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Symptomatic cerebral vasospasm after glioblastoma resection and carmustine wafers implantation. A case report☆,☆☆

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ABSTRACT

Local chemotherapy with carmustine-impregnated wafers showed safe and effective in the treatment of malignant glioma, with infrequent, though sometime serious, adverse effects.

We report a rare case of cerebral vasospasm following glioblastoma removal with carmustine wafers implantation in a 57-years-old man. After surgery, the patient awoke with aphasia, due to vasospasm of the left middle cerebral artery. Intra-arterial infusion of nimodipine was performed, with rapid vasospasm resolution and quick recovery.

Cerebral vasospasm is an extremely rare adverse effect after carmustine wafers implantation in glioma surgery, with only one case reported. In our case, intra-arterial nimodipine was rapidly effective. Although rare, such a potentially disastrous complication should be considered when a new neurological deficit unexpectedly occurs after carmustine wafers implantation, and vascular investigation should be undertaken.

1. Introduction

For the last ten years, local chemotherapy with carmustine-impregnated wafers (Gliadel®, Eisai Inc., Woodcliff Lake, NJ, USA) in the treatment of malignant glioma has demonstrated an improvement of median overall survival with acceptable safety profile [1–3].

Carmustine wafer, which is designed to release biodegradable 1,3-bis-2-chloroethyl-1-nitrosurea (BCNU), has the advantages of bypassing the blood-brain barrier, delivering BCNU directly to peritumoral tissue, and avoiding systemic toxicity [4,5]. Carmustine wafers are placed along the wall of the surgical site, and the chemotherapeutic agent is released continuously, diffusing into the parenchyma over approximately 3–8 weeks, with peak release in the first 2 weeks [5]. However, several adverse events have been associated with Gliadel® implantation, the most common of which include seizures, brain edema, and intracranial hypertension [3]. Other uncommon adverse events are reported in the literature, including wound healing defects, intracranial infections, cerebral hemorrhage, cerebrospinal fluid leakage, hydrocephalus, and cyst formation [1,2,4,6]. According to the current literature, only one case of carmustine wafer-related vasospasm with cerebral infarction has been described [7].

We report a case of symptomatic vasospasm after implantation of carmustine wafers in a patient treated for left frontotemporal glioblastoma (GBM).

2. Case report

A 57-year-old man was admitted to ER for sudden onset of confusion, amnesia and insomnia. Magnetic resonance imaging (MRI) revealed a mass located in the left temporal lobe and insula with perilesional edema, showing inhomogeneous ring enhancement (Fig. 1).

The patient was referred to our department and underwent surgery for tumor resection via left frontotemporal craniotomy. The resection was extended to the deep area of the frontal lobe and the insula, which appeared infiltrated. Sylvian arteries were preserved, except some small branches supplying the tumor. We obtained CT-confirmed subtotal resection (> 95%) of the tumor (Fig. 2a). Eight carmustine wafers were placed on the wall of the resection cavity and secured with Tabotamp strips.

Histopathological examination revealed typical findings of WHO grade IV glioma. On postoperative day one, once sedation was interrupted and patient awoke, he showed moderate aphasia, with no other neurological deficit. CT and CT-angiography (CTA) were performed and revealed persistence of brain edema around the surgical cave, without

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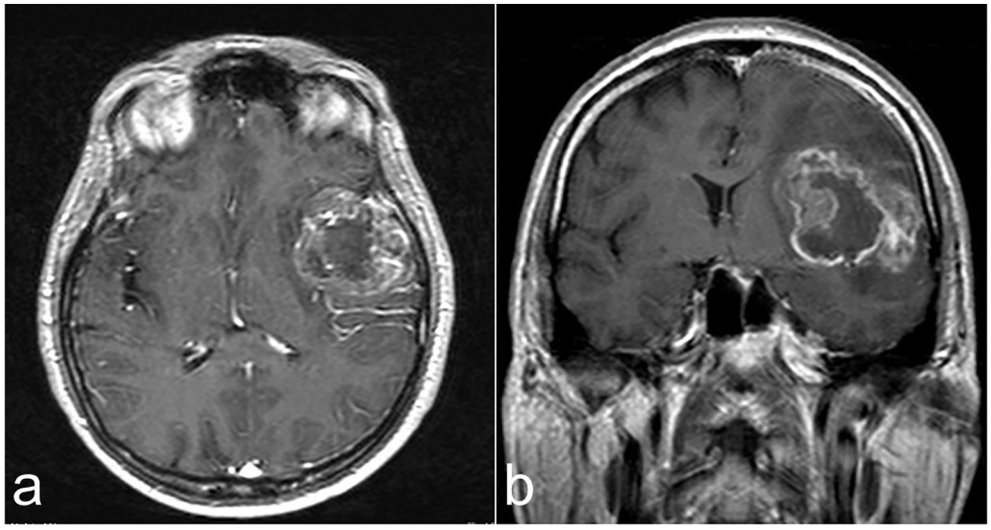

Fig. 1. Preoperative contrast-enhanced MRI. Axial (a) and coronal (b) images, compatible with high grade glioma.

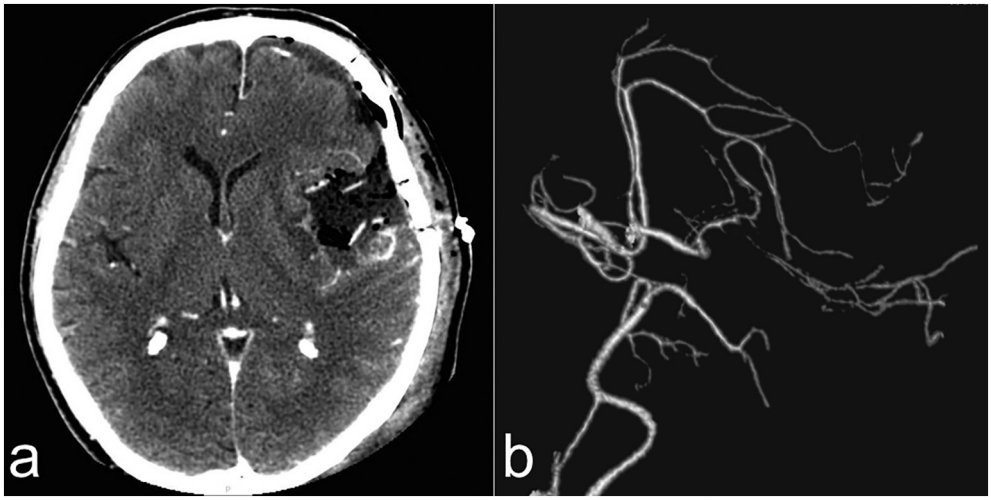

Fig. 2. Postoperative CT. a) Contrast-enhanced image showing normal postoperative findings, with carmustine wafers lying on the wall of surgical cavity, and small enhancing remains in the posterior lateral border; b) CT-angiography revealed vasospasm of the left middle cerebral artery (M2-M3 branches).

postoperative bleeding (Fig. 2a). However, vasospasm was shown at the M2 segments of the left middle cerebral artery and M3 insular branches (Fig. 2b), which was confirmed by digital subtraction angiography (DSA) (Fig. 3a). In the same session, 5 mg nimodipine were infused in 30 min in the left internal carotid artery through a 5F catheter [8], with increased size of M2 and better visualization of insular branches (Fig. 3b). Oral nimodipine (60 mg 6 times daily) was continued for 7 days and then tapered off. Aphasia resolved in two days. Transcranial Doppler monitoring showed vasospasm disappearance after 72 h. The patient was discharged on the 18th postoperative day and underwent radiotherapy and temozolomide chemotherapy. At last follow-up, 15 months after operation, he is free of symptoms and tumor recurrence on MRI (Fig. 4).

3. Discussion

Implantation of carmustine-impregnated wafers (Gliadel®) has demonstrated a survival benefit in patients with malignant glioma [1–3]. However, a number of adverse reactions have been commonly reported [1–4,6], while vasospasm was described in only one case report before [7].

The present case is, at our knowledge, the second reported case of symptomatic cerebral vasospasm associated with carmustine wafers implantation, confirming vasospasm as a possible rare side effect. The mechanism of vasospasm induced by Gliadel® remains unclear, although the vasoactive effect of carmustine has been already described in different situations. Shingleton et al. [9] reported that high-dose intravenous carmustine (800 mg/m^2) has been associated with retinal artery narrowing and obstruction. With carmustine wafers the local concentration at the implantation site is 1200 times higher than concentration achieved by systemic administration [5]. Possibly, local toxicity of carmustine or foreign body reaction to the wafer material may trigger local inflammatory response leading to vasospasm [7]. More specifically, in a rabbit lung model, BCNU inhibited glutathione reductase activity, resulting in increase of induced vasospasm, due to hydrogen-peroxide-induced prostanoid formation and calcium shift [10].

Vasospasm and cerebral infarction are rare complications of brain tumor surgery in general. In a large series of 470 skull base tumors, the incidence of vasospasm was 1.9% only [11]. In a systematic review of cerebral vasospasm following tumor resection, < 50 cases were found, and most of them were benign lesions [12], while only one case related to GBM is reported [13]. These data reinforce the hypothesis that, in our case, local carmustine may have played a causative role. In fact,