Histopathological patterns of papillary tumour of the pineal region

Ewa Matyja1, Wiesława Grajewska1, Paweł Nauman1, Wiesław Bonicki2
1Department of Experimental and Clinical Neuropathology, M. Mossakowski Medical Research Centre, Polish Academy of Sciences,
2Department of Neurosurgery, M. Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, 3Department of Pathology,
The Children’s Memorial Health Institute, 4Department of Neurosurgery, Institute of Psychiatry and Neurology, Warsaw, Poland

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Abstract

Papillary tumour of the pineal region (PTPR) is a rare neoplasm that has been formally included in the 2007 WHO classification of central nervous system tumours. The critical diagnosis of this neoplasm is often difficult because of its similarity to other primary or secondary papillary lesions of the pineal region, including parenchymal pineal tumours, papillary ependymoma, papillary meningioma, choroid plexus papilloma and metastatic papillary carcinoma.

We present the variability of the histopathological pattern in three cases of PTPR. All cases showed predominant epithelial-like morphology but with various degrees of papillary formation and intensity of cellular pleomorphism. One tumour was highly cystic and exhibited cellular sheets containing vessels covered by several layers of uniform columnar to cuboidal tumour cells. The second tumour showed distinct papillae covered by layers of polymorphous cells with atypical, often hyperchromatic nuclei. Numerous cells displayed foamy, eosinophilic or clear, sometimes vacuolated cytoplasm. The third case consisted of solid cellular areas composed of pseudostratified columnar cells, most often arranged in perivascular pseudorosette formations. The cells lining papillary structures exhibited marked polymorphism with atypical, often plump nuclei. Mitotic figures were rare and areas of necrosis were observed only in one case.

Immunohistochemical staining showed diffuse immunoreactivity for neuron-specific enolase, S-100 protein, cytokeratin and vimentin. Focal reaction for synaptophysin and chromogranin A and epithelial membrane antigen (EMA) were observed. The tumours lacked expression of GFAP. The Ki-67 labelling index was relatively low but its focal increase was noted in two cases. The final diagnosis of PTPR was based on both predominant papillary morphology and immunohistochemical results. PTPR should be considered in diagnosis of pineal tumours but their natural history, therapeutic strategy and prognosis remain controversial.

Key words: papillary tumour, pineal region, histopathology, immunophenotype, differential diagnosis.

Communicating author:
Ewa Matyja, MD, PhD, Department of Experimental and Clinical Neuropathology, Medical Research Centre, Polish Academy of Sciences,
5 Pawinskiego St., 02-106 Warsaw, Poland, e-mail: matyja@cmdik.pan.pl

Original article
Introduction

Neoplasms of the pineal region are uncommon and account for less than 1% of all intracranial tumours. They include tumours of diverse origin such as germ cell tumours, pineal parenchymal tumours, astrocytomas, ependymomas and meningiomas [9,15]. Several histological subtypes of primary tumours in the pineal region exhibit distinct papillary features, i.e. papillary ependymoma, papillary meningioma and chordoid plexus tumours. Moreover, metastatic papillary carcinomas might also be located in the pineal region. The differential diagnosis of these papillary tumours is often difficult and requires a wide spectrum of immunohistochemical analysis [28].

In the last edition of the World Health Organization Classification of Tumours of the Central Nervous System (2007), a new tumour of papillary appearance named papillary tumour of the pineal region (PTPR) has been included [22,34]. It is a very rare entity and since its first description by Jouvet et al. in 2003 [21], about 58 cases of PTPR have been reported [2,3,5,6,8,11,14,17,19,24,25,28,32,35,37,38]. PTPR display distinctive clinical and immunophenotypic features and their natural history and treatment strategy are not fully established. This tumour is considered histopathologically as WHO grade II or III.

We present a histopathological and immunohistochemical study in three additional cases of PTPR with various pattern of predominant epithelial-like morphology, distinct papillary formation and variable cellular pleomorphism.

Material and methods

Biopsy tissue was fixed in 10% neutral buffered formalin, embedded in paraffin, and routinely stained with haematoxylin and eosin (H&E). Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded specimens according to the labelled avidin-biotin complex (ABC) method with 3,3’-diaminobenzidine (DAB) as a chromogen, using antibody to: AE1/AE3 (dilution 1 : 100), CAM 5.2 (dilution 1 : 100), S-100 protein (polyclonal, 1 : 800), epithelial membrane antigen (EMA, dilution 1 : 50), neuron-specific enolase (NSE, dilution 1 : 100), synaptophysin (dilution 1 : 200), chromogranin A (dilution 1 : 100), vimentin (dilution 1 : 100), glial fibrillary acidic protein (GFAP, polyclonal, dilution 1 : 5,000) and Ki67 antigen (clone MIB-1, dilution 1 : 100). All antibodies were from Dako, Glostrup, Denmark.

Clinical data

Three patients (30-year-old and 28-year-old women, 32-year-old man) presented with headache, vomiting, and visual disturbances. In all cases, the brain magnetic resonance imaging (MRI) showed a well-circumscribed, heterogeneous mass in the pineal region, accompanied by supratentorial, obstructive hydrocephalus. In one patient (Case 1), the lesion in the pineal region demonstrated a significant cystic component. All patients underwent surgical tumour resection. The histopathological analysis of neoplastic tissue revealed predominant papillary architecture. Postoperatively, the patients received radiotherapy and chemotherapy. Recurrence of the tumour was encountered in one case (Case 3) after 1.5 years.

Histopathological pattern

All tumours exhibited epithelial-like morphology with papillary or pseudopapillary structures. The combination of solid, densely cellular areas and regions with a loose papillary growth pattern was evidenced.

The first tumour (Case 1) was highly cystic (Fig. 1A) and showed a predominant pseudopapillary appearance (Fig. 1B) with vessels covered by several layers of uniform neoplastic cells (Fig. 1C). The tumour cells were monomorphic with small rounded nuclei with a poorly visible nucleus and usually clear, eosinophilic, sometimes vacuolated cytoplasm (Fig. 1D).

The highly cellular, solid areas revealed ependymal differentiation with numerous perivascular pseudo-rosettes formed by cuboidal or columnar tumour cells (Fig. 1E). A few true rosettes around small lumina could be observed. Mitotic figures were encountered only occasionally. In addition, large areas of necrosis were seen (Fig. 1F). Immunohistochemically, the tumour showed strong reaction for cytokeratins CAM5.2 and AE1/AE3 (Fig. 2A) and diffuse immunoreactivity for neuron-specific enolase, S-100 protein and vimentin. Slight positivity for epithelial membrane antigen was observed (Fig. 2B). Positive reaction for synaptophysin was seen only in a few neoplastic cells (Fig. 2C), whereas expression of chromogranin A was negative. The tumour tissue did not exhibit GFAP expression. The Ki-67 labelling index was relatively low, but its focal increase was noted (Fig. 2D).

The second tumour (Case 2) showed both densely cellular areas (Fig. 3A) and distinct papillae covered by layers of polymorphic cells with atypical, often...
hyperchromatic nuclei (Fig. 3B). Papillary structures were formed by fibrovascular cores that were covered by columnar, often multilayered cells with eosinophilic cytoplasm (Fig. 3C). Perivascular pseudorosettes were often formed by pleomorphic cells resembling astroblastic or ependymal pseudorosettes (Fig. 3D). Immunohistochemical staining revealed intense reaction for NSE (Fig. 4A), S-100 protein and cytokeratins AE1/AE3 (Fig. 4B). Positive reaction of epithelial membrane antigen (Fig. 4C) and slight immunexpression for synaptophysin (Fig. 4D) and chromogranin A (Fig. 4E) could be focally seen. The Ki-67 labelling index was relatively low, but its focal increase was encountered. GFAP expression was limited to the tumour stroma (Fig. 4F).

The third case (Case 3) consisted of solid cellular areas composed of pseudostratified columnar cells, most often in a perivascular arrangement (Fig. 5A). The majority of cells displayed foamy, eosinophilic or clear, sometimes vacuolated cytoplasm with pleomorphic nuclei (Fig. 5B). Pseudopapillary structures with a central fibrovascular core predominated but areas with distinct papillary structures could also be seen (Fig. 5C). Focally the cells exhibited marked pleomorphism with large, atypical, bizarre nuclei (Fig. 5D). Some vessels exhibited hyalinization or slight endothelial cell proliferation. Immunohistochemical staining revealed intense reaction for NSE and cytokeratins AE1/AE3 (Fig. 6A). Immunostaining for S-100 protein was observed in perivascular structures (Fig. 6B). Focally, the neoplastic cells displayed slight positive reaction of epithelial membrane antigen and diffuse immunexpression for synaptophysin (Fig. 6C). The tumour tissue lacked chromogranin A and GFAP.
expression. The Ki-67 labelling index was focally increased (Fig. 6D).

In all cases, the final diagnosis of PTPR was based on predominant papillary morphology and results of immunohistochemical studies.

**Discussion**

The pineal region is a rare site of primary CNS tumours. However, histologically different neoplasms including pineal parenchymal tumours, germ cell tumours, gliomas, ependymomas, dermoid cysts and meningiomas might arise in this region [9,15]. The management strategy of these heterogeneous lesions remains controversial [27]. The biopsy specimen from pineal region tumours might not provide any useful material for accurate diagnosis. Cytology smear is occasionally helpful in the diagnosis of PTPR [10].

Two groups of primary pineal tumours are distinguished in the current 2007 WHO classification: pineal parenchymal tumours, which originate from the pineal gland (pineocytoma, pineal parenchymal tumour of intermediate differentiation, pineoblastoma and papillary tumour of the pineal region) and germ cell tumours [22].

Papillary tumour of the pineal region (PTPR) is a very rare neuroepithelial tumour located in the region of the pineal gland in adults of mean 31.5 years old (age range from 5 to 66 years), with slight predominance of females [34]. So far, only a few paediatric cases of PTPR have been described [3,12,29]. This novel tumour type is considered as WHO grade II or III due to its potential malignant behaviour. The main clinical symptoms are non specific and include headache, secondary to hydrocephalus related to ce-
Papillary tumour of the pineal region

rebral aqueduct compression. MRI usually reveals
a well-circumscribed tumour, often with cystic com-
ponents [5,39].

PTPRs are characterized by papillary features and
epithelial morphology associated with immunoreac-
tivity for cytokeratins and markers of ependymal dif-
ferentiation. Originally such tumours were described
under different names, i.e. papillary pineocytoma,
choroid plexus papilloma and others. For the first
time PTPR was reported as a distinct entity in 2003 by
Jouvet et al. [21], but was included in the WHO Clas-
ification of Tumours of the Central Nervous System
in 2007. This tumour is considered to derive from
remnants of specialized ependymal cells of the subcom-
missural organ (SCO) [21]. The SCO may be present
in multiple locations near the third ventricle; thus PTPR
histogenesis is similar to chordoid gliomas of the
anterior third ventricle. The SCO ependymal cells
during development transiently express GFAP, which was
focally positive in this neoplasm, and in the later pe-
riod of development they are characterized by
vimentin and cytokeratin staining [33].

Immunohistochemically and ultrastructurally,
PTPR demonstrates a combination of epithelial,
ependymal and neuroendocrine differentiation [21,
22]. PTPR displays immunoreactivity for cytokeratin,
sometimes in a dot-like intracytoplasmic pattern, but
generally lacks expression of GFAP or synaptophysin.
The intense expression of Bcl-2 was reported in one
case of PTPR with a high proliferation index and its
relation with neoplastic malignancy has been sug-
gested [13]. In the cases presented here, the immu-

![Fig. 5. Case 3. Histopathology of PTPR, H&E. A) Solid cellular area and perivascular structures. B) Vessel lined by layers of columnar tumour cells with eosinophilic cytoplasm. C) Papillary growth pattern and central fibrovascular cores. D) Areas with uniform, clear tumour cells (left) and polymorphic neoplastic cells with atypical nuclei (right). Bars: A, C, D – 100 µm; B – 250 µm.](image-url)
nophenotype revealed a variable pattern of neuronal and epithelial markers. Our three cases of PTPR exhibited characteristic papillary architecture. One tumour was highly cystic (Case 1) and two other tumours (Cases 2 and 3) were composed of solid areas and regions with a loose papillary growth pattern and revealed marked pleomorphism of neoplastic cells (Case 3).

The critical histological diagnosis of PTPR is difficult because of its morphological and immunomorphological similarities to other primary or secondary tumours of the pineal region with papillary features, including papillary ependymoma, papillary meningioma, choroid plexus papilloma/carcinoma or metastatic papillary carcinoma [28].

Distinction of PTPR from other pineal parenchymal tumours is mainly based on diffuse expression of neuronal markers in pineal parenchymal tumours, whereas the majority of PTPR are negative or only occasionally exhibit focal, weak synaptophysin positivity [36]. Papillary structures are very rarely encountered in pineal parenchymal tumours and only a few such cases have been reported so far, including papillary pineocytoma in a child [31]. Recently, a unique case of pineal parenchymal tumour of intermediate differentiation with papillary features was described and the authors suggested its focal transformation to PTPR [7]. Thus, a continuum of primary pineal tumours ought to be considered.

More often, PTPR might be misdiagnosed as ependymoma [16] or choroid plexus papilloma/carcinoma. Both papillary ependymoma and PTPR exhibited epithelial and vascular components but ependymoma is characterized by distinct GFAP expression.
[16], whereas PTPR is only occasionally slightly immunostained for glial markers. Both these tumours might exhibit EMA immunoreactivity, including dot-like staining typical for ependymomas. Nevertheless, PTPR is positive for cytokeratins, which are not seen in ependymomas.

Occasionally, papillary glioneuronal tumour (PGNT), a rare glioneuronal neoplasm, ought to be considered in differential diagnosis with PTPR. However, PGNT is composed of pseudopapillary structures created by GFAP-positive astrocytes covering hyalinized vessels and interpapillary neurocytic elements with strong reactivity for synaptophysin [20]. This tumour was mainly located supratentorially with a predilection for the temporal lobe.

Distinction of PTPR from the papillary subtype of meningioma is based on lack of cytokeratin expression in meningeal neoplastic cells and ultrastructural examination [1].

The differentiation of PTPR and choroid plexus tumours or metastatic carcinoma is particularly difficult, as all these tumours exhibit strong expression of cytokeratins. PTPR usually showed immunostaining for AE1/AE3, CAM 5.2 and CK18, whereas metastatic carcinomas were usually positive for cytokeratins CK7 and CK20, which are usually low or absent in PTPR. A very helpful marker in differential diagnosis between PTPR and metastatic papillary thyroid carcinoma or papillary lung adenocarcinoma is immunexpression of TTF1. Most choroid plexus tumours exhibit Kir7.1 immunoreactivity, which is not expressed in PTPR [17]. Moreover, choroid plexus tumours are rarely located in the third ventricle in adults [25].

The biological behaviour of PTPR is variable and the tumour might correspond to WHO grade II or III. However, the precise histological criteria of grading has not been defined [22,30]. Data on the clinical follow-up of PTPR are scarce and the clinical course is uncertain [4,5]. Aggressive behaviour of PTPR with frequent local recurrence was confirmed in 31 cases by a retrospective multi-centre study [14].

PTPR might display local recurrences and CSF dissemination despite surgical resection and radiotherapy [36]. Cases of PTPR with leptomeningeal seeding and multiple lesions or spinal metastasis have been reported [18,26]. It has been suggested that unpredictable biological behaviour connected with different tumour growth and recurrence rates is probably related to the heterogeneous characteristics of these tumours, demonstrating a large spectrum of differentiation [23].

So far only one study has demonstrated genomic instability of PTPR with numerous chromosomal aberrations, particularly losses on chromosome 10 and gains on chromosome 4 [17]. Gene expression profiling might be useful as diagnostic markers to identify genes and classify tumours of the pineal region [12].

In conclusion, PTPR should be considered in the differential diagnosis of pineal tumours. They are epithelial-like tumours with papillary features, exhibiting epithelial, ependymal and neuroendocrine differentiation. The clinical course and prognosis of PTPR are difficult to predict because of their histological variability.

References


