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Malignant papillary glioneuronal tumor of the pineal gland: Case presentation and literature review of a distinct entity

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 58
Final Diagnosis: Papillary glioneuronal tumor of the pineal gland
Symptoms: Headache • loss of memory • hydrocephalus
Medication: —
Clinical Procedure: —
Specialty: Oncology • neurology • neurosurgery

Objective: Rare disease

Background: The authors report the third case of a rare papillary glioneuronal tumor of the pineal gland and only the second case reported with anaplastic features in this particular location. The authors also review the literature of papillary glioneuronal tumors.

Case Report: Our patient is a 58-year-old Caucasian male who presented with diffuse headaches and loss of short-term memory. There were no deficits on physical exam. MRI Brain was performed demonstrating a large heterogeneously enhancing mass within the pineal gland causing obstructive hydrocephalus. He was taken to the operating room for supracerebellar-infratentorial approach for biopsy of the mass using neuronavigation. He required an endoscopic third ventriculostomy post-operatively for worsening hydrocephalus. Pathology demonstrated a rare malignant papillary glioneuronal tumor. It was recommended that patient undergo chemotherapy and radiation, however he refused treatment. He died six months after his initial diagnosis due to a condition unrelated to his intracranial tumor.

Conclusions: This is an unusually rare tumor of the pineal gland, with only one other malignant case noted in this location. We review the literature of this rare entity that should be considered on the differential diagnosis of a pineal gland mass.

Key words: glio-neuronal • pineal gland • immunostaining • GFAP • synaptophysin

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Background

The authors present a most unusual case of a malignant papillary glioneuronal tumor of the pineal gland. This is only the second reported case of such a high grade glioneuronal tumor in the pineal gland, and the third overall papillary glioneuronal tumor of the pineal gland. We review the literature and discuss the epidemiology, natural history, pathologic diagnostic recommendations, and recommended treatment for this pathology.

Case Report

Our patient is a 58-year-old Caucasian male who presented with diffuse headaches and loss of short term memory. There were no focal deficits on physical exam. MRI Brain was performed demonstrating a large heterogeneously enhancing mass within the pineal gland compressing the tectum and aqueduct of sylvius causing obstructive hydrocephalus. The mass measured 2.0×2.0 cm in size, and was hyperintense on T2 and hypointense on T1 (Figure 1A–D). It was posterior to the massa intermedia.

Intervention

He was taken to the operating room for supracerebellar-infratentorial approach for biopsy of the mass using neuro-navigation. Post-operatively he had continued hydrocephalus, and was taken to the operating room for a cerebral spinal fluid diversion procedure, an endoscopic third ventriculostomy. He had an uneventful hospitalization and was eventually

discharge to home. Because of histological features, it was recommended that patient undergo chemotherapy and radiation; however he refused treatment. He died six months after his initial diagnosis due to an abdominal condition unrelated to his intracranial tumor.

Pathology

Pathology demonstrated a rare high grade glioneuronal tumor (Figure 2A–K). Histology showed a mixture of neoplastic astrocytic and neuronal cells in roughly equal proportions. There was marked nuclear anaplasia, increased mitotic activity, and microvascular proliferation. No definitive necrosis was seen. Neoplastic astrocytes were strongly reactive for GFAP, while neuronal cells were immunoreactive for synaptophysin. No rosettes were seen. Papillary architecture was noted. Double label immunostaining with GFAP and Ki67 highlighted the proliferating astrocytes, and a similar double stain using MAP-2 and Ki67 showed proliferating neuronal cells. The Ki67 was found to be 20%. EGFR, CAM 5.2, and p53 markers were all negative. A diagnosis of malignant papillary glioneuronal tumor was made.

Discussion

Pineal tumors account for 0.5% of all intracranial tumors [1]. Pineal region pathology is diffuse but critical diagnosis of the exact pathology is important, as treatment options and prognosis are very different depending on the specific tumor type.

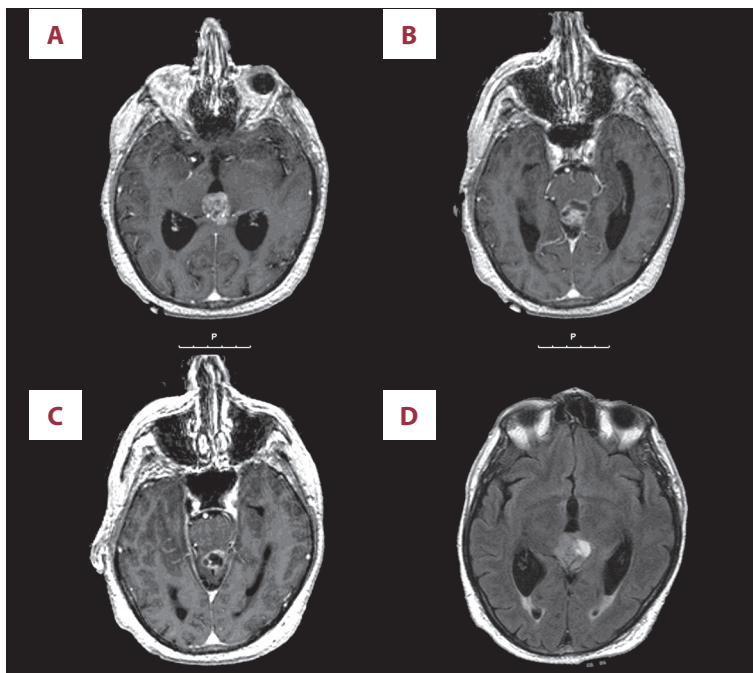


Figure 1. Axial contrast enhanced MRI Brain demonstrated the heterogeneously enhancing mass in the pineal gland with extension to the tectum causing obstructive hydrocephalus.

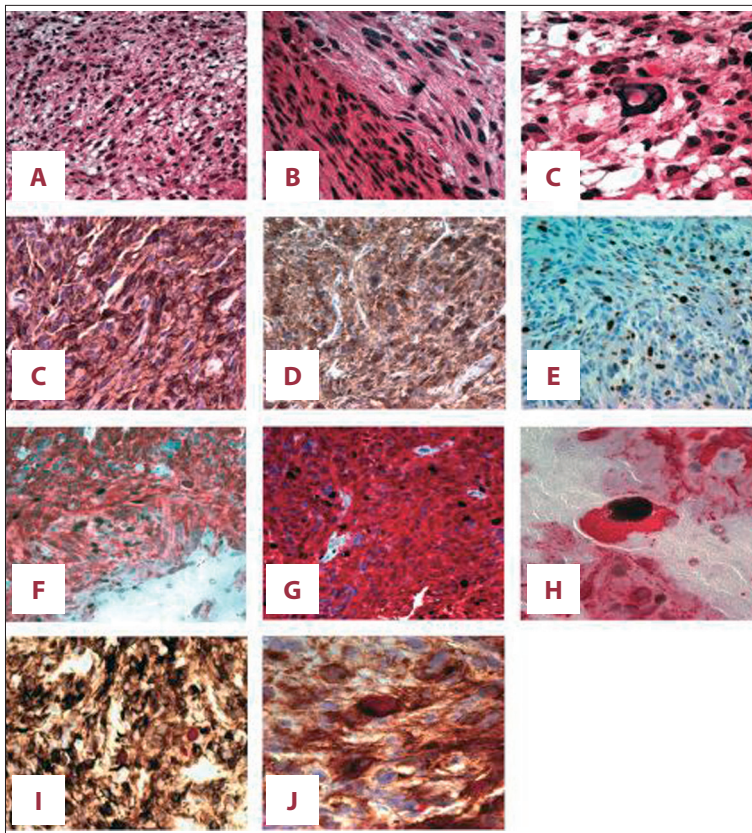


Figure 2. Immunohistochemical slides of malignant papillary glioneuronal tumor of the pineal gland. (A) Hematoxylin and Eosin staining at 20× magnification showing glial processes. (B) Hematoxylin and Eosin Stain 20× showing glial architecture. (C) Hematoxylin and Eosin staining at 40× showing abnormal nuclei pattern. (D and E) Synaptophysin positive indicating neuronal nature of the tumor. (F) Ki67 proliferative index strongly positive at 20%. (G and H) GFAP and Ki67 staining at 20× showing the strong proliferative index of the abnormal glial cells. (I) GFAP and Ki67 immunostaining at 100× demonstrating the strong proliferative index of the abnormal glial cell. (J and K) MAP and Ki67 combined immunostaining demonstrating the high proliferative indices within the abnormal neuronal cells.

Table 1. Comparison of patient characteristics and treatment options of the two known cases of glioneuronal tumor of the pineal gland.

Paper	Age	History	Imag	Size Mass	Contrast	T1	T2	Tx	Survival
Aryan 2004	78M	Personality changes, gait changes	Obst HCP	2.0 cm Localized	Heterog.	Iso	Hyper	ETV Biopsy	Still alive at 3 months
Husain 2011	4 M	Vomiting	Obst HCP	>2 cm Ventricular spread	Heterog.	–	–	Biopsy VPS	–
Kaloostian 2011	58M	Decreased memory, headache	Obst HCP	2.0 cm Localized	Heterog.	Iso	Hyper	Biopsy ETV	Died 6 months (unrelated to tumor)

Papillary glioneuronal tumors (PGNT) were first described in 1998 by Komori et al. [2]. These tumors were noted to have a pseudopapillary pattern with mixed astrocytic, ganglionic and neurocytic differentiation [3]. Histologically these tumors show compact pseudopapillary appearance with hyalinized blood vessels covered by glial fibrillary acidic protein, suggesting astrocytic differentiation, along with areas that are synaptophysin positive, suggesting neuronal differentiation [3]. Ki67 positivity is reported to be low [3]. Classically these tumors are described in young patients, with rare cases affecting the elderly [2,4]. Since that time, WHO in 2007 has classified these

distinct tumors in a group of their own [4] suggesting that these tumors low grade and exhibit benign pathophysiology.

Although most mixed papillary glioneuronal tumors have an indolent course, there are a few published cases of a more aggressive type. Newton et al. described a 19 year old woman with visual seizures and a aggressive papillary glioneuronal tumor in the occipital lobe with a ki67 of 26% [5]. Jahavery et al. described two cases of aggressively behaving papillary glioneuronal tumors. These tumors, one in the frontal lobe and the other along the lateral ventricle, recurred months after their

Table 2. Comparison of Pathological and Immunohistochemical analyses of the two cases of glioneuronal tumor of the pineal gland.

Paper	GFAP	Synapto.	H&E	EM	GFAP + KI67	MIB + KI67	Necrosis	Giant cells
Aryan 2004	+	+	Mitotic fig, Anaplasia, Vascular	Triangle shaped cells with glial filaments	Not done	20%	Not seen	–
Husain 2011	+	+	No Mitosis or Anaplasia or vascularity	Not Done	Not Done	<1%	Not seen	Negative
Kaloostian 2011	+	+	Mitotic Fig, Anaplasia, Vascular	Not done	+	20%	Not seen	Negative

initial resection and had a substantial increase in their KI67 compared to their initial pathology [6]. Ishizawa et al. reported a case of an aggressive papillary glioneuronal tumor in the parietal lobe with an increase in mini-gemistocytic cells up to 10% [7]. In our case, pathology demonstrated a similar combined glioneuronal tumor with aggressive features, of the pineal gland. As noted above, the tissue stained strongly for both GFAP and synaptophysin indicating a dual glioneuronal nature to this tumor. Necrosis was not identified. The proliferative index was 20%. We confirmed on histology that this tumor was neither metastatic in nature, nor a meningioma or intraparenchymal pineal tumor.

Aryan et al. reported the first case of papillary glioneuronal tumor of pineal gland in a 78-year-old man who presented with personality changes and gait disturbance [3]. Husain et al. recently reported a case involving a 4-year-old child with obstructive hydrocephalus with a tumor involving the pineal gland and the ventricular system (Table 1) [8] without anaplastic features or high vascularity. It seems that glioneuronal tumors in the pineal gland may occur in any group, with older patients having a greater predilection for anaplastic features (Table 2), however the number of cases is too small to postulate this trend.

The presentation common among these groups is obstructive hydrocephalus, as observed in all three patients illustrated in the table, caused by a mass approximately 2.0 cm or greater in size (Table 1). In all three cases, the pineal mass is heterogeneously enhancing, with hypointensity on T1 and hyperintensity on T2 MRI (Table 1). Both adult patients were managed

with an endoscopic third ventriculostomy and biopsy (Table 1). One patient survived at least three months and the other six months (although he died from complications of diverticulitis). No data on the survival of the child was available. All cases exhibited strong GFAP and synaptophysin staining (Table 2). Two of the three cases (adult patients) exhibited high proliferative indices with anaplastic components (Table 2).

In review of other malignant tumors of the pineal gland, glioblastoma multiforme cases have been reported with similar presentation [1–15]. This case is clearly not a glioblastoma; necrosis was not seen, synaptophysin was strongly positive, and giant cells were not encountered on pathology. This is a glioneuronal tumor, recently classified entity is clinically and pathologically distinct from other tumors. Since 1998, mixed glioneuronal tumors arising from the cerebrum, cerebellum, ventricular wall have been reported, but the pineal gland are an extremely rare location and one with anaplastic features is even rarer, and it should be considered on the differential diagnosis for primary pineal gland tumors.

Conclusions

It may be surmised that glioneuronal tumor may arise from anywhere in the central nervous system and may showcase a wide spectrum of histological features. More cases and follow up data on these patients must be reported for a more accurate analysis of the natural history, population incidence, location predilection, histology, genetic features and most importantly treatment, of glioneuronal tumors of the pineal region.

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