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Case Report

Glioblastoma with primitive neuronal component: A case report and considerations of fluorescence-guided surgery

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ABSTRACT

Background: Glioblastoma with primitive neuronal components (GB/PNC) is an extremely rare type of glioblastoma characterized by presenting histological and cytogenetic features of both entities. The mixed nature of these tumors limits the imaging diagnosis and supposes a therapeutic dilemma.

Case Description: We present the case of a 77-year-old female with a GB/PNC who is treated with surgery and adjuvant radiochemotherapy according to the STUPP protocol, where an abnormal uptake of 5-aminolevulinic acid (5-ALA) is evident during surgery in probable relation to the mixed nature of GB/PNC.

Conclusion: GB/PNC is extremely rare tumors. Given its low prevalence, there are no studies that refer to the macroscopic characteristics of the tumor as well as evidence of the effectiveness of adjuvant treatment. Fluorescence-guided resection with 5-ALA is the surgical treatment of choice in surgery for high-grade gliomas; however, in GB/PNC, it may not be as useful since PNC may have less fluorescent marker uptake and be more dimly visualized when excited by light using the surgical microscope.

Keywords: 5-aminolevulinic acid, Fluorescence, Glioblastoma, Primitive neuronal components

INTRODUCTION

Glioblastoma with primitive neuronal components (GB/PNC) is a rare and emerging variant of GB, accounting for almost 0.5% cases of GB.[10] Primitive neuronal tumors are aggressive neoplasms of the central nervous system (CNS) that derives from cells of the primitive neuroectoderm. These neoplasms generally appear in children; however, when they are associated with glial growth that they are more frequent in adults. Until few years ago, these tumors were called primitive neuroectodermal tumors (PNET), but after the last classification of tumors of the CNS by the World Health Organization (WHO), this term fell into disuse and began to be called tumors with PNC.[6] Histologically, GB/PNC have characteristics of both entities, and some of the genetic alterations present in each type of tumor may coexist in GB/PNC.[2] The low prevalence of these tumors and few cases published to date make it difficult to understand the pathophysiology of GB/PNC and although there are therapeutic strategies for glioblastomas and tumors with PNC, there is currently no standard treatment regimen for GB/PNC. Most of the times, these tumors are treated with surgery combining radiation therapy and chemotherapy according to specific therapeutic regimes for glioblastomas and tumors with PNC. Despite the optimization of

treatment, it has not been possible to elucidate aspects related to surgical treatment or the efficacy of adjuvant therapy, and the prognosis is unfavorable in most cases.

We present the case of a 77-year-old female patient with a GB/PNC that is treated with surgery and radiochemotherapy according to the STUPP protocol and where an abnormal uptake of 5-aminolevulinic acid (5-ALA) during surgery in probable relationship with the mixed nature of GB/PNC.

CASE REPORT

We present the case of a 77-year-old woman with a history of hypertension, dyslipidemia, and atrial fibrillation who presented with hemiparesis and left hemihypoesthesia of 4 months of evolution. Magnetic resonance imaging (MRI) showed an expansive intracranial lesion at the right frontoparietal level with abundant perilesional edema, areas that enhance paramagnetic contrast and a marked restriction of diffusion in the peripheral region [Figure 1]. Suspecting a high-grade primary brain tumor, a fluorescence-guided total resection with 5-ALA was performed, showing a tumor tissue of solid consistency, pale appearance, and with poor uptake of fluorescent marker [Figure 2]. The intraoperative histological study suggested a high-grade glial tumor. After surgery, the patient gradually recovered her motor balance, although the left hemihypoesthesia persisted. The definitive histological study revealed a GB/PNC with a high cellular proliferation index (Ki-67 95%) [Figures 3 and 4]. The isocitrate dehydrogenase (IDH)-1 R132H mutation was negative. IDH sequencing and the IDH-2 mutation were not determined. The study of the 1p19q codeletion was negative. The average methylation percentage of O6-methylguanine-DNA methyltransferase (MGMT) was 66.2% [Figure 5]. The patient received the first line of adjuvant treatment with conventional radiotherapy and chemotherapy with temozolomide according to the STUPP protocol. Two weeks after completing radiotherapy treatment, the patient suffered a worsening of her neurological state and died.

DISCUSSION

GB/PNC is a rare variant of GB that exhibits very aggressive behavior. As with "conventional" GBs, they are considered Grade IV tumors according to the classification of CNS tumors of the WHO.[2] GB/PNC has characteristics of both types of tumor. As with "conventional" GBs, GB/PNC shows aggressive behavior with a high risk of local recurrence. On the other hand, they have a higher risk of leptomeningeal spread, as occurs with tumors with PNC. To date, the etiopathogenesis of GB/PNC is unknown, although the most consistent hypothesis is neuroblastic metaplasia, that is, the presence of foci of tumor primitive neuronal cells in pre-existing, generally secondary glioblastomas.[9]

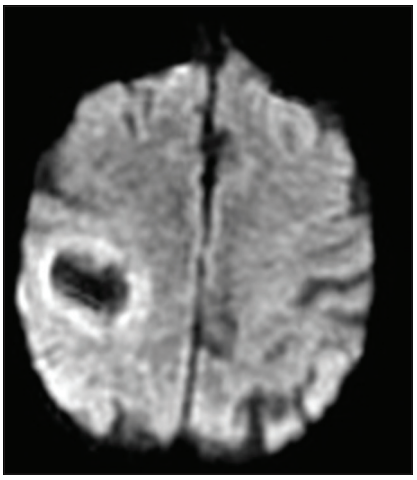

Figure 1: Magnetic resonance imaging with diffusion sequence shows an important restriction of diffusion in the peripheral region.

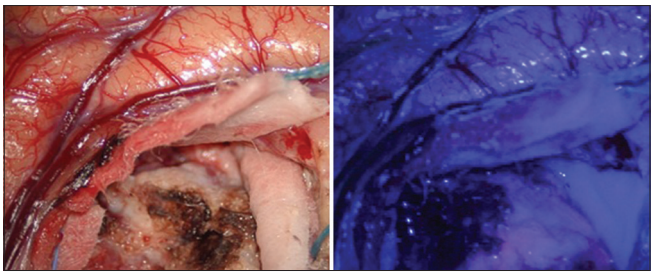

Figure 2: Intraoperative image showing a tumor lesion in the subcortical region with a weak fluorescence of the tumor tissue after administration of 5-aminolevulinic acid.

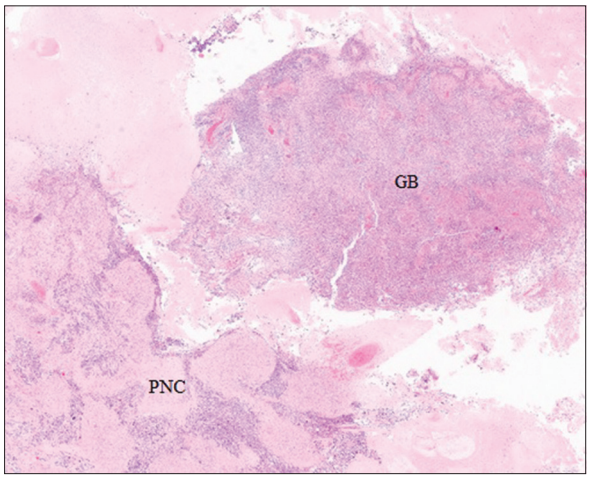

Figure 3: Hematoxylin-eosin stain showing both tumor components and transition area (×2).

Genetically, GB/PNC can present genetic alterations similar to "gliomas," such as the 10q and 1p/19q deletions or the amplification of the gene encoding the epidermal growth factor receptor, and characteristics similar to those traditionally called "Primitive neuroectodermal tumors

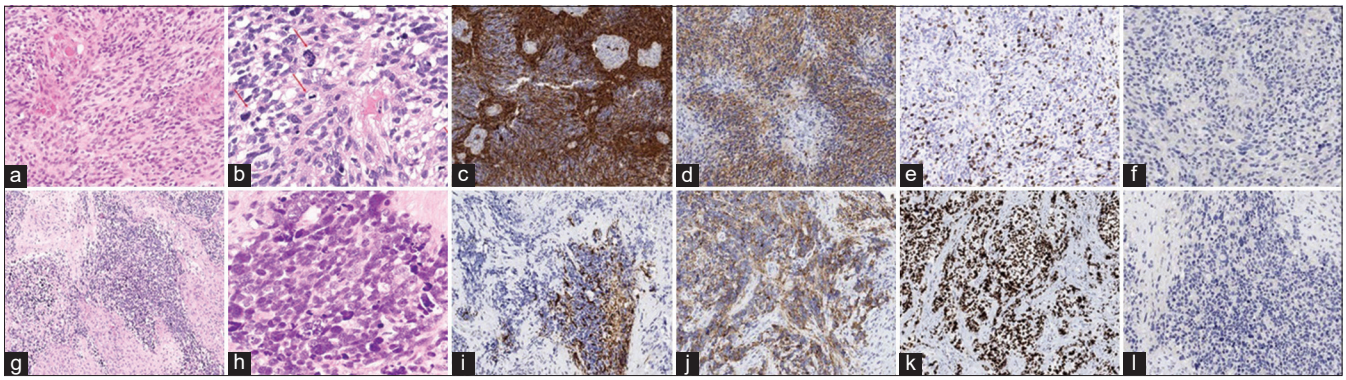

Figure 4: (a) Hematoxylin-eosin stain showing a tumor with dense cellularity and glomeruloid vessels GB-compatible (×10). (b) Hematoxylin-eosin stain showing atypical cellularity with marked nuclear pleomorphism and abundant mitosis (×20). (c) Gliofibrillar acid protein (GFAP) staining showing glial line hypercellularity (×10). (d) Synaptophysin staining showing negative immunoreactivity (×10). (e) MIB-1 staining showing the proliferation index of glioblastoma (×10). (f) Anti-isocitrate dehydrogenase (IDH)-1 R132H immunohistochemistry showing absence of IDH-1 mutation (IDH wild-type GB) (×10). (g) Hematoxylin-eosin stain showing solid-looking primitive nodules presenting neuronal differentiation separated by a desmoplasic stroma (×10). (h) Hematoxylin-eosin stain showing high nuclear-cytoplasmic ratio, karyorrhexis, and occasional cell wrapping (×20). (i) GFAP staining showing low GFAP expression within the foci of the primitive neuronal component in contrast to the glioma component (×10). (j) Synaptophysin staining showing positive immunoreactivity in primitive cells (×10). (k) MIB-1 staining showing a high Ki-67 labeling index with nuclear positivity for more than 90% of tumor cells PNC-compatible (×10). (l) Anti-IDH-1 R132H immunohistochemistry showing a negative study for primitive neuronal component (×10).

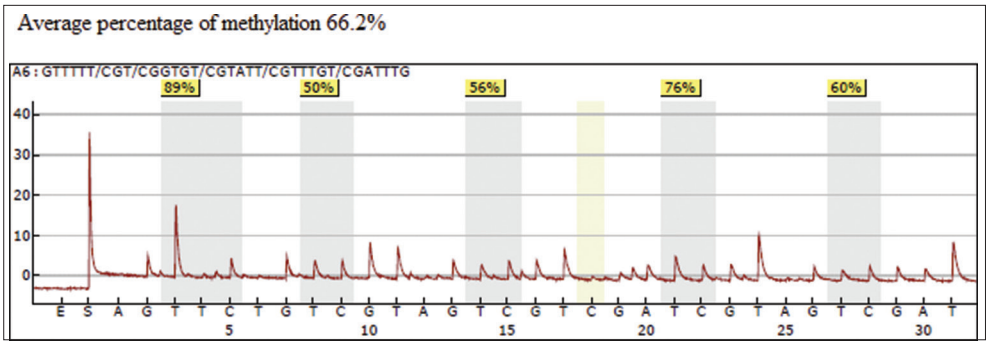

Figure 5: Average percentage of MGMT methylation.

(PNET)," such as the high Ki-67 index or the amplification of the N-myc or C-myc genes. Cases of GB/PNC have been discovered with mutations in the enzyme IDH-1, which supports the origin of these tumors from secondary GB and seems to have a positive prognostic value.[11] Likewise, mutations of the gene encoding the MGMT promoter have been identified. Histologically, GB/PNC shows the characteristics of both malignancies. On the one hand, they present areas of high-grade glial growth with high expression of gliofibrillar acid protein (GFAP) and, on the other hand, areas of undifferentiated neuroepithelial hypercellularity with low expression of GFAP and neuronal immunophenotype (S-100, synaptophysin, neuronal nuclei, neuron-specific enolase, and neurofilament protein).[2]

Regarding imaging, although the MRI findings do not allow a distinction to be made between a "conventional" GB and a GB/PNC; the reduction of the apparent diffusion coefficient and the restriction in diffusion may be more evident probably due to the hypercellularity of the PNC.[1] In our case, it was not possible to determine the existence of a GB/PNC by MRI. The MRI showed a heterogeneous lesion with wide contrast uptake at the edges, a marked restriction of the peripheral diffusion and an area of central necrosis, being the radiological diagnosis of glioblastoma.

The treatment of these tumors is based on surgery, radiotherapy, and chemotherapy. Surgery plays a primary role in the treatment of high-grade gliomas and has been associated with increased survival in those patients treated with complete resection and adjuvant radiochemotherapy compared to conservatively treated patients.[5]

Guided fluorescence with 5-ALA facilitates surgical resection of high-grade gliomas since it allows to differentiate tumor tissue from healthy brain parenchyma during surgery. Once administered to the patient, 5-ALA is absorbed by the different tissues of the body and especially by malignant

glial cells. When applying a light with a wavelength of 400–410 nm on the tumor tissue using a surgical microscope, protoporphyrin IX emits intense, strong pink fluorescence, allowing the extent of the malignant glioma to be determined and the resection to be guided.

5-ALA is a natural precursor to hemoglobin that is metabolized in the mitochondria, causing fluorescent protoporphyrins, such as protoporphyrin IX. The accumulation of protoporphyrin IX by tumor cells depends on the activity of certain mitochondrial enzymes, such as ferrokelase. High levels of ferrokelase have been shown to promote the accumulation of protoporphyrin IX in tumor cells of glioblastomas, bladder cancer, and lung cancer.[8] Likewise, low levels of certain membrane transporters, such as the ATP-binding transporter member 2 of the G superfamily (ABCG2), are also associated with an increase in the accumulation of protoporphyrin IX in glioblastoma tumor cells.[3]

In relation to CNS tumors, the concentration of protoporphyrin IX is considerably higher in malignant glial cells than in neurons, healthy glial cells, or neoplastic non-glial cells. Marbacher *et al*.,[7] determined the percentage of patients who had positive uptake with 5-ALA in a retrospective review of 512 patients with brain tumors operated on by resection or stereotactic biopsy. The results of their study showed positive uptake in 88.4% of high-grade gliomas, in 40% of low-grade gliomas, in 77.3% of meningiomas, and in 52.3% of brain metastases, among other tumors. So far, there is no evidence in the literature on the behavior of GB/PNC when treated with fluorescence-guided surgery. In our case, despite being a malignant glioma, the intensity of the fluorescence was low. The mixed tumor nature and the presence of areas with primitive neural components with little uptake of 5-ALA could explain this phenomenon.

Due to the low prevalence, there is no standard treatment for GB/PNC. Most of the data are derived from small series or case reports. The largest series correspond to Varlet *et al*.[12] and Perry *et al*.[9] and in them aggressive therapy with radical surgery plus chemotherapy with temozolomide and adjuvant radiotherapy is recommended, being able to associate platinum-derived drugs early to avoid recurrences derived from PNC. In other more recent studies, the possibility of associating cisplatin or carboplatin with standard treatment with temozolomide is suggested to reduce the risk of cerebrospinal fluid spread from PNC derived tumor cells.[4] As with "conventional" GBs, the response rate to treatment is higher in tumors with the presence of MGMT promoter methylation; however, in GB/PNC, there is no standard therapeutic protocol. Despite the correct treatment, the prognosis of these tumors remains unfavorable and, as with glioblastomas, it represents a therapeutic challenge for all professionals.

CONCLUSION

GB/PNC are extremely rare malignant tumors of the brain. The existence of a mixed tumor progression limits the image diagnosis and supposes a therapeutic dilemma. Fluorescence-guided resection with 5-ALA is the surgical treatment of choice in surgery for high-grade gliomas; however, in GB/PNC, it may not be as useful since PNC may have less fluorescent marker uptake and be more dimly visualized when excited by light using the surgical microscope. To date, there is no standard treatment protocol for GB/PNC and in the reports or case series described in the literature, there is a tendency to recommend a combined therapy for both tumors. In spite of everything, the prognosis remains unfortunate and the contribution of new cases or studies with a greater casuistry can contribute to the understanding of the pathophysiology and establish a targeted therapeutic approach for these malignancies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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