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*Case Report*

# Unusual extraneural metastasis of glioblastoma

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## ABSTRACT

**Background:** Glioblastoma (GB) is the most common and aggressive malignant brain tumor in adults. Extracranial metastases are very rare, been described in the lungs, soft tissue, or the intraspinal space.

**Case Description:** Through a PubMed-based bibliographic search, the authors reviewed the cases reported in the literature to date, emphasizing the epidemiology and pathophysiology of this rare condition. A clinical case of a 46-year-old man with an initial diagnosis of gliosarcoma, who received complete surgical and adjuvant treatment and later recurred as GB with incidental finding of a lung tumor, whose pathology reported metastasis of the primary, is illustrated.

**Conclusion:** Understanding the pathophysiology, it is likely that the incidence of extraneural metastases may continue to increase. Considering improvements in diagnostic techniques that allow early diagnosis, as well as advances in neurosurgical therapy and multimodal management with the aim of improving patient survival, the period in which malignant cells can spread and form extracranial metastases could increase. When screening should be performed to detect metastases in these patients is still not clear. The neuro-oncologists should pay attention to the systematic survey for extraneural metastasis of the GB. Timely detection and early treatment improve overall quality of patients' life.

**Keywords:** Extracranial metástasis, Glioblastoma, Gliosarcoma, Tumor

## INTRODUCTION

Glioblastoma (GB, World Health Organization [WHO] Grade IV) is the most common primary brain tumor in adults, accounting for 45% of malignant primary central nervous system tumors.[10] Gliosarcoma (GS) refers to the presence of mesenchymal differentiation in the setting of GB. Despite advances in treatment, both variants remain incurable disease with a median survival of 9 and 15 months (GS vs. GB), becoming a therapeutic challenge.[18] Being malignant gliomas highly invasive, extracranial metastases are very rare, and the mechanisms behind extracranial dissemination are still unclarified. Among the best documented sites of dissemination are the lung, lymph nodes, bone (especially vertebrae), and liver.[5,12,19] At present, surgical resection is regarded as the first choice for the treatment of these tumors. However, whether postoperative adjuvant radiotherapy and chemotherapy can improve its prognosis, and which other factors may be related to the prognosis, have not yet reached a consensus.[16]

## ILLUSTRATIVE CASE

A 46-year-old man with no other medical history was referred after presenting recurrent severe headache, dizziness, and dysarthria of 3 months evolution. A contrast-enhanced magnetic resonance study (MRI) showed an 8-cm intraaxial frontoparietal mass on the left side of the brain, with significant vasogenic edema causing mass effect and anatomical distortion of the lateral ventricles [Figure 1]. No other neoplastic lesions were found in a preoperative tomographic study of the chest and abdomen. The patient was scheduled for surgery with the intention of gross total resection, which was achieved through a bicoronal approach due to the size of the tumor. Among the intraoperative findings were a heterogeneous tumor with diffuse infiltration of the brain parenchyma, and the pathology report revealed a GS. After surgery, the patient completed adjuvant scheme according to the Stupp protocol of radiotherapy with concurrent and adjuvant temozolomide.

Two years after diagnosis, he presented to the emergency department with seizures. A control MRI revealed a new lesion in the left temporal area with a 5 cm diameter [Figure 2]. A new surgical intervention was scheduled, however, between the preoperative evaluations, a chest tomography was requested, with an incidental finding of a tumor mass located in the left lung [Figure 3]. The patient was informed of his oncological condition and accepted surgery as part of the treatment. Initially, a frontotemporal approach was performed with gross total excision of the temporal lesion. Subsequently, video-assisted thoracoscopic surgery was performed for lung tumor excision. No intraoperative complications were reported during the procedures [Figure 4]. The histopathological report of the surgical specimens revealed a GB isocitrate dehydrogenase (IDH)-wildtype with partial methylated MGMT promoter, and pulmonary metastasis. At present, the patient is under control continuing treatment with chemo and radiotherapy, 6 months after the recurrence with a Karnofsky index of 80%.

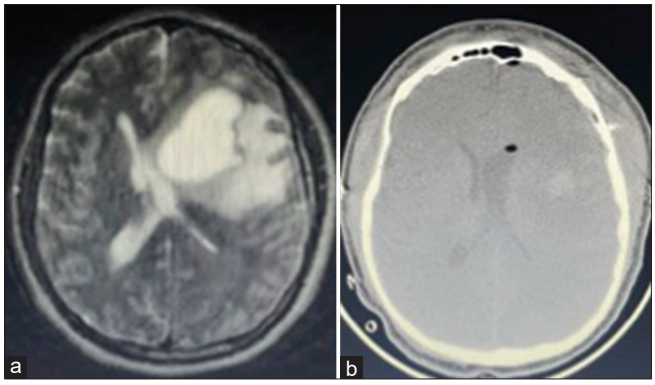


**Figure 1:** (a) T2-weighted axial magnetic resonance imaging showing a tumor within the left frontal lobe with vasogenic edema causing significant mass effect and midline shift. (b) 8-h postoperative tomography.

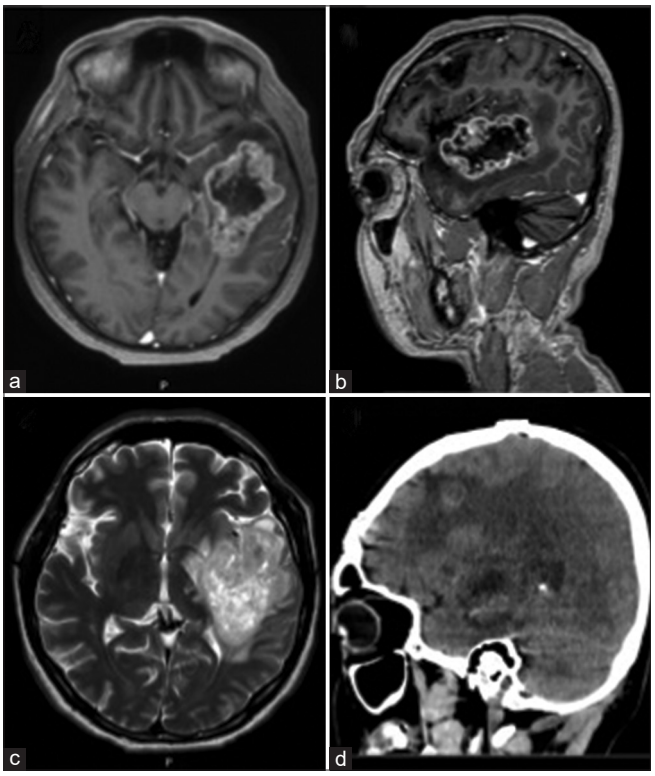


**Figure 2:** (a and b) Contrast-enhanced T1-weighted axial and sagittal magnetic resonance imaging (MRI) showing extensive tumor recurrence within the temporal lobe and deep structures; (c) T2-weighted axial MRI; (d) 10-h postoperative tomography showing tumor resection area.

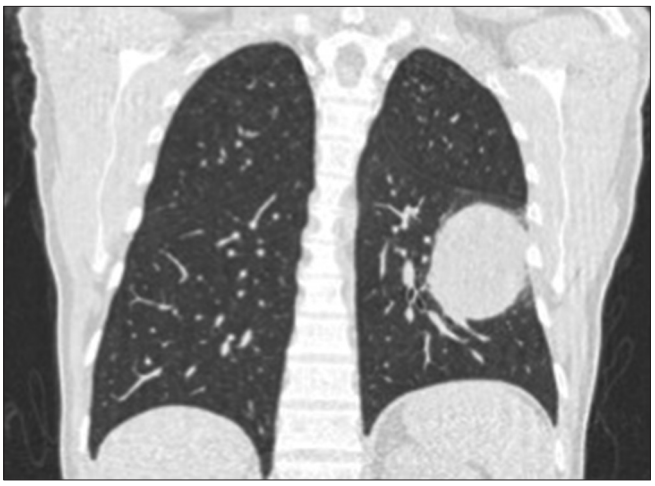

**Figure 3:** Chest computed tomography with coronal plane shows the tumor mass found in the left lung. The patient did not present pulmonary symptoms, it was considered an incidental finding, which was later confirmed to be associated with the primary tumor.

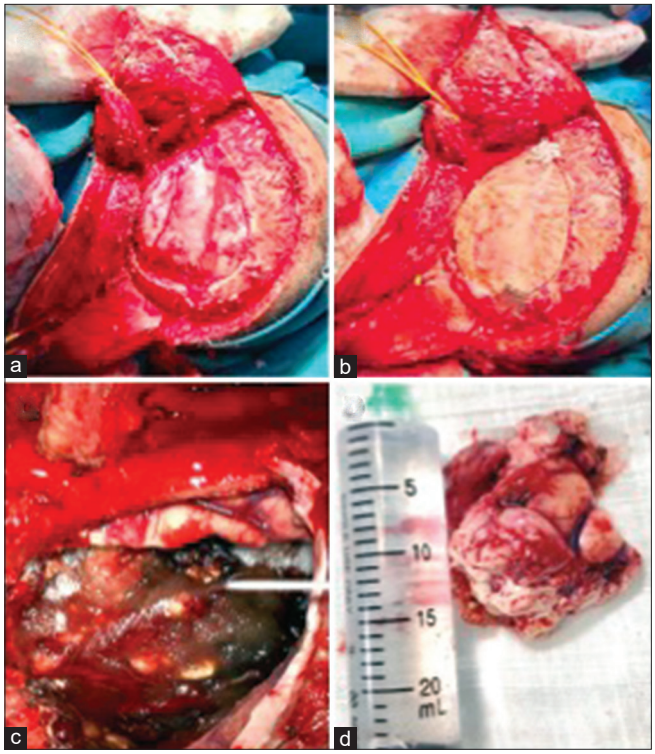


**Figure 4:** (a and b) During the second surgical intervention, an extended frontotemporal approach was performed to obtain a better visualization of the tumor and subsequent cranioplasty. (c) After resecting the tumor, due to its malignant characteristics and high vascularization, bleeding was controlled with hemostatic agents. (d) The surgical specimen that after pathological analysis reported a glioblastoma.

## DISCUSSION

GB and GS are high grade malignant gliomas defined by the WHO as Grade IV astrocytomas.[1,10] GS is a rare tumor (2% within all adult GB) histologically presenting both glial and sarcomatous features, defined by the WHO as a variant of IDH-wildtype GB characterized by a biphasic tissue pattern with alternating areas displaying glial and mesenchymal differentiation.[1,16,21]

Both tumors are clinically similar affecting mainly 50–70-year-old adults, predominantly men. Furthermore, both tumors show similarly poor survival outcomes (GS 9 months compared to a median 15-month survival for other forms of GB)[7,11,18] and are typically treated using the same aggressive protocol including maximal safe resection with concomitant radiotherapy and chemotherapy.[5,6] Despite the notable progress in surgical treatment, chemo, and radiotherapy over the last decades, survival has not been able to increase in the same proportion.

GS can be divided into primary or secondary forms, with the primary form being the most common, while the secondary forms arise after recurrence of a classic GB.[6,21] There is an interesting description of secondary forms of GS after chemoradiation of primary GB. This association is well known in other forms of tumors including meningiomas, gliomas, and fibrosarcomas.[16] However, this classification must not be confused with the terms primary and secondary to refer to mostly IDH-wildtype versus IDH-mutant GB, respectively, the latter of which mostly arise from lower-grade astrocytoma precursors.

Extracranial dissemination of both tumors is very rare (0.5% of cases); GS has been described as having a greater propensity to metastasize, but mechanism behind this infrequent condition remains unclear.[4,19] Lung and pleural metastases have been estimated to occur in around 60%, followed by lymph nodes (50%). Liver and bone metastases (vertebrae 70%) are seen in approximately 30%.[3,13-15,17,19] The rarity of extraneural metastases may be explained by the significant protective mechanisms of the central nervous system (CNS) (blood-brain barrier and meninges), as well as the immune response outside it. In addition, it is hypothesized that the rarity of extraneural metastases may be due to the aggressive nature of GB, shortening survival before tumor cells could metastasize.[5]

There are several postulates in the literature to explain extraneural dissemination: (1) lymphatic spread through the participation of meningeal lymphatics; (2) hematogenous spread through the intratumoral vascular network that characterizes high-grade gliomas, with invasion of the endothelium and connective tissue. The affinity of sarcomatous neoplasms to spread through this route corroborates the greater potential for metastasis of GS; (3) Dissemination through cerebrospinal fluid.[2,4,5,9] This diverse settlement of malignant cells in various anatomic locations and types of tissues confirms a versatile route for these cells to migrate. The tumor in the reported patient could have metastasized through multiple possible pathways, including those described above.

At present, GB is still considered one of the most difficult tumors to treat. Maximal safe resection is the cornerstone of treatment, followed by postoperative radiotherapy plus concomitant and adjuvant chemotherapy continues to be the standard treatment.[8,20] Extracranial metastasis has no well-established treatment. With limited data, we suggest surgical treatment in these cases considering the oncological and functional status of the patient, and considering the dismal prognosis added by distant dissemination. Although these metastases carry a poor prognosis, the diagnosis and treatment of such lesions offer palliative benefit and may improve patient quality of life.[5]

## CONCLUSION

We report an unusual case of secondary GS metastasis. We believe that possibly the incidence of extraneural metastases may continue to increase, since the pathophysiology of this disease (GB) is better understood, added to innovative

surgical techniques aided by neuronavigation, intraoperative neuroelectrophysiologic assessment, and the use of fluorescent materials, better imaging techniques, and multimodal management. Considering the latter whose objective is to improve patient survival, we believe that the period in which malignant cells can spread and form extracranial metastases could increase. When screening should be performed to detect metastases in these patients is still not clear, however, we believe that attention should be given to the systematic study of GB extraneural metastases, especially in those patients with a known GB who have survived a significant period following their initial diagnosis and present with extraneural symptoms with no other explainable cause, or their primary tumor recurs following treatment. Timely detection and early treatment will improve the general quality of life of patients.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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