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Case Report

Pediatric tumors with multilayered rosettes: a diagnostic dilemma: A rare case of Astroblastoma in a 2-year-old child

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Abstract

Background: Diagnosing pediatric CNS tumors with multilayered rosettes can be challenging due to its extreme rarity. Spectrum includes Astroblastomas, Ependymomas, Embryonal tumors with multilayered rosettes which share similar histomorphological features despite being molecularly distinct. Here, we present a case of tumor exhibiting multilayered rosettes, which was later confirmed as Astroblastoma.
Methods: A 2-year-old female child seen with a 8-month history of headache, seizures and fever. CT scan and MRI was done which revealed a solid cystic lesion in the left frontal region. Complete surgical resection of the tumor was performed, and tissue was sent for histopathology.
Results: Microscopic examination revealed a highly cellular tumor composed of tumor cells arranged in multilayered papillae along with numerous similar multilayered pseudo rosettes and true rosettes. At places, tumor cells were arranged in trabecular pattern composed of thin fibrovascular core and regimented nuclei. Frequent foci of microvascular proliferation and necrosis was seen. Prominent perivascular and stromal sclerosis was seen. Differential diagnosis of Astroblastoma, Embryonal tumor of multilayered rosettes and Ependymomas was made. A complete IHC panel was advised which revealed strong positivity for GFAP, dot like positivity for EMA, focal OLIG2 and Synaptophysin positivity and Ki-67 index was high while IDH-1, L1CAM and P65 were negative which confirmed diagnosis of Astroblastoma.
Conclusion: Our case report focuses on Astroblastoma, addressing its diagnostic challenges, particularly the critical role of radiological correlation. This correlation is pivotal in distinguishing Astroblastoma from similar glial tumors like Ependymoma which has subtle histological differences and shared immunohistochemical markers.

Keywords: CNS rosettes, Childhood CNS neoplasms, Supratentorial rosette forming tumors, MN1 altered CNS tumors.

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1. Introduction

Diagnosing pediatric CNS tumors with multilayered rosettes can particularly be challenging due to its extreme rarity and the overlap in features with other glial neoplasms.[1] The spectrum includes Astroblastomas, Ependymomas, Embryonal tumors with multilayered rosettes (EMTRs) which share quite similar histomorphological features despite being molecularly distinct.

Astroblastoma is a rare neuroepithelial tumor with very few cases documented in the Indian population.[2]

Here, we present one such intriguing case of a CNS tumor exhibiting multilayered rosettes.

2. Case Presentation

A 2-year-old female child presented with a 8-month history of headache, seizures, and sporadic fever. MRI showed a solid cystic lobulated intra-axial mass in the left frontal lobe abutting the anterior horn of the left lateral ventricle. The solid part appeared hypointense on T1 with isotense T2

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sequences showing heterogenous post contrast enhancement of the solid component (**Figure 1**).

Complete surgical resection of the tumor was performed and sent for histopathology. The gross specimen was solid cystic, received in multiple bits, overall measuring 5*5 cm. Microscopic examination revealed a highly cellular tumor composed of tumor cells arranged in multilayered papillae and pseudopapillae along with numerous multilayered perivascular pseudo rosettes (**Figure 2**A). At other places, tumor cells were arranged in trabecular pattern composed of central thin fibrovascular core and regimented nuclei with vague palisading (**Figure 2**B). Frequent foci of microvascular proliferation was seen. (**Figure 2**C). Prominent perivascular stromal sclerosis and palisading necrosis was seen (**Figure 2**D). Features were consistent with a high grade neoplastic pathology and a differential diagnosis of Astroblastoma, Embryonal tumor with multilayered rosettes (EMTRs) and Supratentorial Ependymoma was given.

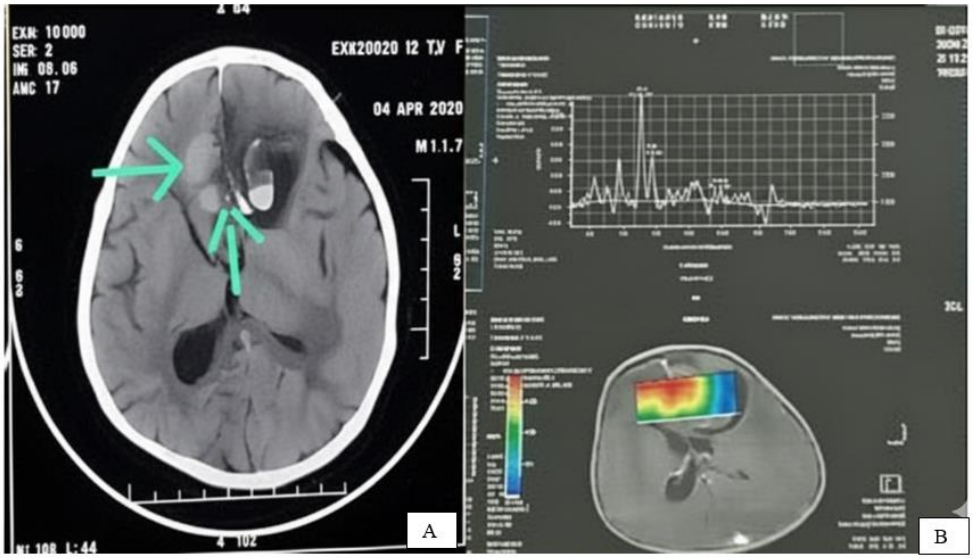

Figure 1: A): A solid cystic mass in left frontal region with midline shift. **B)**: The solid component was T1 hypointense and T2 isointense with post contrast enhancement

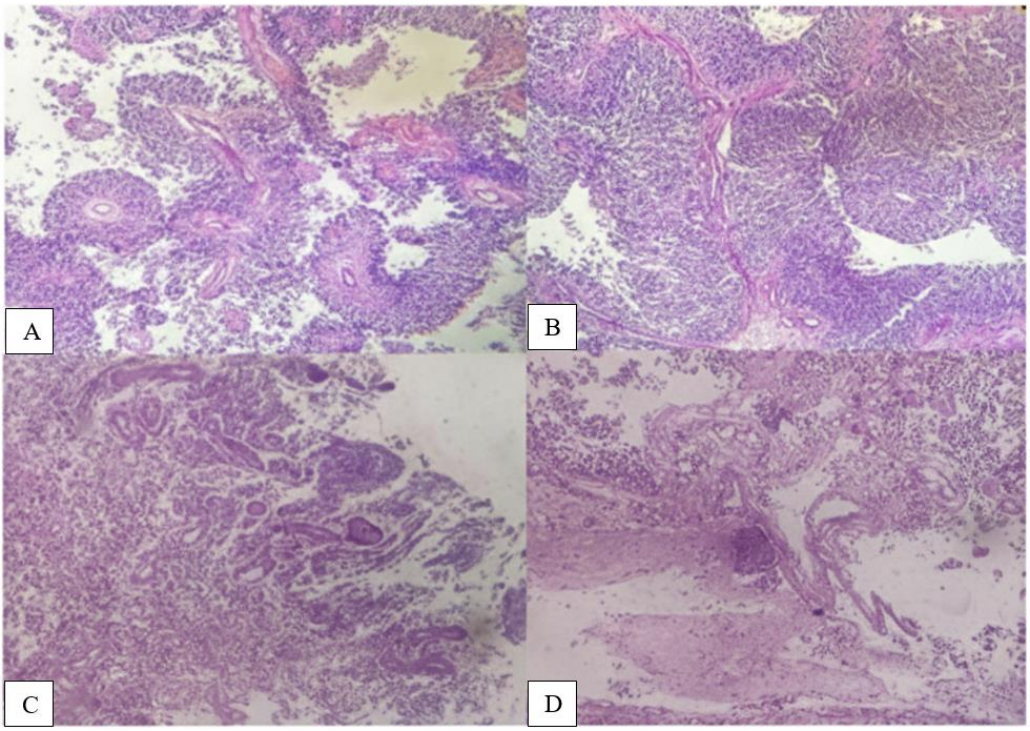

Figure 2: A): Tumor cells arranged in papillae and numerous multi-layered pseudorosettes. **B):** Tumor cells arranged in trabecular pattern composed of thin fibrovascular core and regimented nuclei. **C):** Foci of microvascular proliferation is noted. **D):** Areas of palisading necrosis and prominent perivascular sclerosis is noted.

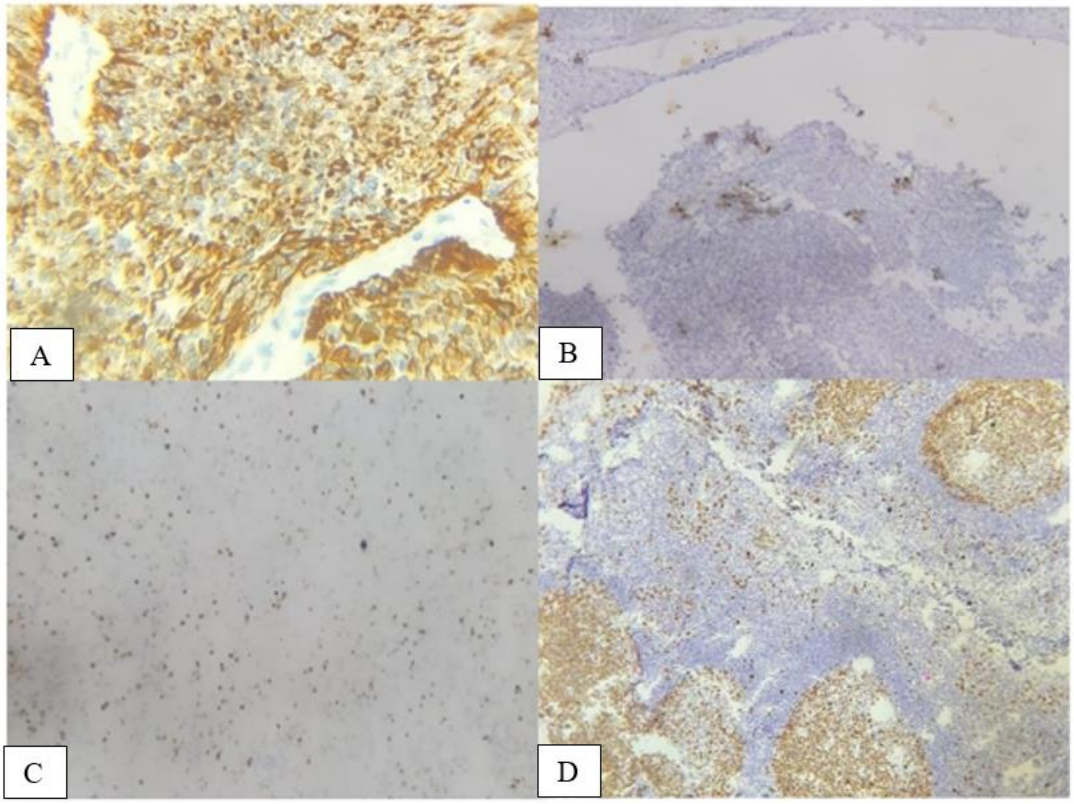

Figure 3: A): Strong positivity for GFAP. **B):** Dot like EMA positivity; Focal OLIG2 positive; **C):** High ki67 index

A comprehensive IHC panel was advised which revealed strong positivity for GFAP (**Figure 3**A), dot like positivity for EMA (**Figure 3**B), focal OLIG2 positivity (**Figure 3**C) and high Ki-67 index (**Figure 3**D) while IDH-1, L1CAM, P65 and CAM 5.2 were negative. Hence, after correlating the clinico-radiological, histopathological and immunohisto-chemical findings, the case was finally diagnosed as an Astroblastoma and MN1 molecular profiling was advised for confirmation. However, the patient was lost on follow up.

3. Discussion

Astroblastoma represents a very small fraction of all brain gliomas (only 0.45%–2.8%), making it an uncommon finding in clinical practice. Astroblastomas were first identified by Bailey and Cushing in 1924.[3] These tumors typically occur in the cerebral hemispheres, their presence in the cerebellum or brainstem is less common. Patient age ranges between 3 month to 40 years and shows a striking female predominance.[4]

Microscopic examination reveals astroblastic pseudorosettes with elongated eosinophilic cells having processes positive for GFAP, and are radially oriented around hyalinized blood vessels. A prominent feature is stromal sclerosis, often with extensive hyalinization and remnant tumor cell cords. The tumor is typically well-circumscribed. Features indicating aggressive behavior include increased mitotic activity, palisading necrosis, high cellularity, vascular proliferation, and a Ki-67 above 4%.[5]

Immunohistochemistry typically shows positivity for Epithelial Membrane Antigen (EMA), D2-40 and GFAP while OLIG2, and S-100 are often variably positive. The 5th edition of the WHO Classification of Tumors of the Central Nervous System redefines Astroblastoma based on molecular features, now termed Astroblastoma, MN1-altered. This tumor is characterized by alterations in the MN1 gene (22q12.1), most commonly through an in-frame fusion with BEND2 (Xp22.13), although other fusion partners have also been identified. These MN1 alterations typically occur in isolation but may be accompanied by copy number variations such as monosomy 16, partial loss of 22q, or loss of the X chromosome. DNA methylation profiling has shown that MN1-altered Astroblastomas form a distinct epigenetic class, clearly separating them from other tumors with similar astroblastic morphology.

While many Astroblastomas exhibit MN1 mutations, others show variability, with some falling into MN1 or BRAF DNA methylation groups. ZFTA fusion and BRAF mutation are mutually exclusive with MN1 alterations and do not support a diagnosis of MN1 altered Astroblastomas.

The histological features noted in MN1 altered Astroblastoma are not entity specific and may be displayed focally or extensively by other tumors that on molecular diagnostic assessment may represent ZFTA fusion positive Ependymomas, BRAF mutant Epitheloid Glioblastomas, BRAF mutant pleomorphic Xanthoastrocytomas, Embryonal neoplasms, IDH wild type Glioblastomas or Embryonal tumors with multilayered rosettes.[6]

Differentiating between Ependymoma and Astroblastomas can be particularly challenging as both types display perivascular pseudorosettes. However, subtle morphological features can help to distinguish between the two-Astroblastic pseudorosettes feature tumor cells with eosinophilic processes arranged radially around blood vessels forming papillary structures with distinct columnar or cuboid borders and a ribbon-like pattern in tangential views, unlike ependymal pseudo rosettes, which have less defined borders and a fibrillary stroma. Perivascular and stromal sclerosis further supports the diagnosis of astroblastoma.[7]

While there's IHC overlap between Ependymomas and Astroblastomas, L1CAM and P65 nuclear staining usually seen in supratentorial Ependymomas are virtually never seen in Astroblastomas.[6]

Distinguishing Astroblastomas from Ependymomas is more straightforward radiologically. They appear well circumscribed, hemispheric, often presenting a cystic mass component and generally located peripherally (i.e., near to or at the surface of the brain). Calcifications are often present, particularly with solid tumors. Astroblastomas demonstrate a bubbly appearance on MRI,[7] showing low peritumoral T2 hyperintensity which is not seen in Ependymomas.[8] These tumors typically present as mixed solid-cystic masses, with the solid component showing a characteristic bubbly appearance. Despite their large size, they demonstrate minimal peritumoral T2 hyperintensity, suggesting limited infiltration into surrounding brain tissue The characteristic radiological appearance of Astroblastoma more likely illustrate heterogeneous hyperintense signal on T2-weighted sequences (T2WS), and fluid-attenuated inversion recovery (FLAIR) images, hypointense to isointense on T1-weighted sequences (T1WS), with characteristic “bubbly” appearance. The tumor show heterogeneous enhancement on contrast based T1WS images. The cystic component demonstrate rim enhancement. Tumor associated vasogenic edema may also be present. Unlike Astroblastomas, Meningiomas show homogeneous enhancement. Calcifications common in Astroblastomas also help distinguish them from Glioblastomas.

While many Astroblastomas exhibit MN1 mutations, others show variability, with some falling into MN1 or BRAF DNA methylation groups.[9] ZFTA fusion and BRAF mutation are mutually exclusive with MN1 alterations and do not support a diagnosis of MN1 altered Astroblastomas.[6]

IDH wild type Glioblastomas are characterized by an infiltrative pattern of growth, distinctive cellular morphology, additional genetic alterations (RET promoter mutations, gain of chromosome 7, loss of chromosome 10) and absence of MN1 alterations unlike Astrocytomas. The calcifications found in Astroblastoma may help distinguishing it from Glioblastomas on radiology.[9]

Embryonal tumors with multi-layered rosettes (ETMRs) have abundant neuropil and true rosettes. Immunohistochemically, ETMRs are typically INI1 (SMARCB1)-positive, while our case showed INI1 loss, ruling out ETMRs.

Astroblastoma treatment primarily involves gross surgical resection. For low-grade lesions with complete resection, follow-up imaging is generally sufficient. In cases of high-grade tumors or incomplete resections, adjuvant therapies are recommended.

4. Conclusion

CNS tumors with multi-layered rosettes, especially in the setting of pediatric population can be quite challenging due to multiple differentials. Astroblastoma should be considered, especially in very young patients with large, well-circumscribed solid-cystic brain lesions along with its typical histopathological and radiological features. This correlation is pivotal in distinguishing it from similar glial tumors especially the more commonly reported Ependymoma which has very subtle histological differences and strikingly overlapping immunohistochemical markers. Molecular testing is the only confirmatory investigation and should be carried out whenever feasible.

5. Source of Funding

None.

6. Conflict of Interest

None.

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