Case Series

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Aggressive CNS Embryonal Tumours: A Series of Three Cases

Pathology Section

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ABSTRACT

Central Nervous System (CNS) embryonal tumours represent a heterogeneous group of aggressive paediatric neoplasms with variable clinical presentations, histopathological features, and outcomes. This case series presents the clinicopathological characteristics of three distinct CNS embryonal tumour cases diagnosed at our centre. The first child presented with cerebellar signs and symptoms, including gait disturbance and vomiting, at three years of age. Clinical and radiological diagnosis was in favour of medulloblastoma. Histopathological examination revealed anaplastic cells with cell wrapping typical of large cell/anaplastic medulloblastoma, which was confirmed with immunohistochemistry. The second case involved a 10-year-old boy with cerebellar symptoms along with signs of myelopathy affecting the lower limbs. Magnetic Resonance Imaging (MRI) revealed a cerebellar tumour with spinal metastasis, raising the possibility of medulloblastoma, which was confirmed histologically. The last case was a one-year-old infant with rapidly progressive neurological deficits and a large supratentorial mass on MRI, suspicious for Atypical Teratoid/Rhabdoid Tumour (AT/RT). Characteristic rhabdoid cells in histopathology, accompanied by loss of SMARCB1 expression in immunohistochemistry, confirmed the diagnosis of ATRT. This series highlights the diverse clinical and pathological spectrum of CNS embryonal tumours, emphasising the importance of a comprehensive diagnostic work-up, including detailed clinicoradiological assessment, histopathological evaluation, and immunohistochemistry in the management. Further research with larger cohorts is warranted to better understand the molecular underpinnings and optimise treatment strategies for these challenging paediatric malignancies.

Keywords: Atypical teratoid/rhabdoid tumour, Central nervous system, Embryonal tumours, Medulloblastoma, SMARCB1

INTRODUCTION

The CNS embryonal tumours, including medulloblastomas and ATRTs, represent a significant challenge in paediatric oncology due to their aggressive nature and complex biological behaviour. Medulloblastomas are the most common malignant brain tumours in children, accounting for approximately 20% of all CNS tumours in this age group. They arise from the cerebellum and are classified into several molecular subgroups that influence prognosis and treatment strategies [1,2].

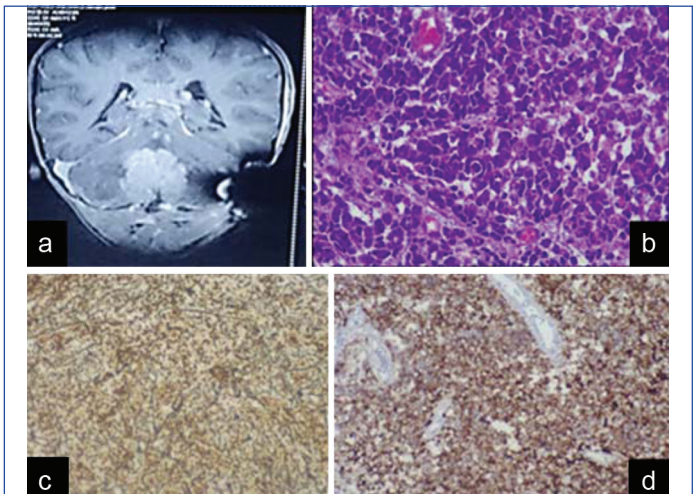
ATRTs, although rarer, are equally aggressive tumours that predominantly affect infants and young children, often presenting with rapid clinical deterioration. This tumour type is characterised by specific genetic alterations, including mutations in the SMARCB1 gene, which play a critical role in its pathogenesis [3,4].

Recent advances in molecular profiling have enhanced our understanding of these tumours, leading to more precise classifications and potential targeted therapies. The integration of histological features with molecular data is essential for accurate diagnosis and management [5,6]. This case series aims to elucidate the clinical and pathological characteristics of two medulloblastoma cases and one ATRT case, contributing to the growing body of knowledge in paediatric neuro-oncology.

Case 1

A three-year-old female child presented to the neurosurgery department with complaints of vomiting, headache, loss of control over micturition, and swaying towards the left side for one month. There was a past history of similar complaints two months prior, which was followed by excision biopsy and ventriculoperitoneal shunt placement. The previous biopsy report indicated medulloblastoma, after which she underwent radiation and chemotherapy at an external hospital. During the present visit, the child was mechanically ventilated following a clinical examination. MRI showed a circumscribed soft-tissue density lesion in the midline of the cerebellum, protruding into the fourth ventricle, consistent with medulloblastoma [Table/Fig-1a]. The clinical diagnosis was medulloblastoma recurrence, and suboccipital craniotomy, excision, and duroplasty were performed.

Microscopy of the lesion revealed a cellular neoplasm composed of cells arranged in diffuse sheets and trabeculae, with areas of necrosis. There were two groups of tumour cells: small round cells and large anaplastic cells. The small round cells had scant to moderate cytoplasm, round nuclei with coarse chromatin, and mild pleomorphism. Nuclear moulding and characteristic cell wrapping were observed [Table/Fig-1b]. The other group of cells was large, with scant cytoplasm and round vesicular nuclei. Reticulin stain did not demonstrate any nodularity [Table/Fig-1c]. Immunohistochemistry (IHC) was performed with synaptophysin, which showed strong and diffuse cytoplasmic positivity [Table/Fig-1d]. The final diagnosis was large cell/anaplastic medulloblastoma, histologically defined. The child succumbed to death one month after surgery.

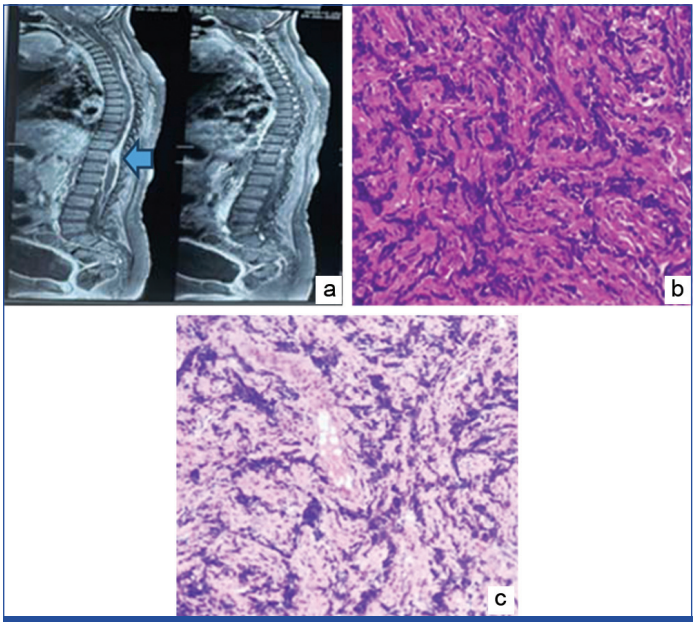


[Table/Fig-1]: a) MRI showing occipital lesion; b) Haematoxylin and Eosin (H&E) stain (40x) shows anaplastic cells with cell wrapping; c) No increase in reticulin fibres/ nodularity in reticulin stain (4x); d) Strong diffuse cytoplasmic positivity with synaptophysin Immunohistochemistry (IHC) (10x).

Case 2

A 10-year-old boy presented with a two-month history of progressive bilateral limb weakness, frequent vomiting, headaches, and urinary incontinence. He had a history of hypertension and was on medication. There was a history of recurrent episodes of headache and vomiting two months prior, which were treated symptomatically. He was admitted to the hospital due to lethargy and worsening of symptoms. Neurological examinations revealed sensory and motor deficits. MRI of the brain revealed a large, well-circumscribed, lobulated, heterogeneous space-occupying lesion in the left cerebellar hemisphere, with dural enhancement and thoracic myelopathy at the D10-D12 level, likely due to an intradural lesion, with the possibility of medulloblastoma grade 3 and evidence of spinal cord metastasis [Table/Fig-2a].

The patient underwent a biopsy of the brain mass, and a laminectomy with decompression was performed at the D10-D12 levels. Histological examination of the brain tissue was inconclusive, while the sections from the spinal mass revealed a syncytial arrangement of densely packed embryonal cells, with indistinct cytoplasm and hyperchromatic, pleomorphic nuclei. There was extensive nuclear streaking and frequent mitoses, but no necrosis or rosettes were observed. The differentials considered were medulloblastoma, high-grade neuroepithelial tumour, and ependymoma [Table/Fig-2b,c].



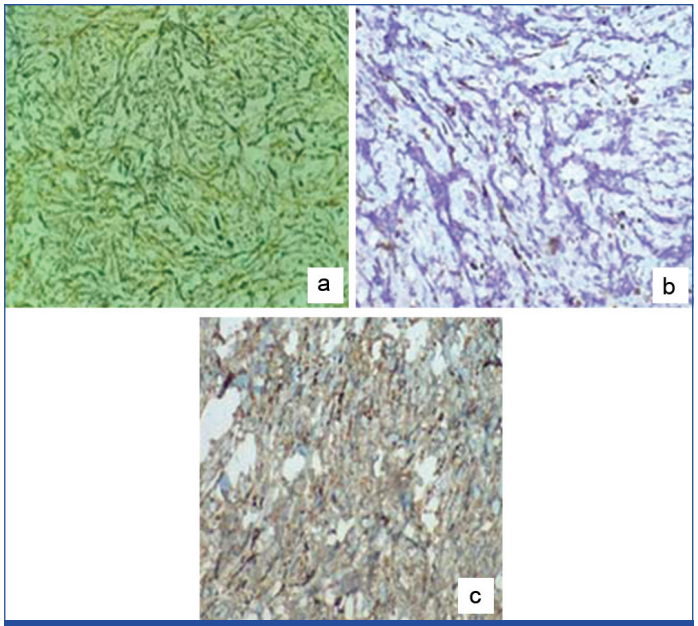
[Table/Fig-2]: a) MRI shows thoracic myelopathy at the D10-D12 level, secondary to an intradural lesion; b) H&E stain from spinal cord mass (40x) with densely packed embryonal cells; c) embryonal cells with extensive nuclear streaking (40x).

To confirm the diagnosis, immunohistochemical markers were utilised. IHC studies for synaptophysin and Neuron-Specific Enolase (NSE) revealed negative results. Additionally, a reticulin stain revealed an abundance of reticulin fibres, which aided in the diagnostic process [Table/Fig-3a-c].

Despite the variability in tumour histology and the expression of various specific lineage markers correlating with age, along with evidence of spinal metastasis and tumour characteristics, a final diagnosis of medulloblastoma, histologically defined, was made. Molecular studies, including DNA methylation profiling and genetic analysis (for WNT and SHH mutations), were advised for further confirmation and treatment. On follow-up, the patient succumbed to the illness, two months after the diagnosis.

Case 3

A one year and 10-month-old male child presented to the neurosurgery department with a one-month history of multiple episodes of vomiting. There was no history of seizures or weakness. Vitals were stable. An MRI of the brain showed an altered signal intensity supratentorial lesion with heterogeneous

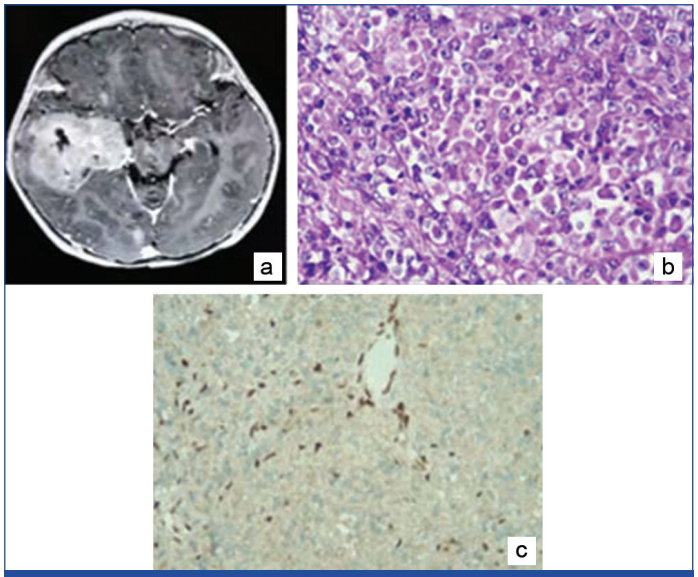


[Table/Fig-3]: a) Reticulin stain (40x): increase in reticulin fibres; b) Negative staining with synaptophysin IHC (40x); c) Negative staining with Neuron Specific Enolase (NSE) IHC (40x).

enhancement centred in the right temporal lobe [Table/Fig-4a]. Possible clinicoradiological differential diagnoses included AT/RT and primitive neuroectodermal tumour. The patient underwent right temporal craniotomy and excision of the lesion.

Histopathology revealed a cellular malignant neoplasm with tumour cells arranged diffusely in sheets. The tumour cells had moderate cytoplasm, round nuclei, coarse chromatin, and prominent nucleoli. A characteristic finding was the presence of aggregates and scattered rhabdoid cells, which exhibited dense eosinophilic cytoplasm, eccentric vesicular nuclei, and prominent nucleoli [Table/Fig-4b]. Numerous mitotic figures and areas of necrosis were noted.

A provisional diagnosis of AT/RT was made, followed by IHC for SMARCB1 [Table/Fig-4c]. The tumour cells were negative for SMARCB1, indicative of a mutation in the SMARCB1 gene, which led to the final diagnosis of AT/RT. Genetic studies were not conducted due to financial constraints. On follow-up, the patient succumbed to the illness five months after diagnosis.



[Table/Fig-4]: a) MRI shows heterogeneously enhancing right temporal lobe tumour; b) H&E stain (40x) with sheets of rhabdoid cells; c) IHC (40x)- SMARCB1 shows loss of expression in the tumour cells with positive internal control.

DISCUSSION

Embryonal tumours hold significant importance in paediatric oncology, representing a substantial portion of malignant brain

tumours in children, accounting for 15-20% of all paediatric CNS tumours. These tumours are known for their diverse histopathological features and varying clinical behaviours, making them a critical focus for clinical research. The case series underscores the complexities of diagnosing and treating embryonal tumours, with particular emphasis on medulloblastoma and AT/RT [7,8].

In a study conducted by Louis DN et al., medulloblastoma shows a bimodal age distribution, with peaks in children under five years (often SHH-activated infants) and again in older children (around 5-9 years) [3]. This is comparable with our first two cases, both of which had the cerebellar symptoms classically reported in medulloblastoma [6].

Medulloblastoma is an aggressive and rapidly growing brain tumour that typically originates in the cerebellum, predominantly affecting children. It is the third most common CNS tumour to develop systemic metastases, following glioblastoma and meningioma. Although it generally remains confined to the brain, it has the potential to spread to other parts of the CNS, including the spinal cord, leading to significant neurological impairments such as motor and sensory dysfunctions [9].

Leptomeningeal spread has an incidence of approximately 1-2% in brain tumours and is most frequently seen in paediatric cases, particularly in medulloblastoma and primary CNS lymphomas. It may present simultaneously with the primary tumour, during recurrence, or, in rare cases, as a primary leptomeningeal process without an identifiable intraparenchymal lesion. This process typically involves the direct deposition of tumour cells into the Cerebrospinal Fluid (CSF), allowing for widespread dissemination along the neuroaxis. In our second case, the patient presented with a dural lesion and spinal metastasis at the time of diagnosis, which is compatible with previously published cases [9-12].

When reporting an embryonal brain tumour, especially in challenging cases where characteristic histological features are absent, IHC becomes crucial for achieving an accurate diagnosis. Most tumour types in this context can mimic each other and can usually be distinguished based on subtle histological features and immunohistochemical profiling using lineage-specific markers.

In rare instances, medulloblastomas may exhibit tumour heterogeneity with alternative lineage differentiation, such as glial or mesenchymal features. In such cases, neuronal markers like synaptophysin and NSE may be negative, while glial markers such as GFAP or other lineage-specific markers may be expressed. This underscores the importance of using a panel of markers and considering molecular profiling for accurate diagnosis and prognosis in medulloblastoma cases [13-18].

AT/RT is a rare and highly aggressive tumour, primarily affecting infants and children under the age of three years. AT/RTs are found in both the supratentorial compartment (~50%) and the posterior fossa (~50%), though rarely in the spinal cord [17]. Our case involves a one-year-old child with a supratentorial tumour, which correlates well with the literature. Histologically, AT/RT is complex, featuring a combination of rhabdoid, primitive neuroepithelial, epithelial, and mesenchymal components, making it prone to misdiagnosis. Immunohistochemically, AT/RTs typically test positive for markers such as vimentin, Epithelial Membrane Antigen (EMA), Smooth Muscle Actin (SMA), and synaptophysin, although none of these are specific.

To avoid diagnostic pitfalls in histology and IHC studies, it is crucial to recognise the hallmark feature of AT/RTs: the loss of nuclear expression of INI1 (SMARCB1), a tumour suppressor gene located on chromosome 22q11.2. This loss typically results from biallelic mutations or deletions of the SMARCB1 gene. Recent studies emphasise the importance of these genetic alterations in the SMARCB1/INI1 gene, which lead to the loss of INI1 protein expression in AT/RTs.

In a study conducted by Al-Hussaini M et al., it was observed that the loss of SMARCB1 is often associated with poor prognosis, and its detection plays a critical role in differentiating these tumours from other CNS malignancies [19]. This aligns with our case, where the nuclear loss of SMARCB1 aided in the diagnosis and indicated an aggressive clinical course.

To enhance diagnosis and therapeutic strategies, specialised studies focused on the genetic and histopathological characteristics of these tumours are essential. These studies will not only aid in classifying embryonal tumours more accurately but also provide valuable insights into potential targeted treatments tailored to the specific biology of the tumours [16,19,20].

CONCLUSION(S)

In conclusion, embryonal tumours of the CNS represent a diverse and challenging group of malignancies, primarily affecting paediatric populations. This case series highlights the critical need for early detection and accurate diagnosis of embryonal tumours through thorough histopathological and immunohistochemical evaluation. The variability in tumour presentation, heterogeneity, and potential for misdiagnosis underscore the importance of careful evaluation and multidisciplinary collaboration in managing these complex cases.

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