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CASE STUDY

Lorlatinib for *ALK*-fused, infant-type hemispheric glioma with lung metastasis: a case report

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Abstract

Infant-type hemispheric glioma, a new subtype of pediatric high-grade glioma, arises in the cerebral hemispheres. Despite better survival outcomes, the treatment of infant-type hemispheric glioma is still facing challenges. Here, we reported a case of *QKI-ALK* fusion, infant-type hemispheric glioma with lung metastasis who achieved a complete clinical response after lorlatinib treatment. This typical case demonstrated the importance of appropriate molecularly targeted treatments in *ALK*-fused tumors, and lorlatinib may serve as an effective complement to conventional chemotherapy and radiotherapy in primary glioma harboring *ALK* fusions and its metastasis.

Introduction

As the most common tumor in the central nervous system (CNS), glioma is a major cause of morbidity and mortality in both children and adults. It is traditionally classified into low-grade glioma (LGG) and high-grade glioma (HGG) according to histological characteristics.[1] Infant-type hemispheric glioma, a new subtype of pediatric HGG defined in the updated 2021 World Health Organization (WHO) classification of tumors of the CNS, arises in the cerebral hemispheres and is frequently confirmed to be malignant histologically.[2,3] Compared with other pediatric HGGs, infant-type hemispheric glioma is more amenable to targeted therapy due to the presence of

receptor tyrosine kinase rearrangements in *ALK*, *ROS1*, *NTRK* family, and *MET*, leading to improved survival outcomes.[1]

Currently, the treatment of infant-type hemispheric glioma is still facing challenges, although better survival outcomes are achieved. Considering that this type of glioma usually presents as an enormous vascular tumor in the developing brain of young children, combined therapies with surgery, radiation, and chemotherapy are highly likely to contribute to various neuroendocrine deficiencies, neurocognitive delays, and shortened lifespan.[3,4] Here we reported a case of infant-type hemispheric glioma harboring *QKI-ALK* fusion who developed lung metastasis but achieved a complete clinical response after treatment with lorlatinib, a tyrosine kinase inhibitor that targets ALK and ROS1.

Case Presentation

A 3-year-old boy presented to our hospital on February 5, 2021, for glioblastoma in the left parietooccipital lobe after surgery. Two months prior to presentation, the patient experienced headache, abdominal pain, drooling, and unconsciousness for 1 h after non-projectile vomiting. Magnetic resonance imaging (MRI) of the head showed a large space-occupying lesion with hemorrhage in the left parietooccipital lobe (Figure 1A, subpanel a). Total resection was performed (Figure 1A, subpanel b), and initial postoperative histopathology suggested an atypical teratoma or a rhabdoid tumor, with INI1 (−) via immunohistochemistry. Targeted sequencing on DNA detected a *QKI-ALK* fusion (Figure 2A), and somatic *SMARCB1* p.R158* and *ALK* p.A1015T (Figure 2B), as well as germline *RAD51C* p.E218Vfs*33 were also identified. After admission to our hospital, MRI showed multiple intracranial lesions with intracerebroventricular dissemination, suggesting a rapidly progressive tumor (Figure 1A, subpanel c). Spinal MRI indicated a few lesions and thread-like enhancement in the periphery of the brainstem and spinal cord. Through pathological consultation, infant-type hemispheric glioma was diagnosed (Figures 1B and 3).

On February 20, 2021, the patient received radiotherapy with concurrent chemotherapy of temozolomide (TMZ, 75 mg/m^2) and bevacizumab (100 mg), including craniospinal irradiation with a cumulative dose of 36 Gy in 20 fractions and local radiotherapy with a dose of 23.4 Gy in 13 fractions. After chemoradiotherapy for 7 weeks, MRI indicated partial response of the intracranial lesions (Figure 1A, subpanel d). On July 9, 2021, the patient suffered from seizures after two courses of TMZ chemotherapy. The MRI showed tumor progression and further dissemination (Figure 1A, subpanel e). On July 19, 2021, the patient was treated with alectinib (150 mg,

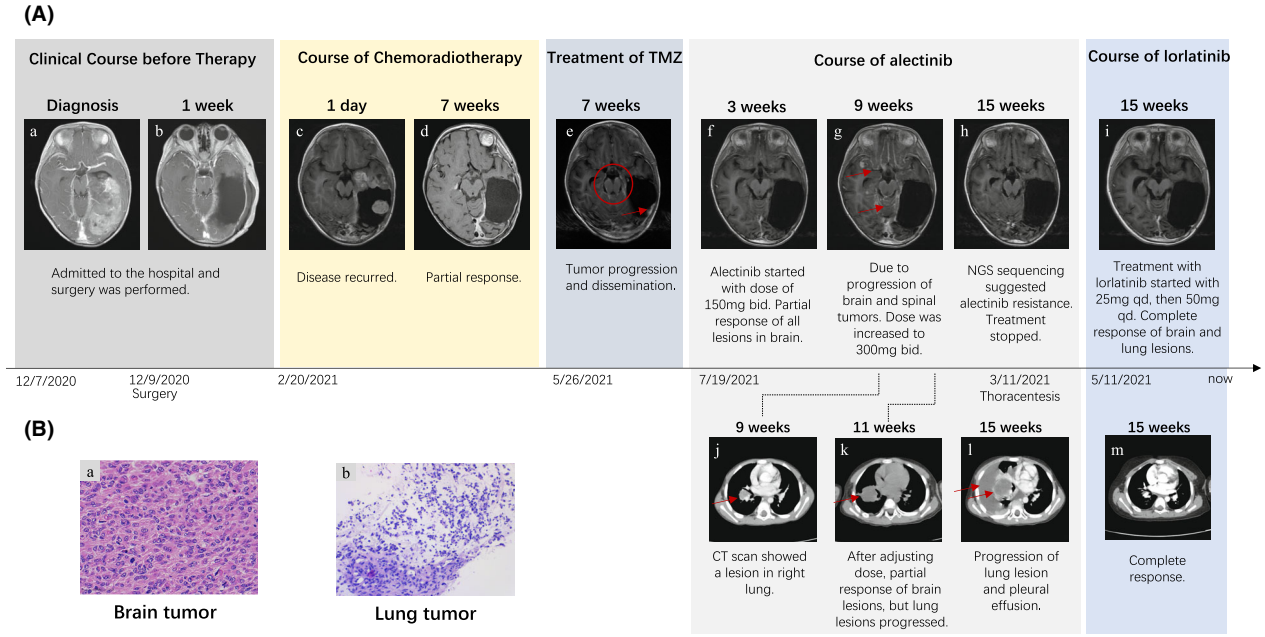

Figure 1. The clinical course of the patient. (A) Serial images of brain (subpanel a to i) and lung (subpanel j to m) over the course of treatment, in which the circle and arrow in subpanel e represent multiple thread-like enhancements around the brainstem and a newly increased abnormal enhancement in the surgical margin, respectively; the arrow in subpanel g represents multiple abnormal thread-like enhancements in the sulcus, while those in subpanel j, k and l refer to obviously abnormal enhancements. (B) Histologic features of the brain (subpanel a) tumor with H&E × 400 and the lung tumor (subpanel b) with H&E × 200.

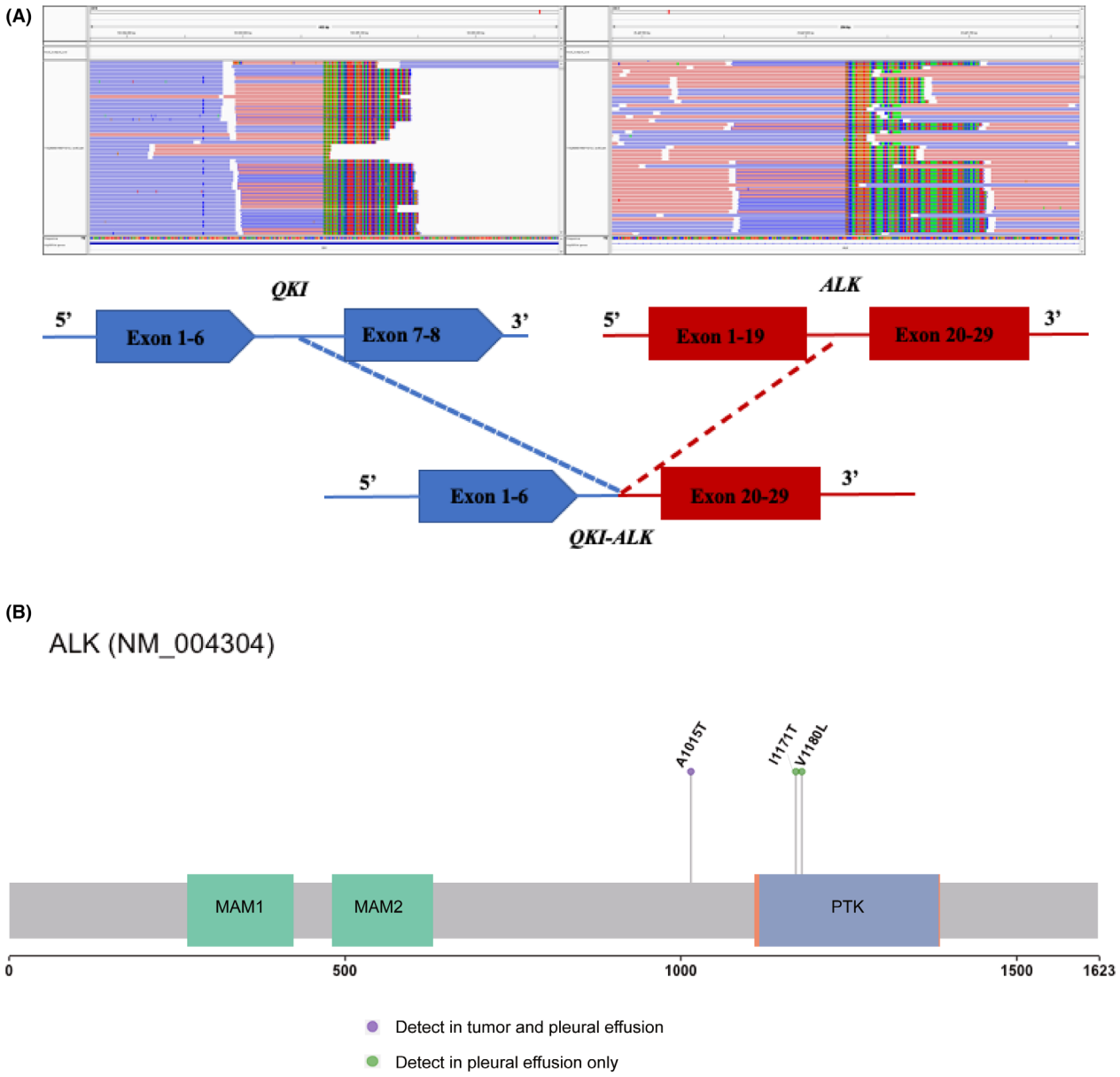

Figure 2. Targeted sequencing results on DNA. (A) A novel *QKI-ALK* oncogenic fusion variant in primary tumor tissue sample. (B) Spectrum of *ALK* variants in primary tumor sample and pleural effusion. MAM, MAM domain; PTK, protein kinase domain.

bid), an ALK inhibitor, and 3 weeks later he achieved partial response in all the intracranial lesions (Figure 1A, subpanel f). In early September, he experienced intermittent nausea and vomiting accompanied by sacrococcygeal pain and mild weakness in the limbs, and seizures occurred on September 22, 2021. MRI revealed the progression of intracranial and spinal lesions (Figure 1A, subpanel g and Figure S1). Furthermore, a mass at the right hilum of the lung was detected through the chest computed tomography (CT) (Figure 1A, subpanel j). Thus, the dose of alectinib was increased to 300 mg, bid. On October 8, 2021, the head and spinal MRI showed reduced intracranial and spinal lesions, but enlarged lung lesions (Figure 1A, subpanel k). B-ultrasound guided-lung biopsy was performed in another hospital, and atypical teratoid rhabdoid tumors were suspected.

The patient was readmitted to hospital due to intermittent nausea and vomiting for nearly 1 week, accompanied by shortness of breath after activity. He was diagnosed with relapsed infant-type hemispheric glioma in the left parietooccipital lobe, atypical teratoid or rhabdoid tumors in the lung and secondary epilepsy. The head MRI

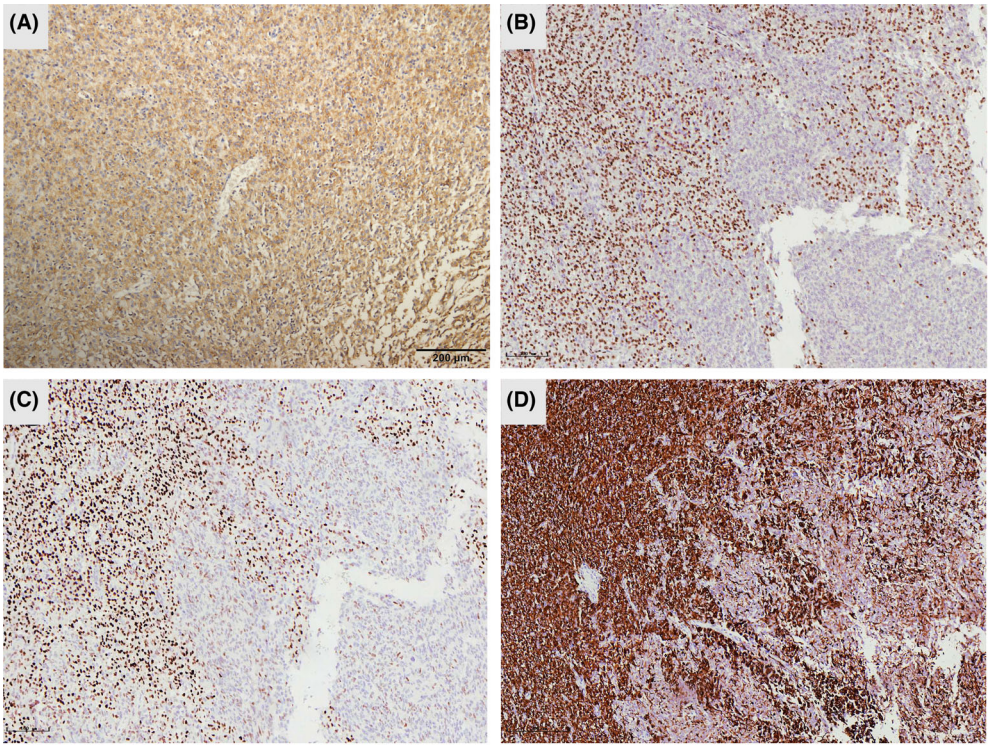

Figure 3. Histologic features of primary brain tumor. (A) A great population of ALK-positive cells are detected, IHC × 100. (B) A great population of INI1-deficient cells are detected, IHC × 100. (C) The tumor cells are positive for glial fibrillary acidic protein (GFAP), IHC × 100. (D) The tumor cells are positive for Olig2, IHC × 100. IHC, immunohistochemistry.

revealed increased abnormally enhancing lesions and tumor cells were detected from cerebrospinal fluid, suggesting tumor progression (Figure 1A, subpanel h). The chest CT showed enlarged space-occupying lesions in the hilum of right lung and significant pleural effusion (Figure 1A, subpanel l). On November 3, 2021, thoracocentesis was performed successfully. Targeted sequencing of 539 tumor-related genes using DNA isolated from the pleural effusion revealed a *QKI-ALK* fusion, somatic mutations in *SMARCB1* p.R158*, *ALK* p.A1015T and *ALK* p.V1180L (Figure 2B), as well as a germline mutation in *RAD51C* p.E218Vfs*33. Two days later, lorlatinib (25 mg, qd) was commenced. On November 9, 2021, the chest CT revealed slightly shrunken lung lesions and significantly decreased pleural effusion. In view of this, the dose of lorlatinib was adjusted to 50 mg, qd. Approximately 15 weeks after lorlatinib use, a complete response was achieved in the brain and lung (Figure 1A, subpanel i and m). At present, the disease is controlled, and the patient continues to receive lorlatinib.

Discussion

Infant-type hemispheric glioma, a rare, rapidly growing HGG, emerges in the cerebral hemispheres of newborns and infants, with molecular aberrations in *ALK*, *ROS*, *NTRK1/2/3*, and *MET*.[5] Kinase fusion-positive tumors clinically respond to targeted treatment, with better outcomes. It is reported that extraneural metastasis of HGG is rare.[6] In this study, we presented a case of infant-type hemispheric glioma harboring *QKI-ALK* fusion who experienced lung metastasis but achieved a complete clinical response after lorlatinib treatment, suggesting that lorlatinib might be effective for infant-type hemispheric glioma harboring *QKI-ALK* fusion.

In our study, targeted sequencing of the brain tumor and pleural effusion revealed the same mutations in *SMARCB1* p.R158* and *ALK* p.A1015T, confirming the pathological finding of brain-to-lung metastasis. In addition, a germline frameshift deletion *RAD51C* p.E218Vfs*33 was also identified, which was evaluated as likely pathogenic according to Clinvar. A previous study revealed that *MYB-QKI* fusion was a molecular subtype of pediatric-type diffuse LGG.[2] However, a targetable *QKI-ALK* fusion was identified in our case of infant-type hemispheric glioma, in which *QKI* was newly found to be the partner of *ALK*, resulting in a *QKI-ALK* fusion.

In common with the subgroups of adult epithelial tumors, the presence of recurrent *ALK*, *ROS*, *NTRK1/2/3*,

and *MET* fusions indicates distinctly targetable aberrations.[7,8] Despite the rarity, the identification of these fusions allows them to be amenable to selection for drugs based on routine diagnostic sequencing panels and screening approaches.[3] Alectinib, a highly selective ALK inhibitor, has been demonstrated to have superior activity within the CNS. Irrespective of previous CNS disease or radiotherapy, alectinib can significantly defer CNS progression in patients with advanced *ALK*-positive non-small cell lung cancer (NSCLC).[9] In our case, the patient initially obtained partial response with alectinib, but tumor progression occurred approximately 15 weeks after alectinib use, which might be associated with a mutation of *ALK* p.V1180L capable of mediating alectinib resistance in NSCLC.[10] Given this, lorlatinib was used for the patient, and a complete clinical response was achieved. As a potent, brain-penetrant, third-generation tyrosine kinase inhibitor targeting ALK and ROS1, lorlatinib presents substantial intracranial and overall activity for *ALK*-positive NSCLC.[11] In an HGG child harboring *ALK* fusions, lorlatinib was found to bring survival benefits,[12] consistent with our findings.

In conclusion, our study is the first to characterize an *ALK*-fused infant-type hemispheric glioma child with lung metastasis who derived survival benefits from lorlatinib. This atypical case demonstrated the importance of appropriate molecularly targeted treatments in *ALK*-fused tumors, and lorlatinib may serve as an effective complement to conventional chemotherapy and radiotherapy in primary glioma harboring *ALK* fusions and its metastasis.

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None.

Author Contributions

MYL, SQL, HNL, QH, ZL, and LBC conceived and designed the study. QJH, JL, JFZ, RYA, JJZ, LCW, YQZ, WMH, and LY participated in data acquisition. ZMZ, XJM, XZ, and CS performed data analysis and interpreted the results. MYL, SQL, and HNL draft the manuscript. ZL and LBC was responsible for reviewing and supervising the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have no conflict of interest.

Ethics Statement

Approval of the research protocol by an Institutional Reviewer Board: N/A. Informed Consent: Yes. Registry and the Registration No. of the study/trial: N/A. Animal Studies: N/A.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Serial magnetic resonance imaging of spine over the course of treatment. The arrows represent obviously abnormal enhancements in spinal cord.