Glioblastoma with Oligodendroglioma Component (GBMO) in an Adolescent

CASE REPORT

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Abstract

Background: Glioblastoma with oligodendroglioma component (GBMO) is a recently classified subtype of glioblastoma, which carries different clinical and prognostic outcomes, being frequently misdiagnosed. Both glioblastoma and GBMO are mainly seen in older ages, such as the 5th and 6th decades of life, being an extremely rare occurrence in children or adolescents and more frequent in male patients.

Case report: A 15-year-old female patient, presented with history of daily headache, not relieved by painkillers, vomiting, blurred vision and strabismus. Magnetic resonance imaging of the brain revealed expansive tumour on left temporo-occipital lobe. Patient was submitted to intracranial exeresis, along with histopathological examination: glial neoplasm with areas of pleomorphism, hyperchromatism, anaplasia, foci of oligodendroglial component, perinuclear halo and ramified capillaries, resembling oligodendroglioma, necrosis and intense mitotic activity. The immunohistochemical analysis revealed positive Glial Fibrillary Acidic Protein (GFAP), synaptophysin, Ki-67 (MindBomb E3 ubiquitin protein ligase 1 – MIB-1) and hyperexpression of Epidermal Growth Factor Receptor (EGFR), indicating GBMO. Subsequently, Fluorescence in situ Hybridization (FISH) showed positive for 19q deletion, negative for 1p deletion and also positive for Isocitrate Dehydrogenase 1 (IDH 1) mutation, suggesting an oligodendroglioma component. Tumour resection was total and symptoms disappeared. Afterwards, she started adjuvant oral chemotherapy with temozolomide. Treatment was completed after 12 cycles adjuvant temozolomide, with no greater symptoms or complications and complete remission.

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Conclusion: GBMO must be considered as a possible diagnosis when confronted with a malignant glioma with oligodendroglial tumour component, independent of age or genre. Necrosis upon histopathological examination has a strong relation to shorter median overall survival. IDH mutation and 19q deletion should be analyzed by immunohistochemistry. Total tumour resection, with adjuvant treatment (chemotherapy with temozolomide and radiotherapy), increases benefits and improves prognosis.

Keywords

Glioblastoma; Oligodendroglial Tumour Component; GBMO; Adolescent; Case Report.

Introduction

Glioblastoma with oligodendroglioma component (GBMO) is a recently classified subtype of glioblastoma (GBM), defined in 2007 by World Health Organization (WHO) as a high grade (grade IV) malignant glioma with oligodendroglial tumour component, which carries different clinical and prognostic outcomes [1].

Furthermore, according to the most recent WHO classification, in 2016, a new addition was made to this diagnosis: the evidence of isocitrate dehydrogenase (IDH) mutation, which is present on about 10% of glioblastomas [2]. This genetic marker has been shown as an important predictor of prognostic and longer survival rate [3, 4, 5].

Moreover, the overall median survival of GBMO and GBM are still controversial, since it has shown a longer survival [4] in GBMO while others did not identify differences whatsoever [5].

Regarding age, although GBMO has been said to have a younger onset than GBM, both are mainly seen on older ages, such as the 5th and 6th decades of life, being an extremely rare occurrence on children or adolescents [3, 5, 6].

About gender, GBMO has been said as more prevalent in men at a 3,25:1 rate [3], but this prevalence is controversial, since many times GBMO is still misdiagnosed as a regular GBM or as anaplastic oli-

goastrocytoma (AOA). However, Karsy et al showed the rarity of this subtype of GBM and, moreover, how rare is its occurrence in children and adolescents [6].

In Brazil, literature about GBMO is scarce, although some cases of GBMs have been reported, most of it was in adults and located in the cerebellum [7]. Furthermore, cases related regarding specifically pediatric patients include a cerebral case, located in the right hemisphere [8].

However, the lack of literature about GBMO shows the importance of producing more studies in this field.

This study describes a 15-year-old female patient, diagnosed with glioblastoma with oligodendroglioma component in the left temporo-occipital cerebral lobe.

Case Report

A 15-year-old girl, presented with history of daily headache, not relieved by painkillers, vomiting, blurred vision and strabismus, for two months. A skull computerized tomography (CT) scan showed a hyperdense lesion, with hypodense center, expansive, in the left cerebral hemisphere, and a magnetic resonance imaging (MRI) of the brain revealed expansive tumour, with calcifications, and hyperdense area in left temporo-occipital lobe, compressing

lateral left ventricle and pushing structures to the right (**Figure 1**).

The patient underwent tumour resection. Histopathological examination showed a glial neoplasm with areas of pleomorphism, hyperchromatism, anaplasia, foci of oligodendroglial component, perinuclear halo and ramified capillaries, resembling oligodendroglioma, necrosis and intense mitotic activity, leading to differential diagnosis between anaplastic oligodendroglioma and GBMO. Immunohistochemical analysis showed positive Glial Fibrillary Acidic Protein (GFAP), synaptophysin, Ki-67 (MindBomb E3 ubiquitin protein ligase 1 – MIB-1) and high expression of Epidermal Growth Factor Receptor (EGFR), indicating GBMO.

The tumour resection was total, and symptoms disappeared. A month after the procedure, postoperative MRI exhibited surgical cavity filled with li-

quor and enhancement on borders of the left parieto-occipital region, along with mastoiditis (**Figure 2**).

About 40 days after the resection, Fluorescence in situ Hybridization (FISH) was tested. The patient initiated the oral treatment with temozolomide (Temodal) 75mg/m² daily for 35 days concomitant with radiotherapy (60 Gy in 30 Gy fractions). During this monitoring, the patient reported side effects such as nausea and vomiting, but had no loss of appetite, changes in diuresis and gastrointestinal disorders.

Subsequently, the results of the FISH analysis were available after nearly two months: negative for 1p36 and positive for 19q13 deletion, and also positive for IDH 1 mutation, suggesting an oligodendroglioma component. Then, the patient started adjuvant oral chemotherapy with the same Temodal, now 200mg/m² daily, from D1 to D5, during each 28

Figure 1: MRI showing hyperdense area on the left temporo-occipital lobe, with compression of lateral left ventricle, pushing structures to the right.

Figure 2: Post-operative MRI revealing surgical cavity filled with liquor and enhancement on borders of the left parieto-occipital region and mastoiditis.

Figure 3: MRI exhibiting no signs of expansive process or haemorrhage after twelfth cycle of Temodal.

days cycle, in a regimen of 12 cycles, and carbamazepine 200mg, twice a day.

After first cycle, a MRI revealed post contrast heterogeneous enhancement on the borders of foramen magnum, with nodular aspect, pointing to residual tissue or postoperative alteration. Patient continued treatment without toxicity, but presenting nausea only.

After second cycle, a new MRI evidenced surgical cavity on the white matter with heterogeneous enhancement on superior and medial border, possibly indicating ischemic injury subacute, pseudoprogression, residual component or tumour recurrence.

At the end of the seventh cycle, the patient was submitted to a MRI again, with no evidences of expansive process or hemorrhage. The surgical cavity was located on the subcortical white matter, and

was very deep on the left temporo-occipital region, with heterogeneous enhancement on superior and medial border, confirming damage after surgery and radiotherapy. However, this finding has not affected patient's overall health, continuing treatment with no greater symptoms or complications.

At the end of the twelfth cycle, another MRI exhibited no evidences of expansive process or haemorrhage (**Figure 3**).

Therefore, the patient was able to continue and complete her treatment after 12 cycles of Temodal, with no greater symptoms or complications and complete remission.

Discussion

Clinical and pathological studies of GBMO are currently scarce. Its exact incidence is unknown and has ranged from 8% to 27% of all GBMs in previous studies [9, 10]. The lack of definitive diagnostic criteria may be the cause of inconsistency. GBMO is a glioblastoma that contains foci that resemble oligodendroglioma, which are variable in size and frequency in the histopathological analysis [1].

A trend for younger patients in the GBMO group compared with the other-GBM group have been described (56.2 y vs 60 y), even though there were no significant differences extent of surgery or treatment [9], being GBMO more prevalent in men at a 3,25:1 rate [2]. However, the patient in this study was a 15 years old female at the time of diagnosis.

Moreover, the origin of the oligodendroglial cells is still unclear. Loss of heterozygosity on 1p and 19q are known as common markers of oligodendroglial tumours [11]. Two recent studies provided a strong evidence for a monoclonal origin: using a microdissection technique, they demonstrated that 2 different parts (astrocytoma and oligodendroglioma) of GBMOs showed a similar genotype [1, 12, 13]. Therefore, it is assumed to result from mixed low-

grade glioma development, which possible results in the malignant transformation [14].

The standard treatment for GBMO consists of maximal surgical resection, radiotherapy, and a concomitant and adjuvant treatment with chemotherapy with temozolomide [9, 14, 15], coinciding with the case reported. The patient was primarily submitted to tumour resection, followed by oral treatment with temozolomide (Temodal) 75mg/m² daily for 35 days with concomitant radiotherapy (60 Gy in 30 Gy fractions). The adjuvant oral chemotherapy included the same Temodal, now 200mg/m² daily, from D1 to D5, during each 28 days cycle, in a regimen of twelve cycles.

Surgical resection is the primary treatment for all tumour types. The surgical goal is total resection, though less aggressive resection is employed for tumour involving eloquent brain. Furthermore, biopsy is typically performed on tumours that are not accessible to confirm the diagnosis and determine the grade of tumour [15]. In this case, the histopathological exam of the total resection showed a glial tumour with a differential diagnosis of anaplastic oligodendroglioma, glioblastoma multiforme (GBM) or glioblastoma multiforme with oligodendroglial component (GBMO).

The guideline to address the impact of cytotoxic chemotherapy on disease control and increase the survival in adults with progressive glioblastoma recommend the use of temozolomide over other medications as procarbazine, at the time of initial therapy [16]. Before the introduction of combined radiochemotherapy with temozolomide, the use of chemotherapy in GBM was not universally recommended [17]. However, the presence of an oligodendroglial component has been regarded by some authors as an indicator of increased chemosensitivity, since GBMO tumors have been reported to frequently contain molecular genetic alterations, such as a loss of heterozygosity (LOH) [3, 11, 17].

Temozolomide is an orally active alkylating agent that is used for patients newly diagnosed with gli-

blastoma multiform. The drug is well tolerated and provides a modest survival benefit [16]. In addition, adjuvant and concomitant temozolomide with radiation was associated with significant improvements [9, 14]. Methylation of the protein O-6 methylguanine DNA methyltransferase (MGMT) increases the response to anchilating agent and thus is a strong predictor for better outcome from temozolomide chemotherapy [9]. In this case, the treatment did not affect patient's overall health, which allowed her to continue the complete treatment with no greater symptoms or complications.

The temozolomide was found to extend average survival from 15 to 24 months [16]. Other study indicates overall survival of 20.1 months, progression free survival of 10.3 months and 2 year survival of 55%, with the standard treatment of surgery followed by radiotherapy and chemotherapy with temozolomide during and after radiotherapy [9]. The patient in this study used radiotherapy, with a concomitant and adjuvant treatment with chemotherapy (temozolomide) within a regimen 12 cycles, completing her treatment with no greater symptoms or complications and complete remission.

Patients whose tumours showed necrosis (high grade tumours) had worse prognosis [9, 14]. The patient of the case had histopathological examination, showing glial neoplasm with areas of pleomorphism, necrosis and intense mitotic activity, leading to differential diagnosis between anaplastic oligodendroglioma, glioblastoma multiform (GBM) and glioblastoma multiform with oligodendroglial component (GBMO).

Moreover, the IDH mutation has been shown as an important predictor of prognosis and longer survival rate [2, 3, 4, 5], also present on 10% of all glioblastomas [2]. The FISH analysis showed IDH 1 mutation.

Although GBMO tumours showed better outcomes associated with the presence of chromosome 1p and 19q deletions [3, 17, 18], the presence of an oli-

godendroglial component as an intrinsic prognostic factor is still unclear. The younger age at diagnosis remains one of the most important prognostic factors for patients with GBMO, as well as a single lesion, both presented by the 15-year-old patient in this case [19, 20]. In multivariate analysis with adjustments for age, sex, preoperative Karnofsky performance status (KPS), and treatment, the presence of an oligodendrogloma component was suggested as a prediction of longer overall survival [14].

Loss of heterozygosity on 19q, known as common markers of oligodendroglial tumours, and EGFR overexpression are also observed [11]. It's possible to confirm that GBMOs carry heterogeneous genetic alterations [11], as presented in this case. Immunohistochemical analysis revealed hyperexpression of EGFR. Furthermore, the results of the FISH tests of the case presented were negative for 1p36 and positive for 19q13 deletion, suggesting an oligodendrogloma component.

A study showed that whereas only one of five patients with 30% or less oligodendroglial cells survived for more than two years, this was true for four of five patients with a predominant oligodendroglial component, reinforcing the idea of better prognosis in GBMO than when the oligodendroglial component is not present [17].

Conclusion

GBMO must be considered as a possible diagnosis when confronted with a malignant glioma with oligodendroglial tumour component, even in females, children and adolescents. The presence of necrosis upon histopathological examination of the tumour has a strong relation to shorter median overall survival, being its analysis advised. IDH mutation and 19q deletion should be analyzed by immunohistochemistry, as both are related to longer survival rate and better prognosis, and can be considered for the classification of the tumour. The primary treatment for GBMO is total tumour resection, with adjuvant

treatment composed by chemotherapy with temozolomide and radiotherapy, which increases benefits and improves prognosis.

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Conflict of interest disclosures

The authors declare that there are no conflicts of interest in this case report.

Consent to publish

Written informed consent was obtained from parents of the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Abbreviations

AOA: Anaplastic Oligoastrocytoma
CT: Computerized Tomography
DNA: Deoxyribonucleic Acid
EGFR: Epidermal Growth Factor Receptor
FISH: Fluorescence in situ Hybridization
GBM: Glioblastoma Multiform
GBMO: Glioblastoma Multiform with Oligodendrogloma component
GFAP: Glial Fibrillary Acidic Protein
IDH: Isocitrate Dehydrogenase
KPS: Karnofsky Performance Status
MGMT-O-6-methylguanine-DNA methyltransferase

MIB-1-MindBomb E3 ubiquitin protein ligase 1
MRI: Magnetic Resonance Imaging
WHO: World Health Organization

Contributions

PCMS conceived and designed the experiment. ALMR, DMN, YGL and MSMG participated in sample collection and performed the experiments. PCMS was involved in patient care. PCMS, FPM, YGL, TSRM and MSMG contributed drafting the manuscript and in the transcription. PCMS, YGL, FPM, ECS and DMN contributed significantly in the critical revision of the manuscript. PCMS, FPM, ALMR, TSRM, SFSC, ECS and MSMG designed and participated in the review and final approval of the manuscript. All authors read and approved the final manuscript.

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