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Primary Leptomeningeal Spread of Glioblastoma : A Rare Case Report

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ABSTRACT

Background : Glioblastoma (GBM) is the most aggressive primary malignant brain tumor in adults and is classified as a CNS WHO grade 4 diffuse astrocytic tumor. Leptomeningeal spread (LMS) represents one of its most severe complications, occurring in up to two-thirds of patients when assessed using advanced imaging or autopsy. However, clinically symptomatic LMS is reported in only 2–4% of cases and is often underrecognized due to overlapping symptoms with tumor progression. Primary, or de novo, LMS at the initial presentation of GBM is exceedingly rare and poses significant diagnostic challenges, particularly because early manifestations may mimic infectious or inflammatory meningoencephalitis. Advances in MRI techniques have improved the early detection of leptomeningeal involvement.

Case Presentation: A woman in her 40s presented with an unknown-onset tonic–clonic seizure and a 10-month history of recurrent seizures despite antiepileptic therapy. Her symptoms had progressed to chronic headaches, left-sided weakness, dysarthria, and declining consciousness. Neurological examination revealed papilledema, left central facial palsy, and left hemiparesis. CT imaging demonstrated a heterogeneous right parietal mass, while advanced MRI with spectroscopy identified an extra-axial enhancing lesion with cystic components suggestive of high-grade glioma with possible leptomeningeal involvement. Gross total tumor resection was performed. Histology revealed hypercellularity, pleomorphic anaplastic glial cells, palisading necrosis, and microvascular proliferation, while immunohistochemistry showed IDH-1 positivity, ATRX loss, and negative p53, confirming Astrocytoma, IDH-1 mutant, CNS WHO grade 4. Five days postoperatively, the patient developed worsening consciousness without radiologic evidence of hemorrhage or increased intracranial pressure. Her condition continued to decline, and she passed away one month later due to multiorgan failure following a septic infection.

Conclusion: This case demonstrates the rare occurrence of primary LMS as the initial manifestation of GBM. Early leptomeningeal involvement should be considered in patients presenting with multifocal neurological deficits or rapidly progressive symptoms. Advanced MRI techniques are essential for early detection, particularly when clinical findings overlap with other intracranial pathologies. Although IDH mutation is often associated with improved prognosis, this advantage may diminish in grade 4 astrocytomas, which can still exhibit highly aggressive behavior. Prompt recognition and comprehensive management are critical, although overall prognosis remains poor.

KEYWORDS: Astrocytoma IDH-mutant; glioblastoma; refractory seizures; status epilepticus; mass effect

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INTRODUCTION

Glioblastoma (GBM) is the most common and most aggressive primary malignant brain tumor in adults, accounting for approximately 45–50% of all malignant gliomas[1,5]. It is classified as a CNS WHO grade 4 diffuse astrocytic tumor, characterized by rapid proliferation, infiltrative growth, extensive necrosis, and microvascular proliferation[5,6]. Despite multimodal therapy consisting of maximal safe resection followed by radiotherapy with temozolomide, GBM remains associated with poor prognosis, with median survival ranging from 12 to 18 months[5,7]. The aggressive biological behavior of GBM predisposes patients to various complications as the disease progresses, including tumor recurrence, intracranial hypertension, seizures, and leptomeningeal spread (LMS).

LMS represents dissemination of malignant glioma cells into the cerebrospinal fluid (CSF) pathways and leptomeningeal surfaces, constituting one of the most devastating end-stage complications of GBM. Studies have shown that up to two-thirds of GBM patients develop LMS within two years, although clinical detection remains limited[2,3]. The reported prevalence of clinically symptomatic LMS in GBM ranges from 2% to 4%, but this likely underestimates the true incidence because most cases remain subclinical or are difficult to identify on routine imaging (2–4,8). Moreover, LMS is frequently underdiagnosed because its manifestations like headache, cognitive decline, multifocal deficits, or seizures were overlap with common features of tumor progression or treatment-related complications[3,4].

Typically, LMS occurs late in the disease course and is detected during tumor recurrence or progressive neurological decline. Approximately 90% of LMS cases are diagnosed after GBM progression, rather than at initial presentation[2,4]. Primary, or de novo, LMS at the time of first GBM diagnosis is exceedingly rare and has been documented only in isolated case reports. Such presentations pose a major diagnostic challenge, particularly because early radiologic findings may mimic infectious, inflammatory, or demyelinating conditions[4,8]. Recent advances in neuroimaging, particularly contrast-enhanced MRI, FLAIR suppression, diffusion-weighted imaging, and MR spectroscopy, have improved early detection of leptomeningeal involvement in gliomas[3,8].

In this report, we present a rare case of primary leptomeningeal spread as the initial manifestation of glioblastoma, diagnosed early with advanced MRI techniques. This case contributes to growing evidence that LMS may occur earlier in the disease course than previously assumed and underscores the importance of considering LMS in atypical or multifocal neurological presentations of GBM.

CASE REPORT

A female patient in her 40s presented to the emergency department (ED) with unknown onset tonic-clonic seizure. The patient had experienced similar types of seizures in the last 10 months which relapsed around once or twice monthly, and was treated using sodium valproate 500 mg twice daily. However, the seizure frequency intensified during the last month. In the ED, the patient experienced focal clonic seizure in her right arm for 4 times with a total duration of 10 minutes. The patient remained unconscious during the seizure. Her present history was significant for progressively worsening headache in the past 2 years, followed by a progressively worsening left-sided body weakness in the past year, slurred speech and gradual decrease of consciousness for one week prior to admission.

She had a 5-year history of monthly hormonal contraceptive injection, and no significant comorbidities or family history. The patient was unconscious with fluctuating GCS (E2V2M5 – E3V4M5) and her vital signs were stable. Neurological examination revealed a papilledema on both eyes, left facial palsy central type, and left-sided motor weakness. Her laboratory results were within normal limit. A head Computed Tomography Scan with Contrast revealed a mixed density mass with irregular border in the right parietal lobe, with a suspicion of high-grade astrocytoma. A head Advanced Magnetic Resonance Imaging with Spectroscopy revealed an extra-axial heterogenous solid mass with cystic component in the right parietal lobe, suggestive of a meningeal glioblastoma (Figure 1).

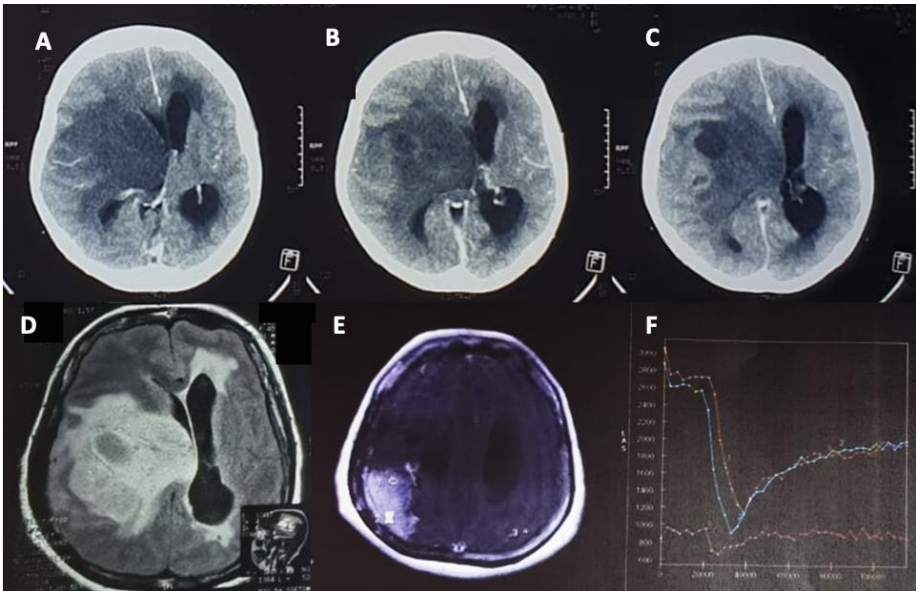

Figure 1. Neuroimaging of the patient suggestive of a primary CNS tumor on Head CT Scan with contrast (A, B, C); Head MRI with Contrast (D, E); and spectroscopy curve (F).

Following a clinicopathologic conference of this case, this patient was planned for craniotomy for accurate diagnosis and surgical removal of the tumor. A gross total removal of the tumor was performed. Intraoperative frozen biopsy and paraffin coupe examination revealed a hypercellular tissue consisted of anaplastic glial cells with oval and pleomorphic nuclei, and dense chromatin. Palisading necrosis and microvascular proliferation were also observed (Figure 2, A and B). Immunohistochemical staining was positive for isocitrate dehydrogenase (IDH-1) in the cytoplasm, negative for alpha thalassemia mental retardation X (ATRX) gene and p53 mutation in the nuclei (Figure 2, C-E). The final pathological result was Astrocytoma, IDH-1 mutant, CNS WHO grade 4.

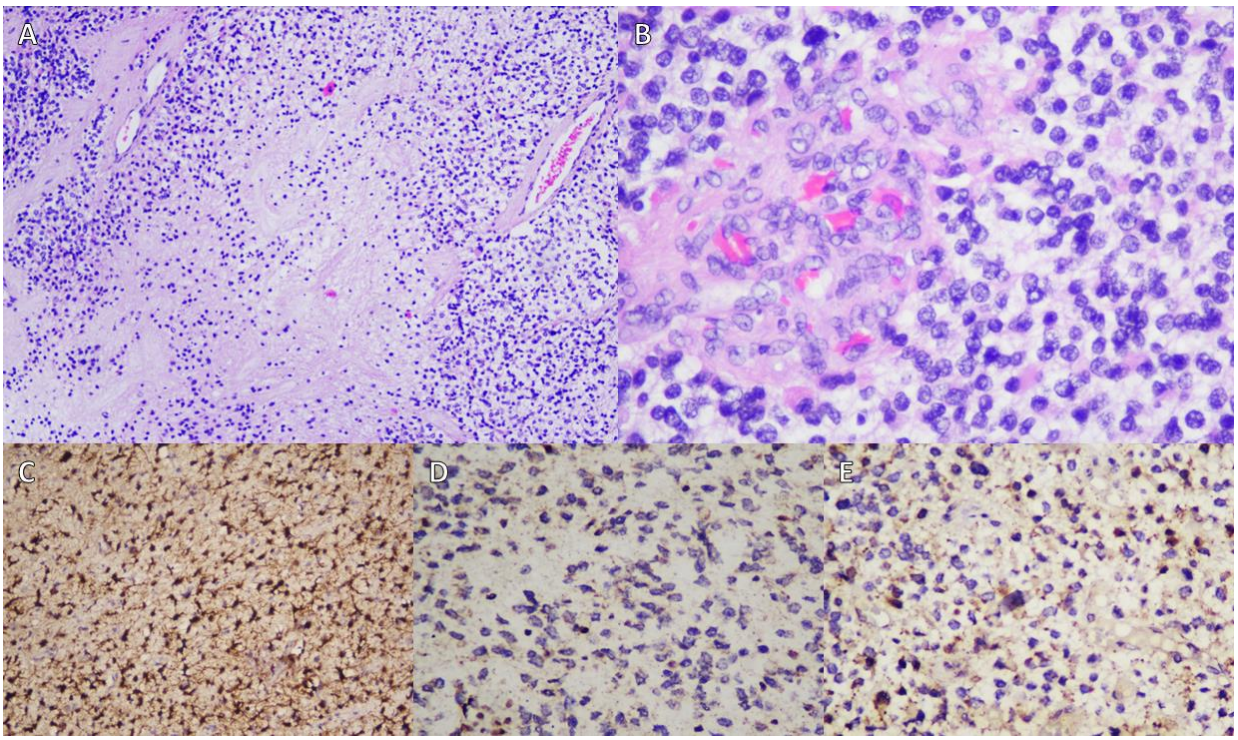

Figure 2. Microscopic examination of the tumor revealed palisading necrosis (100x) (A) and diffuse infiltrative growth pattern with pleomorphic nuclei and microvascular proliferation (400x) (B). Immunohistochemical staining of the tumor positive IDH-1 antibody (200x, C), negative ATRX antibody (400x, D) and negative p53 antibody (400x, E). This finding suggestive of an astrocytoma, IDH-1 mutant, CNS WHO grade 4.

Following the tumor resection, the patient was planned for chemoradiation therapy based on the pathological findings. However, the patient became stuporous and unable to follow verbal command on the fifth day after surgery. An evaluation computed tomography scan of the head revealed no signs of raised intracranial pressure nor intracranial hemorrhage. Her condition gradually deteriorated and she passed away one month later due to multiorgan failure following a septic infection.

DISCUSSION

Glioblastoma (GBM) is the most aggressive primary malignant brain tumor in adults and is classified as a CNS WHO grade 4 diffuse astrocytic tumor characterized by rapid proliferation, extensive necrosis, and microvascular proliferation[1,5]. Despite significant advances in multimodal treatment including maximal safe resection and chemoradiation, GBM continues to carry a poor prognosis with median survival of 12–18 months[1,6,7]. One of the most devastating complications of GBM is leptomeningeal spread (LMS), which represents dissemination of malignant glial cells into the CSF pathways and leptomeninges.

LMS in GBM is increasingly recognized as part of its natural disease progression. Large cohort studies demonstrate that up to two-thirds of GBM patients may develop LMS within two years when assessed through autopsy or advanced imaging, although the clinically recognized rate is much lower[2,3]. Symptomatic LMS is reported in only 2–4% of cases but is widely believed to be underdiagnosed due to nonspecific clinical features, overlap with tumor progression, and limitations of conventional imaging[2,4,8]. The mechanisms of LMS are multifactorial. Tumor cells may access the subarachnoid space through: (1) Direct invasion from cortical or ventricular surfaces, (2)Perivascular or perineural spread, or (3) Disruption of the ependymal lining, especially in high-grade lesions with necrosis and angiogenesis[2,8]. In this case, the tumor's right parietal location, heterogeneous enhancement, necrotic areas, and mass effect likely increased the risk of early leptomeningeal involvement.

Most LMS cases occur late in the disease course, with 90% diagnosed after GBM recurrence[2,4]. The presentation of LMS at the time of initial GBM diagnosis is exceedingly rare and has been documented only in isolated case reports. Early LMS is diagnostically challenging because clinical symptoms such as headache, seizures, cognitive decline, and multifocal deficits mimic intracranial hypertension, tumor progression, or treatment-related effects[3,4].

This patient presented with longstanding headaches, progressive unilateral weakness, dysarthria, fluctuating consciousness, and increasing seizure frequency over recent months. The presence of papilledema indicated elevated intracranial pressure, consistent with mass effect and possible CSF flow impairment.

Conventional CT may suggest high-grade lesions but has limited sensitivity for LMS. MRI is the imaging modality of choice, yet even standard contrast-enhanced MRI may miss early leptomeningeal disease. Advanced MRI techniques, including FLAIR suppression, DWI/ADC analysis, MR spectroscopy, and multiplanar postcontrast sequences, substantially improve diagnostic accuracy[3,8]. In this case, advanced MRI with spectroscopy detected a heterogeneous extra-axial enhancing lesion with cystic components, raising suspicion for a high-grade tumor with potential leptomeningeal involvement. This early detection played a

key role in directing the decision for surgical intervention.

Histopathological examination confirmed features typical of high-grade glioma: hypercellularity with anaplastic glial cells, pleomorphic nuclei, palisading necrosis, microvascular proliferation. IHC also showed: Positive IDH-1, Loss of ATRX, Negative p53, that supporting the diagnosis of Astrocytoma, IDH-1 mutant, CNS WHO grade 4. While IDH-mutant status is generally associated with a better overall prognosis and younger patient age, its presence does not preclude aggressive tumor biology, especially when accompanied by extensive necrosis and mass effect.

Despite gross total resection, the patient developed stupor on postoperative day 5 without radiologic evidence of hemorrhage or increased intracranial pressure. Postoperative neurological decline in GBM may result from early LMS–related CSF pathway dysfunction, metabolic derangement, systemic infection, postoperative inflammation or edema, microcirculatory tumor infiltration not visible on CT. In this case, the patient later developed septic infection leading to multiorgan failure, a known postoperative complication that dramatically worsens outcomes.

CONCLUSION

Primary LMS can occur at initial GBM diagnosis, although rare. Advanced MRI techniques are essential to identifying early leptomeningeal involvement. Clinical symptoms alone are insufficient to distinguish LMS from GBM progression; vigilance is required in patients with multifocal deficits or rapidly worsening status. Although IDH-mutant astrocytomas are generally associated with a more favorable prognosis, this advantage may be lost once the tumor reaches grade 4, which can still exhibit highly aggressive behavior. Early recognition and intervention provide the best opportunity for improved outcomes, though prognosis remains guarded.

ETHICAL CONSIDERATIONS

Written informed consent for publication of clinical details and images was obtained from the patient's family. All images have been anonymized.

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