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 xanthoastrocytoma (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

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.¹⁸,³⁴ The glioma group is largely comprised of pilocytic astrocytomas, fibrillary astrocytomas, anaplastic astrocytomas, glioblastomas, ependymomas, and oligodendrogliomas.¹⁸,²⁰ 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. 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.
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. PXAs were first described by Kepes et al. in 1979 and are currently recognized as WHO grade II tumors. The majority of PXAs have been reported in children and young adults. Lesions are often cystic, typically occurring supratentorially, with a predilection for cortical and leptomeningeal involvement. Only three cases of histologically confirmed PXA in the pineal gland have been reported, of which two were benign, and one featured anaplastic elements. Notably, four cases of PXA-like tumors have been reported in the pineal gland, including PGCAs and an atypical pleomorphic astrocytoma.

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.

MRI characteristics of pineal PXA/PGCA are variable. Srinivas et al. described an enhancing homogenous lesion with a speck of calcification. In contrast, Thakar et al. described a lesion with solid and cystic components.
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, difficulty walking | Gait disturbance, Parinaud syndrome | Isointense T1, hyperintense T2, heterogeneous, calcifications | Yes |
| PGCA (Ohta et al) | 67 | F | 3 year headache | Normal | T1 hypointense, contrast enhancement | Yes |
| PGCA (Snipes et al) | 25 | F | Right hand fine movements altered | Papilledema, incomplete Parinaud syndrome | T2 isointense | Yes (VPS) |
| Atypical pleomorphic astrocytoma (Nitta et al) | 30 | M | Sudden right weakness and loss of consciousness | Right hemiparesis, left homonymous lower quadrantanopsia | 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.

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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. Additionally, PGCA features coarse granular cells containing d-periodic acid Schiff-stained material. It has also been proposed that the presence of retinal S-antigen and a lack of desmoplasia are distinguishing factors between PXA and PGCA. Ohta et al. also report focal immunostaining for synaptophysin.

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. 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. 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. 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...
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, 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.

**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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