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Pediatric-type diffuse high-grade glioma with systemic metastasis: A case report

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Pediatric-type diffuse high-grade gliomas (pHGG) are rare, aggressive central nervous system malignancies newly classified in the 2021 World Health Organization classification. Extracranial metastasis of pHGG is uncommon, mostly in H3K27M-mutant diffuse midline gliomas. We report that a 26-year-old H3-wildtype and IDH-wildtype (RTK1 subtype) male developed extensive extracranial metastases after surgery. Despite radiochemotherapy, the disease spread. This case shows extracranial metastasis potential in pediatric-type gliomas, especially RTK1. Recent studies indicate about half of Adolescent and Young Adult (AYA) high-grade gliomas are pediatric-type, and around 40% of extracranial metastases occur in AYA patients. Recognizing this metastatic potential, especially in AYA, is significant for better outcomes.

Extracranial systemic glioma metastasis is rare, particularly in children, where cases of extracranial metastases in pediatric glioma are exceedingly uncommon.[1,2] Lun et al. undertook a retrospective analysis of 88 cases of extracranial glioblastoma between 1928 and 2009, revealing that the median age was 38 years (range 6–64 years).[1] Among these, only 13 patients were under the age of 18, accounting for 14.7% of the total. The study indicated that the incidence of extracranial metastases in pediatric glioma patients is significantly lower compared to adults.

The fifth edition of the World Health Organization (WHO) classification of central nervous system tumors, published in 2021, distinguished pediatric-type gliomas from the broader glioma category for the first time, further subdividing them into pediatric-type diffuse low-grade gliomas and pediatric-type diffuse high-grade gliomas (pHGG).[3] pHGG are highly aggressive central nervous malignant tumors, with a relatively low incidence rate.[4,5] Notably, the age of diagnosis is not a defining criterion for pediatric-type gliomas,[6] as some young adult patients may also be diagnosed with these tumor types. Consequently, certain biological characteristics of pediatric-type high-grade gliomas, including the conditions of extracranial metastasis, remain incompletely known. Recently, a few case reports have revealed the occurrence of extracranial systemic metastasis in pediatric-type high-grade gliomas. Nearly all of these cases were diffuse midline gliomas with H3K27M mutations,[7–9] while metastases in other types have rarely been reported.

Here, we present a case of a young adult with a pHGG, H3-wildtype and *IDH*-wildtype, RTK1 subtype, who developed multiple extracranial metastases involving the pancreas, lungs, and bones following surgical treatment.

Case Presentation

A 26-year-old previously healthy man presented to his local hospital with an acute headache. Cranial magnetic resonance imaging revealed abnormal signal lesions in the right frontal lobe and basal ganglia, initially suspected to be gliomas with hemorrhage extending into the ventricles (Figure 1A–D). The patient underwent an emergency craniotomy at the local hospital, with a gross total resection of the right deep supratentorial lesion. Intraoperative findings revealed a tumor in the right frontal lobe with a gelatinous appearance and indistinct margins, accompanied by peritumoral edema.

Pathological examination of the resected specimen showed a tumor composed of round and oval cells with diffuse brain tissue infiltration, nuclear atypia, and brisk mitotic activity. Some areas exhibited a perinuclear halo, resembling oligodendroglioma, along with focal necrosis and microvascular proliferation. These histological features were consistent with a high-grade diffuse glioma (Figure 1E–G).

Immunohistochemical analysis revealed a Ki-67 labeling index of approximately 45% (Figure 1H). The tumor cells were positive for GFAP and Olig2, and negative for ATRX, H3K27M, IDH1, BRAF (VE1) (Figure 1I–J), while P53 showed positive expression only in a few cells. Genetic profiling via next-generation sequencing (NGS) demonstrated a homozygous deletion of *CDKN2A/2B*, mutations in *ATRX* and *TP53*, amplification of the *PDGFRA* gene, and mutations in the *MUTH* and *MSH6* genes (Figure 1K)(see Supplementary Table 1). No mutations were found in *IDH1*, *IDH2*, H3, *TERT*, *EGFR*, and *BRAF* genes; chromosomal abnormalities such as chromosome

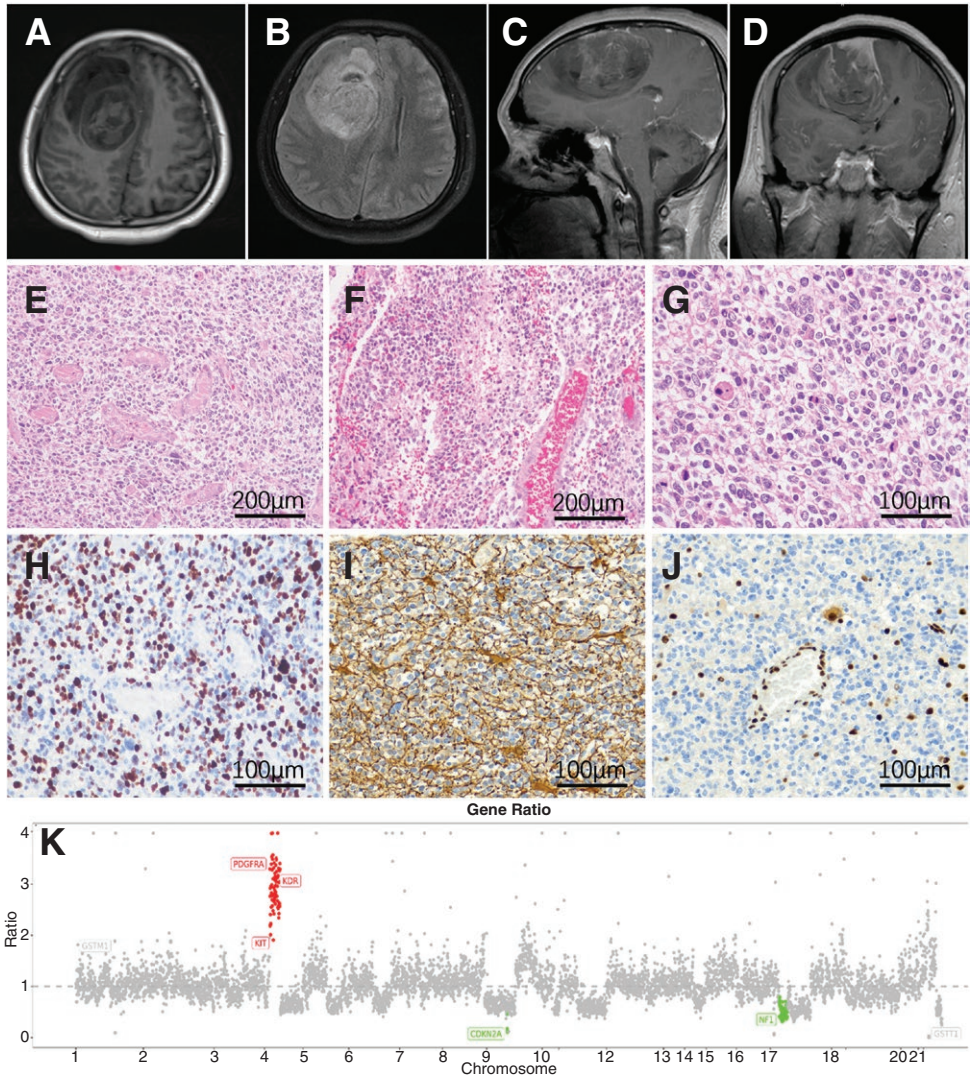

Figure 1. Preoperative MRI showed abnormal signal intensities in the right frontal lobe and basal ganglia, with indistinct margins from the surrounding brain tissue, low signal intensity on T1-weighted images **(A)** and high signal intensity on T2-weighted images **(B)**. T1 sagittal imaging showed the mass to be low density **(C)**. T1 coronal imaging showed uneven hypodensity within the lesion, with significant perilesional edema and midline shift **(D).** H&E stain of resected tissue showed oval to round tumor cells **(E)**, with focal necrosis and microvascular proliferation **(F)**. Marked atypia, frequent mitotic figures, and perinuclear halos were observed in some areas **(G)**. The Ki-67 index of the tumor cells was approximately 45% **(H)**. Immunohistochemical staining showed diffuse positive expression of *GFAP* **(I)**, and the absence of *ATRX* expression, with endothelial cells of blood vessels and other non-neoplastic cells demonstrating positive expression **(J)**. Copy number profiling of DNA methylation sequencing revealed amplification of *PDGFRA*, and the deletion of *NF1* and *CDKN2A* **(K)**.

7 gain or chromosome 10 loss were absent, and 1p/19q co-deletion was not detected. Based on histopathology, immunohistochemistry, and molecular findings, the tumor was integratedly diagnosed as a diffuse pediatric-type high-grade glioma, H3-wildtype and *IDH*-wildtype (see Supplementary Table 2). Whole-genome DNA methylation analysis further confirmed the diagnosis as an RTK1 subtype diffuse pediatric-type high-grade glioma, H3 wildtype and *IDH*-wildtype (classifier version 12.3, score 0.81) (Figure 2).

The patient subsequently underwent standard radiochemotherapy, for PTV1, radiotherapy (RT) was delivered at 2.00 Gy/fraction (Gy/f) to a total dose of 60.00 Gy in 30 fractions; for PTV2, RT was delivered at 1.70 Gy/f to a total dose of 51.00 Gy in 30 fractions. Temozolomide (TMZ) (200 mg orally nightly for 5 days, followed by a 23-day rest period, repeated every 28 days) was administered as adjuvant chemotherapy. However, his condition failed to improve over the following five months. Neurological symptoms persisted, and the quality of life declined. The patient later experienced a sudden syncope, and further clinical examination raised suspicion of pancreatic cancer. PET-CT imaging identified a space-occupying lesion in the tail of the pancreas, approximately 2.24 cm in diameter, with additional tumors in both lungs, lymph nodes in the left lung, and bones throughout the body

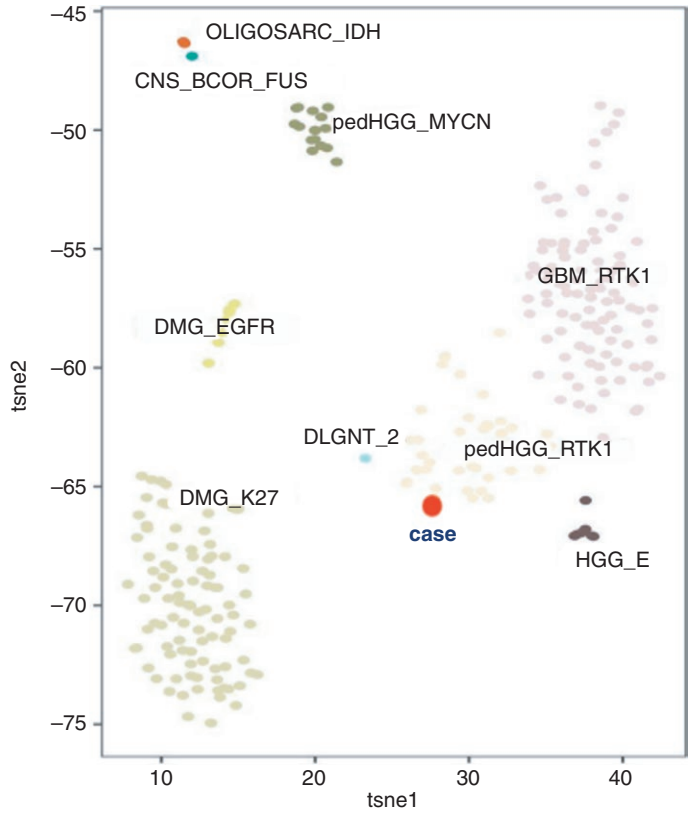

Figure 2. Whole-genome DNA methylation profiling analysis result confirming the tumor to be H3-wildtype and IDH-wildtype, classified as RTK1 subtype.

(Figure 3A–D). Additionally, there was no evidence of scalp or skull metastases, as confirmed by the imaging studies. Brain imaging also revealed a malformed right frontal lobe with a cerebrospinal fluid (CFS) cystic cavity, alterations of the entire ventricular system, and paraventricular edema. The clinical preliminary diagnosis was pancreatic cancer with extensive systemic metastasis.

To confirm the diagnosis, a percutaneous needle biopsy of an iliac bone lesion was performed. Histopathological analysis showed small patchy pleomorphic cells with marked atypia and frequent mitotic figures (Figure 3Eand F). Immunohistochemical findings indicated a Ki-67 of approximately 80%. The tumor cells were positive for GFAP, Olig2, Vimentin, and focal S100, but negative for CK, EMA, CEA, MUC6, and E-cadherin (Figure 3G–I). Considering the patient's medical history of brain tumor, these findings supported a pathological diagnosis of pediatric-type high-grade glioma, H3 wildtype and *IDH* wildtype, with extracranial systemic metastasis.

The patient continued to receive radiochemotherapy and symptomatic treatment at an oncology hospital. Despite these efforts, his condition progressively worsened, and he ultimately succumbed to the primary disease 9 months after his initial craniotomy (see Supplementary Figure 1).

Discussion

While high-grade gliomas are highly aggressive, extracranial metastases are rare and usually confined to intracranial dissemination.[10] The 2021 WHO classification of central nervous system tumors classified the clinical, pathological, and molecular differences between pediatric and adult gliomas in detail, and first recognized pHGG as a distinct category.[11] These tumors are relatively rare, accounting for only 15%–20% of pediatric intracranial tumors.[12] Given that the 2021 classification was recently introduced, the reported incidence of pHGG remains notably low.

Recently, some studies have revealed that approximately half of gliomas in adolescent and young adult (AYA) patients (aged 15–39 years) may be pediatric-type gliomas.[12,13] In a retrospective analysis by Michael et al. of 92 glioblastoma cases with bone metastases, 40 occurred in AYA patients, representing 43.5% of the total.[14] It is estimated that about half of AYA metastases may be pediatric high-grade gliomas. Although pediatric gliomas occur less frequently than adult gliomas, the incidence of extracranial metastasis in pediatric high-grade gliomas may be higher, emphasizing the need for focused research and treatment for children and AYA high-grade glioma patients.[15–17]

In adult-type high-grade gliomas, the most common extracranial metastatic sites include the lungs, pleura, lymph nodes, bones, and liver. Less common sites include the kidneys, pericardium, retroperitoneum, adrenal glands, spleen, pancreas, and subcutaneous tissues.[14,18,19] Analysis of 88 glioblastoma extracranial metastasis cases by Lun et al. identified differences in metastatic sites between pediatric and adult glioma patients.[1] Bone and lung metastases were common to both groups; however, pediatric patients

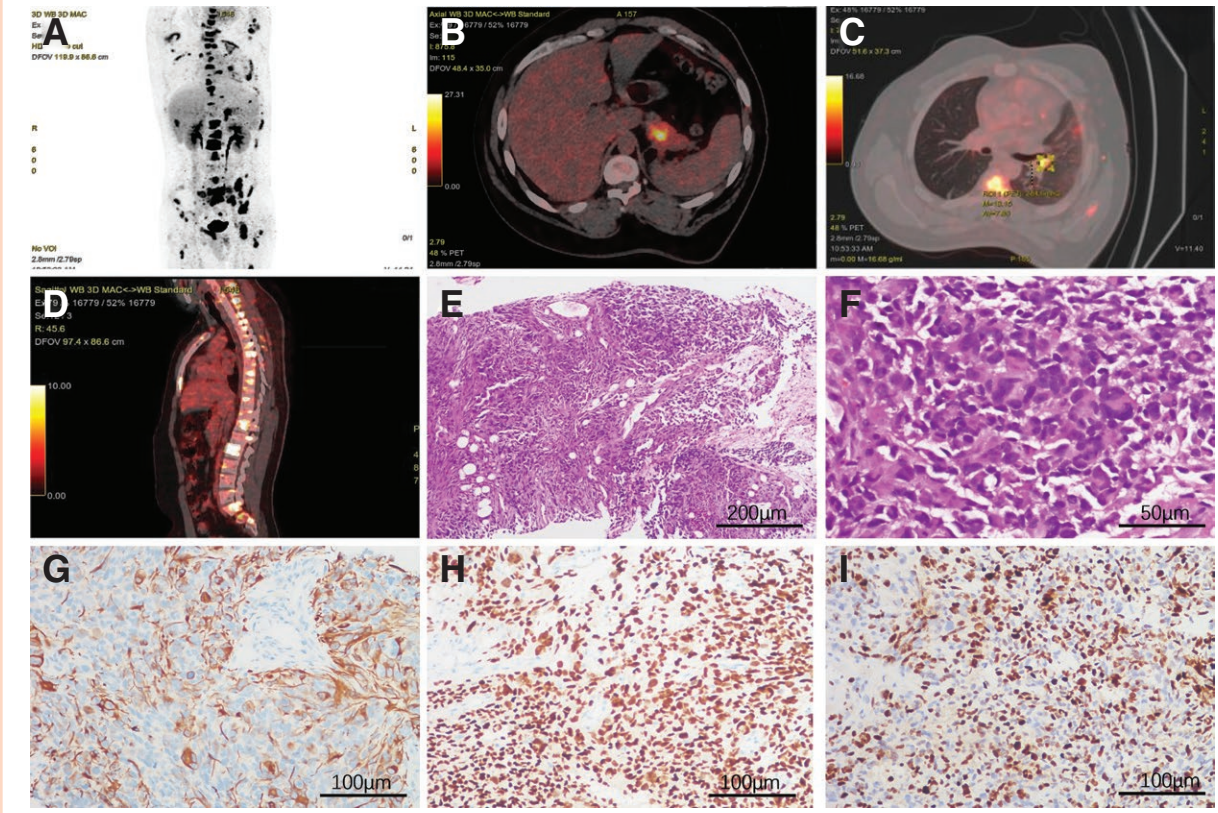

Figure 3. PET-CT scan findings demonstrated widespread metastatic involvement of the tumor throughout the body **(A)**. A distinct space-occupying lesion in the tail of the pancreas **(B)**. The scan detected areas of increased uptake in the upper lobes of both lungs **(C),** revealing the evidence of multiple skeletal metastases of the tumor **(D)**. H&E staining of the pancreatic mass showed the pleomorphic tumor cells in small clusters **(E)**, exhibiting marked atypia with frequent mitotic figures **(F)**. The Ki-67 index of the tumor cells was approximately 80% **(G).** Immunohistochemical staining showed low positive expression of GFAP **(H)**, and focal positive expression of Olig2 that was cytoplasmic and nuclear **(I)**.

were more likely to experience metastases to the spinal cord and leptomeningeal regions, while adult patients more commonly had metastases to lymph nodes, pleura, and liver.

Pediatric-type high-grade gliomas are now categorized into 4 subtypes: H3K27-altered, H3G34-mutant, H3-wildtype and *IDH*-wildtype, and infant-type hemispheric glioma.[20] Almost all cases of extracranial metastases in pHGG involve H3K27M-mutant diffuse midline gliomas. H3K27M mutation appears to play a critical role in metastasis, increasing tumor aggressiveness and metastatic potential.[21] To our knowledge, the patient described here is the second reported case of pediatric high-grade glioma, H3-wildtype and *IDH*-wildtype (RTK1 subtype), with multiple extracranial metastases. The pHGG_RTK1 subtype, associated with a median overall survival of approximately 21 months, is characterized by frequent *PDGFRA* amplifications and the absence of other typical adult-type glioma-associated molecular abnormalities, such as mutations in the *IDH1*, *IDH2*, *BRAF*, and H3 genes.[22,23]

The pHGG-H3wt *IDH*wt were divided into 3 subtypes, the RTK1 and RTK2 subtypes characterized by the RTK signaling pathway, and the MYCN subtype, defined by the amplification of the *MYCN* gene, often linked to worse prognosis and more aggressive tumor behavior.[22] The precise incidence of the RTK1 subtype remains unknown; however, it is commonly associated with hereditary cancer predisposition syndromes such as constitutional mismatch repair deficiency (CMMRD) syndrome, Lynch syndrome, and Li-Fraumeni syndrome.[24,25] In this case, there was the detection of the mutation of the *MSH6* gene by NGS the patient's primary brain tumor. However, the immunohistochemistry revealed normal expression of mismatch repair-related proteins, including MLH1, MLH2, MLH6, and PMS2.

The mechanisms of extracranial metastases in gliomas remain unclear, but are hypothesized to involve several factors: (1) the "seed and soil" hypothesis, where interactions between tumor cells (seeds) and the organ microenvironment (soil) promote colonization and metastasis; (2) immune evasion strategies, such as immunosuppressive microenvironments and molecules, which facilitate systemic tumor spread; and (3) circulating tumor cells that breach the blood–brain barrier and disseminate via the bloodstream.[26–30] Additionally, ventriculoperitoneal shunting may increase the risk of intracranial tumor spreading to the abdominal cavity through CSF.[31]

Distinctions in metastatic mechanisms between pediatric and adult gliomas remain poorly understood. Some

reports suggest that extracranial metastasis may be related to specific molecular features, including specific genetic mutations and changes in epigenetic regulation, which significantly impact the development and therapeutic response of gliomas.[32] For example, the H3K27M mutation, a hallmark of diffuse midline gliomas, alters histone H3 methylation status and destabilizes gene transcription, promoting tumorigenesis and metastasis.[33] Despite the growing importance of molecular features in glioma diagnosis, our understanding of the molecular basis of extracranial metastasis remains limited, constraining our ability to predict metastasis risk and develop targeted therapies.[34]

This case illustrates the rare metastatic potential of gliomas. After 5 months, the patient developed syncope, with PET-CT scan results suggesting pancreatic cancer with systemic metastases, neglecting the history of glioma and the emergence of new cerebral symptoms. With the progress of glioma treatment, which extends the survival time of patients, we need to be more alert to the occurrence of systemic metastasis, even in the context of local control of the primary brain tumor. However, the direct impact of these therapeutic advances on metastatic potential still requires further research. Clinicians should consider systemic metastases when peripheral lesions appear, even in the absence of cerebral symptoms, and conduct detailed investigations to ensure timely and accurate treatment, ultimately improving patient prognosis.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords:

Pediatric-type glioma; RTK1; Extracranial metastasis; Molecular subtype; Methylation;

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Conflict of interest statement

The authors have declared that no competing interest exists.

Author contributions

Clinical data collection: J.W., R.Z., X.S., and P.W. DNA methylation array analysis: C.R. Conducted the molecular studies: C.R., Y.C., and L.H. Pathology diagnosis: R.Z., X.S., and X.W. Manuscript writing: J.W. and X.W.

Data availability

No datasets were generated or analyzed during the current study.

Ethics approval and consent to participate

This study was approved by the Clinical Ethics Committee of the First Affiliated Hospital of Fujian Medical University and the patient's family gave consent.

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