CASE REPORT

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# Longer survival of a patient with glioblastoma resected with 5-aminolevulinic acid (5-ALA)-guided surgery and foreign body reaction to polyglycolic acid (PGA) suture

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## Abstract

In recent years, there is a growing evidence that using 5-aminolevulinic acid (5-ALA)-guided resection of a cerebral glioblastoma, associated with chemoradiotherapy determine a prolonged survival of these patients, even though this period do not exceed 15 months. 5-ALA is a natural biochemical precursor of heme that is metabolized to fluorescent porphyrins, particularly protoporphyrin IX (PPIX) and no foreign reaction were noted until now. However, foreign body reaction developing in neurosurgery is documented in a few number of cases to suture material, surgical hemostatic material, or surgical glove starch, but up to now we could not find any article about granulomatous inflammation to polyglycolic acid (PGA) suture after brain tumor resection. Here we present a case of a delayed foreign body granuloma to PGA suture diagnosed after 10 months following fluorescence-guided surgery with 5-ALA for resection of a cerebral glioblastoma that was difficult to diagnosis both clinically and on magnetic resonance imaging (MRI). Moreover, the survival time was longer. We correlate the appearance of foreign body granuloma with the patient's persistent pre- and postoperative lymphocytosis. We also suggest that the chronic inflammation inhibited the proliferation of any tumoral cells which could remain in the tumor bed because we did not noticed on serial MRI scans a rapidly tumor growth during the first 10 months after the initial surgery as we have expected to be for a glioblastoma.

***Keywords***: glioblastoma, relapse, foreign body granuloma, 5-ALA-guided surgery, polyglycolic acid suture.

## Introduction

Glioblastoma is the most common type of primary brain tumor in adults, accounting for approximately 45% of all these neoplasias, whose incidence has risen slowly in recent decades, and its peak age of onset moved to 75–84 age group [1]. The glioblastoma treatment includes surgical resection, radiotherapy and chemotherapy. However, the best treatment option is to remove as much as possible of the tumor volume, but in the same time to keep to a minimum its morbidity. In the past, surgery alone or combined with radiotherapy led to median survival of 12 months. Nowadays, median survival extended to 15 months with maximum safe surgical resection and concurrent chemo-radiotherapy using temozolomide and external beam radiotherapy [2].

There is a growing evidence that a maximal cyto-reduction (more than 98% of the original tumor) is an important prognostic factor for patient's survival [3], but this aim is difficult to achieved due to the infiltrative character of these tumors. In recent years, this difficulty seem to be eradicated in some prospective randomized studies that used fluorescence 5-aminolevulinic acid (5-ALA)-guided surgery [4, 5]. 5-ALA is a natural biochemical precursor of heme that is metabolized by a series of enzymatic reactions to fluorescent porphyrins, particularly protoporphyrin IX (PPIX). Systemic administration of 5-ALA results in an overload of the cellular porphyrin metabolism and accumulation of PPIX in various epithelia and cancer tissues. Glioblastoma tumor cells synthesize and accumulate porphyrins after application of 5-ALA. PPIX formation induced by 5-ALA is significantly higher in malignant tissue than in normal brain. In the presence of blue light, the fluorescence determined by PPIX (photodynamic effect) in certain target tissues can be used for photodynamic diagnosis [6]. Some studies have shown that 5-ALA-guided resection of glioblastomas determines a longer period without tumor progression and a longer survival because this method gives a complete tumoral cytoreduction [4–6]. However, even if a maximum cytoreduction is achieved, glioblastomas could recur rapidly and the prognosis is poor.

There are very rare cases where the tumor relapse is mimicked by the development of other injuries in the tumor bed, like foreign body reaction, abscess, or tumor radio-necrosis [7, 8]. Postsurgical abscess has elements of identification on imaging, but foreign body reaction or radiation necrosis lend characteristics from tumor

relapse because it appears on magnetic resonance (MR) images to be indistinguishable from recurrent tumor.

Foreign body reaction developing after intracranial surgery is documented in few number of cases, and these were meningioma [9, 10], primitive neuroectodermal tumors [8], gliomas [11], pituitary adenomas [11], and aneurysmal embolizations [12].

Intracranial foreign body reaction was diagnosed after a period of time ranging from two months [8] up to 19 years after surgery [9]. Throughout the time, the authors used various terms to describe these foreign body reactions and these were: gauzoma [13], gossypiboma [14], textiloma [11], or muslinoma [11], depending on the foreign body which caused chronic granulomatous inflammation. In neurosurgery, the foreign body reaction can have diverse etiologies, *i.e.*, the non-absorbable suture material, like silk [15], surgical hemostatic agents, be it absorbable, like gelatin sponge (Gelfoam) [8, 16], oxidized cellulose (Surgicel) [17], microfibrillar collagen (Avitene) [18], or cotton [19–21], rayon [21], surgical glove starch [22], bone wax [23], or polytetrafluoroethylene used as a graft material [24], but until now we could not find any article about granulomatous inflammation to polyglycolic acid (PGA) suture after brain tumor resection.

Here we present a case of a delayed foreign body granuloma to polyglycolic acid suture diagnosed after 10 months following fluorescence-guided surgery with 5-ALA for resection of a cerebral glioblastoma.

## Case presentation

A 49-years-old man was admitted in the 2nd Clinic of Neurosurgery, "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iaşi, Romania, for confusion, aphasic syndrome and left crural monoparesis. Cranio-cerebral computed tomography (CT) scan performed in emergency and the subsequent brain magnetic resonance imaging (MRI) scan revealed an intracranial right fronto-insular infiltrative tumor, with significant peri-lesional edema and central necrosis (Figure 1, a and b).

The surgical intervention was decided and the patient received 20 mg/kg 5-aminolevulinic acid administrated orally, two hours before surgery. The operation was performed with OPMI® PENTERO® 900 from ZEISS equipped with a fluorescent 400 nm UV light and filters.

Microsurgical removal was started using standard white light (Figure 2a). After switching to the violet-blue excitation light, a vivid red porphyrin fluorescence marked malignant glioma tissue (Figure 2b) and the tumor boundaries were visualized distinct from healthy brain tissue, allowing the complete resection of the tumor, confirmed by postoperative MRI (Figure 4a). Intraoperative dural closure was made using polyglycolic acid suture. The surgically removed specimen was submitted to the Department of Pathology. The histopathological examination revealed a corticalized malignant tumor made up of pleomorphic glial cells with marked nuclear atypia and with glomeruloid microvascular proliferation (Figure 3, a and b). As demonstrated by immunohistochemical stainings, glial fibrillary acidic protein (GFAP) were consistently expressed by tumor cells (Figure 3c), which also showed a high MIB1/Ki67 labeling index (25%) (Figure 3d). A final pathological diagnosis of glioblastoma grade IV was made.

Postoperative evolution was favorable, with remission of the neurological deficits. After one month, the patient was referred to the Regional Institute of Oncology from Iaşi, for the post-operative radiotherapy (60 Gy/30 fractions to the tumor lodge five times a week for six weeks) and chemotherapy with temozolomide, according to standardized scheme.

The gadolinium-enhanced MR image performed at three months after surgery (Figure 4b) showed no evidence of tumor relapse. However, a frontal cicatricial area with liquidian signal, surrounded by local gliosis and peripheral moderate irregular linear contrast, suggested scarring and post-radiotherapy features (Figure 1b). The main hematological derangements included: neutropenia – 45.5% [normal values (N): 54–57%], eosinophilia – 6.8% (N: 2.4–2.7%), basophilia – 0.9% (N: 0.2–0.6%), and lymphocytosis – 41.7% (N: 25–40%).

At 10 months after surgery, the patients came back to our Clinic as he presented cephalalgia. Again, the main hematological derangements included lymphocytosis – 42.9% (N: 25–40%).

The gadolinium-enhanced MR image of the brain demonstrated a right frontal cicatriceal area with hypo-signal in T1, associating deep inhomogeneous contrast without significant edema around and without mass effect on neighboring structures. These features suggested a recurrent glioblastoma (Figure 4, c and d) and a new surgical intervention using 5-ALA was decided. A vague intraoperative fluorescence activity was observed within the lesion (Figure 5, a and b).

Intraoperative cytopathological exam revealed fibrous tissue with newly formed vessels and some inflammatory cells. The histopathological exam (Figure 6, a–d) showed a proliferation of fibrous connective tissue with newly formed vessels and many giant multinucleated cells aggregated around a foreign material (amorphous refractive material with a string appearance considered to be PGA). Few lymphocytes and plasmacytes infiltrated the area and many "foamy" cells agglomerated nearby. In the periphery of this area, a small fragment of nervous tissue with activated astrocytes showing plump cell bodies and eccentric nuclei could be seen, but no tumoral cell could be found. The final pathological diagnosis was foreign body reaction to PGA suture and glial reaction of the surrounding nervous tissue.

After another five months, MRI scan (Figure 7a) revealed a frontal lobe lesion with irregular borders, central necrosis and intense, heterogeneous enhancement of the margins, with no significant mass effect. At 18 months from the first intervention, the patient returned to our Clinic for frontal lobe syndrome, left brachial monoplegia and left crural monoparesis. The main hematological derangements included lymphocytosis – 45.3% (N: 25–40%). The gadolinium-enhanced brain MR image (Figure 7b) demonstrated intra-axial frontal parenchymal area with inhomogeneous structure and peri-lesional edema. A quasi-total tumoral resection was done. The histopathological exam revealed a recurrent glioblastoma (Figure 8). Favorable postoperative course was slow, but the patient could not move. After another four months, *i.e.*, at 22 months after his first surgery, the patient died due to the tumor expansion.

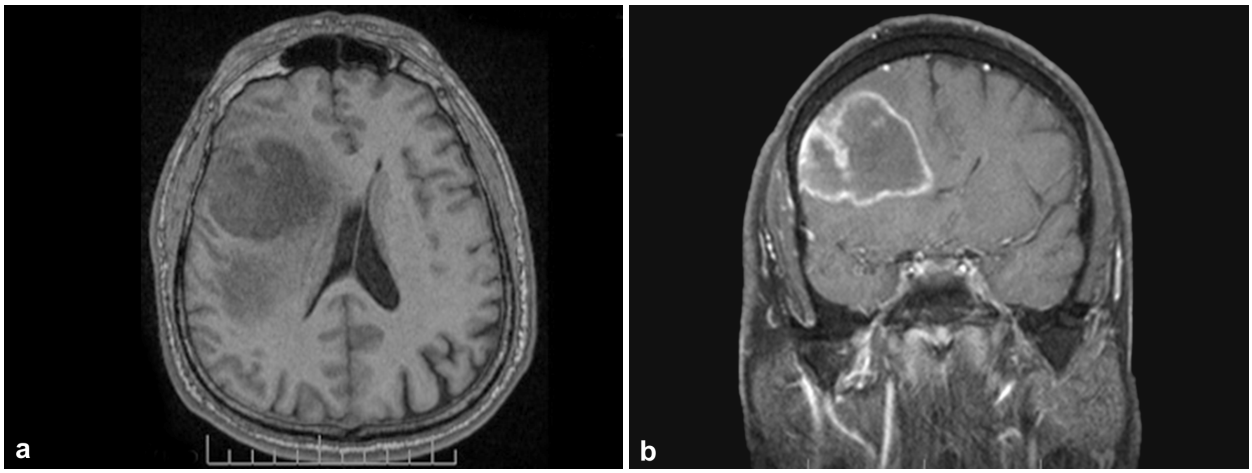


**Figure 1** – ***Preoperative brain MRI scan with gadolinium: axial T1 (a) and sagital T1 (b) showed a left large irregular fronto-insular mass with central necrosis and a nodular zone.***

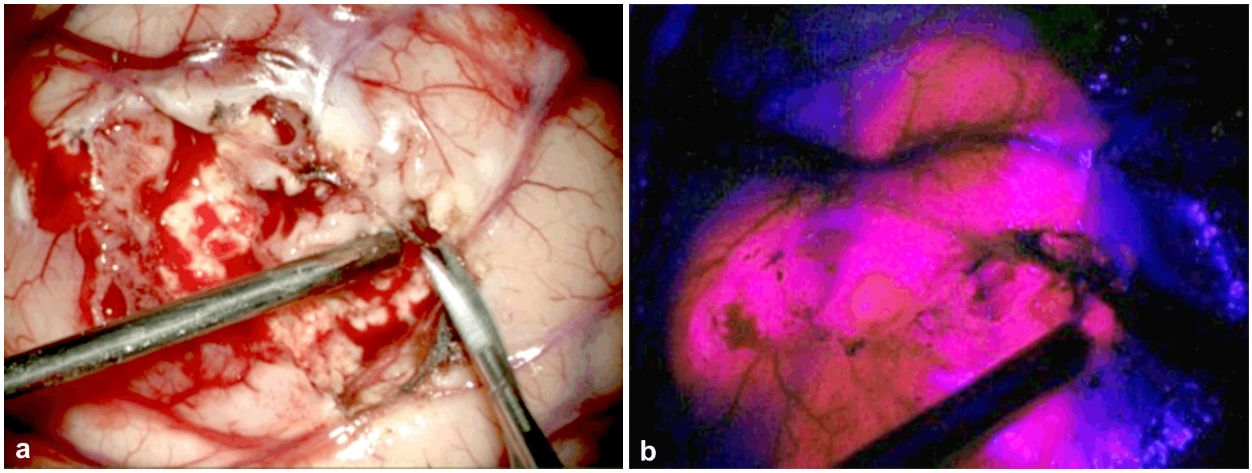


**Figure 2** – ***Intraoperative photograph: tumoral mass appearance under white (a) and blue (b) light.***

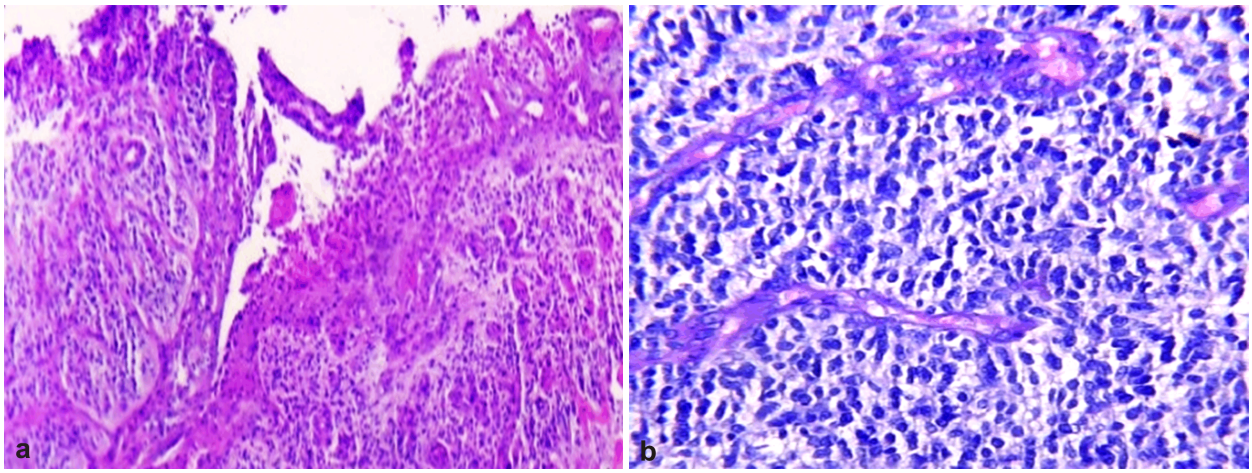


**Figure 3** – ***Microphotographies of the resected specimens on first intervention demonstrated the existence of a glioblastoma grade IV: (a) Cortical tumor made up of anaplastic astrocytes and glomeruloid vessels; (b) A higher objective showed the pleomorphism of the tumoral astrocytes. HE staining: ×200 (a); ×400 (b).***

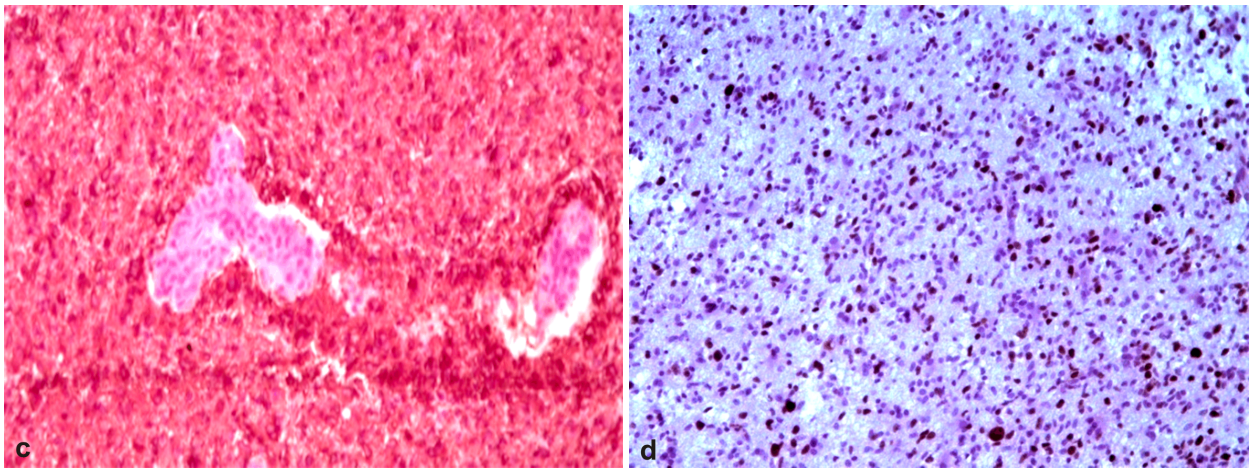


**Figure 3 (continued) –** ***Microphotographies of the resected specimens on first intervention demonstrated the existence of a glioblastoma grade IV (Immunostaining, ×200): (c) Tumoral cells presented GFAP positivity; (d) Tumoral cells showed a high MIB-1/Ki67 index.***

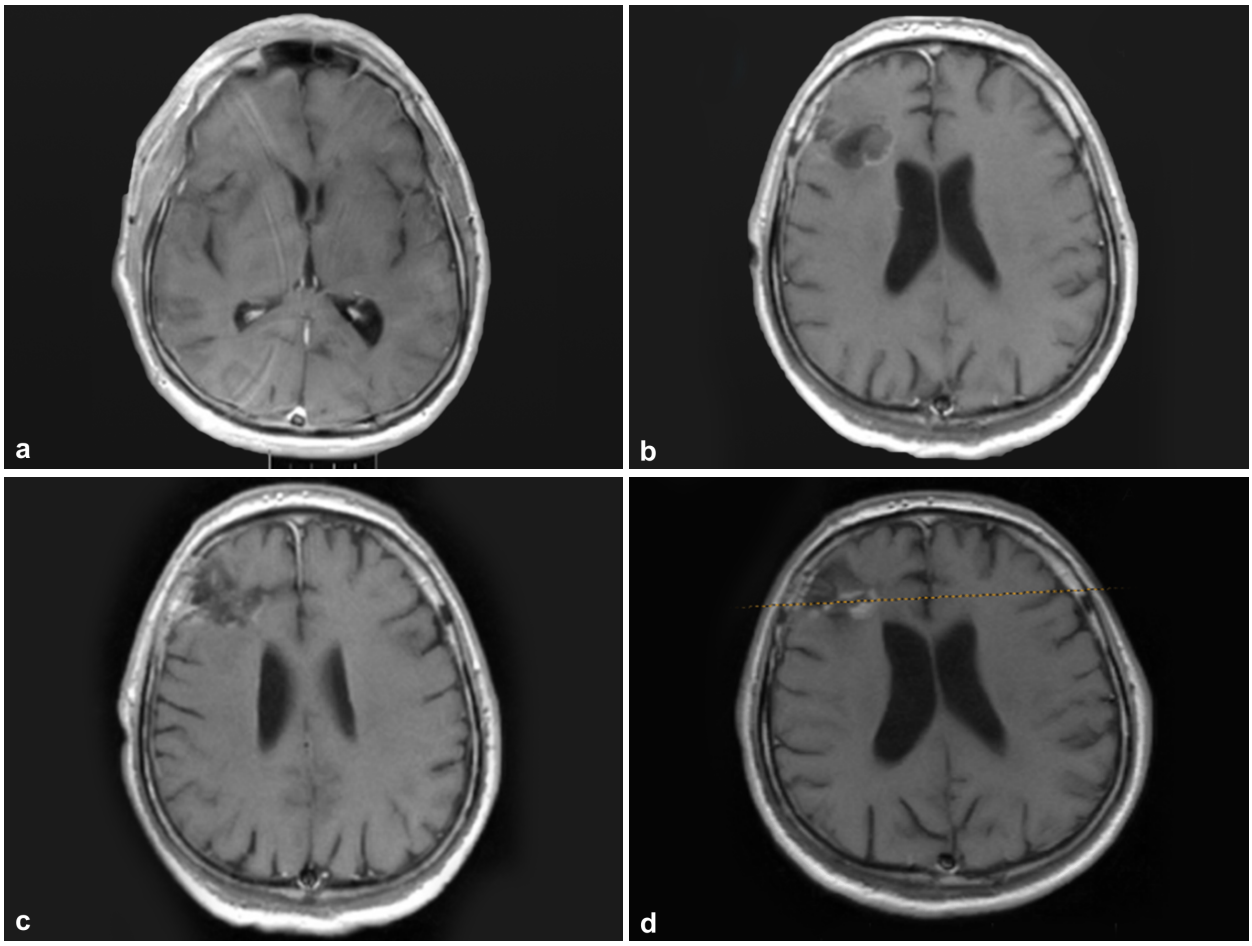


**Figure 4 –** ***(a) Postoperative axial T1 with gadolinium MRI scan demonstrated the complete resection of tumor; (b) Brain MRI scan after three months did not reveal any recurrent tumor on axial T1 with gadolinium; (c and d) Brain MR images after 10 months from the first intervention showed a small mass with heterogeneous peripheral enhancement on T1 axial scans.***

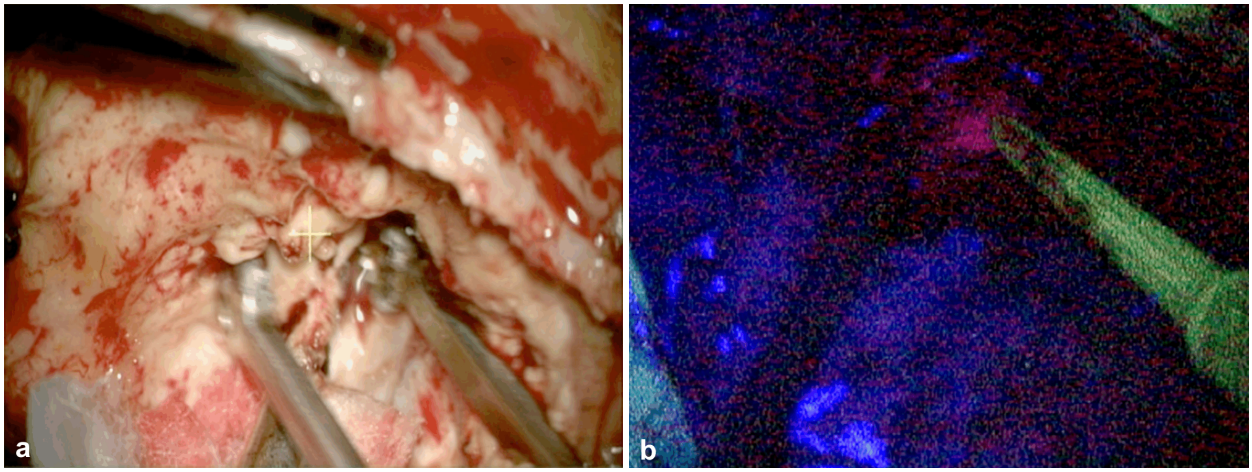


**Figure 5** – ***Intraoperative photograph from the second intervention: lesion appearance under white (a) and blue (b) light.***

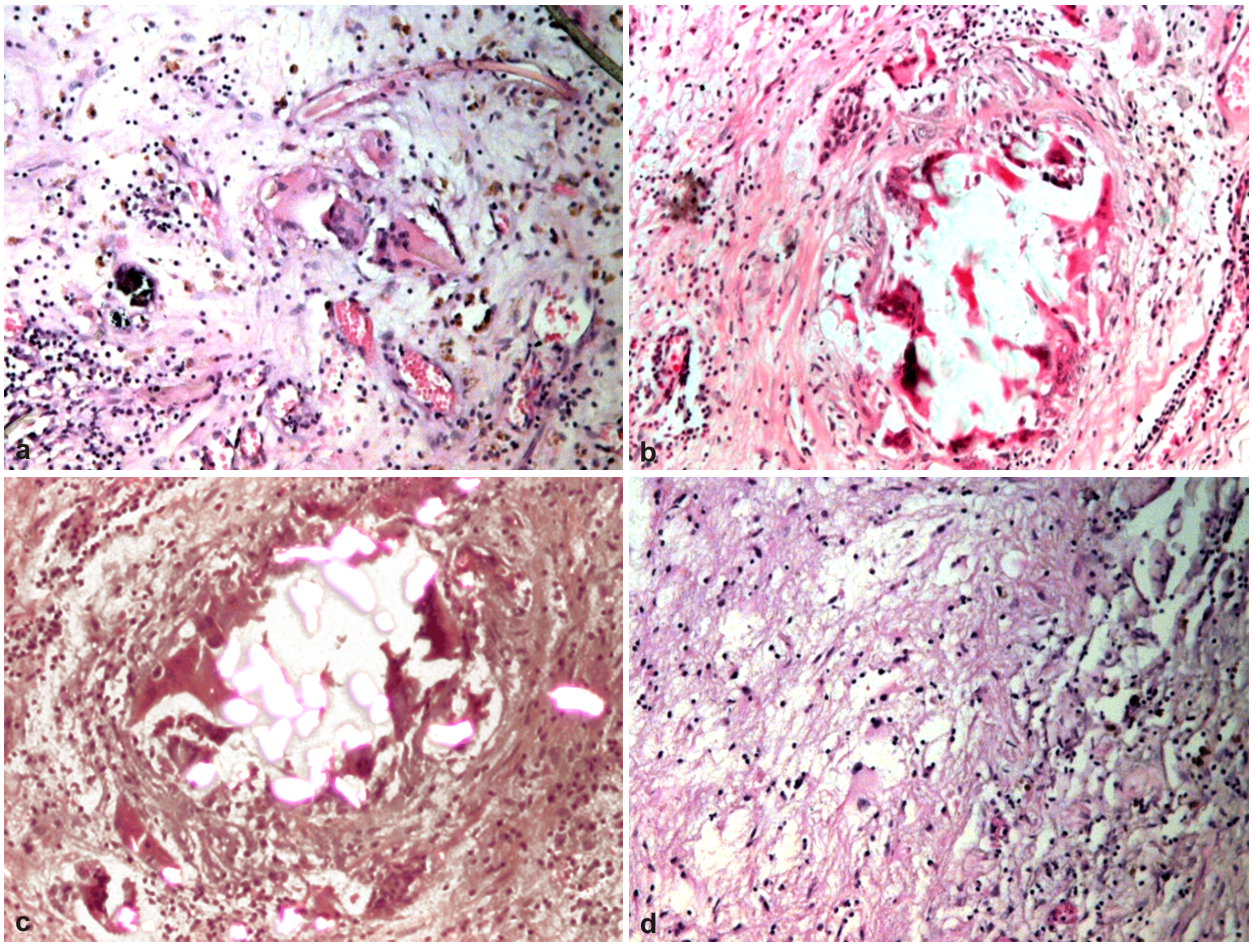


**Figure 6** – ***Microphotographies of the specimens resected on the second operation (HE staining, ×200): (a) Fragments of PGA suture surrounded by foreign body giant cells, and few lymphocytes; (b) Foreign body granuloma centered by fragments of PGA suture; (c) Same aspects in polarized light showing the birefringence of PGA suture; (d) Astrocytic reaction of the nervous tissue from its vicinity.***

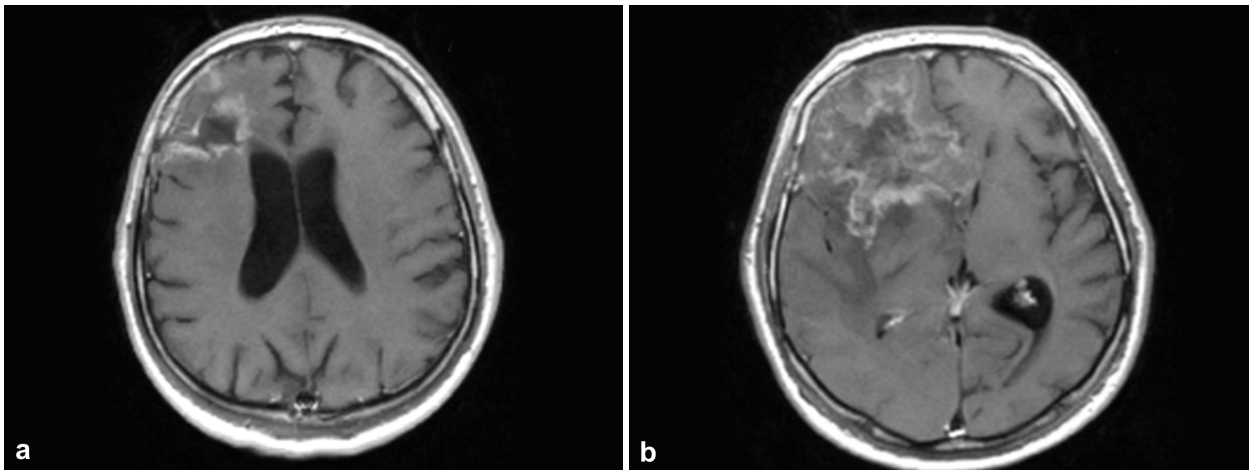


**Figure 7** – ***Brain MRI scan at 15 months (a) and 18 months (b) after the first intervention showed tumoral relapse and rapid growth.***

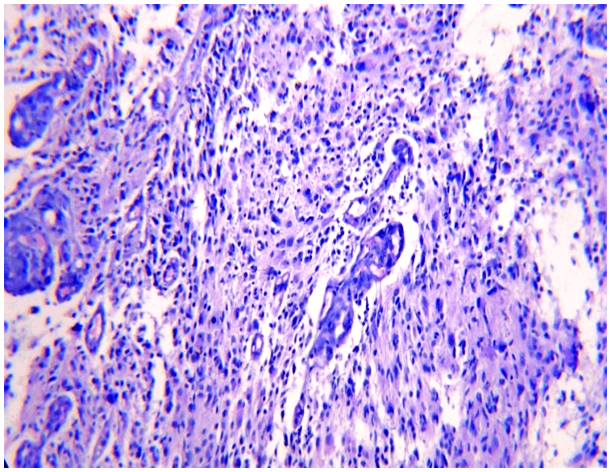

**Figure 8** – ***Microphotography of the specimens resected on the third operation demonstrated a recurrent glioblastoma, grade IV (HE staining, ×200).***

## Discussion

Glioblastoma has a very high growth rate, *in vivo* studies demonstrating an increase of the tumor volume of 1.4% daily, and the tumor diameter doubling in 49.6 days [25].

The extent of glioblastoma resection determines the length of life expectancy. Therefore, improving intra-operative tumor visualization using 5-ALA is of major importance in establishing the prognosis of these patients [5, 6].

5-ALA was used in cerebral glioblastoma surgery for the first time in 1998 by the German physician Walter Stummer [26], and from its approval, in 2007, numerous studies have reported its use not only in gliomas, but in other various brain tumors such as meningioma or metastases [27–29]. Due to its safety and high tumor specificity, 5-ALA is currently used in many neurosurgical centers in the whole world [30–32], including Romania, *i.e.*, in Iaşi [33, 34]. However, granulomatous inflammation to 5-ALA have not been reported up to the present.

Patients treated with 5-aminolevulinic acid-guided surgery had higher 6-month progression free survival and higher overall survival than did those treated with classical surgery in white light [30, 31] because 5-ALA-guided microscopy greatly aided the surgeon in visualizing abnormal tissue and therefore in obtaining an extensive resection and an overall survival of approximately 14 months [30–32].

Gross total resection of glioblastoma is defined as the absence of contrast enhancement on post-operative T1-weighted MRI scans performed within 72 hours after brain surgery. We achieved this goal in the case of our patient. However, our patient's lifetime was 22 months, with seven months longer than the average reported in the literature, but we believe that not only the resection performed under the guidance of 5-ALA fluorescence was the cause, but in this case also intervened the development of a delayed granulomatous reaction to PGA sutures remnants from dural closure.

PGA suture was the first synthetic absorbable suture, which was manufactured in the early 1970s and then used in various combinations with other biodegradable polymers in medicine [35, 36]. PGA suture is a synthetic, absorbable, sterile, multifilament braided surgical suture composed of 100% glycolic acid that, after its use, suffers a progressive hydrolysis and enzymatic cleavage that would be completed between 60 or 90 days [37]. As a result, the PGA sutures lose about 50% of their strength after two weeks and 100% in four weeks [38]. PGA degradation is carried out in two major phases: in the first 21 days appears the diffusion of water into the amorphous regions of the matrix and simple hydrolytic chain scission of the ester groups. The second stage of degradation takes the next 28 days and involves degradation of the crystalline areas of the polymer, which becomes predominantly when the majority of the amorphous regions have been eroded. At this stage, these small fragments may trigger a foreign body reaction. A metabolic stage follows, in which non-toxic degradation products (lactic acid and glycolic acid, respectively) are transformed in carbon dioxide and water, which eliminate through the respiratory route [39].

In some cases, the degradation products of PGA and various chemicals that are added to strengthen the polymer

can cause inflammatory reactions [40], but very few articles have proven the appearance of foreign body reactions when using this kind of suture. In orthopedics, its usage as biodegradable suture anchors for treating tendon and ligament pathology in hand surgery determined intraosseous foreign body reaction and massive osteolysis after 12 months from the initial intervention [41, 42]. Such events were also reported when using PGA in oral surgery as biodegradable implants [43] and were considered to be a delayed type of hypersensitivity [44].

PGA is generally well tolerated in cranial and spinal usage [45], although in rare situation it can cause postoperative complications such as postoperative fistula after the use of a combination of polyglycolic acid mesh and fibrin glue in dural repair [46].

PGA sutures have been reported to produce only rarely a mild inflammation [47], but so far no study outlined foreign body reaction to PGA suture.

From a histopathological point of view, PGA suture used for closing the dura begins to degrade by depolymerization, leading to simultaneously healing of the dura mater [35]. However, in our case, a foreign body granuloma developed after several months from the initial intervention for glioblastoma resection. On microscopy, we have seen a biomaterial-mediated foreign body reactions at dural level, in close contact with gliotic nervous tissue.

As our case demonstrated by polarized light microscopy, in certain circumstances, around partial depolymerisated PGA fragments, a great number of multinucleated foreign body giant cells appeared trying to degrade the suture remnants. The granulation tissue initially associated with the presence of the foreign body tended to progress to fibrosis. Lymphocytes finally contribute to foreign body granulomatous reactions. In the case we presented, around the foreign body granulomas we noticed an extended area of foamy macrophages, which are the marker of nervous tissue necrosis from the neighborhood. The process of cortical necrosis probably was the consequences of some small ligaturated vessels during hemostasis. As Mogoantă *et al.* [48] stated, the presence of foamy macrophages probably was triggered from the first day of nervous tissue ischemia. Firstly, the microglial cells proliferate and assume an amoeboid morphology, becoming activated and ready to phagocyte the dying neurons. However, around an infracted area, microglial proliferation and activation occurred gradually from one to 12 weeks after the ischemic insult [49] and the important influx of macrophages could sustain the inflammation [50].

Also, we found numerous activated astroglia into the nervous tissue nearby the foreign body granuloma. Activated astrocytes showed a swelled cell body and an eccentric nucleus as Pirici *et al.* showed around the older ischemic lesions and around cavitation processes [51]. It seems that the increased number of activated microglia after ischemic injury can be the cause of astrocytic hypertrophy (*i.e.*, reactive astrogliosis) [49].

Our case presented preoperative persistent lymphocytosis, since the first hospitalization. In this situation, we presume that granuloma formation to PGA, which is non-toxic and immunologically inert, could be the result of this lymphocytosis as foreign body granuloma formation is the result of a delayed hypersensitivity where CD4+ T-cells have the central role. Eventually, an uncontrolled T1-helper lymphocytes response could be the trigger as foreign body granuloma is the result of type IV hypersensitivity that includes T-lymphocytes and monocytes and/or macrophages. Cytotoxic T-cells cause direct damage whereas T-helper cells secrete cytokines, which activate cytotoxic T-cells and recruit and activate monocytes and macrophages [52].

We also believe that, in this case, the process of foreign body granuloma formation inhibited proliferation of any tumor cells that remained in the tumor bed because we have noticed that during the first 10 months after the first surgery, serial MRI scans did not showed any rapidly tumor growth as we have expected to be for a glioblastoma. In addition, histopathological examination performed on specimens obtained from the second operation did not reveal any tumor cells, but only foreign body reaction and gliosis into the neighboring nervous tissue. Anyway, after removal the foreign body granuloma from the tumor bed, glioblastoma began to grow, and a new total resection was done after seven months.

Old literature has reported that infection or foreign body reactions occurring after resection of malignant brain tumor could extend the life expectancy and delay relapses, but these cases were seen as anecdotal reports. In 1999, Bowles & Perkins reported a survival greater than 10 years in patients with operated and subsequently infected anaplastic astrocytomas and glioblastomas [53]. For the first time, in 2009, Bohman *et al.* published a retrospective single-center study in which 17 patients with glioblastoma presented postoperative infections. They found that their patients survived longer [54]. Two years later, De Bonis *et al.* [55] published another retrospective study on 197 primary glioblastoma with/without postoperative infections and found a prolongation of postoperative survival with 15 months in patients with infection *versus* those without infections. Trying to explain this association, many authors have formulated various hypotheses about the influence of the inflammatory biological mechanisms that influence the natural history of tumor behavior. Two theories were proposed. Some authors considered that the infection in or near the tumor bed can stimulate the patient's immune response and may promote longer survival by increasing the immune response cascade of cytokines and chemokines and by anti-carcinogenic properties. Others proposed the idea of local competition between tumor cells on one side and the inflammatory and bacterial replication for growth and survival on the other side [54, 55]. This has led to further studies on immunotherapy and genetically modified bacteria to be used in the treatment of primary glioblastoma [56]. In 2016, Chen *et al*. [57] published a study on 369 patients with postoperative infection at one month after resection of primary glioblastoma but they did not find any survival benefit. However, phagocytes associated with chronic granulomatous disease produce high levels of tumor necrosis factor-alpha and interleukin-8, contributing to the inflammatory response [58].

Our case supports Ha *et al.* theory [59] that the presence of inflammation in the tumor bed can decrease a glioblastoma proliferative rate, since T2-helper lymphocytes response ultimately works with the tumor cell to drive the angiogenic response.

Glioblastoma relapse is indistinguishable from postoperative foreign body granuloma if this occurs in tumor bed a few months after the surgical removal of the tumor, because these two diseases are mimicking each other in clinical and neuroimaging studies. The excessive inflammatory reaction may be misdiagnosed as a recurrent tumor, radiation necrosis, abscess, resolving infarction or hematoma, or even unrelated primary or metastatic neoplasm, depending on the particular clinical history of each patient [20]. In the presented case, the gadolinium-enhanced MRI of the brain suggested tumor relapse or radiation necrosis. The differential diagnosis between tumor recurrence and postoperative granulomas could be performed using positron emission tomography and single photon emission tomography that can identify certain parameters (isometabolism, uptake in macrophages, etc.) to support the differentiation [60] between these two pathologies, but in our case we did not have this opportunity. Therefore, the correct diagnosis in this case could not be determined but only based on histopathological examination of the surgical specimens that revealed a foreign body reaction to PGA suture.

The proof that foreign body reaction inhibited tumoral growth was the fact that, unlike the first postoperative period, after the resection of the granuloma, the underlying glioblastoma cells began to grow with a high rate and imposed a third operation after another seven months and the death of the patient at 22 months from his first diagnosis.

## Conclusions

Even if until now there were no reported foreign body reactions developed to PGA suture used for closing the dura mater after resection of a brain tumor, these reactions may occur and they are difficult to distinguish, both clinically and radiologically, from glioblastoma relapse. However, if brain imaging and clinical aspects become suggestive for tumor recurrence or radiation necrosis, the neurosurgeons should include the foreign body reactions into the differential diagnosis of the lesion. In addition, it is indicated a new operation to determine the true nature of that space-occupying lesion, but at the same time, it can add an extra few months in the life of the patients who were already treated with 5-ALA-guided resection, because it allows a wide resection of the tumor with positive prognosis.

### Conflict of interests

The authors declare that they have no conflict of interests.

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