Brainstem pilocytic astrocytoma with H3 K27M mutation: case report

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In this report, the authors present the first case of adult brainstem pilocytic astrocytoma (PA) with the H3 K27M mutation. A 53-year-old man was incidentally found to have a 2.5-cm partially enhanced tumor in the tectum on MRI. The enhancement in the lesion increased over 3 years, and gross-total removal was performed via the occipital transtentorial approach. The resected tissue indicated PA, WHO Grade I, and genetic analysis revealed the H3 K27M mutation. However, although the radiological, surgical, and pathological findings all corresponded to PA, this entity can easily be misdiagnosed as diffuse midline glioma with the H3 K27M mutation, which is classified as a WHO Grade IV tumor according to the updated classification. This case highlights the phenotypic spectrum of PA, as well as the biology of the H3 K27M–mutated gliomas, and may prove to be an exception to the rule that diffuse midline gliomas with the H3 K27M mutation behave in an aggressive manner. Based on the findings of this case, the authors conclude that, in addition to detecting the existence of the H3 K27M mutation, an integrated approach in which a combination of clinical, pathological, and genetic information is used should be applied for accurate diagnosis and determination of the appropriate treatment for diffuse midline gliomas.

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The 2016 revision of the WHO’s classification of tumors of the CNS has newly defined diffuse astrocytic tumors developing in midline structures including the brainstem, thalamus, and spine—and that have a specific mutation in histone 3 (H3) at amino acid 27 resulting in the replacement of lysine by methionine (H3K27M)—as “diffuse midline glioma, H3 K27M-mutant.” This new entity is associated with a poor prognosis and a 2-year overall survival rate of < 10%, despite the development of modern therapies. Accordingly, it is designated a WHO Grade IV tumor, with the existence of the H3 K27M mutation as the sole criterion, regardless of the presence of mitotic activity, microvascular proliferation, or necrosis.

We describe the first case of adult brainstem pilocytic astrocytoma (PA) harboring the H3 K27M mutation. The tumor presented typical clinical, pathological, and DNA ploidy phenotypes of PA.

Case Report

History and Presentation

A mass lesion in the midbrain tectum was incidentally diagnosed on CT scans obtained after a minor head injury in a 53-year-old man. On MRI, the tumor showed low intensity on T1-weighted images (Fig. 1A), mixed high intensity on T2-weighted images (Fig. 1B), and partial enhancement by gadolinium uptake (Fig. 1C). Computed...
tomography showed partial calcification in the tumor and mild ventricular dilation. A methionine-PET (MET-PET) study showed moderate uptake in the enhanced lesion (tumor/normal ratio: 2.73; Fig. 1D). The patient exhibited no neurological deficit, and he was consequently followed up with MRI every 6 months. Three years later, MRI showed increased tumor size and enhancement of the lesion (Fig. 1E–G), whereas MET-PET examination showed no significant upregulation of the signal intensity in the enhanced lesion (Fig. 1H). The patient showed mild ataxia due to hydrocephalus.

Operation and Postoperative Course

First, endoscopic third ventriculostomy was performed for hydrocephalus, after which the ventricle size was reduced. A week later, gross-total removal of the tumor via the occipital transtentorial approach was performed. The boundary between the tumor and normal tissue was clear, and necrotic changes were observed in the enhanced lesion. The extent of resection of the tumor was estimated to be > 95%, as calculated using MRI before and after the tumor resection (Fig. 1I–K). The patient showed mild ataxia and blurred vision after the surgery, although the symptoms fully resolved in 1 month. Postoperatively, he did not receive any adjuvant therapy, based on the original WHO classification (Grade I), rather than on the revised classification (Grade IV). At the latest follow-up, 8 months after the surgery, the patient was free from recurrence.

Pathological Findings

The surgically resected specimens were composed of several small pieces, measuring between 0.5 × 1.0 cm and 1.0 × 2.0 cm. All specimens were embedded into 2 blocks and showed essentially identical histological features. The majority of the lesions consisted of densely fibrillary or fascicular areas with long spindle cells. The nuclei were oval with faint chromatin, although small numbers of cells with large nuclei and increased chromatin were present. The overall cellularity was low, but the background was densely gliotic. Numerous Rosenthal fibers were diffusely scattered, whereas only a few scattered eosinophilic granular bodies were observed. Narrow, loose, or microcystic areas with small round cells interposed between the dense cellular areas were noted, giving a vague biphasic appearance (Fig. 2A).

The tumor tissue was sharply demarcated from the adjacent cerebellar cortex, and there was a thick layer of gliosis at the boundary (Fig. 2B). Dilated or “wickerwork” vessels were conspicuous, a few of which were glomeruloid (Fig. 2C). Aggregate hyalinized vessels were occa-
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sionally associated with coagulative necrosis in the loose or collagenous background (Fig. 2D). Microcalcification was present, and mitosis was rare. On immunohistochemical investigation, the tumor cells were diffusely positive for glial fibrillary acidic protein, vimentin, and nestin (Fig. 2E), whereas the loose areas were focally positive for only oligodendrocyte transcription factor 2. The Ki-67 index was low (average of 10 independent fields, 3.32%; maximum, 7.4%; Fig. 2F), and phospho-histone 3–positive mitoses were rare. The cells were negative for isocitrate dehydrogenase R132H (Fig. 2G), whereas they were diffusely and strongly positive for H3 K27M (Fig. 2H). The p53 protein was only focally positive (< 5% of the tumor cells), and the alpha-thalassemia/mental retardation syndrome X-linked protein expression was retained. According to the revised WHO classification, this tumor corresponded to a diffuse, midline, H3 K27M–mutant glioma, Grade IV.

Genetic Analysis

The tumor samples were subjected to molecular genetics screening to ensure diagnostic accuracy. Consistent with the immunohistochemical findings, the H3 K27M
mutations, leading to ab -

BRAF V600E

3D), line, H3 K27M–mutant glioma. Moreover, the DNA con-

integrated diagnosis of the present case as diffuse, mid -
in situ hybridization, respectively—instead supporting the

mutation detected by Sanger sequencing and break-apart fluorescence

(Fig. 3B) nor KIAA1549-BRAF fusion (Fig. 3C) was
detected on MRI and observed intraoperatively were in -

detectable in the tumor by both immunohistochemical analysis and

oncogenic fusions of the BRAF and KIAA1549 genes and, in -

less aggressive clinical course compared with pediatric PA,

and biological behavior of PA is largely unclear. There

have been some reports that adult PA shows a more ag- 

progressive manner. Considering that this is a newly defined

event, the frequency of such exceptional cases is unclear, 

and the accumulation of additional cases is needed. Thus, 

the treatment strategy should be determined not only by 

detecting the H3 K27M mutation but also by considering 

the clinical, pathological, and genetic information of each

individual patient.

Conclusions

The present case suggests that the H3 K27M mutation 

may not always indicate infiltrating astrocytoma morphol-

ogy or Grade IV malignancy. Additional studies are re-

quired to elucidate the prognostic impact of the H3 muta-

tion in PA, as well as to establish proper criteria for the
diagnosis of midline gliomas.

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Nitta. Acquisition of data: Nitta, Masui, Maruyama, Ichimura, Nakano, Sawada, Koriyama, Tsuzuki, Yasuda, Hashimoto, Niwa. Analysis and interpretation of data: Nitta, Komori, Masui, Ichimura. Drafting the article: Nitta, Morita. Critically revising the article: Nitta, Muragaki, Komori, Ichimura. Reviewed submitted version of manuscript: Nitta, Muragaki, Komori. Approved the final version of the manuscript on behalf of all authors: Nitta. Administrative/technical/material support: Kawamata. Study supervision: Muragaki, Komori, Kawamata.

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