Tumors of Pineal Cell Origin

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16.1 Introduction

Pineal tumors are rare pathological entities that present with a broad spectrum of clinical, imaging, and histopathological characteristics that make them sometimes difficult to define. Tumors of pineal cell origin (TPCOs) are the second most common entity, after tumors of germ cell origin [1]. Unlike in other regions of the brain, gliomas in this region account for 14–22% of all tumors [2].

TPCOs are classified according to their differentiation, from best differentiated to anaplastic, into pineocytomas, pineal parenchymal tumors of intermediate differentiation (PPTIDs), papillary tumors of the pineal region (PTPRs), and pineoblastomas. Pineocytomas are considered World Health Organization (WHO) grade I tumors, PPTIDs and PTPRs WHO grade II or III, and pineoblastomas grade IV [1].

16.2 Epidemiology

TPCOs are the second most common tumors of the pineal region, accounting for a median prevalence of roughly 30–40% [3]. However, owing to the very low overall incidence (0.8 in 100,000 patient years), the prevalence in individual studies varies widely between 5.6% [4] and 41.6% [5]. There appears to be a slightly higher incidence in the Asian population [3]. The existing prevalence data are extremely heterogeneous, given the small series, and should be interpreted accordingly.

Pineocytomas typically appear in the young and middle-aged adult population, whereas in children they make up less than 10% of the pineal region tumors reported [6, 7]. The male-to-female ratio is 0.6:1. **PPTIDs** have a prevalence of roughly 33% among all pineal region tumors [8], appearing equally often in the young adult (second and third decades of life) as well as in the pediatric population [9]. A slight female preponderance is noted, with a male-to-female ratio of 0.8:1. **PTPRs** are reported in both the adult and pediatric populations. Because the entity was unrecognized until recently, and due to only 181 cases reported so far in the literature [1], no data on the incidence is

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available. One study included patients aged 5 to 66, with a median age of 30 [10]. In this case the male-to-female ratio is 1:1. **Pineoblastomas** amount for about 24–50% of all pineal region tumors and are primarily a pediatric tumor [6], with some reports describing adult patients with pineoblastomas as well [8, 11]. The male-to-female ratio is 0.7:1.

Data pertaining to the Brain Tumor Registry of Japan [12] database show a cumulative 5-year survival rate of 84.1% for pineocytomas and 46.1% for pineoblastomas.

16.3 Clinical Presentation and Diagnostics

The most common reported clinical presentation was raised intracranial pressure due to obstructive hydrocephalus [7]. Given the location, eye movement disturbances, in particular vertical gaze palsy ranging all the way to a complete Parinaud syndrome, were present in as many as 75% of the patients [7]. Because of its regulatory endocrine function, diabetes insipidus (18%), hypopituitarism (5%), and pubertas praecox (2%) were also reported [5–7]. Lesions that infiltrate or compress the thalamus and the posterior limb of the internal capsule cause hemihypesthesia, hemiparesis, and dyscoordination.

Diagnostic workup includes imaging studies, usually an (angio) computed tomography (CT), magnetic resonance imaging (MRI), or both, cerebrospinal fluid (CSF) sampling, and a biopsy or resection to confirm the histological diagnosis.

Pineocytomas appear on CT as intermediate density lesions, similar to the surrounding white matter. The essential feature distinguishing pineocytomas from germ cell tumors is that they "explode" the calcifications of the pineal gland and displace these to the edge of the lesion, as opposed to germ cell tumors that "engulf" the calcifications [13, 14]. Given that they are slow-growing tumors, a thin-slice, contrast-enhanced 3 Tesla MRI is necessary to differentiate them from pineal cysts. On T1-weighted imaging they appear hypointense or isointense to brain parenchyma, with vividly enhancing solid components, and on T2-weighted imaging they appear isointense to brain parenchyma with multiple cysts [13, 15].

Pineoblastomas appear on CT hyperdense to the adjacent white matter, due to their hypercellularity. They also characteristically show the "exploded" pineal calcifications, lining the periphery of the lesion. On MRI, they appear isointense or hypointense to adjacent parenchyma, with vivid patchy enhancement and restricted diffusion on apparent diffusion coefficient (ADC)/diffusion weighted imaging (DWI) due to hypercellularity (ADC usually around 400–800 mm^2/s). T2-weighted imaging shows a tumor isointense to adjacent brain with cysts and necrosis [13–15].

PPTIDs and **PTPRs** are virtually indistinguishable from pineocytomas on CT and MRI. What differentiates **PPTIDs** from **pineocytomas** is the rapid growth of the latter on serial MRIs and sometimes the low ADC values [13], whereas **PTPRs** may have a high T1 signal owing to secretory inclusions [16].

For **PPTIDs**, **PTPRs**, and **pineoblastomas,** complete neuraxis scanning is necessary, as these lesions have been reported to exhibit cerebrospinal fluid (CSF) dissemination in between 7% and as much as 45% of cases [14]. Figures 16.1 and 16.2 show MRI images of two patients from the Erasmus University Medical Center (Erasmus MC).

In the diagnosis of pineal germ cell tumors, biochemical markers such as alpha-fetoprotein

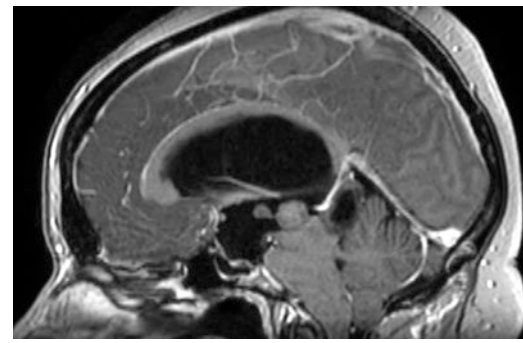

Fig. 16.1 Sagittal MRI, T1 sequence, gadolinium-enhanced. A T1 isointense circular mass is visible just above the tectal plate. Contrast enhancement is scarce. The vein of Galen is draped on its upper side en route toward the sinus rectus. The patient received a third ventriculocisternostomy and biopsy, which revealed a probable PPTID

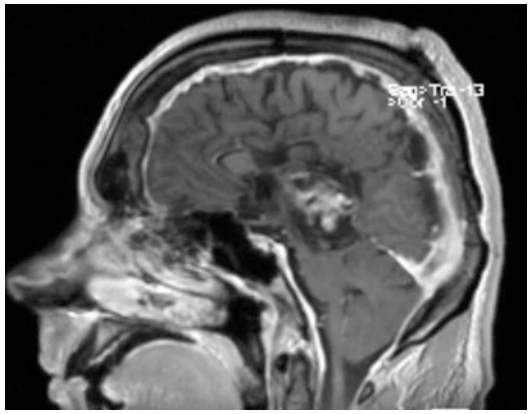

Fig. 16.2 Sagittal MRI, T1 sequence, gadolinium-enhanced. A T1 heterogeneous hypointense and isointense lesion is visible posteriorly to the mesencephalon with compression on the tectal plate and culmen. The tumor was previously operated on via a transcallosal approach. The pathology revealed a pineocytoma

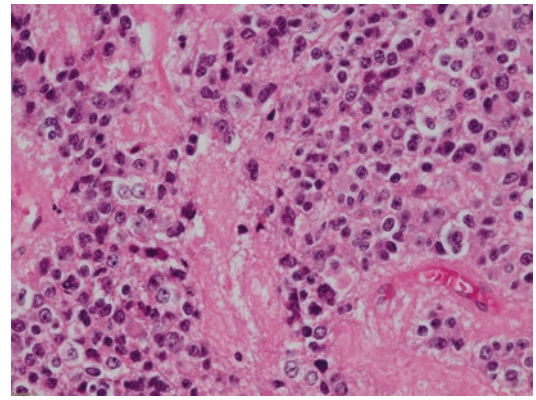

Fig. 16.3 (Hematoxylin–Eosin [H–E] staining, 400×) A patient of the Erasmus Medical Center, MRI depicted in Fig. 16.2. Pineocytoma. The tumor is moderately cellular, composed of sheets of slightly variable cells with moderate amounts of eosinophilic cytoplasm. The nuclei are round—oval, with inconspicuous or regular small nucleoli and fine chromatin. Cell processes form typical pineocytomatous rosettes

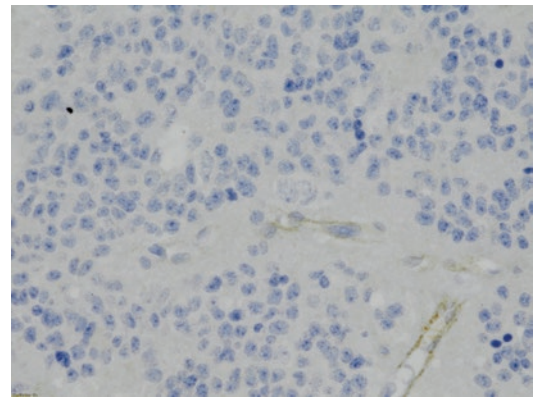

Fig. 16.4 (Immunohistochemistry [IHC], Ki-67 staining, 400×) Same patient as in Figs. 16.2 and 16.3. Ki-67 staining of the nuclei is below 1%, indicating very low proliferative activity. (Courtesy of Dr. R. M. Verdijk, Neuropathologist, Erasmus MC, Rotterdam)

and beta-human chorionic gonadotropin are helpful; there are no biomarkers that help the diagnosis of TPCOs, but biomarkers can help in the differential diagnosis with primary germ cell tumors. Other markers for germ cell tumors that might add to the diagnosis are placental alkaline phosphatase [17] and lactate dehydrogenase isoenzyme 1 [18], but these are not part of the routine screening in all centers. The absence of these markers does not rule out a germ cell tumor, however, and a ventriculostomy and biopsy soon after presentation are recommended.

To date, melatonin levels [19] and hydroxyindole-O-methyltransferase (HIOMT) enzyme levels (which catalyzes the final step in melatonin secretion) [20] in serum and CSF have been suggested to aid the diagnosis of TPCO, but no proper, adequately powered studies have been conducted.

A biopsy, either stereotactic or open, or resection material will be used to acquire the histopathologic diagnosis.

16.4 Pathology

Pineocytomas are circumscribed, grayish-tan tumors well delineated from brain parenchyma. Cystic or hemorrhagic changes are sometimes present macroscopically. Microscopically, they are composed of cells reminiscent of pinealocytes, with characteristic pineocytomatous pseudorosettes [1]. In stark contrast, **pineoblastomas** are macroscopically poorly defined, infiltrative tumors with a pinkish-gray hue. Microscopically, they exhibit small, round, blue cells, with a high nuclear-cytoplasmic ratio, and also exhibit rosettes, but unlike pineocytomas, these are the Homer Wright (pseudo) rosettes also seen in medulloblastoma or olfactory neuroblastoma [1] (Figs. 16.3 and 16.4).

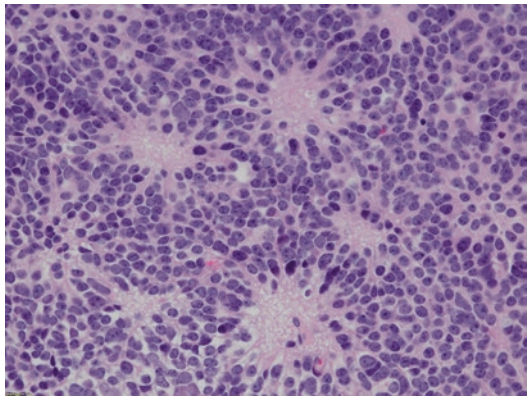

Fig. 16.5 (H–E, 400×) Pineocytoma. The tumor is moderately cellular, composed of sheets of uniform cells with moderate amounts of eosinophilic cytoplasm. The nuclei are round to oval, with inconspicuous or regular small nucleoli and fine chromatin. Cell processes form typical pineocytomatous rosettes

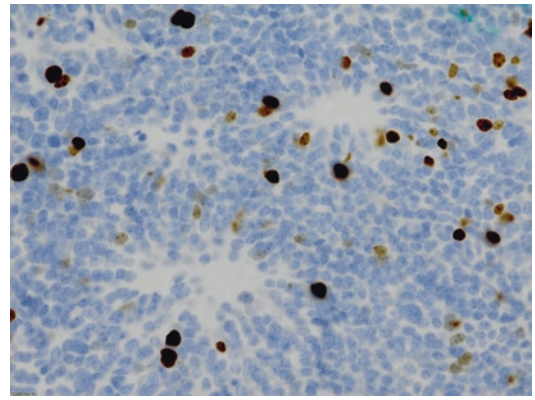

Fig. 16.6 (IHC, Ki-67 staining) Same patient as depicted in Fig. 16.5. Ki-67 staining of the nuclei in this case is around 5%, indicating slight proliferative activity, which is still acceptable for pineocytoma. Pineocytomatous rosettes are not expected to be present in pineal parenchymal tumor of intermediate differentiation or pineoblastoma. (Courtesy of Dr. R. M. Verdijk, Neuropathologist, Erasmus MC, Rotterdam)

PPTIDs and **PTPRs** show intermediate forms, even though they most often microscopically resemble pineocytomas without rosettes. **PPTIDs** exhibit either a lobulated pattern, in which lobules are divided by vessels, or a diffuse pattern, reminiscent of oligodendrogliomas [1]. **PTPRs** range microscopically from solid to predominantly papillary, with areas of necrosis, in a pattern suggestive of an ependymoma [9, 10].

Immunohistochemistry is used to look at tissue-specific antigens (neuronal and glial- neurofilament, glial fibrillary acidic protein (GFAP), synaptophysin, nestin), proliferation (Ki-67), and apoptosis markers and specific pineal markers hydroxyindole-O-methyltransferase (HIOMT). A wealth of markers is currently being studied for diagnosis and prognostic purposes, but consensus remains lacking as to the proper combination. Ki-67-positive nuclei are a well-known and often-used method to determine the proliferation index that usually aids diagnosis. **PTPRs** have a fairly characteristic immunohistochemical profile [21] (Figs. 16.5 and 16.6).

16.5 Management

Surgery, radiation, and chemotherapy are all tools used in the management of TPCOs. Pineal tumors, given their location, should only be treated in centers with considerable neurosurgical experience [7, 22, 23].

The workup of a new TPCO includes: serum and CSF biomarkers, through either the lumbar tap, if deemed safe, or during ventriculostomy procedures (alpha-fetoprotein and beta–human chorionic gonadotropin), contrast-enhanced MRI and T1, T2, DWI, ADC, time-of-flight (TOF) sequences, and CT venography (CTV) or MRI venography (MRV) for preoperative planning.

A benign pineal cyst with negative CSF markers may be followed up without intervention. The same holds true for asymptomatic, small tumors with negative CSF markers (incidental findings), which may be first followed up with serial MRIs. Very often, however, these patients present when they are already symptomatic, usually with obstructive hydrocephalus [7], in which case the primary goal is to resolve the hydrocephalus and to obtain the proper diagnosis. We most often resort to an endoscopic third ventriculocisternostomy with subsequent endoscopic biopsy when feasible. Reports suggest that this approach enjoys low morbidity [24, 25]. It can be argued, however, that, when feasible, a direct approach to the tumor might accomplish both objectives and help avoid a second surgery. If germ cell tumors are still in the differential diagnosis, then a biopsy

should be performed and a first craniotomy avoided, since germinomas, but not non-germinomatous germ cell tumors (NGGCTs), are most effectively treated with chemotherapy and radiation [26].

For both benign as well as malignant TPCOs, an approach that maximizes the extent of resection should be chosen. Reports so far suggest that for benign tumors, surgery alone may be curative [23, 27], while for malignant tumors it might slightly improve the outcome [5, 27]. Obviously, given the infiltrative nature of malignant tumors, a gross total resection cannot be achieved, and adjuvant therapies need to be employed.

The choice of approach for resection depends on the displacement of the surrounding neurovascular structures by the tumor and on certain characteristics of the anatomy of the patient. The pineal stem is continuous with both the habenular (dorsally) as well as the posterior commissure (ventrally). The tip projects in the quadrigeminal cistern, where it is surrounded by the quadrigeminal plate. The principal vessel that provides vascularization is the middle posterior choroidal artery (MPChA) en route to the velum interpositum in the roof of the third ventricle. The main obstacle to approaches of this area is the vein of Galen, which originates 3–5 mm behind the pineal gland and runs in a superoposterior angle to drain in the straight sinus. Dorsally, the superior vermian and precentral cerebellar veins join the vein of Galen. Ventrally, the internal cerebral veins and pineal vein join the vein of Galen.

Taking these anatomical aspects into account, as well as the changes brought about by the tumor (the vein of Galen is usually pushed upward, the internal cerebral veins are either displaced laterally together or apart, the MPChA and the lateral posterior choroidal artery are also pushed laterally), the proper surgical corridor is defined.

The three approaches used for this region are occipital transtentorial [28], infratentorial supracerebellar [29], and interhemispheric retrocallosal [22]. The occipital transtentorial approach is preferred for tumors that extend more cranially or more laterally, into the aqueduct, or more towards the thalamus, where visualization of the walls of the third ventricles is essential. For smaller tumors growing more caudally or which displace the quadrigeminal plate caudally, but without much lateral extension, an infratentorial supracerebellar approach (possibly in the sitting position) offers a relatively unobstructed pathway to the tumor, except for the precentral and anterior vermian veins. The interhemispheric retrocallosal approach offers a wide exposure and excellent visualization, at the cost of potential venous injury (internal cerebral vein or vein of Galen) and hemialexia, pure word blindness, or visual agnosia if the splenium is injured.

Radiotherapy, either stereotactic or fractionated, together with chemotherapy [30, 31] should be used in conjunction with surgery, especially for higher-grade tumors and/or incomplete resections. Spinal irradiation should only be carried out in cases of documented spinal seeding. The decision regarding the proper treatment regimen should be taken in a multidisciplinary team with neuro-oncologic expertise [23].

16.6 Controversies

The two main controversies in the treatment of TPCOs are the timing of surgery and the choice of approach.

Nowadays, most centers choose an endoscopic third ventriculocisternostomy together with an endoscopic biopsy in the same session in order to establish the diagnosis. Ideally, the burr hole should be planned in such a way as to allow achieving both goals (ventriculostomy and biopsy) without damage to the fornix or other neurovascular structures due to the angle of the endoscope. This is often a daunting task. Reports in the literature so far also suggest the possibility of placing two burr holes to achieve the same outcome, but if one is deemed safe, then it is the approach of choice [32, 33]. Some reports suggest the possibility of CSF seeding through the procedure [24]. Another issue is the possibility of sampling errors, especially in germ cell tumors with mixed cell populations. All of these issues must be taken into account when deciding on the surgical strategy.

In large tumors with specific imaging characteristics of a pineocytoma and negative markers, in which a gross total resection is expected, resection will also resolve hydrocephalus, thus avoiding two surgeries. The balance, however, is still in favor of a more conservative approach [23].

The second controversy regards the choice of approach. This choice depends on the anatomy of the individual patient, the displacement of anatomy by the tumor, and last but not least, on the experience of the surgeon. The risk of damage to the surrounding structures, such as contralateral hemi-neglect after lesions of the pulvinar, hemialexia, pure word blindness, or visual agnosia after lesions of the splenium, visuospatial dyscoordination after lesions of the quadrigeminal plate, and vertical gaze palsy after injury of the posterior commissure, should be taken into account. In the pediatric population, surprisingly, despite conventional wisdom deterring neurosurgeons from damaging the internal cerebral vein—vein of Galen complex—sacrifice of these veins or of bridging veins did not lead to any deficit [22, 34]. The authors postulate that this is due to the extended network of valveless veins allowing massive redistribution of flow when one vein is sacrificed. They also speculate that venous infarctions attributed to the sacrifice of bridging veins is actually due to brain retraction and venous congestion. Proper preoperative workup should therefore include either a CTV or an MRV.

Ultimately, the approach that delivers the most direct route to the tumor, allowing for maximum removal without damage to surrounding structures, should be chosen. More often than not, this is the approach the surgeon is most familiar with.

16.7 Conclusion

Tumors of pineal cell origin are rare tumors originating in the cells of the pineal gland itself. Differentiating them from germinomas is essential, and the surgical approach needs to be tailored to the symptomatology of the patient and the anatomical relations of the tumor. The approaches used to maximize resection and minimize the chance of surgical morbidity are highly complex, and these tumors should be treated in centers with plentiful experience in dealing with pineal region lesions.

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