

5-Aminolevulinic Acid Fluorescence Discriminates the Histological Grade of Extraventricular Neurocytoma

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Extraventricular neurocytomas are rare brain tumors that have a diverse range of clinical characteristics. We describe two cases involving fluorescence-guided resection of extraventricular neurocytoma using 5-aminolevulinic acid (5-ALA) and evaluate the efficacy of the technique. We found that the tumor reactions to 5-ALA differed depending on the histologic grade. This finding shows that the 5-ALA fluorescence reaction may potentially be used as a biomarker of the clinical behavior of these tumors. To our knowledge, this is the first report in which fluorescence-guided resection was utilized for the resection of extraventricular neurocytomas.

Key Words Extraventricular neurocytoma; Fluorescence guided surgery; 5-aminolevulinic acid.

INTRODUCTION

Fluorescence guidance has been actively investigated as a tool that facilitates the gross total resection of brain tumors and has emerged as an additional preoperative technique, especially for surgeries involving high-grade gliomas [1-3]. Several reports that describe the application of fluorescence-guided resection of metastatic brain tumors, meningiomas [4], hemangioblastomas [5], pleomorphic xanthoastrocytomas, and ependymomas have been published, demonstrating the usefulness of the technique.

Extraventricular neurocytoma (EVN) is a rare type of brain tumor that displays a diverse range of clinical behaviors without established predictive markers. The limited number of EVNs and the heterogeneous radiological findings make the diagnosis of these tumors difficult prior to surgery, and glioma is the most common radiological tentative preoperative diagnosis. The degree of resection, however, is very important for patient prognosis in both classic and atypical EVNs [6,7].

We describe two cases of EVN that involved resections using 5-aminolevulinic acid (5-ALA) for fluorescence guidance. Interestingly, the fluorescent reaction of the tissue in one case differed from the reaction in the other case; however, the individual fluorescent reactions were consistent with the patho-

logic grading. To the best of our knowledge, this is the first report on the use of fluorescence-guided resection of EVN.

CASE REPORT

Case 1

A 33-year-old woman presented with a 6-month history of severe headaches. Magnetic resonance (MR) imaging revealed a lesion with diffuse high T2 signal intensity, focal areas of cystic changes, and increased perfusion in the left temporal lobe (Fig. 1A, B). Based on a presumed diagnosis of low-grade glioma with possible anaplastic foci, the patient underwent fluorescence-guided surgical resection. The patient was administered 20 mg/kg of 5-ALA 4 hours before the induction of general anesthesia. A Leica M720 OH5 microscope (Leica, Wetzlar, Germany) equipped with an FL400 Fluorescence Module was used for the investigation of 5-ALA fluorescence. Resection of the tumor was performed using intraoperative evoked potential monitoring, and all operative fields were assessed for fluorescence. There was no fluorescence at all in the operative field (Fig. 1C, D) and maximal safe resection was achieved. The pathological diagnosis was classic extraventricular neurocytoma (World Health Organization grade II). Hematoxylin-eosin staining showed that the tumor was

composed of uniform round cells with or without clear cytoplasm. Some scattered cells showed astrocytic differentiation (Fig. 1E), and the mitotic rate was low (2/10 high power field). Immunohistochemical staining was positive for glial fibrillary

acidic protein and synaptophysin, and the Ki-67 labeling index was 2.84% (Fig. 1F). The patient developed postoperative transient sensory aphasia, from which she fully recovered within one month. No adjuvant treatment was administered, and

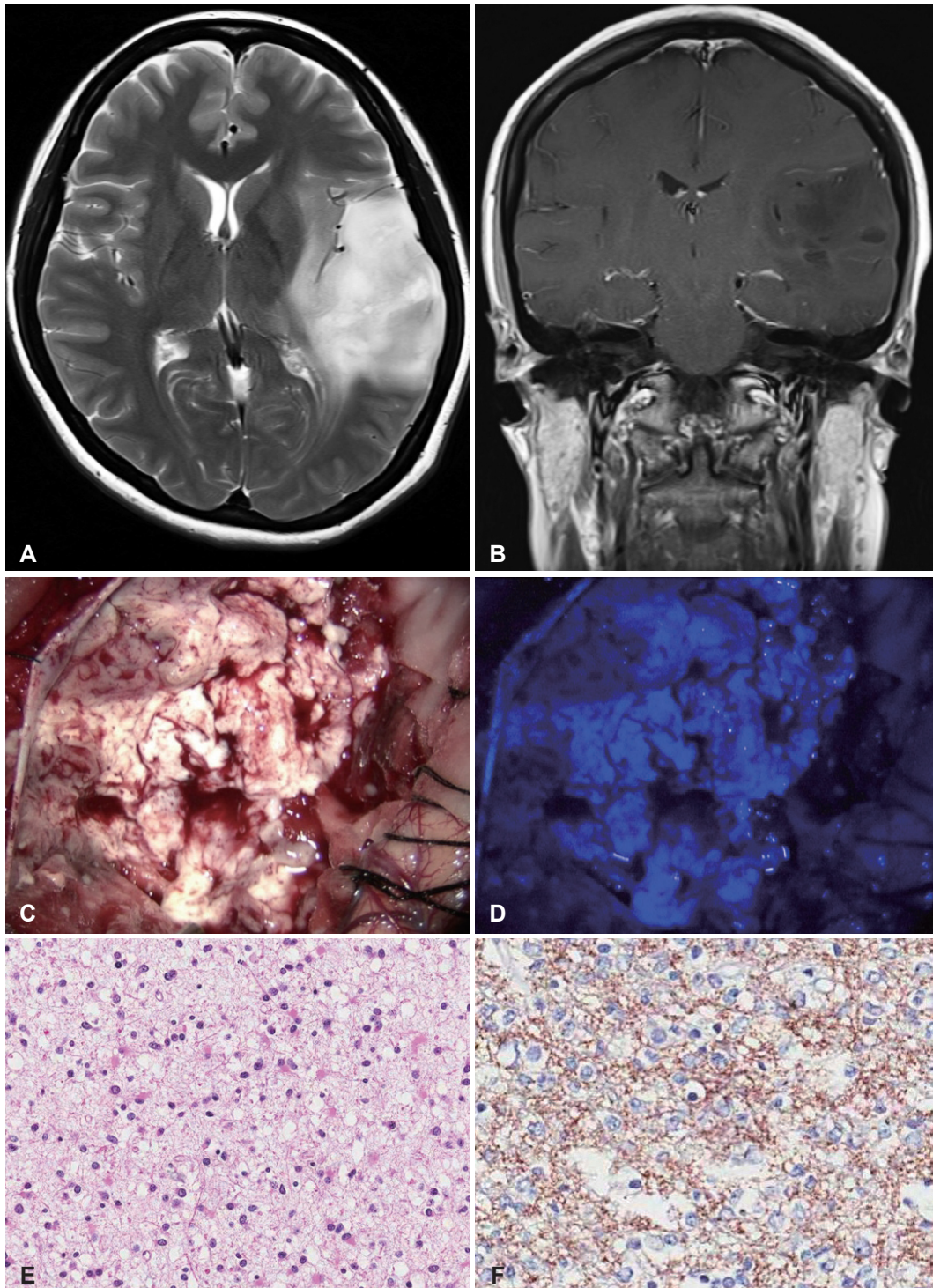


Fig. 1. A: A transaxial T2-weighted MR image showing a diffuse high signal mass in the left temporal lobe. B: The mass was not enhanced in the coronal T1-weighted MR image with contrast. C and D: No fluorescence reaction was observed in any tumor tissue during surgery. E: The tumor composed of uniform round cells with or without clear cytoplasm (hematoxylin-eosin staining). F: Immunohistochemical staining for synaptophysin showing diffuse, strong reactivity in the tumor cells. MR: magnetic resonance.

no evidence of recurrence was observed at the regular imaging follow-up at 24 months after surgery.

Case 2

A 16-year-old girl presented with an episode of convulsion without any neurological deficits. MR images showed an intraaxial mass with faint focal enhancement and high T2 signal

intensity in the right high frontal lobe (Fig. 2A, B). The patient underwent fluorescence-guided tumor resection after a presumed diagnosis of low-grade glioma with anaplastic foci. The same procedure as that described for the above Case 1 was performed. Fluorescence was observed in some areas of the tumor tissue (Fig. 2C, D), and frozen biopsies were obtained from multiple sites. Three tissues that showed strong red flu-

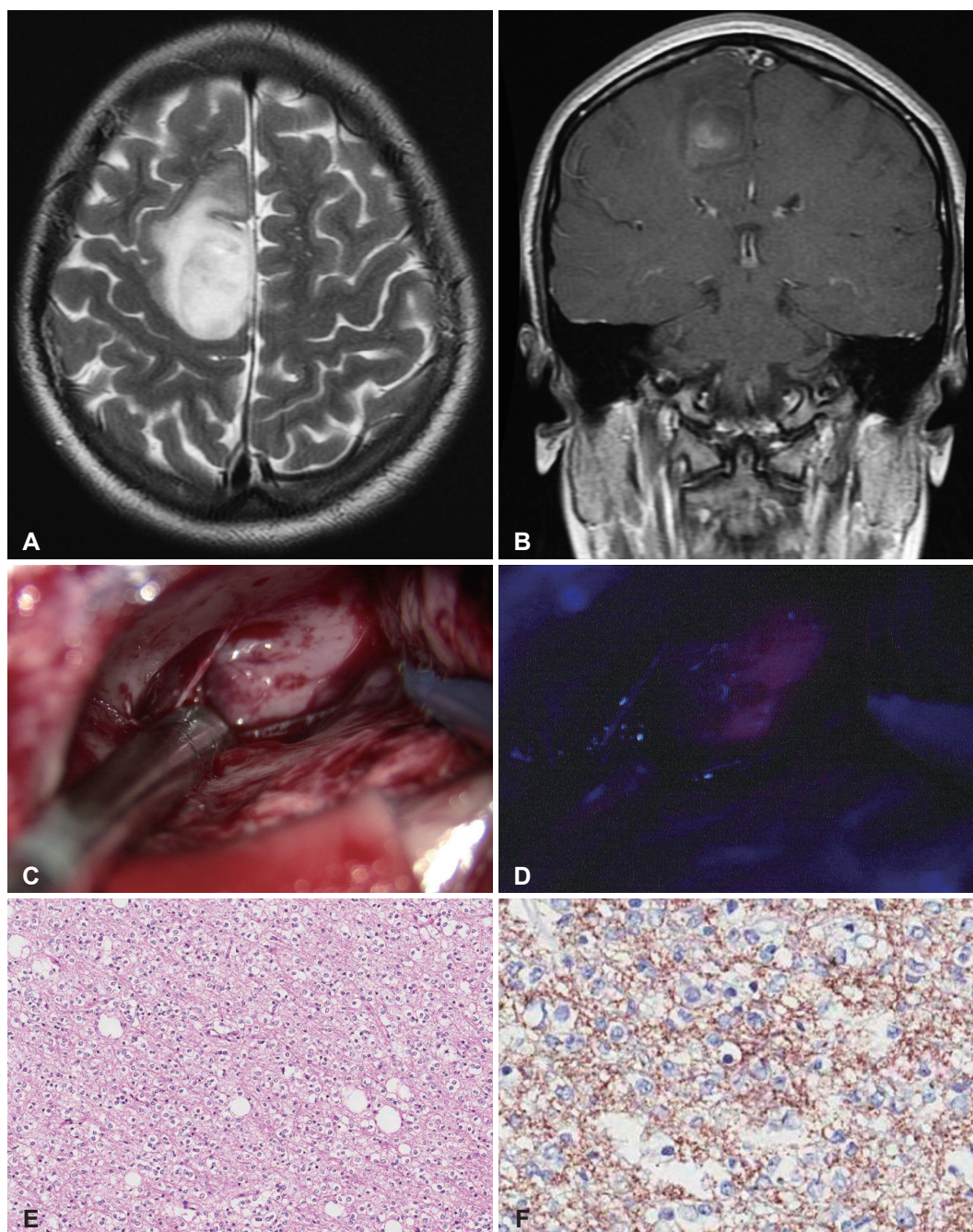


Fig. 2. A and B: A preoperative MRI scan showing a right high frontal mass with high signal intensity on a T2-weighted image and focal enhancement on a T1-weighted image with contrast. C and D: Intraoperatively, the mass showed positive fluorescence reaction and was red after illumination with ultraviolet light of 440-nm wavelength. E: The tumor was composed of monotonous round cells with clear cytoplasm (hematoxylin-eosin staining). F: Immunohistochemical staining for synaptophysin showing diffuse, strong reactivity in the tumor cells. MRI: magnetic resonance imaging.

orescence was confirmed as high-grade tumors, whereas all other tissues that showed no fluorescence were determined to be low-grade tumors. During the tumor resection, motor-evoked potentials were decreased. We therefore decided not to proceed with the resection. The lesion with the positive fluorescence was totally removed grossly, but some remnant tumor was observed on postoperative MR images. The patient developed transient foot drop postoperatively, which almost completely resolved one month later. The histological diagnosis was compatible with atypical EVN, which was composed of monotonous round cells with a clear halo (Fig. 2E, F). Astrocytic differentiation was also found, and endothelial hyperplasia and focal necrosis were present. The mitotic rate was 4/10 HPF, and the Ki-67 labeling index was elevated at 7.3%. The patient received adjuvant radiotherapy due to the residual tumor and atypical features. At the 28-month follow-up, the patient returned to her normal activities without any clinical or radiological evidence of tumor recurrence.

DISCUSSION

Since central neurocytomas were first described by Hassoun et al. [8] in 1982, there has been a series of reports about neurocytomas that arise from the brain parenchyma without any connection to the ventricular system [9]. These so-called 'extraventricular neurocytomas' were named as the counterpart to central neurocytomas, which are typically located in the lateral ventricle near the foramen of Monro [6]. In the recent 2007 World Health Organization classification, EVN was recognized as a new entity to distinguish it from central neurocytomas [10]. EVNs are rare, and their clinical characteristics still need to be evaluated. The radiological findings of EVNs mimic gliomas and are effectively treated with complete resection, regardless of histological grade [6,7]. When EVNs display atypical histological features such as vascular proliferation, necrosis, increased mitotic activity and an increased proliferation index, they are classified as atypical EVNs [6,7]. However, the impact of these histological features on predicting the clinical behavior of these tumors is unknown, and the total resection of the tumor is the best indicator of prognosis, regardless of histological grade [6,7]. Rades et al. [7] reviewed 85 cases of atypical neurocytomas, including 21 cases of atypical EVN, and concluded that patients who underwent complete resection achieved better local control and better survival rates compared to patients who underwent incomplete resection. They also showed that the patients who underwent incomplete resection appeared to benefit from radiotherapy. Brat et al. [6] reported on 35 EVNs from three large institutes and showed that none of the 14 completely resected tumors recurred within the follow-up period, whereas ten of the 19 incom-

pletely removed tumors recurred, regardless of adjuvant radiotherapy. Recurrence occurred in five of ten classic EVNs and five of nine atypical EVNs after incomplete removal. In the Brat report, only one of ten atypical EVNs was completely resected.

Gross total resection of benign brain tumors plays a significant role in prognosis. In malignant brain tumors, gross total resection and overall prognosis seem to be highly correlated [2]. Fluorescence-guided resection of brain tumors has been extensively studied as a potential tool to help neurosurgeons achieve maximal resection of gliomas. Recently, fluorescence-guided surgery for brain tumors using 5-ALA has become more widespread in clinical practice. The proposed mechanisms of the increased 5-ALA uptake into neoplastic brain tissue include the following: induced low permeability of the blood-brain barrier, the presence of adaptable specific membrane transporters, the reduced activity of ferrochelatase, the lowering of the available iron due to chelators, the increased activity of the enzymes that are involved in protoporphyrin IX synthesis, elevated intracellular 5-ALA uptake, and decelerated protoporphyrin IX outflow from the cell [1]. Various types of tumors were investigated for the use of 5-ALA for tumor resection, and the efficacy of the technique has been demonstrated in the literature [4,5]. To our knowledge, however, the fluorescence reaction for EVN has yet to be reported.

In our 2 cases, the maximal safe resection under fluorescence guidance and intraoperative evoked potential monitoring was performed in both patients who had EVN adjacent to eloquent areas, and there were no permanent postoperative neurological deficits. There were some areas that exhibited the fluorescence reaction for 5-ALA within the tumor tissue, and these areas correlated with histological EVN grade. We discovered that the 5-ALA fluorescence reaction may help increase the likelihood of complete resection of highly malignant cell burden and may facilitate the intraoperative diagnosis of histological grade in EVNs. Furthermore, the histological grading system of EVNs has not been systemically determined, the 5-ALA fluorescence reaction may have a potential role as a biomarker for the prognosis of EVN. Further study on the clinical experience with the 5-ALA fluorescence reaction in EVNs is needed to confirm its role in the clinical evaluation and treatment of these tumors.

In summary, the 5-ALA fluorescence reaction discriminated the histological grade of EVN and was helpful in terms of achieving complete resection and determining the intraoperative diagnosis in atypical cases. This finding shows that the 5-ALA fluorescence reaction may be a potential biomarker of the clinical behavior of EVNs.

Conflicts of Interest _____

The authors have no financial conflicts of interest.

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