The first description of central nervous system gliosarcoma (GSM) was reported by Strobe (1895), who characterized GSM as a tumor composed of glial and sarcomatous components. Sixty years later, Feigen and Gross (1955) and Rubinstein (1956) once again mentioned the term gliosarcoma, suggesting that the sarcomatous component was originated in the proliferation of newly formed blood vessels. Histological analysis has shown that GSM consists of a primary central nervous system neoplasm, containing glial and mesenchymal elements, with the glial component considered indistinguishable from that found in typical glioblastoma (GBM). The mesenchymal component may present itself as fibrosarcoma.

Several hypotheses sought to explain the origin of this dysmorphic tumor, including the following:

- A common origin of the glial and sarcomatous malignant components, with both originating from the same precursor clone cell.

**ABSTRACT**

**Background:** Central nervous system (CNS) gliosarcoma (GSM) is a rare primary neoplasm characterized by the presence of glial and sarcomatous components. **Objective:** In this report, we describe the clinical and neuroimaging aspects of three cases of GSM and correlate these aspects with pathological findings. We also provide a brief review of relevant literature. **Methods:** Three patients were evaluated with magnetic resonance imaging (MRI), and biopsies confirmed the diagnosis of primary GSM, without previous radiotherapy. **Results:** The analysis of conventional sequences (T1, T1 after contrast injection, T2, Fluid attenuation inversion recovery, SWI and DWI/ADC map) and advanced (proton 1H MR spectroscopy and perfusion) revealed an irregular, necrotic aspect of the lesion, peritumoral edema/infiltration and isointensity of the solid component on a T2-weighted image. These features were associated with irregular and peripheral contrast enhancement, lipid and lactate peaks, increased choline and creatine levels in proton spectroscopy, increased relative cerebral blood volume (rCBV) in perfusion, multifocality and drop metastasis in one of the cases. **Conclusion:** These findings are discussed in relation to the general characteristics of GSM reported in the literature.

**Keywords:** brain neoplasms; gliosarcoma; immunohistochemistry; spectroscopy.
A GBM metaplastic transformation (with GSM being an unusual histological variant of GBM), the monoclonal origin of which is based on molecular and cytogenetic studies, with particular reference to changes in chromosomes 7, 10 and 3. The presence of similar mutations in the p53 gene of both histological components corroborates the hypothesis that the sarcomatous area results from de-differentiation of the previously glial region, that loses expression of the glial fibrillary acidic protein (GFAP) to become sarcomatous.

- Malignant transformation of astrocytes adjacent to a pre-existing sarcoma.
- The coexistence of two distinct tumors.

The World Health Organization (WHO) defines GSM as a high-grade tumor (Grade IV) that accounts for ~2% of tumors in this class. This classification is similar to that for GBM, the most common primary brain tumor that accounts for ~54% of all malignant brain tumors. GSM is an exceptionally rare tumor, corresponding to 1-5% of all GBM diagnoses, which may have a secondary origin (diagnosed after radiotherapy of the central nervous system). Some authors suggest that GSM has a higher frequency as a primary tumor and appears “de novo”. The detection of primary central nervous system sarcomas is extremely rare, just like metastatic sarcomas. Overall, our knowledge of these tumors is still very limited. The epidemiology and natural history of GSM are similar to those of GBM, and none of the clinical or radiological findings described so far can accurately distinguish between them. For this reason, diagnostic confirmation is achieved only with a histopathological examination.

Little has been established regarding specific treatment for GSM, which is usually treated using the same therapeutic strategy like that used for GBM (surgical resection followed by chemotherapy - usually temozolomide, and radiotherapy). Although GSM is considered to be a chemoresistant tumor, survival may be slightly increased by concomitant radiotherapy and treatment with temozolomide (75 mg/m²/day 1 h prior to radiotherapy and at the weekends, and 150 mg/m² for five cycles after completion of the radiotherapy treatment). Complete cure of GBM is rare, with a life expectancy of 16-18 months (for patients undergoing surgery, chemotherapy and radiotherapy) and six months for untreated patients. GSM has an even more restricted prognosis.

RESULTS

Patient 1

A 68-year-old female patient, with a history of non-Hodgkin’s lymphoma of the splenic marginal zone diagnosed seven years before and in clinical follow-up since then, sought medical attention with complaints of memory and visual field loss, associated with behavioral changes, emotional lability and tinnitus. The patient had no record of treatment to date. Fifteen days after the onset of symptoms, the patient underwent radiological evaluation with MRI. The exam showed a left temporo-parieto-occipital lesion and a second left parietal lesion, both with a similar appearance, which suggested multifocality. The specific findings for each MRI sequence are listed in Table 1, and the main features are shown in Figure 1.

Image examination guided the surgical procedure, which consisted in partial resection. Histopathological analysis confirmed the diagnosis of GSM, with a malignant fusocellular tumor with mitoses and necrosis, reticulin-positive, p53-positive in more than 50% of nuclei, GFAP-positive area with necrosis, associated with behavioral changes, emotional lability and tinnitus. The patient had no record of treatment to date. Fifteen days after the onset of symptoms, the patient underwent radiological evaluation with MRI. The exam showed a left temporo-parieto-occipital lesion and a second left parietal lesion, both with a similar appearance, which suggested multifocality. The specific findings for each MRI sequence are listed in Table 1, and the main features are shown in Figure 1.

Patient 2

A 50-year-old male patient, with a history of systemic arterial hypertension, varicose veins of the lower limbs (that had already undergone surgical treatment without complications)
and polyglobulia, sought medical attention with a complaint of holocranial headache for about three to four months, which evolved with motor aphasia and mental confusion. The pre-operative radiological examination was done in another service. In the postoperative period, after partial resection, the diagnosis of GSM was confirmed histopathologically (a malignant biphasic tumor) and another MRI showed a new lesion in the left cerebral hemisphere (temporal lobe). Two months after a partial surgical resection, MRI revealed a lesion in the right splenium of the corpus callosum, indicating progression of the disease, that evolved with growth of the solid/contrast enhanced components of the lesion. The specific findings for each MRI sequence are listed in Table 1 and illustrated in Figure 2. The patient died eight months after the diagnosis of GSM.

### Patient 3

A 63-year-old female patient, with a history of epilepsy, systemic arterial hypertension and deep venous thrombosis, sought medical attention due to a focal convulsive crisis on the left side, that evolved with left hemiparesis over a two-month period. The patient underwent cranial MRI, which showed an expansive lesion in the right frontal lobe. The specific findings for each MRI sequence are listed in Table 1 and the main ones are illustrated in Figure 3. Analysis of the image guided the surgical management, with GSM being confirmed histopathologically with a malignant tumor. GFAP-positive, mutant IDH1 (R132H; clone H09) negative in neoplastic cells, p53-positive in up to 30% of nuclei.

The patient was referred to follow-up in neurosurgery, oncology and radiotherapy outpatient clinics with palliative care and died three months after the diagnosis.

The main magnetic resonance findings in these cases were:

- Irregular appearance of the lesion.
- Internal necrosis.
- Perilesional edema/infiltration.
- Isointense aspect of the solid component on T2-weighted.
- Irregular enhancement by paramagnetic/gadolinium contrast medium.

### Table 1: MRI findings for the three cases of GSM described in this report.

| MRI sequence                      | Patient 1                                      | Patient 2                                      | Patient 3                                      |
|-----------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| T1-weighted                       | Isointense solid portion; Hypointense central component (necrosis) | Isointense solid portion; Hypointense central component (necrosis) | Isointense solid portion; Hypointense central component (necrosis) |
| T1-weighted after administration of gadolinium (T1 C+) | Heterogeneous enhancement of the solid portion and subependymal enhancement | Heterogeneous enhancement of the solid portion | Heterogeneous enhancement of the solid portion |
| T2-weighted                       | Isointense solid portion; Hyperintense central component (necrosis) | Isointense solid portion; Hyperintense central component (necrosis) | Isointense solid portion; Hyperintense central component (necrosis) |
| FLAIR                             | Isointense solid portion; Hypointense central component (necrosis) | Isointense solid portion; Hypointense central component (necrosis) | Isointense solid portion; Hypointense central component (necrosis) |
| SWI                               | Did not present low signal foci | Low signal foci (hemorrhagic/neofomed vessels) | Low signal foci (hemorrhagic/neofomed vessels) |
| DWI/ADC map                       | Presence of restriction in the solid portion | Presence of restriction in the solid portion | Presence of restriction in the solid portion |
| Proton spectroscopy (solid portion) | Lipid and lactate peaks Increased creatine Increased choline | Lipid and lactate peaks Increased creatine Increased choline | - |
| Perfusion                         | rCBV increased in the solid area | rCBV increased in the solid area, including in the splenium lesion of the corpus callosum and in the peritumoral region | rCBV increased in the solid area |
| Additional findings               | Axial SPIR C+: gadolinium enhanced area in the spinal cord (T8 and T10 levels), consistent with drop metastasis Multifocality (presence of a second lesion in the left parietal region) | Two months after partial surgical resection: Axial T1 C+ showed the onset of lesion in the right of the splenium, indicating disease progression | - |
• Peaks for lipids and lactate and an increase in creatine and choline in proton spectroscopy.
• Increase in relative cerebral blood volume (rCBV) during the perfusion of the enhanced component of the lesion.
• Multifocality of the lesion in one case.
• A drop metastasis in one case.

DISCUSSION

Clinical findings
Gliosarcomas are rare CNS primary tumors that occur in ~4% of all malignant gliomas and affect mainly adults (especially in the fifth and sixth decades of life) and males (male:female frequency ratio of 1.8:1). The clinical course is frequently associated with a poor prognosis, including a survival of less than three months in more than half of the cases (a faster evolution compared to that observed in the present study, in which the survival varied from three to eight months after diagnosis). GSM is indistinguishable from GBM when the diagnosis is only based on clinical and neuroimaging characteristics.

The pathophysiology of the neurological signs and symptoms of GSM has not yet been fully clarified, although the focal manifestations vary according to the site of the tumor (the most affected regions are supratentorial and in the left hemisphere, especially the frontal and temporal lobes). The general signs and symptoms are often characterized by changes in the level of consciousness, nausea, vomiting and headache (intracranial hypertension), reflecting the compressive aspect resulting from the rapid tumor growth; this

![Image](https://example.com/image1.png)

Figure 1. (A) Axial image T1-weighted without gadolinium showing an irregular lesion, with a central hypointense component (corresponding to the area of necrosis) associated with intense perilesional edema. (B) Coronal image T2-weighted demonstrating isointensity of the solid component and hypersignal of the internal component (necrosis), as well as hyperintensity in the peritumoral white matter. (C) Axial image T1-weighted after administration of gadolinium. Note the irregular and peripheral enhancement by the contrast medium. (D) Axial image of ADC map showing marked hypointensity at the periphery that coincided with the gadolinium-enhanced lesion area (non-necrotic area). The high cellularity restricted the diffusion of water molecules. (E) Perfusion map showing increased relative cerebral blood volume (rCBV) in the tumor. (F) Axial SPIR image after contrast administration. Note the gadolinium-enhanced area (arrow) in the spinal cord at T8 and T10 that was consistent with drop metastasis.

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may be associated with perilesional edema, as well as the toxic effects of tumor necrosis itself.

**Histopathological and immunohistochemical findings**

The histopathological criteria that define GSM consist of the detection of a biphasic tumor with two distinct populations of malignant cells, namely, glial cells with an astrocytic and anaplastic appearance that fulfill the criteria for GBM; and highly variably mesenchymal cells represented mainly by a fibrosarcomatous component. This component was characterized by elongated/spindle-like cells arranged in bundles, associated with necrosis, mitosis and atypia. However, components of a liposarcomatous, muscular, melanocytic or chondromatous types have also been described, although they are considerably rarer.

Immunohistochemically, glial and sarcomatous components can also be differentiated by their expression of glial fibrillary acidic protein (GFAP), that is frequent in the glial component and absent in the sarcomatous component. Another important marker is reticulin, typically present in sarcomatous components. Thus, glial components are typically GFAP-positive and reticulin-negative, whereas the opposite is true for sarcomatous components, i.e., GFAP-negative and reticulin-positive.

Other molecular markers have also gained prominence, such as mutations in the p53 gene, studies of which are ongoing. These mutations are rare in GSM, but were detected in most cases in one of the largest studies that correlated image findings with histopathological/molecular characteristics; these mutations may have a monoclonal origin and appear to influence the tumor pathogenesis.

**Figure 2.** A 50-year-old male patient with a complaint of holocranial headache for 3-4 months, that evolved with motor aphasia and mental confusion. (A) Axial image T1-weighted showing a tumor in the left cerebral hemisphere (temporal lobe). The solid component was isointense and associated with hypointense necrosis, with a predominant solid component in the anterior tumor region. (B) Axial image T2-weighted (at the same level as Figure 2A) showing the isointense solid component associated with a hyperintense internal area (necrosis). (C) Axial image T1-weighted after administration of gadolinium obtained two months after Figures 2A and 2B. Note the presence of a lesion in the right splenium that indicated disease progression. (D) Axial image T1-weighted after gadolinium administration obtained six months after Figures 2A and 2B. Note the progression of the lesions (evident growth of the solid and gadolinium-enhanced components). (E) MRI study with proton spectroscopy, in which the voxel was positioned in the solid, medial posterior component and an echo time of 35 ms was used. MRI indicated the presence of lipid and lactate peaks, as well as an increase in creatine and choline.
Isocitrate dehydrogenase (IDH) has been studied as a possible marker in immunohistochemistry, particularly because of its important role in the development of gliomas. For example, IDH1 mutation-positive gliomas usually show an enhanced survival compared to tumors with wild-type IDH1, although the role of IDH1 in the evolution of GSM is unknown. Some data suggest that GSM is universally associated with wild-type IDH, with the IDH1 mutation being a rare event in this tumor (no IDH2 mutation was found in other studies). It is unclear whether IDH mutations are harbored in primary GSM.

Radiological findings

Topographically, GSM is mostly supratentorial, with the temporal lobes being most frequently affected, followed by the frontal, parietal and occipital regions; intraventricular locations are rare. GSM cannot be differentiated from GBM using currently available imaging methods. In the

Figure 3. A 63-year-old female patient with a focal convulsive crisis on the left who evolved with left hemiparesis over a two-month period. (A) Axial image in SWI showing intralesional low-signal multifocal zones consistent with neovascularization/flow voids. (B) Axial image FLAIR showing an isointense lesion with peritumoral edema. (C) Axial image T1-weighted after the administration of gadolinium. Note the irregular contrast enhancement. (D) Perfusion map showing increased relative cerebral blood volume (rCBV) in the tumor.
In the present study, we focused on MRI, using both conventional and advanced sequences.

In computed tomography (CT) and MRI, GSM is typically described as an expansive lesion with well-delimited and irregular contours, associated with perilesional edema. However, the CT findings are extremely variable and frequently demonstrate hyperattenuating signs of the solid component, with a mean attenuation from 15 to 28 UH, that corresponds to the viable tumor portion/fibrous component; there may also be hypoattenuating signs (typical of the central portions of necrosis), in addition to the presence of thick, peripheral ring enhancement. Although calcification (possibly corresponding to chondroid or osteoid metaplasia) is described in the literature, this phenomenon was not observed in the three patients described here.

On the T1 and T2-weighted sequences of MRI, GSM is characterized as an irregular, heterogeneous tumor that may be correlated with bleeding at different stages. Consequently, the solid component can be described as hypo-isointense on T1 and as hypo/iso/hyperintense on T2. Similarly, the necrotic component can be described as hypointense on T1 and hyperintense on T2 (as shown in Figures 1A, 1B, 2A and 2B).

On the FLAIR sequence, GSM is usually hyperintense, but there are reports of iso to hypointensity, in agreement with the finding shown in Figure 3B. Irregular enhancement of the solid components may occur after the injection of paramagnetic contrast medium (gadolinium). Such enhancement may be located peripherally in cases of central necrosis, as shown in Figure 1C. The SWI or T2* sequence may also provide additional information, seen that areas of variable magnetic susceptibility (high heterogeneity) demonstrate hypointensity within the tumor and may correlate with bleeding or neoformed vessels/flow voids (Figure 3A).

On DWI/ADC mapping sequences, GSM has previously been associated with hyperintensity on DWI and hypointensity in the solid component on the ADC map (compatible with restricted diffusion), with the latter possibly extending to regions of “peritumoral edema”, which would suggest neoplastic infiltration. In the present study, DWI/ADC mapping revealed restricted diffusion in the solid component of the tumor, primarily because of the high degree of cellularity (Figure 1D); this restriction was not seen in the peritumoral region.

Although these typical MRI findings (central necrosis associated with irregular peripheral enhancement) cannot differentiate GSM from GBM, two characteristic that may allow the differential diagnosis of GSM have been described, namely, the presence of predominantly necrotic lesions associated with dural nodular thickening; and the presence of predominantly solid lesions.

Other techniques related to unconventional MRI can provide additional diagnostic information but are still not well-established in the literature. Two of these techniques are perfusion and proton spectroscopy. In the perfusion image, rCBV is typically increased in high-grade astrocytomas (including GSM and other high-grade glomas) in both tumoral and peritumoral regions, also observed in case 1 described above (Figure 1E). In cases of metastasis, there may be a reduced rCBV in peritumoral regions compared to a normal brain tissue, with this reduction probably being related to vasogenic edema, abnormal capillary extravasation and reduced blood flow secondary to the compression of the microcirculation by this extravascular fluid.

Spectroscopy provides noninvasive means of assessing the metabolic characteristics of a specifically selected area of brain tissue and may aid in determining the tumor grade and differentiation, with the corresponding values usually being expressed in parts per million (ppm). Various metabolites are suggested as possible markers for GBM and metastasis, and spectroscopic analyses indicate possible similarities in the levels of such markers, between GSM and other high-grade gliomas. Lipids are common metabolites in the necrotic tissue characteristic of high-grade tumors and in intracellular lipid droplets in areas of hypoxic tissue. Creatine has been found to increase in concentration to a similar extent in GSM and GBM, in contrast to metastasis, in which creatine concentration is low.

The peak in lipids and lactate is similar among GSM, metastasis and some cases of GBM, and usually occurs in areas of necrosis. Initially, ischemia leads to an increase in lactate, but as the damage progresses to necrosis, a lipid peak appears. The lipid peak in the solid component which specifically correlates with the typical fatty component of metastases and with the mesenchymal component of GSM (more than with the glial component); this peak also correlates with a poor prognosis in high-grade tumors and necrosis. Based on these characteristics, it has been suggested that a tumor with increased lipid and lactate in its solid portion, together with a near-normal or enhanced creatine value, may be GSM, rather than GBM. Characteristics similar to these were observed here in case 2 (Figure 2E), along with an increase in choline, and suggested cell proliferation.

Computed tomography (CT) and MRI are also relevant for investigating metastases secondary to GSM, in view of this tumor’s well-known capacity for dissemination. GSM disseminates, mainly, via a hematogenous route, a characteristic of tumors with sarcomatous components. This dissemination results in extraneural metastatic foci, with the most frequently affected sites being the lungs, liver and lymph nodes; such foci are more common in young males who have already undergone adjuvant radiotherapy.

A drop metastasis involves metastasis originating from the subarachnoid or leptomeningeal spread and is in the intrarachial compartment. MRI will characterize such metastasis by the presence of nodular lesions, as shown in Figure 1F. Multilocularity is a rare characteristic and was observed in only one of the three patients studied.
CONCLUSION

We have described three cases of GSM that were confirmed by histopathological examination, in addition to presenting the corresponding findings for MRI, proton spectroscopy and perfusion. Most of the findings were consistent with data previously reported for GSM in the literature, although we also observed two less common features (multifocality and drop metastasis).

Based on these findings and previous literature reports, we consider the diagnosis of GSM to be possibly positive when there are predominantly necrotic lesions or when the lesion is predominantly solid, especially if increased the diffusion and restricted diffusion in the solid component of the tumor. For analyses involving magnetic resonance proton spectroscopy sequences, GSM should be considered when there is an increase in the lipid and lactate peaks in the solid portion of the tumor, and increases in the creatine peak and choline levels.

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