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Patient with Diffuse Midline Glioma, H3 K27-altered, Carrying an FGFR1 Mutation Who Experienced Thalamic Hemorrhage: A Case Report and Literature Review

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Abstract

Diffuse midline glioma (DMG), H3 K27M-altered, is a tumor with a poor prognosis mainly found in children. An adolescent patient presented with thalamic hemorrhage, which initially could not be diagnosed as DMG by pathological analysis. A neoplasm in the lateral ventricle close to the previous thalamic hemorrhagic lesion was detected 12 months after the hemorrhage. Thus, endoscopic resection was performed, and a diagnosis was made. Gene expression profiling demonstrated mutation in genes, such as *H3F3A* and *FGFR1*. *FGFR1* mutation was associated with intratumoral hemorrhage in low-grade gliomas and contributed to longer survival than wild-type *FGFR1* in DMG H3K27M. Our findings suggest that patients with DMG, H3 K27-altered, with *FGFR1* mutation may be predisposed to intratumoral hemorrhaging and/or have a longer survival time than patients without *FGFR1* mutation.

Keywords: intratumoral hemorrhage, diffuse midline glioma, H3 K27-altered, FGFR1, gene expression profiling

Introduction

Diffuse midline glioma (DMG), H3 K27-altered, is a rare pediatric type of invasive high-grade glioma in the midline of the spinal cord, brain stem, thalamus, etc. Patients with diffuse intrinsic pontine gliomas or thalamic DMG harboring an H3K27M mutation have a poor prognosis, with an overall median survival of 11 months.[1] DMG can occur at any age but is most common in children.[2] Here, we report thalamic DMG, H3 K27-altered, in an adolescent with an intratumoral hemorrhage in the thalamus. However, the initial diagnosis was difficult because pathognomonic image findings were absent on the computed tomography (CT) scan, and pathogenic evidence was not detected with neuroendoscopy. Since intratumoral hemorrhage of DMG, H3 K27-altered, is rare and the number of reported cases is limited, we reviewed the literature. Additionally, gene abnormalities coexisting with DMG, H3 K27-altered, have been reported. A mutation in fibroblast growth factor receptor 1 (*FGFR1*) was detected via gene expression profiling in this patient, and its association with disease prognosis and hemorrhage susceptibility in DMG is discussed.

Case Report

The patient was a 19-year-old woman with no past medical history. She had sudden onset of headache and vomiting and was subsequently transported to our hospital owing to paralysis of her left upper and lower extremities, including loss of consciousness (Glasgow coma scale: E1V1 M4). Brain CT displayed a right thalamic hematoma with ventricular casting and slight hydrocephalous (Fig. 1a). The intraventricular hematoma was drained through emergency ventricular drainage to improve the hydrocephalus as quickly as possible. Cerebral angiography on the 14th day after the hemorrhage was normal. Subsequently, after three weeks, the mass effect of the thalamic hematoma remained, and her hydrocephalus worsened after the temporary ventricular drain was removed, which prevented infection owing to its long-term placement (Fig. 1b). Therefore, an endoscopic third ventriculostomy and hematoma evacuation was performed with a flexible neuroendoscope

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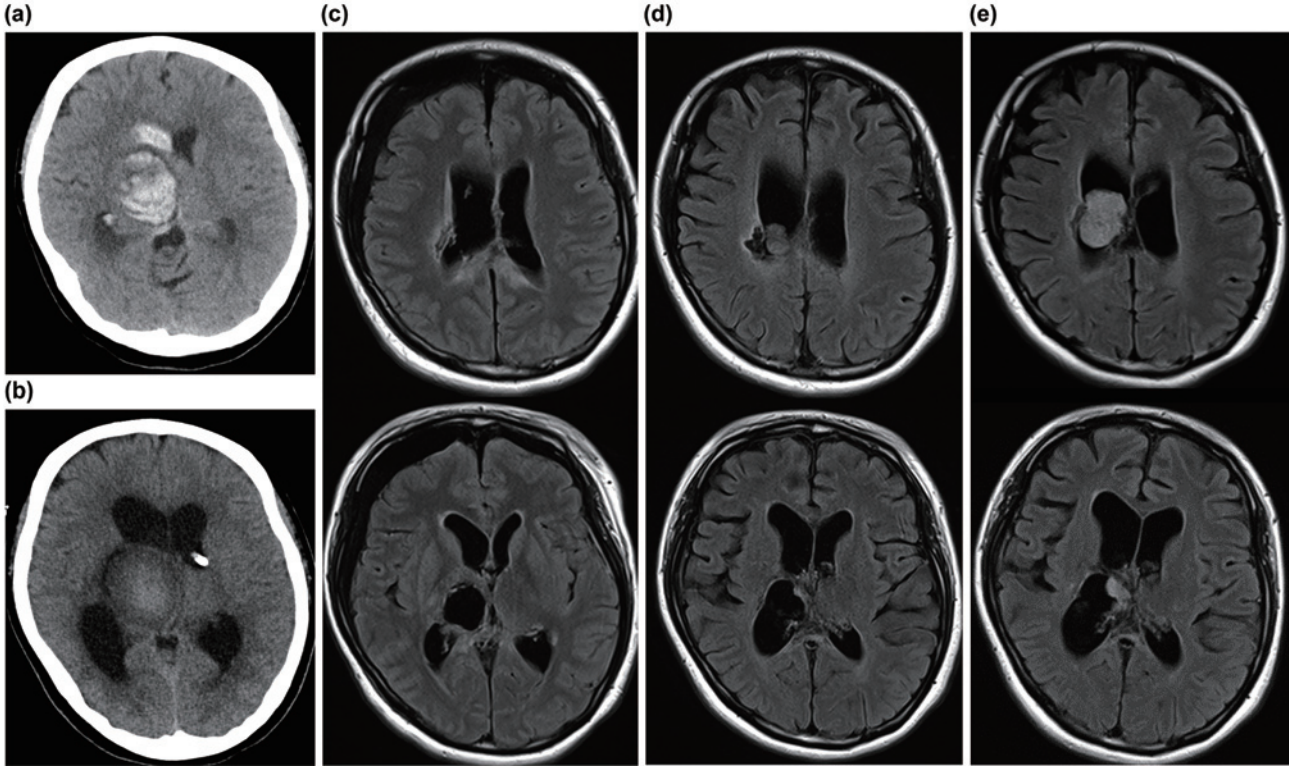

Fig. 1 The patient's brain computed tomography (CT) and magnetic resonance imaging (MRI) fluid-attenuated inversion recovery (FLAIR) images. Brain CT (a and b) and the brain MRI FLAIR (c-e) images are shown.
a. On the day of the hemorrhage. b. Three weeks after the placement of an external ventricular drain, showing hematoma persistence and worsening hydrocephalus. c. Four days after removing the hematoma by neuroendoscopy. Top: No lesion was detected in the ventricle. Bottom: The hematoma was removed. d. Ten months after the hemorrhage. Top: The right lateral ventricle displayed a new high-intensity 15-mm mass lesion. Bottom: The thalamus was normal. e. Twelve months after the hemorrhage. Top: The mass lesion had increased to 30 mm. Bottom: A 10-mm lesion appeared at the right thalamic hemorrhage scar.

(VEF-V, Olympus Corp., Tokyo, Japan) on the 29th day after the hemorrhage. Although pathological analysis of the hematoma and the attached tissue was performed, there was no evidence of a tumor. Brain magnetic resonance imaging (MRI) after endoscopic hematoma evacuation demonstrated no lesions in the ventricle (Fig. 1c). A second cerebral angiography displayed no abnormalities. Her hydrocephalus stabilized four months after the hemorrhage, and her modified Rankin Scale grade was 4. She was transferred to a rehabilitation hospital, where she could walk again using orthotics, and then returned to school. A follow-up brain MRI (fluid-attenuated inversion recovery), which was taken 10 months after the hemorrhage, displayed a 15-mm high-intensity neoplasm within the right lateral ventricle, in a region continuous with the previous thalamic lesion (Fig. 1d). Twelve months after the hemorrhage, the lateral ventricular neoplasm had grown to 30 mm in diameter, and another small neoplasm was observed at the scar of the right thalamic hematoma (Figs. 1e and 2a and b). Since the initial hemorrhage was regarded as an intratumoral hemorrhage, another operation was planned. During the preoperative period, cerebral angiography was performed again (Fig. 2c), which displayed tumor staining in the pericallosal artery, the lenticulostriate artery, and the posterior choroidal artery with an arteriovenous shunt. Endoscopic tumor resection using a rigid endoscope (Endoarm 4K, Olympus Corp., Tokyo, Japan) was performed 13 months after the initial hemorrhage. A postoperative spinal MRI displayed contrast-enhanced lesions on the surface of the spinal cord (Fig. 2d). In the previous surgery, intraoperative findings included hemosiderin deposits in the ventricular wall, but no findings suggested a tumor (Fig. 3a). In this surgery, the intraoperative endoscopy displayed a gross tumor-like mass within the right brain ventricle and a small lesion, which was thought to be dissemination, on the ventricle wall nearly at the foramen of Monro (Fig. 3b). A rapid intraoperative diagnosis was a high-grade glioma. These were considered to be high-grade glioma dissemination.

Pathological diagnosis

Immature tumor cells with an oval nucleus and cell process showed dense and diffuse proliferation, and microvascular proliferation was observed (Fig. 4a). In high-

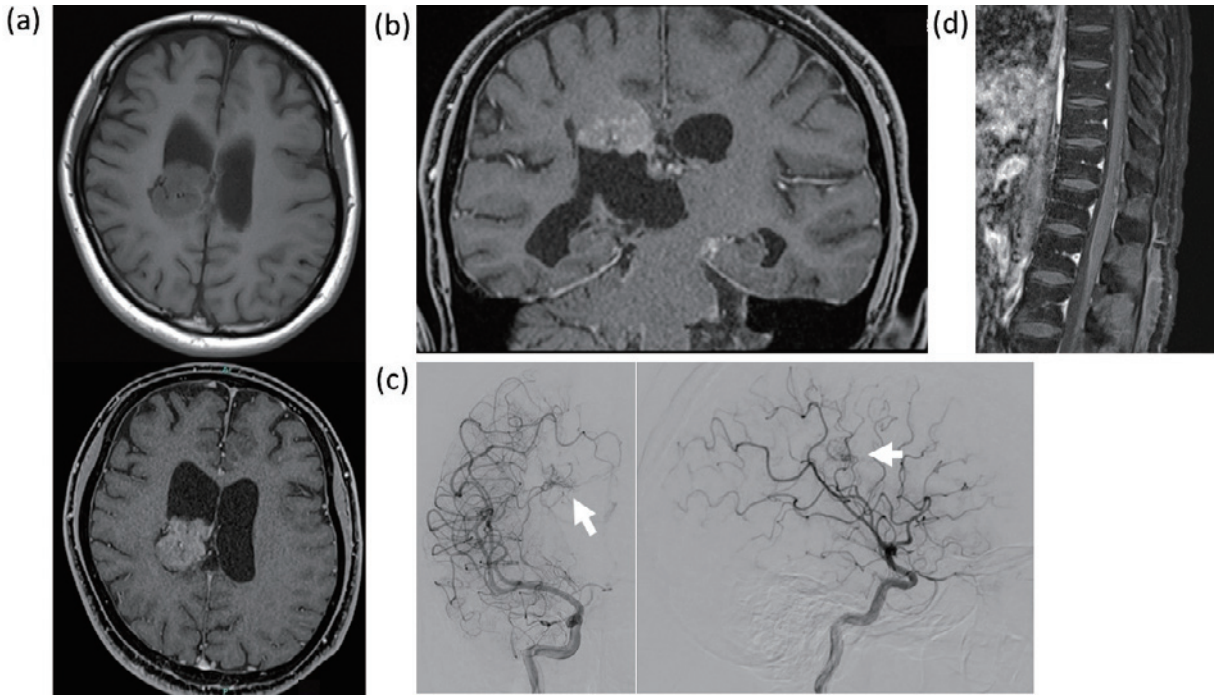

Fig. 2 Preoperative brain magnetic resonance image (MRI), digital subtraction angiography, and postoperative spine MRI.
a. The right lateral ventricle displayed a 30-mm mass lesion 12 months after the hemorrhage. Top: Axial T1-weighted MRI. Bottom: Axial gadolinium contrast-enhanced T1-weighted MRI. b. Coronal gadolinium contrast-enhanced T1-weighted MRI displayed a neoplasm within the right lateral ventricle in a region continuous with the previous thalamic lesion. c. Cerebral angiography mainly displayed tumor staining (arrows) in the lenticulostriate artery. Left: Frontal view of internal carotid angiography. Right: Lateral view of internal carotid angiography. d. Sagittal gadolinium-enhanced T1-weighted spine MRI. The slight enhancement of the spinal cord pia mater at the Th11-Th12 level indicated dissemination.

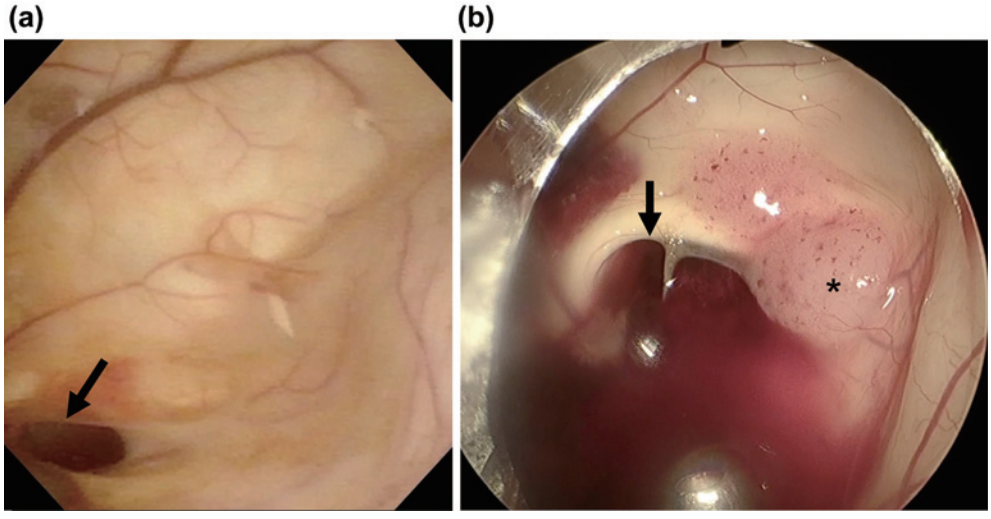

Fig. 3 Endoscopic surgery images.
a. On day 29 after the hemorrhage. After removing the hematoma, the ventricular wall showed hemosiderin deposition, but tumor lesions were absent. b. 13 months after the hemorrhage. Tumor dissemination was observed near the foramen of Monro. Arrows indicate the right foramen of Monro, and the asterisk indicates disseminated lesions on the ventricular wall.

magnification images, nuclear atypia and mitosis were apparent (Fig. 4b). Immunostaining of H3K27M was positive (Fig. 4c), and H3K27me3 expression immunostaining was negative. The Ki-67 index was approximately 20% (Fig. 4d). Immunostaining showed positivity for TP53. Isocitrate dehydrogenase 1/2 sequencing demonstrated an absence of

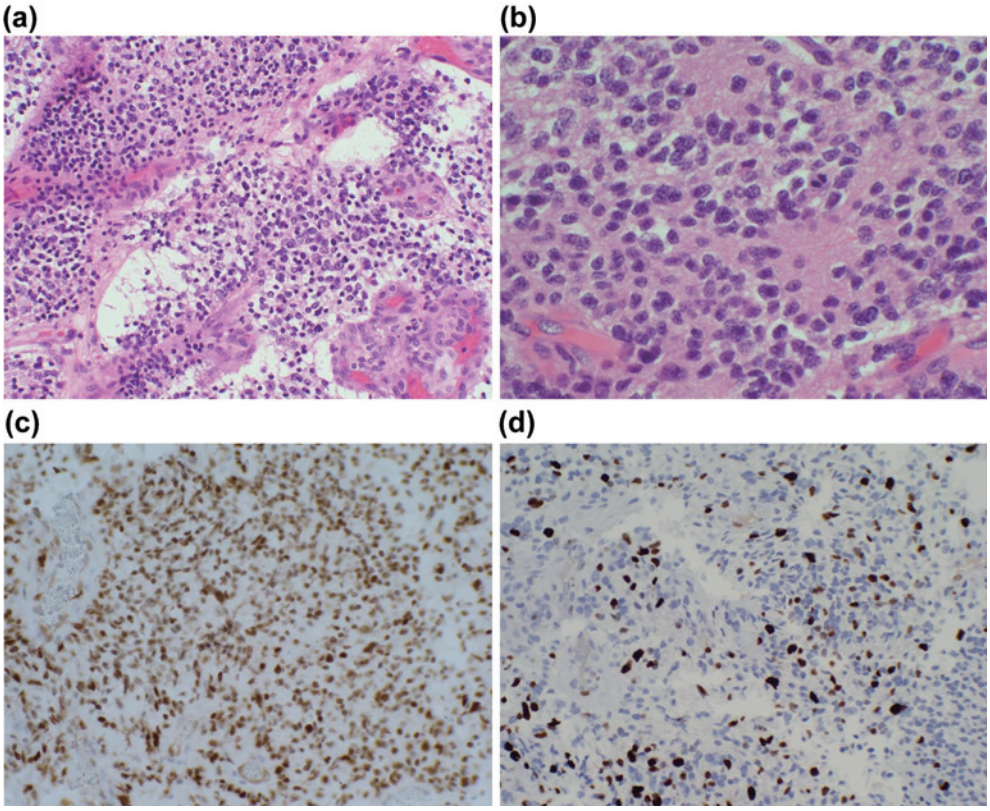

Fig. 4 Pathological findings of the tumor.
a. Hematoxylin and eosin (HE) staining demonstrated that the tumor cells had round, irregular nuclei and fine granular nuclear chromatin. Microvascular proliferation was present (Magnification: 20×). b. HE staining showing densely arranged tumor cells with processes, demonstrating nuclear atypia and mitosis (Magnification: 40×). c. Immunostaining of the tumor for the H3K27M mutation demonstrated its expression in tumor cell nuclei. d. Ki-67 staining demonstrated a Ki-67 index of about 20%.

mutation, and fluorescence in situ hybridization did not detect 1p19q codeletion. Gene expression profiling with FoundationOne® CDx (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) detected mutation in *H3F3A* K28M, *FGFR1* K656N and N546D, *MUTYH* splice site 892-2A > G, *BRAF* P764T, *CARD11* G290R, *CDK12* R1333C, *JAK3* P196T, *FAM123B* S85N, and *ATRX* R1403fs*87. The final diagnosis was DMG, H3 K27-altered.

Outcome

Postoperatively, a total of 59.4 Gy of radiation therapy in 33 days was performed on the entire brain and spinal cord, concomitantly with oral temozolomide (TMZ) (75 mg m^2/day) treatment for 42 days. TMZ (150 mg/m^2/day) for 5 days every 4 weeks and biweekly bevacizumab (10 mg/kg) was administered in an outpatient setting. A brain MRI taken 15 months after the first thalamic hemorrhage displayed a partial tumor response. The patient had moderate paralysis in her lower left limb and used a wheelchair 19 months after the hemorrhage.

Ethical considerations

Institutional Review Board approval was not required, as this is a case study. The patient provided written informed consent to publish this case report.

Discussion

As Vuong *et al.* (2022) reported in a meta-analysis of 929 cases, DMG, H3 K27-altered, is more common in young patients.[2] Patients with the H3K27M mutation have a poor prognosis, with a mean survival time of <1 year.[3] Most DMGs, such as those in the thalamus, initially cause symptoms owing to dysfunction of the thalamus or motor paralysis following a mass effect. However, previous case reports described a patient with thalamic anaplastic astrocytoma with disturbance of consciousness caused by intratumoral hemorrhage, but there was no information regarding whether the tumor had a H3K27M mutation.[4,5] The DMG H3K27M mutant was classified by the revised World Health Organization 2016 classification of central nervous system tumors. Since then, intratumoral hemorrhage in DMG patients has only been reported in 3 cases,[6-8] as shown in Table 1[6,7] (Table 1 only included cases with detailed patient information). The location of the hemorrhage varied, including the thalamus,[7] spinal cord,[6] and

Table 1 Literature review

Authors	Age, sex	Symptoms	Tumor location	Treatment	Prognosis	FGFR1 mutation
Uppar A, *et al.* 2019	28-year-old female	Hemiplegia	Cervical spine	Gross total removal External decompression	Died on postoperative day 23	Not reported
Miyazaki T, *et al.* 2019	26-year-old female	Headache and vomiting	Left thalamus	EVD & VPS for first bleeding. Pregnancy continuation.	Re-bleeding in thalamus on postpartum day 2. Died 3 weeks after re-bleeding.	Not reported
Present case	19-year-old female	Became unconscious	Right thalamus	Neuroendoscopic surgery	Survived 19 months after thalamic hemorrhage. mRS 4	K656N and N546D

Abbreviations. EVD, external ventricular drainage; VPS, ventriculoperitoneal shunt; mRS, modified Rankin scale

corpus callosum.[8] Two patients died within 1 month of the hemorrhage.[6,7] However, detailed genetic analysis was not performed in these case reports, other than analysis of the H3K27M mutation. In the present patient, since the tumor caused a stroke, a diagnosis was made, as a neoplasm was detected in the ventricle about 1 year after the hemorrhage. Our findings suggest that midline intracranial hemorrhage, such as thalamic hemorrhage, of an adolescent or young adult patient should be suspected intratumoral hemorrhage of diffuse midline gliomas.

In the present patient, many genetic abnormalities, including *FGFR1* mutation, were detected by tumor gene expression profiling. Since Ishi Y *et al.* reported spontaneous hemorrhaging may be associated with *FGFR1* mutation in low-grade gliomas in pediatric and young adult patients without clear pathogenesis,[9] we suspected that the FGFR1 mutation in DMG, H3 K27M-altered, was a predisposing factor for intratumoral hemorrhage in this patient. There is no information on *FGFR1* mutation in the other cases exhibited in Table 1, and the discussion of bleeding associations is limited only to low-grade glioma studies.[9] Schüller *et al.* reported that 9 out of 83 DMG patients (10.8%) had *FGFR1* mutation (p.K656E or p.N546K), which was significantly associated with longer overall survival, independently of patient age and tumor location.[10] Furthermore, Vuong *et al.* analyzed 669 patients with DMG and found *FGFR1* mutation in 12.4% of them, with a more favorable prognosis than patients with DMG with wild-type *FGFR1*[11] (median overall survival of 14.2 vs 10.9 months, respectively). The patient, with *FGFR1* mutation, showed hemorrhaging and longer survival (followed up to 19 months) than the other cases shown in Table 1. The association of intratumoral hemorrhage and disease prognosis with *FGFR1* mutation in DMG patients requires future studies.

In conclusion, our results suggest that patients with DMG, H3 K27-altered, with *FGFR1* mutation may be predisposed to intratumoral hemorrhaging and/or have a longer survival time than patients without *FGFR1* mutation.

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Conflicts of Interest Disclosure

The authors declare no conflicts of interest or personal or institutional financial interests regarding any drugs, materials, or devices described in this article.

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