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An integrative molecular tumor board approach to pediatric B atypical choroid plexus papilloma with an equivocal residual lesion: a case report

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Case Report

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Abstract

Background

Choroid plexus tumors are rare pediatric intracranial neoplasms comprising benign choroid plexus papilloma, atypical choroid plexus papilloma, and choroid plexus carcinoma. DNA methylation profiling refines risk stratification, distinguishing pediatric choroid plexus tumors into low-risk pediatric A and high-risk pediatric B subgroups, and may support treatment decisions when histology and clinical behavior are discordant.

Case presentation

A 2.6-year-old white boy from Germany presented with raised intracranial pressure from a large left lateral ventricular mass. Subtotal resection and second-look surgery left > 1.5 cm² residual tumor. Histopathology was discordant between choroid plexus papilloma and atypical choroid plexus papilloma, whereas methylation profiling confirmed a choroid plexus tumor of pediatric subgroup B; staging showed no dissemination. Because of young age and lower-grade appearance, close surveillance was chosen. At 3-month follow-up, local progression required two further resections, reducing residual tumor to < 1.5 cm². Histology then favored atypical papilloma bordering on carcinoma. Precision-oncology molecular analysis revealed no actionable target and broad chemoresistance. Individualized systemic chemotherapy was initiated, but further progression occurred, with a new enhancing lesion along the surgical tract. Subsequent resection achieved near-total removal, including the suspicious tract areas, and viable atypical papilloma was confirmed at the primary site and tract. Given the uncertain significance of minimal residual enhancement, further therapy was deferred. Approximately 30 months after diagnosis, the child remains in radiological remission.

Conclusions

This case highlights the diagnostic and therapeutic complexity of pediatric B atypical choroid plexus papilloma. Integrating histology, methylation profiling, precision-oncology results, repeated maximal safe resections, and individualized interdisciplinary decision-making achieved durable remission while limiting treatment-related morbidity.

Background

Choroid plexus tumors (CPT), derived from choroid plexus epithelium, are very rare intracranial neoplasms occurring predominantly in young children (age-standardized incidence ~ 1.0 per million), with a pronounced peak in the first year of life (6.1 per million). [1, 2] The 2021 WHO classification distinguishes three grades: benign choroid plexus papilloma (CPP, grade 1); atypical CPP (aCPP, grade 2), with elevated mitotic activity; and choroid plexus carcinoma (CPC, grade 3). [3, 4, 5] Genome-wide DNA

methylation profiling further resolves pediatric supratentorial CPT into a low-risk ("pediatric A") and a high-risk ("pediatric B") subgroup, complementing histopathology in clinical decision-making and prognostication. [6, 7]

Complete resection of CPP is generally curative, [8, 9] but histological subtype predicts progression-free survival, and postoperative chemotherapy shows efficacy in selected aCPP with residual disease or relapse. [10] We present a pediatric B aCPP case in which discordant histopathology, aggressive behavior, and molecular findings required highly individualized interdisciplinary counseling.

Case presentation

Initial Diagnosis

A 2.6-year-old white boy presented with gait instability, irritability, and recurrent vomiting, consistent with raised intracranial pressure from obstructive hydrocephalus. Brain MRI revealed a large intraventricular mass arising from the left lateral ventricle and reaching into the adjacent parenchyma (Fig. 2A). An urgent subtotal resection was performed on the day of diagnosis. Histopathology was discordant between two independent reference pathology centers: the local center diagnosed CPP (WHO grade 1), whereas central review (Münster) favored aCPP (WHO grade 2). DNA methylation (Heidelberg brain tumor classifier v12.8) classified the tumor as CPT (calibrated score 0.97), pediatric subgroup B (0.93).

Craniospinal MRI showed no dissemination (M0). Cerebrospinal fluid (CSF) cytology was not obtained at diagnosis. The family history was unremarkable, with no known childhood cancers or hereditary tumor predisposition syndromes. The overall clinical course is summarized in Fig. 1.

Initial surgery and surveillance

After the initial subtotal resection, a second-look surgery was performed eight days later to remove additional tumor tissue. However, residual tumor tissue remained, with postoperative MRI demonstrating > 1.5 cm^2 (2.4 x 1.1 x 2.2cm^3; 2.9cm^3; axial × coronal × sagittal) residual disease (R+). Considering the patient's young age, the initial histopathological impression of a lower-grade lesion, and the intention to postpone or avoid the potential long-term toxicities of adjuvant chemotherapy or radiotherapy, a strategy of close radiological surveillance ('watchful waiting') with serial MRIs was adopted.

Disease progression

At the three-month follow-up, MRI revealed local progression of the tumor (3.2 x 1.7 x 3cm^3; 8.16cm^3; axial × coronal × sagittal) to > 1.5 cm^2, without spinal spread (CSF cytology was not performed). Due to this early relapse, the multidisciplinary tumor board recommended repeat surgery. Following the first procedure, a substantial residual tumor (1.7 x 1.7 x 2.1cm^3; 3.03cm^3; axial × coronal × sagittal) of > 1.5

cm² persisted, necessitating a second re-resection to maximize tumor clearance after eight days. The second operation achieved a near-total resection, leaving only minimal residual disease too small to measure (R+, < 1.5 cm²; Fig. 2B).

Histopathological examination of the recurrent tumor demonstrated more aggressive characteristics compared to the initial specimen. While the local pathology described the lesion as a “higher-grade choroid plexus tumor,” central review favored aCPP, bordering on a CPC, with up to 18 mitoses per 10 high-power fields but without necrosis or marked nuclear pleomorphism, so that criteria for carcinoma were not met (Fig. 3).

Molecular tumor board assessment

Comprehensive molecular profiling was produced and kindly provided within the prospective precision-oncology *INFORM* registry (INdividualized therapy FOr high-Risk childhood Malignancies); whole genome and whole-exome sequencing of tumor and germline, RNA sequencing, and DNA methylation array identified no high-evidence actionable target. [11, 12, 13, 14] The only prioritized alteration was low-evidence *FOLR1* (folate receptor 1) overexpression, for which no approved matching drug is available. The tumor mutational burden was very low (0.2), copy-number analysis showed chromothripsis of chromosome 5p with *TERT* affected but not expressed and germline analysis revealed no cancer predisposition syndrome. Ex vivo drug sensitivity profiling within INFORM was performed as previously described [12] and tested a panel of 79 clinically relevant drugs. The tumor was classified as a non-responder, showing broad in vitro resistance to conventional agents such as cisplatin, etoposide, and vincristine – key components of the initially recommended Carboplatin/Etoposide/Vincristine (CarbEV) regimen, often used in pediatric brain tumors. Specifically, ifosfamide and cyclophosphamide were not covered by the assay, and methotrexate showed intermediate activity, whereas platinum compounds, etoposide, and vinca alkaloids were least active. The only above-average in-class effects were seen with investigational *MDM2* (idasanutlin), indicative for *TP53* wildtype and BCL-XL inhibitors. Given the subtotal resection, borderline malignant histology, and proven clinical aggressiveness, the INFORM tumor board, expert consultation, and interdisciplinary discussion concluded that the drug-screening results should inform the adjuvant treatment decision to prevent further progression.

According to the forthcoming European ERN guideline, CarbEV is the standard chemotherapy regimen for patients with choroid plexus papilloma requiring adjuvant chemotherapy. However, internationally established alternatives (ifosfamide, carboplatin, etoposide (ICE); Headstart-based approaches) are considered therapeutically equivalent, particularly for choroid plexus carcinoma. Given the aggressive biological behavior of the present atypical choroid plexus papilloma and the histopathological description of carcinoma-like features bordering on choroid plexus carcinoma, this equivalence was considered transferable to the present case.

Based on the drug screening, an adjuvant approach containing alkylating agents and high-dose methotrexate—such as a Headstart/HIT-SKK–analogous regimen—was favored over CarbEV, without

high-dose chemotherapy with stem-cell rescue at that stage.

Molecularly informed decision for systemic chemotherapy

Before initiating systemic therapy, a staging lumbar puncture showed no unequivocal tumor cells; the pan-cytokeratin marker LU-5 showed no specific labeling of vital cells, consistent with continued M0 status, although the limited sample quality does not entirely exclude CSF dissemination. Two months after the second relapse surgery, the patient received two cycles of systemic HIT-SKK (cyclophosphamide/vincristine, methotrexate/vincristine) chemotherapy without intraventricular methotrexate, which was omitted because of postoperative limitations in ventricular access, toxicity concerns, and the absence of robust evidence of efficacy in choroid plexus tumors. Treatment was initially well tolerated without severe acute toxicities, followed by imaging reassessment to guide further management.

Further course and outcome

Interim MRI after the first cycle demonstrated stable disease, but during the second cycle of chemotherapy, the solid component and an associated cyst enlarged (compared to the post-surgery baseline), with new contrast enhancing bandlike lesion along the surgical tract (Fig. 2C; arrows 1 and 2). This lesion raised concern for reactive scar tissue versus tumor spread along the surgical pathway. Chemotherapy was stopped and a fifth operation achieved gross-total removal of the progressive residual mass and the associated cyst, with extensive resection of tissue within the surgical tract. Intraoperatively, the tract appeared fibrotic. No contrast-enhancing tissue remained within the surgical tract, while a very small nodular lesion persisted on the tract wall which, given the possibility of tumorous seeding in this location, was considered suspicious for residual disease (Fig. 2D; arrows). Viable aCPP was confirmed at the primary site and within the tract, without high proliferative activity; no gross leptomeningeal spread was seen. The residual lesion was deemed too small for a meaningful re-resection, leaving the decision between continuation of adjuvant therapy versus a watchful waiting approach. As no clear evidence-based recommendation exists for this situation, management had to be individualized again. Various empirical systemic regimens, and continuation of intensive HIT-SKK, were considered to lack meaningful evidence in persistent aCPP. Radiotherapy, which has a limited but occasionally effective role in relapsed choroid plexus tumors, was reserved for possible future progression. Given uncertainty about the residual lesion's viability and the excellent survival expected even after further relapse, a watchful-waiting strategy was favored.

The patient was closely observed without chemotherapy in the ensuing weeks. Four weeks later, only a minute focus remained, barely discernible at the tract wall (Fig. 2E, arrow). The recent MRI (approximately 18 months after diagnosis; Fig. 2F) demonstrated neither definite tumor residue nor relapse; the contrast-enhancing nodule seen along the ventricle during the second chemotherapy cycle was no longer visible, and only nonspecific irregularities along the ventricular lining and surgical tract remained, interpreted as post-surgical changes (gliosis or scar tissue) rather than active tumor. Clinically, the child recovered well without new focal neurological deficits and remained developmentally age-

appropriate. At the latest follow-up, approximately 30 months after the initial diagnosis, the patient remains in radiological remission and will continue close surveillance with serial MRI and clinical evaluation.

Discussion

Diagnostic delimitation and treatment decisions are often challenging in CPP and aCPP. In CPP, gross-total resection typically yields excellent outcomes without adjuvant therapy. In contrast, aCPP, particularly within the pediatric B molecular subgroup, carries a higher risk of relapse and progression, making management more challenging. [1, 10]

Histopathological assessment yielded discordant results, ranging from CPP to aCPP bordering on carcinoma, reflecting well-known grading difficulty. DNA methylation profiling was decisive in assigning the pediatric B subgroup, strengthening the rationale for closer surveillance and potential adjuvant therapy and underscoring the value of integrating molecular diagnostics with histopathology to refine prognostication and treatment decisions. [7]

From a therapeutic perspective, the initial decision to adopt a watchful waiting strategy was reasonable given the patient's age, the lower-grade impression of the tumor, and the desire to avoid long-term treatment-related morbidity. However, the tumor progressed rapidly, necessitating repeated resections. INFORM analysis revealed no actionable target and broad ex vivo chemoresistance.

In the context of aggressive clinical behavior and carcinoma-like histopathological features, these findings supported an individualized treatment approach using a Headstart/HIT-SKK–analogous regimen without high-dose chemotherapy, rather than CarbEV, followed by early imaging reassessment after two cycles. Nevertheless, systemic HIT-SKK chemotherapy failed to control disease progression. These findings underscore the limitations of currently available adjuvant regimens in aCPP pediatric B subgroup and suggest that surgery remains the most effective therapeutic modality in such cases.

The clinical course was further complicated by a new contrast enhancing lesion along the surgical tract on MRI, raising concern for either postoperative scar or tumor seeding. This rare observation illustrates a diagnostic dilemma with significant therapeutic implications. Ultimately, the presence of a minimal residual lesion prompted an individualized management decision, as no evidence-based recommendations exist for this situation. Leptomeningeal dissemination in choroid plexus tumors is not confined to carcinoma but also occurs in lower-grade tumors, underscoring the need for vigilance when new enhancing changes develop along the surgical corridor. [15]

Under continued surveillance, the child remains clinically stable and in complete remission on MRI. This outcome emphasizes the value of repeated maximal safe resections combined with careful surveillance, which proved more decisive than adjuvant chemotherapy in achieving durable control. Importantly, the multidisciplinary and individualized approach helped to avoid unnecessary treatment-related morbidity.

Molecular subgrouping should be integrated into treatment algorithms for CPT. The limited efficacy of conventional chemotherapy highlights the urgent need to strive for complete resection whenever feasible and to develop novel therapeutic strategies, including targeted or immunotherapeutic approaches when complete resection is not possible or needing multiple re-resections. Prospective data collection will be essential to define clearer recommendations, particularly for the management of residual disease in aCPP.

The main strength of this report is its integrative diagnostic approach, combining reference histopathology, genome-wide DNA methylation profiling, comprehensive molecular profiling and ex vivo drug-sensitivity testing within an established precision-oncology programme, together with interdisciplinary decision-making across several reference centers and a documented clinical course of approximately 30 months. Several limitations should be acknowledged. As a single case, the observations are not generalizable and should be regarded as hypothesis-generating. The biological significance of the residual enhancing lesion along the surgical tract remained uncertain, as it could neither be histologically confirmed nor safely re-resected. Finally, ex vivo drug-sensitivity profiling is not yet validated as a routine predictive tool, and the follow-up—although reassuring—remains limited relative to the potential for late relapse in choroid plexus tumors.

Conclusion

In CPT with borderline histopathological and molecular features, distinguishing CPP, aCPP, and biologically aggressive carcinoma-like lesions can remain difficult despite extensive diagnostic work-up. Treatment of recurrent or progressive aCPP requires individualized interdisciplinary assessment, integrating histopathology, molecular profiling, radiological evolution, surgical feasibility, and - where available - functional drug-screening results. Systematic collection of comprehensive clinical, molecular, treatment, and outcome data is needed to refine risk stratification and improve evidence-based decision-making for patients with CPP/aCPP.

Patient perspective

As the patient is a very young child, this perspective is provided by his parents/legal guardians. All diagnostic and treatment decisions, including those reached in the interdisciplinary and molecular tumor boards, were discussed with the family at each step, and the chosen strategy was pursued in agreement with them. The child is currently clinical and neurological in good conditions and remains in regular neuro-oncological and imaging follow-up.

Abbreviations

aCPP
atypical choroid plexus papilloma
CarbEV

carboplatin/etoposide/vincristine
CPC
choroid plexus carcinoma
CPP
choroid plexus papilloma
CPT
choroid plexus tumor
CR
complete remission
CSF
cerebrospinal fluid
ERN
European Reference Network
HIT-SKK
pediatric infant brain-tumor chemotherapy protocol (Säuglinge und Kleinkinder)
HPF
high-power field
ICE
ifosfamide/carboplatin/etoposide
INFORM
INdividualized therapy FOr high-Risk childhood Malignancies
MRI
magnetic resonance imaging
PR
partial remission
TMB
tumor mutational burden
WHO
World Health Organization

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The authors confirm that written consent for submission and publication of this case report, including any accompanying images and associated text, have been obtained from the patient's parents/legal guardians. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Author Contribution

Conceptualization: C.F., D.O.-S., G.C. Data curation: C.F., D.O.-S., B.B., C.T., G.C. Formal analysis: C.F., D.O.-S. Investigation: G.C., M.H., S.S.-S. Visualization: C.F., D.O.-S., B.B., C.T. Supervision: D.O.-S. Writing – original draft: all authors. Writing – review & editing: all authors.

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Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

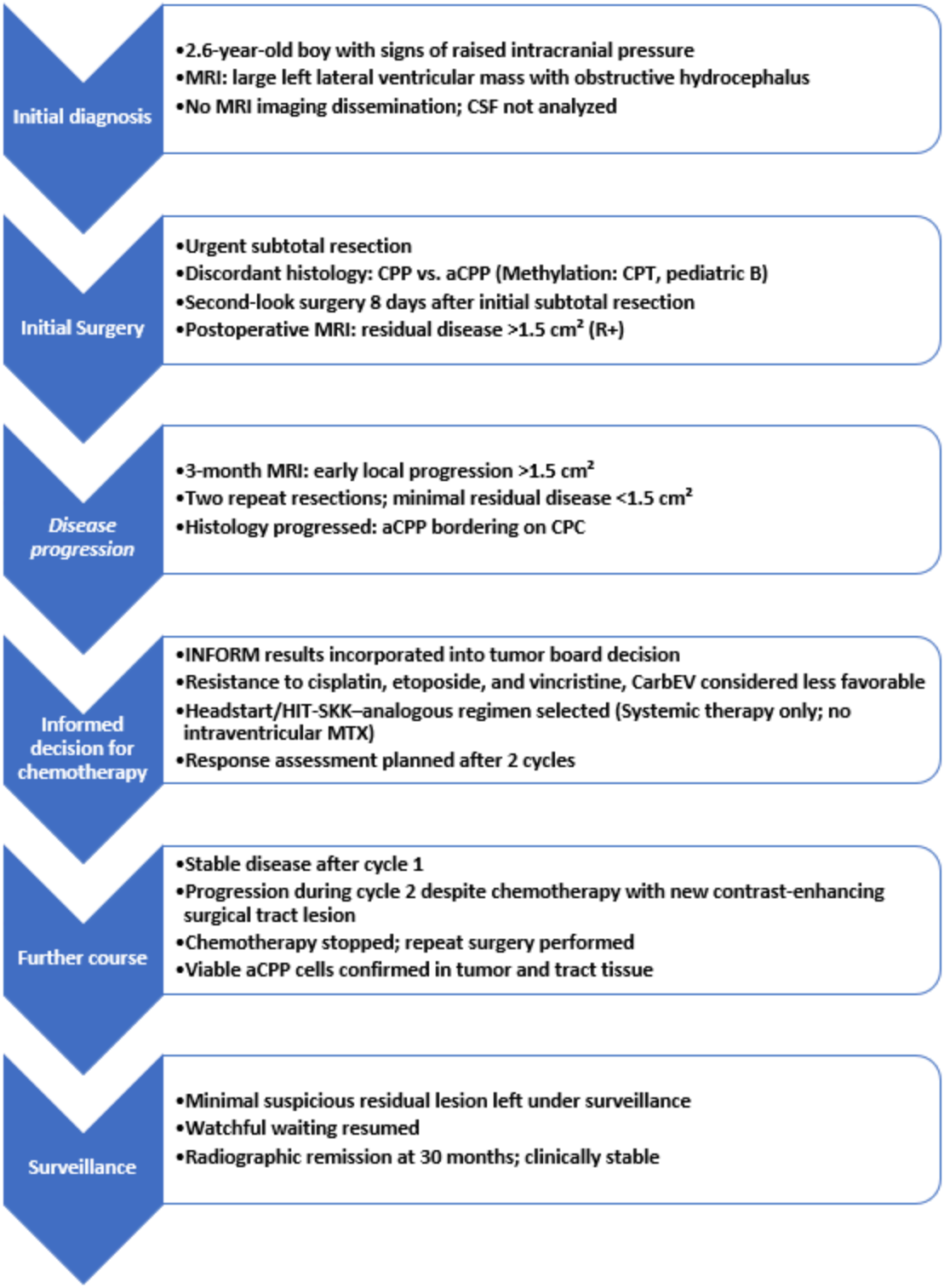


Figure 1

Clinical course and treatment timeline, summarizing surgeries, histopathological and molecular diagnoses, systemic chemotherapy, and imaging milestones from initial diagnosis to most recent follow-up.

Alt text: Vertical timeline of the clinical course from initial diagnosis to most recent follow-up, marking in sequence the diagnostic surgeries, histopathological and DNA-methylation diagnoses, systemic HIT-SKK chemotherapy, subsequent resections, and the key MRI milestones leading to radiological remission.

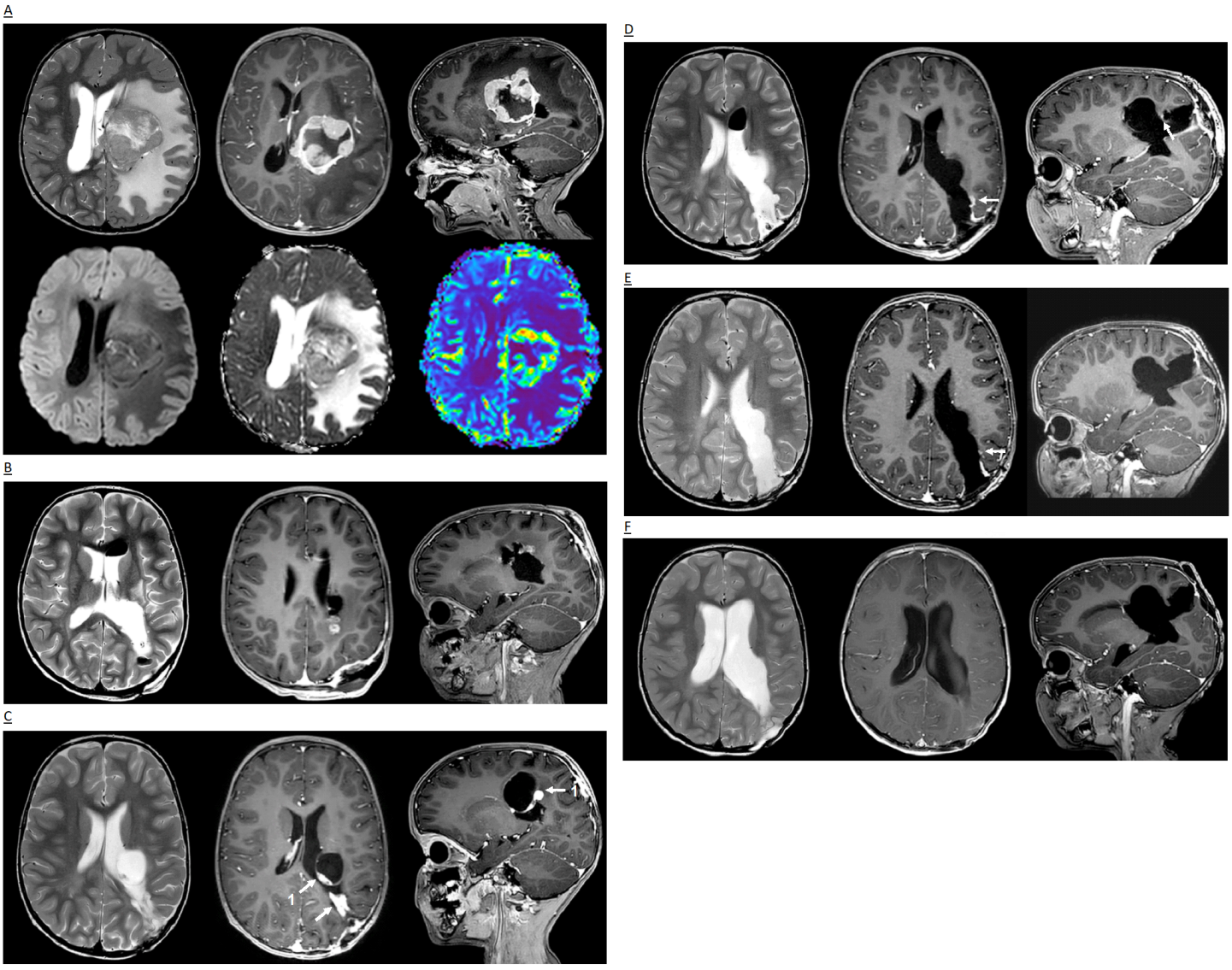


Figure 2

Magnetic resonance imaging (MRI) at sequential time points.

Axial T2-weighted and axial and sagittal contrast-enhanced T1-weighted images.

A At initial diagnosis. Nodular, confluent, predominantly parenchymal mass with elevated cerebral blood volume and central necrosis — an unusual appearance for a choroid plexus tumor, involving the plexus but not the typical intraventricular location or ventricular dilation.

B Early postoperative imaging after the second resection of local progression.

C Local progression: increased solid components and enlargement of the adjacent cyst (arrows 1), with new enhancement of unclear origin along the surgical tract (arrow 2), atypical for scar 5 months after surgery — differential diagnosis includes implantation metastases under HIT-SKK chemotherapy.

D Early postoperative imaging after complete resection of the recurrent, partly solid and partly cystic lesion; a residual enhancing nodule remains on the tract wall (here shown in two directions, arrows).

E Follow-up imaging: the tract-wall nodule is barely discernible (arrow), consistent with partial (PR) or complete remission (CR); residual postoperative changes possible.

F Most recent MRI, approximately 18 months after diagnosis: no reliably detectable enhancement, suggesting non-specific changes rather than residual tumor; minor ventricular-margin irregularities interpreted as postoperative, rated overall as complete remission.

Alt text: Six magnetic resonance imaging panels (axial T2-weighted and axial and sagittal contrast-enhanced T1-weighted) shown in chronological order. They depict the large left lateral ventricular mass at diagnosis, the early postoperative appearance after resection, local progression with a new enhancing band-like lesion along the surgical tract, gross-total removal with a small residual nodule on the tract wall, and progressive regression of that nodule to radiological remission at follow-up.

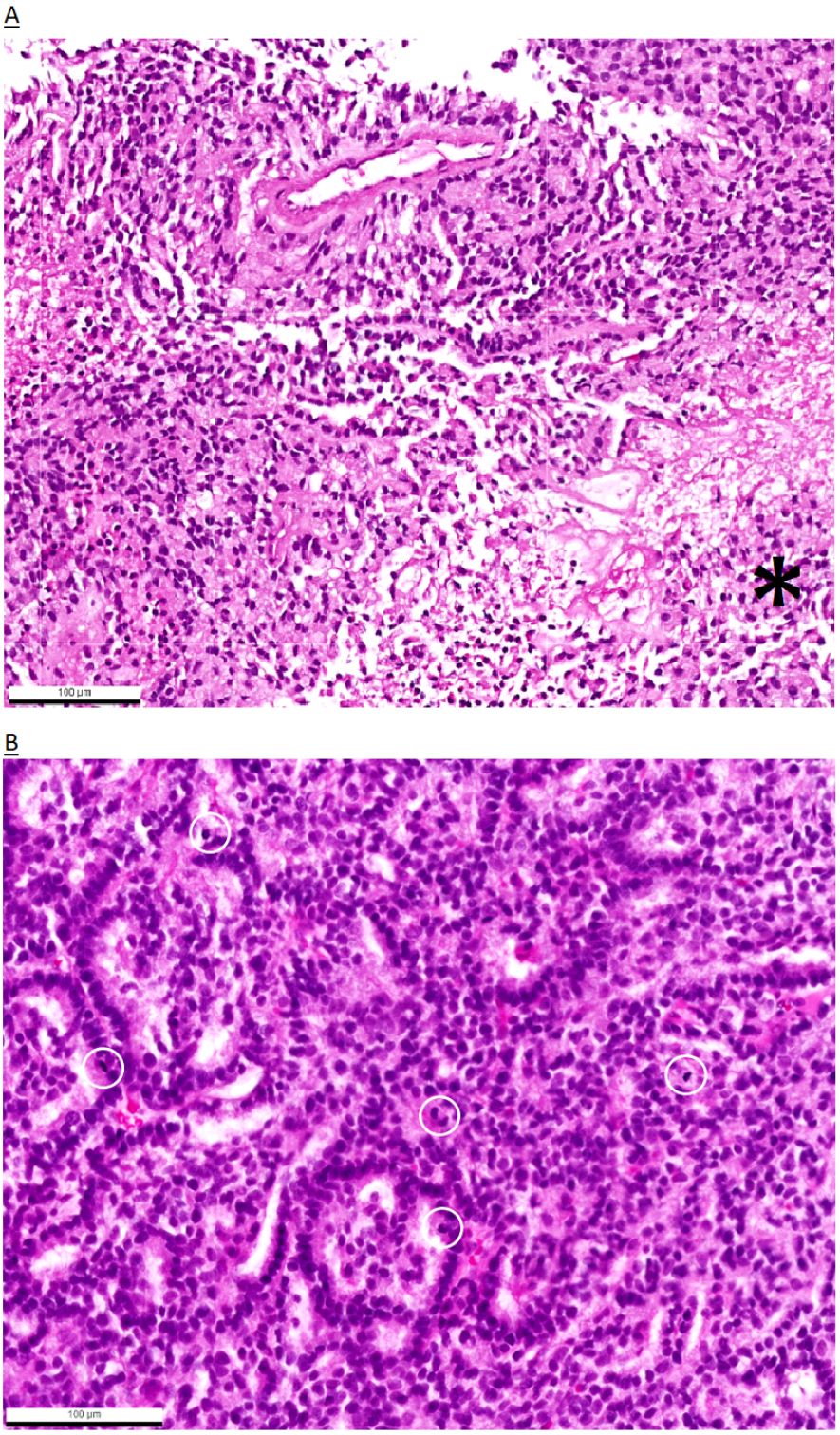


Figure 3

Histological features of the primary and recurrent atypical choroid plexus papilloma.

A Hematoxylin and eosin (H&E)-stained section of the primary atypical choroid plexus papilloma showing moderately increased mitotic activity with 3 mitoses per 10 high-power fields, focal blurring of the papillary growth pattern, and necrosis (asterisk).

B The recurrent tumor shows increased cellular density, more pronounced blurring of the papillary architecture, and increased mitotic activity with up to 18 mitoses per 10 high-power fields (white circles). However, necrosis and marked nuclear pleomorphism are absent, and the tumor therefore does not meet the diagnostic criteria for choroid plexus carcinoma. Scale bars denote 100 μm.

Alt text: Two hematoxylin–eosin photomicrographs at the same magnification with a 100-μm scale bar. The left panel shows the primary tumor with a papillary architecture and scattered mitoses; the right panel shows the recurrent tumor, which is more cellular with more numerous mitoses (marked), while criteria for choroid plexus carcinoma are not met.