ALA-Porphyrin Science

A pitfall of fluorescence-guided surgery with 5-aminolevluinic acid for the treatment of malignant brain tumor –case report–

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Summary.

This report presents the case of a 65-year-old man with complex partial seizures caused by a glioblastoma in the right temporal lobe. Magnetic resonance imaging showed a heterogeneously enhanced mass in the right temporal lobe; however, there was no invasion into the inferior horn of the right ventricle. The patient underwent fluorescence-guided resection with 5-aminolevulinic acid (ALA). During the operation, both the residual tumor and the right surface of the hippocampus were strongly fluorescent under the violet-blue excitation light. However, histological examination showed no tumor invasion into the hippocampus and disruption of the ependymal layer of the ventricular wall. We present this case to emphasize the possibility of false-positive 5-ALA–induced fluorescence near the ventricle in malignant gliomas.

Keyword:
Choroid plexus, ventricle, cerebrospinal fluid, false positive

Introduction

The treatment of malignant brain tumors is challenging. Malignant gliomas such as glioblastoma are highly aggressive brain tumors that diffusely invade the surrounding normal brain tissues. Despite the recent encouraging advances of technology in neurosurgery, the mean survival time of patients with glioblastoma remains to be ~12 months [1, 2]. 5-Aminolevulinic acid (ALA) is a natural biochemical precursor of heme that induces synthesis and accumulation of fluorescent porphyrins such as protoporphyrin IX (PpIX) in various cancerous tissues [3]. It also results in PpIX accumulation within malignant glioma tissues. Porphyrin fluorescence can be visualized using a modified neurosurgical microscope and has been identified in residual malignant gliomas during surgery [4]. This method was established as a fluorescence-guided procedure in neurosurgery and has led to improved prognosis in patients with malignant glioma [5].

We treated a patient with glioblastoma by fluorescence-guided surgery with 5-ALA. During the surgery, we observed a marked fluorescence of the ventricular wall. However, no tumor was detected in this ventricular wall by either radiological or pathological examination. Here, we present a rare case and discuss the pitfall of fluorescence-guided surgery using 5-ALA for the treatment of malignant glioma.

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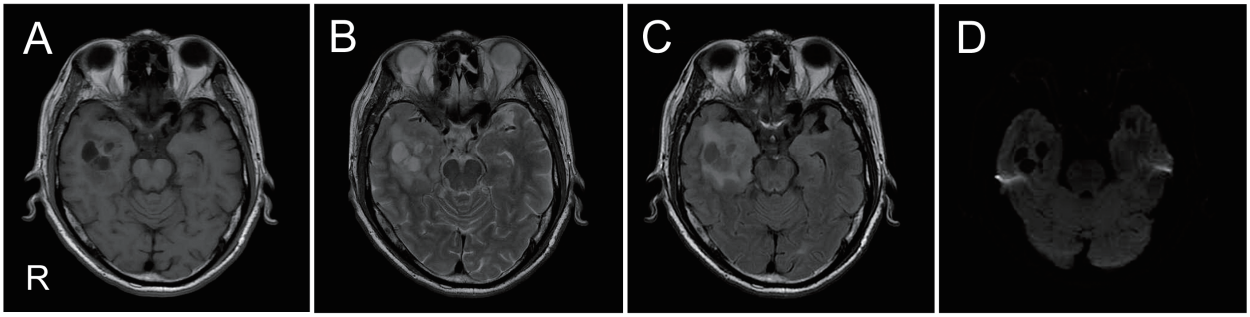

Figure 1: Magnetic resonance image obtained on admission. Axial T1-weighted image (T1WI) (a), a T2-weighted image (T2WI) (b), a fluid-attenuated inversion recovery (FLAIR) (c), and a diffusion-weighted image (DWI) (d). T1WI, T2WI, and FLAIR show a right temporal mass with heterogeneous signal intensity. Note the extensive peritumoral edema (a–c). DWI showing slightly high signal intensity in the tumor (d).

Case

A 65-year-old right-handed man experienced paroxysmal hallucination of odor and disturbed consciousness for 3 months before the diagnosis. The patient experienced a generalized seizure and was transferred to a local hospital. After receiving an anticonvulsant, he was referred to our hospital.

On admission, neurological examination showed no deficits. Electroencephalogram showed a slow wave in the right temporal lobe. Magnetic resonance imaging (MRI) showed a multi-cystic and heterogeneously enhanced mass with surrounding brain edema in the right temporal lobe (Figs. 1, 2). MRI showed that the inferior horn of the right lateral ventricle was compressed and dislocated upward, and that the tumor was located within the right temporal lobe and did not invade the right lateral ventricle (Fig. 2C). According to the results of clinical and radiological examination, we diagnosed a complex partial seizure caused by the high-grade glioma in the right temporal lobe. Thus, we planned to perform tumor resection and right selective hippocampectomy to treat the temporal epilepsy.

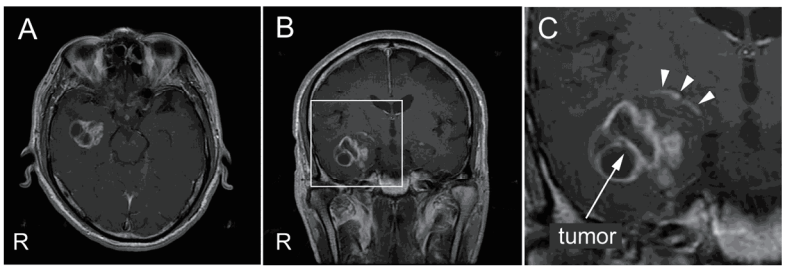

Figure 2: Contrast-enhanced T1WI taken on admission: (a) axial image, (b) coronal image, and (c) magnified view of b. The tumor is enhanced by the contrast reagent. Note that the tumor does not invade the inferior horn of the right ventricle. The arrowheads indicate the choroid plexus in the inferior horn of the right ventricle.

We confirmed the dominance of memory and speech in the left hemisphere using the Wada test. Thereafter, the patient underwent right frontotemporal craniotomy using a neuronavigation system. According to the previous studies on fluorescence-guided resection using 5-ALA [4, 5], 5-ALA (20 mg/kg) was administered orally to the patient 3 hours before the induction of general anesthesia. The surgery was performed using a modified neurosurgical microscope (OPMI/Pentero,

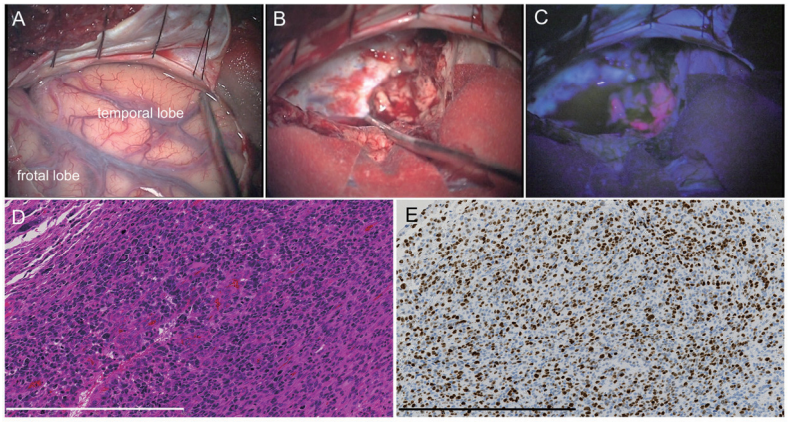

Figure 3: Intraoperative photograph of the tumor resection (a–c) and the pathological findings (c, d). After the right temporal lobe and the tumor were partially resected (a, b), the residual tumor was fluorescent under the violet-blue excitation light (c). The tumor showing high cellularity, nuclear atypia, endothelial proliferation (d), and high proliferative activity (e). Hematoxylin and eosin stain (d) and MIB-1 stain (e). Scale bar, 400 μm (d, e).

Carl Zeiss, Oberkochen, Germany), which enabled switching from conventional white xenon illumination to violet-blue excitation light. The right temporal lobe and the tumor were resected under conventional illumination; the microscope was then switched to violet-blue illumination to resect the residual tumor under fluorescence visualization (Figs. 3A-C). Next, the right hippocampus was exposed and resected at 2.5 cm from the tip. The hippocampal surface and the ventricular wall were strongly fluoresced under the violet-blue illumination (Figs. 4A, B).

After the operation, the patient received extended focal conventional radiotherapy (total, 60 Gy) and chemotherapy with temozolomide. The patient was then discharged without any other neurological deficit except for a slight defect in the left visual field (Fig. 5) and was administered temozolomide according to the Stupp protocol[6].

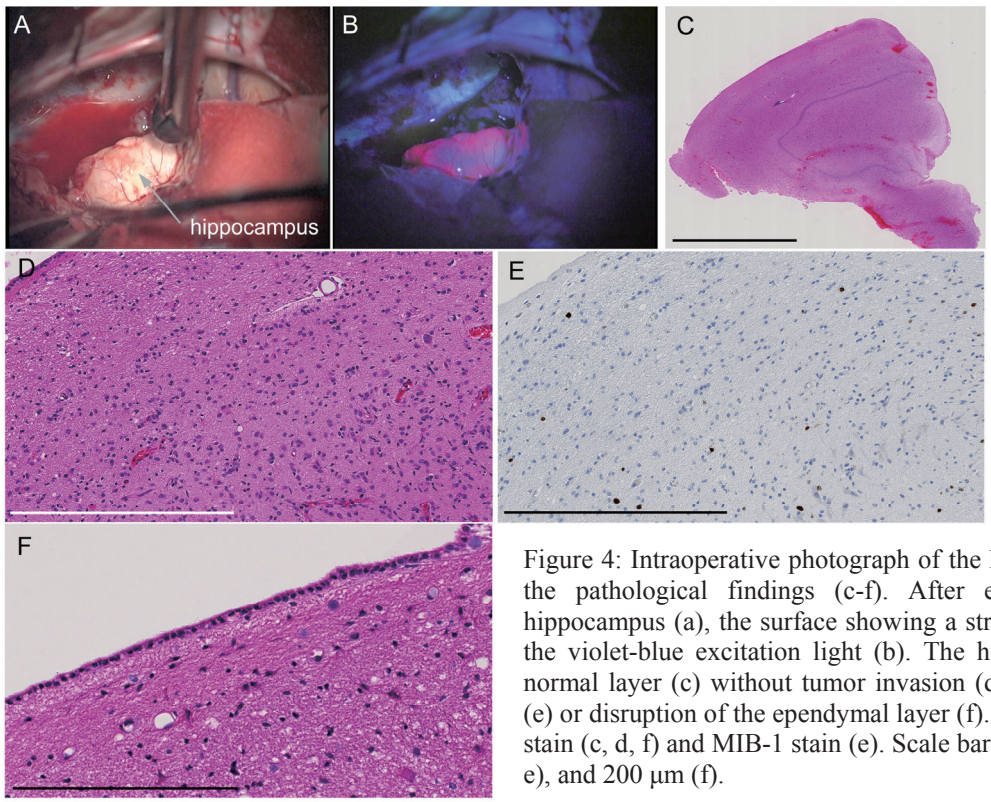

Figure 4: Intraoperative photograph of the hippocampus (a, b) and the pathological findings (c-f). After exposure of the right hippocampus (a), the surface showing a strong fluorescence under the violet-blue excitation light (b). The hippocampus showing a normal layer (c) without tumor invasion (d), high mitotic activity (e) or disruption of the ependymal layer (f). Hematoxylin and eosin stain (c, d, f) and MIB-1 stain (e). Scale bars: 4 mm (c), 400 μm (d, e), and 200 μm (f).

Histological examination of the tumor showed high cellular density, marked nuclear atypia, necrosis, high mitotic activity, and endothelial proliferation; thus, the tumor was diagnosed as a glioblastoma (Figs. 3D, E). On the contrary, the hippocampus presented as a normal layer without the presence of tumor cells under the ventricular surface or disruption of the ependymal cell layers of the ventricular wall (Figs. 4C-F). MRI at 7-month follow-up showed an enhanced lesion along the surface of the tumor resection cavity, suggesting tumor recurrence. However, there was no evidence of ventricular wall and hydrocephalus enhancement associated with cerebrospinal fluid (CSF) dissemination (Fig. 6).

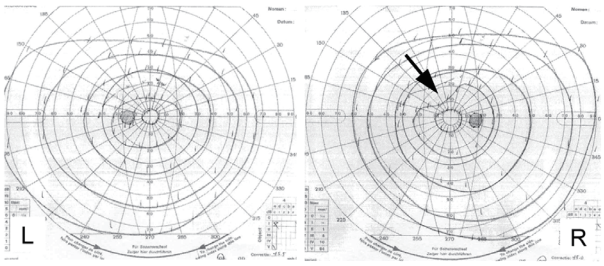

Figure 5. The Goldman visual field test showing a partial postoperative defect in the right eye (arrow).

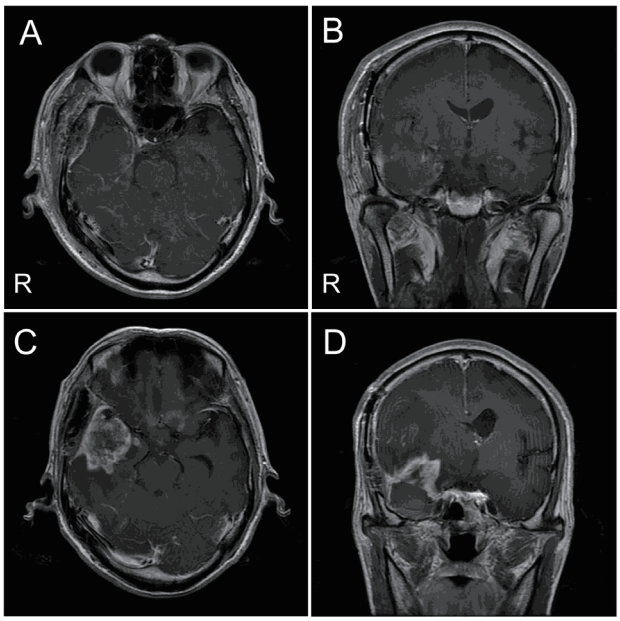

Figure 6: Postoperative (a, b) and follow-up (c, d) magnetic resonance imaging (MRI) on a contrast-enhanced T1WI. Postoperative MRI showing gross total removal of the tumor (a, b). Follow-up MRI obtained 7 months after the surgery showing rim enhancement of the tumor resection cavity, suggesting tumor recurrence (c, d). However, no ventricular wall enhancement or hydrocephalus suggestive of cerebrospinal fluid dissemination was noted.

Discussion

In this study, we presented the case of a patient with glioblastoma who showed strong 5-ALA–induced fluorescence of the ventricular wall. However, pathological examination did not showed any invasion of tumor cells or disruption of the ependymal layer of the ventricle. There was also no evidence of CSF dissemination on follow-up MRI after the operation.

5-ALA–induced accumulation of PpIX in the brain is depend on several factors including disruption of the blood–brain barrier (BBB), high cellular density, high MIB-1 labeling index as an indicator of proliferative activity, and neovascularity as an indicator of BBB abnormality [7]. Therefore, high-grade gliomas, which have the abovementioned characteristics, show a strong 5-ALA–induced PpIX accumulation. The surgical technique with 5-ALA–induced fluorescence for tumor resection can increase the gross total removal rate of high-grade gliomas and lead to improved prognosis [5].

However, some papers have reported false-positive cases of 5-ALA–induced fluorescence in central nervous system lesions, such as inflammatory cell infiltration, peritumoral edema

(reactive astrocyte), radiation necrosis, and demyelinating changes [8, 9]. In the present case, the ventricular wall showed strong 5-ALA–induced fluorescence despite no tumor invasion or disruption of the ependymal layer of the ventricular wall. Therefore, there is a possibility that 5-ALA–induced fluorescence near the ventricle may be false positive. Therefore, we should pay close attention while manipulating this region during glioma surgery.

A recent paper reported the implication of 5-ALA–induced fluorescence of the ventricular wall on postoperative communicating hydrocephalus associated with CSF dissemination in glioblastoma [10]. In the present case, there was no infiltration of tumor cells or disruption of the ventricular wall. Moreover, the pattern of tumor recurrence showed focal recurrence in the tumor resection cavity rather than CSF dissemination. Thus, the mechanism of 5-ALA–induced fluorescence remains unclear.

Some studies have reported that 5-ALA–induced fluorescence has been detected not only in the choroid plexus but also in the ventricular wall of the contralateral side of the lesion in a rat brain tumor model[11]. This group suspected that tumor-borne porphyrin leaked into the blood through a defective BBB and then spread into the CSF via subsequent transportation through the choroid plexus [11, 12]. There is no diffusion barrier between the CSF and the surrounding brain; thus, porphyrin is readily taken up into the surrounding ventricular wall [13]. Taken together, the evidence suggests that 5-ALA–induced fluorescence of the ventricular wall does not necessarily indicate tumor invasion in patients with glioblastoma.

Conclusion

Fluorescence-guided surgery with 5-ALA for malignant gliomas is very useful. However, we recommend that tumor invasion should be confirmed using intraoperative pathological examination in the area of 5-ALA–induced fluorescence near the ventricle in malignant glioma.

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