American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2019; 20: 914-919
DOI: 10.12659/AJCR.916020

Received: 2019.03.04
Accepted: 2019.03.28
Published: 2019.06.27

Gliosarcoma in a Young Filipino Woman: A Case Report and Review of the Literature

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Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 28
Final Diagnosis: Gliosarcoma
Symptoms: Foot drop
Medication: —
Clinical Procedure: —
Specialty: Neurosurgery

Objective: Unusual clinical course

Background: Gliosarcoma (GS) is a rare variant of glioblastoma (GBM), which is typically seen in patients age 40–60 years and located in the supratentorial region. We present an unusual case of GS in a young patient with an unusual presentation, which eventually led to the finding of this neoplasm.

Case Report: Our patient was a 38-year-old woman originally from the Philippines who was transferred to our institution with an isolated left foot drop that developed over the course of several months. Subsequent neuroimaging revealed an extensive mixed cystic and solid mass in the posterior mesial right frontal lobe. Subtotal surgical resection revealed a multi-lobed tumor with a malignant glioma-like surface component overlying a smooth, well-encapsulated, avascular, sarcoma-like component. Neuropathologic examination of the resected tumor revealed a biphasic histologic pattern of predominantly sarcomatous components with fewer adjacent-area glial components. Post-operatively, the patient was left with a mild worsening of left leg segmental strength. She was referred to our neurooncologist colleagues for adjuvant treatment options.

Conclusions: Our case is unique in that it represents a rare neoplasm in a patient whose demographics are atypical for this type of tumor, as well as the unusual presentation of isolated foot drop.

MeSH Keywords: Gliosarcoma • Signs and Symptoms • Young Adult

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/916020

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Gliosarcoma is classified as a WHO grade IV variant of glioblastoma, accounting for 1–8% of glioblastoma cases and less than 0.5% of all intracranial tumors [1–5]. It remains clinically difficult to distinguish GS from glioblastoma, although recent studies have identified a few distinctions, such as a higher tendency to metastasize both intra- and extra-cranially, as well as poorer survival rates of patients with GS compared to those with GBM [1,6–9]. Additionally, GS more frequently invades the periphery of cerebral lobes than does conventional GBM [2,5]. These tumors usually present at 40–60 years of age (average age, 54 years) and are more common in males, particularly those of white ethnicity [2,4,10]. They generally arise supratentorially, and are usually found in the temporal lobe followed by frontal and parietal lobes [11]. Recent literature suggests that patients with GS will usually present with symptoms of increased intracranial pressure or seizures, and less frequently with hemiparesis, hemihypoesthesia, visual field deficits, or language deficits [2,11]. Two distinct patterns of imaging findings have been described: the first is a meningioma-like appearance consisting of a well-circumscribed mass with strong homogeneous enhancement, while the second appears as a malignant glial tumor with heterogeneous and ill-defined borders with ring or patchy enhancement [2,12]. The characteristic pathologic feature is a biphasic histologic pattern consisting of a mix of glial and mesenchymal components.

We present here an unusual case of a young patient in which the only presenting symptom was foot drop, which eventually led to the finding of her brain tumor, histologically diagnosed as gliosarcoma.

Case Report

A previously asymptomatic 38-year-old woman of Filipino origin was transferred from her local healthcare facility to our institution after experiencing a fall. She complained of progressive weakness of her left foot over the course of several months, which had led to worsening ability to walk. She mentioned noticing the presence of a left foot drop. On further inquiry, she denied any other limb weakness or paresthesia, visual or speech disturbances, nausea, vomiting, or headaches. She further denied any episodes of seizures or alteration in mental status throughout this time period. Her past medical history was largely non-contributory apart from tuberculosis, which was medically treated 2 years prior to immigrating to Canada.

Neurologic examination revealed decreased segmental strength in her left lower extremity with grade 3/5 power in hip flexion, hip extension, knee flexion, and knee extension, and grade 2/5 power in dorsiflexion, plantar flexion, and extensor hallux longus dorsiflexion. A deep-tendon reflexes exam showed increased left patellar and left Achilles tendon reflex, as well as clonus in the left foot and upgoing left plantar reflex.

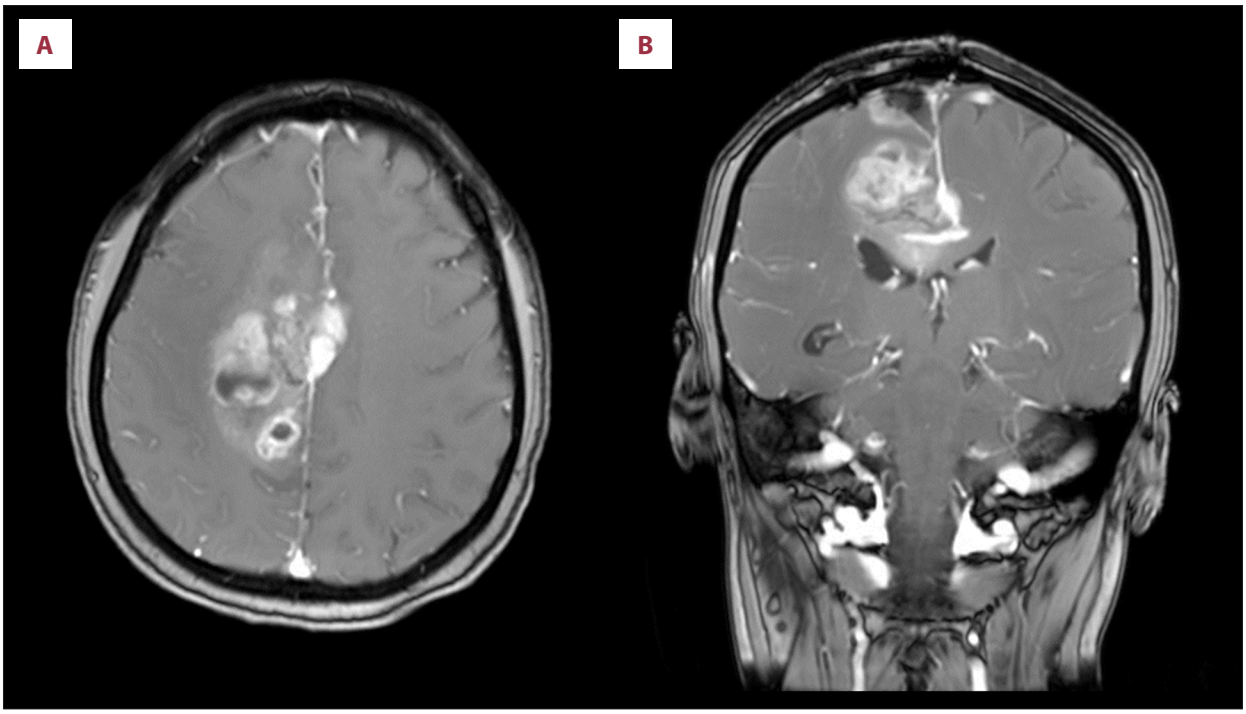

Figure 1. Contrast-enhancing solid and cystic mass seen on axial (**A**) and coronal (**B**) views of MRI, along with leptomeningeal involvement.

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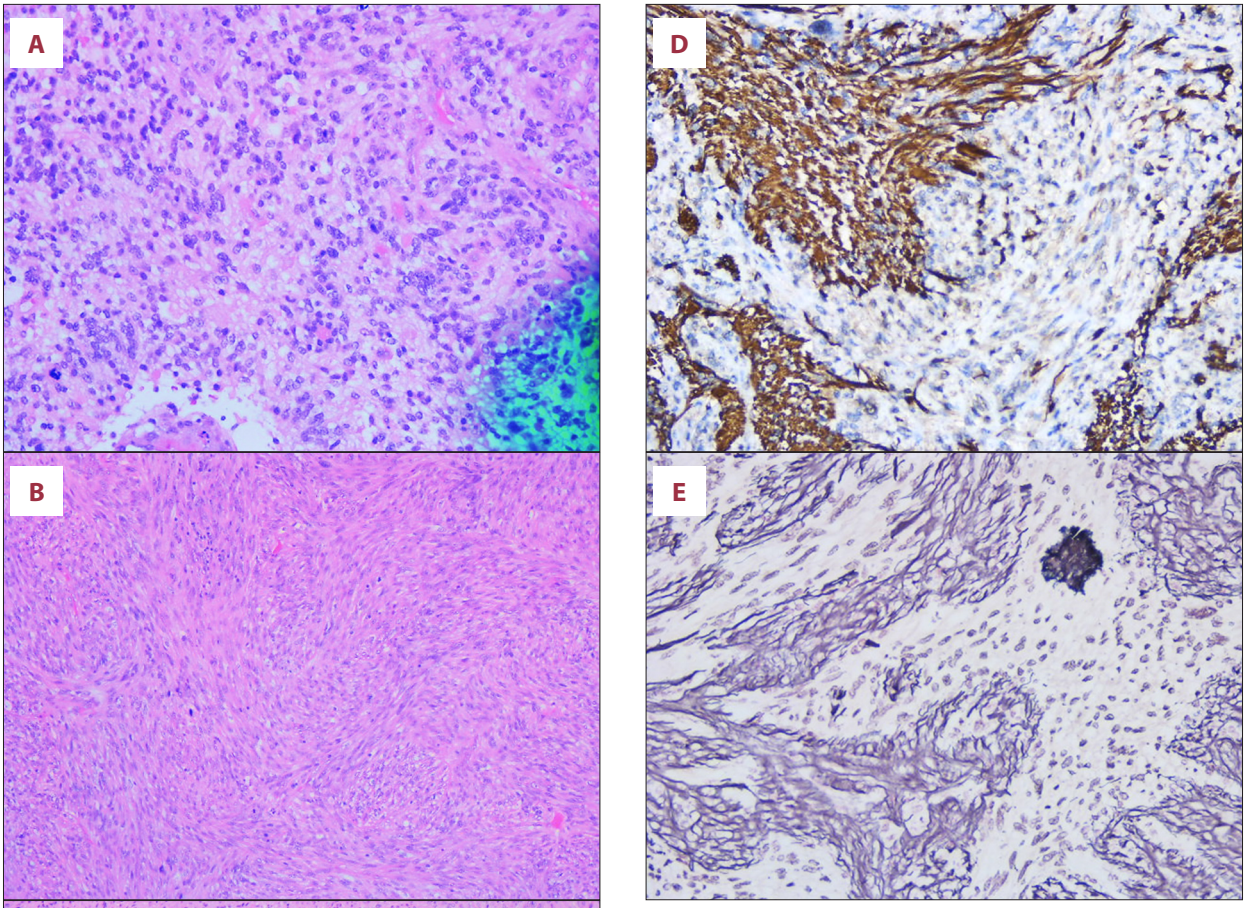

Figure 2. Histopathological examination of the tumor revealed dual presence of glial elements (**A**) and sarcomatous elements (**B**). Necrosis (**C**) was also present within the tumor. The glial elements were strongly GFAP-immunopositive (**D**), while the sarcomatous elements were reticulin-rich (**E**) but GFAP-negative.

CT head without contrast revealed an intra-axial mass at the posterior right mesial frontal lobe, with a partly cystic and partly calcified appearance. MRI head (Figure 1) confirmed the presence of an extensive mixed cystic and solid mass located in the right parafalcine region involving the posterior medial right frontal lobe. The tumor was seen extending across the midline with mild leptomeningeal involvement in the medial right sulcus and minimally in the left medial sulcus. The mass showed moderate hyperintensity on T2 and flair sequences and heterogeneous enhancement upon gadolinium contrast administration, along with mild peri-tumoral edema and dilatation of the right posterior and temporal horns.

The surgical approach was aimed at obtaining a tumor biopsy tissue for histological diagnosis in order to adapt the ensuing therapeutic approach and to relieve the mass effect of the lesion. A right posterior frontal craniotomy near the midline was performed, allowing for descent along the interhemispheric fissure. The abnormal tissue was first encountered on the medial aspect of the right frontal lobe, which had been retracted laterally. Upon initial debulking, this tissue seemed to show significant abnormality and moderate vascularity, grossly resembling a malignant glioma in macroscopic appearance. Underlying this tissue, a well-encapsulated, multi-lobed, and highly avascular structure was identified, with a rather smooth demarcation and a firm, rubbery texture. An intraoperative preliminary pathologic examination had already revealed suspected mixed cytoarchitectural patterns. The initial part of the tumor

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found on the surface of the brain was submitted for intraoperative consultation and was histologically compatible with a glioma, although this specimen did not reveal high-grade features such as microvascular proliferation or mitotic activity. The second specimen that was submitted for intraoperative consultation, however, showed histological characteristics resembling a sarcoma.

Gross total surgical resection was not deemed possible as the main bulk of the tumor was distorting the motor area of the left leg. Post-operatively, the patient did show more weakness of her left leg, remaining with grade 2 power throughout her left leg on physical examination. The clinical evolution following surgery was otherwise uneventful. She was discharged from the hospital and seen by our neuro-oncology colleagues to be evaluated for adjuvant chemoradiotherapy.

Neuropathologic examination of the tumor specimen (Figure 2) revealed features consistent with a gliosarcoma, WHO grade IV, typified by the dual presence of GFAP-positive neoplastic glial cells with adjacent sarcomatous elements. The former consisted of clusters of cells exhibiting nuclear pleomorphism and scant-to-moderate eosinophilic cytoplasm, while the latter was characterized by a wavy arrangement of spindle-shaped cells with pericellular reticulin staining. Molecular studies revealed the tumor to be IDH wild-type without MGMT promoter hypermethylation. Tests for BRAF, H3F3A/B, and TERT were also negative for mutations.

Over the next 10 months after surgery, the patient completed 6 cycles of temozolomide and 43 days of radiation treatment with a total dose of 6039.4 cGy. At the initial follow-up visits, her neurological status had improved, particularly the power of her left lower extremity, which had improved to 4/5, including dorsiflexion and plantar flexion. However, her most recent follow-up visit showed a decline in her neurological status, with more weakness in her left lower extremity, requiring use of a wheel chair, but she was still able to stand and walk for short distances. A follow-up brain MRI showed stable subtotal resection of the lesion, so the decision was made to keep her on low-dose dexamethasone to reduce the mass effect from the surrounding vasogenic edema, and we added etoposide to help stop or at least slow the growth of the tumor.

Discussion

Gliosarcoma (GS) was first defined in 1895 as a highly malignant brain tumor that resembles glioblastoma (GBM) based on the typical age of onset, location, and overall prognosis [13]. The term GS was subsequently reintroduced as referring to a subtype of GBM with a biphasic histological pattern consisting of both glial and malignant mesenchymal components [14]. The latter component of GS was first believed to originate from neoplastic transformation and proliferation of endothelial cells lining intra-tumoral vessels within malignant astrocytoma [1,15]. However, further studies did not seem to be able find conclusive evidence that could confirm the consistent presence of endothelial markers in such tumors. Later studies instead suggested a monoclonal origin of glial and sarcomatous components of GS, as both neoplastic tissues seemed to comprise cells with identical genetic aberrations (mutations in p53 and PTEN), homozygous p16 co-deletion, and co-amplification of MDM2 and CDK4 [16,17].

Gliosarcoma typically presents at age 40–60 years, with only a few studies, such as Singh et al. (2015), obtaining a median age at presentation as low as 45 years old [2,4,5,11,18], and even more unusual, rare cases of childhood onset have also been described [19]. Furthermore, the published literature suggests a male predominance for gliosarcoma, with a male-to-female sex ratio of around 1.5–2.5: 1 [4,11,18]. In our case, the patient's demographics were atypical, as very few cases of gliosarcoma in female patients younger than 40 years have been reported in the literature [10].

More interestingly, multiple studies have reported that gliosarcoma more commonly affects middle-aged men, especially those of white ethnicity. Kozak et al. (2009) reviewed 353 cases of patients diagnosed with gliosarcoma between 2002 and 2009 in their center, of which 91.5% were white, while less than 2.8% were of Asian or Pacific Islander origin [4]. More recently, Smith et al. (2018) reported nationwide cancer registry demographic descriptions identifying 85–88.9% of gliosarcoma patients were of non-Hispanic white ethnicity [4,20,21]. As such, compared to the published literature, this young Filipino woman's ethnicity is a quite atypical presentation for gliosarcoma.

Studies have also reported varying patient symptomatology upon clinical presentation. Singh et al. (2015) studied 16 cases of histologically-proven gliosarcoma (14 primary, 2 secondary) that were operated on over a 5-year period from 2009 to 2014. Of these patients, 11 (69%) had features of raised intracranial pressure, and 3 (20%) presented in an obtunded state. Five (31%) of these patients had a history of 1 or more episodes of seizures [2]. In a retrospective review by Cachia et al. (2015) of 34 cases of pathologically-diagnosed gliosarcoma (24 primary, 10 secondary), 20 (59%) patients initially presented with symptoms of headaches, while hemiparesis, seizures, and hemihypoesthesia were less common [11]. In Kakkar et al.'s (2017) review of 4 cases of gliosarcoma in younger adults, the predominant presentation in all 4 patients was headaches [10]. Although it may be clinically difficult to distinguish gliosarcoma from glioblastoma, some studies have revealed distinctive factors in gliosarcoma – mainly its increased metastatic potential, higher rates of dural attachment, and meningioma-like

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appearance [2,6,19,22]. Rare cases of gliosarcoma associated with prior history of radiation have also been described [23], but to the best of our knowledge, our patient did not have any such history of intracranial radiation.

Gliosarcoma is histologically characterized by a biphasic cytoarchitectural pattern of a combination of glial and sarcomatous components, both of which harbor identical chromosomal aberrations and cytogenetic imbalances suggestive of a monoclonal cellular origin [13]. Both tumor components show highly malignant characteristics on histopathology – high cellularity, necrosis, and high mitotic activity [1,2]. The glial component typically shows astrocytic appearance with GFAP-positive atypical cells, while the sarcomatous component is usually composed of reticulin-rich spindle-shaped cells, frequently resembling fibrosarcoma [2,3]. Rare examples of osteosarcomatous, angiosarcomatous, and rhabdomyomatous differentiation have also been described [19,24,25]. The literature seems to suggests that primary gliosarcomas are typically IDH wild-type and are usually MGMT-unmethylated [18], as was the case with our patient. In a review by Oh et al. (2016) of 36 patients with pathologic diagnosis of gliosarcoma, mutations in either IDH1 or IDH2 were absent in all 36 cases [26]. Cachia et al.'s (2015) review also did not reveal any IDH1 mutations in any of the 24 cases of primary gliosarcoma. One case of secondary gliosarcoma in this cohort was found to harbor an R132H IDH1 mutation [11].

Management of gliosarcoma continues to be based on the therapeutic approach to conventional glioblastoma – a maximal safe surgical resection followed by adjuvant radiotherapy and concurrent temozolomide chemotherapy [1,27]. Treatment options tailored specifically to gliosarcomas are difficult to determine due to the paucity of such cases and consequent lack of large-scale studies to determine more precise therapy. Patients with gliosarcoma generally have poor overall survival outcomes, with a median survival estimated at 8.3–16.7 months, based on the last 15 years of data reported [4,18,28,29]. This prognosis remains worse than that of glioblastoma, with studies such as Damodaran et al. (2014) demonstrating significantly worse median overall survival in primary gliosarcoma patients than in glioblastoma patients (9.7 months in GS *vs.* 12.2 months for GBM patients) [7,9].

Conclusions

We have presented an unusual case of histologically-proven gliosarcoma in a patient with atypical demographics (young, female, non-white), with a highly unusual presentation of isolated foot drop rather than one of the more common presentations of headaches, seizures, or hemiparesis. It is important for neurosurgeons and neuropathologists to be aware of such aggressive brain tumors in young adults and that the clinical presentation of these neoplasms may also be atypical. Treatment options for gliosarcoma are still extrapolated from glioblastoma treatment trials, which is partially due to the paucity of gliosarcoma cases. This offers an incredible opportunity to explore different chemotherapeutic regimens and different modalities of radiotherapy through multiinstitutional trials in an effort to standardize management of gliosarcomas.

Conflict of interest

None.

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