

Clinical Study

Intractable vomiting as an early clinical symptom of cerebrospinal fluid seeding to the fourth ventricle in patients with high-grade astrocytoma

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Key words: dissemination, fourth ventricle, high-grade astrocytoma, magnetic resonance imaging, vomiting

Summary

Object. Cerebrospinal fluid (CSF) seeding of high-grade astrocytoma is common, but the early clinical symptoms are not well characterized. Here, we report five patients with disseminated high-grade astrocytoma in the fourth ventricle region who presented with intractable vomiting prior to the detection of the metastatic deposits with enhancement.

Patients and methods. From 1994 to 2000, 133 patients of high-grade astrocytoma were treated in our institute and were followed up until December 2002. Follow-up magnetic resonance (MR) imaging was performed in all patients every 2–3 months. The CSF seeding was defined as leptomeningeal enhancement. Signs and symptoms of CSF seeding were checked at the monthly outpatient examination.

Results. Among them, 5 patients aged from 27 to 58 years (mean 43.8 years) with one anaplastic astrocytoma and four glioblastomas showed intractable vomiting without signs of high intracranial pressure as evaluated by MR imaging or ocular fundus examination prior to the detection of the fourth ventricle dissemination. Fourth ventricle dissemination appeared 1–3 months after vomiting in five patients. One patient with glioblastoma received gamma knife radiotherapy for a fourth ventricle lesion appearing as a high intensity area on T2-weighted imaging before the appearance of the enhanced nodule, and this lesion was cured. Four patients died of progression of the fourth ventricle lesion.

Conclusion. Intractable vomiting may be an early clinical symptom of CSF seeding to the fourth ventricle in patients with high-grade astrocytoma. Early detection and immediate radiotherapy for this lesion are recommended to control fourth ventricle dissemination.

Introduction

A cerebrospinal fluid (CSF) seeding of the high-grade astrocytoma has been believed to be rare. However, postmortem and radiological studies have shown that the incidence of multifocal spread of high-grade astrocytoma is higher than expected [1–5]. Recent developments in the clinical management of high-grade astrocytoma, including surgical techniques, radiological procedures, and chemotherapy, now provide better local control of the primary lesion and longer survival time, but such successes increase the chances of symptomatic dissemination. Spinal dissemination with intracranial dissemination was found in 6 of 68 cases (8.8%) in our series of high-grade

astrocytoma, and five patients died of extensive brain and spinal dissemination or nodular mass enlargement at the upper cervical cord [6]. The CSF seeding of high-grade astrocytoma to the fourth ventricle region adjacent to brain stem is a life-threatening event, so determination of the early clinical symptoms and/or signs may provide indicators for early treatment [7].

Here, we report five patients with disseminated high-grade astrocytoma in the fourth ventricle who presented with intractable vomiting prior to the detection of the metastases by magnetic resonance (MR) imaging. Intractable vomiting may be an early clinical symptom of CSF seeding to the fourth ventricle in patients with high-grade astrocytoma.

Case studies

Clinical materials

From 1994 to 2000, 133 patients of high-grade astrocytoma (66 anaplastic astrocytoma and 67 glioblastoma) were treated in our institute and were followed up until December 31, 2002. Eighty-five patients had died, and 48 patients were alive and actively followed at the time of this study. Median survival times of patients with anaplastic astrocytoma and glioblastoma were 55.9 and 17.6 months, respectively. Seven patients (5.3%) developed CSF seeding around the fourth ventricle and all of them died. In these cases, five patients (71.4%; 3 males and 2 females) aged from 27 to 58 years (mean 43.8 years) presented with metastatic high-grade astrocytoma of the fourth ventricle manifesting as intractable vomiting prior to the detection of the metastases. Their pre- and postoperative performance status (PS) was classified using the Eastern Cooperative Oncology Group scale ranging from 0 to 4. Histological diagnosis was obtained according to the World Health Organization classification. Immunohistochemical analysis of multiple markers including glial fibrillary acidic protein, epithelial membrane antigen, vimentin and MIB-1 was performed in all cases.

Treatment and follow-up examination

All patients had undergone surgical removal of primary high-grade astrocytoma (1 anaplastic astrocytoma and 4 glioblastomas) and subsequent radiochemotherapy in our institute. Symptoms of CSF seeding were evaluated at monthly outpatient examinations, and head MR imaging was performed every 2–3 months. The CSF seeding was defined as the appearance of enhanced nodules or diffuse enhancement in the leptomeningeal space by MR imaging with contrast medium. Spinal MR imaging was performed if any symptoms indicated spinal dissemination or head MR imaging disclosed intracranial dissemination. The postoperative PS was determined between 1 and 3 months after surgery. To rule out the presence of high intracranial pressure, ocular fundus finding was routinely checked at outpatient examination. The routine evaluation by MR imaging was performed to rule out the supratentorial mass lesion and hydrocephalus that can cause high intracranial pressure.

Case 1

A 55-year-old male with glioblastoma presented with headache in December 1993. MR imaging showed a lesion in the left frontal lobe. He was admitted to our hospital on February 7, 1994. He was disoriented on admission and his PS was 2. He underwent gross total resection on March 3, followed by a total dose of 63 Gy local irradiation with megavoltage equipment and subsequent intra-arterial administration of 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU). He was discharged without neurological deficit (PS = 0) on June 5, 1994. He began to suffer intractable vomiting that could not be improved by conventional medication at the beginning of July 1994, although MR imaging on July 29 showed no evidence of tumor recurrence or CSF seeding in the fourth ventricle (Figure 1A–C). He presented with vomiting and vertigo on August 27. MR imaging suggested CSF seeding to the fourth ventricle region on October 11 (Figure 1D–F). He underwent partial resection and subsequent chemotherapy, but died of progression of the fourth ventricle lesion on July 12, 1995.

Case 2

A 27-year-old male with glioblastoma presented with generalized convulsion on October 14, 1996. MR imaging demonstrated a left frontal lobe lesion extending to the ipsilateral motor cortex, septum pellucidum, and caudate nucleus. He was admitted to our hospital on November 14, 1996. His consciousness was clear on admission (PS = 0). He underwent partial removal of the primary lesion on November 26. He received a total dose of 60 Gy local irradiation and subsequent administration of ranimustine and vincristine sulfate. He was discharged without neurological deficit on January 20, 1997 (PS = 0). He suffered intractable vomiting and truncal ataxia in the middle of May 1997. MR imaging showed no evidence of tumor recurrence or CSF seeding in the fourth ventricle region (data not shown) on May 30. However, MR imaging revealed a high intensity lesion without enhancement in the fourth ventricle region on June 23 (Figure 2A–C). He underwent stereotactic radiosurgery using a gamma knife (peripheral dose 15 Gy) and subsequent intrathecal administration of methotrexate as an outpatient. The lesion in the fourth ventricle had completely disappeared 6 months after the gamma knife therapy.

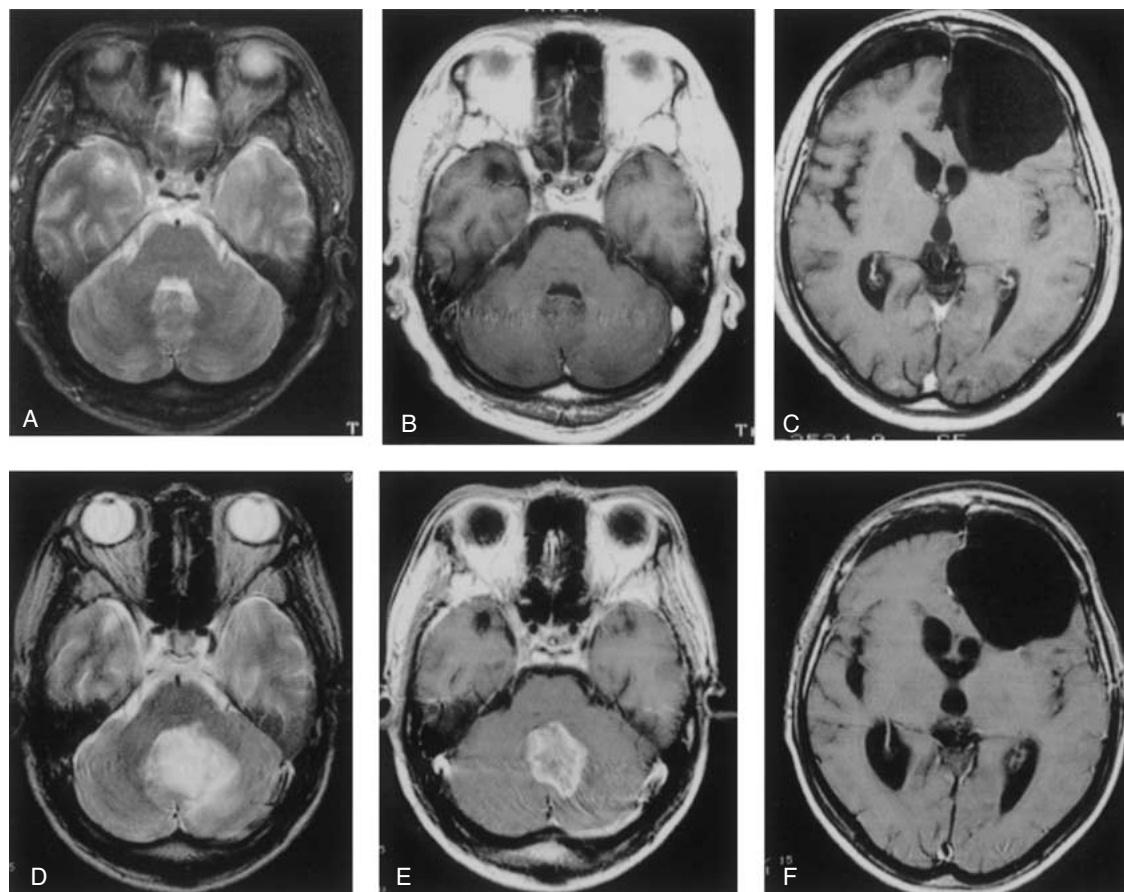


Figure 1. Case 1. T2-weighted (A, D) and T1-weighted MR images with gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA) (B, C, E, F). The CSF seeding was not evident around the fourth ventricle 1 month after presentation with intractable vomiting (A–C), but appeared 2 months later (D–F).

(Figure 2D–F). He died of progression of the supratentorial CSF seeding on November 22, 1998, but there was no evidence of the recurrence of the fourth ventricle lesion.

Case 3

A 58-year-old female with glioblastoma presented with headache in April 1998. MR imaging showed a left frontal lobe lesion extending to corpus callosum. She was admitted to our hospital on May 19, 1998. She was almost alert on admission (PS = 2). She underwent two-staged gross total resection on May 27 and June 4. She then received a total dose of 60 Gy local irradiation and subsequent intravenous administration of ACNU. She was discharged (PS = 2) on July 24. She suffered intractable vomiting on September 12, 1998.

MR imaging showed no evidence of tumor recurrence or CSF seeding in the fourth ventricle region on October 9 (Figure 3A–C). She became comatose on November 20, 1998. MR imaging suggested CSF seeding in the fourth ventricle region (Figure 3D–F). She underwent partial removal of the fourth ventricle lesion, but her consciousness did not recover postoperatively and she died of progression of the fourth ventricle lesion on January 9, 1999.

Case 4

A 32-year-old female with anaplastic astrocytoma presented with headache in July 2000. MR imaging showed a right temporal lobe lesion extending to the ipsilateral basal ganglia and bilateral thalami. She was admitted to our hospital on August 29.

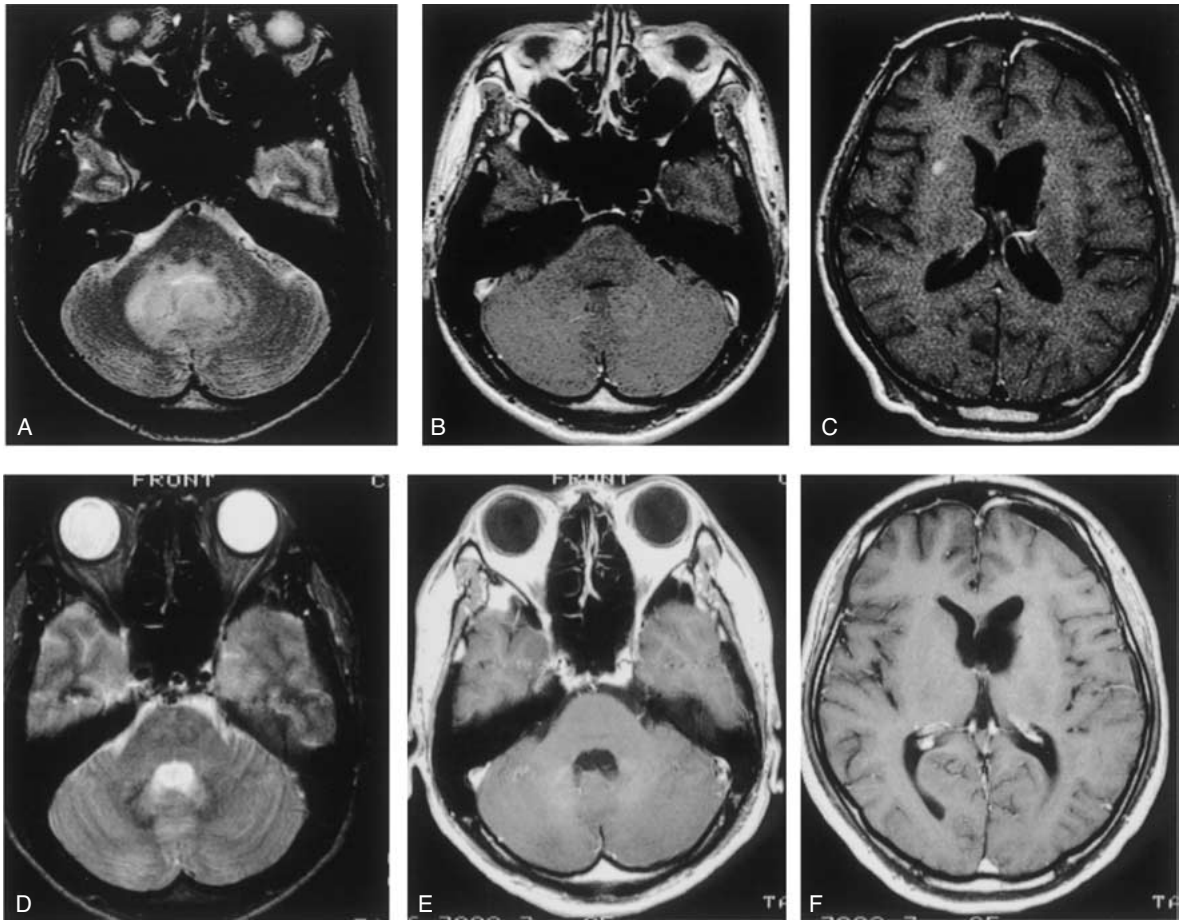


Figure 2. Case 2. T2-weighted (A, D) and T1-weighted MR images with Gd-DTPA (B, C, E, F). T2-weighted imaging showed a high intensity lesion around fourth ventricle 1 month after presentation with intractable vomiting (A–C). Complete disappearance of the high intensity lesion was obtained 6 months after gamma knife therapy (D–F).

Her consciousness was clear on admission but she had left hemiparesis (PS = 2). She underwent right temporal lobectomy on September 6. She then received a total dose of 72 Gy local irradiation and subsequent intravenous administration of ACNU. She was discharged without neurological deficit (PS = 0) on November 3, 2000. She suffered intractable vomiting in December 2000. MR imaging showed no evidence of tumor recurrence or CSF seeding in the fourth ventricle region on January 23, 2001 (Figure 4A–C). MR imaging suggested multiple CSF seeding including the fourth ventricle region on March 9 (Figure 4D–F). Stereotactic radiosurgery using a gamma knife (peripheral dose 17 Gy) and ventriculoperitoneal shunting were performed. She died of progression of the fourth ventricle lesion on July 7, 2001.

Case 5

A 47-year-old male with glioblastoma presented with intracerebral hemorrhage in the right basal ganglia on August 21, 2000. MR imaging detected an enhanced lesion in the right frontal lobe. His consciousness was clear on admission (PS = 0). He underwent subtotal removal on February 27, 2001. Stereotactic radiosurgery using a gamma knife (peripheral dose 15 Gy) was performed for the residual tumor on March 6, and then a total dose of 60 Gy local irradiation and subsequent intravenous administration of ACNU. He was discharged with left hemiparesis (PS = 2) on May 1. Immediately after discharge, he complained of intractable vomiting. MR imaging showed no evidence of tumor recurrence or CSF seeding in the fourth

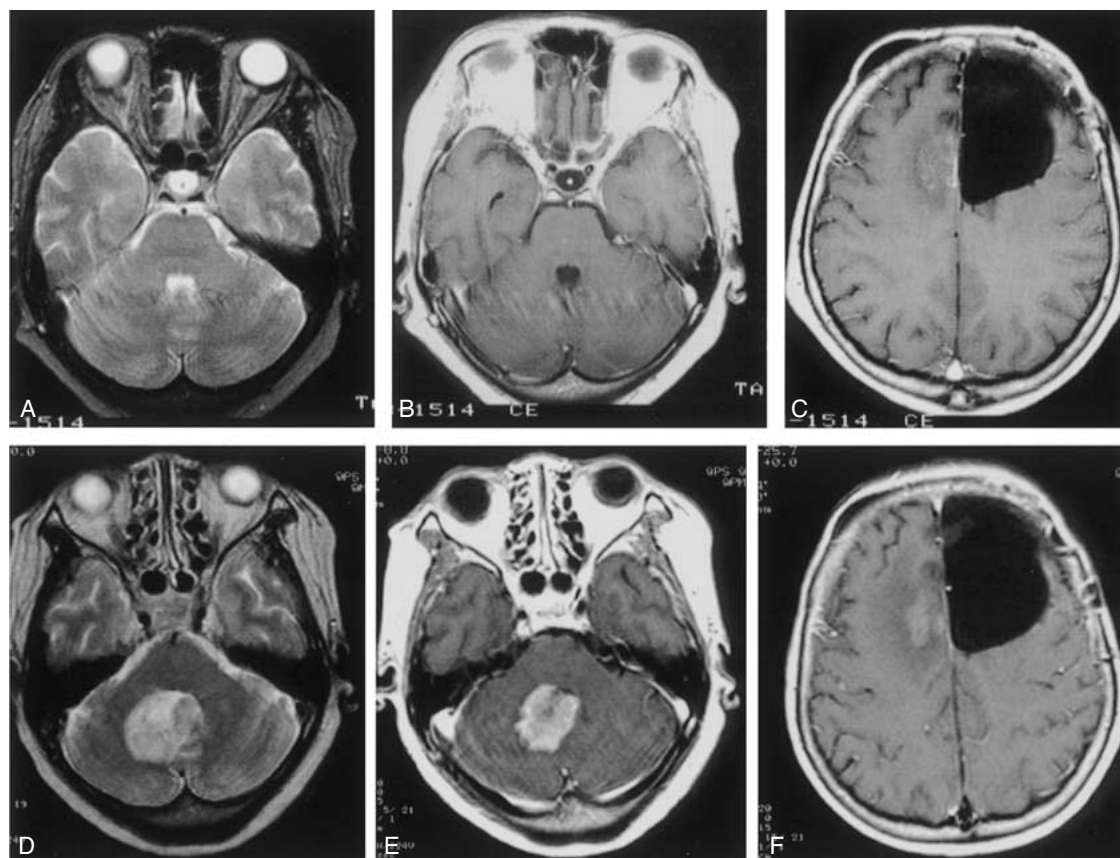


Figure 3. Case 3. T2-weighted (A, D) and T1-weighted MR images with Gd-DTPA (B, C, E, F). The CSF seeding was not evident around the fourth ventricle 1 month after presentation with intractable vomiting (A–C), but appeared 1 month later (D–F).

ventricle region on June 22 (Figure 5A–C). MR imaging suggested multiple CSF seeding in the posterior fossa including the fourth ventricle region on August 1, 2001 (Figure 5D–F). Additional local irradiation was begun, but was interrupted because of severe nausea and vomiting. He died of progression of the fourth ventricle lesion on November 4, 2001.

Discussion

The present study indicates that intractable vomiting may be an early clinical symptom of CSF seeding to the fourth ventricle region in patients with primary high-grade astrocytoma. The CSF seeding of high-grade astrocytoma to the fourth ventricle region was previously found in three patients presenting with intractable vomiting [7]. In our series, the initial evaluation by MR imaging after presentation with intractable

vomiting failed to detect any metastatic lesion around the fourth ventricle, whereas subsequent MR imaging 1–3 months later detected the responsible lesion. These observations indicate that intractable vomiting in patients with high-grade astrocytoma as in the present series could be a warning sign of CSF seeding around the fourth ventricle, and that careful and repeated evaluation using MR imaging is warranted.

The underlying mechanism of the occurrence of the intractable vomiting prior to the detection of CSF seeding to the fourth ventricle region is unclear. Nausea and vomiting are common symptoms generally caused by the activation of the vomiting center in the medulla oblongata which are induced directly by lesion in the posterior fossa. In our series, vomiting center was not directly affected by any mass lesion as demonstrated by MR imaging in all cases, but it is conceivable that small population of the tumor cells that could not be detected by MR imaging contributes

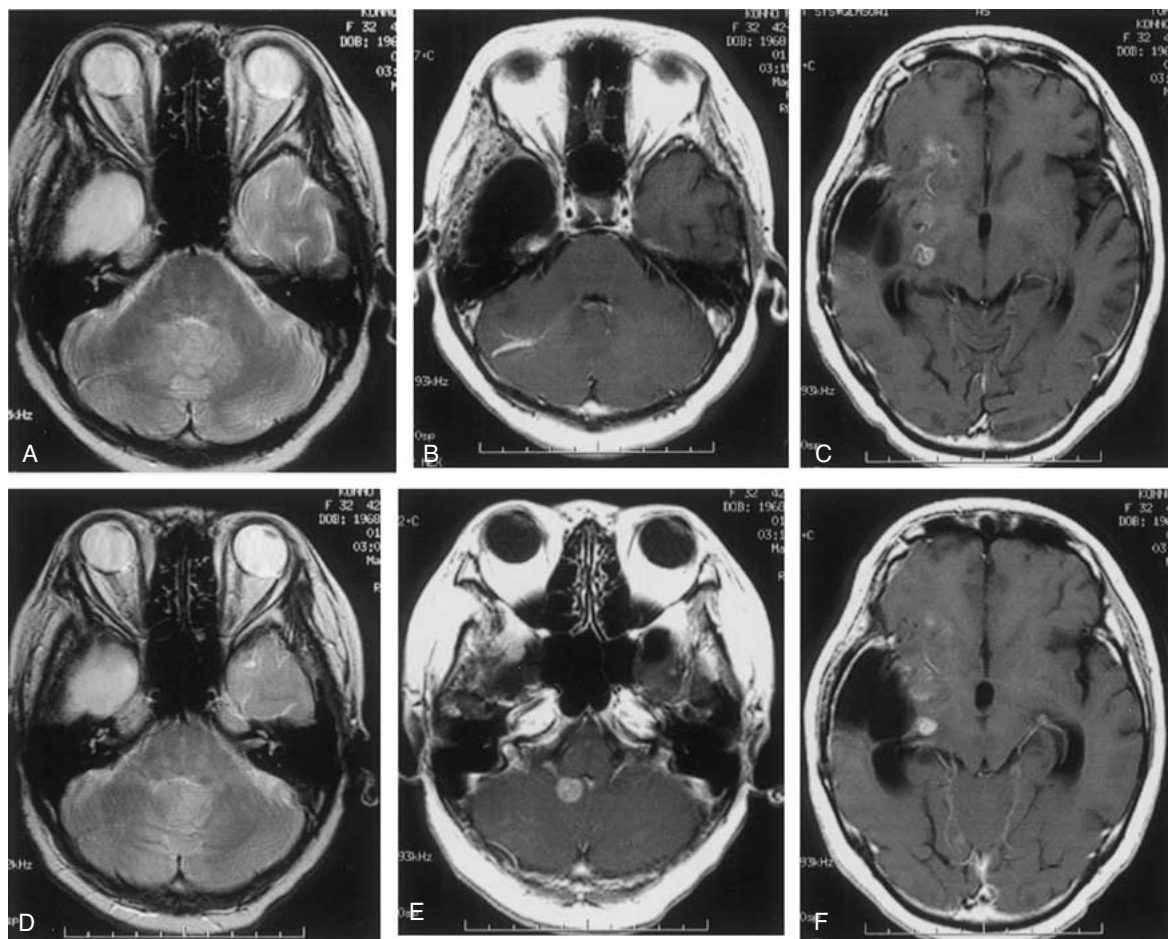


Figure 4. Case 4. T2-weighted (A, D) and T1-weighted MR images with Gd-DTPA (B, C, E, F). The CSF seeding was not evident around the fourth ventricle 1 month after presentation with intractable vomiting (A–C), but appeared 2 months later (D–F).

to the biological stimulation to the vomiting center, thereby causing intractable vomiting. Further evaluation using MR imaging with better resolution or with different condition would address this important issue.

Gamma knife radiosurgery cured the fourth ventricle lesion in our Case 2. Similarly, 2 patients with metastatic glioblastoma in the fourth ventricle obtained complete remission within weeks after completion of stereotactic radiosurgery [7]. Therefore, metastatic deposits of high-grade astrocytoma may be radiosensitive, in contrast to primary high-grade astrocytoma. Primary glioblastoma is considered to be resistant to radiation and complete response is exceptional. This resistance may be due to the relatively high number of anoxic tumor cells adjacent to the necrotic

cavity in large tumors [6,8–10]. Therefore, the small lesion in Case 2 may have been radiosensitive. Besides stereotactic radiosurgery, we do not rule out the possibility that early conventional irradiation can also cure the metastatic deposit of high-grade astrocytoma. Early detection and immediate radiation therapy could be beneficial especially for lesions around the fourth ventricle adjacent to the brain stem. We need to be very careful to recognize any high intensity lesion without enhancement around the fourth ventricle on T2-weighted MR imaging as an early finding of CSF seeding (Figure 2A). Treatment after the appearance of contrast enhancement may fail to interrupt the progression of the tumor around the fourth ventricle. In fact, four patients (Cases 1, 3, 4, and 5) of our series died of progression of the fourth ventricle lesion although

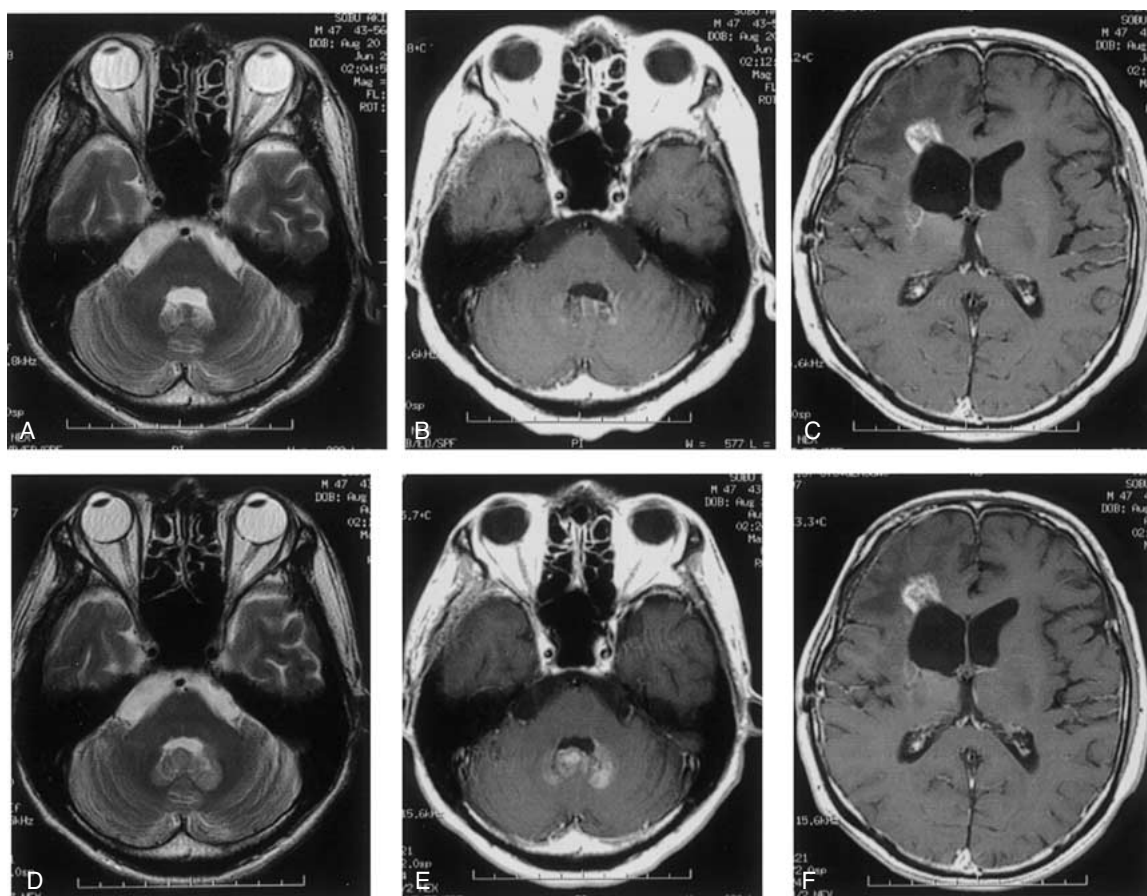


Figure 5. Case 5. T2-weighted (A, D) and T1-weighted MR images with Gd-DTPA (B, C, E, F). The CSF seeding was not evident around the fourth ventricle 1 month after presentation with intractable vomiting (A–C), but appeared 2 months later (D–F).

the primary lesion had been well controlled until their death.

The exact mechanism of CSF seeding to the fourth ventricle region is undetermined. Since all patients in the present series received local irradiation to the supratentorial lesion rather than whole brain irradiation, the lack of postoperative irradiation to the fourth ventricle region may have contributed to the dissemination to this region. Alternatively, genetic factors such as PTEN gene mutation or high MIB-1 labeling index are significantly associated with CSF seeding in patients with glioblastoma [11]. Postoperative whole brain irradiation could be the treatment of choice for malignant astrocytoma with PTEN gene mutation and high MIB-1 labeling index. These issues require future studies.

In summary, intractable vomiting may be an early clinical symptom of CSF seeding to the fourth ventricle in patients with high-grade astrocytoma.

We recommend thorough and repeated evaluation of the fourth ventricle region by MR imaging in patients treated for primary high-grade astrocytoma who subsequently present with intractable vomiting. Early stereotactic radiosurgery for the high intensity lesion by T2-weighted imaging before the appearance of contrast enhancement may be beneficial to control such fourth ventricle dissemination.

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