

Histone-mutant glioma presenting as diffuse leptomeningeal disease

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Practice points

- Histone-mutant high-grade glioma can present with diffuse leptomeningeal disease in the absence of a discrete mass lesion, representing a diagnostic challenge.
- Leptomeningeal dissemination can occur on initial presentation or later in the course of the disease.
- Differential diagnosis of radiographic diffuse leptomeningeal enhancement includes inflammatory conditions such as neurosarcoidosis, infections such as human T-lymphotropic virus, and primary or metastatic CNS malignancy.
- A variety of primary CNS tumors, including glioblastoma, medulloblastoma, ependymoma and primary CNS lymphoma, can involve the leptomeninges.
- Cerebrospinal fluid cytology has limitations, and negative cytology does not preclude a diagnosis of leptomeningeal disease due to primary CNS or systemic malignancy. Emerging cerebrospinal fluid analysis technologies such as circulating tumor cell and cell-free DNA analysis may provide additional methodologies to establish a diagnosis and potentially represent biomarkers to track the course of leptomeningeal disease.
- Definitive diagnosis may require biopsy, which also provides tissue for molecular analysis for identification of potential oncogenic drivers, has a crucial role in treatment planning and informs prognosis.

Glioblastoma multiforme is the most common malignant primary brain tumor in adults. Histone H3 mutations have been identified in pediatric and adult gliomas, with H3K27M mutations typically associated with a posterior fossa midline tumor location and poor prognosis. Leptomeningeal disease is a known complication of histone-mutant glioma, but uncommon at the time of initial diagnosis. We describe a case of glioblastoma with H3K27M mutation that initially presented with progressive vision loss due to diffuse leptomeningeal disease in the absence of a mass lesion other than a small cerebellar area of enhancement and with cerebrospinal fluid cytology negative for malignant cells on two occasions, highlighting the importance of including primary CNS malignancies in the differential of diffuse radiographic leptomeningeal enhancement.

Lay abstract: Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. Histones are molecules around which DNA winds. GBM and other gliomas sometimes have genetic alterations called mutations in histone genes. Of these, a specific alteration in histone 3 called H3K27M has been described in a variety of primary brain tumors. In adult gliomas, the H3K27M mutation is typically associated with tumors located within the brainstem or other structures in the midline of the central nervous system and a poor prognosis. Although previously reported, involvement of the leptomeninges (the thin membranes covering the brain and spinal cord) is uncommon at the time of initial diagnosis of gliomas harboring H3K27M mutations. We describe a case of GBM that initially presented with vision loss due to diffuse leptomeningeal involvement. Imaging and laboratory studies, including two cerebrospinal fluid analyses by lumbar puncture, did not establish a diagnosis. Brain biopsy confirmed the presence of a tumor, and genetic testing performed on the tumor tissue identified the histone mutation. This case highlights the importance of including primary central nervous system malignancies as a possible diagnosis when there is diffuse radiographic leptomeningeal enhancement.

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Glioblastoma multiforme (GBM) is the most common malignant brain tumor in adults, representing 14.5% of all tumors with an incidence of three cases per 100,000 and 10,000 new cases diagnosed in the USA each year [1,2]. Histone H3 mutations have been identified in pediatric and adult gliomas including GBMs [3,4]. The presence of a H3K27M mutation is typically associated with a posterior fossa midline tumor location, young age at presentation and poor prognosis [3,4]. According to the 2016 WHO criteria ‘diffuse midline glioma, H3K27M mutant’ is recognized as a distinct entity and represents a grade IV tumor, but the alteration has been reported in high-grade gliomas involving other locations [5–9]. H3K27M mutations have also been reported in ependymomas, pilocytic astrocytomas, pediatric diffuse astrocytomas and gangliogliomas [10].

Leptomeningeal disease is a known complication of gliomas, with an estimated incidence of 25% on post-mortem studies [11–14]. Leptomeningeal dissemination can occur in H3K27M-mutant gliomas and has been reported at the time of initial diagnosis [15–17]. Establishing the diagnosis of leptomeningeal disease can be challenging, in part due to limitations of conventional cerebrospinal fluid (CSF) analysis in the setting of both glioma and other systemic malignancies [18–21]. Emerging CSF cell-free DNA analysis techniques can improve the diagnostic yield from CSF sampling while providing molecular profiling information with the potential to assess treatment response and disease progression, but have yet to gain widespread adoption [22–24].

Here we present a rare case of glioblastoma harboring an H3K27M mutation in a patient who presented with progressive vision loss due to diffuse leptomeningeal disease.

Case presentation

A 50-year-old man presented with a 3-month history of progressive bilateral vision loss. Complete loss of vision in the left eye occurred over the course of less than 1 month, with the patient retaining the ability to identify shapes, colors and light in his right eye at the time of presentation. He was additionally noted to have bilateral abducens palsies, raising concern for increased intracranial pressures. He was evaluated at a community hospital, where imaging revealed bilateral optic nerve sheath enhancement as well as a 9 × 10 mm left cerebellar T2 hyperintense, contrast-enhancing lesion (Figure 1A & B). Imaging of the spine revealed a nodular lesion in the cervical spine and leptomeningeal enhancement (Figure 1C & D). CSF analysis was significant for elevated protein at 483 (mg/dl), nucleated cells at 13 (cells/μl) and angiotensin-converting enzyme level elevated at 3.7 (U/l). Cytology and culture were negative. Elevated opening pressure on the lumbar puncture, in conjunction with the vision loss, led to placement of a ventriculoperitoneal shunt. CT imaging of the chest, abdomen and pelvis revealed no evidence of systemic malignancy or sarcoidosis. Differential diagnosis included inflammatory etiologies such as neurosarcoidosis, infectious etiologies including mycobacterial and fungal meningitis, as well as leptomeningeal disease from primary CNS or systemic malignancy. He was therefore referred to a tertiary care center for further evaluation.

Repeat MRI brain scanning redemonstrated the left cerebellar lesion along with diffuse intracranial leptomeningeal disease, more prominent at the skull base than at the vertex, and evolution of the cerebellar T2 hyperintensity into a mass-like, heterogeneously contrast-enhancing lesion (Figure 2A & B). MRI of the orbits identified meningeal enhancement along bilateral optic nerves (Figure 2C) with MRI of the cervical, thoracic and lumbosacral spine demonstrating diffuse leptomeningeal involvement (Figure 3A–C). Repeat CSF analysis was significant for elevated protein at 730 (mg/dl), 23 nucleated cells (cells/μl), glucose 93 (mg/dl), negative cytology and negative flow cytometry for leukemia or lymphoma. Due to progressive vision loss, the patient was empirically treated with corticosteroids and later with a single dose of cyclophosphamide for presumed neurosarcoidosis while workup was in progress. In an effort to stabilize the patient’s vision and assess him for neurosarcoidosis, a left optic nerve sheath biopsy was performed, which showed no inflammatory or neoplastic process. Due to progressively worsening vision, a right optic nerve sheath fenestration and biopsy was recommended by ophthalmologists. While the tissue did not show specific pathological findings, the patient had stabilization of vision following the procedure. In order to establish a tissue diagnosis, the left cerebellar lesion was ultimately biopsied. Pathology confirmed diagnosis of GBM, *IDH* wild-type by genetic sequencing, with *MGMT* unmethylated (Figure 4A & B).

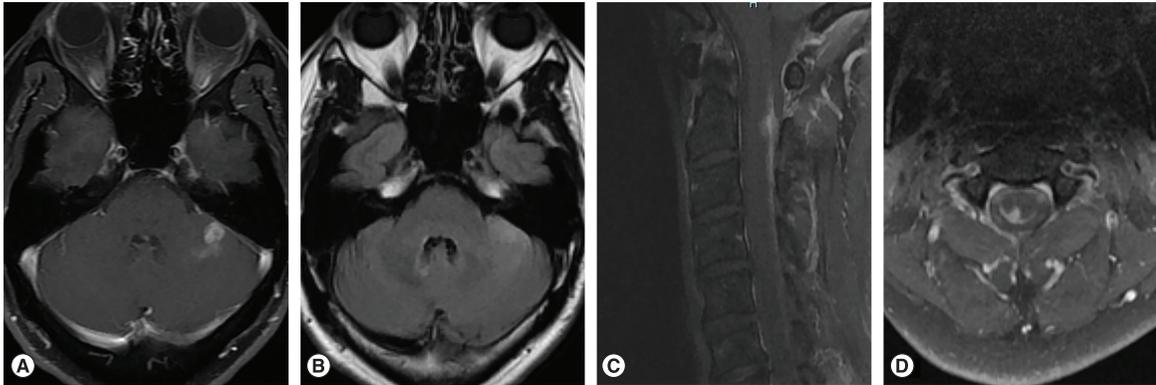


Figure 1. MRI brain and cervical spine at initial presentation. (A) Axial T1 contrasted MRI with sub-centimeter lesion in the anterior left cerebellar hemisphere, with **(B)** hazy T2 hyperintensity. **(C)** Sagittal and **(D)** axial T1 contrasted cervical spine MRI with leptomeningeal enhancement dorsal to and invading into the cervical spinal cord.

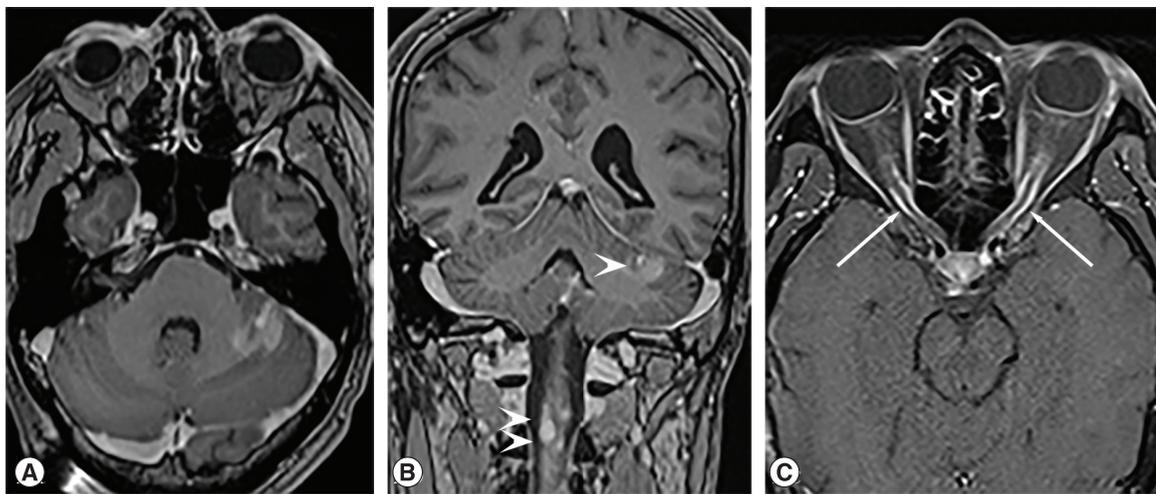


Figure 2. MRI brain demonstrating optic nerve and cerebellum involvement. (A) Axial T1 contrasted MRI with evolution of the left cerebellar lesion. **(B)** Coronal T1 contrasted MRI with the cerebellar lesion (single arrowhead) and progression of the cervical lesion (double arrowhead). **(C)** Axial T1 contrasted MRI of the orbits, highlighting the enhancement of the optic nerve sheath (arrows).

Immunohistochemistry identified the H3K27M mutation, which was confirmed by molecular profiling of tumor tissue (Figure 4C).

After consideration of treatment options at multiple centers, the patient was ultimately treated with craniospinal irradiation with concomitant and adjuvant temozolomide chemotherapy. MRI scans of the brain and cervical spine 1 month after completion of craniospinal irradiation and concomitant temozolomide demonstrated increased diffuse leptomeningeal enhancement. Over the following 2 months, the patient developed progressive gait difficulty, with bowel and bladder dysfunction consistent with clinical progression of leptomeningeal disease, confirmed on imaging and refractory to treatment with high-dose steroids. Patient and family requested no further tumor-directed treatment. He was enrolled in hospice and died 9 months after the initial onset of symptoms.

Discussion

This case represents an unusual presentation of H3K27M-mutant glioma with progressive vision loss and diffuse leptomeningeal disease. Though extensive radiographic leptomeningeal involvement was evident on initial imaging, CSF cytology was negative for malignant cells on two occasions. Optic nerve involvement was evident on MRI of the orbits, but two optic nerve sheath biopsies failed to establish a tissue diagnosis; therefore biopsy of the evolving cerebellar lesion was ultimately required to diagnose the H3K27M-mutant glioma.

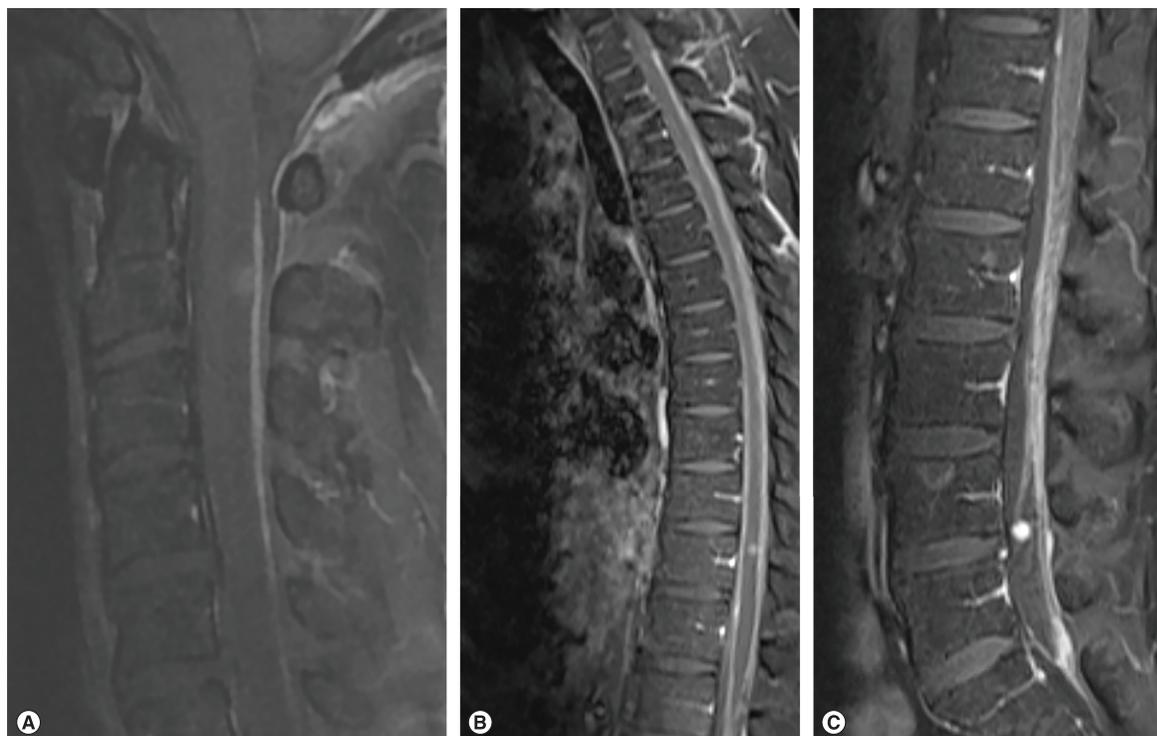


Figure 3. MRI spine demonstrating diffuse leptomeningeal disease. T1 contrasted MRI in sagittal plane of the spine. Note the diffuse leptomeningeal enhancement with focal invasion of the (A) cervical cord, (B) lower thoracic cord, and (C) nerve root-associated lesions in the lumbar thecal sac.

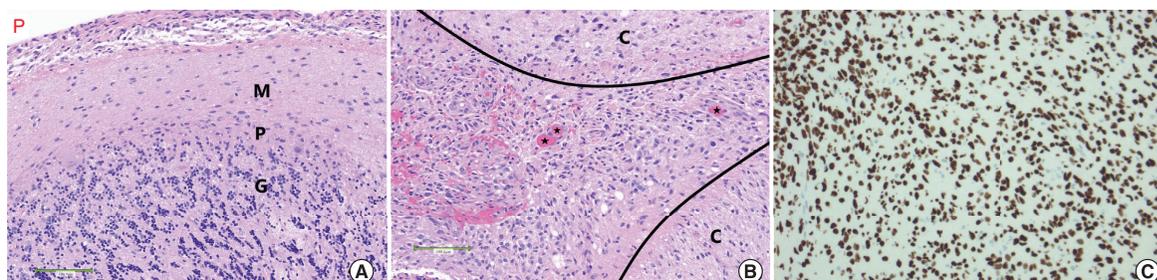


Figure 4. Pathology slides demonstrating tissue diagnosis. (A) H&E stained section shows cerebellar cortex with diffuse glioma infiltrating pia and cerebellar cortex (scale bar = 100 μ m). (B) An area of tumor between cerebellar folia (right and upper part of image) within the leptomeninges shows a cellular malignant glioma with focal microvascular proliferation (scale bar = 100 μ m), indicating WHO grade 4 histology. (C) Immunohistochemical (IHC) staining ($\times 20$): H3K27M shows strong nuclear positivity in tumor cells.
*Microvascular proliferation within the leptomeninges.
C: Cerebellar folia; G: Granular layer; M: Molecular layer; P: Purkinje cell layer; P (red): pia mater with diffuse glioma.

The differential diagnosis of leptomeningeal contrast enhancement is broad, including infectious etiologies such as human T-lymphotropic virus infection, inflammatory conditions such as neurosarcoidosis, and leptomeningeal metastasis from systemic malignancy [25–29]. In this case, the enhancement pattern and elevated CSF angiotensin-converting enzyme level initially led to consideration of neurosarcoidosis, but low-level elevation is nonspecific and should be interpreted with caution [30,31].

Conclusion

Although uncommon, histone-mutant high-grade gliomas can lead to leptomeningeal dissemination early in the course of disease, representing a diagnostic challenge and precluding gross total tumor resection [15–17,32]. Primary CNS malignancies should be considered in the setting of radiographic leptomeningeal enhancement, even without

a mass lesion. Besides high-grade gliomas, other primary CNS tumors such as diffuse leptomeningeal glioneuronal tumor, pilocytic astrocytoma, medulloblastoma, ependymoma, pineoblastoma and primary CNS lymphoma can involve the leptomeninges [33]. Although H3K27M-mutant tumors can affect adult and pediatric populations, patients with advanced age are more likely to have leptomeningeal dissemination as a presenting feature [34]. The limitations of CSF cytology analysis should be remembered; even in the setting of repeated sampling, conventional cytology may not isolate malignant cells, as exemplified in this case.

Future perspective

In the future, widespread use of CSF cell-free DNA analysis may expedite diagnosis of leptomeningeal glioma. Further molecular understanding may identify glioma subtypes with propensity for leptomeningeal dissemination, allowing improved risk stratification and treatment.

Author contributions

T Nadkarni, K Hamilton and U Sener were involved in data analysis and manuscript composition. All authors were involved in manuscript revision.

Financial & competing interests disclosure

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No writing assistance was used in preparation of this manuscript.

Ethical conduct of research

This is a case report with no experimental intervention performed as part of the study. As such, informed consent was not obtained from the included patient, in accordance with regulations of the Institutional Review Board at West Virginia University.

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