Recurrent Papillary Tumor of Pineal Region Misdiagnosed as Pineocytoma 9-Years Ago

Abstract
Primary tumors of the pineal gland occur infrequently with a preponderance of either parenchymal tumors or germ cells tumors. Papillary tumor of the pineal region is a rare neuroepithelial lesion that arises exclusively in the pineal region. They have been designated as either Grade II or Grade III lesions as per the 2016 WHO classification of central nervous system tumors. Clinically, they usually present with obstructive hydrocephalus and visual disturbance. On imaging, these tumors are solid-cystic, heterogeneously enhancing, and show T2 hyperintensity. Pathologically, they can closely resemble a Grade I pineocytoma and immunohistochemistry is essential to differentiate the two. No definite guidelines exist to confirm the ideal protocol of treatment. Evidence regarding the role of radiation after surgery is limited to case reports and series. Adjuvant therapy is usually recommended for tumors with subtotal excision, high proliferative/mitotic index, or proven metastasis. We describe a case of a 29-year-old male with a recurrent papillary tumor of the pineal region, 9 years after primary surgery where it was misdiagnosed as a pineocytoma. The tumor was effectively controlled with surgical excision, cerebrospinal fluid diversion, and adjuvant radiation for 8 years before showing two recurrences within a span of 6 months with a rising proliferation index.

Keywords: Cytokeratin, papillary, pineal, pineocytoma

Introduction
Pineal tumors comprise <1% of all central nervous system (CNS) tumors in adults and approximately 3%-5% of all CNS tumors in children.[1] Although papillary tumors of the pineal region (PTPR) were officially recognized in the WHO classification of CNS tumors in 2007, they were probably known and reported earlier as papillary pineocytomas.[2] This tumor occurs exclusively in the pineal region, most frequently in adults (mean age of 31 years), with a marginal predilection for the female sex.[3] Surgical excision is imperative, not only to improve the overall survival (OS) but also for the need to obtain adequate specimens for immunohistochemical diagnosis which may not always be feasible by biopsy alone.

Case Report
A 29-year-old male presented to the clinic with a history of blurring of vision 9 years ago for which he was evaluated and diagnosed as a case of pineal region tumor [Figure 1a]. He underwent subtotal resection of the same and the pathology report was suggestive of a pineocytoma. Subsequently, he had a turbulent clinical course, developing acute hydrocephalus within 1 month of the surgery for which a ventriculoperitoneal (VP) shunt was inserted. Postoperatively, there was a stable residue of <2 cm which was observed for 2 years [Figure 1b]. The residue then started increasing in size and adjuvant three-dimensional conformal radiation therapy (RT) (54 Gy in 30#) was given. Post-RT imaging showed no tumor residue [Figure 1c]. For 4 years, he was clinically asymptomatic following which he developed shunt malfunction. He underwent multiple shunt revisions (VP and ventriculo-pleural) and eventually an endoscopic third ventriculostomy was performed with removal of previous shunts. A recurrence of the lesion was noted 8 years after the first surgery with clinical worsening, i.e., imbalance on walking and diplopia. The pineal mass was lobulated, solid-cystic, and heterogeneously

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enhancing in nature [Figure 2]. Spine screening showed no evidence of metastasis. A redo surgery was performed through the previous supracerebellar infratentorial approach and subtotal resection with debulking was achieved. Histopathology showed a tumor composed of cuboidal cells and perivascular rosettes. There was absence of pineocytomatous rosettes, mitosis, necrosis, or microvascular proliferation. Immunohistochemistry (IHC) analysis showed negative glial fibrillary acidic protein, focally positive synaptophysin and epithelial membrane antigen, positive S100, and pancytokeratin (AE1/AE3). Ki-67 proliferation index was <1%. These findings were consistent with a PTPR (WHO Grade II) [Figure 3]. The pathology findings were reconfirmed by a second pathologist in another institute. Due to the low proliferative index and absence of mitosis, it was decided to withhold any form of adjuvant treatment. However, the symptoms recurred within 6 months of the second surgery and there was radiological progression of the lesion without spine metastasis [Figure 4a]. A re-exploration was performed to debulk the tumor further [Figure 4b]. The tumor now showed additional features of necrosis and a markedly increased Ki-67 score of 9%. A VP shunt was later re-inserted for ventriculomegaly. Cerebrospinal fluid (CSF) was devoid of any malignant cells. He was referred for RT which has been unfortunately delayed due to the nationwide lockdown currently. At 6 months of follow-up [Figure 4c], the patient is now clinically stable and able to perform day-to-day chores with some help.

**Discussion**

The pineal gland is histologically composed of a mixture of primary cells known as pinealocytes, glial cells, and germ cells. Correspondingly, the predominant primary pineal tumors can be classified as pineal parenchymal tumors, pineal germ cell tumors or glial tumors. The 2016 update of CNS tumors by the WHO lists pineal tumors as pineocytoma (WHO Grade I), pineal parenchymal tumor of intermediate differentiation (WHO Grade II/III), pineoblastoma (WHO Grade IV), and the relatively new, pathological entity papillary tumor of the pineal region (WHO Grade II/III).[4] PTPR, as a separate pathology, was described in 2003 by Jouvet et al.[5] Their case series of six patients with uniform pathological features, hypothesized them to be of ependymal origin from the circumventricular subcommissural organ.

PTPR is composed of an admixture of epithelial cells, papillae, and cells of ependymal differentiation. WHO grades them as either Grade II or III tumors. This differentiation can be done on the basis of mitotic count (< or > than 5/10 hpf) and MIB-1 score (< or >10%).[6] Recurrence is fairly common and strongly dependent on the mitotic rate and...
proliferation index with rates as high as 63%–68% reported in the two largest series of PTPR in literature.\cite{3,7} PTPR shows a propensity to spread to the brain parenchyma rather than showing spinal leptomeningeal metastasis, which tends to occur in higher grades of pineal parenchymal tumors.\cite{6} IHC for cytokeratin marker is essential to rule out a pineocytoma (Grade I) from a PTPR (Grade II/III), since pineocytomas too can show pseudopapillae formation.\cite{8}
In our case, the pathology findings 8 years ago showed small uniform round cells with rosettes classically suggestive of a pineocytoma. An IHC analysis for cytokeratin markers was not done which, in hindsight, would have most probably confirmed the diagnosis of PTPR masquerading as a pineocytoma. This tumor was then effectively controlled with adjuvant radiation for 8 years till a recurrence of PTPR was noted with MIB-1 index <1%. The second recurrence within 6 months and a markedly increased MIB-1 of 9% shows a unique tumor capable of recurrence even after 9 years of follow-up.

Radiologically, these tumors are solid-cystic, well-defined in nature with a characteristic T1 hyperintensity and show mild heterogeneous enhancement on contrast administration. The lesion is usually centered on the posterior commissure and obstructive hydrocephalus due to blockage of the aqueduct is fairly common.

The common differential diagnosis includes pineal parenchymal tumors, choroid plexus papilloma, papillary ependymoma, papillary metastatic carcinoma, and papillary meningioma. Although there have been reports favoring the role of a biopsy followed by adjuvant radiation or radiosurgery, a multicenter study of 44 cases of PTPR has found that only gross total resection along with younger age group statistically influences OS. Maximal safe resection of the lesion with a concurrent CSF diversion maneuver also provides adequate tissue samples for immunohistochemical analysis. The same study has also reported an average progression-free survival of around 5 years. Adjuvant RT offers substantial local control in appropriate cases and hence may be offered to patients with subtotal resection or if the lesion pathologically shows a high mitotic count (≥3/10 hpf) with a high MIB-1 index (≥10%). Adjuvant chemotherapy or targeted therapy in the form of bevacizumab (antibody against vascular endothelial growth factor) must be reserved for patients with recurrence or proven metastasis.

Conclusion

Primary pineal tumors by itself are a rare entity and papillary pineal tumors are even rarer to occur. Their description has been gradually increasing in literature since 17 years ago when it was formally described. IHC for cytokeratin marker is necessary for its diagnosis as it shares pathological features with a more benign pineocytoma. Although these tumors can show an aggressive histology with a WHO grading of II or III, gross total resection and younger age groups are known to offer a good outcome. The role of adjuvant treatment in the form of radiation or chemotherapy is not yet proven, though it may be considered in cases of incomplete resection or a high proliferative index. There is marked tendency for recurrence to occur, even as late as 10 years, and hence a long-term follow-up is essential to diagnose it early.

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Conflicts of interest

There are no conflicts of interest.

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