

Tarik Tihan

34.1 Overview

- Pineal parenchymal tumors range from the indolent pineocytoma (PC) to pineal parenchymal tumors of intermediate differentiation (PPTID) and finally to the highly malignant pineoblastoma (PB).
 - Pineocytoma (ICD-O 9361/1) is a rare, slow-growing pineal neoplasm (WHO grade I) composed of mature-appearing pineocytes and forming pineocytomatous rosettes.
 - Pineal parenchymal tumor of intermediate differentiation (ICD-O 9362/3) is a rare, intermediate-grade malignant tumor (WHO grade II or III) with diffuse sheets of tumor cells with low or moderate level of mitotic activity.
 - Pineoblastoma (ICD-O 9362/3) is a highly malignant embryonal tumor (WHO grade IV) typically seen in children; it has primitive, blastlike cells and frequent recurrence or dissemination.
- A recently described rare neoplasm, papillary tumor of the pineal, is typically a tumor of adults and will not be discussed in this chapter [1].
- Pineal region masses can also cause significant cerebrospinal fluid (CSF) obstruction leading to headaches, nausea and vomiting, and other signs related to increased intracranial pressure. These symptoms are not specific to pineal parenchymal neoplasms.
- Pineocytoma (PC) is less common in the pediatric age group; the rare PC typically presents with signs of increased intracranial pressure and occasionally visual disturbances. The few studies on PC in children report a more frequent local recurrence than in adults, but this finding requires validation with the current WHO grading scheme.
- Pineal parenchymal tumor of intermediate differentiation (PPTID) is even less frequent in children and its clinical presentation is less well defined; it is considered similar to PC. These tumors have a greater tendency for local recurrence, but an objective comparison of recurrence risk between PPTID and PC is not possible on the basis of the available data [2].
- Pineoblastoma (PB) is the most common pediatric pineal parenchymal tumor, and the majority of tumors occur within the first two decades of life. The interval between initial symptoms and the need for surgical intervention is much shorter than for other pineal parenchymal tumors. Signs and symptoms of intracranial pressure are often present and may worsen rapidly with cerebrospinal dissemination.

34.2 Clinical Features

- All primary pineal parenchymal neoplasms, as well as other pineal region masses, may be associated with Parinaud syndrome in the young (dorsal midbrain syndrome), which includes upward gaze paralysis, accommodative paresis, nystagmus, and eyelid retraction.

34.3 Neuroimaging

- Neuroimaging does not provide specific information that can reliably distinguish pineal parenchymal tumors from other neoplasms such as germinomas [3].
- PC is often a well-defined mass that is typically less than 3–4 cm. These tumors are hypointense or isointense on T1-weighted images, and hyperintense on T2-weighted images. The tumors avidly enhance upon gadolinium administration. Some PCs demonstrate calcifications on CT or MRI (Fig. 34.1).

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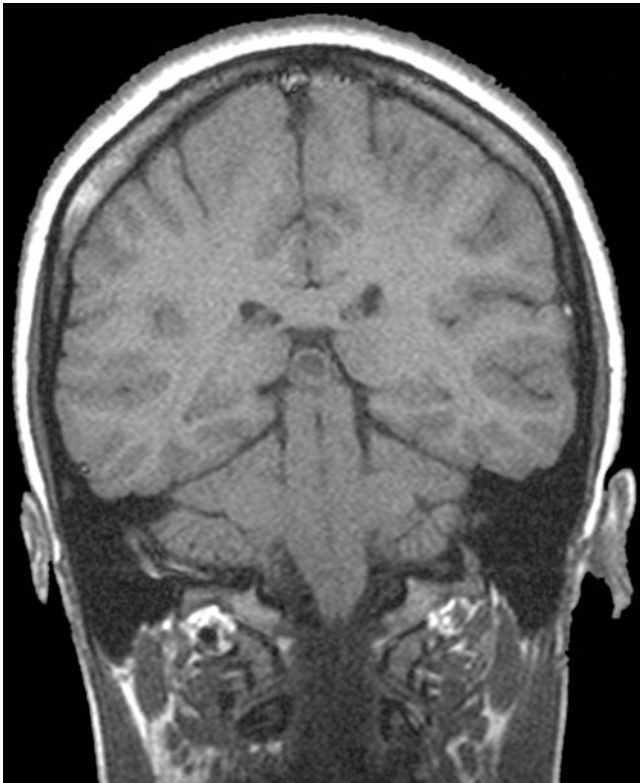


Fig. 34.1 Coronal noncontrast T1-weighted image of a pineal mass in a 17-year-old boy, showing a small cystic pineal gland. The lesion was histologically confirmed as a pineocytoma (PC)

- PPTID is often indistinguishable from PC and may also demonstrate calcifications or hemorrhage on imaging studies. PPTID may be more solid and diffusely enhancing than PC.
- PB is often a large tumor, rarely seen in association with unilateral or bilateral retinoblastoma. The tumors are often larger, with brighter T2-weighted signals, and are hypointense on T1-weighted images. There is marked gadolinium enhancement, and the tumors are much more variable in their appearance, with calcifications, necrosis, or hemorrhage. The boundaries of PB may not always be well defined (Fig. 34.2).



Fig. 34.2 Sagittal, contrast-enhanced T1-weighted MR image of a pineoblastoma (PB) in a 4-year-old child, with mass effect and hydrocephalus

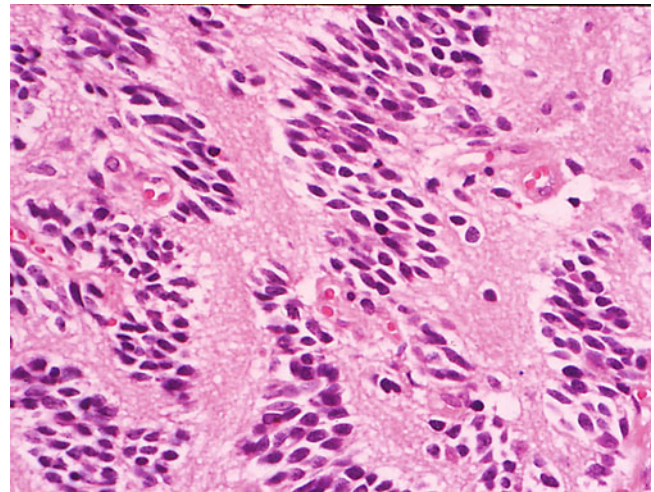


Fig. 34.3 Typical histological appearance of pineocytoma (PC). The tumor is sparsely cellular and is composed of monomorphous, small, mature neuronal cells and neuropil-like background

34.4 Histopathology

- PCs are macroscopically gray, granular, and discrete masses that often fill the pineal recess and the subjacent aqueduct.
 - The tumors are composed of cells with large nuclei, open chromatin density, and ample surrounding cytoplasm (Fig. 34.3).
- The tumor cells are typically monomorphous with only occasional cells with nuclear pleomorphism or hyperchromasia.
 - Necrosis or mitotic figures are exceptionally rare. In some foci, cytological atypia can be interpreted as “degenerative change.”
 - PCs often harbor pineocytomatous rosettes formed by conglomeration of tumor cell processes in a circular or stellate form and are slightly more eosinophilic than the neuropil.

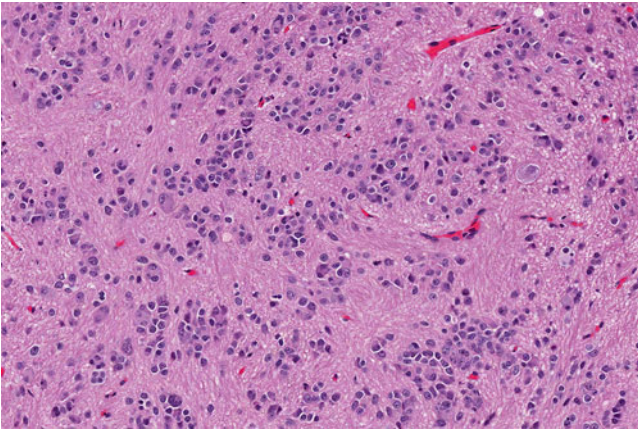


Fig. 34.4 Histological features of pineocytoma. Less common features include a rich, neuropil-like matrix and rare ganglion-like cells

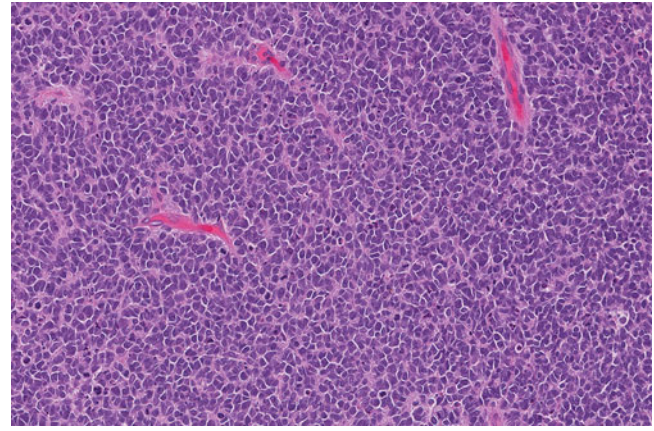


Fig. 34.6 Cytologic atypia in PPTID showing rare multinucleated cells and large, bizarre yet degenerative-appearing nuclei

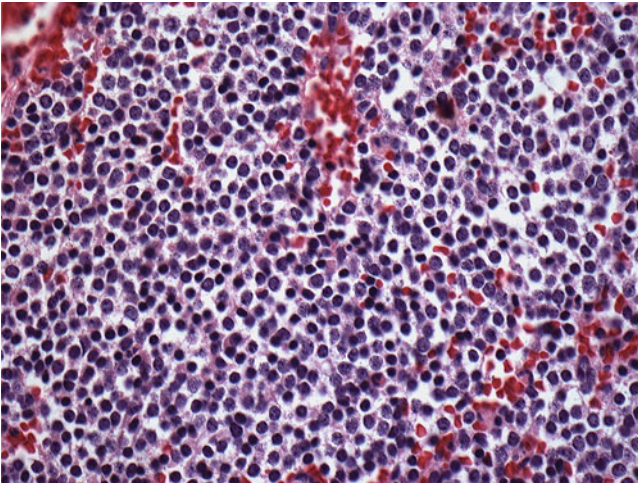


Fig. 34.5 Pineal parenchymal tumor of intermediate differentiation (PPTID) composed of a mixture of small and mature cells presenting a mixed appearance between pineocytoma and pineoblastoma

- The structure of a pineocytomatous rosette is similar to a pineoblastic or Homer-Wright rosette, but it is conspicuously less cellular and larger; the majority of cells have ample cytoplasm.
- PCs can show isolated or clustered large ganglion-like cells and focal islands of neuropil, but these findings are rare (Fig. 34.4).
- PPTID shows focally diffuse or lobular architecture. Some PPTIDs resemble pineocytoma with more hypercellularity and occasional mitoses and abundant neuropil, but others look like small blue round cells with no mitoses and intervening neuropil (Fig. 34.5).
 - The tumors have high or moderate cellularity with focally overlapping nuclei, cells with scant cytoplasm, and scattered mitotic figures.
 - PPTID may harbor focal PC-like areas admixed with sheets of tumor cells or lobules with increased cellularity (Fig. 34.5).
- Rarely, these tumors contain giant cells or moderate nuclear atypia (Fig. 34.6), and occasionally Homer Wright–type rosettes or large ganglion-like cells.
- Grading of PPTID is controversial, and a clear distinction between grade II and grade III neoplasms has not emerged. The use of proliferation rate and a grading scheme to segregate WHO grade II from grade III tumors showed no survival difference [4].
- A grading scheme based on mitotic rate and neurofilament staining was proposed earlier [5]:
 - WHO grade II PPTID has fewer than six mitoses per ten high power fields and strong immunostaining with neurofilament antibody.
 - WHO grade III PPTID has more than six mitoses per ten high power fields and little or no staining with neurofilament antibody.
- PB is macroscopically soft, gelatinous, and focally hemorrhagic and necrotic. These irregular neoplasms can be quite large.
 - PB has been described as similar to medulloblastoma or supratentorial primitive neuroectodermal tumor (PNET). The most recent WHO classification has abandoned the term PNET, and refer to such tumors as Embryonal Tumor, NOS as of 2016. The tumors are composed of small, blue round cells with scant cytoplasm and hyperchromatic nuclei (Fig. 34.7).
 - The cells are often arranged in sheets or discohesive clusters. The tumor cells typically form Flexner-Wintersteiner rosettes in which the cells are radially arranged around a small luminal structure (Fig. 34.8).
 - In addition, neuroblastic-type Homer-Wright rosettes identical to those seen in medulloblastomas can be observed (Fig. 34.9).
 - PB has conspicuous mitotic figures, which can be numerous in some areas. Occasional giant cells, hemorrhage, and calcification are also commonly present.

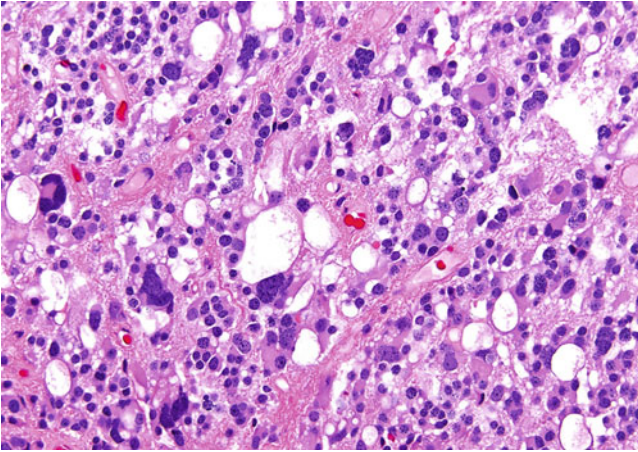


Fig. 34.7 Pineoblastoma composed of highly cellular, small blue round cells with numerous mitotic figures

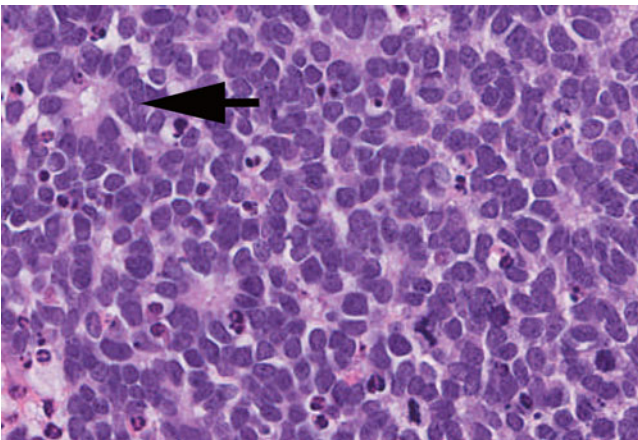


Fig. 34.8 Retinoblastic (Flexner-Wintersteiner) rosette in pineoblastoma (*arrow*)

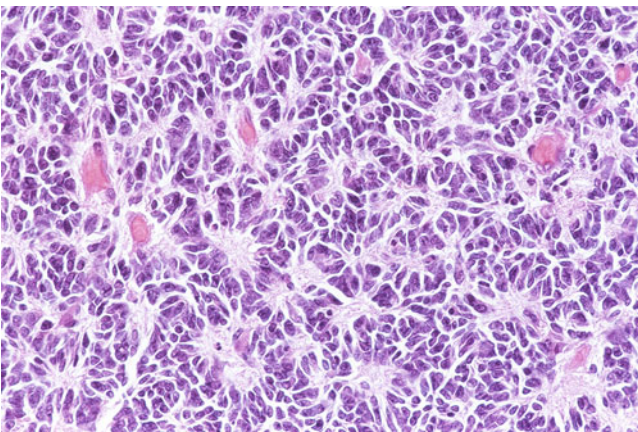


Fig. 34.9 Neuroblastic (Homer-Wright) rosettes in pineoblastoma

- Rare tumor cells may harbor melanin pigment, but the pigment more often is hemosiderin.

34.5 Immunohistochemistry

- As a general rule, with the increasing grade of the tumor, neurofilament immunostaining decreases and Ki-67 proliferation rate increases [6]. A WHO grade III PPTID has only focal neurofilament staining (Fig. 34.10).
- PC typically demonstrates strong positivity for S-100 protein, neuron-specific enolase (NSE), synaptophysin, and chromogranin, with variable immunoreactivity to neurofilament proteins [7].
 - The tumors are also focally positive for glial fibrillary acidic protein (GFAP), retinal-S antigen, and rhodopsin.
- PPTID is similar to PC, with strong positivity for synaptophysin, NSE, and S-100 protein. Antibodies for neurofilament proteins stain the tumors focally, and in some cases isolated cells within the tumor show intense staining.
 - The staining for GFAP and retinal-S antigen is variable; some tumors may be negative for these two markers.
- PB exhibits a less pronounced retinoblastomatous differentiation but is often equally positive for synaptophysin as the other pineal parenchymal tumors.
 - Chromogranin is positive in only a small percentage of tumors and in a limited number of tumor cells (Fig. 34.11).

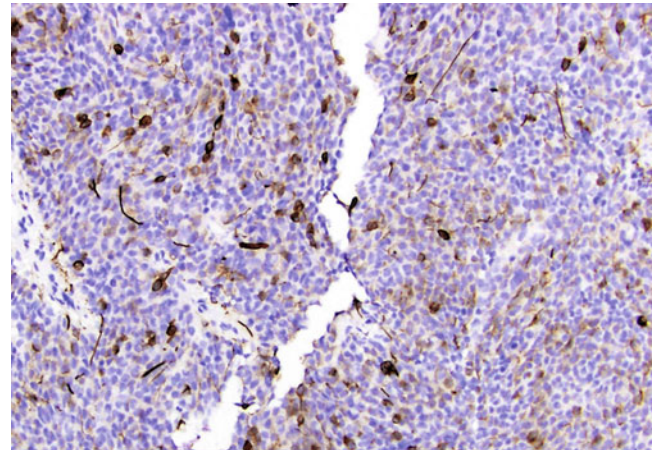


Fig. 34.10 Immunohistochemical staining for neurofilament protein in PPTID, with only patchy staining. With a high rate of mitotic figures, this tumor was graded as WHO grade III, but this patient did not have recurrence following near-total gross resection

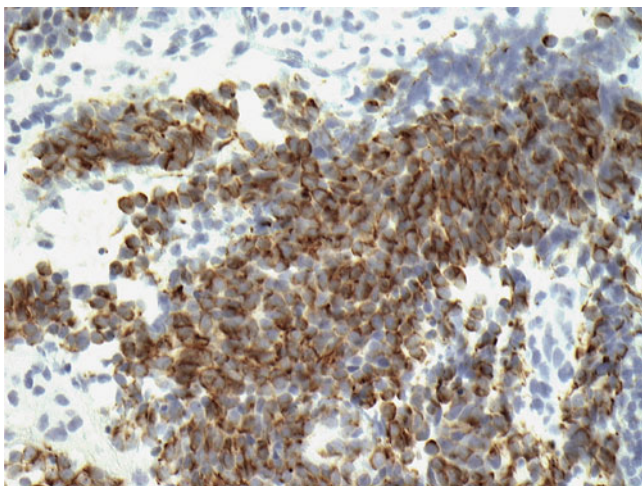


Fig. 34.11 Immunohistochemical staining for chromogranin in pineoblastoma. Note the patchy staining of the cytoplasm

- S-100 protein and retinal-S antigen are typically negative, with rare weak positivity only in an occasional tumor.

34.6 Molecular Pathology

- The *RBI* gene encodes a protein that acts as a cell cycle checkpoint at the G1 phase. Some patients suffering from retinoblastoma and PB harbor germline losses of the *RBI* gene.
- Trilateral retinoblastoma, a heritable form of bilateral retinoblastoma in association with PB, has a rather dismal prognosis. The disease is associated with germline deletion of the *RBI* gene from chromosome 13.
- A subgroup of PB demonstrates *DICER1* mutations, including some patients with germline mutations of this gene [8].

34.7 Prognosis

- The following characteristics were found to influence outcome in pineal neoplasms [9]:

- Tumor histological grade
- Tumor volume
- Tumors with a pineoblastomatous component have a much worse overall survival than the other histological types.
- Gross total resection seems to portend a better prognosis, even for patients with PB [10].
- Aggressive chemotherapy and radiotherapy has been suggested to increase survival for patients with PB [11].

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