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Symptomatic Remote Cyst after BCNU Wafer Implantation for Malignant Glioma

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Abstract

A 43-year-old man was operated on for right frontal oligoastrocytoma. 14 years after the surgery, magnetic resonance imaging and positron emission tomography revealed a new lesion near the surgical cavity. He underwent gross total resection of the lesion and implantation of *bis*-chloroethylnitrosourea (BCNU) wafers after intraoperative pathological diagnosis of recurrent high-grade glioma. A few days after the operation, the level of consciousness gradually worsened and left hemiparesis developed. A computed tomography scan revealed a cyst remote to the surgical cavity which did not exist 3 days prior. We performed anterior cyst wall fenestration and removed all wafers. The characteristic pathological finding at the wafer implantation site was severe inflammation within and around small vessels. This inflammatory reaction was not seen on the surface of the brain parenchyma. After surgery and rehabilitation, the patient's Karnofsky Performance Status stabilized to a pre-incident score of 90 and he returned to work. The exact pathophysiological mechanism of the cyst was not clear, but check-valve and/or osmotic gradient mechanisms related to BCNU wafer implantation could have contributed to this phenomenon. As remote cyst development happened a week after surgery, surgeons should be aware of such a rare condition when implanting wafers as consciousness impairment and hemiparesis may occur. Close radiological follow-up is therefore necessary.

Key words: BCNU wafers, carmustine wafers, cyst formation, symptomatic remote cyst, malignant glioma

Introduction

bis-Chloroethylnitrosourea (BCNU, carmustine) wafer implantation is a common adjuvant therapy for malignant glioma.[1,2] After tumor removal, the wafers are placed on the walls of the resection cavity and BCNU is slowly released over a period of 2 weeks. A phase III, randomized, controlled trial demonstrated a significant improvement in the median overall survival time of 120 patients by 2.3–13.9 months.[1] Some complications of BCNU wafer implantation, such as edema formation, hydrocephalus, and wound site complications, are known and the formation of tumor bed cysts is also considered as a complication.[3] This is because BCNU wafers sometimes form a space-occupying cyst in and/or around the resection cavity which forms a so-called tumor bed cyst and several previous reports describe this phenomenon.[4,5] However, remote cyst formation after BCNU implantation on the cavity walls has not been described previously. Herein, we report a first case of remote cyst formation causing hemiparesis and consciousness impairment after BCNU wafer implantation. We also discuss pathological findings of the brain parenchyma around wafers and the cyst wall.

Case Report

A 43-year-old Japanese man was diagnosed with a right frontal brain tumor and underwent gross total resection. After pathological diagnosis of oligoastrocytoma by the 2007 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) criteria, he subsequently underwent radiation therapy (60.4 Gy) with two rounds of vincristine (2 mg) and nimustine (140 mg). After completing the chemoradiotherapy, the patient was discharged and visited a regional hospital regularly for follow-ups. He did not develop any neurological sequelae other than occasional episodes of epilepsy [Karnofsky Performance Status (KPS) was 90].

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14 years after the first operation, in spite of being asymptomatic, T_2-weighted magnetic resonance imaging (MRI) revealed a new high-intensity area around the surgical cavity (Fig. 1a) and positron emission tomography using ^{11}C-methionine showed a high integration degree in that area (Fig. 1b). The lesion was diagnosed as a tumor recurrence and tumorectomy/BNCU wafer implantation on the surgical cavity wall after intraoperative pathological diagnosis of recurrent high-grade glioma (HGG) was performed uneventfully as follows: The previous operation (14 years prior) had fused the dura mater to the cerebral surface and sharp dissection was needed to detach it. The lateral ventricle was opened during tumor resection and we reconstructed the ventricle wall with a hemostatic gelatin sponge and fibrin glue before implanting 6 wafers on the resected cavity (Figs. 2a and 2b). MRI revealed no residual tumor and no adverse events, except for a small cerebral infarction (Fig. 1f, white arrow), occurred the day after surgery (Figs. 1c–1f).

There were no new neurological symptoms soon after surgery, however, the level of consciousness gradually worsened and left hemiparesis developed gradually over 4 days after surgery. Although no new lesions appeared on computed tomography (CT) scans 4 days post-surgery (Fig. 3a), on the 7th post-surgical day CT scans revealed a cyst with a maximal diameter of 37 mm, located away from the surgical cavity, and compressing the right primary motor area (Fig. 3b). The intensity of the fluid in the cyst was almost the same as the cerebrospinal fluid (CSF) (Figs. 3c–3f), however, fluid-attenuated inversion recovery (FLAIR) images showed the different intensities between surgical cavity and the cyst. Though the signal intensity was relative value, the mean of tumor resected cavity, contralateral lateral ventricle, and cyst were 194, 153, and 497 respectively under the same imaging parameters (Figs. 4a–4c). The surgical removal of the wafers and fenestration of the anterior wall of the cyst was then performed as follows: The exposed cyst

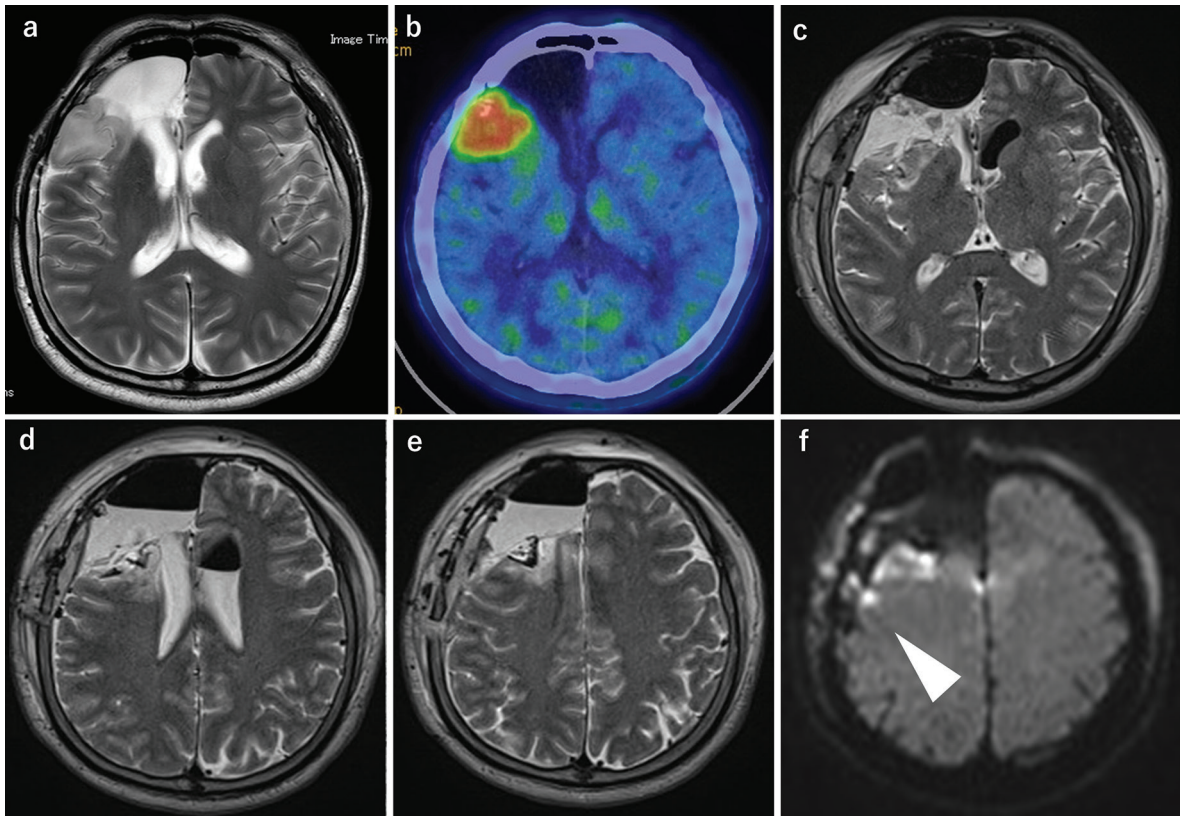

Fig. 1 Perioperative neuroimaging. A T_2-weighted magnetic resonance imaging (MRI) (a) and ^{11}C-methionine positron emission tomography (b) indicating the recurrence of the tumor next to the previous surgical cavity in the right frontal lobe. T_2-weighted MRI on the day after surgery showing the postoperative cavity after recurrent tumor resection with open anterior horn of the right lateral ventricle (c). BCNU wafers placed on the surface of the cavity after closing the lateral ventricle with an absorbable compressed gelatin sponge (d and e). The diffusion-weighted MRI shows a small high intensity spot-like area in the right frontal lobe (f, *white arrow head*), the small cerebral ischemia area located apart from the surgical cavity.

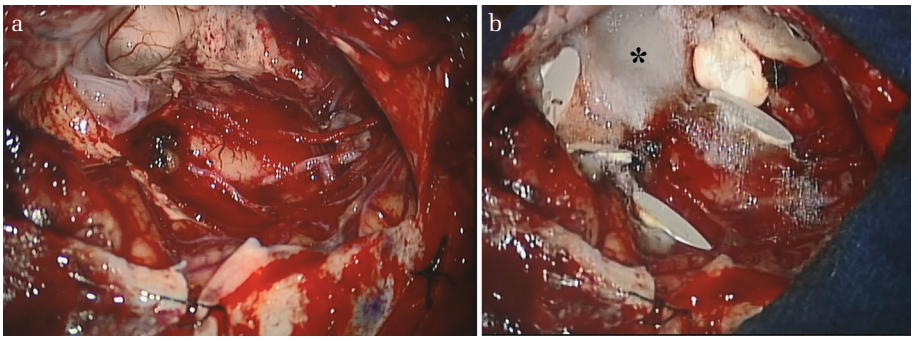

Fig. 2 Operative findings of the tumor resection. Operative findings showing the tumor resected cavity before (a) and after (b) occlusion of the ventricle and implantation of 6 wafers. The upper right side indicates the frontal cranial base and the upper left indicates the medial side. The *asterisk* showing the lateral ventricle reconstructed by the gelatin sponge.

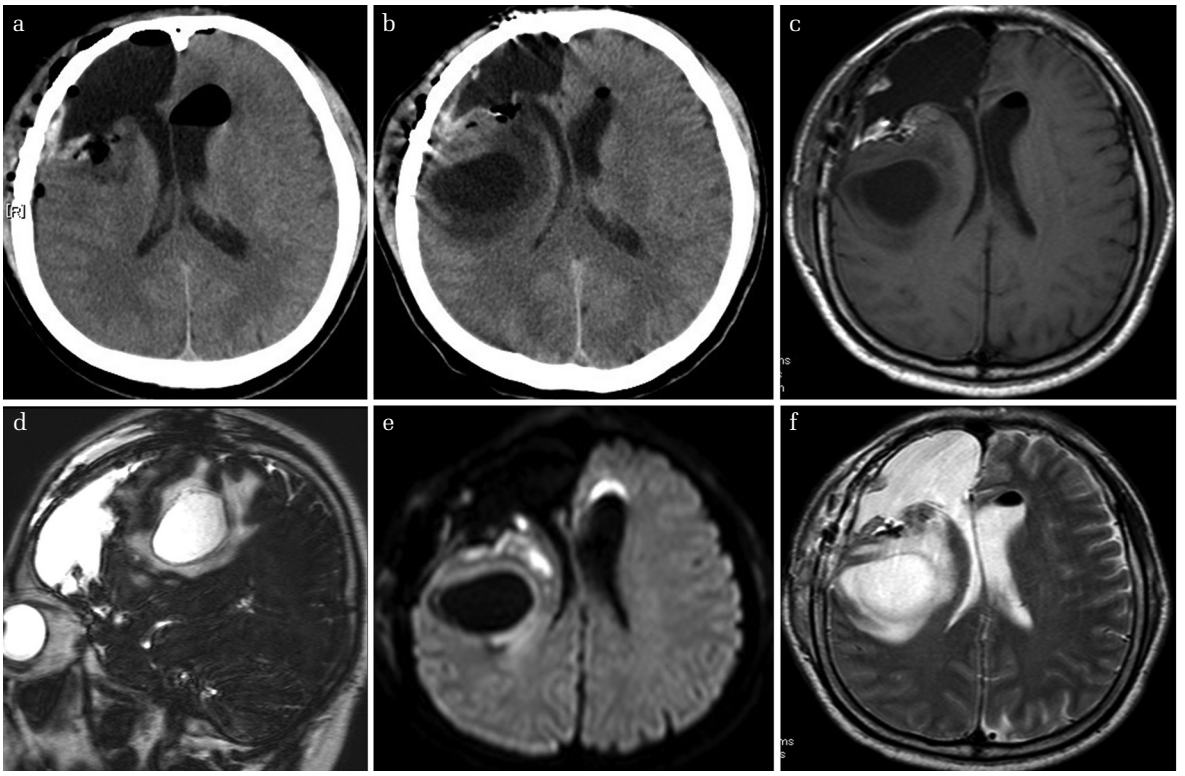

Fig. 3 Consecutive postoperative neuroimaging. Computed tomography (CT) scan on 4th day after the surgery shows no cyst formation (a). CT and MRI on the 7th day after the surgery reveals remote cyst formation (b–f). The cyst is apart from the resection cavity on sagittal T_2-weighted MRI (d). No abscess evidence on diffusion-weighted images (e). Signal intensity of liquid content of the cyst is almost the same as the cerebrospinal fluid (CSF) on T_2-weighted MRI (f).

was visible on the brain surface immediately after reopening the sutured dura mater (Figs. 5a and 5b) and was located away from the initial surgical cavity with a distance of one to two gyri between them. We punctured the cavity with the dissector and transparent fluid resembling CSF effused with moderate pressure (Figs. 5b and 5d). We removed the anterior wall of the cyst and connected the cyst directly to the tumor-resected cavity. We also removed the BCNU wafers and opened the lateral ventricle previously occluded by the hemostatic gelatin sponge (Fig. 5e). After fenestration, consciousness level and left hemiparesis gradually improved while subsequent CT revealed a decrease in cystic portion (Figs. 5c and 5f). Pathological analysis of the cyst wall revealed no inflammatory or tumor cells (Figs. 6a and 6b) but there was an inflammatory reaction at the attachment site of the BCNU wafers (Fig. 7a). These inflammatory cell infiltrations were predominant within and around small vessels which were a short distance from the BCNU wafers (Figs. 7a and 7b). After 3 months of rehabilitation, the patient returned to work with a KPS of 90 as before the operation. The final pathological diagnosis was recurrent HGG compatible with anaplastic oligodendroglioma (*NOS* in the 2016 WHO classification of CNS tumors)

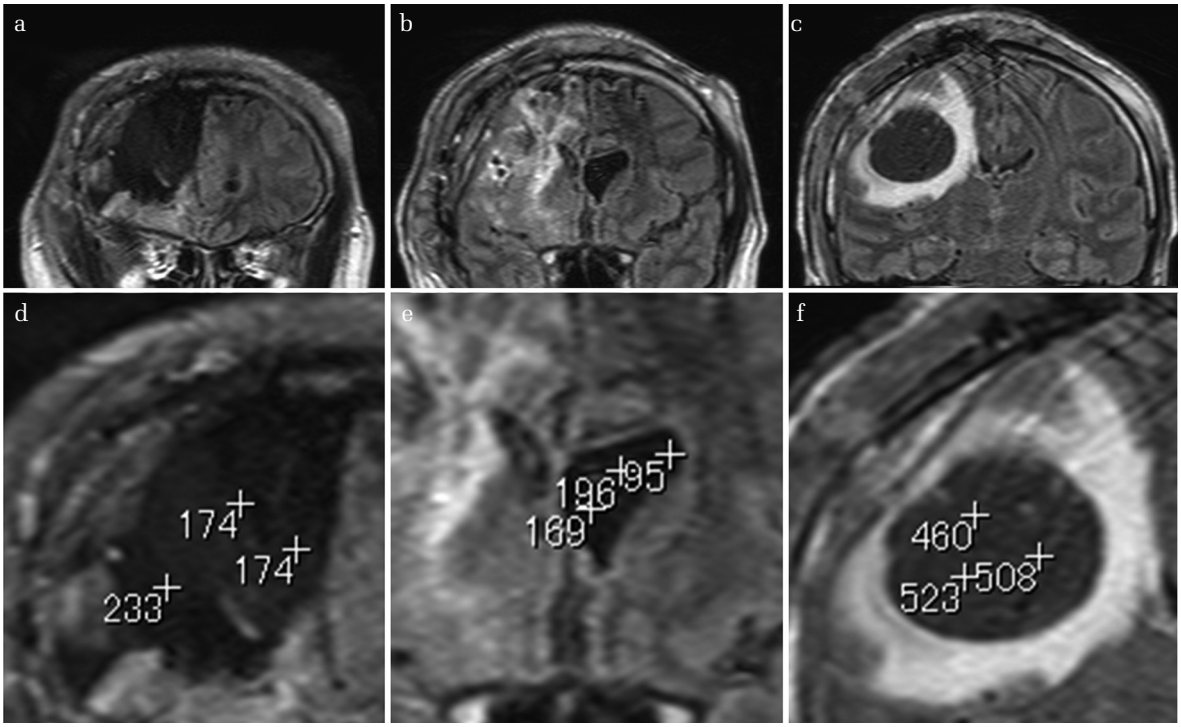

Fig. 4 Intensity difference of tumor resected cavity, lateral ventricle, and cyst on fluid-attenuated inversion recovery (FLAIR) images. FLAIR images taken under the same imaging parameters show the different intensities in the tumor resected cavity (a), a contralateral lateral ventricle as a control value of CSF (b), and the cyst (c). Each column (a–c) shows same coronal FLAIR image (upper, original images; lower, magnified images with intensity values of randomly selected three points).

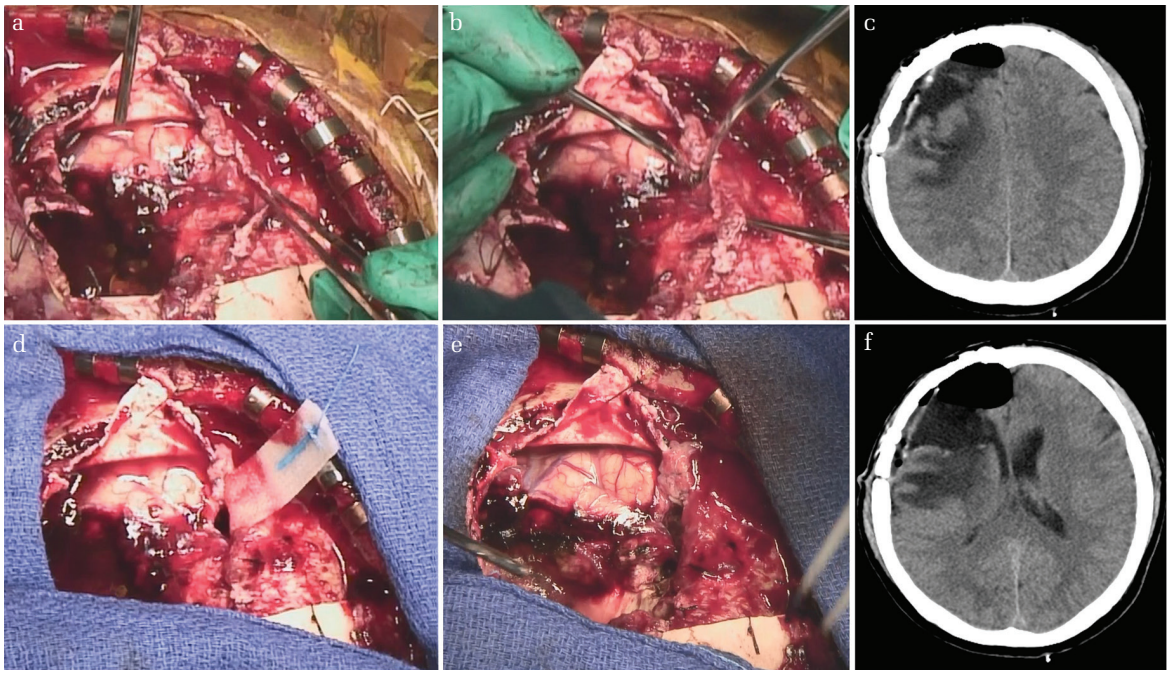

Fig. 5 Operative findings of the cyst fenestration. Operative findings showing the cyst before opening (a and b) and after opening (d). The cyst was easily punctured (b and d). The posterior wall of the tumor resected cavity and the anterior wall of the cyst are partially removed, and the cyst and the tumor resected cavity are connected to each other (e). The left side of the images corresponds to the frontal cranial base, and the lower side of the images corresponds to the medial side of the head. CT scans the day after cyst fenestration show the disappearance of the cyst (c and f).

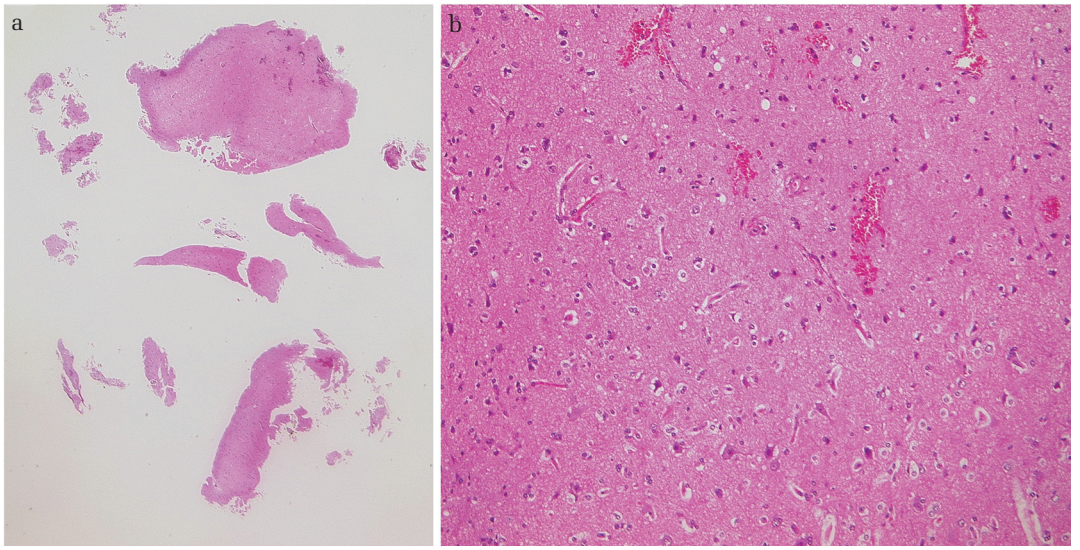

Fig. 6 Pathological examination of the cyst wall. No inflammatory cell infiltration or tumor cells on the anterior wall of the cyst (a and b).

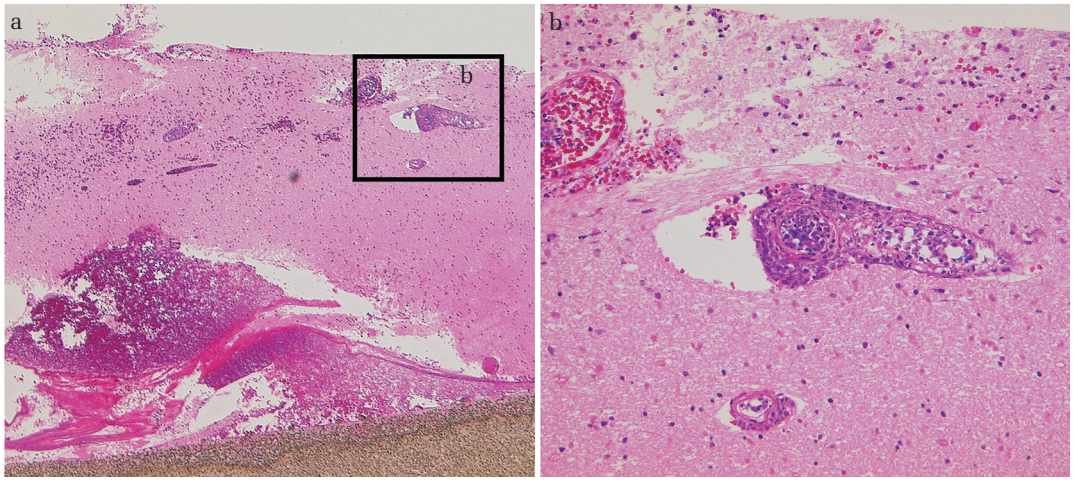

Fig. 7 Pathological examination of the resected cavity wall attached to BCNU wafers. Inflammatory cell infiltration in small vessels apart from the attachment surface. The inflammatory reaction is weaker on the surface than in the distant vessels (a). Enlarged image shows inflammatory cells in a small vessel (b).

and the patient received adjuvant temozolomide. There is no evidence of recurrence at over 26 months after the first operation for recurrent HGG.

Discussion

In the present case, the symptomatic remote cyst formation occurred after BCNU wafer implantation. BCNU wafers have been widely used for glioma adjuvant therapy after being approved by the United States Food and Drug Administration in 1997.[6] Although considered efficacious as an antineoplastic, BCNU adverse events such as wound complications, CSF leakage, local edema, seizures, and hydrocephalus have been reported.[3,7–9] Tumor bed cysts have also been reported previously as a space-occupying cyst in the resection cavity.[4,5,10] However, to the best of our knowledge, this is the first case of a symptomatic remote cyst associated with BCNU wafers.

Although it was not obvious on CT scans up to 4 days post-surgery, we eventually detected the remote cyst on the 7th day. Judging from such radiological findings, the formation of the cyst seems to have occurred after the 4th day. Based on the cystic fluid examination and pathological findings of the cyst wall, abscess or hemorrhage were not observed and could not be related to or cause cyst formation. Similarly, the tumor recurrence could not be directly related to cyst formation as the cyst was characterized by acute formation and no tumor cells in the cyst wall. Therefore, the detailed pathophysiology of this remote cystic formation remains obscure. In our case, the lateral ventricle was opened and reconstructed with a hemostatic gelatin sponge. A previous report about a tumor bed cyst identified a statistically negative correlation between tumor bed cyst enlargement and ventricular opening, since the reactive fluid draining into the CSF limits the enlargement of the tumor bed cyst in case of

a ventricular opening.[4] This idea was reinforced by another report where fluid concentrations were calculated from the Ommaya reservoir inserted into the resected tumor cavity. The average drug concentration in ventricular opening cases was 2.05 μmol/l versus 4.49 μmol/l in non-opened cases.[11] From this previous data, we speculate that the check-valve phenomenon and/or osmotic gradient effect could be the pathophysiological mechanism leading to cyst formation. Retrospective analysis of MRI on the 1st day after surgery revealed a small cerebral ischemic area near the resected cavity (Fig. 1f, white arrow). As the remote cyst was formed at the same location (the ischemic area), we can hypothesize that the small ischemic lesion was also associated with the large remote cyst. As BCNU wafers cause some inflammatory change in attached tissues and the arachnoid membrane damage occurred during opening the adherent dura matter, there was a possibility of generating a check-valve mechanism through the healing process within a few days after surgery. The ischemic, necrotic lesion could then become a semi-isolated area due to the check-valve mechanism of the damaged arachnoid cyst. The BCNU concentration both in the resected cavity and lesion was elevated just after the surgery. As the resected cavity had a connection with the lateral ventricle and the ischemic lesion became semi-isolated, the drug concentration in the ischemic lesion could become relatively higher than in the resected cavity. Thus, the osmotic gradient effect was generated, and the ischemic lesion could pull CSF and create a cavity which was further enlarged from this hydrostatic pressure. The intensity difference between the tumor resected cavity and the cyst on FLAIR imaging would support our hypothesis. We are not aware of previous reports on such a cystic formation related to ischemic lesions. However, coagulative necrosis occurs from 3 to 37 days as a natural course of a cerebral infarction[12] and such coagulative necrosis can be seen histopathologically and macroscopically at autopsy. Thus, this necrotic process could have damaged the blood-brain barrier and locally compromised fluid regulation, leading to the formation of a cyst. As BCNU wafers are a very unique type of local chemotherapy and we have never seen formation of subacute cysts after neurosurgery without them, this points to an association between BCNU wafers and remote cyst formation. Although further reports are needed to determine the incidence of such remote cysts, their formation after BCNU wafer implantation should be kept in mind, especially if imaging shows any ischemic areas near the resection cavity.

In conclusion, we experienced a symptomatic remote cyst formation after BCNU wafer implantation for recurrent HGG. The cyst was formed within several days in the postoperative period. We hypothesized that a check-valve or osmotic gradient effect related to different BCNU concentrations was one of the mechanisms of the cyst formation. This indicates that any imaging anomalies, especially those indicative of ischemia, should be monitored after wafer implants, even up to a week after an uneventful surgery.

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Conflicts of Interest Disclosure

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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