Clinical Reasoning: A 59-Year-Old Woman Presenting With Diplopia, Dysarthria, Right-Sided Weakness, and Encephalopathy

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Section 1

A 59-year-old woman with a history of *FLT3-ITD* mutant acute myeloid leukemia (AML) presented for evaluation of horizontal diplopia, progressive dysarthria, right facial weakness, and somnolence. She was initially diagnosed with AML 15 months prior to the current presentation. Complete remission was attained 9 months from AML diagnosis after induction chemotherapy with daunorubicin, cytarabine, and midostaurin, and consolidation chemotherapy with high-dose cytarabine followed by allogenic stem cell transplantation. The patient relapsed 4 months after transplantation, prompting reduction of immune suppression and initiation of the FLT3 inhibitor gilteritinib. She developed graft vs host disease of the skin, necessitating maintenance tacrolimus and dexamethasone. She again achieved complete remission on gilteritinib. Five months following gilteritinib initiation, she presented to her outpatient oncologist for evaluation of 10 days of intermittent horizontal diplopia associated with left eye pain and a new headache. On examination, she had new left eye esotropia and veered left with ambulation, while the remainder of the neurologic examination was intact. Her medication regimen at this time included gilteritinib, tacrolimus, dexamethasone, and prophylactic acyclovir, trimethoprim-sulfamethoxazole, and fluconazole.

Questions for Consideration:

1. What is the differential diagnosis?
2. What are next steps in diagnostic workup?

GO TO SECTION 2

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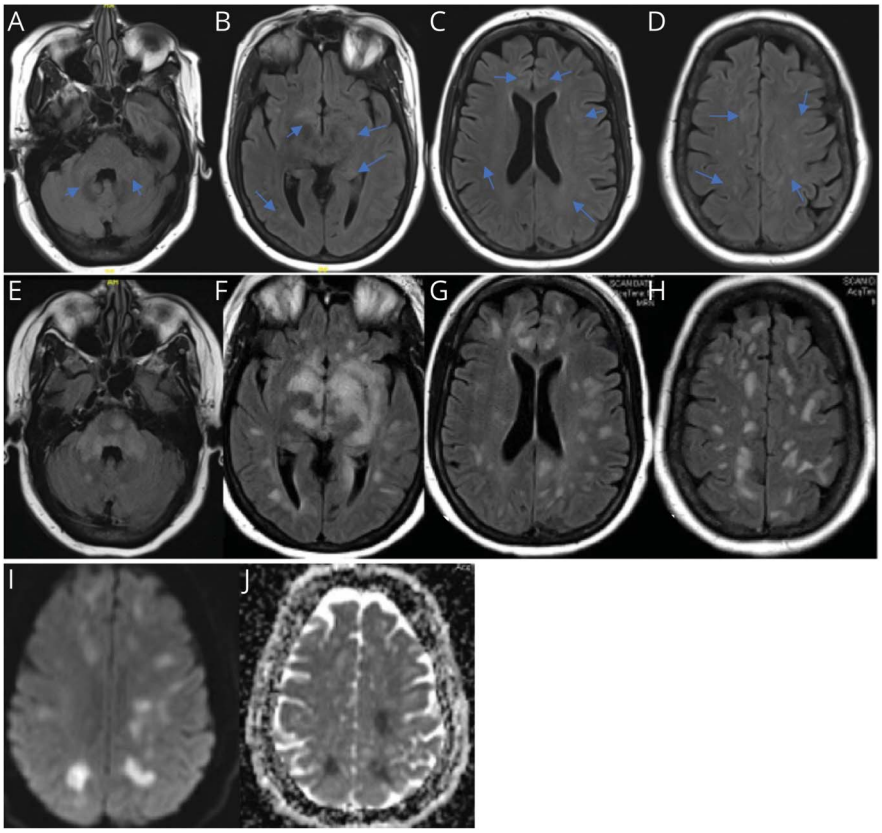
Section 2

The development of neurologic deficits in our patient raised concern for disease progression, opportunistic infections, and treatment complications. A diagnostic workup was pursued. Lumbar puncture yielded clear CSF with pleocytosis of unspecified predominance (leukocytes 24 and 34 cells in tubes 1 and 4, respectively), elevated protein (52 mg/dL; normal range: 15–45 mg/dL), glucose 74 mg/dL (normal range: 40–70 mg/dL), negative gram stain/culture, negative Epstein-Barr virus (EBV) and JC virus PCR, and positive cytology consistent with new CNS involvement of leukemia. A brain MRI showed bilateral oculomotor nerve enhancement and diffuse T2 fluid-attenuated inversion recovery (FLAIR) patchy hyperintensities (figure 1, A–D). Intrathecal triple chemotherapy (cytarabine 50 mg, hydrocortisone 50 mg, methotrexate [MTX] 12 mg) and concurrent whole brain radiation therapy (WBRT) (total 2,400 cGy across 12 fractions) were initiated due to concern for disease progression. One week later, after 2 doses of intrathecal chemotherapy and 2 fractions of WBRT, a repeat lumbar puncture demonstrated CSF disease clearance via negative cytology. However, the patient declined further, presenting to our emergency department (ED) for further evaluation. Persistent horizontal diplopia was now accompanied by a progressive encephalopathy marked by somnolence, inattentiveness, and disorientation. She had a right-gaze preference, asymmetric pupils (right > left), right lower motor neuron facial palsy, dysarthria, right upper extremity weakness, and a moderate-amplitude, high-frequency, bilateral hand tremor. Nuchal rigidity was absent.

Questions for Consideration:

1. What are the next steps in diagnostic workup?
2. Which empiric treatments would you initiate?

Figure 1 Progression of CNS Disease Demonstrated by Interval Neuroimaging



(A–D) Brain MRI axial fluid-attenuated inversion recovery (FLAIR) sequences obtained on day of initial presentation to the outpatient clinic demonstrate nonspecific FLAIR hyperintensities (subtle findings denoted by blue arrows). (E–H) Brain MRI axial FLAIR sequences obtained 6 days later (at time of emergency department presentation/hospital day 1) demonstrate progressive worsening of nonspecific FLAIR hyperintensities. No areas of restricted diffusion were noted on this MRI from hospital day 1. (I, J) Brain MRI axial diffusion-weighted imaging and apparent diffusion coefficient sequences demonstrate new, multifocal areas of restricted diffusion (obtained on hospital day 2).

GO TO SECTION 3

Section 3

The patient's rapid decline led to concerns for infection, multifocal strokes as may occur in vasculitis, treatment-related complications, or worsened oncologic disease. An emergent noncontrast head CT and CT angiography of the head and neck revealed multiple hypodensities involving bilateral basal ganglia and the supratentorial white matter, without any vessel abnormalities. A brain MRI displayed multifocal, confluent, and nodular deep white and gray matter abnormalities with multifocal edema in a perivascular distribution (figure 1, E–H). The patient's right-sided weakness was attributed to left internal capsule lesions, right gaze preference to left pontine lesions, and encephalopathy to the diffuse involvement of the cerebrum and brainstem. A clinical–radiographic dissociation was noted, as radiographic disease burden exceeded appreciated clinical deficits. A repeat lumbar puncture yielded clear CSF with 2 leukocytes, mildly elevated protein (46.8 mg/dL; normal range: 10.0–44.0 mg/dL), glucose 96 mg/dL (normal range: 40–70 mg/dL), negative gram stain/culture, and negative cytology. Other CSF and serum infectious studies (herpes simplex virus 1/2, EBV, human herpesvirus 6, cytomegalovirus, treponemal antibody) resulted negative. Serum tacrolimus level was subtherapeutic. A 24-hour EEG showed nonspecific slowing. Despite empiric meningoencephalitis coverage with vancomycin, cefepime, metronidazole, and acyclovir, the patient progressively deteriorated over the ensuing 24 hours. Clinically, she remained afebrile but hypertensive, became increasingly disoriented and lethargic, and had occasional verbal output, but no spontaneous movement. Repeat brain MRI performed approximately 24 hours from initial ED neuroimaging demonstrated worsened diffuse multifocal areas of T2 FLAIR prolongation supratentorially and infratentorially and new diffusion restriction involving various vascular territories bilaterally (figure 1, I–J). MRI of cervical, thoracic, and lumbar spine was unremarkable.

Question for Consideration:

1. How do these findings refine your differential diagnosis?

GO TO SECTION 4

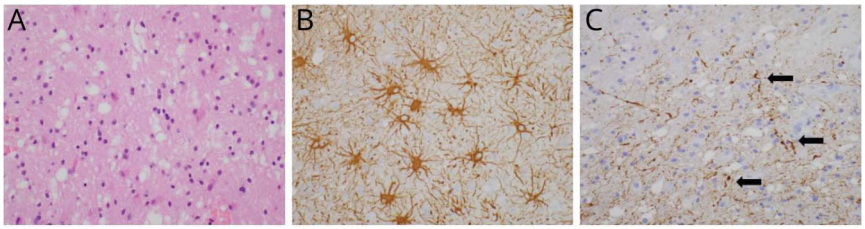
Section 4

The patient's hypertension and tacrolimus use initially raised concern for posterior reversible encephalopathy syndrome (PRES). PRES may manifest as confusion, headache, transient deficits, or seizures.[1] However, the patient's decline despite adequate blood pressure control and removal of tacrolimus made PRES less likely. The rapidity of deterioration and radiographic findings, particularly areas of diffusion restriction on repeat imaging, led to speculation of a treatment-related neurotoxicity vs vasculitis. The patient's outpatient treatment regimen, notably cytarabine and MTX, poses a risk of toxic leukoencephalopathy. High-dose cytarabine can cause cerebellar signs, intrathecal cytarabine may cause myelopathy, and intrathecal cytarabine with concurrent irradiation increases the risk of necrotizing leukoencephalopathy.[2,3] Our patient's examination and imaging were not consistent with cytarabine toxicity. In contrast, MTX toxicity was a probable etiology that was more strongly suspected, particularly once infectious etiologies were excluded. On hospital day 5, empiric leucovorin and IV folic acid were initiated for suspected MTX toxicity and a brain biopsy of the right frontal cortex white matter was performed. Histopathology demonstrated diffuse vacuolization, gliosis, axonal injury suggested by axonal swellings/spheroids, and mild chronic inflammation with reactive perivascular lymphocytes without evidence of vasculitis (figure 2, A–C).

Question for Consideration:

1. What modifications would you make to your treatment plan?

Figure 2 Pathology From Brain Biopsy Performed on Hospital Day 5



The patient's brain biopsy showed fragments of (A) white matter with diffuse vacuolization (hematoxylin & eosin, 400×), (B) gliosis (glial fibrillary acidic protein immunostain, 400×), and (C) axonal swellings (neurofilament protein immunostain, arrows, 400×).

GO TO SECTION 5

Section 5

The biopsy findings provided evidence of a toxin-induced leukoencephalopathy, compatible with a clinical concern for MTX-induced toxicity. The patient received IV folic acid 1 mg once followed by oral folate 1 mg daily, IV leucovorin 25 mg every 6 hours for 2 days, and IV aminophylline 2.5 mg/kg daily for 7 days. Concurrently, dexamethasone was increased to 40 mg every 6 hours. Empiric meningoencephalitis coverage was discontinued once infectious studies resulted negative. Following initiation of treatment for MTX toxicity, the patient's mental status slowly improved, albeit with intermittent delirium. On her day of discharge (hospital day 24), she was fully oriented and conversant; however, right-sided weakness persisted. Steroids were weaned and after months of rehabilitation, she approached her pretoxicity baseline.

Discussion

Our patient's case is complex due to the myriad of pathologies that could account for progressive neurologic decline in an immunosuppressed oncologic patient. Once infectious causes were excluded, the development of progressive deficits and encephalopathy in a patient with leukemia, actively receiving both intrathecal chemotherapy and WBRT, placed toxic adverse effects vs disease progression at the top of the differential.

AML with CNS involvement can cause increased intracranial pressure. This may manifest as headache, altered consciousness, cranial nerve palsies, intracranial hemorrhage, visual changes, and spinal cord compression.[4] However, our patient's cytology was negative on 2 repeat lumbar punctures despite rapid deterioration, thus making disease progression a less likely etiology. MTX, regardless of administration route, portends a risk of systemic and neurologic toxicities. There is an increased risk of MTX neurotoxicity when administrated intrathecally or with concurrent radiation, as compared to oral or IV administrations without concurrent radiation. It is hypothesized that folate deficiency or direct neuronal damage account for its resultant neurotoxicity.[3,5,6] Clinical manifestations of MTX neurotoxicity are variable and may include focal deficits, aphasia, encephalopathy, seizures, or signs of increased intracranial pressure.[5,7,8] Suspicion of MTX neurotoxicity warrants a thorough diagnostic evaluation with neuroimaging, lumbar puncture, EEG, and close clinical monitoring. Radiographic patterns range from leukoencephalopathy to restricted diffusion. Resultant restricted diffusion may be reflective of infarction or cytotoxic edema. Utilization of MRI perfusion sequences or simply following the evolution of these diffusion-restricted lesions through time via interval imaging helps to elucidate the represented process. In our patient's case, magnetic resonance perfusion was not performed. However, repeat neuroimaging demonstrated a reversibility of areas previously seen to have diffusion restriction, without any findings suggestive of prior ischemia. Thus, we conclude that the areas of diffusion restriction seen on the brain MRI on hospital day 2 were reflective of reversible MTX-induced cytotoxicity.

Early implementation of treatment for MTX neurotoxicity is advised to lessen disease severity; however, this is not well-standardized. Reviewed literature advocates for use of multiple agents to reverse the effect of MTX along various steps of the folate synthesis pathway, in addition to steroid treatment.[6,9,10] In our patient's case, other more common diagnoses were considered, in addition to MTX toxicity. This led to a 5-day lapse in empiric treatment for MTX toxicity. However, once infectious etiologies and disease progression were excluded, MTX toxicity was highly suspected and empiric treatment with leucovorin, folate, and aminophylline were administered. Leucovorin and folic acid administration are first-line.[9] Adjuvant aminophylline use is supported by findings of increased CSF adenosine levels in pediatric patients with MTX neurotoxicity[6]; however, no validated clinical trials have yet been performed.[6,8]

There is variability in practice regarding rechallenging with MTX.[7] Successful rechallenge following MTX neurotoxicity has been reported; however, providers may opt to remove MTX entirely from subsequent regimens. In some cases of MTX rechallenge, patients receive prophylactic aminophylline; in others, leucovorin rescue is prophylactically administered within 24–36 hours of intrathecal MTX rechallenge.[7]

This case describes the severe neurologic consequences that may result from MTX-induced toxicity, highlighting the importance of its recognition and early initiation of rescue therapy.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Giovanna S. Manzano, MD	Massachusetts General Hospital and Brigham and Women's Hospital, Boston, MA	Reviewed patient's medical record and drafted case report, created figure 1
Matthew Torre, MD	Brigham and Women's Hospital, Boston, MA	Reviewed brain biopsy pathology, created figure 2
Marlise R. Luskin, MD, MSCE	Dana-Farber Cancer Institute, Boston, MA	Revision of report for intellectual content and oncologic clinical course
Henrikas Vaitkevicius, MD	Brigham and Women's Hospital, Boston, MA	Revision of report for intellectual content

References

1. Hodnett P, Coyle J, O'Regan K, Maher MM, Fanning N. PRES (posterior reversible encephalopathy syndrome), a rare complication of tacrolimus therapy. *Emerg Radiol.* 2009;16(6):493-496.
2. Baker WJ, Royer GL, Weiss RB. Cytarabine and neurologic toxicity. *J Clin Oncol.* 1991;9(4):679-693.
3. Sandoval C, Kutscher M, Jayabose S, Tenner M. Neurotoxicity of intrathecal methotrexate: MR imaging findings. *Am J Neuroradiol.* 2003;24(9):1887-1890.
4. Patkowska E, Szczepaniak A, Barańska M, et al. Primary and secondary central nervous system involvement in acute myeloid leukemia. *J Leuk.* 2019;7(2):1-12.
5. Feinsilber D, Leoni RJ, Siripala D, Leuck J, Mears KA. Evaluation, identification, and management of acute methotrexate toxicity in high-dose methotrexate administration in hematologic malignancies. *Cureus.* 2018;10(1):e2040.
6. Bernini JC, Fort DW, Griener JC, et al. Aminophylline for methotrexate-induced neurotoxicity. *Lancet.* 1995;345(8949):544-547.
7. Bhojwani D, Sabin ND, Pei D, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. *J Clin Oncol.* 2014;32(9):949-959.
8. Inaba H, Khan RB, Laningham FH, Crews KR, Pui CH, Daw NC. Clinical and radiological characteristics of methotrexate-induced acute encephalopathy in pediatric patients with cancer. *Ann Oncol.* 2008;19(1):178-184.
9. Howard SC, McCormick J, Pui C-H, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. *Oncologist.* 2016;21(12):1471-1482.
10. Saini AG, Sahu JK, Mahapatra S, Bansal D, Singhi P. Progressive neurotoxicity after intrathecal methotrexate and cytarabine in a child with acute myeloid leukemia. *Clin Oncol.* 2018;3:3.

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