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Case Report

Atypical pleomorphic neoplasms of the pineal gland: Case report and review of the literature

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Abstract

Background: Pineal region tumors are rare and diverse. Among them exist reports of pleomorphic xanthroastrocytoma (PXA) and pleomorphic granular cell astrocytoma (PGCA) of the pineal gland. These related tumors are remarkably similar sharing pleomorphic histologic features with only minor immunohistochemical and ultrastructural differences.

Case Description: We present a case of a 42-year old right-handed woman presented with a longstanding history of migraine headaches which had worsened over the two months leading up to her hospitalization. MRI revealed a 1.7 × 1.3 × 1.6 cm intensely enhancing lesion originating in the pineal gland. The tumor closely resembled PGCA but did not strictly fit the diagnostic requirements of either PGCA or PXA.

Conclusion: The present case highlights the exotic nature of pineal region tumors with pleomorphic cell histology. Given the diverse range of tumors encountered in the pineal region, pathological confirmation is mandatory. Favorable clinical outcomes demonstrate that surgical resection alone can yield excellent long-term results for tumors falling within the spectrum of pleomorphic lesions of the pineal gland.

Key Words: Pineal gland, pleomorphic granular cell astrocytoma, pleomorphic xanthoastrocytoma

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INTRODUCTION

Pineal region tumors are rare, representing less than 0.5–2% of all intracranial tumors.[8,40] Broadly, these tumors can be divided into germ cell tumors, glial cell tumors, and pineal parenchymal tumors as well as a diverse group of miscellaneous tumors. The pineal parenchymal group extends the range from benign to malignant including pineocytoma, parenchymal tumors of intermediate differentiation, and pineoblastoma.[4,34] The glioma group is largely comprised of pilocytic astrocytomas, fibrillary astrocytomas, anaplastic astrocytomas, glioblastomas, ependymomas, and oligodendrogliomas.[16,20] Tumors with pleomorphic histology are exceptionally rare in this location with only seven reports in the literature.[18,26,28,32-34] These cases roughly fall into the diagnostic categories of pleomorphic xanthoastrocytoma (PXA) or pleomorphic granular cell astrocytoma (PGCA). In this report we present a surgical case of a pineal tumor with pleomorphic histology and

discuss the diagnostic and therapeutic considerations for these exotic tumors.

CASE PRESENTATION

A 42-year-old right-handed female presented with a longstanding history of migraine headaches, which had worsened over the 2 months leading up to her hospitalization. She was otherwise healthy with no additional past medical history, taking only rizatriptan and fenoprofen. Her neurological examination was normal.

Magnetic resonance imaging (MRI) revealed a 1.7 × 1.3 × 1.6 cm intensely enhancing lesion originating in the pineal gland and inseparable from the superior aspect of the tectum inferiorly. The lesion appeared slightly hyperintense relative to cerebrospinal fluid (CSF) on T1-weighted images (WI) [Figure 1] and resulted in inferior displacement of the tectum causing partial obstruction of the aqueduct of Sylvius with associated dilation of the lateral and third ventricles. Fluid-attenuated inversion recovery (FLAIR) sequences demonstrated paraventricular hyperintensity suggestive of transependymal flow due to early obstructive hydrocephalus. Serum levels of human chorionic gonadotropin and α-fetoprotein were negative.

The patient initially underwent successful endoscopic third ventriculostomy for relief of obstructive hydrocephalus. CSF glucose and protein were 38 and <10 mg/dL, respectively. Surgical resection took place 18 days later through a supracerebellar, infratentorial approach with the patient in the sitting position.[5] The tumor seemed to arise from the pineal gland itself with areas of calcification along the dorsal surface. Gross total tumor resection was obtained and the patient was sent to the intensive care unit in satisfactory condition.

Postoperatively the patient did well with a transient mild Parinaud syndrome and gait disturbance that resolved over the following 2 weeks. Follow-up MRI on postoperative day 3 demonstrated complete resection of the tumor [Figure 2].

On hematoxylin and eosin stain [Figure 3], the tumor cells exhibited highly pleomorphic, hyperchromatic nuclei. Frequent multinucleated and enlarged cells with giant, bizarre-shaped nuclei were seen. There were many vessels with hyalinized walls, but no areas of vascular proliferation or necrosis. Rare mitotic figures were seen with a low Ki67 proliferation index reaching up to 1.6% in some areas. Reticulin staining did not reveal peri-tumoral reticulin fibers. Immunohistochemically, the tumor was positive for and synaptophysin and class III β-tubulin with diffuse, weak epidermal growth factor receptor (EGFR) staining. Glial fibrillary acidic protein (GFAP) staining primarily demonstrated focal positivity resembling a reactive process but there were discrete areas of diffuse positive staining of tumor cells.

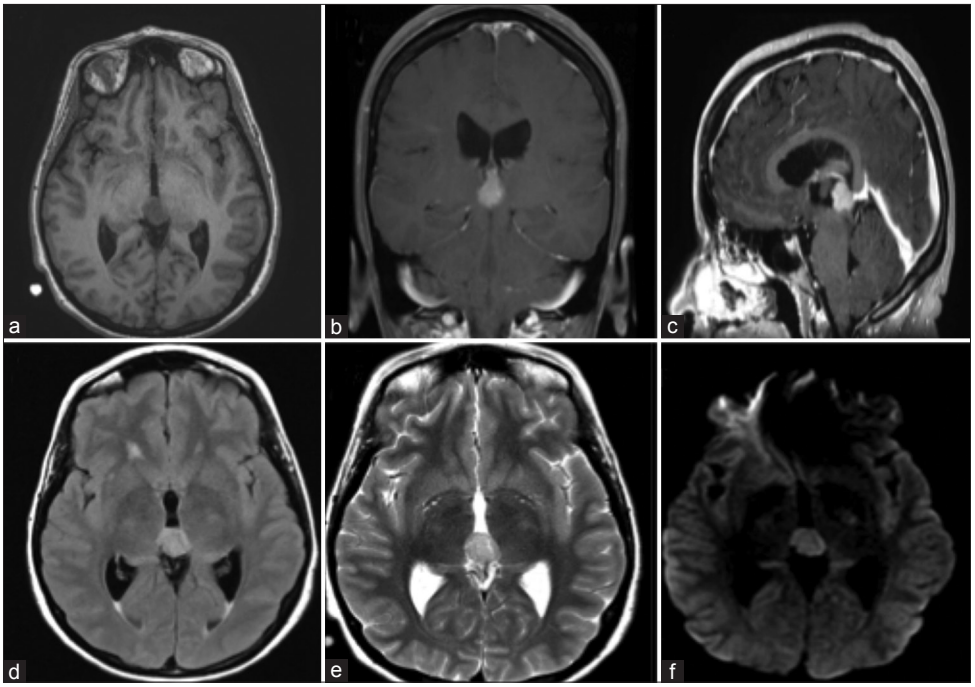

Figure 1: Preoperative Magnetic Resonance Images. (a) Axial T1-weighted image demonstrating lesion in the pineal region with evidence of early hydrocephalus. (b) Coronal contrast enhanced T1-weighted image showing an enhancing lesion extending inferiorly. (c) Sagittal contrast enhanced T1-weighted image demonstrating enhancing lesion displacing the quadrigeminal cistern and dorsal midbrain. (d) Axial FLAIR demonstrating moderate hyperintense lesion. (e) Axial T2-weighted image showing moderate hyperintense lesion. (f) Axial DWI showing moderate hyperintense lesion

There was scattered positive immunostaining for p53, Phosphatase and tensin homolog (PTEN), and Olig2, while staining for IDH-R132H mutation, CK, HMB45, and CD34 were negative.

DISCUSSION

Pineal region tumors are rare, representing 0.5–2% of all intracranial tumors.[8,40] PXAs were first described by Kepes *et al.* in 1979 and are currently recognized as WHO grade II tumors.[11,19] The majority of PXAs have been reported in children and young adults.[6] Lesions are often cystic, typically occurring supratentorially, with a predilection for cortical and leptomeningeal involvement.[11,17,19] However, rare lesions have been reported in the cerebellum, cerebellopontine angle (CPA), spinal cord, hypothalamus, sella, and retina, as well as occurring multifocally.[1,3,7,13-15,21,22,24,25,29-31,36,38,39] Only three cases of histologically confirmed PXA in the pineal gland have been reported, of which two were benign,[33,34] and one featured anaplastic elements.[18] Notably, four cases of PXA-like tumors have been reported in the pineal gland, including PGCAs[28,32] and an atypical pleomorphic astrocytoma.[26]

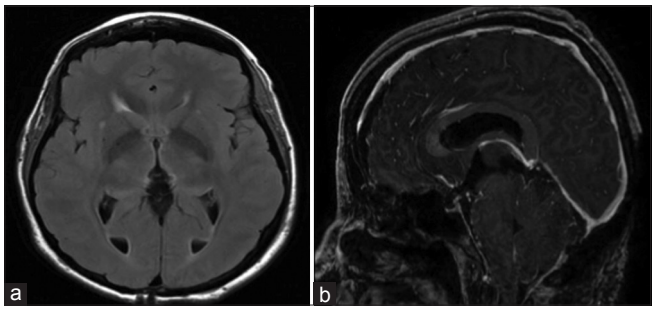

Figure 2: Postoperative Magnetic Resonance Images (a) Axial T1-weighted MRI demonstrating normal postoperative changes. (b) Sagittal T1-weighted postcontrast MRI demonstrating normal postoperative changes

Symptoms of pineal PXA/PGCA at presentation are commonly due to hydrocephalus from mass effect from aqueduct compression and include headache, nausea, and vomiting [Table 1]. Patients may also present with Parinaud syndrome and less commonly, gait disturbances, seizures, and cranial nerve palsies.[4,35]

MRI characteristics of pineal PXA/PGCA are variable. Srinivas *et al.* described an enhancing homogenous lesion with a speck of calcification.[33] In contrast, Thakar *et al.* described a lesion with solid and cystic components,

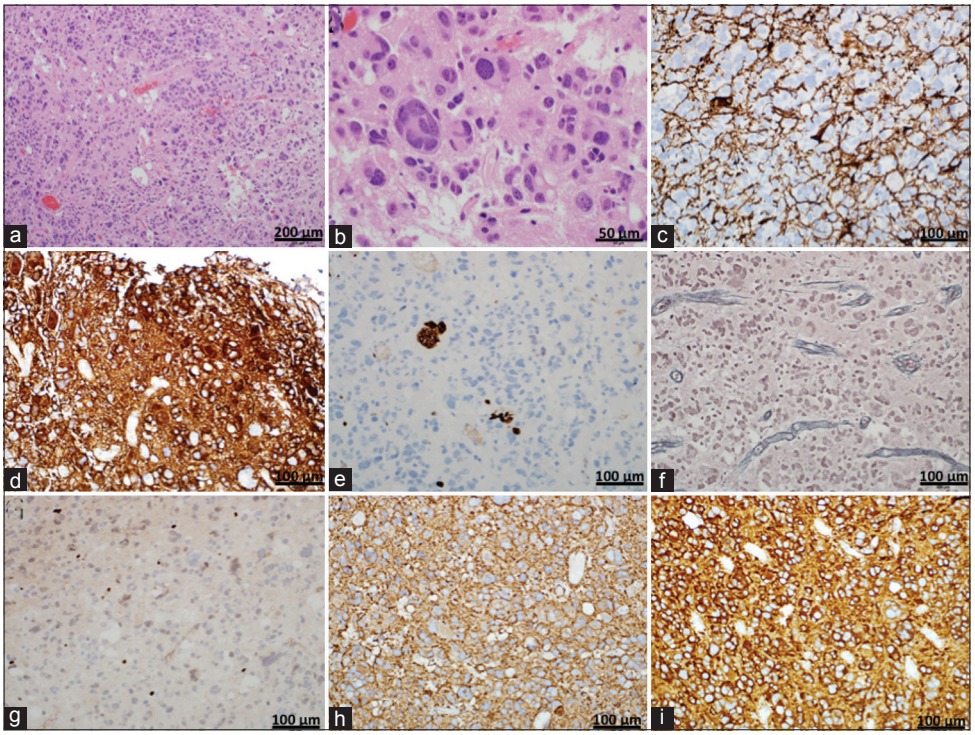

Figure 3: Histology (a and b) Hematoxylin and eosin stained section demonstrating a moderately cellular neoplasm with highly pleomorphic, hyperchromatic nuclei. Frequent multinucleated and enlarged cells with giant, bizarre-shaped nuclei are present. Vessel walls are hyalinized and no areas of vascular proliferation or necrosis are noted. Rare mitotic figures are seen. (c and d) Photomicrograph of GFAP immunostaining demonstrating primarily focal positivity resembling a reactive process with discrete areas of diffuse positive staining. (e) Photomicrograph showing representative Ki-67 immunostaining. Cells show a low proliferation index with focal areas up to 1.6%. (f) Photomicrograph showing representative reticulin immunostaining. Staining can be seen in perivascular connective tissue but there is no reticulin network between the tumor cells. (g) Photomicrograph of Olig2 immunostaining demonstrating scattered positive cells. Magnification: ×20 (h) Photomicrograph of synaptophysin immunostaining demonstrating a diffuse, strongly positive pattern. (i) Photomicrograph of Class III β-tubulin immunostaining demonstrating a diffuse, strongly positive pattern

Table 1: Summary of clinical presentations of pleomorphic neoplasms of the pineal region in the literature

Case	Age	Sex	Presentation	Examination	Imaging	Hydrocephalus
PXA (Srinivas *et al*)	30	M	1-month headache	Papilledema	Isointense T1, hyperintense T2, contrast enhancement, calcifications	Yes (VPS)
PXA (Thakar *et al*)	15	M	1-month history of headache and vomit	Papilledema	Hypointense T1, heterogeneous T2, contrast enhancement, cystic component	Yes
Anaplastic PXA (Katayama *et al*)	61	M	1 month cognitive impairment, difficutly walking	Gait disturbance, Parinaud syndrome	Isointense T1, hyperintense T2, heterogeneous, calcifications	Yes (ventriculostomy)
PGCA (Ohta *et al*)	67	F	Headache, gait disturbance	Normal	T1 hypointense, contrast enhancement	Yes
PGCA (Snipes *et al*)	25	F	3 year headache	Right hand fine movements altered	contrast enhancement	Yes (VPS)
PGCA (Snipes *et al*)	38	M	5 days of headache, nausea and vomiting	Papilledema, incomplete Parinaud syndrome	T2 isointense	Yes (VPS)
Atypical pleomorphic astrocytoma (Nitta *et al*)	30	M	Sudden right weakness and loss of conciousness	Right hemiparesis, left homonoymous lower quadrantonopsia	Partial enhancement	Yes (VPS)
Atypical pleomorphic astrocytoma (Bruce *et al*)	42	F	2-month history of headache	Normal	Hyperintense T1, hyperintense T2, hyperintense FLAIR	Yes (ventriculostomy)

PXA: Pleomorphic xanthroastrocytoma, FLAIR: Fluid-attenuated inversion recovery,

hypointense on T1WI and heterogenous on T2WI, with a contrast-enhancing solid component and a larger, peripherally enhancing cystic component located ventrally.[34] The favorable prognosis of these tumors coupled with the lack of a unique radiological appearance emphasizes the need for histological confirmation of all pineal lesions.

Histologically, PXA tumor cells appear markedly pleomorphic with bizarre, multinucleated giant cells that vary in size and shape. Intracytoplasmic lipid droplets are often present. There is variable infiltration of the underlying brain parenchyma.[11] Mitoses can sporadically be present but necrosis is usually not seen. A basement membrane surrounding the tumor cells might suggest an origin in a subpial astrocyte population.[26] GFAP immunoreactivity is usually positive within the cytoplasm of pleomorphic cells and a reticulin stain shows a rich reticulin network among the tumor cells. Granular bodies with various degrees of eosinophilia are also a regular feature of the tumor.[11] PXAs also contain neuronal antigens, such as betaIII tubulin, synaptophysin, and neurofilament proteins.[12]

Pleomorphic granular cell astrocytoma (PGCA) is a tumor with many histologic features that resemble PXA. However, unlike PXA, it has large numbers of mitochondria and does not have reticulin fibers or a basement membrane between adjacent cells.[26,28] Additionally, PGCA features coarse granular cells containing d-periodic acid Schiff-stained material.[26] It has also been proposed that the presence of retinal S-antigen and a lack of desmoplasia are distinguishing factors between PXA and PGCA.[32] Ohta *et al*. also report focal immunostaining for synaptophysin.[28]

Nitta *et al*. described a pineal gland tumor that could not strictly be defined as PXA or PGCA and was labeled an atypical pleomorphic astrocytoma.[26] This tumor resembled PXA/PGCA in its histopathological and morphological features but lacked the d-periodic acid Schiff-stained material, and was negative for retinal S-antigen. Furthermore, electron microscopy failed to demonstrate increased mitochondria within the tumor cells. Despite inconclusive studies, the overall favorable prognosis remained consistent with PXA/PGCA and the patient was followed for 7 years without signs of recurrence following surgery without adjuvant therapy.

Similarly, the tumor reported here lacks specific criteria to meet a strict diagnostic category. While it demonstrates pleomorphic nuclei, a strong reticulin network as seen in PXA is lacking. Of even greater peculiarity is the GFAP staining, which, in most areas, resembles a reactive astrocytic process. However, there are discrete areas in which the tumor cells themselves are GFAP positive. This is similar to what was encountered in the atypical pleomorphic astrocytoma described by Nitta *et al*. While the tumor reported here has features of PXA and of PGCA, perhaps it is best described as a pleomorphic neuroepithelial neoplasm of the pineal gland.

Astrocytes of the pineal gland are largely believed to give rise to these pleomorphic tumors.[20] In the presented case, the tumor appears to predominantly contain an astrocytic signature only insofar as a reactive process. There are, however, limited focal areas with tumor cells that stain positive for GFAP. Kumar *et al*. noted that involvement of adjacent brain is variable with tumors of the pineal region.[20] In addition to the native astrocytes and interstitial cells of the pineal gland, ependymal cells of the third ventricle and glial cells from the brainstem may also contribute to tumor mass. It is possible that the range of tumor histology

Table 2: Summary of treatment and outcome of pleomorphic neoplasms of the pineal region in the literature

Case	Approach	Postop deficits	Expression markers	Additional treatment	Outcome
1 - PXA (Srinivas *et al*)	Occipital transtentorial	Upward gaze palsy	Ki67<1%, GFAP+, S100+, CD34-	No additional treatment	No recurrence at 1 year
2 - PXA (Thakar *et al*)	Occipital transtentorial	-	GFAP+	No additional treatment	No recurrence at 1 year
3 - Anaplastic PXA (Katayama *et al*)	Interhemispheric transtentorial	Parinaud syndrome	Ki67 32.7%, GFAP+, S100+, Synaptophysin-, CD34-	Biopsy only + TMZ + vincristine + INF-b + local radiation therapy (54 Gy)	Tumor reduction at 10 months
4 - PGCA (Ohta *et al*)	Occipital transtentorial	Left homonymous hemianopsia	Ki67 6%, GFAP+, S100+, Synaptophysin+, EMA-, CD68-, PAS+	No additional treatment	No recurrence at 2 years
5 - PGCA (Snipes *et al*)	Unknown	-	GFAP+, S100+	56 Gy	No recurrence at 8 years
6 - PGCA (Snipes *et al*)	Unknown	Posterior fossa diffuse edema with comatose state	GFAP+, S100+, Vimentin+	45 Gy + reoperation on residual tumor	No recurrence at 1.5 years
7 - Atypical pleomorphic astrocytoma (Nitta *et al*)	Occipital transtentorial	-	S100+, Vimentin-	No additional treatment	No recurrence at 7 years
8 - Atypical pleomorphic astrocytoma (Bruce *et al*)	Supracerebellar infratentorial	Parinaud syndrome	Ki67 1.6%, GFAP+, Synaptophysin+, EGFR+, CD34-	No additional treatment	No recurrence at 3 months

PXA: Pleomorphic xanthroastrocytoma, PGCA: Pleomorphic granular cell astrocytoma, GFAP: Glial fibrillary acidic protein, EGFR: Epidermal growth factor receptor

encountered among these pleomorphic neoplasms is a result of varying degrees of contribution from the local cell populations.

Interestingly, the pathological and immunohistochemical variability seen among PXA, PGCA, and the atypical tumor described here and encountered by Nitta *et al*. are of less clinical consequence than the overall proliferation indexes of these tumors. All seven reported pleomorphic tumors of the pineal gland shared favorable outcomes [Table 2]. This suggests that absence of frequent mitoses and necrosis may be more predictive of favorable clinical outcome in these pleomorphic neoplasms. As a result, surgical treatment alone appears curative across the larger family of these neoplasms.

Pineal region tumors span a highly diverse spectrum of histologies ranging from benign to malignant. Accurate histologic diagnosis is essential for optimal clinical management but can be difficult to achieve because of the propensity for mixed tumor pathologies and heterogeneity in the pineal region. In this case, the patient was managed with craniotomy and open microdissection to achieve the goals of definitive diagnosis by maximizing the amount of tissue provided to the pathologists. Open microsurgical procedures have the added benefit of facilitating gross total resection while minimizing the potential for tumor-associated hemorrhage. Alternate approaches including stereotactic biopsy or endoscopic biopsies are acceptable but provide only limited tissue sampling and ignore the benefits of tumor debulking achievable with open resection, especially for benign, encapsulated tumors. While multiple studies have demonstrated safety and efficacy of endoscopic techniques[2,9,10,27,37] the decision between endoscopic biopsy and open craniotomy depends on several factors including ventricular size, the relative position of the tumor, the dimension of the massa intermedia, the surgical goals of resection/tissue sampling, and, particularly, the vascularity of the tumor and the likelihood of biopsy-associated hemorrhage.[23]

CONCLUSION

The present case highlights the exotic nature of pineal region tumors with pleomorphic cell histology. Given the diverse range of tumors encountered in the pineal region, pathological confirmation is mandatory. Favorable clinical outcomes demonstrate that surgical resection alone can yield excellent long-term results for tumors falling within the spectrum of pleomorphic lesions of the pineal gland.

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