Diffuse midline glioma, H3K27-altered, of the conus medullaris presenting as acute urinary retention: illustrative case

Sabir Saluja, BS,1 Bayan Razzaq, MD,1 John A. Servider, MD,1 Roberta Seidman, MD,2 and Harry Mushlin, MD1

Departments of 1Neurosurgery and 2Pathology, Stony Brook University School of Medicine, Stony Brook, New York

BACKGROUND Diffuse midline glioma (DMG), H3K27-altered, is a rare, highly malignant central nervous system neoplasm that arises in midline structures. They are more commonly encountered in children and are rarely encountered in adults, usually in the thalamus or spinal cord. The presence of the H3K27 mutation in the H3F3A gene automatically classifies a tumor as World Health Organization grade IV. These tumors carry a grim prognosis, with an overall median survival of less than 1 year.

OBSERVATIONS The authors report the case of a 38-year-old male presenting with acute-onset urinary retention who was found to have an expansile, well-circumscribed mass involving the conus medullaris at the level of T12–L1. A T12–L1 laminectomy and tumor debulking were performed. Pathology revealed glial cells with astrocytic morphology among Rosenthal fibers, microvascular proliferation, and cellular atypia. The H3K27 mutation was confirmed.

LESSONS DMG, H3K27-altered, is a rarely encountered entity that can present in numerous midline structures. If localized to the conus medullaris, it may present as acute-onset urinary retention in a previously asymptomatic patient. Further investigation is needed to characterize its molecular and clinical features in adults to improve the management of those presenting with these tumors.

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KEYWORDS H3K27; diffuse midline glioma; conus medullaris; spinal cord tumor
urgency and difficulty with voiding. He reported improvement in pain whenever he was able to void more fully. He denied testicular pain or swelling, hematuria, and fever. Strength was 5/5 in all 4 limbs, with no motor drift. Sensation to light touch was decreased in the right lower extremity and perianal area.

Magnetic resonance imaging of the thoracic and lumbar spine was performed, which revealed a well-defined, expansile lesion with mild surrounding edema, involving the conus medullaris at the level of T12–L1 (Fig. 1). The lesion measured 2.1 × 1.8 × 4.64 cm in the transverse, anteroposterior, and cranial-caudal planes, respectively. Apparent diffusion coefficient (ADC) images revealed restricted diffusion in a hypointense mass at T12–L1 situated along the midline. The lesion was further delineated as an enhancing mass with surrounding edema and lacking central necrosis on T2-weighted and T1-weighted imaging. These radiological findings, along with the patient’s young age and no prior history of malignancy, raised the possibility of a spinal astrocytoma or ependymoma.

The patient underwent T12-L1 laminectomy and intradural exploration for resection of the tumor. Upon opening the dura, the conus medullaris appeared swollen and discolored. Using a microscope, a subtotal tumor resection was performed with neuro-monitoring of motor-evoked potentials (MEPs) and electromyography (EMG). Results of MEP and EMG were stable and guided delineation of the margins of the tumor and healthy spinal tissue. The dura was closed in a watertight fashion, and the wound was closed in standard fashion. The operation concluded, and the patient awoke, moving all 4 extremities voluntarily.

Postoperatively, the patient was alert and oriented and hemodynamically stable. He maintained full strength in all 4 extremities but was unable to contract his gluteus muscles. Additionally, he reported numbness and tingling around the anus and penis, as well as diminished sensation to his right lateral foot. He continued to have difficulty voiding and required reinsertion of a Foley catheter. The patient remained in the hospital for 12 days and was discharged to an acute rehabilitation center. He was examined 6 weeks later at a follow-up office visit. At the follow-up, there was slight improvement in his right foot paresthesia and he was awaiting another void trial. The patient was awaiting radiotherapy with adjuvant chemotherapy.

A sample of the tumor was collected during the operation and sent for histopathological analysis (Fig. 2). The sample contained an infiltrative neoplasm with glial cells, some spindled and arranged in a vaguely fascicular pattern, but most of the neoplasm lacked architectural patterning. Nuclei were pleomorphic with cellular atypia. Mitotic activity was found in some areas of the neoplasm. Rosenthal fibers were abundant. There was focal, mild, subtle (incipient) microvascular proliferation. Necrosis was not found. Additionally, the sample contained foci of perivascular lymphocytic infiltration composed of mostly B cells and few T cells and plasma cells, consistent...
with an inflammatory reaction. Molecular pathology later revealed the presence of several mutations: H3F3A, K27M; PPM1D, S421*; NF1, P185L; GLI3, V778I; and TERT, Q355H. The presence of the H3K27 mutation confirmed the diagnosis of DMG, H3K27-altered, CNS World Health Organization (WHO) grade 4 in this patient.

**Discussion**

**Observations**

We describe the case of a 38-year-old male presenting with acute urinary retention and an extensive intramedullary spinal cord tumor at T12–L1, later confirmed to be DMG, H3K27-altered. Currently, there have been fewer than 20 reported cases of spinal cord DMG, H3K27-altered, in adults and only 1 other case localized to the level of the conus medullaris.5–9

The radiographic features of DMG, H3K27-altered, are highly variable among the few reported cases. Nevertheless, identifying relevant features at presentation can improve prognostication and the choice of treatment. In our case, a well-defined, contrast-enhancing mass with surrounding edema was apparent. In contrast, most adult cases of DMG, H3K27-altered, have been reported to be partially enhancing or nonenhancing and do not usually present with edema.6,10 Diffusion-weighted imaging (DWI) is increasingly utilized in the diagnosis of CNS gliomas, as it can offer insight into cell density, and thus histological grade, noninvasively. Significant diffusion restriction in the volume of the lesion was present on ADC, likely indicating a high-grade, poorly differentiated neoplasm. In a healthy 38-year-old male with no past medical history, diffusion restriction in the surrounding edema was apparent. In contrast, most adult cases of DMG, H3K27-altered, have been reported to be partially enhancing or nonenhancing.

The diagnosis of DMG, H3K27-altered, is confirmed with the presence of the H3.3, 3.1, or 3.2 K27 mutation in the H3F3A gene. The pathogenesis is the result of a total decrease in methylation of histone H3, leading to downstream epigenetic changes that augment the tumor’s malignant potential.11,12 Wild-type H3 variants also rarely present, possessing mutations in genes such as EGFR or TERT. Moreover, the majority of reported cases comprise tumors located in the brain; spinal cord tumors are less likely to harbor the H3K27 mutation in H3F3A and are more associated with mutations in NF1 and TERT.13 The presence of the H3K27 mutation has been associated with a fatal prognosis; compared with DMGs that harbor alternative mutations, neither the pathological features nor survival appear to be significantly different.14

As per the 2021 WHO guidelines, the presence of the H3K27 mutation indicates a high-grade, aggressive tumor, regardless of the apparent histopathological grade.15 However, retrospective studies have reported DMG, H3K27-altered, to be more common than previously thought, with up to 15% of adults with DMGs harboring the mutation. Ultimately, the epidemiology of DMG, H3K27-altered, is not well defined given the paucity of cases reported, along with the heterogeneity in tumor location, age, and patient-specific molecular pathology. Thus, the impact of tumor location in the prognosis of DMG, H3K27-altered, has yet to be conclusively investigated.11,12

The interactions between associated genes and tumor location are likely complex and multifactorial; our case is a unique addition to the sparse body of literature regarding this tumor.

**Lessons**

DMG, H3K27-altered, remains a rare condition with limited reported data regarding its epidemiology, clinical characteristics at presentation, effective treatment, and clinical management. We describe the clinical presentation, investigations, and postoperative follow-up of the second reported case of DMG, H3K27-altered, presenting at the level of the conus medullaris and the first case with diagnostic findings on DWI.

**References**

Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Saluja, Razzaq, Servider, Mushlin. Acquisition of data: Razzaq, Servider. Analysis and interpretation of data: Razzaq, Servider, Seidman, Mushlin. Drafting of the article: Saluja, Razzaq, Servider, Mushlin. Critically revising the article: all authors. Reviewed submitted version of the manuscript: all authors. Administrative/technical/material support: Seidman. Study supervision: Mushlin.

Correspondence
Sabir Saluja: Stony Brook University School of Medicine, Stony Brook, NY. sabir.saluja@stonybrookmedicine.edu.