Case Report
pISSN 1738-2637 / eISSN 2288-2928
J Korean Soc Radiol 2017;77(6):416-420
https://doi.org/10.3348/jksr.2017.77.6.416

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Diffuse Midline Gliomas Harboring the *H3* K27M-Mutation in the Bilateral Thalamus and Midbrain: A Case Report and a Review of the Literature

양측 시상과 중뇌에 발생한 히스톤 *H3* K27M 변이 미만성 중간선 교종: 증례 보고 및 문헌 고찰

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The diffuse midline glioma *H3* K27M-mutant was only added recently to the World Health Organization (WHO) Classification of Tumours of the Central Nervous System. While similar tumors are found in the midline, this particular mutation represents the majority of diffuse gliomas in the brainstem. Classified by WHO as grade IV tumors, these are aggressive and bear a poor prognosis for the patient. This report describes a case involving a 37-year-old woman with a histologically confirmed diffuse midline glioma *H3* K27M-mutant in the bilateral thalamus and midbrain. The following discussion describes typical characteristics observed with computed tomography and magnetic resonance imaging. Given the rarity of diffuse intrinsic pontine gliomas in adults and the general lack of studies investigating this poorly understood entity, we report critical findings for contribution to the existing scarce literature on the topic.

Index terms
Brain Stem Neoplasms
Thalamus
Midbrain
Magnetic Resonance Imaging

Received May 30, 2017
Revised July 10, 2017
Accepted July 25, 2017
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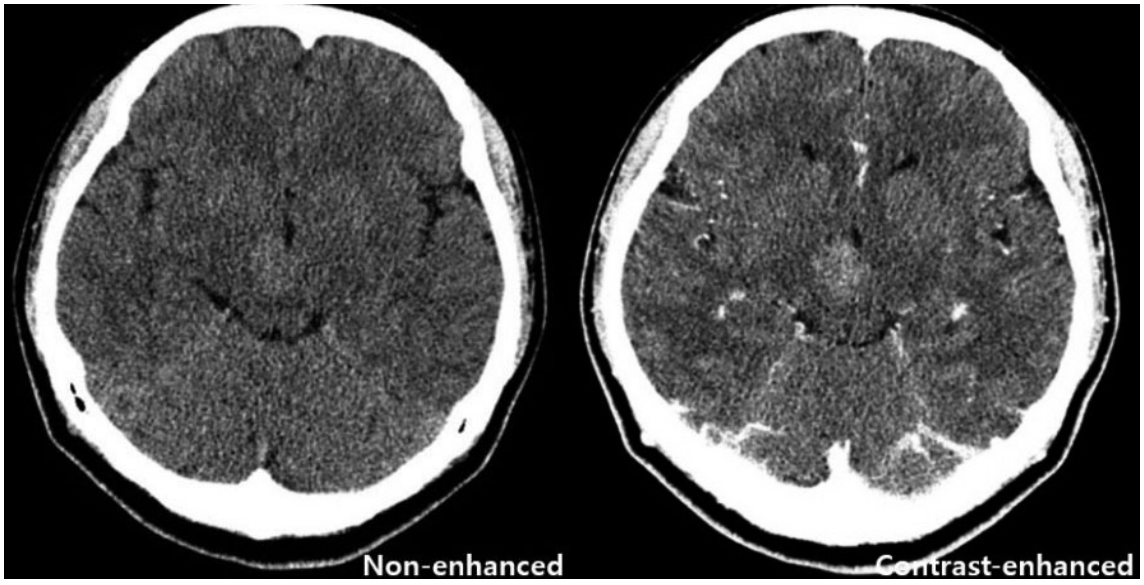
INTRODUCTION

The diffuse midline glioma *H3* K27M-mutant is a distinct subtype of the infiltrative tumor, which represents a majority of diffuse brainstem gliomas. Recently, this subtype was recognized as a new diagnostic entity in the forthcoming edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System (1). Typically, diffuse midline gliomas *H3* K27M-mutant cases occur in the pons and thalamic regions (2). Herein, we report a case involving a 37-year-old woman with a histologically confirmed diffuse midline glioma *H3* K27M-mutant in the bilateral thalamus and midbrain. The following discussion describes the typically observed computed tomography (CT) and magnetic resonance imaging (MRI) characteristics of this entity. We also performed a review of the relevant literature of this aggressive disease.

CASE REPORT

A 37-year-old woman presented with dizziness. This symptom gradually progressed for one year without any associated neurological symptoms. General physical and neurological examinations did not reveal any other abnormalities. Further, laboratory investigations, including examination of the cerebrospinal



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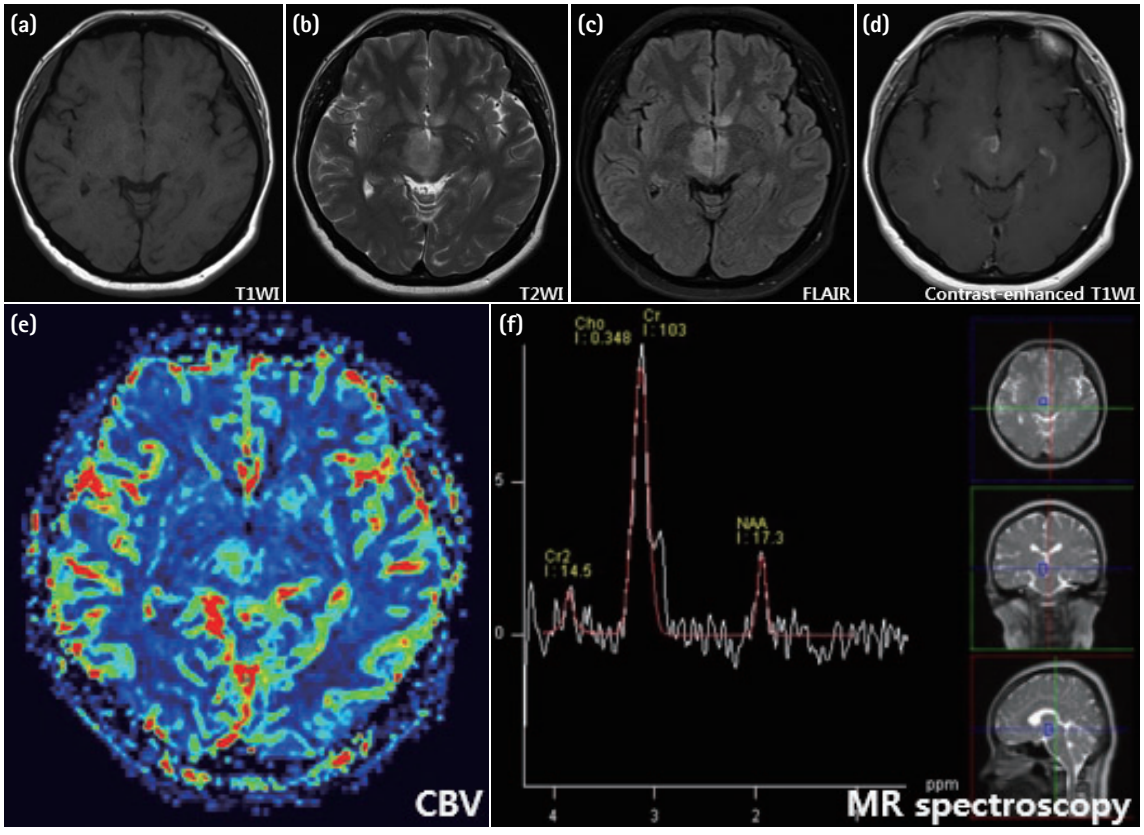

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Fig. 1. Diffuse midline glioma, *H*3 K27M-mutant in the bilateral thalamus and midbrain in a 37-year-old woman, presenting with dizziness.
A. Axial non-enhanced computed tomography scan revealing an ill-defined hyper-attenuated mass in the right thalamus.
B. (a) Axial pre-contrast T1WI revealing a homogeneously hypointense lesion in the right thalamus. **(b)** Axial T2WI demonstrating a hyperintense lesion in the bilateral thalamus. **(c)** Axial FLAIR image revealing a hyperintense lesion in the bilateral thalamus. **(d)** Axial post-contrast T1WI revealing a focal irregular enhancement in the right thalamus. **(e)** CBV parameter map revealing an increased signal in the right thalamus. **(f)** MR spectroscopy: an increased choline peak and a markedly decreased N-acetylaspartate peak are apparent in the right thalamus.
CBV = cerebral blood volume, FLAIR = fluid-attenuated inversion recovery, MR = magnetic resonance, T1WI = T1-weighted image, T2WI = T2-weighted image

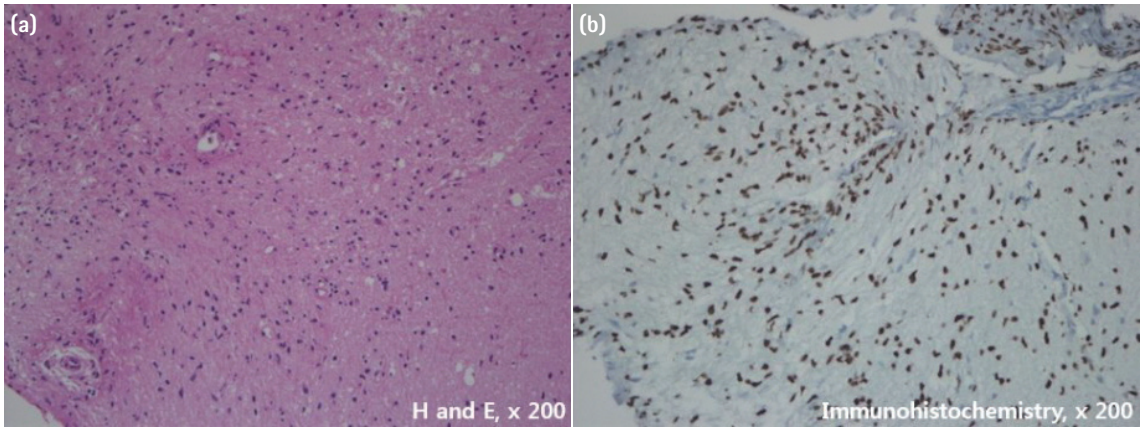

Fig. 1. Diffuse midline glioma, *H3* K27M-mutant in the bilateral thalamus and midbrain in a 37-year-old woman, presenting with dizziness.
C. Photomicrograph: **(a)** hematoxylin and eosin stain, demonstrating dense cellularity and occasional nuclear atypia. **(b)** Immunohistochemistry for histone *H3* K27M-mutant protein revealing the nuclei of a majority of tumor cells (brown stain) with only few normal, residual cells (blue) (original magnification × 200).

fluid, yielded negative results.

Contrast-enhanced brain CT revealed an ill-defined, hyperattenuated lesion, with subtle enhancement in the bilateral thalamus, measuring 1.7 × 2.0 × 2.1 cm (Fig. 1A). The MRI revealed a diffuse infiltrative lesion located in the bilateral thalamus and midbrain. There was a mild mass effect observed with iso-signal intensity in T1-weighted images, and high signal intensity in T2-weighted images and fluid-attenuated inversion recovery images. This lesion exhibited heterogeneous enhancement in the right thalamus, following injection of gadolinium (Fig. 1B). Proton magnetic resonance spectroscopy images of the center of the mass were also obtained. An increased choline-to-creatine ratio and a decreased concentration of N-acetylaspartate were observed. Additionally, perfusion MRI revealed elevated cerebral blood volume and cerebral blood flow at the site of enhancement.

Stereotactic biopsy was subsequently performed. The lesion exhibited proliferation of well-differentiated fibrillary astrocytes, demonstrating moderately increased cellularity and occasional nuclear atypia, consistent with diffuse astrocytoma. Immunohistochemistry was performed using a polyclonal antibody recognizing histone H3.3 and H3.1 tail epitopes, which identified the lesion as histone *H3* K27M-mutant protein (Fig. 1C).

DISCUSSION

The WHO Classification of Tumours of the Central Nervous System uses an integrated diagnostic scheme, incorporating both morphological and molecular features. Emerging evidence indicates that diffuse brainstem gliomas arise in the thalamus, pons and spinal cords of children and young adults. These gliomas are associated with poor prognosis and are categorized as WHO grade IV tumors, regardless of histological features (2).

One narrowly defined group of tumors that primarily occur in children (and infrequently in adults), is characterized by the *H3* K27M-mutation encoded by the histone *H3* gene *H3F3A*. These tumors exhibit a diffuse growth pattern and are generally found somewhere around the midline. Less commonly, mutations in the related *HIST1H3B* gene has also been reported. A newly defined entity, termed "diffuse midline glioma *H3* K27M-mutant," includes tumors previously referred to as diffuse intrinsic pontine gliomas. Identification of this phenotypically and molecularly defined set of tumors can now provide a rationale for therapies directed against the these specific mutations (2).

Retrospective analyses of 47 cases of diffuse midline gliomas positive for histone *H3* K27M-mutant by Solomon et al. (2) indicates that the age of patients at the time of diagnosis range from 2 to 65 years of age (median age of 14 years). However, patients with pontine gliomas tend to be younger (median age 7 years) than those with thalamic (median age 24 years) or spinal (median age 25 years) gliomas. Most of the tumors in these studies were located in the pons (36%), followed by the thalamus (32%), spinal cord (19%), third ventricle (6%), hypothalamus (2%), cerebellum (2%), pineal region (2%), and lastly the midbrain (0%) and medulla

(0%). Additionally, Aboian et al. (3) reviewed 24 specific cases of diffuse midline gliomas with histone *H*3 K27M-mutant in pediatric patients, where most of the tumors were found to be in the pons (46%), followed by the thalamus (25%), vermis/fourth ventricle (17%), cervical spine (8%), subcallosal (4%), with none in the midbrain (0%). Our particular case presented with a very rare midbrain location of the histone *H*3 K27M-mutant.

The clinical features of the *H*3 K27M-mutation vary depending on the tumor location, where symptoms may include the following: headache, cranial nerve palsy, sensory disturbance, visual disturbance, gait disturbance, motor weakness, personality changes, confusion, memory loss, apathy, emotional lability, and dementia (4, 5). The diffuse midline glioma *H*3 K27M-mutant is found in critical midline structures such as the spinal cord and brainstem, which preclude surgical resection in most cases. However, it is unclear whether the poor prognosis stemming from these tumors is due to the burden of the tumor, given the exceeding difficulty of resection, or whether it is a direct manifestation of the *H*3 K27M-mutation. Although the *H*3 K27M-mutation appears to be found more commonly in diffuse midline gliomas, the mutation also appears to be found infrequently in diffuse gliomas arising peripherally in the cerebral hemisphere. Given that the hallmarks of diffuse non-midline gliomas with *H*3 K27M-mutation remain undefined and unclear at present, we believe these tumors should not be specified as WHO grade IV (6).

CT findings of brainstem gliomas typically reveal a hypodense or isodense mass (7). The MRI findings usually demonstrate T2 hyperintensity and a heterogeneously enhancing infiltrative mass with T1 hypointensity (7). Importantly, imaging features vary according to tumor type and location. Guillamo et al. (4) have reported four patterns detected in adult brainstem gliomas, identified by MRI: patterns representing non-enhancing diffusely infiltrative tumors; contrast-enhancing localized masses; isolated tectal tumors; and others (posterior exophytic, diffusely infiltrative with enhanced nodule). Forty-six percent of tumors exhibited contrast enhancement that was associated with shorter survival. Presumed "necrosis" on MRI (defined as a zone of irregularly shaped T1 hypointense signal surrounded by contrast enhancement) was found in 20% of cases and strongly correlated with shorter survival. In another study, contrast enhancement was also an unfavorable factor, particularly when the area of enhancement surrounded a low-signal site suggestive of necrosis. In children, however, the prognostic value of contrast enhancement remains controversial (8). Aboian et al. (3) retrospectively reviewed imaging features of pediatric patients with midline gliomas with or without the histone *H*3 K27M-mutation. They found that diffuse midline gliomas with *H*3 K27M-mutant exhibited variable imaging features, with thalamic gliomas showing contrast enhancement and necrosis in 50% of patients, pontine gliomas exhibiting contrast enhancement to a variable degree in 67%, and cervical spine gliomas being uniformly enhancing. When they compared diffuse midline gliomas according to the presence or absence of histone *H*3 K27M-mutation, there was no significant correlation between border characteristics or enhancement, or presence of edema or infiltrative appearance.

Radiological differential diagnosis in typical cases of diffuse brainstem gliomas may indicate conditions such as brainstem encephalitis, demyelinating disease (e.g., multiple sclerosis or acute disseminated encephalomyelitis), neurofibromatosis type 1, and osmotic demyelination. All of these conditions can present with solitary or multifocal, poorly delineated hyperintensity on T2/fluid-attenuated inversion recovery MRI (9). In our case, the lesion involved the bilateral thalamus and midbrain. Lesions involving the bilateral thalamus and midbrain include lymphoma, basilar artery occlusion or artery of Percheron infarction, deep vein thrombosis, flavivirus encephalitis, and Creutzfeldt-Jakob disease (8, 10). Although imaging may suggest tumor grade on the basis of contrast enhancement, definitive grading requires histopathological examination of the excised tissue. Accordingly, stereotactic biopsy is the preferred mode for definitive diagnosis of diffuse midline glioma. Although image-guided stereotactic biopsy of the brainstem is considered to be a safe and reliable procedure, the optimal methods and routes of biopsy remain debatable (10).

Here, we present a rare case of diffuse midline glioma, *H*3 K27M-mutant that extended to the bilateral thalamus and midbrain. The radiological findings of diffuse midline glioma, *H*3 K27M-mutant are commonly observed in the pons and thalamic regions; however, in our case, it led to an even more challenging diagnosis in clinical practice. Although it is often difficult to differentiate diffuse midline glioma, *H*3 K27M-mutant from other similar diseases, it should be considered in the radiological differential diagnosis in patients with bilateral, brain-

stem lesions.

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양측 시상과 중뇌에 발생한 히스톤 *H*3 K27M 변이 미만성 중간선 교종: 증례 보고 및 문헌 고찰

김인겸 · 김진우* · 황윤준 · 이병훈 · 서정욱

*H*3 K27M 변이 미만성 중간선 교종은 2016년 World Health Organization (이하 WHO) Classification of Tumours of the Central Nervous System에서 새로 추가된 진단이다. 이 진단은 기존의 미만성 뇌간 교종으로 대표된다. *H*3 K27M 변이 미만성 중간선 교종은 WHO grade IV로 분류되고 예후가 좋지 않다. 본 저자들은 37세 여자 환자에서 발생한 *H*3 K27M 변이 미만성 중간선 교종의 영상 소견 및 병리학적 소견을 보고하고자 한다. 성인에서의 미만성 뇌간 교종의 희귀성과 그에 대한 연구가 드물다는 점을 고려하면, 이 증례 보고는 기존의 부족한 문헌에 중요한 정보를 제공할 수 있을 것이다.

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