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Glioblastoma Multiforme of the Pineal Region

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Abstract:

Glioblastoma multiforme (GBMs) tumors are exceedingly rare tumors in the pineal region. We present three cases in which patients presented with a pineal/posterior third ventricular region mass and review all the previously reported cases in the literature. Pineal region GBM seems to be a very aggressive tumor with a high rate of leptomeningeal and ependymal metastatic disease. Patients usually present with signs and symptoms of hydrocephalus and Parinaud's syndrome. The clinical and radiological characteristics of pineal GBM do not differentiate it from other malignancies of this region, thus surgical biopsy is generally required for definitive diagnosis. Glioblastoma should be considered in the differential diagnosis of the pineal region tumors, especially when evidence of leptomeningeal or ependymal metastatic disease is present.

Key Words: glioblastoma multiforme; hydrocephalus; leptomeningeal dissemination; malignant glioma; Perinaud's syndrome; pineal region; spinal metastases

Abbreviations: GBM, glioblastoma multiforme; CT, computed tomography; MRI, magnetic resonance imaging

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Introduction

Tumors of the pineal region comprise only 0.4–1% of intracranial tumors in adults [1]. Although they are comparatively rare, tumors of the pineal region consist of a wide variety of infrequent tumor types [2, 3]. Histologically, they are divided into germ cell and non–germ cell pineal parenchymal derivatives [1, 3-5]. Germ cell tumors arise from transformation of displaced embryonic tissue in the region of pineal gland [1, 3]. The non–germ cell-derived tumors arise from malignant transformation of specialized pineal parenchymal cells (pinocytes) giving rise to either pineocytomas or pineoblastomas or from transformation of surrounding astroglia [1, 3].

Arising from the surrounding glial stroma, gliomas are a very rare subtype of pineal regions tumors [3, 6]. Malignant gliomas, or glioblastoma multiformes (GBMs), of the pineal region are extremely rare; only 13 cases have been reported in the literature previously (Table 1) [4, 6-12]. We report 3 cases of pineal GBM in adult patients and review the literature and discuss the natural history and treatment options in this rare location.

Case reports

Case 1

This 40-year-old man presented with sudden onset of intractable nausea and vomiting with blurry and double vision. He also reported a six-month history of progressive headache and recent sinus surgery for his headaches, without any subsequent relief. A computed tomography (CT) scan of the head (Fig. 1a) showed triventricular

hydrocephalus and a well-circumscribed lesion arising in the pineal region. Focal areas of punctuate calcification and avid enhancement of the mass were found. Magnetic resonance imaging (MRI) (Fig. 1b) of the brain confirmed the finding of a densely enhancing mass in the pineal region with extension of T2 hyperintensity into the mid-brain. The patient underwent an endoscopic third ventriculostomy and biopsy of the lesion. The pathological findings showed a high-grade glioma that was consistent with GBM.

As a result of this diagnosis, the patient underwent stereotactic posterior fossa craniotomy via the supracerebellar/infratentorial approach for resection of the tumor. He tolerated this procedure well, although postoperatively he had some gaze difficulties and diplopia, which subsequently improved. The final pathology report showed a GBM with frequent giant cells, mitotic figures, high proliferation index, microvascular proliferation with endothelial cell hyperplasia, and tumor necrosis with focal pseudopalisading (see Fig. 2a,b). Upon further review of the preoperative MRI, ominous enhancing nodules in the subarachnoid space of the cerebellar folia, as well as in the anterior sylvian fissure and right internal auditory canal (Fig. 1c,d), were noticed consistent with disseminated cerebellar involvement. Given this finding, the patient received whole-brain radiation concurrent with temozolomide (Temodar) therapy. One month after his surgery, the patient developed signs and symptoms of hydrocephalus and, as a result, a ventriculoperitoneal shunt was implanted. The patient died 5 months after the initial diagnosis.

Case 2

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This 43-year-old man presented to an outside hospital with a 1-month history of severe headaches and disequilibrium. The intensity of his headaches was severe enough to cause him weakness and decreased level of consciousness. He denied any nausea, vomiting, or other focal symptoms. He underwent an MRI of the brain (Fig. 3a), which disclosed a heterogeneously enhancing pineal/posterior third ventricular region mass and hydrocephalus. He underwent a right-sided craniotomy for third ventriculostomy and biopsy of his mass at an outside hospital. His symptoms rapidly resolved, but the biopsy was nondiagnostic. Six weeks after his ventriculostomy, the patient developed new fullness in the retro-orbital area with worsening of his dysequilibrium. A follow-up MRI showed interval increase in the size of the tumor, and the patient was referred to our hospital for further evaluation. On examination, the patient had a well-healed right frontal surgical incision and was otherwise neurologically intact. The patient underwent right-sided frontal craniotomy with transcortical/subchoroidal approach to the third ventricular tumor with gross total resection. The patient tolerated the procedure well but postoperatively developed mild vertical diplopia and limited upgaze. The pathology findings showed a GBM with occasional giant cells, frequent mitotic figures, high proliferation index, and prominent microvascular proliferation with endothelial hyperplasia (Fig. 2c). Tumor necrosis was not seen. The patient received a full course of radiation therapy to 5940 cGy in 33 fractions with a full course of chemotherapy. A follow-up MRI of the brain (Fig. 3b,c) revealed intraventricular dissemination, and the patient died 7 months after the diagnosis.

Case 3

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A 52-year-old woman presented to the emergency department for evaluation of worsening severe headaches over the past several months. In addition, she reported blurring and double vision, as well as mild nausea and vomiting. On examination, the patient was somnolent but oriented when awake. She had upgaze palsy without ptosis or nystagmus. An MRI of the brain (Fig. 4a) showed obstructive hydrocephalus and an enhancing mass in the pineal region. She underwent an endoscopic third ventriculostomy with endoscopic biopsy of pineal lesion. The amount of tissue was very small but showed a high-grade glioma with small foci of necrosis (Fig. 2d). The patient tolerated the procedure well and her symptoms were improved. The patient also received fractionated radiation therapy. Two months later, the patient presented with worsening mental status. A follow-up MRI of the brain revealed significant reduction in the size of the enhancing mass, however, new enhancement of the ependymal lining of the lateral ventricles and leptomeninges, which was consistent with leptomeningeal spread of her GBM, was observed. An MRI of the spine revealed diffuse leptomeningeal carcinomatosis (Fig. 4b,c). The family elected to withdraw medical support, and the patient died 2 months after the diagnosis of her tumor.

Discussion

Histopathological classification of pineal region tumors includes a variety of benign and malignant tumors [1, 3]. Gliomas of the pineal region include pilocytic astrocytoma, fibrillary astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, and oligodendroglioma [3]. Well-differentiated astrocytomas are more common [1, 3],

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however, malignant glioblastomas multiformes of the pineal region are rare, with only 13 individual cases reported in the literature (Table 1).

Glioblastomas are very aggressive tumors that are characterized by necrosis and neovascularity [1]. They are the most common primary tumors of the central nervous system, comprising up to half of all primary brain tumors [13, 14]. Primary GBM of the central nervous system has a generally poor prognosis, with median survival after diagnosis of 10 to 12 months [14]. Pineal GBM, although very rare, seem to have an even worse prognosis and very short survival time.

In their single-case report, Gasparetto et al. [6] included a table summarizing the 11 previously reported cases. Toyooka et al. [10] recently reported another case of pineal GBMs in a patient who developed central neurogenic hyperventilation. Our three additional patients bring the number of reported cases to 16. In the following sections, we examine the clinical presentations, radiographic findings, treatment, and prognosis associated with pineal region GBMs.

History and clinical presentation

The most common presenting symptoms in our patients were visual disturbances, headache, nausea, and vomiting secondary to obstructive hydrocephalus. These symptoms are representative of pineal region tumors, which present with general symptoms deriving from the mass effect and direct invasion of surrounding tissue [2, 4, 15]. As expected, the clinical syndromes associated with pineal region masses tend to arise from proximity to the sylvian aqueduct, which can obstruct cerebrospinal fluid flow, with resultant obstructive hydrocephalus [15]. Eighty-three percent of patients described

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in the literature have presented with signs or symptoms of increased intracranial pressure and hydrocephalus. Thirty-three percent of patients presented with dementia, memory problems, or decreased mental status, which could be secondary to long-standing hydrocephalus.

As with other pineal region tumors, pineal GBMs can compromise the superior colliculus, either through direct compression or through tumor invasion, causing Parinaud's syndrome (vertical gaze palsy, nystagmus on attempted convergence, and loss of accommodation). Fifty-eight percent of patients with pineal GBMs presented with either visual or gaze disturbances. Presenting visual symptoms include diplopia, blurry vision, nystagmus, and upgaze palsy. Seven patients presented with visual finding consistent with Parinaud's syndrome.

The clinical signs and symptoms of pineal region GBM and the duration of presenting symptoms are not sufficiently different from other tumors in the pineal region to enable diagnosis based on clinical history and presentation alone. Tissue biopsy is generally necessary to identify the tumor conclusively.

Histology

Microscopic evaluation of our cases of pineal GBM showed moderately cellular, infiltrative tumors with moderate to marked nuclear pleomorphism (Fig. 2). Giant cells were very present in the two cases that underwent resection. In one case (case 1), the giant cells were frequent. All of the tumors showed immunopositive staining of the neoplastic cells for glial fibrillary acidic protein (GFAP). Mitotic figures and MIB-1 proliferation indices were markedly elevated (focally up to 50%) in the 2 cases that

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received more extensive resections. Proliferation index could not be performed on case 3 because of the limited amount of tissue. Tumor necrosis was present in two of the cases, while prominent microvascular proliferation with endothelial hyperplasia was present in the remaining case. All of the cases met present histological WHO criteria for the diagnosis of GBM. The tissue from our cases did not show small cell features or rosettes of pineoblastoma.

Radiographic Studies

Pineal GBM are typically expansile, heterogeneously contrast-enhancing masses with areas of low density on CT studies and hypointensity on T1-weighted MRI representing necrosis. Because of their aggressive expansion and growth, peripheral areas of tumor infiltration and edema are always found extending beyond the region of enhancement. Contrast-enhanced MRI with intravenous gadolinium contrast is the most sensitive technique to evaluate pineal region masses. Pineal GBM are hypointense on T1-weighted MRI imaging and hyperintense on T2-weighted MRI imaging. CT scans are very helpful in visualizing possible areas of calcification.

Leptomeningeal dissemination seems to be very common in pineal GBMs. Two of our patients had evidence of either leptomeningeal or ventricular dissemination at presentation. Although in 1 of the cases the ventricular and leptomeningeal dissemination was not realized until the diagnosis of pineal GBM was made via surgical biopsy and the images were reviews postoperatively.

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Close examination of the MRI studies of patients with pineal region masses is very important, and evidence of leptomeningeal or ventricular dissemination should increase the suspicion for GBM.

Therapy

Treatment of pineal region tumors depends on accurate histological diagnosis to customize the treatment plan to specific pathologies [2, 15, 16]. Unfortunately, definitive diagnosis of pineal GBM cannot be made on the basis of clinical or neuroradiological evaluations alone. It is essential to obtain tissue diagnosis by surgical resection or biopsy when feasible, either by endoscopic or stereotactic open surgery. Endoscopic tumor biopsy combined with third ventriculostomy is a suitable initial procedure. However, our experience with 2 of our 3 patients presented in here suggests endoscopic biopsy may not be sufficient to establish the diagnosis because of limitations of sample size and tissue sampling. Thus, excisional biopsy maybe required.

Most patients present with signs and symptoms of hydrocephalus, requiring surgical treatment. Endoscopic third ventriculostomy may be an appropriate treatment of hydrocephalus; however, in two of our patients the endoscopic third ventriculostomy failed, and the placement of ventriculoperitoneal shunt was required. The high incidence of ventricular dissemination seems to decrease the efficacy of third ventriculostomy in patients with pineal GBM.

The role of aggressive surgical resection in the management of pineal GBM is not clear. Two patients reported in the literature that underwent surgical resection developed leptomeningeal metastases, although two other patients had evidence of disseminated

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metastases before surgery. Whether surgery promotes ventricular dissemination is not known, yet the close proximity of pineal GBM to the cerebrospinal fluid and ventricular system may increase the risk of leptomeningeal and ependymal dissemination.

In patients in whom gross total resection can be safely performed, surgery may have a role in combination with chemotherapy and radiation therapy. The four patients who underwent surgery and received chemotherapy and radiation therapy lived longer overall (4–11 months, mean survival 7 months) than those who did not. However, the two patients who underwent surgery and radiation therapy alone lived 4 and 6 months, respectively (mean 5 months). The patients who underwent radiotherapy alone lived an average of 3.3 months (2, 4, and 4 months each). No patients underwent chemotherapy and radiation therapy alone without surgical resection, making it difficult to make any reasonable conclusion regarding the role of surgery in the treatment of these tumors. Surgical treatment of hydrocephalus in combination with chemotherapy and radiation therapy may be another alternative treatment option, without resection. This option would eliminate the complications associated with resection and may decrease the progression of ventricular and leptomeningeal disseminations.

Prognosis

The overall prognosis of patients diagnosed with pineal region GBM seems to be very poor. The poor prognosis may be related to direct invasion of bilateral thalamus and dorsal midbrain, as well as to leptomeningeal and ventricular dissemination. All three of our patients developed leptomeningeal dissemination and local recurrence. Two of our patients developed progressive failure to thrive, somnolence, weight loss, and malaise

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before death. Our last patient developed obstruction hydrocephalus, which was most likely the cause of her death.

None of the reported patients lived beyond one year after diagnosis. The combination of aggressive surgical resection in combination with chemotherapy and radiation therapy seems to prolong survival only by 2–4 months; however, whether longer survival is due to a combination of chemotherapy and radiation therapy or to the addition of surgery is not known. The small number of reported patients and limited clinical information makes it impossible to make any meaningful conclusion regarding the prognosis of pineal region GBM.

The rate of leptomeningeal and ventricular dissemination seems be very high in patients with pineal GBM. This may be an important factor in the aggressive behavior of this tumor, requiring appropriate early adjunct therapy. All patients with a known clinical history presented with signs of hydrocephalus and eventually required either third ventriculostomy or placement of ventriculoperitoneal shunts. In the presence of extensive leptomeningeal and ventricular dissemination, endoscopic third ventriculotomy may not be appropriate, instead requiring placement of ventriculoperitoneal shunts early in the course of the disease.

Following successful treatment of their resultant hydrocephalus, patients with pineal GBM may be expected to remain asymptomatic for a few months. Despite aggressive multimodality treatments, median survival for patients with pineal GBM, however, remains approximately 6 months.

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Conclusions

Pineal region GBM is extremely rare and is associated with a poor prognosis. Most patients present with sign and symptoms of hydrocephalus and Parinaud's syndrome, requiring placement of a ventriculoperitoneal shunt or endoscopic biopsy and third ventriculostomy. The risk of leptomeningeal and ventricular dissemination seems to be very high, and preoperative evidence of leptomeningeal seeding should increase the suspicion of pineal GBM. The role of surgical resection remains unclear; however, early chemotherapy and radiation therapy in combination with treatment of hydrocephalus seems to improve prognosis slightly.

Acknowledgments

We thank Kristin Kraus for her editorial assistance in preparing this paper.

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Figure legends:

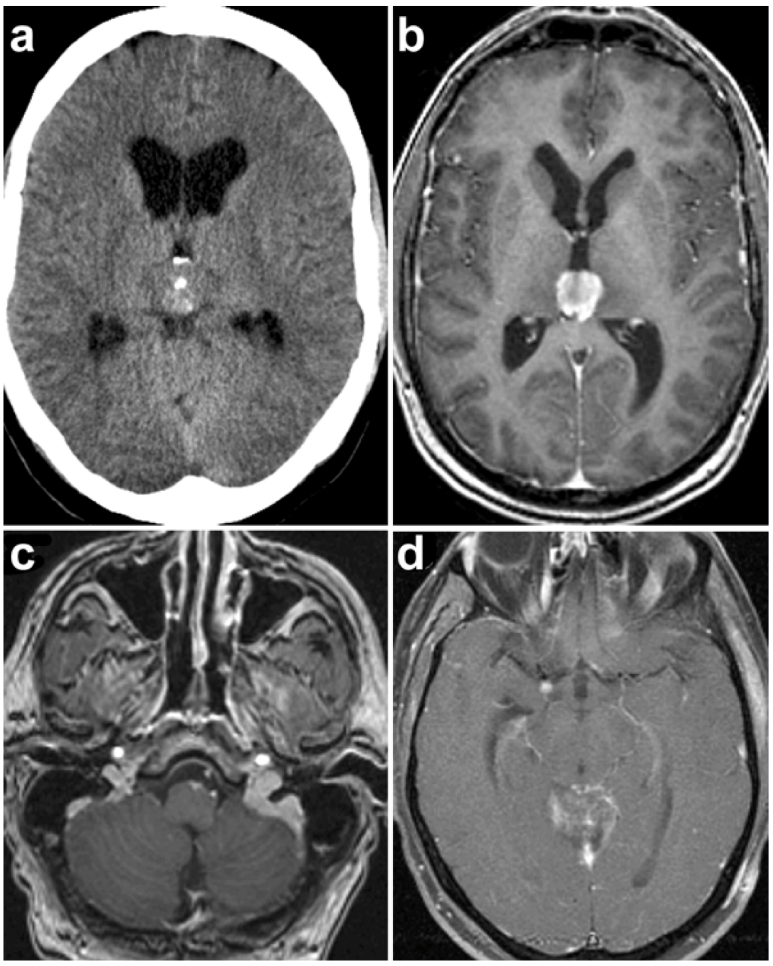

Fig. 1: Noncontrast computed tomography scan of the head showing calcified pineal region mass (a). Axial contrast-enhanced T1-weighted magnetic resonance imaging of the brain with contrast showing heterogeneously enhancing mass with central necrosis (b) and enhancing leptomeningeal disease anterior to the medulla and within the cerebellar folia (c). (d) Enhancing mass along the medial aspect of right temporal lobe representing an additional metastatic focus.

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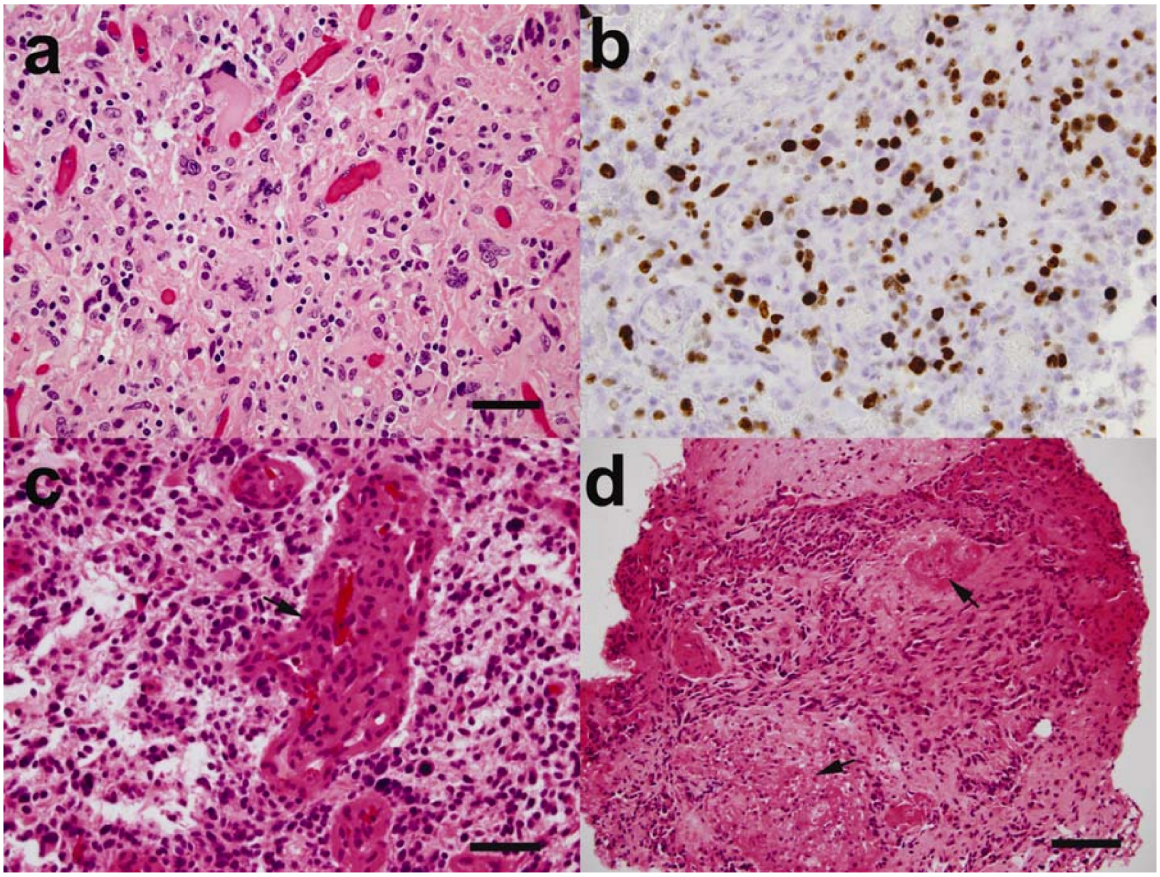

Fig. 2: (a) Hematoxylin and Eosin-stained, high-magnification view of a glioblastoma multiforme with giant cells infiltrating and extensively effacing the normal pineal architecture (Case 1). Scale bar = 50 microns. (b) High-magnification view of the same glioblastoma multiforme as above immunohistochemically stained with marker MIB-1 to illustrate the relatively high proliferation rate. (c) Representative high-magnification view of Case 2 GBM showing prominent microvascular proliferation with endothelial hyperplasia (arrow). Scale bar = 50 microns. (d) Low-magnification view of Case 3 biopsy specimen showing a glial neoplasm associated with foci of necrosis (arrows). Scale bar = 100 microns.

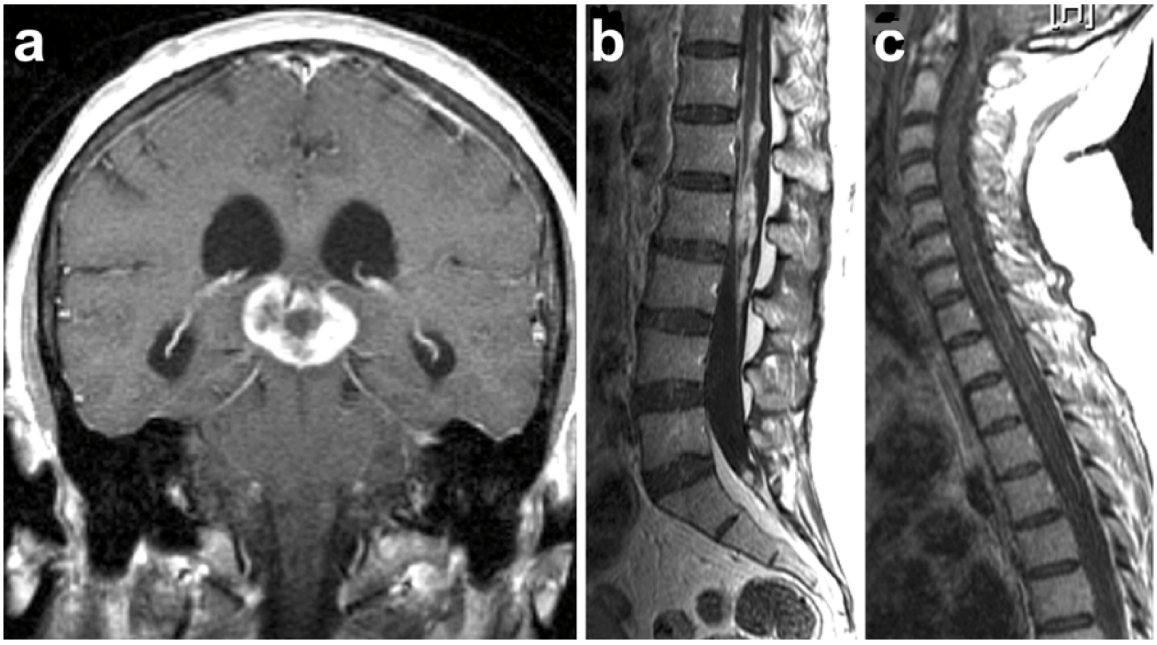

Fig. 3: Axial contrast-enhanced T1-weighted magnetic resonance imaging scans of the brain showing heterogeneously enhancing mass in the pineal region (a) and ependymal metastatic disease along the ventricular margins (b,c).

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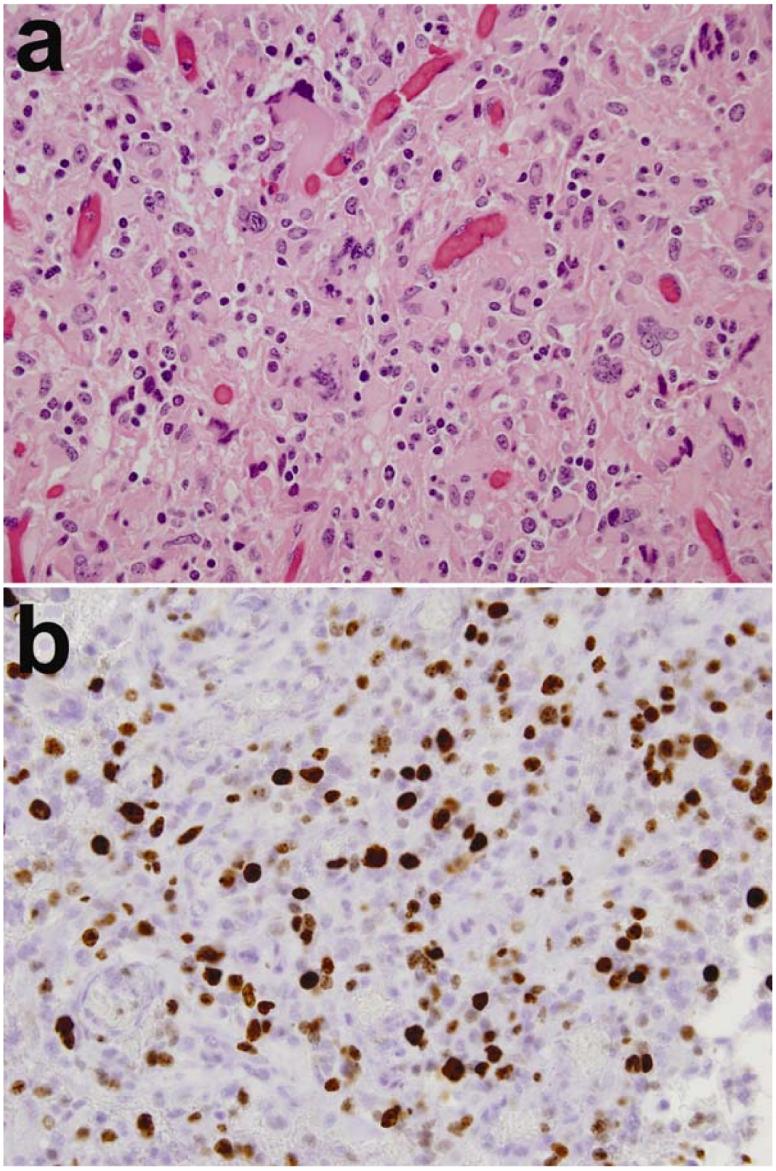

Fig. 4: Coronal T1-weighted magnetic resonance imaging of the brain with contrast showing heterogeneously enhancing mass with central hypointensity in the pineal region (a). Sagittal contrast-enhanced T1-weighted magnetic resonance imaging of the lumbar spine (b) and cervical spine (c) with contrast showing enhancing leptomeningeal deposits over the surface of the spinal cord and conus medullaris and coating the spinal nerve rootlets.

Table 1. Summary of reported cases of patients with pineal region glioblastoma multiforme in literature

Reference	# of patients	Sex	Age (year)	Clinical presentation	Radiographic findings	Leptomeningeal dissemination	Treatment	Survival (months)
Vaquero et al. [12]	1	-	-	-	-	-	-	-
Bradfield et al. [16]	2	F/F	53/5	-	-	-	Radiation and Shunting	-
De Girolami et al. [5]	3	-	-	↑ ICP in all three patients, vertical gaze palsy in one	-	-	Radiation for all 3 patients; surgery in one	-
Pople et al. [11]	1	F	6	HA, vomiting, diplopia, ↓VA, CN IV palsy, papilledema, upgaze palsy	HCP, pineal mass with heterogeneous enhancement	Yes	Surgery, radiation, chemotherapy	4
Cho et al. [4]	1	M	63	↑ ICP and changing behavior	HCP and hyperdense pineal mass with ring enhancement	-	Surgery and radiation	6
Frank et al. [7]	1	F	52	↑ ICP, oculomotor nerve disturbance	HCP, and 3rd ventricle mass	-	Radiation	4
Kalyanaraman [8]	1	F	68	↑ ICP, Parinaud's syndrome, ataxia, confusion	HCP, and calcified midline mass	-	Surgery and radiation	4
Norbut et al. [9]	1	M	36	↑ ICP	HCP, and calcified midline mass	Yes	Radiation	4
Gasparetto et al. [6]	1	F	29	↑ ICP, fever, and seizures	Hypodense pineal mass with heterogeneous enhancement	No	Surgery	2
Toyooka st al. [10]	1	M	49	HA, diplopia, memory disturbances	HCP, and heterogeneous enhancing pineal mass	Yes	Surgery, radiation, chemotherapy	11
Amini et al.	1	M	40	↑ ICP, HA, nausea and vomiting, diplopia, and blurry vision	HCP, calcification on CT, MRI with and heterogeneous enhancing pineal mass with central necrosis	Yes	Surgery, radiation, chemotherapy	5
Amini et al.	1	M	43	↑ ICP, HA, dysequilibrium, weakness and decreased mental status	HCP and heterogeneous enhancing pineal mass with central necrosis	Yes	Surgery, radiation, chemotherapy	7
Amini et al.	1	F	52	↑ ICP, HA, diplopia, up gaze palsy, and nausea	HCP and heterogeneous enhancing pineal mass with central necrosis	Yes	Radiation	2

ICP, intracranial pressure; HA, headache; HCP, hydrocephalus

Table 2. Summary of demographics, presenting symptoms, radiographic findings, and prognosis of patients with pineal glioblastoma multiforme.

Sex	Female 7 (58%) Male 5 (52%)
Age *(years)*	5–68 (mean 40.8) 29–68 (mean 47.2) (adult only) 5–6 (mean 5.5) [2 (12.5%) pediatric cases]
Symptoms	Elevated ICP – 83% Visual and gaze disturbances – 58% Dementia, memory and personality changes – 33%
Radiology	CT: hyperdense to hypodense pineal mass, with possible calcification; MRI: T1 hypointense, T2 hyperintense, heterogeneous enhancement with central necrosis.
Mean survival *(months)*	4.9 (overall) 7 (surgery, chemotherapy, and radiation) 5 (surgery and radiation) 3.3 (radiation alone) 2 (surgery alone)

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