ABSTRACT

Glioblastoma (GBM) is the most aggressive primary tumor of the central nervous system (CNS) in adults. Its growth has been always described as locally invasive. This tumor rarely penetrates dura mater and invades extracranial structures. We present a case of GBM, which occurred in a 39-year-old man, with final involvement of the nasal cavity. The patient was operated four times in three years, and a personalized adjuvant chemotherapy regimen was administered in a neo-adjuvant fashion. Histopathological features of the tumor are described. To our knowledge, there are only 9 cases reported in the literature showing this growth pattern and the last case was reported in 1998.

KEYWORDS: Glioblastoma, Recurrence, Surgery, Temozolomide, Long-term survival, Nasal cavity, Dura mater

INTRODUCTION

Glioblastoma (GBM) is the most malignant primary cerebral tumor in adults. Despite its aggressive biological nature, invasion of the dura mater and subsequent growth into the facial cavities are very rare. Some authors reported the spontaneous dura mater and bone involvement by GBM and anaplastic oligodendroglioma (11, 14) without subsequent extracerebral growth. When the dura mater is surgically disrupted, extracerebral growth may be observed (5). Spontaneous dural penetration associated with extracerebral growth of GBM was previously reported (1,3,6,14). All of them, except one (3), were reported before the World Health Organization (WHO) central nervous system (CNS) tumor classification in 1993.

We report here a case of histologically proven GBM that was treated by repeated operations and adjuvant therapy. The last recurrence of this tumor presented with spontaneous dura mater penetration and nasal cavity invasion.

CASE REPORT

A 39-year-old man presented with progressive headache. Magnetic resonance imaging (MRI) showed a gadolinium-enhanced tumor, which was located in the left frontal lobe and invaded anterior supratentorial structures towards the midline (Figure 1A, B). On August 2006, the patient underwent the first operation. The lesion was subtotally removed and the histopathological diagnosis was GBM, grade IV grade glioma according to the WHO classification system. The status of MGMT gene promoter was methylated. The patient underwent 60 Gy radiotherapy delivered in 30 fractions and concurrent and subsequent chemotherapy with temozolomide according to standard schedules. The status of MGMT gene promoter was methylated. The patient underwent 60 Gy radiotherapy delivered in 30 fractions and concurrent and subsequent chemotherapy with temozolomide according to the WHO classification system. The status of MGMT gene promoter was methylated. The patient underwent 60 Gy radiotherapy delivered in 30 fractions and concurrent and subsequent chemotherapy with temozolomide according to standard schedules. The patient was followed-up with periodic neuroimaging studies and clinical examinations for two years. Six months later, there was evidence of tumor recurrence (Figure 2A). After standard adjuvant treatment with temozolomide, the tumor growth slowed down until March 2008 (Figure 2B). On June 2008, there was again...
evidence of tumor recurrence (Figure 2C). MRI images showed a contrast-enhancing lesion on the basal surface of left frontal lobe, surrounded with edema on T2-weighted images. Therefore, re-operation was performed twenty-five months after the first surgical procedure and subtotal tumor removal was achieved (Figure 2D). The postoperative course was uneventful (Karnofsky Performance Scale score was 100). Histopathological analysis confirmed the diagnosis of recurrent GBM. Eleven weeks after surgery, MRI scans revealed a second lesion on the basal surface of left frontal lobe, surrounded with edema on T2-weighted images. Therefore, re-operation was performed twenty-five months after the first surgical procedure and subtotal tumor removal was achieved (Figure 2D). The postoperative course was uneventful (Karnofsky Performance Scale score was 100). Histopathological analysis confirmed the diagnosis of recurrent GBM. Eleven weeks after surgery, MRI scans revealed a second lesion. The tumor also involved the corpus callosum. The patient underwent personalized adjuvant chemotherapy regimen. A re-challenge with temozolomide following a dose-dense schedule was performed. A metronomic daily administration of temozolomide, 50 mg per square meter of body-surface area was used. At the 5th month of medical treatment, neuroradiological control imaging showed decrease of the lesion size, with the disappearance of corpus callosum involvement (Figure 3B). On January 2009, the patient underwent re-operation for the third time and the tumor was totally removed (Figure 3C). The surgical approach was performed through the operculum, and anterior dura mater was left intact. Postoperative neurological examination was normal. Adjuvant chemotherapy was started again and there was a four-month interval between the surgery and the third relapse of the tumor. On the 4th month after surgery, MRI revealed the third recurrence of GBM which invaded the nasal fossa by penetrating the anterior dura mater, the basal surface of left frontal lobe, extending down to olfactory scrolls, causing lateral drift of the left optic bulb (Figure 4A-D). The patient underwent transnasal biopsy of the lesion showing the presence of necrosis and glial fibrillary acidic protein (GFAP)-vimentine-Ki67 positive cells (40%). The diagnosis was again GBM. Last 2 surgical procedures were performed by neurosurgical and maxillo-facial teams. Firstly, surgical removal of residual tumor fragments in the frontal lobe and dural reconstruction by Tachosil®, Floseal® and Surgicel® with titanium plate were performed (Figure 5A-C). Secondly, nasal part of the GBM was totally removed with the endoscopic technique. In the early postoperative period, the patient was in good clinical condition. Two months later, the patient died due to septic shock secondary to meningeal infection. Histopathological specimens showed massive dural infiltration by glioblastoma cells at the site of a primitive tumor (Figure 6A), and nasal mucosa infiltration by glioblastoma cells forming solid nests. There were cells with pleomorphic nuclei and the classic glassy and eosinophilic cytoplasm of astrocytes on high magnification (Figure 6B, C). Immunohistochemical evaluation revealed the cytokeratin positivity in the epithelial cells of the respiratory mucosa and strong positivity for GFAP (Figure 6D, E).

**DISCUSSION**

GBM, the most common primary brain tumor in adults, is usually fatal. The standard care for a newly diagnosed GBM is surgical resection, followed by adjuvant radiotherapy and chemotherapy (temozolomide). The prognosis for these gliomas is poor. Median survival after the diagnosis is approximately 1 year (9). With adjuvant treatments, this prognosis can improve. Temozolomide is an oral alkylating agent, used in conventional schedule at a dose of 150 to 200 mg per square meter of body-surface area for 5 days of a 28-day cycle. 75 mg per square meter daily for up to seven weeks is useful to deplete the DNA-repair enzyme O6-methylguanine-DNA methyltransferase (MGMT). The MGMT gene is located on chromosome 10q26 and encodes a DNA-repair protein that removes alkyl groups from the O6 position of guanine. Restoration of the DNA consumes MGMT protein and the cells must replenish. In case of missing MGMT protein, chemotherapy can induce DNA-lesioning and trigger cytotoxicity and apoptosis.

MGMT promoter methylation in GBM is associated with benefit of temozolomide treatment (4). Through this treatment, survival of GBM patients have been increased (15). GBM does not usually show leptomeningeal invasion. In fact, dura mater is the most important barrier for extracranial extension. There are biological differences between the invasive behavior of gliomas and non-neuroepithelial tumors. Leptomeningeal cells and associated acellular components of dura mater may

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**Figure 1:** MRI scan of the lesion at its first appearance in June 2006, as it appears on contrast-enhanced axial (A) and coronal (B) T1 sequence.
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Figure 2: Post-contrast axial T1 MRI shows first recurrence of the disease after surgery and concomitant radio-chemotherapy (A); MRI contrast-enhanced T1 axial scan after 15 cycles of conventional temozolomide, administered 5 days of every 28, 200 mg/m² body surface (B); MRI enhanced axial T1 image, showing tumor relapse after twenty-two months from surgery (C); MRI post-contrast T1-weighted axial image showing the surgical cavity after second operation (D).

Figure 3: T1 post-contrast axial MRI scan shows disease progression after 3 months from the re-operation (A); after only two cycles of temozolomide given with an intensified schedule, with the administration of daily 50 mg/m² body surface, the lesion enhancement slowed down (B), and a third surgical approach was then reconsidered and performed, resulting in total removal of the lesion (C).
constitute a barrier against glioma cell invasion (11). However, our case is an exception. According to Brandes et al. (3), dura mater invasion of the GBM was very rarely described in the literature and only eight cases have been previously reported. Dura mater invasion could be attributed to a slow and progressive herniation of the tumor due to an increase of intracranial pressure, or a direct invasion of herniated normal cerebral tissue. Kawano et al. (7) proposed three routes for extradural extension of gliomas: 1. Perivascular or dural slit growth; 2. Through cranial or spinal nerves; 3. Direct destruction of the dura mater. Pompili et al. (14) described two cases of dural spread of gliomas, a GBM and an oligodendroglioma, in 1993. The first case showed severe intracranial hypertension, perforation of the dura mater and the bone defect of the cranial base. In the second case, surgery probably facilitated the extraneural invasion of the tumor.

Figure 4: Axial (A), sagittal (B), and coronal (C) T1 weighted post-contrast MRI shows the extracranial invasion of the nasal fossa by the lesion. The tumor extends for 6 cm on the craniocaudal axis, and causes lateral drift of left optic bulb. The involvement of left bulb appears evident on the straight sight (D).

Figure 5: Intraoperative images shows the endophytic intracranial component of the lesion (A) and cranial anterior fossa reconstruction (B,C).
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The individualized metronomic chemotherapy schedule deserves special considerations. This peculiar second line chemotherapy was only used by Perry and coworkers (13, 12). This gave rise to a new perspective. The treatment was well tolerated, and the good response allowed further surgical approach. It may be called “neo-adjuvant chemotherapy.”

We are not able to ensure the role of this chemotherapy on the transdural spread of the GBM. Therefore further clinical observations are needed. In the future, atypical extracranial tumor spread may be more common because of longer survival of the patients with GBM due to multidisciplinary approach.

**REFERENCES**


Another hypothesis could be a congenital fistula of dura mater with or without congenital absence of anterior fossa components. In this situation, the tumor may grow extracranially. It seems that surgical intervention and radiation-induced damage of the dura mater can possibly cause the extradural extension of glioma (5). In contrast, without previous craniotomy and radiotherapy, rapid growth of the GBM may promote spontaneous penetration of the tumor into the dura mater and bones (16). Gliosarcoma shows this behavior more commonly than GBM. Murphy et al. (10) presented a case extending to the orbital and nasal cavities with bony destruction. In this case, the tumor was located in the temporal base and intraoperative ACNU (1-(4-amino-2-methyl-5-pyrimidiny1)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride) infusion might have damaged both dura mater and meningeal artery. This effect was never reported for temozolomide.

The mechanism of tumor spread is not known yet. More studies are needed to elucidate this mechanism in the future. In fact, improvements in adjuvant treatment and survival of GBM patients may lead to presentation of more cases with abnormal dural penetration. Our patient underwent four surgical procedures and surgical intervention for recurrent GBM was reported in about 28% of cases. Three or more procedures were performed in about 10% of cases (2, 8). Our patient benefited from these four surgical procedures and advanced chemotherapeutic regimens. He was accepted as a long-term survivor (8) because he lived for 3 years and two months after the first surgery.

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**REFERENCES**


**Figure 6:** Hematoxylin and eosin stains shows the massive dural infiltration by glioblastoma cells in the site of primitive tumor (A) and respiratory mucosa infiltrated by glioblastoma cells forming solid nests (B). At higher magnification cells with pleomorphic nuclei and the classic glassy and eosinophilic cytoplasm of astrocytes are evident (C); immunohistochemical evaluation demonstrate the cytokeratin positivity in the epithelial cell of the respiratory mucosa (D) and the strong immunoreactivity of neoplastic cells for GFAP (E).


