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

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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 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.

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 T2-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 T2-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...
Gliadel-Induced Cerebral Infarction

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: T2-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: T2-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: T1-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 T1-weighted image showing the location of Gliadel (arrows). MRI: magnetic resonance imaging.
Brain edema is the most common AE induced by Gliadel; it occurs in 25% of patients and accounts for significant postoperative morbidity.$^{1,6,7}$ 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/m²) 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.

Fig. 3 Angiographic findings at day 13 (A, B) and day 39 (C, D). A: Digital subtraction angiography (DSA) 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 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/m²/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.
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.

**References**

1. Gutenberg A, Lumenta CB, Braunsdorf WE, Sabel M, Mehdorn HM, Westphal M, Giese A: The combination of carmustine wafers and temozolomide for the treatment of malignant gliomas. A comprehensive review of the rationale and clinical experience. *J Neurooncol* 113: 163–174, 2013
2. Attenello FJ, Mukherjee D, Datoo G, McGirt MJ, Bohan E, Weingart JD, Olivi A, Quinones-Hinojosa A, Brem H: Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. *Ann Surg Oncol* 15: 2887–2893, 2008
3. Bock HC, Puchner MJ, Lohmann F, Schütze M, Koll S, Ketter R, Buchalla R, Rainov N, Kanelharid SR, Rohde V, Giese A: First-line treatment of malignant glioma with carmustine implants followed by concomitant radiotherapy: a multicenter experience. *Neurosurg Rev* 33: 441–449, 2010
4. Meeni P, Metellus P, Parot-Schinkel E, Loiseau H, Capelle L, Jacquet G, Guyotat J: Neuro-oncology Club of the French Society of Neurosurgery: Biodegradable carmustine wafers (Gliadel®) alone or in combination with chemoradiotherapy: the French experience. *Ann Surg Oncol* 17: 1740–1746, 2010
5. Quinn JA, Jiang SX, Carter J, Reardon DA, Desjardins A, Vredenburgh JI, Rich JN, Gururangan S, Friedman AH, Bigner DD, Sampson JH, McLendon RE, Herndon JE, Threatt S, Friedman HS: Phase II trial of Gliadel plus O6-benzylguanine in adults with recurrent glioblastoma multiforme. *Clin Cancer Res* 15: 1064–1068, 2009
6. Westphal M, Hilt DC, Borte Y, Delavault P, Olivares R, Warnke PC, Whittle JR, Jääskeläinen J, Ram Z: A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel® wafers) in patients with primary malignant glioma. *Neuro-oncology* 5: 79–88, 2003
7. Aoki T, Nishikawa R, Sugiyama K, Nonoguchi N, Kawabata N, Mishima K, Adachi J, Kurisu K, Yamasaki F, Tominaga T, Kumabe T, Ueki K, Higuchi F, Yamamoto T, Ishikawa E, Takeshima H, Yamashita S, Arita K, Hirano H, Yamada S, Matsutani M; NPC-08 study group: A multicenter phase I/II study of the BCNU implant (Gliadel® Wafer) for Japanese patients with malignant gliomas. *Neur Mol Med* (Tokyo) 54: 290–301, 2014
8. Gallego JM, Barcia JA, Barcia-Marino C: Fatal outcome related to carmustine implants in glioblastoma multiforme. *Acta Neurochir (Wien)* 149: 261–265; discussion 265, 2007
9. McGirt MJ, Villavicencio AT, Bulsara KR, Friedman HS, Friedman AH: Management of tumor bed cysts after chemotherapeutic wafer implantation. Report of four cases. *J Neurosurg* 96: 941–945, 2002
10. Bregy A, Shah AH, Diaz MV, Pierce HE, Ames PL, Diaz D, Komotar RJ: The role of Gliadel wafers in the treatment of high-grade gliomas. *Expert Rev Anticancer Ther* 13: 1453–1461, 2013
11. Weber EL, Goebel EA: Cerebral edema associated with Gliadel wafers: two case studies. *Neuro-oncology* 7: 84–89, 2005
12. Giese A, Bock HC, Kanelharid SR, Rohde V: Risk management in the treatment of malignant gliomas with BCNU wafer implants. *Cen Eur Neurosurg* 71: 199–206, 2010
13. Hammond DA, Belden CJ, Ho AC, Dal Pan GJ, Herskovits EH, Hilt DC, Brem H, Pomper MG: The surgical bed after BCNU polymer wafer placement for recurrent glioma: serial assessment on CT and MRI imaging. *AJR Am J Roentgenol* 180: 1469–1475, 2003
14. Shingleton BJ, Bienfang DC, Albert DM, Ensminger WD, Chandler WF, Greenberg HS: Ocular toxicity associated with high-dose carmustine. *Arch Ophthalmol* 100: 1766–1772, 1982
15. Fung LK, Ewend MG, Sills A, Sipos EP, Thompson R, Watts M, Colvin OM, Brem H, Saltzman WM: Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide, and paclitaxel from a biodegradable polymer implant in the monkey brain. *Cancer Res* 58: 672–684, 1998