Case report of a unique phenomenon: leptomeningeal spread in glioblastoma multiforme

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Abstract

Leptomeningeal spread (LMS) of glioblastoma multiforme (GBM) is a rare event, presenting challenges in both diagnosis and treatment. Here, we describe the case of a 59-year-old GBM patient who experienced LMS during his treatment. Despite multimodal therapy, including surgery, chemotherapy, and radiotherapy, the patient's condition rapidly deteriorated. The case illustrates the difficulty in treating GBM and the restricted ability of available therapies to stop LMS. This manifestation is uncommon, which highlights the need for increased awareness, ongoing study, and development of tailored treatments. Key factors influencing LMS include tumour size, age, and anatomical location. Diagnostic challenges arise due to the rarity of LMS in GBM and its atypical presentation. Therapeutic interventions targeting LMS are lacking, with poor prognosis and low survival rates. To improve patient outcomes, more studies should be done on creating efficient treatment regimens and figuring out the markers associated with LMS development in GBM.

Keywords: Glioblastoma Multiforme, Radiation, Leptomeningeal.

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Introduction

Leptomeningeal spread is the infiltration of cancer cells into the layers of tissues surrounding the brain and spinal cord, collectively known as the leptomeninges.[1] The most aggressive and malignant type of primary brain tumours, Glioblastoma multiforme (GBM) is known for its continuous development and invasiveness.[2] The reported rates of leptomeningeal spread in GBM range from 2% to 3.1% in malignant gliomas, with frequency linked to age and tumour size.[3] Since there are no established guidelines for treating LMS in GBM patients, the condition is regarded as an end-stage consequence. With a mean of 4.7 months, the post-diagnosis survival period ranged from 0.2 to 9.7 months.[4]

There is a dearth of literature on this phenomenon and this case report aims to expand the limited literature on leptomeningeal dissemination in GBM by thoroughly examining a single instance. The goal is to clarify the distinctive characteristics and challenges linked to this uncommon manifestation by means of a comprehensive review of clinical presentations, radiographic findings, and histological studies.

Informed consent from the patient's brother and approval of the IRB committee was obtained for this study.

Case Report

A 59-year-old middle-aged man with a known history of ischaemic heart disease and diabetes mellitus sought medical attention in November 2023 at Jinnah Postgraduate Medical Centre, Karachi. He complained of severe headaches and diplopia that had progressively worsened over the past two weeks. Neurological examination revealed no focal deficits, while imaging studies, including MRI, identified a 30x35x37mm solitary mass consistent with GBM grade 4 in the right temporal lobe. T1, T2W, and FLAIR images revealed an unusual signal intensity within the lesion, with enhanced solid and cystic components. Notably, marked perilesional oedema was causing cortical effacement, ventricular compression, and midline shift (Figure 1a).

This case was discussed in the multidisciplinary neuro-oncology tumour board meeting, and craniotomy was recommended for accurate diagnosis and excision of the tumour. The patient underwent neuronavigation-guided right temporal craniotomy and temporal lobectomy. During surgery, the frozen section was suggestive of high-grade glioma, and intraoperative findings showed a firm, greyish-coloured, highly vascular lesion with multiple thrombosed vessels adherent to the posteromedial

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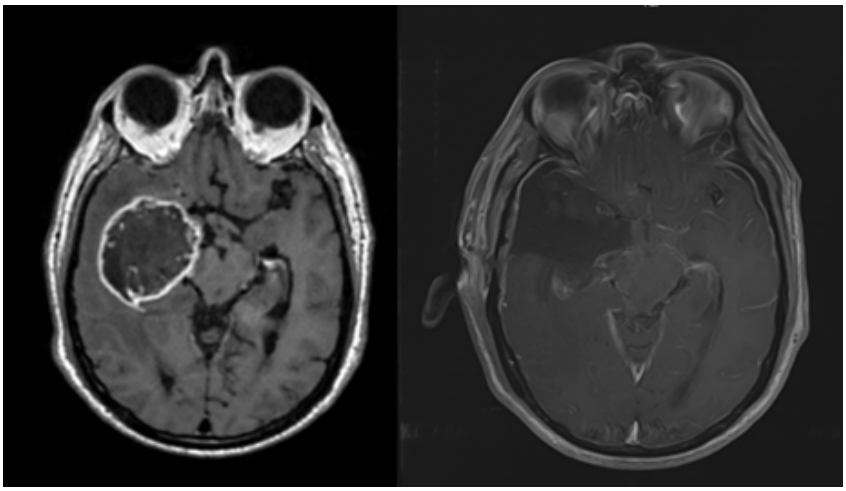

Figure-1: MRI of the brain with contrast Axial view T1+contrast; a: Diagnostic MRI, b: Post-operative MRI within 24 Hours.

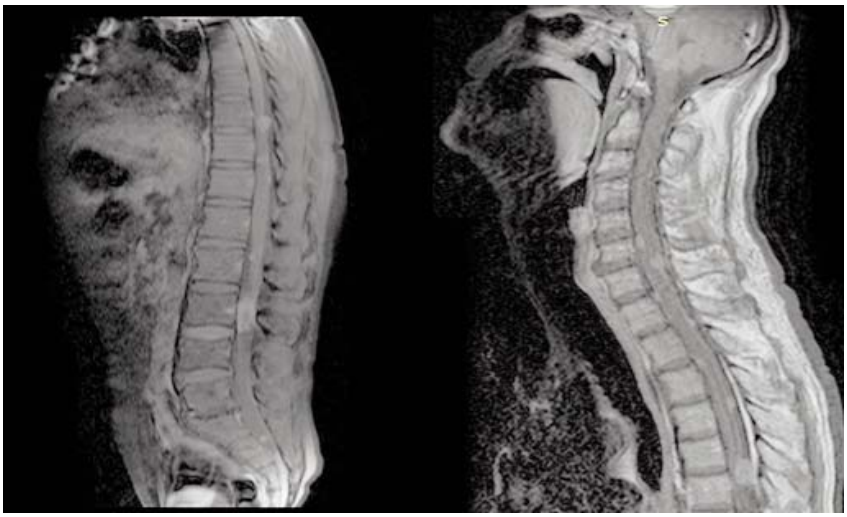

Figure-2: Follow-up MRI of the whole spine scan: Sagittal view T1+contrast showing leptomeningeal spread.

aspect of the brainstem, so it was left as residue. Post-operative MRI was conducted within 24 hours of surgery to evaluate the extent of the residue. An 18 x 26 mm residue enhancing lesion was observed posterior and medial to the resection cavity (Figure 1b). Histopathological examination of the excised tumour revealed characteristics such as cellular pleomorphic, hyperchromatic nuclei, moderate to scant cytoplasm, microvascular proliferation, and necrosis. Immunohistochemical analysis demonstrated a pattern that was IDH-wild type, with positivity for GFAP, Olig 2, and synaptophysin, confirming the diagnosis of GBM grade IV.

Therefore, concurrent chemo-radiation therapy was initiated. Radiation therapy began on a tomotherapy machine with a dose of 60 Gy in 30 fractions at 2 Gy per fraction for a period of six weeks, along with concurrent Temozolomide (TMZ). He was prescribed adjuvant TMZ on the 28th day of the completion of chemo-radiation. A follow-up MRI of the brain after three months of completion of CCRT was compared with the prior scan which showed no significant interval changes in the appearance and size of the lesion, representing stable disease.

The patient was on adjuvant TMZ and completed three-month cycles, after which he started experiencing generalised weakness. A follow-up MRI of the brain revealed the presence of dural band deposits in the cervical spine cuts. This led to the decision to conduct a comprehensive whole-spine MRI, exposing multiple lesions with a distinct nodular sugar-coating of the dura (Figure 2). A re-evaluation of the histopathological examination aimed to observe neuroendocrine differentiation.

Despite the positive synaptophysin result, no neuroendocrine component was identified. The complexity of the case prompted a review by the multidisciplinary tumour board. Leptomeningeal spread of GBM is an exceedingly rare phenomenon, particularly in middle-aged men who were already undergoing adjuvant chemotherapy.

In the light of the situation, the tumour board recommended radiation therapy as part of palliative treatment to target the disseminated tumour cells within the leptomeninges. Craniospinal irradiation (CSI) was initiated, with a dosage of 36 grays administered in 20 fractions at 1.8 Gy per fraction. Unfortunately, despite these therapeutic efforts, the patient's condition rapidly deteriorated. By the second week of radiation therapy, the patient manifested motor weaknesses and eventually succumbed to death.

Discussion

This case revealed a rare phenomenon of leptomeningeal spread in GBM, which was identified during a follow-up scan after receiving multimodality treatment. Glioblastoma, the most common malignant brain tumour, typically exhibits localised development in the parenchyma of the brain. The propensity of GBM to

extend beyond the central nervous system into the bloodstream is exceptionally rare, with reported locations outside the CNS including the pleura, cervical lymph nodes, bones, and lungs. It is crucial to note that the spread within the CNS is usually attributed to the progression or recurrence of primary GBM, and this was not observed in this case.[5] GBM has an aggressive clinical history; therefore, its low propensity to metastasise is note-worthy. In glioblastoma, no molecular marker significantly predicts the probability of Leptomeningeal disease (LMD). BRAF V600E point mutations are highly likely to elevate the risk of LMD, but this specific analysis was not conducted in the patient under discussion.[6]

Leptomeningeal disease is uncommon in GBM at the time of diagnosis, estimated to have a prevalence of only 2-4%.[7] Leptomeningeal spread is more frequently associated with certain CNS malignancies, such as medulloblastoma, apendymoma/pineoblastoma, and most commonly in paediatric patients, posing a challenge for clinicians due to their rare occurrences and scarce literature in adult population.

The patient under discussion was a middle-aged male, which was another uncommon manifestation. GBM is a type IV brain cancer that occurs in patients between the ages of 70 and 80, rather than at earlier ages. Its prevalence rate increases with age.[8] The primary causes of metastatic spinal dissemination are the metastasis of GBM cells with CSF, insufficient surgical protection, an open ventriculus cerebri, or a tumour that is close to the ventriculus cerebri. There is no proven risk factor for LMS of GBM in this case.

Supratentorial primitive neuroectodermal tumour (sPNET) is a primitive, embryonal malignant CNS neoplasm, and carries a high risk to spread through CSF. The diagnosis and differentiation of GBM from sPNET is particularly challenging for the neuropathologist. A variety of neuroendocrine, neuronal, and glial immunohistochemical markers, such as synaptophysin, neuron specific enolase (NSE), neuro-filament proteins, and glial fibrillary acidic protein (GFAP), are often demonstrated in sPNETs and are generally interpreted as evidence of differentiation along the neuronal or glial lineage.[9] Glioblastomas do not exhibit synaptophysin, a protein hallmark of neuroendocrine differentiation, because of their glial origin. The case introduces diagnostic complexities, as synaptophysin readings were positive, indicating potential neuroendocrine differentiation. The multidisciplinary tumour board played a crucial role in re-evaluating the histopathological findings and the lack of a clear neuroendocrine component was identified, emphasising the rarity of this phenomenon.

The pathophysiology of LMS is poorly understood, presenting two patterns of CSF dissemination: low seeding with large early tumour growth, or high seeding with limited initial tumour progression. In the present case, the primary size of the lesion was 30 x 35 x 37 mm, and on the follow-up scan, no initial tumour progression was identified, while 90% of LMS cases are diagnosed during the progression and/or recurrence of GBM within a period of two years. Despite a multimodal treatment approach, including surgery, chemotherapy, and radiotherapy, leptomeningeal spread led to a rapid deterioration in the patient's condition. The prognosis for leptomeningeal metastases is dismal, with a two- to three-month survival rate, emphasising the need for more effective therapeutic interventions targetting this rare manifestation.[10]

The case underscores the need for future research focussing on the development of safe and efficient treatment plans, diagnostic measures, and identifying markers linked to the advancement of leptomeningeal spread in GBM.

Conclusion

In conclusion, this case highlighted rarity and aggressive nature of leptomeningeal spread (LMS) in glioblastoma multiforme (GBM), which posed significant diagnostic and therapeutic challenges. The patient's rapid clinical deterioration despite multimodal therapy reflects the limited efficacy of current treatment strategies for LMS.

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KF: Conception and design of the work, data acquisition, analysis, and interpretation, final approval.
YA: Writing and drafting the work, revision.
FS: Data interpretation, final approval.