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CASE REPORT

Diffuse midline glioma with extra central nervous system metastases in the pediatric, adolescent, and young adult population

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Abstract

Diffuse midline gliomas (DMG) are malignant infiltrative gliomas enriched in the pediatric population and characterized by loss of the *H3 K27me3* epigenetic marker, most frequently via mutation of the *H3-3A* gene. Few cases of extra-central nervous system (CNS) DMG metastasis with redemonstrated *H3-3A p.K28M* (*H3K27M*) mutation in metastatic tissue are reported in the literature. Here, we report two such patients, both females (ages 7 and 10), with DMG and extra-CNS metastasis who died 5 years after initial diagnosis. Both patients significantly exceeded the median life expectancy for DMG, raising the possibility that prolonged overall survival permitted progression to a rarely observed disseminated state of disease. There was absence of *TP53*/*p53* modulating pathway mutation seen in classic DMG in the thalamic biopsy of the first patient, as well as the metastatic disease for the second patient, which may contribute to the prolonged survival observed. Molecular analysis of metastatic disease is important, as clinically and prognostically relevant alterations that vary from the primary site of disease may be detected, which shed light on clonal evolution patterns and further our understanding of disease biology.

Keywords Diffuse midline glioma · Diffuse intrinsic pontine glioma · Extra central nervous system metastasis · Spine · Metastases · Separation surgery

Introduction

Diffuse midline gliomas (DMG) are malignant infiltrative gliomas enriched in the pediatric population. Molecularly, DMG are characterized by loss of the *H3 K27me3* epigenetic marker, most frequently via mutation of the *H3-3A* gene. The estimated 2-year survival is less than 10% [1]. Few cases of extra-CNS DMG metastasis are reported in the literature (Table 1) and molecular profiling of these metastases is sparse. Here, we report two cases with molecular profiling of metastatic disease.

Methods

A retrospective chart review identified the cases of patients with DMG who developed extra-CNS metastases. The study was approved by the Weill Cornell Medical College and Memorial Sloan Kettering Cancer Center Internal Review Boards. Relevant demographics, clinical history, imaging, and operative notes were reviewed. MSK-IMPACT, a next-generation sequencing platform, was used for molecular sequencing [2, 3]. A systematic literature review was conducted to identify additional cases of pediatric DMG with extra-CNS metastases.

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Table 1 Molecular and pathologic characterization for two cases of metastatic diffuse midline glioma

Case	Primary site			Metastatic disease		
	Pathology	IHC	Molecular sequencing	Pathology	IHC	Molecular sequencing
1	None	N/A	N/A	Highly cellular proliferation of spindled cells with hyperchromatic irregular nuclei, fibrillar processes, mitoses and apoptotic bodies Ki67 40%	Strong, positive nuclear staining for *H3K27M*	Mutations in *BRAF p.G464V, PTPN11 p.R498L, PDGFRA, KIT*
2	Moderately cellular infiltrating glial neoplasm with predominantly astrocytic cytomorphology Ki67 4%	Strong nuclear staining for *H3K27M*	Mutations in: *BRAF p.V600E, H3-3A, TERT*	Metastatic diffuse midline glioma involving bone and soft tissue	Tumor expression of *H3K27M*	Mutations in: *BRAF p.V600E*, *H3-3A*, *TERT*, and *TP53*

DMG diffuse midline glioma; *IHC* immunohistochemistry

Clinical case presentation

Case 1

A 7-year-old female presented with headaches and difficulty with ambulation. MR imaging revealed T2 hyperintensity in the pons (Fig. 1A), and she was diagnosed with DMG by radiographic appearance. She initially underwent multiple treatments at outside institutions, including conventional external beam radiation therapy, chemotherapy including panobinostat, and direct delivery of radioimmunotherapy through convection-enhanced delivery and intra-arterial delivery of bevacizumab. Four years after diagnosis, she complained of back pain and was found

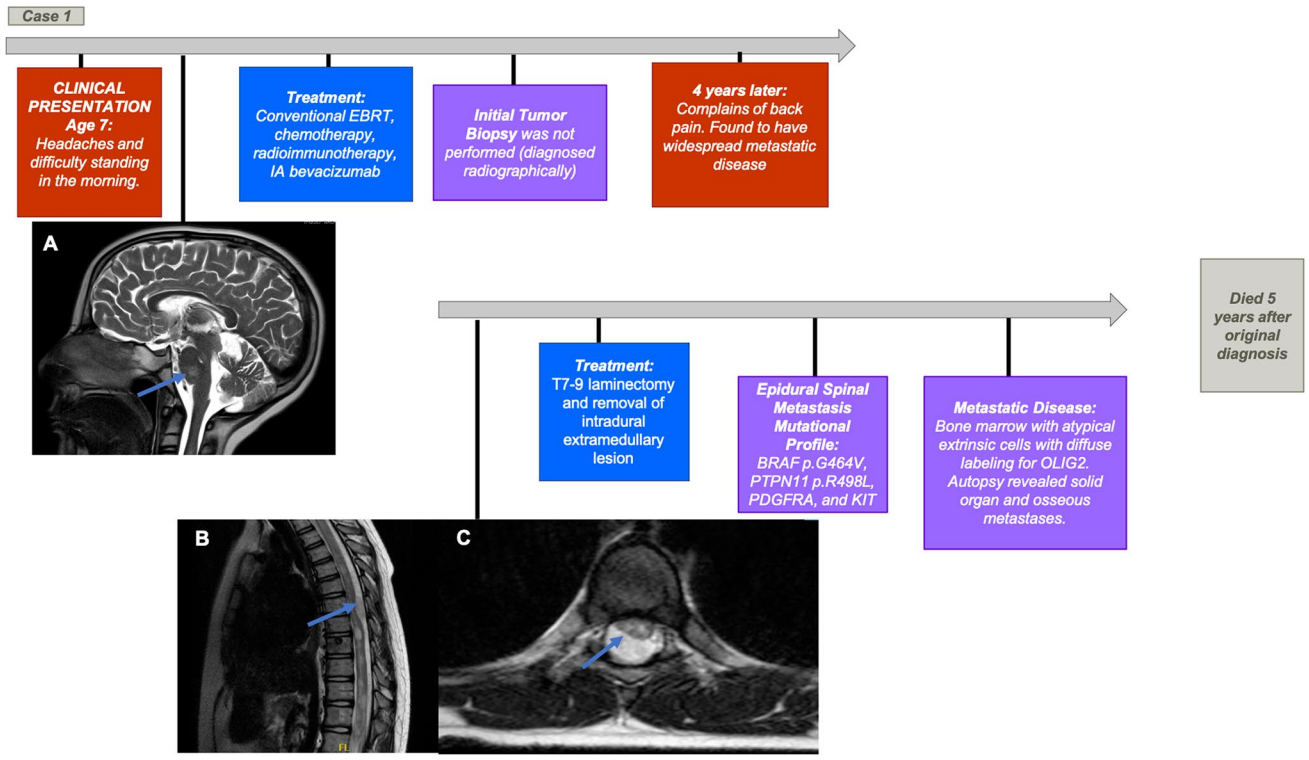

Fig. 1 Case 1 timeline with **A** sagittal T2 HASTE showing extensive T2 hyperdense signal in the pons (blue arrow). **B** Sagittal T2 and **C** axial T1 with contrast demonstrate enhancing intradural extramedullary lesions at T7-8 (blue arrow)

to have multiple lesions including thoracic intradural extramedullary compression lesions at T7/8 (Fig. 1B, C) and multiple non-enhancing, expansive intramedullary lesions throughout the spine. She underwent T7 to T9 laminectomy and palliative decompression. Pathology was consistent with DMG *H3K27M* mutant tumor. The histology of the spinal metastases revealed a highly cellular proliferation of spindled cells with hyperchromatic irregular nuclei, fibrillar processes, mitoses, and apoptotic bodies. Ki67 labeling index was approximately 40%. Immunohistochemical (IHC) staining was positive for *H3K27M*. Next-generation sequencing revealed mutations in *BRAF p.G464V, PTPN11 p.R498L*, *PDGFRA*, and *KIT*. Bone marrow biopsy demonstrated atypical extrinsic cells with strong and diffuse immunolabeling for *OLIG2*. She died two months later, 5 years after initial diagnosis, and autopsy revealed both solid organ and osseous metastases.

Case 2

A 10-year-old female underwent MR brain for participation in a voluntary research study. MR brain (Fig. 2A) demonstrated a T2 hyperintense lesion centered within the right thalamus measuring approximately 4 cm in maximal dimensions. She underwent an initial biopsy for diagnosis and ventriculoperitoneal shunt placement given ventricular trapping and enlargement. Biopsy was consistent with *H3-3A K27M* thalamic DMG. Histology revealed a moderately cellular infiltrating glial neoplasm with predominantly astrocytic cytomorphology and a Ki-67 labeling index of 4%. IHC was strongly positive for the *H3K27M* mutation. Next generation sequencing demonstrated a mutation in *BRAF p. V600E*, *TERT* promoter, and *H3-3A*. She was treated with 5940 cGy of radiation over 33 fractions to the thalamus. Two years after radiation, she had progressive disease with bithalamic tumor and was started on BRAF inhibitor Dabrafenib and MEK inhibitor Trametinib. Five years after the initial diagnosis, she experienced upper extremity weakness and midscapular pain. MR imaging demonstrated diffuse marrow infiltration from C7 through T3 with unstable pathological fractures at T1 and T2 (Fig. 2B) and grade 2 epidural spinal cord compression (Fig. 2C). She underwent C5-T5 posterior instrumented fixation and T1-2 laminectomies with spinal cord decompression. Pathology was consistent with a primary glial tumor, as it stained positive for *H3K27M* on immunohistochemistry. The tumor was consistent with metastatic DMG with *H3K27M* mutation. Next-generation sequencing revealed mutations in *BRAF p.V600E*, *H3-3A K27M*, *TERT*, and *TP53,* which was not present in the original tumor. She underwent emergent radiation to C4-T7 with 2000 cGy delivered in 5 fractions, and the next day was started on encorafenib and binimetinib. She died three months later of widespread metastatic disease, and an autopsy was not performed.

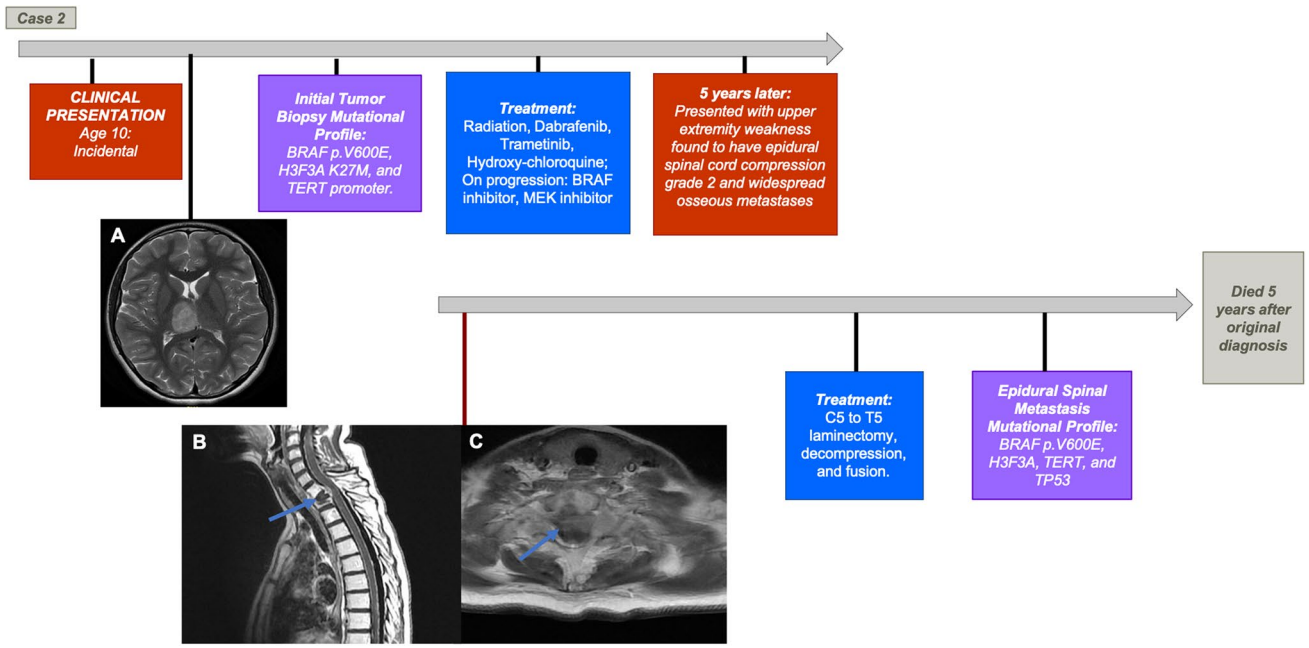

Fig. 2 Case 2 timeline with **A** sagittal T2 of brain showing T2 hyperintense lesion centered within the right thalamus. **B** Sagittal T1 with contrast of high thoracic spine demonstrating pathological collapse at T1-2 with destruction of the vertebral body (blue arrow). **C** Axial T1 with contrast demonstrating grade 2 epidural spinal cord compression (blue arrow)

Table 2 Cases of extra central nervous system diffuse midline glioma metastasis

Ref (author, year)	Age (y), sex	Location	Tumor molecular	Additional alteration	Tx:	Time to met	Location of extra-CNS met	Molecular for met	Additional tx for metastatic disease	OS (mo)
Paul et al. 2018[11]	11, M	LV, HT, MB	*H3-3A K27M* mutation	N/A	STR	3.5 mo	Osseous	*H3-3A K27M* mutation	N/A	9
Paul et al. 2018[11]	12, F	Tectal/pineal	*H3-3A K27M* mutation	N/A	STR	5.5 mo	Osseous	*H3-3A K27M* mutation	N/A	13
Bhatt et al. 2020[5]	15, F	4 V, IDEM	*H3K27M* mutation	N/A	None	At dx	Osseous	HGG *H3K27M* mutation	None	0.5
Li S et al. 2020 [9]	36, F	Pons	*H3K27M* mutation	N/A	LP, RT, CT	At dx	Osseous	*H3K27M* mutation	None	13
Mohiuddin et al. 2021[10]	20, F	Thalamus	*H3-3A H3K27M* mutation	BRAC2, TP53	RT, CT	3 mo	Osseous	Non-diagnostic	Proton beam, CT, bevacizumab	11
Mohiuddin et al. 2021[10]	17, F	Hippocampus, MB	*H3-3A H3K27M* mutation	TP53, CDK2, CDK4, TERT, KRAS	CSI, CT	1.75 mo	Osseous, solid organ	*H3K27M* mutation	None	5
Handis et al. 2021[7]	16, F	IDIM	*H3K27M* mutation	N/A	RT, CT	At dx	Osseous	*H3K27M* mutation	N/A	5
Silva et al. 2022[12]	8, F	Pons	*H3 K27me3* loss	EZHIP	CSI	At dx	Muscle, brachial plexus	N/A	RT	14
Lazow et al. 2022[8]	12, F	BS, CB, ID	*H3K27M* mutation	MET, CDK6, EMSY, PIK3CG, TP53	LP, CSI	At dx	Osseous, solid organ	*H3K27M* mutation	MET inhibitor	9
Aftahy et al. 2023[4]	24, M	IDIM/ IDEM	Non-diagnostic		CSI, CT	At dx	Osseous	*H3K27M* mutation	RT	3
De Martino et al. 2023[6]	11, M	Pons	*H3K27M* mutation		CT, RT	5 mo	Osseous	*H3K27M* mutation	None	6
De Martino et al. 2023[6]	11, F	CB	*H3K27M* mutation		CT, RT	6 mo	Osseous	Non-diagnostic	CT	24
Rathi et al. 2024[13]	17, F	Spinal	*H3K27M* mutation	P53	None	At dx	Osseous	*H3K27M* mutation	None	N/A
Current paper	7, F	Pons	*H3K27M* mutation	BRAF, PTPN11, PDGFRA, KIT	RT, CT, RadioIT	4 years	Osseous, solid organ	*H3K27M*	Surgery	60
Current paper	10, F	Thalamus	*H3K27M* mutation	BRAF, TERT	RT, BRAF/MEK inhibitor	5 years	Osseous	*H3K27M*, *BRAF*, *TERT*, *TP53*	None	60

4V fourth ventricle, *BS*, brainstem, Bx biopsy, *CB* cerebellum, *CT* chemotherapy, *CSI* craniospinal irradiation, *DMG* diffuse midline glioma, *Dx* diagnosis, *EM* extramedullary, *HGG* high-grade glioma, *HT* hypothalamus, *ID* intradural, *IM* intramedullary, *IMRT* intensity-modulated radiation therapy, *LMD* leptomeningeal disease, *LR* lateral rectus, *LV* lateral ventricle, Met metastases, *MB* midbrain, *Mo* months, *N/A* Not available, *RadioIT* radioimmunotherapy, *RT* radiotherapy, *STR* subtotal resection, *Tx* treatment, *VB* vertebral body

Review of literature

A review of PubMed for cases of DMG with extra-CNS metastatic lesions was performed (Table 2). We excluded cases of leptomeningeal spread and iatrogenic peritoneal spread after placement of ventriculoperitoneal shunt. Thirteen cases were identified [4–13]. The median age of diagnosis was 16.2 years (range 8 to 36) with 10 females and 3 males. Of the thirteen patients, 7/13 of the patients had metastatic disease at the time of diagnosis [4, 5, 7–9, 12, 13]. For the six patients without metastatic disease known at the time of diagnosis, the average time to development of metastatic disease was 4.2 months (range 1.75 to 6). All patients except one had osseous metastases. Two patients had solid organ metastases. 12/13 (92.3%) of the patients had sampling of the site of metastases, and 10/12 had confirmed *H3K27M* mutation (83.3%). Two biopsies at the metastatic disease site were non-diagnostic. The median time from diagnosis to death was 9 months (0.5 months to 24 months). No patients had pathologic fractures requiring surgical stabilization and spinal cord decompression.

Discussion

Extra-CNS metastases of DMG are a rare occurrence, and there are only a handful of cases in the Literature regarding metastatic DMG, which are summarized here. Both of our patients significantly exceeded the median Life expectancy for DMG by surviving 5 years after diagnosis, raising the possibility that prolonged overall survival permitted progression to a rarely observed disseminated state of disease. However, this finding was inconsistent with the Literature review of cases of metastatic DMG, with the median overall survival of 9 months. Both of our patients developed metastatic disease years after initial diagnosis (4 and 5 years), while greater than 50% of the patients reported in the Literature had metastatic disease at diagnosis. Those who did not have metastatic disease at diagnosis developed disease a median of 4.2 months after initial diagnosis. Another factor that may have contributed to the prolonged survival in our cases was the absence of *TP53/p53* modulating pathway mutation that is seen in classic DMG [14, 15]. *TP53* wildtype is favorable and is associated with a subset of *MAPK*-driven DMG which our two patients represent [16–18]. Recent studies have found that the rare co-occurrence of *H3K27M* with *MAPK*-activating mutations, *FGFR1* or *BRAF* alterations, may lead to increased survival, providing an explanation for these findings [19]. Absence of *TP53/p53* modulating pathway mutation was absent in the metastatic disease of our first patient and thalamic biopsy of our second patient.

Our cases and literature search highlight the high rate of osseous metastases in extra-CNS metastases of DMG. All patients (93.3%, 14/15) except one had osseous metastases. Bone metastases are thought to occur via hematogenous spreading or the vertebral venous plexus, and metastasis-initiating cells may play a role in distant tumor growth [20–23]. While extra-CNS metastasis of DMG is a rare occurrence, this information helps elucidate potential mechanisms behind metastatic spread. Our second case represents the first literature report of a case of a patient with metastatic DMG with a pathological spine fracture with high-grade epidural disease necessitating emergent separation surgery and spinal fusion.

Molecular analysis of metastatic disease is vital for multiple reasons. First, as demonstrated in our first cases and three cases in the literature, biopsy of the metastatic disease site can provide diagnosis when there is no primary sample or when the biopsy is inconclusive. Alternatively, when a primary sample is available, molecular analysis of metastatic disease is important to detect clinically and potentially prognostically relevant alterations that may vary from the primary disease site. Targetable mutations may expand treatment eligibility for novel therapies, as was seen in our patient with *BRAF p.V600E* mutation who was treated with a *BRAF* inhibitor. Furthermore, identification of alterations in metastatic disease sites of DMG can shed light on clonal evolution patterns and further our understanding of the biology of disease.

Conclusion

For diffuse midline glioma, molecular profiling of metastatic disease is important to detect clinically and prognostically relevant alterations and mutations that may differ from the primary site of disease. In addition, metastatic DMG has a high rate of osseous involvement.

Author contribution AGL and MR drafted the original manuscript. AGL, ALG, MR, and RH were involved in initial acquisition and analysis of data. DP, SFS, MAK, JPG, MHB, WCN, and MMS were involved in acquisition and interpretation of data. All authors critically revised the work. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors approved the version to be published.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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