5-Aminolevulinic acid a biomarker for worse prognosis in IDH-wildtype brain tumors? Evolution of a Fluorescence-Positive Diffuse Astrocytoma: Case Report

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Introduction: In 2017, the U.S Food and Drug Administration (FDA) approved 5-Aminolevulinic Acid (5-ALA) as an intraoperative optical imaging agent in patients with suspected high-grade gliomas (HGGs). However, the application of 5-ALA for low-grade gliomas is still less accepted.
Case Report: A 74-year-old male patient was diagnosed with a right parietal lesion suggestive of a low-grade brain tumor in a surgical resection using 5-ALA, which led to the detection of tiny fluorescence spots during the surgery. The frozen section was consistent with Diffuse astrocytoma, IDH-wildtype (WHO grade II). The patient’s postoperative MRI showed complete resection. Eight months after surgery, he began experiencing symptoms again and was admitted with a brain MRI finding consistent with recurrent infiltrating astrocytomas. This required reoperation of the brain tumor resection with 5-ALA. Unlike the first surgery, they observed a high fluorescence intensity; the pathological finding was Glioblastoma, IDH-wildtype (WHO Grade IV). Post-surgical brain MRI showed total resection of the tumor. The patient was discharged four weeks after surgery and continued with specialized clinical follow-up.
Conclusion: The use of 5-ALA increasingly approaching its use as a prognostic tool for aggressive clinical behavior. This case report expand knowledge for potentially using to prognosticate IDH-wildtype II tumors.

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ABSTRACT

Introduction: In 2017, the U.S Food and Drug Administration (FDA) approved 5-Aminolevulinic Acid (5-ALA) as an intraoperative optical imaging agent in patients with suspected high-grade gliomas (HGGs). However, the application of 5-ALA for low-grade gliomas is still less accepted. Astrocytoma, IDH mutant tumors are diffuse infiltrating astrocytic tumors where there is no identifiable border between the tumor and normal brain tissue, even though the borders may appear relatively well-marginated on imaging. Generally, it is considered that 5-ALA cannot pass through a normal blood brain barrier (BBB). Thus, 5-ALA fluorescence may mean disruption of BBB in grade II glioma.

Case Report: A 74-year-old male patient was diagnosed with a right parietal lesion suggestive of a low-grade brain tumor in a surgical resection using 5-ALA, which led to the detection of tiny fluorescence spots during the surgery. The frozen section was consistent with Diffuse astrocytoma, IDH-wildtype (WHO grade II). The patient's postoperative MRI showed complete resection. Eight months after surgery, he began experiencing symptoms again and was admitted with a brain MRI finding consistent with recurrent infiltrating astrocytomas. This required reoperation of the brain tumor resection with 5-ALA. Unlike the first surgery, they observed a high fluorescence intensity; the pathological finding was Glioblastoma, IDH-wildtype (WHO Grade IV). Post-surgical brain MRI showed total resection of the tumor. The patient was discharged four weeks after surgery and continued with specialized clinical follow-up.

Conclusion: The use of 5-ALA continues to be a great contributor to the improvement of complete resection of primary brain tumors, especially HGG. Besides, fluorescence is increasingly approaching its use as a prognostic tool for aggressive clinical course, regardless of the initial grade of the tumor. This case report is an effort to expand knowledge for
potentially using 5-ALA to help prognosticate brain tumors. Nevertheless, more clinical prospective studies must be conducted.

Keywords

Brain tumor

5-ALA

Diffuse Astrocytoma

INTRODUCTION

Diffuse astrocytoma IDH wild-type is an uncommon diagnosis, and the pathology of the disease is controversial [1-3]. The grading of astrocytoma, IDH mutant is based on histological features, as well incorporating molecular markers (introduced in the 5th edition (2021) WHO classification of CNS tumors)[1]. IDH-mutant adult-type astrocytomas are typically diagnosed in young adults median age of 36 years for grades 2 and 3 (combined), and 38 years for grade 4). This is substantially younger than glioblastoma IDH wildtype tumors (median 50-60 years of age). There is a substantially higher incidence in men of all ages and of all grades tumor. Tumors with normal IDH genes referred to as “IDH-wildtype” tend to behave far more aggressively. It is well documented that pathological classification has a elevated interobserver discrepancy and consequently incorrectly predicts clinical outcomes. Additional clinical research studies have presented that the genetic status of these tumors is further reflective of their subtypes than the histologic grading. 5-Aminolevulinic Acid (5-ALA) is an orally administered prodrug that improves Glioblastoma (GBM) visualization during surgery, allowing safer and more extensive tumor resection. Prognosis is similar to that of primary GBM [1-3]. Although it’s a low-grade glioma, it exhibits molecular and clinical features of high-
grade glioma and may represent an early stage of primary glioblastoma [3-4]. For that reason, even the mere existence of this type of tumor is in doubt [4,5]. 5-ALA improves the delimitation of malignant tissue during surgery, obtaining a positive predictive value (PPV) of 95.7% (when used for the diagnosis of GBM by biopsy) [5-7]. 5-ALA achieve a better extent of resection (EOR), simultaneously decreasing residual fluorescence tissue (Gadolinium T1 MRI), which led to an increase in overall survival (27.0 months CI95% 22.4 - 31.6) compared to patients with residual fluorescence tissue (17.5 months CI95% 12.5-22.5) [6,8].

The FDA approval of 5-ALA as an intraoperative optical imaging agent in patients with suspected high-grade gliomas (HGGs) occurred in 2017 [1,7]. However, the application of 5-ALA for low-grade gliomas is still less accepted [8-11]. In this case report, we discuss the case of a histologically low-grade glioma with positive fluorescence that develops a poor outcome.

**CASE PRESENTATION**

This is a 74-year-old male patient, right-handed, history of hypertension (HTN), various cardiovascular interventions, and polypharmacy. Referred symptoms were left-hand numbness and tingling sensation, associated with the left side of the face and tongue numbness, as well as slurred speech. Magnetic resonance imaging (MRI) of the brain revealed a right parietal lesion, with mass-effect and solid consistency, suggestive of a low-grade brain tumor, which led to the decision to biopsy the lesion. The result of the biopsy suggested low-grade glioma but awaits permanent sections to a definitive diagnosis. Surgery for complete resection was scheduled one month later. The patient underwent Awake Stereotactic Frameless Craniotomy using 5-ALA (1500 mg oral route, 2 hours before surgery) fluorescence guidance and neuronavigation. Patient was not on any drugs that may affect 5-ALA fluorescence. Tiny spots of fluorescence were observed during surgery (weak fluorescence). The frozen section was consistent with Diffuse astrocytoma, IDH-wildtype (WHO grade II), mitoses, necrosis, CDKN2A/B homozygous deletion and microvascular
proliferation were absent. Post-surgical brain MRI showed complete resection (Figure 1). The patient was discharged with clinical and imaging follow-up every three months to monitor the lesion.

Eight months post-surgery, the patient became symptomatic again and was admitted to the emergency room. MRI findings indicated recurrent infiltrating astrocytoma, extensive adjacent vasogenic edema, mass effect, and resolving hemorrhage. The patient underwent reoperation with 5-ALA fluorescence guidance resection and neuronavigation. In contrast to the first surgery, high-intensity fluorescence was observed, well related to HGG. A new sample was sent to pathology, resulting in Glioblastoma, IDH-wildtype (WHO Grade IV).

Post-surgical brain MRI showed complete resection of the tumor (Figure 2). The patient was discharged four weeks after surgery and continued with specialized clinical follow-up. One month after discharge, he showed improvement in symptoms, mild left muscular weakness, no aphasia, normal coordination, and mild gait difficulty—the last MRI reported an overall improvement in the operative cavity and no mass effect. To gain a deeper understanding of the patient’s case, a timeline of their evolution was drawn (Figure 3).

DISCUSSION

From the authors’ knowledge, this is the first report of a 5-ALA fluorescent diffuse astrocytoma IDH-wildtype and its tracing until malignant transformation. The IDH-mutant astrocytomas are now graded 2, 3 or 4 established on histological and molecular features, but remarkably a grade 4 tumor is no longer a glioblastoma, but reasonably just an astrocytoma, IDH mutant WHO CNS grade 4. Glioblastoma is currently measured a separate entity and different and must be IDH-wildtype, and is therefore discussed separately. Essentially, the identification of astrocytoma, IDH mutant is an adult-type diagnosis, different from a variety of other pediatric-type diffuse astrocytomas. In a previous retrospective clinical study, So Youn Ji., et al [10],
evaluate the performance of 5-ALA in 827 cases of gliomas. Their survey agreed with most of the literature by finding fluorescence in 95% of GBM. While in a lower percentage, the grade I to III gliomas also showed a certain degree of fluorescence during surgery (55%, 24.1%, 26.3% of cases, respectively). There were 20 cases of diffuse astrocytomas or oligoastrocytomas. Only two of the cases reported focal fluorescence and a total of 15 cases that underwent resection, including those that had focal fluorescence. Paradoxically, there was no improvement in EOR for positive fluorescence low-grade gliomas [10,11]. Generally, it is considered that 5-ALA cannot pass through a normal blood brain barrier (BBB). Thus, 5-ALA fluorescence may mean disruption of BBB in grade II glioma. According to the literature, the rates of 5-ALA induced fluorescence in WHO grade II tumors vary [8,10–13] (Table 1).

As shown in our case, the clinical relevance of positive fluorescence in low-grade gliomas is poorly understood, however, due to the recurrence of the tumor and its aggressiveness, we agree that it’s directly related to an increased proliferation rate and anaplasia as referred to in studies [14-16]. We consider that fluorescence during surgery could have been a red flag for poor prognosis in this patient. Jaber M., et al [13]. reported a shorter overall survival (51.6 months [34.8-68.3] vs 68.2 months [62.7-73.8], \( P = .002 \)) and shorter periods of malignant transformation (43.0 months [27.5-58.5] vs 64.6 months [57.7- 71.5], \( P = .015 \)) in patients with low grade glioma with positive fluorescence against those without [13-15,16]. In contrast, the patient in the case had faster malignant transformation (8 months). However, these types of tumors could have a clinical course and survival more akin or only slightly longer than glioblastoma IDH Wild type [1–4]. We also consider that 5-ALA helped improve the EOR in this patient.

**CONCLUSION**

The use of 5-ALA continues to be a great contributor to the improvement of complete resection of primary brain tumors, especially HGG. Besides, fluorescence is increasingly
approaching its use as a prognostic tool for aggressive clinical behavior, regardless of the initial grade of the tumor. This case is reported in an effort to extend knowledge for future research for the use of 5-ALA in brain tumors as a prognostic tool. Nevertheless, more studies with greater power should be designed to achieve a definitive conclusion.

Conflict of Interest

None declared.

References


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https://doi.org/10.1227/NEU.0b013e31828c3974.


https://doi.org/10.1371/journal.pone.0076988.


**Figure 1. Evolution of first surgical intervention.** Preoperative MRI: Right mid parietal gray matter lesion related to a low-grade glioma. (A, Coronal T2; B, Axial FLAIR; C, sagittal T2; D diffusion tensor imaging DTI); Intraoperative images. Correlation between the different moments of the surgery (E, white light; F, 5 ALA fluorescence in blue light); Postoperative MRI: complete resection of the tumor (G, coronal T1; H, coronal T2; I, axial T1; J, sagittal T1); Brain tumor pathology: increased cellularity and increased cytologic atypia, histiocytic reaction and chronic inflammation, ki-67 positive, 3+, nuclear on 5% of cells (K, Diffuse astrocytoma, IDH-wildtype, WHO Grade II).

**Figure 2. Evolution of second surgical intervention.** Preoperative MRI: Finding consistent with recurrent infiltrating astrocytoma (A, coronal T2; B, axial FLAIR; C, sagittal T1 GAD; D, diffusion tensor imaging DTI, three-dimensional axial and sagittal); Intraoperative images. Correlation between the different moments of the surgery (E, white light; F, 5-ALA fluorescence with blue light); Postoperative MRI: complete resection of the tumor (G, coronal T2; H, axial T2; I, sagittal T1; J, axial); Brain tumor pathology: areas of necrosis, diffuse infiltrative pattern, ki-67 positive, 3+, in 3% of tumor cells. (K, Glioblastoma, IDH-wildtype, WHO Grade IV)

**Figure 3. Timeline of the clinical case**

<table>
<thead>
<tr>
<th>Authors and year</th>
<th>Cases with positive fluorescence*</th>
<th>Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>So Young Ji, et al. (2019)</td>
<td>21 (25%)</td>
<td>87</td>
</tr>
<tr>
<td>Authors</td>
<td>Fluorescence (%)</td>
<td>Cases</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Ewelt C, et al. (2011)</td>
<td>1 (8%)</td>
<td>13</td>
</tr>
<tr>
<td>Widhalm G, et al. (2013)</td>
<td>4 (9%)</td>
<td>33</td>
</tr>
<tr>
<td>Jaber M, et al. (2016)</td>
<td>13 (16%)</td>
<td>82</td>
</tr>
<tr>
<td>Marbacher S, et al. (2014)</td>
<td>8 (40%)</td>
<td>20</td>
</tr>
</tbody>
</table>

*Table 1. Fluorescence in WHO Grade II gliomas*
This image contains a series of medical images and a timeline of events:

**A** - MRI scans showing a cerebral tumor.

**B** - Additional MRI scans with a tumor highlighted.

**C** - Another MRI scan with a tumor visible.

**D** - A 3D rendering of the brain with highlighted areas.

**E** - A close-up image of a tissue sample with red and pink colors.

**F** - Another close-up image with purple and pink colors.

**G** - A series of MRI scans showing different angles of the brain.

**H** - Another set of MRI scans with a tumor highlighted.

**I** - A third MRI scan with a tumor visible.

**J** - A final MRI scan showing the tumor.

**K** - A histological image of the tissue sample.

**Timeline Events:**

- **April 07**: Cerebral tumor observed on MRI.
- **May 21**: First surgery; weak fluorescence; diagnosis of Diffuse astrocytoma, IDH-wild type.
- **November 28**: New onset symptoms; recurrent diffuse astrocytoma on MRI.
- **December 03**: Second surgery; high-intensity fluorescence; diagnosis of Glioblastoma, IDH-wild type.
- **January 24**: Follow up MRI with overall improvement.

**Other Events:**

- **April 10**: Biopsy.
- **May 30**: Patient discharge.
- **December 11**: Patient discharge.