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H3K27M mutant diffuse midline glioma: a case report

Y. LUO[1], L. ZENG[1], X.-Q. XIE[2], F. WANG[1], Y.-Z. LIU[3], J.-B. KANG[4], X.-F. LI[5], D.-B. WU[6], B.-L. QU[7]

[1]Department of Medical Oncology, Cancer Center, West China Hospital, West China Medical School, Sichuan University, Sichuan, P.R. China
[2]Department of Critical Care Medicine, West China Hospital, Sichuan University, Sichuan, P.R. China
[3]Department of Radiotherapy, Beijing Hospital, Beijing, P.R. China
[4]Department of Radiotherapy, The Fifth Medical Center of PLA General Hospital, Beijing, P.R. China
[5]Department of Radiotherapy, First Hospital of Shanxi Medical University, Taiyuan, Shanxi, P.R. China
[6]Cancer Hospital, Ansteel Group Hospital, Anshan, Liaoning, P.R. China
[7]Department of Radiotherapy, Chinese PLA General Hospital, Beijing, P.R. China

Abstract. – OBJECTIVE: Diffuse midline glioma with H3K27M mutation is a new tumor type of WHO central nervous system tumor classification. It often occurs in the midline structure and usually has a poor prognosis.

CASE REPORT: A 38-year-old male patient presented with 2 years history of right limb with facial numbness, tumors in the left thalamic region and lateral ventricle was detected by imaging. The patient underwent the first surgery.

RESULTS: The pathological examination results: Glioblastoma. He recovered well after surgery and received a total of 30 times of radiotherapy and temozolomide for one year. Fourteen months later, tumours were observed in the left thalamic region and left parieto-occipital lobe, the patient underwent the second operation. Immunohistochemistry showed: H3K27M(+). He experienced limitation of right limb movement after surgery and started taking oral apatinib 250 mg qd. After one-year, multiple tumors were found in the left brainstem, bilateral ventricles, bilateral basal ganglia, etc. The patient was given radiotherapy 7 times and then took apatinib 250 mg qd. Now the patient is still alive.

CONCLUSIONS: H3K27M mutant diffuse midline glioma is characterized by diffuse infiltrative growth. Its pathological classification is diverse, imaging features lack specificity, and prognostic factors are complex. Traditional radiochemotherapy has limited effects, molecular targeted therapy, especially intervention of epigenetic regulation is being explored.

Key Words:
H3K27M mutant, Diffuse midline glioma, Prognosis, Case report.

Introduction

Diffuse midline glioma with H3K27M mutation is the new tumor type of WHO central nervous system tumor classification (2016), which not only has traditional morphology, but also combines the diagnosis of molecular pathology[1]. It occurs mostly in children and has fewer adults. It often occurs in the midline structure, such as the thalamus, brainstem, and spinal cord. It is accompanied by a mutation of histone H3K27M, and its growth is diffuse and invasive. Histological changes are visible from low grade to high grade, but the biological manifestations are highly malignant, so the new classification regards it as a new type, which is classified as grade IV, with a very poor prognosis and a 2-year survival rate < 10%[2].

Case Report

A 38-year-old male patient presented with 2 years history of right limb with facial numbness, there was no evident limb movement disorder, dizziness, headache, tinnitus, decreased vision or drinking water choking cough. He

Corresponding Authors: Feng Wang, MD; e-mail: wangfeng5024@126.com
Baoli Qu, MD; e-mail: qubl6212@sina.com

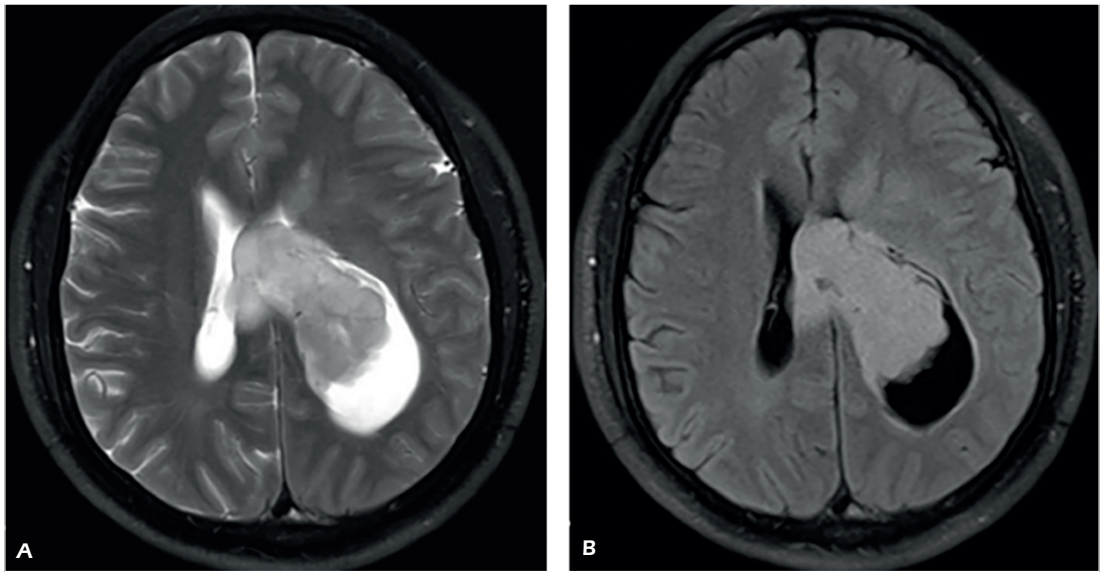

Figure 1. Irregularly shaped mass shadows were observed in the left thalamic region and lateral ventricle, with the size of 6.4×4.3 cm measured in axial view. Left ventricular enlarged, and midline shifted to right.

did not pay attention. After that, limb numbness was gradually aggravated. In May 2017, the patient underwent a head enhanced MRI scanning in our hospital (Figure 1): irregularly shaped mass shadows were observed in the left thalamic region and lateral ventricle, with the size of 6.4×4.3 cm measured in axial view. Left ventricular enlarged, and midline shifted to right. The subject underwent surgery in our hospital in May 2017. Pathological examination results: Glioblastoma (grade IV), Ki67 50%. IDH1, IDH2 gene, and TERT gene promoter mutation were not detected by gene detection, MGMT gene promoter methylation was not detected. He recovered well after surgery, and reexamination of MRI showed relevant changes after the surgery (Figure 2). The patient received a total of 30 times of radiotherapy

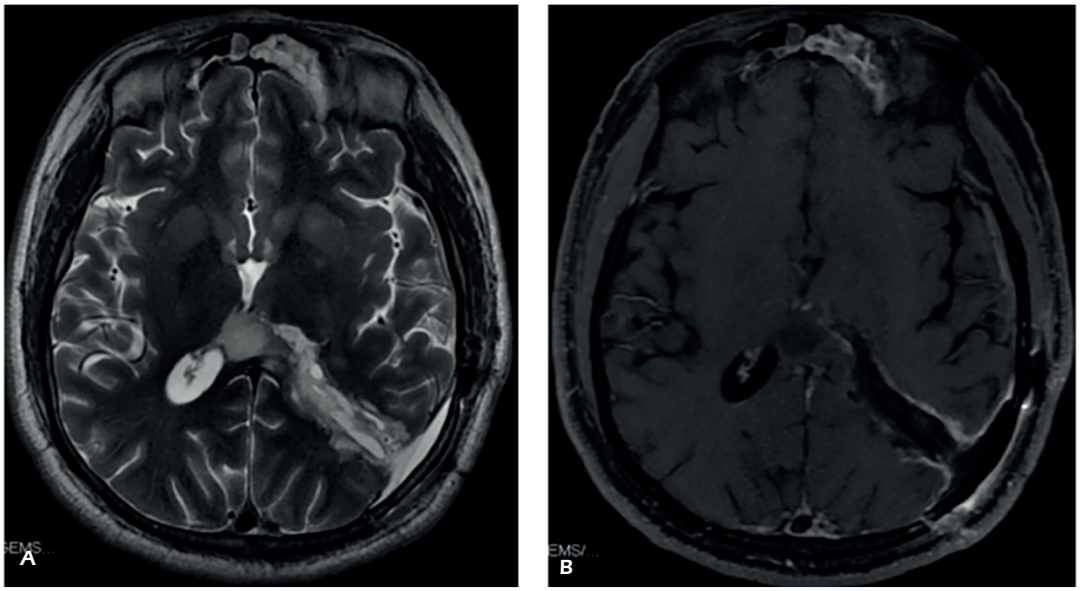

Figure 2. A, B, Glioblastoma (grade IV), Ki67 50%. IDH1, IDH2 gene, and TERT gene promoter mutation were not detected by gene detection, MGMT gene promoter methylation was not detected. The patient recovered well after surgery, and reexamination of MRI showed relevant changes after the surgery.

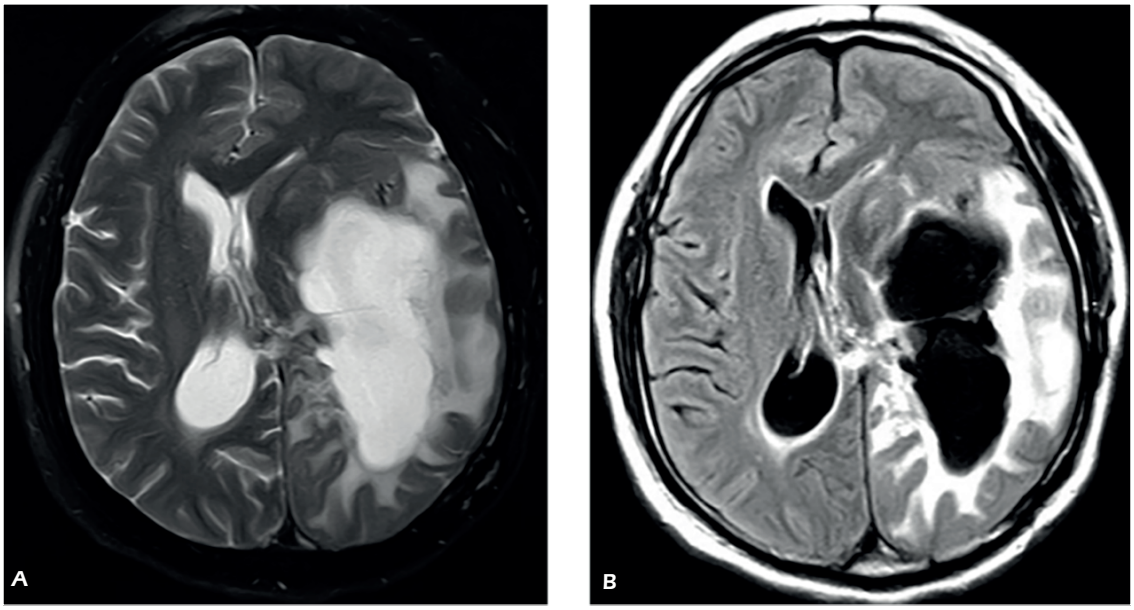

Figure 3. A, B, Large patchy long T1 and long 2 signal shadows were observed in the left thalamic region and left parieto-occipital lobe, and there was a patchy edema around it. The left ventricle narrowed, the midline shifted to the right. Slightly longer T1 and longer T2 signals were observed in the left cerebellopontine angle region, approximately 2.5×2 cm in size. A T2 long signal could be seen in the left maxillary sinus, ethmoid sinus, and frontal sinus.

since September 2017, while temozolomide 100 mg qd was given. After radiotherapy, temozolomide 300 mg d1-5, q28d was administered until June 2018. He was in good conditions and there was no limit to physical activity. In July 2018, the patient began to experience nausea and vomiting, and suddenly, he became unresponsive, irritable, without convulsion or incontinence. MRI head enhancement scan showed (Figure 3): large patchy long T1 and long 2 signal shadows were observed in the left thalamic region and left parieto-occipital lobe, and there was a patchy edema around it. The left ventricle narrowed, and the midline shifted to the right. Slightly longer T1 and longer T2 signals were observed in the left cerebellopontine angle region, approximately 2.5×2 cm in size. A T2 long signal could be seen in the left maxillary sinus, ethmoid sinus, and frontal sinus. We considered tumor recurrence. The subject underwent surgery again on July 31, 2018. Postoperative pathological immunohistochemistry showed (Figure 4): GFAP(+), O1igo2(+), ATRX(+), H3K27M(+), IDH1(-) EMA(-), NeuN(-), Ki67 (+, 2%). Pathological diagnosis: left temporo-parieto-occipital diffuse midline glioma, H3K27 mutant (WHO grade 4, 2016 edition). He experienced limitation of

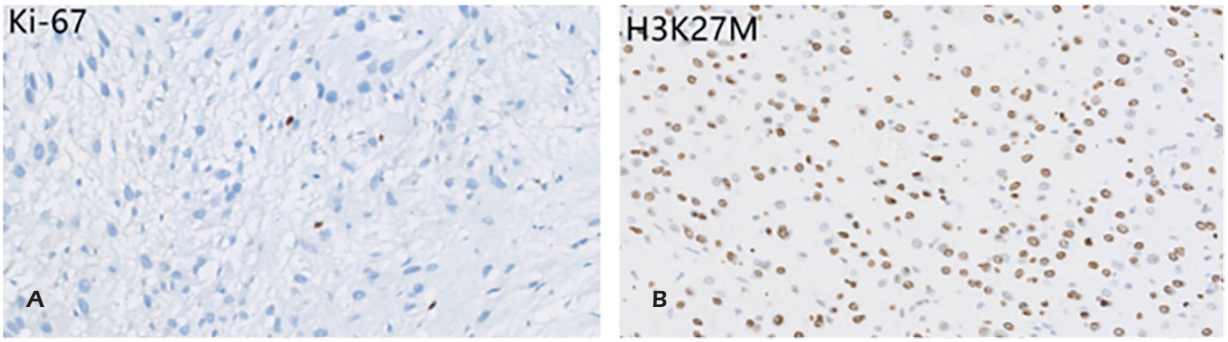

Figure 4. A, B, GFAP(+), O1igo2(+), ATRX(+), H3K27M(+), IDH1(-) EMA(-), NeuN(-), Ki67 (+, 2%). Pathological diagnosis: left temporo-parieto-occipital diffuse midline glioma, H3K27 mutant (WHO grade 4, 2016 edition).

right limb movement after surgery. The head MRI showed postoperative changes (Figure 5). He started taking oral apatinib 250 mg qd since November 2018. In July 2019, MRI brain tumor multimodal enhancement scan found that a long T1 and long T2 signal measuring 4.6 cm × 3.8 cm could be seen in the left part of the brainstem. The mass protruded into the left cerebellopontine angle cistern. Bilateral periventricular area, callosal region, bilateral basal ganglia, and the left frontal lobe had multiple irregular slightly long T1 and long T2 signals (Figure 6). So, we considered the tumor progressing again, the patient was given radiotherapy 7 times. Due to high fever, headache, convulsions, and vomiting, the radiotherapy was stopped. After the patient's physical condition gradually improved, he continued to take apatinib 250 mg qd. At present, he has right limb movement disorder, occasional headache, and part of life is self-care.

Discussion

H3K27M mutant diffuse midline glioma is most common in the pons and the thalamus. The average age of diagnosis is 7-11 years. The average age of the pons is about 7 years old, the thalamus is 11 years old, and the patients with spinal cord tumors are mostly adults. The clinical symptoms and signs are related to the tumor site. The supratentorial lesions may cause clinical symptoms such as hemiplegia, headache, vomiting, and blurred vision because of increased intracranial pressure, while the infratentorial lesions are manifested as limb movement and sensory disturbance, ataxia, symptoms, and signs caused by cranial neuropathy. In terms of imaging performance, the disease is similar to other gliomas. MRI shows a long T1 and T2 signal, with or without enhancement, no specificity, and huge variability[3]. However, with the continuous advancement of medical imaging technology and the development of radiomics, specific imaging performance will be slowly explored[4]. The morphological changes of the disease are quite different, astrocytoma is the most common, oligodendrocyte is also common, and glioblastoma can also be seen, as well as neuropil-like structures, hairy cell myxoid features, ependymoid, sarcomatoid changes, etc[5]. The most characteristic feature of this disease is the mutation of H3K27M, which is located on the coding gene H3F3 on histone H3.3. Histone H3.3 affects gene expression through epigenetic regulation and participates in biological processes such as cell proliferation and differentiation[6]. The mutation of H3K27M can cause the decrease of its own methylation level, which affects the stability of gene transcription and causes the occurrence and development of tumor[7].

The prognosis of glioma is closely related to the grade, but the diffuse midline glioma with H3K27M mutation is special, histolog-

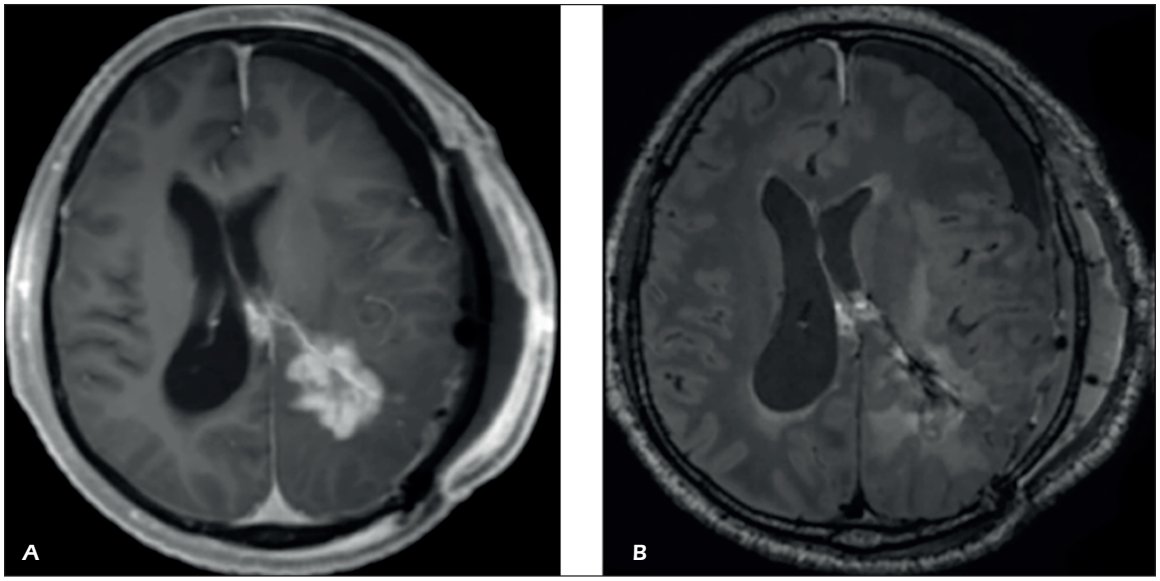

Figure 5. A, B, The patient experienced limitation of right limb movement after surgery. The head MRI showed postoperative changes.

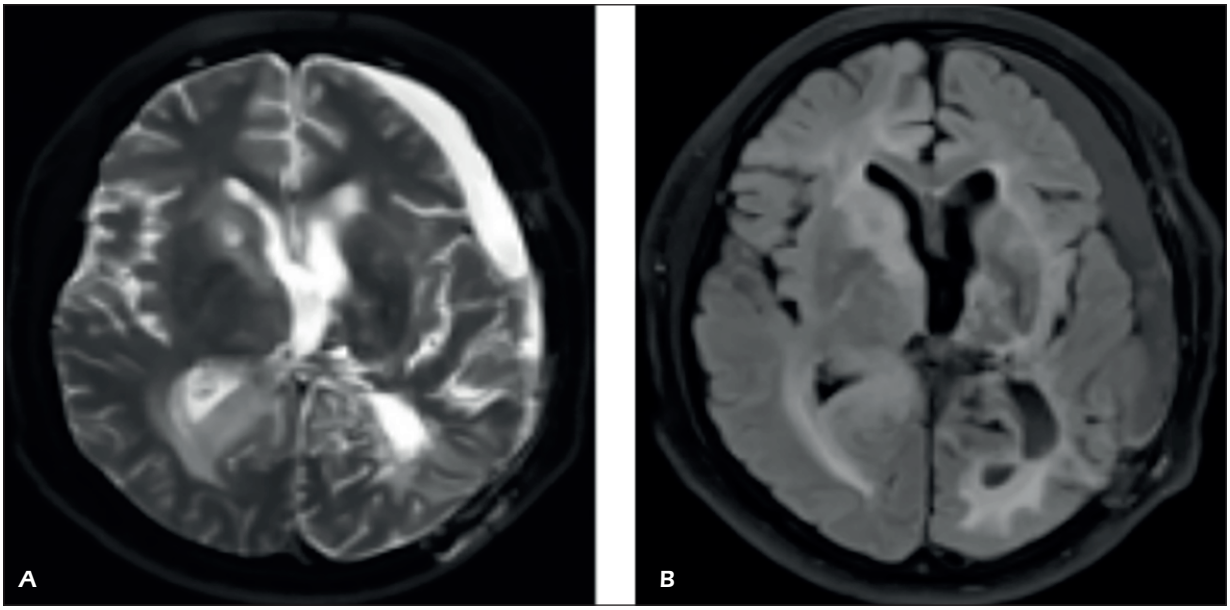

Figure 6. A, B, A long T1 and long T2 signal measuring 4.6 cm×3.8 cm could be seen in left part of the brainstem. The mass protruded into the left cerebellopontine angle cistern. Bilateral periventricular area, callosal region, bilateral basal ganglia, and the left frontal lobe had multiple irregular slightly long T1 and long T2 signals.

ical grade has a very limited role in judging prognosis[8]. As in this case, histopathology is a glioblastoma, but the survival time is relatively long. Karremann et al[9] have shown that the prognosis of H3K27M mutant glioma is not related to the extent, location, and grade of the tumor, H3K27M mutation is an only independent prognostic factor, H3K27M mutation indicates poor prognosis. However, in actual clinical practice, the prognosis of the disease is still very different. Feng et al[10] have also shown that different sites may have different prognosis. The prognosis of patients occurring in the thalamus is better than the brainstem, because the expression of the gene of cyclin-dependent kinase 6 (CDK6) is different in brainstem and thalamus with H3K27M mutation[10]. The survival time of this case is more than 2 years, and the first site is just in the thalamus where the prognosis was relatively good. To further search for the prognostic factors of the disease, molecular markers have become a research hotspot, including PDGFR, 17p, c-MET, p53, etc. There are also researchers using next-generation sequencing methods to explore very concealed prognostic-related molecules[11,12]. Specimens are not limited to tumor tissue, cerebrospinal fluid becomes an important source of specimens because of its operability[13].

Conclusions

At present, the treatment of this disease is very difficult, the brain stem and thalamus are the most common sites of disease, but also the key anatomical region of the nervous system, the position is very deep, and the operation of the surgical is very difficult. Traditional radiotherapy and chemotherapy effects are limited. To date, the drugs targeting PDGFR, EGFR, anti-angiogenic drugs, PARP1 inhibitors, CDK4/CDK6 inhibitors, and various multi-kinase inhibitors have not shown efficacy. Now, the intervention of epigenetic regulation has become a hot spot, H3K27M mutations cause changes in the methylation level. Histone demethylase JMJD3 and histone methyltransferase EZH2 are involved in the methylation process and are expected to be potential therapeutic targets. However, different studies have not yielded consistent results, and further exploration is needed[14-17].

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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