Follow-up of a postoperative pregnant woman with low-grade oligodendroglioma

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ABSTRACT

Central Nervous System (CNS) neoplasms do not usually comprise the epidemiological profile of women of childbearing age, affecting more men in a ratio of 2:1 in the fourth or fifth decade of life. There is no consensus in the literature on risk factors and related family history in relation to the individual's gender, however, some studies suggest a neuroprotection deficit due to the absence of estrogen, which, in women, could be related to the indiscriminate use of hormonal contraceptives alone, such as capsules and/or progesterone injections, since estrogen has been proven to play an important role in the deployment of central nervous system cells.

The symptomatology secondary to grade II oligodendrogliomas usually refers to epilepsy and headache, which are accompanied by little improvement to medications. Resolution, in this case, consists of surgical tumor resection and usually has a good prognosis when diagnosed early.

In the cases of young women diagnosed with oligodendrogliomas and undergoing a well-disciplined clinical-surgical therapy, family planning is possible and of great importance. They usually have uneventful gestational development and a smooth delivery, as long as they are assisted by a multidisciplinary team. To this end, physicians must take advantage of scientific evidence that supports the use of medications and the choice of imaging method to monitor the evolution of the case.

In cases of malignant CNS neoplasia, local chemotherapy may be an option. Surgical reapproach should be considered with great caution and the decision should always prioritize the health of the mother over that of the developing fetus.

Keywords: Pregnancy, Neoplasm, Glioma, Oligodendroglioma, Woman, Epilepsy.

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INTRODUCTION

Central nervous system (CNS) tumors diagnosed before or during pregnancy represent a rare occurrence. It is estimated that only 0.1% of pregnancies occur concomitantly with the diagnosis of malignant neoplasms, and only a portion correspond to intracranial tumors8. The possibilities of diagnostic and follow-up tests are limited, since ionizing imaging should be minimized in order to avoid its teratogenicity on the developing fetus6, in this case, cranial computed tomography scans are discarded, assuming magnetic resonance imaging as the ideal method10.

Epileptic seizures are the second most prevalent chronic neurological disease in pregnancy, being the most severe13. According to *The International League against epilepsy*, epilepsy can be classified according to ictal and interictal clinical features into: partial/focal and generalized. Focal seizures occur in a specific, localized brain region, while generalized seizures occur throughout the cortex.

Regarding the management of pregnancy during the course of the neoplasm, it is a fact that women should not be prevented from receiving the best treatment during the perinatal evolution. Treatment should depend on the clinical-radiological presentation of the tumor, its histological type, the mother's gestational age, and the woman's personal decision12: surgical reapproach should be considered with extreme caution, since physiological stressors can be harmful to both the mother and the fetus1, and chemotherapeutic agents are capable of crossing the placental barrier by passive diffusion, causing effects on the developing fetus related to teratogenicity6, however, gestational age has to be taken into account, as it is important to define the effect exerted by a teratogen9.

The occurrence of an ongoing pregnancy during the treatment of a tumor has a strong psychological impact, as it evolves in a stage of life where the woman is in her youth and in an important emotional moment11. There are controversies regarding the relationship between pregnancy and cancer prognosis, some suggest that hormonal changes may adversely affect the outcome, but there is no consensus regarding the outcome of maternal death9. Pregnancy can cause worsening of neurological symptoms related to some types of tumors, precipitating obstetric emergencies5 and it is known that the evolution of the pregnant woman should be monitored by a multidisciplinary team aiming primarily at the well-being of the mother and secondarily at the well-being of the fetus.

OBJECTIVES

The objective of this study is to report the case of a patient who became pregnant during the oncological postoperative period of grade II oligodendroglioma, a pathology that progressed with epileptic seizures, and surgical resolution was indicated. The focus of this study is to track the multidisciplinary decisions regarding the follow-up of the same.

METHODOLOGY

This is a case report study, whose information was collected through a review of medical records and personal reports, using photographic records obtained with the consent of a young patient in a public hospital in the interior of Western São Paulo, in 2024. For this, communication and writing tools, such as Word 2023, and literature review were used.

CASE REPORT

ANAMNESIS

A 27-year-old Caucasian female patient, married, incomplete high school, cook, sought public neurology service in November 2021 complaining of seizures with sudden onset 1 month earlier, accompanied by aura. She reports a frequency of seizures of around 2/3 per week, lasting 15 minutes each. There is no causal relationship with stress or other triggering reasons. He denies other associated symptoms.

Patient denies smoking or use of illicit drugs, reports social alcoholism (around 400/600 mL of fermented beverage per week). She had undergone only one cesarean section during the delivery of her first child, denies previous comorbidities or continuous use of medications.

She denies a family history of neoplasms.

GYNECOLOGICAL HISTORY

G2Pc2A0. The patient presented menarche at 11 years of age. She had an irregular menstrual cycle until she was diagnosed with Polycystic Ovary Syndrome at the age of 18, when she underwent fertility treatment to successfully become pregnant. She had her first child by cesarean section, at term, without intercurrences. She reported the need for a cesarean section due to the absence of cervical dilation during labor.

She started monthly injections of progesterone-based contraceptives after the birth of her first child and continued using them for 5 years, ceasing 2 years before the neoplastic diagnosis of the central nervous system. She reported the permanence of the irregularity of the menstrual cycle after stopping contraception.

There is no family history of miscarriages or gynecological diseases.

PHYSICAL EXAMINATION OF SURGICAL ADMISSION

The patient was admitted to the hospital in good general condition, acyanotic, afebrile, anicteric, hydrated, flushed and eupneic. The cardiovascular system presented rhythmic sounds in 2 beats, normophonetic, without adjacent murmurs; The respiratory system was unabnormal: breath sounds were present bilaterally and there were no adventitious sounds. Abdomen unchanged.

Regarding the neurological physical examination, the patient entered the service with 15 points on the Glasgow scale16, without focal neurological deficits, isochoric and photoreactive pupils, oriented in time and space, calm and collaborative.

ANCILLARY EXAMS

The patient underwent magnetic resonance imaging of the skull on May 16, 2022, using *Fast spin-echo, FLAIR,* echoplanar, and gradient-echo sequences, weighted on T1, T2 diffusion, and T2-weighted sequences, using gadolinium.

The analysis showed an intra-axial expansive lesion, with an infiltrative aspect, with a geometric center at the transition between the right middle and upper frontal gyrus. The signal was low on T1-weighted sequences and high on T2-weighted sequences (*Figure 1*), with no evidence of calcification or hemorrhage, and no signs of enhancement after gadolinium administration. No changes were identified in the rest of the parenchyma and/or ventricles. The characteristics of the image favor glial primary neoplastic nature.

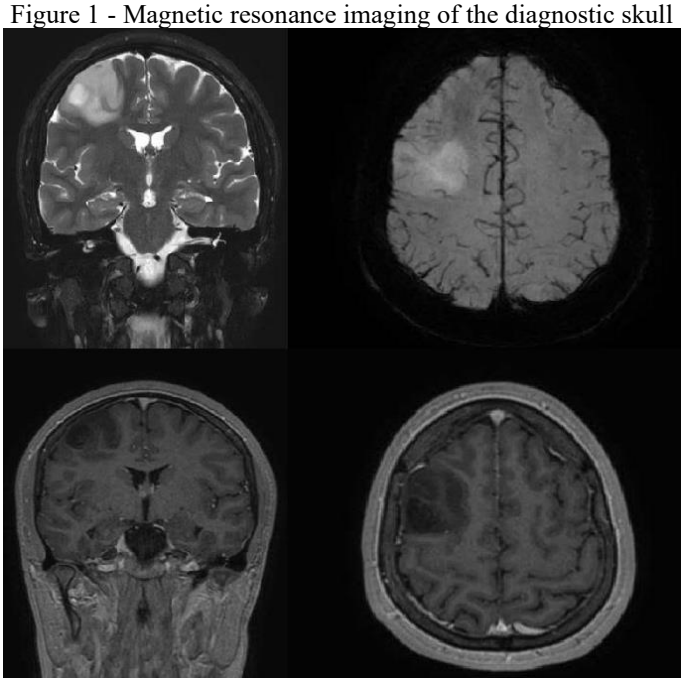
An electroencephalogram was requested during wakefulness and spontaneous sleep without sedation (EEG), which concluded that the baseline activities remained organized and symmetrical for age, in addition to the absence of epileptiform paroxysms.

After performing surgery, the anatomopathological report of August 30, 2022 showed that the set of findings favors oligodendroglial differentiation, but the absence of specific studies did not allow the identification of the 1p/19q codeletion, making the neoplastic grading uncertain. There was an isolated presence of immature microvascularization, without necrosis and/or high mitotic activity, which was inconclusive for a high histological grade, not allowing aggressive behavior to be excluded.

Cranial MRIs of the immediate postoperative period (August 14, 2022 – *figure 2*) and subsequent follow-up (December 11, 2022 – *figure 3*) showed signs of surgical manipulation, without the presence of tumor masses, with preserved brain parenchyma, a ventricular system of normal shapes and dimensions, anatomical grooves and cisterns, and centromedian structures without significant deviations.

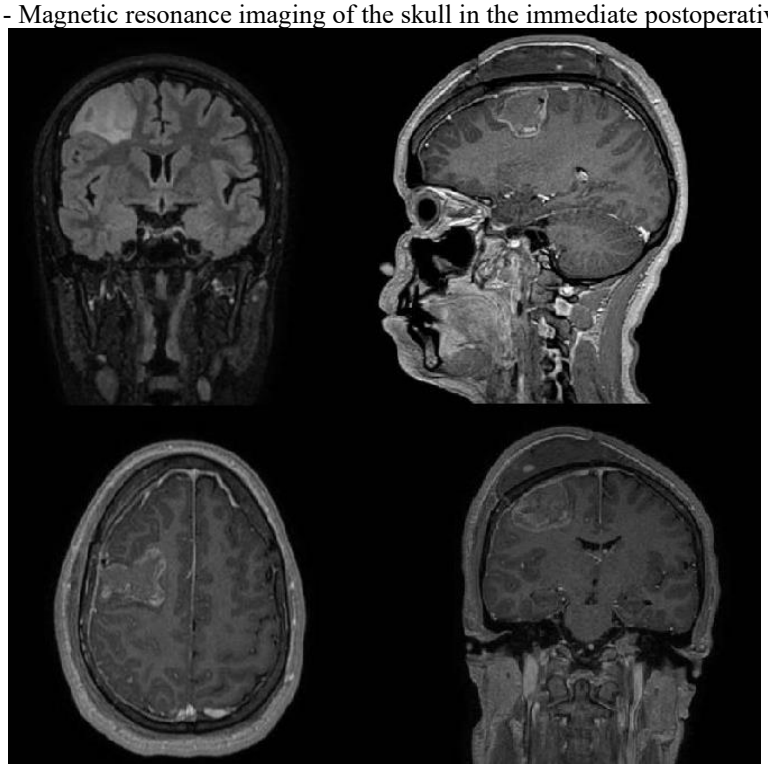
Magnetic resonance imaging (MRI) scans performed during pregnancy had the same characteristics as the previous ones.

Figure 1 - Magnetic resonance imaging of the diagnostic skull



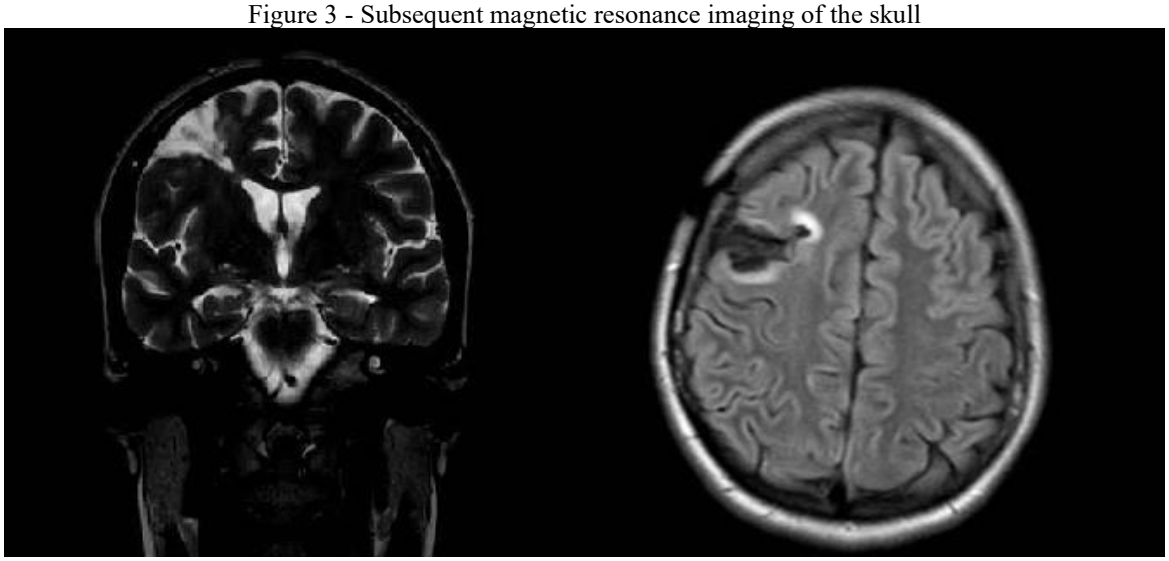
Source: Medical record

Figure 2 - Magnetic resonance imaging of the skull in the immediate postoperative period



Source: Medical record

Figure 3 - Subsequent magnetic resonance imaging of the skull



Source: Medical record

DIAGNOSTIC HYPOTHESIS

Neoplastic central nervous system syndrome; Epilepsy secondary to tumor growth.

CONDUCT AND EVOLUTION

The patient received a prescription with sodium valproate 250mg every 12 hours at the time of seeking medical assistance and reported persistence of tonic-clonic seizures. During hospitalization, she received Oxcarbazepine associated with valproic acid and Diazepam, but suffered two seizures assisted during medical care. He was discharged from the hospital to schedule a subsequent elective surgical intervention with guidance to improve lifestyle habits and prescription of Levetiracetam 250mg at the target dose of 1000mg per day. The patient reported that even this last therapeutic option had no effect on the crises.

During the surgical hospitalization, the patient entered the service with no changes in the physical examination. On August 12, 2022, the patient underwent tumor resection microsurgery without intercurrences. Osteoplastic craniotomy and duroplasty associated with partial excision of the intraaxial lesion were chosen. She remained in the intensive care unit for three days, oriented, calm and collaborative, where she was discharged with bilateral nystagmus. In the ward bed, the patient underwent a new magnetic resonance imaging (see topic 4.3.) and remained with slowed speech, slight asymmetry of the face to the left, and preserved strength.

The patient was discharged with sodium valproate and was referred for oncological follow-up after postoperative MRI ruled out significant changes. The patient reported the absence of seizures since the surgical intervention.

Six months after surgery, the patient returns to the public health system pregnant with her second child, the result of an unplanned pregnancy. She reported that she did not use any

contraceptive method. She was advised to remain assisted only with non-ionizing imaging methods, performed at 6-month intervals. She was referred for follow-up of a high-risk pregnancy that replaced the medication Sodium Valproate with Levetiracetam. The multidisciplinary counseling advised to carry the pregnancy to term, with cesarean delivery. There were no complications during the gestational period. The newborn was male, weighing 3,600 grams, without the need for neonatal resuscitation.

Both mother and child are discharged from the hospital system uneventfully, in good general condition.

DISCUSSION

Oligodendrogliomas are neoplastic tumors of the central nervous system, originating from oligodendrocytes, and have the differentiation between low grade (grade 2) and high grade (grade 3) according to malignancy, according to the WHO. They usually originate in the white matter of cerebral hemispheres with a diffuse pattern and in the cortex with infiltrative characteristics3,17,18. They are tumors very similar to astrocytomas, however, on the radiological image, the presence of small gyriform calcifications of Oligodendrogliomas does not differ them to a high degree, i.e., it does not suggest an insidious character17,19. The doubt of this report remained regarding the malignant characteristics of the tumor, since it was not possible to observe the genetic behavior regarding the 1p/19q codeletion, however, the favorable evolution of the patient and the slow growth of the neoplastic mass suggest benign characteristics, therefore, grade II. since neoplastic oligodendroglial cells do not have specific markers, they can be positive for S-100, Leu-7 and vimentin19.

This type of glioma is a rare neoplasm that usually affects the fourth or fifth decade of life, predominantly in men. The frontal lobe is affected in 50-65% of patients18. It usually has a good prognosis in relation to other gliomas and this case was able to prove that even though this tumor develops outside the common epidemiological profile, in women in the second decade of life, grade II oligodendrogliomas present with good expectation in their evolution, even allowing uneventful gestational development and a healthy neonate.

Few risk factors have been described for glioma-like tumors, and these have a low relationship with family history3,19. Some studies suggest that brain tumors are more prevalent in men due to the neuroprotection exerted by estrogen (female steroid hormone) on specific receptors: estrogens could bind to nuclear or membrane receptors and stimulate many tumor signaling pathways3.

Estrogens act in several areas of the brain exerting neuroprotective and neurotrophic functions, acting against oxidative stress, stimulating neural growth factors, increasing the concentration and number of receptors for noradrenaline, serotonin and dopamine, etc.[20]. Even

though steroid production occurs in secondary sites, they are able to cross the blood-brain barrier, regulating the CNS and even acting on dendritic branching and myelination3. In the embryonic sphere, sex hormones are responsible for determining apoptosis, neuronal migration and neurogenesis21.

Several studies have shown that combined hormone replacement was neuroprotective for menopausal women3. In the case of women of childbearing age, the excess of progesterone and absence of estrogen can trigger a cascade of emblematic effects: this report evidenced the long-term use of progesterone-based contraceptives, important information that may explain the early onset of a central nervous system neoplasm in a woman of childbearing age. Other studies have been inconclusive regarding the relationship between the onset of glioma and the woman's age in relation to steroid hormones3,18. The epidemiological profile of the tumor *per se*, already described earlier in this study, reveals that this glioma arose in a peculiar way and a possible justification would be the indiscriminate use of progesterone-based substances, which would have been harmful when taking into account the loss of the neuroprotective effect of estrogen. This information becomes even clearer when compared with the literature: a case-control study was conducted in premenopausal women and the chance of developing glioma was 2.8 times higher in those who underwent hormone replacement with progesterone alone than in those who used a combination of progesterone and estrogen3.

The symptoms of neoplastic growth confirm those described in the studies. Although all tumors have symptoms dependent on the brain areas affected, oligodendrogliomas usually present with epileptiform seizures and long-term severe headaches18,19. The patient in this case had seizures that led her to seek medical attention in a short period of time. The availability of resources and the long waiting list of the public service in question was a diagnostic obstacle, since it took 6 months for the imaging test to be performed after the symptomatic onset and the diagnostic hypothesis to be established. In cases of fast-growing tumors, this fact would prove to be a major adverse factor, and could cause death even before a treatment was established.

Epilepsy is a chronic neurological condition that is characterized by recurrent neuronal electrical discharges caused by several factors. These discharges have paroxysmal features and may manifest with motor symptoms, called seizures, and non-motor symptoms. Epileptic seizures are the second most prevalent chronic neurological disease in pregnancy, being the most severe. An estimated 60 million people worldwide suffer from epilepsy, of this number, half are women and 0.3-0.5% of births are to epileptic mothers. Epilepsy has an idiopathic (40%) or secondary (60%) cause, the latter includes: trauma, medications, infections, tumors, CNS vascular problems, etc. There is also a classification according to the affected brain area, called partial/focal (only one area of the brain) or generalized (the whole brain). The generalized crisis was observed in this report, since it is responsible for triggering seizures, i.e., seizures with motor involvement and loss of consciousness,

usually related to the cerebral cortex, where the tumor developed infiltrative characteristics [13,14,15,24,25]. Epilepsy can only be considered cured if there is no recurrence of seizures within 2 years, with therapeutic weaning without recurrence, or with surgical resolution28.

The initial symptomatic therapy was sodium valproate, the mechanism of which is to increase brain concentrations of the neurotransmitter GABA. This drug is usually effective in treating idiopathic epilepsy, but it has shown little beneficial effect in this patient, since its diagnosis arose secondary to the expansive growth of the tumor mass. Some previous studies suggest that valproate is associated with polycystic ovary syndrome, menstrual irregularities and even decreased fertility28. Menstrual irregularity was observed in this case, but there were no hindrances regarding the issue of fertility. Other therapeutic drug options were installed during the patient's hospitalization, however, this report shows that the symptomatology only ceased with the surgical removal of the tumor, proving that epileptic seizures of secondary cause are definitively resolved by treating the underlying cause14,15,22.

Sodium valproate has a high teratogenicity22, and FEBRASGO (Brazilian Federation of Gynecology and Obstetrics Associations) recommends its replacement with an antiepileptic drug that is less harmful to fetal development during the gestational period29. As soon as pregnancy was confirmed, the patient was instructed to use Levetiracetam, a drug whose mechanism of action is not fully understood, but it is believed that it acts on the protein 2A of the synaptic vesicles, reducing the occurrence of epileptic seizures. The interruption of the seizures was attributed to the removal of the tumor, so it is not possible to conclude solely through this study whether this medication reaches satisfactory therapeutic levels in the control of tonic-clonic seizures during pregnancy. However, the fetus was born healthy without malformations or alterations in neonatal examinations, and it is possible to conclude, then, that in this case Levetiracetam was a safe medication that did not present teratogenic adverse effects.

The definitive therapy chosen follows the recommendation in the literature: surgical resection to avoid subsequent malignant progression of the tumor, for which the prognosis is excellent, with an expectation of survival after 5 years in 81% of cases, without the need for radiotherapy/chemotherapy in the absence of signs of postoperative progression, with periodic monitoring of imaging exams every 6 months23, conduct duly followed by the health professionals responsible for this patient.

Pregnancy *per se* can lead to worsening of neurological symptoms, such as seizures in pre-existing gliomas. Female hormone levels increase up to 200 times during pregnancy and this can cause an increase in the vascularization of tumors5, triggering recurrence in those who have not been completely resected due to increased blood supply and increased mitotic activity. However, in the case of low-grade gliomas, the course of pregnancy rarely intervenes in its prognosis. Systemic therapy should be used with caution, since several factors influence its teratogenicity: drug

concentration, placental passage, etc.6. In case of malignancy of some tumors, health professionals could opt for local chemotherapy with carmustine, enjoying a good safety margin, but it should still be avoided during the first trimester of pregnancy5.

Family planning is one of the focuses of encouragement of the Brazilian Unified Health System (SUS) and is an extremely important tool for epileptic women of childbearing age to be able to have children15,25. It is known that the physiology of the current pregnancy is capable of altering the frequency and intensity of crises14 and poor medication adherence before pregnancy will cause a worsening of the condition during the course of pregnancy. The risk of malformations in infants becomes two or three times higher when the occurrence of cleft palate and cleft lip, cranioencephalic anomalies, heart defects and poor closure of the neural tube13, but this occurs with the use of teratogenic anticonvulsant drugs or the occurrence of severe crises due to the lack of control of the pathology15. Several other consequences have been reported in the literature, such as: fetal distress, premature termination of pregnancy, and even fetal death. Well-controlled epilepsy *per se* , with adequate use of medication, results in more than 90% of healthy pregnancies13,14,15,26,27. Thus, family planning in addition to good prenatal care becomes even more important in the face of patients of childbearing age who have some comorbidity, especially epilepsy, a serious neurological condition with serious repercussions25.

Delivery should be planned to occur after the 37th week of gestation, in order to avoid harmful effects on the fetus related to prematurity, but the route chosen should be cesarean section. In case of prematurity, where delivery is not plausible to be postponed, cortisone is a systemic drug used for fetal lung maturation that is safe and beneficial for the mother. If the patient needed chemotherapy, it should occur 3 weeks before the expected date of delivery6. Fortunately, the patient in this case had a good postoperative evolution, with no signs of tumor recurrence, and it was not necessary to undergo radiotherapy/chemotherapy, with non-ionizing imaging at 6-month intervals, which evidenced surgical therapeutic success of her neoplasm and complete cessation of seizures.

CONCLUSION

The reported case shows that multidisciplinary integration of professionals is necessary for the therapeutic success of individuals treated in health institutions. The installation of a therapy, whether clinical or surgical, must be accompanied by a series of decisions based on scientific evidence and take into account the clinical, personal and social profile of each individual. This fact brings to light that, although the evolution of medicine makes the pathological diagnosis easier, the investigation must be carried out thoroughly before starting drug therapy in a patient, especially in relation to those pathologies that arise secondary to other conditions, thus achieving success in an integrated way, bringing well-being to those who undergo medical care.

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