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Pineal parenchymal tumor of intermediate differentiation: imaging spectrum of an unusual tumor in 11 cases

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Abstract
Introduction Pineal parenchymal tumor of intermediate differentiation (PPTID) was recognized in the 2007 World Health Organization (WHO) classification as a new pineal parenchymal neoplasm, intermediate in malignancy (WHO grade II or III) between pineocytoma (grade I) and pineoblastoma (grade IV). The imaging spectrum of this new tumor has not been previously delineated. We describe the imaging spectrum in 11 pathologically proven PPTIDs and identify findings that may suggest the preoperative diagnosis of this newly recognized entity.
Methods Electronic medical records over the last 9 years and teaching files between the years 1985 and 1995 were searched for atypical pineal lesions. Additional cases were added from the teaching files of contributing authors.
Results Imaging studies in nine patients (9/11) showed bulky, aggressive pineal region masses with local brain invasion; two patients (2/11) demonstrated circumscribed pineal masses. Two patients had spinal metastases at presentation. On computed tomography (CT), five patients had classic "exploded" calcifications characteristic of pineal parenchymal tumors. All tumors were heterogeneously hypointense on T1WIs and heterogeneously hyperintense on T2WIs. Post-contrast scans showed marked heterogeneous (10/11) or uniform (1/11) enhancement. Cystic foci were identified in eight cases. Intratumoral hemorrhage was present in one case.
Conclusion While no singular neuroimaging feature is pathognomonic of PPTID, these tumors are usually larger, demonstrate local invasion, and appear much more heterogeneous than pineocytoma. Because PPTIDs have a higher grade and increased potential for recurrence as compared to pineocytomas, it is important to consider this diagnosis as shorter follow-up, and adjuvant therapy may be indicated in selected cases.

Keywords Pineal parenchymal tumor · Pineal parenchymal tumor of intermediate differentiation · Pineal tumors

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Introduction

Pineal parenchymal tumors (PPT) are uncommon, accounting for less than 1% of all intracranial neoplasms. Prior to 2007, only two PPTs were recognized: pineocytoma, an

indolent tumor designated grade I, and pineoblastoma, a highly malignant primitive neuroectodermal tumor assigned World Health Organization (WHO) grade IV. It has long been suggested that PPTs are in fact a significantly more heterogeneous group with considerable morphological variation [1–4]. Some PPTs demonstrate transitional histopathology that does not precisely fit into either the pineocytoma or the pineoblastoma category.

The 2007 WHO classification of tumors of the central nervous system designated a new PPT, pineal parenchymal tumor of intermediate differentiation (PPTID) to describe the group of tumors intermediate in malignancy between pineocytoma and pineoblastoma [5]. Although definite grading criteria for PPTIDs have yet to be established, WHO grade II or grade III has been suggested.

Only a few scattered cases of PPTID have been reported in the pathology literature. To our knowledge, this new entity has not been described in the radiology literature. We describe the imaging spectrum of PPTID eleven histologically proven cases and suggest features that may differentiate this newly described entity from pineocytoma and pineoblastoma. Compared to pineocytoma, these tumors have a higher potential for local invasion, recurrence, and dissemination, and it is important to consider this diagnosis for adequate preoperative staging and appropriate treatment planning and follow-up.

Materials and methods

Case material

In this institutional review board-approved study, electronic medical records over the last 9 years and hard copy teaching files from our institution between 1985 and 1995 were reviewed. Radiology database was searched using the key words "pineal tumor," "pineal mass," "pineocytoma," and "pineoblastoma." One hundred and six cases of pineal region tumors were reviewed, and one case of pathologically proven PPTID was identified. During review of teaching files of atypical pineal masses, we identified one additional atypical pineal tumor and suspected a diagnosis of PPTID based on imaging features, clinical behavior, and the original histopathology report. The original tumor blocks were reviewed by a board-certified pathologist with a confirmation of the diagnosis 13 years after the patient's demise. Eight additional cases of PPTIDs were gathered from the case collections of the contributing authors.

Imaging

Seven patients had CT imaging. In three of the patients, only non-enhanced CT (NECT) was performed. In three patients, only contrast-enhanced CT (CECT) was performed. One patient had both NECT and CECT.

MR imaging was obtained using multiple different 1.5 and 3T scanners and standard parameters for each sequence. All patients had magnetic resonance (MR) imaging. Precontrast T1WIs were available in ten patients. T2WIs were available for all cases. FLAIR images were available for 8/11. GRE images were available for 3/11. Diffusion-weighted images were available for 4/11. Contrast-enhanced T1WIs were available for 10/11. Magnetic resonance spectroscopy (MRS) was performed in one patient.

Images were evaluated by two board-certified neuroradiologists and assessed for size, signal characteristics, presence of intra-lesional cysts, calcification, hemorrhage, and local invasion. Enhancement characteristics and presence of CSF dissemination at presentation were also evaluated. As images were submitted without original datasets, maximal tumor diameter was estimated using a calibrated scale.

Results

Case material

Eleven pathologically proven cases of PPTID were evaluated. Patient demographics were available in all cases and detailed clinical history was available in ten patients (Table 1). Patient age at presentation ranged from 4.5 to 75 years (mean, 23 years). Male:female ratio was 7:4. Presenting symptoms included headache (8/11), Parinaud syndrome (3/11), gait disturbances (3/11), other unspecified visual symptoms (2/11), and seizures (1/11).

Imaging (Table 2)

General features: Nine patients showed aggressive pineal region masses with local brain invasion. Two patients had a well-circumscribed mass without signs of regional invasion. Two patients had spinal metastases at presentation. Approximate size of tumor at presentation varied from 1 to 6 cm (mean, 2.5 cm). In two patients (case 1, 6), the preoperative studies were not available and size at presentation was not known.

Computed tomography: Three patients had only NECT, three had only CECT, and one had both. Five patients demonstrated the classic peripheral "exploded" calcifications characteristic of pineal parenchymal tumors. Gross hemorrhage was seen in one patient on NECT. Three (3/4) patients with CECT demonstrated heterogeneous enhancement and one (1/4) demonstrated uniform enhancement.

Table 1 Case summaries

Case no.	Age[a] (years), gender	Size (cm)	Presenting symptoms	Treatment/results	Follow-up period (years)
1	15, F	–[b]	HA, Parinaud syndrome	Ventricular shunting, CTx and XRT. Death following multiple recurrences 21 years after initial presentation. Pathology at autopsy: "pineoblastoma with transitional features and retinoblastomatous differentiation." Pathology reviewed after 13 years with final diagnosis of PPTID	21
2	57, F	2.6	HA, diplopia, seizure	Surgical resection. No recurrence after 6 months	2
3	75, F	6	Parinaud syndrome, gait disturbance, R hand weakness	Initial pathology on biopsy: "aggressive PC." Marked tumor regression following XRT	1
4	36, M	4	HA	Surgical resection. Initial pathology: "aggressive PC"	Lost to follow-up
5	28, M	1	No history	Surgical resection	Lost to follow-up
6	32, M	–[b]	HA, Parinaud syndrome, visual sym, gait disturbance	Ventricular shunting followed by partial surgical resection and XRT. Initial pathology: "mixed pineocytoma–pineoblastoma." Recurrence after 10 years with continued growth to date	14
7	50, F	6	HA, incontinence	Surgical resection	Lost to follow-up
8	10, M	1	HA, fatigue, decline of achievement	Surgical resection. Initial pathology: pineoblastoma. Recurrence after 4.5 years treated with surgical resection	4.5
9	13, M	1.5	HA	Partial surgical resection followed by CTx and XRT with persistent meningeal disease. Currently on RT	1
10	18, M	3	HA	Partial surgical resection followed by XRT. Stable at 6 months follow-up	0.5
11	4.5, M	3.5	Gait disturbance, loss of skills	Partial surgical resection followed by CTx and XRT with tumor reduction in 1 year. No recurrence to date	8

HA headache, *CSF* cerebrospinal fluid, *XRT* radiotherapy, *CTx* chemotherapy

[a]At presentation

[b]Size at presentation not known

Magnetic resonance: On MR, the tumor was heterogeneously hypointense on T1WI and heterogeneously hyperintense on T2WI in all cases, and showed strong heterogeneous (10/11) or uniform (1/11) enhancement following contrast administration. Cystic-appearing foci were identified in eight cases. MRS was performed in one patient and demonstrated elevated choline (Cho), decreased *N*-acetylaspartate (NAA), and a lactate doublet.

Follow-up: Follow-up was available in eight patients (Table 1). Follow-up period ranged from 6 months to 21 years. Including our presumed case, a total of three patients had documented tumor recurrence. The first patient (case 1) originally presented at age 15 years with headache and Parinaud syndrome. A heterogeneous invasive pineal mass was found and initially presumed to be a pineal teratoma. Tumor recurrence with local invasion was later treated with debulking and histopathologic diagnosis of "pineoblastoma." The patient expired 21 years after initial diagnosis following multiple recurrences. The autopsy diagnosis, made prior to the introduction of the 2007 WHO classification, was "pineoblastoma with transitional features and retinoblastomatous differentiation." Based on the history and imaging characteristics, we suspected this case to be a PPTID. The original tumor blocks were reviewed by a board-certified pathologist and confirmed to be a PPTID. The second patient (case 6) underwent partial resection of a pineal tumor 1 year after presentation with an initial histopathological diagnosis of "mixed pineocytoma–pineoblastoma." Pathology was reviewed with a diagnosis of PPTID, and the patient received postoperative radiation. The patient returned 10 years after initial surgery with tumor recurrence and was treated with radiosurgery. Follow-up imaging to date continued to demonstrate evidence of recurrence, and the patient is awaiting surgery at this time. The third patient (case 8) underwent macroscopically complete resection with an initial diagnosis of pineoblastoma. Pathology was reviewed with a diagnosis of PPTID. Relapse, 4.5 years after initial resection, was treated with surgical resection and revealed similar histology. The patient was lost to further follow-up.

Table 2 Imaging appearance

Case No.	CT appearance	MR appearance	Local invasion	Dissemination
1	CECT: heterogeneous CE	T1: heterogeneously low, T2: heterogeneously high, cystic foci, FLAIR: heterogeneously high	+	–
2	–	T1: heterogeneously low, T2: heterogeneously high, cystic foci, FLAIR: heterogeneously high, T1+: heterogeneous CE, MRS: high Cho, NAA, lactate doublet	+	–
3	CECT: heterogeneous CE, exploded Ca++	T1: heterogeneously low, T2: heterogeneously high, cystic foci, FLAIR: heterogeneously high, GRE: foci of susceptibility, T1+: heterogeneous CE DWI: no diffusion restriction	+	Spine intradural drop metastasis, separate mass in fourth ventricle, vermis. CSF negative
4	NECT: hyperattenuating, exploded Ca++	T1: heterogeneously low, T2: heterogeneously high, FLAIR: heterogeneously high, GRE: foci of susceptibility, DWI: no diffusion restriction	+	–
5	NECT: hyperattenuating, CECT: uniform CE	T2: well circumscribed, heterogeneously high, FLAIR: heterogeneously high, T1+: uniform CE		–
6	Not available	T1: heterogeneously low, T2: heterogeneously high, cystic foci, FLAIR: heterogeneously high, GRE: foci of susceptibility, T1+: heterogeneous CE	+	–
7	NECT: hypoattenuating, exploded Ca++	T1: heterogeneously low,T2: heterogeneously high, cystic foci T1+: heterogeneous CE	+	–
8	–	T1: heterogeneously low, T2: heterogeneously high, cystic foci, FLAIR: heterogeneously high, DWI: no diffusion restriction	+	–
9	NECT: hypoattenuating, exploded Ca++	T1: well circumscribed, heterogeneously low, T2: heterogeneously high, cystic foci, FLAIR: heterogeneously high, DWI: no diffusion restriction		Meningeal dissemination, CSF negative
10	CECT, CTA: heterogeneous CE, exploded Ca++	T1: heterogeneously low, T2: heterogeneously high, cystic foci T1+: heterogeneous CE	+	–
11	–	T1: heterogeneously low, T2: heterogeneously high, cystic foci T1+: heterogeneous CE	+	–

CECT contrast-enhanced CT, *NECT* non-enhanced CT, *CE* contrast enhancement, *CSF* cerebrospinal fluid

Discussion

PPTID was introduced as a separate PPT in 2007 to describe a group of tumors intermediate in malignancy between pineocytoma and pineoblastoma [5]. This category was first reported by Schild et al. in 1993 [1], and it is believed that PPTID may account for at least 20% of all pineal parenchymal tumors [5]. These tumors are thought to lie along a spectrum from pineocytoma to pineoblastoma. Although some authors include "mixed pineocytoma–pineoblastoma," "malignant pineocytoma," and "pineoblastoma with lobules" in this category [6], this is not the recommended terminology. The existence of a spectrum from pineocytoma to pineoblastoma has also been supported by a number of shared clinical, morphological, and genetic features [1, 2, 7–10].

Histopathologically, PPTIDs are composed of diffuse sheets or large lobules of uniform cells and characterized by moderately high cellularity, mild to moderate nuclear atypia, and low to moderate mitotic activity [5]. On immunohistochemistry, these tumors are positive for synaptophysin and neuron-specific enolase. There is variable labeling with antibodies to neurofilament protein, chromogranin A, retinal S-antigen, and S-100 protein [5, 9, 11].

Only a limited number of cases have been reported in the pathology literature, and histological grading of these tumors remains controversial. PPTID may correspond to WHO grade II or III and includes both prognostically favorable and unfavorable lesions. Definite grading criteria have not yet been established [5]. It has been suggested that a grading system based on mitotic activity and neurofilament protein immunoreactivity can distinguish low- from high-grade PPTID [9]. Grade II has been proposed for tumors with less than six mitoses and positive immunolabeling for neurofilaments. Grade III has been proposed for tumors with greater than six mitoses without immunostaining for neurofilaments, and these were associated with poorer outcome.

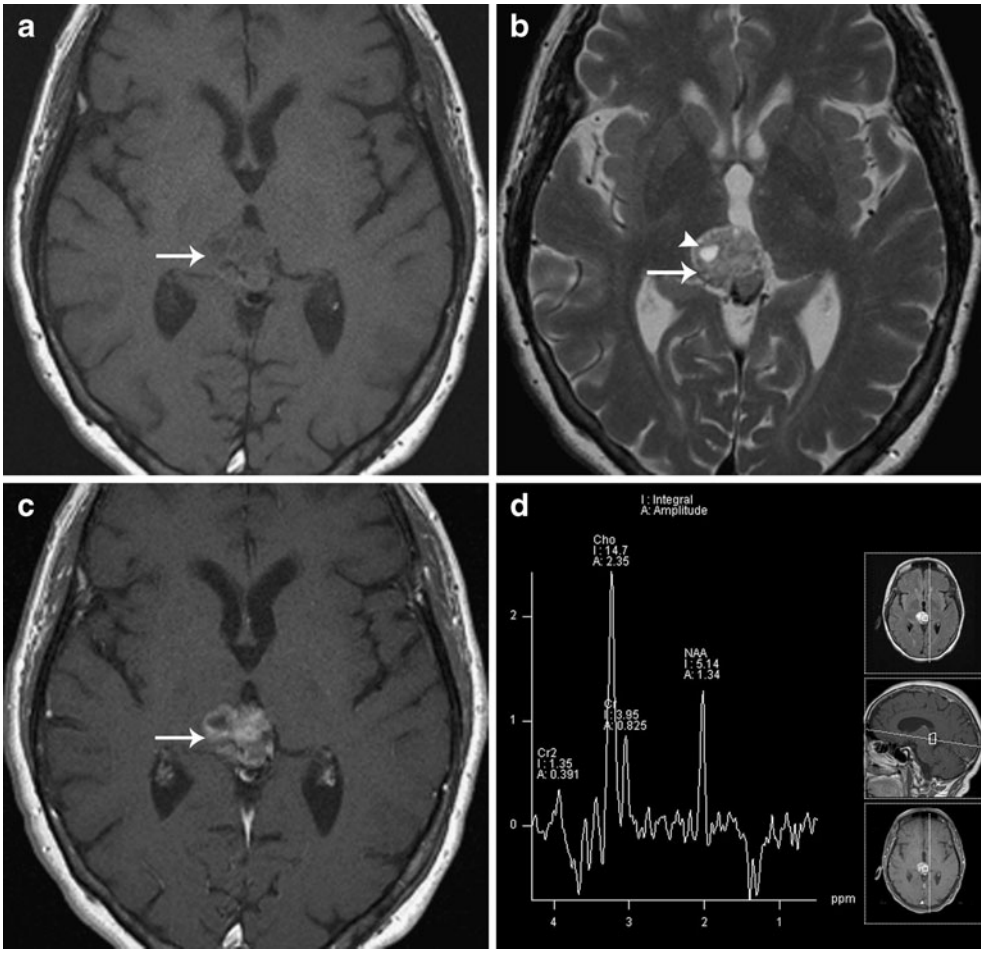

Fig. 1 **a** Axial T1WI in a 57-year-old female patient presenting with HA, diplopia, and seizures (case 2) shows a heterogeneously hypointense pineal mass (*arrow*) with invasion of the right posterior thalamus and tectal plate. **b** Axial T2WI in the same patient shows a heterogeneously hyperintense pineal mass (*arrow*) with T2 hyperintense cystic-appearing focus (*arrow head*). **c** Axial T1 post-contrast MR in the same patient shows heterogeneously enhancing pineal mass with local invasion into the adjacent thalamus (*arrow*). **d** MRS in the same patient shows elevated Cho, decreased NAA, and a lactate doublet at 1.33 ppm

According to one study, grade III tumors have comparatively worse 5-year survival, higher recurrence, more rapid progression time, and higher rate of extrapineal spread. This study also associated tumor size greater than 2.5 cm, along with higher grade, to correlate with an unfavorable outcome [12]. In six of our patients, tumor size was greater than 2.5 cm. Follow-up imaging and clinical stability was available only in three of these patients without evidence of recurrent disease. However, in one of our cases with recurrent disease, tumor size at the time of diagnosis was

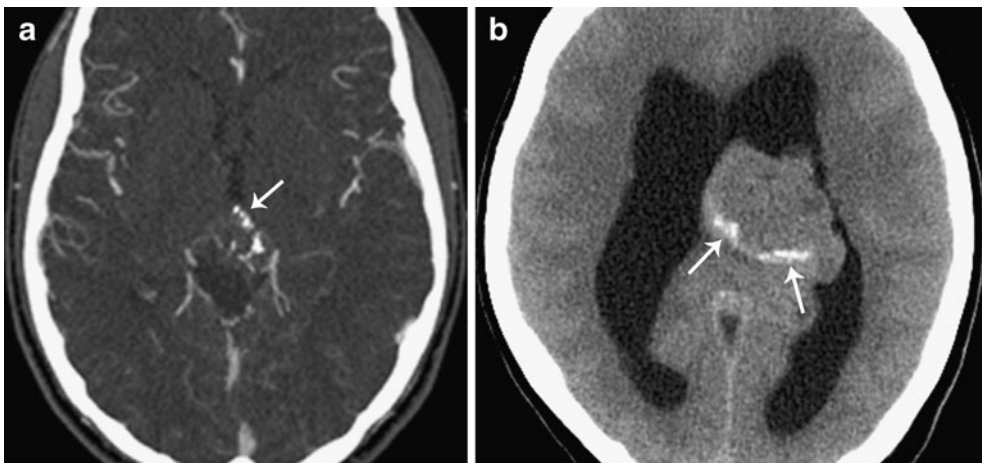

Fig. 2 **a** Axial CTA image in an 18-year-old male presenting with HA (case 10) shows a pineal mass with peripheral "exploded" calcifications (*arrow*). **b** Axial non-contrast CT image of a 50-year-old female patient presenting with HA and incontinence (case 7) shows a heterogeneous pineal mass with peripheral "exploded" calcifications (*arrows*). Note the hydrocephalus related to compression of the cerebral aqueduct

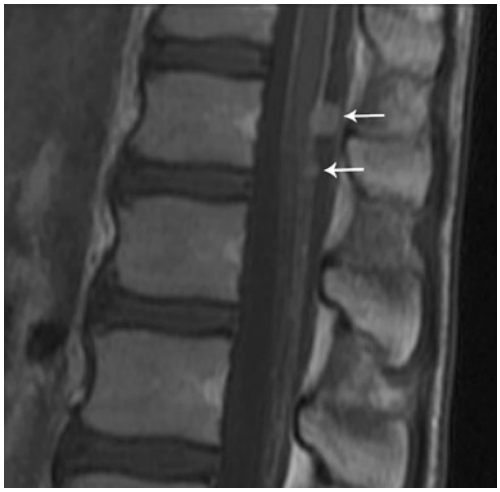

Fig. 3 Sagittal T1 post-contrast MR in a 13-year-old male patient presenting with HA (case 9) shows enhancing spinal leptomeningeal metastases (*arrows*) at initial presentation

1 cm, with recurrence 4 years following initial surgery. Initial tumor size in our second case with recurrent disease and our presumed case of PPTID were not available.

PPTIDs have a broader age spectrum than either pineoblastoma or pineocytoma [1, 2, 9]. Pineocytomas are indolent tumors that are primarily seen in adults but may occur at any age and are typically less than 3 cm. Pineoblastomas are highly malignant, occur primarily in children, and are typically greater than 3 cm. The mean age of presentation in our series was 23 years (median, 28). The youngest patient in our series was 4.5 years and the oldest was 75 years. Tumor size ranged from 1 to 6 cm in maximum diameter (mean, 2.5 cm). Although review of literature suggests a slight female preponderance [5], in our series, the male:female ratio was 7:4.

Imaging features of pineocytoma and pineoblastoma have been described in the radiology literature and are well recognized, but the imaging spectrum of PPTID has not been previously described. All tumors in our series were heterogeneously hypointense on T1 and heterogeneously hyperintense on T2 and FLAIR imaging (Fig. 1a, b). Ten (91%) tumors showed heterogeneous enhancement (Fig. 1c). Eight (73%) tumors displayed cystic foci, suggesting necrosis or cystic degeneration. One (9%) tumor showed uniform enhancement. One (9%) tumor in our series demonstrated intratumoral hemorrhage. MR spectroscopy performed in one of our patients demonstrated elevated Cho and decreased NAA, characteristic of aggressive tumors (Fig. 1d).

Aggressive pineal region tumors often present with obstructive hydrocephalus due to tectal invasion or mass effect on the tectum with compression of the cerebral aqueduct [9]. Invasion of surrounding brain parenchyma at presentation was seen in nine (82%) of our patients. There was imaging evidence of obstructive hydrocephalus on CT and/or MR in six (55%) of our patients.

The principle differential diagnosis of this entity includes germinoma, pineocytoma, pineoblastoma, and the extremely rare papillary tumor of the pineal region [13–17]. Germinomas usually present in young male patients and on CT typically demonstrate "engulfed" calcifications, in comparison to the "exploded" calcifications seen in PPTs (Fig. 2a, b). Pineocytomas are slow growing indolent tumors and only rarely show progression. Pineoblastomas are highly malignant PNETs of the pineal gland with frequent invasion into the adjacent brain and up to 45% CSF dissemination. Hemorrhage and necrosis occur more commonly in pineoblastomas, although calcifications are rare. Both germinoma and pineoblastoma commonly have CSF dissemination and invasion of the adjacent brain. PTPRs are extremely rare and have been described as well-circumscribed masses with frequent cystic regions.

While no singular neuroimaging feature is pathognomonic of PPTID, these tumors are usually larger, demonstrate local invasion, and appear much more heterogeneous

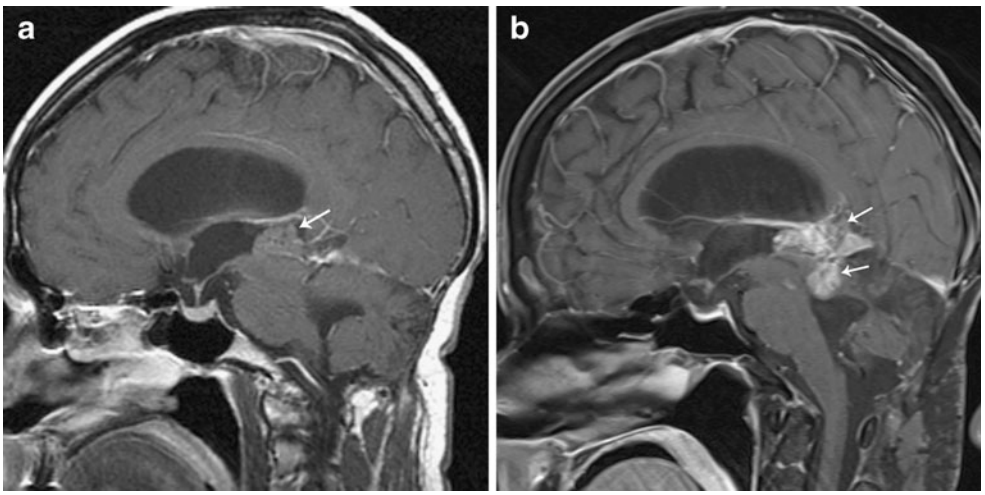

Fig. 4 **a** Sagittal T1 post-contrast MR shows a heterogeneously enhancing pineal mass (*arrows*) with invasion of the tectal plate related to recurrent tumor. This was the first recurrence in this 32-year-old male patient (case 6), 10 years after partial resection and radiation therapy. **b** Sagittal T1 post-contrast FS MR in the same patient, 12 years after surgery, showing continued growth of the recurrent PPTID (*arrows*) with more extensive local invasion

than pineocytoma. Based on these features, we were able to make the preoperative diagnosis of PPTID in our most recent case. In addition, using these features, we also correctly suspected a diagnosis of PPTID in case 1.

Prognostically, PPTIDs appear to have a variable behavior. Due to the rarity of this entity, there is restricted data regarding the biological behavior and recurrence rate [18]. PPTID is occasionally associated with central nervous system or extraneural metastases. Two patients in our series had CSF dissemination at presentation (Fig. 3). Of note, both had negative CSF cytology. Two of our patients had recurrent disease (Fig. 4). In both cases, recurrence was local. One series found the first relapse to be local in 22% and spinal leptomeningeal in 4% [12]. Given the potential for CSF seeding, pre-operative imaging of the entire neuraxis should be considered for initial staging. In one study, the recurrence rate of PPTID was reported to be 26–56% with extra-pineal spread 4.3–33% [12]. There is also a single case report of a PPTID with transformation into pineoblastoma at relapse [4].

Tumor behavior is thought to be related to spectrum of differentiation, and the prognosis of PPTID is not as favorable as pineocytoma [18]. PPTIDs are usually slowly progressive and compatible with long-term survival even with subtotal resection. Postoperative adjuvant therapy using radio- and chemotherapy has been suggested for these tumors, as most pineal tumors cannot be totally resected safely [18–20].

Conclusion

Radiologists should consider the diagnosis of PPTID in an older child or adult with an atypical or aggressive-appearing, locally invasive pineal region mass. The clinical course of PPTIDs can be relatively benign despite histological pleomorphism. Although survival even with subtotal resection is common, these tumors have a higher grade and increased potential for local recurrence. Given the potential for leptomeningeal seeding, preoperative imaging of the entire neuraxis at the time of diagnosis may be warranted. The histopathology of tumors initially diagnosed as “pineocytoma versus pineoblastoma” and “aggressive pineocytoma” prior to 2007 should be reviewed as these may be PPTIDs. Treatment of this tumor entity has not been established and shorter follow-up and adjuvant therapy may be indicated in selected cases.

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Conflict of Interest We declare that we have no conflict of interest.

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