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Diffuse midline gliomas, H3K27M-altered, of the pineal gland: the first synaptophysin-positive case and a systematic review

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ABSTRACT

Diffuse midline gliomas (DMGs) with H3K27M alterations are rare, aggressive, World Health Organization (WHO) grade 4 tumors arising in midline central nervous system (CNS) structures, characterized by a lysine-to-methionine substitution at histone H3K27, which disrupts epigenetic regulation via global loss of H3K27 trimethylation. The pineal gland is an exceptionally uncommon site of origin. We report the first case of a synaptophysin-positive, H3K27M-altered DMG in the pineal gland of a 7-year-old female, characterized by hypercellularity, moderate atypia, high mitotic activity, and a Ki-67 index of 30%. Immunohistochemistry confirmed positivity for glial markers: glial fibrillary acidic protein (GFAP), oligodendrocyte transcription factor 2 (Olig2), loss of hypotrimethylation of lysine 27 on histone H3 (H3K27me3), and synaptophysin expression, an unusual feature for DMGs. Methylation profiling established the diagnosis.

A systematic review identified seven cases of pineal H3K27M-altered DMG (age ranged from 7 to 65 years, with three pediatric and four adult) revealing notable immunohistochemical heterogeneity, limited molecular data (only our case had available methylation profiling) and a synaptophysin expression limited to our pediatric case. Sparse clinical outcome data precluded robust prognostic comparisons.

These findings underscore the biological heterogeneity and diagnostic challenges of pineal DMGs and underscore the necessity of comprehensive molecular and immunohistochemical assessments to optimize diagnosis and guide emerging targeted therapies.

Keywords: epiphysis; H3K27me3; synaptophysin; diffuse midline glioma; H3K27M

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Introduction

Histone H3, a core component of the nucleosome, plays a critical role in regulating chromatin structure and gene expression through post-translational modifications. These modifications, particularly at specific lysine residues, modulate transcriptional activity by altering the accessibility of DNA to the transcriptional machinery. The H3K27M mutation, characterized by a lysine

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(K) to methionine (M) substitution at position 27 of the histone H3 protein, disrupts normal epigenetic regulation. This alteration results in global hypotrimethylation of lysine 27 on histone H3 (H3K27me3), a repressive mark critical for silencing developmental and oncogenic pathways. Consequently, the H3K27M mutation contributes to widespread transcriptional dysregulation that drives oncogenesis in diffuse midline gliomas (DMGs) [1–7].

DMGs are highly aggressive central nervous system (CNS) tumors that most commonly arise in the thalamus, brainstem, and spinal cord. The World Health Organization's 2021 classification of central nervous system tumors (WHO-CNS2021) distinguishes between adult-type and pediatric-type gliomas, with pediatric-type gliomas further subdivided into high-grade and low-grade entities. H3K27M-altered DMGs are classified as high-grade (grade 4) pediatric-type gliomas. Importantly, the term "pediatric-type" does not limit these tumors to children: this distinction reflects the molecular characteristics and biological behavior of the tumor rather than the age of the patient [1, 8].

Pineal DMGs are extremely rare, with very few documented cases, including the current one.

The report includes a unique case of a synaptophysin-positive pineal DMG, highlighting its diagnostic challenges and therapeutic implications.

This systematic review aims to consolidate the immunohistochemical and molecular data on H3K27M-altered pineal diffuse midline gliomas (DMGs), though the limited and heterogeneous cases reported in the literature prevent definitive conclusions.

Materials and methods

Search strategy

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. A Boolean search string was performed in PubMed, Scopus, Embase, and Web of Science using the keywords: "H3K27M", "pineal", "pineal gland", "diffuse midline glioma", and "H3K27me3". Given the extreme rarity of this lesion, no temporal restrictions were applied to the search to ensure inclusion of all relevant publications.

Inclusion criteria

Studies documenting confirmed histologic diagnoses of pineal DMGs with or without molecular profiling were included. Cases without sufficient histologic data were excluded.

Results

Case overview

The current case involved a 7-year-old female presented with a brief clinical history of headache, morning vomiting and progressive neck pain and evidence. The brain magnetic resonance imaging (MRI) revealed a large lesion in the pineal region, characterized by hemorrhagic areas, small cystic components, and heterogeneous contrast enhancement. Diffusion-weighted imaging (DWI) demonstrated intralesional focal areas with low ADC values, suggestive of increased cellularity. Magnetic resonance spectroscopy (MRS) showed a marked reduction in N-acetyl aspartate, with inversion of the choline/N-acetyl aspartate ratio and no evidence of lipid or lactate peaks. A computed tomography (CT) scan excluded the presence of calcifications.

There was also evidence of signal alteration in the right thalamus due to tumor infiltration, along with multiple metastatic lesions in the brain and spine. The pituitary stalk appeared normal. The pineal lesion caused obstruction of the mesencephalic aqueduct, resulting in decompensated supratentorial hydrocephalus (Fig. 1). Despite the site of disease, the patient did not present symptoms related to involvement of pineal gland. The neuroradiological findings were suggestive of a biologically aggressive lesion in the pineal region. The initial diagnostic hypothesis was a germ cell tumor. However, serum and cerebrospinal fluid (CSF) markers (alpha-fetoprotein and beta-human chorionic gonadotropin), assessed after the neuroradiology, were found to be negative. Based on the findings, urgent surgery was performed (Fig. 2). This included a third ventriculostomy and an endoscopic biopsy to obtain a histological diagnosis and determine the therapeutic strategy. A secure external ventricular drain (EVD) was also placed. The procedure was completed without complications. However, since the ventriculostomy was insufficient to resolve the established hydrocephalus, the patient then

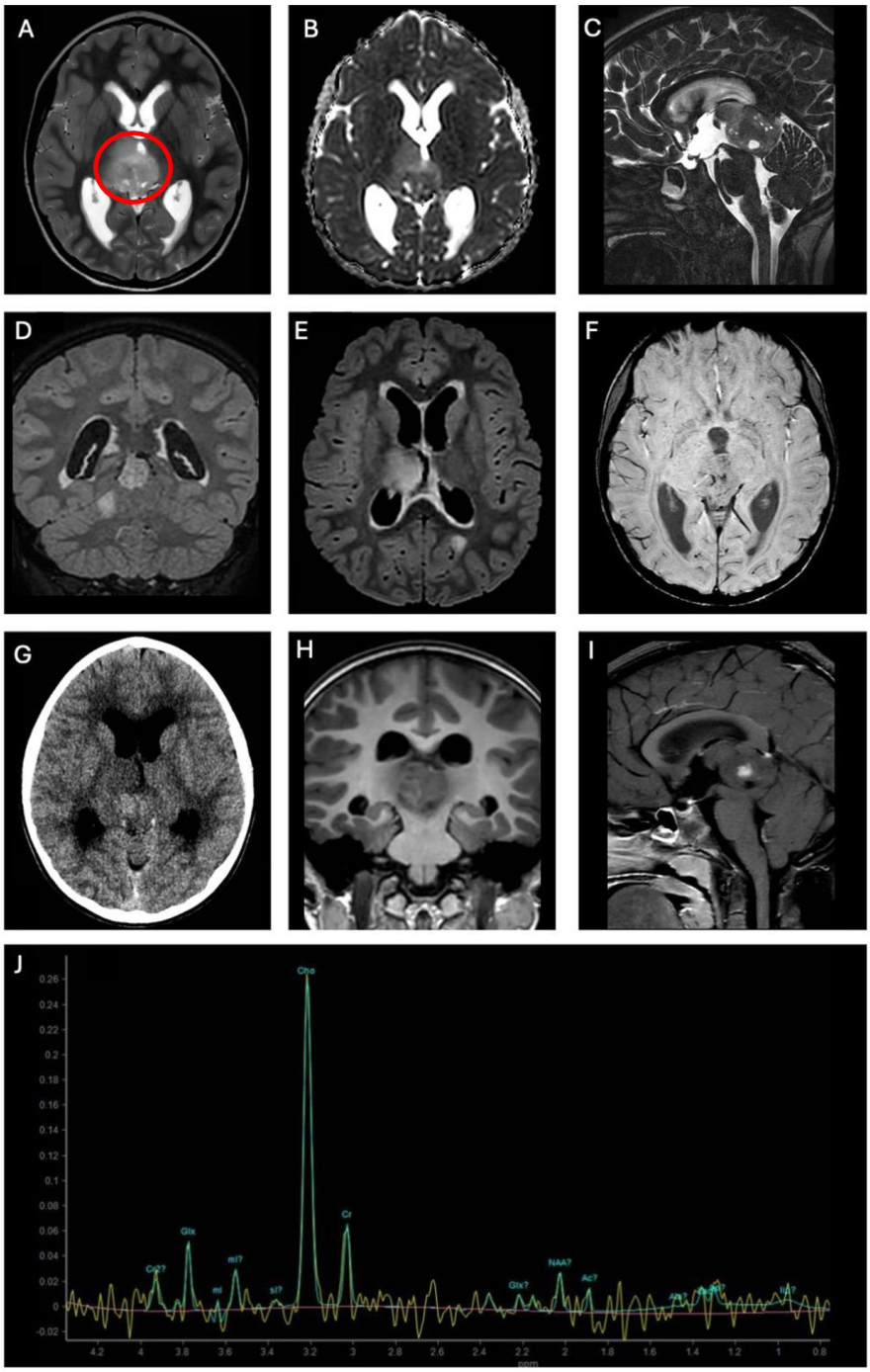

Figure 1. A. Axial T2-weighted magnetic resonance imaging (MRI) shows a large pineal lesion [craniocaudal diameter (dCC) 24 mm x anteroposterior diameter (dAP) 30 mm x laterolateral diameter (dLL) 30 mm, red circle] with heterogeneous signal intensity and infiltrative extension into the right thalamus; **B.** The apparent diffusion coefficient (ADC) map reveals low values within the lesion, indicative of high cellularity, and a slightly higher signal in the right thalamus, raising suspicion for neoplastic infiltration; **C.** A sagittal high-resolution T2-weighted image demonstrates impression on the midbrain with subsequent aqueductal obstruction and hydrocephalus with bowing of the floor of the third ventricle. Mass effect on cerebellar vermis is also noted; **D., E.** Post-contrast fluid-attenuated inversion recovery (FLAIR) images show hyperintense cortical lesions in the right cerebellar hemisphere and the left parietal lobe, consistent with metastases. There is also enlargement of the lateral ventricles accompanied by transependymal edema, indicating decompensated hydrocephalus; **F., G.** Susceptibility weighted imaging (SWI) detects small hypointensities without corresponding calcifications on computed tomography (CT), suggestive of microhemorrhages; **H., I.** Coronal T1-weighted MRI reveals a slightly heterogeneous hypointense lesion, with focal contrast enhancement visible on the sagittal post-contrast T1-weighted images; **L.** Magnetic resonance spectroscopy (MRS) reveals a marked reduction in N-acetyl aspartate, with inversion of the choline/N-acetyl aspartate ratio, and no evidence of lipid or lactate peaks

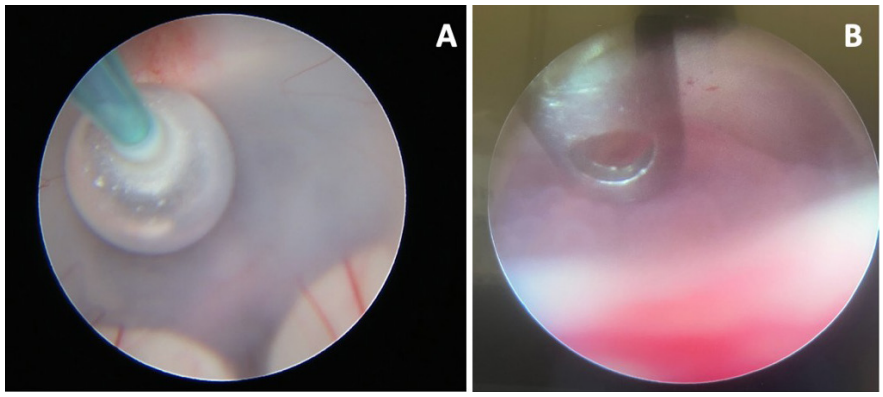

Figure 2. Endoscopic view of the third ventricle floor (**A**) and pineal tumor (**B**)

underwent ventriculoperitoneal shunt placement. Histology (Fig. 3) showed a hypercellular lesion composed of rather monomorphic, medium-sized elements with numerous mitoses [13 mitoses/10 high-power field (HPF)], in the absence of necrosis and/or vascular endothelial proliferation. Immunohistochemistry (IHC) shows the following profile: glial fibrillary acidic protein positive (GFAP+), oligodendrocyte transcription factor 2 positive (Olig2+), synaptophysin+, loss of nuclear expression for H3K27me3, high proliferation index Ki-67 (30%), octamer-binding transcription factor 4 negative (OCT4–), sal-like protein 4 negative (SALL4–), cluster of differentiation 30

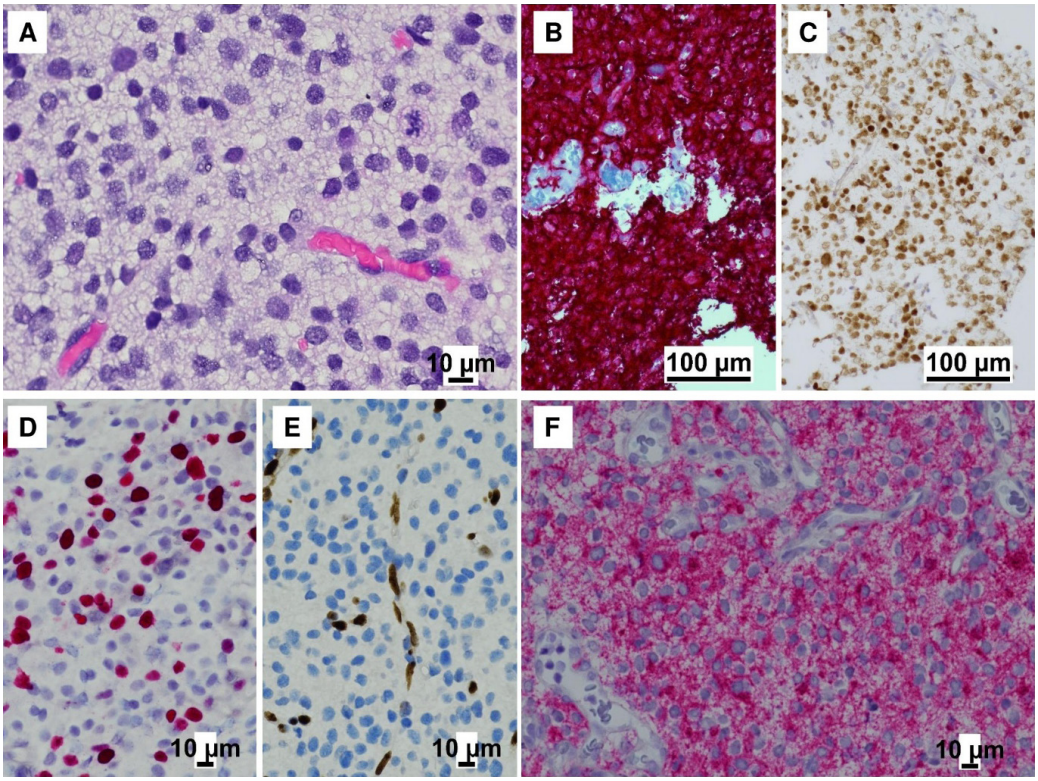

Figure 3. A. Photomicrograph showing a moderately cellular neoplasm with mild to moderate nuclear atypia and atypical mitosis in the absence of necrosis and/or vascular proliferation [hematoxylin and eosin (H&E), x60]; **B.** Immunohistochemistry (IHC) for glial fibrillary acidic protein (GFAP), strongly and diffusely positive; **C.** IHC for oligodendrocyte transcription factor 2 (Olig2) with diffuse nuclear positivity; **D.** IHC for cell proliferation index Ki-67, extremely high; **E.** IHC for hypotrimethylation of lysine 27 on histone H3 (H3K27me3), showing loss of expression in neoplastic cells (and internal positive control in capillary endothelium); **F.** IHC for synaptophysin, widely positive

negative (CD30–), beta-human chorionic gonadotropin negative(βHCG–). The two main diagnostic hypotheses that open up in the study of this lesion are germinoma, pineal parenchymal tumor (PPT) such as pineoblastoma; other possibilities involve DMG, astrocytoma (grade 3, according to WHO-CNS2021 criteria) and metastasis (less consistent in pediatric age). One of these hypotheses actually constitutes the final diagnosis, definitively reached with the help of the methylation profile. Although the topographic site (epiphysis) and neuroradiologic suspicion are consistent with the hypothesis of a germ-cell tumor, the IHC rules it out: OCT4– and SALL4– exclude germinoma and yolk sac tumor; CD30– excludes embryonal carcinoma; βHCG– excludes choriocarcinoma. Instead, the other hypotheses could be considered immunohistochemically: pineal parenchymal tumors (PPTs) by location and as typically synaptophysin+, DMG as H3K27me3– and grade 3 diffuse astrocytoma as GFAP+, Olig2+ and mitotically active (but in the absence of necrosis and/or microvascular proliferation) [1]. However, let us approach these data analytically: a PPT (and in particular a pineoblastoma), while expressing synaptophysin, should not express GFAP and Olig2, typical glial markers. The GFAP+/Olig2+ profile strongly supports the diagnosis of glioma, and the loss of expression for H3K27me3 points to DMG rather than other entities [1–8, 10]. The peculiarity of this case, which required methylomic profiling, is the aberrant expression of synaptophysin, which is completely unusual for a DMG: only in the context of glioblastoma, the possibility of neuroectodermal synaptophysin+ differentiation, although rare, has long been known histologically [1]. The analysis of the methylation profile, finally confirmed the diagnostic hypothesis and classified the lesion as a high-grade pediatric-type diffuse glioma, and specifically as a DMG, H3K27M-altered, according to WHO-CNS2021.

Given the histological report and due to the presence of metastases, a treatment with whole cranio-spinal radiation was proposed, combined with adjuvant chemotherapy with vinorelbine and nimotuzumab [anti-epidermal growth factor receptor (EGFR) agent]. The parents, aware of the severity of the disease and, in particular, of the dismal prognosis, despite their daughter's good clinical and neurological condition and after repeated consultations with both treating physicians and psychologist, refused in full agreement any therapeutic approach preferring to prioritize quality of life. After three months, an MRI scan performed due to clinical deterioration showed progression of the disease, both locally and in metastatic sites; she was therefore admitted to hospital for palliative care and finally died for disease progression seven months after diagnosis.

Systematic review findings

Overall findings

The conducted review identified 7 articles reporting a total of 7 cases [11–17]; however, one of these articles was retracted by the authors [15]. Therefore, the final number of included articles was 6, corresponding to 6 reported cases. When combined with our own case, this brings the total number of cases to 7 (Fig. 4). The seven cases, summarized in Table 1, reveal significant heterogeneity, with implications for diagnosis and treatment. Notably, methylation profiling was performed only in the present case, highlighting a gap in the molecular characterization of other reported cases. This diversity underscores the challenges in establishing standardized diagnostic protocols. Main systematic review findings were: age range: 7–65 years (mean 30.7 years); IHC markers: GFAP: assayed in 2 cases, all positive Olig2: detected in 2 cases, positive in all; synaptophysin: assayed in 1 case (present case), positive but Solomon et al. [11] reported a focal synatophysin expression in DMG with rabdoid features located in the spinal cord; H3K27me3: assayed in 2 cases, lost in all; Ki-67: proliferation index ranged from 9.3% to 37%; alpha-thalassemia/mental retardation syndrome X-linked (ATRX): tested in 3 cases, positive in 2, negative in 1; tumor protein p53: reported in 2 cases, positive in 1, negative in 1; BRAF V600E: detected in 2 cases, negative in all; OCT4: assayed in 2 cases, negative in all; SALL4, CD30, βHCG: only analyzed in this present case, negative.

To note, molecular analysis, when performed, revealed wild type isocitrate dehydrogenase (IDH) and BRAFV600E, no EGFR amplification, no losing of Ch. 10, no promoter of the telomerase reverse transcriptase gene (pTERT) mutation or O6-methylguanine-DNA methyltransferase (MGMT) methylation.

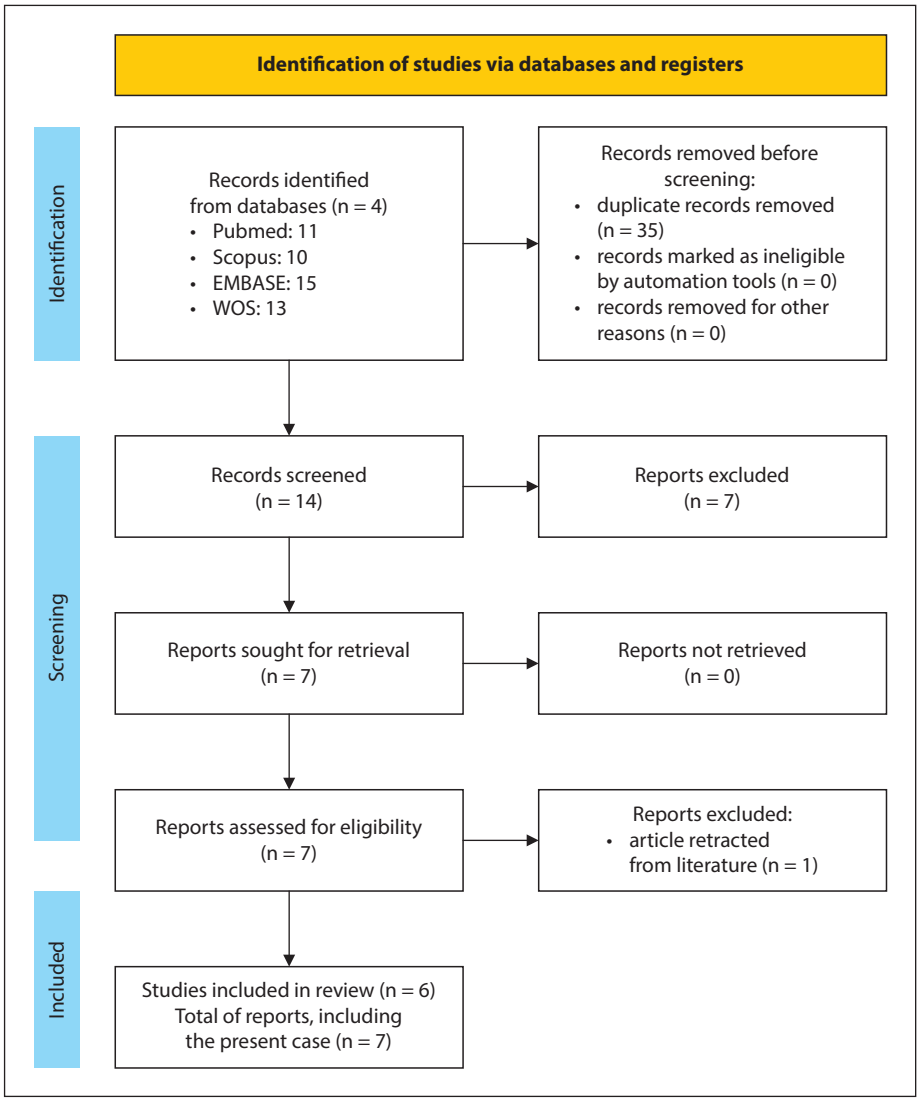

Figure 4. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses(PRISMA) flow-chart of the systematic review conducted

Comparing pediatric and adult populations

Demographics: Among the seven cases, pediatric patients accounted for less than a half (three out of seven). There was a slight male predominance overall, with both sexes represented in each group. IHC and Molecular Features: Among pediatric cases (ages 7, 12, 12), one case had an H3K27M mutation, and two cases had loss of H3K27me3, which is consistent with a diagnosis of DMG; the Ki-67 proliferation index was high in both pediatric cases assessed (30% and 37%, respectively); synaptophysin expression was observed in one of the pediatric cases, which is a very unusual finding for DMG and is more typical of pineal parenchymal tumors. Among adult cases (ages 21–65), some cases reported ATRX loss and Ki-67 indices, with lower Ki-67 indices than in pediatric cases (9.3% in one adult); H3K27M status was not consistently reported in adults, and methylation profiling was generally unavailable. Methylation profiling: methylation data were available only for our pediatric case, which limited meaningful comparisons between groups. Clinical outcomes: clinical outcome data were quite varied and often not systematically reported, with only one death by disease (age 7, our case) and two patients currently living at time of publication (ages 22 and 12). Thus, any reliable comparison of prognosis or survival between pediatric and adult patients is precluded in this cohort.

Table 1. Main features extrapolated from the systematic review about diffuse primary midline gliomas of the pineal gland

Case	Author [year]	Gender	Age	Immunohistochemistry	Synaptophysin expression	Methylation profile	Molecular features	Treatment	Follow up [months]	Dead/Alive (D/A)
1	Solomon et al. (2016) [11]	M	65	ATRX+; p53–; BRAF V600E–	Negative	NA	EGFR ampl – Ch.10 loss –	NA	NA	NA
2	Meyronet et al. (2017) [12]	F	21	NA	NA	NA	IDH wt, BRAFV600E wt, EGFR ampl –, pTERT–, MGMT meth–	Biopsy	3	NA
3	D'Amico et al. (2018) [13]	M	38	ATRX–; Ki-67 9.3%	NA	NA	NA	Subtotal resection, XRT, CHT	23	NA
4	Gilbert et al. (2018) [14]	F	12	NA	NA	NA	NA	Biopsy, later resection, XRT, CHT	NA	NA
NA	Jiang et al. (2019) [15]*	NA	NA	NA	NA	NA	NA	NA	NA	NA
5	Lim et al. (2020) [16]	F	22	GFAP+; Olig2+; ATRX+; p53+ (15%); OCT4–; LIN28A–; CAM5.2–; CD45–; desmin–; INI1–	NA	NA	IDH wt, MGMT meth –	Biopsy, XRT, CHT	7	A
6	Ono et al. (2021) [17]	M	12	H3.3K27M+; H3K27me3–; Ki-67 37%	NA	NA	IDH wt, BRAFv600E wt, MGMT meth –	Subtotal resection, XRT, CHT	72	A
7	Present case	F	7	H3K27me3–; GFAP+; Olig2+; Ki-67 30%; OCT4–; SALL4–; CD30–; βHCG–	Positive	YES	NA	Biopsy	7	D

ATRX — alpha-thalassemia/mental retardation syndrome X-linked; p53 — tumor protein 53; EGFR — epidermal growth factor receptor; ch. — chromosome; NA — data not available; IDH — isocitrate dehydrogenase; pTERT — promoter of the telomerase reverse transcriptase gene; MGMT — O6-methylguanine-DNA methyltransferase; XRT — radiotherapy; CHT — chemotherapy; GFAP — glial fibrillary acidic protein positive; Olig2 — oligodendrocyte transcription factor 2; OCT4 — octamer-binding transcription factor 4 negative; LIN28A — lin-28 homolog A; CAM5.2 — anti-cytokeratin monoclonal antibody cocktail; CD45 — cluster of differentiation 45; INI1 — integrase interactor 1; wt — wild type; ampl — amplification; meth — methylation; SALL4 — sal-like protein 4 negative; CD30 cluster of differentiation 30; βHCG — beta-human chorionic gonadotropin

*Article retracted by the Authors.

Limitations

Due to the extremely limited number of reported cases and frequent absence of complete immunohistochemical and molecular data, it is not possible to make a robust comparison between pediatric and adult pineal DMGs based solely on the available cases. The rarity of these tumors and the heterogeneity of the reported data further limit the ability to draw meaningful statistical or clinical conclusions.

Discussion

Literature context on DMGs and targeted therapies

DMGs harboring H3K27M mutations are highly aggressive tumors with a poor prognosis, especially in pediatric patients, in whom they most commonly present as diffuse intrinsic pontine gliomas (DIPGs). DMGs in adults more frequently involve the thalamus and spinal cord and may have a slightly better prognosis; however, overall outcomes remain unfavorable across age groups. There are molecular distinctions, with H3.1 K27M mutations predominating in children and H3.3 K27M mutations predominating in adults. There is also a higher incidence of ATRX loss and TERT promoter mutations in adult cases. Despite these insights, data specific to pineal gland DMGs is extremely limited, precluding definitive conclusions on age-related differences in this rare location. Therapeutically, radiotherapy remains the mainstay of treatment, often combined with chemotherapy. Emerging targeted therapies, notably ONC201 — a selective dopamine D2 receptor antagonist and caseinolytic protease P (ClpP) agonist — have shown promising efficacy in H3K27M-mutant gliomas by inducing apoptosis and disrupting metabolic and epigenetic pathways. However, their effectiveness in pineal DMGs specifically requires further investigation [18, 19].

Insights from the systematic review of pineal DMGs

Our review identified only nine reported cases of H3K27M-altered DMGs in the pineal gland, highlighting their rarity. Three of these cases involved pediatric patients, and the present case is unique in that it demonstrates synaptophysin positivity. The immunohistochemical profiles of the cases were heterogeneous, with variable expression of ATRX, p53, and Ki67 proliferation indices ranging from 9.3% to 37%. Synaptophysin expression, which is typically absent in DMGs but common in pineal parenchymal tumors (PPTs), was observed exclusively in our pediatric case. Methylation profiling was largely limited to pediatric cases, which restricted molecular comparisons between age groups. Clinical outcome data were sparse and inconsistently reported, which limited prognostic assessments.

Diagnostic challenges and hypotheses regarding synaptophysin positivity

The staining for synaptophysin was convincingly positive as it was expressed by monomorphic frankly neoplastic cells in hypercellular areas; nevertheless, this aberrant synaptophysin expression in pineal DMGs poses a significant diagnostic challenge because synaptophysin is typically associated with pineal parenchymal tumors rather than DMGs. This finding necessitates a reevaluation of the histological and immunohistochemical diagnostic algorithms used for neoplasms in the pineal region (Fig. 5). Comprehensive molecular and methylation profiling is critical to avoid misclassification and guide appropriate treatment.

While no direct molecular link has been established between the H3K27M mutation and synaptophysin expression, several hypotheses could explain this phenomenon. First, synaptophysin positivity could reflect aberrant differentiation driven by epigenetic dysregulation resulting from H3K27M-induced global hypotrimethylation of H3K27me3. This could lead to ectopic activation of neuronal or neuroendocrine markers. Alternatively, synaptophysin positivity may represent biological variability or an incidental epiphenomenon. These possibilities remain speculative due to the absence of targeted molecular studies. Further epigenetic and functional analyses are necessary to determine whether synaptophysin expression affects tumor behavior or therapeutic response.

Future directions

Further studies are needed to: expand the molecular characterization of pineal DMGs; evaluate the efficacy of targeted therapies; refine diagnostic criteria to include atypical IHC findings.

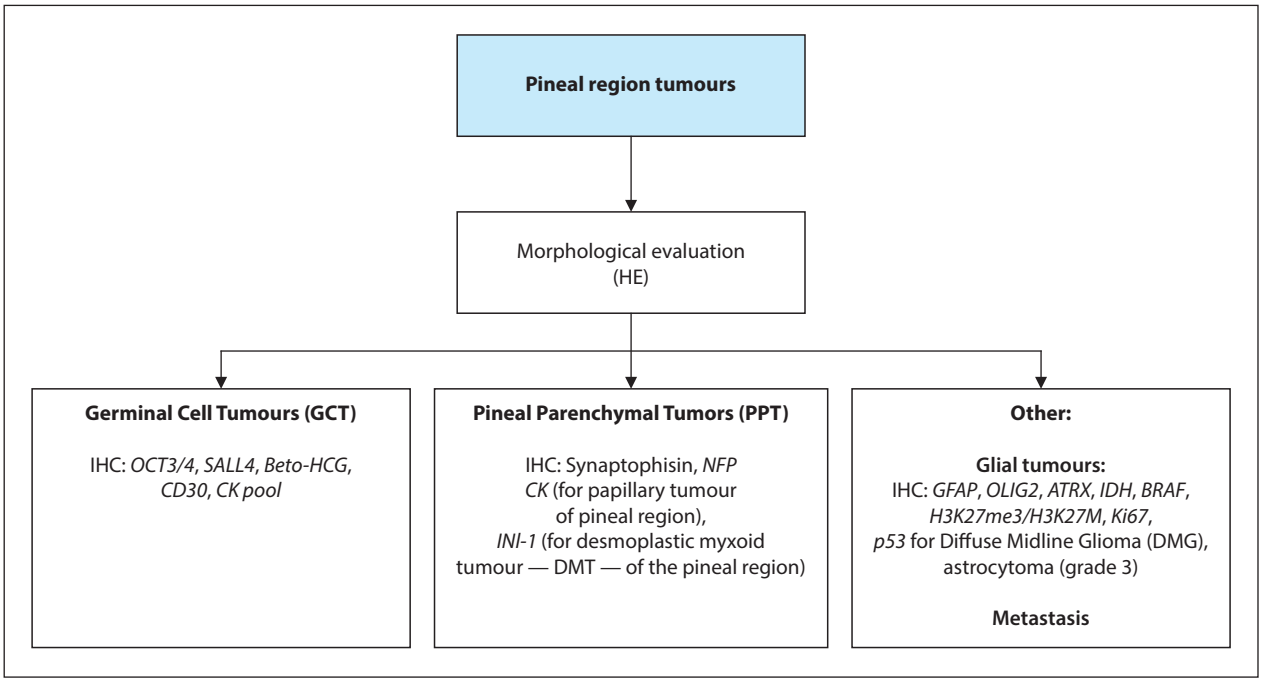

Figure 5. Diagnostic flow chart in diagnosis of pineal region tumours

Conclusions

This systematic review expands our understanding of pineal DMGs, highlighting their biological heterogeneity and diagnostic complexity. The current case — a synaptophysin-positive DMG — illustrates the evolving landscape of CNS tumor diagnosis and highlights the clinical utility of molecular/methylation profiling. Continued research into these rare tumors is essential to improve patient outcomes.

Author contributions

G.G.: conceptualization, supervision, writing — original draft; M.P., C.M.C., A.R. — data curation, formal analysis, writing — original draft; C.T.A. — data curation, methodology, validation; M.S.V., A.V., M.R. — data curation, writing — original draft; V.G.V.: writing — review and editing.

Conflict of interest

The authors declare no conflict of interests.

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Declaration of patient consent

Obtained.

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