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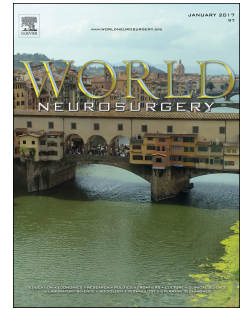
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**Title Page****Title**

Papillary tumor of the pineal region in children: presentation of a case and comprehensive literature review

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**Abstract**

The papillary tumor of the pineal region (PTPR) is a rare grade II-III pineal lesion with peculiar histologic and immunohistochemical features. These tumors mostly occur in adults, rarely in children (19 cases reported up to now).

We present a 3-year-old boy who was re-operated for a recurrent PTPR (grade II). The gross total resection of the lesion, through an occipital interhemispheric approach in sitting position, was followed by adjuvant radiochemotherapy. Histological examination revealed tumor progression (grade III), and the MIB-1 proliferation index was higher than 25%. The patient continues to do well with no evidence of recurrence more than 3 years following surgery.

A comprehensive literature review regarding the PTPR, including the current management in children, is reported.

PTPR are extremely rare in children, and immunohistochemistry is needed for their differentiation from other pineal tumors. These tumors present a big rate of recurrence, and a multidisciplinary management (microsurgical resection followed by radio- and/or chemo-therapy) is needed in most of the cases to achieve favorable outcomes.

**Key words:**

Children, Immunohistochemistry, Multidisciplinary management, Microneurosurgery, Papillary tumor of the pineal region, Pineal region lesions, Radiochemotherapy

**Abbreviations and Acronyms**

EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; INI-1, integrase interactor 1; MAP 2, microtubule associated protein 2; PHH3, phosphohistone-H3; PTEN, phosphatase and tensin homolog; PTPR, papillary tumor of the pineal region

## Introduction

The papillary tumor of the pineal region (PTPR) is a new entity introduced in the 2007 World Health Organization nomenclature to describe a rare grade II-III pineal lesion with particular histologic and immunohistochemical features. These tumors mostly occur in the adult population, and are extremely rare in children.<sup>1-3</sup>

Herein, we present the case of a 3-year-old boy who was initially operated abroad for acute hydrocephalus due to a PTPR, and then, after few months, was admitted to our department for a tumor recurrence.

Our purpose is to report the multidisciplinary management of this case, which presented a good response after the gross total resection of the lesion and adjuvant radiotherapy and chemotherapy, with no recurrence after 3 years.

Moreover, we present a comprehensive literature review regarding the PTPR while describing the current management of this new entity in children.

## Case presentation

A three-year-old boy with a grade II PTPR was admitted to our department for re-evaluation. Nine months prior, he presented with acute hydrocephalus, and underwent subtotal resection of the lesion abroad. Follow up brain MRI revealed the persistence of a giant heterogeneously enhancing pineal region lesion with a small cystic component (Fig. 1). Ventriculomegaly was also present. The boy did not present neurological deficits.

The patient underwent an occipital interhemispheric approach in sitting position with gross total tumor resection (Fig. 1). The postoperative course was uneventful.

Based on the operative video analysis, microsurgical aspects may be detailed as follows:

- after a left occipital craniotomy, the dura is opened under the microscope based on the superior longitudinal sinus;
- strong dural retraction with vicryl stitches along the opening provides a hemostasis of the epidural space;
- the cerebrospinal fluid is released from the posterior interhemispheric cistern along the interhemispheric approach;
- after a careful access the tumor is recognized, and, under a high magnification, tissue samples are taken for immediate histological studies;

- internal debulking of the tumor is performed using ring forceps and long bipolar forceps as well;
- small vessels running on the surface of the tumor are coagulated and cut. After a careful dissection and devascularization of the lesion, the tumor is softly but constantly pulled out using long ring microforceps in the right hand and thumb regulated suction tube in the left hand;
- the tumor is shrunk with bipolar coagulation, and a piecemeal reduction of the tumor is performed;
- water dissection is used to separate deep borders of the lesion from the surrounding tissue, and continuous irrigation as well is used to keep a clean surgical field;
- the final steps include a painstaking detachment of tumoral remnants from the inferior sagittal sinus, and a meticulous hemostasis of the surgical site.

After surgery, the histologic diagnosis was grade III PTPR. According to immunohistochemistry, the lesion was positive for pancytokeratins (Cytokeratin 5,6,8,18), vimentin, microtubule associated protein 2 (MAP 2), S100 protein, integrase interactor 1 (INI-1), CD99, transthyretin, CD56, epithelial membrane antigen (EMA, focal positivity), and synaptophysin (weak focal positivity). On the other hand, the lesion was negative for neurofilament protein (SMI-32), glial fibrillary acidic protein (GFAP), and chromogranin A (Fig. 2).

The MIB-1 proliferation index was higher than 25%, and the mitosis-specific marker phosphohistone-H3 (PHH3) determined 15 mitosis/mm<sup>2</sup>. Compared with the previous histologic result from the first surgery, this tumor recurrence had more necrosis, more mitosis, and the MIB-1 proliferation index was higher too.

Four weeks after the surgery, the patient received focal fractionated radiotherapy of the pineal tumor bed. A total of 54Gy was divided in a daily dose of 1,8Gy. In February 2015, the patient started chemotherapy based on an ependymoma protocol of cisplatin-cyclophosphamide-vincristine-etoposide, which was delivered in four intravenous cycles, each lasting 21 days: 1) days 1, 8, and 15 for the first three cycles: vincristine, 1.5 mg/m<sup>2</sup>, 2) days 1, 2, 3: etoposide, 100 mg/m<sup>2</sup>, 3) day 1: cisplatin, 100 mg/m<sup>2</sup>, and 4) days 2, 3: cyclophosphamide, 1000 mg/m<sup>2</sup>.<sup>4</sup> The cisplatin dose had to be reduced from 100mg/m<sup>2</sup> to 80mg/m<sup>2</sup> because the patient had only one kidney for a congenital malformation.

The patient continues to do clinically well with no evidence of developmental delay and without recurrence more than 3 years following surgery (Fig.1).

### **Discussion and literature review**

The PTPR is a grade II-III pineal lesion introduced in the 2007 World Health Organization nomenclature, with no major changes in the last 2016 World Health Organization classification of brain tumors.<sup>1-3</sup>

According to the French Register of pineal tumors, true pineal tumors represent: pineal parenchymal tumors (27%), germ cell tumors (27%), gliomas (17%), and papillary tumors (8%). Pineal parenchymal tumors are represented by: pineocytomas (13%), pineal parenchymal tumors with intermediary differentiation (66%), and pinealoblastomas (21%).<sup>5</sup>

The first pineal tumor with a papillary aspect, reported as papillary pineocytoma, was described by Trojanowski in 1982.<sup>6</sup> In 2003, Jouvet et al. introduced the term “PTPR”.<sup>7</sup>

Other pineal region tumors with expression of papillary features comprise: ependymoma, choroid plexus tumor, papillary meningioma, germ cell tumor, and papillary metastatic carcinoma<sup>6</sup>

It is currently believed that the PTPR could derive from the subcommissural organ; thus, PTPR, as well as the ependymal cells arising from the subcommissural organ itself, highly express cytokeratin 18 (CK18).<sup>7-9</sup>

### *Histology*

PTPR are tumors characterized by an epithelial-like growth pattern in which vessels are covered by a layer of tumor cells forming perivascular pseudorosettes.<sup>10,11</sup> Light microscopy shows a papillary architecture; vascular connective tissue is composed of several layers of large cuboidal or columnar epithelial-like growth pattern cells.<sup>9</sup> Cells' cytoplasm is clear, and sometimes vacuolated. Nuclei are small and rounded. Mitotic figures are rare and areas of tumor necrosis are very frequent.<sup>7,11,12</sup> PTPR cannot be diagnosed by light microscope, thus immunohistochemical tumor profiles must be acquired.<sup>10</sup>

### *Immunohistochemistry*

Cytokeratin KL1 and cytokeratin 18 are constantly expressed by PTPR. PS100, vimentin, and neuron-specific enolase are frequently positive as well. Transthyretin, synaptophysin, and chromogranin immunolabeling are inconstantly positive. Tumor cells do not express GFAP nor EMA, but GFAP expression would be recognized in the perivascular areas of the tumor.<sup>7,12</sup> Immunolabeling for antineural cell adhesion molecule and nestin is frequently positive, but immunolabeling for anti-NF, anti-antigen S, anti-tau protein, anti- $\alpha$ -fetoprotein, and anti-placental alkaline phosphatase antibodies is negative.<sup>7</sup>

Some studies determined that phosphatase and tensin homolog (PTEN) mutations and activation of the PI3K/Akt/mTOR signaling pathway may play a role in the biology of PTPR, thus opening the possibility to the use of PI3K/Akt/mTOR inhibitors in therapy for patients with PTPR.<sup>13,14</sup>

Studies in serum and cerebrospinal fluid were negative for the tumor markers alpha-fetoprotein and human chorionic gonadotropin.<sup>10</sup>

### *Genetics*

Regarding chromosomal alterations, losses of chromosome 10 were very frequent in different studies. Losses of chromosomes 3, 14, 22, and X were also identified; and gains of chromosomes 8, 9, and 12 were common, as well. Other chromosomal alterations include a homozygous PTEN deletion, and 2 point mutations in exon 7 of PTEN (G251D and Q261stop).<sup>13,14</sup> Fèvre-Montange reported that PTPRs showed high expression of SPDEF, KRT18, and genes encoding proteins reported to be expressed in the subcommissural organ, such as ZFH4, RFX3, transthyretin, and CGRP.<sup>15</sup>

### *Imaging*

Chang et al. reported an intrinsic T1 hyperintensity centered on the posterior commissure, associated with T2 hyperintensity and gadolinium enhancement as a regular presentation in 4 PTPRs.<sup>16</sup> However, fat content related to teratomas, as well as melanin, calcification and extracellular methemoglobin, usually seen in melanotic tumors, and hemorrhagic metastases, choriocarcinomas or teratomas, must also be excluded.<sup>17</sup> Opposite to this description, other authors just reported MRI heterogeneous mass isointense on T1.<sup>10</sup>

### *The biological behavior of PTPRs*

PTPRs grading and prognosis are still unclear so far, and reports of long survival cases contrast with those with local tumor recurrence. Histological grading of PTPRs correspond to WHO grade II or III.<sup>1,2,18</sup> Variables related to decreased progression-free survival are represented by: more than 3 mitoses per 10 high-powered fields, or a Ki-67 proliferation index of more than 10%.<sup>14,19</sup> Some authors reported the isocitrate dehydrogenase 1 and 2 mutations in PTPR cells as a predictor of wild-type genotypes, as similarly described in gliomas.<sup>20</sup>

### *Differential diagnosis*

Regarding to the differential diagnosis, as mentioned above, different tumors present papillary architecture. However, the two main differential diagnoses are: papillary ependymomas, and choroid plexus tumors. Choroid plexus tumors share with PTPR a comparable immunohistochemical profile, but with a different morphologic appearance. On the other hand, ependymomas present similar morphologic appearance with different antigenic

expression. Choroid plexus tumors present exclusively papillary architecture lined by a single cell layer without the massive component, and, unlike PTPR, areas of necrosis are extremely rare. Choroid plexus carcinomas are well differentiated and with higher degree of anaplasia. Regarding the immunohistochemical analysis, potassium inwardly-rectifying channel Kir 7.1 and stanniocalcin-1 are only expressed by choroid plexus tumors.<sup>21</sup> Ependimomas show a constant expression of EMA and GFAP, with no expression of cytokeratin KL1.<sup>12</sup> Finally, only papillary tumors express MAP 2.<sup>21</sup>

Papillary meningiomas, in contrast with PTPR, present a dense membrane expression of EMA. Vimentin and protein S100 are expressed by papillary meningiomas in 40% of cases. Papillary tumors of the pineal parenchyma, such as papillary pineocytoma, present massive expression of synaptophysin and antigen S, while cytokeratins and vimentin are not expressed.<sup>21</sup>

DNA methylation profiling using Illumina 450k arrays reliably distinguished PTPR from ependimomas and pineal parenchymal tumors of intermediate differentiation. The group of PTPR with a higher global methylation had a tendency toward shorter progression-free survival.<sup>14</sup> The overexpressed SPDEF gene, known to be present in the rodent subcommissural organ, has a remarkable expression in PTPR compared with ependymal tumors, choroid plexus tumors, and samples of other central nervous system tumor entities.<sup>14</sup> Some papillary tumors of the midline, such as papillary thyroid carcinoma and papillary craniopharyngioma, conceal BRAF-V600E mutations. However, PTPR demonstrated negativity for BRAF-V600E.<sup>22</sup>

### *Management*

In a multicentric retrospective study of 31 patients by Fèvre-Montange et al., gross total resection was the only factor that tended to have a significant positive effect on disease progression. A complete open resection was achieved in 21 cases and, after heterogeneous schemes of radiotherapy after complete (9) or incomplete (6) resection, 21 patients presented local (19), local and spinal (1), or only spinal (1) progression in a mean follow up of 4.2 years (range, 0.2–16.5 years). The overall survival was 73% at 5 years, and 58% at 10 years.<sup>11</sup>

Regarding to the radiotherapy, based on the above-mentioned study, this tumor appears to have a high potential for local recurrence during the 5 years after initial surgery, suggesting the need for tumor bed boost radiotherapy after surgical resection. However, no strong evidence is available. On the other hand, spinal dissemination seems to be rare.<sup>11,12</sup>

Radiotherapy may consist of craniospinal irradiation with a boost to the primary site, whole brain radiotherapy with a boost to the primary site, focal irradiation of the pineal area only, and radiosurgery. In a study published



by Fauchon, the median pineal dose in 22 of the 26 irradiated cases was 54 Gy (CI 95 %: 12.0–60.0 Gy). Despite relatively high cumulative doses (more than 100 Gy in 3 cases), only 2 cases presented irradiation-related side effects: a thalamic radionecrosis associated with diplopia and hypersomnia, and a thalamo-tectal radionecrosis associated with motor deficiency and Parinaud's syndrome.<sup>23</sup>

Some authors reported favorable outcomes after biopsy procedures followed by radiotherapy. In a case reported by Smruti, an endoscopic third ventriculostomy with a simultaneous endoscopic biopsy followed by postoperative radiotherapy (50.4 Gy) resulted in a complete regression of the tumor with no evidence of recurrence at 25 months.<sup>24</sup> Similarly, Riis et al. described a case of a PTPR treated with stereotactic radiosurgery in a Gamma Knife unit after stereotactic biopsy of the tumor. Five years after treatment with a dose of 12 Gy on the 50% isodose, the tumor size was still decreasing.<sup>25</sup>

Ishida et al. studied the safety and efficacy of stereotactic 125iodine brachytherapy for the treatment of PTPRs. 100% local tumor control was achieved with a median follow-up of more than four years. No significant clinical nor radiological side effects of 125iodine brachytherapy were detected during the follow-up period, and all symptoms improved significantly.<sup>20,26</sup>

Chemotherapy has been proposed in specific cases: rapid spinal dissemination, first-line radiotherapy based treatment, and in patients with local recurrences. However, the evidence remains weak to support this modality treatment.<sup>21</sup> Adjuvant chemotherapy is mainly based on cisplatin and etoposide protocols. Those referred in the literature include: carboplatin-VP16- vincristine, carboplatin plus either etoposide or vincristine, temozolomide and, ACNU (3-[(4-amino-2-methyl-5-pyrimidinyl) methyl]- 1-(chloroethyl)-1-nitrosourea) chemotherapy.<sup>10,23,27–29</sup> Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, which has demonstrated activity in ependymoma, should be considered for inoperable recurrent PTPR, or in those amenable/responsive to radiation or standard cytotoxic treatments.<sup>30,31</sup>

#### *Papillary tumor of the pineal region in children*

Regarding to the management of PTPRs in children, even though the proportion of PTPRs between children and adult population is suggested to be between 16-19%, the literature is scarce.<sup>11,22</sup> Table 1 lists the published cases.<sup>10–12,22,23,32–37</sup> We found 19 cases in children younger than 17 years old. Although some information was not available in this small population of cases, some conclusions from all 20 patients could be outlined. No difference regarding the sex was found, and the mean diameter of the tumor was 30 mm. In 3 cases, unavailable information was found regarding the follow up. The mean follow up of the rest 17 cases was 67.5 (3-180)

months. 8/17 (47%) patients had a tumor recurrence or regrowth during the follow up. The mean time of the first recurrence was 34.5 (10-60) months. At the last follow up, 15/17 (88%) patients were alive and symptom free or with controlled disease, while one patient had a progressive disease after 115 months, and another patient died 61 months after starting the treatment. A gross total resection along the course of the disease was performed in 15/17 (88%) cases, while in the remaining two cases (12%) a partial resection followed by radio and chemotherapy was carried out, with stable disease after 15 and 21 months. Only 3 (20%) of the 15 patients who underwent a gross total resection did not receive complementary therapy during the course of the disease. Concurrently, those cases did not recur during 3, 12, and 15 months of follow up.<sup>10-12,22,23,32-37</sup>

Summarizing our results, 17 out of 20 pediatric patients in the literature had follow-up information, and a gross total resection was achieved in 15 of them along the course of the disease. Only one of the two patients with partial resection had a non-recurrent stable disease.. Four of the 8 patients who presented a local recurrence/regrowth during the follow-up, had a second recurrence (3 local recurrences, and one spinal and ventricular recurrence). Three cases recurred three times (a repeated spinal recurrence, a local recurrence, and another ventricular recurrence). One patient had 4 local recurrences of the disease. The unique patient with spinal disease died.<sup>10-12,22,23,32-37</sup>

Compared to the epidemiology in the general population, where 68% of PTPR recurred in a mean follow up of 4.2 years (with an overall survival of 73% at 5 years, and 58% at 10 years), in children population only the 47% of PTPR recurred in a mean follow up of 6,5 years.<sup>11</sup> The survival rate of the entire children group was 94% with only one dead patient 5 years after starting the treatment. However, only 40% of the kids had a follow up over 5 years.<sup>11</sup> This difference could be explained by the fact that a gross total resection was achieved in 88.24% of the pediatric cases and only in the 68% of the adults. However, the reason could be also found in a different, more aggressive and infiltrative biological behavior of the tumor in adults. In this regard, measurements of the DNA methylation, determination of the isocitrate dehydrogenase 1 and 2 mutations in PTPR cells, over the well-known mitotic and Ki-67 proliferation index, could represent important tools for evaluating the progression-free survival rate. Moreover, future perspectives on genetic features will be essential to determine the malignancy grade of the lesion.<sup>14,19,20</sup>

Surgery was performed by different approaches: the occipital interhemispheric, the suboccipital supracerebellar, the traschoroidal, and the endoscopic translaminar terminalis represented the main used routes.<sup>10-12,22,23,32-37</sup>

Regarding the posterior routes to the pineal regions, the sitting position may offer several advantages over the horizontal position, and several protocols may be effectively used in the clinical setting in order to prevent its

major complications.<sup>38–45</sup> Biopsy through an endoscopic approach, associated with a third ventriculostomy, followed by radiotherapy was an option too. Whatever approach is selected, skillful and clean microneurosurgery preserving the normal anatomy is imperative during pineal region operations.<sup>35,44–47</sup>

Common radiotherapy schemes included external beam radiotherapy, and proton beam radiotherapy with doses of 50–54 Gy as a part of the initial treatment and treatment for the recurrences.<sup>10–12,22,23,32–37</sup> A local recurrence in a 13 years old boy (who initially underwent a gross-total resection, craniospinal radiation, and chemotherapy) was controlled by a partial resection followed by stereotactic radiosurgery (20 Gy). The patient had subsequently other two local resections that were managed with stereotactic radiosurgery alone (22, and 20Gy). At 180 months follow-up the patient is able to work as a computer scientist.<sup>36</sup>

The main schemes of chemotherapy were based on ACNU, Carboplatine-VP16-vincristine, 9 cycles of gemcitabine–oxaliplatin as second line chemotherapy for the case with the spinal recurrence, and cisplatin-cyclophosphamide-vincristine-etoposide in our case.<sup>10–12,22,23,32–37</sup>

### *Conclusion*

Even though PTPRs in children have a big rate of recurrence during the first 5 years, they have a good control of the disease. Radiotherapy and chemotherapy are important tools in the management of the disease, as well as of their recurrences after gross total resection. Stereotactic radiosurgery might be an important tool for the management of local recurrences of the tumor with good cognitive function at long term follow-up.

### **Disclosure**

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**Figure Legends**

**Fig.1** Sagittal cerebral MRI scans. Preoperative MRI showing a pineal lesion (A), which underwent a subtotal resection abroad (B). The histologic diagnosis was a grade II papillary tumor of the pineal region. 9 months MRI revealing a regrowth of the tumor (C). The patient underwent an occipital interhemispheric approach with gross total removal at our department (D), followed by adjuvant radiochemotherapy. Histological examination revealed tumor progression (grade III). The patient continues to do well with no evidence of recurrence more than 3 years following surgery (E)

**Fig.2** Photomicrographs of surgical specimens. Hematoxylin and eosin staining showing an epithelial-like growth pattern with vessels covered by a layer of tumor cells forming perivascular pseudorosettes (A). Some necrotic areas were present (B). Immunohistochemistry was positive for pancytokeratins (C), cytokeratin 18 (D), S100 protein (E), CD56 (F), and negative for glial fibrillary acidic protein (G)



| Author                             | Age (years)<br>Sex | Size mm | Surgical treatment                   | Histopathology             | Radiotherapy                   | Chemotherapy             | Follow up (Months) | 1st recurrence and treatment                                   | 2nd recurrence and treatment      | 3rd recurrence and treatment | 4th recurrence | Final status   |
|------------------------------------|--------------------|---------|--------------------------------------|----------------------------|--------------------------------|--------------------------|--------------------|--|-----------------------------------|------------------------------|----------------|--|
| Buffenoir, 2008 <sup>12</sup>      | 13 M               | 31      | ETV+B, GTR                           | MI: 1-10/10HPF             | Yes, 50 Gy, bed and ventricles |                          | 24                 | No   |                                   |                              |                | Alive  |
| Nakamura, 2009 <sup>10</sup>       | 11 M               | ~20     | PR, VPS, GTR (3 months later)        | MIB-1: 2.6%                | Yes, 50,4 Gy                   | Yes, ACNU                | 180                | No   |                                   |                              |                | Alive  |
| Fevre-Montange, 2006 <sup>11</sup> | 14 M               | NAI     | GTR                                  |                            |                                |                          | NAI                | NAI  |                                   |                              |                | NAI  |
|                                    | 5 F*               | 28      | GTR                                  |                            |                                | Yes                      | 61                 | LR at 21 months: GTR+RT  | VR+SR: 9 cycles of GEMOX          | SR                           |                | Death  |
|                                    | 13 M*              | NAI     | ETV+B, GTR                           |                            | Yes, 50 Gy                     |                          | 33                 | No   |                                   |                              |                | Alive  |
|                                    | 14 M*              | 50      | GTR                                  |                            |                                | Yes                      | 122                | LR at 44 months: RT  | LR at 53 months                   | LR at 88 months              | LR             | Alive  |
|                                    | 11 F*              | 32      | B+RT, GTR                            |                            | Yes                            |                          | 115                | LR: GTR+CMT  | LR at 72months: GTR+RT (54Gy)+CMT |                              |                | Alive, progressive disease                           |
| Hua, 2015 <sup>32</sup>            | 10 F               | ~20     | GTR (SOTA), ETV                      | Ki67 ~5%                   |                                |                          | 15                 | No   |                                   |                              |                | Alive  |
| Li, 2011 <sup>33</sup>             | 1,25 M             | 10      | ETV, B (TFCA), B+PR (TFCA), ETV, VPS | MIB-1: 5%–8%; MI: 3/10HPF. |                                | Yes, 4 cycles of VMCCyCi | 15                 | Local regrowth (after 2 cycles of CMT): PR+ CMT+PBRT (6 weeks) |                                   |                              |                | Alive, left oculomotor nerve deficit, stable disease |
| Abela, 2013 <sup>34</sup>          | 3 F                | 35      | GTR (SCIT)                           | Ki67 10-15%, MI: 4-6/10HPF |                                |                          | 39                 | LR at 3 year: PR+ PBRT 54Gy                                    |                                   |                              |                | Alive, Parinaud's syndrome, stable disease           |

|                                 |      |                 |                      |   |                   |           |     |  |                              |   |  |                       |
|---------------------------------|------|-----------------|----------------------|---|-------------------|-----------|-----|--|------------------------------|---|--|-----------------------|
| Fauchon, 2013 <sup>23,§</sup>   | 7 F  |                 | GTR                  |   | Yes, 54Gy         | Yes       | 95  | No   |                              |   |  | Alive                 |
|                                 | 16 F |                 | PR                   |   | Yes               | Yes       | 21  | No   |                              |   |  | Alive, stable disease |
|                                 | 15 M | 30              | B, GTR               |   |                   |           | 3   | No   |                              |   |  | Alive                 |
| Cimino, 2015 <sup>22</sup>      | 1 F  | 23              | GTR                  | Ki67: 6%; MI: 1/10HPF                                   |                   |           | 12  | No   |                              |   |  | Alive                 |
|                                 | 10 F |                 |                      | Ki67:3%; MI: <1/10HPF                                   |                   |           | NAI | NAI  |                              |   |  | NAI                   |
|                                 | 11 F |                 |                      | Ki67:19,6%; MI: 7/10HPF                                 |                   |           | NAI | NAI  |                              |   |  | NAI                   |
| Iacoangeli, 2017 <sup>35</sup>  | 10 M | 24 (recurrence) | GTR (SCIT)+ TEV, VPS | MIB-1: 5%   | Yes, 54Gy         |           | 120 | LR at 3 year: GTR (microscopic+endoscopic technique)     |                              |   |  | Alive                 |
| Gutenberg, 2011 <sup>36,†</sup> | 13 M | 50              | VPS, GTR (OC)        | Low mitotic activity                                    | Yes, Craniospinal | Yes, CaEV | 180 | LR at 60 months: PR+SRS(20Gy)                            | LR at 96 months: GKRT (22Gy) | Yes (lateral ventricle close to the foramen of Monro after 8 months): GKRT (20Gy) |  | Alive, symptom free   |
| Marcol, 2007 <sup>37,#</sup>    | 10 F | ~20-30          | VPS, GTR (SCIT)      | MI: 10/10HPF  | Yes               | Yes       | 72  | No   |                              |   |  | Alive, symptom free   |
| Present Case                    | 2 M  |                 | PR (SOA)             | WHO Grade II, LR: MIB-1>25%; 15 mitosis/mm <sup>2</sup> |                   |           | 40  | Yes, LR at 10 months: GTR (OIH) + RT: 54Gy + CMT: CiCyVE |                              |   |  | Alive, symptom free   |

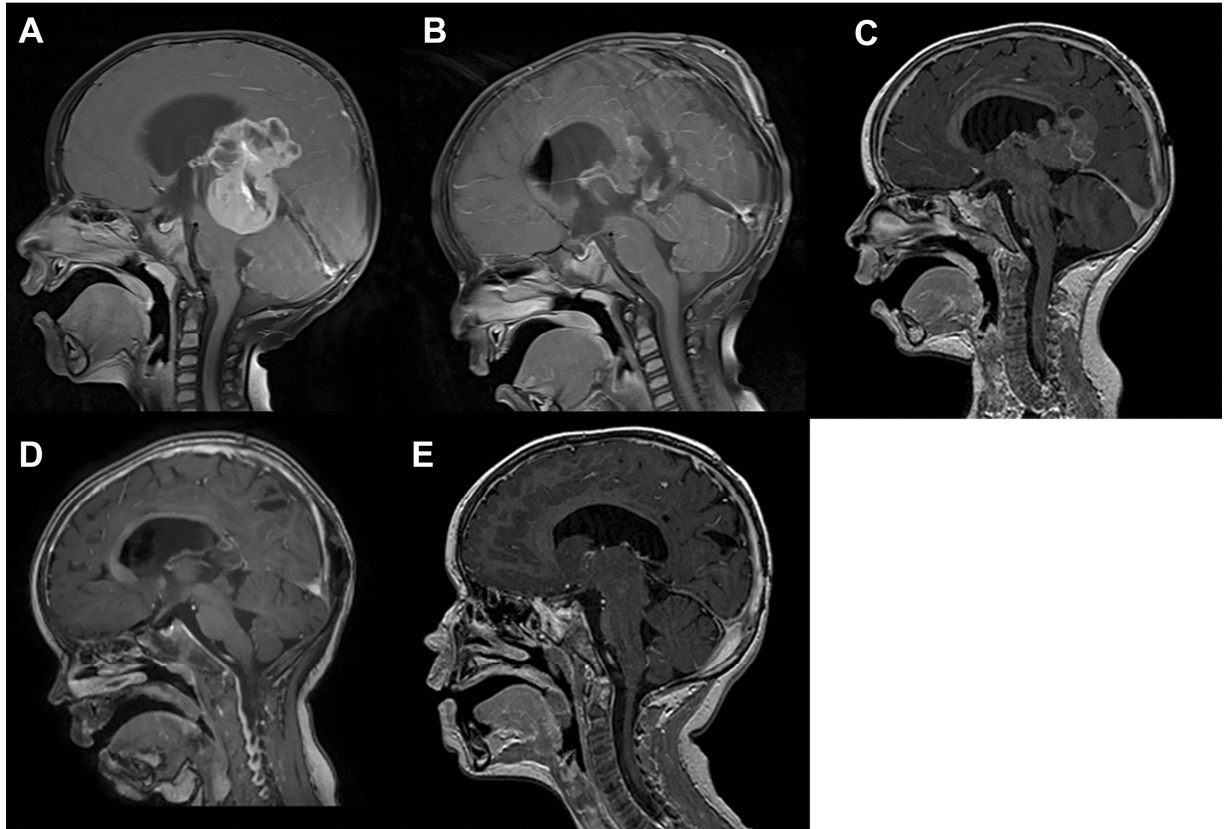
\*These cases were published initially by Fèvre-Montange et al.<sup>11</sup>, and later updated by Fauchon et al.<sup>23</sup>

§One case was also reported by Jeruc and Popovic with no available information in the literature

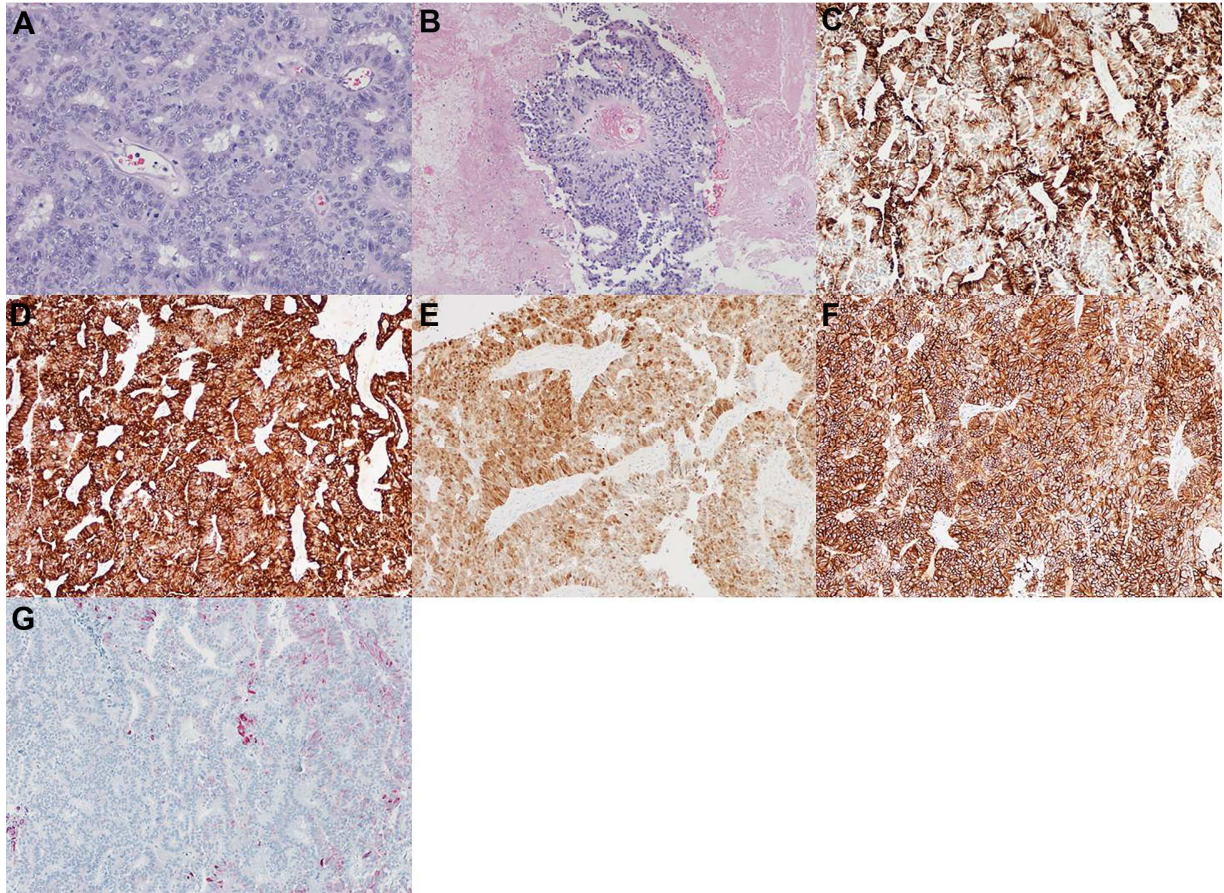
†Initially reported as an anaplastic plexus papilloma (WHO grade III)

#Reported as a papillary pineocytoma

ACNU, nimustina; B, biopsy; Ca, carboplatine; Ci, cisplatin; CMT, chemotherapy; Cy, cyclophosphamide; E, etoposide; ETV, endoscopic third ventriculostomy; GEMOX, gemcitabine-oxaliplatin; GKRT, gamma knife radiation therapy; GTR, gross-total resection; HPF, high-power field; LR, local recurrence; M, methotrexate; MI, mitosis; NAI, not available information; OC, occipital craniotomy; OIH, occipital interhemispheric approach; PBRT, proton-beam radiation therapy; PR, partial resection; RT, radiotherapy; SCIT, supracerebellar infratentorial approach; SOA, suboccipital approach; SOTA, suboccipital transtentorial approach; SR, spinal recurrence; SRS, stereotactic radiosurgery; TFCA, transfrontal transchoroidal approach; V, vincristine; VPS, ventriculo-peritoneal shunt; VR, ventricular recurrence; WHO, World Health Organization



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**Title**

Papillary tumor of the pineal region in children: presentation of a case and comprehensive literature review

**Highlights**

Papillary tumors of the pineal region (PTPRs) are rare grade II-III pineal lesions

Immunohistochemistry is needed for their differentiation from other pineal tumors

We describe a successful multidisciplinary management of a PTPR in a 3-year-old boy

A comprehensive literature review, including the current management in children, is reported

**Title**

Papillary tumor of the pineal region in children: presentation of a case and comprehensive literature review

**Disclosure**

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