Primary Glioblastoma Multiforme in the pineal region: a case report with diagnostic imaging findings, treatment response, and literature review

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Glioblastoma multiforme (GBM) is one of the most common primary tumors of the central nervous system, comprising up to half of all primary brain tumors; however, primary GBM of the pineal region is extremely rare. To our knowledge, there are only 18 reported cases. We report a rare case of pineal GBM in a 32-year-old male who presented with headache, visual image distortion, and vertigo. Computed tomography, magnetic resonance imaging, and cerebral angiography revealed a tumor mass in the pineal region. The mass was diagnosed as a glioblastoma following subtotal removal. After combined surgery and concurrent chemoradiotherapy treatment, our patient survived longer than 1 year after the initial diagnosis. Here, we present the radiographic features and treatment strategy of pineal GBM, with a review of the literature.

The pineal region is defined as the space delimited superiorly by the splenium of the corpus callosum and the choroid plexus of the third ventricle, anteriorly by the third ventricle, anteroinferiorly by the lamina quadrigemina, inferiorly by the anterior face of the cerebellum culmen, and laterally by the thalamus and medial faces of the cerebral hemispheres [1]. It consists of the pineal body, the posterior portion of the third ventricle, tela choroidea, and velum interpositum. Thus, a tumor in the pineal region could have originated from the pineal gland itself, the posterior portion of the third ventricle, or the quadrigemina cistern [1, 2]. Although glioblastoma multiforme (GBM) is one of the most common primary tumors of the central nervous system, comprising up to half of all primary brain tumors [3, 4], primary GBM of the pineal region is extremely rare, with only 18 reported cases [1, 2, 5-15].

We report a rare case of pineal GBM in a 32-year-old male, compare the findings in this patient with those in the literature in terms of clinical and radiological characteristics and angiographic findings, and discuss the treatment response.

CASE PRESENTATION

A 32-year-old male with no related illness experienced intermittent headaches, which were accompanied by visual image distortion, neck stiffness, vertigo, and vomiting for 1 month prior to admission to our hospital. Contrast medium-enhanced axial brain computed tomography (CT) was performed 1 month after the initiation of symptoms and revealed a 3.3 × 3.1-cm², well-defined, lobulated, intra-axial enhanced tumor mass, which was posterior to the third ventricle and superior to the supracerebellar
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cistern (Fig. 1). Subsequent magnetic resonance imaging (MRI) demonstrated an intra-axial tumor, which was hypointense on T1-weighted images, hyperintense on T2-weighted images, and heterogeneously enhanced by gadolinium contrast medium administration. It was located in the pineal region, with poor distinction from the nearby tectum, midbrain, and thalami, and was complicated by obstructive hydrocephalus (Fig. 1). Diagnostic cerebral angiography with injection from the bilateral common carotid, internal carotid, and vertebral arteries revealed a deep-seated tumor with prominent tumor staining in the delay and capillary phases. The tumor was located in the pineal region, for which the blood supply was derived primarily from the thalamoperforating arteries and posterior choroid arteries, with a tumor mass effect displacing the internal cerebral vein (Fig. 2).

The patient underwent a first operation for the placement of a right ventriculo-peritoneal shunt to relieve the obstructive hydrocephalus about 8 days after first admission. Cerebrospinal fluid (CSF) cytology revealed only atypical cells and lymphocytes. A biopsy was not immediately performed after discussion with the patient, because the tumor was in close proximity to nearby draining veins. However, the possibility of pineal GBM or lymphoma was suggested, because of tumor infiltration over the corpus callosum, demonstrating the typical “butterfly” tumor appearance.

The patient received a first cycle of induction chemotherapy, with cisplatin (CDDP 20 mg/m² daily for 5 days; total dose administered, 175 mg) and etoposide (VP-16 100 mg/m² daily for 5 days; total dose administered, 875 mg), about 40 days after first admission. However, despite the chemotherapy, mild progression of the tumor (3.3 × 3.1 cm² progressing to 3.7 × 4.5 cm²) was observed during a follow-up CT study 24 days after initiation of induction chemotherapy. Thus, a second operation with MR-navigated subtotal removal (80%) of the tumor mass was performed. An initial intra-operative frozen section revealed grade II astrocytoma. However, after subtotal resection of the tumor mass, subsequent pathology confirmed the tumor to be glioblastoma multiforme (grade IV astrocytoma) of the pineal region.

Post-operative MRI was arranged 7 days later and demonstrated that only a small amount of tumor in this area had been resected by the prior surgical intervention, while most of the bulky tumor in the ventricular system and splenium of corpus callosum remained apparently unchanged. He was then referred for concurrent chemo-radiotherapy treatment, which consisted of a total radiation dose of 60 Gy in 30 fractions and chemotherapy with

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**Figure 1.** a. Brain axial CT revealed a calcified mass in the pineal region (see arrow), resulting in obstructive hydrocephalus. b and c. MR images revealed an intra-axial tumor, presenting with hypointensity on T1-weighted image (not shown), (b) hyperintensity on FLAIR axial image 9000/105/180 degrees (TR/TE/flip angle), and (c) T1-weighted sagittal image 420/20/90 degrees (TR/TE/flip angle) with gadolinium administration showing heterogenously enhancing tumor located in pineal region. b. Tumor invasion over corpus callosum splenium, demonstrating typical “butterfly” tumor appearance in GBM.
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Temozolomide, 120 mg/day for 31 days. Follow-up MRI 4 months after the second operation revealed residual tumor over the pineal region and the posterior body and splenium of the corpus callosum, but intraventricular extension and leptomeningeal spreading were newly observed. Progressive, widespread CSF dissemination was noted in a follow-up MRI about 7.5 months after the second surgery.

Figure 2. A diagnostic cerebral angiography was arranged to evaluate for the angiographic characteristic of this tumor. a. and b. A prominent tumor stain persisted through the arterial (see arrow in a) and capillary phase (see arrow in b) of left internal carotid artery angiography (left anterior oblique, 30 degrees). (a) The blood supply was mainly derived from thalamoperforating arteries and posterior choroid arteries. c. Venous phase demonstrates displacement of the internal cerebral vein, suggestive of the presence of an underlying bulky tumor mass.

Figure 3. An MRI follow up study was performed about 7.5 months after surgical resection. a. FLAIR axial image 9000/105/108 degrees (TR/TE/flip angle) showed more prominent protrusion of the tumor mass is found along with intraventricular extension (see arrow in a). b. T1-weighted coronal image with gadolinium contrast medium enhancement 420/20/90 degrees (TR/TE/flip angle) diffuse leptomeningeal carcinomatosis (see arrow in b).
Table 1. Summary and comparison of the 19 available reported cases of the pineal glioblastoma multiforme

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Clinical findings</th>
<th>Radiological findings</th>
<th>Treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradfield [6]</td>
<td>5/F</td>
<td>N/A</td>
<td>OHD Mass in posterior 3rd ventricle No LMS</td>
<td>OP, RTX</td>
<td>27 mons</td>
</tr>
<tr>
<td>DeGirolami [7]</td>
<td>3 cases</td>
<td>3 patients VPG in 1 patient</td>
<td>N/A</td>
<td>OP, RTX</td>
<td>N/A</td>
</tr>
<tr>
<td>Kalyanaraman [8]</td>
<td>68/F</td>
<td>ICP, PAS, GD, Confusion</td>
<td>CEM, OHD</td>
<td>OP, RTX</td>
<td>4 mons</td>
</tr>
<tr>
<td>Norbut [9]</td>
<td>36/M</td>
<td>OHD, PAS, GD</td>
<td>OHD, CEM</td>
<td>OP, RTX</td>
<td>4 mons</td>
</tr>
<tr>
<td>Frank [10]</td>
<td>52/F</td>
<td>ICP, PAS, Hearing loss, Tremor</td>
<td>OHD Mass in posterior 3rd ventricle</td>
<td>RTX</td>
<td>4 mons</td>
</tr>
<tr>
<td>Edwards [11]</td>
<td>12/F</td>
<td>N/A</td>
<td>N/A</td>
<td>OP, RTX, CTX</td>
<td>18 mons</td>
</tr>
<tr>
<td>Vaquero [12]</td>
<td>63/M</td>
<td>Headache, Behavioral change</td>
<td>REM</td>
<td>OP, RTX</td>
<td>6 mons</td>
</tr>
<tr>
<td>Pople [13]</td>
<td>6/F</td>
<td>Headache, PAS</td>
<td>OHD, LMS on post treatment CT</td>
<td>OP, RTX, CTX</td>
<td>4 mons</td>
</tr>
<tr>
<td>Cho [14]</td>
<td>63/M</td>
<td>ICP, Behavioral change</td>
<td>OHD Hyperdense REM</td>
<td>OP, RTX</td>
<td>6 mons</td>
</tr>
<tr>
<td>Gasparetto [1]</td>
<td>29/F</td>
<td>ICP, Headache Fever Seizure</td>
<td>Ill-defined hypodense HEM No LMS</td>
<td>OP</td>
<td>2 mons</td>
</tr>
<tr>
<td>Amini [5]</td>
<td>43/M</td>
<td>CP, Headache, Disequilibrium, Decreased mental status</td>
<td>OHD, HEM, LMS: on F/U MR</td>
<td>OP, RTX, CTX</td>
<td>7 mons</td>
</tr>
</tbody>
</table>
operation (Fig. 3) despite further chemotherapy with temozolomide since the previous MRI. Palliative radiotherapy was given to both the brain and spine during the patient’s last admission after the MRI. Unfortunately, he experienced myelosuppression and pancytopenia during the radiotherapy, which improved after granulocyte colony stimulating factor administration. He was discharged to a nursing home for palliative care about 1 year after initial symptom onset, and was lost to follow-up since then.
**DISCUSSION**

A tumor of the pineal region is considered a rare intracranial tumor, comprising only 0.4-1% of intracranial tumors in adults [5]. Germinomas are the most common histological type, comprising 50-60% of all pineal tumors. Although gliomas account for 33% of pineal neoplasms, most are low-grade astrocytomas; primary glioblastoma multiforme of the pineal region has only been reported in 19 cases, including the patient in this study [2, 11, 16]. Due to overlap of clinical and radiological characteristics of pineal GBM with other pineal region tumors, GBM is difficult to diagnose based on clinical history and presentation alone. Thus, recognition of the typical clinical and radiological characteristics should be a first step when considering pineal GBM as a tentative diagnosis, but a surgical biopsy may be required for a definite diagnosis.

The clinical characteristics and radiological findings in this patient were generally consistent with previous reports (Table 1). The patient presented with symptoms related to obstructive hydrocephalus and Parinaud’s syndrome, which included headache, visual image distortion, neck stiffness, vertigo, and vomiting. These symptoms occur primarily because pineal region masses tend to arise in proximity to the Sylvian aqueduct, which can obstruct CSF flow, with resulting obstructive hydrocephalus [17]. All cases previously reported had signs or symptoms of increased intracranial pressure and hydrocephalus [2], as did ours.

Owing to the location of a pineal GBM, the tumor mass can frequently compromise the superior colliculus, through either direct compression or tumor invasion. This may explain the development of symptoms of Parinaud’s syndrome, including diplopia, blurry vision, nystagmus, loss of accommodation, and upgaze palsy, in nine (47%) of the previously reported patients [2, 5]. Due to overlap of clinical and radiological characteristics of pineal GBM with other pineal region tumors, GBM is difficult to diagnose based on clinical history and presentation alone. Thus, recognition of the typical clinical and radiological characteristics should be a first step when considering pineal GBM as a tentative diagnosis, but a surgical biopsy may be required for a definite diagnosis.

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Reported CT findings include an expansile, calcified, or heterogeneously contrast-enhancing pineal mass due to tumor vascularity, with areas of low density attributable to central necrosis. The lesion may be found in the pineal region only, or with intraventricular spread and invasion of adjacent structures [1, 2, 5]. Compared with other imaging modalities, CT was most useful for visualizing possible areas of calcification [5] and may help in identifying calcifications in pineal GBM.

MRI was reported to be superior to CT in analyzing the tumor characteristics and its relationship to neural and vascular structures [1]. Contrast-enhanced MRI using intravenous gadolinium contrast medium was the most sensitive technique for evaluating pineal region masses. Pineal GBM were hypointense on T1-weighted MRI and hyperintense on T2-weighted MRI. These tumors were usually variable in shape, often irregular, with a wall thicker than 2 mm and a size larger than 20 mm [18]. On T2-weighted MR images, infiltration into surrounding structures such as the midbrain and thalamus was seen as hyperintensity extending beyond the margin of the enhanced mass. Heterogeneous enhancement with a centrally located non-enhanced portion in T1-weighted MRI indicated hypervascularity and central necrosis, demonstrating the aggressive nature of this tumor. [2, 5] The typical “butterfly” appearance of tumor invasion across the corpus callosum splenium, which suggests the possibility of GBM, had been clearly demonstrated in this patient since the initial MRI (Fig. 1) and appeared to be aggravated on follow-up MRI. Leptomeningeal and ventricular enhanced nodules were also noted on follow-up MRI, indicating the aggressive nature of this tumor.

Differentiation between GBM and lymphoma by conventional MRI is often difficult and sometimes impossible [19]. Diffusion-weighted MRI characteristics of the lesion have been reported by various authors as the first key in differentiating these two entities. The apparent diffusion coefficient (ADC) value is inversely proportional to cellular density, which reflects inherent diffusion facilitation by the lesion [20]. Diffusion is usually facilitated in primary neoplasms, but not in abscesses or lymphomas [20]. Although there is no consensus as to the ADC threshold for determining whether diffusion is facilitated, Al-Oakili et al. adopted a value of $1.1 \times 10^{-3} \text{mm}^2/\text{s}$ from a meta-analysis study [20], and Toh et al. suggested an optimal ADC cut-off value of $0.818 \times 10^{-3} \text{mm}^2/\text{s}$ (sensitivity, 100%; specificity, 90%; accuracy, 95%) to differentiate between these two tumor lesions [19]. For any lesion having an ADC value higher than the suggested threshold, high-grade glioma such as GBM is favored over...
lymphoma. These findings were also consistent with those in our patient (Fig. 4). We observed an average ADC value higher than \(1.1 \times 10^{-3}\) mm\(^2\)/s in two studied regions of interest, which included an average ADC value of \(1.63 \times 10^{-3}\) mm\(^2\)/s for the main pineal tumor (Fig. 4a, b) and an ADC value of \(1.16 \times 10^{-3}\) mm\(^2\)/s for the tumor-infiltrated splenium (Fig. 4c, d).

In addition to the CT and MRI findings, this is the first report of a diagnostic cerebral angiography performed in a pineal GBM patient. Cerebral angiography revealed a deep-seated hypervascular tumor in the pineal region, with a prominent mass effect displacing the internal cerebral vein. The blood supply was derived from the thalamoperforating and posterior choroidal arteries. The posterior thalamoperforating arteries primarily supply the thalamus, subthalamic nucleus, and nuclei and tracts of the upper midbrain, and the medial posterior choroidal artery supplies the thalamus, midbrain, tectal plate, pineal gland, splenium, caudate nucleus, pulvinar, habenula, and medial geniculate body [21]. The blood supply to the tumor may help in understanding the frequent tumor invasion of the thalamus, midbrain, splenium, and tectum.

The treatment of pineal region tumors depends on accurate histological diagnosis, to allow the treatment plan to be customized to specific pathologies [5]. Prompt recognition of this rare tumor by its clinical and radiological findings is crucial for early treatment planning. The overall prognosis of a patient with a pineal glioblastoma is poor; despite aggressive multimodality treatments, median survival for patients with pineal GBM remains approximately 6 months [2, 5].

The benefit of aggressive surgical resection in the treatment of pineal GBM is unclear [2]. The patient in our study demonstrates the difficulty in total removal of the tumor by surgery. Although the surgeon believed that he had removed 80% of the tumor mass, the post-operative MRI 7 days later suggested that only a small amount of tumor in this area had been resected by the surgical intervention. Most of the bulky tumor in the ventricular system and splenium of corpus callosum had remained apparently untouched.

The effect of chemotherapy alone was also discouraging in this patient; despite induction chemotherapy, mild progression of the tumor was still noted by follow-up CT 24 days later. It has been reported that longer survival time was observed in patients who underwent surgery and chemotherapy, with an average survival period of 7 months [5]. This was also established in our patient, in that he had survived about 1 year after the initial diagnosis as of his last discharge; only the patient reported by Edwards has survived longer [11].

The benefit of ventriculoperitoneal shunting over ventriculostomy was demonstrated in this patient. No recurrent hydrocephalus was seen after placement of the ventriculoperitoneal shunt, and thus early placement is encouraged to prevent complications from chronic or recurrent hydrocephalus.

**CONCLUSIONS**

Despite the rarity of pineal GBM, early recognition of its clinical and radiological findings is important in planning early adjunct treatment. The benefits of early ventriculo-peritoneal shunt placement and concurrent chemo-radiotherapy after surgery were also shown in preventing complications from chronic hydrocephalus and in prolonging survival in our patient. Chemotherapy or surgery alone is discouraged. The angiographic findings provided in this case also helped in recognizing the expected vascular characteristics and may assist in predicting and understanding the tumor invasion pattern.

**REFERENCES**

原發於松果體區域的多型性神經膠母細胞瘤：一個結合影像診斷、治療成果以及文獻回顧的病例報告

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雖然多型性神經膠母細胞瘤佔了在中樞神經系統裡面超過一半的原發性腫瘤，但是位於松果體區域的多型性神經膠母細胞瘤卻是非常的稀少。到目前為止，僅有 18 篇發表過的病例。我們報告一例原發於松果體區域的多型性神經膠母細胞瘤的罕見個案。一位 32 歲男性以頭痛、視覺扭曲以及暈眩作為初始症狀。安排了電腦斷層、核磁共振影像及腦部血管攝影等檢查後發現了一個位於松果體區域的腫瘤，並發現了腫瘤有跨越胼胝體侵犯的典型 "蝴蝶樣" 特色，且具有高度水分子表觀擴散係數 (ADC value) 而懷疑了多型性神經膠母細胞瘤的可能性。經部份切除後的腫瘤病理切片檢查進一步證實為多型性神經膠母細胞瘤。自初次診斷後，病患於是接受了手術以及合併了放射線治療與化學治療，並存活了至少超過一年。於是本篇主要提出了此病例個案的影像學特徵與治療方式，並回顧了過去文獻及進一步的相關探討。