


Recurrent pineal parenchymal tumor of intermediate differentiation with intratumoral hemorrhage: A case report and review of the literature

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Yu-Li Chen¹, Li-Hsin Tai^{2,3}  and Ann-Shung Lieu^{1,2,4} 

Abstract

Pineal apoplexy is a rare clinical condition. Its common symptoms include headaches, nausea, vomiting, ataxia, and gaze paralysis. These symptoms are mainly caused by obstructive hydrocephalus or direct compression of the cerebellum or midbrain. There have been no previous reports on the development of a recurrent pineal parenchymal tumor of intermediate differentiation (PPTID) with intratumoral hemorrhage. We report a case of PPTID with intratumoral hemorrhage. A 44-year-old woman developed recurrent PPTID following tumor removal and ventriculoperitoneal shunting in 2010. She visited the emergency department in April 2021 for sudden-onset dizziness and generalized weakness. Blurring of vision occurred and progressed over the previous month. Neurological examination revealed upward conjugate gaze paralysis. Brain computed tomography revealed a hyperdense lesion in the pineal region, and a recurrent tumor with hemorrhage was suspected. Magnetic resonance imaging of the brain confirmed a pineal tumor with intratumoral hemorrhage. The pineal tumor and hematoma were surgically removed via the suboccipital transtentorial approach. The patient was discharged from the hospital 2 weeks after the surgery. The pathological findings were consistent with the diagnosis of recurrent PPTID. PPTID is a rare tumor, accounting for less than 0.1% of primary central nervous system tumors. Pineal apoplexy is rare, and its incidence and clinical significance remain unclear. There have only been nine reported cases of pineal apoplexy, associated with pineal parenchymal tumors. The recurrence of PPTID with apoplectic hemorrhage after 10 years has not been reported. Despite its rarity, PPTID with apoplexy should be considered in patients with PPTID who develop sudden-onset neurological symptoms.

Keywords

Pineal parenchymal tumor of intermediate differentiation, pineal apoplexy, tumor recurrence, neuro-oncology

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Introduction

Pineal parenchymal tumor of intermediate differentiation (PPTID) is a pathological classification of pineal tumors.¹ It was first classified by the World Health Organization (WHO) in 2007, and it accounts for less than 0.1% of primary central nervous system tumors.¹ PPTID affects patients of all age groups. Its incidence peaks twice: during adulthood and senescence. On brain computed tomography (CT), PPTID are lobulated, vascular pineal

¹Division of Neurosurgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
²College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
³Chang Gung Memorial Hospital Kaohsiung Branch, Kaohsiung, Taiwan
⁴Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Corresponding author:

Ann-Shung Lieu, College of Medicine, Kaohsiung Medical University, No. 100, Tzyou 1st Road, Sanmin District, Kaohsiung 80708, Taiwan.
Email: e791125@gmail.com



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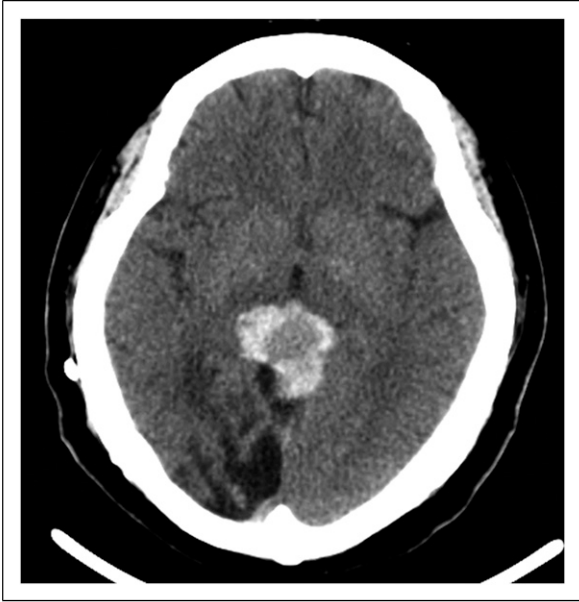


Figure 1. A hyperdense lesion in the pineal region on non-enhanced CT examination.

region masses that can extend into adjacent structures such as the ventricles or thalami.² The magnetic resonance imaging (MRI) features of PPTID typically show a well-defined mass with heterogeneous enhancement and areas of necrosis. On T1-weighted images, the tumor usually appears hypointense, while on T2-weighted images, it appears hyperintense. PPTID can also cause hydrocephalus, which may be visible on an MRI.³ Pineal hemorrhagic apoplexy is a rare clinical manifestation. Moreover, there have only been nine reported cases of apoplectic pineal tumors, including the present case.⁴ Its common symptoms include headaches, nausea, vomiting, ataxia, syncope, and gaze paralysis. These symptoms are mainly caused by obstructive hydrocephalus or direct compression of the adjacent structures.³ There is currently no established standard treatment for PPTID, but achieving gross total resection is the most important factor for optimal outcomes. After surgery, radiotherapy is commonly used to eliminate any possible remaining tumor cells. The role of chemotherapy in PPTID treatment is still being studied, and its effectiveness is

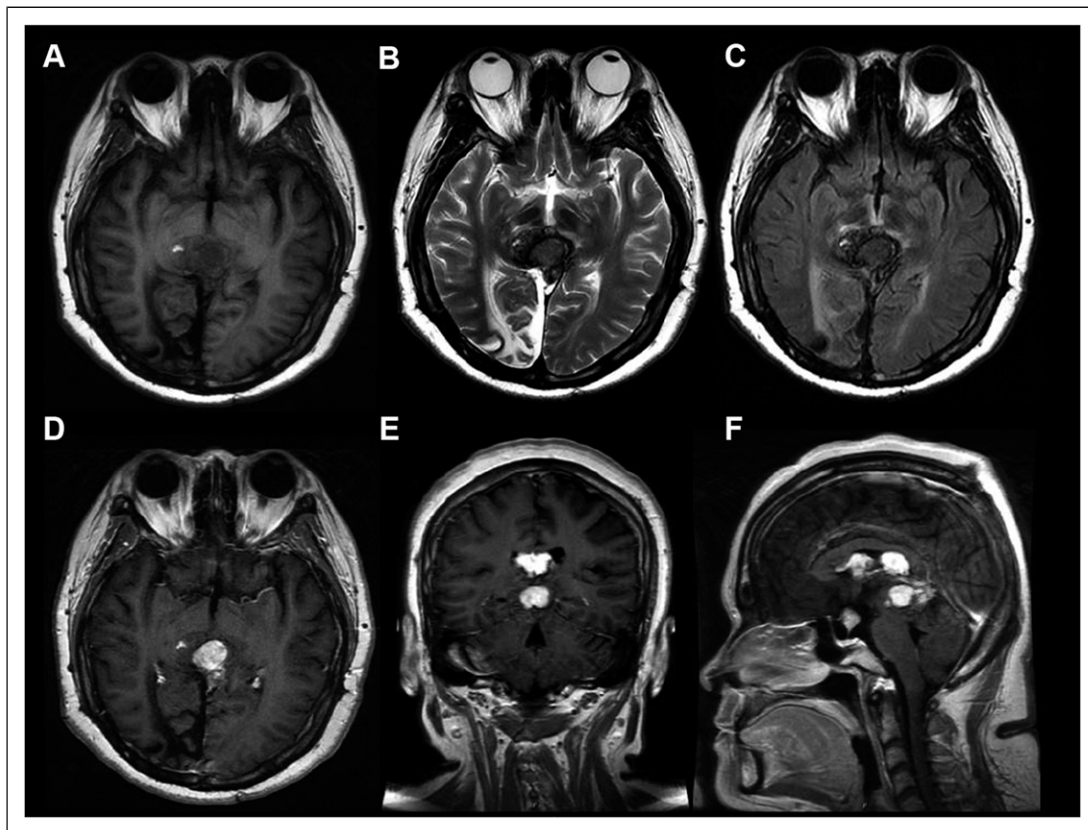


Figure 2. (A) T1-weighted axial magnetic resonance image shows a hypointense lesion in the pineal region. (B) T2-weighted axial view shows an isointense lesion with perifocal edema in the pineal region. (C) T2 fluidattenuated inversion recovery (FLAIR) axial view shows an isointense lesion with perifocal edema in the pineal region. (D) T1 axial view with contrast shows an enhanced lesion in the pineal region. (E) T1 coronal view with contrast shows an enhanced lesion in the pineal region and ventricles. (F) T1 sagittal view with contrast shows an enhanced lesion in the pineal region and ventricles.

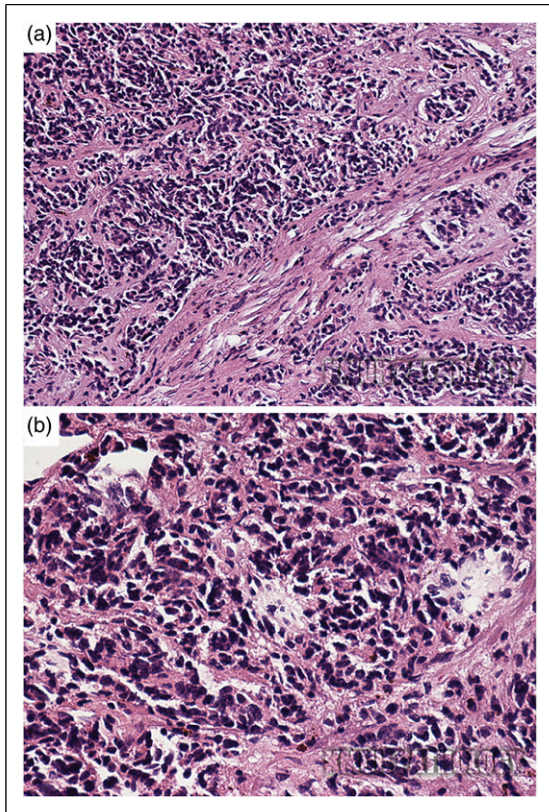


Figure 3. Histological analysis reveals that the moderate tumor cells are composed of small round cells, most of which have uniform nuclei, fine chromatin, and small nucleoli. Low to moderate levels of mitotic activity and nuclear atypia are observed.

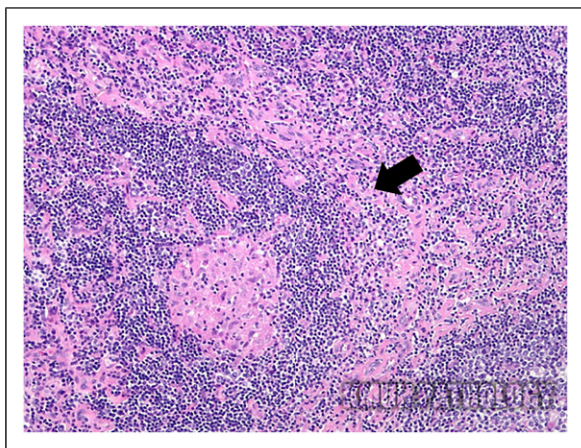


Figure 4. Small irregular flower-like pineocytomatous rosettes are focally observed.

uncertain.⁵ The clinical prognosis is reportedly related to the histopathological grade. Recurrent PPTID with intratumoral hemorrhage has not been reported. This study reports the first case of recurrent PPTID with hemorrhagic apoplexy.

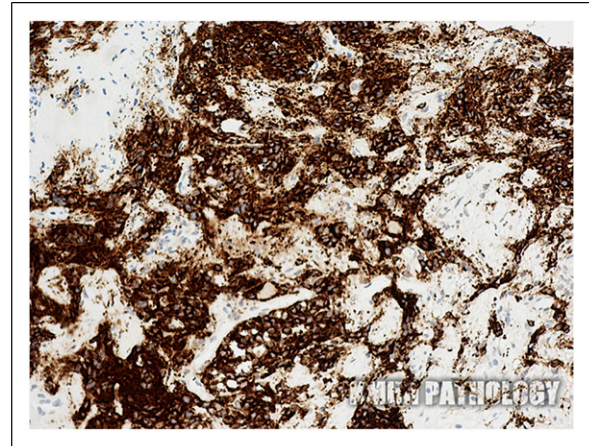


Figure 5. The darker staining in immunohistochemistry is positive for synaptophysin.

Case report

A 44-year-old woman without hypertension, antiplatelet use, or anticoagulant use developed recurrent PPTID 10 years after she received tumor removal and ventriculoperitoneal shunting. In 2010, after she received total pineal tumor resection, it was recommended that she undergo postoperative radiotherapy; however, she missed the follow-up due to personal reasons. She visited our hospital's emergency department in April 2021, presenting with sudden-onset dizziness and generalized weakness. The blurring of vision had progressed since 1 month before the visit. Neurological examination revealed upward conjugate gaze paralysis. The non-enhanced brain CT revealed a hyperdense lesion in the pineal region and lateral ventricles (Figure 1). A recurrent tumor with hemorrhage was suspected. After admission, a brain MRI confirmed a pineal tumor with hemorrhage (Figure 2). Later, the patient underwent subtotal tumor removal and hematoma removal via the suboccipital transtentorial approach. The patient was discharged 2 weeks postoperatively. The neurological examination when she was discharged showed still-existing upward conjugate gaze paralysis.

On gross inspection, the tumor was gray and had a soft texture. Histological analysis revealed moderate tumor cells composed of small round cells, most of which had uniform nuclei, fine chromatin, and small nucleoli. Low to moderate mitotic activity and nuclear atypia were observed (Figure 3). Some small, irregular, and flower-like pineocytomatous rosettes were focally observed (Figure 4). Immunohistochemical analysis revealed that the tumor was positive for synaptophysin (Figure 5), neurofilament protein (Figure 6), and neuron-specific enolase. Meanwhile, it was negative for Sallike protein 4, cytokeratin AE1/AE3, and leukocyte common antigen. The Ki-67 proliferation index was 12% (Figure 7). The tumor was diagnosed as a grade II PPTID according to WHO standards.

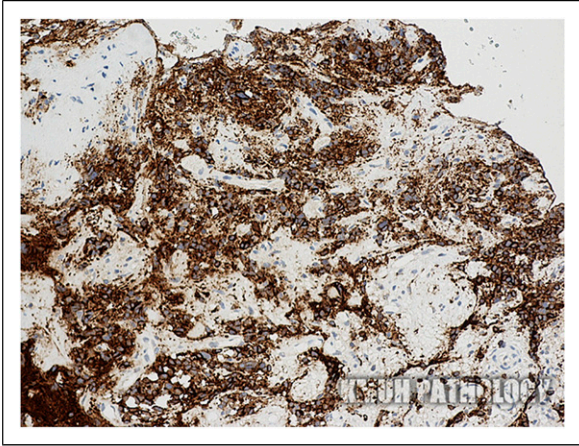


Figure 6. The darker staining in immunohistochemistry is positive for neurofilament protein.

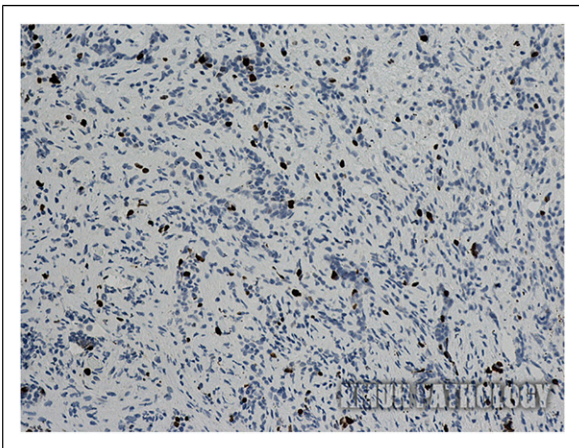


Figure 7. The Ki-67 proliferation index is 12% (observed as darker staining in this figure).

Two weeks after the subtotal tumor removal surgery, a non-enhanced brain CT scan showed a residual tumor in the pineal region and lateral ventricles (Figure 8). Although the preoperative brain MRI showed an occupied tumor in the ventricles, the spinal MRI did not provide any evidence of cerebrospinal fluid seeding. Therefore, we treated the residual PPTID with radiotherapy. Stereotactic radiotherapy (30 Gy in 10 fractions) was administered. The patient remained asymptomatic until the 1-year and 11-month follow-up visit (Figure 9).

This case report was approved by the institutional review board of our hospital. A signed patient permission form was obtained from the patient.

Discussion

Pineal parenchymal tumors originate from the melatonin-producing cells of the pineal gland and account for approximately 30% of pineal region tumors.⁶ These tumors

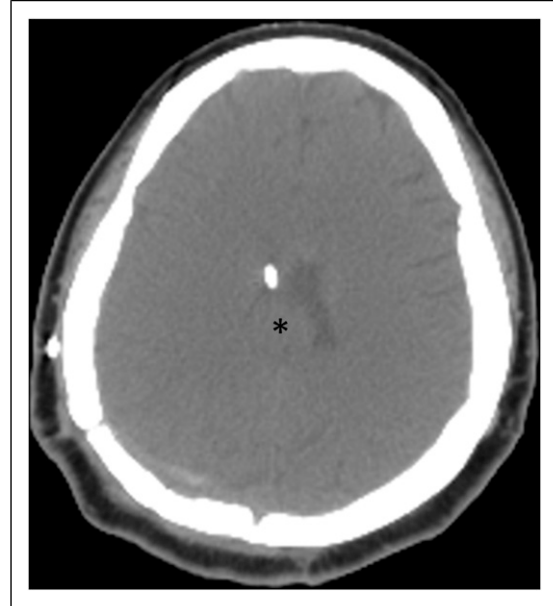


Figure 8. The postoperative non-enhanced CT 2 weeks after the subtotal tumor resection shows an isodense lesion (asterisk) in the pineal region. The size of the tumor was about 2.3 cm.



Figure 9. The follow-up non-enhanced brain CT 1-year and 5-month after the subtotal tumor resection shows an isodense lesion (asterisk) in the pineal region. The size of the tumor was about 1.8 cm.

vary in histopathological features, with pineocytomas being the most benign and pineoblastomas being the most malignant. PPTID falls between these two ends of the spectrum.⁵ PPTID was first defined by the WHO in 2007.¹ According to the mitotic activity and neurofilament

Table 1. Cases of pineal tumor with apoplexy.

Author, year	Age (years), sex	Risk factors	Symptoms and signs	Physical examination	Clinical finding	Pathology	Treatment	Outcome
Steinbok et al., 1977	13 y, M	N/A	HA, Parinaud's syndrome	Neck stiffness, papilledema	HCP, SAH	Pineocytoma	Shunt, radiotherapy	Progression free survival for 4 years; died 7 years after onset
Steinbok et al., 1977	33 y, F	N/A	HA, Parinaud's syndrome, photophobia	Papilledema, positive Kernig's sign	HCP, SAH	Pineocytoma	Shunt, radiotherapy	Died 4 years after onset
Burres and Hamilton, 1979	54 y, M	Anticoagulant use, hypertension	HA, diplopia, Parinaud's syndrome	Papilledema, pinpoint pupils without light reflex, positive Babinski sign	HCP	Pineocytoma with gangliogliomatous differentiation	Shunt, radiotherapy, subtotal resection	Died 1 year after onset
Fujii et al., 1981	11 y, M	N/A	HA, Parinaud's syndrome	Papilledema, sluggish light reflex, neck stiffness	Acute HCP	Choriocarcinoma	Shunt, radiotherapy	Died 1 month after onset
Harada et al., 1993	58 y, F	N/A	Syncope, Parinaud's syndrome, HA	Papilledema	HCP	Pineocytoma with astrocytoma differentiation	Shunt, total resection	Transient Parinaud's syndrome, progression free survival for 3 months
Matsumoto et al., 1997	58 y, M	Shunt placement	HA, gait ataxia, Parinaud's syndrome	Papilledema	Acute HCP	Pineocytoma	Shunt, total resection, radiotherapy	Progression free survival for 3 months
Wang et al., 2013	31 y, F	N/A	HA, photophobia, Parinaud's syndrome	N/A	HCP	PPTID	Shunt, total resection	Progression free survival for 5 years
O'Connell et al., 2019	43 y, M	N/A	HA, visual disturbance	N/A	HCP	Pineocytoma	Total resection	N/A
Our case, 2021	44 y, F	N/A	Dizziness, Parinaud's syndrome	N/A	HCP	Recurrent PPTID	Subtotal resection, radiotherapy	Progression free survival for 1 year and 11 months

N/A, not applicable; HA, headache; HCP, hydrocephalus; SAH, subarachnoid hemorrhage; PPTID, pineal parenchymal tumor of intermediate differentiation.

staining, PPTIDs are classified as grade II (fewer than six cells undergoing mitoses with a positive neurofilament staining) or grade III (more than or equal to six cells undergoing mitoses with a negative neurofilament staining).⁷

Takase et al. reported that microsurgery was the most suitable treatment option to achieve gross total resection. The decision to administer postoperative radiotherapy is based on the pathological grade, residual tumor, cerebrospinal fluid seeding, and clinical manifestations. Chemotherapy may increase the effect of radiotherapy, although its side effects remain uncertain.³ In our patient, after the first surgery, there was no evidence of cerebrospinal fluid seeding. Although the tumor was believed to have been gross total resection during the first surgery, we still recommended radiotherapy at that time due to concerns about any small residual or possible further dissemination or recurrence. However, due to the patient's reasons, she did not undergo radiotherapy at the time. According to Fauchon et al., the five-year survival rates for PPTID were 74% and 39% for grades II and III, respectively. Meanwhile, the recurrence rates were 26% and 56%, respectively.⁸ The patient in the present case was postoperatively diagnosed with PPTID, WHO grade II. She had progression-free survival for 10 years, and the PPTID recurred 10 years after the first surgery.

Based on a literature review by Majovsky et al., there have been eight cases of pineal hemorrhagic apoplexy associated with pineal tumors.⁴ The symptoms and signs of pineal apoplexy include headache, lethargy, unsteady gait, extraocular motor manifestations, and generalized hyperreflexia.³ Some symptoms are exacerbated in the context of acute hemorrhage, resulting in hydrocephalus or midbrain compression. Pineal tumor apoplexy causes acute clinical deterioration of neurological function owing to acute intratumoral hemorrhage.⁴ Various causes of pineal tumor bleeding have been identified. Apuzzo et al. reported that pineal tumor bleeding was likely related to anticoagulant therapy.⁹ Burres et al. proposed other possible causes of pineal tumor hemorrhage, including hypertension, external or interstitial irradiation, craniocerebral trauma, tumor histology, tumor growth characteristics, hemorrhagic diathesis, and idiopathic causes.¹⁰ Harada et al. reported a case of pineal tumor hemorrhage caused by an external ventricular drain or a ventriculoperitoneal shunt.¹¹ Matsumoto et al. reported a case of pineal tumor hemorrhage associated with ventriculoperitoneal shunt placement.¹² According to Wang et al., pineal tumor apoplexy may occur spontaneously.¹³ Majovsky et al. reported that space-occupying lesions compress the surrounding structures of the pineal gland and interfere with the arterial blood supply and venous return of the pineal gland, resulting in bleeding.⁴ The patient in the present case had no history of hypertension, trauma, or anticoagulant use. Although she underwent ventriculoperitoneal shunt insertion, the bleeding

did not occur until 10 years later. The bleeding was mostly caused by the recurrent pineal tumor. Majovsky et al. compiled 30 cases of pineal apoplexy from the PubMed database, of which 8 are pineal tumors.⁴ There were seven cases of pineal parenchymal tumors, and one of choriocarcinoma.⁴

The most common pineal tumor is germinoma, which accounts for about 40% of pineal tumors.¹⁴ However, we proposed that pineal parenchymal tumors are more prone to bleeding than other pineal tumors. Table 1 shows that out of 9 cases of pineal tumors with apoplexy, 8 (89%) are pineal parenchymal tumors, while 1 (11%) is a germ cell tumor. All nine cases are hemorrhagic apoplexy. Hemorrhage is more frequently seen in pineal parenchymal tumors compared to other pineal tumors. As the pineal gland, mainly composed of pinealocytes, is a small gland in the brain with a rich blood supply primarily from the posterior choroidal arteries,^{15, 16} we hypothesize that these histological features may explain our finding that bleeding, or pineal apoplexy, occurs more frequently in pineal parenchymal tumors, which arise from pinealocytes, compared to other pathology types of pineal tumors.

Conclusions

PPTID is a rare disease that accounts for less than 0.1% of primary central nervous system tumors. Pineal apoplexy is rare, and its incidence and clinical significance remain unclear. We noted that pineal parenchymal tumors are more prone to tumor bleeding than other pathology types of pineal tumors. We proposed that this is attributed to the high vascularity of pineal glands and the pathological changes in pineal parenchymal tumors. There have only been eight reported cases of pineal tumors with hemorrhagic apoplexy. The recurrence of PPTID with apoplectic hemorrhage after 10 years has not been reported. Despite its rarity, PPTID with apoplexy should be considered in patients with PPTID presenting with sudden-onset neurological symptoms.

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Author contributions

Yu-Li Chen, MD researched the literature and wrote the first draft of the manuscript. Li-Hsin Tai, MD researched the literature, collected information for series review and Table 1, and joined the article revision. Ann-Shung Lieu, MD, PhD participated in protocol development, obtaining ethical approval, patient recruitment, and data analysis. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

This case report was approved by the institutional review board at the Kaohsiung Medical University Hospital (Kaohsiung, Taiwan).

Informed consent

A signed patient permission form for medical research was obtained.

ORCID iDs

Li-Hsin Tai  <https://orcid.org/0000-0001-5982-3755>

Ann-Shung Lieu  <https://orcid.org/0000-0001-7441-1898>

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