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Clinical Reasoning: A 22-Year-Old Man With Multifocal Brain and Osseous Lesions

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Abstract

The evaluation of patients with disseminated processes with CNS and osseous involvement is often challenging. A 22-year-old healthy man developed left-sided weakness, paresthesias, and neck pain over several weeks. On clinical examination, he was noted to have decreased right eye visual acuity, left-sided pyramidal weakness and numbness, and bilateral hyperreflexia. MRI revealed multifocal widespread abnormalities: nonenhancing lesions throughout the infratentorial brain, pituitary gland, right frontal lobe, and optic nerves, in addition to an enhancing intramedullary cervical spinal cord lesion, extensive nodular leptomeningeal enhancement of the spine, and numerous enhancing bony lesions throughout the vertebrae and iliac bones. CSF analysis was notable for normal opening pressure, protein 465 mg/dL, glucose 21 mg/dL, and normal cell count. Extensive serum and CSF analysis for infectious, inflammatory, and neoplastic etiologies was unrevealing, and the diagnosis was ultimately revealed after additional staining of tissue biopsy specimen from sacral and cerebellar biopsies. This case highlights the differential diagnoses for widely disseminated disease affecting the CNS and bones and informs pediatric and adult clinicians of important recent developments regarding this diagnostic entity.

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Section 1

A 22-year-old healthy man developed left-hand weakness, paresthesias, and neck pain over several weeks. He initially underwent chiropractic treatment for presumed nerve impingement without improvement. One month later, he presented to a local hospital with worsening left arm weakness and paresthesias, as well as new left leg weakness, headache, nausea, and vomiting. Examination revealed an alert mental status; decreased visual acuity in the right eye; mild weakness

in the left triceps, wrist extensors, finger extensors, and ankle dorsiflexors; decreased sensation throughout the left hemibody to touch; and bilateral hyperreflexia. Vital signs, comprehensive metabolic panel, complete blood count, and human immunodeficiency virus testing were unremarkable.

Questions for Consideration:

1. What localizations could account for these symptoms?
2. What diagnostic categories should be initially considered?
3. What additional studies should be pursued next?

GO TO SECTION 2

Section 2

The patient's presentation is notable for left-sided pyramidal weakness and hyperreflexia involving the arms and legs, localizing to an upper motor neuron process at the level of the cervical spine, brainstem, white matter tracts, or the primary motor cortex. Assuming that the decrease in monocular visual acuity is due to the same underlying process, possible localizations for this symptom include (1) a solitary or multifocal lesions causing elevated intracranial pressure and papilledema or (2) multifocal lesions, with involvement of the right optic nerve or retinal fibers. The bilateral hyperreflexia further supports either multifocal lesions or more caudal involvement of the brainstem or spinal cord rather than a single lesion in the contralateral primary motor cortex or white matter tracts. The differential diagnosis for subacute, progressive CNS processes in young adults is broad and includes indolent infections, neoplasms, autoimmune diseases, toxic/metabolic etiologies, and mitochondrial and other genetic disorders. The initial workup should include MRI of the brain and spine with and without contrast, CSF analysis, and

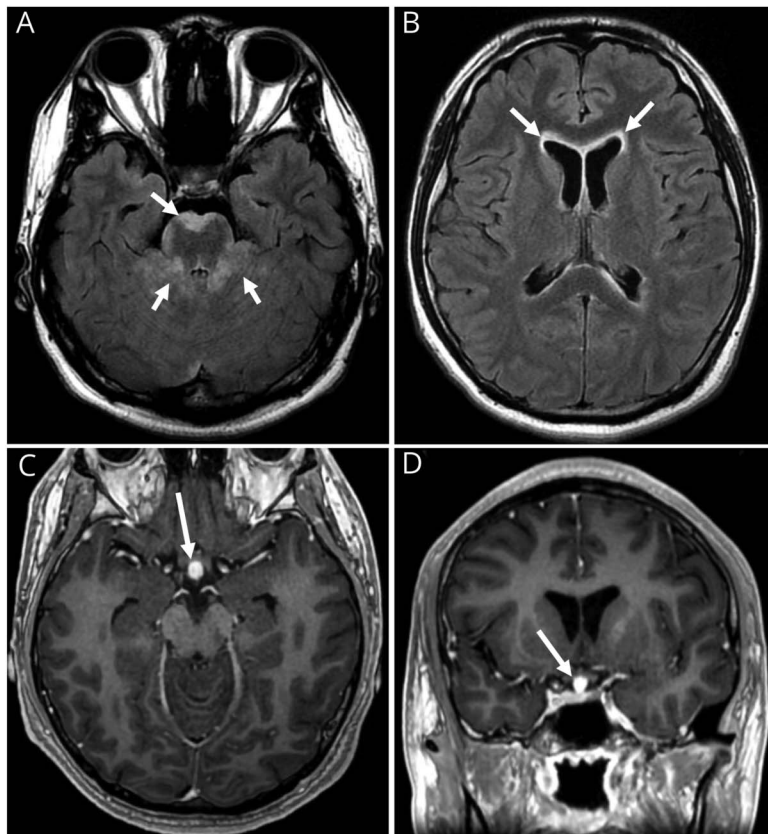
consideration of further serum studies pending the MRI and CSF results.

MRI of the brain revealed nonenhancing T2/fluid-attenuated inversion recovery hyperintense nodular lesions throughout the infratentorial brain, right frontal lobe, septum pellucidum, pituitary gland, and optic nerves (Figure 1). Spinal MRI demonstrated an intramedullary enhancing lesion spanning C5-C7, enhancement of the conus, and smaller nonenhancing lesions throughout the spinal cord (Figure 2). There were also numerous enhancing bony lesions throughout the vertebrae and both iliac bones and extensive nodular leptomeningeal enhancement of the spine. Lumbar puncture revealed normal opening pressure, 13 red blood cells, 5 white blood cells (54% monocytes, 46% lymphocytes), markedly elevated protein (465 mg/dL), low glucose (21 mg/dL), and unrevealing cytology and flow cytometry.

Questions for Consideration:

1. Considering the imaging characteristics and CSF profile, what specific etiologies could explain his presentation?
2. What additional workup should be considered?

Figure 1 Brain MRI at Presentation



(A) Axial fluid-attenuated inversion recovery demonstrating multiple hyperintense pial nodules coating the brainstem and cerebellar vermis. (B) Axial FLAIR demonstrating diffuse subependymal hyperintense lesions coating the ventricular surface. (C) Axial T1 postcontrast demonstrating an enhancing nodule of infundibular stalk. (D) Coronal T1 postcontrast demonstrating an enhancing nodule of infundibular stalk.

Figure 2 Spinal MRI at Presentation



(A) Sagittal T1 postcontrast demonstrating enhancing osseous lesion of C2 (thick arrow) and intramedullary cord mass at C5 and C6 levels (small arrow). (B) Sagittal T1 postcontrast demonstrating multiple enhancing osseous lesions. On precontrast T1-weighted imaging, these lesions are hypointense, marrow replacing lesions. (C) Axial T1 postcontrast demonstrating enhancement within the thecal sac. (D) Axial T1 postcontrast demonstrating enhancing osseous lesions in the lumbar spine.

GO TO SECTION 3

Section 3

Infectious causes of disseminated CNS and osseous lesions with markedly elevated protein and hypoglycorrhachia include tuberculosis (TB), *Cryptococcus* species (spp), and endemic mycoses such as *Coccidioides* spp. An acellular CSF profile can be seen in each of these infectious etiologies, though would be unusual in an immunocompetent host. Extrapulmonary manifestations of TB that resemble this case include basilar-predominant nodular lesions, intramedullary enhancing lesions, diffuse leptomeningeal enhancement throughout the spinal cord, vertebral lesions due to Pott disease, and other sites of bony involvement.¹ Fungal infections such as *Cryptococcus* and *Coccidioides* can also present with subacute onset meningioencephalomyelitis, occasionally with vertebral and other osseous involvement.² The tapeworm *Echinococcus granulosus* can also cause osseous and CNS lesions; however, these lesions are typically cystic in nature unlike this case.³ His extensive infectious workup was unrevealing, including serum and CSF cryptococcal antigen and *Coccidioides* antibodies (by complement fixation and immunodiffusion), serum and CSF fungal and acid-fast bacilli cultures, CSF mycobacteria PCR, and serum tuberculosis interferon-gamma release assay.

Malignant etiologies should also be considered. Particularly, given the lytic appearance of the vertebral lesions, metastatic carcinomas including renal cell carcinoma, lung cancer, melanoma, and gastrointestinal malignancies are possible etiologies.⁴ Systemic non-Hodgkin lymphoma can present with secondary CNS involvement and lytic bone lesions, although this is more common in the setting of relapse rather than the initial presentation.⁵ Histiocytic disorders such as Langerhans cell histiocytosis and Erdheim-Chester disease (ECD) are associated with skeletal involvement and a variety of CNS

lesions, although the osseous lesions in ECD are more commonly sclerotic lesions of the long bones.⁶ Although primary CNS tumors rarely disseminate outside of the CNS and leptomeninges, there have been reports of systemic metastasis in glioblastoma, oligodendroglioma, diffuse midline glioma, and others.^{7,8} This patient underwent PET demonstrating hypermetabolic activity in the lower cervical spinal cord lesion and multiple vertebral and sacral bony lesions and 3 lumbar punctures without evidence of atypical or clonal cell populations on CSF flow cytometry and cytology.

Neurosarcoidosis is one of the few autoimmune etiologies that can cause hypoglycorrhachia, along with basilar-predominant brain involvement, intramedullary lesions, and nodular leptomeningeal enhancement.⁹ Osseous involvement, including multifocal lytic-appearing vertebral lesions, is another extrapulmonary manifestation of sarcoidosis.¹⁰ Our patient's serum angiotensin-converting enzyme level was normal, although this test is insensitive for neurosarcoidosis. Furthermore, the absence of hilar lymphadenopathy or other pulmonary manifestations does not exclude this disease because extrapulmonary disease can be the presenting symptom in a minority of patients with sarcoidosis.⁹ Neuro-Behçet is another noninfectious etiology that can present with basilar-predominant leptomeningitis, intramedullary cord lesions, and hypoglycorrhachia; however, osseous involvement is typically limited to nonerosive arthritis rather than disseminated lytic bone lesions.¹¹ Among the other categories initially considered, his presentation is less consistent with toxic-metabolic, genetic, or mitochondrial disorders, given the hypoglycorrhachia and imaging characteristics.

Questions for Consideration:

1. What diagnostic tests should be pursued next?
2. Given these imaging findings, what complications may arise during his clinical course?

GO TO SECTION 4

Section 4

The patient's neurologic status progressively worsened because he developed spastic paraparesis, urinary retention, and hydrocephalus requiring external ventricular drain placement. He had multiple episodes of acute altered mental status with forced gaze deviation concerning for seizures. He underwent biopsy of the right sacral bone and cerebellum lesion, which demonstrated some atypical cells but was inconclusive on initial analysis. He received empiric intravenous methylprednisolone 1 g daily for 5 days and intravenous immunoglobulin 2 g/kg because there was some concern for an underlying neuroinflammatory process (possibly granulomatous); however, he continued to worsen clinically and radiographically. He was ultimately started on empiric tuberculosis treatment and then transferred to our institution for further evaluation.

Further immunohistochemical staining of the sacral and cerebellar specimens was positive for histone H3 K27M alteration, establishing the diagnosis of *diffuse midline glioma (DMG), H3 K27M-altered*, World Health Organization (WHO) grade IV, with diffuse osseous metastases. He received 1 week of palliative craniospinal irradiation and ultimately died 5 months after symptom onset.

Discussion

Diffuse intrinsic pontine glioma (DIPG) was previously conceptualized as an aggressive primary midline CNS malignancy affecting pediatric patients. In 2016, the WHO Classification of CNS Tumors replaced DIPG with a new entity, *DMG, H3 K27M-mutant*, based on the observation that post-translational modifications to histone H3 K27 conferred a poor prognosis among pediatric DIPG cohorts (median overall survival, mOS 10–14 months).¹² The 2021 WHO Classification of CNS Tumors modified the name to *DMG, H3 K27-altered*, and includes gliomas with H3 K27 alteration regardless of midline location in the brain or spinal cord.¹³ Given the prognostic implication of this histone alteration, these tumors are designated as WHO grade IV tumors regardless of the histologic appearance.

Although previously viewed as a disease of childhood, DMG is increasingly identified among adults, with retrospective analysis suggesting that 15% of adult midline gliomas harbor H3 K27 alterations.¹⁴ In contrast to children, survival is generally longer among adults (mOS 8.4–27 months), and outcomes among H3 K27M-altered and H3 wild-type high-grade midline gliomas are similar.^{12–14} The diencephalon, spinal cord, and brainstem are common sites of involvement, often with heterogenous parenchymal enhancement.^{12,14} Current treatment strategies are extrapolated from glioblastoma multiforme and other aggressive CNS tumors, including craniospinal irradiation with or without adjuvant chemotherapy (e.g., temozolomide) and/or surgical resection.¹⁴

However, ongoing clinical trials are investigating novel treatment approaches, including imipridones such as ONC201 (TNF-related apoptosis inducing ligand–inducing compounds), panobinostat (histone deacetylase inhibitor), chimeric antigen receptor T-cell therapy, and several others.¹⁵ Several trials have also expanded enrollment to include adults with DMG.¹⁵

Leptomeningeal dissemination occurs in a minority of adults with DMG¹³; however, widely disseminated osseous metastases, as described here, are rare and contributed to diagnostic uncertainty.⁷ Among the previously reported adult cases, diffuse osseous involvement was present at diagnosis in 3 adult patients who generally had an aggressive clinical course (OS 4–13 months) similar to this case.⁷ The diagnosis of DMG among adults is likely to increase as immunohistochemical staining for this histone alteration becomes more widely available. Furthermore, cell-free DNA and other circulating biomarkers are being investigated as noninvasive alternatives for diagnosis, particularly among patients at higher risk for biopsy.¹⁵ As such, recognition of this atypical presentation of DMG is important for guiding diagnostic workup and prognostication, and for advancing treatment given the increasing number of clinical trials.

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Appendix (continued)

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Sara C LaHue, MD	Department of Neurology, School of Medicine, and Department of Neurology, UCSF Weill Institute for Neurosciences, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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