Case Report

Pineal region ganglioglioma: A neoplasm with a bimodal age distribution

Osama A. Al-Dalahmah1, Linda Wang2, Susan J. Hsiao1, Chun-Chieh Lin3, Mahesh M. Mansukhani1, Peter Canoll1, Jeffrey N. Bruce1, George Zanazzi3,4

1Department of Pathology and Cell Biology, Columbia University Irving Medical Center, 2Department of Neurosurgery, Columbia University Irving Medical Center, New York, 3Department of Pathology and Laboratory Medicine, Dartmouth-Hitchcock Medical Center, 4Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, United States.

E-mail: Osama A. Al-Dalahmah - oaan2288@cumc.columbia.edu; Linda Wang - lmm2181@cumc.columbia.edu; Susan J. Hsiao - sjh2155@cumc.columbia.edu; Chun-Chieh Lin - chun-chieh.lin@hitchcock.org; Mahesh M. Mansukhani - mm322@cumc.columbia.edu; Peter Canoll - pc561@cumc.columbia.edu; Jeffrey N. Bruce - jnb2@cumc.columbia.edu; *George Zanazzi - george.j.zanazzi@hitchcock.org

ABSTRACT

Background: Gangliogliomas arise very rarely in the pineal region, where their natural histories and pathologic features are poorly understood.

Case Description: In this report, we describe a 36-year-old woman who presented with a seizure followed by worsening headache, dizziness, confusion, and intermittent left facial numbness over the next few weeks. A head CT scan showed a partially calcified pineal region mass with hydrocephalus. After an endoscopic third ventriculostomy, the patient underwent a resection of the tumor that contained dysplastic ganglion cells and piloid glial cells. Molecular profiling of this CNS WHO Grade 1 ganglioglioma revealed polysomies of chromosomes 7 and 9, and a BUB1 variant of uncertain significance, without known MAP kinase pathway alterations. From a review of the literature, we found two distinct age distributions for pineal ganglioglioma, with modes at 1 and 36 years of age.

Conclusion: Although very rare, this tumor should be considered in the differential diagnosis of pineal region tumors in children and young adults.

Keywords: Epiphysis, Glioneuronal, Targeted next-generation sequencing, Tumor, Chromosome 7 polysomy

INTRODUCTION

Pineal region tumors constitute 2.8% of intracranial tumors in children and adolescents in the United States, and 0.05% in adults.[25] In an analysis of the Surveillance, Epidemiology and End Results database of tumors diagnosed from 1973 to 2005, Al-Hussaini et al.[1] found that 43% of the pineal region tumors were in adults. While there is a predilection for pineoblastoma in children, pineocytoma and pineal parenchymal tumor of intermediate differentiation most frequently occur in adults (reviewed in WHO Classification of Tumours Editorial Board[39]). Glial and glioneuronal tumors originating in the pineal gland or in adjacent structures have diverse epidemiological features, depending on the tumor type.[23]

Gangliogliomas are tumors characterized by dysplastic ganglion cells and neoplastic glial cells that most commonly occur in children and young adults. Together with gangliocytomas, they comprise...
0.4% of all central nervous system tumors. While gangliogliomas can be found throughout the central nervous system, from the cerebral hemispheres to the spinal cord, most tumors occur in the temporal lobe and present with focal seizures. Complete surgical resection of these well-circumscribed, variably cystic lesions leads to an excellent prognosis for most of these patients, and hence they correspond to CNS WHO Grade 1. A small subset of these tumors show aggressive behavior and anaplastic histologic features, which correspond to CNS WHO grade 3 (reviewed in WHO Classification of Tumours Editorial Board[39]). Most gangliogliomas appear to have few genomic alterations, and they reside predominantly in \textit{BRAF} and other genes of MAP kinase pathways.[28]

Although a ganglioglioma in the pineal region was first described in 1928,[14] these tumors are not well-understood due to their rarity. In this report, we present a case of a 36-year-old woman who initially experienced a seizure and was found to have pineal region ganglioglioma, CNS WHO Grade 1.

\textbf{CASE HISTORY}

The patient is a 36-year-old right-handed woman who collapsed and was found unresponsive, stiff, drooling, and tremulous, but with no rhythmic shaking, tongue-biting, or urinary incontinence. She became responsive again within 4–5 min. Head CT and subsequent MRI at an outside hospital revealed a mass in the pineal region. The patient was started on dexamethasone and levetiracetam.

She experienced worsening headache, dizziness, confusion, and intermittent left facial numbness. Head CT revealed a partially calcified mass centered in the pineal region with moderate lateral ventricle and third ventricle hydrocephalus. An endoscopic third ventriculostomy was performed. Headache, left-sided facial numbness, and confusion diminished. Serum AFP and beta-HCG levels were normal. Brain MRI showed a 3.0 × 2.1 cm heterogeneously enhancing mass in the pineal region [Figure 1a]. Susceptibility weighted-images demonstrated magnetic susceptibility artifact within the mass, corresponding to the calcifications seen on CT.

Two and a half weeks later, the patient underwent a right parietal craniotomy followed by an interhemispheric approach to the tumor. The posterior surface of the tumor was partially attached to the cerebellum, and the right lateral aspect of the tumor seemed to blend into the dorsal midbrain. A gross total resection of the tumor was performed [Figure 1b].

\textbf{Pathology}

Multiple fragments of tan-gray and red soft tissue were received. Hematoxylin and eosin-stained sections of the resection specimen showed highly pleomorphic tumor cells, with large ganglioid cells containing vesicular nuclei and distinct nucleoli interspersed between variably sized ovoid cells and spindle-shaped bipolar cells containing fibrillary, eosinophilic cytoplasmic processes [Figure 2a]. Scattered Rosenthal fibers and eosinophilic granular bodies were present [Figure 2b]. A subset of the ganglioid cells were binucleated or multinucleated [Figures 2c and d]. Areas of perivascular inflammation [Figure 2e], vascular hyalinization [Figure 2f], and corpora arenacea [Figure 2f] were noted. No rosettes, necrosis, mitoses, or microvascular proliferation

\textbf{Figure 1:} Preoperative and postoperative imaging of the pineal region neoplasm. (a) Axial T1-weighted MRI shows a mass, measuring 3.0 × 2.1 cm, at the level of the pineal gland with heterogeneous, mostly solid enhancement. (b) Axial T1-weighted MRI after resection reveals minimal linear enhancement along the margin of the surgical cavity.

\textbf{Figure 2:} Histologic features of the pineal region neoplasm. (a) Hematoxylin and eosin-stained sections of the resection specimen show a pleomorphic neoplasm with thick, fibrillary, cytoplasmic processes. Some cells have ovoid nuclei, and some have spindle-shaped nuclei. (b) Eosinophilic granular bodies and Rosenthal fibers are noted on a frozen section. Low magnification (c) and high magnification (d) photomicrographs reveal many ganglioid cells with prominent nucleoli. (e) Collections of mixed chronic inflammatory cells can be seen around some blood vessels. (f) Tumor cells are present adjacent to hyalinized blood vessels and corpora arenacea.
were identified. The Ki67 proliferation index was low, with <1.0% of tumor cells staining positive.

Gliarial fibrillary acidic protein (GFAP) immunoreactivity was diffusely positive in the glial component [Figure 3a] and a subset of the gangliocytic and multinucleated cells, and OLIG2 was expressed in the majority of tumor cells [Figure 3b]. Phosphorylated neurofilament [Figure 3c] and granular synaptophysin immunoreactivity, including in the somata and axons of some gangliocytic tumor cells [arrow, Figure 3d], confirmed that the tumor was a ganglioglioma. Highly branched CD34-positive cells, present in the majority of gangliogliomas, were abundant [Figure 3e]. Platelet-derived growth factor receptor alpha and p53 were positive in a small subset of tumor cells, and PTEN and ATRX were preserved. The tumor lacked IDH-1 (R132H) and BRAF (V600E) mutations by immunohistochemistry.

**Molecular diagnostics**

To begin to evaluate the molecular alterations in this tumor, paraffin-embedded sections were incubated with chromosome 7 reference alpha-centromeric (CEP7, red) and EGFR (black) in situ hybridization DNA probes [Figure 3f]. Polysomy of chromosome 7, with an average of 4.25 copies per cell, was detected without selective EGFR amplification. Additional fluorescent in situ hybridization experiments revealed polysomy of chromosome 9, with detection of 3–5 copies of a reference CEP9 probe in 83.5% of cells. Of note, no cells showed homozygous deletion of CDKN2A.

Targeted next generation sequencing was performed with the Columbia Combined Cancer Panel, a 467-gene panel.[36] Sixty-six million total reads were obtained on the tumor sample, resulting in an average coverage of ×878. The tumor mutational burden was low (1.57). A somatic variant of uncertain significance (NM_001211.5:c.973G>A, p.G325S), which has not been previously reported, was identified in exon 8 of the spindle checkpoint kinase BUB1B. Canonical MAP kinase pathway alterations found in gangliogliomas, including the BRAF p.V600E mutation,[28] were not identified.

**DISCUSSION**

We present a report of ganglioglioma, atypically located in the pineal region, in a 36-year-old woman who presented with a seizure followed by worsening headache, dizziness, confusion, and intermittent left facial numbness. CT and MRI showed a large, heterogeneously enhancing mass in the pineal region causing obstruction of the aqueduct of Sylvius and hydrocephalus. Following a right parietal craniotomy with interhemispheric approach for tumor resection, examination of the tumor revealed a ganglioglioma, CNS WHO Grade 1, with polysomies of chromosomes 7 and 9 and a BUB1 variant of uncertain significance. Postoperative MRI showed gross total resection. We reviewed our large institutional cohort of 221 patients with pineal region tumors that were resected over a 25 year-period from 1994 to 2019, and this was the only ganglioglioma.[20]

We reviewed the literature and found 24 additional cases of ganglioglioma in the pineal region [Table 1].[3,7-9,10,13-16,19,21-22,24,31,33,37-38] Two cases that have historically been classified as pineal region gangliogliomas were not available for review and therefore not included in the analysis.[27,33] Fifteen case reports included data on patient age. From these cases, two major peaks emerged: one in childhood (mean 7.75, mode 1, range 1–16, n = 8) and one in young adulthood (mean 36.3, mode 36, range 32–40, n = 7). Eighteen cases provided information on patient gender and revealed a slight female predominance, with 11 female patients compared to seven male patients. These demographics are consistent with those of our patient, a woman in her mid-thirties.

We found that pineal gangliogliomas, like other pineal region lesions, tend to present with signs and symptoms of increased intracranial pressure due to compression of the aqueduct of Sylvius, resulting in headache, nausea, vomiting, and papilledema. Features associated with Parinaud syndrome are also commonly seen, including vertical gaze palsy resulting in diplopia and pupillary light-near dissociation. In the case of our patient, the clinical presentation was also notable for a seizure, a common presentation of gangliogliomas in general.
due to their typical location in the temporal lobe, but an uncommon presentation for most lesions of the pineal region including gangliogliomas. There may be a higher prevalence of epileptic seizures in some patients with pineal cysts, but the mechanisms are not well understood.  

Pineal gangliogliomas, like other gangliogliomas, are characterized by dysplastic neurons and intermixed glia, with immunohistochemical staining positive for markers of both cell lines, such as neuron-specific enolase, neurofilament, synaptophysin, and GFAP. The immunophenotype of the

### Table 1: Gangliogliomas involving the pineal region.

| Reference          | Age/sex | Presentation                                                                 | Treatment | Tumor grade | Outcome                        |
|--------------------|---------|-----------------------------------------------------------------------------|-----------|-------------|-------------------------------|
| Horrax, 1928       | 40/M    | HA for 15 mo, poor vision for 1 yr, drowsiness and ataxia for 4 mo; two Sz with right face, arm, leg numbness; dysphagia, dysarthria | Decompn  | NA          | Died                           |
| Camins, 1978¹      | NA      | NA                                                                          | NA        | NA          | NA                            |
| Camins, 1978¹      | NA      | NA                                                                          | NA        | NA          | NA                            |
| Demakas, 1982      | 1/F     | Increasing lethargy, decreased activity, regression of development           | VPS, STR, Rtx | NA          | “Doing well” approximately 1.5 yr later |
| Dorne, 1986        | 39/M    | HA starting 13 yr prior, transient vertigo starting 6 mo prior              | Bx, Rtx  | NA          | Radiographic persistence of enhancing tumor 2 yr later |
| Hunt, 1989         | 1/F     | Nausea, vomiting, lethargy, regression of motor function                   | Bx, Rtx  | low         | Recurrence 6 yr later         |
| Tokoro, 1993       | 36/M    | Gait disturbance, dementia, urinary urgency, impotence                      | GTR       | NA          | No recurrence at 2 yr         |
| Johnson, 1995      | 10/M    | Behavioral changes starting 3 mo prior, followed by abulia, dizziness, ataxia, urinary incontinence | Bx, Rtx  | low         | No recurrence at 2 yr         |
| Chang, 1996        | 6/F     | Hydrocephalus at 4 mo, premature thelarche                                | VPS, GTR  | low         | NA                            |
| Faillot, 1998      | 38/M    | Symptoms of increased ICP, diplopia                                        | GTR       | NA          | No recurrence at 1 yr         |
| Fagundes-Pereyra, 2001 | 14/M    | HA starting 8 yr prior, and 2 mo of vomiting, seizure, ataxia, diplopia and bilateral papilledema | GTR       | low         | No recurrence at 0.5 yr       |
| Tender, 2004       | 16/F    | HA, cognitive and emotional difficulties, confusion, gait unsteadiness     | GTR, VPS  | low         | No recurrence at 1 yr         |
| Leston, 2009       | 36/F    | Symptoms of increased ICP, vomiting                                        | NA        | NA          | NA                            |
| Radovanoivc, 2009  | NA      | NA                                                                          | NA        | NA          | NA                            |
| Radovanoivc, 2009  | NA      | NA                                                                          | NA        | NA          | NA                            |
| Sajko, 2009        | NA/F    | NA                                                                          | VPS, resection | NA          | NA                            |
| Woo, 2013          | 33/F    | NA                                                                          | VPS, excision, Rtx | low         | Recurrence 12 yr later        |
| Mottolese, 2015    | NA/F    | NA                                                                          | NA        | low         | NA                            |
| Mottolese, 2015    | NA      | GTR, Rtx                                                                     | GTR       | NA          | NA                            |
| da Costa, 2016     | 32/F    | HA                                                                          | GTR, TMZ, Rtx | high       | NA                            |
| Lüdemann, 2017     | 11/M    | HA, double vision                                                           | STR, TMZ, Rtx | high       | No recurrence at 3 mo         |
| Lin, 2020          | 3/F     | NA                                                                          | bx        | low         | No recurrence at 2.3 yr       |
| Lin, 2021          | NA      | NA                                                                          | NA        | NA          | NA                            |
| Lin, 2021          | NA      | NA                                                                          | NA        | NA          | NA                            |
| Lin, 2021          | NA      | NA                                                                          | NA        | NA          | NA                            |
| Al-Dalahmah, 2022  | 36/F    | Sz, HA, confusion, intermittent left facial numbness                        | ETV, GTR  | low         | No recurrence at 1 mo         |

F: Female, M: Male, NA: Not available, HA: Headache, Sz: Seizure; ICP: Intracranial pressure, Decompn: Decompression, VPS: Ventriculoperitoneal shunt, ETV: Endoscopic third ventriculostomy, STR: Subtotal resection, GTR: Gross total resection, Bx: Biopsy, Rtx: Radiotherapy, Tmx: Temozolomide, mo: Month, yr: Year. 'The two cases listed here from this reference were diagnosed as "mixed astrocytoma-ganglieneuroma" by the authors.
pineal ganglioglioma in our case was overall similar to that of general non-pineal gangliogliomas, with diffusely positive staining for GFAP in the glial component of the tumor [Figure 3a] in combination with positive staining for phosphorylated neurofilament [Figure 3c], and synaptophysin [Figure 3d], and NeuN in the gangliocytic component. The glial component of gangliogliomas can vary in composition, but has been known to resemble other neoplasms, including pilocytic astrocytomas. The differential diagnosis for a pineal ganglioglioma also includes gangliocytoma and ganglioneuroblastoma which lack a glial component. Pineal gangliogliomas should also be distinguished from pineocytomas with astrocytic differentiation and pleomorphic pineal parenchymal tumors with gangliocytic differentiation. Pleomorphic gliomas of the pineal region lack a gangliocytic component. The genetic features of pineal gangliogliomas are not known, but the most common chromosomal abnormality found in non-pineal gangliogliomas is gain of chromosome 7 and polysomy of chromosome 7 was in fact detected by cytogenetic analysis in our case, with an average of 4.25 copies per cell measured across 40 representative cells. Several studies have found associations between the BRAF V600E mutation and gangliogliomas, with reports of a mutation present in approximately 20–60% of cases. However, of the pineal gangliogliomas reviewed here, only two cases, reported by Lüdemann et al. and Ho et al. investigated this connection and found evidence of a mutation (BRAF V600E for both cases). Our case tested negative for the BRAF V600E mutation. Instead, polysomy of chromosome 9 and a variant of unknown significance in the mitotic checkpoint inhibitor BUB1B (p. G325S) were detected in this tumor.

In general, pineal gangliogliomas are low-grade tumors most often corresponding to CNS WHO Grade I, similar to gangliogliomas found elsewhere in the brain. The Ki-67 proliferation index in our case was <1.0%, similar to the mean for non-pineal gangliogliomas (1.1–2.7%). As a whole, gangliogliomas rarely undergo malignant transformation, and progression of pineal gangliogliomas is even less common. There have been two reports of high-grade gangliogliomas of the pineal region with clinical information: an 11-year-old boy and a 32-year-old woman. As with other gangliogliomas throughout the central nervous system, pineal gangliogliomas appear to recur at a low rate. Almost all cases reviewed here were of patients with primary tumors presenting for the 1st time, and surgical resection was curative in most cases. Four patients represented after initial treatment with residual or recurrent disease. Furthermore, additional adjuvant therapy was required for patients with pineal gangliogliomas with higher-grade features. Overall, the prognosis for pineal gangliogliomas appears to be similar to that of non-pineal gangliogliomas, which is typically favorable: usually surgical excision is sufficient, with one series reporting a 5-year survival rate of 89% and a 10-year survival rate of 84%.

CONCLUSION

We present a case of a rare pineal region ganglioglioma in an adult woman. Review of our large institutional cohort of 221 pineal region tumors, resected over 25 years, did not reveal any additional gangliogliomas. A literature search found 24 additional cases of pineal region gangliogliomas without pineal parenchymal tumor differentiation. There is a bimodal age distribution, with modes at age 1 and age 36 years. Despite being rare, gangliogliomas should be part of the differential diagnosis of tumors in the pineal region.

Ethics approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the research committee of University of Helsinki and with the 1964 Declaration of Helsinki and its amendments or comparable ethical standards.

Declaration of patient consent

Patient’s consent not required as patient’s identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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