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Small cell glioblastoma of the sella turcica region: a case report and review of the literature

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Abstract

Background: Glioblastomas in the sellar region are very rare; in most cases, the tumor originates from the optic nerve/optic chiasm. Only 4 cases of sellar glioblastoma with a non-optic origin have been reported. We present such a case with detailed clinical, imaging and histopathological information. A review of similar published cases is also presented.

Case presentation: A 42-year-old woman presented with endocrinological abnormalities including, amenorrhea and lactation, symptoms of diabetes insipidus and signs of elevated ICP. MRI showed a giant heterogeneously enhancing lesion involving the intrasellar, parasellar and suprasellar regions, with hyper cellularity and signs of infiltration of adjacent structures. Intraoperative examination revealed the tumor to be independent from the optic pathways but it showed infiltration of the hypothalamic region. Histopathological examination demonstrated uniformly packed small cells and negative staining for GFAP, which was consistent with a diagnosis of small cell glioblastoma.

Conclusion: This is the first report of a small cell glioblastoma in the sella turcica region. Glioblastomas in the sellar region with no clear evidence of an optic origin should be viewed as an independent disease entity. The typical characteristics of this tumor raise the specter of its inclusion as a rare subtype of glioblastomas. Further accumulation of experience is needed to better differentiate these cases and to offer optimal treatment.

Key words: Small cell glioblastoma, sellar turcica region, optic nerve, hypothalamus
Introduction

Glioblastoma is the most common primary central nervous system (CNS) neoplasm of neural epithelial origin. Despite decades of research, the prognosis of the affected patients remains extremely poor. The frontal, parietal, and the temporal lobes are the most commonly affected anatomical locations.

The sella turcica is one of the most anatomically complex regions of the CNS which harbors various structures with diverse histomorphology; pathological lesions of these diverse tissues often have similar imaging manifestations. Gliomas of the sella turcica region are rarely encountered, but may originate from the glial cells of the optic nerve/chiasm, the hypothalamus or the pituitary/pituitary stalk; in some cases, the origin may not be clearly discernible[1-3]. A vast majority of these gliomas are of low grade; WHO grade IV gliomas are extremely rare[4, 5].

In our retrospective case series of 27 sellar gliomas reported over a period of 15 years[6], only one case of glioblastoma was recorded; even this particular case manifested a rare disease pattern of a small cell glioblastoma with a very high cellular proliferation. In this report we provide a detailed description of this case, for which the initial differential diagnosis was between sellar chordoma, pituitary adenoma, craniopharyngioma, germ cell tumor, lymphoma, glioma and metastatic lesion based on imaging examination. A review of all reported cases is also provided to further illustrate the features of these cases.

Case report

Clinical presentation

A 42-year-old woman was admitted to our department with chief complaints of right frontal-temporal headache with projectile vomiting since 1 month, and amenorrhea and lactation since 3 months. During the course of the disease, the patient experienced progressive worsening of
symptoms of diabetes insipidus with a daily urine output of approximately 4000 mL. Physical
examination revealed tachycardia (96 beats/min), thyroid tenderness, decreased visual acuity, bi-
temporal visual deficit, and signs of disorientation and memory loss. Laboratory examination
revealed hypernatremia and hyperchloremia (Na\(^+\) 158.7 mmol/L; Cl\(^-\) 120.9 mmol/L), decreased
TSH (0.005 µIU/mL; reference level: 0.27-4.2 µIU/mL), elevated FT3 (14.79 pmol/L; reference:
3.1-6.8 pmol/L), FT4 (34.770 pmol/L; reference: 12.0-22.0 pmol/L), TT3 (5.27 nmol/L;
reference: 1.3-3.1 nmol/L), TT4 (228.20 nmol/L; reference 66.0-181.0 nmol/L). Pituitary
function tests revealed markedly elevated serum prolactin level (1768.94 mIU/L; reference:
70.81-566.5 mIU/L). There was no significant past history. Thyroid iodine uptake test confirmed
hyperthyroidism.

*Imaging examination*

MRI brain showed a large hourglass shaped lesion (size: 3.55 cm×2.96 cm×5.34 cm) involving
the intra-sellar and the suprasellar region. The margins of the lesion were not well-defined; the
lesion was relatively homogenous with slightly hyptointense T1 and hyperintense T2 signals (Fig
1a-b); On DARK-FLUID and diffusion weighted imaging (DWI) sequences, the lesion was
slightly hyperintense. Following intravenous Gd-DTPA injection, the lesion showed significant
heterogenous enhancement; the lesion had enveloped the internal carotid arteries on both sides
and had infiltrated the bilateral cavernous sinuses, the floor of the third ventricle and the
hypothalamus region. The sellar floor was mildly enlarged; the imaging of the pituitary gland
was unclear. The bony structures of the sellar floor and the clivus were irregular in shape, with
patchy signals of T1 hypointensity, T2 hyperintensity, DARK-FLUID hyperintensity and
significant heterogenous contrast enhancement (Fig. 1c-f). Large areas of cerebral edema were
seen in the right temporal lobe, which had caused compression of the right lateral ventricle. The
initial differential diagnosis was between sellar chordoma, pituitary adenoma, craniopharyngioma, germ cell tumor, lymphoma, glioma and metastatic lesion.

Operation and postoperative course

A right pterional approach was selected for tumor removal. Following exposure of the sellar region, the tumor mass was found occupying the space anterior to the optic chiasm and between the right carotid artery and the right optic nerve. The tumor was gray, firm and well-demarcated from the optic nerves and the optic chiasm. The tumor blood supply was not abundant. The tumor mass occupying these spaces was removed with an ultrasound aspirator. Further dissection revealed the expansion of the lamina terminalis posterior to the optic chiasm. Opening of the space between the optic chiasm and the lamina terminalis demonstrated tumor extension to the hypothalamus which was partially resected under an operating microscope. A total of 2.0 cm×2.0 cm×3.0 cm of the tumor mass was removed; the bilateral optic nerves, the optic chiasm, optic tract, the carotid artery and the right anterior cerebral artery A1 segment and its perforating arteries were preserved. Intraoperative pathology revealed malignancy of glial cell origin; hence, further resection of the tumor was not insisted. Postoperatively the patient experienced aggravation of diabetes insipidus, mild hydrocortisone deficiency and persistence of hyperthyroidism, which was controlled with pituitrin, corticosteroid replacement and supportive treatment. The patient received adjuvant temozolomide and fractionated radiation therapy. Two months later the patient died of disease progression.

Pathology

Histopathological examination of surgical specimen showed hypercellular tissue comprising of small round to oval shaped cells with relatively homogenous appearance and distribution.
Mitosis was frequently observed among tumor cells, and the nucleus to cytoplasm ratio was high. No cells with fried egg appearance were seen. Areas of microvascular proliferation were observed without signs of coagulative tumor necrosis. Immunohistochemical staining showed 60% positivity for Ki-67, and <10% positivity for MGMT. The tumor tissue stained positive for Oligo-2, Syn, CD56, S-100, Vimentin, and negative for GFAP, Neu-N, CgA, Oct3/4, LCA, CD20 and CK (Fig. 2).

Discussion

Gliomas occurring in the sella turcica region represent a relatively uncommon subgroup of CNS neural epithelial tumors. Most of the tumors in the region are optic/chiasmatic gliomas, which comprise approximately 2% of all brain tumors; a majority of these occur in pediatric patients and are low -grade gliomas[7]. Malignant optic gliomas are very rare and typically affect adult patients. Only 46 clearly documented cases are on record, of which 25 were grade IV glioblastomas[8]. Patients with an optic or chiasmatic glioblastoma typically present with a history of rapid deterioration in visual acuity and loss of visual fields. In the past, optic neuritis was an important differential diagnosis[9]; decades ago when CT was the dominant imaging modality, these cases were typically misdiagnosed as craniopharyngiomas based on their appearance as supra-sellar masses[10, 11]. In the era of magnetic resonance imaging when soft tissue imaging has become exceedingly accurate, the diagnosis of optic glioblastoma is often based on MRI findings; lesions are typically characterized by the bulging or expansion of the optic nerve or the optic chiasm, often with T1 contrast enhancement[12-14]. In these reports, intraoperative observation was often consistent with the preoperative MRI evaluation; expansion of the optic nerve and/or the optic chiasm were the most prominent features of the mass, and decompression of the tumor typically led to amelioration of visual dysfunction.
In contrast to these reports, we believe that certain glioblastomas occurring in the sellar region belong to an entirely different type of disease. For example, our case does not exhibit the above-mentioned features. Though the huge volume of the tumor mass which had occupied the entire sella turcica region rendered the identification of the optic nerve and the optic chiasm impossible on conventional MRI, intraoperative examination clearly showed that the tumor did not originate from the optic pathway. This possibly explains the patient’s clinical history and the main complaints. The main presenting symptoms were those of endocrine dysfunction (including amenorrhea, lactation and diabetes insipidus), which were likely caused by the stalk effect and impaired release of ADH due to tumor compression and infiltration. Though the visual acuity and the visual field were affected, a rapid deterioration was not reported by the patient, which is consistent with the huge volume of the tumor, whose clinical course might have been indolent in the early stage; otherwise, even a small mass in the optic pathway could have caused obvious visual symptoms. Therefore, in this case, the tumor was a sellar glioblastoma which possibly originated from the hypothalamus, pituitary/pituitary stalk or lamina terminalis, but not primarily from the optic pathway. A review of literature revealed only 4 documented cases which presented similar diagnostic challenge (Summarized in Table 1). Lemm D et al reported 2 cases of suprasellar glioblastomas that resembled craniopharyngiomas[15]. The first case was that of a 70-year-old man who presented with loss of appetite, rapid visual loss and motor dysfunction. Endocrinological investigations revealed hypopituitarism and elevated PRL. MRI showed an enhancing lesion centering on the hypothalamus which had distorted the lamina terminalis. Intraoperatively the tumor was found to be located above the pituitary gland; the histopathological diagnosis was glioblastoma. The second case was that of a 45-year-old woman who presented with visual field defect (which rapidly developed over a course of 3–4 weeks),
headache, diminished appetite, and amenorrhea. Hormone tests suggested hypogonadotropic hypogonadism. MRI showed a predominantly solid intra-sellar, suprasellar mass with cystic changes, which had extended ventrally and had displaced the optic chiasm and the optic nerves. Intraoperatively, the tumor could be separated from the pituitary gland but the right tumor margin was adherent to the adjacent structures; due to this only a partial resection was performed. The histopathological diagnosis was glioblastoma. Ali Mahta et al. reported a 42-year-old man who presented with rapid deterioration in visual acuity over a period of 2 months. The endocrinological profile was normal. MRI revealed an enhancing sellar mass with suprasellar extension which had elevated the optic chiasm and caused a shift of the optic nerves. T2 sequences showed small central hypointense foci due to which the tumor was preoperatively diagnosed as pituitary macroadenoma. Intraoperative examination revealed that the elevated optic chiasm was not infiltrated by the tumor; posteriorly, the tumor had infiltrated the hypothalamic region; histopathological examination of surgical specimen revealed a glioblastoma[16]. Kazem Anvari[17] reported a 62-year-old man who presented with elevated ICP, hypopituitarism, impaired visual acuity, visual field defects and oculomotor nerve dysfunction. MRI showed sellar mass with suprasellar extension which had lifted the optic chiasm; the imaging findings mimicked those of a pituitary adenoma. A transphenoidal approach was selected for resection; however, only a partial resection was performed; the pathological diagnosis was glioblastoma.

The imaging differential diagnosis of sella turcica mass includes a broad spectrum of diseases. The most commonly encountered entity in the suprasellar region is craniopharyngioma. Indeed, in our previous study of patients with sellar glioma, more than 90% were misdiagnosed as craniopharyngiomas. On comparing the retrospective case series of sellar gliomas and
craniopharyngiomas, we identified cystic changes and calcification as two imaging manifestations which could help differentiate between the two entities. Compared with craniopharyngiomas, sellar gliomas are less likely to develop cystic changes and calcification[6]. Other manifestations, such as intrasellar extension, hypointensity on T1, hyperintensity on T2 and heterogeneous enhancement, are usually common to both craniopharyngiomas and suprasellar malignancies. Imaging diagnosis of craniopharyngioma could be supplemented with CT owing to better delineation of sites of calcifications as compared to that with MRI. A recent study demonstrated the value of DWI in differentiating between craniopharyngiomas and germ cell tumors in the suprasellar region[18]. This highlights the potential of advanced MRI imaging modalities in facilitating accurate diagnosis of sellar masses, possibly including malignant gliomas. DWI in the present case suggested hypercellularity of the mass, but did not show clear signs of cystic change or calcification; therefore, craniopharyngioma was not on the top of the list of possible diagnoses.

Chordomas are congenital neoplasms which may originate from the clivus, and extend into the sella turcica region; these may invade the bony structures of the skull base and the adjacent neural and vascular structures[19]. Typical MRI findings of chordomas include heterogeneous T1 with hypo, iso or hyper-intensity, heterogeneous hyperintensity on T2, and heterogeneous contrast enhancement. CT facilitates the differential diagnosis by clear delineation of signs of bone destruction[20, 21]. In our case, there were signs of clivus involvement and heterogeneous enhancement; therefore this diagnosis was suspected. Another differential diagnosis for this case was giant pituitary adenoma. Extensive suprasellar extension of pituitary adenomas often appears as an hourglass-shaped mass, owing to confinement of the superior extension of the mass by the sellar diaphragm. A typical giant pituitary adenoma is a mass of relatively iso intense T1 and T2
signals, with hetero or homogenous enhancement and regular margins. The mass may contain areas of cystic changes. Sellar floor enlargement or encroachment is common[22]. The distribution and signal of the tumor in the present case were not consistent with the diagnosis of adenoma. In the coronal and sagittal planes, the focus of tumor mass appears to be located at the suprasellar region with irregular margins, and the signal was low on T1 and high on T2. A complete benign pituitary adenoma is not likely to present such features; however, it is possible for its more malignant counterparts. Other rare types of suprasellar masses with similar imaging findings may include germ cell tumors, lymphomas and metastatic lesions. About 6-13% of germ cell tumors involve the sella turcica region, and these cases may present with diabetes insipidus. These tumors are often lobulated, with moderate T1 and high T2 signals and exhibit significant contrast enhancement. CT is able to better delineate areas of calcification, while MRI shows better anatomical relations. Even though these manifestations are not specific, serum tumor marker including HCG, AFP and CEA could further facilitate the diagnosis[23-25]. Lymphoma of the suprasellar region does not have very specific manifestations either; these typically appear iso-intense on T1 and hyperintense on T2 sequences. A pertinent point for differential diagnosis of the present case from lymphoma was the homogenous contrast enhancement of lymphoma, which reflects its homogenous malignant cell composition[25-29]. Metastatic lesions from a variety of histological origins accounted for 14% of nonadenomatous sellar diseases in a cohort of 346 patients [30], which may present with diabetes insipidus as the primary clinical manifestation. These lesions may appear isointense on T1-weighted images and hyperintense on T2 weighted images, exhibit homogenous enhancement with gadolinium, and are more likely to invade the surrounding structures[31].
In the 2007 and 2016 WHO classification of CNS tumors, small cell glioblastoma is classified as an uncommon variant of glioblastoma, which implies that more clinical evidence is required to classify this subgroup as a subtype of glioblastomas[32, 33]. Small cell glioblastomas account for approximately 5-10% of all glioblastomas. These tumors are characterized by monomorphic small glial tumor cells which typically exhibit high mitotic index. This pattern has been reported to be highly aggressive and resistant to treatment. Indeed, despite our attempts to achieve maximal surgical excision and postoperative temozolomide and radiation therapy, the tumor remnant continued to progress and the patient survived only for 2 months post surgery. The histopathology of small cell glioblastoma may sometimes be difficult to differentiate from anaplastic oligodendroglioma as the astrocyte marker GFAP is seldom expressed. But in this case the small cells did not exhibit typical features of an oligodendroglioma, and its insensitivity to adjuvant therapies further supported the diagnosis. Hiroaki Takeuchi et al. summarized the clinicopathological features of small cell glioblastomas in their case-series report of 14 patients[34]. They reported several pathological features including limited microvascular proliferation, necrosis, and lymphocytic infiltration, negativity for IDH1 R132H in all patients, and no 1p/19q co-deletion. The tumors are multifocal, more likely to affect older patients and are associated with a very poor prognosis. In our previous study of 880 cases of gliomas, 263 cases were those of glioblastoma; of these, 15 (5.7%) cases exhibited the small cell pattern. The average Ki-67 positivity in these cases was 48% (range, 30-80%) as against 29% (range, 5-60%) for rest of the cases (data not shown). The prognostic value of Ki-67 positivity in patients with GBM is not clear; however, a report suggested that Ki-67 index predominantly affects the pattern of failure in GBM patients treated with a multimodal approach[35]. In the present case, Ki-67 positivity was extremely high (60%), which possibly was associated with treatment failure. Extensive review
of published literature suggests that this is the first report of small cell glioblastoma in the sellar region.

**Conclusion**

Glioblastoma in the sella turcica region is a very rare disease entity. Optic or optic chiasmatic gliomas account for a vast majority of malignant gliomas in this region. However, in a very small proportion of these tumors (as illustrated in the present case), a direct origin in the optic pathway is not found. Such tumors are suspected to originate from the hypothalamic/pituitary axis, and these patients typically present with endocrinological abnormalities. MRI imaging may facilitate the exclusion of optic gliomas in these cases as the typical feature of optic nerve expansion is often absent. However, preoperative differential diagnosis from other common sellar lesions is challenging, and intraoperative investigation and pathology examination is required for confirmation. Small cell glioblastoma is an uncommon pattern of glioblastoma which exhibits higher proliferation and treatment resistance and is associated with poor prognosis. This is the first report of this pattern of glioblastoma in the sellar region, and we believe the accumulation of such cases in the future may depict a distribution of subtypes and patterns of glioblastoma that are encountered in other CNS locations. Since the sella turcica region is characterized by complex anatomical structures, the efficacy of surgical resection in the region is poorer than that for other locations. Despite the rarity of these tumors, further research on non-surgical therapeutic modalities is warranted to improve outcomes of these patients.
References


Figure legends

Fig. 1 MRI findings of small cell glioblastoma. A) T1 sagittal; The scanning revealed a sellar-suprasellar hypointensive lesion of irregular margin B) T1 coronal; The lesion was hourglass-shaped with lateral infiltration and elevation the of the third ventricle floor. C) T1 contrast enhancement sagittal; Heterogenous enhancement of the lesion, sellar floor and the clivus. D) T1 contrast enhancement coronal; The lesion invaded the cavernous sinus enveloping the bilateral carotid arteries. E and F) T1 contrast enhancement axial; showing cavernous sinus invasion and lateral extension

Fig. 2 HE staining (100×); B) HE staining (400×); C) HE-stained section (200×) showing microvascular proliferation; D) Ki-67 staining; E) MGMT staining
Table 1 Summary of the reported cases of glioblastoma of the sellar turcica region (cases without evidence of optic origin)

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Age (years)/Sex</th>
<th>Clinical features</th>
<th>Radiological features</th>
<th>Suspected diagnosis</th>
<th>Surgical approach</th>
<th>Possible origin</th>
<th>Pathology</th>
<th>Ki-67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng et al.*</td>
<td>42/F</td>
<td>Headache, Amenorrhea and lactation, Diabetes insipidus, Visual loss and visual field defect</td>
<td>Suprasellar and intrasellar mass, Gd-DPTA heterogeneous enhancement</td>
<td>Giant adenoma, Chordoma, Craniopharyngioma, Germ cell tumor, lymphoma</td>
<td>Pterional</td>
<td>hypothalamus, pituitary/pituitary stalk or lamina terminalis</td>
<td>Small cell glioblastoma</td>
<td>60%</td>
</tr>
<tr>
<td>Patient ID</td>
<td>Gender</td>
<td>Symptoms</td>
<td>Lesion Type</td>
<td>Location</td>
<td>Hypothalamic Distortion</td>
<td>Other Conditions</td>
<td>Percent</td>
<td></td>
</tr>
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<td>------------</td>
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<td>------------------------</td>
<td>-----------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Lemm et al. 70/M</td>
<td>M</td>
<td>Loss of appetite, visual loss, ataxia and left hemiparesis</td>
<td>Craniopharyngioma, Germinoma, Glioma, Metastasis</td>
<td>Centered on the hypothalamus, lamina terminalis</td>
<td>Distorted</td>
<td>Lymphoma, Sarcoidosis</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Lemm et al. 45/F</td>
<td>F</td>
<td>Visual field defect, suprasellar</td>
<td>Craniopharyngioma, Germinoma, Glioma</td>
<td>Transsphenoidal</td>
<td></td>
<td></td>
<td>15%</td>
<td></td>
</tr>
</tbody>
</table>
diplopia, headache, amenorrhea, hypogonadotrophic hypogonadism predominantly solid, partially multicystic tumor, compression of the optic chiasm and lateral displacement of both optic nerves.

Mahta et al. 42/M visual loss and visual field defect suprasellar macroadenoma Pterional hypothalamus glioblastoma 15%
homogeneous contrast enhancement, optic chiasm elevate, optic nerves shifted intra- and suprasellar mass, heterogeneous enhancement, macroadenoma optic chiasm compressed

Headache, Visual loss and visual field defect, diplopia

Anvari et al. 62/M transsphenoidal Pituitary gland glioblastoma

heterogeneous macroadenoma
enhancement, optic chiasm compressed NA
M, male; F, female; NA, not available

* The present case
Highlights:

1. This is the first report of sellar non-optic small cell glioblastoma

2. Differences between sellar optic and non-optic glioblastomas are discussed.

3. Sellar non-optic glioblastomas are very rare; a review of all reported cases is presented.
List of abbreviations:

Central nervous system (CNS); thyroid stimulating hormone (TSH); free triiodothyronine (FT3); free thyroxine (FT4); Total-triiodothyronine (TT3); Total thyroxine (TT4); Magnetic resonance imaging (MRI); diffusion weighted imaging (DWI); anterior communicating artery (ACoA)