Dextromethorphan for Methotrexate Neurotoxicity:
Lessons from Pediatrics

A Case Report

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Background & Significance

- Presented is the report of an adult patient with leukemia who developed methotrexate-induced neurotoxicity (MTX-NTx) following intrathecal administration.
- Prompt resolution of neurotoxicity (as determined via encephalopathy) following a single dose of dextromethorphan (DXM) invokes compelling clinical considerations.
- Neurotoxicity is an uncommon though well-described following MTX administration in the treatment of childhood leukemias (Ashfar et al., 2014).
- Current literature is primarily restricted to the pediatric realm and involves scheduled, weight-based dosing.
- This case presents a unique situation with respect to both patient age and treatment via a single dose of dextromethorphan well below published regimens.
- Current mechanistic understanding supports methotrexate as an antifolate compound which inhibits production of dihydrofolate reductase, thereby limiting cancer cell synthesis and repair of DNA. Resultant accumulation of homocysteine is toxic to vascular endothelium, resulting in metabolites which are excitatory agonists of NMDA receptors (Dracthman et al., 2002; Quinn & Kamen, 1996). Figures 1 & 2 detail cases of MTX-NTx in pediatric patients.
- Dextromethorphan's non-competitive antagonism of the NMDA receptor is speculated to act in protective fashion (Vijayanathan et al., 2011; Fernández-Fernández et al., 2017; Bettachi et al., 1999) though additional pathways related to adenosine, biopterine, and homocysteine have been raised (Quinn & Kamen, 1996)

Case

- The patient is a 60-year-old Caucasian male presenting for their sixth cycle of R-HyperCVAD plus intrathecal MTX for treatment of ALL.
- On Day 1, the patient received methotrexate.
- The patient tolerated the regimen until the evening of Day 4, at which time they became disoriented and agitated.
- Psychiatry was consulted on Day 5, wherein clinical assessment was supportive of encephalopathy/delirium in keeping with the Confusion Assessment Method (CAM) algorithm.
- Supportive imaging was completed with both CTH w/o contrast and MRI brain w/ and w/o contrast showing no evidence of acute process in an otherwise unremarkable series.
- Given the temporal relationship of chemotherapy initiation and altered mental status, it was felt the principal causative agent existed with the current chemotherapy regimen.
- The consulting psychiatry team recommended a one-time dose of PO dexamethasone to be given at 1 mg/kg. This dosing was determined to be in keeping with previously published regimens in pediatric populations.
- Ultimately, the primary team administered a one-time dose of 60 mg DXM PO (a weight-based dosing of approximately 0.7 mg/kg). No rationale was provided as to the departure, although it was presumed secondary to ease of administration given the oral suspension existed in a form of 30 mg/5 mL.

Results

- The patient received the indicated DXM dosing on the evening of Day 6. They were reassessed by the consulting psychiatry team on the morning of Day 7, approximately 15 hours after receiving DXM.
- The patient was appreciated to have made significant improvement in mentation with only minimal evidence of lingering cognitive fatigue. The patient denied recollection of any events since Day 4 of their treatment. Bedside mental status examination was notable only for mild attentional deficits.
- The Confusion Assessment Method (CAM) diagnostic criteria for delirium were not met at this time.
- The patient was reassessed the morning of Day 8 and was again without alterations in mental status. Previously appreciated attentional deficits had resolved. No further adverse or unanticipated events were noted.
- The patient was discharged home on Day 8.
- Longitudinal observation during the following 18 months produced multiple episodes of demonstrated tolerability with administration of oral MTX. Intrathecal MTX has not been re-attempted.

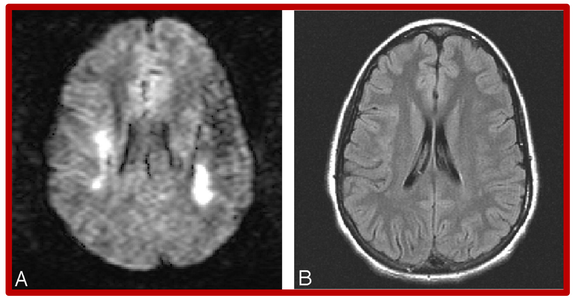

Figure 1. A pediatric patient presenting with nonfluent aphasia and bilateral UE weakness following intrathecal MTX administration. Image A is an axial DW image evidencing restricted diffusion in the centrum semioval accounting for the arm weakness. Image B is an axial FLAIR at 39 months s/p neurotoxicity showing minimal abnormal T2 signal intensity consistent with demyelination. Neurological deficits had resolved.

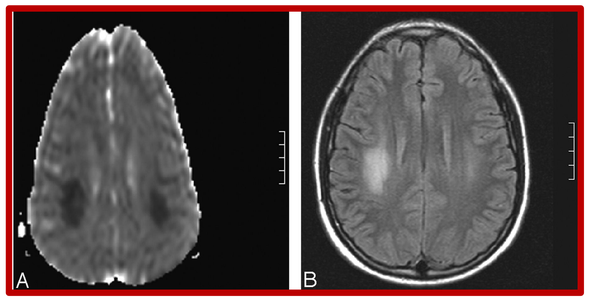

Figure 2. A pediatric patient presenting with nonfluent aphasia and left-sided hemiparesis/hemisensory loss. Image A is an axial ADC showing asymmetric areas of restricted diffusion in the centrum semiovale. The right-sided motor lesion correlated with left-side hemiparesis. Image B is an axial FLAIR imaged obtained eight weeks s/p neurotoxicity showing confluent areas of presumed demyelination in the right centrum semiovale. Neurological deficits had resolved.

Conclusions & Implications

- This case presents a unique circumstance in which an adult patient evidencing sub-acute MTX-NTx following intrathecal MTX administration displayed a robust response to a single administration of PO DXM at a dosing below published reports.
- This finding underscores the dearth of evidence in employing this treatment in the adult population. Such an outcome raises consideration of this intervention in the prevention and treatment of MTX-NTx across the age-span.
- Subsequent administration of PO MTX on later encounters raises consideration for a dose-response and/or administration-response relationship which may guide future chemotherapy regimens in cohorts of this patient.
- The utility of dextromethorphan may extend to treatments for other states of glutamatergic excess. Werling et al. reviews the utility of DXM in various CNS injury models (ischemia, seizure, TBI, etc.) and describes protection of dopamine neurons in Parkinsonian models, potentially secondary to inhibition of an inflammatory response.

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In-text:
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Figure:
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