Archives of Clinical and Experimental Surgery, 2024
VOL 13, NO. 06, PAGE 01-08

CASE SERIES

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Extra-Cranial Metastases of Glioblastoma Multiform: Cases Reports and a Review of the Literature

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ABSTRACT

Introduction: Glioblastoma Multiforme (GBM) is the most common and aggressive malignant glioma. Despite the well-known invasiveness in the Central Nervous System (CNS), yet they are considered to be typically confined because extra-cranial metastasis of glioblastoma rarely occurs.

Case presentation: We describe two cases, the first is about a 58-year-old woman with a diagnosis with GBM, which was subsequently taken to surgery with total resection and progress with recurrence in the temporal lobe finally presented a spinal cord metastasis. The second case of a fifteen-year old patient who initially presented with a low-grade glioma, which was managed with surgical resection, radiation therapy and a ventriculoperitoneal shunt because of obstructive hydrocephalus. Despite of the treatment, the tumor progressed to GBM, associated with peritoneal metastasis.

Conclusion: Glioblastoma extracranial disease is rare, and reporting cases could help to collect data that might orient about mechanism of dissemination, and develop future investigations on this topic.

ARTICLE HISTORY
Received: 18-Oct-2024, Manuscript No. EJMACES-24-150300;
Editor assigned: 21-Oct-2024, PreQC No. EJMACES-24-150300 (PQ);
Reviewed: 04-Nov-2024, QC No. EJMACES-24-150300;
Revised: 11-Nov-2024, Manuscript No. EJMACES-24-150300 (R);
Published: 18-Nov-2024

KEYWORDS
Brain neoplasms; Glioma; Ventriculoperitoneal shunt; Neoplasm metastasis; Case report

Abbreviations
GBM-Glioblastoma Multiforme; CNS-Central Nervous System; CSF-Cerebro Spinal Fluid; BBB-Blood Brain Barrier; ECM-Extra Cellular Matrix; VPS-Ventriculo Peritoneal Shunt; CTC-Circulating Tumor Cells

Introduction

Malignant gliomas are the most common type of primary malignant brain tumor, accounting for 80% of patients with CNS cancers. There is an annual worldwide incidence of malignant gliomas of 5-7 per 100,000 of the population [1,2]. Worldwide, this accounts for 2% of all primary tumors and 7% of years of life lost from cancer before the age of 70 [2].

Prognosis is poor, because GBM is an aggressive CNS neoplasm with average survival time varying from 6 to 18 months [1-5]. Up to 90% of patients die within two years of diagnosis glioblastoma multiforme is highly invasive, infiltrating the surrounding brain parenchyma [3]. It is considered to be typically confined to the CNS because extra-cranial metastasis of GBM only rarely occurs [1,3]. Reported incidence of GBM metastasis is 0.4 to 2.7% [2,4,6,7].

We report two case of GBM spreading outside the brain in order to contribute to the construction of knowledge on this topic. It should be noted that while the incidence of cases is not very high, it is not negligible. In addition, this pathology has a high mortality and morbidity for patients.

Case Presentation

Case number 1

A 58-year-old woman with no prior medical history was admitted with dysgeusia, severe headache, dysphagia, right limb weakness, and deviation of the mouth commissure to the left side. A Computed Tomogram (CT) scan was obtained, showing a mass in the basal ganglion region and left insula. Brain Magnetic Resonance Imaging reported a 31 × 23 mm nodular mass with well-defined contours, possibly an insular Glioblastoma Multiforme (GBM) (Figures 1A-1F). She underwent surgery, and macroscopically complete resection was performed. Pathology reported a GBM with poor expression of *P53*, a Ki67 index of 20%, PD-L1 expression of 70%, and negative IDH1 and PTEN. She received radiotherapy plus temozolomide, followed by monthly temozolomide at 270 mg. She was re-operated on 04/14/2019 due to tumor recurrence located in the left temporal lobe

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(19 × 20 × 20 mm). Pathology reported a recurrence with PD-L1 expression of 70%, Ki67 index of 30%, and negative IDH-1 and PTEN, with poor expression of *P53*. A second treatment line (irinotecan plus bevacizumab) was initiated. A week later, she returned to the emergency department with severe cervicalgia associated with paresthesia and hemiparesis in the left hemibody. Due to discordance with initial symptoms, a cervical spine MRI was performed, which reported a nodular enhancement mass occupying the central and lateral portion of the medulla from C2 to C5 with specific contours, measuring (52 × 11 × 10 mm) (Figure 1G-1I). No new surgical intervention was performed due to the risk outweighing the benefit. The patient died with a total survival of 17 months from the initial diagnosis.

Case number 2

A 15-year-old female with no prior medical history presented with a one-month history of progressively worsening headaches. Imaging revealed a right thalamic tumor, and a stereotactic biopsy confirmed a Grade II astrocytoma, with a Ki-67 proliferative index of less than 2%. Two months post-diagnosis, the patient developed hydrocephalus, necessitating the placement of a programmable Ventriculo Peritoneal Shunt (VPS). She subsequently received fractionated radiation therapy, totaling 5400 cGy, which resulted in clinical and radiological stability on follow-up imaging.

Three years after the completion of radiotherapy, follow-up Magnetic Resonance Imaging (MRI) revealed tumor progression towards the posterior aspect of the thalamus, with extension into the right temporal lobe. The patient underwent five sessions of hypofractionated radiosurgery (600 cGy each) targeting both previously irradiated areas and newly affected regions. Ten months later, she presented with severe headaches, vomiting, and left hemiparesis. MRI demonstrated edema and a small amount of bleeding, which were interpreted as radiation effects. Dexamethasone was initiated, resulting in improved strength and reduced headaches. She was discharged on oral steroids.

Twelve months after the last radiosurgery, the headache reappeared and was associated with left hemiparesis (Figures 2A-2F). MRI showed significant growing of the tumor (Figures 2A and 2B). Stereotactic biopsy was obtained to clarify the diagnosis. Pathology reported GBM, with a Ki-67 proliferation index of 40% (Figures 3A-3E). Given the impossibility of surgical resection, temozolomide was started.

Three weeks afterwards, the patient presented with abdominal pain and intermittent cramping, which was associated with a feeling of fullness and episodes of fever. Ultrasonography revealed ascites and an abdominopelvic CT-scan revealed nodular lesions in the uterus, ovaries, liver, right kidney and peritoneum (Figures 2C and 2D). Diagnostic laparoscopy was performed. Peritoneal lesions and some ovarian tumors were found (Figures 2E and 2F). Several of these lesions were biopsied showing the connective tissue infiltrated by malignant tumor cells. Immunohistochemistry was positive for the GFAP, S100, vimentin and WT1, with a Ki-67 proliferation index of 50%. These results were compatible with high-grade astrocytoma (Figures 3F-3J). Patient presented rapid deterioration until she died 13 months after hypo-fractionated therapy and 4 years and 3 months after her initial diagnosis.

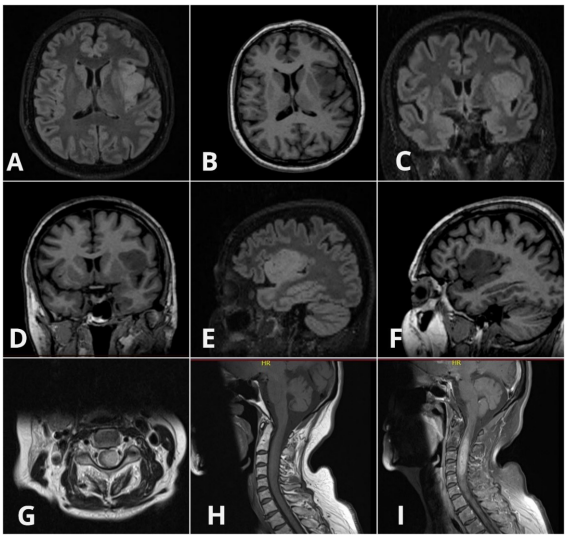

Figure 1. A-B) Axial FLAIR and T1-weighted images brain MRI that shows a mass in the left insular with a little deviation from the midline; C-D) Coronal FLAIR and T1-weighted images brain MRI that evidences a circumferential mass in the left insula and presence of vasogenic edema; E-F) Sagittal section in sequences FLAIR and T1-weighted images expose a oval mass ivading the insula; G-I) Axial T2 and sagittal T1-weighted without and with contrast of the Spinal cord widening due to a hyperintense lesion in T2, isointense on T1 and with contrast enhancement. Length of that mass is approximately two intervertebral spaces.

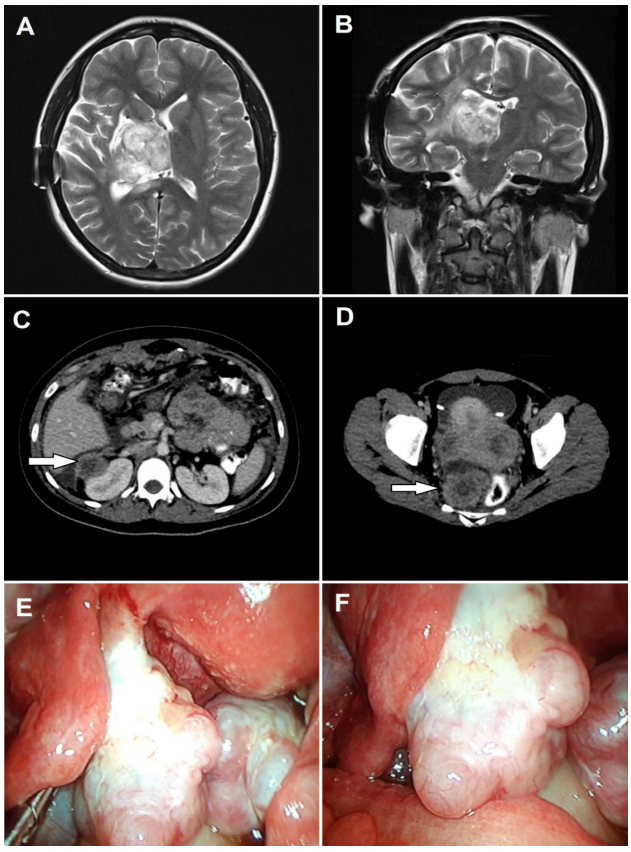

Figure 2. A) Axial T2-weighted brain MRI that evidences a right thalamic high signal lesion that compromises the third ventricle; B) Coronal Axial T2-weighted brain MRI that evidences a right thalamic high signal lesion that compromises the third ventricle with vasogenic edema surrounding the mass; C) Axial abdominal CT-scan that evidences a low-density nodular lesion anterior to the right kidney; D) Axial pelvic CT-scan that shows the distal end of the VPS catheter and multiple nodular lesions of the ovaries; E-F) Laparoscopic image that shows nodular lesions in the ovaries.

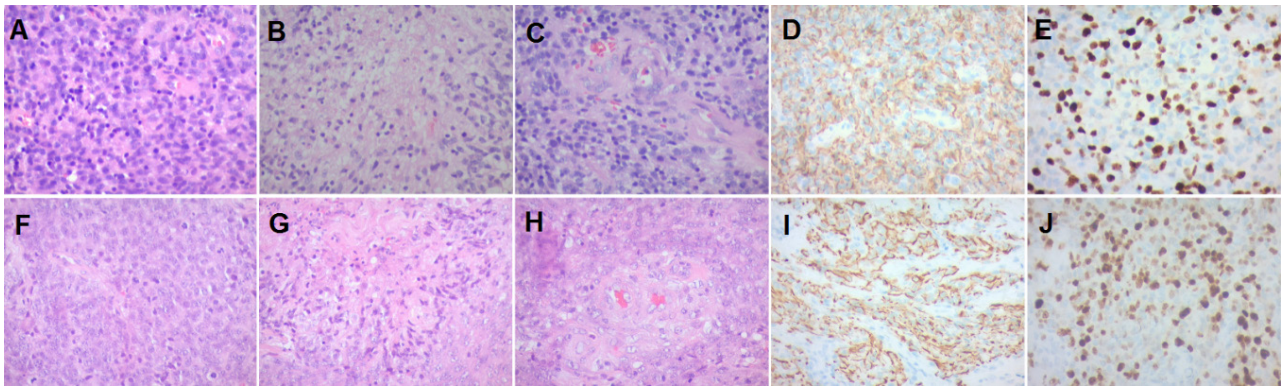

Figure 3. A-E) Histopathologic findings and comparison of biopsy of brain; F-J) Abdominal samples.

A and F) Tumoral cells with important pleomorphism and mitotic activity; B and G) Pseudopalisading necrosis; C and H) Microvascular proliferation; D and I) The tumoral cells are positive for GFAP; E and J) The tumoral cells have a high proliferation index measured by KI67. All of these characteristics are consistent with GBM in both samples.

The presented Table 1, contrasts two cases of Glioblastoma Multiforme (GBM) illustrating distinct clinical trajectories and management strategies. Case 1, involving a 58-year-old patient, demonstrated rapid disease progression with initial surgical intervention and subsequent recurrence, leading to metastasis to the cervical spine and ultimately death within 17 months of diagnosis. In contrast, Case 2, a 15-year-old patient, initially treated with radiotherapy for a Grade II astrocytoma, later experienced tumor progression despite additional radiosurgery, culminating in metastasis to multiple abdominal organs and death 4 years and 3 months post-diagnosis. This comparative overview underscores the variable course of GBM, emphasizing the challenges in treatment efficacy and disease management across different age groups and initial tumor grades (Tables 2 and 3).

Table 1. Glioblastoma Multiforme (GBM) illustrating distinct clinical trajectories and management strategies of cases.

Event	**Case 1**	**Case 2**
Initial presentation	Dysgeusia, severe headache, dysphagia, limb weakness, left-sided mouth commissure deviation	Progressive headaches
Imaging findings	CT: Basal ganglion mass; MRI: 31 × 23 mm insular GBM	Thalamic tumor
Initial surgery	Complete resection of insular GBM	Stereotactic biopsy
Pathology (Initial)	GBM, poor *P53*, Ki67: 20%, PDL-1: 70%, IDH1/PTEN negative	Grade II astrocytoma, Ki67: <2%
Treatment	Radiotherapy+temozolomide; maintenance temozolomide	Fractionated radiotherapy (5400 cGy)
Recurrence	Left temporal lobe GBM (19 × 20 × 20 mm)	Thalamic tumor progression to temporal lobe
Pathology (Recurrence)	GBM, PDL-1: 70%, Ki67: 30%, IDH-1/PTEN negative, poor *P53*	GBM, Ki67: 40%
Second line treatment	Irinotecan+bevacizumab	Hypofractionated radiosurgery
Emergency presentation	Cervical spinal cord metastasis, cervicalgia, paresthesia, hemiparesis	Headaches, vomiting, left hemiparesis
Metastasis	Not specified	Abdominal metastases (uterus, ovaries, liver, kidney, peritoneum)
Outcome	Death at 17 months from diagnosis	Death at 4 years and 3 months from diagnosis

Table 2. Characterization of the tumors 1.

	Pathology	**Location**	**Ki67**	**PDL-1**	***P53* expression**	**IDH**	**PTEN**	**GFAP**	**S100**	**Vimentin**	**WT1**	**Size**
Patient 1 Pathology 1	GBM IV WHO	Basal and left insular	20%	70%	Poor	-	-	ND	ND	ND	ND	31 × 23 mm
Patient 1 Pathology 2	GBM IV WHO	left temporal lobe anterior pole	30%	70%	Poor	-	-	ND	SD	ND	ND	19 × 20 × 20 mm
Patient 1 metastasis	ND	Spinal cord from C2 to C5	ND	ND	ND	ND	ND	ND	ND	ND	ND	52 × 11 × 10 mm
Patient 2 Pathology 1	Astrocytoma grado II WHO	Right Talamus with an extension to the right temporal lobe	2%	ND	ND	ND	ND	ND	ND	ND	ND	SD
Patient 2 Pathology 2	GBM grade IV	Basal ganglia	40%	ND	ND	ND	ND	ND	ND	ND	ND	SD
Patient 2 metastasis	high-grade astrocytoma	Uterus, ovaries, liver, right kidney and peritoneum	50%	ND	ND	ND	ND	+	+	+	+	SD
Note: GBM-Glioblastoma Multiforme; GFAP-Glial Fibrillary Acidic Protein; ND-No data												

Discussion

Gliomas are exceedingly adept at infiltrating the CNS, with glioma cells capable of remodelling the Extra Cellular Matrix (ECM) and migrating along nerve tracts, meninges, and vasculature [8]. Despite their aggressive behavior, gliomas do not routinely metastasize outside the CNS. In fact, due to the rarity of extra-cranial metastasis, gliomas are the only malignant tumors that are not staged [8]. The reasons behind the preferential metastasis within the CNS rather than outside it remain incompletely understood.

Several factors contributing to the low incidence of extra-cranial metastasis from Glioblastoma (GBM) have been proposed, including short survival periods, the dense dura around intracranial veins preventing tumor cell penetration, the Blood-Brain Barrier (BBB), immune system suppression of extra-cranial GBM cell growth, the absence of true lymphatic channels in the CNS, and the inability of GBM cells to invade extra-cranial connective tissue [6,7,9].

However, despite these traditional concepts and proposed barriers, extra-cranial primary brain tumor metastases have been documented in the literature [7]. The first reported case of extra-cranial metastasis of a glial tumor was described by Davis in 1928 [10]. Since then, additional cases have been reported with metastases to the pleura, heart, peritoneum, intra-abdominal organs, regional lymph nodes, vertebral bones, parotid glands, skin, scalp, and bone marrow [2–5,7–9,11–16].

The increase in reported cases of extra-cranial metastases of GBM is generally attributed to improved overall survival and local control from radical surgery and advancements in adjuvant therapy (concurrent temozolomide with radiation therapy followed by maintenance temozolomide) [4,8,11,15]. Extra-cranial metastases of gliomas frequently occur late in the disease course (median of 2 years), and survival is poor after the onset of metastatic disease [4,13].

Primary brain tumors can metastasize through various routes. Five main pathways have been described: Hematogenous spread *via* the vessels of the primary brain tumor; hematogenous spread following tumor invasion of the dural veins; hematogenous and/or lymphatic spread after infiltration of the skull and extra-cranial soft tissues; spread *via* Cerebro Spinal Fluid (CSF); and spread *via* ventriculoatrial, ventriculopleural, or ventriculoperitoneal shunts [15,16]. The newly discovered glymphatic system, which drains the interstitial fluid of the brain parenchyma, and its probable connection to the recently discovered lymphatic system of the CNS, may constitute another route for primary brain tumors to spread to the deep and superficial cervical lymph nodes [17,18]. There is substantial evidence that the lymphatic system drains not only interstitial fluid but also a significant fraction of CSF into the cervical lymph nodes [5].

The BBB may be a significant obstacle for extra-cranial spread of GBM [5]. It is supported by the fact that many cases reported in the literature presented metastases after neurosurgical procedures. These could facilitate the migration of GBM cells by breaches of the BBB and the innate defense system, because incomplete closure of the dura could create a direct communication between malignant cell tumors and extra-meningeal vessels and lymphatic channels [5]. Additionally, tumor cells could easily invade fragile vessels during post-operative repair [11].

It is well known that GBM cells can spread *via* the CSF pathway [4]. Cells entering the CSF can find a route to spread quickly, especially when there is a shunt. Seeding of tumoral cells or "Drop metastases" have been reported in patients with GBM and VPS [2,3,5,11,14]. We hypothesize that this is what happened to our patient as this would explain the rapid spread of the GBM in the peritoneum and intra-abdominal organs, among them, ovary, which is an extraordinary rare site of glioma cells implantation. Regarding those reports, its pathophysiology remains unknown in GBM. Several biological and molecular pathways may explain this behavior, such as *P53* gene mutations, overexpression of insulin growth factor, appearance of a sarcomatous component in the original glioblastoma or clonal selection [15].

The breach of the BBB in neurosurgical procedures may not explain completely primary brain tumor metastases. There are cases of extra-cranial metastases without prior neurosurgical procedures [19-22] and it is thought that approximately 10% of extra-cranial glioma metastases occur in patients without previous surgery, suggesting that other routes of dissemination exist [2,9]. Glioma cells actively seek out blood vessels and migrate along them through the perivascular spaces (Virchow-Robin spaces), but there is also now more evidence that the GBM cells can actually disrupt the BBB by themselves [23]. Müller et al., provide evidence to support this theory, having reported that approximately 20.6% of GBM patients have detectable levels of Circulating Tumor Cells (CTC) in their blood [6,8]. How these cells interact at this level with the immune system is not clearly known, and this could be critical in systemic spread.

Malignant gliomas are highly molecular and genetically heterogeneous tumors with core defects primarily in three signalling axes: The tyrosine kinase receptor pathway, the anti-apoptotic retinoblastoma pathway and the cell cycle regulatory (*p53*) axes [1,24]. Any of

these possible pathways could explain the enhanced aggressive infiltration and dissemination of GBM. At present, however, the molecular pathways that predispose these patients to have extra-cranial metastasis are unknown [7]. One proposed molecular mechanism is the Epithelial-Mesenchymal Transition (EMT), which is a transcriptional cascade that enables epithelial cells to lose their cell polarity and their dependence on cell-cell adhesion, allowing them to gain migratory and invasive properties reminiscent of mesenchymal cells. EMT is thought to be essential for tumor metastasis in systemic cancers and may play a role in GBM metastasis [8].

Despite all of this data, many fundamental questions remain about the relevance of CTC in GBM. In Müller et al., most patients with detectable CTC did not developed extra-cranial metastases [6]. Just as there are biological obstacles to reach the systemic circulation, there may be intrinsic biological obstacles that prevent tumors from infiltrating and surviving beyond the neural environment [7]. This may be explained by the "seed *versus* soil" hypothesis first posited by Stephen Paget in 1889, whereby the distant site where CTCs have lodged is not conducive to the subsequent development of metastasis or where the immune system could not allow for extra-neural tumor survival [8]. These may explain why extra-cranial GBM is not observed at a higher rate than currently reported [9].

As primary brain tumors traditionally have been considered incapable of metastasizing and affected patients typically die from intracranial progression, GBM patients have served as a pool for organ donors. Unfortunately, this has led to the discovery of a new entity: Secondary extra-cranial metastases of GBM from organ transplantation [8]. In order to be successful, transplant recipients must be placed on significant immunosuppression medication. It is well known that the immune system plays a critical role in the prevention of malignancy, and that immunosuppressed patients are prone to develop malignant tumors [8]. In the case of transplantation, there is controversy because it is clear that organ donors with prior malignancies may increase the risk of malignancy in the organ recipient, because some tumor cells may be present in the graft and, due to the immunosuppression, the recipient's immune system is unable to control these transplanted malignant cells.

It is also hypothesized that the immune system plays a critical role in the prevention of CTC and tumor seeding occurring in distant extra-neural organs. It is known that radiotherapy, temozolamide and corticosteroids depress the immune system response and may facilitate the spread of tumors throughout extra-neural tissues [25–28]. Thus, it is not clear whether the long-course of corticosteroids given to our patient, favored tumor invasion. We hypothesized that this could occurred in case number 2.

There is currently no standard strategy to prevent metastases of primary brain tumors, especially following neurosurgical procedures. There has been attempts at control using VPS filters, watertight dural closure, calvarial reconstruction, changing instruments between intra-dural and extradural segments of the operation and postoperative prophylactic craniospinal irradiation [9,29]. These strategies have not shown any beneficial effects and there are no randomized trials to support them.

Conclusion

These cases do not allow to consider hypothesis about risk factors to study with an extracranial hypothesis due to GBM. It also calls us to actively look for these metastases in patients with long survival, since the symptoms can be very unspecific of an extracranial metastasis.

This case may lead us to consider variables like the presence of VPS, longer courses of corticosteroids or any condition that impair the cellular immune response and can induce tumor growing and facilitate its extra cranial invasion. Considering reviewed data, it could be reasonable to evaluate how much steroid therapy patients need, due to the potential (not yet well-established) risk of tumor progression. In addition, patients with VPS should be followed up closely, due to the potential abdominal dissemination.

Through this study it is impossible to draw conclusions or causal relationships. Therefore, it is key and we hope to motivate research in this area. In this sense, it is considered that a contribution will be made from a study in order to establish hypotheses about risk factors for extracranial metastases, clinical outcomes, prognosis and treatment.

Ethical Considerations

This paper was made under the national normative that is the answerable to regulate the clinical investigation in Colombia. According the resolution 8430 of 1993, the law 2378 of 2008 and definitely the international research ethics agreements (the Helsinki Statement). Because it is a retrospective study and no additional intervention will be performed in patients, this study is considered risk free. However, understanding that no investigation does not require any risk for the participants and relying on article 8 of resolution 8430 We are committed to ensuring that the confidentiality and privacy of patients is maintained. The identification information of each patient will be encrypted to avoid traceability by outsiders.

Limitations of the Study

From the methodological strategy of the case report, we know that conclusions or associations cannot be drawn. The two cases that were presented do not have a standardized genetic assessment of the tumor. Which slightly limits the ability to observe certain aspects of tumors. We understand that during the first case a biopsy was not performed to verify with certainty the diagnosis of GBM metastases. However, the patient's clinical context was futile to expose the patient to a procedure that was not going to change the behavior.

Acknowledgements

We extend our gratitude to all the family members who agreed to provide the information necessary for the confidential preparation of this manuscript. There is no more altruistic act than caring for the well-being of others without expecting anything in return, and their contributions continue to enrich lives even in their absence. We also appreciate Dr. Helen Reina for her assistance in writing and copy-editing this manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval

Ethics approval was obtained from the institutional review board of Fundación Clínica Valle del Lili, Cali, Colombia. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent for Publication

Additional informed consent was obtained from all individual participants. The identification information of each patient will be encrypted to avoid traceability by outsiders.

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

Brian Bravo-Gamboa: Data collection, Literature review, manuscript drafting.

Danielle Floyd-Aristizábal: Data collection, Literature review, manuscript drafting.

Alejandro Enríquez-Marulanda: Data analysis, Literature review, manuscript editing.

Luis Alberto Escobar: Pathological analysis, data interpretation.

Oscar Rojas: Surgical data collection, manuscript review.

Javier Lobato-Polo: Surgical data collection, Study conception and design, overall supervision of the manuscript preparation, manuscript review.

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