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Severe, Fatal Methotrexate-related Neurotoxicity in 2 Adolescent Patients With ALL

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Summary:

Neurotoxicity is a well-documented adverse effect of methotrexate in the treatment of pediatric cancers. The spectrum of symptoms is broad, can include stroke-like episodes and seizures, and classically resolves within days. The majority of patients tolerate subsequent doses without recurrence of symptoms. The population of patients who experience persistent and irreversible neurological symptoms is poorly described, with the existing literature suggestive of a relationship with radiation therapy. The authors present a case series of 2 patients with pre-B-cell acute lymphoblastic leukemia who developed severe and ultimately fatal methotrexate-related neurotoxicity in the absence of radiation.

Keywords

methotrexate; neurotoxicity syndromes; pediatric; pre-cursor cell lymphoblastic leukemia-lymphoma

Oral, intravenous (IV) and intrathecal (IT) methotrexate (MTX) are essential medications in the treatment of many childhood malignancies, including acute lymphoblastic leukemia (ALL). MTX-related neurotoxicity is a well-documented adverse effect, despite leucovorin rescue. Between 3% and 15% of patients receiving MTX will develop neurotoxicity symptoms, with a highly variable presentation that can include altered mental status (AMS), seizures, and stroke-like episodes.¹ Episodes of neurotoxicity typically occur 3 to 11 days from the last dose of MTX and last minutes to days and typically resolve within 2 weeks.^{2,3} Patients who have neurotoxicity rarely have a recurrence of symptoms when rechallenged with MTX but rarely patients can develop recurrences and severe neurological deficits.^{4,5}

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The pathophysiology of MTX toxicity is largely unknown but is thought to be related to interrupted folate metabolism resulting in axonopathy and demyelination.^{6–8} Nonclinical signs of leukoencephalopathy include radiologically noted white matter changes or elevations in cerebrospinal fluid (CSF) homocysteine and excitatory neurotransmitters, which can also be seen in asymptomatic patients.^{9,10} The risk factors include age > 10 years, patients with high-risk ALL, higher cumulative number of IT doses, higher ratio of 42-hour plasma MTX concentration to leucovorin rescue, genetic polymorphisms, and concurrent radiation, the latter of which is thought to be due in part to increased permeability of the blood-brain barrier.^{1,2,11,12} In addition to supportive care, dextromethorphan (N-methyl-1-aspartate receptor antagonist) or aminophylline (adenosine receptor antagonist) have been utilized in the management of MTX-neurotoxicity.^{13,14}

Despite preventative measures, some patients develop severe MTX-related neurotoxicity that is unrecoverable.^{15–17} Although few adult studies do discuss severe and fatal MTX-related leukoencephalopathy without radiation,¹⁸ these cases are rare and infrequently described in the pediatric literature.^{4,5,17} In this case series, we present 2 female young adult patients with ALL who developed severe MTX-related neurotoxicity and leukoencephalopathy in the absence of radiation.

OBSERVATIONS

A retrospective review was conducted for 2 patients undergoing treatment for ALL who developed severe neurological compromise with simultaneous evolution of imaging consistent with MTX leukoencephalopathy. These patients were separated by several years and both treated at Children's Hospital Los Angeles in Los Angeles, CA.

To find comparable previously published cases, a literature review was conducted in February 2019 in PubMed. All English language papers containing “methotrexate” and MESH term “neurotoxicity syndromes” were reviewed (n = 81) and then inspected to ascertain whether they obtained information about irreversible deficits or death in the absence of radiation in pediatric patients aged 21 and under.

Case 1

A Hispanic female individual, diagnosed at age 15 with high-risk B-ALL, central nervous system no blasts, was treated on study per Children's Oncology Group (COG) protocol AALL1131. Her induction course was uneventful and she was found to be minimal residual disease negative. During cycle 4 of her maintenance therapy (age 17), without any previous neurological effects from methotrexate, 37 days from last IT dose and 3 days from last weekly oral dose, she developed fever and headache, progressing over 4 days to include auditory hallucinations, cranial nerve II–VI deficits, and vertigo with evolving changes on brain magnetic resonance imaging (MRI) (Fig. 1). Electroencephalogram showed diffuse slowing without evidence of seizure.

She was in the pediatric intensive care unit for 3 months with encephalitis progressing to static encephalopathy. Her infectious workup was notable only for rhinovirus positivity. MTX-neurotoxicity was made as a diagnosis of exclusion and on the basis of

consistent evolution of imaging findings (Fig. 1). Given the uncertainty of diagnosis, she received aminophylline, steroids, IVIG, plasmapheresis, and rituximab. After 2 months, neurological status progressed to using eye opening/closing, eyebrow raising, and speech cards to communicate, phenotypically resembling locked-in syndrome. She received a tracheostomy and gastrostomy tube. She remained on the pediatric floor for an additional 2 months for home-ventilation training and was discharged after a 5-month hospital stay. She died unexpectedly 11 days after discharge, with the exact cause of death unknown, but presumed to be progressive encephalopathy.

Case 2

A Hispanic female individual, diagnosed at age 20 with high-risk B-ALL, central nervous system < 5 leukocytes with blasts present, was initially treated on study per COG AALL1131. Her end of induction bone marrow was minimal residual disease negative at end-induction and cleared malignant cells from her CSF by her second lumbar puncture. On day 38 of induction, 9 days after last IT MTX, she presented with 45 minutes of AMS, manifesting as agitation, emotional lability, and phrase repetition. She retained a full recollection of the event. MRI showed left cortical vein thrombosis with underlying petechial hemorrhages in the left parietal lobe, yet it was unclear if these findings fully explained her global symptomatology.

On day 12 of her consolidation, 12 days from last dose of IT MTX, she re-presented with a 3-hour episode of headache, aggression, and emotional lability. She improved and was discharged after an 8-day stay without a clear understanding of the underlying cause after repeat MRI was unchanged from prior. She tolerated her next 3 weekly doses of IT MTX well.

During Interim Maintenance I, 11 days from the last IT MTX and high-dose IV MTX (5000 mg/m²/dose) with standard leucovorin rescue, level monitoring, and clearance and 45 days postdischarge from prior admission, she re-presented with fever, headache, and diffuse tingling. Three days later, she developed roving eye movements, slurred speech, and ataxia and had subsequent evolution of her MRI (Fig. 2). Initial electroencephalogram showed diffuse slowing without evidence of seizure.

She was in the pediatric intensive care unit for 2 months with encephalopathy. Her infectious workup was negative. MTX-related encephalopathy was made as a diagnosis of exclusion and on the basis of the evolution of MRI findings. She received antimicrobial therapy, dextromethorphan, and aminophylline without improvement. Her intensive care unit course was complicated by dystonia, dysautonomia, respiratory failure, tube feeding dependence, and pneumonia. She required mechanical ventilation for 1 month. She did not experience neurological recovery. With a focus on comfort care, she died from the progression of encephalopathy after an almost 3-month hospital stay.

CONCLUSIONS

Several similarities are noted in the 2 cases. Both patients were young adult female individuals undergoing treatment for high-risk B-ALL. Both were of Hispanic origin, which

has been suggested to be linked to a genetic predisposition.¹⁹ In addition, they both presented with fever and headache before developing AMS. Although the timing from the last dose to the onset of symptoms falls within the expected window for patient 2, it is weeks outside the expected window for patient 1. However, patient 1 was receiving weekly oral MTX during maintenance therapy, and rare cases of severe neurotoxicity and leukoencephalopathy have been reported in patients with rheumatoid arthritis receiving oral MTX alone.^{20,21} Patient 2 presented with recurrent psychiatric symptoms before the onset of severe encephalopathy, however, had imaging at that time not suggestive of MTX-related leukoencephalopathy. A potential explanation may be a concurrent unrecognized infectious etiology with a simultaneous appearance of MTX leukoencephalopathy on imaging, yet the clinical course and evolution of MRI images make this seem unlikely.

At this time, definitive criteria do not exist to characterize the acute radiographic changes of MTX-related neurotoxicity. However, it is generally accepted that MRI imaging should demonstrate transient diffuse high signal intensity changes in the white matter on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging.²² It is also notable that transient restricted diffusion is a feature found along multiple vascular territories involving the deep cerebral white matter.¹ In 2 separate case series, restriction diffusion abnormalities were acutely found either in the frontoparietal or frontal lobe regions.^{1,17} In both studies, follow-up MRI showed resolved diffusion-weighted imaging changes with small residual T2-weighted and FLAIR changes. Given the previously described findings in pediatric patients who experienced MTX-related neurotoxicity, the acute radiographic changes and time course of the 2 patients we have described are consistent with the diagnosis.

Although most patients with MTX-related neurotoxicity improve, our case series may be helpful to provide clinical guidance in similar cases of severe toxicity. When placed in the context of existing documented cases of persistent methotrexate neurotoxicity (Table 1), these 2 patients again demonstrate that symptoms, once beyond the anticipated recovery period, are unlikely to resolve. Unlike previously reported cases, these 2 patients died within months of the onset of symptoms, with the cause of death thought to be linked to sequelae of their neurotoxicity. These cases support that pediatric patients can develop severe MTX-related neurotoxicity in the absence of radiation and may prove helpful in prognostication of long-term recovery when symptoms persist beyond the anticipated recovery period of 2 weeks.

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FIGURE 1.

Case 1, a 15-year-old Hispanic woman being treated for pre-B-ALL CNS 1, developed a headache, diplopia, and fever 37 days following an ITT dose of MTX. Four days into her symptoms, she developed hallucinations, CN II–VI deficits, and vertigo. A brain MRI demonstrated diffuse abnormal T2-weighted and FLAIR hyperintensities within the white matter of the frontal and parietal lobes bilaterally (A), within the splenium of the corpus callosum, and the periventricular white matter. There was notable restriction diffusion within the dorsal pons, medulla, superior colliculi, and midbrain (B). Three weeks into her symptoms, there had been interval progression of symmetric signal abnormality involving the frontoparietal regions (C), and progressive involvement of the deep white matter and

gray nuclei (D). Fifty-six days into symptoms, the restriction diffusion signals had resolved on MRI, with progressive T2/FLAIR changes within the deep structures, brainstem and proximal cervical spine (E). ADC indicates apparent diffusion coefficient; ALL, acute lymphoblastic leukemia; CN, cranial nerve; CNS1, central nervous system no blasts; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; ITT, intrathecal triple therapy; MRI, magnetic resonance imaging; MTX, methotrexate.

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FIGURE 2.

Case 2, a 20-year-old Hispanic woman being treated for pre-B-ALL CNS2 developed altered mental status 9 days after the last dose of ITT MTX during induction chemotherapy. She developed agitation, inappropriate laughter, and full-body paresthesias. An MRI showed bilateral restricted diffusion in the centrum semiovale and left precentral regions without associated T2/FLAIR hyperintensities initially (A). Five days later, she demonstrated progressively restricted diffusion within the centrum semiovale (B). A repeat MRI 28 days into her symptoms showed extensive T2/FLAIR changes in the corona radiata and centrum semiovale of both cerebral hemispheres, with no evidence of restricted diffusion (C). ADC indicates apparent diffusion coefficient; ALL, acute lymphoblastic leukemia; CNS2, central

nervous system < 5 leukocytes with blasts present; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; ITT, intrathecal triple therapy; MRI, magnetic resonance imaging; MTX, methotrexate.

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TABLE 1.
Pediatric Cases of Persistent Methotrexate Neurotoxicity in the Absence of Radiation

Patient No.	Diagnosis	Age (y)	Sex	Therapy Protocol	Days since IT MTX	Stage of Therapy	Initial Physical Findings	Treatment	Persistent Deficits
1	ALL	17	F	Per COG AALL1131	37	Maintenance cycle 4	Auditory hallucinations, cranial nerve deficits, respiratory distress requiring ventilation	Antimicrobials aminophylline steroids IVIG plasmapheresis rituximab	Quadriplegia, ventilator dependence
2	ALL	20	F	Per COG AALL1131	11	Interim maintenance	Confusion, disinhibition, tingling, slurred speech, ataxia, respiratory distress requiring ventilation	Antimicrobials, dexamethorphan, aminophylline	Encephalopathy
3	ALL	17	M	UKALL2003	6	Consolidation	Disorientation, agitation, dysphasia	Antimicrobials	Deficit in executive functioning (particularly word processing)
4	ALL	14	F	UKALL2003	6	Consolidation	Quadripareisis, aphasia, respiratory distress requiring ventilation	Aminophylline folinic acid	Quadriplegia and dysarthria
5	ALL	17	M	UKALL2003	8	Consolidation	Arm monoparesis, confusion, aphasia	Anticonvulsants Antimicrobials	Persistent impairment in short-term memory and ataxia
6	ALL	7	F	CoALL 08-09	4	Induction	Somnolence, respiratory distress requiring ventilation, impaired speech, and motor function	Antimicrobials antifungals antivirals folinic acid aminophylline	Persistent limitations in cognitive function

Patients 1 and 2 reflect the patients in this series reflecting cases 1 and 2, respectively, and patients 3 to 5 reflect the survey findings from Bond et al.⁴ in the UKALL-2003 trial, and patient 6 obtained from Löbel et al.⁵ Of note, patient 6 received nitrous oxide during her intrathecal methotrexate administration and this was felt by the author to be a possible contributing factor.

ALL indicates acute lymphoblastic leukemia; IVIG, intravenous immunoglobulin.