Intractable vomiting from glioblastoma metastatic to the fourth ventricle: Three case studies

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Dissemination of malignant glioma to the fourth ventricle with metastatic deposits and intractable vomiting is rare. Leptomeningeal extension of malignant glioma is an uncommon condition that has been reported in patients with end-stage disease and is usually unresponsive to any treatment modality. We describe 3 patients with progressing recurrent glioblastoma multiforme in whom leptomeningeal invasion manifested itself as intractable vomiting due to tumor metastases in the floor of the fourth ventricle. All patients received additional radiation therapy focused to the posterior fossa, with complete resolution of vomiting occurring within 10 days after irradiation. The remission of symptoms in these patients persisted until their death 3-4 months after the repeat radiation therapy. These reports indicate that additional focused radiation should be considered because of its significant therapeutic effect in alleviating intractable nausea and vomiting in patients with glioma metastasized to the posterior fossa. *Neuro-Oncology 4, 129–133, 2002 (Posted to Neuro-Oncology [serial online], Doc. 01-053, February 1, 2002. URL <neuro-oncology.mc.duke.edu>)*

The clinical picture of tumor invasion of the leptomeninges is well recognized as a problem of systemic cancer (Wasserstrom et al., 1982), but is less frequent in gliomas. A secondary type of leptomeningeal extension of malignant glioma, also called secondary gliomatosis, has been reported and is associated with dissemination of cerebral or spinal intraparenchymal glioma (Awad et al., 1986; Kandt et al., 1984; Poisson et al., 1995; Whelan et al., 1987; Yung et al., 1980).

Leptomeningeal dissemination usually develops as a late complication in patients who were treated previously with radiation and chemotherapy before disease progression occurred. In most cases, leptomeningeal propagation of glioma is considered untreatable and is seen as an end-stage complication of malignant glioma. Due to the nonregional nature of this complication, chemotherapy is sometimes attempted, but it has limited therapeutic efficacy (Davila et al., 1993; Delattre et al., 1989; Kandt et al., 1984; Poisson et al., 1995).

We describe 3 patients with advanced recurrent malignant glioma in whom leptomeningeal spreading occurred with tumor deposits in the fourth ventricle causing intractable nausea and vomiting. One patient failed to respond to intrathecal chemotherapy delivered through an Ommaya reservoir. All 3 patients were treated with focused radiation delivered to the posterior fossa that resulted in complete resolution of symptoms within days after radiation.

Case Studies

Case 1

A 46-year-old patient was diagnosed with a left temporoparietal GBM,[2] presenting with mild headaches, memory deficits, and mild dysphasia. The patient underwent an awake craniotomy with cortical mapping in which near total resection of the tumor was achieved. He had an uneventful recovery and was referred for adjuvant chemotherapy followed by irradiation of the tumor bed (70 Gy in 40 fractions over 8 weeks). Six months later, the patient developed nausea and vomiting that were unresponsive to all oral and parenteral anti-emetic therapies. MRI showed diffuse leptomeningeal extension in

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[2]Abbreviations used are as follows: CSF, cerebrospinal fluid; GBM, glioblastoma multiforme.

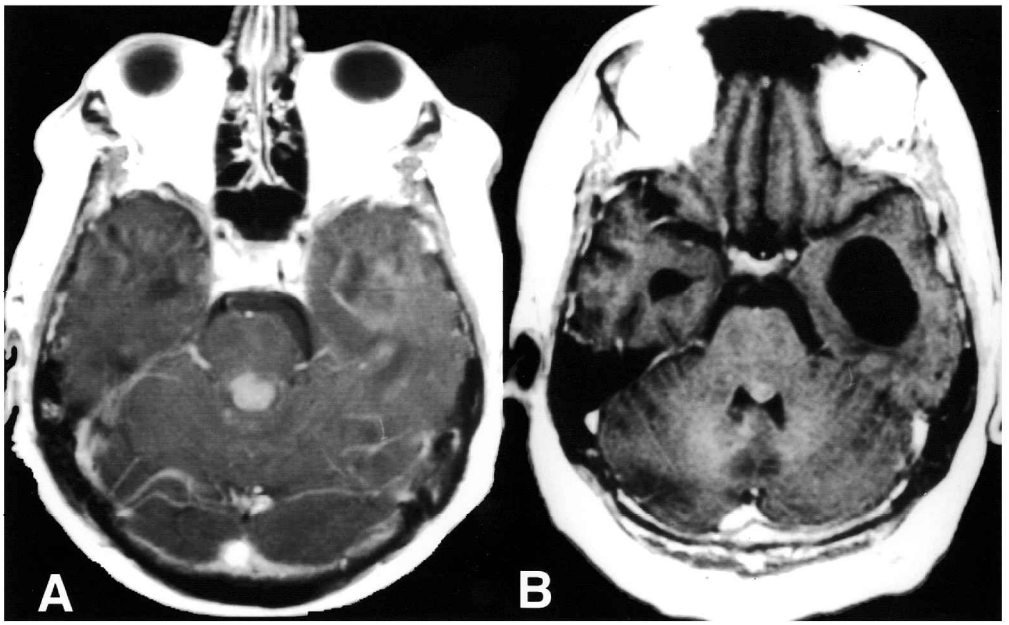

Fig. 1. Gadolinium-enhanced T1-weighted spin-echo MRI in the axial plane (A) demonstrating pathological enhancement of the leptomeninges with solid metastasis to the fourth ventricle. Complete regression of the tumor 3 weeks after delivery of focused radiation to the fourth ventricle (B).

both cerebral hemispheres and the posterior fossa, with solid tumor deposits in the corpus callosum, pineal region, and the fourth ventricle floor (Fig. 1A). Because the fourth ventricular tumor deposit was considered the cause of intractable vomiting, the patient had received an additional course of radiation focused on the posterior fossa (30 Gy in 10 fractions over 12 days). Within 10 days after completing radiotherapy, the patient's nausea and vomiting resolved completely; anti-emetic medications were discontinued; and his symptoms did not recur prior to his death from tumor progression 4 months later. Three weeks after completing radiotherapy, MRI of the patient showed complete regression of the fourth ventricle mass (Fig. 1B).

Case 2

A 27-year-old patient was diagnosed with a brain tumor presenting with a seizure disorder. He had undergone a left frontal craniotomy in which gross total resection of an anaplastic oligodendroglioma was performed. The patient had received 5 courses of procarbazine/CCNU/vincristine chemotherapy that was interrupted due to tumor progression detected on an MRI scan. The patient underwent re-operation for resection of his tumor. Histologic examination indicated that the tumor had degenerated into a GBM. The patient was referred for radiation therapy (60 Gy in 30 fractions over 6 weeks). Three months later (2 weeks after completing the radiotherapy), he developed intractable nausea and vomiting resistant to all oral and parenteral anti-emetic medications, resulting in weight loss of 15 kg. MRI showed leptomeningeal dissemination with metastatic deposits within the fourth ventricle (Fig. 2A and 2B). In the belief that the fourth ventricular tumor mass was responsible for his symptoms, the patient was given an additional radiation dose (21 Gy) to the posterior fossa in 7 fractions over 9 days. The patient's nausea and vomiting resolved completely within 7 days after irradiation, but no follow-up MRI was available in this patient. The patient did not experience recurrence of the symptoms prior to his death 3 months later.

Case 3

A 37-year-old patient underwent gross total resection of a right temporoparietal GBM followed by radiation therapy (60 Gy in 30 fractions over 6 weeks). A few months later, the patient presented with intractable nausea and vomiting. MRI revealed metastatic deposits in the fourth ventricle (Fig. 3A). The placement of an Ommaya reservoir was performed. The patient was treated with intrathecal chemotherapy as well as a combination of 6-thioguanine and lomustine. The symptoms persisted 1 month later despite treatment. The imaging studies were unchanged. A decision was made to proceed with delivering focused radiation to the posterior fossa (45 Gy in 15 fractions over 3 weeks). The patient had dramatic symptomatic improvement. Imaging studies demonstrated complete regression of the tumor immediately after completion of the irradiation to the fourth ventricle (Fig. 3B). Two months later the patient experienced multifocal progression of the disease without involvement of the fourth ventricle (Fig. 3C). There was no recurrence of symptoms prior to his death from tumor progression 4 months after the additional focused radiation.

Discussion

Secondary leptomeningeal dissemination of malignant glioma (secondary gliomatosis) is not uncommon (Awad

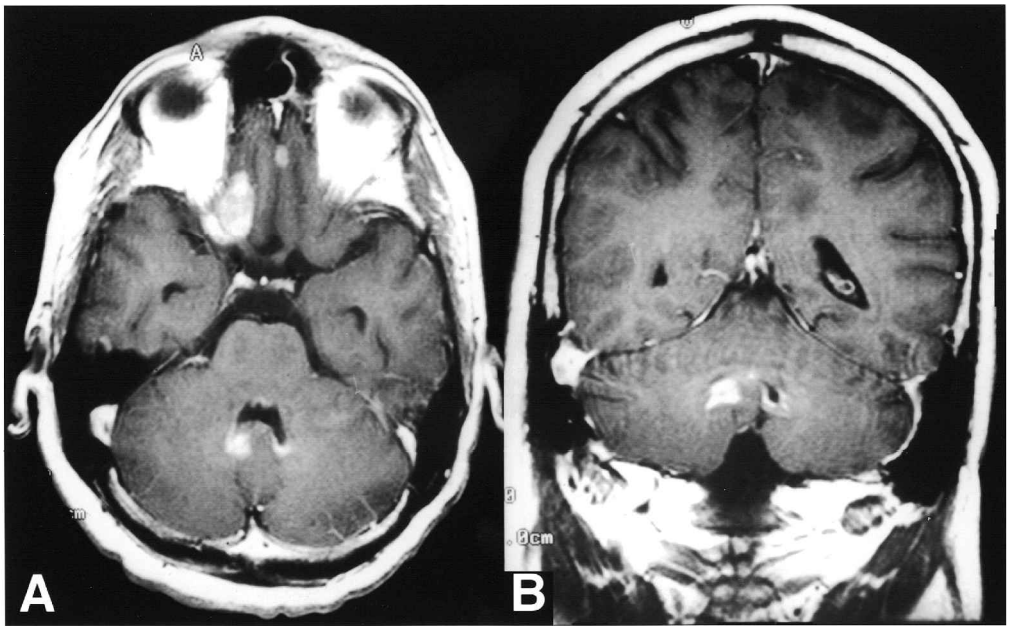

Fig. 2. Axial (A) and coronal (B) gadolinium-enhanced T1-weighted spin-echo MRIs obtained due to intractable vomiting (a few months after surgical resection of GBM) demonstrating enhancement of the metastatic deposits around the fourth ventricle.

et al., 1986; Kandt et al., 1984; Poisson et al., 1995; Whelan et al., 1987; Yung et al., 1980) as opposed to the primary type, which is rare (Beauchesne et al., 1998; Olivera-Leal et al., 1997). Whereas with primary leptomeningeal gliomatosis, astrocytoma arises in the leptomeninges from malignant transformation of heterotopic neurological tissue (Dietrich et al., 1993; Fayet et al., 1994; Park et al., 1996), the secondary type is associated with dissemination of cerebral or spinal intraparenchymal glioma. Distant metastases of cerebral glioma to the spinal cord via CSF pathways have also been reported (Nakagawa et al., 1990); however, they respond poorly to spinal irradiation (Delattre et al., 1989). Secondary gliomatosis arises rarely in patients with low-grade glioma (Civitello et al., 1988). Secondary gliomatosis may be the presenting symptom of glioma in rare cases (Davila et al., 1993; Herman et al., 1995). In many instances of secondary CSF dissemination of malignant glioma, the primary lesion is very small and can only be found at autopsy (Ashworth and Gordon, 1994). However, as previously indicated, secondary meningeal invasion by malignant glioma usually presents in patients with a previously established diagnosis of this tumor. Because most gliomas do not involve the leptomeninges to any clinically significant degree, one may assume that their propensity to invade the meninges depends on the biologic behavior of the tumor or on some other factors, such as invasiveness, proximity to leptomeningeal or ventricular surfaces, or CSF factors promoting distant spreading of tumor cells (Ashworth and Gordon, 1994; Dietrich et al., 1993; Onda et al., 1989; Yung et al., 1980). Onda et al. (1989) examined autopsy findings in a clinicopathologic series of 14 patients who had leptomeningeal dissemination of malignant glioma. They identified 2 groups of patients with CSF dissemination of glioma. The primary tumor showed only slight local invasion of the brain in one group and tended to seed the CSF pathways and involve the meninges, but in the other group it showed extensive local infiltration and only slight dissemination. In the first group, there was almost no expression of cells positive for glial fibrillary acidic protein in the primary tumors, whereas in the second group, all primaries contained many cells positive for glial fibrillary acidic protein. It appears that glioblastomas showing poor astrocytic differentiation based on immunohistochemistry tend to shed tumor cells more vigorously and to seed the CSF, but are less invasive at the primary site than those with many cells positive for glial fibrillary acidic protein. All patients from the first group and 2 from the second group (9 of 14 patients) had tumor involvement of the fourth ventricle; however, only 2 of them showed massive solid tumor deposits as seen in our patients. The symptoms of the 2 patients with a mass in the fourth ventricle, described by Onda et al. (1989), included cerebellar signs and disturbance of consciousness, whereas our patients presented mainly with severe, intractable nausea and vomiting that were probably related to local irritation of the area postrema region. Focused radiation delivered to this region alleviated all symptoms despite persistent leptomeningeal involvement outside the field of radiation.

The cases presented are unique in terms of the radiosensitivity they manifested. The metastatic deposits around the fourth ventricle resolved completely within weeks after completion of radiation in patients 1 and 3 (Figs. 1B and 3B). Primary GBM, on the other hand, is notorious for its resistance to radiation, and complete response on MRI scan after treatment is exceptional. One of the traditional explanations to the radioresistance of GBM is the high number of anoxic tumor cells adjacent to the necrosis inherent in larger tumors (Kocher et al., 2000; Leith et al., 1994; Okunieff et al., 1993). In the

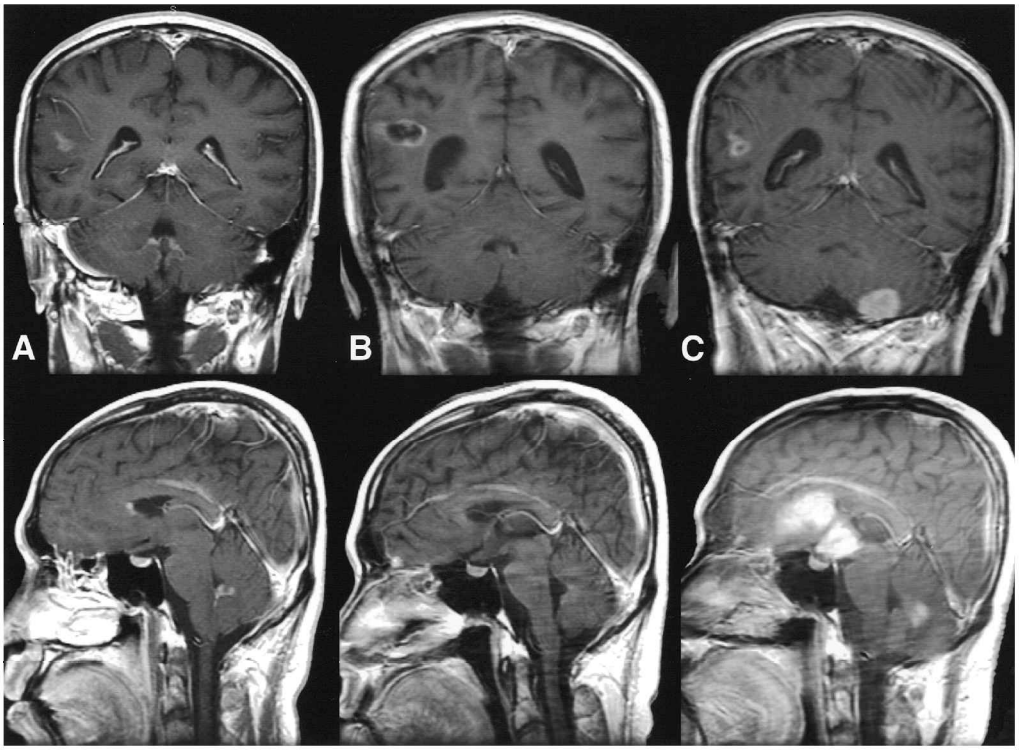

Fig. 3. Coronal and sagittal gadolinium-enhanced T1-weighted MRIs in a patient with GBM demonstrating pathologic enhancement with solid metastasis to the fourth ventricle (A). Complete regression of the tumor immediately after delivery of focused radiation to the fourth ventricle (B). Two months later, evidence of multifocal progression of the tumor without involvement of the fourth ventricle (C).

cases presented, however, the patients had small deposits that lacked a necrotic component by MRI criteria and that were well vascularized (Figs. 1A, 2A, 2B, and 3A). Their radiosensitivity may be related to their small size, good vascular supply, and absence of necrosis.

The radiation was given as a palliative measure. The different doses of radiation ranging from 21 Gy to 45 Gy were given empirically, reflecting the wide range of doses prescribed for palliation and were not dependent on field size.

Summary

Dissemination of malignant glioma to the fourth ventricle with metastatic deposits and intractable vomiting, as seen in our 3 patients, is rare. Although this complication represents a catastrophic terminal event in the course of the disease, symptomatic tumor deposits may be successfully treated by selectively focused irradiation. The intractable vomiting seen in our patients responded rapidly and completely to such local therapy.

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