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5-ALA fluorescence–guided resection of a recurrent anaplastic pleomorphic xanthoastrocytoma: illustrative case

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BACKGROUND 5-aminolevulinic acid (5-ALA)–induced fluorescence of neoplastic tissue is known to occur in a number of high-grade gliomas. This fluorescence helps surgeons maximize safe resection by distinguishing previously indiscernible neoplastic tissue from brain parenchyma. Still, the effectiveness of 5-ALA has not been fully explored for all central nervous system tumors. Consequently, the full spectrum of tumors that would benefit from fluorescence-guided surgery using 5-ALA is unknown.

OBSERVATIONS This report describes successfully utilizing 5-ALA to achieve complete resection of a recurrent anaplastic pleomorphic xanthoastrocytoma (APXA).

LESSONS APXA tumor cells accumulate sufficient amounts of 5-ALA and its fluorescent metabolite to produce visible intraoperative fluorescence. However, further investigation is needed to determine if 5-ALA fluorescent labeling routinely occurs in patients with APXAs.

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KEYWORDS 5-aminolevulinic acid; fluorescence-guided surgery; recurrent astrocytoma; anaplastic; pleomorphic xanthoastrocytoma

Resection is the cornerstone of treatment for primary central nervous system (CNS) tumors. More extensive tumor resection appears to significantly impact recurrence rate, malignant transformation, response to adjuvant treatment (e.g., radiotherapy and chemotherapy), progression-free survival, and overall survival.[1–5] To achieve maximal safe cytoreduction of aggressive forms of primary CNS tumors, intraoperative real-time fluorescence with 5-aminolevulinic acid (5-ALA) is currently widely used by neurosurgeons.[6] Following oral administration, 5-ALA leads to the accumulation of a naturally occurring fluorophore of the heme synthesis pathway, protoporphyrin-IX (PPIX) in high metabolically active cells, such as tumor cells, and causes a pink fluorescence under ultraviolet light, allowing surgeons to discern tumor from the normal brain parenchyma, which does not accumulate PPIX.[5] Currently, 5-ALA is only routinely used in patients with suspected high-grade gliomas (HGGs) as it seems that fluorescence intensity is positively correlated with tumor grade.[7] Indeed, 5-ALA labeling significantly improves the rate of gross-total resection of grade IV gliomas, but its effectiveness in resection of lower grade gliomas (grades I to III) is not well established.[7–9] In this report, we present the first reported case of 5-ALA used for resection of a recurrent anaplastic pleomorphic xanthoastrocytoma (APXA), a rare form of glioma thought to be less aggressive than standard astrocytomas.

Illustrative Case

History and Presentation

A 46-year-old right-handed male with chronic lymphocytic leukemia (CML) diagnosed 3 years earlier taking dasatinib daily presented with headaches and a right visual field cut. Magnetic resonance imaging (MRI) revealed a heterogeneously enhancing mixed solid and cystic left occipital brain lesion extending into the occipital horn of the left lateral ventricle, with mass effect causing effacement of the left cerebellar sulci, entrapment of the temporal horn of the left lateral ventricle, and 5 mm of rightward midline shift (Fig. 1A). A stereotactic left occipital craniotomy was performed for resection and diagnosis. Pathology was consistent with a World Health Organization (WHO) grade III APXA

ABBREVIATIONS 5-ALA = 5-aminolevulinic acid; APXA anaplastic pleomorphic xanthoastrocytoma; CML = chronic lymphocytic leukemia; CNS = central nervous system; FDA = Food and Drug Administration; FGS = fluorescence-guided surgery; GTR = gross-total resection; HGC = high-grade glioma; MRI = magnetic resonance imaging; PPIX = protoporphyrin-IX; TMZ = temozolomide; WHO = World Health Organization.

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and ATG7-RAF1 gene fusion. Postoperative MRI demonstrated residual nodular enhancement along the anterolateral aspect of the resection cavity, indicating near gross-total resection (GTR) (Fig. 1B). After recovering from surgery, the patient was treated with chemoradiation therapy per the Stupp protocol, receiving fractionated radiotherapy and concurrent temozolomide (TMZ) for 6 weeks followed by 12 cycles of TMZ. Treatment was completed 19 months after initial presentation, and regular MRI scans showed no evidence of disease progression. The patient was doing well clinically, with residual right hemianopsia.

Surveillance MRI 23 months after initial presentation demonstrated growth of the enhancing region in the anterior-lateral aspect of the resection cavity (Fig. 2A). At this time, it was difficult to distinguish whether this enhancement represented treatment effect or tumor recurrence. Therefore, follow-up MRI in a shorter interval was recommended. MRI with a perfusion study 2 months later showed a growing area of enhancement in the anterior-lateral region of the resection cavity, primarily at the atrium of the left ventricle (Fig. 2B). Nonelevated relative cerebral blood volume of this area suggested treatment effect. Two subsequent MRI studies, each a month apart, demonstrated slight interim growth of the known anterior-lateral enhancement and new growth of a smaller inferior and lateral focus. The patient also reported new symptoms of right-sided visual hallucinations that improved after starting Keppra. MRI 6 weeks after the previous MRI showed an increased size of three sites in the resection cavity (Fig. 2C). MRI spectroscopy was concerning for disease recurrence with an elevated choline/creatinine ratio and a reduced N-acetylaspartate peak. At this time, following a multidisciplinary discussion between his surgeon, neuro-oncologist, and radiation oncologist, surgery was recommended for definitive diagnosis and, if it was tumor, resection of the lesions. The patient was in agreement with the surgical plan.

Operation

The patient underwent a revision left occipital craniotomy for possible tumor recurrence versus treatment effect with an intraoperative optical imaging agent dosed 2 hours prior to induction of anesthesia. After removing the prior craniotomy skull plate and opening the dura, the most superficial lesion was visualized as grossly abnormal under loupes and white light visualization and removed en bloc. The pathological report from a frozen specimen of this lesion confirmed recurrent glioma. Surgery proceeded using the intraoperative microscope for resection of the remaining lesions. The left lateral ventricle was entered medially, and the choroid plexus was visualized. No apparent tumor was seen in the ventricle. The microscope blue light was then turned on, and an area within the inferior portion of the atrium fluoresced pink (Fig. 3). A small piece of enhancement tracking lateral to this periarterial lesion also had avid fluorescence. All fluorescent 5-ALA–labeled tissue under blue light was resected. The surgery was completed without complication, and the patient maintained his preprocedure neurological baseline. No adverse effects related to 5-ALA occurred, including the absence of common side effects such as skin reactions and abnormal liver function tests. The patient was discharged on postoperative day 3.

Postoperative Imaging and Histological Findings

Postoperative MRI revealed resection of the previously demonstrated enhancing nodular foci adjacent to the resection cavity with no evidence of residual enhancement (Fig. 4).

Histological examination of the resected tissue showed a moderately cellular tumor composed of solid nests and sheets of epitheloid cells, with readily apparent mitotic figures and some with pleomorphic nuclei, consistent with recurrent APXA WHO grade III. Molecular testing revealed an ATG-RAF1 gene fusion and a homozygous deletion

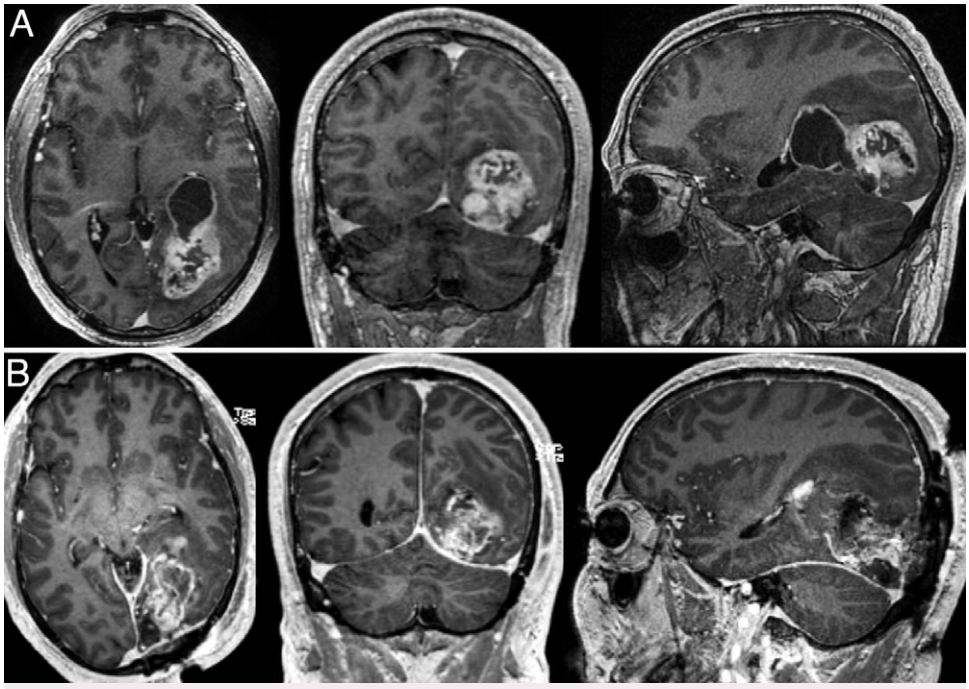

FIG. 1. Initial axial, coronal, and sagittal T1-weighted postcontrast images (**A**) showing a large mixed cystic and solid heterogeneously enhancing lesion in the left occipital lobe that extends into the left lateral ventricle. Postoperative MRI (**B**) showing that a majority of the mass had been resected with a small residual enhancing component anterior to the resection cavity.

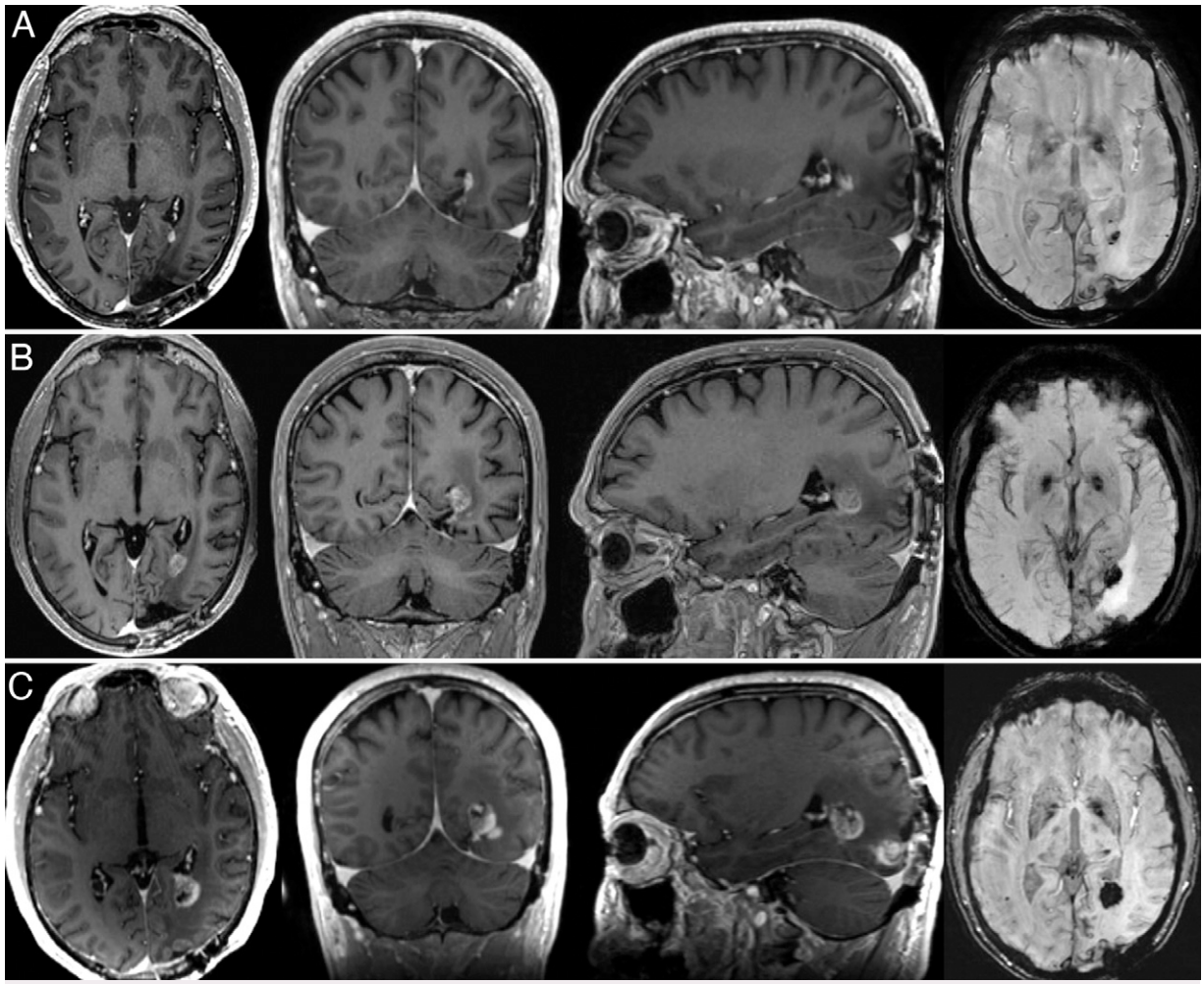

FIG. 2. Surveillance MRI (**A**) showed a focal enhancing nodularity within the resection cavity and extending into the left atrium, which correlated with an area of focal new susceptibility (*upper right*). Follow-up MRI (**B and C**) demonstrated interval progression of the enhancing nodule. The sequences, from left to right, are axial, coronal, and sagittal T1-weighted postcontrast and axial susceptibility-weighted imaging.

of CDKN2A. Tumor cells were in a perivascular distribution, as well as diffusely infiltrating into the brain parenchyma. Additionally, reactive gliosis, macrophage infiltration, and chronic inflammation consistent with treatment-related changes were evident in the surrounding brain parenchyma. The tumor was overall similar in histological appearance and molecular profile to his previously resected APXA.

Given the findings of recurrent tumor, the patient was recommended to resume TMZ therapy and started the first cycle one month postoperatively.

Discussion

Observations

In 2006, a landmark randomized phase 3 study by Dr. Walter Stummer demonstrated that fluorescence-guided surgery (FGS) using 5-ALA enabled surgeons to achieve more complete resections of HGGs.[6,9–11] Since Stummer's landmark trial, studies have repeatedly demonstrated that 5-ALA improves the extent of resection achieved in patients with glioblastomas and other WHO grade III tumors.[5,11–15] In 2017, the United States Food and Drug Administration (FDA) approved 5-ALA as an intraoperative optical imaging agent in patients with suspected grade III or grade IV gliomas.[6]

5-ALA is an endogenous nonfluorescent intermediate in the heme synthesis pathway. When given orally, exogenous 5-ALA preferentially accumulates in proliferating tumor cells. Once inside the cell, it is incorporated into the heme biosynthesis pathway where it is eventually metabolized into PPIX, a fluorogenic substrate.[5,8] Under blue-violet light, PPIX causes tumor-specific tissue to fluoresce pink.[5,8] Unfortunately, fluorescence is not a universal feature of all neoplasms. For example, in histopathological analyses of radiologically suspected gliomas, all tumors showing visible fluorescence were classified as at least WHO grade III gliomas, while those that did not show any visible fluorescence were classified as low-grade gliomas.[16] In other studies, a significantly higher mitotic rate, cell density, nuclear pleomorphism, and proliferation rate were found in tumors with fluorescence compared to tumors without visible fluorescence,[8,17] indicating that visible 5-ALA fluorescence is associated with the degree of malignancy.

Fluorescence induced by 5-ALA is often heterogeneous in intensity, ranging from bright to absent.[9] Bright fluorescence identifies tumor tissue

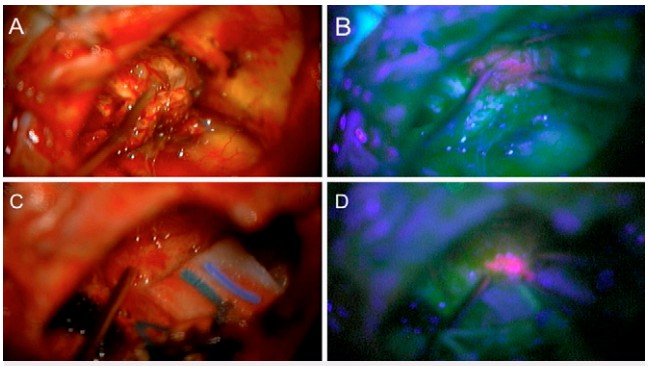

FIG. 3. The tumor was indistinct from the brain parenchyma using white light microscopy (**A and C**) but became discernable under blue light (**B and D**).

with a positive predictive value of 95 to 100%.[9] However, a lack of fluorescence does not necessarily mean the absence of tumor cells. In fact, some studies report that a substantial portion of nonfluorescing tissue specimens—as much as 40% to 60%—contain tumor cells.[18] Additionally, vague tissue fluorescence typically occurs when tumor cells are invading normal tissue, although tissue samples infrequently show solid tumor and rarely normal tissue.[18]

Currently, 5-ALA is only FDA-approved for new or recurrent glioblastoma multiforme (WHO grade IV), anaplastic astrocytoma (WHO grade III), anaplastic oligodendroglioma (WHO grade III), and anaplastic ependymoma (WHO grade III).[9] Ascertaining additional tumors that reliably fluoresce after 5-ALA administration is an area of great interest within neurosurgical oncology. To this end, 5-ALA is increasingly being used off-label to study its fluorescence in other central nervous system tumors. For example, several studies have reported positive 5-ALA fluorescence in meningiomas, with fluorescence rates ranging from 83% to 94%.[9,14,19–22] 5-ALA FGS has also been described for hemangioblastomas, which reportedly fluoresce well despite being low-grade vascular tumors.[9,23,24] Other studies report PPIX accumulation and positive fluorescence in CNS lymphomas,[25–27] germ cell tumors,[28] papillary glioneuronal tumors,[29] brain metastases,[27,30,31] medulloblastoma,[32] subependymomas,[33] and ependymomas.[33,34] A few case studies report using 5-ALA for the intraoperative visualization of pleomorphic WHO grade II xanthoastrocytomas. In each case a strong, homogeneous 5-ALA–induced fluorescence was observed.[35–37] To the best of our knowledge, there are no documented reports of 5-ALA fluorescence in APXA.

Pleomorphic xanthoastrocytomas and APXA are rare WHO grade II and WHO grade III astrocytic tumors, respectively.[38] Standard treatment includes a combination of maximal safe resection, radiation, and chemotherapy.[36,38] The extent of resection significantly impacts patient outcomes, with more extensive tumor resection correlating with more favorable outcomes.[36,38] Unfortunately, tumor margins are not always visible intraoperatively, making it difficult to resect all tumor tissue. If GTR is not achieved, the tumor may recur or undergo a malignant transformation. With conventional white-light microscopy, the deeper region of recurrent tumor was not readily apparent. After the blue light was turned on, the once indistinguishable tumor avidly fluoresced pink, and margins between APXA and normal brain became discernable. As a result, complete resection of the patient's recurrent APXA was achieved, as assessed by postcontrast MRI.

It is important to note, especially for cases such as this one in which the differential is recurrent tumor versus treatment effect, that fluorescent tissue does not always harbor tumor cells. For example, Kamp et al.[28] detected solid or vague 5-ALA-induced fluorescence without histological evidence of tumor in 13 of 313 patients with recurrent glioma. Similarly, Utsuki et al.[23] encountered false-positive fluorescence in 5 of 11 patients with recurrent gliomas. In both studies, false-positive regions corresponded to peritumoral areas marked by inflammatory changes. Interestingly, immune cells, like tumor cells, accumulate PPIX when incubated with 5-ALA, mimicking tumor fluorescence. This is further supported by documented reports of 5-ALA–induced fluorescence observed in other nontumorous inflammatory conditions, including cerebral abscesses and cerebral infarctions.

It is hypothesized that an immune response coupled with a compromised blood-brain barrier may cause 5-ALA–induced false-positive fluorescence in patients with glioma treated with adjuvant radiation therapy. Hydrophilic porphyrins like uroporphyrin and coproporphyrin produced during 5-ALA metabolism leak across the compromised blood–brain barrier.[39,40] Once across, these are metabolized to the fluorescent porphyrin PPIX, which selectively accumulates in peritumoral sites with inflammatory treatment-related changes. Therefore, critical differential diagnoses to consider in patients previously or currently receiving radiation treatment are treatment-related changes, including pseudoprogression and radiation-induced necrosis, which are

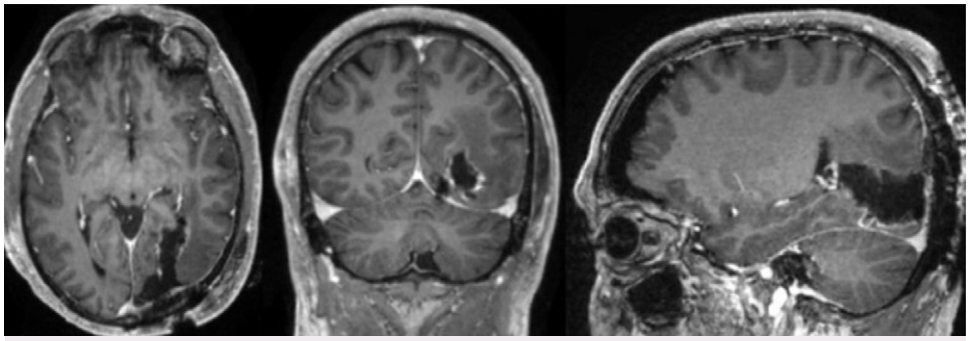

FIG. 4. Postoperative axial, coronal, and sagittal MRI after redo left posterior occipital craniotomy for resection of previously demonstrated nodular enhancing foci, showing no evidence of residual enhancement along the inferomedial aspect of the resection cavity.

histologically marked by an inflammatory infiltrate of reactive astrocytes, macrophages, and neutrophils.[18]

Nevertheless, 5-ALA FGS is highly beneficial in the setting of recurrent gliomas. In one analysis, the positive predictive value for fluorescing tissue that looked abnormal under white light was 97%.[18,41] This study also noted that, in general, infiltrating tumors of primary WHO grade III and IV gliomas demonstrated weak fluorescence, whereas infiltrating zones of recurrent cases included both strong and weak fluorescence intensities.[18,41] Interestingly, the strong fluorescent areas often appeared normal under white light, but biopsies revealed areas of dense cellular infiltrating tumor.[18,41] Furthermore, the resection of false-positive tissue resulted in neither new temporary nor permanent neurological deficits in several case series and case reports, indicating the fluorescent tissue is likely not functionally intact. Ultimately, visualization and identification of fluorescent tissue via 5-ALA can be highly useful in the recurrent setting when the area of abnormality may not look grossly obvious under white light, and biopsy of fluorescent tissue for intraoperative frozen section analysis may help guide surgical decision making.

Lessons

5-ALA fluorescent labeling aids neurosurgeons in achieving maximal safe resection of tumors when its fluorescent metabolite PpXI accumulates in neoplastic cells to cause fluorescence of tumor tissue under blue light. PpXI accumulation is variable, and not all neoplastic tissue accumulates sufficient amounts to produce visible intraoperative fluorescence. Questions remain regarding which tumors fluoresce when 5-ALA is used as an adjuvant for resection. Recently, investigating the use of 5-ALA in various CNS neoplasms to identify tumors in which 5-ALA FGS can be used to achieve maximum safe resection has become of great interest within neurosurgical oncology. This present case illustrates that APXA may be among those tumors to present with visible intraoperative fluorescence, even in the setting of recurrence, and that these patients may benefit from 5-ALA FGS, although additional research is needed.

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Disclosures

Dr. Jones reported a patent for MGH25618 pending. No other disclosures were reported.

Author Contributions

Conception and design: Jones, Muñoz. Acquisition of data: Jones, Muñoz. Analysis and interpretation of data: Jones, Muñoz. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Jones. Study supervision: Muñoz.

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