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H3K27M-mutant spinal cord and hemispheric tumor with prolonged survival: illustrative case

Eva Liu, MD,[1] Hsuan Ming Su, MD,[1] Patrick Toyota, MD,[1] Braeden D. Newton, MD,[1] Nicole Coote, MD,[1] Kristen Marciniuk, MD, PhD,[1] Roland Nicholas Auer, MD, PhD,[2] and Daryl R. Fourney, MD[1]

[1]Division of Neurosurgery, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; and [2]Department of Pathology and Laboratory Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

BACKGROUND H3K27M-altered diffuse midline glioma (DMG) is a recently classified tumor in the 2021 WHO classification of central nervous system tumors. Pediatric patients with H3K27M-altered DMG have a universally poor prognosis, with a median survival of 9–15 months. The prognosis of adult patients with the same tumor type is more variable, with rare cases of prolonged survival.

OBSERVATIONS The authors report the case of a 32-year-old male who presented with Brown-Séquard syndrome secondary to a heterogeneously enhancing intramedullary mass extending from T7 to T10. The lesion was resected, and the patient was diagnosed with an H3K27M-altered DMG. The patient presented again 29 months later with a nonenhancing right-sided temporal mass. This was again determined to be an H3K27M-mutated glioma with a molecular signature similar to the intramedullary mass. He received postoperative radiation therapy after each surgery and continued to survive well at the 42-month follow-up.

LESSONS The authors report the rare case of an adult-onset H3K27M midline glioma in the spinal cord and subsequent dissemination to the right temporal lobe with prolonged survival. This suggests that H3K27M-altered DMGs are heterogeneous entities with variable prognoses based on location and age.

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KEYWORDS intramedullary tumor; H3K27M mutation; high-grade glioma

H3K27M-altered diffuse midline glioma (DMG) is a central nervous system tumor that was first described in the 2016 WHO classification and was more recently revised in the updated 2021 WHO classification.[1] It has received the designation of "pediatric-type," as it is a tumor that primarily occurs in children.[1] The term "H3K27M-altered" refers to the K27M mutation of histone 3, which is believed to be the main driver mutation in this type of tumor.[2]

Pediatric patients with H3K27M-altered DMG have a universally poor prognosis, with a median survival of 9–15 months.[3] The prognosis for adult patients with the same tumor type is more variable, and there have been case reports of prolonged survival.[2–4]

In adults, DMG arises from numerous midline structures, most commonly the thalamus and spinal cord.[5] Very rarely does DMG develop in hemispheric regions. There are 8 cases of H3K27M-altered DMGs involving nonmidline structures in the literature.[6]

We present the unique case of an adult-onset H3K27M-altered spinal cord DMG with subsequent spread to the right temporal lobe with prolonged survival. The patient remains well at our latest follow-up.

Illustrative Case

A previously healthy 32-year-old male was referred to the neurosurgery department at a tertiary care center with new-onset Brown-Séquard syndrome. He initially presented with low back pain, which did not improve with physiotherapy. The patient then developed left leg numbness and temperature loss as well as progressive right leg weakness.

On examination, the patient had an impaired gait with a right foot drop. His strength in the right leg was 4/5 in all myotomes, and the left leg showed full strength. He had diminished sensation to light or sharp touch on the left side up to the T10 spinal level. He had 3+ reflexes at the patella bilaterally, 4+ at the right ankle, and 3+ at the left ankle. There was sustained clonus at the right ankle.

Spine MRI was urgently performed and showed a heterogeneously enhancing intramedullary mass extending from T7 to T10, with a small syrinx at the caudal end (Fig. 1). The patient underwent a T6–10 laminectomy and resection of the intramedullary tumor, with monitoring of

ABBREVIATIONS DMG = diffuse midline glioma.

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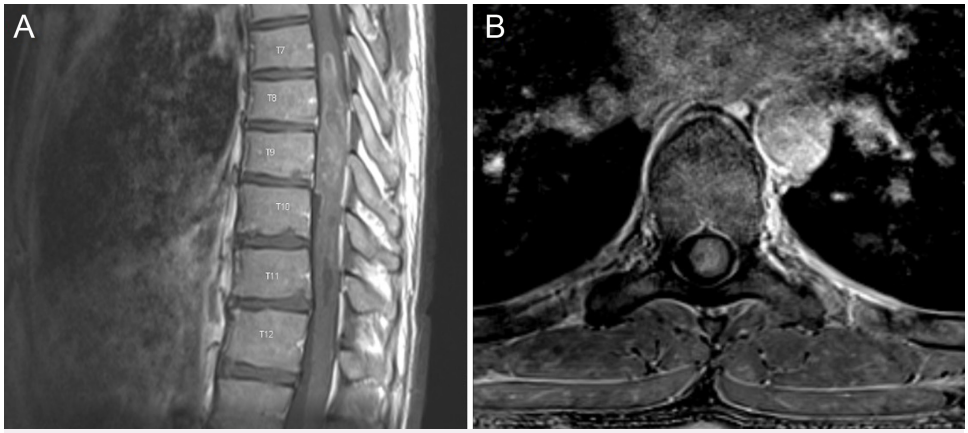

FIG. 1. A: Sagittal T1-weighted gadolinium-enhanced MR image showing an abnormal, heterogeneously enhancing intramedullary mass extending from T7 to the superior aspect of T11. Irregular multifocal syrinx is seen down to T12. **B:** Axial T1-weighted gadolinium-enhanced MR image showing the same mass at T8.

both motor evoked potentials and somatosensory evoked potentials. A midline myelotomy was performed, and a plane was developed between the tumor and spinal cord. On the right, the tumor extended to the arachnoid and was adherent to the spinal cord at the anterior and inferior surface. A gross-total resection was achieved. There was a significant drop in motor evoked potentials and somatosensory evoked potentials during the procedure, but our electrophysiologist thought that the waves suggested that this change was likely temporary and would improve with time. Postoperatively, the patient recovered well and was transferred to the inpatient rehabilitation unit. His examination prior to transfer to rehabilitation was as follows: left L2 grade 4/5, left L3 grade 4/5, left L4 grade 4/5, left L5 grade 4/5, left S1 grade 4/5, right L2 grade 3/5, right L3 grade 4/5, right L4 grade 0/5, right L5 grade 1/5, and right S1 grade 4–/5. There was mild spasticity throughout the lower extremities, worse on the right than on the left, but not severe. His proprioception was very limited on the right side to the level of the knee but preserved on the left. He was able to ambulate with crutches for short distances, climb stairs using the railing, and use a wheelchair for long distances.

Pathology results showed grade IV DMG, H3K27M mutant. The pilocytic astrocytes, Rosenthal fibers, and clefts lined by vascular arcades were reminiscent of pilocytic astrocytoma grade I. However, there were atypical features, including more proliferative arcades and exuberant vessels with occlusive endothelial hyperplasia (Fig. 2). The patient underwent radiation therapy, with 45 Gy delivered in 25 fractions, and he also received temozolomide. Follow-up MRI showed no recurrence or residual disease in the spine.

At the 29-month follow-up, the patient presented with new-onset presyncope, and MRI of the brain was performed, which showed a nonenhancing lesion in the right temporal lobe measuring 2.4 × 1.8 × 1.7 cm (Fig. 3). This was a de novo lesion not shown on previous imaging. After discussion with the patient, the lesion was initially managed conservatively with serial imaging. The rationale for monitoring was that the patient was asymptomatic and the lesion was small. The right temporal lesion was stable on serial imaging. At the 36-month follow-up, the patient had an episode of sudden loss of consciousness with a postictal period, which was suspicious for seizure. The decision was then made to proceed with resection. A right-sided temporal craniotomy and resection of the right temporal mass were performed. The patient had no postoperative neurological deficits following the second surgery. The pathology results from the right temporal lobe again showed grade IV DMG, H3K27M, similar to his spinal cord lesion

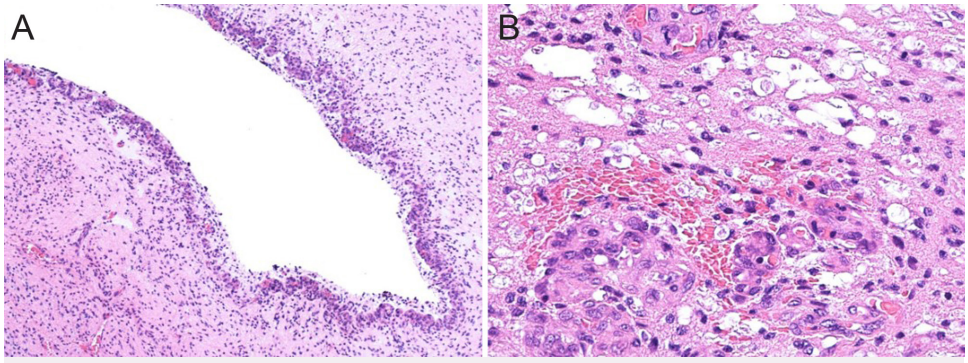

FIG. 2. A: The cleft of the thoracic spine tumor lined by vascular arcades. **B:** Vascular proliferation within the tumor. H&E, original magnification ×10 (A) and ×40 (B).

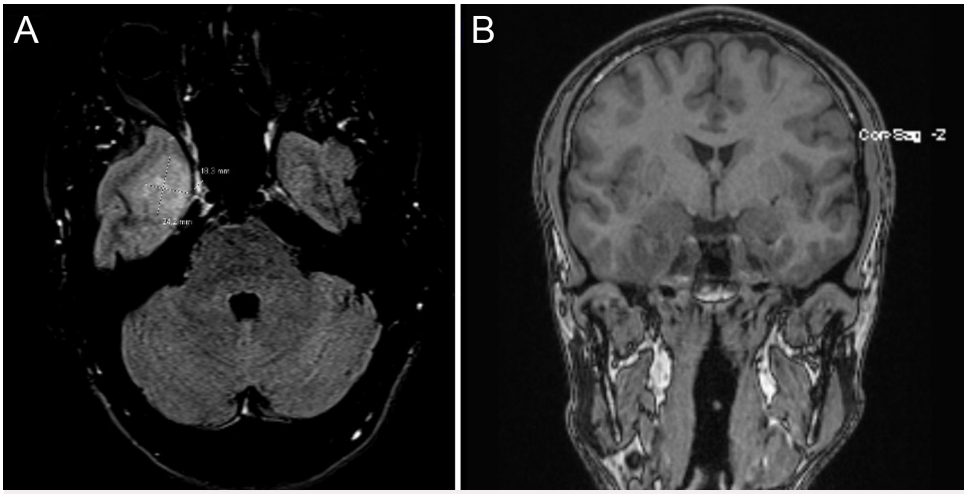

FIG. 3. A: Axial T2-weighted FLAIR sequence showing nonenhancing right temporal mass measuring 2.4 × 1.8 × 1.7 cm. **B:** Coronal MPRAGE sequence showing nonenhancing mass in right temporal lobe.

(Fig. 4). The Ki-67 proliferative index was up to 10% in the thoracic spine lesion and 15%–20% in the right temporal lesion. The patient received 60 Gy in 30 fractions.

There were no complications, and the patient remained well at the 42-month follow-up from his index surgery. The most recent images of both the thoracic spine and right temporal region showed no recurrence (Fig. 5).

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

The most recent 2021 WHO classification of central nervous tumors divided diffuse gliomas into those that primarily occur in adults ("adult-type") and those that primarily occur in children ("pediatric-type").[1] The term "primarily" is used because pediatric-type tumors can sometimes occur in adults and adult-type tumors can sometimes occur in children. This division could be seen as progress toward the eventual separation of adult- and pediatric-type tumors, which could be prognostically and biologically distinct.[1]

H3K27M-altered DMG is one of the tumors that received the designation of "pediatric-type" in the 2021 update. It is most often found in children and carries a poor clinical prognosis. While it is rare in adults, some reported cases have shown prolonged survival, depending on the tumor's location. In 2019, Peters et al. reported on an adult patient with cervical H3K27M DMG who survived 31 months, which has been the longest overall survival in the literature to date.[4] In 2023, Sato et al. reported the case of an adult patient with conus medullaris H3K27M DMG, who survived 6 years after undergoing cordectomy.[6]

The commonality between the 2 cases of prolonged survival is that the initial tumor was located in the spinal cord. Even though the case numbers are limited, it appears that gross-total resection followed by chemotherapy and radiation therapy can result in prolonged survival in rare cases.[7] One of the challenges of H3K27M-altered DMGs in children is that these tumors commonly develop in the brainstem, thalamus, hypothalamus, or pineal gland, regions that carry a universally poor prognosis.[8] There is 1 reported case of an H3K27M-altered DMG in the spinal cord in a pediatric patient in 2021, with no tumor recurrence

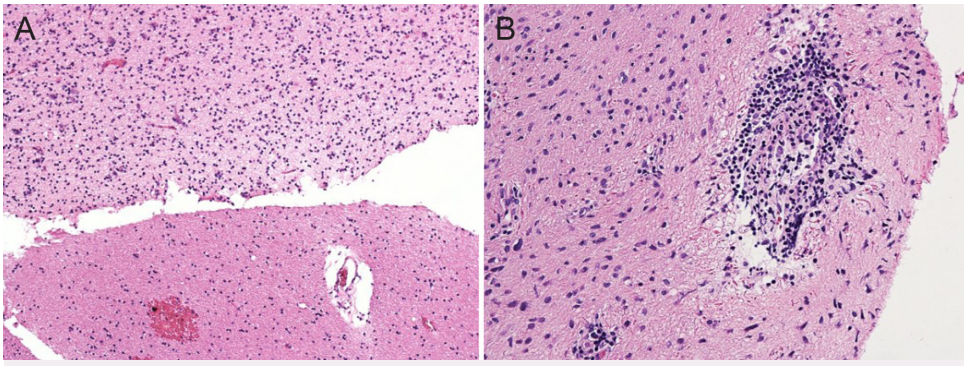

FIG. 4. A: Direct comparison of right temporal tumor and normal brain at magnification. **B:** Pseudoencephalitis within the tumor. H&E, original magnification ×10 (A) and ×20 (B).

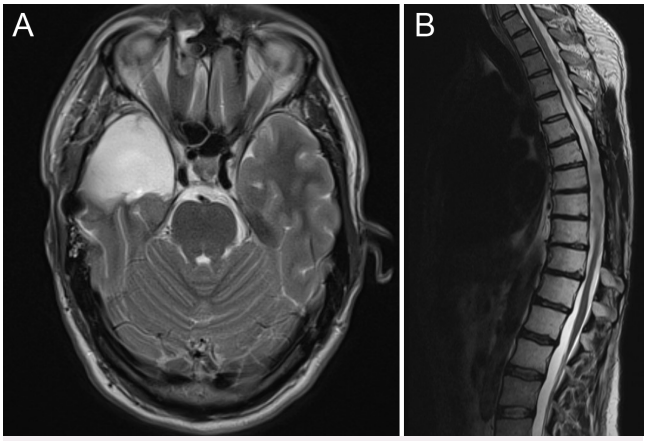

FIG. 5. A: The most recent postoperative brain image showing no residual or recurrent disease. **B:** The most recent postoperative spine image showing stable intra-axial and extra-axial cysts from T3 to T10 but no disease progression.

at 18 months.[9] There are 3 other cases of pediatric H3K27M spinal cord DMGs in the literature, but none with long-term survival.[10–12] H3K27M-altered spinal cord tumors can represent a different entity than intracranial cases. A recent paper published in *Neurospine* found no significant difference in prognosis between the H3K27M-altered and wildtype high-grade intramedullary astrocytomas.[13]

In our case, recurrence occurred 29 months postoperatively in the right temporal lobe. There are 8 other cases of supratentorial H3K27M-altered DMG in the literature, 4 of which were in the corpus callosum.[2] The patient survival in these cases ranged from 3 to 42 months.[2]

Lessons

We present the rare case of an adult-onset H3K27M DMG in the spinal cord with subsequent dissemination to the right temporal lobe. The patient underwent resection of both the spinal cord and intracranial lesion and remains well at the 40-month follow-up. Our case demonstrates that H3K27M-altered DMGs are a heterogeneous group of tumors with varying presentations. There are significant prognostic differences between the pediatric and adult types of the tumor.

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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: Liu, Toyota, Newton, Coote, Marciniuk, Auer, Fourney. Acquisition of data: Liu, Su, Newton, Coote, Auer, Fourney. Analysis and interpretation of data: Liu, Su, Toyota, Auer, Fourney. Drafting the article: Liu, Su, Toyota, Coote, Fourney. Critically revising the article: Liu, Su, Toyota, Newton, Coote, Marciniuk, Fourney. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Liu. Administrative/technical/material support: Auer, Fourney. Study supervision: Fourney.

Correspondence

Eva Liu: University of Saskatchewan, Saskatoon, SK, Canada. eva.liu@usask.ca.