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Letter to the Editor

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An unusual case of metastatic diffuse midline glioma in an adult

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To the Editor:

The diffuse midline glioma (DMG), H3 K27-altered, is a relatively new diagnostic entity first included in the 2016 WHO classification of tumors of the central nervous system as DMG, H3 K27M-mutant, and further characterized in the 2021 WHO classification as DMG, H3 K27-altered (1). DMG is considered a pediatric-type high-grade glioma as it most often affects a younger patient population but cases of DMG in adults are reported (1). This is a diffusely infiltrative glioma involving the midline structures of the central nervous system and it has a characteristic loss of the trimethylation of histone 3 (H3); the class includes tumors formerly referred to as diffuse intrinsic pontine glioma (1). These tumors may or may not demonstrate high-grade histologic features, including microvascular proliferation and necrosis, but regardless have a poor prognosis with an abysmal survival rate of <10% at 2 years following diagnosis (2). In addition to the H3 K27-mutant subtype, this tumor includes H3-wildtype tumors with EZHIP overexpression and tumors with loss of the trimethylated histone 3 with concurrent *EGFR* mutation (3).

Here, we illustrate a case of an adult patient who presented with headaches and was found to have a thalamic lesion; subsequently, significant leptomeningeal enhancement surrounded the brainstem on MRI. He was ultimately diagnosed with DMG, H3 K27M-altered, with the H3 K27M variant. Several months after his initial diagnosis, he was found to have metastases to the bone marrow. To our knowledge, this is only the second report of a case of an adult patient with metastatic DMG.

A 39-year-old man with a history of migraines presented for headache and worsening dizziness. A brain MRI showed a 2 × 1 cm non-enhancing T2/FLAIR hyperintense lesion with ill-defined borders and intermediate diffusivity in the posterior left thalamus and posteromedial temporal lobe (Fig. 1A). As this lesion was not thought to be the source of his symptoms, close clinical follow-up was recommended but no interventions were performed. Three months later, his MRI showed mild increase in size and expansion of the lesion in the left temporal lobe suggestive of infiltrative glial neoplasm as well as subtle leptomeningeal enhancement along the ventral surface of the brainstem (Fig. 1B). One month later, the leptomeningeal enhancement markedly progressed to diffusely fill the intracranial subarachnoid spaces as well as the subarachnoid space of the thecal sac with the greatest enhancement circumferentially encasing the spinal cord (Fig. 1C, D). Lumbar puncture revealed increased opening pressure, elevated cerebrospinal fluid (CSF) protein levels, and monocyte-predominant pleocytosis. Flow cytometry analysis was unremarkable. Infectious disease work-up involved analysis of the patient's CSF via polymerase chain reaction which did not reveal any of the following entities: *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitides*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, CMV, enterovirus, HSV1/2, HHV-6, parechovirus, VZV, *influenza A/B*, *Cryptococcus*

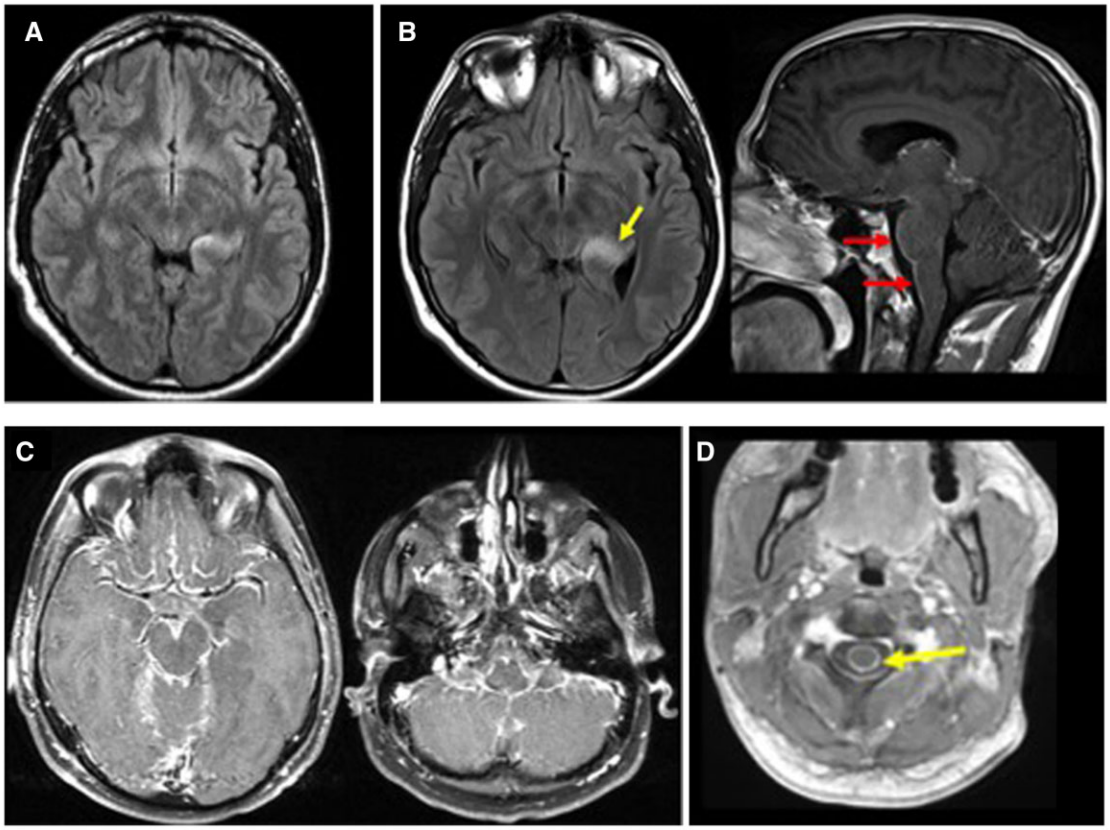

Figure 1. **(A)** MRI at initial presentation showing a 2 × 1 cm nonenhancing T2/FLAIR hyperintense lesion in the posteromedial left temporal lobe and thalamus; **(B)** follow-up MRI 3 months later showing mild increase in size and expansion of the component in the posteromedial left temporal lobe (yellow arrow) and new subtle leptomeningeal enhancement along the ventral surface of the brainstem (red arrows); **(C)** MRI an additional month later showing marked progression of leptomeningeal enhancement in the supratentorial compartment; **(D)** spine MRI showing leptomeningeal enhancement encasing the spinal cord (yellow arrow).

neoformans/gattii, or *Escherichia coli*. CSF was also evaluated for Lyme antibody and cryptococcal antigen levels, which were undetectable. Quantiferon Gold and HIV antigen/antibody testing were also performed on venous blood and were negative. A paraneoplastic panel (Quest Diagnostics, Western Blot analysis) was performed on CSF and covered the following antibodies: Hu, Ri, Yo, DNER, CRMP5/CV2, Amphiphysin, GAD65, and AGNA/SOX1. None were detected. An autoimmune panel to screen for antibodies (Quest Diagnostics including analysis of the following: ANCA, MPO, PR-3, ANA, RF, Ro, La, Sm, SM/RNP, Scl-70, Ribosomal P, Reticulin IgA, Mitochondrial antibody, Actin IgG, C3, C4, thyroid peroxidase antibody, striated muscle antibody, myocardial antibody, and gastric parietal cell antibody) was performed on venous blood and was within normal limits. The radiologic and clinical differential at this point primarily included disseminated glial neoplasm and inflammatory conditions.

A biopsy of the right temporal lobe and Sylvian fissure arachnoid membrane was performed and showed a dense infiltrate of small to medium-sized neoplastic cells filling and expanding the subarachnoid space without parenchymal involvement (Fig. 2). The tumor cells demonstrated variable amounts of GFAP-positive cytoplasm and positivity for S100, SOX10, synaptophysin (focal), and NeuN (subset), while being negative for IDH1-R132H, Melan A, keratins, inflammatory markers, and Oct3/4. Ki-67 proliferative index was up to 15%. Given these features, the main histologic differential included anaplastic diffuse leptomeningeal glioneuronal tumor (DLGNT) versus DMG, H3 K27-altered. Molecular studies showed mutations in *ATRX* (VAF 23.4%) and *H3F3A* p.K28M c.83A>T (VAF 19.4%) with intact 1p/19q and no *KIAA::BRAF* fusion. Though methylation profiling analysis yielded results below the established threshold, potentially due to relatively low tumor purity, the classification suggested midline glioma, H3K27-altered, WHO grade 4. Given the sequencing and methylation findings, a final diagnosis of DMG, H3K27-altered was rendered.

The patient was treated with temozolomide and concurrent craniospinal radiation. Six months after the biopsy, he developed severe anemia. His hemoglobin level was as low as 6.0 g/dL (reference range: 13.5–17.5 g/dL), which was out of proportion to what would be expected from anemia seen following radiation and temozolomide treatment. CT chest/abdomen/pelvis showed diffuse sclerosis of multiple osseous

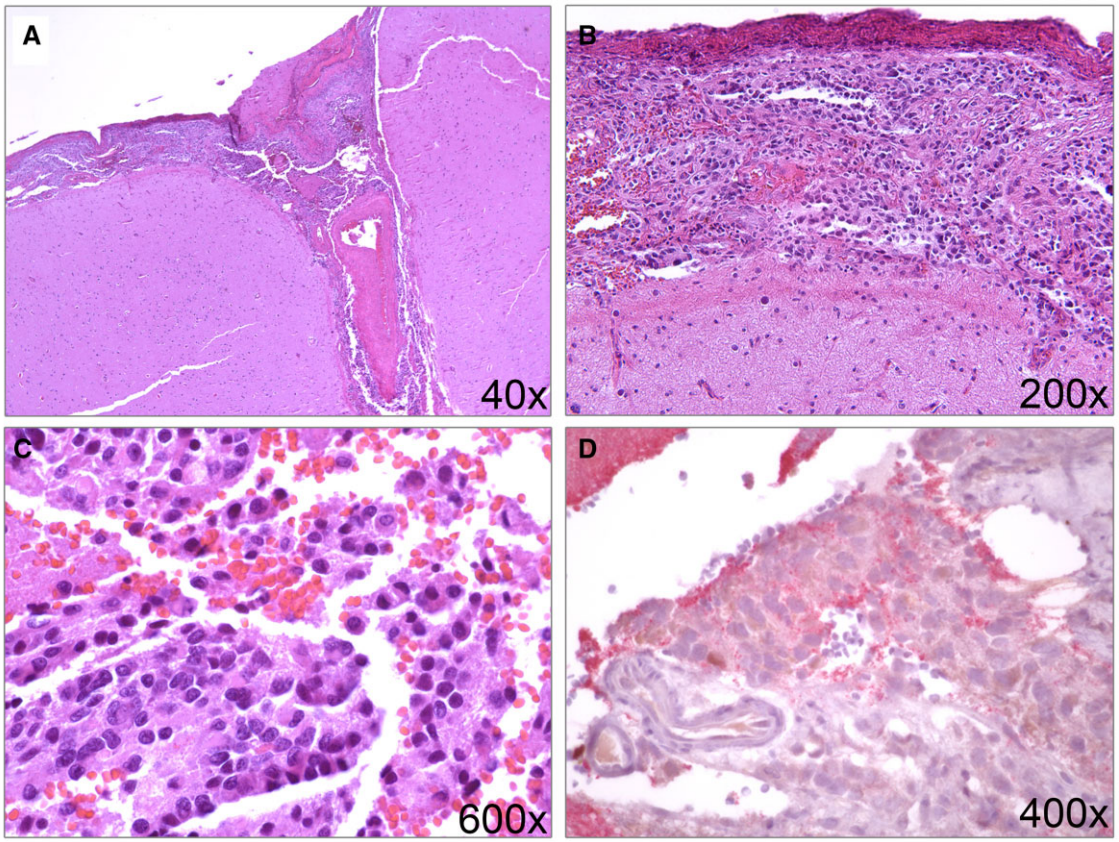

Figure 2. **(A–C)** H&E images of the temporal lobe biopsy in region of meningeal enhancement depicting tumor cells localized to the subarachnoid space. **(D)** Synaptophysin stain highlights a few tumor cells.

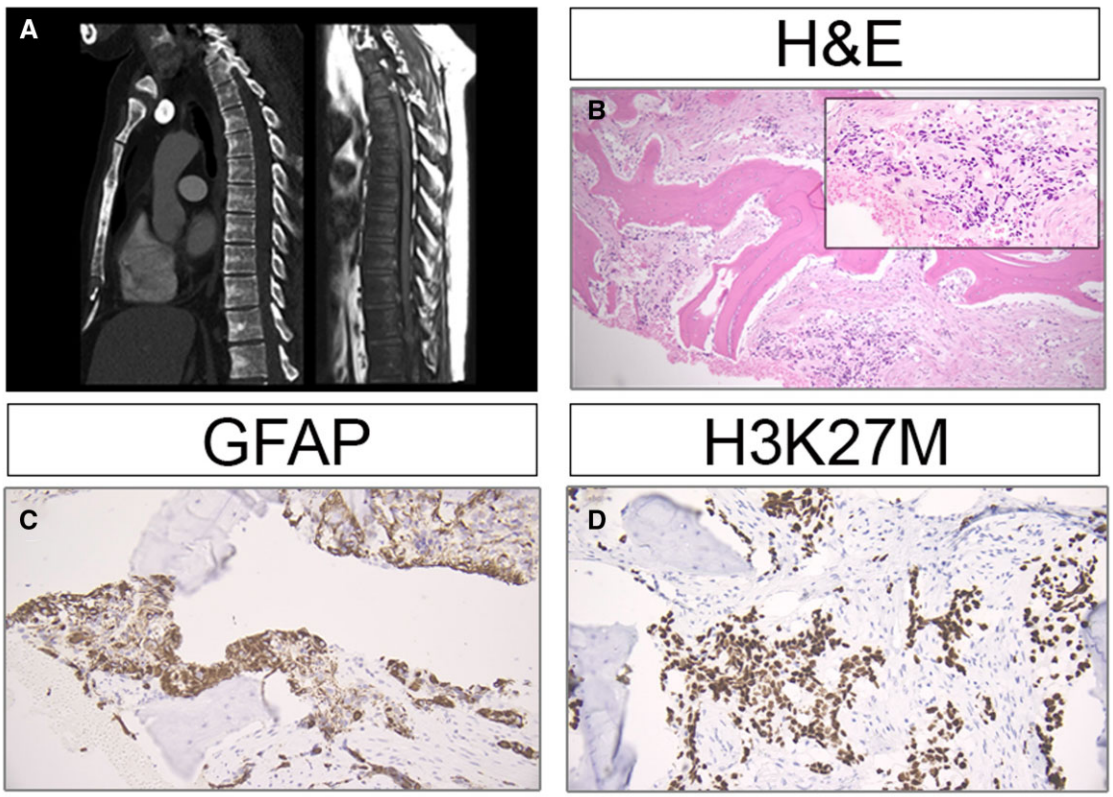

Figure 3. **(A)** CT showing widespread patchy sclerosis throughout the spine and sternum, corresponding to diffuse hypointensity on T1-weighted MRI consistent with diffuse marrow replacement. **(B)** H&E of bone depicting metastatic glioma (inset demonstrating cytology at higher power). **(C, D)** GFAP and H3K27M immunostains highlighting metastatic glial cells.

structures, including bones of the chest wall, with a radiologic differential including treatment-related changes, medication-induced fibrosis, or metastatic disease. These findings prompted bone marrow biopsy of the iliac crest which showed near complete replacement of the bone marrow by metastatic DMG, confirmed by a positive H3K27M immunostain (Fig. 3). No sequencing was performed on this specimen as it had been de-calcified during processing, and no clot was obtained as the bone marrow tap was dry. The patient was re-admitted shortly after this biopsy due to global clinical decline including worsening oral intake, fatigue, and decreased responsiveness. He was transitioned to hospice and passed away 8 months following his initial diagnosis.

We present the second reported case of an adult patient with DMG with focal neuronal differentiation and extraneural metastases. Overall, metastases from primary glial malignancies are extremely rare but have been identified in lymph nodes, lung, bone, liver, and salivary gland (4–7). DMG has a tendency to spread distantly, including to the spinal cord and leptomeninges (1). Additionally, accounts of distant metastases, including osseous metastases, are also reported; however, the majority of metastatic cases found in the literature are in pediatric patients; only one true metastasis, to the femur, has been reported in an adult (4, 5, 8). Further insight regarding the molecular mechanisms underlying the tumor's propensity to spread more aggressively than other primary gliomas lend insight into the factors that allow glial tumors to metastasize outside of the CNS. Some hypotheses include iatrogenic spread during surgery or via surgical interventions such as ventriculoperitoneal shunting (9). Other theories posit that glioma cells might penetrate vessels, especially in cases of sarcomatoid metaplasia (10). Another possibility may be related to what is coined the "glymphatic system," a cerebral clearance mechanism that predominantly functions during sleep to remove wastes via a network of vessels (11). This glymphatic system has been identified to also clear wastes through a meningeal lymphatic system which drains to cervical lymph nodes (12). Our patient had a ventriculoperitoneal shunt, but no seeding of the peritoneum was noted and no direct invasion into bone by tumor was identified. It is possible that tumor spread via a hematogenous mechanism given the distant bony tumor deposits, although this is merely speculation and the route of metastasis in our case remains unclear.

Additionally, while our patient's tumor is an intra-axial infiltrating glioma, a DMG has been reported presenting entirely within the leptomeninges with only focal or even absent parenchymal infiltration (13). Tumors presenting exclusively with meningeal involvement must be distinguished from DLGNT, which are often, though not always, histologically lower grade with an oligodendrocyte-like morphology. When DMG involvement is limited to the leptomeninges, histologic differentiation from DLGNT can be challenging. However, molecular features of DLGNT include 1p deletion, and MAPK pathway alterations, most commonly the *KIAA1549::BRAF* fusion (1), in contrast to the epigenetic changes and genetic variants that characterize DMG. However, while molecular studies revealing H3-alterations can help narrow down a diagnosis, tumors with unusual combinations of molecular features, including the H3 K27M mutation with 1p/19q codeletion, have been reported (14).

Finally, the utility of methylation profiling is increasingly recognized for the classification of CNS tumors (15) and is particularly useful as an additional piece of data to incorporate with histology, immunostains, and sequencing results when making a diagnosis of a neuroepithelial neoplasm. As this particular case only had a suggested methylation profile match, it is possible that contamination of the specimen by smooth muscle cells, inflammatory cells, and adjacent glial cells could have lowered the tumor purity resulting in a result below the established threshold.

In summary, this case, complete with molecular analysis, including methylation profiling, illustrates not only the extensively infiltrative nature of DMG, but its metastatic potential, in a rare case in an adult.

CONFLICT OF INTEREST

The authors have no duality or conflicts of interest to declare.

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