Child's Nervous System
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CASE REPORT

Spinal intramedullary H3K27M mutant glioma with vertebral metastasis: a case report

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Abstract
A new entity of gliomas, named "diffuse midline glioma (DMG), H3K27M mutant (grade IV)," which represents a specific molecular profile, was introduced to the World Health Organization (WHO) classification 2016 of central nervous system tumors. Many midline localizations have been described for this glioma, and mainly the hypothalamus, pons, thalamus, and spinal cord are sites of predilection in pediatric and young adult patients. We report the case of spinal intramedullary DMG, H3K27M mutant (WHO grade IV), that showed an unusual presentation with multiple vertebral metastases.

Keywords High-grade glioma · H3K27M · Vertebral metastasis · Midline glioma

Introduction

H3K27M mutant diffuse midline gliomas (DMGs) are high-grade glial tumors that most commonly occur in the pediatric age group. As they are diffuse, radical resection is impossible. Despite numerous clinical trials, the prognosis remains poor, with a median survival of 1 year from diagnosis [1].

These gliomas arise mainly in the pons, thalamus, and spinal cord, with incidence rates of 36%, 31%, and 19%, respectively [2], affecting pediatric and adult populations. Spinal cord intramedullary tumors comprise 1–2% of all primary central nervous system (CNS) tumors in pediatric patients. Nearly 85% of them are glial tumors, and 10–15% have histological features consistent with a high-grade glial tumor [3–6].

This work was aimed at reporting an unusual case of pediatric H3K27M mutant diffuse spinal diffuse midline glioma presenting with vertebral metastasis.

Case report

A 16-year-old female patient was referred to our department with complaints of intractable pain in the spinal axis, paraplegia, urinary and fecal incontinence, and blindness, all of which developed within 2 weeks. The physical examination finding was consistent with complete paraplegia and atonic anal sphincter, and the blood test results were normal.

Radiology

Whole spinal magnetic resonance imaging (MRI) revealed spinal intradural and intramedullary mass lesions with heterogeneous contrast enhancement between the T7 and L3 vertebral segments. It also revealed spinal pial seeding, especially at the level of the cauda equina with extensive vertebral body metastasis. Cranial MRI revealed multiple intracranial pial and parenchymal disseminations, which were more prominent around the optic nerves, chiasm, and cerebellum (Fig. 1).

Surgery

As the patient presented with systemic metastasis, we performed an open biopsy for tissue diagnosis. The surgical approach was through a midline lumbar skin incision. Three-level osteoplastic laminotomy was performed through the L2 and L4 lumbar laminae. After opening the dura, the tumor was observed to be infiltrating the spinal cord diffusely and was

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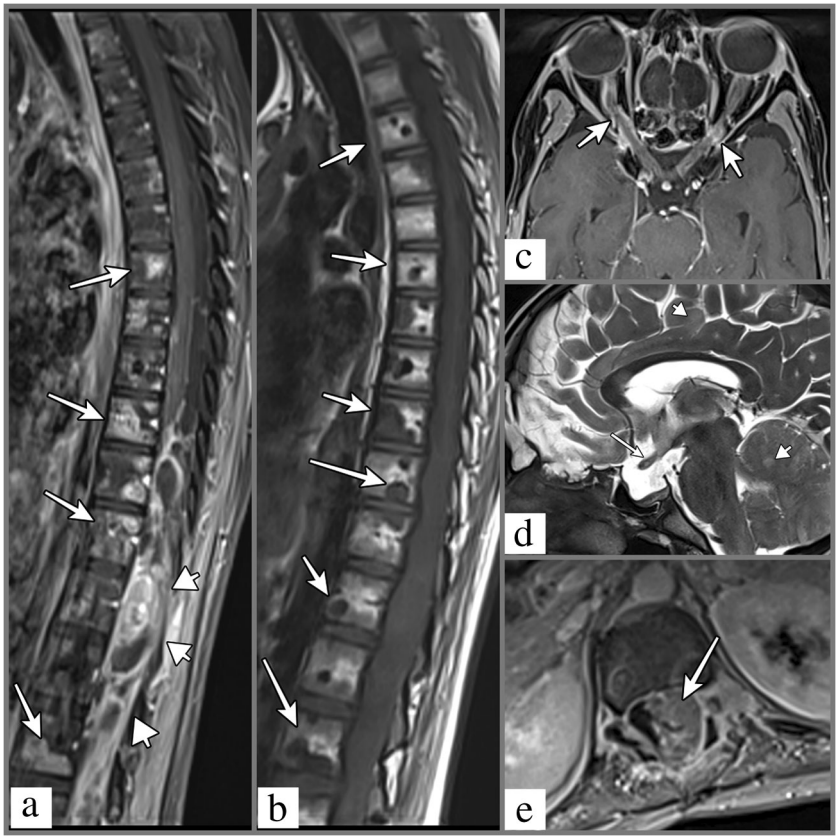

Fig. 1 **a** Sagittal section, T1-weighted MRI with contrast, shows intradural tumor with heterogeneous contrast enhancement (arrowheads) along with multiple vertebral body metastases (arrows). **b** Sagittal section T1-weighted MRI scan shows multiple osteolytic vertebral body metastases (arrows). **c** Axial section cranial MRI shows diffuse optic nerve sheet enhancement upon contrast administration which designates optic nerve seeding. **d** Sagittal section T2-weighted MRI scan which shows chiasmal (arrow) and brain and cerebellar parenchymal diffuse lesions (arrowheads). **e** Axial section T1-weighted spinal MRI with contrast shows intramedullary tumor with exophytic components which shows heterogeneous contrast enhancement

highly hemorrhagic. Biopsies were obtained for histopathological diagnosis and molecular tests.

Pathology

Histopathological evaluation revealed an infiltrating hypercellular glial tumor composed of pleomorphic cells, with high mitotic activity. The targeted Sanger sequencing revealed an H3K27M mutation in the tumor (Fig. 2).

After morphomolecular integrated diagnosis of DMG, H3K27M mutant, we performed computed tomography with contrast enhancement of the thoracic and abdominal cavities. It revealed no systemic metastases except for the vertebral metastases that were also histopathologically proven by needle biopsy as metastasis of the DMG. Additional molecular analysis was not performed on the biopsy from the metastatic site owing to the positive H3K27M immunostaining of the neoplastic cells. The patient received radiotherapy (RT), including the whole cranial and vertebral axis. The patient also received chemotherapy with vincristine (1.5 mg/m^2 once daily), procarbazine (100 mg/m^2 once daily), lomustine (100 mg/m^2 once daily), cyclophosphamide (1000 mg/m^2 once daily), and urometaxan (400 mg/m^2 three times a day). Although this combination protocol was not specifically approved for metastatic histone mutant spinal gliomas, it has been widely used for the treatment of aggressive and disseminated childhood gliomas [7–9]. After RT and 2 chemotherapy cycles, the tumor did not regress. Afterward, the patient and her family did not accept any further treatment, and all oncological treatments were stopped. Unfortunately, she died 5 months after the surgery owing to disease progression.

Discussion

The current understanding of DMG, H3K27M mutant, was based on molecular analyses in pediatric and adult patients that revealed a characteristic recurrent lysine-to-methionine substitution at codon 27 (K27M) in histone H3 variants encoded predominantly by H3.3 gene-H3F3A (75–80% cases) and H3.1 gene-HIST1H3B (25%) [10]. Pediatric DMGs are highly malignant tumors with poor clinical outcomes. Over 70% of patients with this neoplasm harbor the H3K27M mutation, which correlates with a poor clinical outcome [11].

Castel et al. conducted a study about diffuse intrinsic pontine glioma in 91 patients. All patients except for one were found to harbor either a somatic H3K27M mutation and/or loss of H3K27 trimethylation. They also discovered a novel K27M mutation in HIST2H3C and a lysine-to-isoleucine substitution (K27I) in H3F3A, which induced a loss of trimethylation. The behavior of the H3.3 group was more

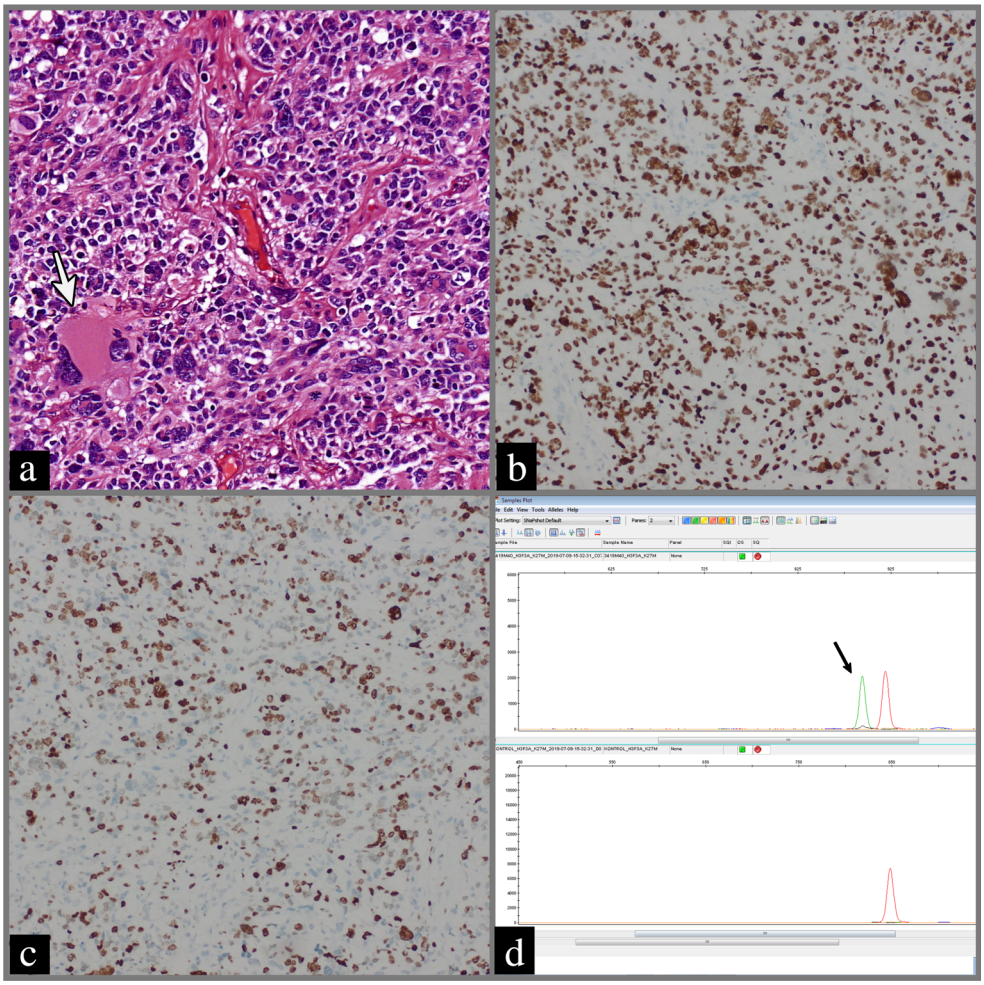

Fig. 2 **a** The tumor is highly cellular consisting of pleomorphic and bizarre cells of glial origin (arrow) (×20). **b** The tumoral cells show diffuse nuclear positivity by anti-H3K27M (mutant-specific) antibody (×10). **c** The Ki67 labeling index is high (×10). **d** The targeted Sanger sequencing test showing the H3K27M mutation: The green peak (arrow) is suggestive of the mutation, in contrast to the negative control result at the bottom

aggressive than that of the H3.1 group [12]. In another study, the H3K27M mutation correlated with worse overall survival and poorer prognosis in infratentorial gliomas, including spinal cord tumors [13].

Extraneural metastasis of high-grade gliomas is extremely rare, and the scarcity of this finding may lead to delayed diagnosis and unnecessary diagnostic considerations [14]. The low incidence rate may be related to the short life spans of patients or to intrinsic biological obstacles. These obstacles may include the absence of a lymphatic system within the brain and spinal cord that would allow systemic dissemination and the lack of nurturing stroma in other organs to facilitate the survival and proliferation of cells [15]. The few cases reported with systemic metastasis are hypothesized to be caused by iatrogenic factors, such as surgical procedures and radiotherapy, which may facilitate tumoral seeding [14]. It is hypothesized that vertebral extraneural metastasis occurs when the metastatic glioma cells disseminate into the cerebrospinal fluid and enter the Batson plexus (in the anterior lumbar cord), which supplies blood to the vertebrae and thus facilitates the metastasis to the vertebrae [16].

Distinct histone H3.3 alterations in various bone and cartilage tumors, including chondroblastoma, osteosarcoma, and giant cell bone tumor, have also been reported [17, 18]. This finding shows that the H3.3 mutation is not exclusive to DMGs and may also occur in bone tumors.

Velz et al. (2018) reported leptomeningeal seeding of a spinal H3K27M mutant glioma in an adult [19]. A recent report described a pediatric H3K27M mutant spinal DMG showing especially bone metastasis [20].

Our case is the second reported case of pediatric DMG with this kind of presentation in the literature. The first pediatric case was presented by Bhatt et al. The patient was a 15-year-old female who presented with bony metastasis affecting the femoral bones, humerus, ribs, sternum, and pelvic bones, in addition to the vertebral column. The dismal evolution was marked by early death at 13 days after the initial presentation [20]. Our patient only had vertebral body seedings within bony structures and died 5 months after diagnosis (Table 1).

From these data, the H3.3 mutation seems to have a strong predilection to occur classically in midline glial tumors and bone neoplasms. This might explain the rare metastatic

Table 1 Pediatric cases of DMG with multiple vertebral metastases

Case	Age (years)	Presentation	Location	Intervention	H3K27M status	Adjuvant treatment	Outcome
1. Bhatt et al.	15	Headache, neck stiffness, paraparesis, back pain	Fourth ventricle + craniospinal pial seeding + vertebral, rib, pelvis metastasis	Open spinal biopsy + bone marrow aspiration from iliac rest	Positive	No	Died 2 weeks after presentation
2. Current case	16	Blindness, back pain, paraplegia, urinary and fecal incontinence	Spinal intramedullary + craniospinal pial seeding + multiple vertebral metastases	Open spinal biopsy + concurrent bone marrow aspiration from vertebral body	Positive	KT + RT	Died 18 weeks after presentation

behavior of DMGs seeding in the skeleton system. This mutation is associated with a dismal prognosis and reduced survival despite adjuvant therapy.

The fulminant evolution of clinical symptoms and presence of a highly infiltrating neoplasm with vertebral and cranial seeding in our patient were suggestive of a high-grade tumor. The findings from the immunohistochemical and molecular studies were consistent with an H3K27M mutant DMG.

Deductively, we can conclude that the coexistence of a midline CNS tumor and multiple bone neoplasms might be suggestive of an H3K27M mutant glial tumor. In similar cases, the prognosis will most probably be poor, and only biopsy can be advocated as a therapeutic strategy. When an H3K27M mutant DMG is detected, systemic screening, especially for bony structures, should be performed to highlight other possible foci of the tumor.

Declarations

Conflict of interest Dr. Chafik Handis attends a pediatric neurosurgery fellowship program in our department which is sponsored by KARL STORZ Company. Preparation for publication of this article (English editing) is partly supported by the Turkish Neurosurgical Society. We have no other conflict of interest to declare.

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