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Primary Gliosarcoma with a Gliomatosis Cerebri Pattern: A Case Report on Radiotherapy Challenges of a Rare Entity

El Amin MARNOUCHE[1]*, Najlae LIMOUNI[1], Mouhcine HOMMADI[1], Maroua BENLEMLIH[1], Mohamed Amine Essaoudi[1], Khalid Andaloussi Sghir[1], Khalid HADADI[1], Mohamed EL MARJANY[1]

[1]Department of Radiation Oncology, Mohamed V Military Training Hospital, Rabat, Morocco

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***Corresponding author:** El Amin MARNOUCHE
Department of Radiation Oncology, Mohamed V Military Training Hospital, Rabat, Morocco

Abstract **Case Report**

Gliosarcoma is a rare variant of isocitrate dehydrogenase IDH-wildtype glioblastoma. Its association with a gliomatosis cerebri growth pattern remains an exceptional occurrence. This case concerns a 51-year-old female presenting with a focal right occipital mass. Histopathology following subtotal resection confirmed gliosarcoma. Despite preserved neurological status post-surgery, magnetic resonance imaging performed four weeks subsequently demonstrated a dramatic aggravation. Imaging demonstrated a Type 2 gliomatosis pattern: a focal enhancing mass and massive, non-enhancing bi-hemispheric infiltration extending through the corpus callosum. The patient was managed with concurrent chemoradiotherapy utilizing Volumetric Modulated Arc Therapy (VMAT) with Simultaneous Integrated Boost (SIB), delivering 60 Gy to macroscopic disease and 54 Gy to the infiltrative component. Despite this aggressive approach, the patient succumbed to rapid disease progression three months after completion of radiotherapy. This report underscores the profound radio-clinical discordance characterized by preserved clinical status masking fulminant radiological aggravation. Furthermore, it highlights the complex radiotherapy challenges, particularly the dilemma of dose prescription, balancing therapeutic efficacy against neurotoxicity in such extensive disease.

Keywords: Gliosarcoma, gliomatosis cerebri, volumetric modulated arc therapy.

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INTRODUCTION

Gliosarcoma (GS) is a rare and aggressive primary central nervous system neoplasm, currently classified as a variant of isocitrate dehydrogenase (IDH)-wildtype glioblastoma (World Health Organization (WHO) Grade 4). Defined by a biphasic histological architecture comprising malignant glial and mesenchymal components, GS accounts for approximately 2% of all glioblastomas and 0.5% to 1% of all intracranial malignancies [1,2]. Clinically and radiologically, GS typically present as a well-circumscribed, firm, peripherally enhancing mass, often mimicking a meningioma or metastasis, thereby contrasting with the infiltrative nature of classic gliomas [3].

Gliomatosis cerebri (GC) is no longer recognized as a distinct entity in the 2021 WHO classification but describes an extensive growth pattern involving at least three cerebral lobes [4]. While this pattern has been identified in approximately 9.4% of IDH-wildtype glioblastomas in recent large-scale analyses [5], the specific association of GS histology with a GC growth pattern remains an exceptional occurrence. Standard management protocols involve maximal surgical resection followed by concurrent chemoradiotherapy (Stupp protocol); however, the prognosis remains dismal, with a median survival ranging from 9 to 14 months [1,6].

This study describes a case of primary gliosarcoma exhibiting a fulminant post-operative aggravation of a gliomatosis cerebri pattern. This report elucidates the radio-clinical discordance, characterized by rapid and extensive radiological progression contrasting sharply with the paucity of clinical symptoms, and discusses the therapeutic challenges posed by this aggressive growth pattern.

OBSERVATION

A 51-year-old female with no significant medical history presented to a referring institution with a one-month history of progressive left-sided hemiparesis and intracranial hypertension. Medical records and

imaging reports from the referring center described a solitary, focal lesion characteristic of a high-grade glioma. Specifically, the MRI identified a heterogeneous, infiltrating right occipital mass measuring 37 x 36 mm, associated with significant perilesional vasogenic edema, right lateral ventricle compression, and subfalcine herniation. While the primary radiological presentation was that of a circumscribed mass, suspected infiltration of the splenium of the corpus callosum was noted. The patient underwent subtotal resection at the external facility. Histopathological examination of the resected specimen confirmed a high-grade malignant neoplasm with a biphasic tissue pattern (Figure 1A).

The tumor was composed of two distinct cell populations: a glial component consisting of GFAP-positive astrocytes with marked nuclear atypia, and a sarcomatous component characterized by fascicles of spindle-shaped cells forming a dense reticulin network. Immunohistochemical analysis showed strong and diffuse positivity for Vimentin in the mesenchymal component (Figure 1B), while the glial component retained GFAP expression. The proliferative index was significantly elevated, with numerous mitoses and areas of necrosis. Based on the 2021 WHO Classification of Tumors of the Central Nervous System, a diagnosis of Gliosarcoma (IDH-wildtype, Grade 4) was established.

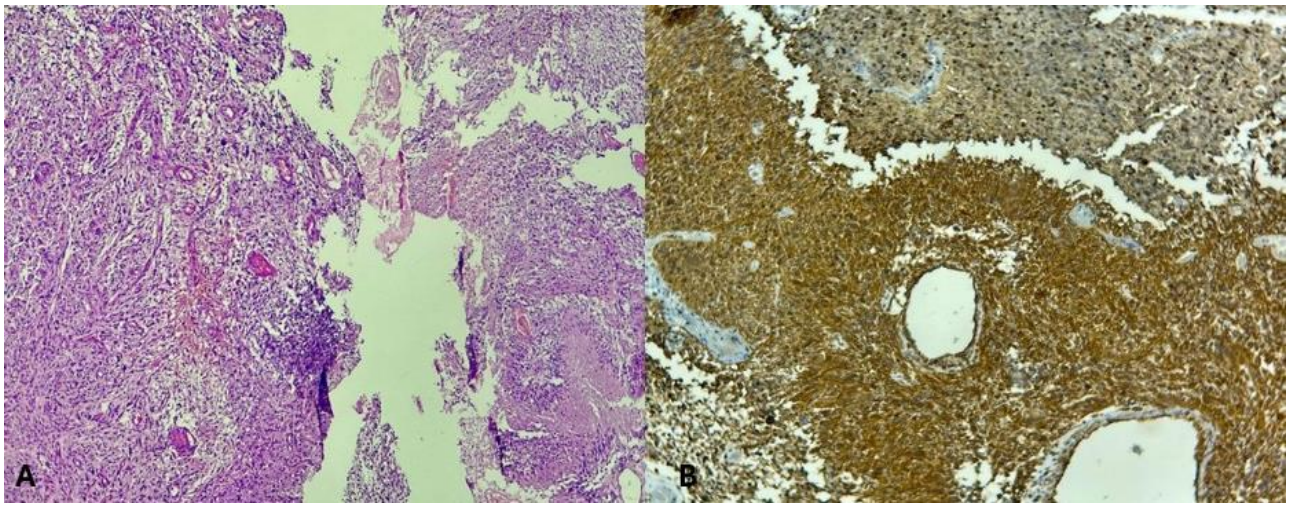


Figure 1 A, B: Histopathological and immunohistochemical features of the resected brain tumor. (A). Hematoxylin and Eosin (H&E, ×10) section revealing a densely cellular, biphasic neoplasm characterized by disorganized fascicles of spindle-shaped and epithelioid cells, indicative of the sarcomatous component; a prominent focus of necrosis is evident, comfirming the high-grade malignant nature of the lesion. (B). Immunohistochemical analysis (×25) demonstrates strong and diffuse cytoplasmic staining with anti-vimentin antibody, confirming the mesenchymal phenotype of the sarcomatous component.

The patient was referred to the Radiation Oncology department for adjuvant management. On admission, the clinical examination was remarkably discordant with the initial severity of the disease; the patient was alert, fully oriented, and had no evident motor or sensory deficits. She complained of persistent headaches despite ongoing corticosteroid therapy.

Magnetic Resonance Imaging (MRI) performed four weeks postoperatively and revealed a significant progression of the disease compared to the initial status. Anatomical sequences identified a focal lesion measuring 21 x 13 mm at the surgical bed, appearing hypointense on the T1-weighted sequence and heterogeneously hyperintense on the T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences, and demonstrating annular enhancement after gadolinium injection (Figure 2: A, B).

The diffuse infiltrative component showed dramatic progression. Extensive T2/FLAIR hyperintensity was observed in the right parieto-occipital region, extending massively through the corpus callosum to the contralateral hemisphere, exerting a mass effect on the midline and the pons (Figure 2: C, D, E). Magnetic Resonance Spectroscopy indicated a collapsed N-acetylaspartate (NAA) peak and an elevated Choline peak, which indicated active tumor proliferation.

Post-operative axial T1-weighted MRI with gadolinium (A) Focal lesion with annular enhancement at surgical bed (arrow). (B) Absence of contrast enhancement in the diffuse infiltrative component.

Post-operative axial T2-FLAIR MRI: Arrows indicate extensive bi-hemispheric hyperintense infiltration involving the corpus callosum (C, D), with mass effect on the midline and pons (E), consistent with a gliomatosis cerebri pattern.

This mixed radiological pattern—combining a focal enhancing mass with extensive, bi-hemispheric diffuse infiltration—was consistent with a gliomatosis cerebri growth pattern. These findings met the radiological criteria for Type 2, characterized by the

involvement of at least three cerebral lobes, complicating the delineation of radiotherapy target volumes.

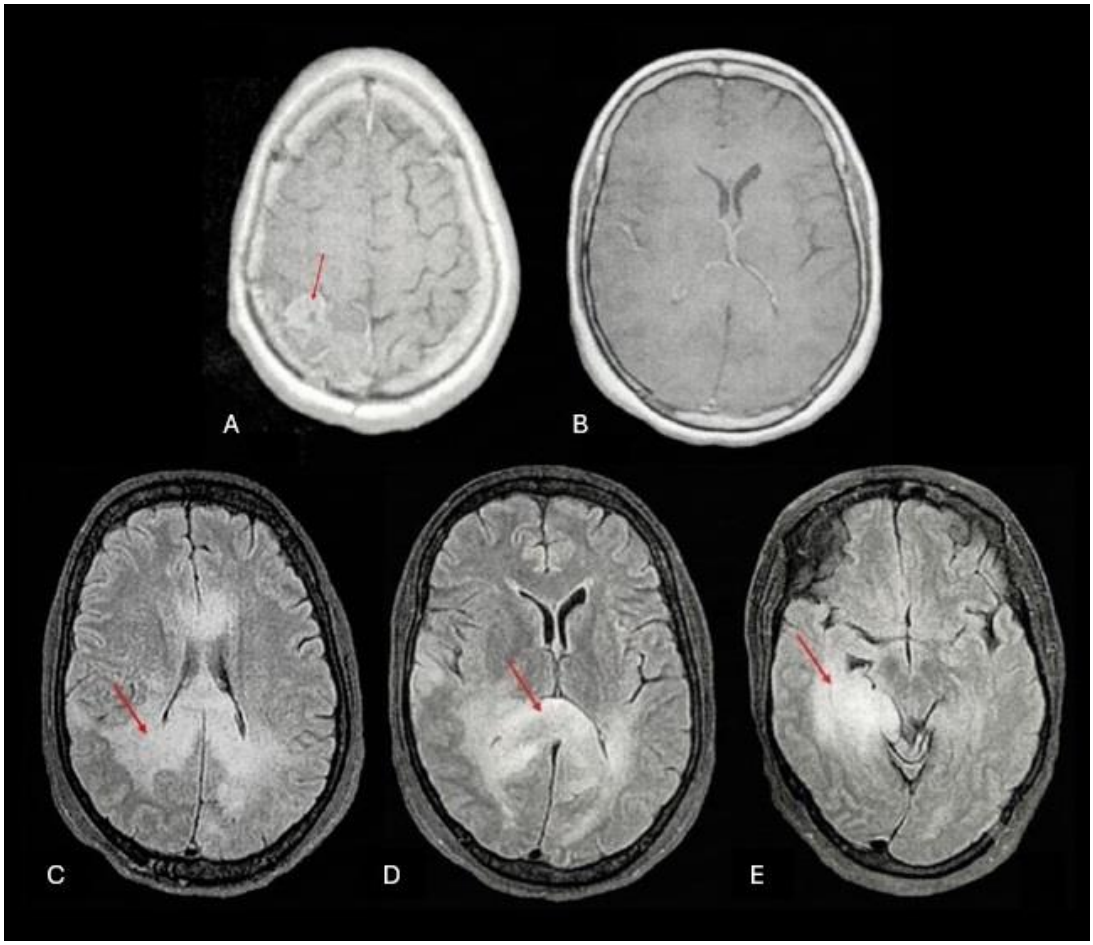


Figure 2: Post-operative neuroradiological assessment

Following multidisciplinary tumor board discussion and the acquisition of informed consent, clinical management involved concurrent chemoradiotherapy (Stupp protocol). To address the complex tumor geometry comprising both a focal mass and diffuse infiltration, a Volumetric Modulated Arc Therapy (VMAT) technique with a Simultaneous Integrated Boost (SIB) was employed. A total dose of 60 Gy in 30 fractions (2 Gy/fraction) was delivered to the resection cavity and residual enhancing disease plus a 2-cm margin (Clinical Target Volume [CTV] 60), while a dose of 54 Gy in 30 fractions (1.8 Gy/fraction) was prescribed to the extensive non-enhancing infiltrative component defined by T2/FLAIR hyperintensity plus a 1-cm margin. The respective Planning Target Volumes (PTVs 60 and 54) were generated by expanding each CTV with a uniform 3-mm margin. The daily administration of concurrent temozolomide was 75 mg/m².

The patient's tolerance of the concomitant phase was favorable, with no severe acute toxicity reported. The initiation of adjuvant chemotherapy with temozolomide occurred four weeks post-radiation at a dose of 150 mg/m² (days 1-5, every 28 days). However, following the second cycle of adjuvant treatment, the patient's neurological status deteriorated precipitously, progressing rapidly to a comatose state. This decline was attributed to uncontainable disease progression despite multimodal therapy. The patient passed away three months after the completion of radiotherapy.

DISCUSSION

Gliosarcoma is a rare entity primarily affecting adults between the fifth and sixth decades of life (median age 53–60 years), and shows a male predominance, with male-to-female ratios ranging from 1.4:1 to 1.8:1 [1,7]. The patient was a 51-year-old female; while her age is consistent with the peak incidence of Gliosarcoma (GS), her gender represents a statistically less common demographic for this pathology. A distinctive feature of this presentation is the association with a gliomatosis cerebri (GC) growth pattern. Shin *et al.,*(2024) recently reported an overall incidence of this pattern in 8.2% of adult-type diffuse gliomas, with a specific predilection for the IDH-wildtype glioblastoma subgroup [5].

The rapid development of a GC pattern following the resection of a focal GS appears to represent a rare phenotypic evolution that underscores the aggressive potential of this variant.

The clinical presentation of GS is typically indistinguishable from that of glioblastoma, dominated by focal neurological deficits and signs of increased intracranial pressure due to the rapid growth and mass effect of the sarcomatous component [1, 7]. The index presentation with hemiparesis and intracranial hypertension aligns with this classic profile. However, the post-operative course illustrates the radio-clinical discordance often described in GC. While GC can manifest insidiously with cognitive decline or mimic cerebrovascular events due to white matter infiltration [8], the patient remained clinically minimally symptomatic at the time of radiotherapy planning, reporting only persistent headaches despite massive bi-hemispheric infiltration. This discordance highlights the capacity of the infiltrative glial component to migrate along white matter tracts while initially preserving neuronal connectivity, delaying clinical decompensation until a critical threshold of tumor burden is reached [9].

Radiologically, GS typically presents as a well-circumscribed, peripherally enhancing supratentorial mass, often mimicking a meningioma or metastasis due to its firm mesenchymal composition [3]. Conversely, the GC pattern is characterized by diffuse T2/FLAIR hyperintensity enlarging anatomical structures with variable contrast enhancement [5]. The literature describes two radiographic subtypes of GC: Type 1 (diffuse infiltration without a mass) and Type 2 (extensive infiltration coexisting with a focal mass) [5]. The present case constitutes a paradigmatic example of Type 2 gliomatosis cerebri. The postoperative MRI revealed a dual pattern: a focal, ring-enhancing mass at the surgical bed (likely the sarcomatous component) and extensive, non-enhancing bi-hemispheric infiltration. The absence of enhancement in the diffuse component may reflect a partially preserved blood-brain barrier in areas of glial invasion, a known diagnostic pitfall that can mimic non-neoplastic conditions [8]. In this context, MR spectroscopy was decisive, revealing a collapsed NAA peak and elevated Choline levels in the parietal lesion, confirming high-grade tumor activity and ruling out post-operative changes.

Within the framework of the 2021 WHO classification of CNS tumors, gliosarcoma is registered as a histological subtype of glioblastoma, IDH-wildtype, CNS WHO grade 4—an assignment that formally consolidates GS under the same molecular nosological umbrella as other IDH-wildtype GBM variants [10].

The diagnosis of GS is predicated on the identification of a characteristic biphasic tissue architecture. The neoplasm comprises two distinct neoplastic populations: a glial component (GFAP-positive) and a sarcomatous component (Vimentin and Reticulin-positive) [11]. Contemporary molecular evidence supports a monoclonal origin for GS, with the prevailing hypothesis positing that the sarcomatous element evolves from the glial component via mesenchymal differentiation [12]. This concept has been substantially refined: glioblastoma is now understood to exhibit extensive transcriptional plasticity, enabling transitions across molecular subtypes—most notably toward a mesenchymal phenotype—in response to microenvironmental cues and therapeutic pressure [13,14]. Critically, the MES-like state may be mechanistically linked to therapy resistance, as it is sustained by master transcriptional regulators, tumor-associated macrophages, and metabolic reprogramming, shifting the view of GS pathogenesis from a static histological curiosity to a dynamic resistance mechanism [14]. Accordingly, the biphasic morphology of GS may reflect, rather than a discrete sarcomatous transdifferentiation, an extreme phenotypic expression along this plastic transcriptional continuum, and one that contributes to its chemoradioresistance.

The management of GS associated with a GC pattern presents a significant clinical challenge. While maximal safe resection is the cornerstone for focal GS [6], the diffuse nature of the gliomatosis component precludes extensive surgery. Consequently, radiotherapy plays a pivotal role. The utilization of historical whole-brain radiotherapy (WBRT) has largely been superseded by focal radiotherapy with extended margins, as WBRT is associated with significant neurotoxicity without a proven survival benefit [10]. Kandula *et al.,*demonstrated that 93% of recurrences in GC occur within the initial T2/FLAIR abnormality, supporting the use of involved-field radiation techniques [15].

The treatment strategy utilized Volumetric Modulated Arc Therapy (VMAT) with a Simultaneous Integrated Boost (SIB). This allowed for the delivery of a curative dose (60 Gy) to the macroscopic disease (resection cavity and enhancing nodule) while simultaneously delivering a high prophylactic dose (54 Gy) to the extensive non-enhancing infiltrative component. The choice of a one-centimeter radial margin around the T2/FLAIR signal to define the CTV 54 was deliberately aligned with the lower bound of the one- to two-centimeter margin range recommended by the EANO guidelines for diffuse adult-type gliomas [16]; this conservative expansion was chosen over the upper 2-cm value to limit the irradiated brain volume and the associated neurotoxicity in the context of an already extensive bi-hemispheric infiltration. The prescription of 54 Gy to the infiltrative component is supported by the series from Kandula et al [15], which reported a median effective dose of 54 Gy for gliomatosis cerebri, demonstrating that dose escalation beyond this level did not correlate with improved survival outcomes while potentially increasing neurotoxicity.

Given the neurotoxicity risks of delivering tumoricidal radiation doses to extensive infiltrative volumes, regional modalities like Tumor Treating Fields (TTFields) have been proposed as a complementary "field treatment. DesJarlais *et al.,*[17] reported a durable response in a glioblastoma patient with a secondary gliomatosis pattern by combining restricted focal radiotherapy with concurrent TTFields to safely target diffuse microscopic disease. In the reported instance, however, despite delivering a high prophylactic dose of 54 Gy to the infiltrative component via VMAT-SIB, the disease exhibited a rapid progression. This contrast underscores the radioresistance inherent to the sarcomatous component of primary gliosarcomas, suggesting that physical dose escalation alone may be insufficient and that integrating field treatments like TTFields warrants future consideration to improve local control in non-enhancing diffuse phenotypes.

Regarding systemic therapy, although the benefit of chemotherapy in GS is debated due to variable MGMT methylation status, the addition of temozolomide (Stupp protocol) remains the standard of care given the potential for chemosensitivity within the glial component, which is sufficient to support this approach, [1,6]

Despite the implementation of an aggressive multimodal therapeutic regimen, the patient's rapid disease progression three months after the completion of radiotherapy underscores the dismal prognosis of this entity. Median overall survival for gliosarcoma (GS) is generally reported between 9 and 14 months [1] [7]. Furthermore, Shin *et al.,*identified the presence of a gliomatosis cerebri (GC) pattern as an independent adverse prognostic factor (Hazard Ratio = 1.25) in IDH-wildtype glioblastoma [5]. The combination of GS histology and a secondary GC growth pattern thus appears to define a phenotype of extreme therapeutic resistance. The fulminant clinical trajectory observed in this patient may plausibly reflect the co-occurrence of molecular alterations classically associated with aggressive IDH-wildtype glioblastoma. According to the 2021 World Health Organization (WHO) Central Nervous System (CNS) classification, TERT promoter mutations are, alongside EGFR amplification and the +7/-10 genotype, sufficient by themselves to assign a CNS WHO grade 4 designation—an observation highlighting their prognostic weight [18]. Furthermore, homozygous CDKN2A/B deletion, although not required for grading, is recognized as a recurrent alteration in this subtype and a contribution to accelerated disease progression [10]. Full molecular profiling, including TERT and CDKN2A/B status, was not available at the time of initial diagnosis, representing a recognized limitation of this report.

CONCLUSION

Gliomatosis cerebri associated with primary gliosarcoma constitutes a rare entity of extreme aggressiveness. This case underscores the clinical significance of radio-clinical discordance, where the absence of major symptoms may mask fulminant tumor progression. The lack of contrast enhancement within the diffuse infiltration should not be misinterpreted as low-grade disease, necessitating evaluation via multimodal imaging (spectroscopy). The prognosis remains dismal despite aggressive multimodal management. Early identification of this growth pattern is crucial for adapting radiotherapy planning and the facilitation of prognostic counseling for the patient. These considerations delineate a management paradigm prioritizing early and transparent prognostic disclosure, enabling patients and their families to make informed decisions in the face of a notoriously chemoradioresistant entity.

Conflicts of Interest:

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Ethical Approval:

As this is a case report, formal ethical committee approval is not required by our institution, provided that anonymity is maintained and consent is obtained. The study was conducted in accordance with the Declaration of Helsinki.

Patient Consent Declaration:

Informed consent has been obtained from the patient's next of kin regarding the publication of this case report and accompanying images. The patient's identity was fully anonymized; thus, no identifying details are included in the manuscript

Author Contributions:

EM, NL: literature search, clinical data acquisition, manuscript drafting, and editing, **MH:** Participation in the clinical management of the patient, data analysis, and manuscript review. **KAS, KH and ME:** Supervision, critical revision of the manuscript for important intellectual content, and final approval of the version to be published

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