Clinical Reasoning: A unique case of acute onset, progressive left hemiparesis

SECTION 1
A 15-year-old, right-handed Hispanic boy with B-cell acute lymphoblastic leukemia (ALL) was transferred for acute onset of stroke-like symptoms. Approximately 6.5 hours prior to arrival, the patient was in his normal state of health. At that time, he developed abrupt onset of headache and left arm tingling described as “ants crawling on my arm.” He described associated dysarthria, dysphagia, and progression of symptoms over the first hour to include left lower extremity paresthesias. By the time of neurologic consultation, he reported some subjective improvement in left leg sensory deficits but was weak throughout his left hemibody. Past medical history was notable for B-cell ALL diagnosed 3 months earlier, for which the patient had undergone induction chemotherapy with vincristine, daunorubicin, pegylated asparaginase, and intrathecal methotrexate (IT-MTX) and cytarabine. He achieved remission and was being treated with consolidation chemotherapy consisting of systemic cyclophosphamide, cytarabine, mercaptopurine, vincristine, pegylated asparaginase, and IT-MTX. His most recent lumbar puncture with IT-MTX was 10 days prior to presentation, at which time CSF analysis had shown white blood cells 2/mm³, red blood cells 2/mm³, and unre- markable cytology (a few normal-appearing lymphocytes). Family history was negative for stroke. The patient denied current tobacco, alcohol, or drug use.

Initial temperature was 98.9°F, blood pressure 112/52 mm Hg, heart rate 110, respirations 20, oxygen saturation 100% on room air. Examination demonstrated intact mental status. Cranial nerves were intact except for a left lower facial droop. Motor examination showed 5/5 strength throughout the right hemibody and 4/5 strength throughout the left. Deep tendon reflexes were 2+ throughout with flexor plantar responses. Sensation was decreased to pinprick over the left lower extremity from the thigh distally. Coordina- tion was intact but gait was slightly wide-based.

Initial laboratory assessment showed white blood cells 3,500/mm³, hemoglobin 7.4 g/dL, platelets 58,000/mm³, international normalized ratio 0.92, creatinine 0.4 mg/dL, all stable from prior values. Electrolytes were within normal limits. CT of the head was negative for acute abnormality.

Question for consideration:
1. What acute therapy, if any, is indicated in this setting?
SECTION 2
The initial management of acute-onset focal neurologic deficits which are concerning for ischemic stroke involves a prompt evaluation of candidacy for fibrinolytic therapy. Current data support the use of IV fibrinolytic therapy within 3 hours of ischemic stroke onset in all adult patients with potentially disabling deficits. IV fibrinolytic therapy has been shown to offer moderate benefit within 3 to 4.5 hours in patients younger than 80 years with disabling deficits who are not on anticoagulation and have no history of stroke and diabetes mellitus. Intra-arterial fibrinolytic therapy in the 3- to 6-hour window has been shown to offer moderate benefit in patients with disabling deficits and large artery occlusion.

In the pediatric population, the management of acute ischemic stroke remains largely supportive. Large-scale randomized controlled trials of fibrinolytic therapy have not been performed in pediatric populations. There is no current consensus on the use of tissue plasminogen activator (tPA) in adolescent patients who otherwise meet adult eligibility standards. In younger children, tPA is not administered outside a clinical trial. Efforts are currently underway in the Thrombolysis in Pediatric Stroke trial to investigate the safety and efficacy of fibrinolytics and intra-arterial therapy in the pediatric population.

In this case, the patient falls outside the accepted age range of Food and Drug Administration approval for fibrinolytic therapy. This patient presented well outside the timeline of accepted use of IV tPA and outside the accepted window for intra-arterial therapy in anterior circulation stroke. He was significantly thrombocytopenic, a contraindication. In addition, he reported a progressive onset of symptoms with some evidence of evolution over time which would be atypical for stroke.

Questions for consideration:
1. What differential diagnoses would you consider at this time?
2. What studies and neuroimaging would you consider to confirm your diagnostic suspicion?
SECTION 3

The differential diagnosis for acute onset of unilateral neurologic symptoms includes ischemic stroke and its mimics. In the pediatric population, this list is broad and includes structural pathology (e.g., intracranial hemorrhage or mass lesion), infectious etiologies (e.g., abscess, empyema, herpes simplex virus encephalitis), demyelinating process (e.g., acute demyelinating encephalomyelitis [ADEM]), metabolic or toxic processes, postictal paralysis, posterior reversible encephalopathy syndrome (PRES), complicated migraine or migraine variant (e.g., hemiplegic migraine), inherited channelopathy (e.g., periodic paralysis), mitochondrial disorders (e.g., mitochondrial encephalopathy with lactic acidosis and stroke-like attacks), conversion reaction, and others. In our patient, intracranial hemorrhage or mass lesion was not demonstrated on CT head. There were no clinical symptoms to support antecedent seizure activity. Blood pressure and metabolic studies including potassium were unremarkable. While headache was a component of his initial presentation, there was no history of prior migrainous symptoms. There was no fever, leukocytosis, or associated infectious symptoms. The patient’s family denied toxic ingestion.

On the morning following admission, the patient clinically worsened, with strength declining to 0/5 in the left upper extremity, 3+/5 in the left lower extremity, left hemianesthesia, significant dysarthria, and worsening dysphagia, necessitating nasal feeding tube. He was transferred to the pediatric intensive care unit for closer monitoring. MRI of the brain was performed and demonstrated abnormal hyperintense signal in the right subcortical white matter on diffusion-weighted imaging (DWI) and corresponding low signal on apparent diffusion coefficient (ADC) sequences (figure). This abnormality was confined to the subcortical white matter and did not respect typical vascular territory. T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences did not demonstrate abnormal signal in the areas of restricted diffusion or elsewhere including the parietal or occipital regions.

Questions for consideration:

1. What diagnosis would you favor based on this evaluation?
2. What management and prognostic information would you share with the patient and family?
MTX toxicity mimicking acute ischemic stroke is an uncommon but described entity. Over the past 5 years, we are aware of 4 pediatric patients at our institution who presented with acute-onset focal neurologic deficits mimicking ischemic stroke after MTX administration (Table). Each developed a combination of hemiparesis, hemisensory deficit, aphasia, dysarthria, or dysphagia. Symptoms began 3–10 days following MTX administration, which is similar to the 5–15 days that is commonly reported. Three patients developed symptoms following IT-MTX and 1 patient developed symptoms following high-dose IV MTX that was complicated by delayed clearance despite aggressive hydration and leucovorin rescue. In each case, symptoms fluctuated over the initial hours and days such that patients reported worsening, improvement, or waxing and waning symptoms. Similar to prior reports, in 1 case, neurotoxicity evolved to include encephalopathy. MRI was performed at admission in all patients and demonstrated restricted diffusion as well as white matter abnormalities on T2-weighted and FLAIR sequences which tends to predominate in the posterior cerebral hemispheres. The presentation and MRI findings in this case were not believed to be consistent with MTX neurotoxicity.

The mechanisms for subacute MTX neurotoxicity are poorly understood. While important risk factors appear to include younger age, higher doses, prolonged leucovorin rescue, and coadministration of high-dose systemic methotrexate, IT-MTX, and HD-MTX appear to include younger age, higher doses, and gradual functional decline. Acute toxicity may include headache, nausea, lethargy, altered mental status, blurred vision, seizure, or increased intracranial pressure developing within 1 day of administration. Stroke-like symptoms have a subacute presentation 5–15 days after IV or intrathecal administration, and have been estimated to occur in approximately 2% of patients receiving MTX. Asparaginase can also cause neurotoxicity, most commonly a true stroke due to acquired antithrombin deficiency. His previous dose of asparaginase was 34 days prior to presentation. Combined with the MRI findings, asparaginase-induced stroke was considered much less likely. PRES is a known complication of oral and IT-MTX but commonly presents with headache, seizures, and altered consciousness with MRI demonstrating restricted diffusion as well as white matter abnormalities on T2-weighted and FLAIR sequences which tends to predominate in the posterior cerebral hemispheres. The presentation and MRI findings in this case were not believed to be consistent with MTX neurotoxicity.

**SECTION 4**

The patient’s clinical presentation, early hospital course, and recent history of IT-MTX administration raised primary concern for MTX neurotoxicity. The MRI findings were inconsistent with stroke, PRES, encephalitis, ADEM, or other process. The patient was briefly intubated for respiratory distress but subsequently stabilized and was transferred back to the floor. He was treated empirically with dexamethasone 0.02 mg/kg/day and symptoms gradually improved with full recovery after 6 days. He was discharged with a diagnosis of subacute MTX neurotoxicity.

MTX is an antineoplastic agent that acts as a folate antimetabolite and inhibits DNA synthesis by inhibiting dihydrofolate reductase. Oral, IV, and intrathecal forms are used for the treatment of various cancers including ALL. Drug toxicity can manifest as myelosuppression, mucositis, nephrotoxicity, hepatotoxicity, and neurotoxicity. Neurotoxicity can present in acute, subacute, or chronic forms. Chronic MTX neurotoxicity develops slowly and may progress to permanent neurologic impairment, dementia, and gradual functional decline. Acute toxicity may include headache, nausea, lethargy, altered mental status, blurred vision, seizure, or increased intracranial pressure developing within 1 day of administration. Stroke-like symptoms have a subacute presentation 5–15 days after IV or intrathecal administration, and have been estimated to occur in approximately 2% of patients receiving MTX. Asparaginase can also cause neurotoxicity, most commonly a true stroke due to acquired antithrombin deficiency. His previous dose of asparaginase was 34 days prior to presentation. Combined with the MRI findings, asparaginase-induced stroke was considered much less likely. PRES is a known complication of oral and IT-MTX but commonly presents with headache, seizures, and altered consciousness with MRI demonstrating restricted diffusion as well as white matter abnormalities on T2-weighted and FLAIR sequences which tends to predominate in the posterior cerebral hemispheres. The presentation and MRI findings in this case were not believed to be consistent with MTX neurotoxicity.

**Table** Summary of patients with subacute MTX neurotoxicity presenting with stroke-like symptoms

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Race</th>
<th>Diagnosis</th>
<th>Presenting symptom</th>
<th>MTX therapy</th>
<th>Days from MTX</th>
<th>Days to recovery</th>
<th>Outcome</th>
<th>Restarted MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>M</td>
<td>H</td>
<td>B-lineage ALL</td>
<td>Headache, left-sided stroke-like symptoms</td>
<td>IT-MTX</td>
<td>10</td>
<td>6</td>
<td>Full recovery</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>F</td>
<td>C</td>
<td>OS</td>
<td>Left-sided stroke-like symptoms</td>
<td>HD-MTX</td>
<td>9</td>
<td>6</td>
<td>Full recovery</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>F</td>
<td>C</td>
<td>T-lineage ALL</td>
<td>Dysarthria, blurred vision, left-sided stroke-like symptoms</td>
<td>IT-MTX</td>
<td>6</td>
<td>6</td>
<td>Full recovery</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>M</td>
<td>H</td>
<td>B-lineage ALL</td>
<td>Headache, left-sided stroke-like symptoms</td>
<td>IT-MTX</td>
<td>3</td>
<td>9</td>
<td>Full recovery</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ALL = acute lymphoblastic leukemia; C = Caucasian; H = Hispanic; HD-MTX = high-dose systemic methotrexate; IT-MTX = intrathecal methotrexate; MTX = methotrexate; OS = osteosarcoma.

* Clinical features including route of MTX, time to onset of symptoms, time to recovery, and whether MTX was restarted in 4 patients over the past 5 years who presented with acute onset stroke-like symptoms found to be secondary to subacute MTX toxicity.

* Systemic MTX elimination was complicated by prolonged clearance despite leucovorin rescue.
of cranial irradiation, no predictive factors or biomarkers have been determined. There is growing evidence to suggest that susceptibility may be related to single nucleotide polymorphisms particularly those involving the methylene tetrahydrofolate reductase gene. It has been proposed that excess MTX in the setting of such genetic alterations may result in abnormal folate metabolism and increased intracellular homocysteine. Further study is required.

The available case reports of MTX toxicity mimicking acute stroke almost invariably involve pediatric patients. This is likely related to the underlying pathophysiology as well as the frequent use of MTX in the treatment of pediatric ALL. Cranial irradiation is thought to disrupt the blood–brain barrier, substantially increasing CNS penetration of MTX. Leucovorin rescue involves administration of 5-formyl-tetrahydrofolate to help salvage purine and pyrimidine biosynthesis, which is disrupted by MTX. Neither leucovorin nor dexamethasone has been shown to be effective in treating MTX neurotoxicity.

Subacute MTX toxicity is an important mimicker of ischemic stroke. It can occur after IV or IT-MTX. Treatment is supportive, and most patients can be successfully rechallenged. This uncommon presentation is an important consideration in that clinical symptoms, MRI findings, management, and prognosis may differ significantly from stroke. Residents and stroke fellows should be aware of this entity so as to avoid unnecessary diagnostic or therapeutic interventions such as fibrinolytics, unnecessary CT scans, or catheter angiograms.

**AUTHOR CONTRIBUTIONS**

R. Strowd: primary consulting neurology resident. Responsible for conceiving the case report, primary manuscript preparation, generation of figure, and final revision and approval of manuscript. M. Vishwas: primary consulting pediatric neurology resident. Responsible for manuscript preparation, revision, and approval. T.W. McLean: primary pediatric attending. Responsible for manuscript preparation, revision, and approval. A. Grefe: primary consulting neurology attending. Responsible for manuscript preparation, revision, and approval.

**REFERENCES**
