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CASE REPORT

Pineal parenchymal tumor of intermediate differentiation: diagnostic pitfalls and discussion of treatment options of a rare tumor entity

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Abstract Tumors of the pineal region are uncommon, comprising approximately 0.4–1% of all intracranial tumors in adults in European and American series. Histopathologically, they are a very heterogeneous group of tumors. Of genuine pineal tumors, pineal parenchymal tumors of intermediate differentiation (PPTIDs) are the least frequently found type. In this paper, we report on the case of a patient with an unexpected and difficult-to-diagnose PPTID. A 2.2×2.2-cm midline mass within the posterior part of the third ventricle with consecutive obstructive hydrocephalus was found in a 44-year-old man presenting with diplopia and gait disturbances. There was no clear connection of the tumor to the pineal gland. Differential diagnosis included all intraventricular and midline tumors, therefore a biopsy was taken. Preliminary histopathological diagnosis was germinoma or primitive neuroectodermal tumor, and the tissue sample was reexamined by a referential neuropathological institute. Final diagnosis was PPTID. The tumor was then resected through a transventricular/transchoroidal approach. Histopathological examination of tumor specimen confirmed the diagnosis of a PPTID. Postoperatively, the patient received gamma-knife radiosurgery. At 1-year follow-up, there are no signs of tumor regrowth. Diagnosis of pineal parenchymal tumors in general and PPTIDs in particular can be troublesome. Their histopathological features are still being defined, as is the biological behavior of the different tumor entities. Thus, treatment options including surgery, radiation therapy, and chemotherapy remain controversial. We recommend surgical removal of PPTID, preferably in toto whenever the size of the tumor permits that kind of excision.

Keywords Pineal parenchymal tumor · Therapy

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Introduction

Tumors of the pineal region are uncommon and account for approximately 0.4–1% of all intracranial tumors in European and American series [16, 33]. An unexplained higher incidence of up to 3.2% is reported in the Japanese literature [28]. Only 14–30% of these tumors are of pineal parenchymal origin, the majority being germ cell tumors [10, 16]. Pineal parenchymal tumors (PPTs) arise from pineocytes or their precursors, and they are distinct from other neoplasms of the pineal region. Of PPT, pineocytomas (PCs) and pineoblastomas (PBs) represent approximately 45% each, with pineal parenchymal tumors of intermediate differentiation (PPTIDs) accounting for the remaining 10% [20]. PB manifests primarily in children, whereas adults aged 25–35 are most frequently affected by PC. PPTs often present with signs and symptoms of occlusive hydrocephalus due to compression of the mesencephal aqueduct. They may also cause local compression of brain tissue with distortion of important anatomical structures, e.g., the quadrigeminal plate. Due to the small

number of reported cases, the classification of PPTs, especially PPTIDs, remains controversial [7, 11]. Little is known about their clinical behavior, and optimum treatment is not yet defined [22, 29].

In this paper, we report on the case of a 44-year-old man presenting with symptoms of occlusive hydrocephalus due to a tumor of the posterior part of the third ventricle without evident relation to the pineal gland. Histologically, the tumor turned out to be a PPTID. In respect to histopathological features, available treatment options are discussed and a treatment recommendation is made.

Clinical presentation and course of treatment

A 44-year-old man presented with a 4-week history of temporary flash-like visual impairment of the left eye accompanied by a feeling of retrobulbic pressure, slight headache, and gait disturbances. An ophthalmologic examination showed a bilateral papilledema. Computed tomography (CT) and magnetic resonance imaging (MRI) scan of the neurocranium were performed, and the patient was then transferred to the neurosurgical department.

Neuroimaging showed a 2.2×2.2-cm-large mass within the third ventricle rostrally to the pineal region. The aqueduct was obstructed, resulting in occlusive hydrocephalus. The tumor showed contrast enhancement on T1-weighted imaging and was hyperintense on T2-weighted imaging (Fig. 1a,b). Differential diagnosis included all intraventricular and midline tumors like meningeoma, ependymoma, plexus-papilloma, neurocytoma, germinoma, and pineal parenchymal tumor. A CT scan revealed microcalcifications indicating germinoma or pineocytoma. A two-dimensional ^{1}HMR spectroscopic imaging with short TE of 30 ms was also performed at 3 T, and quantitative analysis spatially transformed data were processed offline using LCModel. Metabolite maps were created by converting the concentration tables into text images, which were imported into the ImageJ image processing software. These results revealed an increased concentration of choline-containing compounds with 3.3 to 4.0 mmol/l (compared to 1.4 mmol/l measured in the normal parietal white matter), a decreased concentration of creatin/phosphocreatin with 4.7 mmol/l (compared to 6.5 mmol/l measured in the normal parietal white matter), a nearly absent concentration of *N*-acetyl-aspartate with 0.3 mmol/l (compared to 8.3 mmol/l measured in the normal parietal white matter), and a slight decreased concentration of myoinositole with 4.9 mmol/l (compared to 5.1 mmol/l measured in the normal parietal white matter). Signals of lipids were lacking. These findings were suspicious of a highly malignant, highly cellular tumor of neuronal origin, e.g., a high-grade ependymoma, although the decrease of NAA suggested for an extracerebral tumor. The missing lipid

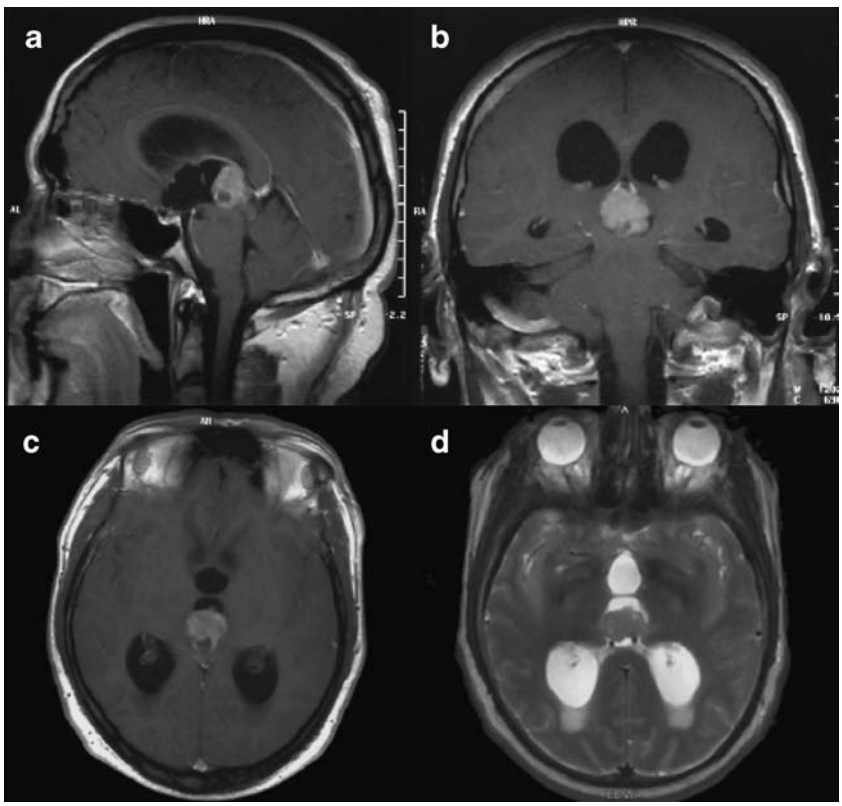

Fig. 1 Preoperative sagittal (**a**), coronal (**b**), and axial (**c**) contrast-enhanced T1-weighted MRI; tumor is hyperdense on T2-weighted imaging (**d**)

peak made a germinoma unlikely; in cases of neurocytomas, higher choline signals are generally present. Regarding patient age and tumor location, a pineal parenchymal tumor seemed unlikely.

Tumor markers including α-fetoprotein (AFP) and the β-unit of human chorionic gonadotrophine (β-HCG) were within margins with 2.0 ng/ml and 0.1 IU/l, respectively, and there were no positive findings for placental alkaline phosphatase (PLAP) either.

In summary, the tumor entity remained unclear, and in respect to the patient's symptoms from obstructive hydrocephalus, we placed an external ventricular cerebrospinal fluid (CSF) drainage into the right lateral ventricle. Furthermore, we performed a stereotactic biopsy of the tumor. There were no intraoperative complications from these procedures. Gait and visual disturbances were relieved by CSF drainage after a few days, and the patient suffered no more headache. A CT scan showed decrease of ventricular size.

A CSF sample showed, like the serum sample, no increased AFP or β-HCG with 0.6 ng/ml and 0.5 IU/l, respectively.

Intraoperative histopathological examination of smear preparations showed a partially pleomorphic tumor with round-shaped cells. Preliminary diagnosis was germinoma or primitive neuroectodermal tumor (PNET; Fig. 2).

Further examination of the paraffin-embedded tissue revealed a highly cellular tumor consisting of predominantly round-shaped cells. Few mitoses could be seen; MIB-Index (Ki67-antigen) was 10%. There was no necrosis visible, and there was no immunoreactivity for glial fibrillary acidic protein, Lu5, PLAP, or chromogranine. The tumor expressed neuronal markers like synaptophysin, neuron-specific enolase, and microtubule-associated protein 2. With regard to the small specimen size due to stereotactic biopsy, the diagnosis of a malignant, neuronally differentiated tumor, e.g., neuroblastoma or PNET was made, and the samples were sent to the German Reference Center for Brain Tumors for further evaluation.

The Reference Center's assessment of the tumor samples resulted in the diagnosis of a PPTID. This diagnosis was unexpected because of the patient's age and because of the tumor lacking a visible connection to the pineal gland on neuroimaging.

Given the diagnosis of a PPTID, we performed surgery to obtain complete tumor removal. As for the tumor being located rostrally to the pineal gland in the posterior part of the third ventricle, we opted for a transventricular/transchoroidal fissure approach. Intraoperatively, a small remnant of tumor had to remain due to the strong tumor adherence to the internal cerebral veins. Histological examination of the resected tissue confirmed the diagnosis of a PPTID (Figs. 3 and 4).

Postoperative MRI revealed the expected small tumor remnant dorsally on the left side of the third ventricle, with some intracranial air but no complications (Fig. 5). There was no more CSF obstruction; thus, the external ventricular drainage was removed 4 days later. An ophthalmologic examination performed postoperatively showed regular bulbar movement and no more diplopia. The left-sided papilla still showed edema which is slowly resolving.

The patient then underwent gamma-knife radiosurgery with a dose of 15.5 Gy. The patient was followed in 3-month intervals, and at 1-year follow-up, he is without radiographic evidence of regrowing tumor and has returned to his workplace without neurological disturbances.

Discussion

In the case presented here, diagnosis of PPTID was difficult to establish. Given the patient's age and tumor location

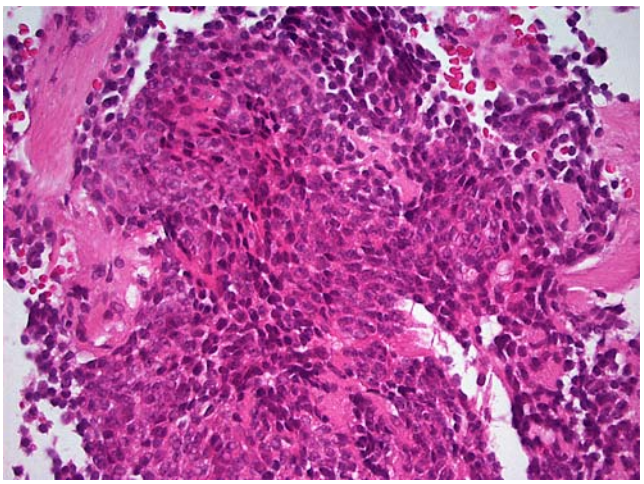

Fig. 2 Paraffin-embedded stereotactic biopsy sample, H & E staining: highly cellular tumor with poorly differentiated, irregularly shaped cells with occasional mitotic figures. Tumor cells are focally arranged around blood vessels

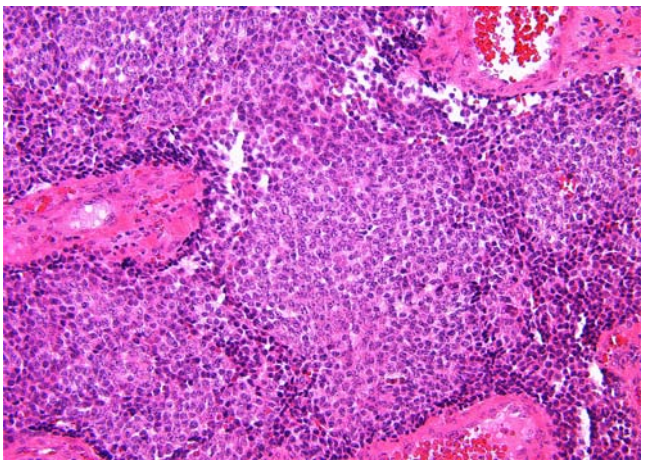

Fig. 3 Paraffin embedded tissue, H & E staining: morphologically undifferentiated tumor with high cellularity, predominantly round-shaped cell nuclei, mild nuclear atypia, and occasional mitoses

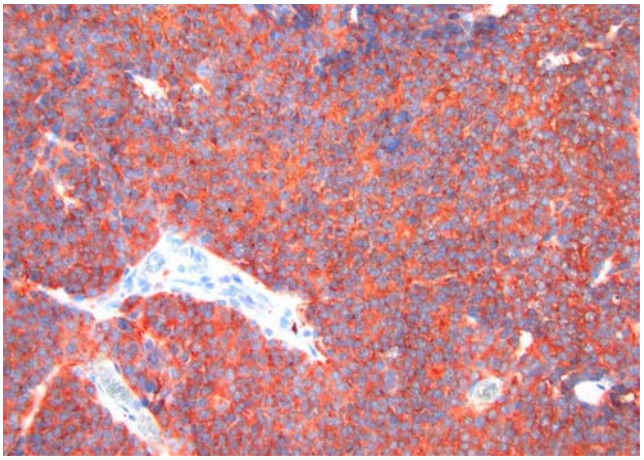

Fig. 4 Immunohistochemical staining for synaptophysin: tumor cells show neuronal differentiation. Vessels are spared

within the third ventricle, apart from the pineal gland, there were a large number of differential diagnoses including all intraventricular and midline tumors.

As the adequate therapeutic strategy of pineal region tumors depends on the tumor entity, it is imperative to confirm tumor diagnosis [5, 6]. Despite many new developments in neuroimaging techniques such as MRI spectroscopy, there is no radiographic test that can definitely predict histology. Therefore, histopathological evaluation of the tumor is essential for diagnosis [27, 31].

Stereotactic biopsy of pineal region tumors is a procedure that can be performed with a limited perioperative risk of mortality (less than 1%) and morbidity (about 1.3%) and with a high diagnostic rate of >95% [14, 15, 23]. As some tumors are extremely radiosensitive, e.g., germinomas, a stereotactic biopsy offers the ability to ascertain a histopathological diagnosis and then initiate radiotherapy. There are, however, the pitfalls of sampling error due to the diversity of histologies and the potential of mixed-cell tumors, argumenting for maximal tissue sampling. Moreover, anomalies may lead to anatomic varieties such as a venous roof over the dome of the tumor, and there remains the risk of bleeding due to injuring these structures or injuring the internal cerebral veins.

PPTs and other intraventricular or pineal region lesions often present with signs and symptoms of hydrocephalus or local brain tissue compression [1, 14, 16, 29]. Sometimes, treatment of hydrocephalus has highest priority and must be performed before any treatment of the tumor itself. External ventricular drainage or endoscopic ventriculostomy should then be performed, the latter technique permitting sometimes a biopsy of the tumor in the same procedure. Definite ventriculo-peritoneal shunting procedures should be avoided before biopsy or surgery given the risk of tumor seeding throughout the CSF [29]. If the tumor can be resected, hydrocephalus might cease after tumor removal, and shunting will not be necessary—then a temporary external ventricular drain may suffice [31]. In case the tumor cannot be resected or will be treated by first-line radiotherapy or chemotherapy, e.g., non-germinomatous germ-cell tumors, thus taking more time to end obstruction of the CSF pathway, a permanent external ventricular CSF drainage bears a high risk of infection. In these cases, a permanent shunting procedure will be necessary. As implantable shunt systems bear the risk of infection or dysfunction, an endoscopic third ventriculostomy can be easily performed with a high success rate and few complications [26].

As there were no diagnostic hints indicating a certain tumor entity in our patient, we decided to perform a stereotactic biopsy and place an external ventricular drainage to treat hydrocephalus. As outlined above, an endoscopic biopsy and third ventriculostomy would have been another option.

PPTs and especially PPTIDs are rare tumor entities. So far, there are only a few more than 100 cases of PPTID reported in the literature, and there is a lot of controversy about the histopathological classification of these tumors [11]. Only limited clinical data regarding their behavior are available, and treatment remains controversial [2, 22, 29, 31].

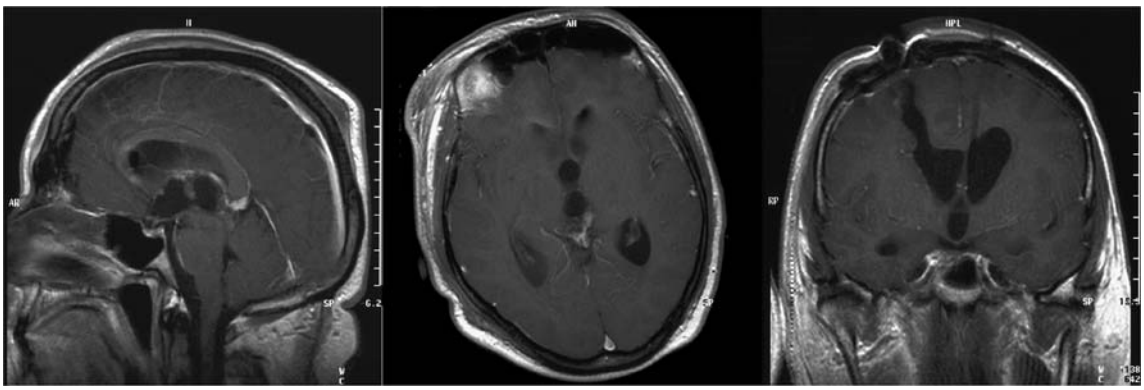

Fig. 5 Early postoperative sagittal, axial, and coronal contrast-enhanced MRI scans

Until 1983, PPTs were divided into only PTs and PBs [3]. PC, being a well-differentiated tumor recapitulating the normal pineal gland, is regarded as the most benign of PPTs. It is usually less aggressively treated than PB which consists of poorly differentiated cells similar to medulloblastomas and is, therefore, sometimes described as a supratentorial primitive neuroectodermal tumor [6, 17].

PPTID is a tumor with histological features resembling both PC and PB. The current WHO classification distinguishes between PCs, PBs, and PPTID. PPTIDs are sometimes also referred to as mixed-type PC/PB, but nomenclature is inconsistent, as some authors distinguish even between PPTID and mixed PC/PB [6, 13, 30]. It is sometimes difficult to distinguish between these entities when it comes to setting a diagnosis, as there seems to be a continuous spectrum from PC to PB. PBs usually occur in children, whereas PCs have a peak in adults aged 25–35 years. In other age groups, these tumors are extremely rare [5, 17, 18, 27].

Treatment options for PPTs consist of surgery, radiotherapy, and chemotherapy. Patients suffering from PCs are usually treated by surgical resection, optionally followed by conventional radiotherapy or gamma-knife radiosurgery [6, 9, 24, 29, 31, 32]. PBs are also treated by surgical resection and/or radiotherapy; sometimes, also platinum-based chemotherapeutic agents are administered [5, 17, 21, 29]. Radiation therapy is performed by either fractionated external beam radiation, gamma-knife radiosurgery, or brachytherapy [8, 9, 12, 19, 24]. The optimal adjuvant therapy protocols for each tumor entity, however, are still not defined.

Prognosis of PPTs seems to depend mainly on histological subtype and characteristics and stage of disease at diagnosis [5, 18]. Although there is no clear evidence of a relationship between the extent of resection and survival, long-term survival is reported sometimes by surgery alone [4, 5, 7]. Usually, outcome is more favorable for PC than PB with 5-year survival rates of up to >80% and ~40–60%, respectively [14, 17, 29, 30]. However, especially for adult patients with PB, prognosis is poor.

It is thought that prognosis of PPTIDs lies in between that of PCs and PBs, but in a large retrospective case control study, survival rates were far better for PPTIDs than for PBs [18]. Jouvet et al. [11] have associated histopathological features of PPTs with survival and proposed a new grading system: They defined pure PCs as type I, pure PBs as type IV, and divided PPTIDs into two types according to the number of mitoses seen and whether positive immunolabeling of neurofilaments can be found. Rickert et al. [25] have found that PPTIDs resemble PBs genomically but PCs prognostically, raising the question of treating PPTIDs similarly to PCs or PBs. In our patient, there were only a few mitoses found, thus corresponding to a type II tumor according to the classification of Jouvet et al.

Conclusion

We present the case of a patient with a third ventricular tumor turning out to be a PPTID. Diagnosing a PPTID can be difficult, and there is no widely accepted treatment strategy for patients with these tumors. Prognosis of PPTIDs is similar to that of PCs, so we advocate a similar treatment regime. If feasible, the tumor should be resected to the largest possible extent and the patient's course be closely followed. Any remaining tumor after surgery or recurrence of tumor should lead to adjuvant radiotherapy.

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