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Diffuse midline glioma H3K27-altered with thoracic epidural metastasis: illustrative case

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BACKGROUND Diffuse midline glioma (DMG) H3K27-altered is a newly recognized diffuse high-grade tumor entity in the 5th edition of the WHO classification of CNS tumors. Spinal extradural metastasis is extremely rare in patients with DMG H3K27-altered, while the occurrence of spinal intramedullary DMG, intradural dissemination, and osseous metastasis has been reported.

OBSERVATIONS The authors report the case of a 6-year-old female presenting with acute-onset urinary retention and paraplegia, who was found to have a pontine DMG, an intradural mass at the level of T1–6, and an extradural lesion at T6–9. The thecal sac was severely compressed by the extradural mass; thus, a T6–9 laminectomy and extradural tumor resection were performed. After the procedure, an amelioration of weakness was observed. The patient was treated with radiotherapy to the spine. Pathology revealed an increase in chromatin, the proliferation of atypical cells, and microvascular proliferation. The H3K27 mutation was confirmed.

LESSONS This case demonstrates an operative view in the metastasis of DMG H3K27-altered to the spinal epidural space without visceral or osseous metastasis. The possibility of spinal epidural metastasis and its surgical treatability should be considered if patients with DMG present spinal cord symptoms.

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KEYWORDS diffuse midline glioma H3K27-altered; extradural tumor; case report

Diffuse midline glioma (DMG) H3K27-altered is a newly recognized diffuse high-grade tumor entity described in the 2021 WHO classification of CNS tumors.[1] DMG H3K27-altered is a rare, highly malignant CNS neoplasm that arises in midline structures. DMGs are encountered more commonly in children and are considered rare in adults. In young children, the most common location is the brainstem or the pons, whereas DMGs in adolescents and adults arise predominantly unilaterally in the thalamus or spinal cord.[1] The presence of an H3K27 mutation in the H3F3A gene automatically classifies a tumor as WHO grade 4.[1] These tumors are associated with a dismal prognosis and an overall median survival of less than 1 year.[2] Large autopsy studies have demonstrated leptomeningeal metastasis in 40% of DMG cases, as well as diffuse spread involving the thalamus, cervical spinal cord, and frontal lobe.[3] In addition, recent studies have reported the occurrence of spinal intradural dissemination[4–6] and osseous metastasis,[5–11] which reflect the progressive nature of DMG H3K27-altered. However, extradural metastasis without bone or visceral metastasis is extremely rare. Here, we report a surgical case of extradural metastasis of pathologically confirmed H3K27-altered.

Illustrative Case

Case Presentation

A 6-year-old female with no significant past medical history presented with acute headache and hemifacial palsy. MRI performed at a previous hospital revealed pontine hyperintensity in FLAIR imaging. The patient was diagnosed with DMG and treated with radiation therapy (RT). The symptoms were ameliorated by RT; however, gait disturbance and urinary retention progressed at 6 months after RT. MRI showed regrowth of the pontine lesion and apparent leptomeningeal dissemination to the cervical spinal cord at the C4–5 level (Fig. 1A–C). The patient was referred to our hospital for further treatment. Physical examination revealed that her strength was 0/5 in both lower limbs, with decreased sensation to touch. Bilateral Achilles and patellar tendon reflexes were not evoked. On the other hand, her deep tendon reflexes of the bilateral biceps brachii and triceps brachii were normoreflexic, and strength was 5/5 in both upper limbs.

MRI of the whole spine revealed an intradural extramedullary mass lesion mainly posterior to the spinal cord at T1–T6, which was

ABBREVIATIONS DMG = diffuse midline glioma; H&E = hematoxylin and eosin; POD = postoperative day; RT = radiation therapy; WT = wildtype.

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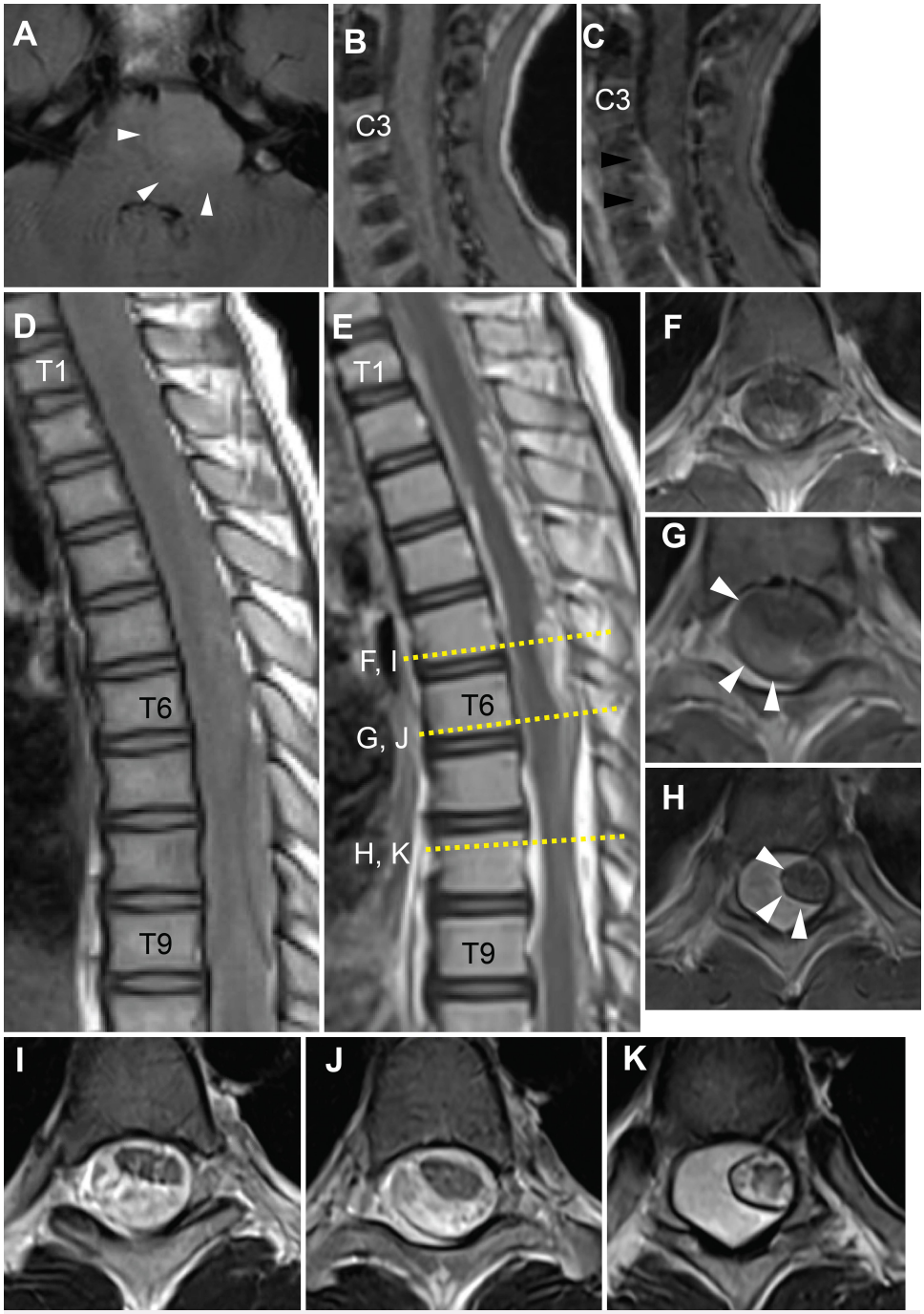

FIG. 1. Preoperative MR images depicting pontine and spinal tumors. **A:** FLAIR image showing a hyperintensity area in the left side of the pons (*white triangles*). Note that the tumor extends outward. **B and C:** T1-weighted (B) and contrast-enhanced T1-weighted (C) images showing a well-enhanced spinal tumor at the C4–5 level (*black triangles*). **D and E:** Sagittal T1-weighted (D) and contrast-enhanced T1-weighted (E) images showing the thoracic spine. Heterogeneous enhancement is shown at the level of T1–6, whereas homogeneous enhancement is shown at the level of T6–9. **F–H:** Axial contrast-enhanced MR images showing heterogeneously enhanced tumor posterior to the spinal cord (F), homogeneously enhanced tumor on the right side of the thecal sac (G), and homogeneously enhanced tumor encasing and compressing the thecal sac (H). *White triangles* indicate the dura. **I–K:** Axial T2-weighted images at the levels of T5, T6, and T8, respectively. Note that the spinal cord is most severely compressed at the level of T8, where the thecal sac is encased by the tumor.

heterogeneously enhanced by gadolinium (Fig. 1D–F). In addition, a strongly enhanced extradural mass was revealed, which surrounded the thecal sac and compressed the spinal cord from the left side at T6–9 (Fig. 1C, E, G, and H). The dura was well depicted in T1-weighted, T2-weighted, and contrast-enhanced T1-weighted images as a black line in the axial and sagittal sections. These radiological findings, along with the history of DMG, suggested the intradural dissemination of DMG and metastasis to the epidural space.

We diagnosed the cause of paraplegia to be spinal cord compression by the epidural lesion because T2-weighted imaging showed severe spinal cord compression at the level of T6–9 as compared with T1–6 (Fig. 1I and J). We performed T6–9 laminectomy followed by resection of the extradural tumor. The tumor was gray, hard, and hemorrhagic (Fig. 2A). However, adhesion of the tumor to the spinal dural sac and root sleeve was not severe. Total resection of extradural tumor was achieved (Fig. 2B). Tumor components anterior to the thecal sac were curetted and aspirated. At the level of T6–9, the fistula communicating between the intradural and epidural space caused by the tumor was not observed. Hence, CSF leakage was not encountered during tumor removal.

Postoperatively, the patient showed gradual recovery of manual muscle testing scores in her bilateral lower extremities. The strength of her lower limbs was 2/5 on postoperative day (POD) 5 and 3/5 on POD 8. However, she continued to have urinary retention. MRI on POD 3 showed expansion of thecal sac at the level of T6–9 (Fig. 2C–E) and no growth of the cervical intradural lesion. On POD 8, she was transferred to the previous hospital, which was near her home, for RT to the spine.

A sample of the tumor was collected during surgery and was sent for histopathological analysis (Fig. 3). Pathology revealed an increase in chromatin, the proliferation of atypical cells with nuclear size variability, and microvascular proliferation. Immunohistochemical analysis demonstrated that the tumor was positive for *GFAP*, *Olig2*, *ATRX*, and *MTAP* and negative for *IDH1*, *R132H*, *MGMT*, and *p53*. The *Ki-67* labeling index was 30%. The presence of an H3K27 mutation was confirmed, supporting the diagnosis of DMG H3K27-altered (WHO grade 4) in this patient.

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

In this case study, we describe a surgically treated pediatric case of epidural metastasis of DMG H3K27-altered. Metastases of pediatric DMG outside the CNS are relatively rare, with only several cases of extra-neural metastasis reported.[8–10,12] In those cases, most of the DMG metastases to the spine were osseous lesions. Other patterns of spinal involvement include leptomeningeal, intramedullary, and intradural extramedullary dissemination.[13,14] Our patient's spinal metastasis was located in the epidural space of the thoracic spine and, in addition to the intradural extramedullary lesion, caused compression of the thecal sac. Surgical findings indicate an absence of direct invasion from the intradural to the extradural space at the thickest part of the extradural tumor, suggesting that the extradural tumor metastasized through a different pathway than intradural dissemination. Although there are no reports of extradural metastasis of DMG, some studies have reported the extradural metastasis of glioma.[15–18] A postmortem study suggested that a glioma spread through the venous system after having gained entrance at either the dural or intracerebral level.[18] In our patient, the venous plexus might be the channel through which metastatic tumor cells reach the epidural space.

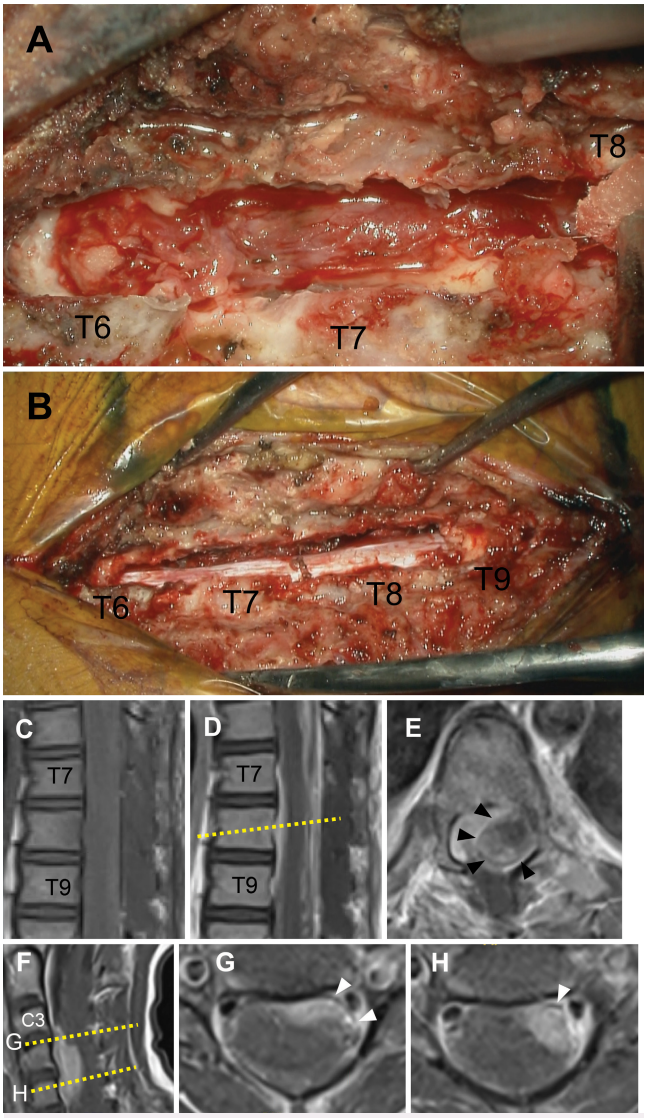

FIG. 2. Surgical findings. **A:** After the laminectomy and removal of flavum, a gray, hard, and hemorrhagic tumor is observed. **B:** The extradural tumor is removed. CSF leakage and direct invasion of the tumor to the dura are not observed. **C–E:** Postoperative T1-weighted (C) and contrast-enhanced T1-weighted (D) images demonstrating removal of the extradural tumor and expansion of the thecal sac as compared with the preoperative MR image (E; *dashed line in panel D*). The *black triangles* indicate the dura. **F–H:** Postoperative cervical contrast-enhanced T1-weighted images at the levels of C3–4 (G; *dashed line in panel F*) and C5 (H; *dashed line in panel F*). Dura is depicted as the *thin black lines* (*white triangles*).

The radiographic features of DMG H3K27-altered are highly variable among the few reported cases. Hohm et al. reported the radiographical difference between DMG H3K27-altered and DMG H3K27-wildtype (WT).[19] In their report, the majority of intracranial H3K27-altered tumors showed hyperintense T2 signal in 93.6% of cases, compared with only 63.6% in WT tumors. There was no clear

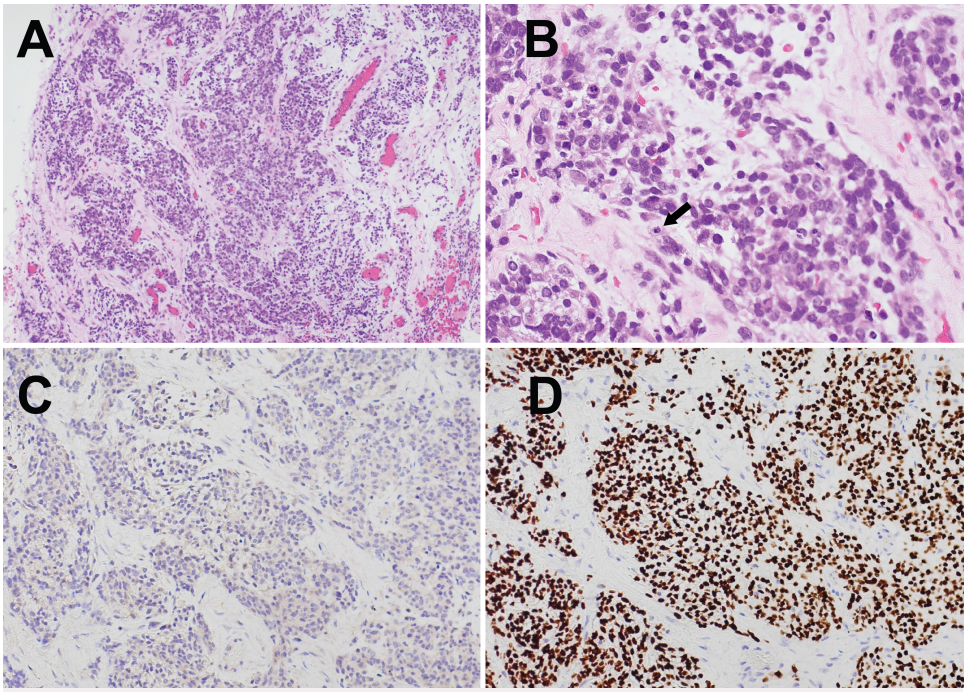

FIG. 3. Microscopic pathology of extradural neoplasm. **A:** Hematoxylin and eosin (H&E) stain showing high cellularity and pleomorphism. Original magnification ×100. **B:** H&E stain demonstrating mitotic figures (*arrow*). Original magnification ×400. **C:** *IDH* R132H immunohistochemistry was negative. Original magnification ×200. **D:** H3K27-altered immunohistochemistry was positive. Original magnification ×200.

tendency of contrast enhancement in DMG. In our case, moderately enhanced lesions were observed in the intradural cervical and thoracic spinal canal at the levels of C3–5 and T1–6. In addition, a strongly enhanced extradural lesion was depicted at T6–9. Thus, contrast enhancement of the tumors can vary in a single patient. Interestingly, dura was well depicted in T2-weighted and contrast-enhanced T1-weighted images as a black line in axial and sagittal sections, which was helpful to identify that the tumor existed in extradural space.

A limitation of this case report is that the specimen was not collected from the intradural tumor at the level of T1–6. Although radiological and surgical findings suggest that intradural and extradural components of the tumors progressed via different pathways, histopathological findings would strengthen differences in the metastasis pathway.

Lessons

Extradural metastasis is extremely rare in cases of DMG H3K27-altered. However, the possibility of spinal epidural metastasis and surgical treatability should be considered if patients with DMG present with spinal cord symptoms.

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Author Contributions

Conception and design: Sawada. Acquisition of data: Sawada, Hattori, Sano. Analysis and interpretation of data: Sawada, Mineharu. Drafting the article: Sawada, Sumita. Critically revising the article: Sawada, Sumita, Sano, Tanji, Mineharu, Kikuchi. Reviewed submitted version of manuscript: Sawada, Sumita, Hattori, Sano, Takada, Mineharu, Kikuchi, Arakawa. Approved the final version of the manuscript on behalf of all authors: Sawada. Study supervision: Mineharu, Arakawa.

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