Case Report
H3 K27-altered diffuse midline glioma of the thalamus with formation of glio-fibrillary globular structures

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Abstract: A case of diffuse midline glioma (DMG), H3 K27-altered, that arose in the right thalamus of a 14-year-old boy is reported. The patient died of tumor spread after a progressive clinical course of approximately 13 months. Histopathologically, the tumor consisted of a mixture of loose proliferation of stellate cells and compact fascicular growth of spindle cells showing a "piloid" feature. Aggregates of globular structures composed of entangled fine glial fibrils ("glio-fibrillary globules, GFGs") were observed. Tumor cells were immunoreactive for S-100 protein and glial fibrillary acidic protein (GFAP), and showed nuclear immunoreactivity for histone H3 K27M and loss of expression of H3 K27me3. Tumor cell nuclei were also negative for alpha-thalassemia/mental retardation syndrome X-linked protein (ATRX) and p16. Although GFGs morphologically resembled "neuropil-like islands" or "neurocytic rosettes" seen in glial or glio-neuronal tumors, they showed immunoreactivity for GFAP, but not for synaptophysin. A GFG is a unique structure that has been described in DMG, H3 K27-altered, by a few investigators. To the best of our knowledge, this structure has not previously been reported in other glial or glio-neuronal tumors. It could be added as a new feature in the histopathological variations of DMG, extending its morphological spectrum. Familiarity with this feature can help prevent misdiagnosis of DMG.

Keywords: Diffuse midline glioma, glio-fibrillary globules, H3 K27M mutation, thalamus

Introduction

Diffuse midline glioma (DMG) is a primary brain tumor that predominantly affects the pediatric population, from infants to adolescents [1-4]. It is classically located in the midline structures, most frequently the pons, and occasionally in the thalamus and spinal cord [1-4]. DMG mostly shows histopathological features of a high-grade astrocytic tumor, but their spectrum is wide, ranging from diffuse astrocytoma (WHO grade 2) to glioblastoma (grade 4) [1-6]. In the current WHO classification, DMG is defined by a specific genetic alteration, i.e., a heterozygous somatic mutation of K27M (methionine substitution for lysine at amino acid residue 27) in either the *H3F3A* or *HIST1H3B* genes, which encode the histone H3 variants H3.3 and H3.1, respectively [3]. The mutation of H3 K27M results in a loss of expression of tri-methylated lysine-27 of histone 3 (H3 K27me3) [1, 7]. H3 K27M mutation is considered an early driving

event in the pathogenesis of DMG [7], and the combination of positive nuclear staining of H3 K27M and loss of nuclear H3 K27me3 expression is the diagnostic hallmark of DMG, H3 K27-altered [3, 8].

A case of DMG, H3 K27-altered, that arose in the thalamus of a 14-year-old boy is reported. Histopathological findings of the tumor were consistent with high-grade astrocytic tumor or glioblastoma, but it showed a unique additional feature, i.e., the appearance of many glio-fibrillary globular structures within the tumor.

Clinical history

The patient was a 14-year-old boy who consulted a physician because of headache, an incongruous feeling of the left extremities, and occasional falls for ten days. Neuroradiological examination showed an intracranial mass lesion, and the patient was referred to the university hospital. On admission, his consciousness
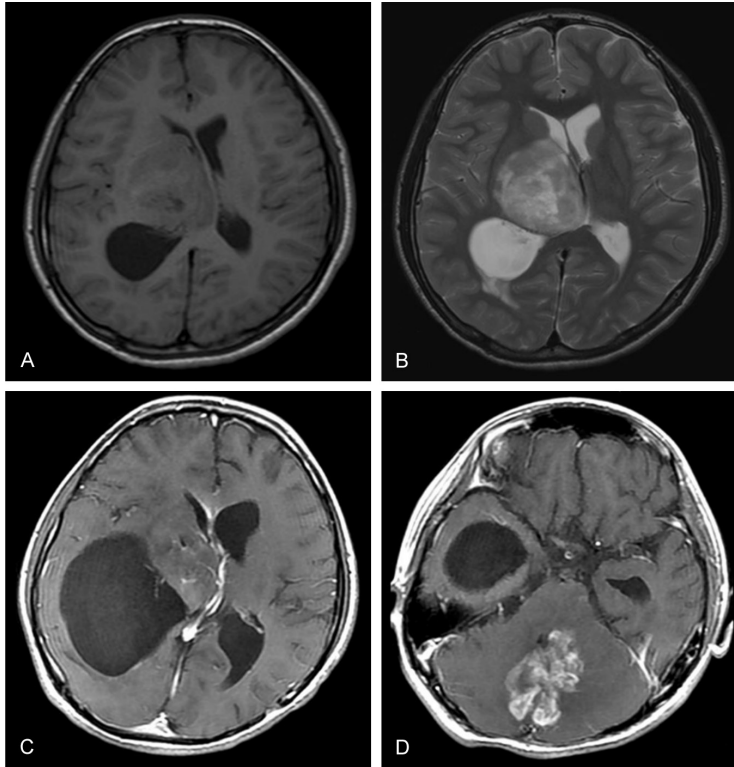
Figure 1. (A, B) Magnetic resonance imaging (MRI) findings on the first admission. A large, relatively well-demarcated tumor involves the right thalamus and head of the caudate, and it protrudes into the lateral ventricle. The signal intensity of the tumor is heterogeneous (A: T1-weighted image, B: T2-weighted image). (C, D) MRI findings after partial excision of the tumor. The tumor invades the cerebellar vermis, and marked dilatation of the lateral ventricle is evident (C, D: T1-weighted image with contrast enhancement).

associated with obstructive hydrocephalus. Emergency craniotomy was performed, and the tumor was partially excised. Postoperative radiation (30 Gy) was given, but the tumor increased progressively (**Figure 1C**, **1D**), and the patient's general condition gradually deteriorated. His consciousness level fell gradually, and the patient died four months after the operation. The total clinical course from the onset of initial symptoms to death was approximately 13 months. An autopsy was not performed.

Pathological findings

Histopathology

The specimen submitted at the time of the craniotomy consisted of many small fragments of tumor tissue, measuring about 23 by 18 mm^2 in aggregate. The tumor was moderately cellular and consisted of diffuse proliferation of medium-sized, round cells having hyperchromatic or vesicular nuclei and stellate cytoplasm (**Figure 2A**) or spindle cells with elliptical nuclei and elongated cytoplasmic processes (**Figure 2B**). The nuclei showed moderate pleomorphism, and a small number of large cells having irregularly shaped nuclei were scattered. The extracellular space was wide and exhibited an edematous or palely basophilic, myxoid appearance. In some areas, spindle cells having long bipolar cytoplasmic processes formed more compact, cellular fascicles (**Figure 2C**). These features resembled the biphasic pattern seen in pilocytic astrocytoma (PA), but neither Rosenthal fibers nor eosinophilic granular bodies were found. The tumor showed brisk mitotic activity (up to five mitotic figures per high-power field) and multiple geographic foci of pseudopalisading necrosis. Proliferation of oligodendrocyte-like cells with clear cytoplasm or primitive neuroectodermal cells was not found. There were neither "ganglion cells" nor cells showing neurocytic differentiation. Because the amount of the specimen was limited, the boundary

was clear, but mild left hemiparesis was noted. Magnetic resonance imaging (MRI) demonstrated a relatively well-circumscribed mass measuring about 50 mm in maximal dimension that involved the right thalamus and head of the caudate and protruded into the lateral ventricle (**Figure 1A**, **1B**). Mild midline shift was observed. The mass showed heterogeneous signal intensity, which was predominantly low on T1-weighted imaging and high on T2-weighted imaging. The contrast enhancement was inhomogeneous. Endoscopic needle biopsy of the tumor was performed, and the pathological diagnosis of high-grade glioma was made. Radiation therapy (60 Gy) and chemotherapy (temozolomide 75 mg/body surface area, 42 days) were started, and the patient was discharged two months later. However, loss of appetite and nausea/vomiting appeared two months after discharge, and MRI demonstrated spread of the tumor to the cerebellar vermis
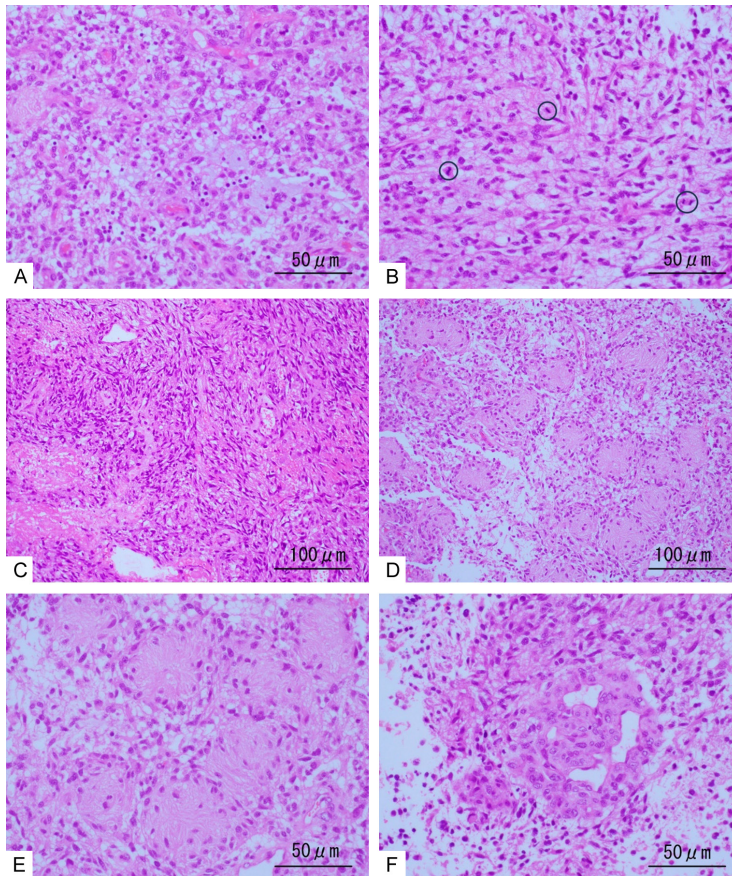
Figure 2. Histopathology of the tumor (hematoxylin-eosin stain). (A) The tumor is moderately cellular and consists of diffuse proliferation of medium-sized cells with round nuclei and stellate cytoplasm on the edematous or myxoid matrix (×400). (B) In some areas, tumor cells are elongated and have elliptical nuclei and long cytoplasmic processes. Three mitotic figures (encircled) are found in this field (×400). (C) A compact, fascicular arrangement of spindle-shaped cells is also observed (×200). (D) Aggregates of globular shape that consist of entangled fine glial fibrils (glio-fibrillary globules) are found in many places (×200). (E) Higher magnification of (D). The nuclei of tumor cells are circumferentially arranged at the periphery of the globules (×400). (F) Reactive proliferation of small vessels forms masses resembling "glomeruloid structures" (×400). Scale bars: 50 μm (A, B, E, F) and 100 μm (C, D).

between the tumor and surrounding tissue could not be evaluated.

A peculiar finding in the tumor was aggregates of well-delineated, globular structures composed of entangled fine glial fibrils (tentatively termed "glio-fibrillary globules, GFGs") (**Figure 2D**, **2E**). They measured approximately 60 to 70 μm in diameter, and the small nuclei of tumor cells were arranged in a circumferential fashion at the periphery. No neuronal perikarya were found within the GFGs. Most GFGs were round, but a small number of them had an elon-

gated and curved columnar shape. Some GFGs were located adjacent to blood vessels, but no small vessels were found within GFGs.

Stromal blood vessels showed prominent hyperplastic changes and occasionally formed vascular masses resembling "glomeruloid structures" (**Figure 2F**). However, the constituent vessels were larger and had thicker walls than those in typical "glomeruloid structures" seen in glioblastoma. Fresh or organized thrombi were occasionally found in the dilated lumina of small vessels. In some areas, many lymphocytes were sprinkled between tumor cells.

Immunohistochemical findings

Immunohistochemical studies were performed using an automated immunostainer (Leica Bond-Max, Leica Biosystems). Monoclonal or polyclonal primary antibodies against the following substances were used: S-100 protein (polyclonal, Leica Biosystems, 1:500), glial fibrillary acidic protein (GFAP) (clone EP672Y, Roche Diagnostics, prediluted), nestin (polyclonal, Immune-Biological Laboratories (IBL), 1:100), oligodendrocyte transcription factor 2 (Olig2) (polyclonal, IBL, 1:200), alpha-thalassemia/mental retardation syndrome X-linked protein (ATRX) (polyclonal, Sigma Aldrich, 1:500), synaptophysin (clone 27G12, Leica Biosystems, 1:200), phosphorylated neurofilament protein (p-NFP) (clone SMI-31, BioLegend, 1:500), epithelial membrane antigen (EMA) (clone M0613, Dako, 1:400), p53 (clone DO-7, Leica Biosystems, 1:400), isocitrate dehydrogenase 1 (IDH1)-R132H (clone H09, Dianova GmbH, 1:100), p16 (clone E6H4, Ventana Medical Systems, prediluted), BRAF V600E (clone VE1, Roche Diagnostics, prediluted), H3 K27M (clone EPR18340, Abcam, 1:500), H3 K27me3 (clone C36B11, Cell
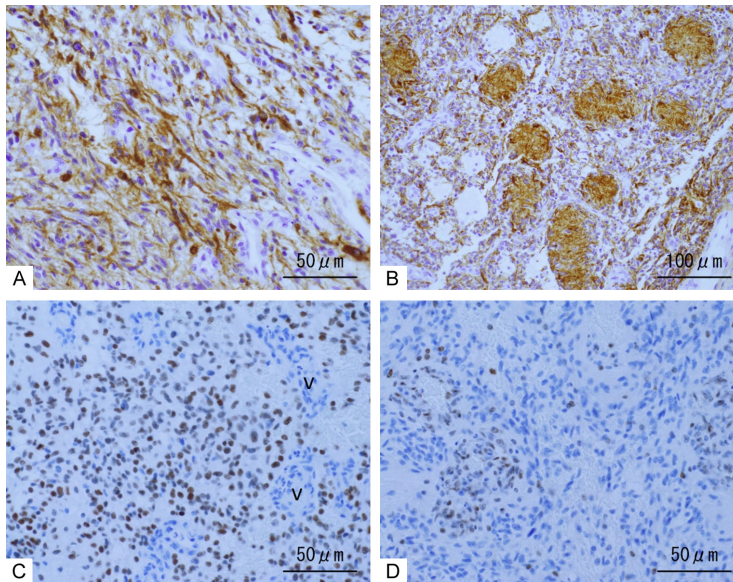
Figure 3. Immunohistochemical findings. (A) Long cytoplasmic processes of tumor cells are immunoreactive for glial fibrillary acidic protein (GFAP) (×400). (B) Glio-fibrillary globules are intensely immunoreactive for GFAP. Note that some of the globules are elongated (lower center) (×200). (C) The majority of tumor cells show nuclear immunoreactivity for H3 K27M. Cells constituting the vascular walls (v) are not immunostained (×400). (D) Tumor cell nuclei have lost expression of H3 K27me3. Cells of the vascular walls serve as a positive internal control (×400). Scale bars: 50 µm (A, C, D) and 100 µm (B).

Signaling Technology, 1:100), sex-determining region Y-box 10 (SOX10) (clone SP267, Ventana Medical Systems, prediluted), alpha-smooth muscle actin (a-SMA, clone 1A4, Dako, prediluted), desmin (clone D33, Dako, 1:200), CD34 (clone QBEnd, Leica Biosystems, 1:400), and Ki-67 (clone MIB-1, Dako, 1:100).

Almost all tumor cells showed intense nuclear and cytoplasmic immunoreactivity for S-100 protein. The cytoplasm of round and spindle tumor cells (**Figure 3A**) and GFGs (**Figure 3B**) were also strongly immunoreactive for GFAP. The majority of tumor cells showed nuclear immunoreactivity for Olig2, and nuclear immunoreactivity for SOX10 was seen in about 20% of tumor cells. Tumor cells and GFGs were not immunoreactive for synaptophysin and p-NFP. The vast majority of tumor cells showed nuclear immunoreactivity for H3 K27M (**Figure 3C**), and, inversely, all tumor cells showed loss of nuclear expression of H3 K27me3 (**Figure 3D**). Nuclear immunoreactivity for ATRX and p16 was also lost. The pattern of immunoreactivity for p53 was consistent with the wild type. Tumor cells were not immunoreactive for IDH1-

R132H, nestin, CD34, BRAF-V600E, and EMA. The Ki-67 labeling index was 37.7%. Immunostaining for a-SMA and CD34 showed prominent proliferation of vascular smooth muscle cells and mild proliferation of endothelial cells, respectively. Vascular smooth muscle cells were not immunoreactive for desmin.

This case is an old one retrospectively identified during a review of the archives of our departments, and, unfortunately, a molecular genetic study could not be performed because a sufficient amount of tissue material was not left in the paraffin block.

Discussion

Gliomas originating in the thalamus (thalamic gliomas) comprise a substantial portion (approximately 15%) of malignant intracranial tumors in the pediatric population, and the vast majority of them show differentiation along the astrocytic lineage [9]. Most astrocytic tumors of the thalamus have previously been dichotomized into diffuse astrocytoma (of low- or high-grade) and pilocytic astrocytoma [9]. However, recent molecular genetic studies demonstrated that the majority of pediatric "diffuse astrocytomas" of the thalamus have a specific genetic aberration, the H3 K27M mutation, and they are currently placed under the category of "diffuse midline glioma (DMG)" [9, 10]. Among H3 K27-altered DMGs, though the localization of H3.1-mutated tumors is restricted to the pons, H3.3-mutated tumors are also found in other midline regions including the thalamus [4, 7].

In contrast with the relatively restricted localization of the tumor, DMG shows a wide histopathological spectrum ranging from diffuse astrocytoma to glioblastoma [1, 4-6]. Ishibashi et al. [11] reported a pediatric case of thalamic DMG in which the progression from low-grade astrocytoma to anaplastic astrocytoma was confirmed. The morphological variations in DMG further include the appearance of giant cells, epithelioid/rhabdoid cells, pilomyxoid fea-

tures, primitive neuroectodermal features, neuropil-like islands, and even sarcomatous transformation [1, 4, 6, 12].

The present case showed histopathological features consistent with glioblastoma (moderate pleomorphism of tumor cells, brisk mitotic activity, pseudopalisading necrosis, and microvascular proliferation), but it also exhibited some features resembling PA, i.e., long cytoplasmic processes reminiscent of "piloid" cells and the "biphasic" growth pattern consisting of a mixture of loose proliferation of stellate cells and compact fascicular growth of spindle cells. In the differential diagnosis, anaplastic PA [13] and "high-grade astrocytoma with piloid features (HGAP)" [14, 15] entered into consideration.

Anaplastic PA (or "PA with anaplastic features") is a rare, aggressive variant of PA [13]. The histopathological patterns of anaplasia show a wide spectrum including the "pilocytic-like" (showing the classic PA pattern but also exhibiting brisk mitotic activity, necrosis, or microvascular proliferation), dense proliferation of anaplastic small cells, appearance of epithelioid/rhabdoid cells, and features consistent with high-grade diffuse astrocytoma [13]. In the present case, the histopathology resembled the classic PA pattern, but Rosenthal fibers and eosinophilic granular bodies were absent. HGAP is a molecularly defined entity that has been established on the DNA methylation profiles, and its morphological spectrum is even more variable than that of anaplastic PA [14, 15]. The histopathological features closely resemble glioblastoma or anaplastic PA, and loss of nuclear expression of ATRX is frequently found [14]. HGAP mostly arises in the posterior fossa [14], and in the past it seems to have often been reported under the diagnosis of "cerebellar glioblastoma". HGAP is basically a glioma in adulthood, and pediatric patients are rare [15]. In the present case, it was difficult to exclude the diagnostic possibility of either anaplastic PA or HGAP on histopathological grounds alone, and immunohistochemistry for H3 K27M and H3 K27me3 finally established the diagnosis of DMG.

It should be added that, although the H3 K27M mutation was considered a major driver in the pathogenesis of DMG [7], some recent studies noted that the occurrence of this mutation was not restricted to DMG. Rare cases of PA of the thalamus [16] or ependymomas of the posterior fossa [17] have been reported to harbor this mutation. Pagès et al. [18] reported that some cases of pediatric ganglioglioma arising in the midline structures harbored the mutation of H3 K27M that was always seen in association with BRAF V600E (a characteristic mutation of ganglioglioma) at a high frequency.

The unique pathological finding in the present case was the appearance of many GFGs that consisted of entangled glial fibrils. On H&E-stained sections, GFGs resembled "neuropil-like islands" that have rarely been described in glio-neuronal tumors [19]. Although "neuropil-like islands" appeared in rare cases of DMG [1, 4, 12], GFGs showed more uniform size and round shape in comparison with the "neuropil-like islands". They consisted solely of cytoplasmic processes of astrocytic tumor cells whose nuclei were arranged circumferentially in the periphery. Immunohistochemically, whereas "neuropil-like islands" were immunoreactive for synaptophysin and not for GFAP [19], GFGs showed the reverse immunohistochemical pattern: immunoreactive for GFAP, but not for synaptophysin. To the best of our knowledge, a report by Wang et al. [20] documented the structures similar to GFGs in a case of DMG under the term of "GFAP-positive anucleate whorled pattern". Auffret et al. [21] also referred to the rare occurrence of the similar structures (under the term of "gliofibrillary tangles") in a new subtype of DMG associated with co-alteration of *BRAF* or *FGFR1*.

GFGs also resembled "neurocytic rosettes" seen in some tumors showing neuronal (or neurocytic) differentiation, such as rosette-forming glio-neuronal tumor (RFGT) [22]. RFGT is a rare kind of mixed glio-neuronal tumor and is also known to frequently have a PA-like component and a myxoid matrix [22], further enhancing the histopathological resemblance to the present tumor. However, RFGT occasionally contains dysmorphic ganglion cells, and the neurocytic rosettes seen in RFGT are not immunoreactive for GFAP, but they are positive for synaptophysin [22], differing from the GFGs in the present case.

The morphogenesis of GFGs is unknown. Perivascular or angiocentric growth of tumor cells accompanied by the formation of a perivascular "anuclear zone" is commonly seen in

ependymoma and occasionally in PA, glioblastoma, or glio-neuronal tumors, and it may produce a feature resembling GFGs in some planes of the sections. However, the angiocentric growth pattern was scarcely observed in the present tumor, and GFGs lacked blood vessels within them.

In conclusion, GFGs are the structures that have been only rarely documented in the previously reported cases of DMG. They add a new feature in the wide histopathological variations of DMG, and familiarity with this morphological feature can help prevent misdiagnosis of DMG, especially in small biopsy specimens. Furthermore, as suggested by Auffrets et al. [21], if these structures are a characteristic pathological feature of DMG associated with co-alteration of *BRAF* or *FGFR1*, the appearance of this feature has a prognostic significance, because the patients having this variant of DMG are expected to have improved overall survival [21].

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Written informed consent to use both clinical data and pathological material was obtained from the parents of the patient.

Disclosure of conflict of interest

None.

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