Case Report

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Pathology Section

Gliosarcoma: A Very Rare Biphasic Histopathological Engima Associated with Very Poor Prognostic Parameters

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ABSTRACT

Gliosarcoma (GS) is rare type of brain tumour characterised by a combination of glial and mesenchymal elements. It is a sporadic and aggressive malignancy, categorised as a variant of Glioblastoma with an Isocitrate Dehyrogenase (IDH) wild-type phenotype. These tumours generally present as well-defined masses and are most frequently observed in adults between the ages of 40 and 60 years, with a slight predominance in males. Common clinical features include focal neurological impairments such as hemiparesis and aphasia, often accompanied by tumour-associated oedema that contributes to elevated intracranial pressure. Due to the rarity of the condition, existing knowledge is primarily based on limited published reports. This report discusses a 57-year-old male who presented to the Emergency Department after experiencing a six-day progression of weakness affecting both the left upper and lower limbs, ultimately leading to significant mobility issues and difficulty walking. However, there was no history of loss of consciousness or vomiting. Upon hospital arrival, on clinical assessment, the patient was found to be drowsy but responsive, with both pupils irregularly dilated. A detailed examination revealed impaired balance and coordination, gait disturbance, numbness and tingling on the left-side of the body, as well as weakness in the left limbs and tongue, contributing to slurred speech and a stuporous state. Following the initial clinical evaluation,Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans were recommended. A CT scan revealed a hetero-dense, intra-axial solid-cystic lesion with relatively well-defined margins located in the right frontal lobe, measuring 4.6×5.0×5.5 cm (craniocaudal×transverse×anteroposterior). The mass was associated with surrounding vasogenicoedema, causing a mass effect on nearby sulci and resulting in compression of the frontal and temporal horns, as well as the body of the right lateral ventricle. MRI findings corroborated the CT results, additionally highlighting a dominant necrotic component within the lesion. These imaging features strongly suggested a brain tumour, with differential diagnoses including high-grade astrocytoma and GS. Surgical management was promptly initiated, and a complete tumour resection was performed via a right Fronto-Temporo-Parietal (FTP) craniotomy. Subsequent histopathological and immunohistochemical analysis confirmed the diagnosis of GS. The patient's family member consent was taken verbally before reporting this case in this current literature. Hence, we are reporting this rare entity to add to the literature and to be considered in the differential diagnosis of high grade malignant glial tumours as GS holds worse prognosis compared to Glioblastoma due to its rapid metastasis.

Keywords: Biphasic tumour, Chemotherapy, Gliosarcoma, Glioblastoma, IDH wild type, Radiotherapy, Surgery

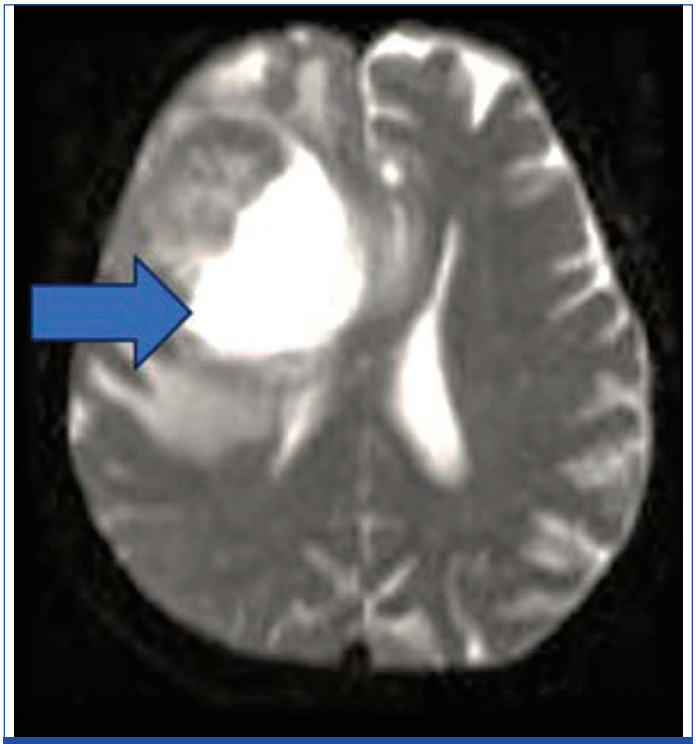
CASE REPORT

In the current case analysis, a 57-year-old male was admitted to our institution for evaluation of a six-day history of gradual weakness affecting the left upper and lower limbs. On clinical examination, bilateral papilloedema was noted. Laboratory findings on admission revealed moderate anaemia, with a haemoglobin level of 8 g/dL (reference range-13.8 to 17.2 g/dL and a total white blood cell count of 8,000/cu mm (reference range: 4,000 to 11,000 cells/µL of blood, or 4.0 to 11.0×10^9/L).

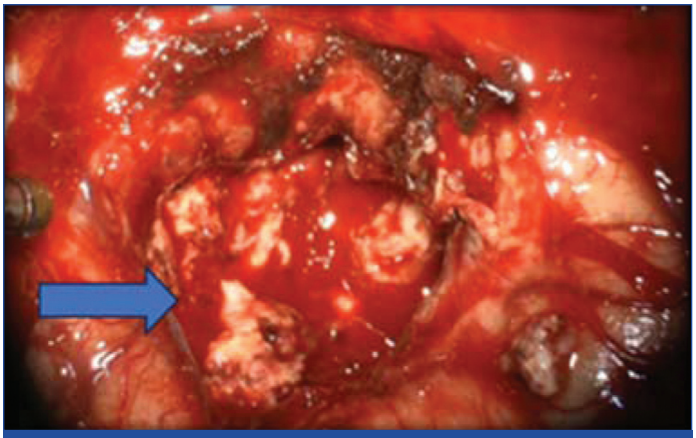
As enclosed brain CT scan image above shows a well-circumscribed [Table/Fig-1], hetero-dense, intra-axial solid-cystic mass measuring 4.6×5.0×5.5 cm (craniocaudal×transverse×anteroposterior). The cystic component of the lesion did not show contrast enhancement. Surgical resection of the lesion was performed promptly [Table/Fig-2].

The excised tissue was sent for histopathological evaluation. The immediate postoperative course was stable; however, the patient's condition gradually declined due to secondary infections, which were accompanied by a rise in the total white blood cell count to 20,000/cu mm (reference range: 4,000 to 11,000 cells/µL) of blood, or 4.0 to 11.0×10^9/L). Despite supportive measures, the patient ultimately succumbed to the illness.

A single soft-tissue bits measuring 6.5×5×3.5 cm with grey white cut surface with few grey brown areas was received. Specimen was all embedded for proper detailed analysis.

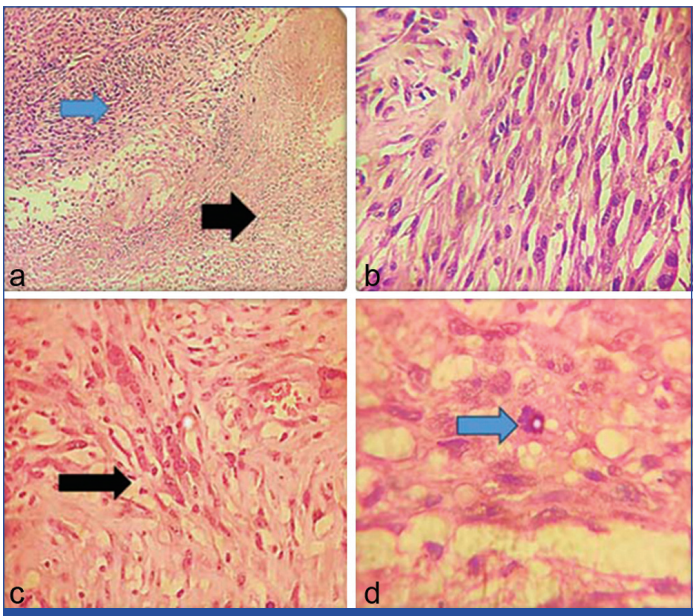


[Table/Fig-1]: CT scan shows well circumscribed hetero-dense (solid-cystic) (blue-arrow) measuring 4.6×5.0×5.5 cm.



[Table/Fig-2]: Intraoperative craniotomy image shows an irregularly bulky tumour (blue-arrow) noted on right frontal lobe extending into anterior body of corpus callosum.

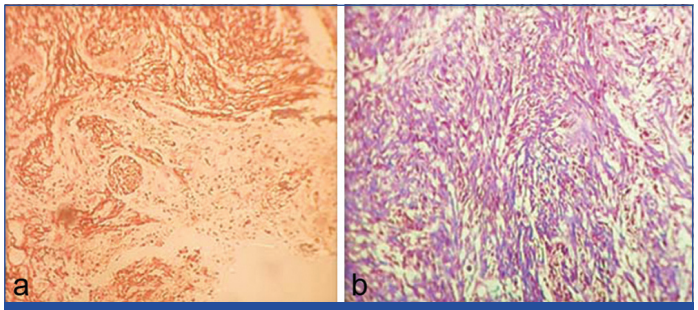
Histopathological analysis from multiple sections from right frontal space occupying lesion of cerebrum shows highly cellular tumour with biphasic configuration composed predominantly of spindle cells arranged in longitudinal, parallel and intersecting fascicles. The periphery of the tumour shows eosinophilic fibrillary background matrix including glial differentiation with round to oval to polygonal tumour cells with moderate to marked nuclear atypia. The spindle shaped cells arranged in fascicles as well as those in periphery and in the intervening areas showing moderate to marked nuclear pleomorphism, hyperchromatism, many bizzare nuclei and tumour giant cells also noted. Numerous mitotic figures also noted [Table/Fig-3].



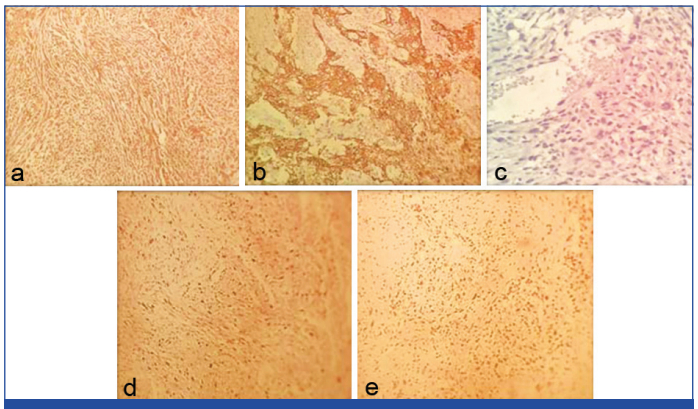
[Table/Fig-3]: a) Highly cellular tumour with biphasic pattern, composed of predominantly spindle shaped cells (black arrow), periphery of the tumour shows glial differentiation (blue arrow) (Hematoxylin and Eosin (H&E), 10x); b) Spindle shaped cells arranged in longitudinal, parallel and intersecting fascicles and glial component showed round to oval to polygonal tumour with moderate to marked nuclear atypia (H&E, 40x); c) Spindle shaped cells showing moderate to marked nuclear pleomorphism, hyperchromatism and multinucleated tumour cells (black arrow) (H&E, 40x); d) Many bizzare cells and numerous mitotic figures noted with atypical mitotic figures (blue arrow) (H&E, 40x).

Histochemical study with reticulin and Masson trichome stain reveals mesenchymal and collagenous component of the tumour, respectively [Table/Fig-4].

Immunohistochemical analysis revealed that **Glial Fibrillary Acid Protein (GFAP)** has strong cytoplasmic positivity in glial components predominantly periphery of tumour and few intervening areas within spindle cell component. Also, GFAP is negative in spindle cell (mesenchymal/sarcomatous) components. **Vimentin**- Diffuse strong cytoplasmic positivity in spindle cell (mesenchymal/sarcomatous) component **(Epithelial Membrane Antigen EMA)**. Negative in tumour cells. **Ki-67 Proliferation Index**- 70-75% positive in tumour cells. **P53**- Strong nuclear positivity in 80-85% tumour cells [Table/Fig-5].



[Table/Fig-4]: a) Reticulin Stain highlights predominantly mesenchymal component of tumour (Blue arrow) whereas the glial component doesn't take the stain (black arrow) (reticulin stain 40X); b) Masson Trichrome Stain highlights collagenisation (of varying degree) of mesenchymalsarcomatous components (green arrow) (Masson Trichrome Stain 40X).



[Table/Fig-5]: a) Vimentin: Diffuse strong cytoplasmic positivity in spindle cells (mesenchymal/sarcomatous) component (Immunohistochemistry [IHC], 10x); b) GFAP: Strong cytoplasmic positivity in glial component predominantly at periphery of tumour and intervening areas (blue arrow). Negative in spindle cells (black arrow) (IHC, 10x); c) Epithelial Membrane Antigen (EMA)- Negative in tumour cells (IHC, 10x); d) KI-67 (Proliferation Index-70-75% on tumour cells (IHC, 40x); e) P53- Strong nuclear positivity (IHC, 40x).

The histopathological and immunohistochemical findings confirmed the diagnosis of high-grade biphasic tumour (predominantly mesenchymal/sarcomatous component and minimal Glial Component) - GS, WHO Grade IV. The medical team proposed adjuvant radiotherapy and chemotherapy as part of a comprehensive treatment plan, but the patient's family declined further intervention. During follow-up, the patient's condition deteriorated rapidly, and he ultimately passed away four months after the initial presentation.

DISCUSSION

As per the 2021 classification by the World Health Organisation (WHO) concerning central nervous system tumours, GS is acknowledged as a rare variant of grade-IV Isocitrate Dehydrogenase (IDH) wild-type glioblastoma, characterised by both glial and mesenchymal differentiation. GS represents a distinct form of Glioblastoma, notable for its dual-component histological structure, featuring intermixed areas exhibiting both glial and mesenchymal differentiation [1]. It accounts for approximately 1% to 8% of all malignant gliomas, making it an extremely rare entity [2]. This type of tumour predominantly occurs in individuals aged 40 to 60 years, with the mean age of onset being over 50 years. It is more frequently observed in males and predominantly arises in the cerebral hemispheres, particularly within the temporal and frontal lobes [2]. GS was initially described by Stroebe H in 1895 as a brain neoplasm characterised by the presence of both glial and mesenchymal components [3]. Later, the biphasic nature of this tumour was more widely accepted following detailed histological evaluations conducted by Feigen and colleagues and also suggested that the sarcomatous component may develop through neoplastic transformation of the hyperplastic blood vessels frequently seen in high-grade gliomas [4]. In terms of clinical presentation, radiological features, dissemination patterns,

and gross morphology, this tumour closely resembles conventional glioblastoma. At present, GS is recognised as a well-circumscribed neoplasm that contains distinctly identifiable glial and metaplastic mesenchymal elements [5]. On microscopic examination, the glial component displays cytological features consistent with astrocytoma WHO grade IV, while the mesenchymal component may vary widely in appearance, potentially arising from fibroblastic, osseous, cartilaginous, adipocytic, or smooth/striated muscle tissue differentiation. Despite this, there is still no universal agreement on the pathological definition, particularly in terms of which component is dominant. As understanding of the clinical and histopathological characteristics of GS advances, there is a growing need for more stringent and standardised diagnostic guidelines.

The clinical presentation of GS differs based on the tumour's size and its specific location within the brain. The overall prognosis remains unfavourable, with reported median survival ranging between 6 and less than 20 months [6]. Commonly observed symptoms include seizures, focal neurological impairments, headaches, and signs indicative of elevated intracranial pressure [7]. While imaging modalities like Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are essential for the preliminary evaluation, a conclusive diagnosis requires histopathological and immunohistochemical analysis of the resected tumour tissue.

In the present case reported, we confirmed the co-existence of distinct gliomatous and sarcomatous components within the tumour. These components demonstrated marked cellular and nuclear atypia, hyperchromatic nuclei, elevated mitotic activity, and a high Ki67 proliferation index. The most frequently affected site for primary GS is the cerebrum, with the temporal, parietal, frontal, and occipital lobes involved in descending order of occurrence [8]. In our case, a monoclonal origin associated with p53 mutation was observed, consistent with findings in previous studies. Several reports have emphasised the diagnostic challenge in distinguishing glioblastoma from GS, as both conditions typically present at similar ages, have a brief clinical course, and share a comparably limited survival period following diagnosis [9,10]. However, the exact pathogenesis of GS is still a subject of ongoing debate. Emerging evidence supports the notion that both glial and mesenchymal components derive from a single progenitor clone, with the mesenchymal differentiation representing an atypical pathway of malignant glioma cell transformation [11]. Huo Z et al., reported two rare cases of primary GS with unusually prolonged survival, supported by an extensive review of the literature [12]. They also defined GS as histopathologically by its distinctive biphasic architecture, combining a glial component with a mesenchymal, sarcomatous component. This unique duality renders it a histopathological paradox and often necessitates detailed immunohistochemical evaluation for accurate diagnosis. The glial component generally stains positive for GFAP, while the sarcomatous portion expresses markers like vimentin and smooth muscle actin [12]. Our findings were consistent with this profile, as we identified neoplastic glial cells exhibiting GFAP immunopositivity, helping to exclude differential diagnoses such as fibrosarcoma or malignant fibrous histiocytoma. In cases where diagnostic uncertainty remains, reticulin staining can aids in delineating the sarcomatous regions, thereby clearly identifying the biphasic nature of GS.

GS is an uncommon and aggressive variant of Glioblastoma Multiforme (GBM), accounting for approximately 2-8% of all GBM cases. It is distinguished by its biphasic histopathological architecture, characterised by the coexistence of two morphologically distinct cellular components: a glial component and a sarcomatous (mesenchymal) component, thereby earning its reputation as a histopathological enigma. Due to its complexity and rarity, GS represents a significant challenge in both diagnosis and management, underscoring the need for heightened awareness, early identification, and ongoing research into more effective treatment modalities to improve outcomes for affected patients.

Therapeutic strategies for GS identical for those for glioblastoma and include surgical excision followed by radiotherapy and chemotherapy. Younger patients are generally better candidates for radiotherapy and tend to have a more favourable prognosis. Unfortunately, our patient was of advanced age and presented late in the disease course. Although a combined regimen of radiation and chemotherapy was recommended, the patient's family declined further treatment. During follow-up, the patient's condition worsened, compounded by secondary infections, ultimately resulting in mortality.

CONCLUSION(S)

The GS is an uncommon but aggressive brain tumour characterised by distinct imaging findings, immunohistochemical markers, and clinical presentation and a biphasic glial and mesenchymal sarcomatous component unlike glioblastoma which is a glial malignant tumour. The prognosis of GS is believed to be worse than glioblastoma and also the propensity for extra-cranial metastasis is higher in GS compared to glioblastoma. Hence, it is important that the awareness of this very rare and distinct biphasic entity of GS and its highly aggressive behaviour by the pathologists, oncologists, oncosurgeons and other specialists is required and any personalised treatment options available may be considered. Hence, we are reporting this rare entity to add to the literature and to be considered in the differential diagnosis of high grade malignant glial tumours.

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