NMC Case Report Journal 2015; 1: 36–39
DOI: 10.2176/nmccrj.2014-0080

*Case Report*

# Cerebral Infarction Related to Carmustine Wafers in Glioblastoma: A Case Report

Mitsutoshi Nakada, Shingo Tanaka, Masahiro Oishi, Katsuyoshi Miyashita, Kouichi Misaki, Masanao Mohri, Yasuhiko Hayashi, Naoyuki Uchiyama, Takuya Watanabe, and Yutaka Hayashi

Implantation of carmustine-impregnated wafers (Gliadel®) into the tumor resection cavity has demonstrated a survival benefit for patients with malignant glioma. However, some precautions should be taken regarding Gliadel implantation. We report a case of a 63-year-old man with glioblastoma who was implanted with Gliadel after a left temporal lobe tumor had been removed, and who later developed vasospasm of the lenticulostriate artery close to the implanted Gliadel, leading to serious cerebral infarction. Therefore, the implantation of Gliadel in cases where important vessels run close to the resection cavity should be considered with great caution.

**Keywords:** carmustine, glioblastoma, vasospasm, cerebral infarction

## Introduction

Carmustine-impregnated wafers (Gliadel®, Eisai, Baltimore, Maryland, USA) are designed to release biodegradable 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU) slowly over a period of 2–4 weeks after their placement on the surface of the surgical cavity resulting from the treatment of high-grade glioma. This results in high local concentrations of carmustine in the surrounding brain tissue to suppress tumor recurrence. Recently, Gutenberg et al. reviewed the literature and identified 19 retrospective and prospective studies investigating the use of Gliadel, and concluded that it resulted in a modest improvement of median overall survival with an acceptable and manageable safety profile.[1] However, many adverse events (AEs) have been associated with the implantation of Gliadel, including cerebral edema, healing abnormalities, cerebrospinal fluid (CSF) leakage, intracranial infections, seizures, hydrocephalus, and cyst formation.[2–7] To the best of our knowledge, ischemia due to vasospasm is not a known complication of Gliadel. Here we present a case of primary glioblastoma (GBM) that showed an acute cerebral infarction certainly caused by vasospasm due to Gliadel.

## Case Report

A 63-year-old man with mild dementia visited a local hospital. Computed tomography (CT) revealed a mass located in the left temporal lobe and insula, which showed apparent ring enhancement (diameter, 40 mm) with irregular margins under a contrast medium (Fig. 1A). Magnetic resonance imaging (MRI) showed that the hyperintense lesion was accompanied with mild perifocal edema on $T_2$-weighted imaging (Fig. 1B).

The patient was admitted to our hospital. He underwent surgery for tumor resection via a left frontotemporal approach. Although the left lenticulostriate artery (LSA) was invisible during the operation (Fig. 2A), the tumor was close to it. Therefore, a small portion of the tumor was deliberately left at the deep area of the temporal lobe. The tumor was resected subtotally, and two Gliadel wafers were placed and secured with fibrin glue at the deep portion of the temporal lobe (Fig. 2B–E) and the posterior portion close to the posterior limb of the internal capsule. Obvious thick clot was not present between Gliadel and the surface of the resected cavity. Postoperative CT at day 1 revealed the subtotal removal of the tumor and the presence of entrapped air near the Gliadel wafers in the tumor resection cavity (Fig. 1D). MRI demonstrated that some edema remained in the area surrounding the tumor cavity. There was no indication of acute infarction events on diffusion-weighted imaging before and after surgery (Fig. 1C, F).

Histopathological examination of the excised tissue revealed typical GBM findings. The postoperative course was uneventful until day 11, without any new neurological deficit. However, consciousness disturbance and right hemiparesis appeared from the morning of day 12. Despite the presence of mild hemiparesis at the beginning, hemiparesis gradually worsened and consequently progressed to complete hemiplegia for 24 h. Emergent CT showed edema in the frontal lobe and the augmentation of air in the tumor resection cavity, although the subdural postoperative air had disappeared (Fig. 1G). MRI revealed severe edema at the basal ganglia on a $T_2$-weighted image (Fig. 1H) and acute ischemic stroke in the left corona radiata (Fig. 1I). Angiography performed at day 13 revealed stenosis of the left LSA, which was just below the entrapped air close to the Gliadel (Figs. 2B, 3A). Ozagrel sodium and edaravone were given to treat the acute cerebral infarction for 2 weeks. The stenosis of the left LSA had improved and perforators from middle cerebral artery were conspicuous at day 39 compared to the finding at day 13, suggesting this was a vasospasm (Figs. 2D, 3C). The air in the cavity had disappeared (Fig. 3D). Because of his GBM diagnosis, he subsequently received radiotherapy with

Department of Neurosurgery, Graduate School of Medical Science, Kanazawa University, Kanazawa, Ishikawa

Received: February 27, 2014; Accepted: June 5, 2014

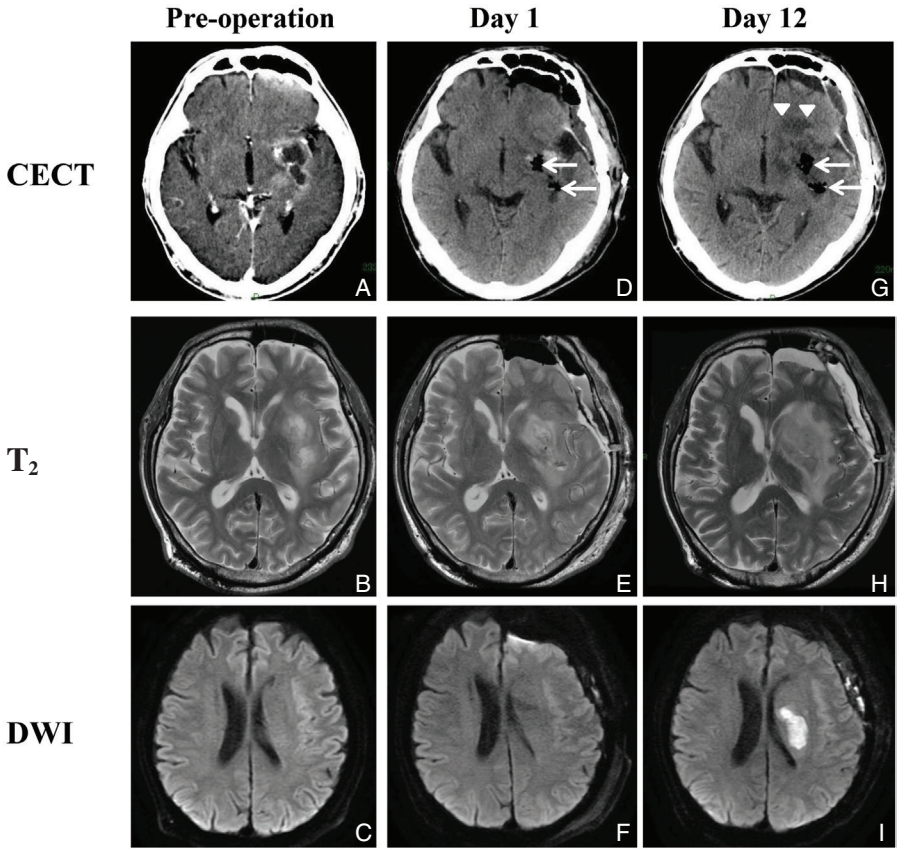


**Fig. 1** CT and MRI findings pre-operatively (A–C), at day 1 after the operation (D–F), and at day 12 (G–I). A: CT with contrast medium showing a ring-enhanced mass with irregular margins (diameter, 40 mm) in the temporal lobe and insula. B: $T_2$-weighted image showing a hyperintense lesion. C, F: Diffusion-weighted MRI (DWI) showing no hyperintense lesions. D: CT showing entrapped air in the resected cavity (arrows). E: $T_2$-weighted image showing mild perifocal edema and subdural air. G: CT showing enlargement of entrapped air in the resected cavity (arrows) with perifocal edema (arrowheads). H: $T_2$-weighted images showing severe edema. I: DWI showing a hyperintense lesion in the left corona radiata, suggesting acute cerebral infarction. CECT: contrast-enhanced computed tomography, CT: computed tomography, MRI: magnetic resonance imaging.

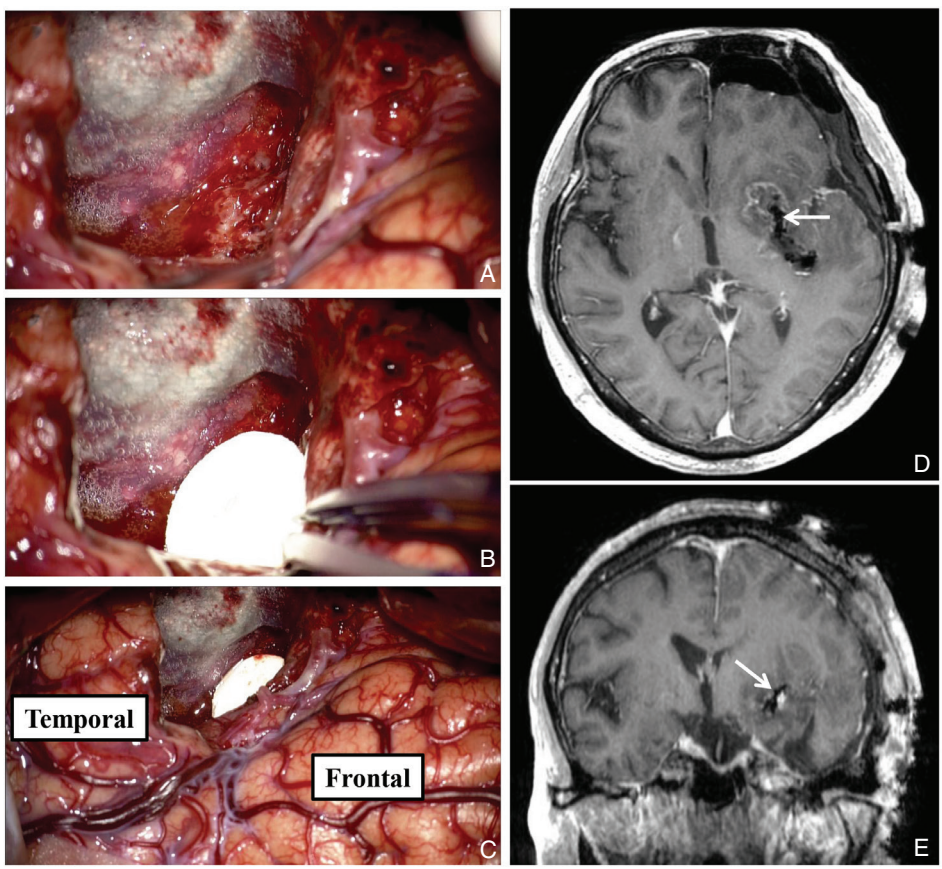


**Fig. 2** Intraoperative pictures (A–C) and postoperative MRI at day 1 (D, E). A: Tumor resected cavity before implantation of Gliadel. B: The location of Gliadel in high magnification (C) and low magnification. Axial (D) and coronal (E) image on $T_1$-weighted image showing the location of Gliadel (arrows). MRI: magnetic resonance imaging.

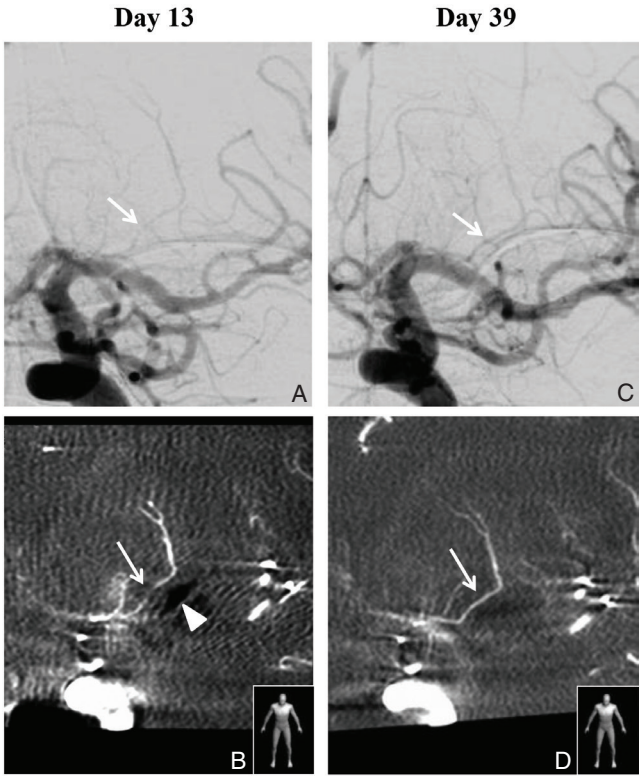


**Fig. 3** Angiographic findings at day 13 (A, B) and day 39 (C, D). A: Digital subtraction angiography (DSA): left internal carotid artery injection (AP view) showing stenosis of a major branch of lenticulostriate arteries (LSAs, arrow). B: Reformatted coronal image of three-dimensional rotational angiography (3DRA) showing stenosis of the left LSA (arrow) below the air related to Gliadel (arrowhead). C: DSA showing recovery of LSA stenosis. D: Reformatted coronal image of 3DRA showing no stenosis and disappearance of air.

a total dose of 60 Gy and temozolomide chemotherapy at 75 mg/m$^2$/day.

Intensive rehabilitation was performed to improve left hemiplegia. However, severe hemiparesis remained at 3 months after the operation.

## Discussion

In a multi-center randomized trial, Westphal et al. analyzed 240 patients with newly diagnosed GBM with post-resection Gliadel implantation and radiotherapy, or placebo wafers and radiotherapy.[6] AEs related to Gliadel included seizures (33.3%), brain edema (22.5%), grand mal convulsions (5%), and intracranial hypertension (9.2%). The rate of AEs was comparable with that in the placebo control group, emphasizing the safety of Gliadel. However, in clinical practice following drug approval, many other AEs have been reported, including healing abnormalities, CSF leakage,[3,5] intracranial abscesses,[3] hydrocephalus,[3,5,8] deep-vein thrombosis,[2] and cyst formation.[9] Recent review papers concerning Gliadel have reported that the rate of severe AEs, including grades 3 and 4, was 43%.[3,10] Here, we report the case of GBM where Gliadel might induce vasospasm resulting in a cerebral infarction with complete hemiplegia.

Brain edema is the most common AE induced by Gliadel; it occurs in 25% of patients and accounts for significant post-operative morbidity.[3,6,7] Weber and Goebel reported that extensive cerebral edema after Gliadel placement led to severe neurological compromise and death.[11] Our case also demonstrated wide edema around the Gliadel. Generally, within the first 10 days after surgery, no significant edema is observed, similar to our case.[12] This complication is addressed successfully with either high-dose steroids or surgical decompression depending on the degree of mass effect.[12] In our case, edema was highly responsive to steroids. Giese et al. recommended dexamethasone treatment before surgery in the case of a substantial mass effect, if Gliadel is planned to be used.[12] If brain edema cannot be sufficiently controlled by steroids, bevacizumab treatment, which decreases the permeability of tumor blood vessels, might be effective.

In our case, the air in the tumor cavity remained at the appearance of vasospasm. Air in the surgical bed is a transient finding that may last up to 3 weeks and does not necessarily represent infection. As expected, the air in our case had disappeared within 3 weeks. The origin of this air remains unclear, but may be due to expansion of the entrapped air in the cavity; it may also be related to the chemical breakdown of the wafer.[13]

We speculated that the patient's cerebral infarction could be attributed to vasospasm possibly induced by Gliadel in our case. This is because the vasospasm was found to be localized just below the Gliadel site, whereas other parts of the main arteries did not show vasospasm. LSA was not exposed on the surface of the resected cavity, and obvious thick clot did not exist between Gliadel and the surface, suggesting vasospasm was not induced by hematoma. Delayed symptoms excluded the possibility of mechanical injury to the vessels caused by the surgery. Moreover, the patient did not have any risk factors for stroke such as diabetes, hypertension, dyslipidaemia, hypercoagulable disorder, or a history of smoking.

The mechanism of vasospasm induced by Gliadel remains unclear. Shingleton et al. reported that high-dose intravenous carmustine (800 mg/m$^2$) has been associated with retinal artery narrowing and obstruction.[14] The controlled release of carmustine from a copolymer takes place over a period of 3 weeks. The local carmustine concentration at the implantation site is 1,200 times higher than concentration achieved by systemic administration of carmustine.[15] Possibly, local toxicity of carmustine or a foreign body reaction to the wafer material may result in the local inflammatory response responsible for the vasospasm. The vasospasm decreases the cerebral blood flow (CBF) at local region where the corresponding vessels govern. Subsequently, cytotoxic edema is induced by the CBF decrease. Cytotoxic edema increase local tissue pressure because of the rigid cranium, resulting in decrease of CBF. Therefore, it seems likely that severe vasospasm in LSA and small perforators accompanied with a vicious spiral of CBF decrease and local pressure increase has led to the serious cerebral infarction.

We reported a case of GBM showing an acute cerebral infarction probably associated with vasospasm related to Gliadel. The clinical aim of this report is to emphasize the relevance of brain toxicity as a possible severe complication of Gliadel use.

## Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors who members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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Corresponding author:
Mitsutoshi Nakada, MD, PhD, Department of Neurosurgery, Graduate School of Medical Science, Kanazawa University, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan.
✉ mnakada@med.kanazawa-u.ac.jp