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Case Report

Glioblastoma mimicking autoimmune meningitis in an adult: A complex diagnostic challenge

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ABSTRACT

Background: Glioblastoma multiforme (GBM) is a highly aggressive primary brain tumor with a poor prognosis. It commonly affects the brain and rarely spreads outside the central nervous system owing to barriers like the blood–brain barrier. We present a rare case of GBM with atypical features mimicking autoimmune meningitis, complicating the diagnosis.

Case Description: A 45-year-old previously healthy man presented with persistent headaches, dizziness, vomiting, neck pain, diplopia from bilateral abducens nerve palsy, and cognitive dysfunction. The cerebrospinal fluid analysis did not confirm meningitis, although initial clinical and radiological findings suggested autoimmune meningitis. Head magnetic resonance imaging (MRI) showed postcontrast leptomeningeal enhancement and meningeal thickening. A spinal MRI revealed a contrast-enhancing lesion at the L1 level with leptomeningeal enhancement of the spinal cord. Despite empirical steroid therapy, his condition worsened, resulting in severe neurological deficits and impaired consciousness. A biopsy confirmed GBM through L1-2 laminectomy. Although adjuvant therapy was scheduled, his health rapidly declined, and he passed away on the 24th day of admission before receiving chemotherapy or radiotherapy.

Conclusion: GBM can rarely present with noticeable symptoms and radiological features resembling autoimmune meningitis, posing diagnostic challenges. GBM cases involving spinal dissemination typically have a poorer prognosis, emphasizing the necessity of thorough diagnostic strategies. These should encompass histopathological biopsy and advanced imaging for optimal management, as delayed intervention significantly impacts survival. This report highlights the importance of maintaining a high level of suspicion for GBM and prompt intervention, including biopsy, in the presence of atypical clinical, radiological, and laboratory signs suggestive of meningitis.

Keywords: Atypical presentation, Autoimmune meningitis, Cerebrospinal fluid analysis, Glioblastoma multiforme, Spinal metastases

INTRODUCTION

Glioblastoma multiforme (GBM) is a prevalent malignant primary brain tumor, constituting 12–15% of all intracranial neoplasms.[1] It is recognized as the most aggressive form of glial tumor and is often linked to a poor prognosis, with a median survival of 11–17 months, despite advancements in multimodal treatment strategies involving radiation therapy, temozolomide administration, and

maximal safe surgical resection. For certain patients, tumor-treating field therapy and oncolytic virus therapy have enhanced the prognosis of GBM.[1,4,11,14,15] While GBM typically manifests as an intramedullary brain tumor, progress in early detection and therapeutic approaches have resulted in improved median patient survival and increased detection of extracranial GBM metastases.[3,13] The majority of GBM metastases occur within the central nervous system (CNS) through leptomeningeal or intramedullary spread to the spinal cord, resulting in spinal-drop metastases.[3,8-11,13-15] Despite the critical importance of early GBM diagnosis, unusual presentations such as leptomeningeal spread to the spine can present significant diagnostic challenges. This report presents a case of GBM with an aggressive course mimicking autoimmune meningitis, highlighting its diagnostic complexities and advocating for a comprehensive diagnostic approach.

CASE PRESENTATION

Initial presentation

A 45-year-old previously healthy man presented with a 1-week history of persistent headache and intermittent dizziness. He was diagnosed with migraine after a head computed tomography (CT) scan revealed no abnormal lesions. Sumatriptan was administered, but it proved ineffective as his symptoms progressed rapidly over 2 weeks, with new manifestations including vomiting, neck pain, speech disturbance, and diplopia caused by bilateral abducens nerve palsy. The patient was admitted to the Department of Neurology at our hospital for further assessment.

Neurological examination

On admission, neurological examination revealed cognitive dysfunction, sensory aphasia, and bilateral ataxia in the lower extremities. A stiff neck was observed, but the motor and sensory systems were intact.

Laboratory examination

Initial investigations revealed leukocytosis of 5.00×10^3/mL with 67% polymorphs, 28% lymphocytes, 5.4% monocytes, and 1.9% eosinophils. The results of tests for infectious disease, immunoglobulin, thyroid function, autoantibodies, and tumor markers were all normal or negative. Tests for antibodies against N-methyl-D-aspartate (NMDA), leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), and myelin oligodendrocyte glycoprotein (MOG) were negative, indicating no evidence of immunodeficiency. Cerebrospinal fluid (CSF) analysis showed an opening pressure of 30 mmH_2O and a cell count of 58/mm^3, protein level of 1,310 mg/dL, and glucose level of 53 mg/dL. There were no increases in CSF adenosine deaminase (ADA), angiotensin converting enzyme (ACE), or soluble interleukin-2 receptor (sIL-2R) levels. CSF polymerase chain reaction (PCR), smears, cultures, and India ink preparations showed negativity for pathogens. Cytology revealed a predominance of lymphocytic inflammatory cells (Class II) with no atypical cells. Head magnetic resonance imaging (MRI) revealed hyperintense changes in the bilateral mesial temporal lobes, including the hippocampal gyrus and periventricular area surrounding both anterior horns of the lateral ventricles, as well as the choroid plexus of both lateral ventricles on Fluid attenuated inversion recovery (FLAIR) [Figures 1a and b]. In addition, postcontrast leptomeningeal enhancement and thickening of the meninges, involving the brainstem and cerebellar sulci, were observed [Figures 1c and d]. An additional MRI scan of the whole spine revealed leptomeningeal thickening and postcontrast enhancement around the entire spinal cord, along with an in-core contrast-enhancing mass lesion at the L1 level [Figure 2]. Various systemic examinations, including CT and gastrointestinal endoscopy, revealed no findings suggestive of cancer.

Diagnostic workup

Possible differential diagnoses at this time included inflammatory diseases of the CNS, such as autoimmune meningitis and herpes encephalitis, based on clinical symptoms, laboratory findings, and radiological findings, although CSF findings could not confirm meningitis.

Treatment and progression

Empirical treatment for herpes encephalitis and autoimmune meningitis was initiated with antiviral medication (acyclovir 500 mg every 8 h for 2 weeks), and steroid pulse therapy (intravenous methylprednisolone 1000 mg for 3 days) was administered. Following steroid pulse therapy, the patient's symptoms, including headache and nausea, temporarily improved; however, a few days later, they rapidly worsened, resulting in an inability to ingest food. The patient also reported severe neck and lower back pain. One week after the first steroid pulse therapy, a second course of steroid pulse therapy was administered following the same protocol. However, the patient showed no improvement, and his neurological condition continued to deteriorate. As the condition progressed, the patient developed bladder and rectal dysfunctions, accompanied by motor weakness in the bilateral lower extremities, which impaired his ability to stand and walk. At this stage, autoimmune meningitis was considered unlikely, and a biopsy of the spinal cord lesions was planned to obtain a definitive diagnosis. Thirteen days after admission, a biopsy of the spinal mass lesion was performed through L1–2 laminectomy. Upon dural opening, swelling of the conus medullaris and cauda equina was observed. A grayish, soft, hemorrhagic tumor was identified on the ventral side

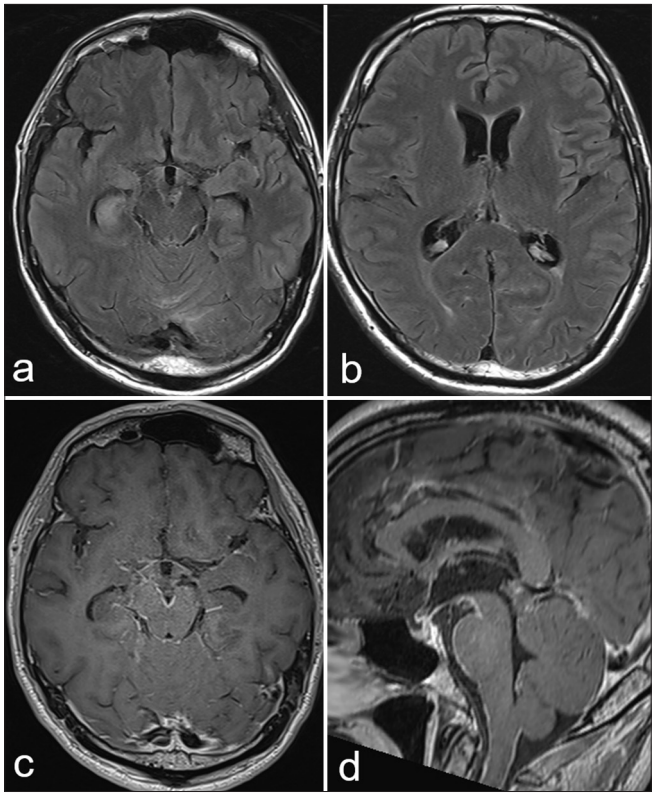

Figure 1: (a and b) Axial images of the brain magnetic resonance imaging in Fluid attenuated inversion recovery (FLAIR) show hyperintense changes of the bilateral mesial temporal lobe and periventricular area surrounding both frontal horns of lateral ventricles, as well as choroid plexus. (c and d) Postcontrast leptomeningeal enhancement and thickening of meninges involving the brainstem can be seen.

of the conus medullaris and cauda equina [Figure 3]. The tumor was strongly adhered to the surrounding nerves, and its boundaries were indistinct. The patient tolerated the procedure well without any surgical complications, and histopathological examination confirmed the diagnosis of GBM, with isocitrate dehydrogenase (IDH-1) negativity, alpha-thalassemia/mental retardation (ATRX) positivity, p53 positivity, oligodendrocyte lineage transcription factor (OLIG2) positivity, and a Ki-67 proliferation index of 50–60% [Figure 4]. Postoperatively, adjuvant therapy involving radiotherapy and chemotherapy with temozolomide was planned; however, the patient's symptoms deteriorated rapidly before treatment could begin. The patient died 11 days after surgery and 24 days after hospital admission before receiving chemotherapy or radiotherapy.

DISCUSSION

Mechanism of extracranial extension of GBM

Primary spinal GBM is a rare entity, and intracranial dissemination from the spinal GBM is extremely rare and has been reported infrequently.[2,12] In the present case, neuroimaging showed simultaneous involvement of both the intracranial and spinal cord regions; however, intracranial symptoms appeared first, followed by symptoms related to the spinal lesions. Considering the clinical course, it is reasonable to conclude that the primary intracranial lesions had disseminated to the spinal cord. GBM typically originates in the subcortical white matter and spreads along white matter tracts.[4,13] Initially, the extracranial spread of GBM, like spinal drop metastasis, was considered rare because of physical barriers, such as the thickened basement membrane, dura mater, and blood–brain barrier.[10] However, approximately 2% of patients who undergo surgical resection of GBMs later develop spinal drop metastasis.[11] While various hypotheses exist regarding spinal cord dissemination, the specific mechanisms and risk factors for its spread remain uncertain. The primary mechanism is believed to result from a surgical breach of the blood–brain barrier or ventricular opening, leading to tumor cell dissemination through the CSF, potentially facilitating tumor seeding.[10,15] Diagnosing spinal drop metastasis before surgery is uncommon;[3,8-11,13-15] However, the literature suggests that ventricular invasion, ventricular epithelial rupture, and decreased immune function may contribute to distant GBM metastases, including spinal drop metastasis.[3,4,10,11] Leptomeningeal spread is hypothesized to occur during the later stages of the disease. However, leptomeningeal spread to the spinal cord was observed at the time of the initial presentation, which is extremely rare.[11] Furthermore, CSF assessment is crucial for diagnosing dissemination, with the presence of tumor cells in the CSF being the most reliable finding; however, Chen *et al*. reported that cytology often yields false negatives.[4] In the present case, no malignant cells were detected in the CSF, potentially complicating the diagnosis. This suggests that while the exact mechanism of extracranial extension, in this case, remains inconclusive, it is vital for neurosurgeons to acknowledge that drop metastasis can occur as part of the natural progression of the disease, independent of surgical manipulation. Hence, GBMs have the potential to metastasize at diagnosis, warranting consideration of spinal imaging in patients with suspected leptomeningeal spread.

Glioblastoma mimicking autoimmune meningitis

GBM typically presents with irregular ring-like enhancement on postcontrast T1-weighted MRI, central necrosis, and surrounding edema. It causes a mass effect, infiltrates surrounding brain tissue, and may show restricted diffusion and vascular enhancement due to its high vascularity. On the other hand, MRI findings of meningitis typically include leptomeningeal enhancement on postcontrast T1-weighted images and mild cerebral edema on T2 and FLAIR images. There is usually no mass effect, although severe cases can show diffuse involvement of the meninges and brain parenchyma.

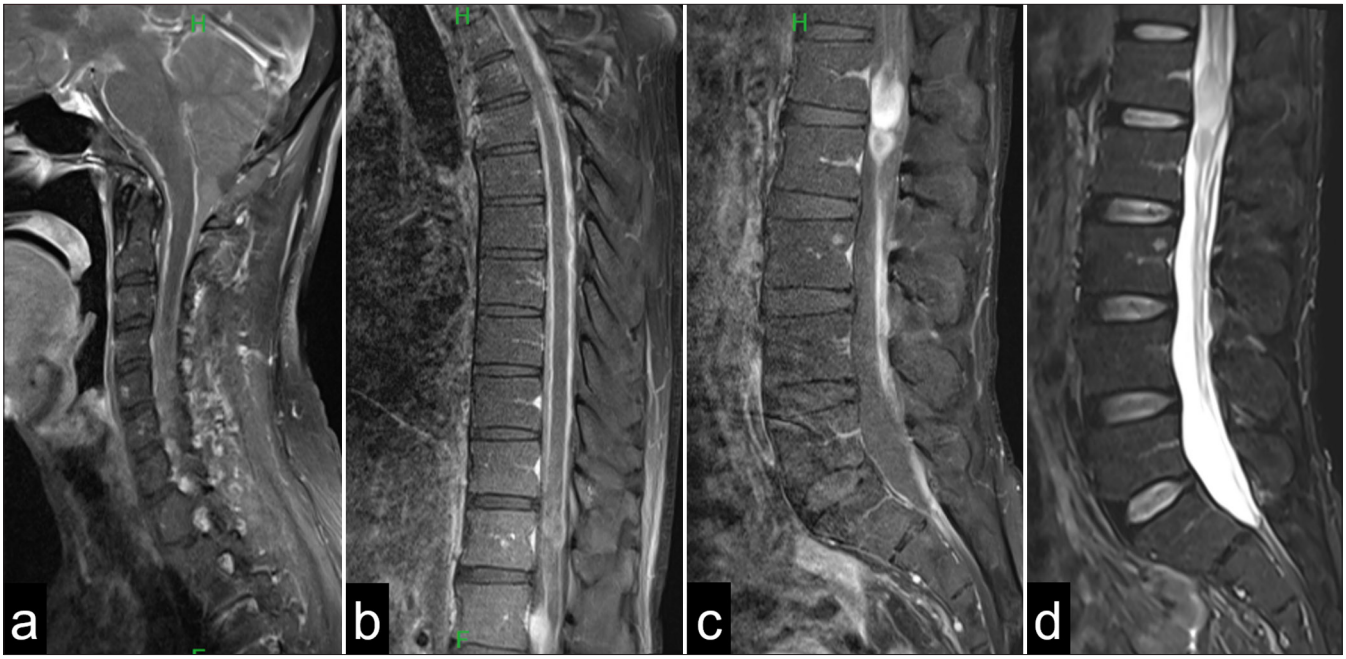

Figure 2: Sagittal magnetic resonance imaging of the (a) cervical spine, (b) thoracic spine, and (c and d) lumbar shows leptomeningeal thickening and postcontrast enhancement around the entire spinal cord. In addition, T2-weighted images reveal a (c) contrast-enhancing and (d) high-intensity mass lesion at the L1 level.

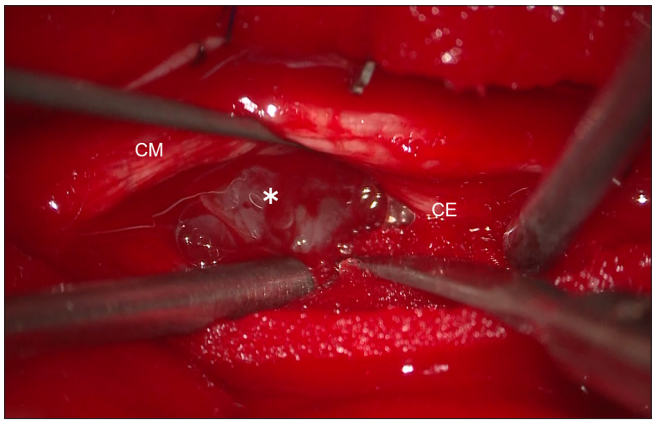

Figure 3: Intraoperative photograph of the spinal cord tumor taken under an operating microscope. The image displays swollen conus medullaris (CM) and cauda equina (CE), along with a grayish, soft, and hemorrhagic tumor ( ) present in the operative field.

In this case, the atypical radiological findings deviated from typical characteristics of GBM, such as irregular margins, contrast enhancement, central necrosis, and extensive surrounding edema, which complicated the diagnosis.[5] The diffuse postcontrast leptomeningeal enhancement of the meninges involving the brainstem and spinal cord resembled meningitis rather than brain tumors. Leptomeningeal GBM can manifest symptoms overlapping with autoimmune meningitis or infectious encephalitis, further complicating diagnosis.[7] This overlap led to a diagnostic delay, exacerbated by the initial conservative treatment for meningitis. The median survival for patients with intracranial GBM ranges from approximately 11–17 months, whereas survival postdiagnosis of leptomeningeal metastasis significantly decreases to an average of 2–3 months.[14] Patients with spinal cord dissemination of GBM typically experience rapid deterioration, and diagnostic delays often result in predominantly palliative management. Timely and accurate diagnosis is pivotal for improving the outcomes. The delay in diagnosis, in this case, precluded timely administration of adjuvant therapies, such as radiotherapy or chemotherapy. Jang *et al*. reviewed 41 cases of primary GBM with spinal cord dissemination and reported a mean overall survival duration of 4.94 months (range: 1–14.9 months). In addition, 35 out of 41 cases showed no malignant cells in CSF analysis, similar to the present case.[6] Their study also highlights the extremely poor prognosis of GBM with spinal cord dissemination, along with the difficulties in diagnosis with laboratory and radiological examinations. Therefore, histopathological confirmation of CNS lesions remains the diagnostic gold standard for complex cases. Biopsy should be promptly pursued when a definitive diagnosis is challenging. In addition, molecular analysis after histopathological diagnosis is crucial for optimizing treatment strategies.[10] The present case highlights the necessity of considering a wide range of differential diagnoses for atypical neurological presentations. Early and precise diagnosis through advanced imaging techniques and histopathological evaluation is critical. Attention to the rare and atypical presentations of GBM is critical for ensuring prompt and effective treatment.

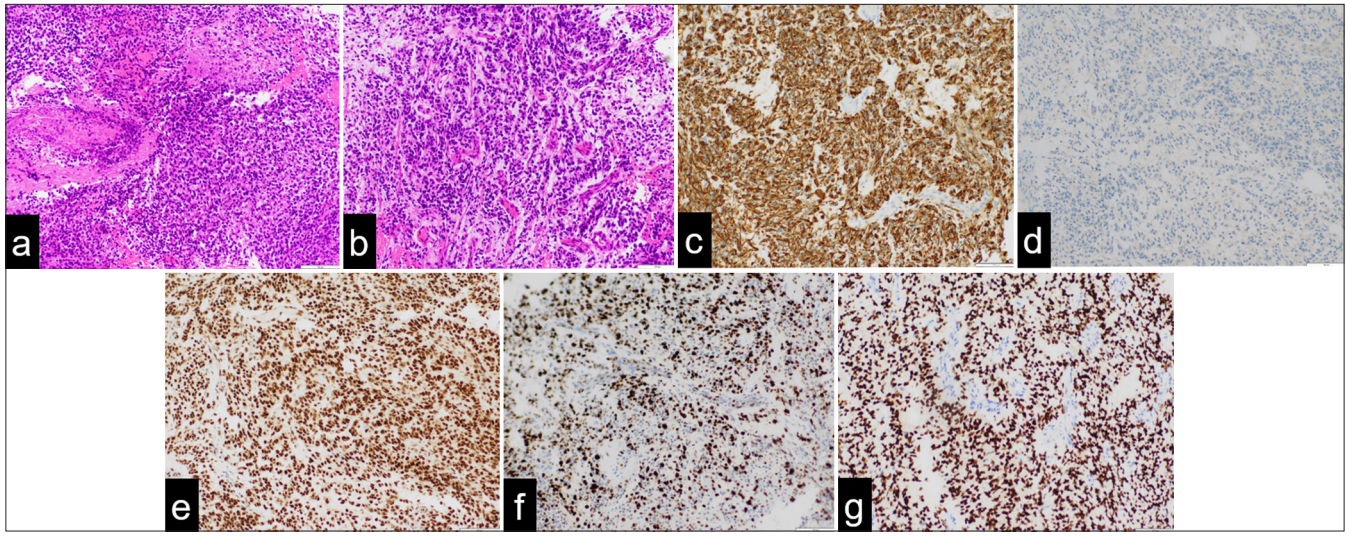

Figure 4: Histopathological findings demonstrate (a) medullary proliferation of tumor cells with variably shaped nuclei and numerous mitotic figures in hematoxylin and eosin (H and E) staining. (b) Diffuse malignant astroglia neoplasm with pseudopalisading patterns around areas of necrosis is observed with H and E staining. (c) Neoplastic cells show high mitotic activity and immunoexpression of glial fibrillary acidic protein. (d) Isocitrate dehydrogenase (IDH) staining reveals that the tumor is IDH wild-type, confirming the absence of IDH1 mutations. (e) Immunohistochemistry reveals strong nuclear staining for alpha-thalassemia/mental retardation (ATRX). (f) The Ki-67 immunolabeling index is approximately 60%. (g) Oligodendrocyte lineage transcription factor 2 (OLIG2) positivity indicates glial lineage. (Original magnification: ×20).

Learning points

We reported a case with an atypical clinical presentation of GBM mimicking autoimmune meningitis in an adult. It is difficult to establish a correct diagnosis without a biopsy in the initial stage because these pathologies share common clinical and radiological features. When some atypical or undoubted findings of meningitis or encephalitis are observed in laboratory examinations, including CSF analysis, the possibility of GBM should be considered even if autoimmune meningitis or viral encephalitis is radiologically diagnosed. Early definitive diagnosis and treatment are extremely important for malignancies such as GBM; therefore, a biopsy should be performed without hesitation to avoid misdiagnosis or delayed diagnosis.

CONCLUSION

Leptomeningeal diffuse GBM presents symptoms and imaging findings similar to those of autoimmune meningitis. The possibility of GBM should be considered if empirical treatment is ineffective, a definitive meningitis diagnosis is inconclusive from CSF examination, and symptoms deteriorate rapidly. GBM with spinal dissemination has a poor prognosis, necessitating prompt definitive diagnosis. Surgical biopsy for histopathological diagnosis should be promptly conducted without hesitation. Healthcare professionals managing CNS disorders must maintain high vigilance for timely diagnosis and effective management of these complex cases.

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