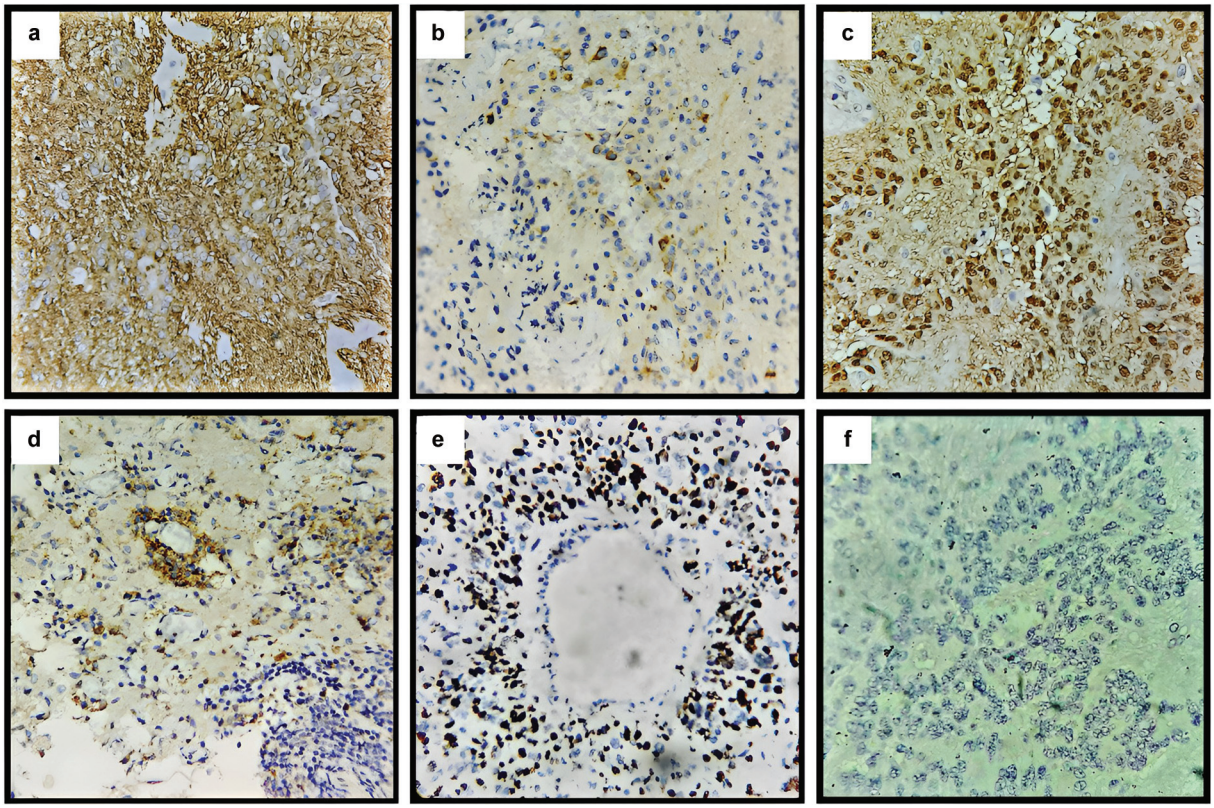

Fig. 3 Immunohistochemistry findings. (**a**) Tumor cells showing diffuse immunoreactivity for glial fibrillary acidic protein (GFAP), immunohistochemistry ×400. (**b**) Perinuclear dotlike and ringlike immunostaining for epithelial membrane antigen (EMA), immunohistochemistry ×400. (**c**) Strong nuclear and cytoplasmic positivity for S100, immunohistochemistry ×400. (**d**) Focal positivity with pancytokeratin (AE1/AE3), immunohistochemistry ×400. (**e**) High Ki-67 proliferation index of around 75%, immunohistochemistry ×400. (**f**) Negative immunostaining with IDH1, immunohistochemistry ×400.

of PF ependymoma, NOS, CNS WHO grade 3 with extensive chondro-osseous metaplasia, at right CP angle was rendered.

The child was clinically stable post-surgical excision of the tumor and had been kept on close follow-up in the pediatric neurosurgery outpatient department. He had shown no signs of recurrence of the tumor at the previous location or elsewhere in the brain parenchyma or spinal cord for 8 months post excision. However, after that his parents had taken him to his native village, due to which he could not attend his regular follow-up visits. On telephonic follow-up at the 10th postoperative month, his father informed that his condition had rapidly deteriorated in the ninth month post-surgical excision and had started experiencing severe headache and recurrent bouts of projectile vomiting and had ultimately succumbed to the illness.

Discussion

Ependymomas comprise a rare group of neuroepithelial neoplasms that constitute a mere 1.6 to 1.8% of all primary CNS tumors and are relatively commonly seen in children as compared with adults. As per the statistical figures from the Central Brain Tumor Registry of the United States, the incidence of ependymoma varies between 0.29 and 0.6 per 100,000 persons annually.[3] They are composed of ependymal differentiated tumor cells arising in close association with the ependymal-lined ventricular system, central canal of the spinal cord, or originate from the cortical ependymal rests. They show a slight male predilection with a male-to-female ratio of 1.3:1.[4] The preponderance of ependymomas to occur at a specific site vastly depends on the age group of the affected patient. A majority (around 90%) of pediatric ependymomas typically occur intracranially, of which most of them typically occur in or around the fourth ventricle, whereas 65% of adult neoplasms characteristically occur in the spinal cord.[5]

The most recent Fifth Edition of WHO Classification of CNS Tumors 2021 recommendations regarding the classification of ependymal tumors have led to a paradigm transition in prognostication and risk stratification for the patients. It has guided neurosurgeons in refining treatment and follow-up management plans as well. It suggests that wherever feasible, ependymomas should be subtyped using a holistic approach considering key histopathological and molecular findings, in adjunct with the anatomic location of the tumor. The application of DNA methylation studies helps classify ependymal neoplasms into three main categories including the following: (1) supratentorial ependymomas, which are characterized by two molecular subgroups involving *ZFTA* (previously known as *C11orf95*) and *YAP1* fusion genes, with *ZFTA* fusions having a worse prognosis in contrast to ependymomas with *YAP1* fusions, which have a favorable prognosis. (2) PF ependymomas, which are further subclassified into Posterior fossa group A (PFA) and Posterior fossa group B

(PFB) based on the DNA methylation profile alignment. Moreover, PFA ependymomas show a globally reduced nuclear expression of H3 p.K28me3 (K27me3) in the tumor nuclei and are characterized by genomic stability in genome-wide copy number analysis studies. PFB ependymomas, on the other hand, demonstrate retained nuclear immunoexpression of H3 p.K28me3, while exhibiting chromosomal instability and aneuploidy in genetic studies. (3) Spinal ependymomas, which can either have a classic or myxopapillary histopathology with relatively favorable outcome or can display aggressive high-grade morphology and behavior with MYCN (MYCN Proto-Oncogene, BHLH Transcription Factor) amplification. Additionally, one molecular subgroup at each anatomical location comprises of tumors with histomorphological characteristics of subependymoma. Moreover, the WHO also suggests defining ependymomas by their anatomic location without molecular classification in those cases where molecular analysis reveals a different alteration from that defined at the particular location, where the term "NEC" (not elsewhere classified) is recommended. Furthermore, where molecular studies fail or are not feasible, the term "NOS" is applied, which is especially implemented in resource-poor countries where molecular cytogenetics are yet to be incorporated into routine clinical practice. Although myxopapillary ependymoma and subependymoma continue to be listed as ependymoma subtypes, papillary, tanycytic, and clear cell histopathological variants are no longer regarded as subtypes. Another important implication of the updated classification negates the application of the term "anaplastic ependymoma." However, in an integrated final diagnosis, CNS WHO grade 2 or 3 can be assigned depending on histopathological features.[6] Therefore, in the present case, a final diagnosis of posterior fossa ependymoma, NOS, CNS WHO grade 3 was rendered owing to the anatomical site of occurrence of the tumor, which was CP angle, suggesting a posterior fossa ependymoma. Moreover, a WHO grade 3 was attributed accounting for the high-grade histopathological features including large areas of tumor necrosis, high mitotic count, high Ki-67 proliferation index, and the presence of numerous atypical mitoses.

Posterior fossa ependymomas usually occur in and around the fourth ventricle. They can arise from its floor, roof, and/or the lateral aspect. However, the CP angle is an extremely rare site for the occurrence of ependymoma, which has been infrequently described in limited reports by Salunke et al,[7] Lan et al,[8] Ebrahimi et al,[9] and Dibs et al[10] and, when present, poses significant diagnostic and management challenges. It can easily masquerade as a vestibular schwannoma on imaging, which is typically known to occur at the CP angle. Other possible mimickers at this site could be a meningioma, vascular aneurysm or ectasia, or less commonly epidermoid cyst, arachnoid cyst, or even metastasis from malignant primaries elsewhere. Moreover, this peculiar location of the tumor also enhances the operative difficulties of a neurosurgeon as they can alter the posterior fossa anatomical landmarks as they grow. However, diligent effort should be made in distinguishing and arriving at an accurate diagnosis as they have diverse management and follow-up protocols, with varying prognostic outcomes for the patients. The pivotal role of histopathology along with the ancillary technique of IHC cannot be emphasized enough and is crucial for precise diagnosis and timely formation of appropriate management plans.

Another exceptionally uncommon and intriguing histopathological finding observed in the present case was extensive chondro-osseous metaplasia within the tumor proper. Quite a few theories have been proposed to explain this rare observation in ependymomas. The most accepted postulate remains that they arise from the metaplastic transformation of either the glial or mesenchymal component of the neoplasm.[11] Another interesting hypothesis suggested for glial tumors is the production of basement membrane–like material by the neoplastic cells, which on condensation may convert into chondroid mesenchyme.[12] Wang et al[13] concluded that the presence of chondro-osseous metaplastic elements in ependymoma was associated with a worse outcome for the patient despite aggressive management, indicating that their presence confers an aggressive behavior to the neoplasm. However, due to the seldom-seen nature of this histomorphological feature, there is no definite

Table 1 The clinicopathological features of the previously described cases of ependymoma exhibiting both chondroid and osseous metaplasia

Sl. no.	Study	Age (y)	Sex	Site of occurrence	Histologic variant of ependymoma	CNS WHO grade	Follow-up and outcome
1	Bannykh and Baehring[14]	61	Male	Left frontal lobe	Anaplastic	3	Death at 6 mo
2	Mridha et al[15]	9	Male	Left cerebellopontine angle cistern	Anaplastic	3	NA
3	Gessi et al[16]	2	Female	Fourth ventricle	Anaplastic	3	NA
		3	Female	Fourth ventricle	Ependymoma	2	NA
		53	Female	Fourth ventricle	Subependymoma/ ependymoma	1	NA
4	Wang et al[13]	5	Male	Fourth ventricle	Ependymoma	2	Death at 18 mo
5	Alkhaibary et al[17]	3	Male	Fourth ventricle	Anaplastic	3	No recurrence at 2 y
6	Present study	7	Male	Right cerebellopontine angle cistern	Posterior fossa ependymoma	3	Death at 9 mo post-surgical excision

consensus regarding its etiopathogenesis and clinical consequences. Larger studies with long-term follow-up of patients need to be undertaken to comprehensively elucidate their characteristics and establish robust guidelines on their clinical implications. The clinicopathological features of the previously described cases of ependymoma exhibiting both chondroid and osseous metaplasia are summarized in ►**Table 1**.[14–17]

Ependymomas are treated by gross total resection with/without adjuvant radiotherapy.[18] Several novel therapeutic drugs targeting ALK (Anaplastic lymphoma kinase), VEGF (Vascular endothelial growth factor), mTOR (Mammalian target of rapamycin), EGFR (Epidermal growth factor receptor), ErbB2 (Erb-B2 receptor tyrosine kinase 2) pathways are under clinical trial for neurofibromatosis 2–associated neoplasms and offer a promising future.[19]

Conclusion

This unique case report elucidates the clinical, radiological, and neuropathological features of a scarcely described presentation of posterior fossa ependymoma occurring at the CP angle, which itself is challenging to diagnose, and, additionally, with concurrent presence of extensive chondro-osseous metaplasia, making it an exceptionally uncommon occurrence. Moreover, histopathological and immunohistochemical evaluation plays a pivotal role in distinguishing challenging masqueraders. Long-term clinical follow-up and diligent and detailed assessment of similar rare presentations in the future are mandatory for the establishment of robust guidelines on the clinical and prognostic impact of this rare co-occurrence and consequently refining treatment guidelines for the patients.

Statement of Ethics

Written informed consent was taken from the patient's guardian to participate in this study and for the publication of any potentially identifiable images or data included in this article. Ethical review and approval are not required and are provided a waiver for the publication of case reports as per institutional requirements.

Authors' Contribution

S.M. had a key role in the conceptualization, drafting, and revision of the manuscript and the collection, analysis, and interpretation of the data. S.S.S. had a major contribution to curation, analysis, interpretation of data, and drafting of the manuscript. S.K. had an important role in diagnosing the case, conceptualization, providing resources, and critically revising the manuscript for important intellectual content.

Conflict of Interest

None declared.

References

1 Rudà R, Bruno F, Pellerino A, Soffietti R. Ependymoma: evaluation and management updates. Curr Oncol Rep 2022;24(08):985–993
2 Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-oncol 2021;23(08):1231–1251
3 Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013–2017. Neuro-oncol 2020;22(12, Suppl 2):iv1–iv96
4 Giridhar P, Nambirajan A, Benson R. Ependymoma. In: Mallick S, Giridhar P, Rath GK, eds. Evidence Based Practice in Neuro-Oncology. Singapore: Springer; 2021
5 McGuire CS, Sainani KL, Fisher PG. Incidence patterns for ependymoma: a surveillance, epidemiology, and end results study. J Neurosurg 2009;110(04):725–729
6 WHO Classification of Tumours Editorial Board. World Health Organization Classification of Tumours of the Central Nervous System. 5th ed. Lyon: International Agency for Research on Cancer; 2021
7 Salunke P, Sharma M, Gupta K, Kovai P, Aggarwal A. Cerebellopontine angle ependymoma in a 2-year- old child. J Neurosci Rural Pract 2012;3(02):200–203
8 Lan Z, Richard SA, Zhang Y. Cerebellopontine angle ependymoma in a young adult: A case report. Medicine (Baltimore) 2019;98 (14):e15019
9 Ebrahimi H, Jelodar S, Karimi Yarandi K, Eftekhar Javadi A, Alimohamadi M. Adult cerebellopontine angle ependymoma presenting as an isolated cisternal mass: a case report. J Med Imaging Radiat Sci 2020;51(04):689–693
10 Dibs K, Prasad RN, Madan K, et al. Cerebellopontine angle ependymoma presenting as isolated hearing loss in an elderly patient: a case report and literature review. Surg Neurol Int 2021;12:572
11 Chakraborti S, Govindan A, Alapatt JP, Radhakrishnan M, Santosh V. Primary myxopapillary ependymoma of the fourth ventricle with cartilaginous metaplasia: a case report and review of the literature. Brain Tumor Pathol 2012;29(01):25–30
12 Kepes JJ, Rubinstein LJ, Chiang H. The role of astrocytes in the formation of cartilage in gliomas. An immunohistochemical study of four cases. Am J Pathol 1984;117(03):471–483
13 Wang X, Zhang S, Ye Y, Chen Y, Liu X. Ependymoma with cartilaginous metaplasia might have more aggressive behavior: a case report and literature review. Brain Tumor Pathol 2012;29 (03):172–176
14 Bannykh S, Baehring JM. Images in neuro-oncology: rapid development of osseous and chondrous metaplasia in recurrent anaplastic ependymoma. J Neurooncol 2007;81(03):257–258
15 Mridha AR, Sharma MC, Sarkar C, Garg A, Singh MM, Suri V. Anaplastic ependymoma with cartilaginous and osseous metaplasia: report of a rare case and review of literature. J Neurooncol 2007;82(01):75–80
16 Gessi M, Kuchelmeister K, Lauriola L, Pietsch T. Rare histological variants in ependymomas: histopathological analysis of 13 cases. Virchows Arch 2011;459(04):423–429
17 Alkhaibary A, AlSufiani F, Alassiri AH, Almuntashri M, Al Qutub ST. Chondro-osseous metaplasia in ependymoma: a rare histopathological finding. Case Rep Pathol 2020;2020:1528698
18 Rudà R, Reifenberger G, Frappaz D, et al. EANO guidelines for the diagnosis and treatment of ependymal tumors. Neuro-oncol 2018;20(04):445–456
19 Neyazi S, Yamazawa E, Hack K, et al. Transcriptomic and epigenetic dissection of spinal ependymoma (SP-EPN) identifies clinically relevant subtypes enriched for tumors with and without NF2 mutation. Acta Neuropathol 2024;147(01):22