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Rare Adult Spinal Diffuse Midline Glioma with Craniospinal Progression: A Case-Based Review

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Abstract

Introduction: Spinal gliomas account for approximately 10% of all gliomas of the central nervous system. Ependymomas and pilocytic astrocytomas are the most prevalent subtypes, whereas diffuse spinal gliomas are relatively rare. The H3K27 mutation is a molecular marker of malignancy. Case Description: We present the clinical case of a 29-year-old female patient with no significant past medical history. In 2021, during pregnancy, she developed lumbar pain with radiation to the left lower limb. This was initially presumed to be pregnancy related and treated symptomatically. Postpartum, the pain worsened, and motor deficit of the left lower limb appeared—asymmetric spastic paraparesis, predominantly on the left, with asymmetric hyperreflexia and sustained clonus in the limb. A cervical-thoracic spinal MRI revealed a large tubular intramedullary lesion extending from C6 to T10. A surgical biopsy was performed, and histopathological analysis revealed a diffuse midline glioma with H3K27M mutation. Initial treatment included radiotherapy followed by chemotherapy. In February 2024, the patient presented with worsening motor function, progressing to paraplegia. No intracranial dissemination was noted at that time. In 2025, a new right cerebellar metastasis was identified. Initially proposed for radiotherapy but was unable to commence due to rapid clinical deterioration. This case highlights an unusually prolonged survival for this lesion subtype, suggesting that further study into prognostic factors and treatment responses is warranted.

Keywords

Diffuse Midline Gliomas, Intramedullary Spinal Cord Glioma, Spinal Surgery, Adjuvant Treatment, Palliative Care

1. Introduction

Diffuse midline gliomas (DMGs), particularly those harboring the H3K27M mutation, represent a highly aggressive category of central nervous system tumors

that predominantly arise within midline structures, including the spinal cord, brainstem and thalamus [1]-[3]. Their diffuse infiltrative nature, molecular signature, and limited responsiveness to conventional therapies have led to their classification as WHO grade IV tumors, regardless of histological features. The introduction of molecular diagnostics has substantially advanced the understanding of DMG biology, identifying unique epigenetic features that drive tumor invasion and treatment resistance.

Although spinal cord DMGs constitute a minority of cases, they pose profund diagnostic and therapeutic challenges. Patients often present with nonspecific or slowly progressive neurological symptoms that may be misattributed to more common benign conditions, resulting in diagnostic delay. Moreover, due to the infiltrative nature of the tumor and involvement of eloquent neural pathways, surgical resection is typically limited to biopsy alone [2].

Despite incremental advances in radiotherapy, chemotherapy, and targeted approaches, prognosis for patients with H3K27M-mutant DMGs remains extremely poor, with median survival typically less than two years [4]. Recent studies have mapped the cellular diversity and spatial architecture of these tumors, offering new insights into mechanisms of therapeutic resistance and dissemination. Nevertheless, effective treatments remain limited, underscoring the need for continued translational research.

This report presents a case of an spinal H3K27M-mutant DMG diagnosed in early adulthood, with unusually long survival. The case illustrates the characteristic clinical course, radiological progression patterns, and therapeutic challenges associated with intramedullary DMG.

2. Case Presentation

A 29-year-old woman with no significant past medical history developed lumbar pain radiating to the left lower limb during late 2020. The symptoms initially appeared during gestation and were attributed to physiological musculoskeletal changes and managed conservatively, with transient symptomatic improvement. In September 2021, following delivery, the patient experienced progressive worsening of symptoms associated with new-onset motor deficit of the left lower extremity. She was subsequently admitted for diagnostic workup. Neurological examination demonstrated asymmetric spastic paraparesis, more pronounced on the left side, with hyperreflexia and sustained clonus.

A neuraxis magnetic resonance imaging (MRI) study revealed a large cervical and dorsal intradural lesion extending from C6 to T10, with a focal hyperenhancing area at T4 - T5 (**Figure 1**). Baseline MRI of the entire neuro-axis performed after definitive diagnosis showed no evidence of intracranial or leptomeningeal dissemination. Cerebrospinal fluid studies were not performed.

The diagnosis was established following D4 - D5 laminotomy with bone flap removal, dural exposure, and biopsy sampling from multiple quadrants of the lesion. Histopathological analysis revealed a diffuse midline glioma, H3K27M-mu-

tant, WHO grade IV. Immunohistochemical evaluation demonstrated variable positivity for glial fibrillary acidic protein (GFAP) and OLIGO2, with negative p53 expression. Immunoexpression was compatible with H3 K27M mutation, while ATRX mutation, IDH1-R132H mutation, and BRAF V600E mutation were negative. Molecular analysis (H21-17737) did not identify V600E/E2/D mutations in codon 600 of the BRAF gene.

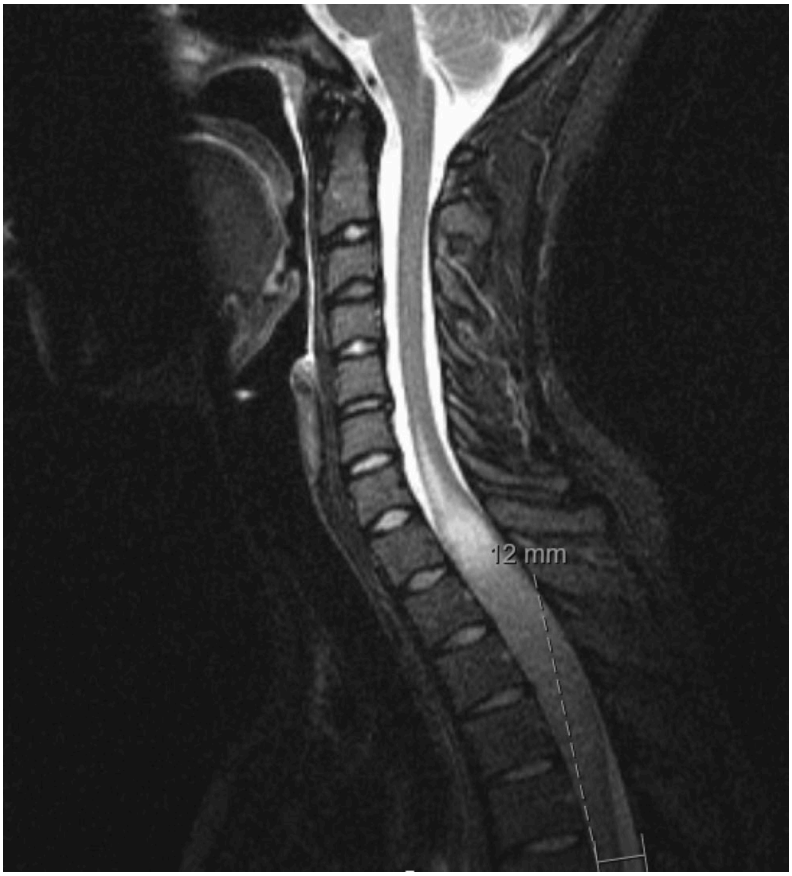

Figure 1. Sagittal T2-weighted MRI of the cervical and upper thoracic spine demonstrating an extensive intramedullary expansile lesion with diffuse cord enlargement. The maximal transverse diameter reaches approximately 12 mm at the mid-thoracic level. The lesion shows characteristic T2 hyperintensity and longitudinal extension, consistent with a diffuse infiltrative intramedullary neoplasm.

Following surgery, the patient received focal radiotherapy consisting of a total dose of 48 Gy delivered in 27 fractions over 5.5 weeks (November 2021 to January 2022). Nine days after completion of radiotherapy, adjuvant PCV chemotherapy was initiated, and the patient completed six cycles, maintaining clinical and neurological stability. PCV was selected as the initial systemic treatment based on its established use in high-grade gliomas and the patient's preserved functional status at diagnosis.

The patient underwent close surveillance with spinal MRI every six months, showing clinical and radiological stability for approximately two years (**Figure 2**).

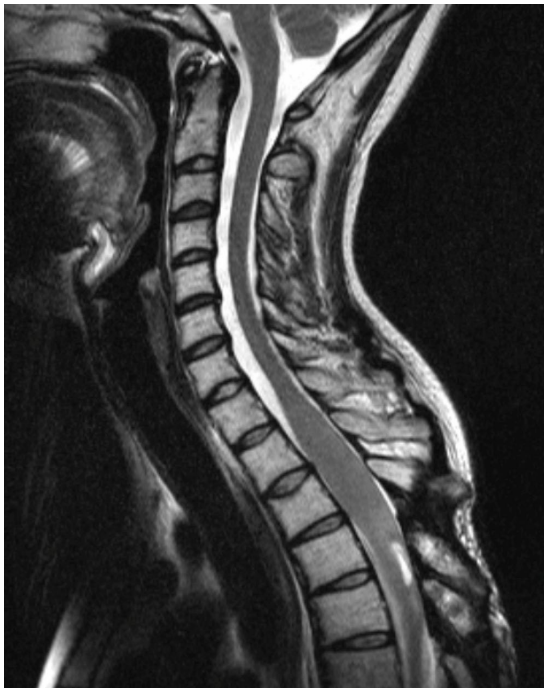

Figure 2. An example of serial magnetic resonance images obtained during follow-up showing stability of the lesion.

In March 2024, she developed progressive neurological deterioration with paraplegia, prompting earlier imaging assessment that demonstrated progression of the cervicodorsal lesion (**Figure 3**). Given disease progression, treatment was changed to temozolomide as an alternative alkylating agent.

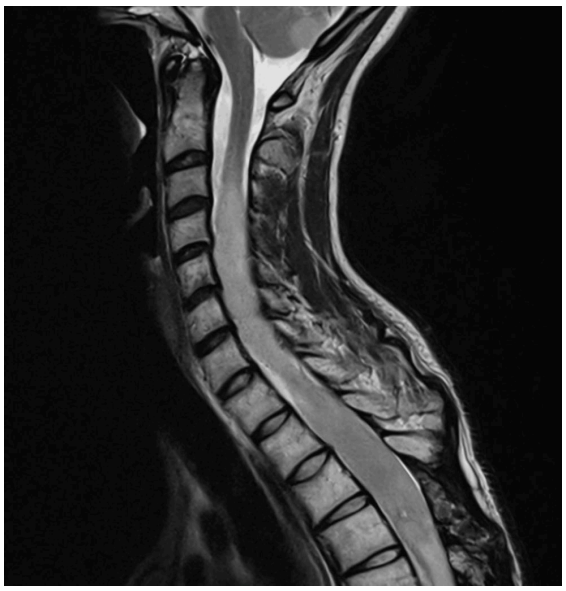

Figure 3. Sagittal T2-weighted MRI of the cervical and upper thoracic spine demonstrating marked intramedullary expansion with diffuse T2 hyperintensity extending longitudinally from the cervical region into the thoracic cord. The spinal cord appears enlarged and infiltrated, consistent with an extensive diffuse midline glioma.

Subsequent MRI studies demonstrated further radiological progression, including cranial extension reaching C2 - C3. Due to progressive disease and the impossibility of re-irradiation, treatment with lomustine and bevacizumab was initiated in January 2025.

Because of altered mental status, the patient was later admitted to the Emergency Department, where cranial CT and MRI revealed advanced disease progression with cerebellar metastasis (Figure 4)—which was considered radiologically presumed metastatic dissemination, without histopathological confirmation. Although radiotherapy of the cerebelar lesions was considered, the patient's rapidly declining clinical condition precluded treatment initiation. She subsequently received palliative care and died shortly thereafter. The overall survival after diagnosis was 45 months.

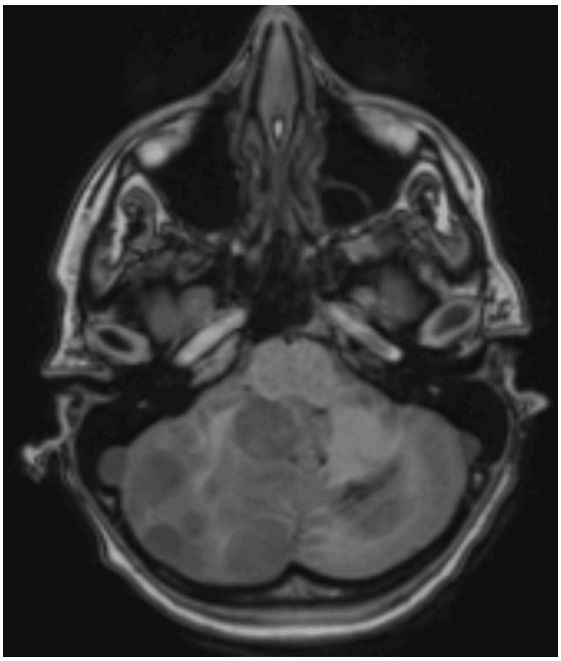

Figure 4. Axial T1-weighted MRI at the level of the posterior fossa demonstrating a heterogeneously lesion within the right cerebellar hemisphere. The lesion produces localized distortion of adjacent cerebellar folia.

3. Discussion

Diffuse midline gliomas with H3K27M mutation are defined by a unique epigenetic dysregulation resulting in global loss of H3K27 trimethylation, which drives widespread transcriptional reprogramming and tumor aggressiveness. Recent work by Liu *et al.* has demonstrated that these tumors consist of diverse and spatially organized cellular states, including progenitor-like, oligodendrocyte-like, and mesenchymal-like populations, each contributing to therapeutic resistance and intratumoral heterogeneity [4]. Such cellular plasticity enables survival under therapeutic pressure and likely contributes to the inevitable disease progression observed in most patients.

In the spinal cord, DMGs are rare but follow a similarly aggressive course. Yao *et al.* reported a series of 33 spinal cases, highlighting early motor impairment, extensive longitudinal tumor spread, and poor overall survival despite multimodal therapy [2]. The present case exhibited these hallmark features, including an exceptionally long rostrocaudal involvement (C6 - T10 at diagnosis) and later cranial extension to C2 - C3.

Notably, the overall survival of 45 months observed in this patient exceeds that reported in most published adult spinal DMG cohorts, in which median survival generally ranges from approximately 10 to 24 months despite combined treatment strategies. While pediatric DMGs may occasionally demonstrate prolonged survival, adult spinal H3K27M-mutant tumors are usually associated with rapid neurological decline and early progression. The comparatively prolonged survival in this case may reflect a combination of factors, including the patient's young age, initially preserved functional status, absence of dissemination at diagnosis, prolonged disease stabilization following radiotherapy and PCV chemotherapy, and the relatively delayed occurrence of intracranial spread. In addition, the absence of ATRX, IDH1, and BRAF alterations may suggest a distinct molecular profile, although the prognostic significance of these findings in spinal DMG remains incompletely understood.

The initial two-year period of stability following radiotherapy and PCV chemotherapy is noteworthy, as adults with spinal DMG occasionally demonstrate slightly more indolent courses than pediatric cases, although the overall prognosis remains dire. Consistent with available literature, radiotherapy provided temporary stabilization but did not arrest eventual progression. Temozolomide, lomustine, and bevacizumab similarly offered limited benefit, aligning with multiple reports indicating only modest palliative effects of conventional chemotherapeutic regimens in DMG.

An important aspect of this case is the development of a cerebellar metastasis, which exemplifies the capacity of DMGs to disseminate beyond the initial site. Increasing evidence indicates that DMGs rely on cell-autonomous signaling pathways to drive infiltration and metastasis, as detailed in the work of Bruschi *et al.*, who identified specific molecular mechanisms enabling widespread CNS dissemination [1]. These findings correlate with the late cerebellar metastasis observed in this patient.

Efforts to identify prognostic markers and therapeutic targets remain ongoing. Dufour *et al.* have shown that particular molecular signatures may correlate with progression and survival, while emerging research highlights metabolic vulnerabilities specific to differentiation states, suggesting new avenues for targeted interventions [5]. For example, Mbah *et al.* demonstrated state-dependent metabolic dependencies in DMG, revealing potential for precision therapy [6].

Nonetheless, despite significant biological insights and promising preclinical strategies, effective clinical treatments remain lacking. This case underscores the urgency of translating molecular advances into tangible therapeutic options and

highlights the critical importance of early recognition, even in contexts such as pregnancy where symptoms may initially be attributed to benign processes [3].

This report has several limitations. As a single-case study, its findings cannot be generalized to the broader population of patients with spinal H3K27M-mutant DMG. In addition, cerebrospinal fluid studies were not performed, limiting assessment of occult leptomeningeal dissemination. The cerebellar lesion was radiologically presumed to represent metastatic disease and did not undergo neuropathological confirmation. Furthermore, although immunohistochemical and selected molecular analyses were available, comprehensive genomic profiling was not performed.

4. Conclusion

H3K27M-mutant diffuse midline gliomas of the spinal cord are rare, highly aggressive tumors with limited therapeutic options and poor prognosis. This case illustrates the potential for prolonged survival despite extensive spinal involvement and late intracranial dissemination, emphasizing the biological heterogeneity of adult spinal DMG. Although multimodal treatment achieved temporary disease stabilization, progression ultimately occurred, reinforcing the need for more effective targeted and molecularly informed therapies.

Note

Written informed consent could not be obtained because the patient was deceased at the time of manuscript preparation. All clinical information has been fully anonymized, and no identifiable personal data or images that could permit patient identification are included in this report.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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