Tectal Low-Grade Glioma with *H3* K27M Mutation

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Key words
- Diffuse midline glioma
- *H3* K27M mutation
- Pediatric tumor
- Pilocytic astrocytoma
- Tectal glioma

Abbreviations and Acronyms
CNS: Central nervous system
PA: Pilocytic astrocytoma
WHO: World Health Organization

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■ BACKGROUND: **In the revised World Health Organization 2016 classification of central nervous system tumors, "diffuse midline glioma, *H3* K27M-mutant" has been added as a new diagnostic entity. However, some confusion exists concerning this diagnostic entity because *H3* K27M-mutant diffuse midline glioma is diagnosed with grade IV regardless of morphologic phenotype. Furthermore, the significance of *H3* K27M mutation in tumors that aren't typical "diffuse midline glioma, *H3* K27M-mutant," such as those with an unusual location and nontypical histology, remains unclear.**

■ CASE DESCRIPTION: **To elucidate further such unusual tumors, we describe here a rare case of pediatric low-grade glioma located in the tectum, which was morphologically a pilocytic astrocytoma (PA) with genetically *H3* K27M mutation but no microvascular proliferation, necrosis, mitoses, or other genetic alterations, insofar as we were able to observe. At the latest follow-up, 28 months after surgery, radiotherapy, and chemotherapy, the patient was found to be free from any neurologic deficits and MRI demonstrated that the tumor was stable without tumor regrowth. This case might be identified as "diffuse midline glioma, *H3* K27M-mutant", grade IV, when applying only the current World Health Organization 2016 classification. In addition, we discuss the morphologically benign gliomas harboring the *H3* K27M mutation based on the literature.**

■ CONCLUSIONS: **We describe here a rare case and present a short literature review of circumscribed/nondiffuse gliomas, particularly in PA with *H3* K27M mutation. However, the significance of *H3* K27M mutation for PA remains unclear, so further studies and clinical data are needed to elucidate the biology and optimal treatment of such tumors.**

INTRODUCTION

The World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) was recently revised in 2016, introducing an integration of phenotype and genotype, which improves the objectivity of the classification, and the adoption of a more homogeneous biological narrow classification, which enables accurate diagnosis, appropriate treatment, and prognosis prediction.[1] In this revision, "diffuse midline glioma, H3 K27M-mutant" including what is referred to as "diffuse intrinsic pontine glioma," has been added as a new diagnostic entity in the classification of "diffuse astrocytic and oligodendroglial tumors."[2] This is because accumulated evidence has indicated that diffuse midline glioma, H3 K27M-mutant at amino acid 27 resulting in the replacement of lysine by methionine (K27M), are present in the majority of high-grade infiltrative astrocytomas associated with aggressive clinical behavior and poor prognoses that arise in the midline CNS structures of children and young adults.[3-13] Furthermore, such histone mutation has been considered to be a highly specific and driver tumorigenesis for pediatric and young adult glioblastoma pathogenesis including diffuse intrinsic pontine glioma.[14,15] However, some confusion does exist in the revised WHO 2016 classification of CNS tumors because H3 K27M-mutant diffuse midline glioma is diagnosed with WHO grade IV regardless of morphologic phenotype. In other words, we should give preference to the molecular genetic features when the histology does not match the molecular parameters. On the other hand, Orillac et al[16] stated in a letter to the editor of *Acta Neuropathol Commun* in 2016 that "the H3 K27M mutation in the midline glioma should not be used as the only the criteria for the diagnosis of WHO grade IV." Moreover, more recently, cIMPACT-NOW (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy—Not Official WHO) Working Committee 3 presented a recommendation for clarifying the diagnostic criteria of "diffuse midline glioma, H3 K27M-mutant," as follows: "the term *diffuse midline glioma, H3 K27M-mutant* should be reserved for tumors that are *diffuse* (i.e., infiltrating), *midline* (e.g., thalamus, brain stem, spinal cord, etc.), *gliomas*, and *H3 K27M-mutant* and should not be applied to other tumors that are H3 K27M-mutant."[17] Thus the significance of H3 K27M mutation in tumors that are not typical "diffuse midline glioma, H3 K27M-mutant," such as those with an

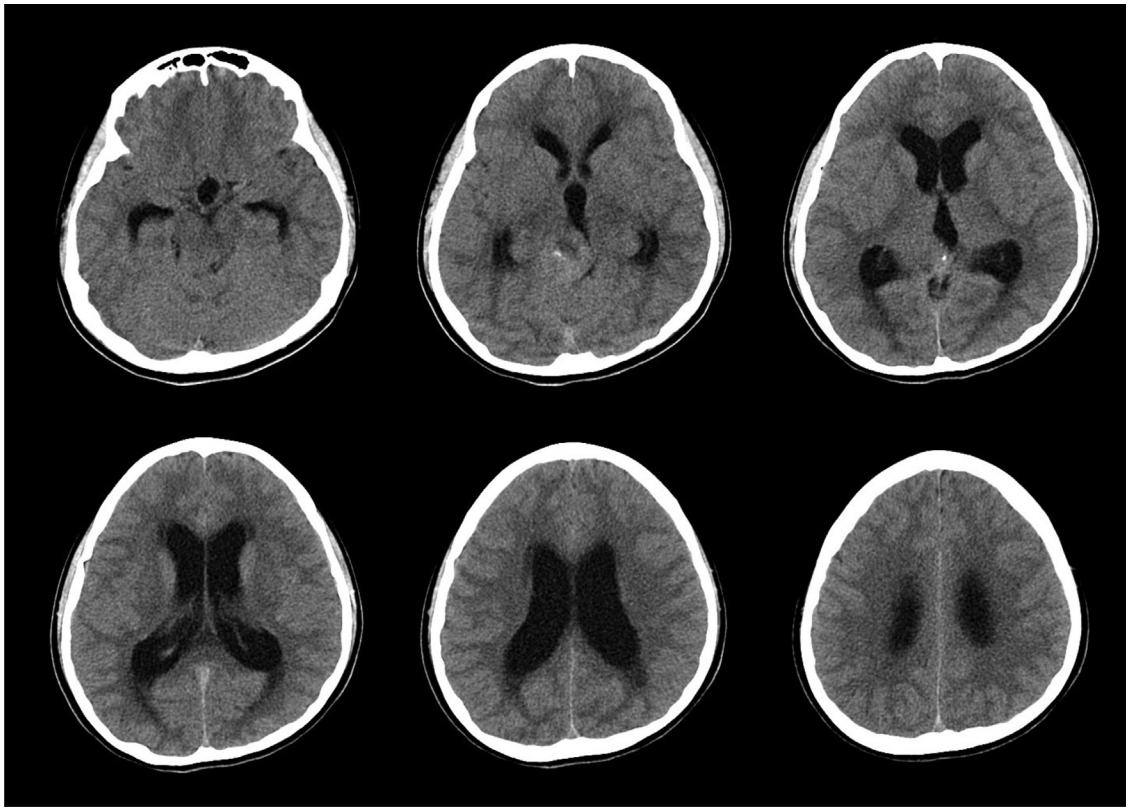

Figure 1. Preoperative computed tomography (CT) scans. Noncontrast axial CT images demonstrate a mass lesion with a small calcification on the right side of the midbrain and ventriculomegaly consistent with noncommunicating hydrocephalus.

unusual location and nontypical histology, remains unclear.

We describe here a rare case of pediatric, midline, tectum glioma harboring the *H3* K27M mutation, histologically a pilocytic astrocytomas (PA) with pleomorphism and a slightly high Ki-67 proliferation index with no microvascular proliferation, necrosis, or mitoses. It might be identified as "diffuse midline glioma, *H3* K27M-mutant" and grade IV when applying only the current WHO 2016 classification. In addition, we present a short literature review of morphologically benign gliomas (circumscribed gliomas, especially PA) harboring the *H3* K27M mutation including tectal gliomas.

CASE PRESENTATION

History and Examinations

A 13-year-old female was referred to our department because her head computed tomography (CT) ordered by an ophthalmologist at our hospital had disclosed an intracranial abnormality (Figure 1). Three days before the CT, she had experienced diplopia accompanied by headache. Before this event, she had been in good health and her family history was unremarkable. At admission, her consciousness level was clear, while she displayed mild headache and esotropia of the left eye (30°), but her eye movement showed no restriction. Neurologic examinations demonstrated no abnormalities except for the ophthalmologic problem. In a fundus examination, her optic discs were found to have mild papilledema. Routine laboratory blood tests including for tumor markers and hormonal tests revealed no obvious abnormalities.

CT scans and magnetic resonance imaging (MRI) of the head demonstrated a relatively well-circumscribed midbrain mass lesion of approximately 30 mm in length (Figures 1 and 2). CT images showed a small calcification within the isodensity mass lesion. The greater part of this lesion exhibited iso to slightly high signal intensity on T1-weighted images and heterogeneous high signal intensity on T2-weighted images, while partial peripheral and spot enhancement could be detected after contrast medium administration on MRI. Perifocal edema was not obviously observed in the adjacent brain, but hydrocephalus due to obstruction of the cerebral aqueduct was clearly evident. The above imaging findings indicated a midline glioma centered within the tectum, causing hydrocephalus due to mass obstruction of the cerebral aqueduct.

Surgery

Three days after admission to our department, endoscopic surgery was performed for a third ventriculostomy, as well as a biopsy for hydrocephalus and diagnosis based on histopathology, respectively.

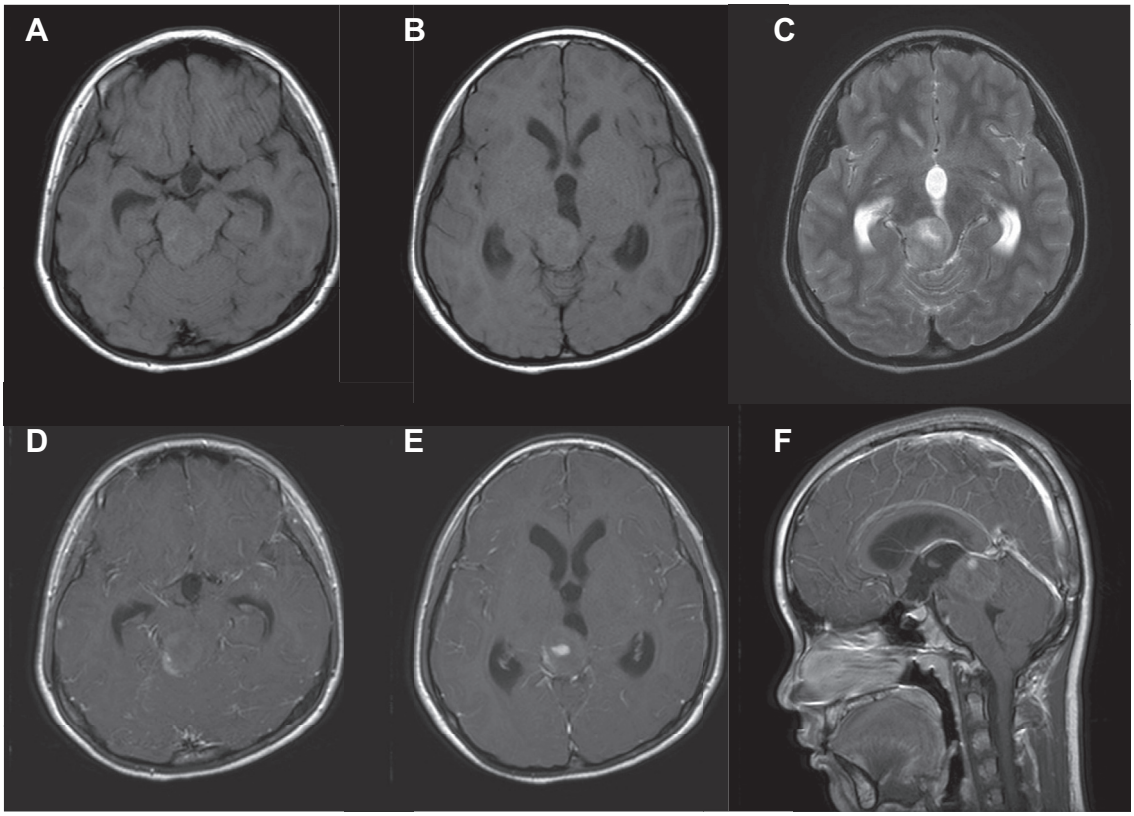

Figure 2. Preoperative magnetic resonance imaging (MRI). (**A** and **B**) Axial T1-weighted images; (**C**) axial T2-weighted image; (**D** and **E**) gadolinium-enhanced, T1-weighted axial images; (**F**) gadolinium-enhanced T1-weighted sagittal image. The relatively well-circumscribed midbrain lesion arising in the tectum displayed isointensity to slightly high signal intensity on T1-weighted images and heterogeneous high signal intensity on T2-weighted images. Gadolinium-enhanced MRI demonstrated a mass lesion with partial peripheral and spot enhancement in the tectum.

However, these procedures were abandoned due to hemorrhage from the choroid plexus near the foramen of Monro, and a cerebrospinal fluid drainage tube was then placed in the right anterior horn of the lateral ventricle. Ten days later, to avoid the risk of severe morbidity, subtotal removal of the exophytic lesion (ı main purpose was to achieve a histologic diagnosis, especially of enhanced sites) was planned and carried out via the occipital transtentorial approach employing the neuroimaging navigation of the Stealth Navigation System (Medtronic Japan CO., LTD.). The main procedures used for surgical removal of tectal tumors are the suboccipital transtentorial approach and infratentorial supracerebellar approach. The former offers a larger view, better control of bleeding, and a smaller working distance. Its disadvantage is the obstructed view by the Galen complex. The infratentorial supracerebellar approach is especially useful in the case of small lesions that develop in the middle area. Its disadvantage is represented by a narrow operative field, especially to the lateral extension, and the risk of a sacrifice bridging vein or precentral cerebellar vein.[18] In addition, because the patient's tentorium was standing, we chose the suboccipital transtentorial approach due to our preference. Mass lesion removal from the space between the precentral cerebellum vein and basal vein of Rosenthal was initiated. The intraoperative findings indicated that the lesion was grayish white and slightly soft. When reaching deeply into the brainstem parenchyma, however, distinct boundaries were not evident. The surgical procedure was therefore terminated after removal of as much material as possible at this stage (partial removal). The immediate pathology of intraoperative frozen-sections indicated a diagnosis of low-grade glioma. One week after the tumor removal, a ventriculoperitoneal shunt was installed.

Histopathologic Investigations

Microscopic examinations of the surgical specimen revealed that the tumor displayed a biphasic pattern with loose areas and dense areas containing numerous Rosenthal fibers (**Figure 3**). However, eosinophil granular bodies were rarely found in the tumor. The overall cellularity was moderate to relatively high. Most tumor cells resembled astrocytoma in their appearance, and some tumor cells appeared to be bipolar neoplastic astrocytes. The tumor cells were characterized by regular round or oval nuclei in the dense areas, but distinct nuclear atypia was observed in

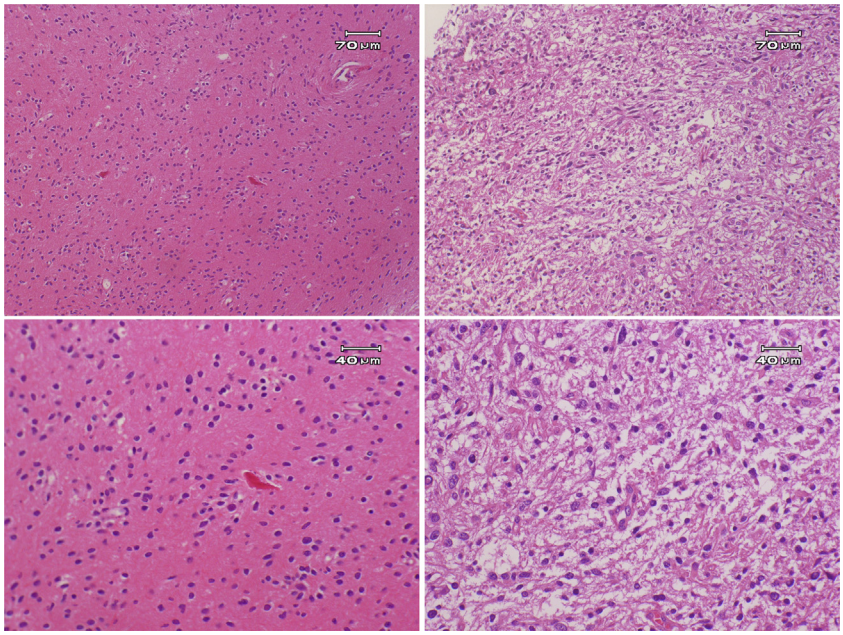

Figure 3. Microscopy of the surgical specimen (hematoxylin-eosin stain, upper: original magnification × 75, bar = 70 µm, lower: original magnification × 150, bar = 40 µm). The tumor displayed a biphasic pattern with alternating dense and loose components. Left images, dense foci; Rosenthal fibers are seen as brightly eosinophilic structures within this part of the tumor. Right images, loose foci; the cells are more loosely packed.

the loose areas. However, there was no microvascular proliferation, necrosis, or mitoses.

The tumor cells were immunohistochemically positive for S100 protein, glial fibrillary acidic protein (GFAP), oligodendrocyte transcription factor 2 (Olig2), alpha-thalassemia/mental retardation syndrome X-linked protein (ATRX), and *H3* K27M, but they were negative for p53 and isocitrate dehydrogenase R132H (mIDH1 R132H). The Ki-67 proliferation index was 4.8% in the most stained areas (Figure 4).

Furthermore, the following findings were indicated by the Japan Children's Cancer Group, which provides central diagnostic services (details omitted). In short, *IDH1* R132, *IDH2* R172, *BRAF* T599, *BRAF* V600, *H3F3A* G34, *HIST1H3B* K27, *TERT* C228, *FGFR1* N546, and *FGFR1* K656 were the wild types, but *H3F3A* K27M was the mutant type as investigated using pyrosequencing. *KIAA1549-BRAF* was not recognized when examined by reverse transcription–polymerase chain reaction. Their central review of the histopathology indicated diffuse midline glioma, *H3* K27M-mutant, WHO grade IV (histologic phenotype: low-grade localized astrocytoma).

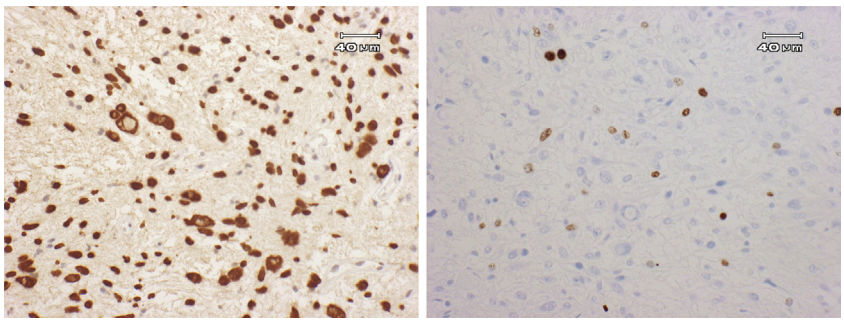

Figure 4. Immunohistochemical staining of the surgical specimen (original magnification × 150, bar = 40 µm). Left, *H3* K27M exhibited strong nuclear positivity in the tumor cells. Right, the Ki-67 index was 4.8% in the most stained areas.

Postoperative Course

The patient's postoperative course was uneventful. The histologic phenotype was low-grade localized astrocytoma consistent with PA, displaying pleomorphism and a slightly high Ki-67 proliferation index, in addition to *H3* K27M mutation. Furthermore, because complete surgical removal of her tumor was not performed, she was treated with focal radiation therapy at a dose of 50 Gy for 25 times of the fraction with adjuvant chemotherapy and concomitant daily temozolomide, followed by maintenance temozolomide (for about 1 year). At the latest follow-up, 28 months after surgery, she was found to be free from any neurologic deficits and MRI demonstrated that the tumor was stable without tumor regrowth (Figure 5).

DISCUSSION

Exhaustive gene expression analyses have demonstrated that specific genetic alterations could drive distinct subsets of glial neoplasms, dependent on not only the histologic phenotype but also the tumor localization and patient age, and could be associated with the prognoses.[13,19,20] The *H3* K27M mutation has been considered to represent one of such genetic alterations in the midline CNS structures of children and young adults.[3-13] However, recent findings have strongly suggested that a wide range of morphologic features including histologically circumscribed/nondiffuse gliomas occurring not only in the pons but also in the spinal cord, thalamus, hypothalamus, and pineal region in both children and adults can (rarely but certainly) harbor the *H3* K27M mutation.[13,21-23] Furthermore, a number of studies including those in the most recent literature, have indicated that the *H3* K27M mutation is associated with a poor prognosis regardless of histologic presentation, tumor location, or patient age.[21,22,24-27] On the other hand, some of the nontypical "diffuse midline gliomas" with the same *H3* K27M mutation including PA, ependymomas, diffuse

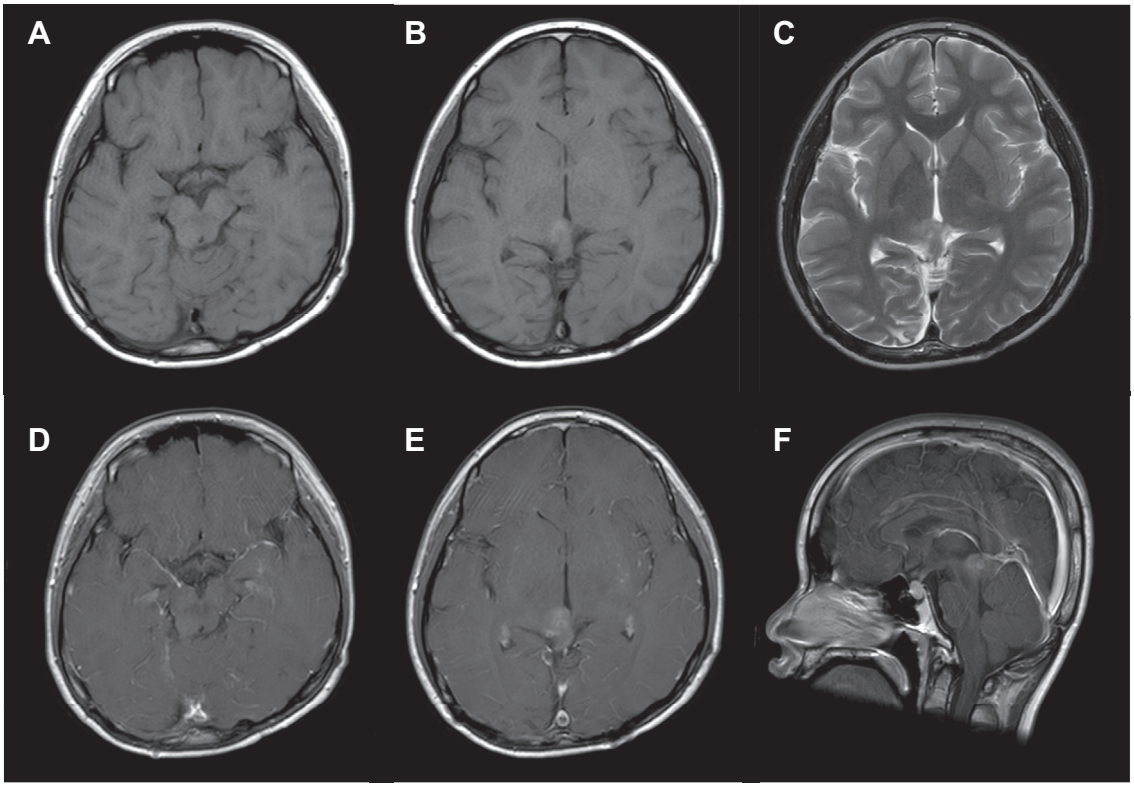

Figure 5. Postoperative magnetic resonance imaging (MRI). (**A** and **B**) Axial T1-weighted images; (**C**) axial T2 weighted image; (**D** and **E**) gadolinium-enhanced T1-weighted axial images; (**F**) gadolinium-enhanced T1-weighted sagittal image. The residual tumor on the midline displayed isointensity to slightly high signal intensity on T1-weighted images and slightly high signal intensity on T2-weighted images. Gadolinium-enhanced MRI demonstrated a lesion with slight enhancement in the tectum.

astrocytoma, and ganglioglioma have been reported without a poor prognosis as WHO grade IV.[16,17,28] The significance of *H3* K27M mutation in gliomas thus remains unclear as regards tumor localization, patient age, and histologic phenotype.

PA, a histopathologic benign tumor (WHO grade I), occurs frequently in children, located mainly in the cerebellum, optic pathways, brainstem, and spinal cord, and is histologically characterized by a biphasic pattern: a compact area containing bipolar cells with Rosenthal fibers and a loose area containing multipolar cells with microcysts, myxoid stroma, and eosinophilic granular bodies. However, PA can display a wide range of tissue patterns, although it rarely exhibits mitoses, hyperchromatic and pleomorphic nuclei, glomeruloid vascular proliferation, or necrosis.[29,30] Moreover, PA may be due to a genetic alteration of the mitogen-activating protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway including *KIAA1549-BRAF* fusion transcripts, *BRAF* V600E, *FGFR1*, *KRAS*, *NF1* mutations, etc.[29,31-37] On the other hand, a small fraction of PA develops anaplastic changes associated with aggressive behavior, although clear criteria for such tumors have not yet been defined.[29,30,36] Recent studies have suggested that PA with anaplasia is associated with molecular alterations including activation of the PI3K/mTOR pathway, *PTEN*, *CDKN2A*, *ATRX*, and *H3* K27M, as well as the presence of alternative lengthening of telomeres (ALT),[29,38,39] although the precise sequence of events leading to PA with anaplasia remains unknown.

Tectal glioma is rare, occurring predominantly in children but accounting for <5% of brainstem tumors in children.[40] Liu et al,[41] in a retrospective study of 45 tectal gliomas, found that 83% were similar to PA and 17% could be aligned with diffuse astrocytoma. However, no *H3* K27M mutation was detected in their study, while *BRAF* V600E mutation and *KIAA1549-BRAF* fusion were observed in 8% and 25%, respectively. Furthermore, large series of clinicopathologic assessments, by Solomon et al in 2016, Pratt et al in 2018, and Kleinschmidt-DeMasters and Mulcahy Levy in 2018, did not reveal cases of tectal gliomas (including PA) with *H3* K27M mutation. Taken together, these findings indicate that tectal PA with *H3* K27M mutation is rare. Our case was found to be a pediatric midline, tectum, low-grade astrocytoma consistent with PA. The case described by Morita et al[42] is the only case of tectum PA with *H3* K27M mutation aside from ours. Our case was similar to theirs including the genetic information and tumor localization, but there was a difference in patient age (their case was a 53-year-old man) and histology including vessel abnormalities (their case had glomerular vessels).

To the best of our knowledge, after undertaking a careful search of the

Table 1. Characteristics of 23 Cases of Pilocytic Astrocytoma (PA) (including PA with Anaplastic Changes) with *H3* K27M Mutation

Source	Age (Years)	Sex	OS (Months)	Status	Location	Initial Histology	Treatment	Co-Occurring Mutations	Other Details
Jones DT et al., 2013[34]	6	F	17.2	L	TH	PA	n/a	FGFR1 mutation Somatic NF1 alteration	
Nguyen AT et al., 2015[42]	10	F	12	D	BS	PA with aggressive features versus HGG	Ch, Re	BRAF V600E mut.: P	
Hochart A et al., 2015[27]	7	F	137	D	SC	PA	Re, Ch, RT	IDH1/2 mut.: N PTEN mut.: N KIAA1549-BRAF fusion: N BRAF mut.: N ACVR1 mut.: N no loss of 16p	TP53 mutation in recurrent tumor Olig2 IHC: P Synaptophysin IHC: N EGFR IHC: N Malignant transformation into glioblastoma after 10 years
Orillac C et al., 2016[16]	24	F	50	L	TH	PA	Re	IDH1/2 mut.: N BRAF V600E mut.: N 3' BRAF duplication: N	High Ki-67 proliferation index and rapid recurrence within 14 months
Reers S et al., 2017[36]	32	M	21	D	SC	PA	Re, P	FGFR1 hot-spot mut.: N KIAA1549-BRAF fusion: N BRAF V600E mut.: N	No evidence for MAPK/ERK signaling pathway activation on IHC
Meyronet D et al., 2017[23]	18	F	24	D	BS	PA or LGG	B, RT	IDH1/2 mut.: N EGFR amp.: N TERT mut.: N BRAF V600E mut.: N	MGMT: not methylated
Meyronet D et al., 2017[23]	21	F	3	D	PF	PA or LGG	B	IDH1/2 mut.: N EGFR amp.: N TERT mut.: N BRAF V600E mut.: N	MGMT: not methylated
Meyronet D et al., 2017[23]	43	F	6	D	SC	PA or LGG	B	IDH1/2 mut.: N EGFR amp.: N TERT mut.: N BRAF V600E mut.: N	MGMT: not methylated
Morita S et al., 2018[41]	53	M	44	L	TE	PA	Re	IDH R132H: N KIAA1549-BRAF fusion: N BRAF V600E mut.: N ATRX IHC: retained	p53 IHC: focally P Olig2 IHC: focally P
Pratt D et al., 2018[21,*]	n/a	F	n/a	n/a	n/a	PA	n/a	n/a	
Pratt D et al., 2018[21,*]	50	n/a	n/a	n/a	SC	PA	n/a	n/a	
Kleinschmidt-DeMasters BK and Mulcahy Levy JM, 2018[20]	49	F	16.2	L	SC	PA	n/a	n/a	Supratentorial leptomeningeal/dural metastasis with glioblastoma transformation 1 year after diagnosis

El Ahmadieh TY et al., 2018[26]	21	F	22	L	TH	PA	Re, RT, Ch	IDH R132H: N BRAF V600E mut.: N BRAF duplication: N	
El Ahmadieh TY et al., 2018[26]	25	M	11	L	TH	PA with anaplasia	Re, RT, Ch	n/a	
Rodriguez FJ et al. in 2019[38]	53	F	6	L	C	PA with anaplasia	RT, Ch	IDH R132H: N BRAF duplication: P BRAF V600E mut.: N ATRX IHC: lost CDKN2A: No mutation	p53 IHC: strongly positive ALT: P
Rodriguez FJ et al. in 2019[38]	4	M	4	D	PF	PA with anaplasia	Re	IDH R132H: N BRAF duplication: N BRAF V600E mut.: N ATRX IHC: lost CDKN2A: no mutation	p53 IHC: strongly positive p16 IHC: partial loss ALT: P
Rodriguez FJ et al. in 2019[38]	36	F	39	L	C	PA with anaplasia	n/a	IDH R132H: N BRAF duplication: N BRAF V600E mut.: N ATRX IHC: lost CDKN2A: no deletion	p53 IHC: N p16 IHC: partial loss ALT: P
Rodriguez FJ et al. in 2019[38]	10	M	25	D	3rd ventricle	PA with anaplasia	Re	IDH R132H: N BRAF duplication: N BRAF V600E mut.: N ATRX IHC: lost CDKN2A: no deletion	p53 IHC: N ALT: P
Rodriguez FJ et al. in 2019[38]	51	M	55	D	SC	PA with anaplasia	Re	IDH R132H: N BRAF duplication: N BRAF V600E mut.: N ATRX IHC: partial CDKN2A: No deletion or mutation	p53 IHC: N ALT: P
Ebrahimi A et al. in 2019[22]	44	M		L	BS	PA		ATRX IHC: retained IDH R132H: N BRAF V600E mut.: N	MGMT: not methylated
Ebrahimi A et al. in 2019[22]	9	M		L	BS	PA		ATRX IHC: retained IDH R132H: N BRAF V600E mut.: N ACVR1: p. G328E	TP53: wild type MGMT: not methylated

OS, overall survival; F, female; L, living; TH, thalamus; n/a, not available; D, deceased; M, male; BS, brainstem; Ch, chemotherapy; Re, resection; BRAF mut., BRAF V600E mutation; P, positive; SC, spinal cord; RT, radiotherapy; IDH mut., isocitrate dehydrogenase mutation; N, negative; MGMT meth, MGMT promoter methylation; P, pineal region; TE, tectum; C, cerebellum; PF, posterior fossa; PA, pilocytic astrocytoma; HGG, high-grade glioma; LGG, diffuse low-grade glioma; P, proton beam therapy; B, biopsy; pTERT mut., TERT promoter mutation; ALT, alternative lengthening of telomeres.

*From supplementary material of Pratt D et al., 2018.[21]

Continues

Table 1. Continued

Source	Age (Years)	Sex	OS (Months)	Status	Location	Initial Histology	Treatment	Co-Occurring Mutations	Other Details
Ebrahimi A et al. in 2019[22]	12	F		L	TH	PA		ATRX IHC: lost IDH R132H: N BRAF V600E mut.: N ACVR1: p. G328E	TP53: mutated type MGMT: not methylated
Ours	13	F	28	L	TE	PA	Re, RT, Ch	FGFR1 mutation: N IDH1/2: N IDH R132H: N TERT mut.: N KIAA1549-BRAF fusion: N BRAF V600E mut.: N ATRX IHC: retained	p53 IHC: N Olig2 IHC: P S100 IHC: P

OS, overall survival; F, female; L, living; TH, thalamus; n/a, not available; D, deceased; M, male; BS, brainstem; Ch, chemotherapy; Re, resection; BRAF mut., BRAF V600E mutation; P, positive; SC, spinal cord; RT, radiotherapy; IDH mut., isocitrate dehydrogenase mutation; N, negative; MGMT meth, MGMT promoter methylation; P, pineal region; TE, tectum; C, cerebellum; PF, posterior fossa; PA, pilocytic astrocytoma; HGG, high-grade glioma; LGG, diffuse low-grade glioma; P, proton beam therapy; B, biopsy; pTERT mut., TERT promoter mutation; ALT, alternative lengthening of telomeres.

*From supplementary material of Pratt D et al., 2018.[21]

literature, we found 23 cases of PA with *H3* K27M mutation as summarized in **Table 1**.[16,21-24,27-29,35,37,39,42,43] After excluding cases that were histologically suspected as PA with anaplastic changes, 16 cases were identified as PA with *H3* K27M mutation (we could not include the cases reported by Reinhardt et al[38] because we were unable to collect sufficient data from their series. However, their cases might be included in the study of Rodriguez et al[29]). On the basis of the available data obtained, except in the cases of anaplastic change, the patient age ranged from 6 to 53 years (mean: 26.8 years). The spinal cord was the most common location ($n = 5$), followed by the thalamus ($n = 4$), brainstem ($n = 3$), tectum ($n = 2$, including our case), and posterior fossa ($n = 1$). The longest survival period was 137 months, and the shortest was 3 months. No one revealed *IDH1/2* mutation including anti-IDH1 (R132H) immunoreactivity. Neither *BRAF* V600E mutation nor *KIAA1549-BRAF* fusion was detected in them. In addition, no one displayed *TERT and MGMT* promoter mutation, either. ATRX immunohistochemistry was performed in 5 cases, and only 1 demonstrated ATRX expression loss. These findings together indicate that most cases of PA with *H3* K27M mutation did not show other genetic alterations except PA with anaplasia, suggesting that *H3* K27M-mutant PA might represent 1 of the glial tumor spectra driven by this mutation as also mentioned by Meyronet et al.[24] However, the significance of *H3* K27M-mutant PA for age of onset, site of onset, and/or prognosis remains unclear. Further studies and clinical data are thus needed concerning the biology and optimal treatment of PA with *H3* K27M mutation.

CONCLUSIONS

We describe here a rare case of pediatric, midline, tectum PA with *H3* K27M mutation without other genetic alterations and present a short literature review of morphologic PA harboring *H3* K27M mutation. The significance of *H3* K27M mutation for PA was unclear, so further studies and clinical data are needed to elucidate the biology and optimal treatment of such tumors.

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