Eosinophilic meningitis triggered by implanted Gliadel wafers: case report

Kiyotaka Saito, MD,1 Kouji Yamasaki, MD,1 Kiyotaka Yokogami, MD, PhD,1 Asya Ivanova, MD,1 Go Takeishi, MD,1 Yuichiro Sato, MD, PhD,2 and Hideo Takeshima, MD, PhD1

1Department of Neurosurgery, Division of Clinical Neuroscience, and 2Department of Diagnostic Pathology, Miyazaki University Hospital, Faculty of Medicine, University of Miyazaki, Japan

Although carmustine (Gliadel) wafers improve local tumor control and extend the overall survival in patients with malignant glioma, adverse effects have been documented. The authors report the first case of eosinophilic meningitis triggered by the placement of Gliadel wafers. A 61-year-old man with a history of alimentary allergy and glioblastoma in the right frontal lobe underwent resection followed by the implantation of Gliadel wafers. Three weeks later he suffered the sudden onset of headache, vomiting, and progressive consciousness disturbance. Computed tomography revealed enlargement of the ventricular system and subdural space on the side of the tumor. His CSF leukocyte count increased up to 3990 cells/mm³; 95% of the cells were eosinophilic granulocytes (EGs), suggesting eosinophilic meningitis. Laboratory examination showed the patient to have various elevated allergy indicators. The administration of corticosteroids failed to improve his condition. Despite the insertion of a lumbar drain his symptoms failed to improve. He underwent a second surgical intervention to remove the Gliadel wafers. Histologically, EGs had assembled around the wafers. Eosinophilic infiltrate was present in the brain parenchyma around small vessels. After ventriculoperitoneal shunting his course was favorable. A drug lymphocyte stimulation test against the Gliadel wafers failed to demonstrate a positive reaction; polifeprosan, the wafer matrix without 1,3-bis(2-chloroethyl)-1-nitrosourea, yielded a positive reaction. These findings strongly suggest that although extremely rare, polifeprosan (the wafer matrix) can elicit an allergic reaction. When eosinophilic meningitis is suspected after the implantation of Gliadel wafers, their immediate removal should be considered.

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Of all neoplastic lesions and across all medical specialties, high-grade gliomas, including glioblastoma, are some of the most difficult tumors to treat. The combination of maximal resection followed by radiation therapy and adjuvant chemotherapy (temozolomide) is the standard treatment leading to the best clinical course. However, the prognosis remains unfavorable and most patients succumb to the disease.

Carmustine wafers (known by their trade name Gliadel) were approved by the US FDA and the European Medicines Agency for the local chemotherapy of malignant gliomas. In Japan, Gliadel wafers were approved in 2012 as an adjuvant treatment for high-grade gliomas. The Gliadel wafer is an implant for intracranial use; it contains 7.7 mg of carmustine (1,3-bis[2-chloroethyl]-1-nitrosourea, BCNU) and the biodegradable copolymer polifeprosan 20,7 which consists of polycarboxyphenoxypropane and sebacic acid in a 20:80 ratio.4 Gliadel wafers, placed along the wall of the tumor resection cavity, release carmustine continuously with diffusion into the parenchyma. Peak release occurs in the first 2 weeks and controlled release continues for approximately 3 weeks.2,7,14 Local chemotherapy with Gliadel wafers is well tolerated and offers a survival benefit to patients with malignant glioma.2,5,11,12,18 However, adverse effects have been reported. Postoperative wound healing abnormalities including wound effusion and CSF leakage account for about 3% of adverse effects.6,11 The incidence of cerebral edema was reported to be about 25%.11,18 Intracranial infection and -hypertension, and cyst formation in the resection cavity, have also
been documented. In this report we present a patient with eosinophilic meningitis that developed after the implanta
tion of Gliadel wafers. To the best of our knowledge, this is the first report of this rare complication.

Case Report

Patient History

This 61-year-old man with a history of alimentary aller
gy to beef presented with consciousness disturbance and
left hemiparesis. MRI demonstrated an intraxial mass in
the right frontal lobe with marked perifocal edema and
midline shift. The lesion had a heterogeneous component
and manifested ring-like enhancement after the admin-
istration of contrast medium (Fig. 1A and B). Preopera-
tively, high-grade glioma, most likely glioblastoma, was
strongly suspected and he underwent resection. Because
intraoperative histopathological study demonstrated the
proliferation of astrocytic cells with high cellularity, sug-
gesting high-grade glioma, 8 carmustine wafers (Gliadel)
were placed. Before their placement, the resection cavity
was completely separated from the ventricular system us-
ing oxicellulose and fibrin glue. Postoperative histopa-
thological examination revealed the lesion to be glioblasto-
ma. His clinical condition improved and MRI confirmed
the gross-total removal of the contrast-enhanced lesion
(Fig. 1C and D). In accordance with the Stupp protocol we
delivered adjuvant chemotherapy with temozolomide and
concomitant radiotherapy.

Examination and Workup

On postoperative Day 21, 2 days after the start of ad-
juvant therapy, the patient experienced new symptoms
including headache, vomiting, and progressive conscious-
ness disturbance. No fever or neck rigidity was present
and no other clinical signs of meningeal irritation were
noted. A brain CT scan obtained on Day 7 showed no ven-
tricular enlargement (Fig. 2A). A blood test performed on
postoperative Day 25 revealed no evident cause of his con-
sciousness disturbance except for a slight elevation of the
eosinophil count. The white blood cell (WBC) count was
7500/μl (reference range 3300–8600/μl) with eosinophils
accounting for 7.7% (reference range 0.7%–7.0%), and C-
reactive protein was 0.09 mg/dl (reference range < 0.14
mg/dl). His baseline kidney and liver function were nor-
mal. Considering the side effects of temozolomide, corti-
costeroids (dexamethasone 6.6 mg daily) were adminis-
ttered; they did not improve his symptoms.

CT studies showed progressive ventricular enlargement
and expansion of the right frontal subdural space (Fig. 2B
and C). We considered the ventricular enlargement and
symptoms to reflect secondary hydrocephalus. On post-
operative Day 41 we performed emergency spinal drainage.
CSF findings were suggestive of eosinophilic meningitis:
the lumbar fluid was cloudy, protein was 224 mg/dl (refer-
ence range 10–40 mg/dl), the WBC count was 3990 cells/
μl (reference range 3300–8600/μl), glucose was 20 mg/dl
(50%–66% serum, serum glucose 93 mg/dl), and 95% of
the cells were eosinophilic granulocytes (EGs).

The workup for eosinophilic meningitis by multiple-dot
enzyme-linked immunosorbsent assay ruled out parasitic
infection. The serum β-D glucan level gave no evidence of
fungal infection. The CSF culture was negative for bacte-
ria and fungi. Cytologically there was no dissemination of
the glioblastoma to the CSF. In blood tests immunoglob-
ulin E (IgE) was 985.2 IU/ml (reference range 3.7–311.6
IU/ml); the eosinophil count continued to increase until
insertion of the lumbar drain on Day 41 (Fig. 3). We diag-
nosed his eosinophilic meningitis to be attributable to an
allergic reaction. An allergy component-specific IgE test
showed that the patient was allergic to latex, cedar pol-
len, Japanese cypress, and kiwi fruit. A drug lymphocyte
stimulation test (DLST) was negative for Gliadel wafers
and temozolomide but positive for polifeprosan (procured
from Eisai Co. Ltd.), the biodegradable copolymer used to
control the release of carmustine from Gliadel wafers. Al-
though the insertion of a lumbar drain markedly reduced
the EG count, his condition did not improve significantly.

Reoperation

On postoperative Day 55 we performed a right fron-
tal craniotomy for debridement and the removal of all 8
Gliadel wafers and the surrounding brain parenchyma.
A catheter was introduced into the left ventricular horn for
ventricular drainage. During the reoperation, the tumor
resection cavity was noted to communicate with the right
anterior horn of the lateral ventricle via a small fissure in

FIG. 1. Axial Gd-enhanced preoperative (A and B) and postoperative (C
and D) MR images. A and B: T1-weighted (A) and T2-weighted (B) im-
ages obtained at the time of admission to our institution. Note the mass
in the right frontal lobe with heterogeneous Gd enhancement and strong
perifocal edema around the tumor. C and D: T1-weighted (C) and T2-
weighted (D) images confirming gross-total tumor resection and showing
placement of the Gliadel wafers (arrows).
Eosinophilic meningitis triggered by implanted Gliadel wafers

Postoperative Course

Histological examination of the Gliadel wafers and brain tissue showed the accumulation of EGs around the wafers from the side of the resection cavity. In addition, eosinophilic infiltrates were observed in brain tissue around small vessels (Fig. 4). After the removal of the Gliadel wafers the EG count in the CSF returned to the normal range (Fig. 3). His hydrocephalus failed to improve. On Day 98 after the first surgery, a right occipital ventriculoperitoneal shunt was placed, which resolved the condition. After adjuvant therapy the patient was deemed stable and admitted to a related hospital for rehabilitation.

Discussion

Glioblastoma is the most aggressive and challenging cancer to treat. Despite the implementation of the current standard treatment (known as the “Stupp protocol”), the prognosis of patients with glioblastoma remains poor. Various additional molecular targeted therapies have been developed. Drugs available in Japan for the treatment of glioblastoma are limited to certain chemotherapeutic agents such as temozolomide and nimustine. Due to its efficacy, the use of Gliadel has increased in Japan. The implantation of Gliadel is not recommended when intraoperative opening of the ventricular system is expected, because the wafers may dislocate and migrate into the ventricular system, leading to obstructive hydrocephalus. However, Bock et al. reported that sealing the ventricular system with fibrinogen-coated collagen fleece effectively separates the resection cavity and prevents Gliadel wafers from dislocating and contaminating the ventricular system. Taking that into consideration, we chose to use Gliadel wafers as adjuvant therapy in this case despite the opening of the ventricular system.

Due to the absence of meningeal irritation and general signs of inflammation, the diagnosis of eosinophilic meningitis was difficult in our patient. Follow-up CT studies showed only an expansion of the lateral ventricles and enlargement of the subdural space ipsilateral to the tumor resection cavity; these are considered to be nonspecific imaging findings. Study of the CSF obtained by lumbar drainage resulted in a diagnosis of eosinophilic meningitis.
The presence of more than 10 eosinophils per microliter in the CSF or CSF eosinophilia of at least 10% is defined as eosinophilic meningitis, a rare clinical condition. Its most common etiology is invasion of the CNS by parasites, especially Angiostrongylus cantonensis, Baylisascaris procyonis, and Gnathostoma spinigerum. Other eliciting factors are fungal infection, syphilis, and tuberculosis. Noninfectious etiologies have also been reported. For example, some patients with lymphoma developed eosinophilic meningitis after ventriculoperitoneal shunting and after the intraventricular administration of antibiotics or iophendylate dye.

Different from eosinophilic meningitis attributable to infection, the noninfectious form does not tend to elicit the classic clinical signs of meningeal irritation such as nuchal rigidity. In our patient, besides the lack of signs of meningeal irritation, elevated allergy indicators led to a suspicion of an allergic reaction to the implanted Gliadel wafers. While our initial DLST results against Gliadel wafers per se failed to show a positive reaction, when we performed the test against the polifeprosan wafer matrix without BCNU the test was positive. We posit that our patient’s allergic reaction to polifeprosan was veiled by the cell-killing effect of BCNU released by the wafers. Polifeprosan contains sebacic acid, which has been reported to be capable of inducing an allergic reaction. It is an organic compound that is a derivative of castor oil obtained by pressing the seeds of the castor oil plant Ricinus communis. Cases of allergic contact dermatitis attributable to exposure to sebacic acid compounds have been reported.

Our patient manifested late-onset elevation of the blood eosinophil count; it was recognized 25 days after the implantation of the Gliadel wafers at the first operation. We believe that this reflects the lasting duration and the released concentration of BCNU from the Gliadel wafers. Fung et al. reported that in the monkey brain, concentrations of carmustine (BCNU) were present in an area up to about 5 cm from the drug implant site for as long as 30 days. The time lag in the manifestation of elevated blood eosinophil levels may be attributable to the prolonged cytotoxicity of BCNU released by the Gliadel wafers and the accumulation of eosinophils might be inhibited early on. Taken together, our observations suggest that anticancer or immunosuppressant drugs may return false-negative DLST results due to cell destruction or the inhibition of immune-, and thus allergic reactions.

Our patient responded to the removal of all 8 Gliadel wafers and subsequent ventriculoperitoneal shunting. Suspecting adverse effects of temozolomide, as an initial treatment we administered corticosteroids to alleviate his symptoms. However, because this did not markedly improve his level of consciousness, headache, and vomiting, we next performed CSF drainage via a lumbar drain. Although the EG count in his CSF and blood was markedly reduced (Fig. 3), it failed to return to the normal range. We posit that the EG count decreased before removal of the wafers on postoperative Day 55 because the antigen concentration in the CSF was markedly reduced after insertion of the lumbar drain on Day 41 (Fig. 3). However, as the tumor resection cavity communicated with the lat-
eral ventricle, the antigen was not removed completely. Based on his allergic diathesis and neurological status we decided to remove all Gliadel wafers and some of the surrounding brain tissue. Histological examination after the second operation revealed eosinophilic aggregates around the Gliadel wafers and the surrounding brain tissue, especially in the perivascular area. Although corticosteroids tend to improve eosinophilic meningitis, their administration had no significant beneficial effects. Only removal of the wafers and placement of a ventriculoperitoneal shunt resulted in his recovery.

To the best our knowledge, this is the first report of a patient with eosinophilic meningitis elicited by the implantation of Gliadel wafers. Because of its rarity, eosinophilic meningitis attributable to Gliadel wafers is difficult to predict, thus it is very important to be aware of their potential adverse effects. Before their placement, special attention must be paid in patients with an allergic diathesis. If there is a strong suspicion of eosinophilic meningitis after the placement of Gliadel wafers we recommend their immediate removal and CSF drainage.

References

Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Saito, Takeshima. Acquisition of data: Yamasaki, Yokogami, Takeshi, Sato, Takeshima. Reviewed submitted version of manuscript: Saito, Ivanova, Takeshima. Approved the final version of the manuscript on behalf of all authors: Saito.

Correspondence
Kiyotaka Saito, Department of Neurosurgery, Division of Clinical Neuroscience, Faculty of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan. email: kiyotaka_saitou@med.miyazaki-u.ac.jp.