Case Report

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A rare case of adult diffuse midline glioma with H3 K27M mutant in the prepontine cistern

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Abstract

Diffuse midline glioma with the H3.3 histone A (*H3F3A*) or H3 clustered histone 2/3 (*HIST1H3B/C*) K27M mutation occurs primarily in children and less frequently in adults involving the midline structures of the central nervous system. This case report describes an adult patient with a diffuse midline glioma H3 K27M mutant in the prepontine cistern, which is an unusual site in clinical practice. The clinical, radiographic and histopathological data from the case are presented. Magnetic resonance imaging showed a progressively enlarged and enhanced nodule in the right prepontine cistern, with diffuse involvement of the meninges and communicating hydrocephalus. Analysis of the cerebrospinal fluid occasionally found suspiciously atypical cells with hyperchromatic nuclei and multiple nucleoli, as well as a severely elevated opening pressure and protein level, slightly elevated white cell count and decreased chloride level. Empirical antituberculosis treatment was administered but eventually proved to be ineffective. The definite diagnosis was made by histopathological analysis of the lesion based on the features of positive H3 K27M mutant protein and diffusely infiltrating growth. A diffuse midline glioma with the H3 K27M mutation may rarely present in an unusual site. A biopsy is recommended at an early stage for suspected cases to facilitate a definite diagnosis.

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Introduction

Diffuse midline glioma with H3 K27M mutant, which results in a substitution of lysine at position 27 with methionine, is listed as a distinct entity that corresponds to histological grade IV in the revised 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) even when mitotic figures, microvascular proliferation and necrosis are not observed.[1] The tumour is recognized as having an oncogenic histone K27M mutation in the H3.3 histone A (*H3F3A*) or H3 clustered histone 2/3 (*HIST1H3B/C*) genes that encode for the histone H3 variants, H3.3 and H3.1, respectively.[2] These mutations give rise to decreased methylation of the histone tails, causing blockage of glial differentiation and consequent gliomagenesis.[3] Diffuse midline glioma H3 K27M mutant occurs primarily in children or less frequently in adults regardless of sex.[4] It presents with a quite typical pattern of diffuse and invasive growth in the midline CNS structures; specifically, the pons in children; and in adults, the spinal cord or thalamus appear to be the most frequently involved structures.[4,5] Despite a shorter overall survival, the K27M mutation has been shown to be closely associated with a poor outcome in the infratentorial structures compared with wild-type counterparts.[6,7]

This case report describes a young female patient with a rare diffuse midline glioma with the H3 K27M mutant originating in the prepontine cistern, which is an unusual site in clinical practice.

Case report

A 20-year-old female patient presented in November 2018 to the Department of Neurology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong Province, China with a 3-month history of daily persistent headaches that deteriorated at night, without complaint of fever, vomiting, visual loss or paralysis during each attack period. No history of hypertension, encephalitis or head trauma was reported. Analgesics were occasionally taken by the patient to relieve the headache. Communicating hydrocephalus was found by computer tomography (CT) at another hospital but no certain diagnosis was made. On admission to the Department of Neurology, The First Affiliated Hospital of Sun Yat-Sen University, the patient had a normal body temperature, heart rate and respiratory rate. Additionally, the patient was alert and there were no signs of mental confusion. Except for fundus venous engorgement, the neurological examination did not find impairment of vision, paralysis of the extremities or abnormality of sensation. There were neither any pathological reflexes nor the meningeal irritation sign present.

An initial magnetic resonance imaging (MRI) scan found an iso-intense nodular lesion ($\sim$11 mm $\times$ 8 mm) in the right prepontine cistern on T1- and T2-weighted imaging (Figures 1a and 1b). Gadolinium-based contrast MRI revealed an enhanced solid lesion with a broad base attached to the adjacent meninges, corresponding to the site of iso-intensity on the T1- and

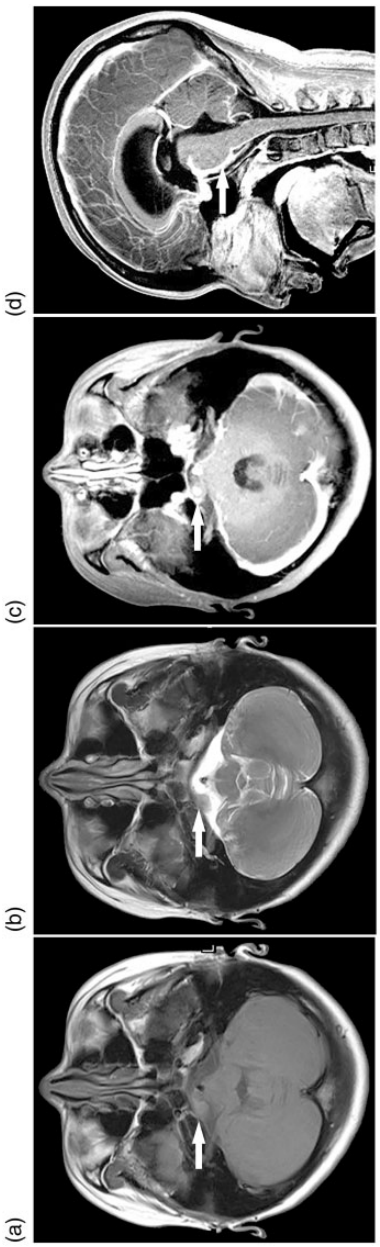

Figure 1. Initial magnetic resonance images of the brain of a 20-year-old female patient that presented with a 3-month history of daily persistent headaches that deteriorated at night. T1- and T2-weighted magnetic resonance images showed an iso-intense nodular lesion (arrow) in the right prepontine cistern (a, b). The lesion (arrow), as well as the adjacent basilar meninges, was obviously enhanced by gadolinium (c, d).

T2-weighted imaging (Figure 1c). Diffuse enhancement of basilar meninges by gadolinium and communicating hydrocephalus were found at the same time (Figure 1d). Positron emission tomography showed a negative accumulation of 18F-fluorodeoxyglucose at the lesion and outside of the CNS. Lumbar puncture demonstrated an abnormal yellow cerebrospinal fluid (CSF) of severely elevated opening pressure (300 mmH_2O), with a white cell count of 18×10^6/l (normal $<10 \times 10^6$/l), protein level of 11419.5 mg/l (normal range, 120–600 mg/l), glucose concentration of 5.3 mmol/l (normal range, 2.3–3.9 mmol/l; simultaneous serum glucose concentration, 7.4 mmol/l) and a chloride level of 112 mmol/l (normal range, 119–129 mmol/l; simultaneous serum chloride level, 101 mmol/l). Meanwhile, suspiciously atypical cells with hyperchromatic nuclei and multiple nucleoli were occasionally found in the CSF. A diagnosis of a neoplastic nodule was suspected but tubercular meningitis was not excluded. Since the patient was unwilling to undergo a biopsy, empirical antituberculosis treatment with 0.3 g isoniazide, 0.45 g rifampin, 1.5 g pyrazinamide and 0.75 g ethambutol was administered orally once a day for 7 days, which was followed by a subsequent ventriculoperitoneal shunt operation. The patient achieved relief from the headache and left hospital after 7 days, with continuation of the antituberculosis treatment. On discharge, a CT scan showed a reduction of the hydrocephalus and CSF analysis revealed a normal opening pressure as well as glucose and chloride concentrations. The white cell count was decreased to 1×10^6/l and the protein level was decreased to 5978.6 mg/l.

One month later, the patient returned to the Department of Neurology, The First Affiliated Hospital of Sun Yat-Sen University because she had been experiencing persistent dizziness and vomiting. A follow-up MRI revealed that the original

nodular lesion in the right prepontine cistern was obviously enlarged (~16 mm × 10 mm) with similar radiological features compared with the initial images (Figure 2a). Slightly blurry plaques without gadolinium enhancement were observed in the cervical cord (Figure 2b). By contrast, diffuse enhancement by gadolinium in the spinal meninges of the cervical, thoracic and lumbar cord was found (Figures 2c and 2d). The diagnosis of a neoplastic nodule was highly suspected. A laminectomy was performed upon the third lumbar segment to obtain a white subdural-extramedullary specimen. Histopathology of the biopsy specimen indicated that moderately cellular nests, consisting of infiltrating and nodular proliferation of pleomorphic cells with hyperchromatic nuclei and scant cytoplasm, were dispersed in the hyperplastic fibrous tissue of the spinal meninges, in support of the morphological characteristics of neoplastic cells (Figure 3A). Furthermore, the cells were strongly positive for the H3 K27M mutant protein (Figure 3B) as well as Ki-67 (median labelling of 70%), glial fibrillary acidic protein and oligodendrocyte lineage transcription factor 2. Taking these findings together, a final diagnosis of a diffuse midline glioma H3 K27M mutant, WHO grade IV was made. The disease was quickly progressive and the patient died 2 months later.

This case report adhered to the ethical guidelines of the Helsinki Declaration (2000) and the CARE (2013) guidelines for case reports. It was approved by the local clinical trial committee at The First Affiliated Hospital of Sun Yat-Sen University. The details of the patient have been completely de-identified and written informed consent to treatment was obtained from the patient. The patient was assessed and treated at the discretion of physician-in-charge according to the usual medical practice.

Discussion

Diffuse midline glioma with H3 K27M mutation is characterized by diffuse and invasive growth in the midline CNS structures.[1] Nonetheless, the clinical and radiographic spectrums of the disease are variable and none of them are decisive for diagnosis.[4,5] Intracranial hypertension is common.[4] The frequently involved midline structures are the brainstem, spinal cord, thalamus, hypothalamus, cerebellum or third ventricle.[4,8] In accordance with previous reports, the present case presented with

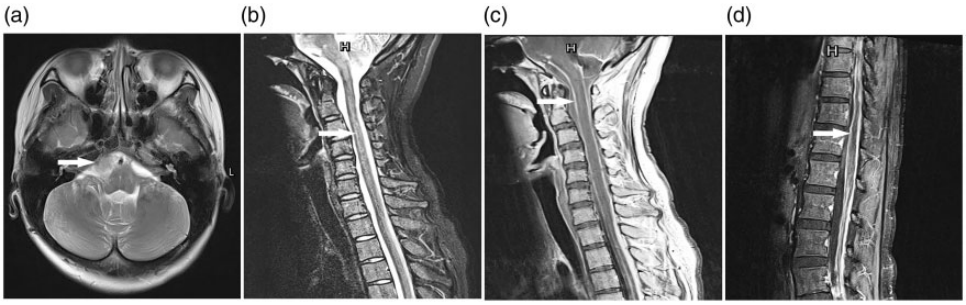

Figure 2. Follow-up magnetic resonance images of the brain and spinal cord of a 20-year-old female patient that presented with a 3-month history of daily persistent headaches that deteriorated at night. The original nodular lesion (arrow) in the right prepontine cistern was enlarged with similar radiological features compared with the initial images (a). Sagittal T2-weighted imaging revealed slightly blurry plaques without gadolinium enhancement (arrow) in the cervical cord (b, c). Diffuse gadolinium enhancement (arrow) in the spinal meninges of the cervical, thoracic and lumbar cord was found (c, d).

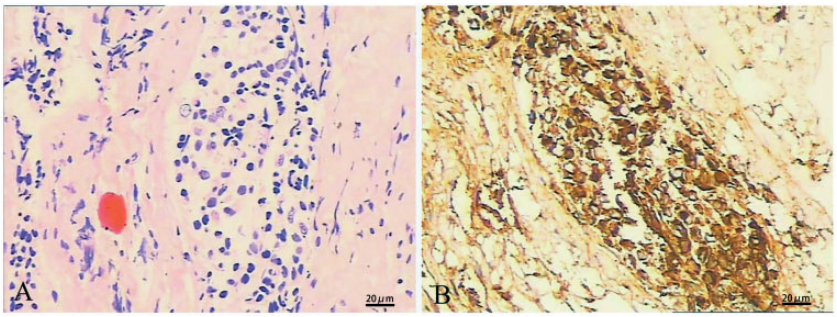

Figure 3. Histological and immunohistochemical examination of a biopsy specimen of the nodular lesion on the third lumbar segment showed infiltrating and nodular proliferation of pleomorphic cells with hyperchromatic nuclei and scant cytoplasm, which were dispersed in the hyperplastic fibrous tissue of the spinal meninges (A). These cells were strongly positive for the histone H3 K27M mutant protein (B), supporting a diagnosis of diffuse midline glioma H3 K27M mutant. Scale bar 20 μm. The colour version of this figure is available at: http://imr.sagepub.com.

a headache due to high cranial pressure hydrocephalus. However, the initial lesion found by MRI was located in the right prepontine cistern, a common site for acoustic neuroma or meningioma but not for diffuse midline glioma with the H3 K27M mutation.[8] No other defined lesion was found in the CNS except for some blurry plaques in the cervical cord. However, upon further consideration of the finding of diffuse infiltration to the meninges, it might be speculated that the neoplastic cells arising from the intramedullary parenchyma had grown and spread elsewhere, including the right prepontine cistern, by CSF flow.

The examination of the CSF in adults with diffuse midline glioma with the H3 K27M mutation has rarely been reported.[9] In contrast to a previously reported paediatric case,[10] the CSF in the present adult case demonstrated a severely elevated opening pressure and protein level, slightly elevated white cell count and decreased chloride level, making it difficult to distinguish from some kinds of infectious diseases in the CNS such as tubercular meningitis. This was compounded by the temporary improvement in the clinical symptoms and CSF parameters following the antituberculosis treatment. Whether the changes to the CSF were specific remains unclear. It may only have been attributed to the diffuse involvement of the meninges or the obstruction of the CSF circulation. More cases are needed to clarify this issue.

The H3 K27M mutation is required for the definite diagnosis of this disease. As shown in the present case, H3 K27M mutant protein, usually together with oligodendrocyte lineage transcription factor 2 (a marker of oligodendrocytes and astrocytes) and glial fibrillary acidic protein (a marker of astrocytes), is without exception positive in the immunohistochemical examination.[11,12] A poor outcome has been associated with the H3 K27M mutation, with a reported median survival time of 19.7 months in adults even if surgical resection and chemotherapy are undertaken.[4] A more effective strategy incorporating the molecular/genetics data and drug development is needed for this disease.

In conclusion, this adult case had a rare diffuse midline glioma with the H3 K27M mutation that presented as a nodular lesion in the right prepontine cistern, which is an unusual site in clinical practice. A biopsy is recommended at the early stage for

suspected cases to make a definite diagnosis based on the histopathological characteristics of positive H3 K27M mutant protein and diffusely infiltrating growth.

Acknowledgement

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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