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Chronic Phase Intracranial Hemorrhage Caused by Ruptured Pseudoaneurysm Induced by Carmustine Wafer Implantation for Insulo-opercular Anaplastic Astrocytoma: A Case Report

Kimitoshi SATO,[1] Mitsuru DAN,[1] Daisuke YAMAMOTO,[1] Yoshiteru MIYAJIMA,[1] Atsuko HARA,[2] and Toshihiro KUMABE[1]

Departments of [1]Neurosurgery and [2]Pathology, Kitasato University School of Medicine, Sagamihara, Kanagawa

Abstract

Carmustine wafers improve the survival of patients with high-grade gliomas, but several adverse events have been reported. A 42-year-old man with left insulo-opercular anaplastic astrocytoma developed a massive intra-cavital hematoma with subarachnoid hemorrhage caused by ruptured pseudoaneurysm of the left middle cerebral artery (MCA) adjacent to the site of carmustine wafers implanted 6 months previously. Intraoperative finding demonstrated a dissection of the insular portion of the MCA, and pathological examination identified the resected pseudoaneurysm. This case demonstrates that carmustine wafers can cause changes in local vessels. Therefore, implantation of carmustine wafers near to important vessels passing close to the resection cavity should be considered with great caution.

Key words: biodegradable 1,3-bis(2-chloroethyl)-1-nitrosourea wafers, carmustine wafers, Gliadel®, pseudoaneurysm, intracranial hemorrhage

Introduction

Local chemotherapy with carmustine-impregnated wafers (Gliadel®, Eisai Inc., Woodcliff Lake, New Jersey, USA), which are designed to release biodegradable 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), has the advantages of bypassing the blood-brain barrier, delivering BCNU directly to peritumoral tissue, and avoiding systemic toxicity. Carmustine wafers are placed along the wall of the cavity after removal of the tumor, and carmustine is released continuously, diffusing into the parenchyma, over approximately 3–8 weeks with peak release in the first 2 weeks.[1–6] This delivery system results in high local concentrations of carmustine in the surrounding brain tissue which suppress tumor recurrence.[4] Many adverse events have been associated with the implantation of carmustine wafers.[2,6–16] Recent reviews of the use of carmustine wafers have reported that the rate of adverse events was up to 42.7–52%.[9,17] However, only one case of vasospasm was reported as an adverse event related to the adjacent vessels.[18]

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Here, we present a first case of primary anaplastic astrocytoma that showed a massive intra-cavital hematoma with subarachnoid hemorrhage caused by histologically-proved pseudoaneurysm induced by the implantation of carmustine wafers.

Case Report

I. History of present illness and examination

A 42-year-old man presented with seizure and was admitted to our hospital. Magnetic resonance (MR) imaging revealed a slightly enhanced tumor with perifocal edema in the left temporal lobe and insula (Fig. 1A). He underwent surgery for tumor removal via a left frontotemporal approach. After gross total resection of the tumor, eight carmustine wafers were placed on the surface of the tumor cavity adjacent to the left M2 portion of the middle cerebral artery (MCA) with interposition of absorbable hemostat (Surgicel®, Ethicon Inc., Somerville, New Jersey, USA) (Fig. 2A, B).

Intraoperatively, no injury to the main trunks, including the M2 portion of the MCA, was observed. Postoperative MR imaging revealed the presence of carmustine wafers on the surface of the resection cavity (Fig. 1B). The pathological

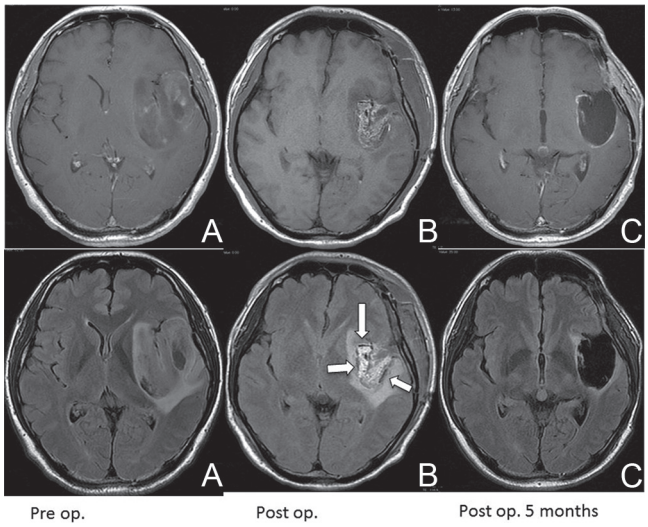

Fig. 1 Axial gadolinium-enhanced T_1-weighted (upper row) and fluid-attenuated inversion recovery (lower row) magnetic resonance (MR) images. A: Preoperative MR images showing a mild enhanced tumor with perifocal edema in the left temporal lobe and insula. B: Postoperative MR images depicting the implanted carmustine wafers (*arrows*) on the surface of the resection cavity. C: MR images obtained 5 months after the operation demonstrating no tumor recurrence. The edema surrounding the cavity had improved. The presence of carmustine wafers was not confirmed.

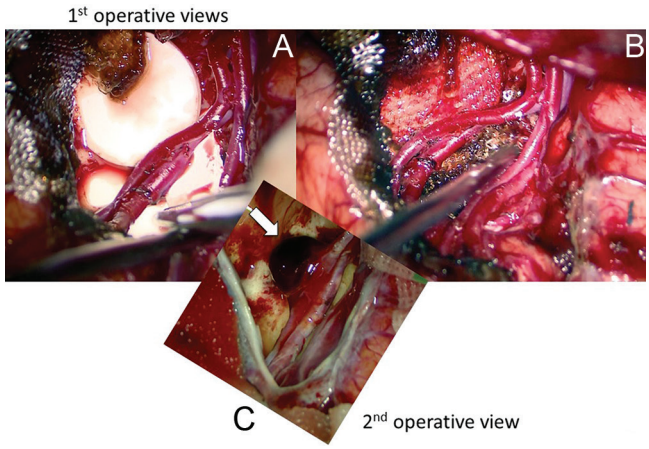

Fig. 2 A, B: First intraoperative views after gross total removal of the tumor showing eight carmustine wafers implanted on the surface of tumor cavity adjacent to the left middle cerebral artery (M2 portion). The carmustine wafers were covered with absorbable hemostat (Surgicel®, Ethicon Inc., Somerville, New Jersey, USA). C: Second intraoperative view after evacuation of hematoma in the resection cavity, corresponding to A, B, showing an aneurysm with a clot (*arrow*) at the M2 portion, running along the surface of the cavity.

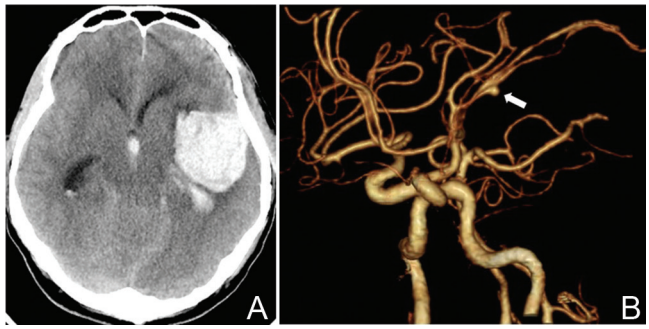

Fig. 3 A: Computed tomography (CT) scan obtained 6 months after the initial operation revealing hemorrhage in the tumor cavity and subarachnoid hemorrhage. B: CT angiogram showing an aneurysm (*arrow*) at the M2 portion of the left middle cerebral artery.

diagnosis was anaplastic astrocytoma. After the operation, the patient underwent 60 Gy of extended local radiation therapy combined with intravenous administration of nimustine hydrochloride (ACNU). He was discharged home without neurological deficits after these initial treatments, and was treated with ACNU bimonthly in the outpatient clinic. MR imaging performed 5 months after the operation revealed no tumor recurrence. The edema surrounding the cavity had improved. The presence of carmustine wafers was not confirmed (Fig. 1C). Six months after the initial operation, the patient suffered sudden onset of severe consciousness disturbance and was transferred to our hospital. Computed tomography (CT) revealed massive hemorrhage in the tumor cavity with subarachnoid hemorrhage (Fig. 3A). CT angiography revealed an aneurysm at the M2 portion of the left MCA (Fig. 3B).

II. Second operation for the hemorrhage

The bone graft was removed and a dural incision was made. The hematoma in the tumor cavity was removed. Carmustine wafers had already been absorbed so was not observed. An aneurysm with a clot was observed at the M2 portion running along the surface of the cavity (Fig. 2C). The M2 portion together with the aneurysm was trapped and excised, and the specimen was submitted for pathological examination. Intraoperative inspection identified a dissection in the intima of the M2 portion near the aneurysm (Fig. 4A). Histopathological examination of the excised tissue revealed ruptured pseudoaneurysm wall covered with clot (Fig. 4B).

Discussion

Carmustine releases into the parenchyma peaks in the first 2 weeks.[4–6,13] Animal studies have demonstrated that some edema could be seen radiographically by day 14 but resolved by day 72. Autopsy revealed that subacute cellular inflammatory response to carmustine wafer was seen on postoperative day 16 and changed to chronic inflammatory response by day 72.[19]

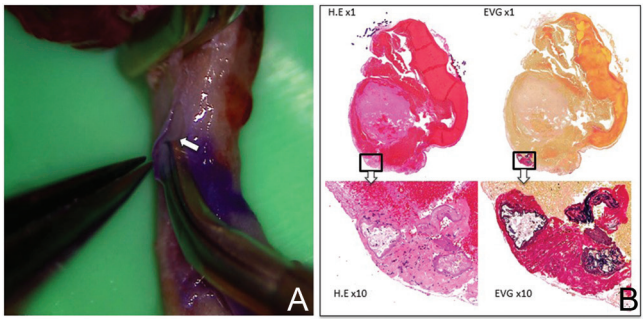

Fig. 4 A: Second intraoperative inspection found a dissection (*arrow*) in the intima of the M2 portion near the aneurysm. B: Histopathological examination of the excised tissue revealed ruptured pseudoaneurysm wall covered with clot. Hematoxylin and eosin (H.E) and Elastica van Gieson (EVG), original magnification ×1 or ×10.

Many clinical adverse events have been reported, including healing abnormalities (0–21.7%), cerebrospinal fluid leakage (0–33.3%), intracranial infection (0–22.2%), hydrocephalus (7–22.2%), deep-vein thrombosis (2.2–22%), seizure (0–50%), intracranial hypertension (9.2%), brain edema (0–25%), pulmonary embolus (0–20%), and cyst formation (11–48%).[1,2,6–16] Pseudoaneurysm formation and its rupture in the chronic phase after implantation of carmustine wafers has not been reported.

Patients with eight carmustine wafers implanted had a 3-fold increased risk of adverse events and a 5.6-fold increased risk of implantation site-related adverse events.[20] In our case, eight carmustine wafers were placed on the surface of tumor cavity, and some of them were adjacent to the M2 portion with interposition of absorbable hemostat. No evidence-based recommendations are available to guide implantation decisions;[4] however, direct wafer contact with large cerebral vessels should be avoided because of a few cases with perioperative significant bleeding events.[4] The reason was suspected to be rupture, dissection, or thromboembolic occlusion of the vessels caused by carmustine wafers.

Theoretically, drug distribution within the brain has four basic mechanisms: (1) diffusion, (2) bulk or convective flow, (3) intravascular invasion and extravasation, and (4) cerebrospinal fluid invasion and extravasation.[3] The mechanism of pseudoaneurysm formation induced by carmustine wafers remains unclear. In addition, previous reports have described the pathophysiological mechanisms of aneurysm formation in patients with brain tumors, including those related to shunting of intratumoral high blood flow, direct invasion of the vessel wall by tumor cells, radiation-induced vasculopathy, and iatrogenic traumatic aneurysm caused by surgical manipulation. However, these potential causes remain speculative and further study is required.[21] In the previous animal study with carmustine wafers implantation, dense fibrosis with hemosiderin-laden macrophages, thick-walled vessels, and recent hemorrhage were observed within 4 mm of the implantation site at 196 days after implantation.[19] Reactions including edema, perivascular lymphocytes, and gliosis, were observed within 8 mm of the implantation site. Meanwhile, no abnormality was observed at 1 cm outside the implantation site.[19] The distance between carmustine wafers and vital organ must be critical. Based on these findings, we considered that the hemorrhage in the present case was caused by disruption of the vessel wall due to carmustine wafers-induced inflammation of the adjacent artery. Therefore, carmustine wafers implantation should be avoided at sites adjacent to the main trunk vessels.

Conflicts of Interest Disclosure

The authors received no financial support for this study. They have no personal, financial, or institutional interests in any of the materials or methods described in this article.

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Address reprint requests to: Toshihiro Kumabe, MD, PhD, Department of Neurosurgery, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara, Kanagawa 252-0374, Japan.
e-mail: kuma@kitasato-u.ac.jp