

Spinal cord diffuse midline glioma with H3K27M mutation: A case report and literature review

Omuriliğin diffüz orta hat gliomu ve H3K27M mutasyonu: Bir olgu sunumu ve literatür derlemesi

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ABSTRACT

Diffuse midline gliomas (DMGs) harboring the H3K27M mutation represent a rare and aggressive category of central nervous system tumors recently classified as WHO grade IV. While predominantly observed in pediatric brainstem gliomas, spinal cord involvement, especially in adults, is uncommon and presents unique diagnostic and therapeutic challenges. We report a case involving a 27-year-old male patient who presented with progressively worsening back pain and sensory disturbances localized below the T12 dermatome. Magnetic resonance imaging (MRI) revealed an expansive intramedullary lesion in the thoracic spine (T10–T12). Surgical intervention achieved a gross total resection, and histopathological evaluation confirmed a DMG characterized by strong positivity for the H3K27M mutation, an elevated Ki-67 proliferation index, and significant p53 expression. Postoperatively, the patient underwent adjuvant radiotherapy (54 Gy) and initiated temozolomide chemotherapy. A follow-up MRI at five months post-treatment showed no evidence of recurrence. Spinal cord DMGs with the H3K27M mutation typically exhibit aggressive biological behavior and predominantly affect individuals under the age of 40. These tumors commonly exhibit high proliferative activity and lack MGMT promoter methylation, suggesting a limited effectiveness of conventional alkylating agents, such as temozolomide. Although gross total resection alone is rarely curative, integrated multimodal therapy can provide meaningful short-term disease control. Continued research into targeted epigenetic therapies is crucial for advancing management and improving patient outcomes.

Keywords: diffuse midline glioma, H3K27M mutation, spinal cord tumor, intramedullary glioma, WHO grade 4 glioma

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Öz

H3K27M mutasyonu taşıyan diffüz orta hat gliomları (DMG), yakın zamanda WHO grade IV olarak sınıflandırılan nadir ve agresif santral sinir sistemi tümörleridir. Çoğunlukla pediatrik beyin sapı gliomlarında görülmekle birlikte, yetişkinlerde omurilik tutulumu seyrek ve özgün tanısal ve terapötik zorluklar içerir. Bu yazıda, giderek artan sırt ağrısı ve T12 dermatomu altında duyu bozukluğu ile başvuran 27 yaşındaki erkek hasta sunulmaktadır. Manyetik rezonans görüntüleme (MRG), T10–T12 seviyelerinde genişleyici intramedüller bir lezyon ortaya koymuştur. Cerrahi müdahale ile total rezeksiyon sağlanmış ve histopatolojik inceleme H3K27M pozitifliği, yüksek Ki-67 proliferasyon indeksi ve belirgin p53 ekspresyonu ile uyumlu DMG tanısını doğrulamıştır. Postoperatif dönemde hasta 54 Gy radyoterapi almış ve temozolomid tedavisine başlanmıştır. Beş aylık takipte tekrarlama izlenmemiştir. H3K27M mutasyonuna sahip omurilik DMG'leri biyolojik olarak agresif seyirli olup genellikle genç erişkinlerde görülür. Yüksek proliferatif aktivite göstermeleri ve MGMT promotör metilasyonunun olmaması, temozolomid gibi alkilleyici ajanlara sınırlı yanıtla ilişkilidir. Total rezeksiyon tek başına kür sağlayamasa da multimodal tedavi kısa süreli hastalık kontrolü sunabilir. Bu tümörlerin yönetiminde ilerleme kaydedebilmek için hedeflenmiş epigenetik tedavilere yönelik araştırmaların sürdürülmesi kritik öneme sahiptir.

Anahtar Kelimeler: diffüz orta hat gliom, H3K27M mutasyonu, omurilik tümörü, intramedüller gliom, WHO grade IV gliom

Introduction

Diffuse midline glioma (DMG), H3K27-altered, is classified as a World Health Organization (WHO) Grade IV tumor entity, characterized by a critical lysine-to-methionine substitution at position 27 on histone H3 (H3K27M). Initially identified predominantly in pediatric brainstem gliomas, these tumors have been increasingly recognized in other midline central nervous system (CNS) structures, including the thalamus and spinal cord. Their aggressive biological behavior contributes significantly to poor prognosis, and the complex genetic and epigenetic underpinnings pose considerable therapeutic challenges.^{1,2}

While spinal cord presentations of DMG remain exceptionally rare, particularly in adults, accurate diagnosis requires heightened clinical suspicion complemented by advanced imaging, histopathological evaluation, and precise molecular characterization. The presence of the H3K27M mutation, which disrupts normal epigenetic regulation by inhibiting the Polycomb Repressive Complex 2 (PRC2), plays a pivotal role in tumor progression and resistance to conventional therapies. Understanding the implications of these

molecular characteristics is crucial, as emerging targeted therapeutic strategies increasingly aim to modulate these specific epigenetic abnormalities.³⁻⁵

This case report presents a rare instance of spinal H3K27M-mutant glioma in an adult patient, providing insights into its clinical course, diagnostic intricacies, and therapeutic management. Furthermore, a comprehensive review of the existing literature is provided to contextualize clinical presentations, molecular diagnostic criteria, current treatment paradigms, and potential future directions for targeted therapeutic interventions.

Case Presentation

A 27-year-old male presented with a one-week history of progressive upper and lower back pain, following an initial two-week period of mild discomfort. The neurological examination revealed hypoesthesia localized to the T12 dermatome and below, without associated motor deficits or other neurological abnormalities. Magnetic resonance imaging (MRI) demonstrated an intramedullary expansile lesion extending from T10 to T12, characterized by T2-weighted

hyperintensity, cord swelling, and surrounding edema. Post-contrast T1 sequences displayed mild, patchy enhancement suggestive of a high-grade glial neoplasm (Figure 1).

The patient underwent surgical resection under general anesthesia in the prone position. Using fluoroscopic guidance, the T10–T12 vertebral levels were localized, and a midline incision was performed. Paraspinal muscles were dissected bilaterally, and a laminectomy was carried out to expose the dura. Upon dural opening, a mass consistent with tumor tissue was identified intradurally. Gross total resection of the lesion was achieved using bipolar cautery, tumor forceps, and Cavitron Ultrasonic Surgical Aspirator (CUSA). Dural closure was completed primarily, and meticulous hemostasis was secured using a Duragen patch and fibrin sealant. Layered

anatomical closure of the surgical wound followed (Figure 2).

Postoperative neurological status remained stable, with persistent hypoesthesia but no additional deficits. The patient subsequently received adjuvant radiotherapy totaling 54 Gy and was placed on maintenance temozolomide therapy. Follow-up MRI performed five months postoperatively showed no evidence of tumor recurrence (Figure 3).

Histopathology and molecular profile

Histopathological examination of the resected spinal mass revealed a diffusely infiltrative glial tumor. Microscopically, the neoplasm exhibited moderate nuclear atypia, hyperchromasia, and scattered mitotic activity. Areas of necrosis and focal microvascular proliferation were

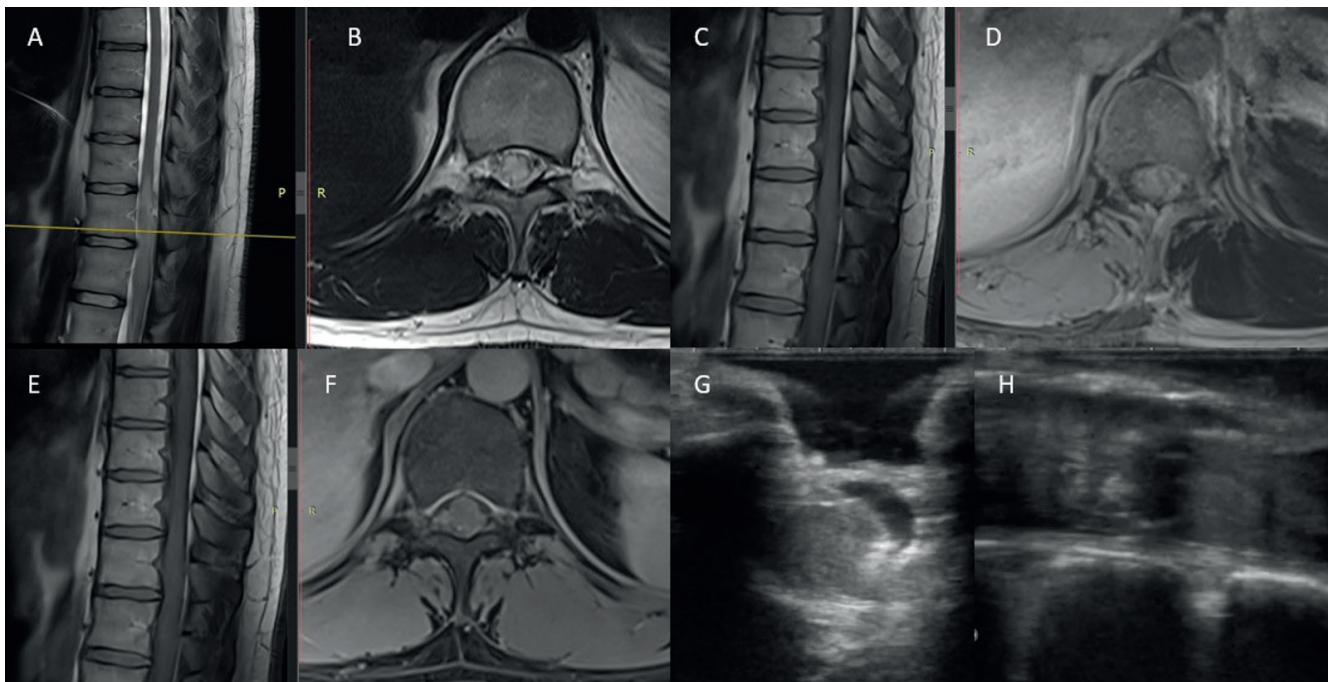


Figure 1. Preoperative MRI and intraoperative ultrasound imaging of the thoracic spinal cord lesion

(A, B) Sagittal and axial T2-weighted MRI images showing an intramedullary expansile lesion extending from T10 to T12 with a hyperintense signal and cord swelling. (C, D) Sagittal and axial T1-weighted post-contrast images demonstrating mild heterogeneous enhancement within the lesion. (E, F) Corresponding sagittal and axial T1-weighted non-contrast images for anatomical reference. (G, H) Intraoperative ultrasound images reveal hyperechoic tumor boundaries within the spinal cord, aiding localization prior to myelotomy.

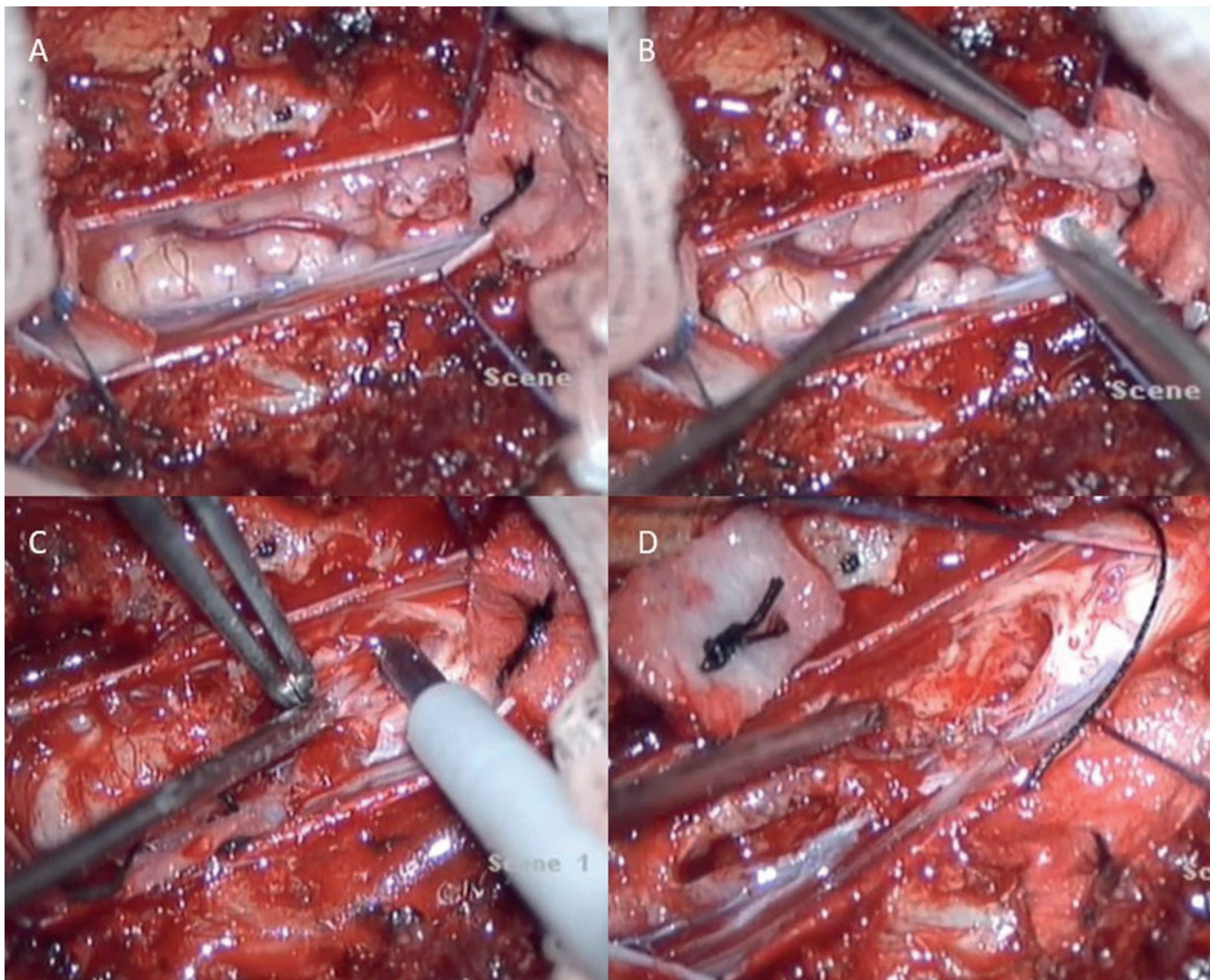


Figure 2. Intraoperative microsurgical images showing key stages of thoracic intramedullary tumor resection

(A) After T10–T12 laminectomy and dural opening, the swollen spinal cord is exposed, revealing a midline bulge suggestive of the underlying tumor. (B) Myelotomy is performed along the midline, and tumor removal is initiated using sharp dissection. (C) Tumor debulking proceeds using standard tumor forceps in combination with a Cavitron Ultrasonic Surgical Aspirator (CUSA) for precise resection. (D) Final inspection of the resection cavity following gross total tumor removal, with dural closure preparation and hemostatic agents visible.

also observed. Immunohistochemical staining was diffusely positive for glial fibrillary acidic protein (GFAP), confirming its astrocytic origin. Importantly, strong positivity for the H3K27M mutant protein was detected, establishing the diagnosis of diffuse midline glioma, H3K27-altered, WHO grade IV.

The Ki-67 proliferation index was elevated at approximately 15%, indicating a high proliferative

potential. Additional molecular analyses showed wild-type status for IDH1/2, retained ATRX expression, and absence of the BRAF V600E mutation. Increased p53 immunoreactivity suggested a TP53 mutation. The MGMT promoter was found to be unmethylated, further indicating likely resistance to alkylating chemotherapy. Testing for TERT promoter mutations was not performed.

These molecular characteristics align closely with established profiles of spinal diffuse midline gliomas harboring the H3K27M mutation, which typically exhibit aggressive clinical behavior and limited responsiveness to standard therapeutic approaches.

Discussion

Diffuse midline gliomas (DMGs) with H3K27M-alteration represent a rare and aggressive category of central nervous system (CNS) neoplasms predominantly observed in pediatric brainstem

locations. Spinal cord involvement, particularly in adults, remains an uncommon and distinct presentation, necessitating careful differentiation from other spinal intramedullary tumors. This case of a 27-year-old male with a thoracic intramedullary DMG underscores critical aspects of clinical presentation, diagnostic challenges, and management paradigms of this complex entity.^{3,6,7}

Radiologically, DMGs share imaging characteristics with other spinal cord tumors such as astrocytomas, ependymomas, hemangioblastomas, and demyelinating diseases. Typical MRI findings include diffuse cord expansion, hyperintense signaling on T2-weighted images, and variable enhancement patterns.⁸ The presence of significant peritumoral edema, as observed in our case, often raises suspicion for high-grade gliomas. Consistent with this, Watanabe et al. highlighted thoracic involvement as a predominant spinal localization, supporting the representativeness of our patient's presentation.³

Molecular profiling has become indispensable in diagnosing and prognosticating DMGs. The hallmark mutation, H3K27M, results in profound epigenetic dysregulation and significantly contributes to tumor aggressiveness. Our patient's tumor displayed classic molecular features, including H3K27M positivity, wild-type IDH status, high Ki-67 proliferation rate, and lack of MGMT promoter methylation, corroborating previous literature. The absence of MGMT methylation, in particular, implies resistance to alkylating chemotherapeutic agents, which explains the limited clinical benefit from temozolomide.^{9,10}

Surgical management strategies remain debated, particularly regarding the extent of resection. While gross total resection is typically associated with better outcomes in other CNS tumors, evidence suggests it may not significantly impact survival in spinal DMGs due to inherent microscopic infiltrative growth patterns. In our case, gross total resection was achievable due

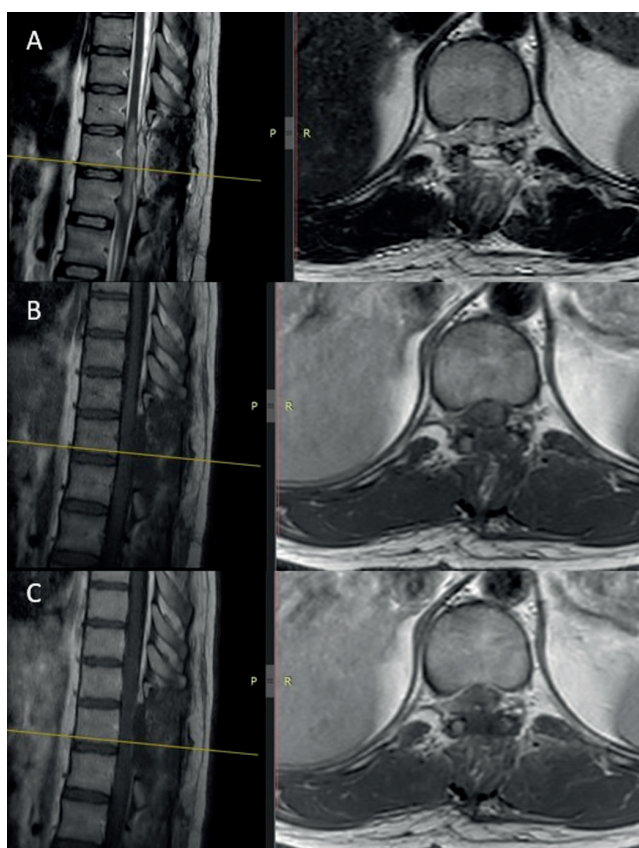


Figure 3. Postoperative spinal MRI demonstrating surgical changes and absence of residual tumor

(A) Sagittal and axial T2-weighted images showing postoperative myelotomy tract and reduced spinal cord swelling at the T10–T12 levels. (B) Sagittal and axial T1-weighted contrast-enhanced images showing no definite residual enhancing lesion, consistent with gross total resection. (C) Follow-up sagittal and axial post-contrast images demonstrating continued absence of recurrence at the surgical site at five months.

to clear tumor margins and lesion accessibility. However, contemporary studies suggest equivalent or superior outcomes with limited surgical intervention combined with adjuvant radiotherapy and chemotherapy, underscoring a conservative surgical philosophy.^{11,12}

The role of chemotherapy, primarily temozolomide, remains uncertain due to the intrinsic resistance mechanisms.^{13,14} Novel agents targeting specific molecular pathways disrupted by the H3K27M mutation, such as histone deacetylase inhibitors (panobinostat), dopamine receptor antagonists (ONC201), and anti-angiogenic therapies (bevacizumab), have shown preliminary promise in preclinical and early clinical trials. Further rigorous evaluation through well-designed prospective trials is critical.¹⁵

Our patient's favorable short-term outcome highlights the potential efficacy of a comprehensive multimodal therapeutic strategy, including surgery, radiotherapy, and chemotherapy. Nonetheless, the prognosis remains guarded given the aggressive biological behavior of spinal DMGs.

Accordingly, longer-term follow-up and larger, systematically analyzed case series are required to clarify the true prognostic value of surgical extent and to better define optimal management strategies for spinal H3K27-altered diffuse midline gliomas. In parallel, future research should prioritize large-scale, multicenter studies incorporating standardized molecular profiling, centralized clinical registries, and the systematic evaluation of targeted therapies aimed at modulating the epigenetic dysregulation central to these tumors, with the potential to substantially improve disease understanding, patient management, survival, and quality of life.

Conclusion

Diffuse midline gliomas (DMGs) with H3K27M mutation in the spinal cord are rare and aggressive tumors that predominantly affect young adults, presenting significant diagnostic and therapeutic challenges. Although universally categorized as WHO grade IV, emerging evidence suggests potential variability in clinical outcomes. Comprehensive molecular profiling is crucial for accurate diagnosis and informing targeted treatment strategies. While the role of aggressive surgical resection remains controversial, a multimodal therapeutic approach incorporating surgery, radiotherapy, and chemotherapy may offer short-term disease control. Future research should focus on multicenter collaboration, detailed molecular stratification, and the development and evaluation of novel targeted therapies aimed at mitigating the aggressive biology associated with H3K27M mutations, ultimately aiming to enhance patient outcomes and survival.

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Ethical approval

This study is a case report, therefore does not require an ethics committee approval.

Author contribution

Study conception and design: CIG, DS, DDB, AA; data collection: CIG, DS; analysis and interpretation of results: CIG, DGG, DDB, AA; draft manuscript preparation: CIG, DS. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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