Primary Extra-axial Glioblastoma: Case Report and Literature Review

Glioblastoma extra-axial primário: relato de caso e revisão da literatura

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Abstract

Glioblastoma multiforme (GBM) is the most frequent and most aggressive primary brain tumor in adults, mainly located in the cerebral hemispheres. In the literature, few cases of primary GBM have been reported to have radiographic and intraoperative features of extra-axial lesions, leading to a diagnostic dilemma. Despite the advances in imaging modalities, the diagnosis of GBM can be challenging, and it is mainly based on the histopathologic confirmation of the excised tumor. We describe the case of a 76-year-old previously healthy female patient who presented to our hospital due to speech disturbances and cognitive impairment. The diagnosis of the tumor type on magnetic resonance imaging (MRI) was difficult, as the findings were suggestive of a malignant meningioma due to the heterogeneous enhancement of a dural-based mass with a dural tail sign. Moreover, the intraoperative findings revealed an extra-axial mass attached to the dura. A histological examination confirmed the diagnosis of glioblastoma with arachnoid infiltration. The patient underwent adjuvant radiotherapy and concomitant temozolomide treatment, she had clinical improvement postoperatively, and was stable during the six months of follow-up. Glioblastoma should be considered in the differential diagnosis of primary extra-axial mass with atypical and malignant features, especially in elderly patients.

Keywords
- brain neoplasms
- glioblastoma
- arachnoid
- extra-axial

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Abstrata

O glioblastoma multiforme (GBM) é o tumor cerebral primário mais frequente e agressivo em adultos, localizado principalmente nos hemisférios cerebrais. Na literatura, poucos casos de GBM primário foram relatados com características radiográficas e intraoperatórias de lesões extra-axiais, o que leva a um dilema diagnóstico. Apesar dos avanços nas modalidades de imagiologia, o diagnóstico de GBM pode ser desafiador, e é baseado principalmente na confirmação histopatológica do tumor excisado. Descrevemos o caso de uma paciente do sexo feminino, de 76 anos, previamente hígida, que se apresentou em nosso hospital devido a distúrbios da fala e alterações cognitivas. O diagnóstico do tipo de tumor na ressonância magnética foi difícil, pois os achados eram sugestivos de meningioma maligno devido ao realce heterogêneo de uma massa dural com um sinal de cauda dural. Além disso, os achados intraoperatórios revelaram uma massa extra-axial aderida à dura-máter. O exame histológico confirmou o diagnóstico de glioblastoma com infiltração aracnoide. A paciente foi submetida a radioterapia adjuvante e tratamento concomitante com temozolomida, apresentou melhora clínica no pós-operatório, e manteve-se estável durante os seis meses de seguimento. O glioblastoma deve ser considerado no diagnóstico diferencial de massa extra-axial primária com características atípicas e malignas, especialmente em pacientes idosos.

Palavras-chave
- neoplasias cerebrais
- glioblastoma
- aracnoide
- extra-axial

Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive primary malignant brain tumor in adults, accounting for 14.6% of all tumors and 48.3% of malignant tumors.[1] It is usually located intra-axially in the deep white matter of the supratentorial region, mainly in the frontal and temporal lobes.[2] Several neoplastic and nonneoplastic (granulomatous, lymphoproliferative, autoimmune) dural-based entities are reported to clinically and radiographically mimic meningioma.[3,4] Glioblastoma multiforme with primary extra-axial involvement has rarely been reported in the literature.[5] Here, we report a case of left temporal GBM with extra-axial features.

Case Report

A 76-year-old, previously healthy, nonsmoker, and nonalcoholic female patient, presented with verbal paraphasia and attention deficit that had begun in the month prior to her visit. Upon neurological examination, expressive aphasia was noted, and the three-word recall test, along with the backward digit span test, was impaired. There were no other neurological signs, such as focal deficits, motor weakness, cranial nerve deficit, gait instability, or pronator drift. The vital signs and the initial laboratory testing were unremarkable.

A brain magnetic resonance imaging (MRI) scan performed upon admission showed a 5.1-cm left temporal tumor broadly abutting the dural surface at its anterior inferior and medial aspects, with heterogeneous enhancement and surrounded by extensive vasogenic edema. The dura showed a thickened appearance and enhancement (dural tail sign, DTS) surrounding the middle cranial fossa. A mass effect was produced by the tumor, with compression of the left lateral ventricle and shift of the midline structures to the right by $\sim$ 3 mm (►**Fig. 1**). The mass also presented a cerebrospinal fluid (CSF) cleft sign (►**Fig. 2**).

A computerized tomography (CT) scan of the chest, abdomen, and pelvis was performed, and failed to reveal a primary tumor. The patient was submitted to appropriate intravenous (IV) hydration, and dexamethasone 8 mg IV every 6 hours to decrease the edema.

The case was discussed in a tumor board meeting, and the main differential diagnoses considered were malignant meningioma and glioblastoma multiforme. The decision was made to proceed with craniotomy to resect the lesion. The patient received standard preoperative medication, including valproate, dexamethasone, cefazolin, and mannitol on the morning of the surgery. Intraoperatively, the tumor was soft, gray, round, extra-axial, and attached to the dura of the left middle cranial fossa inferiorly, and it was indenting but easily resectable from the temporal lobe superiorly and medially. A gross total resection was performed under microscopic magnification.

A postoperative brain MRI showed complete resection of the middle cranial fossa tumor (►**Fig. 3**). The postoperative course was smooth, and the patient demonstrated progressive clinical improvement in her neurological status. The histopathological result of the specimen was consistent with an isocitrate dehydrogenase 1 (IDH1) mutated glioblastoma with arachnoid infiltration (►**Fig. 4**). Moreover, there was a glial proliferation of the neoplastic cells within the arachnoid, along with fibrous and angiomatous components, containing necrotic sites, pleomorphism, and a multinucleate and a moderate to marked anisonucleosis with important mitotic activity. The neoplastic cells expressed glial fibrillary

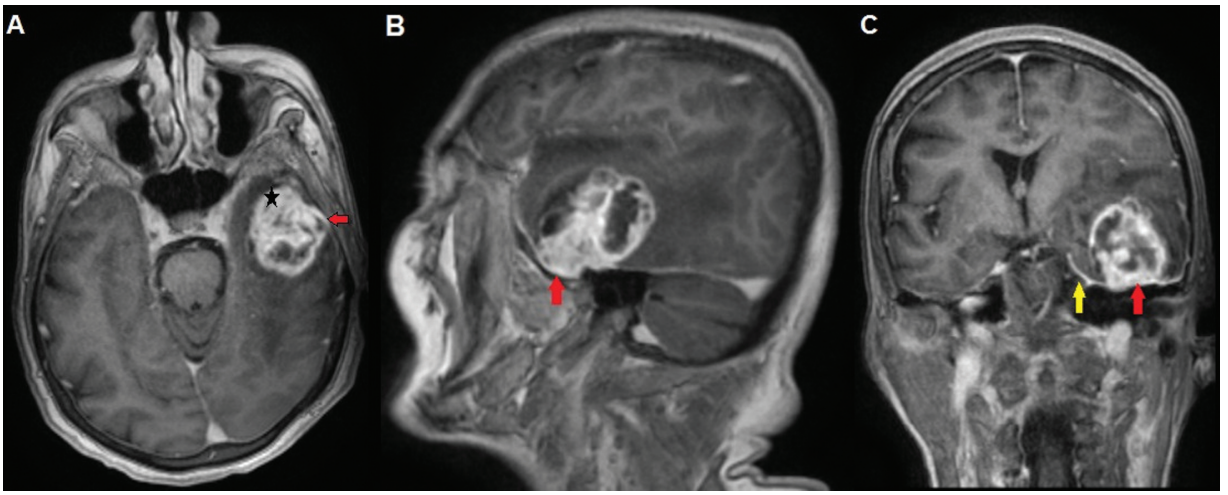

Fig. 1 Axial (**A**), sagittal (**B**), and coronal (**C**) T1-weighted MRI scans with contrast demonstrating a heterogeneously-enhancing mass (asterisk) with broad dural contact anteroinferiorly (red arrow) with a dural tail sign (yellow arrow).

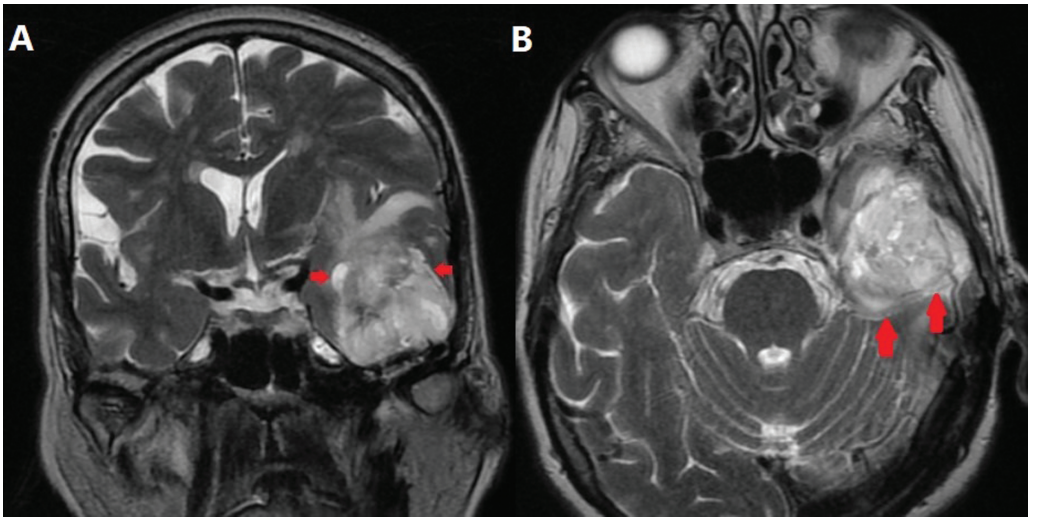

Fig. 2 Coronal (**A**) and axial (**B**) T2-weighted MRI scans showing CSF cleft sign (red arrows).

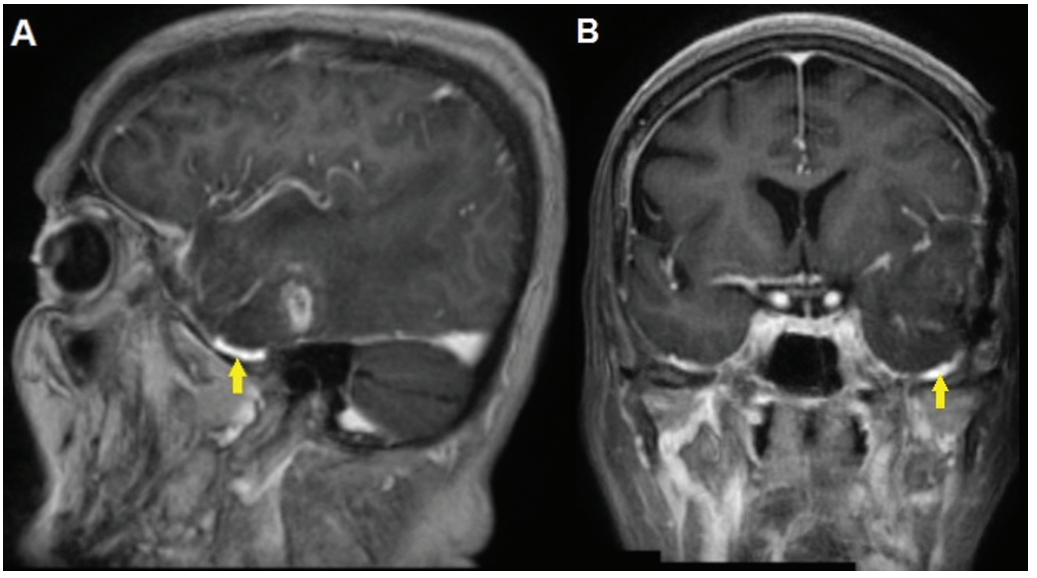

Fig. 3 Sagittal (**A**) and coronal (**B**) T1-weighted MRI scans with contrast showing complete surgical resection of the left middle fossa tumor with thickened enhancing dura at the site of dural invasion (yellow arrow).

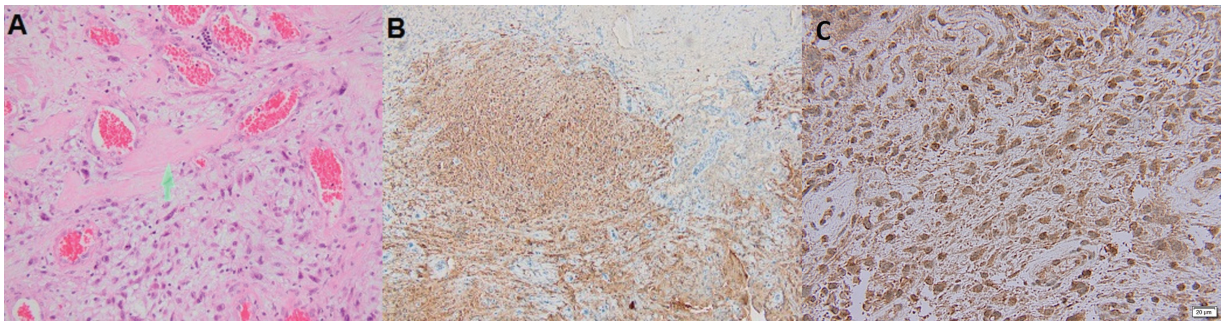

Fig. 4 (A) Fibrous and vascular connective tissue (arachnoid: green arrow) invaded by astrocytes with marked atypia and mitotic figures (hematoxylin and eosin stain, original magnification: X200); (**B**) cluster of invasive cells positive for GFAP infiltrating the connective tissue (arachnoid) (GFAP immunoperoxidase staining, original magnification: X100); (**C**) immunohistochemical staining reveals strongly positive results for the anti-IDH1 R132H mutation (original magnification: X400).

acidic protein (GFAP), and 30% were expressing p53. They were positive for S-100 protein and IDH1. The IDH1 mutation was assessed by immunohistochemistry (►**Fig. 4**).

After the surgery, the patient was treated with radiotherapy and concomitant temozolomide followed by adjuvant temozolomide. The last examination six months after the surgery confirmed that the patient was doing well.

Discussion

Extra-axial brain tumors, which are responsible for approximately half of all intracranial neoplasms in the United States, include a wide spectrum of pathologic tumors grouped by their primarily extraparenchymal involvement, typically involving the meningeal layers of the brain.[6] According to the most recent data from The Central Brain Tumor Registry of the United States (CBTRUS, 2012–2016), the most commonly occurring malignant brain tumor was glioblastoma (14.6% of all tumors), and the most common non-malignant tumor was meningioma (37.6% of all tumors).[1] Besides, 1% to 3% of meningiomas are classified as malignant meningiomas, which are characterized by higher rates of recurrence, morbidity, and mortality.[7] Meningioma exhibits a broad-based dural contact, inward displacement of the cortical gray matter, and DTS.[8]

On the other hand, glioblastoma is usually an intra-axial tumor located in the subcortical white matter of the brain hemispheres.[9] Moreover, GBM can extend to the dura, and rarely shows dural thickening and DTS.[10,11] The onset of GBMs occurs at a median age of 64 years, but they can occur at any age, including during childhood. Ionizing radiation is one of the few known risk factors to show an increased risk of glioma development. Radiation-induced GBM typically occurs years after therapeutic radiation for another tumor or disease, or due to environmental exposure to vinyl chloride, pesticides, smoking, petroleum refining, and synthetic rubber.[12] Around 10% of all GBMs are IDH-mutant, which develop secondarily to progression from a World Health Organization (WHO) grades II or III astrocytoma.[13] The vast majority of IDH-mutated gliomas occur in persons younger than 55 years of age. In a study cinducted by Robinson and Kleinschmidt-DeMasters,[14] from a total of 578 gliomas tested for IDH1 mutation, 88 were IDH-mutant gliomas, and only 4 occurred in persons aged 70 or older. The median overall survival in cases of IDH-mutant GBMs carry is significantly better than that of IDH-wildtype GBMs following the standard treatment (31 months versus 15 months respectively).[15] The standard treatment for GBM is surgery, which consists of maximum surgical resection of tumor tissue, even if complete resection is not possible, followed by a course of chemotherapy and/or radiotherapy. Currently, temozolomide, which is approved by the US Food and Drug Administration (FDA), is the preferred chemotherapeutic agent for GBM, and it can be tailored based on the characteristics of the patient.[16]

As therapeutic options remain scarce and prognosis, poor, alternative options such as targeted therapies and immunotherapy are actively examined in clinical trials. Apart from prolonged progression-free, but not overall, survival afforded by the vascular endothelial growth factor antibody, bevacizumab, no pharmacological intervention has been demonstrated to change the course of the disease.[17–19]

The classic imaging feature of GBM is a ring-enhancing intra-axial lesion on MRI or CT; however, peripheral lesions rarely present dural thickening and DTS.[9–11] "Dural thickening", "DTS", "flare sign," and "meningeal sign" are synonyms referring to the thickening of the dura adjacent to an intracranial neoplasm on contrast-enhanced T1-weighted MRI scans. Originally thought to be pathognomonic for meningioma, DTS was reported in CNS lymphoma, metastasis, multiple myeloma, GBM, chordoma, schwannoma, pleomorphic xanthoastrocytoma, hemangiopericytoma, medulloblastoma, eosinophilic granuloma, and pituitary adenoma.[11] Additionally, gliosarcoma, which accounts for 1% to 8% of glioblastomas and demonstrates both glial and sarcomatous differentiation, when it's located peripherally in the brain, may simulate meningioma by having DTS and homogenous enhancement.[20] The CSF cleft sign, which is defined as a thin rim of CSF between the tumor body and the brain parenchyma, may be more advantageous in differentiating intracranial extra-axial tumors from intra-axial tumors.[21] However, malignant or grade-III meningioma may lack the CSF cleft sign or clear demarcation between the tumor and the brain parenchyma.[22]

In the literature, there is limited data regarding the diagnostic confusion between malignant meningioma and GBM, and primary extra-axial involvement of GBM is rarely

Table 1 Major characteristics of primary extra-axial GBM case reports

Authors, year	Sex/Age (years)	Location	Duration of symptoms	Treatment	Prognosis
Derrig et al.,[24] 1986	Female/62	Base of right middle cranial fossa	6 weeks	Resection, neon heavy-particle radiation	Dead after 6 months
Gheyi et al.,[23] 2004	Male/68	Right frontoparietal calvarium	Few days	Near total resection, EBRT	Dead after 143 days
Wu et al.,[26] 2011	Male/60	Left cerebellopontine angle	2 months	Subtotal resection	Dead after 2 months
Patel et al.,[5] 2016	Female/57	Right temporoparietal	1 month	Resection followed by concurrent WBRT and TMZ	Not available
	Male/60	Left parasagittal	Not availabel	Resection followed concurrent WBRT and TMZ + 12 months of adjuvant TMZ	Dead after 28 months
Lee et al.,[27] 2017	Female/71	Left cerebellopontine angle	3 months	Navigation-assisted SB followed by conventional WBRT concurrent with TMZ	Alive after 1 year of the diagnosis
Karthigeyan et al.,[28] 2017	Female/27	Left petroclival	4 months	Subtotal Resection + Radiotherapy	Not available
Taghipour Zahir et al.,[25] 2018	Male/60	Right frontal calvarium	1 year	Biopsy followed by WBRT and concomitant TMZ + adjuvant TMZ	Dead after 7 months
Present case report	Female/76	Left temporal	1 month	GTR followed by WBRT and concomitant TMZ + adjuvant TMZ	Alive after 6 months

*Abbreviations: EBRT, external-beam radiation therapy; GBM, gliobastoma multiforme; GTR, gross total resection; TMZ, temozolamide; SB, stereotactic biopsy; WBRT, whole-brain radiation therapy.

reported. Patel et al.[5] described two cases of glioblastoma mimicking meningioma, with the first case being a heterogeneous-enhancing right temporoparietal mass with broad contact along the right tentorium, CSF cleft sign, and DTS, and the second, a case of a left parasagittal, heterogeneous-enhancing mass abutting the falx with DTS. Moreover, Gheyi et al.[23] reported a case of right frontoparietal mass with both extra- and intra-axial components causing inward displacement of the adjacent dura and calvarial destruction. Derrig at al.[24] also presented a case of GBM involving the cavernous sinus and Gasserian ganglion with retrograde extension along the trigeminal nerve. Taghipour Zahir et al.[25] described a case of GBM presenting as a right frontal calvarial mass. Additionally, two cases of primary extra-axial GBM within the cerebellopontine angle were reported by Wu et al.[26] and Lee et al.[27] Lastly, Karthigeyan et al.[28] described a case of extra-axial left petroclival giant-cell GBM. ►**Table 1** summarizes the major characteristics of the aforementioned cases of primary extra-axial GBM.

The case herein reported reveals that GBM may present as an extra-axial mass based on imaging and intraoperative findings, which render the diagnosis challenging, while the gold standard of diagnosis is still made through surgical pathology. Because of the scarcity of reports of cases of extra-axial GBM in the literature, further studies have to be conducted to define this new entity and whether the prognosis differs from that of intra-axial GBM.

Conclusion

The present report demonstrates that, although GBM is the most common primary intra-axial malignant brain tumor, it could present as an extra-axial mass with infiltration of the meningeal layers despite the absence of a history of previous trauma, surgery or radiotherapy. Glioblastoma should be considered in the differential diagnosis of extra-axial masses with atypical malignant features, especially in elderly patients.

Conflict of Interests

The authors have no conflict of interests to declare.

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