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# Adult cerebellar glioblastoma: case report and review of the literature

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## Abstract

Glioblastoma is the most common and malignant primary brain tumor but its occurrence in the cerebellum is very rare. Giving its low occurrence the treatment modalities and outcome of this glioblastoma location are still poorly understood. We present the case of an adult woman with a cerebellar glioblastoma treated at the Clinical Hospital of Montevideo, and we perform a non-systematic review of the literature concerning the clinical, radiological and pathological features of this tumor, as well as its treatment modalities, prognostic factors and outcome.

**Keywords**: Cerebellar glioblastoma; Treatment modalities; Prognostic factors; Outcome

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## Introduction

Glioblastoma multiforme (GBM) is the most common and malignant primary brain tumor, accounting for about 15-20% of all intracranial tumors [1, 2] and 50% of primary intracranial tumors [3-5]. The incidence in Europe and North America is about 2 to 3 annual cases per 100000 habitants [6, 7] and there are reports suggesting that its incidence is increasing [8-11]. It usually affects people in the sixth and seventh decade of life [3]. There are two types of GBM, those who develop "de novo" (primary GBM) and those who develop after malignant transformation of a low grade or lesser grade glioma (secondary GBM) [3, 6]. This tumor arrives from the white matter or deep gray matter neighboring the white matter of the cerebral hemispheres [1].

The occurrence in the cerebellum is extremely rare and the reason for its very low frequency is still unknown. Most of the available data about cerebellar glioblastoma is reduced to case reports and some case series. Cerebellar GBM has different clinical and some radiological features compared with supratentorial GBM, and also a different mechanism of occurrence has been suggested

[12]. The treatment and prognostic factors in cerebral GBM are well established, but in cerebellar GBM, giving its low occurrence, there is still no consensus regarding its outcome and treatment modalities.

The authors report the case of an adult female with a cerebellar glioblastoma and make an extensive non-systematic review of the literature concerning its clinical and radiological features, as well as pathological findings, treatment, prognostic factors and outcome.

## Case presentation

We present the case of a 50-year-old woman with a past history of breast cancer treated with surgery and adjuvant chemotherapy 3-years before. She was under control by oncologist without evidence of recurrent disease. 2-months prior to admission she started with progressive gait disturbances and later developed headache and nausea. The day of admission at the Emergency Medical Center, she was lucid, but presented intense headache and vomiting. The neurological examination revealed trunk ataxia and left cerebellar signs (dysmetria and bradykinesia).

The head computed tomography (CT) scan showed a large midline mass in the posterior fossa, compromising the vermis and partially both cerebellar hemispheres, with heterogeneous contrast enhancement and poorly defined margins. It had severe mass effect with collapse of the IV ventricle and posterior fossa cisterns. Supratentorial hydrocephalus with transependymal edema was present **(Fig. 2)**. Despite the imaging findings, the presumptive diagnosis was brain metastases, based on its frequency and the patient's antecedent. She was taken urgently to the operating room. An external ventricular drainage was placed in the right frontal horn, followed by a sub-occipital craniotomy with tumor resection. We found an infiltrative lesion without a demarcable plane with the surrounding cerebellar parenchyma. A gross total removal was achieved and the piece was sent for histological examination. The patient remained intubated, under sedation and went to the Intensive Care Unit (ICU). The immediate postoperative course was uneventful. The control CT didn't show complications in the surgical bed **(Fig. 3)** and she was extubated 24 hours after surgery **(Fig. 4)**. The ventriculostomy was removed on the third postoperative day and she was discharged from the ICU 48 hours later.

In the following days, the patient presented a wound infection, that was successfully treated with antibiotics. She started physiotherapy and the cerebellar signs improved, being able to walk unaided. The successive scans didn't show further ventricular dilatation and she was discharged from Hospital 20 days after admission.

The histopathological examination revealed a highly cellular lesion, with increased mitosis, cellular and nuclear pleomorphic, proliferative blood vessels and necrosis; consistent with the diagnosis of glioblastoma multiform (WHO grade IV). **(Fig. 4)**. She received external beam radiotherapy (EBRT) with a total dose of 50 Gy, divided into 25 doses of 200 cGY. Four months after surgery and during radiotherapy (RT) a

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magnetic resonance imaging (MRI) showed a small lesion in the left cerebellar hemisphere adjacent to the fourth ventricle, hypointense in T1, hyperintense in T2 and flair with mild peripheral enhancement, interpreted as a tumor recurrence. We decided to continue with RT, which was completed with good tolerance. After 11 months of follow up, the patient is independent for activities of daily living, with mild cerebellar signs and no evidence of disease progression.

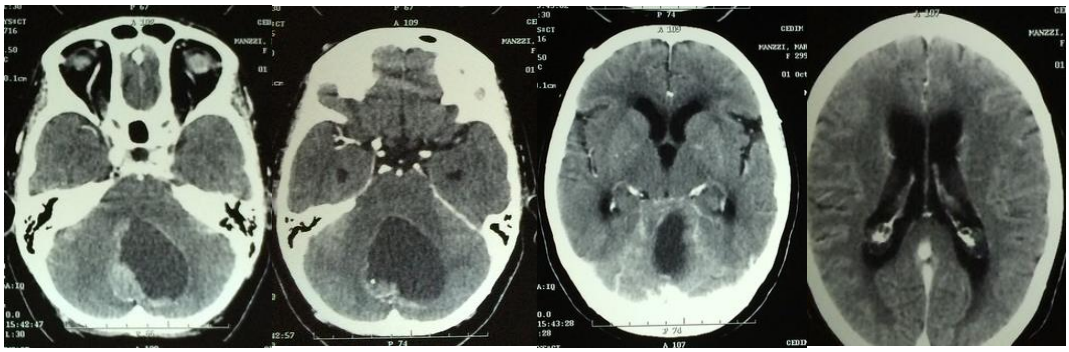

**Figure 1**.
Cranial CT scan. Midline heterogeneous enhancing mass with severe mass effect in the posterior fossa and supratentorial hydrocephalus.

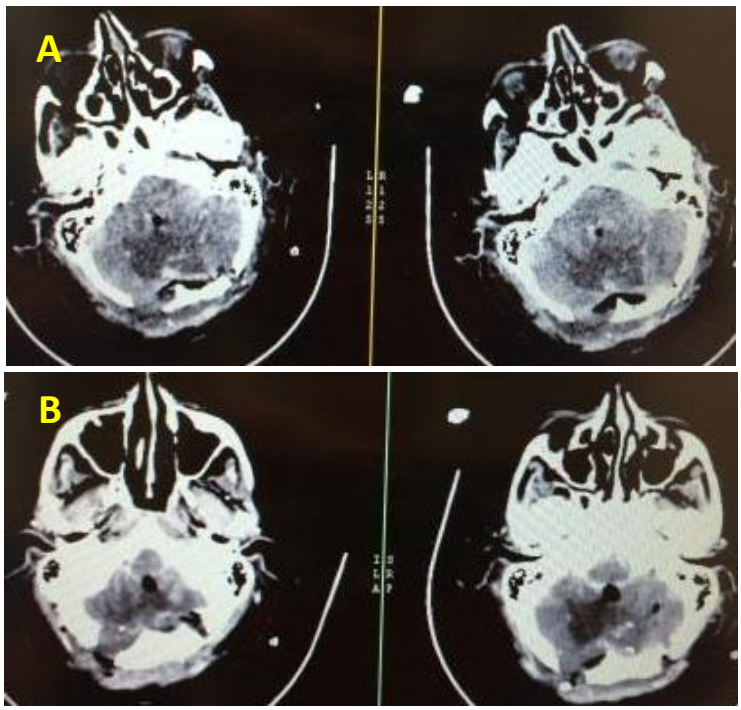


**Figure 2.**
A) Postoperative CT without contrast, showing no hemorrhagic complications in the surgical bed.
B) Absence of pathological enhancement after contrast administration.

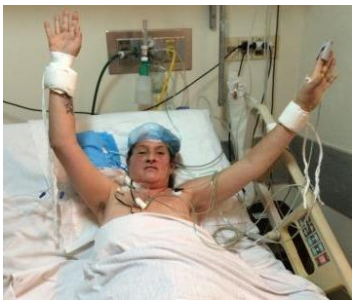

**Figure 3.**
The patient after extubation, without new focal deficit.

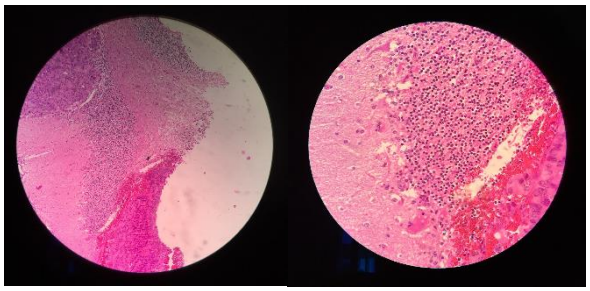

**Figure 4.**
Histological examination

## Discussion

Cerebellar GBM is a very infrequent tumor, accounting for about 0,4 to 3,4% of all glioblastomas [13-16]. In an early study, about 70% of the cases occurred in adults with an average age of 46,7 years, and 30% in children with an average age of 10,4 years17,18. The reasons for its low incidence remains uncertain. As it was suggested, if we consider that the cerebellum represents about 10% of the total brain volume, one should expect an incidence of cerebellar GBM of 10%19,20, but this does not occur. One reason that could explain this point, is the minimal or absent substance P (SP) signaling in the normal adult cerebellum, which has been implicated as an initiating and growth-enhancing path in glioblastomas [21]. Also, it has been proposed that cerebellar astrocytes have less tendency to anaplastic transformation [11, 22]. About the etiologic origin of glioblastoma in the posterior fossa, some authors suggest that a clinically silent supratentorial GBM could give rise to symptomatic infratentorial tumors by dissemination of its cells via the cerebrospinal fluid (CSF) pathways [7, 23, 24]. Another theory says that infratentorial GBM could arise de novo in the posterior fossa or from a lower grade glioma, without dissemination from a supratentorial location [7]. It has been suggested that radiation therapy might be a cause for inducing cerebellar GBM. There are reports of this entity following pilocytic astrocytoma, medulloblastoma and other posterior fossa midline tumors [22, 25-27], most of them receiving RT after surgery with the possibility of anaplastic progression. Furthermore, a malignant cerebellar astrocytoma was described after RT for craniopharyngioma [28, 29]. Anyway the potential role of this kind of therapy in the pathogenesis of cerebellar GBM remains uncertain. As we said previously, there are two types of GBM: primary GBM, which represents approximately 90% of the cases, and secondary GBM which represents the remaining 10% [6].

The former generally occurs in older patients and is characterized by the absence of heterozygosity 10q (LOH 10q) (about 70%) and frequently has epidermal growth factor receptor (EGF R) amplification, while secondary GBM

occurs mostly in younger patients and usually has p53 mutation [3], as well as inmuno-positivity for IDH1 and inmunonegativity for EGFR [12, 30, 31]. The inmunoreactivity rates for p53, EGFR and IDH1 in primary GBM are 11 - 37%, 63 - 76% and 4% respectively, while in secondary GBM are 75-97%,10% and 71% respectively [12, 32, 33]. It has been seen that cerebellar GBM occurs in younger patients compared with its supratentorial counterparts. The median age of appearance in cerebellar GBM was [39, 9] years in the study of Tsung *et al*., [14] and [50, 3] in the study conducted by Weber [34], compared with a median age of 64 year in supratentorial GBM [15]. Furthermore, there are reports of cerebellar glioblastomas showing p53 mutation, negativity for EGFR [3, 12, 30, 31, 35] and histology of low grade glioma [12, 30, 35].

Considering all of these features Utsuki *et al*. suggested that cerebellar GBM have a different mechanism of ocurrence compared with supratentorial GBM [12], with the first exhibiting mostly characteristics of secondary glioblastoma. Amplification of EGFR has been correlated with relative resistance to RT [36]. Saito *et al*., observed longer survival in patients with cerebellar glioblastoma and negativity for EGFR, compared with supratentorial GBM, suggesting that the better prognosis is attributable to its higher radiosensitivity [31].

Our case is probably a primary GBM, taking into account the absence of a past history of lesser grade glioma. Apart from the younger age, cerebellar GBM is also less frequent in whites and has a smaller size compared with supratentorial GBM [11]. The last probably because of the lower tolerance of the posterior fossa to expansive lesions. The duration of symptoms before presentation varies from 1 to 4 months; a period of time significantly shorter compared with the most common tumors of the posterior fossa [2]. Patients usually present ataxia and symptoms of increased intracranial pressure (IIPC) like headache and nausea [34, 35], as it was observed in our patient. Vomiting can also be present as well as other cerebellar signs. Dizziness, neck pain and mental confusion also has been described [22]. As we see these symptoms are nonspecific and can be present in many others expansive cerebellar lesions. Some authors report cases with mild initial manifestations, like vertigo or floating sensation that may overlook the presence of a cerebellar tumor leading to a delay in diagnosis and treatment [35]. The presentation of a cerebellar GBM as a cerebellar hemorrhage has also been reported [2].

Infratentorial glioblastomas generally have a closer relationship with the ventricular system compared with supratentorial glioblastomas, however the rate of spinal metastasis is quite similar [7]. These ones, which are often asymptomatic, as well as brain stem metastasis are well known in the late stages of supratentorial GBM.

Extracranial metastasis in glioblastomas are extremely rare, accounting for about 0,44% of the cases [4]. Pang *et al*., reported a case of extraneural metastasis of cerebellar GBM, suggesting that an open dura-mater in the posterior fossa might allow the tumoral

cells to make contact with extrameningeal tissues, with the possibility of lymphatic and vascular invasion [37]. About the location of this tumor, some studies describe a midline or near midline location [18, 35], concurring with our case, while others describe a lateral location [34]. In the study conducted by Weber, which includes 45 patients treated at different institutions 73,3% of the tumors were located in the cerebellar hemispheres [34].

In the case reported by the authors the presumptive diagnosis was cerebellar metastasis, taken into account the patient's past history of breast cancer and its high frequency, being the most common differential diagnosis for posterior fossa masses in adults [18]. Giving its very low occurrence the diagnosis of cerebellar glioblastoma is rarely made preoperatively, even though the advances in magnetic resonance imaging have increased the accuracy of the diagnosis [1, 22, 29, 38]. In the present case CT reveals a midline lesion with poorly defined margins after contrast administration. These are two features that can led to the presumptive diagnosis of glioblastoma in the posterior fossa according to Kuroiwa *et al*., (although we must consider that these authors findings are based on MRI images).

Others are prominent heterogeneous ring like enhancement (due to necrosis) and multi-centricity or extra-axial metastasis related to a disproportionally large tumor [18]. We must say that compared with its supratentorial counterpart, cerebellar glioblastoma has a higher rate of multifocality [5], accounting for 33% of the cases in the study of Weber *et al*., [34]. A mixed signal in T1 and T2 weighted MRI images may be due to intratumoral hemorrhage [18]. The lack of peritumoral edema and little mass effect are described as features that suggest cerebellar GBM in contrast to metastasis. These ones usually have more peritumoral edema and mass effect on the fourth ventricle with supratentorial hydrocephalus [3, 39]. Standard MRI sequences usually are insufficient for the differential diagnosis between metastatic disease and glioblastoma1. Perfusion and spectroscopy are very useful tools to increase the accuracy of the diagnosis. The former shows significantly higher relative cerebral blood volumes in the peritumoral region in high-grade gliomas compared with metastasis, while spectroscopy demonstrates an increased choline to creatine ratio in the peritumoral area of malignant gliomas [40], as well as a reduced N-acetyl aspartate (NAA) peak due to neuron loss [1].

Apart from metastasis [5, 7, 18] the differential diagnosis includes other common tumors like medulloblastoma, ependymoma [18], cystic astrocytoma1, hemangioblastoma [1, 7, 18] and lesions of other natures like cerebellar abscess [1, 5] or even infarction [5]. The latter can show contrast enhancement after one or two weeks ("fogging effect"), probably due to reduction of edema and protein leakage from cell lysis [29]. As it is known diffusion weighted imaging (DWI) is useful in the differential diagnosis between abscesses and tumors. The cavity content of abscesses exhibits high signal intensity in DWI and low apparent diffusion coefficient (ADC) values, while the solid compon-

ent of tumors usually shows low signal in DWI and high ADC values [1].

In a recent study, it was suggested that positron emission tomography-computed tomography (PET/CT) may be useful in the diagnosis of a cerebellar mass lesion [13]. When dealing with a glioblastoma patient the treatment modality depends on several factors like age, patient's general condition according to Karnofsky performance status (KPS) scale, tumor location and its relationship with eloquent areas, histological grade, genetic profile and proliferative index [6]. Older age, preexisting neurological deficit and poor functional status are associated with a worse prognosis in patients with GBM [41-43]. Gross total resection while keeping minimal surgical morbidity followed by radiation therapy with concurrent and adjuvant temozolomide according to Stupp protocol, is the treatment modality of choice in supratentorial glioblastoma with an overall survival (OS) of 14, 6 months [3, 4 3, 44]. More recent trials with novel agents combined with the standard chemotherapy report a survival of 19,6 months, with an OS of 37% at 2-year [14, 45]. Age and extent of resection are independent predictors of survival in primary GBM [46].

In cerebellar GBM, giving its low occurrence, the standard of treatment and prognostic factors are not so clear, with older reports describing a poorer prognosis compared with supratentorial GBM, others describing similar outcome between them and the most recent suggesting a slightly better prognosis in cerebellar GBM. Considering its location near the brain stem, the extent of resection may be limited and also the application of some adjuvant therapies like brachytherapy, because of the potential radiation injury to the brain stem [20]. These, are some of the reasons which led physicians and neurosurgeons to think that cerebellar GBM has a poorer outcome. In the analytic review of Djalilian and Hall the median survival of cerebellar GBM was 11 months [20], and in the retrospective study from the Rare Cancer Network conducted by Weber, the OS was 9,9 months and the progression free survival (PFS) was 5,7 months [34]. In the former study surgical resection compared with only biopsy, and external beam radiation therapy were correlated with extended survival, (P = 0.0036) and (P = 0,0001), respectively [20]. In the study of Weber, adjuvant therapy had a positive impact on PFS, while brain stem invasion was correlated with a shorter OS and PFS. Surprisingly, survival was negatively influenced by the extent of surgery, on multivariate analysis (P = 0,03) [34].

In supratentorial GBM the extent of surgical resection is reported as a significant factor in PFS and OS14. In their review of 21 patients with cerebellar GBM treated at the University of Texas MD Anderson Cancer Center between 1990 and 2010, Tsung *et al.*, found no correlation between extent of resection (EOR) with PFS and OS, but in this study surgical resection was nearly 100%, so this factor could have been biased. Furthermore, brain stem invasion did not affect survival. The authors argued that the variability in treatment and the impact of adjuvant chemotherapy may have affected this result; the last factor extended PFS from 2,8 to 10,1 months (P < 0,0001) but did

not significantly affect OS. In this study, a KPS ≥ 80 significantly affected survival and the presence of leptomeningeal disease was associated with a worse OS (6,1 *vs* 24,1 months; P = 0,0001) and PFS (3,3 *vs* 9 months; P = 0,019)14. The overall survival of this cohort was 18,4 months, longer than that reported by Weber *et al*., and Djalilian and Hall for cerebellar GBM and better than the 14, 6 months reported by Stupp *et al*., for supratentorial GBM [14, 20, 34, 44].

In another retrospective study, brainstem invasion, extent of resection and gamma knife radiosurgery (GKRS) were significantly associated with OS and PFS [47]. The survival of cerebellar glioblastoma patients in this study was 14, 3 months, comparable to that of supratentorial GBM reported by Stupp *et al*., and the PFS was 9, 4 months, better than the 7, 9 months reported by Tsung *et al*., [14, 44, 47]. The authors suggest that GKRS combined with chemotherapy may be a feasible postoperative adjuvant treatment [47]. The lack of a cohort receiving the standard treatment of supratentorial GBM was a limitation of this single institution retrospective study.

Three more recent studies of cerebellar GBM, based on the Surveillance, Epidemiology and End Results (SEER) database, were publish-ed. In one of them, Babu *et al*., found no differences between cerebellar and supratentorial GBM, in terms of overall survival and prognostic factors. Radiotherapy and surgical resection were seen to be independent favorable prognostic factors in multivariate analysis (P < 0,0001 and P = 0,028 respectively), while age > 40 was associated with a worse survival (P = 0,0001) [15]. In the same manner, the study conducted by Adams revealed that radiotherapy (P < 0,001) and younger age (P < 0,001) were factors significantly associated with prolonged survival in patients with cerebellar GBM. The authors make mention of the lesser ability to cope neurological insults caused by the tumor, surgery and/or adjuvant therapy that older patients may have, apart from the possibility of a more aggressive-behaving tumor. Asian or Pacific Islander race was another factor correlated with longer survival in this study (P = 0.046) [11]. The median survival for cerebellar GBM was 8 months and for supratentorial GBM was 9 months, with one, two and five-year survival rates of 21%, 13%, and 2%; and 12%, 7% and 1%, respectively. Extent of resection was associated with longer survival (P = 0,019), but only in univariate analysis [11].

The third study, also showed mortality risk reduction in younger patients (P < 0,0001) and with radiotherapy (P < 0,0001). The median survival of patients with supratentorial and cerebellar GBM was 8 months, but as the study progressed a slight advantage in survival time was seen in the last group [16].

It has been suggested by some authors that an absence of IDH-1 mutation, a negative MGMT methyla-tion, and meningeosis carcinomatous are negative predictors of a good response to chemotherapy and long overall survival [l4]. In the case presented by the authors, the MRI made four months after surgery showed a small tumor recurrence in the

left cerebellar hemisphere adjacent to the fourth ventricle. We decided in conjunction with oncologists to continue with the planned radiotherapy. About this point, it is reported that tumor recurrence usually occurs within 2 cm of the original tumor bed (greater than 95% of cases) [43, 48]. Despite radiation therapy is a well-established treatment after surgery, the irradiation field is not well defined and most patients have been treated with limited fields, including posterior fossa, brain stem and upper cervical spinal cord [5]. Weber *et al*., recommend that the treatment protocol for cerebellar GBM should be the same as for supratentorial GBM. They do not recommend routinely craniospinal irradiation, unless cerebrospinal fluid dissemination is present [34]. In a recent study, a long-term control of spinal metastases from cerebellar glioblastoma was achieved combining intravenous bevacizumab with temozolomide and radiation therapy [4].

In our case, the patient did not receive the standard treatment of supratentorial GBM, but after 11 months of follow up, has a good clinical condition, with minimal neurological deficit.

**In conclusion**; cerebellar GBM is a very infrequent tumor. The minimal or absent SP signaling in normal adult cerebellum, as well as a less tendency of the cerebellar astrocytes to anaplastic transformation are some of the theories proposed to explain its low incidence. It has clinical and radiological differences compared with its supratentorial counterpart and also a different mechanism of occurence has been suggested. Younger age, surgical resection and radiotherapy are factors independently associated with longer survival, while leptomeningeal disease is associated with worse survival.

In general terms, despite the apparent pathogenic differences between supratentorial and cerebellar GBM, with the last showing a pattern of secondary glioblastoma like p53 mutation, inmunonegativity for EGFR and inmunopositivity for IDH-1, several authors agree that its treatment should be the same as for supratentorial GBM, with a similar or slightly better prognosis in terms of survival.

## Competing interests

Author declare that I have no competing interest.

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