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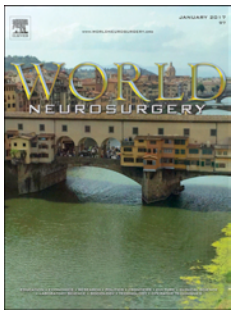

Recurrent pineocytoma-like papillary tumor of the pineal region – a case report and literature review

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Title: Recurrent pineocytoma-like papillary tumor of the pineal region – a case report and literature review.

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Abbreviations list: WHO – World Health Organization, PTPR - papillary tumor of the pineal region, CK - cytokeratins, broad spectrum, CK18 - cytokeratin 18, EMA - epithelial membrane antigen, MRI – magnetic resonance imaging, GFAP – glial fibrillary acidic protein, NSE - neuron-specific enolase, CSF - cerebrospinal fluid, S100 - S100 protein, SYN - synaptophysin, VIM -vimentin, Ki67 - antigen Ki-67, RT - radiotherapy, WBRT - whole brain radiotherapy, SRS - stereotactic radiosurgery, RChT - radiochemotherapy, ChT - chemotherapy

Abstract

Background

Papillary tumors of the pineal region (PTPRs) are malignant WHO grade II/III tumors, however they may perfectly mimic benign tumors, e.g. pineocytomas (WHO grade I).

Case Description

We present a case of a 28-year-old male with a 35mm tumor of the pineal region. Considering the typical radiological and pathological presentation, the tumor was firstly diagnosed as pineocytoma. However, despite first total resection the tumor recurred after 7 years. The recurrent neoplasm was composed mainly of papillary structures with low-grade atypical cells positive for CKAE1/AE3 and CK18. This lead to the final diagnosis of PTPR. The patient underwent adjuvant radiotherapy, which vastly improved his neurological condition and resulted in significant tumor regression.

Conclusions

This case exemplifies that PTPRs can perfectly mimic pineocytomas and simple staining for cytokeratins may warrant the correct diagnosis and better treatment allocation.

Introduction

Papillary tumors of the pineal region (PTPRs) comprise rare neuroepithelial neoplasms arising from ependymocytes of the subcommissural organ.[1–4] Although a diagnosis of PTPR may be suggested basing on magnetic resonance imaging, PTPRs show no pathognomonic features on neuroimaging.[4,5] Similarly, the microscopic image of PTPRs may be heterogenous and thus misleading.[4] Apart from the characteristic papillary structures, PTPR can present with solid areas mimicking other tumors of the pineal region, such as benign pineocytoma.[2,4,6–8] The most distinctive feature of PTPR is the positive staining with cytokeratins, including cytokeratin 18 (CK18).[3,4] The differential diagnosis between PTPR and pineocytoma is especially important, as PTPR's grading corresponds to WHO grade II/III, while pineocytoma is a WHO grade I tumor.[4,9,10] The recurrence rate for pineocytoma stands below 10%.[4,11] In turn, papillary tumors of the pineal region tend to recur in the majority of cases and radiation oncology may often be beneficial for patients with PTPRs.[9,10]

In the context of thorough literature review (Table 1), we present a case of a patient with pineal region tumor with the typical histological image of a pineocytoma, which recurred after 7 years as a papillary tumor of the pineal region.

Case description

In 2007, a 28 years-old man with bronchial asthma and aortic aneurysm presented with headache and impaired vision. A primary neuroimaging examination revealed a tumor located in the pineal region. On MRI, the tumor was 35 mm in diameter and presented as a heterogeneous mass with intrinsic T1 hyperintensity (Figure 1A-B).

Because of the size and extension into both the aqueduct and third ventricle, the tumor was excised in two consequent surgeries (October 2007 *via* supracerebellar infratentorial approach and December 2007 *via* parietal interhemispheric approach). The tumor histopathologically consisted of solid and highly-cellular areas with small, uniform cells that formed typical rosettes (Figure 2A-B). Atypia, mitoses and necrosis were absent. The tumor was focally positive for synaptophysin and NSE, while negative for GFAP (Figure 2C). Ki67 index was 1%. All stainings were routinely executed in our Department with utilization of EnVisionTM FLEX+ system (Agilent Technologies, Santa Clara, CA 95051, United States). Considering the typical presentation, the tumor was diagnosed as WHO grade I pineocytoma.

Unexpectedly, after 7 years (in 2014) the patient presented with impaired vision and paresis and a recurrence was confirmed on neuroimaging (Figure 3A-B). The recurrent tumor underwent gross total resection. On the histopathological examination, the tumor was positive for synaptophysin and Ki67 index was 3% and it was considered as a late recurrence of an incompletely resected pineocytoma. However, 2 years later (in 2016), a radiological examination revealed the tumor in the region of the cerebral aqueduct and fourth ventricle (Figure 3C-D). The bone opening from the previous surgeries was extended by C1 laminectomy, as the medulla was compressed by the tonsils below C1 level and the recurrent tumor was excised subtotally (Figure 3E-F). The microscopical image of the tumor was starkly different from the primary specimen. It presented with papillary structures composed of cells with moderate atypia and higher Ki67 index (Figure 4A-C). A stainings for broad spectrum cytokeratins and CK18 revealed strong positivity of the papillary structures and the tumor was diagnosed as a papillary tumor of the pineal region, WHO grade II/III (Figure 4D). Subsequently, the primary tumor was stained for CK18, which also revealed a strong positivity (Figure 2D).

In 2017, the patient underwent cerebrospinal fluid (CSF) analysis and MRI of the spinal region, which excluded CSF dissemination. Hence, the patient underwent adjuvant local intensity-

modulated radiation therapy (54.0 Gy in 1.8 Gy fractions). After the consultation with Medical Oncology Department no adjuvant chemotherapy was administered. The therapy was well tolerated and no significant (≥3 according to Common Terminology Criteria for Adverse Events v.4.03) treatment-related toxicity was observed. There were no treatment breaks due to treatment complications. Six months later, his neurological condition improved and pronounced shrinkage of the tumor was observed (Figure 3 G-H). The patient is under close follow-up and remains stable with no new symptoms.

Discussion

Papillary tumor of the pineal region was first described in 1982, but was referred to as a pineocytoma with papillary features and its aggressive course was emphasized.[12] Subsequently, it was recognized as a separate entity in 2003[2] and it was first introduced in the WHO Classification of Tumors of the Central Nervous System in August 2007[13], basing on 38 cases worldwide, just before the time the patient was initially diagnosed. Since then the tumor has drawn more attention and a few years later the 2016 WHO Classification reported 181 cases of pineal tumors with the papillary morphology.[4]

In principle, the differentiation between pineocytoma and papillary tumor of the pineal region should be relatively straightforward (Table 1). Pineocytomas are composed of sheets of small, uniform, round cells forming large pineocytomatous rosettes. In turn, PTPRs present, at least partially, papillary structures lined by slightly polymorphic cells forming ependymal rosettes and pseudorosettes. On the other hand, a relatively large morphological variability is possible in case of these tumors.[8] The architecture may range from mostly papillary to solid with pseudorosettes, while the cells from small and uniform to highly polymorphic and atypical. Moreover, due to imperfect sampling, especially in small biopsies, the papillary structures may be absent in the analyzed specimen (while presumably present in the residual tumor). What is crucial, a simple staining for broad spectrum cytokeratins should efficiently indicate the PTPR cases even lacking the papillary structures in the resected specimen.

The precise definition and clinical behavior of PTPRs is still the matter of a debate. The most common opinion is that this is not a single entity but rather a spectrum of grade II and grade III tumors. This might explain the variation in the initial presentation and reported behavior of the tumors. A maximal safe resection remains a standard of care, however, a recent paper by Mallick S *et al.* showed that only one third of the patients were suitable for a gross total resection and the other one third were managed with a biopsy only.[14] In the largest pooled analysis of 127 patients, the reported median progression free survival was 5 years and overall survival was 14 years.[14] The role and extent of adjuvant therapy is not well-established, and its use depends widely on local practice. The report by Mallick et al. has shown that adjuvant radiotherapy may bring the benefit in overall survival however, due to the heterogeneity of the analyzed group, definitive conclusions cannot be drawn.[14] Conventional fractionation to 50.4-54.0Gy is the most common

regimen, however, other are also in use.[9] The described late recurrences may suggest that the current management of the disease is suboptimal.[15] Hence, there is an acute need for novel diagnostic markers as well as uniform treatment and follow-up guidelines.

Taking into consideration both pathological and clinical aspects, we believe that cytokeratin stains should be routinely implemented in the diagnostic panel for all low grade pineal parenchymal tumors. Case-wise the addition of a single staining should only slightly increase the diagnostic costs, since these tumors are relatively rare, so the overall additional financial burden would be hardly observed. As mentioned, the distinction between pineocytomas and PTPRs are crucial from patient management perspective.

Conclusions

Our case shows that papillary tumors of the pineal region (WHO grade II/III) can perfectly mimic pineocytomas (WHO grade I). Thus, in all cases of the rare tumors of the pineal region, a simple staining for cytokeratins, especially for cytokeratin 18, may lead to the correct primary diagnosis and result in a better treatment allocation.

Compliance with Ethical Standards:

Ethical approval: For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participant included in the study.

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Contributions: Author MB, Author BT, Author MB and Author RK conceived and designed the study, and wrote, edited and reviewed the manuscript. Author KW, DJK, DJ, JF and WP consulted the case, wrote, edited and reviewed the manuscript. All authors gave final approval for publication. Author MB takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript. The first and second author contributed equally.

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Figure legends:

Figure 1 MRI at first diagnosis - a circumscribed, slightly-lobulated lesion shows prominent diffuse contrast enhancement on axial (A) and sagittal (B) T1-weighted image.

Figure 2 Histopathological texture of the primary tumor. A-B. Solid areas of uniform cells form pineocytomatous rosettes. C. The tumor is weakly for synaptophysin. D. The tumor is positive for CK18.

Figure 3 MRI images: at 1st tumor recurrence on axial (A) and sagittal (B) T1-weighted image; at 2nd tumor recurrence on axial (C) and sagittal (D) T1-weighted image; after resection of 2nd tumor recurrence on axial (E) and sagittal (F) T1-weighted image; performed 6 months after radiotherapy on axial (G) and sagittal (H) T1-weighted image.

Figure 4 Histopathological texture of the primary tumor. A-B. Papillary structures of cells with moderate atypia. C. Ki67 proliferation index is 5-7%. D. The tumor is positive for CK18.

Table legend:

Table 1 Clinical, radiological and pathological features of PTPRs in the literature review. We reviewed MEDLINE and EMBASE database via Ovid search engine with search queries as stated in keywords of the manuscript. After deduplication, we screened 120 found articles for case, case series and cohort studies on PTPRs and we selected 64 articles reporting clinical, radiological and pathological features of PTPRs. The current case is depicted in the first row. Abbreviations: CK (cytokeratins, broad spectrum), CK18 (cytokeratin 18), GFAP (glial fibrillary acidic protein), EMA (epithelial membrane antigen), S100 (S100 protein), NSE (neuron-specific enolase), SYN (synaptophysin), VIM (vimentin), Ki67 (antigen KI-67), + (positive), +/- (focally positive), - (negative), RT (radiotherapy), WBRT (whole brain radiotherapy), SRS (stereotactic radiosurgery – either gamma knife or LINAC), RChT (radiochemotherapy), ChT (chemotherapy)

Ref	N	Age Sex	Radiology	Surgical approach	Architecture	Cytology	Immunohistochemistry	Further therapy, genetic analyses and follow-up	
16	1	3M	Solid and cystic, heterogeneously enhancing tumor	Occipital interhemispheric approach in sitting position	Pseudorosettes and necrotic areas	Epithelial-like	CK +, CK18 +, GFAP -, EMA +/-, S100 +, SYN -, VIM +, Ki67 25%	RChT (54Gy with cisplatin, cyclophosphamide, vincristine, etoposide); no recurrence during 5 years of follow-up	
17	2	27M	Pineal tumors with obstructive hydrocephalus	No data	Papillary	No data	GFAP +, EMA +, SYN +	SRS; no recurrence during 15 and 20 years of follow-up, respectively	
		46F		Infratentorial supracerebellar approach					
18	1	34M	Solid and cystic tumor	Infratentorial supracerebellar approach	Papillary with pseudorosettes	Polygonal cell with eosinophilic or clear cytoplasm	CK +, GFAP -, EMA -, S100 +, NSE -, SYN -, Ki67 5%	Observation, no recurrence during 57 months of follow-up	
19	1	27W	Lobulated tumor	Suboccipital craniotomy	First tumor – pineocytoma-like rosettes, Recurrent tumor - papillary	Cells with oval to round nuclei and dispersed chromatin	CK +, GFAP -, Ki67 5%	Early recurrence after three months; RT after second surgery, no recurrence during 39 months of follow-up after RT	
20	1	60W	Hemorrhagic tumor	No data	Papillary with pseudorosettes	Columnar and cuboidal cells with eosinophilic cytoplasm	CK18 +, GFAP -, EMA -, S100 +, SYN -, VIM +	No recurrence during 2 years of follow-up	
21	1	34W	Circumscribed tumor with hydrocephalus	No data	Solid and papillary with rosettes	Epithelial-like cells with vacuolated cytoplasm and moderate nuclear pleomorphism	CK18 +, GFAP -, EMA -, S100 +, NSE -, SYN -, Ki67 5%	No data	
22	1	37M	Heterogeneously enhancing tumor with hydrocephalus	Occipital transtentorial approach	First tumor - solid with some papillary structures Second tumor - more papillary structures	Oval cells with low mitotic activity	CK +, CK18 +, GFAP +, EMA +, S100 +, NSE +, Ki67 8%	Losses of 3, 10 and gain of 8 chromosomes (CGH); *MGMT* not methylated; mutations in codons 546 and 656 of *FGFR1* Negative for *BRAF* V600E	Combined RChT (1st - carboplatin and etoposide plus 40 Gy in 20 fractions; 2nd - oral temozolomide (150 mg/m2, days 1–5, 28-day cycle) and intravenous bevacizumab (7.5 mg/kg, day 0, every 4 weeks) Follow up of one year - stable disease
15	1	62M	Circumscribed tumor with hydrocephalus	Suboccipital craniotomy with laminectomy	Papillary with pseudorosettes	Epithelial-like, columnar cells with oval nuclei	CK18 +, GFAP -, NSE +, SYN -, VIM +, Ki67 10%	RT (36Gy/g – 1.8 Gy/g per fraction), no recurrence during 8 years of follow-up	
23	1	17W	Heterogeneous, solid and cystic tumor with hydrocephalus	Midline suboccipital craniotomy with infratentorial supracerebellar approach	Papillary with pseudorosettes	Eosinophilic cytoplasm and round to oval nuclei with dispersed chromatin	CK +, GFAP NSE +, SYN -, Ki67 15-20%	Complete response	
24	1	10W	Heterogeneously enhancing solid and cystic tumor	Suboccipital transtentorial approach	Papillary with pseudorosettes	Hyperchromatic cytoplasm and irregular nuclei	CK +, CK18 +, GFAP -, EMA -, S100 +, NSE +, SYN -, Ki67 5%	No recurrence during 15 months of follow-up	
25	1	31M	Heterogeneous	Right parieto-occipital	Papillary	Epithelial-like,	CK +	Adjuvant RChT with temozolomide; no recurrence during	

			tumor with hydrocephalus	craniotomy with interhemispheric, transcallosal approach		columnar and cuboidal cells		9 years of follow-up
26	3	18W	MRI - solid tumor in the pineal region without contrast enhancement	No data	At first pineocytoma-like, at recurrence papillary	oval to elongated with monomorphic nuclei containing vesicular chromatin, moderate atypia,	CK +, CK18 +, GFAP -, S100 +, NSE -, SYN -, VIM +	Adjuvant RT – late recurrence after 7 years, excision and adjuvant RT – no recurrence after 14 months of follow-up
		30W	MRI – heterogeneously enhancing solid tumor of the pineal region		Papillary with occasional solid foci			Adjuvant RT – no recurrence after 30 months of follow-up
		50M	MRI – heterogeneously enhancing solid-cystic tumor of the pineal region, hydrocephalus		Papillary			Adjuvant RT – no recurrence after 8 months of follow-up
27	1	29M	Heterogeneous tumor with hydrocephalus	No data	Papillary	Epithelial-like	CK +, CK18 +, SYN +, Ki67 2%	Radiotherapy
28	1	25M	Heterogeneously enhancing tumor with hydrocephalus	No data	Papillary with pseudorosettes	Epithelial-like without atypia	CK +, CK18 +, GFAP -, EMA -, SYN +, Ki67 3%	Radiotherapy; Chromosomal abnormalities: losses of 3, 7, 10, 14, 18, Y; gains of 3, 8, 9, derivative 5
9	8	37 yrs. median (25-56 range) 4M: 4W	MRI - all tumors exhibited heterogeneous enhancement on T1 postcontrast imaging, and most (75%) had cystic components	supracerebellarinfratentorial (n = 3), interhemispheric-transventricular (n = 4), and endoscopic transventricular (n = 1)	No data	No data	CK +, CK18 +, EMA -, S100 +	5 received adjuvant radiotherapy, follow-up of 60 months (range, 10-170 months), 1 death
29	1	17M	Heterogeneously enhancing tumor with hydrocephalus	No data	Papillary	No data	CK +, Ki67 20%	No recurrence during 6 months of follow-up
6	2	37M	MRI - solid and cystic, heterogeneously enhancing tumors	Supracerebellar infratentorial approach	Papillary and solid foci with pseudorosettes	Epithelial-like with little atypia	CK +, GFAP -, EMA -, SYN -, Ki67 1-2%	Adjuvant RT 10 years without recurrence
		45W						Adjuvant RT 2 years without recurrence
30	21	35 (10-56), M:W= 1.3:1	No data	No data	Increased cellularity 4/21 Solid growth 11/21 Necrosis 8/21 Increased proliferative activity (Ki67≥10%) 8/20	Nuclear pleomorphism 4/21 Increased mitotic activity 10/21	CK +, EMA -	4 patients adjuvant chemotherapy, 13 adjuvant radiotherapy, Recurrence-free survival – 66 (CI: 42-90) months, 3 deaths
31	1	24M	Enhancing tumor with hydrocephalus	No data	Papillary	No data	CK +, GFAP -, SYN -, Ki67 20%	RT and bevacizumab, no recurrence during 8 years of follow-up
32	1	59W	Enhancing tumor	No data	Papillary with	Epithelial-like with	CK +, GFAP -, EMA -, S100 +, NSE -, SYN +,	RT, no recurrence during 6 months of follow-up

			with hydrocephalus		necrosis, pseudorosettes and anaplastic component	small, blue cell areas	Ki67 15-50%	
33	1	20M	Heterogeneous tumor with hydrocephalus	Radiosurgery	Solid and papillary	No atypia	CK +, GFAP -, EMA -, S100 +, NSE +	No recurrence during 62 months of follow-up
10	44	29 median (5–66 range) M:W= 21:23	MRI – pineal region mass with contrast enhancement	More infratentorial-supracerebellar approach than transcallosal approach	No data	No data	No data	8 patients received adjuvant chemotherapy and 28 received adjuvant radiotherapy, median follow up of 63.1 months, 12 deaths
34	1	3W	Solid and cystic, heterogeneously enhancing tumor with hydrocephalus	Suboccipital supracerebellar approach	Solid and papillary with pseudorosettes	Epithelial-like	CK +, GFAP -, S100 +, NSE +, SYN -, Ki67 10-25%	Observation; recurrence after 3 years, alive 6 years
35	2	48M	MRI – heterogeneously enhancing cystic and solid tumors of the pineal region	No data	Solid with pseudopapillary foci	Epithelial-like with focal atypia	CK +, CK18 +, GFAP -, EMA -, S100 +, NSE +, SYN -, VIM +, Ki67 1%	No data
		35M			Prominent papillary			
36	46	35 yrs. median (5-71 range) M:W= 24:22	No data	No data	30/46 papillary 16/46 solid and papillary Pseudorosettes present	Small to medium cells without atypia	CK +, CK18 +, GFAP -, EMA -, S100 +, NSE +, SYN -, VIM +, Ki67 1-30%	15/46 tumors recurred, follow-up of 4.5±0.8 years
37	1	22M	Enhancing tumor	Right lateral infratentorial supracerebellar approach	Papillary with rosettes	Small round to oval cells with eosinophilic cytoplasm	CK +, GFAP -, EMA -, S100 +, NSE +, VIM +, Ki67 4%	RT; no recurrence during 12 months of follow-up; IDH1 wild-type
38	1	45M	Heterogeneous, lobulated tumor	Infratentorial supracerebellar approach	Papillary	Epithelial-like without atypia	CK +, GFAP -, EMA +/-, NSE +, SYN -, Ki67 4%	No recurrence during 15 years of follow-up
39	1	70M	Cystic, heterogeneously enhancing tumor with hydrocephalus	No data	Solid and papillary	Uniform, columnar, epithelial-like	CK +, GFAP -, EMA -, S100 +, NSE +, SYN -, VIM +, Ki67 10-20%	RT; no recurrence during 9 months of follow-up
40	1	47M	Solid and cystic, enhancing tumor with hydrocephalus	No data	Pseudopapillary	Epithelial-like with moderate pleomorphism	CK +, GFAP -	No data
8	3	30W	MRI – well circumscribed, heterogeneous masses in the pineal region, cystic component in one	No data	Cystic, pseudopapillary and solid, pseudorosettes	Epithelial-like with little to moderate atypia	CK +, GFAP -, EMA +, S100 +, NSE +, SYN +, VIM +, Ki67 5%	RChT, no recurrence
		28W			Solid and papillary with pseudorosettes			RChT, no recurrence

		32M	hydrocephalus		Solid, papillary and pseudopapillary			RChT, recurrence after 1.5 year
41	1	20M	Cystic, non-enhancing tumor	endoscopic approach through a right frontal burr hole	Papillary with rosettes	Epithelial-like without atypia	CK +, GFAP -, S100 +, SYN +, Ki67 8-10%	RT with complete response; no recurrence during 25 months of follow-up
42	2	48M	MRI - heterogeneously enhancing mass in the pineal region, hydrocephalus	Suboccipital supracerebellar approach	Papillary and pseudopapillary with rosettes and pseudorosettes	Epithelial-like with little to moderate atypia	CK +, CK18 +, GFAP +/-, EMA -, S100 +, NSE +, SYN -, VIM +, Ki67 15-20%	RChT; no recurrence during 14 months of follow-up
		36W						RChT; no recurrence during 18 months of follow-up
43	1	42W	Enhancing tumor	Midline infratentorial-supracerebellar approach	Papillary with rosettes and pseudorosettes	No data	CK +, GFAP -, S100 +	Recurrence after 2 years (ChT: TMZ); no recurrence during 5 years of follow-up
44	3	31M	Solid and cystic, enhancing tumor with hydrocephalus	No data	Papillary	Polygonal cells with clear to eosinophilic cytoplasm	CK +/-, GFAP +/-, EMA -, S100 +, NSE -, SYN -, VIM +, Ki67 2-4%	RT (54Gy); no recurrence during 4.5 years of follow-up
		37F		No data	Solid and papillary		CK +/-, GFAP -, EMA -, S100 +, NSE -, SYN -, VIM +, Ki67 1-2%	Observation; no recurrence during 2.5 years of follow-up
		43M		No data	Nests, sheets and papillae		CK -, GFAP -, EMA -, S100 +, NSE +, SYN -, VIM +, Ki67 2-4%	RT (54Gy); no recurrence during 18 months of follow-up
45	2	25F	Solid and cystic, enhancing tumor without hydrocephalus	Supracerebellar infratentorial approach	Papillary	Cuboidal to columnar cells with round nuclei	CK +, GFAP +/-, EMA -, S100 +/-, NSE +/-, SYN -, VIM +, Ki67 5%	RT (54Gy); recurrence after 23 months; 22q11.2 deletion
		42M	Solid and cystic, enhancing tumor with hydrocephalus	No data	Solid and papillary	Eosinophilic cytoplasm and oval nuclei	CK +, GFAP +/-, EMA -, S100 +/-, NSE +/-, SYN -, VIM +, Ki67 5%	RT (50.4Gy); no recurrence during 13 months of follow-up
46	1	29F	Solid and cystic, enhancing tumor with hydrocephalus	Suboccipital transtentorial approach	Solid and papillary	Eosinophilic cytoplasm and vesicular or hyperchromatic nuclei	CK +, EMA +, S100 +, SYN +/-, Ki67 10%	Radiotherapy (50.4Gy)
47	1	1M	Solid and cystic, enhancing tumor with hydrocephalus	Transchoroidal approach	Solid and papillary with pseudorosettes	Eosinophilic cytoplasm with vacuoles and hyperchromatic nuclei	CK +, GFAP -, EMA -, S100 +, Ki67 5-8%	ChT (vincristine, methotrexate, etoposide, cyclophosphamide, cisplatin); recurrence during 2nd cycle
48	3	13M	Cystic, enhancing tumor with hydrocephalus	Occipital craniotomy	Solid and papillary with pseudorosettes and necrosis	Eosinophilic cytoplasm with vacuoles and monomorphic nuclei	CK +/-, GFAP+/ -, EMA +/-, S100 +, NSE +, SYN +, VIM -	ChT (carboplatin, VP16, vincristine) and RT to craniospinal axis; recurrence after 5 years (RT 20Gy); recurrence after 3 years (SRS 22Gy); recurrence after 8 months (SRS 20Gy); no recurrence during 5 years of follow-up; gains at 4,8,9p, 11,12p12q21; losses at 1p32pter, 10, 15q
		26F	Enhancing tumor with hydrocephalus	Parietal parasagittal approach and suboccipital approach	Solid and papillary with pseudorosettes and necrosis	Eosinophilic cytoplasm with vacuoles and monomorphic nuclei	CK +/-, GFAP +/-, EMA +/-, S100 +, NSE +, SYN -, VIM +	RT with I-125 seeds; recurrence after 7 years (RT 46Gy); recurrence after 3 years (surgery); recurrence after 18 months (RT 30.6 Gy); recurrence and spinal metastasis after 12 months (surgery); death after another 3 months;

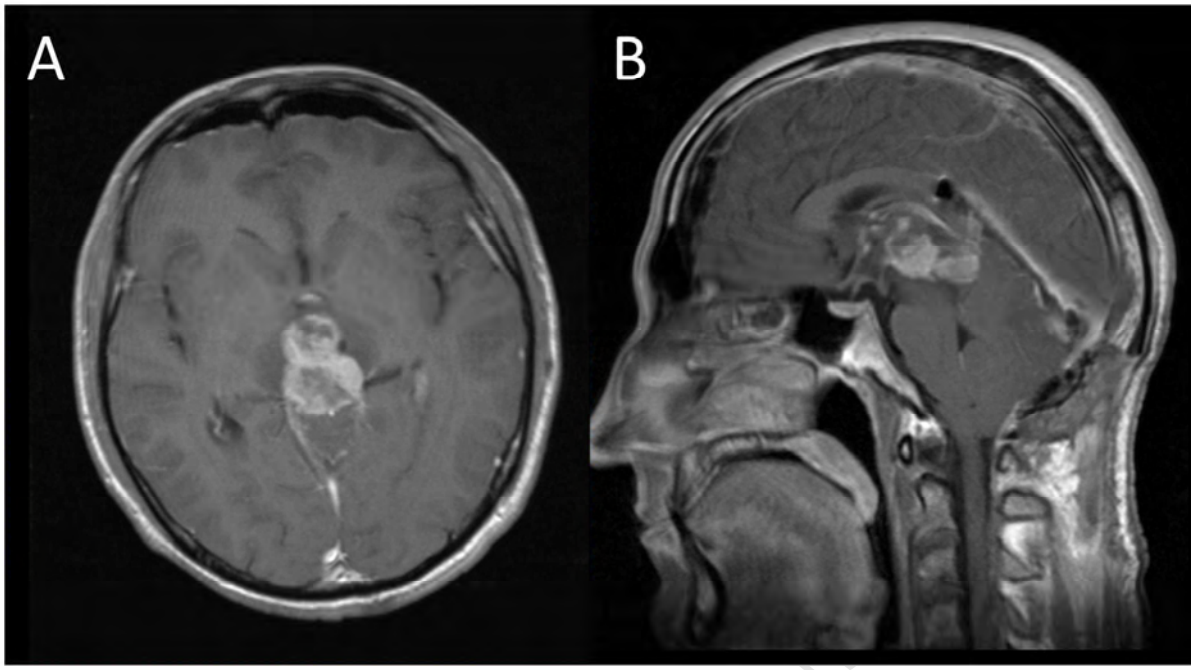
								gains at 3,8,9p,12p11qter; loss at 10
		53M	Solid, homogeneously enhancing tumor	Median suboccipital craniotomy	Solid and papillary with pseudorosettes and necrosis	Eosinophilic cytoplasm with vacuoles and monomorphic nuclei	CK +/-, GFAP +/-, EMA +/-, S100 +, NSE +, SYN -, VIM +	No adjuvant therapy; no recurrence during 8 months of follow-up; gains at 4,5,9p13pter, 13q, 18q; losses at 17
49	1	18F	Solid and cystic, enhancing tumor with hydrocephalus	No data	Solid and papillary without necrosis	Eosinophilic cytoplasm and round to oval nuclei	CK +, GFAP -, EMA -, S100 +, NSE +	No data
50	1	21M	Heterogeneous enhancing tumor with hydrocephalus	No data	Pseudopapillary with pseudorosettes	Columnar and cuboidal cells with round to oval nuclei	CK18 +, GFAP -, SYN +/-	Subtotal resection, recurrence within 2 months, 55Gy RT, 3 years later dissemination, 50Gy over posterior fossa, recurrence after 2 years treated with surgery, recurrence after another 2 years treated with ChT (etoposide+carboplatin), recurrence after 6 years treated with TMZ and 2 resections
51	1	47M	Tumor with hydrocephalus	Occipital interhemispheric approach	Solid with pseudorosettes	Moderately pleomorphic cells	CK +, GFAP +/-, S100 +, SYN -	Radiosurgery, recurrence after 7 years, excision, recurrence free during 42 months of follow-up
52	4	21M	Solid and cystic, enhancing tumor with hydrocephalus	No data	Solid and papillary	Cytoplasm with vacuoles and oval or round, mildly pleomorphic nuclei	CK +, GFAP +/-, EMA +, S100 +, VIM +	RT, recurrence within 2 years treated surgically
		19F	Solid and cystic tumor	No data				RT, no recurrence during 22 months of follow-up
		47M	Solid and cystic, enhancing tumor	No data				Observation, recurrence within 1 year treated with RT, no further recurrence during 2 years of follow-up
		35M	Heterogeneous enhancing tumor	No data				RT
53	1	29F	Enhancing tumor with hydrocephalus	No data	Solid and papillary	Eosinophilic cytoplasm and round to oval nuclei	CK +/-, GFAP -, EMA -, SYN +	Gross total resection, no adjuvant therapy; no recurrence during 10 months of follow-up
54	1	29M	Heterogeneous tumor with hydrocephalus	Supracerebellar approach	Papillary with rosettes	Eosinophilic cytoplasm and round-to-oval nuclei	CK +, EMA +/-, SYN +, Ki67 3-4%	Subtotal resection, early progression within 4 months, clear progression after 8 months; patient refused reoperation, platinum-based RChT
55	1	39F	Solid and cystic, enhancing tumor	No data	Pseudopapillary	Eosinophilic or clear cytoplasm and hyperchromatic nuclei	CK -, CK18 -, GFAP -, EMA -, S100 +/-, NSE +/-, SYN -, VIM +, Ki67 3-5%	SRS, recurrence and progression after 6 months, 12Gy and 14Gy RT, further dissemination; death 11 months from diagnosis
56	1	17M	Homogeneously enhancing tumor	No data	Papillary with pseudorosettes	Columnar cells	CK18 +, GFAP +/-, EMA +, NSE +, SYN +, Ki67 7.4%	WBRT 30Gy with local 20Gy; recurrence after 9 years, GKR 20Gy, recurrence after 17 months treated with etoposide+cisplatin, SRS 18Gy, 41 months later recurrence treated with RT (14Gy)
57	1	11M	Heterogeneous, enhancing tumor with hydrocephalus	Occipital transtentorial approach	Papillary	Well-differentiated tumor cells with round to oval nuclei	CK +, GFAP -, EMA +/-, S100 +/-, NSE -, SYN +/-, VIM +/-, Ki67 2.6%	Extended local RT (50.4Gy) and systemic ChT (nimustine), followed by gross total resection; no recurrence during 15 years of follow-up
58	1	25F	Enhancing tumor with hydrocephalus	Bilateral frontal craniotomy	Papillary with rosettes	Granular eosinophilic cytoplasm and round to oval eccentric nuclei	CK +, CK18+, GFAP -, EMA -, S100 +/-, Ki67 7.8%	No adjuvant therapy
59	3	31M	Enhancing tumor with hydrocephalus	Krause approach	Solid and papillary with rosettes and	Columnar cells with eosinophilic	CK+, GFAP +/-, EMA +, S100 +/-, SYN +, Ki67 4%	RT; no recurrence during 10 months of follow-up

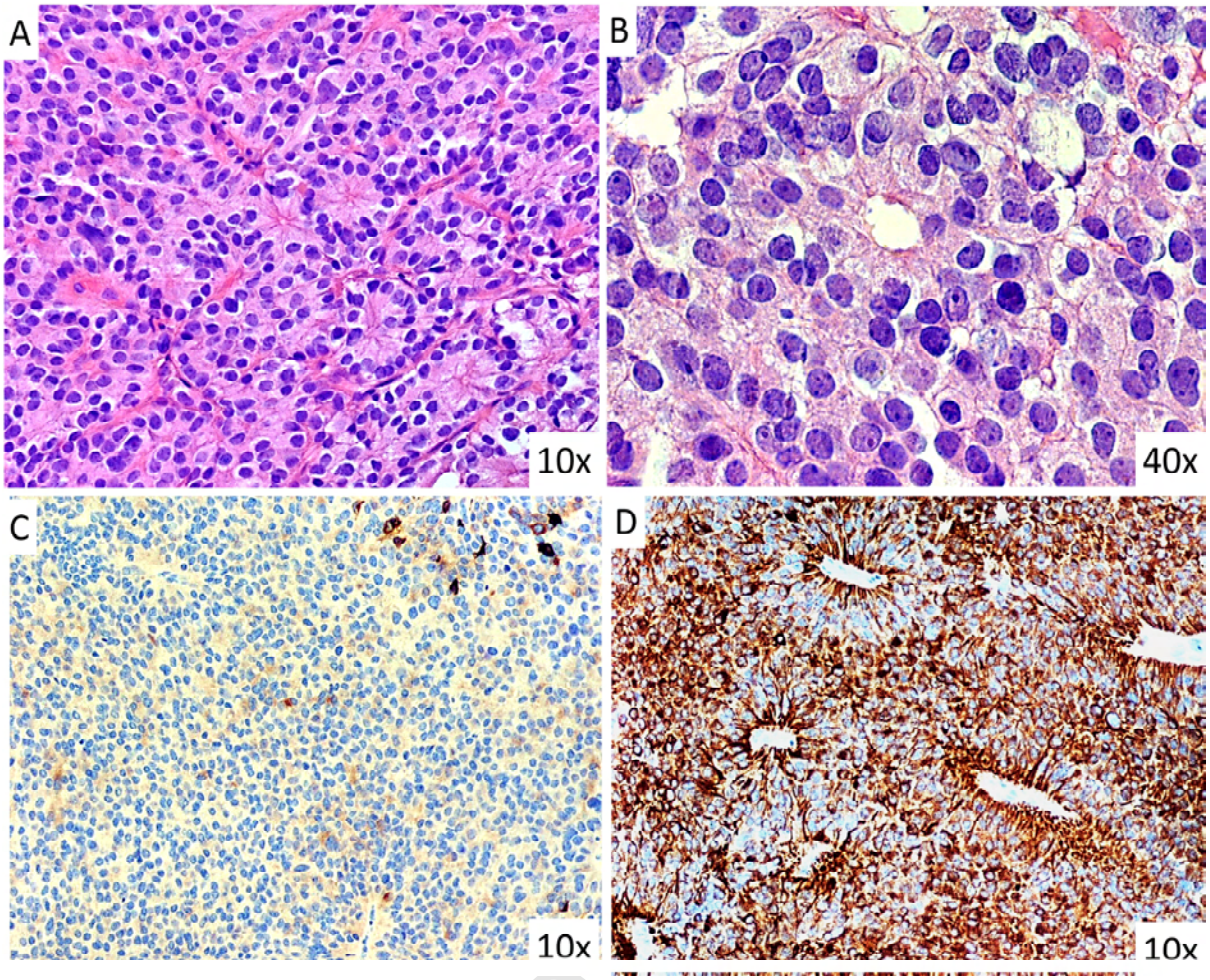
		32F	Heterogeneously enhancing tumor with hydrocephalus	Suboccipital craniotomy and supracerebellar approach	pseudorosettes	Cytoplasm and round to oval nuclei	CK+, GFAP -, EMA -, S100 +/-, SYN +, Ki67 3%	RT; no recurrence during 20 months of follow-up
		22M	Solid, enhancing with hydrocephalus	No data			CK+, GFAP +/-, EMA +, S100 +/-, SYN +, Ki67 8%	RChT; no recurrence during 15 months of follow-up
60	1	56M	Enhancing tumor with hydrocephalus	Infratentorial-supracerebellar approach	Papillary	No data	CK +, S100 +/-, Ki67 8%	Gross total resection 29 months after diagnosis; conformational RT (45Gy) after 4 months, no recurrence during 3 months of follow-up
61	1	18M	Solid and cystic, enhancing tumor	No data	Papillary	Epithelial-like cells with uniform, vesicular nuclei	CK +, S100 +/-, NSE +, SYN +, VIM +/-	ChT (two cycles of ifosfamide, cisplatin and etoposide), RT (36Gy to the spinal axis and 39.6Gy WBRT with boost to posterior fossa pineal region) with poor response; death within 12 months since diagnosis
62	1	43M	Solid and cystic, enhancing tumor with hydrocephalus	Occipital transtentorial approach	Papillary	Columnar and cuboidal cells with mildly non-uniform, round to oval nuclei	CK +/-, GFAP +/-, EMA +-/, S100 +, NSE +, SYN -, VIM +, Ki67 13.1%	RT (WBRT 24Gy and 30Gy to the pineal region) with intravenous nimustine; then nimustine every 2 months; no recurrence during 1 year of follow-up
63	1	42F	Heterogeneous, enhancing tumor	No data	Papillary with rosettes and pseudorosettes	Columnar and cuboidal cells with vacuolated cytoplasm	CK +, CK18+, GFAP -, EMA +/-, S100 +/-, NSE +, SYN -, Ki67 8%	No data
64	1	48F	Solid and cystic, enhancing tumor with hydrocephalus	Occipital transtentorial approach	Papillary with pseudorosettes	Polygonal cells with clear cytoplasm and pleomorphic nuclei	CK +, GFAP -, EMA -, S100 +, SYN -, VIM +	No recurrence during 8 months of follow-up
65	1	22M	Solid and cystic, enhancing tumor with hydrocephalus	Infratentorial-supracerebellar approach	Solid and papillary with rosettes and pseudorosettes	Eosinophilic, non-fibrillary cytoplasm and indistinct borders, large pleomorphic nuclei	CK +, GFAP +/-, S100 +/-, NSE +/-, SYN +/-, VIM +/-, Ki67 4.5%	RT, no recurrence during 26 months of follow-up
66	1	13M	Solid and cystic, enhancing tumor with hydrocephalus	Infratentorial supracerebellar approach	Papillary with diffuse areas and pseudorosettes	Columnar or cuboidal cells with eosinophilic or clear cytoplasm and oval nuclei	CK +, GFAP -, S100 +, VIM +	RT (50Gy); no recurrence during 24 months of follow-up
67	1	33M	Cystic, enhancing tumor	Infratentorial supracerebellar approach	Solid and papillary with pseudorosettes	Columnar or polygonal cells with clear cytoplasm, mild atypia and nuclear pseudoinclusions	CK +, GFAP -, EMA -, S100 +, SYN +/-, VIM +, Ki67 3%	Near total resection and RT (55Gy); no recurrence during 38 months of follow-up
68	3	37F	Solid and cystic, enhancing tumor with hydrocephalus	Supracerebellar infratentorial approach	Solid and papillary with pseudorosettes	Eosinophilic cytoplasm and round-to-oval nuclei	CK +, GFAP -, EMA -, S100 +, NSE +, SYN -, VIM +	SRS (15Gy), no recurrence during 60 months of follow-up
		51F		Supracerebellar infratentorial approach				WBRT (30Gy), no recurrence during 56 months of follow-up
		54F		Transcallosal-transventricular approach				Stereotactic SRS (15Gy)
69	1	19F	Solid and cystic, heterogeneously	Midline infratentorial-supracerebellar	Solid and papillary with rosettes and	Columnar and cuboidal cells with	CK +, GFAP +/-, EMA -, S100 +/-, SYN +/-, VIM +	Stereotactic RT (60Gy); no recurrence during 22 months of follow-up

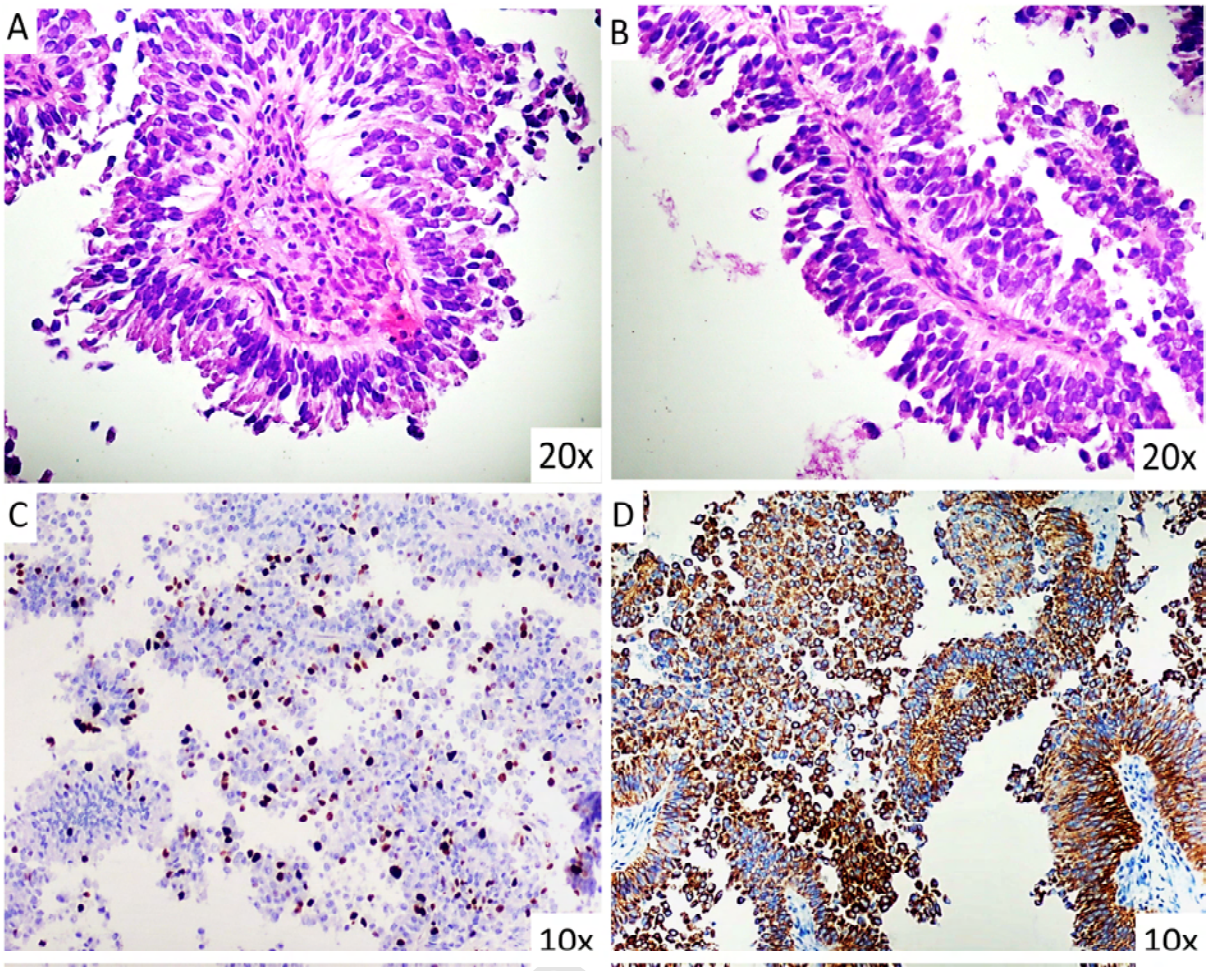
			enhancing tumor with hydrocephalus	approach	pseudorosettes	eosinophilic or clear cytoplasm and monomorphic nuclei		
70	1	35M	Enhancing tumor with hydrocephalus	Transcallosal-transventricular-transchoroidal approach	Papillary with rosettes and pseudorosettes	Columnar and cuboidal cells with clear cytoplasm and round to oval nuclei	CK +/-, GFAP -, EMA +, S100 +, NSE +, SYN -, VIM +, Ki67 3-5%	No recurrence during 16 months of follow-up
7	1	29F	Solid and cystic tumor with hydrocephalus	No data	Solid and papillary with pseudorosettes	Columnar and cuboidal cells with vacuolated cytoplasm	CK +, GFAP -, EMA +, S100 +/-, SYN -, VIM -, Ki67 5%	RT (50 Gy) with resection and ChT (ifosphamide, cisplatin, etoposide); no recurrence during 9 months of follow-up
2	6	19M	Well circumscribed tumor	No data	Papillary with rosettes and pseudorosettes	Vacuolated cytoplasm and round to oval nuclei	CK +, GFAP -, EMA +, S100 +, NSE +, SYN +/-, VIM +	Recurrence after 17 months, treated with surgery and RT; alive after 24 months
		28F						RT and recurrence; alive after 57 months
		56F						RT and recurrence; alive after 24 months
		53M						SRS; alive after 23 months
		37F						Spinal dissemination treated with RChT; alive after 24 months
		42F						RChT, 2 recurrences, ChT
71	1	11M	Solid and cystic, enhancing tumor with hydrocephalus	Supracerebellar approach	Papillary with rosettes	Well-differentiated cells with round to oval nuclei	GFAP -, S100 +/-, NSE +	RT and gross total resection; no recurrence during 18 months of follow-up
12	1	58M	Enhancing tumor with hydrocephalus	No data	Solid and papillary with rosettes and pseudorosettes	Moderately differentiated cells with abundant cytoplasm and moderately pleomorphic nuclei	GFAP +/-	RT

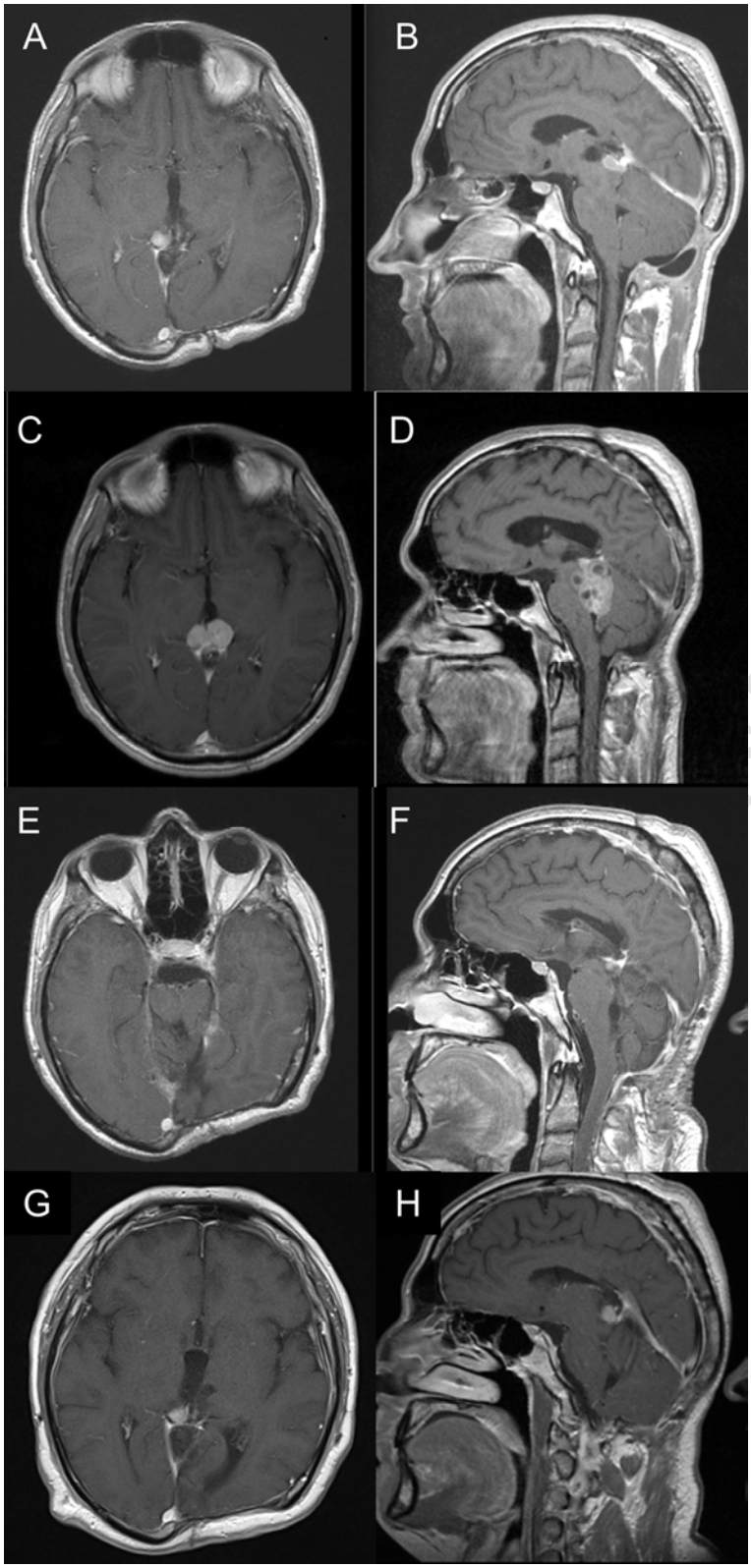
Abbr. list: CK (cytokeratins, broad spectrum), CK18 (cytokeratin 18), GFAP (glial fibrillary acidic protein), EMA (epithelial membrane antigen), S100 (S100 protein), NSE (neuron specific enolase), SYN (synaptophysin), VIM (vimentin), Ki67 (antigen KI-67), + (positive), +/- (focally positive), - (negative)

RT (radiotherapy), WBRT (whole brain radiotherapy), SRS (stereotactic radiosurgery – either gamma knife or LINAC), RChT (radiochemotherapy), ChT (chemotherapy)









Highlights:

- PTPRs are WHO grade II/III tumors, however they may mimic benign tumors, such as pineocytomas
- Adjuvant radiotherapy results in better prognosis in PTPRs
- We present a recurrent pineocytoma-like PTPR (WHO grade II/III)
- Only morphology of recurrent tumor and CK-positivity lead to the correct diagnosis
- We show that a simple, positive staining for cytokeratins is a diagnostic clue for pineocytoma-mimicking PTPRs

Abbreviations list:

WHO – World Health Organization, PPTRPTPR - papillary tumor of the pineal region, CK - cytokeratins, broad spectrum, CK18 - cytokeratin 18, EMA - epithelial membrane antigen, MRI – magnetic resonance imaging, GFAP – glial fibrillary acidic protein, NSE - neuron-specific enolase, CSF - cerebrospinal fluid, S100 - S100 protein, SYN - synaptophysin, VIM -vimentin, Ki67 - antigen Ki-67, RT - radiotherapy, WBRT - whole brain radiotherapy, SRS - stereotactic radiosurgery, RChT - radiochemotherapy, ChT - chemotherapy