



Case Report

Papillary tumor of the pineal region: Is stereotactic radiosurgery efficient for this rare entity?

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ABSTRACT

Background: Papillary tumors of the pineal region are rare neuroepithelial lesions that were described for the 1st time in the WHO 2007 classification. Management of such lesions remains controversial.

Case Description: We describe the case of a 26-year-old female who presented with intracranial hypertension syndrome secondary to a 1.9 cm³ lesion of the pineal region causing hydrocephalus. The patient benefited from an endoscopic third ventriculostomy and a biopsy of her lesion in favor of a papillary tumor of the pineal region. After discussion of the surgical risks, the patient refused the surgical option and a stereotactic radiosurgery (SRS) was performed. She improved both clinically (allowing her to regain autonomy) and radiologically (reduction of 60% of tumor volume) at 1 year follow-up.

Conclusion: Because of the rarity of the lesion, literature is yet not able to find consensus concerning management of such lesion, but SRS has proven efficiency for these Grades II or III lesions with high recurrence rates. Therefore, it should be considered as a primary therapeutic option allowing good outcome with low risks for the patient.

Keywords: Papillary tumor, Pineal region, Stereotactic radiosurgery

INTRODUCTION

Papillary tumor of the pineal region (PTPR) is a neuroepithelial tumor defined as Grade II or III, depending on its malignancy and frequency of local recurrence.^[9,10] First included in the 2007 WHO classification, PTPR is a rare entity that accounts for 0.5–1% of primary central nervous system tumors^[13] and is characterized by a combination of papillary and solid areas with particular immunohistochemical (IHC) features.^[9,15] Because of the rarity of PTPR, the treatment of such lesions remains controversial, with the options of surgery, radiotherapy, stereotactic radiosurgery (SRS), or chemotherapy.^[9] We report a case of a PTPR successfully managed with biopsy and complementary SRS and review the literature analyzing the effects of SRS on PTPR.

CASE REPORT

A 26-year-old female with no medical history presented with progressive headaches, vomiting, and visual loss over a 3-month period. The physical examination showed a Glasgow Coma Scale of 15, no motor or sensory deficits, and equal and semi-mydiatic pupils with only light perception in both eyes at the ophthalmological examination. The computed tomography (CT) scan and contrast magnetic resonance imaging (MRI) showed obstructive hydrocephalus secondary to a pineal region tumor. This lesion was hypointense on T1-weighted sequences and heterogeneously hyperintense on T2 with small cystic portions noted in the mass. Solid portions were heterogeneously enhanced after contrast injection. The tumor extended into the third ventricle, elevating both internal cerebral veins, but no extension into the fourth ventricle or the thalamus was noted. The lesion measured 15 mm × 10 mm. The serum laboratory workup for germ cell tumor markers (α fetoprotein and β -HCG) was negative [Figure 1].

Given the location of the lesion and its accessibility by transventricular biopsy, an endoscopic right ventricular approach was chosen both to treat the obstructive hydrocephalus endoscopic third ventriculostomy (ETV) and obtain tumor specimens for pathology. The postoperative protocol was determined based on the results of the first procedures. The transventricular biopsy was achieved through a two burr hole approaches: one in front of the coronal suture for the ETV (using the Decq Neuroendoscopy set [Karl Storz, Germany] with 30° endoscope, 2.9 mm in diameter and 30 cm in length, ventriculostomy forceps and a Fogarty balloon catheter) and the second, 5 cm in front of the coronal suture, to perform the biopsy using the same set and tumor forceps. The tumor was reddish and nonhemorrhagic, originating from the pineal region. Three tumor specimens

were collected. A CSF sample was tested for pathological cells and biological markers and was negative for both.

Pathology revealed an epithelial-looking tumor with papillary features and denser cellular areas in a vascularized conjunctive tissue. In papillary areas, the vessels were covered by layers of large, pale to eosinophilic columnar cells. The nuclei were round to oval, with stippled chromatin and pleomorphic nuclei. The mitotic count ranged from 0 to 10 mitoses per 10 high-power fields. Necrotic foci were noted. Vessels were hyalinized and had a pseudoangiomatous morphology, with multiple lumina and an absence of microvascular proliferation [Figure 2].

The IHC profile showed reactivity to epithelial membrane antigen (EMA), synaptophysin, glial fibrillary acid protein (GFAP), vimentin, PS100, pancytokeratin, and Ki67 estimated at 2%, indicating a PTPR.

In the postoperative period, the patient showed significant improvement in intracranial hypertension syndrome symptoms (disappearance of headaches and vomiting), no motor or sensitive deficit, and a slight ophthalmological improvement at the examination (2/10 on both eyes).

Given the pathological findings in the tumor specimen, two treatment options were possible and explained in detail to the patient: surgical resection through one of the selected approaches or Gamma Knife-based SRS. The latter option was preferred, as the patient did not accept the risks associated with surgery and could be achieved 1 month after the biopsy.

The patient was fitted with a Leksell stereotactic frame (Model G, Elekta Instruments, AB Stockholm, Inc.) under local anesthesia. Gadolinium-enhanced T1-weighted reconstructions were generated and the treatment planning was performed using GammaPlan software (Elekta

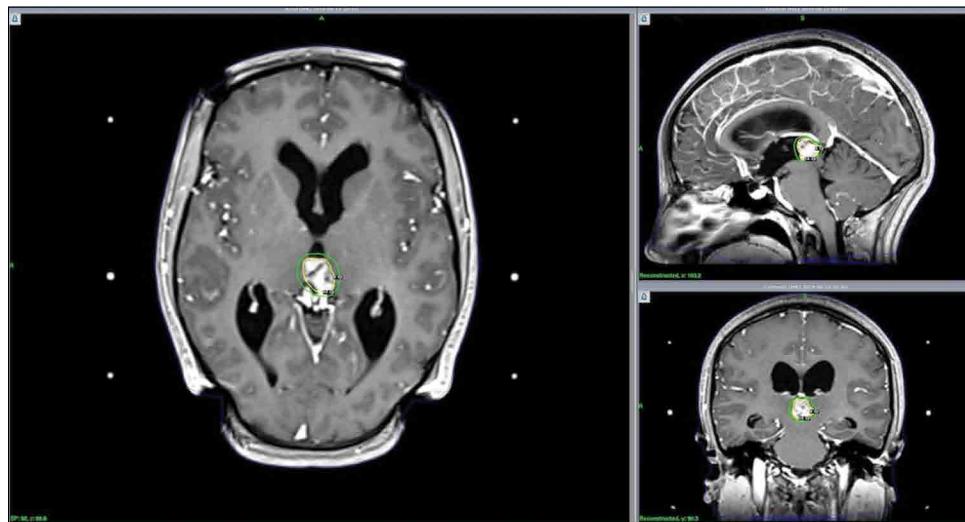


Figure 1: Axial, sagittal, and coronal T1 injected magnetic resonance imaging, with stereotactic radiosurgery planning from the GammaPlan software Elekta Instruments, Inc., version 11.0.3 delivering a 14 Gy at 50% isodose for a 1.9 cm³ pineal region lesion.

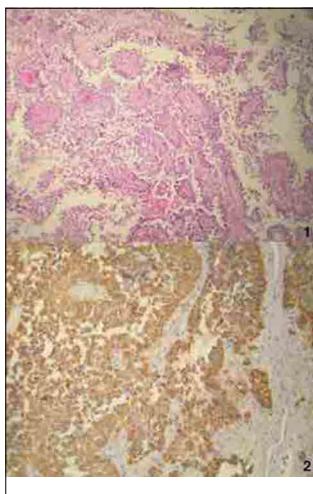


Figure 2: Papillary tumor of the pineal region. (1) The vascular axes of neoplastic papillae often harbor multiple capillaries. Neoplastic cells detached from the papillary vascularized core, leading to an apparent clear perivascular space. (2) Cytokeratin AE1-AE3 is diffusely expressed in the epithelial-like neoplastic cells and predominates in perivascular areas.

Instruments, Inc., version 11.0.3). The patient was treated 2 weeks after the biopsy for a tumor with a volume of 1.9 cm^3 . We delivered a 14 Gy dose at 50% isodose with 40 shots of 4 mm using a Leksell Gamma Knife ICON machine (Elekta Instruments, AB Stockholm, Inc.). The beam time was 88 min for a dose ratio of 2.681 Gy/min. The mean dose delivered to the brainstem was 0.4 ± 0.8 ; as such, the 10 Gy isodose volume was difficult to measurable. In the context of tumor location, the superior and inferior colliculi were initially considered as organs at risk; however, considering the mean dose to the brainstem, local dose distributions were not measurable. The frame was removed at the end of the procedure and the patient was discharged the same day.

The patient follow-up occurred at 3, 6, and 12 months. Her neurological examination showed progressive improvement of the intracranial hypertension syndrome symptoms as well as her visual status. On MRI, we observed a significant tumor reduction at 6 and 12 months (30% and 60% volume reduction, respectively) and the previously reported aqueductal compression had disappeared at 6 months [Table 1].

Because of the malignancy of the lesion and the high risk of recurrence, the patient will attend follow-up appointments every 6 months, including a physical examination and serial imaging. This will continue for the first 5 years, and yearly until the 10-year follow-up period is complete.

DISCUSSION

Tumors of the pineal region are rare and account for <1% of all brain tumors. Papillary tumors are the most recently

Table 1: Volumetric and tumor characteristics evolution at 6 and 12 months.

| Tumor characteristics | Initial | 6 months | 12 months |
|-------------------------|--------------------|---------------------|---------------------|
| Tumor volume | 1.9 cm^3 | 1.33 cm^3 | 0.76 cm^3 |
| % of volume reduction | – | 30 | 60 |
| Aqueductal compression | Yes | No | No |
| Internal cerebral veins | Elevated | Elevated | Not elevated |

identified pathological pineal region tumors, described by Jouvet *et al.* in 2003. The tumors originate from a distinct ependymal cell of the sub-commissural organ with epithelial-like growth patterns and, as described in our patient, fibrovascular papillae with a well-defined secretory function.^[13,15] Immunohistochemistry is mandatory for the diagnosis. Staining for S100, NCAM, neuron-specific enolase, and transthyretin is frequent. PTPR is usually variably reactive for GFAP, synaptophysin, chromogranin, and neural antigens.^[15] In our case, it showed positivity for GFAP and synaptophysin in addition to the classical positivity for PS100, the other markers could not be explored due to their unavailability at the time of diagnosis. Ki67 immunolabeling and mitotic rates vary widely, with a mean of 6%.^[15] No correlation between Ki67 positivity and biological behavior has been proven, but some authors have reported that higher proliferative activity is found in younger patients. Heim *et al.*, in a series of 21 patients, highlighted an association between increased mitotic/proliferative activity and higher recurrence, but further studies and larger samples are needed to prove the relationship between Ki67, the degree of malignancy, local infiltration, and metastatic activity [Table 2].

Slight female predominance has been observed in the literature.^[9] Classically, patients present with headache, visual loss, and intracranial hypertension symptoms. On MRI, as described in our presented case, PTPR presents as a mixed lesion with solid and cystic components arising from the pineal gland and with a heterogeneous enhancement pattern after contrast injection.^[9] The tumor causes compression of the cerebral aqueduct, leading to obstructive hydrocephalus.^[9,12,15] Nodular lesion enhancement after contrast injection secondary to leptomeningeal dissemination was previously described by Kim *et al.*^[8]

Because of the rarity of the lesion, multiple therapeutic options have been described, but a standard treatment has yet to be determined. Surgical resection, mostly using an infratentorial supracerebellar approach, has been used as the primary therapeutic strategy to improve outcome, recurrence, and survival rates.^[1,15] Yamaki *et al.*, in their systematic review of PTPR, showed better survival rates at 36 months in patients who benefited from surgical resection. However, they concluded that compared to other rates of resection, gross total resection did not improve patient

Table 2: Microscopic and IHC profile of the patients lesion and literature review.

| Study | Pathology | | General features | Vessels | Cells | Mitotic count | IHC profile | | | | | | Ki67 (%) |
|---|--|--|---|-------------------|--------------|---------------|-------------|---|----|---|----|----|----------|
| | EMA | S100 | Synaptophysin | GFAP | Chromogranin | Cytokeratin | NCAM | | | | | | |
| Canizares Méndez <i>et al.</i> ^[1] | Papillary structures Pineal gland parenchyma with calcifications | Perivascular pseudorosettes | Polygonal with extensive eosinophilic cytoplasms | 1/10 | - | + | - | - | - | + | NA | 5 | |
| Lancia <i>et al.</i> ^[9] | Papillary structures, focal necrosis | Rosette-like structures, vascular | Oval or round nuclei, dispersed chromatin | Seldom mitosis | NA | + | NA | + | NA | + | NA | 5 | |
| Hua <i>et al.</i> ^[6] | Papillary structures and a palisade arrangement | Vascular pseudostratified columnar epithelium | Cytoplasm hyperchromatic, irregular nuclei | NA | - | + | NA | - | NA | + | NA | 2 | |
| Our study | Papillary features, dense areas, vascularized conjunctive tissue | Covered by pale to eosinophilic columnar cells | Round to oval Stippled chromatin | 0–10 | + | + | NA | + | NA | + | NA | NA | |

IHC: Immunohistochemical, EMA: Epithelial membrane antigen, GFAP: Glial fibrillary acid protein

outcome.^[15] Given that PTPR occurs in deep location in the brain surrounded by important brainstem structures, upfront or adjuvant therapy (radiotherapy, chemotherapy, or SRS) has been proposed.^[15]

The effectiveness of radiotherapy (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, or radiosurgery; each protocol depending on the center and the initial diagnosis) and chemotherapy (mainly based on cisplatin-VP16 protocols) has been studied by Fauchon *et al.* who reported that there is no improvement in overall survival after these treatments.^[4] Edson *et al.* expressed their concerns about the long-term side effects of adjuvant radiotherapy for PTPR. In their review, seven patients were treated by radiotherapy 2–9 weeks after surgery, consisting of whole-brain radiotherapy (30 Gy); SRS (15 Gy); proton radiotherapy to the surgical bed (54 Gy); or whole ventricular intensity-modulated radiation therapy with a boost (36 Gy and 18 Gy). Using focal radiotherapy followed by craniospinal irradiation or whole ventricular intensity-modulated radiation therapy, side effects were observed on cognition and quality of life.^[3]

SRS is well known to be a safe alternative as a primary or adjuvant treatment for deeply located lesions. The first use of SRS for PTPR was in 2010 by Kim *et al.*^[8] The procedure locally controlled the tumor but did not avoid leptomeningeal dissemination at 8 months. Fauchon *et al.* considered in their review that SRS, as an adjuvant therapy, led to better local control of PTPR.^[4] They reported two patients who benefited from SRS following biopsy and partial resection of the lesion. Both patients experienced tumor recurrence after an undefined time, and one of them died.^[4] Shakir *et al.* reported a patient who received SRS after partial lesion resection and adjuvant chemotherapy. Gradual regression was observed with tumor control at the 9-year follow-up.^[14]

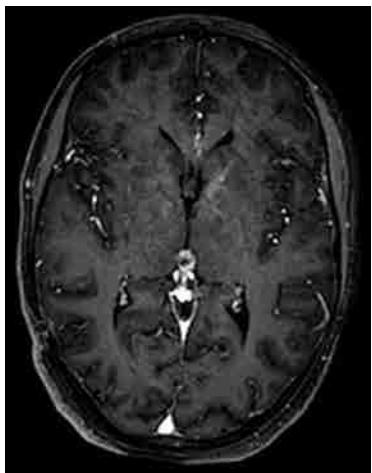
Iorio-Morin *et al.*, in their report on SRS of pineal region tumors, considered SRS at tumor progression. They found 33% of local control at 5 years, with one patient experiencing a total disappearance of the tumor. They advocate for a second SRS treatment for recurrence or tumor progression.^[7] Yianni *et al.* and Cardenas *et al.* reported two and one patients, treated for PTPR by SRS alone, respectively, with a local tumor control at 1–7 years.^[2,10,16] Another patient reported by Riis *et al.* who had sustained tumor regression at 5 years after SRS.^[11] Fernández-Mateos *et al.* reported two cases treated with no recurrence at 15–20 years.^[5] [Figure 3] summarizes all the published cases of PTPR treated by SRS in the literature.

Although details about the treatment planning protocol used are not always available, all groups used a peripheral prescription dose of 10–15 Gy [Table 3], achieving optimal treatment and local control of the lesion regardless of

Table 3: Literature review of PTPR treated with stereotactic radiosurgery.

| Study | Number of patients | Tumor size | Intent SRS | Dose isodose 50% | Follow-up | Regression rate (%) | Recurrence | Type of treatment for recurrence | Second recurrence |
|--|--------------------|----------------------|--------------------------------------|------------------|------------------------|---------------------|------------------------------|----------------------------------|-------------------|
| Riis <i>et al.</i> , 2013 ^[11] | 1 | 12.3 mL | Primary | 12 Gy | 5 years | 66 | No | - | - |
| Iorio-Morin <i>et al.</i> , 2017 ^[7] | 6 | NA | 1 recurrence 5 primary / adjuvant | 15 Gy | 5 years | - | 5/6 | SRS | 1 |
| Cardenas <i>et al.</i> , 2010 ^[2] | 1 | 20×21 mm | Primary | - | 7 years | 7 mm | Yes | GTR | No |
| Shakir <i>et al.</i> , 2015 ^[14] | 1 | 4.2 cm ³ | Adjuvant + chemotherapy (STR) | - | 9 years | 70% | No | - | - |
| Yianni <i>et al.</i> , 2012 ^[16] | 2 | - | - | 15 Gy | 1 year | - | - | - | - |
| Kim <i>et al.</i> , 2010 ^[8] | 1 | 24.4 cm ³ | Primary | 12.5 Gy | 11 months | - | Leptomeningeal dissemination | - | - |
| Fauchon <i>et al.</i> , 2013 ^[4] | 2 | 32 mm NA | Primary Adjuvant | 12 Gy - | 91 months 36 months | - | Yes Yes | - | - |
| Fernandez-Matéos <i>et al.</i> , 2018 ^[5] | 2 | 13 cc 4.1 cc | Primary Primary | 10 Gy 12 Gy | 15 years 20 years | - | No No | - | - |
| Our case | 1 | 1.9 | Primary | 15 Gy | 1 year | 60% | No | - | - |

PTPR: Papillary tumor of the pineal region

**Figure 3:** One year posttreatment magnetic resonance imaging, axial T1 injected sequences showing 60% reduction of tumor volume.

the volume with minimal toxicity to the brainstem and the colliculi, as described in our case, consistent with the principle of SRS. The protocols allow the physician to keep the

10 Gy volume (V-10) to <1 cc for the brainstem. Fernández-Mateos *et al.* delivered <6 Gy to the colliculi and 4 Gy to the brainstem. Our protocol managed a nonmeasurable V-10, effectively precluding dose dissipation to the colliculi and the rest of the brainstem.

Unfortunately, there are limited cases of PTPR reported in the literature and, as such, a significant comparison between the different therapeutic modalities is not possible. Thus, the authors agree that prospective studies with larger cohorts are needed to determine the best therapeutic option to offer the patients. At present, the choice should be made by balancing the risks and benefits according to the surgeons' technicity, the availability of the techniques, and the patients' preference.^[15] We believe that SRS is a good option to treat tumors considered Grade II or III, allowing minimal side effects, maximum safety, and local control of the lesions. In the case presented here, SRS resulted in 60% reduction in the tumor volume and the disappearance of the cerebral aqueduct compression without any complications, and the patient regained autonomy 1 year after treatment.

CONCLUSION

PTPR are rare lesions with unpredictable courses. SRS may be considered as a primary or adjuvant treatment option due to its potential long-term local control of these surgically challenging lesions.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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