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5-Aminolevulinic Acid—A Biomarker for Worse Prognosis in IDH-Wildtype II Tumors? Evolution of a Fluorescence-Positive Diffuse Astrocytoma: A Case Report

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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, isocitrate dehydrogenase (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 (World Health Organization [WHO] grade II). The patient's postoperative magnetic resonance imaging (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). Postsurgical brain MRI showed total resection of the tumor. The patient was discharged 4 weeks after surgery and continued with specialized clinical follow-up.

Keywords
- brain tumor
- 5-ALA
- diffuse astrocytoma

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Conclusion The use of 5-ALA continues to be a great contributor to the improvement in 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.

Introduction

Diffuse astrocytoma isocitrate dehydrogenase (IDH)-wildtype 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) World Health Organization [WHO] classification of central nervous system [CNS] tumors).[1] IDH-mutant adult-type astrocytomas are typically diagnosed in young adults median age of 36 years for grades II and III (combined), and 38 years for grade IV. This is substantially younger than glioblastoma (GBM) 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 an 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 GBM visualization during surgery, allowing safer and more extensive tumor resection. Prognosis is similar to that of primary GBM.[1–3] Although it is a low-grade glioma, it exhibits molecular and clinical features of high-grade glioma and may represent an early stage of primary GBM.[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 of 95.7% (when used for the diagnosis of GBM by biopsy).[5–7] 5-ALA achieves a better extent of resection (EOR), simultaneously decreasing residual fluorescence tissue (gadolinium T1 magnetic resonance imaging [MRI]), which led to an increase in overall survival (27.0 months confidence interval [CI] 95%: 22.4–31.6) compared with patients with residual fluorescence tissue (17.5 months CI 95%: 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, 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. 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 1 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. Postsurgical brain MRI showed complete resection (►**Fig. 1**). The patient was discharged with clinical and imaging follow-up every 3 months to monitor the lesion.

Eight months postsurgery, 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 GBM, IDH-wildtype (WHO grade IV).

Postsurgical brain MRI showed complete resection of the tumor (►**Fig. 2**). The patient was discharged 4 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 (►**Fig. 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 II, III, or IV established on histological and molecular features, but remarkably a grade IV tumor is no longer a GBM, but reasonably just an astrocytoma, IDH mutant WHO CNS grade IV. GBM is currently measured as separate entity and different and must be IDH-

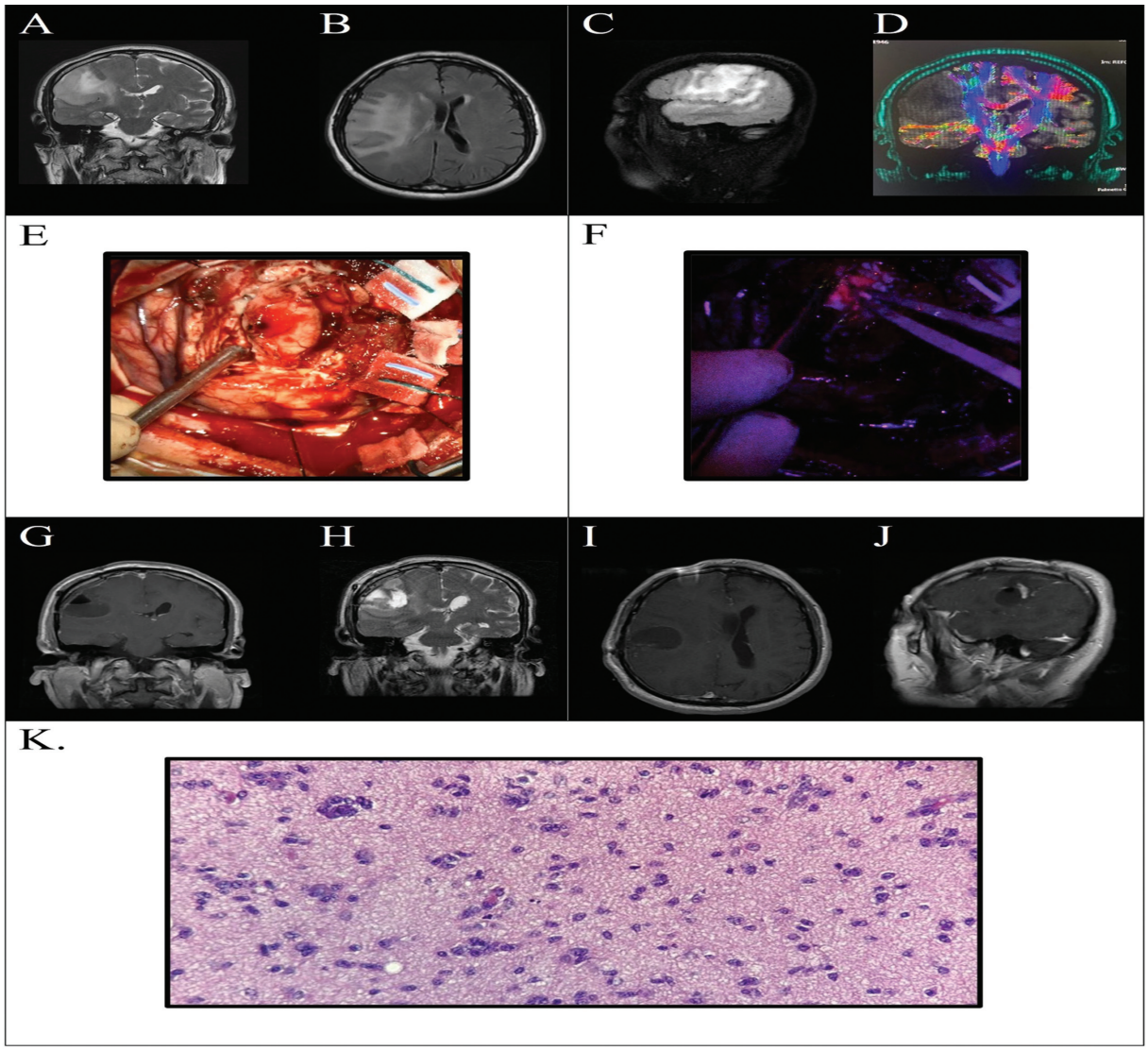

Fig. 1 Evolution of first surgical intervention. Preoperative magnetic resonance imaging (MRI): Right mid-parietal gray matter lesion related to a low-grade glioma. (**A**) Coronal T2; (**B**) axial fluid-attenuated inversion recovery; (**C**) sagittal T2; (**D**) diffusion tensor imaging); intraoperative images. Correlation between the different moments of the surgery (**E**), white light; (**F**) 5-aminolevulinic acid fluorescence in blue light. Postoperative MRI: complete resection of the tumor, (**G**) coronal T1; (**H**) coronal T2; (**I**) axial T1; and (**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, isocitrate dehydrogenase-wildtype, World Health Organization grade II.

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[11] 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 is 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 et al[13] reported a shorter overall survival (51.6 months [34.8–68.3] vs. 68.2 months [62.7–73.8], $p = 0.002$) and shorter periods of malignant transformation (43.0 months [27.5–58.5] vs.

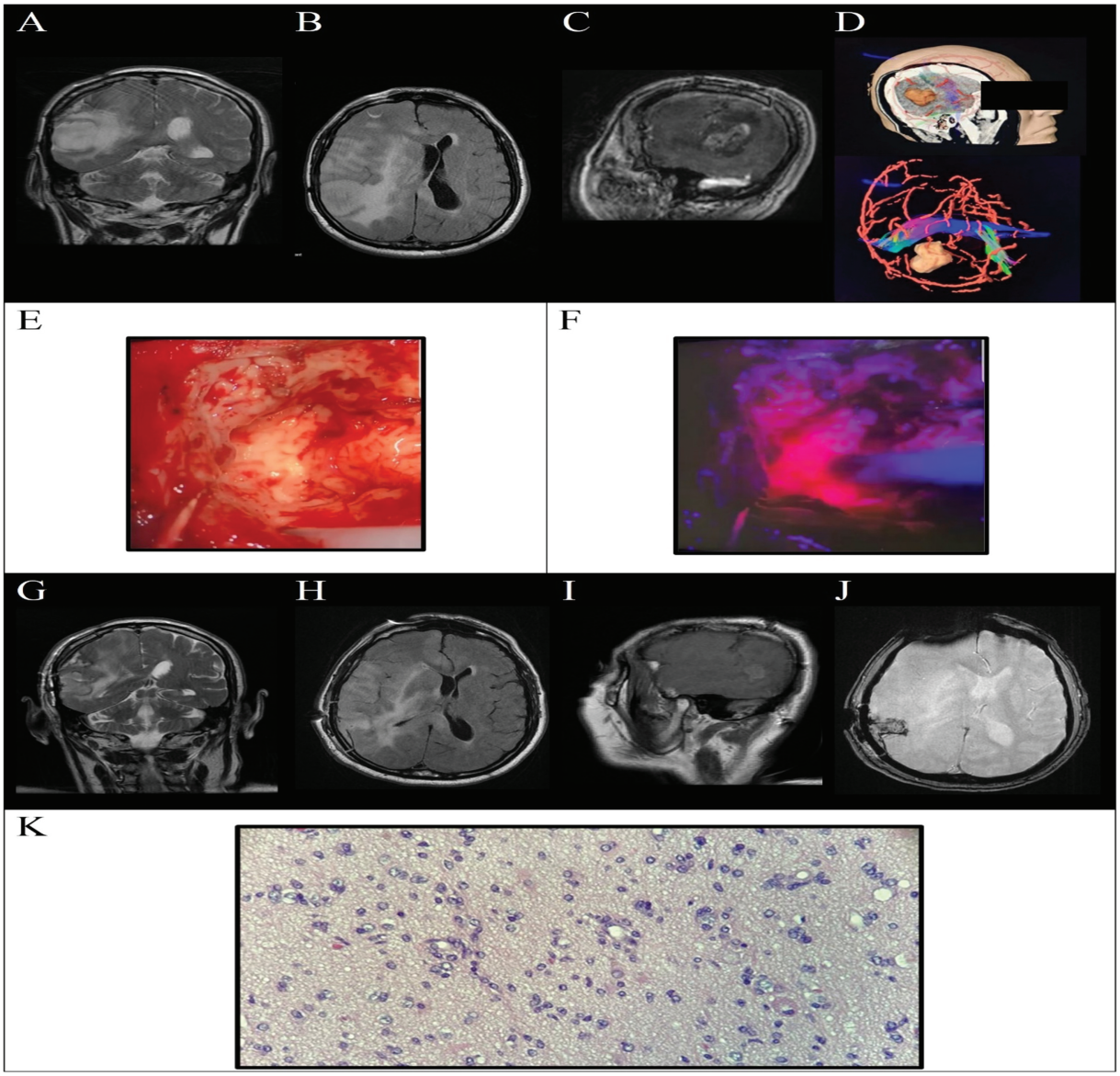

Fig. 2 Evolution of second surgical intervention. Preoperative magnetic resonance imaging (MRI): Finding consistent with recurrent infiltrating astrocytoma (**A**) coronal T2; (**B**) axial fluid-attenuated inversion recovery; (**C**) sagittal T1 gadolinium; (**D**) diffusion tensor imaging, three-dimensional axial and sagittal. Intraoperative images. Correlation between the different moments of the surgery (**E**) white light; (**F**), 5-aminolevulinic acid 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, isocitrate dehydrogenase-wildtype, World Health Organization grade IV).

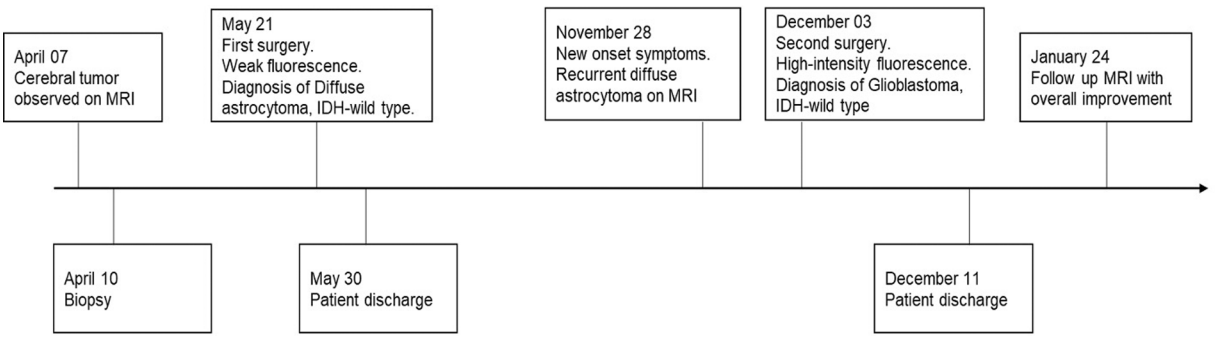

Fig. 3 Timeline of the clinical case. IDH, isocitrate dehydrogenase; MRI, magnetic resonance imaging.

Table 1 Fluorescence in World Health Organization grade II gliomas

Authors and year	Cases with positive fluorescence	Total cases
So Young Ji et al (2019)[11]	21 (25%)	87
Ewelt et al (2011)[12]	1 (8%)	13
Widhalm et al (2013)[9]	4 (9%)	33
Jaber et al (2016)[14]	13 (16%)	82
Marbacher et al (2014)[13]	8 (40%)	20

64.6 months [57.7–71.5], $p = 0.015$) in patients with low-grade glioma with positive fluorescence against those without.[13–16] 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 GBM 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 in 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.

Authors' Contributions

All authors contributed to manuscript conceptualization, investigation, manuscript edition, review and writing.

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