

Pediatric H3K27M-mutant diffuse midline glioma with vertebral metastasis: A case report and literature review

XIAOHUI GE*, YU YANG*, WENYAN WANG, LEI TIAN,
GE ZHANG, ZHESEN TIAN and XIAOYING XUE

Department of Radiotherapy, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei 050000, P.R. China

Received May 13, 2023; Accepted November 7, 2023

DOI: 10.3892/ol.2023.14181

Abstract. H3K27M-mutant diffuse midline glioma (DMG) is a type of high-grade glial tumor, which occurs in the midline structure and develops mostly in children. Extranuclear metastases (ENM) are exceedingly rare in patients with H3K27M-mutant DMG. A 9-year-old male patient presented with a headache, nausea and vomiting. Following magnetic resonance imaging and immunohistochemical molecular testing examination, the patient was diagnosed with H3K27M-mutant DMG and received chemoradiotherapy plus five cycles of chemotherapy with temozolomide intermittently as an adjuvant therapy. The treatment resulted in a slight reduction of the tumor volume. However, 2 months later, the patient was admitted to hospital with complaints of drooping of the mouth, and waist and back pain. Magnetic resonance imaging and positron-emission tomography-computed tomography revealed an unusual presentation with multiple vertebral metastases and craniospinal leptomeningeal dissemination. Following discussion between the members of a multidisciplinary medical team, the patient underwent one cycle of chemotherapy with cyclophosphamide, vincristine and cisplatin. However, the condition did not improve and the patient died 4 weeks after the diagnosis of ENM. The mechanisms underlying the development of these rare metastases remain unclear. The present case report provides insights into the clinical characteristics and potential metastasis mechanisms

of this aggressive disease and may help to elucidate new pathways for the management of ENM.

Introduction

According to the World Health Organization (WHO), H3K27M-mutant diffuse midline glioma (DMG) is a grade IV malignancy that occurs at any age with no sex predilection, but commonly occurs in children aged 5-11 years old, rarely occurs in middle-aged and elderly people (1). Although epidemiological data remain scant for H3K27M-mutant DMG, the incidence of pediatric diffuse intrinsic pontine glioma (DIPG) is estimated to be 0.54 cases per 1million person-years (2). H3K27M-mutant DMG represents 10-15% of pediatric brain tumors and occurs at a prevalence of ~75% in DIPG (3). Furthermore, pediatric DMG is mainly located in the brainstem, thalamus, or spinal cord, and is often identified in a relatively advanced stage, this indicate a low degree of resection and the patient often has some serious symptoms, such as headache, vomiting, nerve palsy, ataxia and even respiratory and cardiac arrest. The prognosis of patients with this disease is poor, with a median survival time of 1 year from diagnosis (1). Glioma is characterized by local recurrence and invasion; nevertheless, extraneural metastases (ENM) are rare, occurring in <2% of patients with glioma (4,5). Thus far, only five cases of ENM in patients with H3K27M-mutant DMG have been reported in the literature (6-10). In the present study, a pediatric case of brainstem H3K27M-mutant DMG is reported, with an unusual presentation involving multiple vertebral metastases and extensive craniospinal leptomeningeal dissemination. Furthermore, the relevant literature is discussed.

Case report

A 9-year-old male patient presented with a headache, nausea and vomiting that had persisted for two weeks. He initially attended at Beijing Tiantan Hospital (Beijing, China) in August 2019 and then was admitted to the Second Hospital of Hebei Medical University in Shijiazhuang on September 2019. Magnetic resonance imaging (MRI) of the brain revealed the presence of a 6.0x5.4x5.9-cm³ irregular, solid and cystic mass in the brainstem, with a slightly dilated supratentorial ventricle (Fig. 1A). Additionally, the tumor appeared hyperintense on T2, hypointense on T1, and T1-weighted with heterogeneous internal

Correspondence to: Professor Xiaoying Xue, Department of Radiotherapy, The Second Hospital of Hebei Medical University, 215 Heping West Road, Xinhua, Shijiazhuang, Hebei 050000, P.R. China
E-mail: xxy0636@163.com

*Contributed equally

Abbreviations: DMG, diffuse midline glioma; ENM, extraneural metastases; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography

Key words: DMG, H3K27M, extraneural metastasis, vertebral metastasis

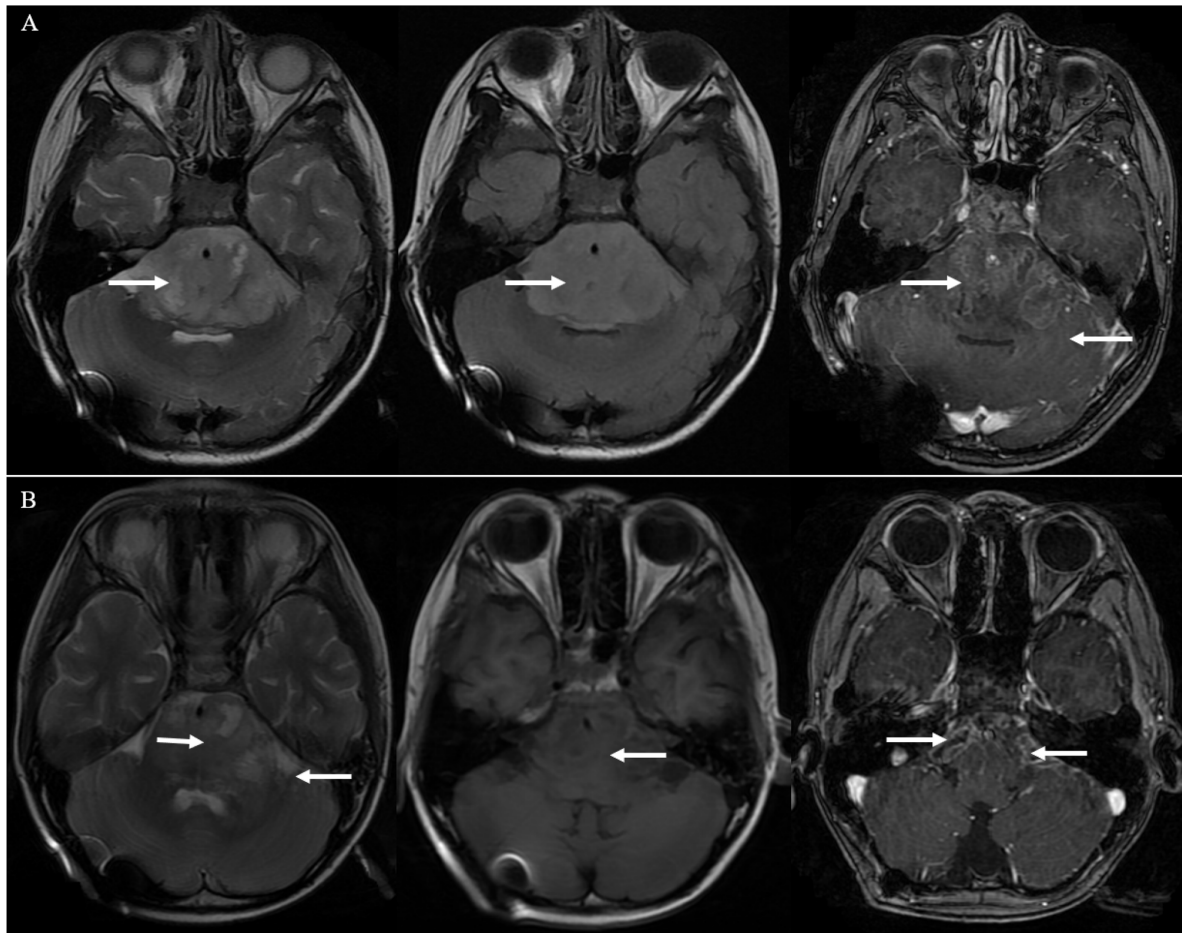


Figure 1. An irregular, solid and cystic mass observed in the brainstem, measured at 6.0x5.4x5.9 cm. (A) Pre-treatment, the tumor appeared hyperintense on T2, hypointense on T1, and heterogeneous internal enhancement on T1-weighted. (B) Post-radiochemotherapy, the irregular, solid and cystic mass was smaller than before treatment and the degree of enhancement was reduced. White arrows indicate the location of the lesion.

enhancement. MRI of the spine did not detect metastases. The patient had headaches and vomiting for supratentorial ventricular dilation caused by tumor compression, so subsequently, both a stereotactic biopsy and right ventriculoperitoneal shunt were performed; postoperative the patient vomiting disappeared and headache was alleviated. Histological sections of PXAs (4 μ m thick) were prepared from 10% formalin-fixed paraffin-embedded tissue blocks for 48 h at room temperature as follows: Tissue chips were placed in a 60°C oven for 20 min, then soaked in xylene for 3 times with 10 min per time, soaked in absolute ethanol for 3 times with 5 min per time and soaked successively in 90, 80, 70% ethanol for 3 times with 5 min per time, soaked successively in tap water and distilled water for 5 min), HE stain (Hematoxylin staining for 5 min and eosin staining for 10 s at room temperature), etc. Images were obtained using a Leica light camera. Histological assessment revealed an anaplastic astrocytic glioma with areas of variable cellularity, atypia and focal mitotic activity (Fig. 2A). Immunohistochemical testing of the tissue demonstrated that H3K27M-mutant protein was expressed in tumor cells (cat. no. GT236902; Gene Tech Co., Ltd; Fig. 2B). As a result, the medical team reached a histopathological diagnosis of H3K27M-mutant DMG (WHO grade IV). Histochemical testing and genetic sequencing would have been beneficial to support the understanding of the present case but were not available.

Chemoradiotherapy was initiated 40 days after the right ventriculoperitoneal shunt surgery. The gross tumor volume (GTV) was defined as the area of T1-weighted and T2-flair abnormal signals. The clinical target volume (CTV) was the expansion of the GTV by 0.5 cm. Subsequently, the planning target volume (PTV) was set as a 3-mm margin around the CTV. The prescribed dose to the PTV was 50 Gy/25 fractions (2 Gy/fraction). Accordingly, the patient received 75 mg/m²/day oral temozolomide throughout the period of radiotherapy for 5 weeks. The tumor volume was slightly reduced 1 month later based on the Response Assessment in Neuro-Oncology criteria (11) (Fig. 1B). Adjuvant chemotherapy with temozolomide was performed intermittently for five cycles. The dose in cycle 1 was 150 mg/m²/day, whilst in cycles 2-5 (all cycles administered on days 1-5, every 28 days) it was 200 mg/m²/day.

Drooping was observed on the right side of the patient's mouth while laughing, and the patient reported waist and back pain 2 months after chemotherapy. MRI demonstrated nodular and patched enhancement in the tumor located in the brainstem and cerebellum. Around the fourth ventricle, the tumor was enlarged compared with prior to treatment. Furthermore, enhanced MRI of the spine showed diffuse metastases in the spinal cord and craniospinal leptomeningeal dissemination with abnormal enhancement. Several lumbar-sacral metastases with bone destruction and abnormal enhancement were also

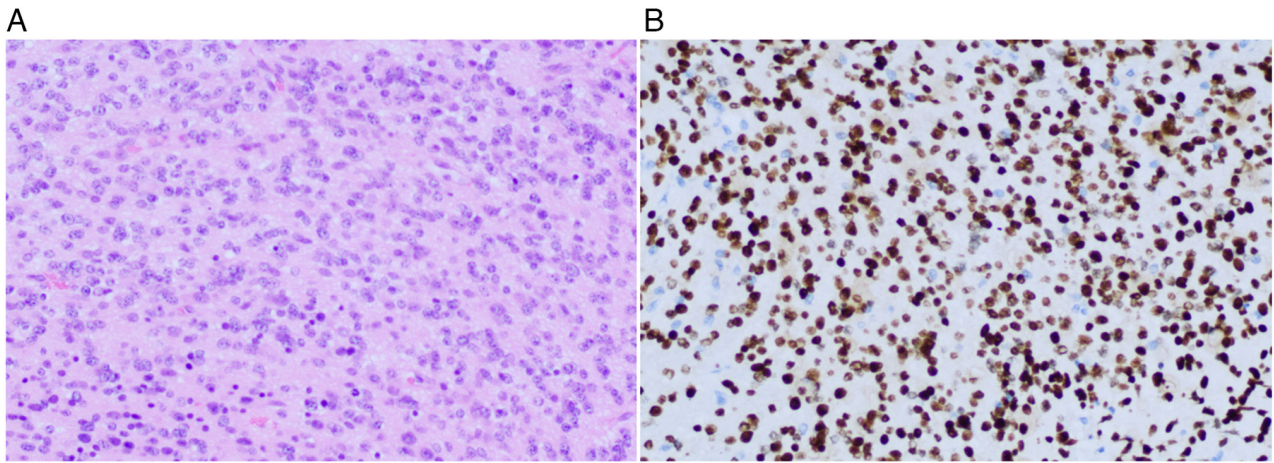


Figure 2. Histological and immunohistochemical assessments of the tumor, leading to a pathological diagnosis of H3K27-mutant brain stem diffuse midline glioma (World Health Organization 2016 criteria, grade IV). (A) Presence of anaplastic astrocytic morphology with areas of variable cellularity, atypia and focal mitotic activity (hematoxylin and eosin stain, magnification, x200). (B) Immunohistochemistry demonstrating H3K27M(+) tumor cells (magnification, x200).

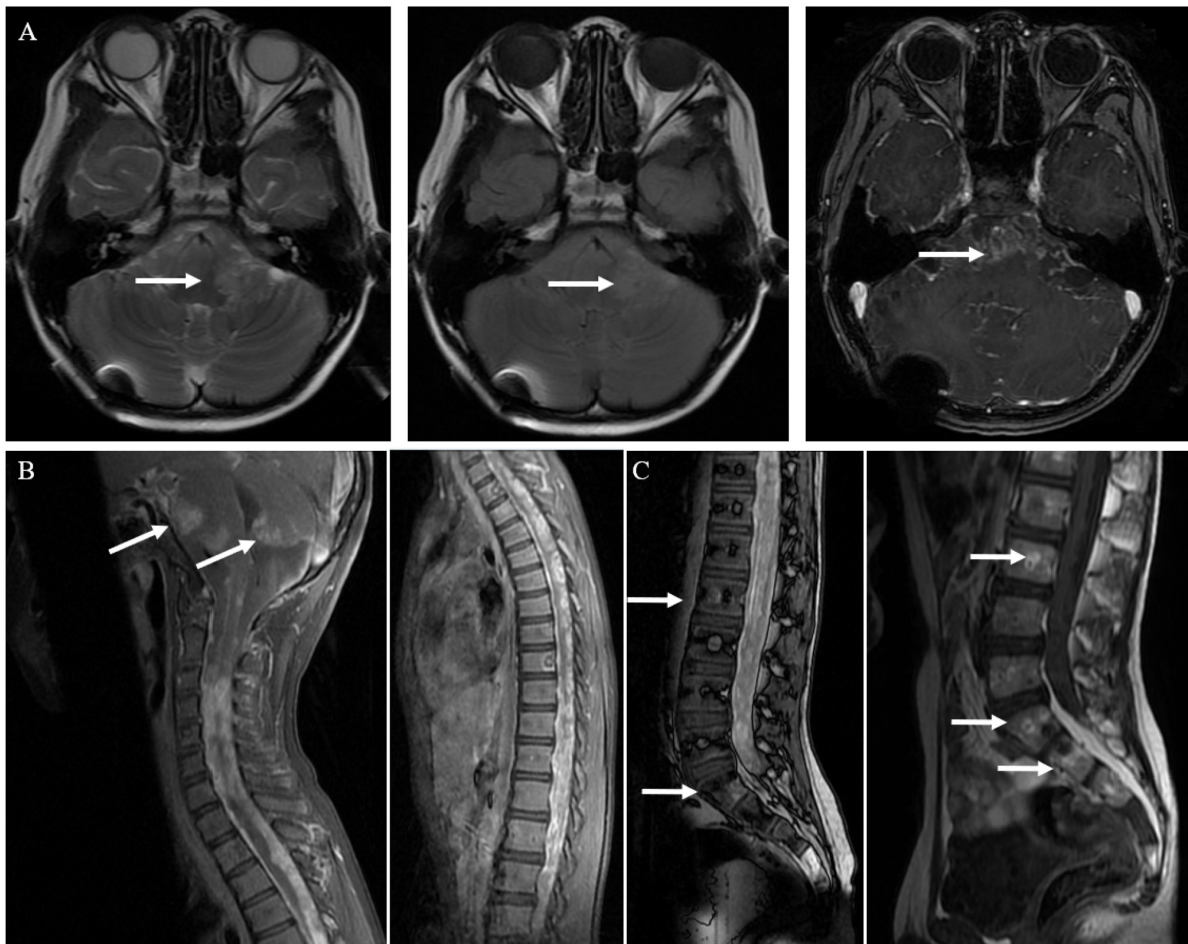


Figure 3. MRI of the head and spine showed diffuse metastases. (A) MRI revealed nodular and patched enhancement of the tumor in the brain stem, cerebellum and around the fourth ventricle, with an increased tumor size compared with that in the previous review. (B) Enhanced MRI scan of the spine showed diffuse metastasis of the spinal cord and meninges with abnormal enhancement, and (C) several lumbar sacral metastases with bone destruction and abnormal enhancement. White arrows indicate the location of the lesion. MRI, magnetic resonance imaging.

noted (Fig. 3). Examination using fluorine-18-fluorodeoxyglucose positron-emission tomography-computed tomography (PET-CT) also demonstrated multiple metastases in the

spinal membrane and a diffuse increase of metabolism in the cervical, thoracic and lumbosacral vertebral areas (Fig. 4). Subsequently, the patient rapidly developed neck pain,

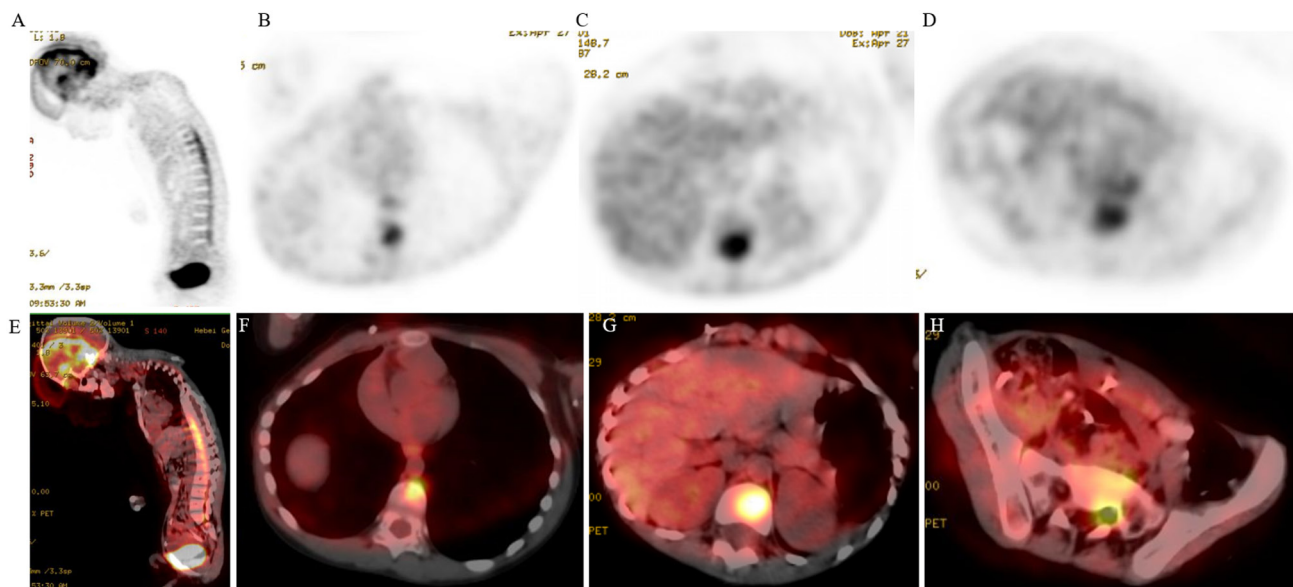


Figure 4. PET-CT showed multiple spine and vertebral metastases. CT demonstrated hypermetabolic lesions in (A) multiple vertebral bodies and the spinal cord, (B) the thoracic spine, (C) the lumbar spine and (D) the sacrum. PET demonstrated hypermetabolic lesions in (E) multiple vertebral bodies and the spinal cord, (F) the thoracic spine, (G) the lumbar spine and (H) the sacrum. PET-CT demonstrated a diffuse increase in metabolism in the cervical, thoracolumbar and sacral vertebral canals, and abnormal hypermetabolism of multiple thoracolumbar vertebral bodies. In combination with magnetic resonance imaging, the findings indicated multiple metastases of the spinal membrane and vertebral bodies. CT, computed tomography; PET, positron emission tomography.

stiffness and urinary retention. Based on discussions between the members of a multidisciplinary medical team, the patient underwent one cycle of chemotherapy with cyclophosphamide 600 mg on day 1, vincristine 1mg on day 1 and cisplatin 20 mg on day 1-3, one cycle every 28 days. Moreover, pain relievers (Tramadol injection 50 mg twice daily) and dehydrating drugs (Mannitol 100 ml twice daily, Dexamethasone 3 mg once a day) were administered to relieve the symptoms. However, the condition did not improve and the patient died 4 weeks after diagnosis of ENM due to disease progression.

Discussion

H3K27M-mutant DMG refers to a tumor type classified as a central nervous system (CNS) tumor by the WHO, based on the molecular signature, with the 2016 WHO classification of CNS tumors recognizing H3K27M-mutant DMG as a clinical pathological entity (1). This malignancy mostly develops in children and seldomly in adults (1). DMG is accompanied by a mutation of histone H3K27M and its growth is diffuse and invasive (12). Karremann *et al* (13) reported that H3K27M mutation was the sole independent prognostic factor, indicating a poor prognosis, meaning that the prognosis of H3K27M-mutant DMG was not associated with the extent, location and grade of the tumor.

High-grade glioma (HGG) accounts for 8-15% of pediatric CNS tumors (14,15) and ~50% of the cases occur in the midline location, namely DMG (16). Notably, diffuse intrinsic pontine glioma refers to the intrinsic pontine type of DMG. In these cases, the H3K27M heterozygous somatic mutation, which occurs in pediatric diffuse intrinsic pontine glioma, has a prevalence rate of 78%. The rate of this mutation in other DMGs, such as thalamic and spinal gliomas, is ~22% (17). The biological manifestation is highly malignant and corresponds to that of a grade IV lesion.

The prognosis of H3K27M-mutant DMG is generally poor, with a 2-year overall survival rate of <10% (18-20).

HGG is highly invasive locally, occasionally spreading along the neuraxis. Autopsy studies have reported that metastases in the neuraxis occur in ~20% of patients with HGG (4,5,7). However, the estimated incidence of ENM from intracranial malignant gliomas is 0.4-2% of all cases (4,5). The most commonly reported sites of HGG-ENM are the lung/pleural cavity (60%), lymph nodes (51%), bones (31%) and liver (22%) (21-23). The low incidence rate may be related to the barrier of the CNS and the short life span of the patients; malignant glioma cells rarely have the necessary time to breach the protective intrinsic biological obstacles and thus, develop into ENM (24,25). It has been reported that iatrogenic factors, encompassing vascular invasion, and cranial nerve perineural and lymphatic spread may be responsible for ENM in a number of cases (4,26). In addition, the most recurrent site of bony metastasis is the axial skeleton; the vertebrae are the most common site (73%), followed by the ribs and sternum (26). This indicates that venous invasion may reflux into the Batson plexus of the spine. Metastatic glioma cells disseminate into the spinal fluid and enter the Batson plexus, which supplies the vertebrae with blood, thus facilitating the metastasis to the vertebrae (4,8).

ENM in H3K27M-mutant DMG is extremely rare. Only five cases of H3K27M-mutant DMG with ENM have been reported (6-10) since it was acknowledged as a clinical pathological entity (1) and was classified as pediatric-type diffuse HGG in 2021 (27). Of the aforementioned five cases, two cases were of peritoneal cavity metastases and three were bony metastases. All five cases involved children. The characteristics and treatment results of the five published cases of H3K27M-mutant DMG with ENM are summarized in Table I.

Stephens *et al* (6) reported a case of H3K27M-mutant glioma with peritoneal cavity seeding in a 4-year-old male

Table I. Cases of H3K27M-mutant diffuse midline glioma with multiple extraneural metastases.

First author, year	Age of patient, years	Presentation	Location of tumor	Intervention	H3K27M status	Adjuvant treatment	Overall survival, months	(Refs.)
Stephens <i>et al</i> , 2019	4	Headache, left facial droop, reduced vision and partial ptosis	Suprasellar cistern lesion, spinal cord metastasis, and intra-abdominal metastases	Surgical debulking, bilateral ventriculoperitoneal shunts and ascitic drainage	+	Radiotherapy and chemotherapy	4	(6)
Bhatt <i>et al</i> , 2020	15	Headache, neck stiffness, paraparesis and back pain	Fourth ventricle, craniospinal pial seeding, vertebral, rib and pelvis metastases	Open spinal biopsy and bone marrow aspiration from iliac rest	+	None	0.5	(7)
Handis <i>et al</i> , 2021	16	Blindness, back pain, paraplegia, and urinary and fecal incontinence	Spinal intramedullary, craniospinal pial seeding and multiple vertebral metastases	Open spinal biopsy and concurrent bone marrow aspiration from vertebral body	+	Radiotherapy and chemotherapy	5	(8)
Lazow <i>et al</i> , 2022	12	Bilateral lower weakness, back pain, bowel/bladder incontinence and diplopia	Osseous (vertebrae, pelvis, sternum, bilateral femurs and humeri) and pulmonary nodules	Open spinal biopsy and left iliac osseous disease	+	Radiotherapy and molecularly targeted therapy-cabozantinib	9	(9)
Mohiuddin <i>et al</i> , 2021	17	Headaches, diplopia, paresthesia, dizziness and short-term memory loss	Left hippocampus, midbrain, spinal cord, chest abdomen, pelvis lymph nodes, liver and omental fat stranding	Stereotactic biopsy and ventriculoperitoneal shunt	+	Radiotherapy and chemotherapy	5	(10)
Present study	9	Headache, nausea, vomiting, mouth skew upon laughing, back pain, neck stiffness and pain, and urinary retention	Brain stem, craniospinal pial seeding, spinal intramedullary, craniospinal pial seeding and multiple vertebral metastases	Stereotactic biopsy and right ventriculoperitoneal shunt	+	Chemoradiotherapy and chemotherapy	10	-

patient. The patient presented with a large, solid and cystic lesion centered on the suprasellar cistern, and received radiochemotherapy for the primary lesion. Moreover, the patient underwent bilateral ventriculoperitoneal shunting due to acute hydrocephalus. Massive ascites developed due to histologically confirmed intra-abdominal glioma metastasis at 14 months after the initial diagnosis. The patient died 1 month later. Another case of H3K27M-mutant DMG with peritoneal metastases, accompanied by spinal cord metastases, involved a 17-year-old female patient. The patient successively underwent chemoradiotherapy and ventriculoperitoneal shunting. Nevertheless, chest, abdominal and liver metastases, and pleural and multifocal soft tissue metastases rapidly developed, and the patient died 5 months after the diagnosis (10). Both of the aforementioned patients underwent bilateral ventriculoperitoneal shunting and the subsequent presentations implied that the dissemination to the peritoneum may have occurred via the ventriculoperitoneal shunts.

Bhatt *et al* (7) was the first to report a pediatric case of H3K27M-mutant DMG with diffuse bony metastases. A 15-year-old female patient presented with a lesion in the fourth ventricle, innumerable intradural lesions and leptomeningeal seeding throughout the neuraxis, as well as several osteoblastic lesions involving the spine, ribs, sternum, pelvis, humerus and femurs. The pathological analysis demonstrated the presence of H3K27M-mutant DMG with metastasis. The patient died 2 weeks after the initial presentation. The second reported case of pediatric H3K27M-mutant DMG with this type of presentation involved a 16-year-old female patient who had multiple vertebral metastases within bony structures and craniospinal pial seedings (8). The patient died 5 months after the diagnosis. The third case involved a 12-year-old with H3K27M-mutant DMG and vertebral and lung metastases, who received radiotherapy and molecularly targeted therapy with cabozantinib (9). The patient expired 9 months after the initial diagnosis.

The present case was the fourth report of a pediatric patient with H3K27M-mutant DMG and multiple vertebral metastases. A pathological biopsy of the vertebrae was not performed in this case. Both MRI and PET-CT demonstrated multiple vertebral lesions and the patient presented with multiple vertebral metastases and extensive craniospinal leptomeningeal dissemination.

The most common cause of bone metastasis may be venous invasion to the Batson plexus of the spine (28). Recent study have reported that malignant tumor cells may migrate through nerve roots (29). All the aforementioned cases reported multiple vertebral metastases with extensive craniospinal pial seeding. This may help glioma cells to metastasize along the nerve roots. Therefore, it is hypothesized that the ENM in these patients may migrate via the spinal nerve roots. However, additional clinical cases are required to assess this hypothesis.

Currently, there is no consensus regarding the optimal treatment for H3K27M-mutant DMG. Due to the location of lesions, surgical treatment continues to be difficult. Therefore, traditional radiotherapy can be used to prolong overall survival. Radiotherapy is an independent clinical parameter influencing overall survival (30), whereas the effects of adjuvant chemotherapy are limited. Drugs targeting vascular endothelial growth factor and epidermal growth factor receptor, as well as

anti-angiogenic and several multi-kinase inhibitors, have not exhibited satisfactory efficacy (31-33). However, programmed cell death-ligand 1/programmed cell death-1 inhibitors may be a beneficial treatment option for such patients (34).

Further research is warranted to develop innovative and effective treatment strategies for patients with H3K27M-mutant DMG. H3K27M mutations alter methylation level and there are numerous molecular pathological mechanisms that remain unknown (16). An enhanced understanding of this mutation and the emergence of targeted drugs may lead to the development of more rational therapeutic methods, which may improve overall survival.

In conclusion, the occurrence of ENM in patients with H3K27M-mutant DMG is exceedingly rare, and the mechanisms underlying the development of such metastases remain unclear. Therefore, the present case report provides insight into the clinical characteristics and metastasis mechanisms of this aggressive disease and may help to elucidate new pathways for the management of ENM. However, additional studies are needed in this field.

Acknowledgements

Not applicable.

Funding

The present study was supported by Hebei Natural Science Foundation (grant no. H2022206430) and the S&T Program of Hebei (grant nos 22377723D and 236Z7718G).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XX designed the study. XG participated in the study conception, performed the study, carried out the literature search and wrote the paper. YY participated in the treatment of the patient, analyzed aggregated data and helped write the manuscript. WW participated in the acquisition of data and the histological examination of the sample. LT and ZT participated in the radiological examination of the images. GZ participated in the acquisition of data and revision of the manuscript. ZT participated in the critical review and substantively revised it. All authors have read and approved the final manuscript. XG and YY confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present case report was approved by the Institutional Review Board of Hebei Medical University (Shijiazhuang, China), ethics approval number:2023-R100.

Patient consent for publication

Consent for publication of the case report and associated images was obtained from the patient's mother.

Competing interests

The authors declare that they have no competing interests.

References

- Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P and Ellison DW: The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A summary. *Acta Neuropathol* 131: 803-820, 2016.
- Mackay A, Burford A, Carvalho D, Izquierdo E, Fazal-Salom J, Taylor KR, Bjerke L, Clarke M, Vinci M, Nandhabalan M, *et al*: integrated molecular meta-analysis of 1,000 pediatric high-grade and diffuse intrinsic pontine glioma. *Cancer Cell* 32: 520-537, 2017.
- Ostrom QT, Price M, Ryan K, Edelson J, Neff C, Cioffi G, Waite KA, Kruchko C and Barnholtz-Sloan JS: CBTRUS statistical report: Pediatric brain tumor foundation childhood and adolescent primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. *Neuro Oncol* 24 (Suppl 3): iii1-iii38, 2022.
- Hamilton JD, Rapp M, Schneiderhan T, Sabel M, Hayman A, Scherer A, Kröpil P, Budach W, Gerber P, Kretschmar U, *et al*: Glioblastoma multiforme metastasis outside the CNS: Three case reports and possible mechanisms of escape. *J Clin Oncol* 32: e80-e84, 2014.
- Beauchesne P: Extra-neural metastases of malignant gliomas: Myth or reality?. *Cancers (Basel)* 3: 461-477, 2011.
- Stephens S, Tolleson G, Robertson T and Campbell R: Diffuse midline glioma metastasis to the peritoneal cavity via ventriculo-peritoneal shunt: Case report and review of literature. *J Clin Neurosci* 67: 288-293, 2019.
- Bhatt NS, Houser K, Belongia M, Ellison DW, Foy A, Jarzembowski J, Kelly T, Maheshwari M, Suchi M and Knipstein J: Diffuse midline glioma with osseous metastases at diagnosis: A case report. *J Pediatr Hematol Oncol* 42: e673-e676, 2020.
- Handis C, Tanrikulu B, Danyeli AE and Özek MM: Spinal intramedullary H3K27M mutant glioma with vertebral metastasis: A case report. *Childs Nerv Syst* 37: 3933-3937, 2021.
- Lazow MA, Leach JL, Trout AT, Breneman JC, Fouladi M and Fuller C: Extraneural metastases of diffuse midline glioma, H3 K27M-Mutant at diagnosis: Case report, review of the literature, and identifying targetable alterations. *J Pediatr Hematol Oncol* 44: e597-e604, 2022.
- Mohiuddin S, Maraka S, Usman Baig M, Gupta S, Muzzafar T, Valyi-Nagy T, Lindsay H, Moody K, Razvi S, Paulino A, *et al*: Case series of diffuse extraneural metastasis in H3F3A mutant high-grade gliomas: Clinical, molecular phenotype and literature review. *J Clin Neurosci* 89: 405-411, 2021.
- Chukwueke UN and Wen PY: Use of the Response Assessment in Neuro-Oncology (RANO) criteria in clinical trials and clinical practice. *CNS Oncol* 8: CNS28, 2019.
- Yi S, Choi S, Shin DA, Kim DS, Choi J, Ha Y, Kim KN, Suh CO, Chang JH, Kim SH and Yoon DH: Impact of H3.3 K27M mutation on prognosis and survival of grade IV spinal cord glioma on the basis of New 2016 World Health Organization classification of the central nervous system. *Neurosurgery* 84: 1072-1081, 2019.
- Karremann M, Gielen GH, Hoffmann M, Wiese M, Colditz N, Warmuth-Metz M, Bison B, Claviez A, van Vuurden DG, von Bueren AO, *et al*: Diffuse high-grade gliomas with H3 K27M mutations carry a dismal prognosis independent of tumor location. *Neuro Oncol* 20: 123-131, 2018.
- Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, Kruchko C, McCarthy BJ, Rajaraman P, Schwartzbaum JA, *et al*: Brain tumor epidemiology: Consensus from the Brain tumor epidemiology consortium. *Cancer* 113 (7 Suppl): S1953-S1968, 2008.
- Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, Wolinsky Y, Kruchko C and Barnholtz-Sloan JS: CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. *Neuro Oncol* 17 (Suppl 4): iv1-liv62, 2015.
- Jones C and Baker SJ: Unique genetic and epigenetic mechanisms driving paediatric diffuse high-grade glioma. *Nat Rev Cancer* 14: 10.1038/nrc3811, 2014.
- Wu G, Broniscer A, McEachron TA, Lu C, Paugh BS, Becksfors J, Qu C, Ding L, Huether R, Parker M, *et al*: Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet* 44: 251-253, 2012.
- Lu VM, Alvi MA, McDonald KL and Daniels DJ: Impact of the H3K27M mutation on survival in pediatric high-grade glioma: A systematic review and meta-analysis. *J Neurosurg Pediatr* 23: 308-316, 2018.
- Navarro RE, Golub D, Hill T, McQuinn MW, William C, Zagzag D and Hidalgo ET: Pediatric midline H3K27M-mutant tumor with disseminated leptomeningeal disease and glioneuronal features: Case report and literature review. *Childs Nerv Syst* 37: 2347-2356, 2021.
- Wang Y, Feng LL, Ji PG, Liu JH, Guo SC, Zhai YL, Sankey EW, Wang Y, Xue YR, Wang N, *et al*: Clinical features and molecular markers on diffuse midline gliomas With H3K27M Mutations: A 43 cases retrospective cohort study. *Front Oncol* 10: 602553, 2020.
- Gamis AS, Egelhoff J, Roloson G, Young J, Woods GM, Newman R and Freeman AI: Diffuse bony metastases at presentation in a child with glioblastoma multiforme. A case report. *Cancer* 66: 180-184, 1990.
- Beauchesne P, Soler C and Mosnier JF: Diffuse vertebral body metastasis from a glioblastoma multiforme: A technetium-99m Sestamibi single-photon emission computerized tomography study. *J Neurosurg* 93: 887-890, 2000.
- Seoane J and De Mattos-Arruda L: Escaping out of the brain. *Cancer Discov* 4: 1259-1261, 2014.
- Piccirilli M, Brunetto GM, Rocchi G, Giangaspero F and Salvati M: Extra central nervous system metastases from cerebral glioblastoma multiforme in elderly patients. Clinico-pathological remarks on our series of seven cases and critical review of the literature. *Tumori* 94: 40-51, 2008.
- Bernstein JJ and Woodard CA: Glioblastoma cells do not intravasate into blood vessels. *Neurosurgery* 36: 124-132; discussion 132, 1995.
- Goodwin CR, Liang L, Abu-Bonsrah N, Hdeib A, Elder BD, Kosztowski T, Bettogowda C, Latterra J, Burger P and Sciubba DM: Extraneural glioblastoma multiforme vertebral metastasis. *World Neurosurg* 89: 578-582.e3, 2016.
- Smith HL, Wadhvani N and Horbinski C: Major Features of the 2021 WHO Classification of CNS Tumors. *Neurotherapeutics* 19: 1691-1704, 2022.
- Li ZG, Zheng MY, Zhao Q, Liu K, Du JX and Zhang SW: Solitary vertebral metastatic glioblastoma in the absence of primary brain tumor relapse: A case report and literature review. *BMC Med Imaging* 20: 89, 2020.
- Zhang W, Cai YY, Wang XL, Wang XX, Li Y, Han GY, Chu YJ, Zhang YX and Hao FR: Bone metastases of glioblastoma: A case report and review of the literature. *Front Oncol* 11: 705455, 2021.
- Jiang H, Yang K, Ren X, Cui Y, Li M, Lei Y and Lin S: Diffuse midline glioma with H3 K27M mutation: A comparison integrating the clinical, radiological, and molecular features between adult and pediatric patients. *Neuro Oncol* 22: e1-1e9, 2020.
- Long W, Yi Y, Chen S, Cao Q, Zhao W and Liu Q: Potential new therapies for pediatric diffuse intrinsic pontine glioma. *Front Pharmacol* 8: 495, 2017.
- Ramaswamy V, Remke M and Taylor MD: An epigenetic therapy for diffuse intrinsic pontine gliomas. *Nat Med* 20: 1378-1379, 2014.
- Wiese M, Schill F, Sturm D, Pfister S, Hulleman E, Johnsen SA and Kramm CM: No significant cytotoxic effect of the EZH2 inhibitor tazemetostat (EPZ-6438) on pediatric glioma cells with wildtype histone 3 or mutated histone 3.3. *Klin Padiatr* 228: 113-117, 2016.
- Yang G, Fang Y, Zhou M, Li W, Dong D, Chen J, Da Y, Wang K, Li X, Zhang X, *et al*: Case report: The effective response to pembrolizumab in combination with bevacizumab in the treatment of a recurrent glioblastoma with multiple extracranial metastases. *Front Oncol* 12: 948933, 2022.



Copyright © 2023 Ge et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.