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CASE REPORT

Pineal parenchymal tumor of intermediate differentiation with papillary features: a continuum of primary pineal tumors?

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Abstract Pineal parenchymal tumors comprise a rare group of primary neoplasms of the pineal gland. We describe a case involving a 29-year-old woman who presented with signs and symptoms of hydrocephalus secondary to a pineal region tumor obstructing the third ventricle. Surgical resection was performed and pathological analysis revealed a novel diagnosis consistent with a pineal parenchymal tumor of intermediate differentiation (PPTID) with transition to a papillary tumor of the pineal region (PTPR). To our knowledge, this particular pineal region tumor pathology has not yet been reported in the literature and highlights the continuum with which primary pineal tumors exist. We provide a review of the existing literature on pineal region tumors, specifically PTPR and PPTID, and offer insight into the management of these rare neoplasms.

Keywords Pineal parenchymal tumor · Obstructive hydrocephalus · Papillary tumor of the pineal region · Pineal parenchymal tumor of intermediate differentiation

Abbreviations

PPTID	Pineal parenchymal tumor of intermediate differentiation
PTPR	Papillary tumor of the pineal region
PPT	Pineal parenchymal tumor
CNS	Central nervous system
WHO	World Health Organization
PC	Pineocytoma
PB	Pineoblastoma
MRI	Magnetic resonance imaging
ETV	Endoscopic third ventriculostomy
PLAP	Placental alkaline phosphatase
CK	Cytokeratin
AFP	Alpha fetoprotein
GFAP	Glial fibrillary acidic protein
NF	Neurofilament
HCG	Human chorionic gonadotropin
EMA	Epithelial membrane antigen
NSE	Neuron specific enolase

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Introduction

The differential for tumors of the pineal region is quite broad and can include nearly any type of intracranial tumor. Among them, pineal parenchymal tumors (PPTs) are a rare occurrence in the central nervous system (CNS), accounting for less than 0.3% of all CNS tumors [1] and approximately 30% of all neoplasms of the pineal region [2]. PPTs arise from pineocytes or their precursors and are therefore distinctly different from other pineal region tumors. The World Health Organization (WHO) has long recognized three major categories of PPTs, which occur along a spectrum

based on aggressive behavior and potential. From benign to malignant, these include pineocytoma (PC), pineal parenchymal tumor of intermediate differentiation (PPTID), and pineoblastoma (PB) [3].

While papillary features have been reported in other tumors of the pineal region, including choroid plexus tumors, ependymoma, meningioma, astroblastoma, germ cell tumors, and metastatic carcinoma [4], papillary structures are an exceedingly rare feature of PPTs. In the present case, we report the first case of PPTID with focal transition to a papillary tumor of the pineal region (PTPR). In addition, we review the existing literature on primary pineal region tumors focusing on PPTID and PTPR in an effort to provide insight into the clinical management of these rare tumors.

Case report

A 29-year-old, otherwise healthy female presented with 2 weeks of bi-frontal, throbbing headaches associated with nausea and vomiting. Physical and neurological examinations were unremarkable. Magnetic resonance imaging (MRI) revealed a 1.5 cm × 1.5 cm × 1.7 cm homogeneously enhancing mass in the pineal region causing obstructive hydrocephalus with associated periventricular interstitial edema that was isointense on T1 imaging and hyperintense on T2 imaging. Based on the location and imaging characteristics, as well as the age of the patient, the differential diagnosis included pineal parenchymal tumor, exophytic tectal glioma and ependymoma. Germ cell tumor was also considered, but excluded based on negative serum markers. The patient was offered neurosurgical intervention (i.e. endoscopic third ventriculostomy (ETV) and biopsy), but declined.

Eight months later, she again presented with recurrent, increasingly severe morning headaches, located in the frontal and occipital regions with associated nausea. The patient also reported worrisome cognitive and memory disturbances, specifically with name-retrieving difficulty. Neurological examination remained non-focal and repeat MRI showed worsening obstructive hydrocephalus and increased size of the pineal region mass (1.6 cm × 1.7 cm × 1.7 cm) (Fig. 1a). Given the patient's worsening symptoms and the increase in the size of the mass, the patient was now amenable to surgery and underwent an uncomplicated ETV and pineal tumor biopsy.

The biopsy specimen was noted to contain pleomorphic cells that stained strongly for synaptophysin (Fig. 2a) with negative staining for placental alkaline phosphatase (PLAP), cytokeratin (CK), alpha fetoprotein (AFP), glial fibrillary acidic protein (GFAP), neurofilament (NF), c-kit, human chorionic gonadotropin (HCG), and chromogranin A. Proliferation index was <3% using Ki67 staining. The diagnosis was consistent with a low to intermediate grade pineal parenchymal neoplasm.

Additional surgery with a goal of gross total resection was recommended, but the patient initially declined only to return 6 months later with more consistent headaches. Repeat MRI demonstrated further growth of the mass to 2.1 cm in maximal diameter (Fig. 1b). At that point, the patient agreed to surgery and underwent gross total resection via an endoscopic-assisted supracerebellar infratentorial approach. Grossly, the tumor was noted to be soft, tan, and was located in the deep pineal gland extending to the posterior third ventricle. It was removed in its entirety using microdissection.

Microscopic evaluation of the gross total specimen revealed a cellular neoplasm with round to oval hyperchromatic nuclei and abundant eosinophilic cytoplasm that formed focal papillary structures (Fig. 2b). There were no areas of increased mitotic activity or necrosis. The tissue was again found to be strongly positive for staining with synaptophysin and exhibited focal positivity for cytokeratin AE1/AE3 (Fig. 2c). The cells were negative for staining with epithelial membrane antigen (EMA) and glial fibrillary acidic protein (GFAP). The mitotic index was 5% with Ki67 labeling. Taken together, these findings were consistent with a PPTID. However, the presence of focal papillary structures and cytokeratin expression suggested transition to a PTPR.

Postoperative MRI confirmed gross total resection (Fig. 1c, d). The patient experienced a post-operative Parinaud syndrome associated with bilateral vertical diplopia that resolved with monocular patching and a slow steroid taper. MRI spine was negative for drop metastases. Given the rarity of pineal parenchymal tumors, a consensus was difficult to reach regarding optimal treatment, specifically whether adjunct therapy should be initiated. Further, this particular case is complicated by its unique histology, rendering its behavior even more difficult to predict. The patient declined aggressive postoperative management with adjunct radiation and chemotherapy and instead opted for serial MRI exams with close clinical follow up to monitor for recurrence. At the time of submission, she is 10 months postoperative without clinical or radiologic evidence of disease recurrence.

Discussion

All subtypes included, pineal region tumors are uncommon, accounting for less than 1% of all intracranial neoplasms [5]. Although a rare location for a CNS neoplasm, the tumor types found in the pineal region are diverse, including those arising primarily from the pineal body

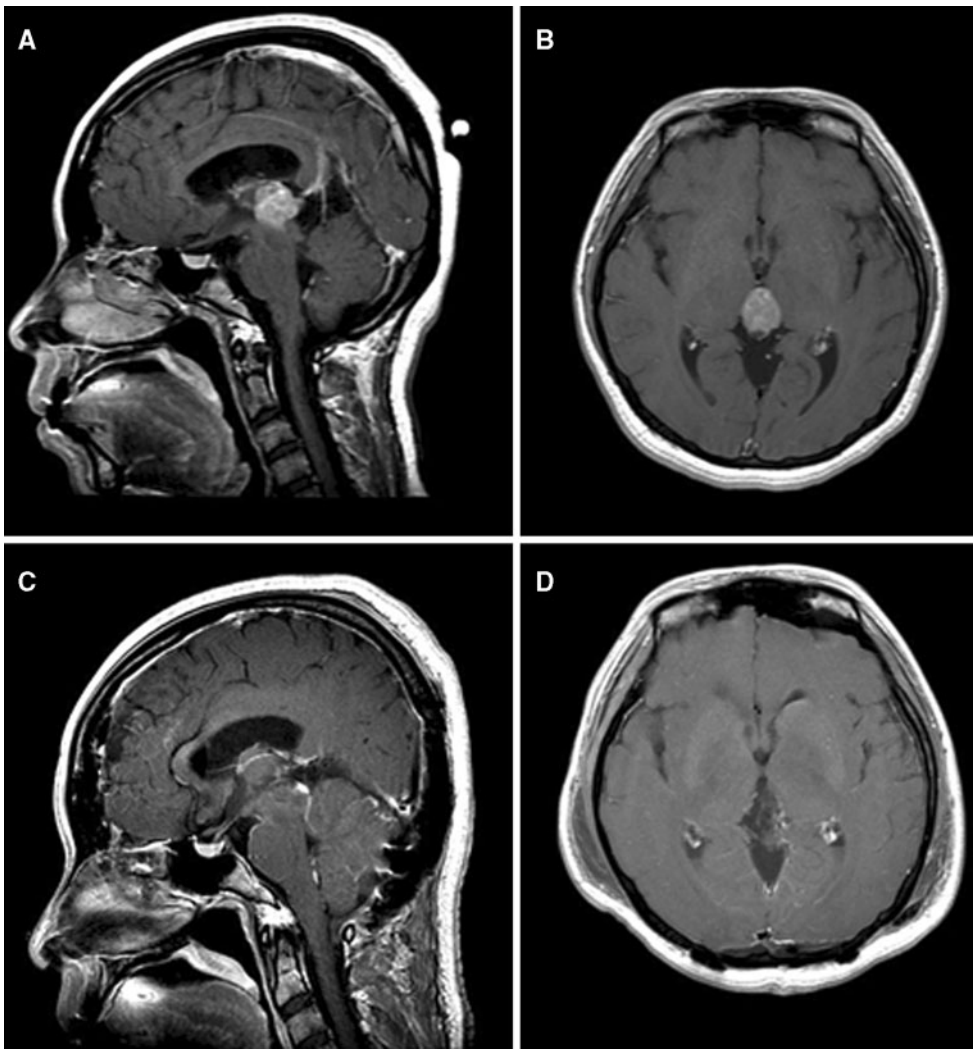

Fig. 1 Magnetic resonance imaging. **a** and **b** Pre-operative saggital and axial images reveal an enhancing mass arising within the region of the pineal body, causing obstruction of the third ventricle. **c** and **d** Post-operative axial and sagittal images demonstrate gross total resection of the pineal mass

(PPTs), as well as germ cell tumors, astrocytoma, ependymoma, meningioma, and metastatic lesions [4]. PPTs are exceptionally rare, comprising 10–30% of all masses of the pineal region [2], with an annual diagnosis limited to approximately 10–50 patients per year in the US [1].

As mentioned, the current WHO classification of pineal region tumors has included three entities: pineocytoma (PC), pineal parenchymal tumor of intermediate differentiation (PPTID), and pineoblastoma (PB) [3]. These tumors are believed to exist along a continuum, as approximately 10% of PPTs are classified as mixed pineocytoma-pineoblastoma [6]. Further evidence includes a recent report of a conservatively managed PC (no surgical resection) that demonstrated transformation to PB [7]. In 2003, papillary tumor of the pineal region (PTPR) was introduced as a distinct pineal tumor thought to arise from the specialized ependyma in the lining of the posterior commissure of the subcommissural organ [8] and subsequently added to the WHO Classification of Tumors of the Central Nervous System in 2007 [3]. Both PPTID and PTPR have a WHO grade of II/III indicating their moderate growth rate and potential for malignant behavior. Although it is difficult to speculate on the origin of this novel tumor, cells from both PPTID and PTPR have neurosecretory features, suggesting the possibility of a common precursor. However, PTPR exhibit epithelial differentiation that PPTID lack. Further study is required to make a more accurate assessment of how this novel tumor evolved.

Papillary architecture is found in a limited subset of pineal region tumors. The most common papillary tumors found in the CNS are papillary ependymoma, choroid plexus tumor, and metastatic papillary carcinoma [4], although rarely they are found to be pineal parenchymal tumors, such as PTPR or PC [6, 9]. To our knowledge, there exists only one previously reported case of PPTID with papillary features [10].

In order to prognosticate and optimize treatment appropriately, an accurate diagnosis of a pineal tumor is of the utmost importance as treatment approaches vary greatly amongst the vast differential of tumors. Though these

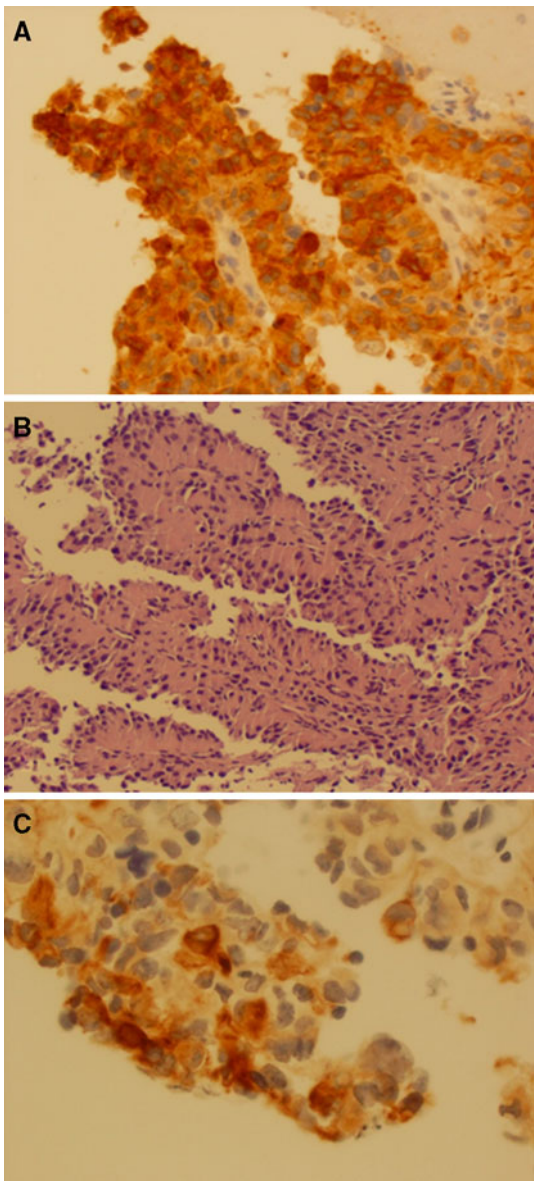

Fig. 2 Pathology. **a** Immunohistochemistry. Using antibodies against synaptophysin, strong cytoplasmic positive staining is evident in the majority of the neoplastic cells. Such a pattern of synaptophysin staining in a pineal region neoplasm, coupled with the lack of GFAP staining and only focal cytokeratin staining is most consistent with a pineal parenchymal tumor rather than ependymal, choroidal, or a papillary tumor of the pineal region. **b** Histology, H&E. Neoplastic proliferation of bland, monotonous population of cells, with round hyperchromatic nuclei and rare mitotic activity in a papillary configuration. **c** Immunohistochemistry. Immunohistochemical staining for pan cytokeratin (AE1/AE3) shows focal reactivity of our papillary tumor for this epithelial intermediate filament marker. This staining, in conjunction with diffusely positive synaptophysin reactivity, illustrates the combined qualities of both PPTID and PTPR differentiation

tumors are rare, our knowledge has evolved over time such that accurate diagnosis can be made using patterns of immunohistochemistry and microscopic features. In one study evaluating 31 PTPR specimens, positive immunohistochemistry results were obtained for neuron specific enolase (NSE): 100%, CK: 100%, S-100: 92%, chromogranin A: 22%, EMA: 20%, synaptophysin: 12%, and GFAP: 12% [11]. Although PTPR occasionally exhibit focal, weak synaptophysin positivity, synaptophysin is considered a good marker to differentiate PTPR from PPT because the staining in PPT is consistently diffuse and strong [12]. The tumor in the present case therefore has a staining pattern consistent with PPTID reported in the literature. However, PPTID are not known to express cytokeratins or contain papillary structures and thus the presence of papillary differentiation and focal positivity for cytokeratin AE1/AE3 was consistent with transition to PTPR.

Because there is variability in the histopathologic characteristics of these tumors, other diagnostic strategies are being actively pursued. For example, it has been shown that PTPR exhibit extreme genetic instability. Although limited by a small sample size, one study thus far has demonstrated numerous chromosomal aberrations in PTPR specimens, particularly losses on chromosome 10 and gains on chromosome 4 [13]. These findings suggest a possible adjunct role for advanced genetic techniques in the diagnosis of pineal tumors.

The rarity of PTPR and PPTID has precluded accurate characterization of their behavior. PTPR and PPTID exist along a histological spectrum, and are classified as WHO grade II or III depending on the microscopic characteristics. Several retrospective reviews have characterized these tumors as having an intermediate prognosis with survival ranging from 39–80% in several series (Table 1). For PPTID in particular, survival has been associated with immunohistochemical and histological features. Better outcomes were observed in those patients with grade II tumors, as well as tumors with less than 6 mitoses, absence of necrosis, and positive immunostaining for NF [14]. The tumor in the present case exhibited 5 mitoses/HPF and no necrosis, but NF was not expressed, indicating that it may have an intermediate, but overall good prognosis. Little is known about prognostic histological characteristics of PTPR at the present time. However, in the future, immunohistochemical analysis, specifically for Bcl-2 expression, may aid in determining prognosis for PTPR [15].

PPTID with transition to PTPR has not yet been described in the literature to date. It is therefore difficult to predict the response of this tumor to the various modalities of treatment used for PTPR and PPTID. Moreover, PPTID and PTPR occur with such infrequency that optimal treatment has not yet been established and a standard of care is thus lacking. Published accounts have characterized PTPR as an infrequently disseminating tumor with high rates of local recurrence [16]. Although controversial, current

Table 1 Reported 5-year survival for pineal region tumors

	Tumor type	Number of subjects	5-year survival
1. Fevre-Montange et al. [11]	PTPR	31	73%
2. Konolov et al. [2]	Malignant PPT	50	44%
3. Fauchon et al. [19]	PPTID, mixed PC-PB	28	Grade I 74%
			Grade II 39%
4. Lutterbach et al. [20]	PPTID	37	80%

PTPR papillary tumor of the pineal region, *PPT* pineal parenchymal tumor, *PPTID* pineal parenchymal tumor of intermediate differentiation, *Mixed PC-PB* mixed pineocytoma-pineoblastoma

practice in the majority of PTPR reported in the literature include aggressive local therapy with maximal surgical resection and adjuvant radiotherapy. The largest published series to date [11], which consists of a retrospective review of 31 patients, showed no significant survival benefit in patients undergoing gross total resection and/or radiation therapy. However, another small study did show increased survival in patients receiving adjuvant radiation [17].

PPTIDs have historically been treated similarly to PBs with varying combinations of surgery, radiotherapy, and chemotherapy, but again there remains a lack of consensus on the combination of treatments. This is due in part to the rarity of these tumors and the variation in malignant potential exhibited within the group. Although generally viewed as first line treatment for PPT, surgical therapy has yielded controversial results [18]. The authors of one series found that the extent of resection was not significantly associated with survival, although the authors acknowledge the study may have been underpowered [19]. However, two other reports demonstrated significant benefit afforded by complete resection [2, 20]. Although conflicting, this data suggests that patients with PPT who underwent successful gross total resection can be managed conservatively based on the individual clinical picture, whereas adequate treatment for patients with subtotal tumor resection should likely include adjunct therapy with radiation and/or chemotherapy. There is a paucity of literature on the efficacy of chemotherapy in the treatment of these tumors, although this approach may be attractive as a means to decrease the radiation burden on this relatively young patient group [1, 19, 21].

The overall prognosis for patients with PPTID and PTPR is extremely difficult to quantify considering the paucity of long term follow up and the variation in treatment between patients. In light of the conflicting reports on treatment for PPTID and PTPR, a treatment plan for this unique tumor including surgical resection followed by adjuvant radiation and chemotherapy seems reasonable. However, it is the authors' opinion that if these aggressive treatments are unacceptable to patients who have undergone total resection, conservative management with serial MRI exams of the craniospinal axis, as in the present case, is an acceptable alternative.

One important aspect to note in this report is that the original biopsy specimen did not provide an accurate diagnosis. Indeed, it has been found that 11% of pineal region tumor biopsies result in inaccurate diagnoses [2]. This highlights the difficulty of obtaining and analyzing sufficient specimen in order to make an accurate diagnosis and serves as a reminder to clinicians to consider possibility of sampling error when recommending treatment options for patients with brain tumors. In the present case, biopsy diagnosis would have provided a stronger argument for immediate neurosurgical intervention, although it is unclear if this would have changed the outcome given this patient's repeated deferment of treatment.

Conclusion

Due to the paucity of PPTIDs and PTPRs reported in the literature, the histological and biological features of these tumors are still being defined. Additionally, the pathological variability of PPTs and their rarity in adults makes it difficult to predict their clinical course and prognosis. However, with time and the diligent dissemination of information, the optimal diagnostic and therapeutic strategies for pineal region tumors will be revealed. The present case is that of an extremely rare tumor consisting of PPTID with focal papillary differentiation consistent with transition to PTPR. It not only serves as an addition to the existing literature, but also highlights the continuum along which PPTs exist.

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