https://doi.org/10.1590/0004-282X20190158

Gliosarcomas: magnetic resonance imaging findings

Gliossarcomas: achados de ressonância magnética

Aya FUKUDA[1], Luciano de Souza QUEIROZ[2], Fabiano REIS[1]

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.

RESUMO

Introdução: O gliossarcoma (GSM) do sistema nervoso central (SNC) é uma neoplasia primária rara, caracterizada pela presença de componentes gliais e sarcomatosos. **Objetivo:** Nosso objetivo é descrever os aspectos clínicos e de neuroimagem de três casos com este diagnóstico e correlacioná-los com os achados patológicos. Também foi realizada uma breve revisão da literatura relevante. **Métodos:** Três pacientes foram avaliados por ressonância magnética (RM), e biópsias confirmaram o diagnóstico de GSM primário, sem radioterapia prévia. **Resultados:** Foram analisadas as sequências convencionais (T1, T1 após injeção de contraste, T2, FLAIR-*fluid attenuation inversion recovery*, SWI, DWI/mapa ADC) e as sequências avançadas (espectroscopia de prótons 1H e perfusão), observando-se aspecto necrótico e irregular da lesão, edema/infiltração peritumoral, isointensidade do componente sólido em T2, associada a realce irregular e periférico pelo meio de contraste, pico de lípides e de lactato e aumento dos níveis de colina e creatina na espectroscopia de prótons, aumento do volume sanguíneo cerebral relativo (rCBV) na perfusão, multifocalidade e "drop" mestástase em um dos casos. **Conclusão:** O presente estudo descreve características do GSM, discutindo as informações na literatura científica, ilustrando algumas particularidades desses tumores.

Palavras-chave: neoplasias encefálicas; gliossarcoma; imuno-histoquímica; espectroscopia.

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[1]. 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[2-4]. 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)[5,6]. The mesenchymal component may present itself as fibrosarcoma[7].

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[8].

[1]Universidade Estadual de Campinas, Faculdade de Ciências Médicas, Departamento de Radiologia, Campinas SP, Brazil.

[2]Universidade Estadual de Campinas, Faculdade de Ciências Médicas, Departamento de Anatomia Patológica, Campinas SP, Brazil.

Aya FUKUDA https://orcid.org/0000-0002-3724-141X; Luciano de Souza QUEIROZ https://orcid.org/0000-0001-8648-6846; Fabiano REIS https://orcid.org/0000-0003-2256-4379

Correspondence: Fabiano Reis; Rua Tessália Vieira de Camargo, 126, Cidade Universitária Zeferino Vaz; 13083-887 Campinas SP, Brasil; E-mail: fabianoreis2@gmail.com

Conflict of interest: There is no conflict of interest to declare.

Received on July 12, 2019; Received in its final form on September 11, 2019; Accepted on October 1, 2019.

- A GBM metaplastic transformation (with GSM being an unusual histological variant of GBM)[9], the monoclonal origin of which is based on molecular and cytogenetic studies, with particular reference to changes in chromosomes 7, 10 and 3[10,11]. 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[12].
- Malignant transformation of astrocytes adjacent to a pre-existing sarcoma.
- The coexistence of two distinct tumors[1,13].

The World Health Organization (WHO) defines GSM as a high-grade tumor (Grade IV) that accounts for ~2% of tumors in this class[1,4,13,14]. This classification is similar to that for GBM[13], the most common primary brain tumor that accounts for ~54% of all malignant brain tumors[15]. GSM is an exceptionally rare tumor, corresponding to 1-5% of all GBM diagnoses[15], which may have a secondary origin (diagnosed after radiotherapy of the central nervous system)[16]. Some authors suggest that GSM has a higher frequency as a primary tumor and appears "de novo"[17]. The detection of primary central nervous system sarcomas is extremely rare, just like metastatic sarcomas are (although they are more common than primary tumors)[18]. Overall, our knowledge of these tumors is still very limited. The epidemiology and natural history of GSM are similar to those of GBM[6,19-25], 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[5,13,19,26].

Little has been established regarding specific treatment for GSM, which is usually treated using the same therapeutic strategy like that used for GBM[27] (surgical resection followed by chemotherapy - usually temozolomide[27], and radiotherapy)[28-31]. Although GSM is considered to be a chemoresistant tumor, survival may be slightly increased by concomitant radiotherapy and treatment with temozolomide (75 mg/m^2/day 1 h prior to radiotherapy and at the weekends, and 150 mg/m^2 for five cycles after completion of the radiotherapy treatment)[32]. Complete cure of GBM is rare, with a life expectancy of 16-18 months (for patients undergoing surgery, chemotherapy and radiotherapy)[33] and six months for untreated patients[29]. GSM has an even more restricted prognosis[4].

METHODS

This retrospective study was approved by the Institutional Ethics Committee of UNICAMP. We reviewed the medical records and MRI results of three patients with GSM, who were treated at the University Hospital/UNICAMP from 2000 to 2018. We analyzed the conventional MRI sequences (T1, T1 C + after injection of paramagnetic contrast medium/gadolinium, T2, FLAIR, SWI and DWI/ADC map) and the advanced MRI sequences (proton spectroscopy and perfusion). The imaging protocols were done in a PHILIPS imager, operating in a magnetic field of 1.5T, with acquisitions in the axial, sagittal and coronal planes.

The inclusion criteria for the patients were the existence of MRI exams, with conventional sequences and at least one of the advanced sequences (as indicated above), as well as a histopathological confirmation of gliosarcoma and the absence of previous CNS radiotherapy.

In agreement with the rarity of this tumor, only 11 cases of GSM were identified in the hospital records from 2000 to 2018, of which only three fulfilled the inclusion criteria indicated above (patient 3, despite having no spectroscopy data, had the complete conventional protocol and also perfusion images). Patients 4 to 11 did not have advanced sequences in the MRI protocol.

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 neoplastic astrocytes (GBM) that transitions to GFAP-negative fusocellular area (GSM).

MRI of the neuroaxis was also done and revealed areas with gadolinium enhancement in the spinal cord (T8 and T10 levels), consistent with a drop metastasis (arrow in Figure 1F). Despite complementary treatment with radiotherapy and chemotherapy, the patient's neurological symptoms worsened, and she required hospitalization, evolving to superior vena cava syndrome and cardiopulmonary arrest. She died five months after the diagnosis of GSM.

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 preoperative 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/ neoformed vessels)	Low signal foci (hemorrhagic/ neoformed 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)[34] and males (male:female frequency ratio of 1.8:1)[35]. 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[36] (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)[36]. 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

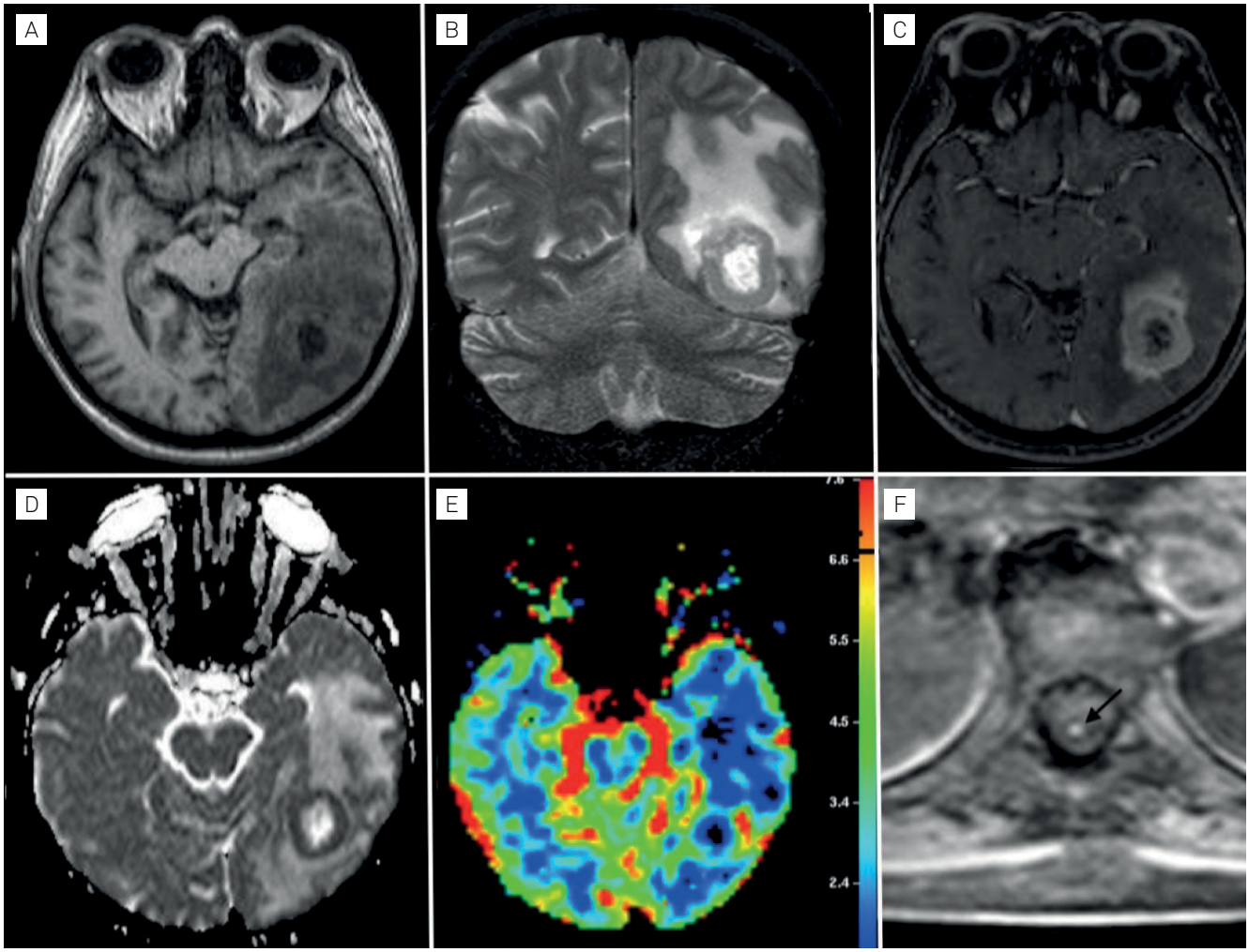

Figure 1. (A) Axial image T1-weighted without gadolinium showing an irregular lesion, with a central hypointense component (corresponding to the area of necrosis) associated with intense perilesional edema. (B) Coronal image T2-weighted demonstrating isointensity of the solid component and hypersignal 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.

may be associated with perilesional edema, as well as the toxic effects of tumor necrosis itself[36].

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[16,24,37,38].

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[39]. 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[40].

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 pathogenetics[35,41].

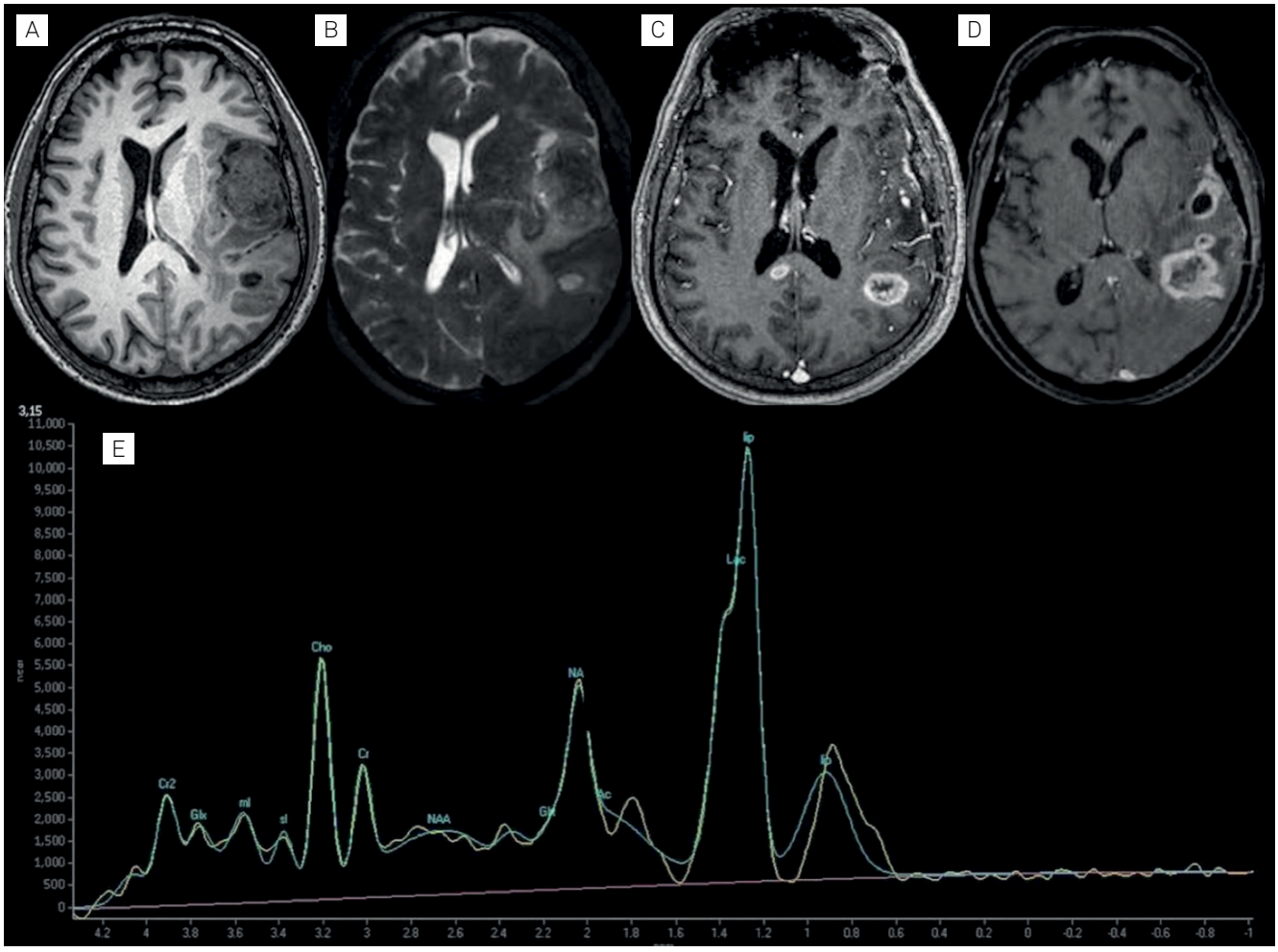

Figure 2. A 50-year-old male patient with a complaint of holocranial headache for 3-4 months, that evolved with motor aphasia and mental confusion. (A) Axial image T1-weighted showing a tumor in the left cerebral hemisphere (temporal lobe). The solid component was isointense and associated with hypointense 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[42]. Some data suggest that GSM is universally associated with wild-type IDH[41,43], with the IDH1 mutation being a rare event in this tumor (no IDH2 mutation was found in other studies)[44]. It is unclear whether IDH mutations are harbored in primary GSM[42].

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[12]. GSM cannot be differentiated from GBM using currently available imaging methods[16]. In the

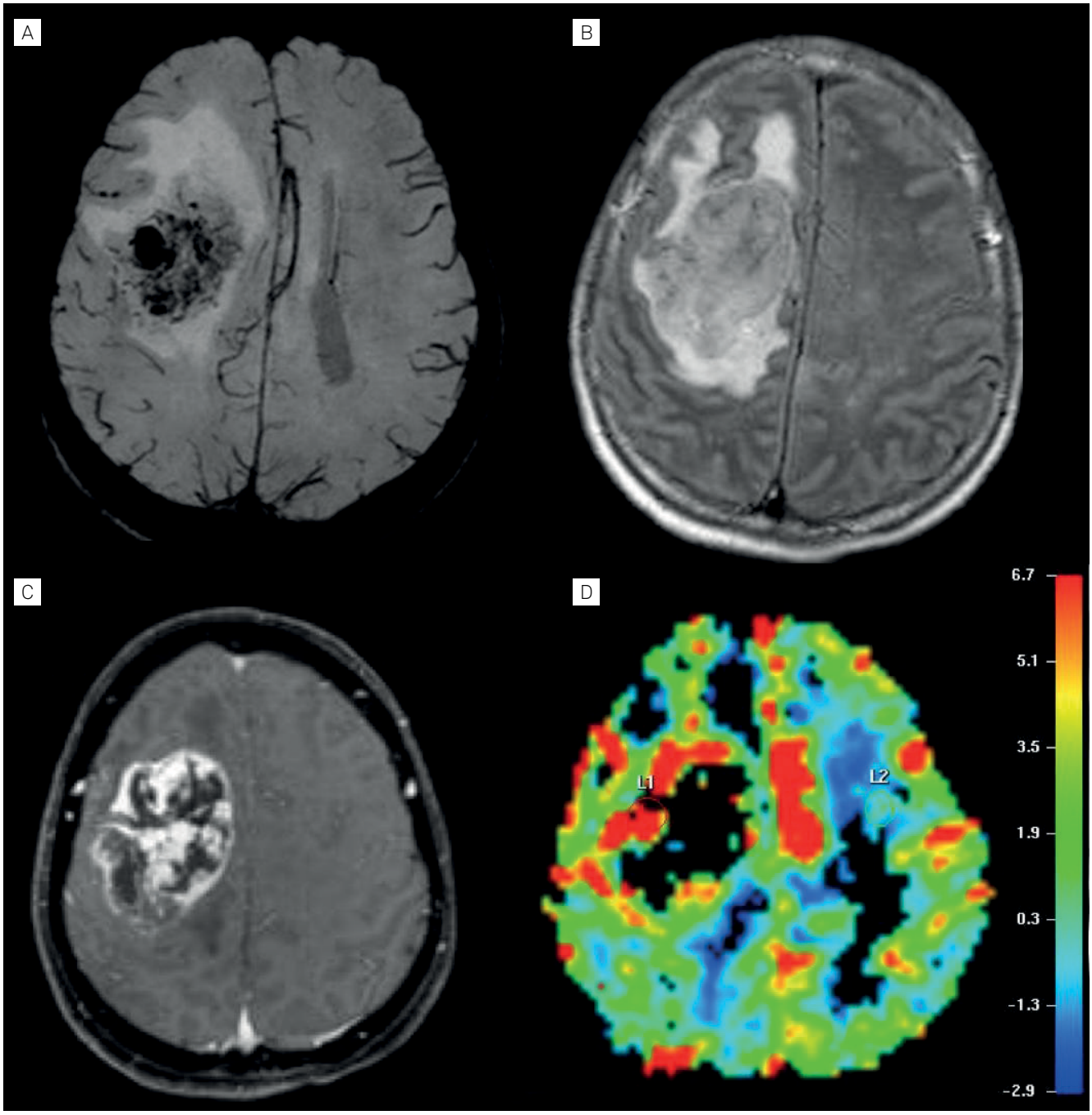

Figure 3. A 63-year-old female patient with a focal convulsive crisis on the left who evolved with left hemiparesis over a two-month period. (A) Axial image in SWI showing intralesional low-signal multifocal zones consistent with neovascularization/flow voids. (B) Axial image FLAIR showing an isointense 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.

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[16,19,28,35,45]. 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[27] (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[19,28,35,45,46]. Although calcification (possibly corresponding to chondroid or osteoid metaplasia) is described in the literature[47], 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[27]. Similarly, the necrotic component can be described as hypointense on T1 and hyperintense on T2[48] (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[49], 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)[45]. Such enhancement may be located peripherally in cases of central necrosis[48], 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)[41].

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)[50], with the latter possibly extending to regions of "peritumoral edema", which would suggest neoplastic infiltration[48]. 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[41].

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 gliomas) in both tumoral and peritumoral regions[48,51,52], 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[48].

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)[53]. 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[53]. 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[46,48,53].

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[54]. 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[46,48,53]. 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[55]. This dissemination results in extraneural metastatic foci, with the most frequently affected sites being the lungs, liver and lymph nodes[52]; such foci are more common in young males who have already undergone adjuvant radiotherapy[55].

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[55], as shown in Figure 1F. Multifocality is a rare characteristic and was observed in only one of the three patients studied[49].

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 added the increased perfusion 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.

References

1. Rodriguez FJ, Scheithauer BW, Jenkins R, Burger PC, Rudzinskiy P, Vlodavsky E, et al. Gliosarcoma arising in oligodendroglial tumors ("oligosarcoma"): a clinicopathologic study. Am J Surg Pathol. 2007 Mar;31(3):351-62. https://doi.org/10.1097/01.pas.0000213378.94547.ae
2. Feigin IH, Gross SW. Sarcoma arising in glioblastoma of the brain. Am J Pathol. 1955 Aug;31(4):633-53.
3. Rubinstein LJ. The development of contiguous sarcomatous and gliomatous tissue in intracraneal tumors. J Pathol Bacteriol. 1956 Apr;71(2):441-59. https://doi.org/10.1002/path.1700710219
4. Schittenhelm J, Erdmann T, Maennlin S, Will BE, Beschorner R, Bornemann A, et al. Gliosarcoma with chondroid and osseous differentiation. Neuropathology. 2007 Feb;27(1):90-4. https://doi.org/10.1111/j.1440-1789.2006.00747.x
5. Kozak KR, Mahadevan A, Moody JS. Adult gliosarcoma: epidemiology, natural history, and factors associated with outcome. Neuro Oncol. 2009 Apr;11(2):183-91. https://doi.org/10.1215/15228517-2008-076
6. Morantz RA, Feigin I, Ransohoff J 3rd. Clinical and pathological study of 24 cases of gliosarcoma. J Neurosurg. 1976 Oct;45(4):398-408. https://doi.org/10.3171/jns.1976.45.4.0398
7. Slowik F, Jellinger K, Gaszó L, Fischer J. Gliosarcomas: histological, immunohistochemical, ultrastructural, and tissue culture studies. Acta Neuropathol. 1985;67(3-4):201-10. https://doi.org/10.1007/bf00687802
8. Actor B, Cobbers JM, Büschges R, Wolter M, Knobbe CB, Lichter P, et al. Comprehensive analysis of genomic alterations in gliosarcoma and its two tissue components. Genes Chromosomes Cancer. 2002 Aug;34(4):416-27. https://doi.org/10.1002/gcc.10087
9. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016 Jun;131(6):803-20. https://doi.org/10.1007/s00401-016-1545-1
10. Romero-Rojas AE, Diaz-Perez JA, Amaro D, Lozano-Castillo A, Chinchilla-Olaya SI. Glioblastoma metastasis to parotid gland and neck lymph nodes: fine-needle aspiration cytology with histopathologic correlation. Head Neck Pathol. 2013 Dec;7(4):409-15. https://doi.org/10.1007/s12105-013-0448-x
11. Dawar R, Fabiano AJ, Qiu J, Khushalani NI. Secondary gliosarcoma with extra-cranial metastases: a report and review of the literature. Clin Neurol Neurosurg. 2013 Apr;115(4):375-80. https://doi.org/10.1016/j.clineuro.2012.06.017
12. Klitzke S, Schlittler LA, Lazaretti N, Villarroel RU, Dallagasperina VW, Azambuja N. Gliossarcoma: um desafio clínico e terapêutico. Rev AMRIGS. 2012 Jan/Mar;56(1):63-6.
13. Miller CR, Perry A. Glioblastoma. Arch Pathol Lab Med. 2007 Mar;131(3):397-406. https://doi.org/10.1043/1543-2165(2007)131[397:G]2.0.CO;2
14. Barresi V, Cerasoli S, Morigi F, Cremonini AM, Volpini M, Tuccari G. Gliosarcoma with features of osteoblastic osteosarcoma: a review. Arch Pathol Lab Med. 2006 Aug;130(8):1208-11. https://doi.org/10.1043/1543-2165(2006)130[1208:GWFOOO]2.0.CO;2
15. Karsy M, Gelbman M, Shah P, Balumbu O, Moy F, Arslan E. Established and emerging variants of glioblastoma multiforme: review of morphological and molecular features. Folia Neuropathol. 2012;50(4):301-21. https://doi.org/10.5114/fn.2012.32361
16. Romero-Rojas AE, Diaz-Perez JA, Ariza-Serrano LM, Amaro D, Lozano-Castillo A. Primary gliosarcoma of the brain: radiologic and histopathologic features. Neuroradiol J. 2013 Dec;26(6):639-48. https://doi.org/10.1177/197140091302600606
17. Osborn AG. Encéfalo Imagem, Patologia e Anatomia. Porto Alegre: Artmed; 2013. p. 489-90.
18. Pardo J, Murcia M, García F, Alvarado A. Gliosarcoma: a rare primary CNS tumor. Presentation of two cases. Rep Pract Oncol Radiother. 2010 Jul;15(4):98-102. https://doi.org/10.1016/j.rpor.2010.05.003
19. Lutterbach J, Guttenberger R, Pagenstecher A. Gliosarcoma: a clinical study. Radiother Oncol. 2001 Oct;61(1):57-64. https://doi.org/10.1016/S0167-8140(01)00415-7
20. Meis JM, Martz KL, Nelson JS. Mixed glioblastoma multiforme and sarcoma. A clinicopathologic study of 26 radiation therapy oncology group cases. Cancer. 1991 May;67(9):2342-9. https://doi.org/10.1002/1097-0142(19910501)67:9%3C2342::aid-cncr2820670922%3E3.0.co;2-b
21. Salvati M, Caroli E, Raco A, Giangaspero F, Delfini R, Ferrante L. Gliosarcomas: analysis of 11 cases. Do two subtypes exist? J Neurooncol. 2005 Aug;74(1):59-63. https://doi.org/10.1007/s11060-004-5949-8
22. Galanis E, Buckner JC, Dinapoli RP, Scheithauer BW, Jenkins RB, Wang CH, et al. Clinical outcome of gliosarcoma compared with glioblastoma multiforme: North Central Cancer Treatment Group results. J Neurosurg. 1998 Sep;89(3):425-30. https://doi.org/10.3171/jns.1998.89.3.0425
23. Sarkar C, Sharma MC, Sudha K, Gaikwad S, Varma A. A clinico-pathological study of 29 cases of gliosarcoma with special reference to two unique variants. Indian J Med Res. 1997 Sep;106:229-35.
24. Perry JR, Ang LC, Bilbao JM, Muller PJ. Clinicopathologic features of primary and post irradiation cerebral gliosarcoma. Cancer. 1995 Jun;75(12):2910-8. https://doi.org/10.1002/1097-0142(19950615)75:12%3C2910::aid-cncr2820751219%3E3.0.co;2-a
25. Parekh HC, O'Donovan DG, Sharma RR, Keogh AJ. Primary cerebral gliosarcoma: report of 17 cases. Br J Neurosurg. 1995 Apr;9(2):171-8. https://doi.org/10.1080/02688699550041511
26. Fukuda T, Yasumichi K, Suzuki T. Immunohistochemistry of gliosarcoma with liposarcomatous differentiation. Pathol Int. 2008 Jun;58(6):396-401. https://doi.org/10.1111/j.1440-1827.2008.02242.x
27. Yi X, Cao H, Tang H, Gong G, Hu Z, Liao W, et al. Gliosarcoma: a clinical and radiological analysis of 48 cases. Eur Radiol. 2019 Jan;29(1):429-38. https://doi.org/10.1007/s00330-018-5398-y
28. Moon SK, Kim EJ, Choi WS, Ryu CW, Park BJ, Lee J. Gliosarcoma of the cerebellar hemisphere: a case report and review of the literature. Korean J Radiol. 2010 Sep/Oct;11(5):566-70. https://doi.org/10.3348/kjr.2010.11.5.566

29. Rees JH, Smirniotopoulos JG, Jones RV, Wong K. Glioblastoma multiforme: radiologic-pathologic correlation. Radiographics. 1996 Nov;16(6):1413-38. https://doi.org/10.1148/radiographics.16.6.8946545

30. Romeike BF, Chen Y, Walter J, Petersen I. Diagnostic utility of IDH1- and p53-mutation analysis in secondary gliosarcoma. Clin Neuropathol. 2011 Sep/Oct;30(5):231-4. https://doi.org/10.5414/np300375

31. Kumar N, Bhattacharyya T, Chanchalani K, et al. Impact of changing trends of treatment on outcome of cerebral gliosarcoma: a tertiary care centre experience. South Asian J Cancer. 2015 Jan/Mar;4(1):15-17. https://doi.org/10.4103/2278-330X.149931

32. Mason WP, Del Maestro R, Eisenstat D, Forsyth P, Fulton D, Laperrière N, et al. Canadian recommendations for the treatment of glioblastoma multiforme. Curr Oncol. 2007 Jun;14(3):110-117. https://doi.org/10.3747/co.2007.119

33. Salcman M. Survival in glioblastoma: historical perspective. Neurosurgery. 1980 Nov;7(5):435-9. https://doi.org/10.1227/00006123-198011000-00001

34. di Norcia V, Piccirilli M, Giangaspero F, Salvati M. Gliosarcomas in the elderly: analysis of 7 cases and clinico-pathological remarks. Tumori. 2008 Jul/Aug; 94(4):493-6.

35. Machuca TN, Prevedello DM, Pope LZ, Haratz SS, Araújo JC, Torres LF. Gliosarcoma: Report of four cases with immunohistochemical findings. Arq Neuropsiquiatr. 2004 Sep;62(3A):608-12. https://doi.org/10.1590/s0004-282x2004000400008

36. Lucena RCG, Mello RJV, Lessa Jr. JR, Cavalcante GM, Ribeiro M. Correlação clínico-topográfica em glioblastomas multiformes nas síndromes motoras. Arq Neuropsiquiatr. 2006 Jun;64(2-B):441-5. http://dx.doi.org/10.1590/S0004-282X2006000300017

37. Meis JM, Ho KL, Nelson JS. Gliosarcoma: a histologic and immunohistochemical reaffirmation. Mod Pathol. 1990 Jan;3(1):19-24.

38. Moreira RK, Koppe D, Zignani J, Marconato MC, Abreu M, Pitrez E. Gliossarcoma de tronco cerebral em paciente pediátrico: relato de caso. Radiol Bras. 2004;37(1):61-63. http://dx.doi.org/10.1590/S0100-39842004000100013

39. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47. https://doi.org/10.1016/j.ejca.2008.10.026

40. Huo Z, Yang D, Shen J, Li Y, Wu H, Meng Y, et al. Primary gliosarcoma with long-survival: report of two cases and review of literature. Int J Clin Exp Pathol. 2014 Aug;7(9):6323-32.

41. Peckham ME, Osborn AG, Palmer CA, Tsai A, Salzman KL. Gliosarcoma: neuroimaging and immunohistochemical findings. J Neuroimaging. 2019 Jan;29(1):126-32. https://doi.org/10.1111/jon.12565

42. Hsieh JK, Hong CS, Manjila S, Cohen ML, Lo S, Rogers L, et al. An *IDH1*-mutated primary gliosarcoma: case report. J Neurosurg. 2017 Feb;126(2):476-80. https://doi.org/10.3171/2016.2.JNS151482

43. Cambruzzi E. The role of IDH1/2 mutations in the pathogenesis of secondary glioblastomas. J Bras Patol Med Lab. 2017 Sep/Oct;53(5):338-44. http://dx.doi.org/10.5935/1676-2444.20170055

44. Lee D, Kang SY, Suh YL, Jeong JY, Lee JI, Nam DH. Clinicopathologic and genomic features of gliosarcomas. J Neurooncol. 2012 May;107(3):643-50. https://doi.org/10.1007/s11060-011-0790-3

45. Meena US, Sharma S, Chopra S, Jain SK. Gliosarcoma: A rare variant of glioblastoma multiforme in paediatric patient: Case report and review of literature. World J Clin Cases. 2016 Sep;4(9):302-05. https://doi.org/10.12998/wjcc.v4.i9.302

46. Zhang BY, Chen H, Geng DY, Yin B, Li YX, Zhong P, et al. Computed tomography and magnetic resonance features of gliosarcoma: a study of 54 cases. J Comput Assist Tomogr. 2011 Nov/Dec;35(6):667-73. https://doi.org/10.1097/RCT.0b013e3182331128

47. Swaidan MY, Hussaini M, Sultan I, Mansour A. Radiological findings in gliosarcoma — A single institution experience. Neuroradiol J. 2012 May;25(2):173-80. https://doi.org/10.1177/197140091202500203

48. Lin JN, Chiang IC, Tsai TC, et al. 3T-Magnetic resonance imaging and proton magnetic resonance spectroscopy findings in gliosarcoma: a case report. Chin J Radiol. 2007;32:81-5.

49. Han L, Zhang X, Qiu S, Li X, Xiong W, Zhang Y, et al. Magnetic resonance imaging of primary cerebral gliosarcoma: a report of 15 cases. Acta Radiolog. 2008;49(9):1058-67.

50. Sampaio L, Linhares P, Fonseca J. Detailed magnetic resonance imaging features of a case series of primary gliosarcoma. Neuroradiol J. 2017 Dec;30(6):546-53. https://doi.org/10.1177/1971400917715879

51. Law M, Yang S, Wang H, Babb JS, Johnson G, Cha S, et al. Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. AJNR Am J Neuroradiol. 2003 Nov/Dec;24(10):1989-98.

52. Stadlbauer A, Gruber S, Nimsky C, Fahlbusch R, Hammen T, Buslei R, et al. Preoperative grading of gliomas by using metabolite quantification with high-spatial-resolution proton MR spectroscopic imaging. Radiology. 2006 Mar;238(3):958-69. https://doi.org/10.1148/radiol.2382041896

53. Raab P, Pilatus U, Hattingen E, Franz K, Hermann E, Zanella FE, et al. Spectroscopic characterization of gliosarcomas — Do they differ from glioblastomas and metastases? J Comput Assist Tomogr. 2016 Sep/Oct;40(5):815-9. https://doi.org/10.1097/RCT.0000000000000419

54. Yamasaki F, Takaba J, Ohtaki M, Abe N, Kajiwara Y, Saito T, et al. Detection and differentiation of lactate and lipids by single-voxel proton MR spectroscopy. Neurosurg Rev. 2005;28(4):267-77. https://doi.org/10.1007/s10143-005-0398-1

55. Ramos R, Morais N, Silva AI, Almeida R. Gliosarcoma with neuroaxis metastases. BMJ Case Rep. 2015 Oct;2015:bcr2015212970. http://dx.doi.org/10.1136/bcr-2015-212970