Unveiling Systemic Barriers to High-Grade Glioma Management in Non-Tertiary Centers: A Case Report and Analysis of Resource-Limited Care Challenges

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AIM: High-grade gliomas (HGGs) are among the most aggressive brain tumors, including gliosarcoma. This report aims to present a case of gliosarcoma managed in a general non-tertiary hospital and to highlight the systemic barriers that delayed diagnosis and treatment.
CASE PRESENTATION: A 53-year-old female was diagnosed with two intra-axial brain lesions and was managed in a general non-tertiary hospital. One lesion was excised and identified as gliosarcoma. Pathological analysis concluded that the excised lesion was World Health Organization (WHO) grade 4 gliosarcoma, isocitrate dehydrogenase (IDH)-wild type, with glial and spindle sarcomatous components, *P53* mutation, C228T (c.-124C>T) variant of the telomerase reverse transcriptase (*TERT*) promoter, and hypermethylated O-6-methylguanine-DNA methyltransferase (*MGMT*) promoter status. The final diagnosis was concluded as gliosarcoma, WHO grade 4, IDH-wild type.
RESULTS: Despite the detailed histopathological and molecular findings, there were delays in radiological imaging, surgical treatment, and possible adjuvant therapy because of several systemic barriers, including initial family opposition and resource-limited conditions. The case also shows the challenges of managing high-grade gliomas in non-tertiary settings and the impact of delayed referral and treatment.
CONCLUSIONS: This report highlights the limitations of care in resource-limited settings and the need for stronger referral systems and better access to timely imaging, surgery, and adjuvant treatment to improve outcomes for patients with HGGs. It also suggests that future WHO guidelines for central nervous system tumors may consider adding diagnostic and prognostic parameters relevant to resource-limited settings, rather than relying only on histological entities or using the term "Not Otherwise Specified" when molecular classification is not achievable.

Keywords: high-grade glioma; gliosarcoma; resource-limited settings; CNS tumors; histopathology; radiology; case report

Introduction

The latest 2021-World Health Organization (WHO) classification of central nervous system (CNS) tumors classifies gliosarcoma as a rare variant of grade 4 glioblastoma, and both are known as high-grade gliomas (HGGs) [1]. Gliosarcoma is found in about 2–8% of all primary glioblastomas and is characterized by the presence of two histological components, gliomatous and sarcomatous [2]. The gliomatous component originates from glial cells and is identified by glial fibrillary acidic protein (GFAP), while the sarcomatous part consists of spindle cells that are positive for reticulin and vimentin stains [3]. In previous molecular studies, gliosarcoma has been profiled mainly as an isocitrate dehydrogenase (IDH)-wild type, with *P53* mutations occurring more frequently than what has been observed in other variants of glioblastoma [4,5].

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The 2021-WHO classification of CNS tumors emphasizes the necessity of comprehensive pathological assessment and classification of tumors as a layered diagnosis incorporating histological entity and molecular markers such as *IDH-1*/*IDH-2* status, telomerase reverse transcriptase (*TERT*) promoter alterations, O-6-methylguanine-DNA methyltransferase (*MGMT*) methylation, and *P53* mutations [1]. In the era of precision medicine, it is believed that histological diagnosis alone is no longer sufficient to provide an accurate diagnosis, predict prognosis, or plan appropriate treatment. This comprehensive diagnostic approach, according to the 2021 WHO classification of CNS tumors, has tremendously improved CNS tumors classification and their management, consequently [6,7]. However, the requirements for advanced molecular profiling have created different diagnostic challenges and systemic barriers, mainly in resource-limited settings [8,9].

The complexity and demands for high resources to manage HGGs go beyond the advanced molecular diagnosis to involve specialized neurosurgery, radiotherapy, chemotherapy, and potential adjuvant therapy [10], all of which remain essential barriers in resource-limited settings such as non-tertiary healthcare centers [11,12]. Non-tertiary centers usually lack the essential infrastructure, well-

trained/specialized healthcare providers, molecular diagnostic pathology, radiological imaging, and other necessary resources to provide timely and comprehensive HGGs care. For instance, limited access to neuroimaging or neuropathology services delays accurate diagnosis [13,14]. Shortage in or lack of well-trained/specialized neurosurgeons may result in suboptimal intervention or delayed surgical treatment [15,16]. Unavailability of radiotherapy facilities is another complexity that may extend treatment delays [17]. Due to cultural beliefs or health literacy, family members and/or patients may resist certain treatment decisions [12,17], which can further delay treatment. These barriers and delays pose challenges to the timely delivery of standard therapy for patients with HGG.

The current report discusses a case of a 53-year-old female who was diagnosed with two intra-axial brain lesions and managed in a general non-tertiary hospital. Besides the systemic barriers discussed above regarding HGGs management in non-tertiary centers, the presence of two-axial lesions in this patient is considered as an additional challenge. Multiple lesions of HGGs are infrequent and mistaken for metastatic secondary tumors [18]. The distinction between primary glial tumors and metastatic tumors is critical as it significantly affects the strategy of treatment and follow-up [19,20]. This critical distinction needs timely and proper neuroradiology and neuropathology services, besides a neurosurgical team [21,22,23]. Besides the case description, this report highlights limitations regarding HGGs management in non-tertiary centers and discusses recommendations to improve outcomes for HGG patients or others in such a context. In addition to that, the current report proposes that future WHO guidelines for central nervous system tumor classifications may include diagnostic and prognostic parameters relevant to resource-limited settings [8,24], other than relying on the histological entities, besides the suggested term "Not Otherwise Specified" in case the molecular classification is not achievable.

Case Presentation

Patient Demographics and Timeline

This case has been reported in line with the case report guidelines: Case Report (CARE) Guidelines to ensure the accuracy and completeness of the report (**Supplementary Material**). A 53-year-old female with no medical or surgical history. The Red Crescent brought her to the Emergency Department at King Khalid Hospital, Najran, Saudi Arabia after two convulsion attacks that lasted for 1 minute each. The patient had no history of head trauma or falling; no weakness, slurred speech, loss of consciousness, pain, and change of bowel habits, or loss of sphincter control. On examination, the patient was vitally stable, conscious, alert, and oriented. She had intact speech, no neck stiffness, or meningeal irritation signs. She was able to move her upper and lower limbs, had no Babinski sign, and her brainstem reflexes were intact.

The patient was brought to the Emergency Department (Day 0) after the aforementioned convulsive attacks. On Day 1, an urgent brain computed tomography (CT) was performed and the patient was admitted for four days. On Day 33, multi-planner and multi-sequential magnetic resonance imaging (MRI) images were acquired using the standard department protocol with intravenous contrast, confirming the presence of two aggressive neoplastic lesions. On Day 140, the patient was scheduled for neurosurgery to excise the tumors. The patient underwent left temporal craniotomy and subtotal tumor excision of the larger lesion. The patient improved and was discharged five days later. The histopathological report was released on Day 145, and part of the samples were sent for molecular pathology analysis. The patient was scheduled for an appointment at the outpatient department after reviewing the molecular pathology results on Day 218. To maintain confidentiality, specific calendar dates have been replaced with elapsed days relative to the initial presentation [25].

Radiological Findings

Brain CT (Fig. 1) revealed the presence of two intra-axial brain lesions on Day 1, and MRI was recommended for further assessment. On Day 33, multi-planner and multi-sequential MRI images were acquired using the standard department protocol with intravenous contrast (Fig. 2). The MRI report, compared to the previous CT scan, confirmed the presence of two large intra-axial lesions. The largest lesion was noted at the left temporal lobe, demonstrating a central fluid-like signal intensity in the T2-weighted MRI sequence and avidly enhancing the thick, irregular wall in the T1 post-contrast image. A few dark foci were observed within the lesion in the gradient echo (GRE) sequence, consistent with a blooming artifact, likely indicating hemorrhage or small calcifications. Moderate surrounding vasogenic edema was observed, which caused a mass effect on the effacement of adjacent sulci and the ipsilateral posterior horn of the lateral ventricle.

The other lesion was observed in the left thalamus and showed intermediate T2/fluid-attenuated inversion recovery (FLAIR) signal intensity. It showed no significant enhancement in the T1 post-contrast image. The lesion compressed the third ventricle and caused a mild right-sided midline shift. No hydrocephalus was observed. Orbits, cerebellar hemispheres, midbrain, and the internal auditory canals were intact. The visualized portion of the paranasal sinuses showed mild mucosal thickening at both maxillary sinuses, with right-sided nasal septum deviation and hypertrophy of both inferior turbinates. Overall, MRI features were consistent with two aggressive neoplastic lesions.

Surgical and Pathological Findings

While the thalamic lesion was neither biopsied nor resected, left frontotemporal craniotomy and subtotal tumor excision of the large lesion were performed via neurosurgery. After the neurosurgical excision of the tumor, gross pathol-

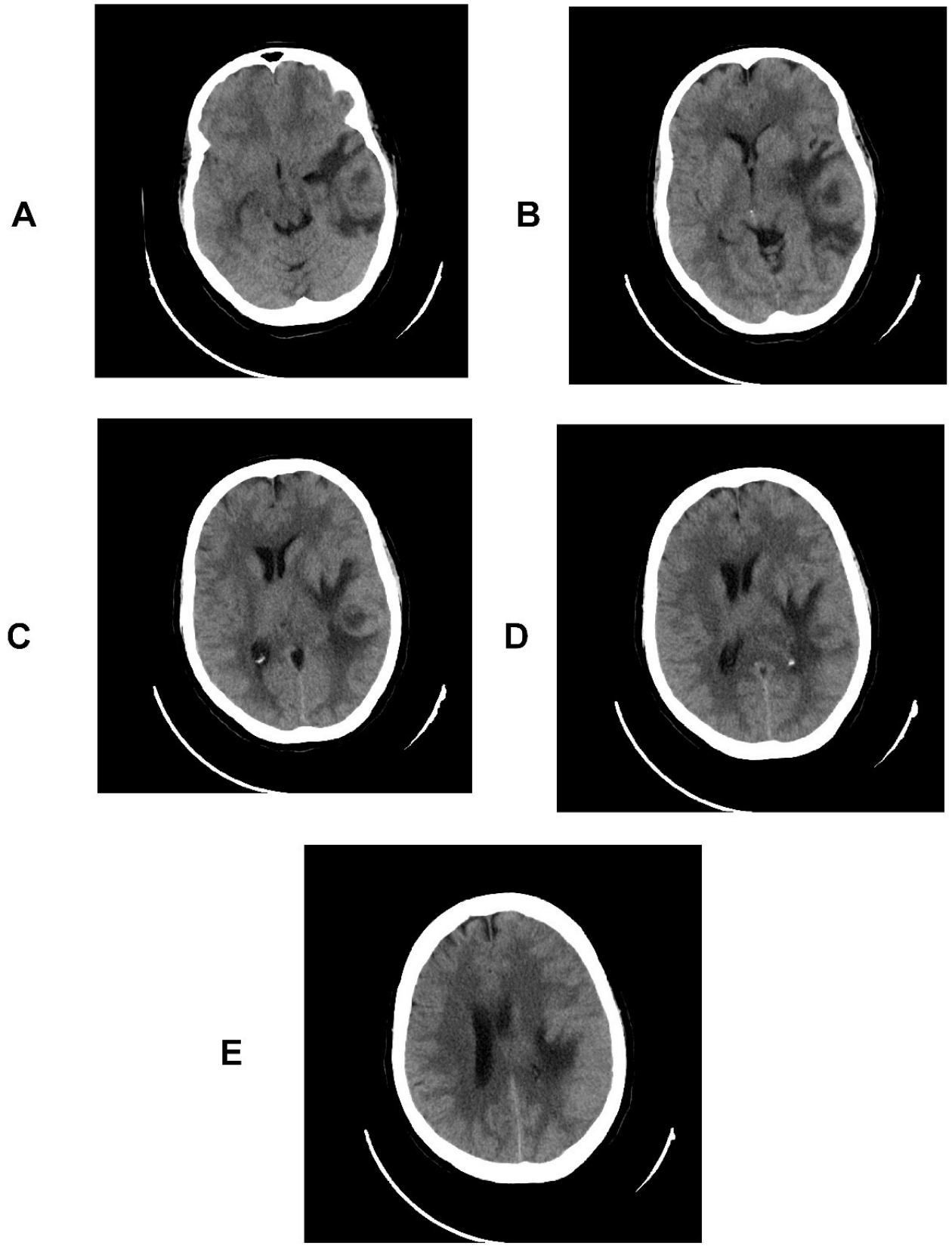

Fig. 1. Representative images for the computed tomography (CT) scan. A multi-axial non-contrast CT scan of the brain at the level of the temporal lobe showed a large heterogeneous intra-axial left temporal soft tissue mass (A) with central hypodensity as a cystic component (B,C). It is surrounded by prominent vasogenic edema (hypodense) and a significant mass effect on the surroundings by effacement of the adjacent cortical sulci and obliteration of the atrium and the occipital horn of the left lateral ventricle (A,B,C). Another ill-defined hypodense lesion occupying the left thalamus causes a mass effect represented by a right-sided midline shift (D,E).

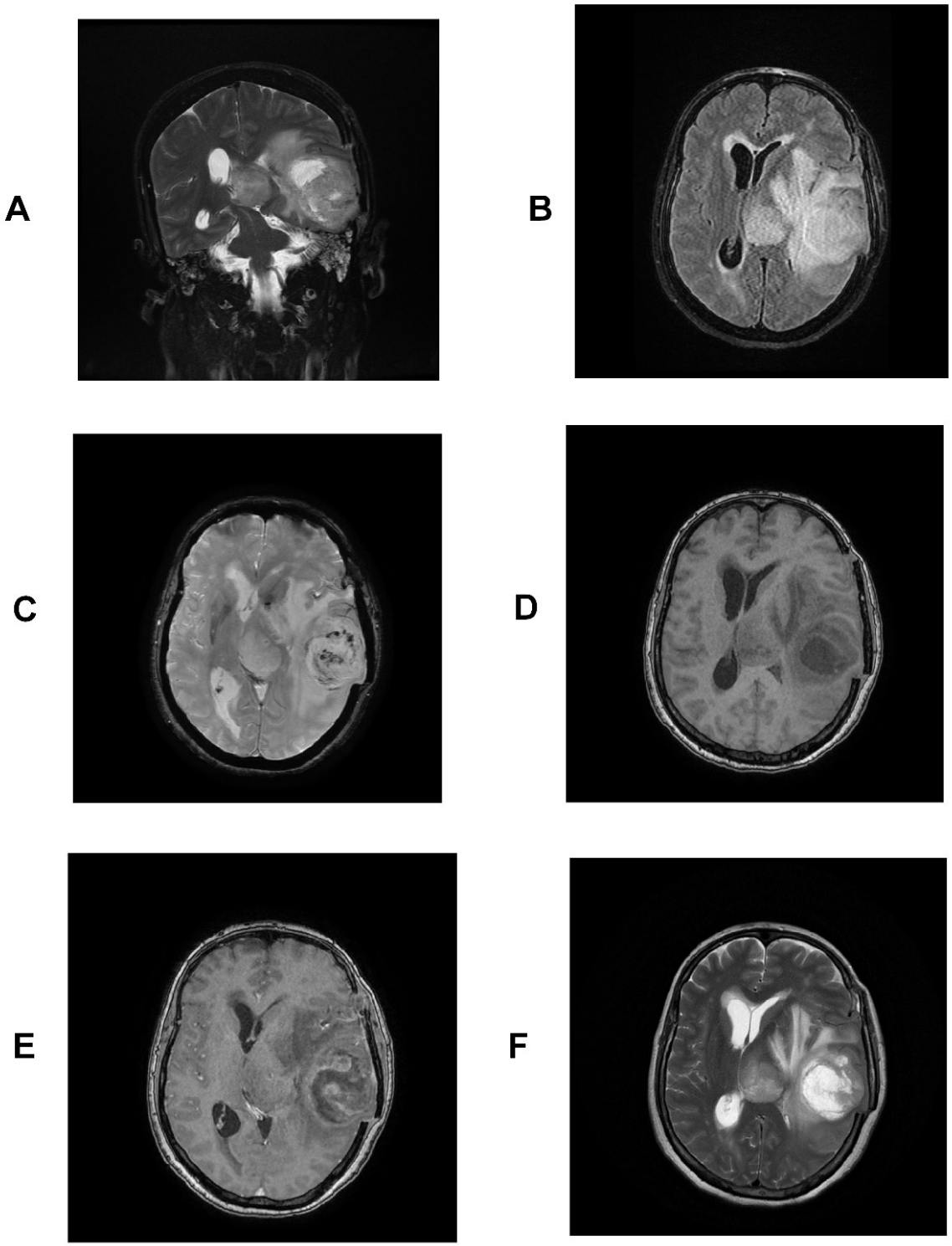

Fig. 2. Representative images for the magnetic resonance imaging (MRI). A multi-sequential MRI confirmed the presence of two large intra-axial lesions. The largest lesion was noted at the left temporal lobe, demonstrating a central fluid-like signal intensity in the T2-weighted MRI sequence (A,F) and avidly enhancing the thick, irregular wall in the T1 post-contrast image (E). A few dark foci were observed within the lesion in the GRE sequence (C), consistent with a blooming artifact, likely indicating hemorrhage or small calcifications. Moderate surrounding vasogenic edema was observed, which caused a mass effect on the effacement of adjacent sulci and the ipsilateral posterior horn of the lateral ventricle. The other lesion was observed in the left thalamus and showed intermediate T2/fluid-attenuated inversion recovery (FLAIR) signal intensity (A,B,F). It showed no significant enhancement in the T1 post-contrast image (D). The lesion compressed the third ventricle and caused a mild right-sided midline shift (F). Overall, MRI features were consistent with two aggressive neoplastic lesions.

Table 1. Primers and tested mutations.

Gene	Primers	Mutations
IDH1	NM_005896.4; chromosome 2	c.395G>A p.(R132H) and c.394C>T p.(R132C)
IDH2	NM_002168.4; chromosome 15	c.515G>A p.(R172K) and c.515G>T p.(R172M)
TERT	NM_198253.3; chromosome 5	p. C228T y p.C250T

IDH, isocitrate dehydrogenase; *TERT*, telomerase reverse transcriptase.

ogy revealed fragmented soft tissue pieces measuring 7 × 7 × 3 cm. The sectioning revealed firm, whitish-tan cut surfaces with hemorrhagic and necrotic areas. On Day 145, the histopathology (Fig. 3) report revealed highly pleomorphic and biphasic glial and spindle tumor cells with pseudopalisading necrosis, microvascular proliferation, and frequent atypical mitosis (Fig. 3A,B). The immunohistochemistry showed that the tumor glial cells were positive for GFAP (Fig. 3C) and S-100 immunostaining (Fig. 3D), while the spindle cell component (sarcomatous component) was positive for vimentin (Fig. 3E). The *P53* immunostaining was positive in the glial and the spindle cells (Fig. 3F), and the Ki-67 proliferative index was approximately 90% (Fig. 3G). The final diagnosis of the histopathology report concluded brain tumors with features consistent with grade 4 glioblastoma/gliosarcoma.

The molecular pathology report was released on Day 218 after testing for *MGMT* gene promoter methylation, and frequent mutations in *IDH1, IDH2*, and *TERT* genes, as shown in Table 1. The test was done using Methylation-Specific Multiplex Ligation-Dependent Probe Amplification (MS-MLPA) analysis and all reported variants were confirmed in an independent assay. The results confirmed a hypermethylation pattern in the promoter region of the *MGMT* gene, and the C228T (c.-124C>T) variant in the *TERT* gene was observed. The molecular pathology report concluded the diagnosis according to the 2021-WHO classification of CNS tumors as a grade 4 gliosarcoma variant of glioblastoma, IDH-wild type. Additionally, the tumor was *TERT*-mutant, *MGMT*-hypermethylated, and *P53*-mutant.

Treatment Recommendations

The oncologist referred the patient to a higher specialized center for further treatment with chemotherapy and radiotherapy. According to the histopathological and molecular reports, the patient was suggested as a candidate for telozolamide, as the test results indicated a hypermethylation pattern in the promoter region of the *MGMT* gene. Additionally, the molecular pathology report recommended the patient for further genetic counseling.

Treatment Delays and Systemic Barriers

Analysis of the timeline and associated barriers in this case revealed remarkably prolonged durations at every stage of treatment with a total duration of approximately seven months. These delays obviously exceeded what is recommended for the proper management duration of HGGs [26]. Available high-grade glioma literature supports prompt diagnostic workup and surgery without unnecessary delay [27,28,29], with postoperative chemoradiotherapy generally initiated within 6 weeks [30,31]. However, the effect of delay may differ by extent of resection and patient subgroup [31,32]. In the current report, the diagnostic radiology required 33 days from the initial presentation to MRI assessment completion. Another delay for 140 days occurred until the surgical intervention was performed, representing a delay of 107 days after the MRI assessment. A further 78 days of delay occurred from the time of tissue excision to the availability of the final molecular report. The total time from the first presentation to the referral was 218 days, which corresponds to roughly seven months.

Apparently, several systemic barriers may contribute to these delays at the different levels. At the diagnostic level, although the center has both CT and MRI facilities, MRI assessment was performed after more than one month, suggesting obstacles in scheduling, executing, approving, or reporting the MRI. Gross pathology and histopathology were completed in a reasonable time, but molecular testing was outsourced to an external reference laboratory and produced a delay of 78 days due to the unavailability of on-site molecular diagnostics.

Surgically, there is a neurosurgical capability since the craniotomy and suboptimal resection were performed. However, there was a 107-day delay after the acquisition of the MRI, indicating the presence of potential contributors as systemic barriers. These contributors may include limited operating rooms for such neurosurgical cases, absence of formalized policy for urgent operation of HGGs, unavailability of well-trained neurosurgeons or other related professions, and documented family opposition. These contributors might be overcome by explicit institutional policies that prioritize HGG patients for surgical intervention, by a dedicated neuro-oncology team with multidisciplinary personnel, by robust referral/consultation systems connecting the regional hospital to tertiary centers [8,11,16], and by structured strategies for family engagement and education on tumor aggressiveness and the significance of urgent intervention. The family opposition likely deferred the urgent surgical intervention due to either limited health literacy or religious/cultural beliefs that drive the preference for conservative or alternative treatments, compared to surgery [12,17].

Discussion

The current report highlights the multiple systemic barriers to optimal HGGs management in resource-limited set-

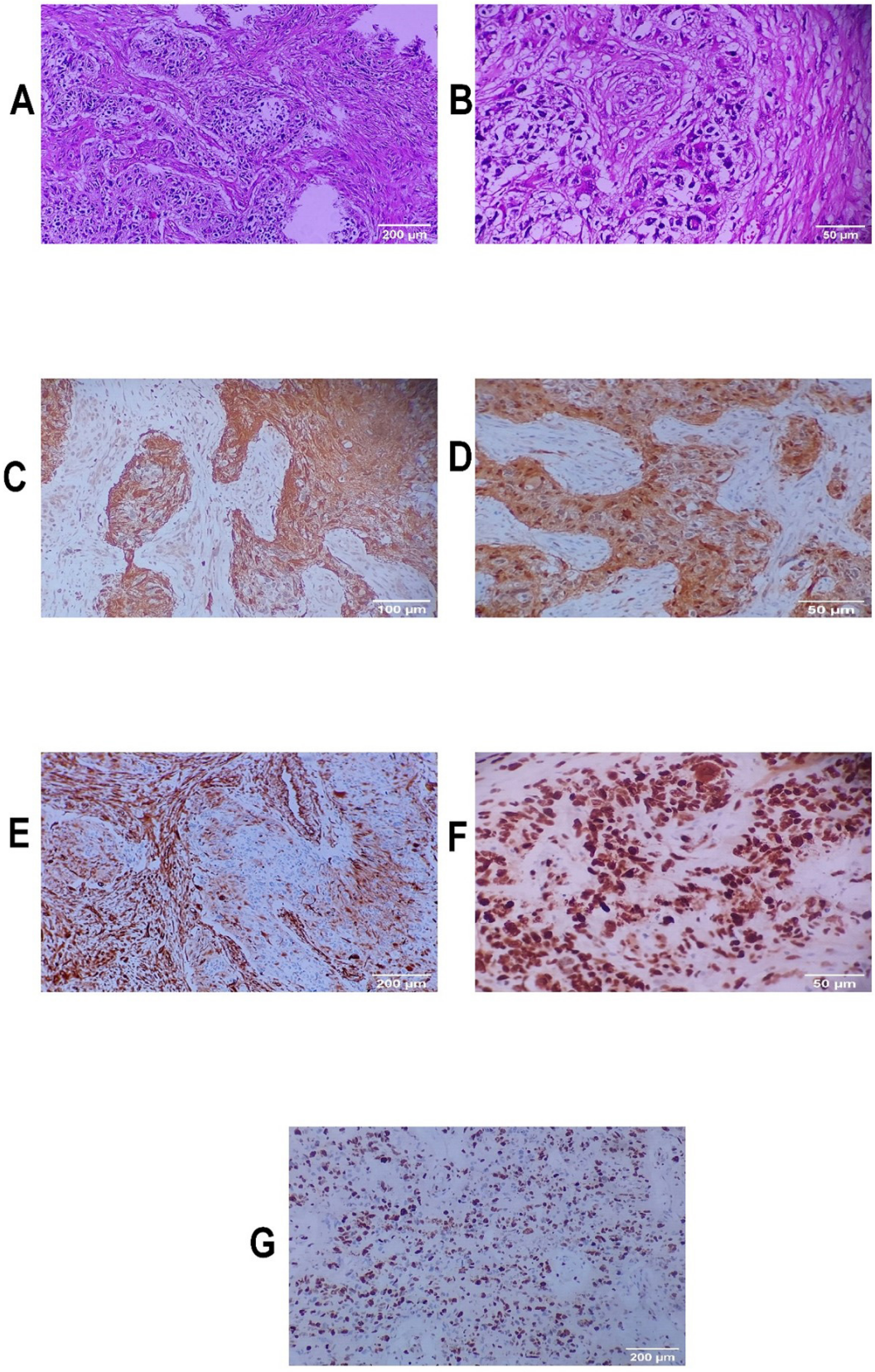

Fig. 3. Representative images for the histopathology and immunohistochemistry. (A) Hematoxylin and eosin section, (B) Another hematoxylin and eosin section, (C) Glial fibrillary acidic protein (GFAP) section, (D) S100 section, (E) Vimentin section, (F) *P53* section, and (G) Ki-67 section.

tings. While the molecular testing in the current report represented a diagnostic strength, the delay in treatment initiation weakened this strength. The reported *MGMT* hypermethylation indicated the patient's sensitivity to temozolomide [10,26]. *MGMT* status is clinically relevant in gliosarcoma, and temozolomide-based therapy has been associated with improved survival, although reported *MGMT* methylation frequencies vary across studies [10,27]. Compared to glioblastoma, gliosarcoma has a more aggressive course with less median survival, even with combined therapy (9–12 months vs. 15–19 months for glioblastoma) [33]. IDH-wild type status is the most reported in gliosarcoma, *P53* mutations occur more frequently (71% of gliosarcomas) in comparison to conventional glioblastoma, and *TERT* promoter mutations are documented in 81–92% of gliosarcomas [5,34,35]. The molecular testing results in this report exhibited consistency with these reports. The tumor was IDH-wild type, *P53*-mutant, and *TERT*-mutant. However, these molecular results remained clinically unrealized due to delays in treatment initiation.

Although gliosarcoma is increasingly recognized as a unique entity of HGGs [4], recent reviews and reports present insights into its optimal management [13,27,28]. Surgical resection and postoperative concurrent radiotherapy/chemotherapy with adjuvant temozolomide is the gold standard of care [27]. The patient in this report experienced remarkable prolonged durations at every stage of treatment, with a total duration of approximately seven months. A large analysis of 107 glioblastoma patients found that initiating radiotherapy before 42 days post-operatively was an independent favorable prognostic factor on multivariate analysis ($p = 0.009$) [31]. Few studies address cumulative delays across diagnostic and treatment phases. However, the rapid growth kinetics of HGGs, particularly gliosarcoma, with high Ki-67 as seen in this patient, suggest that delays allow tumor progression, increasing operative difficulty and reducing resection extent [36,37]. There are different reports presenting some rare presentations and locations of HGGs [38,39]. The presentation of HGGs with multiple lesions is an infrequent and rare example, and might be mistaken for metastatic secondary tumors [18]. The distinction between primary glial tumors and metastatic tumors is crucial because it directly influences treatment planning and follow-up [19,20]. Making this distinction requires prompt, coordinated input from neuroradiology, neuropathology, and neurosurgery [21,22,23]. Multiple-lesion presentation is generally associated with a worse prognosis and potentially a more aggressive nature, compared to single-lesion presentation [19,20]. In this case, the thalamic lesion was never definitively diagnosed. It was neither biopsied nor resected, creating ongoing diagnostic uncertainty. This illustrates another systemic barrier in resource-limited settings and how it compromises treatment planning for complicated and rare cases.

This case report discusses the profound systemic barriers to optimal management of gliosarcoma as HGGs in a non-tertiary healthcare center within resource-limited settings. While comprehensive histopathological and molecular diagnostics were successfully achieved, demonstrating diagnostic excellence, cumulative delays in diagnostic imaging (33 days), surgical intervention (140 days), and treatment planning (218 days to diagnostic completion) substantially exceeded evidence-based thresholds. Additionally, the thalamic lesion was not biopsied or resected, leaving its diagnosis unresolved. The systemic barriers were discussed and highlighted in this report include infrastructure limitations for both diagnostic and therapeutic purposes, suboptimal surgical services, the absence of a neuro-oncology team, the nonexistence of on-site molecular diagnostics, the absence of explicit referral/consultation policies, and patient-family cultural or religious factors. Addressing these different barriers is mandatory and requires different national interventions that align with health system transformation and the 2030 vision [40]. These interventions include, but are not limited to:

1. Initiation of formal neuro-oncology networks connecting expertise in tertiary centers to others in non-tertiary ones.
2. Implementation of explicit referral/consultation policies.
3. Development of regional molecular diagnostics.
4. Standardization of national diagnostic and therapeutic measures.
5. Supporting psychosocial aspects and education of families and patients.

Finally, in the international context, the current report proposes that future WHO guidelines for central nervous system tumors classification may include diagnostic and prognostic parameters relevant to resource-limited settings, other than relying on the histological entities, besides the suggested term "Not Otherwise Specified" in case the molecular classification is not achievable, as pointed in the 2021-WHO guidelines.

Conclusions

This case highlights the profound systemic barriers to the timely diagnosis and management of gliosarcoma in a non-tertiary, resource-limited setting, and it underscores the need for stronger referral pathways, improved access to imaging and surgery, and better support for multidisciplinary neuro-oncology care.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

SMA is the sole contributor to this manuscript. The author confirms sole responsibility for the conception and design of the study; the acquisition, analysis, and interpretation of data; the preparation of the manuscript; and being accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The report was conducted in accordance with ethical principles consistent with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of clinical details and images for educational and research purposes, with patient identifiers removed to protect privacy per international research ethics guidelines. The study was approved by the Scientific Ethics Committee at Najran University, Saudi Arabia, under the decision HAPO-11-N-102 and approval number 202602-076-042556-092572.

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Conflict of Interest

The author declares no conflict of interest.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

During the preparation of this work, the author used Perplexity to enhance language and readability. After using this tool, the author carefully reviewed and edited the text as needed and assumes full responsibility for the final content of the publication.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.4749.

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