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Review article

Papillary tumor of the pineal region. Report of two cases and literature review

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ABSTRACT

Papillary tumor of the pineal region (PTPR) was introduced to the WHO classification in 2007. This rare tumor of little known natural history and unpredictable behavior was described in fewer than 100 cases. Its optimal treatment is not established yet. We report another two cases of PTPR in whom tumors were totally removed via supracerebellar infratentorial approach and both were treated with radiotherapy. In a 37-year-old man the operation was delayed 6 years after the first tumor diagnosis and subsequent shunt placement. He has no complaints 10 years after the onset of the disease. A 45-year-old woman has no complaints 24 months after surgery. Our experience and the data from literature indicate that a total tumor removal is the major prognostic factor.

1. Introduction

Pineal region tumors of atypical papillary histological appearance were sporadically described already years ago [1,2]. Clinical data were scarce as the surgical treatment of pineal tumors was not commonly performed then. In 2003 Jouvet et al. described papillary tumors of the pineal region (PTPR). On the basis of 6 histologically examined cases, they came to conclusion that it was a distinct type of the pineal tumor [3]. Its characteristic histopathological picture was described. Some years later, in 2007, the tumor was included into the new revision of the WHO classification of CNS tumors [4]. The biological behavior of PTPR is variable and may correspond to the WHO grades II or III [4]. This rare tumor has been described in fewer than 100 cases [5,6]. The optimal treatment options have not been established yet [4,7–9]. The majority of cases described till now were confirmed histologically, but their treatment differed. Surgery (biopsy, attempt at gross total removal, treatment of hydrocephalus) remains the main option, but still seems insufficient in particular cases. Radiotherapy and chemotherapy as adjuvant treatment options are commonly used, but their value needs to be evaluated. This is the reason that we report two additional cases of PTPR because only the multicenter study and growing experience may in future give better indications for optimal therapy.

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2. Materials and method

Among 65 pineal region tumors treated surgically in our institution in years 1998–2013, histological examinations revealed 2 cases of PTPR. Both tumors were totally removed macroscopically via supracerebellar infratentorial approach. Post-operative materials were submitted to pathology, where formalin-fixed paraffin embedded tissue blocks were prepared. Initial haematoxilin and eosin staining of tissue slides was followed by additional immunohistochemical and PAS stainings. The antibodies used in tumor diagnosis were: cytokeratin (clone AE1/AE3, dilution 1:50), EMA (clone E29, 1:100), CEA (clone Il-7, 1:50), GFAP (clone 6F2, 1:100), NF (clone 2F11, 1:100), NSE (clone BBS/NC/VI-H14, 1:100), synaptophysin (clone DAK-SYNAP, 1:50) and Ki-67 (clone MIB-1, 1:100), all manufactured by DAKO, Denmark. Postoperatively both patients underwent 3D conformal radiotherapy to tumor beds with margins, with photon energy 6 MeV. Each one received dosis of 5400 cGy in 30 equal fractions during about 6 weeks.

Case 1. KK, male, 37 years, admitted because of a headache, hypoacusis, tinnitus and visual worsening lasting 10 days. 6 years earlier the diagnosis of a pineal tumor with hydrocephalus was established in another hospital and the patient underwent shunt placement. On admission, only hypoacusis was found. Routine blood tests, serum alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (βCG) levels were normal. MRI with significant contrast enhancement revealed a pineal tumor of heterogenous morphology with cystic components, 49 mm × 31 mm × 27 mm in size. The tumor penetrated the third ventricle, pressed cerebral peduncles and cerebellar vermis (Fig. 1). As the shunt worked correctly there was no hydrocephalus.

At the time of surgery, the tumor was grayish, soft, contained cysts with yellow fluid, did not bleed. The borders were clear except for the right thalamus, which seemed infiltrated. Postoperatively the patient had diplopia, nausea and improvement of hearing. Discharged home on the 9th postoperative day with diplopia. Later he proceeded to adjuvant radiotherapy. 47 months after the operation and more than 9 years from the onset of the disease he feels well, is professionally active, with no complaints and with no residual tumor in MRI scans (Fig. 1).

Histologically the tumor was composed of epithelioid cells forming papillary structures and solid areas (Fig. 2A). Among tumor cells with little atypia, foci of highly atypical cells were observed. Despite conspiciuous cell morphology, increased mitotic activity was absent in such areas. No tumor necrosis, nor vascular proliferations were found (Fig. 2B). In immunohistochemical stainings neoplastic cells were positive to cytokeratin (Fig. 2C). The same cells were found to be EMA-, CEA-, GFAP-, NF- and synaptophysin-negative. Low Ki-67 labeling index of tumor cells reflected low proliferative activity of the neoplasm (Fig. 2D). In cytoplasm of neoplastic cells PAS-positive granules were found (Fig. 2E). Based on histology and immunophenotype of neoplastic cells, diagnosis of PTPR was made (Fig. 2).

Case 2. BA, female, 45 years, with a 2-month history of imbalance, all limbs painful and weak, urinary incontinence for 2 years, arterial hypertension for 3 years. On admission neurological examinations showed imbalance, left side hemiparesis, hypoestesia on the right side of the trunk, bilateral ataxia. Cranial nerves were normal. Routine blood tests, serum AFP and βhCG levels were normal. MRI scan revealed a heterogenous, strongly contrast enhanced mass in the pineal region, the third ventricle, cerebral aqueduct and quadrigeminal cistern with small cystic components. The tumor was 22 mm × 15 mm × 14 mm in size and caused obstructive hydrocephalus with periventricular edema (Fig. 3). At operation it was grayish, soft, infiltrating right thalamus. Postoperatively she had ocular discoordination with the Parinaud syndrome, psychomotor slowing and pneumocephalus. She was discharged home on the 21st postoperative day. Radiotherapy was used. 17 months later no

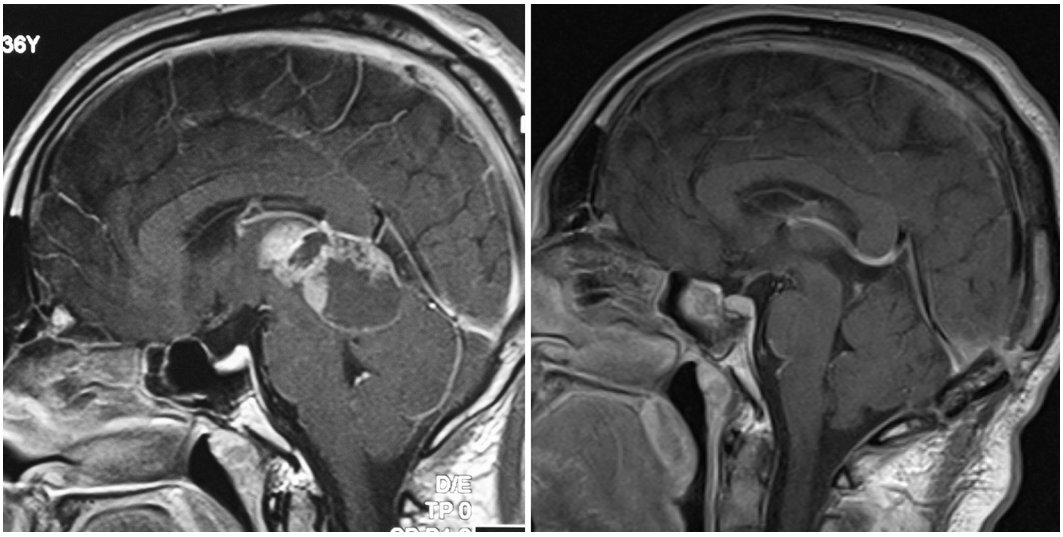

Fig. 1 – Case no. 1. MRI of papillary tumor of the pineal region, sagittal section, contrast enhancement. Right – preoperative examination. Left – 4 years after the operation.

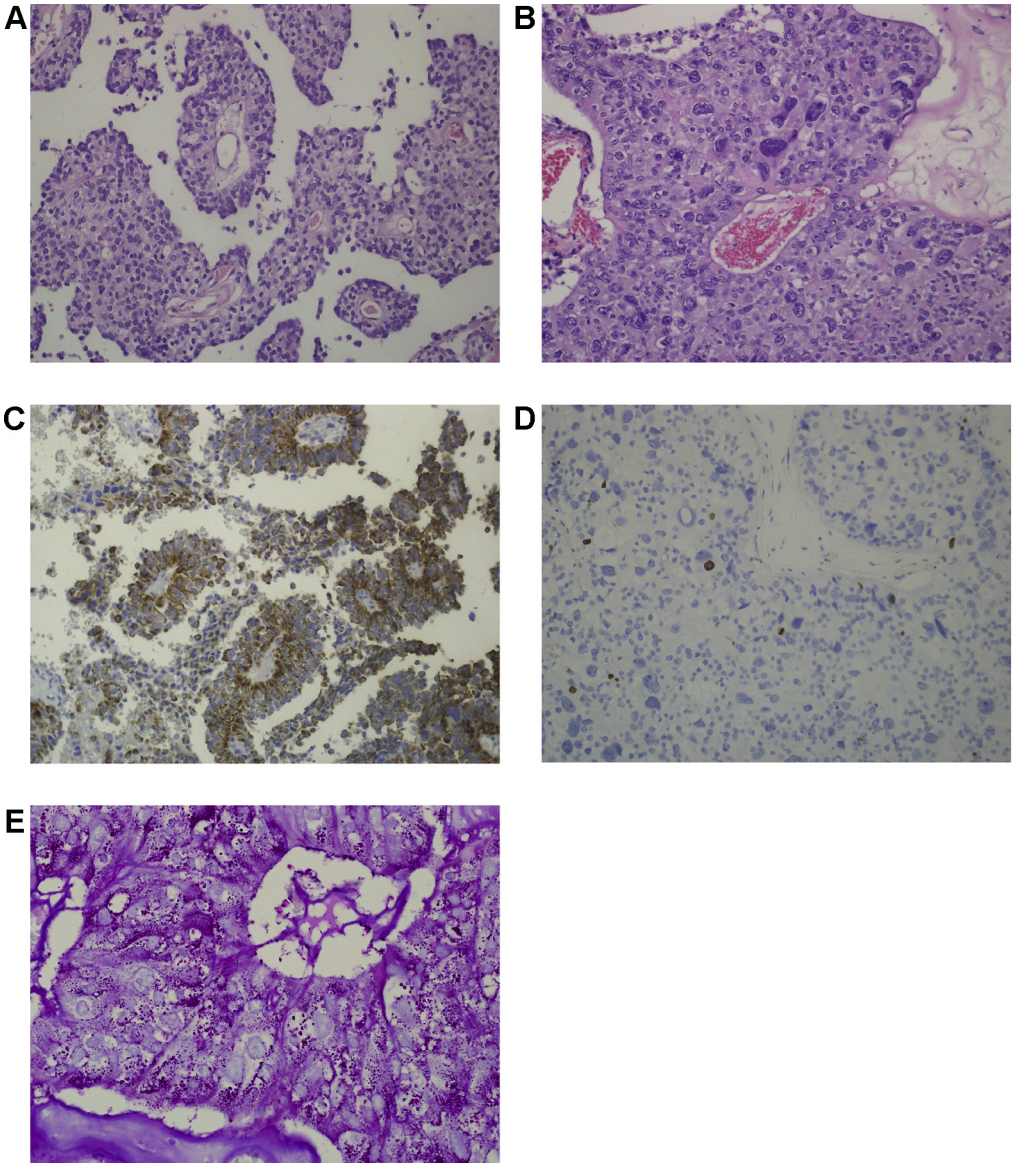

Fig. 2 – Case no. 1. Tumor histology. A – Papillary areas of tumor (H&E staining, 200×). B – Area of tumor cells with greater atypia, but without increased mitotic activity (H&E, 200×). C – Expression of cytokeratin by neoplastic cells in immunohistochemistry (anti-CK, 200×). D – Minimal nuclear staining of tumor cells with anti-Ki-67 antibody (anti-Ki67, 200×). E – PAS-positive cytoplasmic granules in tumor cells – such finding might correspond to ultrastructural features of partial secretory differentiation of tumor cells (PAS staining, 400×).

residual tumor was found in MRI exam (Fig. 3), hydrocephalus disappeared and the patient felt well though imbalance and slight diplopia persisted.

Histologically the tumor was composed of monomorphous population of medium-sized epithelioid cells with little atypia, forming papillary structures with vascular stalk. Solid areas of tumor cells were also present, accompanied with perivascular pseudorosettes (Fig. 4A). No foci of necrosis, conspicuous mitotic activity, nor vascular proliferation were present. The tumor cells were immunopositive to cytokeratin (Fig. 4B). Immunopositivity to neuron specific enolase (NSE) was detected (Fig. 4C), but the tumor cells were immunonegative to other neuronal markers, such as synaptophysin or neurofilament (NF) (Fig. 4D), as well as to glial fibrillary acidic protein (GFAP). Similarly to Case No 1 few tumor cells expressed Ki-67 antigen (Fig. 4E). The neoplastic cells were PAS-negative. The histological diagnosis of WHO grade II PTPR was established (Fig. 4).

3. Discussion

PTPR is a pineal tumor encountered both in adults and in children [10–13]. The average age of patients is 32–34 years

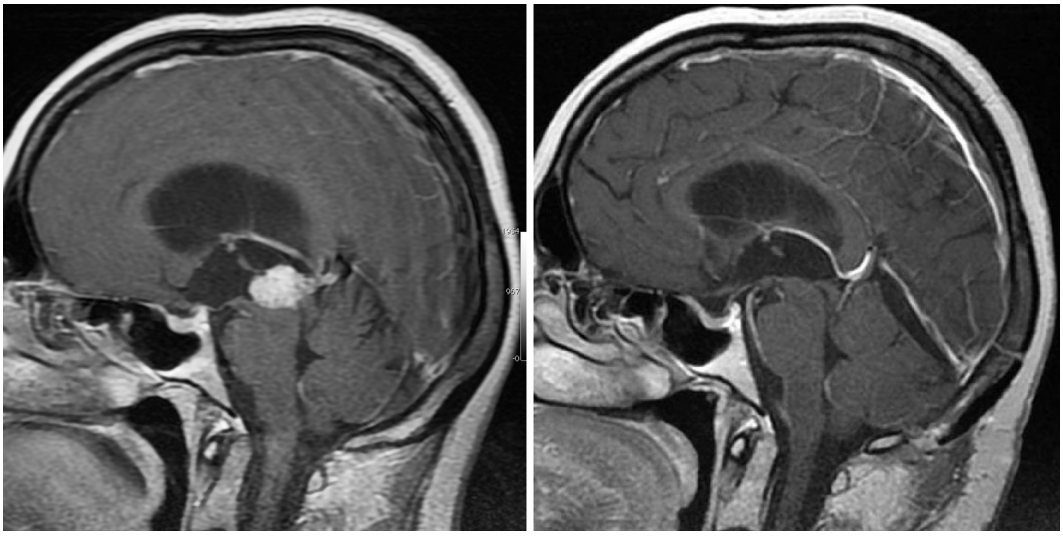

Fig. 3 – Case no. 2. MRI of papillary tumor of the pineal region, sagittal section, contrast enhancement. Right – preoperative examination. Left – 4 months after the operation.

[4,14]. Symptoms do not differ from those of other pineal tumors. They mainly consist of a headache due to obstructive hydrocephalus, visual impairment, gait disturbances. Tumors at the time of diagnosis are quite big, being 5–50 mm in diameter (average 29 mm) and nearly in half of the patients they cause hydrocephalus [14]. In the majority of MR imaging reports of PTPR, the tumor looks like a heterogeneously enhanced pineal region mildly lobulated mass with cystic compartments [3,15–17]. The intrinsic hyperintensity on non-contrast T1-weighed sequences in the absence of fat, hemorrhage, melanin or calcifications is considered to be a characteristic MRI appearance of this tumor [15]. This, however, is not true in all cases [18,19]. Histological diagnosis of PTPR is difficult, as the tumor may resemble other pineal region tumors with papillary features. PTPR may sometimes be distinguished from papillary ependymoma, papillary meningioma, choroid plexus papilloma or carcinoma and even metastatic papillary carcinoma on the basis of thorough immunohistochemical staining only [3,7,20]. Before the definition of PTPR was given these kinds of tumors had been sometimes diagnosed erroneously according to old experiences, but nowadays after reexamination and additional stainings done they seem PTPR [21,22]. It is postulated that this tumor derives from specialized ependymocytes of the subcomissural organ in the third ventricle [3].

Cases reported in the relevant literature, rarely in larger series, show that the natural course of the disease is unpredictable. Therefore establishing optimal treatment indications seems difficult. PTPR is considered to be the WHO II or III grade, however the exact histological grading criteria have not been explained precisely yet [4,7,14,23]. Tumor might exhibit slow progression and long clinical course, as was in the case no. 1 reported here [24–26]. However local recurrences are frequent [5,11,14,27], CSF spinal dissemination or meningeal spread may occur [3,5,8,14,28–31].

Treatment modalities differ. The most common choice is an attempt at gross total surgical tumor removal and postoperative adjuvant radiotherapy. In the series of 72 cases collected from the literature by Poulgrain et al. [14], surgical tumor removal was performed in 87% of the patients. In 11% only the biopsy was done. In many cases the coexisting hydrocephalus had to be treated. Radiation with different methods and extent was used in 61% of cases.

In a quite extensive retrospective multicenter study of 44 cases of PTPR, the statistical analysis showed that the extent of the surgery was the only clinical factor associated with a better overall survival [8]. Radiotherapy did not influence the overall survival nor progression-free survival. This analysis proved chemotherapy also ineffective. This study confirmed a high risk for PTPR recurrence (58% at 5 years, 70% at 6 years).

On the other hand, tumor regression after radiotherapy [10,32] or even tumor disappearance [33] was observed. Whole brain irradiation, local radiotherapy, gamma knife surgery, stereotactic linac radiosurgery were all used with different protocols [32,34,35]. A good local control of tumor was achieved in a few cases treated with interstitial brachytherapy with $_{125}$Iodine seeds [36].

When surgery and radiotherapy were ineffective, long lasting tumor regression could be sometimes obtained after chemotherapy with temozolomide [37]. Temozolomide with etoposide, etoposide with carboplatin, ACNU were all used in PTPR treatment with various results [30,38,39]. A successful long-term response to bevacizumab, an antiangiogenic antibody against vascular endothelial growth factor, in a refractory recurrent multifocal PTPR was recently described [6].

No optimal therapy of PTPR is established yet, so even in the same institution patients are treated differently according to the individual neurosurgical and oncological evaluation of a case, its histological pattern and other factors which may be difficult to identify [31,40,41].

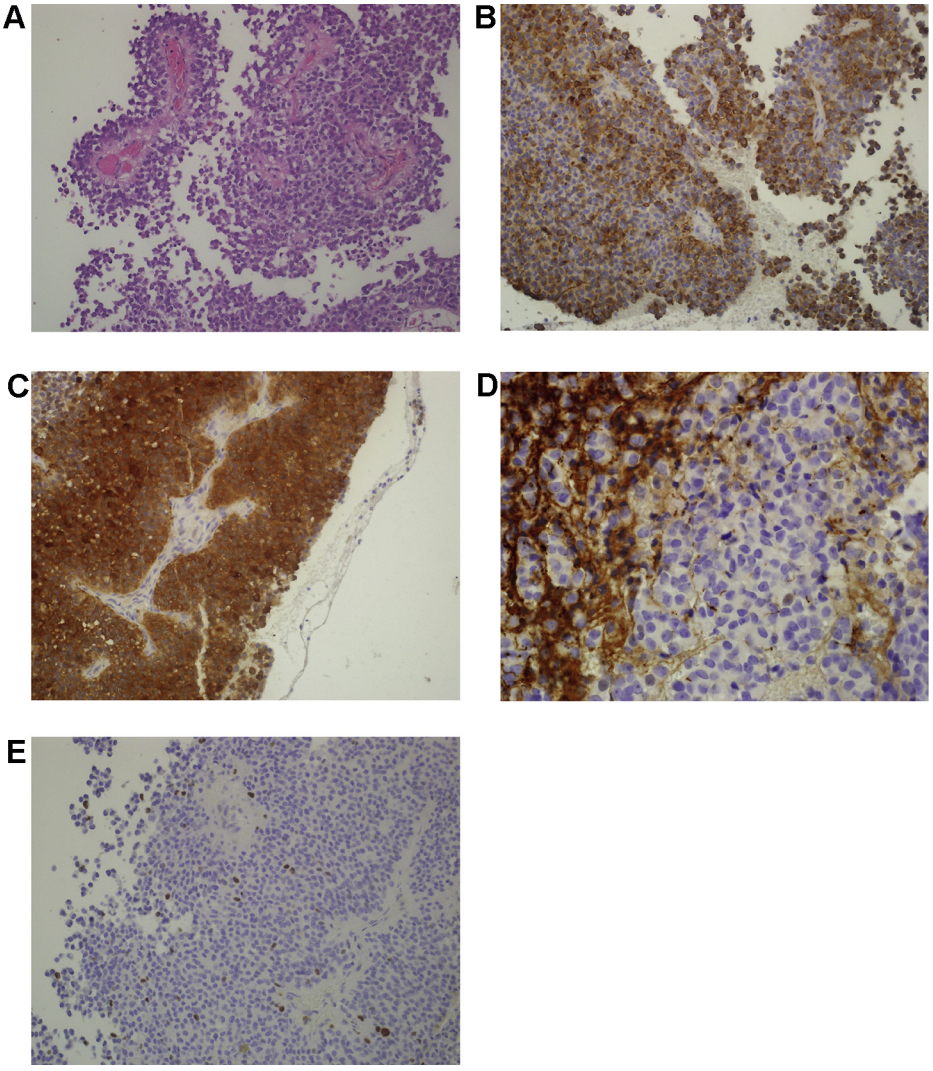

Fig. 4 – Case no. 2. Tumor histology. A – Neoplastic papillary structures (H&E, 200×). B – Expression of cytokeratin by tumor cells (anti-CK, 200×). C – Expression of NSE by tumor cells (anti-NSE, 200×). D – NF-negative tumor cells infiltrating adjacent NF-positive non-neoplastic tissues of pineal region (top left) (anti-NF, 400×). E – Low Ki-67 labeling index of tumor cells reflecting low proliferative activity of the neoplasm (anti-Ki-67, 200×).

4. Conclusions

PTPR is a very rare tumor of the pineal region with unpredictable course and proclivity for local recurrence and seeding. Sometimes, however, the course of the disease is long. The only positive prognostic clinical factor improving an overall survival rate is gross total resection of the tumor mass. Other methods do not offer the permanent cure. For that reason, and because of the heterogenous tumor nature, all kinds of biopsies (stereotactic or endoscopic) should be avoided and the goal of the surgery should be a complete tumor resection. Further experience with a larger number of cases is needed to establish optimal treatment guidelines.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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