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

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Giovanna S. Manzano: 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; Additional contributions: Creation of Figure 1.
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Section 1

A 59-year-old woman with a history of FLT3-ITD mutant acute myeloid leukemia (AML) presents for evaluation of horizontal diplopia, progressive dysarthria, right facial weakness and somnolence. She was initially diagnosed with AML 15-months prior to current presentation. Complete remission (CR) 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. She relapsed four months after transplantation, prompting reduction of immune suppression and initiation of the FLT3-inhibitor, gilteritinib. She developed graft versus 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 exam 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?

Section 2

The development of neurologic deficits in our patient raised concern for disease progression, opportunistic infections, and treatment complications. A diagnostic work-up was pursued. Lumbar puncture yielded clear CSF with pleocytosis of unspecified predominance (WBC’s 24 and 34 cells in tubes 1 and 4, respectively), elevated protein (52 mg/dL; range: 15-45 mg/dL), glucose 74 mg/dL (range: 40-70 mg/dL), negative gram stain/culture, negative EBV and JCV PCR’s, and positive cytology consistent with new CNS involvement of leukemia. A brain MRI showed bilateral oculomotor nerve enhancement and diffuse T2 FLAIR patchy hyperintensities (Figure 1A-D). Intrathecal triple chemotherapy (cytarabine 50mg, hydrocortisone 50mg, methotrexate (MTX) 12mg) and concurrent whole brain radiation therapy (WBRT) (total 2400 cGy across 12 fractions) were initiated due to concern for disease progression. One week later, after two doses of intrathecal chemotherapy and two fractions of WBRT, a repeat lumbar puncture demonstrated CSF disease clearance via negative cytology. However, the patient further declined, 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. Additionally, 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?

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 non-contrast 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 1E-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 WBC’s, mildly elevated protein (46.8 mg/dL; range: 10.0-44.0 mg/dL), glucose 96 mg/dL.
(range: 40-70 mg/dL), negative gram stain/culture, and negative cytology. Other CSF and serum infectious studies (HSV1/2, EBV, HHV6, CMV, treponemal antibody) resulted negative. Serum tacrolimus level was sub-therapeutic. A 24-hour EEG showed non-specific slowing. Despite empiric meningoencephalitis coverage with vancomycin, cefepime, metronidazole, acyclovir, the patient progressively deteriorated over the ensuing 24-hours. Clinically, she remained afebrile but hypertensive, became increasingly disoriented and lethargic, 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 supra- and infratentorially and new diffusion restriction involving various vascular territories bilaterally (Figure 1 I-J). MRI C-, T- and L-spine were unremarkable.

**Question for consideration:**

1. How do these findings refine your differential diagnosis?

**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, and/or seizures. 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 versus vasculitis. Her outpatient treatment regimen, notably cytarabine and methotrexate, 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. Our patient’s exam 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 intravenous (IV) folic acid were initiated for suspected MTX-toxicity and a brain biopsy of a 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 2A-C).

**Question for consideration:**

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

**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 1mg once followed by oral folate 1mg daily, IV leucovorin 25mg every 6 hours for 2 days, and IV aminophylline 2.5mg/kg daily for 7 days. Concurrently, dexamethasone was increased to 40mg every 6 hours. Empiric meningoencephalitis coverage was discontinued once infectious studies resulted negative. Following initiation of treatment for MTX-toxicity, her mental status slowly
improved albeit with intermittent delirium. On 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 re-approached her pre-toxicity 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 versus 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 even, spinal cord compression. However, our patient’s cytology was negative on two 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 intravenous administrations without concurrent radiation. It is hypothesized that folate deficiency and/or direct neuronal damage account for its resultant neurotoxicity. Clinical manifestations of MTX neurotoxicity are variable and may include focal deficits, aphasia, encephalopathy, seizures and/or signs of increased intracranial pressure. Suspicion of MTX-neurotoxicity warrants a thorough diagnostic evaluation with neuroimaging, lumbar puncture, EEG, and close clinical monitoring. Radiographic patterns range from leukencephalopathy 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, MR 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 methotrexate along various steps of the folate synthesis pathway, in addition to steroid treatment. 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. Adjuvant aminophylline use is supported by findings of increased CSF adenosine levels in pediatric patients with MTX-neurotoxicity; however, no validated clinical trials have yet been performed.
There is variability in practice regarding re-challenging with methotrexate. Successful re-challenge following MTX-neurotoxicity has been reported; however, providers may opt to remove methotrexate entirely from subsequent regimens. In some cases of methotrexate re-challenge, patients receive prophylactic aminophylline; in others, leucovorin rescue is prophylactically administered within 24-36 hours of intrathecal methotrexate re-challenge.

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

Appendix 1. Authors

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References


**Figures**

**Figure 1. Progression of CNS disease demonstrated by interval neuroimaging.** *A-D*: Brain MRI axial FLAIR sequences obtained on day of initial presentation to outpatient clinic demonstrating nonspecific FLAIR hyperintensities (subtle findings denoted by blue arrows). *E-H*: Brain MRI axial FLAIR sequences obtained six days later (at time of emergency department presentation/hospital day #1) demonstrating 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 DWI and ADC sequences demonstrating new, multifocal areas of restricted diffusion (obtained on hospital day #2).
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 (H&E, 400x), (B) gliosis (GFAP immunostain, 400x), and (C) axonal swellings (neurofilament protein immunostain, arrows, 400x).
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