

Papillary Tumor of the Pineal Region with Leptomeningeal Seeding: A Case Report and Literature Review

Kazem Anvari*, MD, Parisa Rabiei*, MD, Hamidreza Hashemian**, MD, Mohammad Farajirad***, MD, Soudh Arastouei*, MD, Zohreh Pischevar Feizabad**, MD

*Cancer Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

**Department of Medical Microbiology and Pathology, Razavi Cancer Research Center, Razavi Hospital, Imam Reza International University, Mashhad, Iran

***Department of Neurosurgery, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

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Abstract

Papillary tumor of the pineal region (PTPR) is an infrequent neoplasm arising from the ependymal cells of the sub-commissural organ. This tumor entity was incorporated into the World Health Organization (WHO) classification of central nervous system tumors in 2007. Given the propensity for local recurrence observed in PTPR cases and the documented instances of leptomeningeal seeding in previous case reports, it presents a substantial risk of significant morbidity. Due to its rarity, there is no established standard for its management. Surgical intervention constitutes the primary treatment modality, while the role of adjuvant radiotherapy remains ambiguous. In this case report, we present the clinical course of a 46-year-old male diagnosed with PTPR who underwent surgical resection followed by adjuvant radiotherapy. 14 months post-initial treatment, the patient manifested intracranial and spinal metastases in the form of leptomeningeal dissemination. Subsequently, systemic chemotherapy utilizing vincristine and carboplatin was initiated, and the patient exhibited no evidence of disease progression over the last six months.

Keywords: Pineal gland, Papillary tumor, Leptomeningeal seeding, Brain neoplasms, Case report

Corresponding Author:

Zohreh Pischevar Feizabad, MD
Cancer Research Center,
Mashhad University of Medical
Sciences, Mashhad, Iran
Tel: +98 51-38426082
Fax: +98 51-38428622
Email: zohreh.pischevar@gmail.com

Introduction

Papillary tumor of the pineal region (PTPR) is a rare pineal parenchymal lesion, compromising less than 1% of all intracranial tumors.¹ It was first introduced by Jouvett in 2003,² and has been

included in the classification of central nervous system tumors since 2007.¹ Pineal region tumors are of four general categories: Pineal parenchymal tumors, germ cell tumors, pineal metastasis, and other rare tumors, including meningioma,

lymphoma, and glial tumors.²

PTPR originates from the subcommissural organ's ependymal cells, showing papillary formations and an epithelial growth pattern.² It has a high propensity to recur locally. Due to its rare occurrence, its management is not standardized. A large study on patients' characteristics, optimal treatment, and survival is lacking, and most patients are presented as case reports or case series.⁴⁻¹⁴

Herein, we present a case of PTPR, who was treated with surgery and adjuvant radiotherapy and experienced recurrence 14 months later.

Case Presentation

A 46-year-old man experiencing a two-week history of nausea, vomiting, severe headache, dizziness, loss of balance, and somnolence was referred to the Department of Neurological Surgery at Mashhad University of Medical Sciences. Brain magnetic resonance imaging (MRI) revealed a 41 mm enhancing mass at the posterior part of the third ventricle, resulting in non-communicating hydrocephalus of the lateral ventricles (Figure 1).

To alleviate intracranial pressure (ICP), a ventriculoperitoneal shunt was placed, and subsequently, a subtotal mass resection was performed during the craniotomy. Pathological assessment of the $1.5 \times 1 \times 0.5$ cm resected

specimen revealed a neoplastic lesion with a diffuse proliferation of atypical cells characterized by round hyperchromatic nuclei, moderate nuclear atypia, clear to acidophilic cytoplasm, and some mitotic activity. These findings were consistent with a pineal parenchymal tumor with intermediate differentiation (Figure 2).

The patient received adjuvant radiotherapy, which commenced two weeks postoperatively, delivering a total dose of 5940 cGy in 33 fractions using a three-dimensional (3D) conformal technique. Pre- and postoperative MRI images were fused and registered on computed tomography simulation images to delineate the treatment volumes. The tumor bed and residual mass were defined as the gross tumor volume (GTV), with a 3D margin of 1.5 cm added to create the clinical tumor volume (CTV) (Figure 3). Due to limited evidence regarding the chemoresistance of the tumor and a lack of data on the role of systemic treatment in recurrence or cases of diffuse involvement, the patient was counseled, and he opted for surveillance with neurological examinations and brain MRIs every 4 to 6 months.

During follow-up, the patient remained clinically stable, with stable disease observed on MRI scans, consistent with the RANO criteria, for 14 months post-radiotherapy. Four months after his last follow-up, he presented to the emergency room with tonic-clonic seizures. On MRI, the mass in the pineal region remained

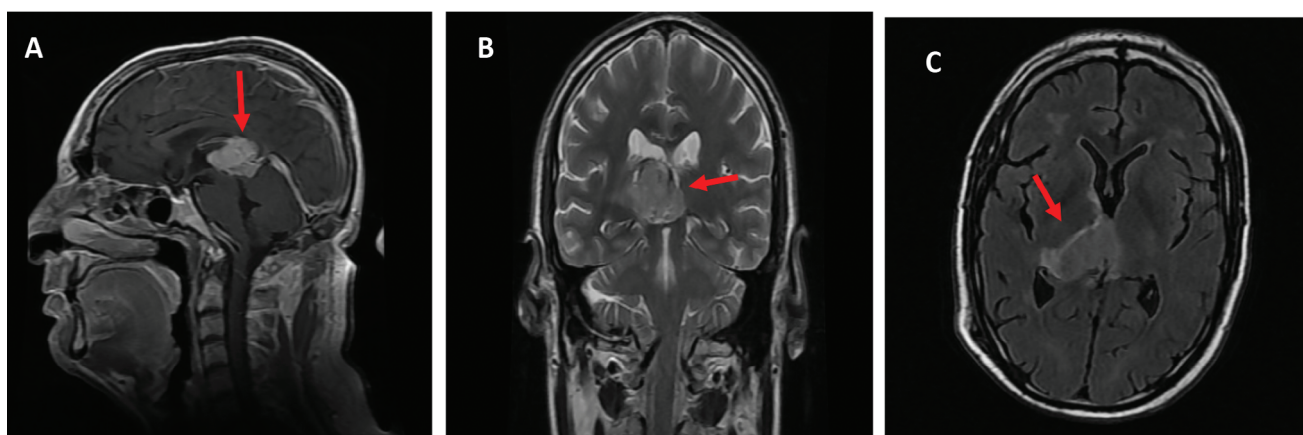


Figure 1. This figure depicts a well-defined enhancing mass situated at the posterior aspect of the third ventricle (indicated by the red arrow). 1A showcases a Gd-T1w sequence, revealing a uniformly enhancing lesion above the tentorium. 1B and 1C feature T2-weighted and FLAIR sequences, respectively, illustrating midline invasion by the abovementioned lesion. Additionally, the lesion displayed heightened signal intensity without notable peritumoral edema.

Gd-T1w: Gadolinium-enhanced T1-weighted; FLAIR: Fluid attenuated inversion recovery

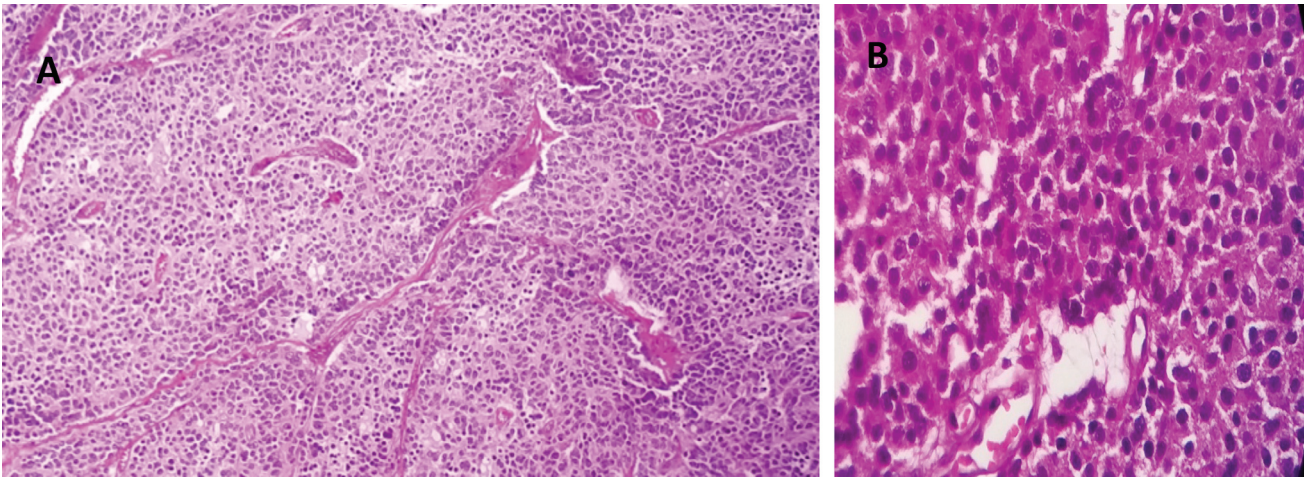


Figure 2. This figure shows, A) Papillary tumors originating from the pineal region exhibit discernible papillary features (H&E, 20× magnification), and B) Areas characterized by higher cellular density (H&E, 400× magnification).

stable, with a slight decrease in size; however, a new lesion, approximately 20 mm in size, had appeared in the right parasagittal region of the posterior parietooccipital lobe, radiologically mimicking meningioma characteristics (Figure 4). Considering the short interval since his last imaging, the clinical presentation of such a large meningioma seemed unlikely.

The new mass was surgically resected, and microscopic examination revealed a lobular proliferative disorder characterized by cell clusters with distinct boundaries, round to oval nuclei with salt-and-pepper chromatin, abundant vessels with a pseudorosette appearance around the vessels, and a clear pseudopapillary appearance. Additionally, there was cerebral parenchymal reaction and expansion in the meninges, along

with a few scattered mitoses (Figure 5). Immunohistochemistry of this new lesion showed positivity for synaptophysin and negativity for glial fibrillary acidic protein (GFAP) and epithelial membrane antigen (EMA), with a Ki67 positivity rate of 30% (Figure 6).

The morphologic and immunophenotypic characteristics suggested the diagnosis of grade 4 pineoblastoma. A pathological review of formalin-fixed slides from both the old and new lesions was conducted to justify the change in pathology, revealing the exact diagnosis of the pineal parenchymal tumor with intermediate differentiation (PTPR) for both lesions. The parasagittal lesion was diagnosed as a metastasis of the primary PTPR, further substantiated by a complete spinal MRI revealing multiple spinal tumoral seedings

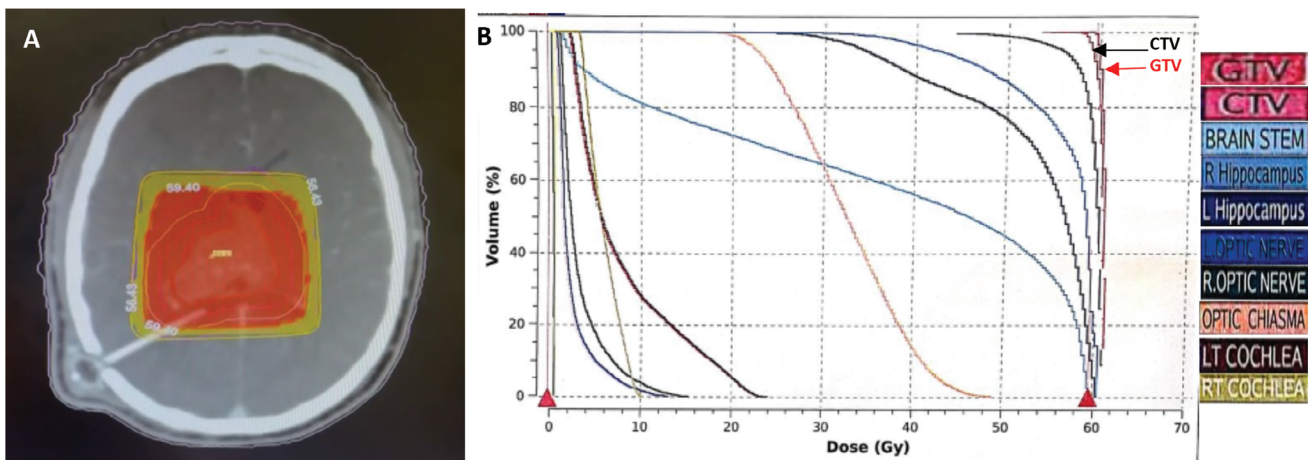


Figure 3. This figure provides insight into A) The transverse plane of treatment planning, highlighting the 95% isodose line in yellow and the 100% isodose line in red. B) The accompanying dose volume histogram depicts the at-risk targets and organs.

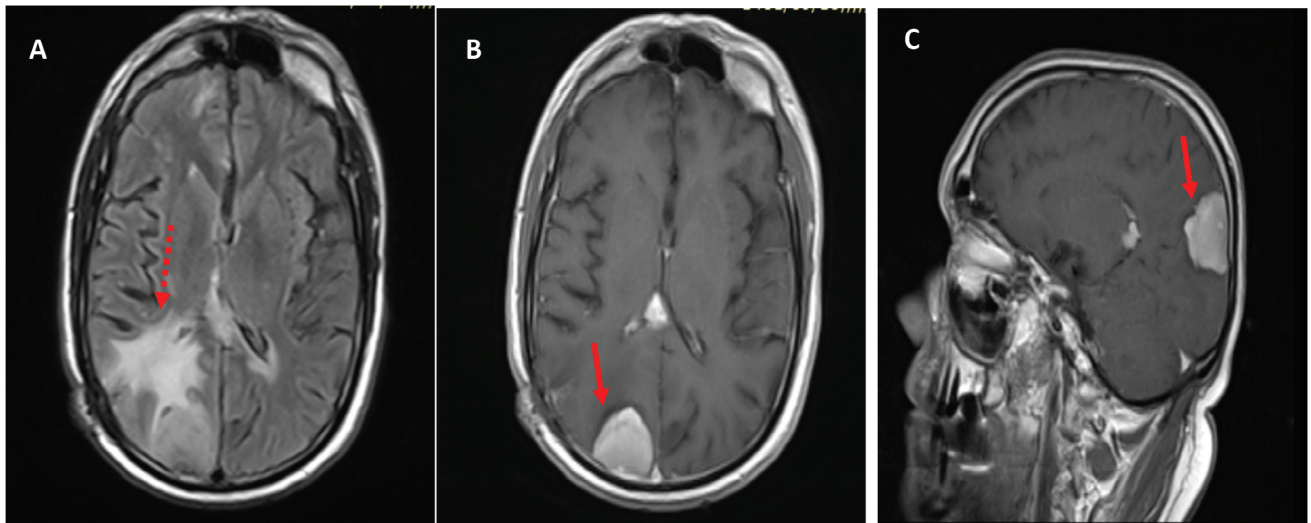


Figure 4. This figure encompasses A) A FLAIR sequence on the transverse plane, revealing the lesion and peritumoral edema (indicated by the round red arrow). 4B and 4C present the transverse and sagittal planes of the Gd-T1w sequence, showcasing a new 20mm enhancing lesion within the right parasagittal region of the posterior parieto-occipital lobe (highlighted by the red arrow), in addition to nodular enhancement within the previous tumor bed, suggestive of residual tumor. FLAIR: Fluid attenuated inversion recovery; Gd-T1w: Gadolinium-enhanced T1-weighted

in the cervical and thoracic spine (Figure 7).

For the palliative treatment of this diffuse recurrence of PTPR, the patient was initiated on systemic chemotherapy, consisting of vincristine at a dose of 1.5 mg/m^2 (with a maximum dose of 2 mg) on days 1 and 8, along with carboplatin at an area under the curve of 2 on days 1, 8, and 15, every 28 days. The patient remains symptom-free after six months of follow-up, with no signs of disease progression observed on recent brain MRI images.

Ethical approval

The Ethics Committee of Mashhad University

of Medical Sciences approved the publication of the present case report (code: IR.MUMS.REC.1402.059).

Discussion

Papillary tumors of the pineal region are sporadic, constituting less than 1% of all adult central nervous system tumors.¹ Its peak incidence is in the third decade of life.² The reported cases ranged in age from 5 to 66 years. In some reports, both genders are affected equally, with a slight dominance for males.³ Our patient was a male in his fifth decade of life, in the age range reported

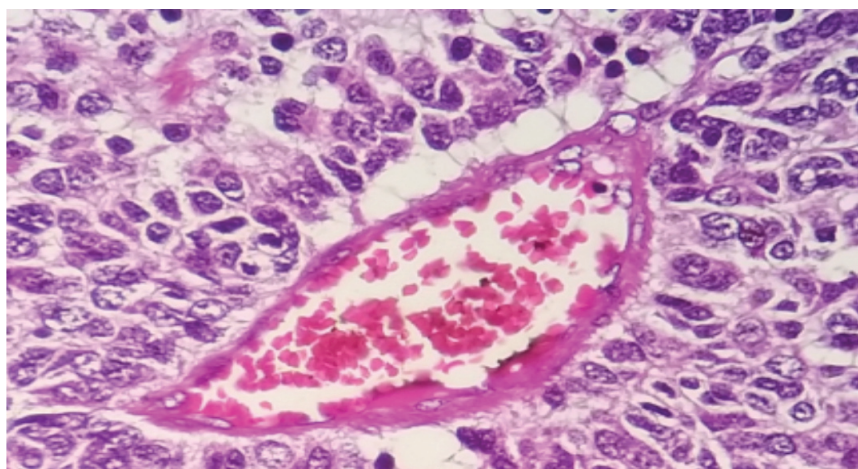


Figure 5. This figure shows a papillary tumor originating from the pineal region is typified by an epithelial appearance, displaying papillary features often manifest as ependymal-like actual rosette formations (H&E, 400× magnification).

in previous reports.

Preliminary symptoms leading to a diagnosis of our patient were headache, nausea, and vomiting, all caused by raised ICP. Due to the anatomical location of pineal tumors, they can cause hydrocephalus, thus increasing ICP. So, the patient may present with symptoms of increased ICP, such as nausea, vomiting, and headache. Visual disturbances and ataxia are also standard presenting features.⁴ The evidence of increased ICP in our patient was presented on his brain MRI. Disseminated disease at the presentation is not a frequent finding. However, it may happen during disease. Our patient had no distant involvement when he was diagnosed. However, at the time of recurrence, there were leptomeningeal metastases. In a report of 17

patients with PPTIDs by Jo Nam et al. (2020), dissemination in the neuroaxis at the time of initial diagnosis was evident in only 3 patients.¹³

A mass-like lesion in the pineal region with subsequent obstructive effects on cerebrospinal fluid flow has a list of differential diagnoses. On imaging, there is no characteristic feature to distinguish PTPR from other lesions of the pineal parenchymal category. A well-defined mass with approximately heterogeneous enhancement, with or without cystic or calcification component that sometimes is a high signal in non-contrast T1-weighted sequences, makes diagnosing PTRP more likely.¹ In Our patient, middle and parasagittal masses were iso signal on T1-weighted sequences, which enhanced homogenously on post-contrast images. Masses were iso- to hyper-signal on T2-

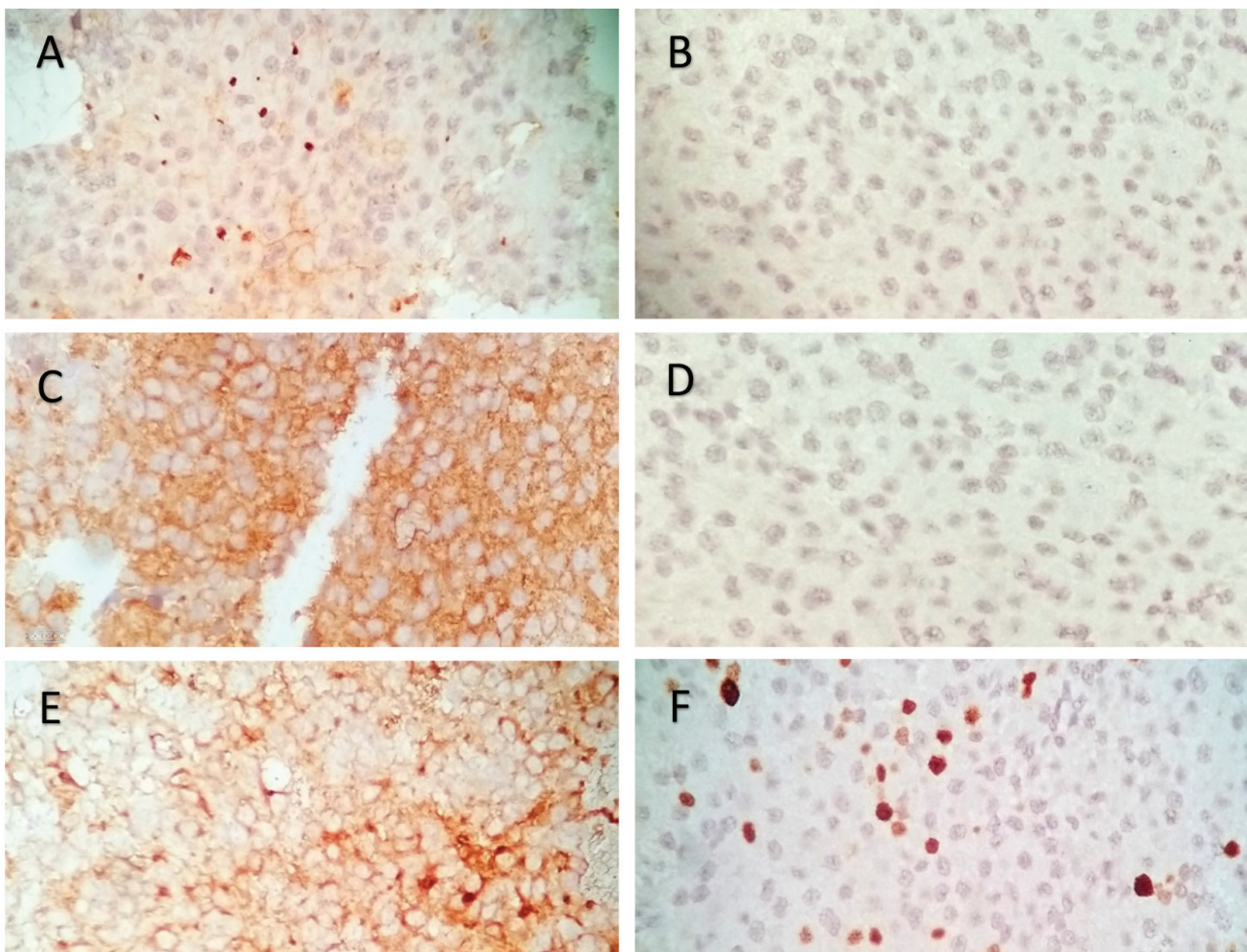


Figure 6. Immunohistochemical staining results are A) Negative immunoreactivity of tumoral cells for EMA. B) Negative immunoreactivity of tumoral cells for GFAP. C) Positive immunoreactivity of tumoral cells for synaptophysin. D) Negative immunoreactivity of tumoral cells for S100 protein. E) Positive immunoreactivity for chromogranin. F) Positive Ki 67 staining was observed in 30% of nuclei.

EMA: Epithelial membrane antigen; GFAP: Glial fibrillary acidic protein

weighted and FLAIR sequences, with substantial surrounding edema, and showed restriction on the diffusion-weighted sequence.

A papillary tumor in the pineal region brings to mind one of the differential diagnoses of papillary pineal parenchymal tumors, papillary ependymoma, choroid plexus papilloma, papillary meningioma, and papillary pineocytoma.⁵ Special cells of the posterior third ventricle near the pineal gland, which are believed to be responsible for PTPR, simultaneously show ependymal and neuroendocrine features. Immunohistochemistry staining helps to differentiate PTPR from other papillary tumors of the pineal region. Cytokeratins, S100, Vimentin, and neuron-specific enolase are positive in this disease. EMA could also be positive. GFAP is generally negative.¹ In contrast to other pineal parenchymal neoplasm, there is a lack of retinal S-antigen and

neurofilament protein expression in PTPR.² In our case, GFAP negativity distinguished PTPR from papillary ependymoma, while CD56 expression and absence of cytoplasmic stanniocalcin-1 and transthyretin helped differentiate it from choroid plexus tumors. Considering that EMA is also positive in meningiomas and S100 can also be positive in 33% of them,⁶ meningiomas became the most important differential diagnosis of this patient's second dural-based lesion, radiologically and pathologically.

Surgery is the mainstay of treatment. While adjuvant radiotherapy has been employed, its role remains unclear.³ Most commonly, it is employed in high-grade tumors or the state of recurrence.³ A systematic review by Yamaki et al. found surgical resection, whether total or partial, to affect survival while reporting adjuvant treatments

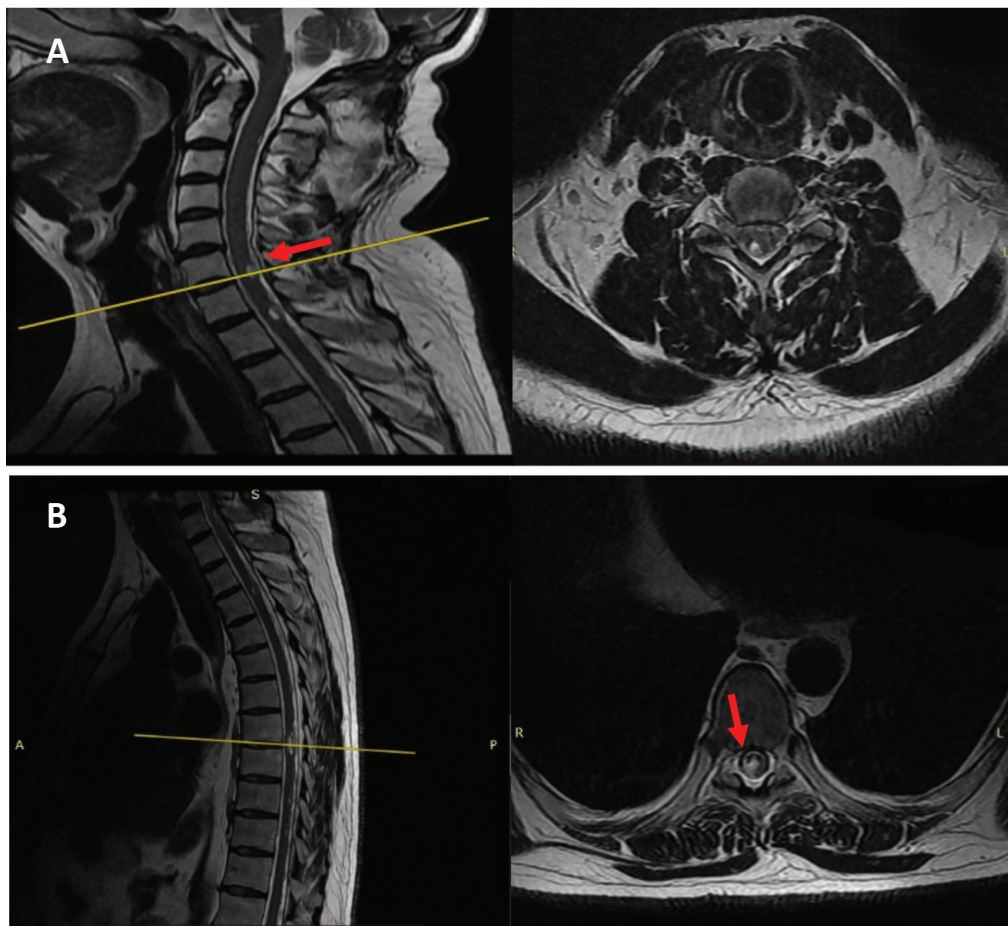


Figure 7. Images of the cervical and thoracic spine are presented, showcasing multiple tumoral implants within the spinal region (indicated by the red arrow).

to have no bearing on survival.⁴ However, a 50-54 Gy dose of radiotherapy could be used as adjuvant treatment in incompletely resected and recurrent disease.³

Reports have described frequent local recurrence in this entity.^{1,4} Leptomeningeal seeding of PTPR has previously been described.^{2,8} As Jouvét et al. described this entity in 2003, they reported 6 cases with 4 local recurrences and one spinal dissemination. All patients were treated by surgery, with adjuvant radiotherapy mostly done following incomplete resection.² Similar to our case, a reported patient experienced recurrence with a mass in the foramen magnum following complete resection of the pineal tumor, with several cerebral foci of metastasis.⁷

Recurrent disease has mostly been treated with radiation therapy.⁸ Systemic therapy has also been used: a patient remained stable on temozolomide for 9 years,⁸ while bevacizumab resulted in progression-free survival of 13 months.⁹ In a case of extensive leptomeningeal recurrence, everolimus resulted in the lesions' regression and disease control for at least two years.¹⁰

Using vincristine and platinum combinations, a 3-year-old child with grade III PTPR was disease-free for 3 years following adjuvant radiotherapy and chemotherapy containing vincristine, cisplatin, cyclophosphamide, and etoposide,¹¹ while a 6-year-old boy remained disease-free for four years following adjuvant radiotherapy and chemotherapy with cisplatin, lomustine, and vincristin.¹² In our case, a decision was made to put the patient on combination chemotherapy based on carboplatin and vincristine.

Conclusion

In conclusion, PTPR represents a rare and recently characterized entity characterized by a pronounced tendency for local recurrence and the potential for meningeal seeding. Despite undergoing surgical intervention and receiving adjuvant radiotherapy, our patient experienced a recurrence marked by extensive leptomeningeal involvement. Given the limited availability of

data, especially concerning treatment modalities, accumulating additional case reports detailing treatment protocols and their respective outcomes and incorporating them into a comprehensive meta-analysis will delineate the optimal therapeutic approach for this condition.

Informed Consent

A written informed consent form was obtained from the patient prior to the publication of the present study.

Acknowledgment

We want to thank the patient for her consent to data publication.

Conflict of Interest

None declared.

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