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CLINICAL VIGNETTE

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Pediatric anaplastic ependymoma — intraoperative cytology and histopathological grading roles in the morpho-molecular era

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Introduction

Intraoperative cytology is nowadays essential for quickly determining the type of pediatric central nervous system (CNS) lesion [1]. This includes distinguishing high-grade ependymoma from other gliomas (low-grade ependymoma, low-grade glioma, high-grade glioma), other neoplasms, and non-neoplastic mimics. Despite the overlap in surgical gross total resection (GTR) goals for resectable tumors, each of these lesions has distinct clinical requirements.

Case report

An 11-year-old girl presented with a large left temporo-parieto-occipital mass. Intraoperative pathological consultation using imprint, smear, and squash cytology techniques was requested to guide the surgical strategy in real time. Cytological preparations revealed features characteristic of a high-grade tumor, including cell crowding, marked nuclear atypia, and atypical mitoses (Fig. 1A–C); the presence of round to oval nuclei with tiny nucleoli and long, thin processes, as well as the tendency for nuclei on cells attached to vessels to be located at the end away from the vessel, points globally towards an ependymoma, grade 3 according to the World Health Organization's 2021 classification of CNS tumors (WHO-CNS2021) [2]. This prompted an aggressive GTR according to international standards, as the extent of resection optimizes progression-free survival (PFS) [3].

Postoperative histology confirmed ependymal perivascular pseudorosettes associated to high-grade features (Fig. 1D), and immunohistochemistry (IHC) was consistent, with diffuse GFAP positivity, dot-like EMA expression, and Ki67 at ~25%. Immunohistochemistry excludes atypical teratoid/rhabdoid tumor (retained INI1) and high-grade glioma. Tissue was submitted for confirmatory fusion and epigenetic analysis. Postoperative magnetic resonance imaging (MRI) confirmed complete resection without detectable residual tumor; postoperative management follows international pediatric protocols.

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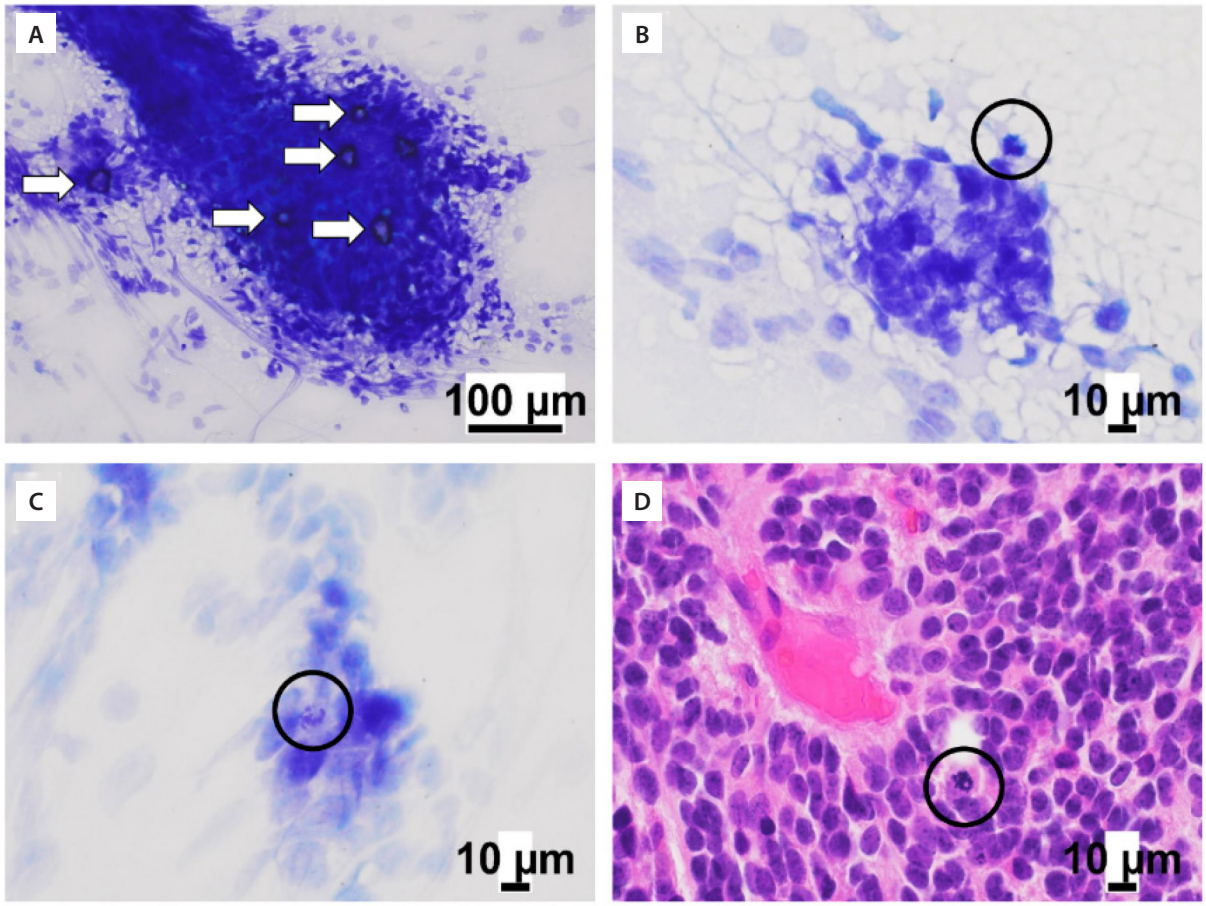

Figure 1. Microphotographs; **A.** An intraoperative cytological preparation showing scattered microcalcifications (arrows) within multilayered aggregates of neoplastic cells (toluidine blue, 20 ×); **B, C.** Intraoperative cytological preparations showing scattered atypical mitoses (circles) within neoplastic elements (toluidine blue, 40 ×); **D.** The definitive histological counterpart (hematoxylin-eosin, 40 ×), confirms that it is an anaplastic ependymoma with scattered atypical mitoses (circle)

Discussion

This case raises two sets of reflections: 1) on the one hand, purely morphological considerations regarding the role of this type of intraoperative diagnosis today; 2) on the other hand, considerations regarding the clinical-pathological significance of assigning morphological grade 3 to an ependymoma, at a time that has seen — from WHO-CNS2016 to the current WHO-CNS2021 classification — an ever-increasing and mandatory need for integrated morpho-molecular diagnosis of CNS tumors.

1. This morphological diagnosis excluded five surgically divergent categories that can be distinguished intraoperatively with good accuracy in pediatric CNS tumors:
   — low-grade ependymoma (WHO grade 2) lacks atypical mitoses and pursues the same GTR goal, though with relatively less urgency, given its more favorable biology;
   — low-grade gliomas, which feature Rosenthal fibers and eosinophilic granular bodies (e.g., pilocytic astrocytoma, ganglioglioma, and pleomorphic xanthoastrocytoma), pursue GTR when safely achievable. However, function-sparing subtotal resection or biopsy is prioritized in eloquent areas;
   — high-grade glioma featuring astrocytic palisading necrosis or microvascular proliferation emphasizes maximal safe cytoreduction, though it is often limited by infiltration;
   — small round blue cell morphology with cellular 'cannibalism', characteristics seen in embryonal and germ-cell tumors (both of which are absent here) [4], would necessitate protocol modifications, including cerebrospinal fluid (CSF) staging and a systemic workup;
   — non-neoplastic mimics, such as abscesses, demyelination, or reactive gliosis showing purulent inflammation, lipid-laden macrophages, or

gemistocytic astrocytes and Rosenthal fibers, respectively, would halt aggressive resection immediately to prevent iatrogenic harm.

Intraoperative cytology was decisive in providing rapid morphological triage among these — above mentioned — five categories. All ependymomas (grades 2 and 3) require GTR according to international standards [3]. However, excluding gliomas, embryonal/germ cell tumors, and non-neoplastic mimics prevented mismatched surgical aggressiveness while confirming the appropriate high-grade ependymoma strategy.

2. Traditionally, the term 'anaplastic' in ependymoma referred to these histopathological features, including microvascular proliferation and necrosis, which indicate a poor prognosis for the tumor. However, recent molecular insights, now incorporated into the WHO-CNS2021, have challenged this straightforward correlation. Integrated molecular profiling classifies ependymomas according to anatomical location and genetic alterations. Supratentorial tumors frequently harbor ZFTA (RELA) or YAP1 fusions, posterior fossa (PF) tumours are categorised into PF-A and PF-B groups based on epigenetic markers such as H3K27me3 loss, and spinal tumours exhibit NF2 mutations or MYCN amplifications [2]. Importantly, these new subgroups reveal discrepancies with traditional morphology, with some tumors exhibiting classical anaplastic features yet lacking aggressive behavior from a topographic and/or molecular viewpoint, while others with low-grade cytology/histology exhibit molecular alterations associated with a worse prognosis [5, 6]. This highlights that 'anaplasia' alone may not fully capture tumor biology or aggressiveness.

Conclusions

Our case study emphasises the importance of rapid intraoperative morphological assessment to inform surgical decisions in CNS lesions, while advocating for subsequent molecular analyses to improve diagnosis, prognosis and therapeutic planning in neoplastic cases. Thus, the evolving concept of 'anaplastic ependymoma' reflects a transition from morphology-driven grading to a more nuanced, biologically informed classification.

Article Information and Declarations

Ethics statement

This study adhered to the ethical principles of the 2024 Declaration of Helsinki.

Author contributions

G.G.: concept, design, definition of intellectual content, experimental studies, data analysis, data interpretation, manuscript preparation, manuscript editing, manuscript review, approval of manuscript for submission, approval of manuscript for submission, guarantor; B.C.: definition of intellectual content, literature search, data acquisition, data interpretation, manuscript preparation, approval of manuscript for submission; G.P.: definition of intellectual content, clinical studies, data acquisition, data analysis, data interpretation, manuscript preparation, approval of manuscript for submission; M.F.: data acquisition, data analysis, approval of manuscript for submission; V.G.V.: definition of intellectual content, experimental studies, manuscript preparation, manuscript review, approval of manuscript for submission

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Conflict of interest

Authors declared no conflict of interest.

Supplementary material

None.

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