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Bone metastases in an adult patient with diffuse midline glioma: a case report

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Diffuse midline glioma—previously known as diffuse intrinsic brainstem glioma (DIPG)—has a poor prognosis with a median survival of 9.2–19.6 months.[1–3] Histone H3 K27M somatic mutation is a unifying feature, found in 80–90% of DIPG patients.[2,4] Unlike pediatric DIPG, adult brainstem glioma only accounts for less than 2% of adult gliomas.[5] A retrospective analysis of 21 adult patients with gliomas with H3 K27M mutations found that 11 (52%) of these patients had glioblastoma, 2 (10%) had astrocytoma, 1 (5%) had oligodendroglioma, and 7 (28%) remained undetermined following histological analysis.[3] Diffuse midline glioma, H3 K27M-mutant behaves like grade IV glioma, even when mitotic figures, microvascular proliferation, and necrosis are absent.[3]The H3 K27M mutation defines a distinct subgroup of adult IDH-wildtype gliomas that are characterized by midline localization, low rates of *MGMT* promoter methylation, and poor prognosis.[3]

Only approximately 0.4–0.5% of primary brain tumors ultimately spread beyond the central nervous system (CNS).[6] Bone is a more common metastatic site beyond the CNS compared to other sites, including the lymph nodes, liver, lungs, and pancreas.[7] We report herein a case of diffuse midline glioma with bone metastases.

Case Report

A 36-year-old Chinese woman complained of a 1-week history of new-onset dizziness, left facial numbness, and increasingly severe gait instability. Magnetic resonance imaging (MRI) of the brain revealed an enlargement of the pons, with a heterogeneous mass (Figure 1A). Also observed were multiple miniscule enhancement lesions in the spine (Figure 1A). Positron emission tomography–computed tomography (PET-CT) showed active metabolism at the site of the mass in the brainstem (Figure 1A).

We advised the patient to undergo a stereotactic biopsy to determine a definitive diagnosis; however, she declined. Instead, she opted for lumbar puncture, and the circulating tumor DNA (ctDNA) of the cerebrospinal fluid (CSF) was profiled by next-generation panel sequencing on cancer-associated genes using patient-matched whole blood, which revealed a *HIST1H3B* mutation (Supplementary Material).

The patient was ultimately diagnosed with diffuse midline glioma with an H3 K27M mutation. She received radiochemotherapy, which included involved-field radiotherapy (PTV 54Gy/27F) and temozolomide (TMZ) chemotherapy (75 mg/m^2/day, from the first to the last day of radiotherapy). One month after the last radiochemotherapy session, MRI revealed a reduction in the mass in the brainstem (Figure 1B).The patient then continued to receive 2 cycles of TMZ chemotherapy (150–200 mg/m^2 for 5 days per every 28-day cycle).

Following chemotherapy, tumor progression was confirmed (Figure 1C), and the patient refused further treatment. Two months later, we observed a larger area of signal abnormalities in the patient's spine and multiple Gd-enhancing lesions that were larger than upon initial imaging (Figure 1D). PET-CT revealed abnormal uptake of 18F-fluorodeoxyglucose in the majority of the bones (Figure 1D). Biopsy of the left femur confirmed the metastases (Figure 2). The patient eventually died with overall survival of 13 months.

Discussion

Diffuse midline glioma with an H3 K27M mutation is a new entity in the revised 2016 World Health Organization Classification

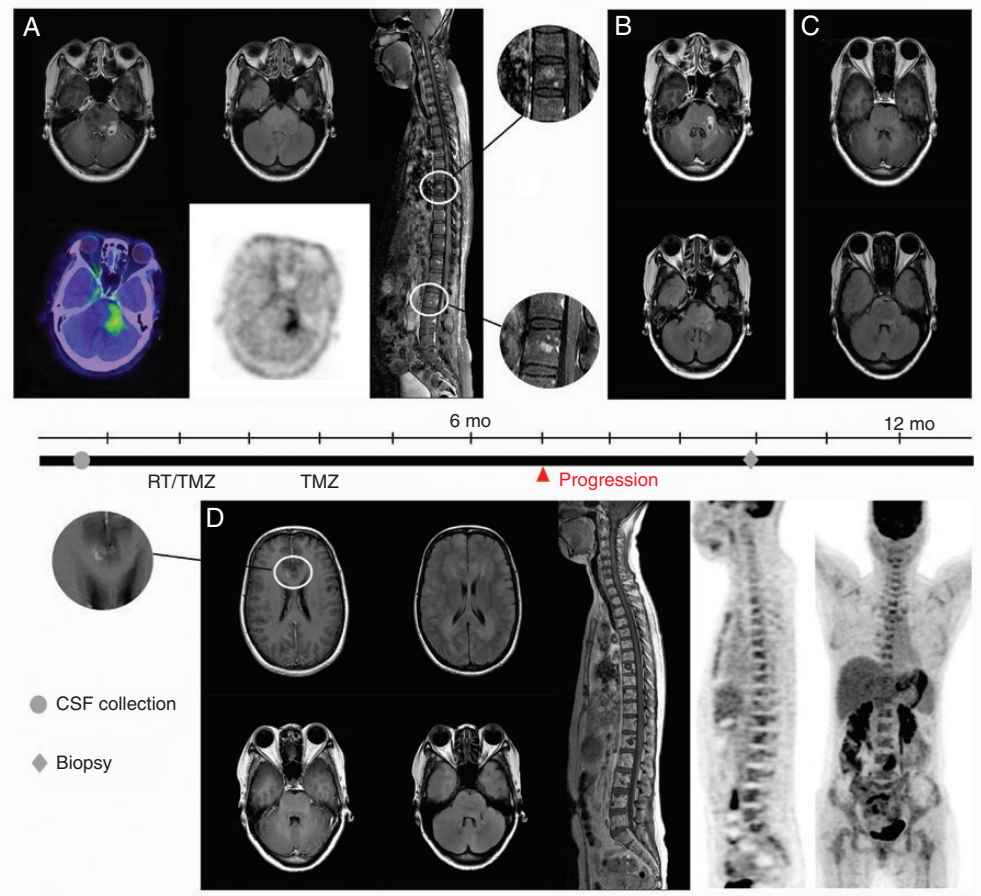

Figure 1. Timeline of treatment of a 36-year-old woman with a brainstem tumor. (A) Post-contrast T1-weighted MRI demonstrated a diffuse involvement and a small enhancement in the left pons. Axial FLAIR showed an enlargement of the pons, with a heterogeneous mass. Post-contrast T1-weighted MRI of the spinal cord indicated multiple miniscule enhancement lesions in the spine. The lesions in the first lumbar vertebrae and the eighth thoracic vertebrae are clearly visible. 18F-DOPA PET-CT images showed increased uptake of the tracer in the left brainstem. (B) Post-contrast T1-weighted MRI showed that the tumor had shrunk following treatment. Increased signal narrowed in brainstem on axial FLAIR image. (C) Post-contrast T1-weighted MRI showed that the original enlargement in the left pons had subsided. However, increased signal enlarged in the brainstem upon axial FLAIR imaging. (D) Post-contrast T1-weighted MRI showed that the original enlargement in the left pons had remained subsided; however, post-contrast T1-weighted MRI indicated an additional small enlargement in the genu of the corpus callosum. Axial FLAIR imaging showed an enlargement of the pons and an extended area of high signal in the whole brain. Post-contrast T1-weighted MRI of the spinal cord showed multiple Gd-enhancing lesions in the whole spine. The lesions in the first lumbar vertebrae and the eighth thoracic vertebrae were larger than before. 18F-FDG PET-CT images showed increased uptake of the tracer in the majority of the bones, such as the whole spine, bilateral proximal humeri, bilateral scapulas, ribs, sternum, bilateral ilia, and bilateral upper femurs.

of Tumors of the CNS. Castel et al.[1] found that patients with *HIST1H3B* mutations had an approximately 2-year earlier onset of the disease, better clinical response to radiotherapy, and longer overall survival (OS) duration. The median OS was 15 months for patients with *HIST1H3B* mutations and 9.2 months for patients with *H3F3A* mutations.[1] Moreover, in patients with *HIST1H3B* mutations, genes known to be inhibited in metastases were downregulated.[1]The *HIST1H3B K27M* mutation has been shown to be associated with a less aggressive diffuse midline glioma. In this case, other mutated genes related to the development of glioma beyond *HIST1H3B* were found, such as *ATRX*, *TP53*, *DAXX*, and *FAT1* (Supplementary Material).[8] *FAT1* is a cadherin and has been described as a tumor suppressor through regulation of cell proliferation, as well as regulating actin-mediated cell migration and carcinoma metastasis,[9] which may explain why the more indolent subtype of this lesion leads to bony metastases.

In the past, pediatric diffuse gliomas were grouped with their adult counterparts, even though it was well known that pediatric and adult gliomas with similar histological features were nevertheless associated with different behaviors. The median survival in patients with diffuse midline glioma was 8–19 months in adults and 7–11 months in pediatric populations,[10] which suggested that diffuse brainstem glioma may be less aggressive in adults. Although similar methylation patterns were identified in both adults and children, the genomic features differentiating pediatric from adult populations remain unclear.

Like other glioma tumors, the evolution of diffuse midline glioma is characterized by local infiltration and relapse

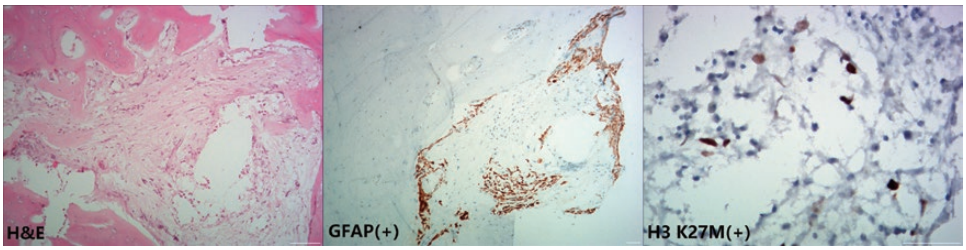

Figure 2. Microscopy images of biopsy tissue from the left femur. Spindle tumor cells have infiltrated into the marrow cavity and the marrow is now absent, H&E ×200. Spindle tumor cells were positive for glial fibrillary acidic protein (GFAP), IHC ×100. Tumor cells were positive for H3 K27M, IHC ×400. H&E, hematoxylin and eosin staining; IHC, immunohistochemical staining; scale bar = 100 μm.

in the majority of cases, with metastases extending beyond the CNS remaining extremely rare. Absence of a lymphatic system and presence of a neuromeningeal barrier may underlie the rare phenomenon of metastasis outside the CNS. However, the absence of a lymphatic system in the CNS is disputed. Louveau et al.[11] discovered functional lymphatic vessels lining the dural sinuses and, therefore, called for a reassessment of the basic assumptions in neuroimmunology. Besides, the unique environmental situations of non-CNS tissue may be inhospitable to further brain tumor growth beyond the confines of the CNS.

Malignant glioma may bypass the possible mechanisms and metastasize outside the CNS in some conditions, such as prolonged survival, presence of a shunt, or repeated intracranial surgery. The invasiveness of the meninges may increase the permeability of the blood–brain barrier, thereby facilitating the hematogenous metastasis of a given tumor. Local inflammation, such as bone flap infection, could lead to vasodilation and increased permeability such that tumor cells could access vascular pathways.[12] The delayed occurrence of metastasis outside the CNS may result from a selection of clones following multimodal treatment, such as radiotherapy and chemotherapy, which may render the tumor cells more aggressive. To summarize, lymphatic metastasis, presence of a shunt, leaky blood–brain barrier, and multimodal treatment selection of clones may be the physiopathological markers of metastasis.

Based on the location of brainstem glioma, it is difficult to perform a safe surgical resection or biopsy, which limits the applications of routine molecular profiling and treatment options. Noninvasive diagnostic approaches provide an alternative to surgery and mitigate unnecessary risk to patients, such as ctDNA from the biological fluids of patients. Tumor-specific plasma methylomes have been confirmed to distinguish gliomas from extracranial cancers and healthy controls.[13] Pan et al.[14] showed that deep sequencing of CSF ctDNA is a reliable technique for detecting tumor-specific alterations in brain tumors. In 91.9% of cases, at least half of the alterations were identified in the CSF, and the mutation detection by CSF ctDNA was found to be more sensitive than plasma ctDNA.[14,15] Therefore, the presence of ctDNA in the CSF may be an early indicator of progression in brain tumors.[15] Ultimately, diffuse midline glioma is an aggressive disease, and its occurrence, development, and treatment strategies are worthy of further investigation.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Advances* online.

Keywords

adult | bone metastasis | diffuse midline glioma

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