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Case Report

Laparosc Endosc Surg Sci 2021;28(4):215-222
DOI: 10.14744/less.2021.92603

Neuroendoscopic management of a pineal glioblastoma: A case report with a systematic literature review

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ABSTRACT

Pineal region glioma histologies are fibrillary astrocytoma, pilocytic astrocytoma, anaplastic astrocytoma, glioblastoma, oligodendroglioma, ependymoma, and choroid plexus papilloma. Malignant tumors of the pineal region are difficult to manage. Glioblastomas are rare aggressive tumors that can cause acute hydrocephalus and life-threatening complications in this area. We present a case of pineal region glioblastoma, who diagnosed and treated with neuroendoscopy as well as radiotherapy and chemotherapy. We also provided a literature review specifically focused on neuroendoscopic treatment of the disease with a comparison between those with and without surgical resection.

Keywords: Biopsy, endoscopic third ventriculostomy, hydrocephalus, pineal region glioblastoma

Introduction

Pineal region pathologies are challenging to treat because of the deep location of this site and its neighboring vital structures.[1] Glioblastoma is the most common brain tumor in adults; however, pineal region glioblastoma (PRG) is very rare. There have only been 40 reported cases to date. The optimal management of PRGs is not yet clear. This case report demonstrates an endoscopic third ventriculostomy (ETV) treatment of acute hydrocephalus in a patient with PRG, as well as neuroendoscopic biopsy through a different trajectory during the same session. We also review the literature, specifically focusing on the neuroendoscopic treatment of the tumor, comparing those with and without surgical resection.

Case Report

A 59-year-old man presented with complaints of headache, dizziness, and inability to hold a drinking glass steady for 3 weeks. A neurological examination revealed motor deficit (4/5) of both upper distal extremities and cerebellar ataxia. Magnetic resonance imaging (MRI) of the brain showed a solid enhancing tumoral mass in the pineal region without hydrocephalus (Fig. 1). The patient refused further investigations and was discharged from the hospital. However, he had gradually worsened over 8 months and returned back to the emergency department with severe headache, confusion, moderate ataxia, and double vision. The brain MRI was repeated and showed progression of the tumor size. The tumor was compressing the midbrain, tectum, posterior third ventri-

Received: 08.11.2021 **Accepted:** 11.11.2021
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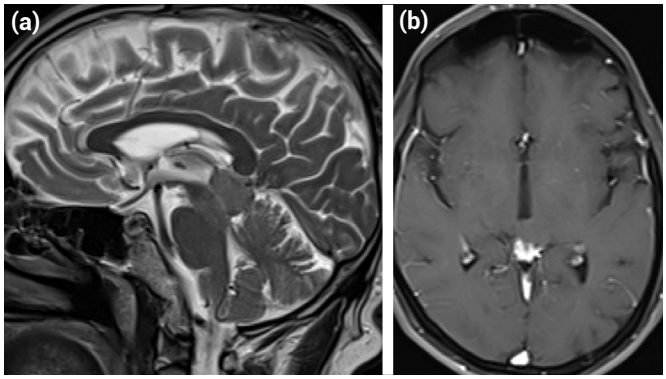

Figure 1. Magnetic resonance imaging (MRI) of the pineal glioblastoma at initial presentation **(a)** Sagittal T2-weighted image shows a mass in the pineal region **(b)** The mass shows heterogeneous enhancement on postcontrast axial T1-weighted image.

cle, and aqueductus cerebri, resulting in hydrocephalus. Post-gadolinium T1-weighted MRI showed heterogeneous contrast enhancement of the mass with scattered necrotic areas, suggesting a high-grade tumor (Fig. 2). Spinal MRI did not reveal leptomeningeal metastasis. Results of laboratory evaluations, including tests for serum alpha-fetoprotein and beta-human chorionic gonadotropin, were within the normal range.

Neuroendoscopic method (Karl Storz, Hopkins, 0 degree, straight forward) was used for the management of the acute hydrocephalus and the diagnostic biopsy from the pineal tumor. We preferred two different trajectories for these procedures. For ETV, we drilled the first burr hole just anterior to the coronal suture on the mid-pupillary line. A pathway was then identified from the frontal lobe through the foramen of Monroe and the floor of the third ventricle immediately anterior to the mammillary bodies. Once the floor of the third ventricle was fenestrated, cerebrospinal fluid was observed flowing from the ventricle to the prepontine cistern. After the classical ETV procedure was completed, we performed the biopsy. A second burr hole was drilled 3 cm anterior to the first one on the mid-pupillary line. A trajectory was then followed from the frontal lobe through the foramen of Monroe toward the Sylvian aqueduct. The lesion was biopsied immediately superior to the opening of the Sylvian aqueduct (Fig. 3). The procedures were completed in 40 min. He recovered well afterward and his level of consciousness, ataxia, and double vision improved. Making ETV treated the hydrocephalus, finally treating the hydrocephalus solved the increased intracranial pressure syndrome.

Pathological examination of the tissue revealed an isocitrate dehydrogenase (IDH) 1 wild-type glioblastoma. Tumor cell cytoplasm positive for glial fibrillary acidic protein immunohistochemical staining (×400) reveals proliferated tumor cells positive for Ki-67 (a nuclear protein associated with cellular proliferation) (Fig. 4). The patient was prescribed curative radiotherapy of 6000 cGy administered in 30 fractions, as well as temozolomide chemotherapy. Nineteen months after surgery, he was alive with the stable tumor (Fig. 5).

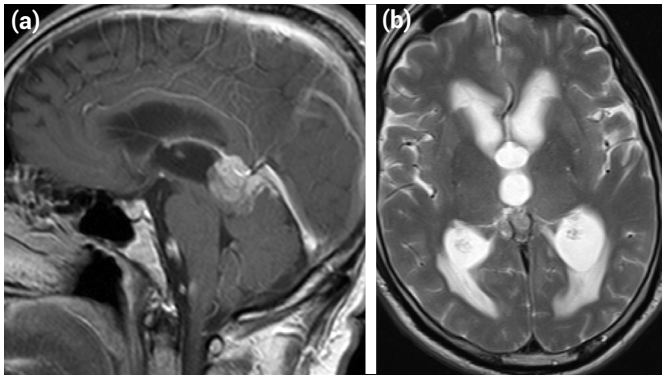

Figure 2. Repeated MRI eight months after the initial examination. (a) Postcontrast axial T1-weighted image shows a larger heterogeneously enhancing mass that fills the pineal region and obstructs the third ventricle outflow, causing hydrocephalus. (b) Axial T2-weighted MRI demonstrates the enlarged mass and acute hydrocephalus.

Figure 3. Histological findings of the pineal region glioblastoma: (a) The photomicrograph of the biopsy specimen (X100 magnification, H+E) reveals atypical astrocytes (black arrow) and a normal choroid plexus (white arrow). (b) Immunohistochemical staining (X100 magnification) shows tumor cells negative for isocitrate dehydrogenase (IDH) 1. (c) Immunohistochemical staining (X400 magnification) reveals tumor cell cytoplasm positive for glial fibrillary acidic protein (GFAP) (d) Immunohistochemical staining (X400 magnification) reveals proliferated tumor cells positive for Ki-67 (a nuclear protein associated with cellular proliferation).

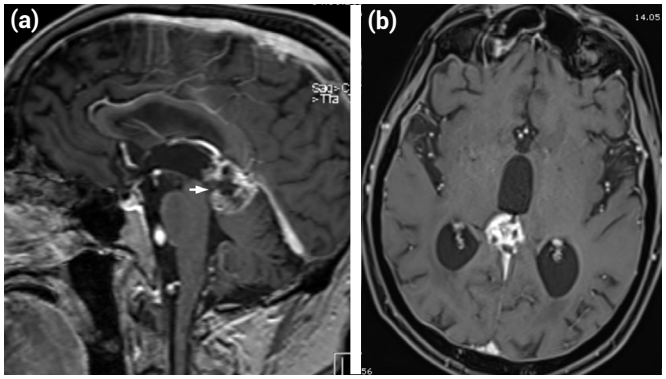

Figure 4. Follow-up MRI after the operation. (a) Sagittal postcontrast T1-weighted image shows heterogeneous enhancement of the pineal mass (white arrow indicates biopsy site) (b) Axial postcontrast T1-weighted MRI shows the pineal mass (arrow) and the ventricles (arrowhead)reduced in size after endoscopic third ventriculostomy. By this stage, the patient had undergone radiotherapy and chemotherapy, and the images demonstrates the stable disease.

Systematic Review of the Literature

A systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[2] A literature search was performed using keywords combination both in PubMed and Google Scholar on March 2020. The keywords combination includes of terms of pineal and glioblastoma. A detailed literature search revealed 49 previously published cases. Six of them were excluded from the study because their treatments were unknown. Forty-three patients were analyzed in two groups, those with and without surgical resection. Groups A and B included 31 and 12 cases, respectively. The PRISMA flow diagram is provided in Figure 6. The results are presented in Table 1, including the presented case.[3-27] The gender of three patients was unknown. Twenty-three of 40 patients were male, and 17 were female. The mean age at presentation is 43.6, ranging from 5 to 74.[3,18]

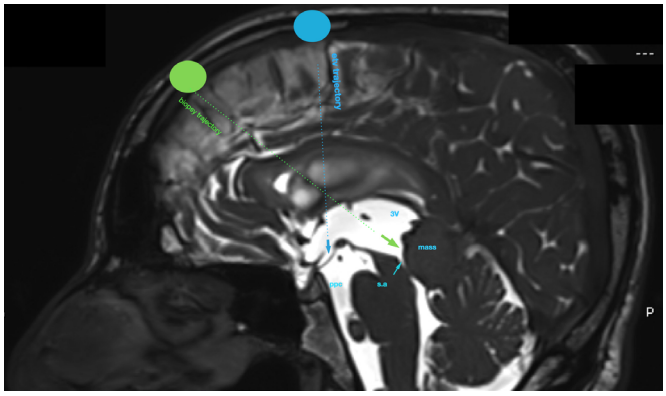

Figure 5. Preoperative sagittal constructive-interference-in-steady-state (CISS) sequence shows the planned trajectory of the endoscopic third ventriculostomy (blue dashed line) via the posterior burr hole (blue circle). The path extends from the frontal lobe through the lateral ventricle and the foramen of Monroe, and finally through the floor of the third ventricle, which is superior to the prepontine cistern. The biopsy trajectory (green dashed) line begins at the anterior burr hole (green circle). It extends from the frontal lobe through the foramen of Monroe, and ends in the superior portion of the Sylvian aqueduct.

Discussion

Tumors arising from the pineal region can be classified into three groups as germ cell tumors, pineal tumors, and glial tumors. Glial tumors in the pineal region can develop from a small amount of astrocytes within the pineal gland or from glial cells in the median posterior aspect of the thalamus or midbrain.[28, 29] The vast majority of gliomas arising in this region are low-grade astrocytomas.[30] PRG is a rare distinct tumor that is most commonly encountered in adults, but also sporadically seen in children.

Clinical Features

Obstruction of third ventricle outflow at the level of the aqueduct causes the most common presenting symptom of PRG. Severe hydrocephalus can provoke nausea and vomiting.[13,15,31] Direct compression of the midbrain, and the superior colliculus in particular, causes loss or deficit of eye movement control (Parinaud vertical gaze palsy), nystagmus on attempted convergence, and loss of accommodation.[8,25] Hypothalamic infiltration or damage, or secretion of AFP and ß-HCG can cause neuroendocrine diseases, such as diabetes insipidus and puberty precox. Our patient presented with chronic headaches presumably from hydrocephalus and motor deficit.

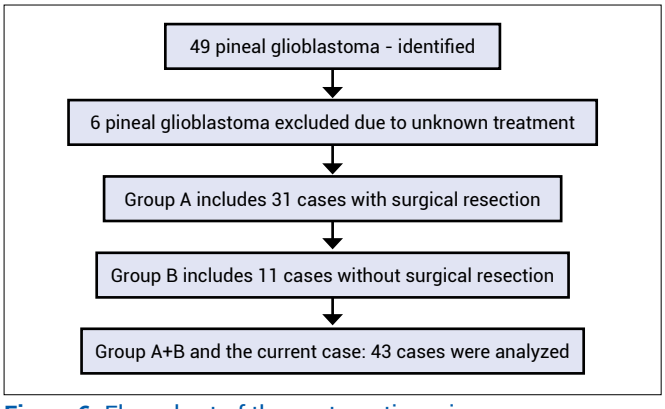

Figure 6. Flow chart of the systematic review.

MRI

The imaging characteristics of PRG do not differentiate it from other malignancies of this region; thus, surgical biopsy is required for the final diagnosis. Key imaging diagnostic features include a heterogeneous irregular ring-enhancing lesion with central necrosis, which may also have a hemorrhagic component. They are usually surrounded by vasogenic-type edema, which in fact usually contains tumor cells. The infiltration of adjacent structures such as the midbrain and thalamus and leptomeningeal metastasis may also be seen. There are no imaging findings that can make the diagnosis prospectively, but ill-defined infiltrative non-enhancing involvement of the adjacent brain parenchyma may raise the suspicion of the disease. Germ cell tumors, pineal parenchymal tumors, astrocytoma of the pineal gland, and pineal metastasis should be considered in the differential diagnosis.[12,31]

Histopathology

The diagnosis depends on both histological and molecular analyses according to the World Health Organization's Classification of Tumors of the Central Nervous System.[33] Histopathological features typically include atypia, mitotic activity, increased cellular density, microvascular proliferation, and necrosis. In addition, glioblastoma was mainly classified according to the status of IDH mutation: IDH wild type or IDH mutant.[32] Furthermore, D'Amico et al. stated that molecular markers such as Ki-67 index, ATRX, lp/19 codeletion, MGMT promoter methylation, expression of EGFRviii, and H3 K27M mutation may also be important for prognosis, and appropriate management of the disease should also be included in the histopathological review of PRGs.[18] In the presented case, the tumor was with negative IDH-1 (wild type) and ATRX staining positivity. Ki-67 labeling index was 9%. However, Ki-67 labeling index alone may not predict the survival in glioblastoma patients arguing against its prognostic importance as an independent factor.[33]

Treatment and Outcomes

Management of PRG is controversial, and the literature focuses on three main approaches: (i) biopsy and radiotherapy/chemotherapy, (ii) radiosurgery alone, or (iii) surgery combined with radiotherapy and chemotherapy. In this study, the median survival in months for all PRG patients was 13.8 months. However, the median survival in months for patients who underwent a debulking surgery "subtotal resection" was 12.8 versus 16.3 only for those who only underwent a biopsy procedure or a shunt (Table 1). These results support the disagreement on the treatment of PRGs and surgical resection does not contribute significantly to improved overall survival. On the other hand, authors have documented various complications after surgical resection. Bradfield and Perez and Oi et al. reported two PRG patients who died in the early post-operative period.[3,9] Pople et al. reported a patient who exhibited lethargy and upward gaze paralysis post-surgery.[7] Gasparetto et al. performed partial resection of a PRG and the patient exhibited hemiparesis postoperatively.[10] In 2005, Toyooka et al. reported a patient who had diplopia after partial resection of a PRG.[11] Amini et al. performed resection (degree of resection unreported) on two PRGs, and both patients exhibited diplopia and upward gaze paralysis after surgery.[12] Orrego et al. reported two PRG patients with post-operative complications of hemiparesis and low Karnofsky performance score.[17] D'Amico et al. performed resection in eight cases of PRG in 2018, and they reported only one complication, a death in the post-operative period.[18] Li et al. reported the most recent surgical resection series in 2020. Five of their six patients underwent surgical resection, and one was treated with radiosurgery. Two of the five patients who underwent resection had complications (hemorrhage and motor aphasia, respectively), and the remaining three had none.[19]

Since tumor progression or dissemination may lead to CSF pathway obstruction, many patients with PRG will develop hydrocephalus. Due to the greater benefits in terms of major complications, infection, reoperation, duration of surgery, and hospital stay than ventriculoperitoneal shunt for patients, the ETV has become the alternative method for the treatment of obstructive hydrocephalus. In this review, we recognized that ETV was preferred in four cases in the treatment of hydrocephalus, including the ours.[12,14,19]

Conclusion

Surgical resection of PRG tends to result in serious complications. These patients' surgical and survival outcome are not satisfactory when compared to the outcomes for those who undergo biopsy alone. Thus; we prefer to manage PRGs, performing neuroendoscopic ETV and biopsy through two burr holes in a single session in selected patients as the presented case. This technique can resolve acute hydrocephalus without the potential complications of shunting. It also provides the surgeon relatively easy access to the pineal region for biopsy.

Disclosures

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Table 1. Summary of reported PNG cases in the literature

Case no.	Author/s	Age (yrs)	Sex	Symptoms	Treatment	Postoperative complication	Survival
1	Ringertz et al. 1954	na	na	na	na	na	na
2	Bradfield et al. 1972	5	f	na	No biopsy, V-P shunt	na	27
3	Bradfield et al. 1972	53	f	na	Resection	Postop death	Post op death
4	De Girolami et al. 1973	na	na	Vertical gaze palsy, increased intracranial pressure	Partial resection+rt	na	na
5	De Girolami et al. 1973	na	na	Increased intracranial pressure	Open biopsy+rt	na	na
6	De Girolami et al. 1973	na	na	Increased intracranial pressure	rt		na
7	Kalyanaraman et al 1979	68	f	Ataxia, confusion	Subtotal resection+rt	Uneventful	4
8	Norbut et al 1981	36	m	Headache, blurry vision	V-P shunt+rt (postmortem		4
9	Frank et al 1985	52	f	Intracranial hypertension, cn CN III palsy6789	biopsy) Str biopsy+rt		4
10	Edwards et al. 1988	12	f	na	na	na	18
11	Pluchino et al. 1989	na	na	na	na	na	na
12	Luo et al. 1989	na	na	na	na	na	na
13	Vaquero et al. 1990	63	m	Headache	Resection+shunt+rt	na	6
14	Pople et al. 1993	6	f	Headache, nausea, diplopia	Resection+shunt+rt+ct	Lethargic, failure of upward gaze	4
15	Bruce et al. 1995	na	na	na	na	na	na
16	Bruce et al. 1995	na	na	na	na	na	na
17	Bruce et al. 1995	na	na	na	na	na	na
18	Bruce et al. 1995	na	na	na	na	na	na
19	Cho et al. 1998	10-15	f	na	Resection+rt	na	6
20	Shin et al. 1998	12	f	na	Partial resection	na	na
21	Oi et al. 2000	na	na	na	Resection	Postop period died (exact time is not reported)	na
22	Gasparetto et al. 2003	29	f	Headache, seizure	Partial resection+shunt	Hemiparesis	2
23	Toyooka et al. 2005	49	m	Headache, memory disturbance	Shunt+partial resection+ct+rt	Diplopia	11

Table 1. CONT.

Case no.	Author/s	Age (yrs)	Sex	Symptoms	Treatment	Postoperative complication	Survival
24	Amini et al. 2006	40	m	Headache, nausea, visual disturbances	ETV+biopsy+resection +shunt+rt+ct	Gaze difficulty, diplopia	5
25	Amini et al. 2006	43	m	Headache, decreased level of conscious	ETV+biopsy+resection +rt+ct	Diplopia, limited upward gaze	7
26	Amini et al. 2006	52	f	Headache, nausea, blurry vision	ETV+biopsy+rt	No complication	2 (refused therapy died of lepromeningeal dissemination
27	Moon et al. 2008	68	m	Headache, vomiting, ataxia	Subtotal resection+shunt	na	2
28	Birbilis et al. 2010	54	f	na	Str biopsy+V-P shunt+ct+rt		40
29	Ozgural et al. 2013	60	m	Headache, ataxia	Shunt+resection+serial str biopsy+rt+ct		24
30	Mansour et al. 2014	69	m	Vertigo, fever, nausea, bladder dysfunction	Biopsy+rt+ct		16
31	Suzuki et al. 2014	65	m	Disturbance of consciousness	Shunt+etv+neur biopsy +resection+rt+ct	na	na
32	Matsuda et al. 2015	31	f	Headache, nausea, vomiting	Shunt+resection+rt+ct	Uneventful	5
33	Nadwi et al. 2016	18	f	Headache	Str biopsy+shunt+rt+ct		>12
34	Sugita et al. 2016	65	f	Disturbance of consciousness	ETV+neur biopsy+ Resection+rt+ct	na	24
35	Sugita et al. 2016	18	m	Headache, CN VI palsy	Resection+rt+ct	na	13
36	Abecassis et al. 2016	na	na	na	biopsy		2
37	Orrego et al. 2017	48	f	Headache, dizziness, nausea, hemiparesis	Shunt+resection+rt	Favorable	12
38	Orrego et al. 2017	50	m	Headache, nausea, CN VI deficit	Resection+rt+ct	Hemiparesis	6

Table 1. CONT.

Case no.	Author/s	Age (yrs)	Sex	Symptoms	Treatment	Postoperative complication	Survival
39	Orrego et al. 2017	56	m	Headache, nausea, ataxia	Shunt+resection+rt+ct	na	29
40	Orrego et al. 2017	25	m	Headache, nausea, Parinaud Syndrome	Resection+rt+ct	na	32
41	Stowe et al. 2017	65	m	Headache, diplopia	Str biopsy+rt+ct		41
42	D'amico RS et al. 2018	51	m	na	Resection+ct+rt	na	na
43	D'amico RS et al. 2018	52	m	na	Resection+ct+rt	Died of peroperative complications	2
44	D'amico RS et al. 2018	38	m	na	Resection+ct+rt	na	20
45	D'amico RS et al. 2018	46	f	na	Resection+ct+rt	na	24
46	D'amico RS et al. 2018	74	m	na	Resection+ct+rt	na	15
47	D'amico RS et al. 2018	36	m	na	Resection+ct+rt	na	8
48	D'amico RS et al. 2018	38	m	na	Resection+rt	na	10
49	D'amico RS et al. 2018	na	na	na	Resection+ct+rt	na	23
50	Sajan A, 2019	39	f	Headache, visual disturbances, aura	Str biopsy+ct+rt		>12
51	Li D et al. 2020	54	f	na	Resection+ct	No deficit	4
52	Li D et al. 2020	54	m	na	Resection+ct	No deficit	6
53	Li D et al. 2020	15	f	na	Gamma knife surgery	No deficit	>42
54	Li D et al. 2020	30	m	na	Resection+rt	No deficit	12
55	Li D et al. 2020	50	m	na	Resection	Motor aphasia	5
56	Li D et al. 2020	54	m	na	Resection	Hemorrhage	>7
57	Present case	59	m	Headache, motor deficit	Endoscopic biopsy +ETV+ct+rt	No deficit	>17

f: female, m: male, na: not available, rt: radiotherapy, ct: chemotherapy, str: stereotaxi".