



5-Aminolevulinic Acid-Induced Fluorescence in Cerebellar Primary Central Nervous System Lymphoma: A Case Report and Literature Review

Serebellar Yerleşimli Primer Santral Sinir Sistemi Lenfomasında 5-Aminolevülinik Asit ile İndüklenmiş Floresans: Olgu Sunumu ve Literatür Derlemesi

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ABSTRACT

5-Aminolevulinic acid (5-ALA)-induced fluorescence-guided resection is a widely used procedure for patients with malignant gliomas. However, the clinical application of 5-ALA for surgery in primary central nervous system lymphoma (PCNSL) is uncommon. Here, we present a case of PCNSL treated using 5-ALA-induced fluorescence-guided resective surgery. A 70-year-old woman presented with cerebellar ataxia, and magnetic resonance imaging revealed an irregularly shaped and homogeneously enhanced mass with surrounding brain edema in the vermis that extended to the right hemisphere of the cerebellum. Under the preoperative diagnosis of a malignant glioma in the cerebellum, the patient underwent 5-ALA-induced fluorescence-guided surgery. Under blue light illumination, the tumor revealed strong 5-ALA-induced fluorescence. The tumor was identified as a diffuse large B-cell lymphoma. After partial resection, the patient received adjuvant chemotherapy and radiotherapy. Importantly, the neurological deficit of the patient improved, and recurrence of the tumor was not observed 21 months post-surgery. Together with previous reports, this case study emphasizes the efficacy of the surgical application of 5-ALA for PCNSL.

KEYWORDS: Glioma, Subventricular zone, Ependyma, Surgery, Diffuse large B-cell lymphoma, Dissemination, 5-ALA

ÖZ

5-Aminolevülinik asit (5-ALA) ile indüklenmiş floresans-eşliğinde rezeksiyon malign gliomalı hastalarda yaygın kullanılan bir tekniktir. Ancak primer santral sinir sistemi lenfoması (PSSSL) olan hastaların cerrahisinde 5-ALA kullanımı sık değildir. Burada 5-ALA ile indüklenmiş floresans eşliğinde rezektif cerrahi uygulanan bir PSSSL olgusu sunuldu. Serebellar ataksi ile başvuran 70 yaşındaki kadın hastada manyetik rezonans görüntüleme, vermisden sağ serebellar hemisfere uzanan, düzensiz sınırlı ve homojen kontrast tutan, çevre beyin dokusunda ödeme nedene olan kitle lezyonunu ortaya koydu. Preoperatif olarak serebellumda malign glioma tanısı düşünüldü ve hastaya 5-ALA ile indüklenmiş floresans eşliğinde cerrahi uygulandı. Mavi ışık aydınlatması altında tümör kuvvetli 5-ALA ile indüklenmiş floresans gösterdi. Tümörün histopatolojik inceleme sonucu diffüz geniş B-hücreli lenfoma olarak geldi. Kısmi rezeksiyondan sonra hastaya ilave kemoterapi ve radyoterapi uygulandı. Önemli olarak, hastanın nörolojik defisiti düzeldi ve cerrahiden 21 ay sonra nüks gözlenmedi. Bu konudaki daha önceki raporlarla birlikte, bu olgu çalışması da 5-ALA'nın PSSSL'da cerrahi uygulamasının etkinliğini vurgulamaktadır.

ANAHTAR SÖZCÜKLER: Glioma, Subventriküler bölge, Ependim, Cerrahi, Diffüz geniş B-hücreli lenfoma, Yayılım, 5-ALA

INTRODUCTION

5-Aminolevulinic acid (5-ALA) is a natural biochemical precursor of heme that induces the synthesis and accumulation of fluorescent porphyrins such as protoporphyrin IX (PpIX) in various cancerous tissues (17). Because 5-ALA can lead to PpIX accumulation within malignant glioma tissues, 5-ALA is primarily applied for fluorescence-guided resection of malignant gliomas by using specifically modified neurosurgical microscopes (10). Recently, 5-ALA has also been identified as a promising intraoperative marker in stereotaxic biopsies for malignant gliomas (5, 15). However, clinical application of 5-ALA in primary central nervous system lymphoma (PCNSL) is currently uncommon (2, 8, 12).

Here, we report a case of cerebellar PCNSL demonstrating strong 5-ALA-induced fluorescence via open resective surgery. Furthermore, we discuss the usefulness of 5-ALA in surgery for PCNSL, and review relevant literature.

CASE REPORT

A 70-year-old woman with diabetes mellitus experienced progressive gait disturbance and consulted our hospital. Neurological examination revealed right-sided dysmetria and an unstable wide gait. Blood sugar level on arrival and HbA1c were 169 mg/dL and 6.2%, respectively. Tests to determine serum soluble interleukin-2 receptor levels indicated no abnormalities (292.0 U/mL). Serological examination for infections and collagen disease was unremarkable. Brain

computed tomography (CT) showed ill-defined mixed density (iso- and hypo) lesion in the cerebellum (Figure 1A). Magnetic resonance imaging (MRI) revealed an irregularly shaped and relatively homogeneously enhanced mass with surrounding brain edema (Figures 1B-F). This intra-axial mass was located mainly in the cerebellar vermis and extended to the right hemisphere of the cerebellum. A diffusion-weighted image showed mild fluid restriction (Figures 1D), and a map of regional cerebellar blood volume from a perfusion-weighted image indicated increased blood flow (Figure 1G). Under the preoperative diagnosis of a malignant glioma in the cerebellum, and according to a previously described protocol (10), the patient underwent 5-ALA-induced fluorescence-

guided surgery. Via a midline suboccipital craniotomy, a small corticotomy was performed at the boundary zone between the cerebellar vermis and right cerebellar hemisphere. The tumor was identified in deep cerebellar white matter (Figures 2A, B). Blue light illumination of the tumor revealed the typical strong red fluorescence under a 410-nm ultraviolet light source (OPMI/Pentero, Carl Zeiss, Oberkochen, Germany) (Figure 2C). Because the pathological examination during the surgery confirmed the suspected malignant lymphoma, the fluorescent tumor tissue was partially resected. Histological examination of tumor specimen showed a high cellular malignancy composed of large cells with elongated, irregular nuclei (Figure 3A). The tumor cells were immunoreactive for

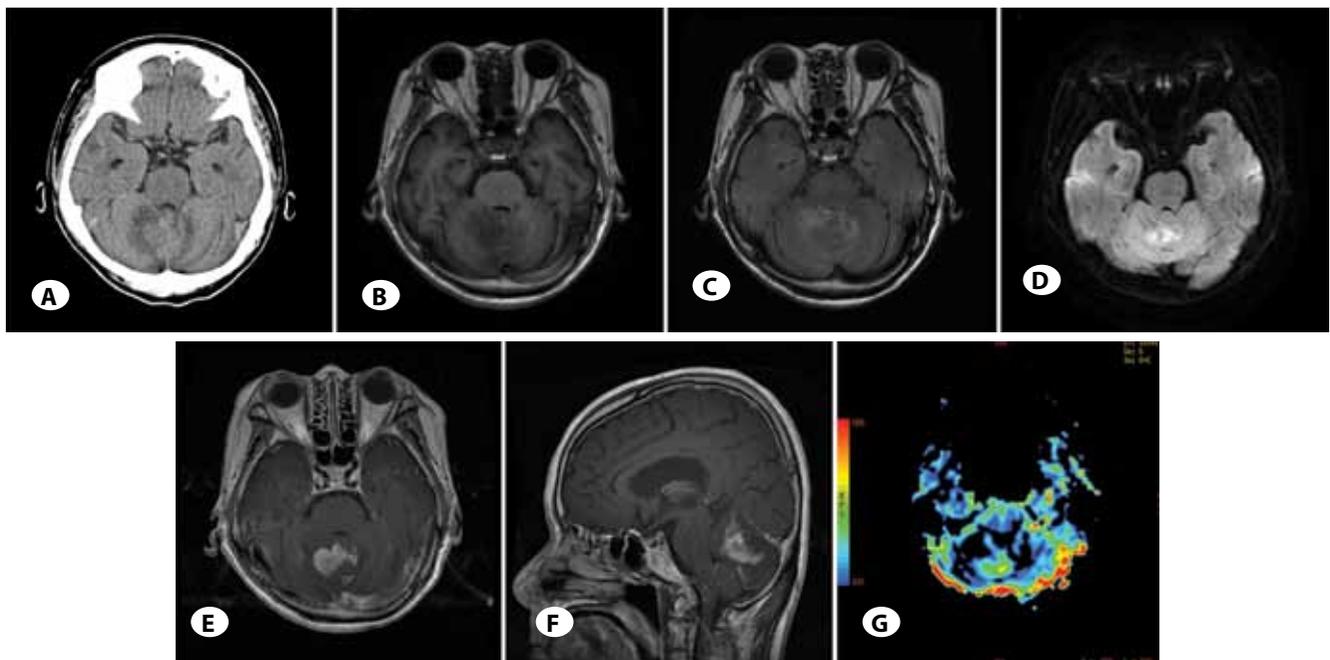


Figure 1: Computed tomography (CT) and magnetic resonance imaging (MRI) performed on admission. Axial CT image (A), T1-weighted image (T1WI) (B), fluid-attenuated inversion recovery (FLAIR) image (C), diffusion-weighted image (DWI) (D), axial (E) and sagittal (F) contrast-enhanced T1WIs (E), and axial image of a regional cerebellar blood volume map on perfusion-weighted image (PWI) (G). MRI demonstrating an irregularly shaped and relatively homogeneously enhanced mass on the vermis extending to the right hemisphere of the cerebellum with surrounding brain edema (B-D). PWI showing high blood flow within the tumor (G).



Figure 2: Intraoperative photograph of the tumor resection (A-C). B and C correspond to the square in A. After the suboccipital craniectomy, a small corticotomy was performed at the boundary zone between the vermis and right cerebellar hemisphere (A). The tumor was identified in deep cerebellar white matter (arrow in B). The tumor was strongly fluorescent under the violet-blue excitation light (C). The asterisk in A is the cerebellomedullary cistern.

a B cell marker (CD20) (Figure 3B), but not for a T cell marker (CD3) (Figure 3C). The proliferation index (Ki-67) was 92% (Figure 3D). These findings were compatible with diffuse large B-cell lymphoma (DLBCL). Whole-spine MRI and body CT showed no abnormalities. Ophthalmological examination excluded intraocular lesions. Thus, we diagnosed the patient with PCNSL.

According to a previously described protocol (6), the patient underwent the first course of high-dose methotrexate therapy

(HD-MTX). Because of mild renal dysfunction, the patient could not receive the next course of HD-MTX. Thus, the patient underwent subsequent radiotherapy. The patient's condition improved without any other neurological deficit. No recurrence of the tumor was detected on MRI performed 21 months after the surgery (Figure 4A, B).

DISCUSSION

The number of clinical cases using 5-ALA for PCNSL is extremely low compared to the number of cases using 5-ALA

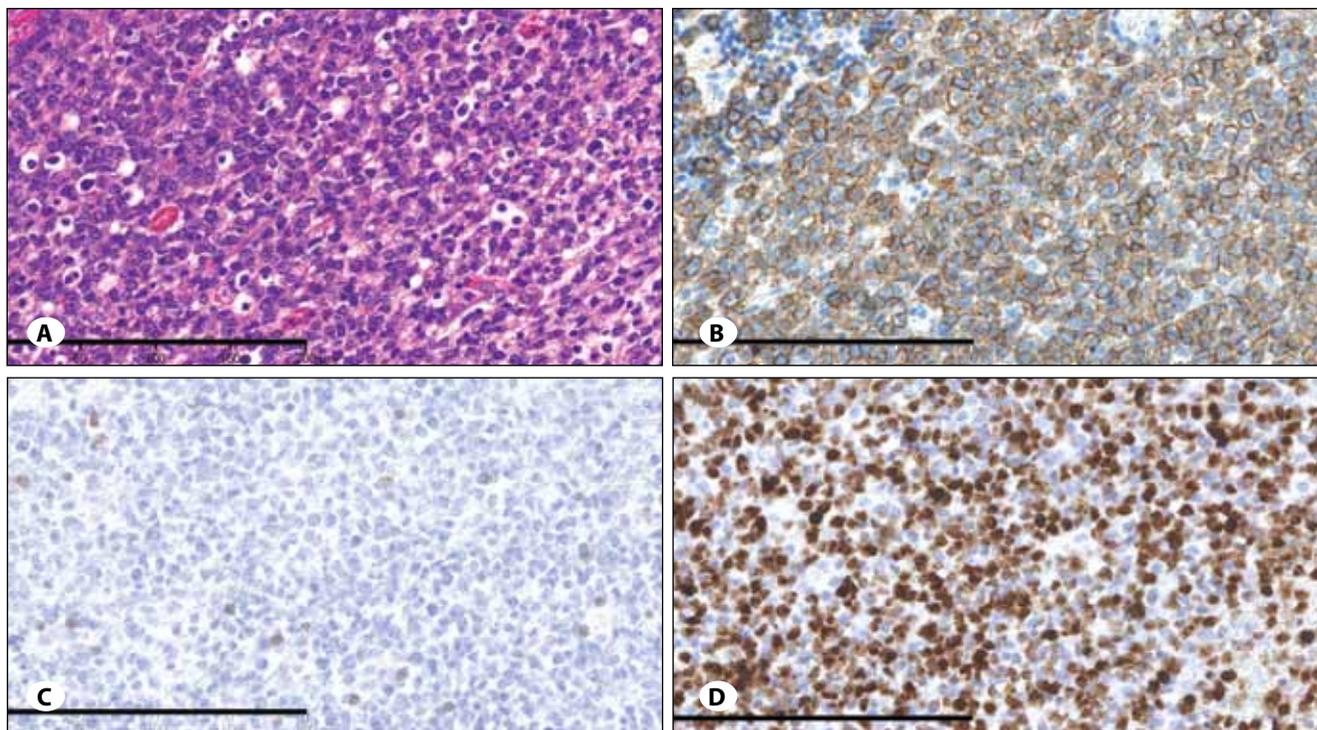


Figure 3: Diffuse large B-cell lymphoma. Hematoxylin and eosin staining from the specimen that demonstrated strong 5-ALA-induced fluorescence lesion showed a high cellular malignancy composed of large cells with elongated, irregular nuclei (A). Immunohistochemical examination showed that the tumor strongly expressed CD20 (B). The tumor lacked CD3 expression, with retained expression in intermingled and small reactive T lymphocytes (C). MIB-1 (Ki-67) shows a high proliferative index (D). Scale bar 200 μ m (A-D).

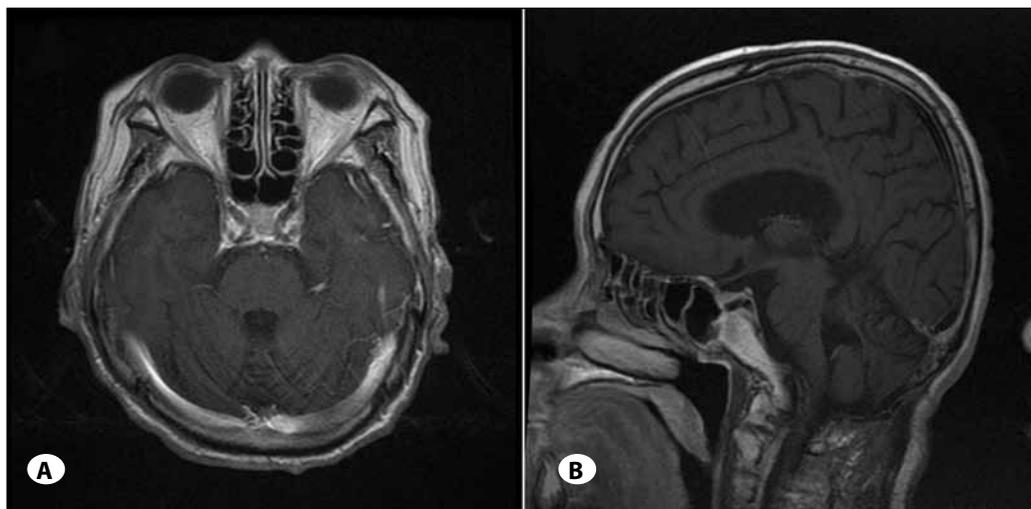


Figure 4: Follow-up MRI performed 21 months after the surgery. Axial (A) and sagittal (B) contrast-enhanced T1WIs. No tumor recurrence was detected. R in A, and A in B mean right side and anterior side, respectively.

Table I: Summary of Studies on CNS Lymphoma Demonstrating 5-ALA-Induced Fluorescence

Summary of CNS lymphoma demonstrating 5-ALA-induced fluorescence						
Authors (year)	Patients (n)	Pathology	Surgery	5-ALA fluorescence status		
				Strong %	Vague %	None %
Moriuchi et al. (2011) (8)	1	DLBCL	stereotaxic biopsy	100	-	-
Utsuki et al. (2011) (12)	20	malignant lymphoma	stereotaxic biopsy (one case), others; no information	60	20	20
Widhalm et al. (2012) (14)	7	CNS lymphoma	stereotaxic biopsy	88	12	-
von Campe et al. (2012)	4	DLBCL	stereotaxic biopsy	100	-	-
Grossman et al. (2014) (2)	1	DLBCL	suboccipital craniectomy	100	-	-
Present case	1	DLBCL	suboccipital craniectomy	100	-	-

Abbreviation: DLBCL, diffuse large B-cell lymphoma.

for malignant gliomas. Only 33 cases of 5-ALA-induced fluorescence-guided surgery have been reported (Table I). Except for one reported case, patients with PCNSL commonly undergo stereotaxic biopsy. Only one case of 5-ALA-induced fluorescence-guided surgery via the open resective approach for PCNSL that was located on the floor of the fourth ventricle has been reported (2). Almost all cases were positive (strong and vague) for 5-ALA-induced fluorescence. However, one study reported that 20% of PCNSL cases lacked 5-ALA-induced fluorescence (12). In the present case, we chose an open resective approach to the cerebellar tumor, without exposing the fourth ventricle, and observed strong 5-ALA-induced fluorescence of the tumor that was histologically compatible with DLBCL. The tumor also had a high proliferation index. Previously, 5-ALA-induced fluorescence intensity in malignant gliomas was correlated with three factors: 1) high cellular density, 2) high proliferation index, and 3) high neovascularity (11). Although the precise pathogenesis of 5-ALA-induced fluorescence in PCNSL is unclear, PCNSL with high cellular density and proliferation index correlates strongly with intense 5-ALA-induced fluorescence. Therefore, in agreement with a previous report (14), we propose that 5-ALA-induced fluorescence in PCNSL plays an important role in tumor detection via open surgery as an intraoperative marker to confirm the precise biopsy target in stereotaxic biopsy.

A recent study showed improved survival following resection, but not biopsy, of PCNSL (13). Interestingly, 5-ALA-induced fluorescence-guided resection may apply to PCNSL in a similar way surgery applies to malignant gliomas (2). Typically, PCNSLs are supratentorial (75–85%) and appear as a mass or multiple masses that commonly contact the subarachnoid or ependymal surface (7). Recently, in patients with malignant gliomas and PCNSL, 5-ALA-induced fluorescence of the ventricular wall adjacent to the tumor was discovered and considered as tumor infiltration or dissemination (1–3). We previously reported glioblastoma presenting with mesial temporal epilepsy in the right temporal lobe (16); the patient underwent tumor resection and right selective

hippocampectomy to treat the mesial temporal epilepsy. During the surgery, the surface of the hippocampus revealed strong 5-ALA-induced fluorescence. However, pathological investigation of the hippocampus showed neither tumor invasion nor disruption of the ependymal layer. Moreover, previous work using a rat brain tumor model found 5-ALA-induced fluorescence not only in the choroid plexus, but also in the ventricular wall of the contralateral side of the lesion (4). A likely scenario involves tumor-secreted porphyrin leaking into the blood through a defective blood-brain barrier, then spreading through the cerebrospinal fluid to the choroid plexus (4, 9), and, consequently, undergoing direct uptake into the ventricular wall. Therefore, if the tumor infiltrates into the subependymal layer, then 5-ALA-induced fluorescence should be observed in the ventricular wall. However, if there is no histological confirmation, 5-ALA-induced fluorescence in the ventricular wall does not necessarily demonstrate the presence of tumor cells. Therefore, we caution that neurosurgeons should carefully interpret 5-ALA-induced fluorescence in the ventricular wall during surgery for PCNSL.

CONCLUSION

The present case demonstrates that 5-ALA-induced fluorescence serves as a useful diagnostic adjunct for PCNSL under the open resective approach. Together with previous studies, we propose that 5-ALA provides highly specific intraoperative tumor identification in PCNSL. Furthermore, these data suggest that the application of 5-ALA may be extended to open surgery and stereotaxic biopsy in PCNSL.

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