Methotrexate-induced Leukoencephalopathy: A Rare but Life-threatening Toxicity

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ABSTRACT

Methotrexate (MTX), an anti-metabolite, is part of various chemotherapy regimens to treat acute lymphoblastic leukemia (ALL) and certain non-Hodgkin's lymphomas (NHLs). It is the major drug used in central nervous system (CNS) prophylaxis. Besides, its common hepatic, pulmonary, and hematologic toxicities, it has been implicated in the development of toxic leukoencephalopathy. Here, we present a case of a 19-year female, diagnosed with T-ALL. She was managed with UK ALL 2011 regimen B induction as a standard of care and intrathecal MTX as CNS prophylaxis. She tolerated induction well; however, during the second block of consolidation, she started developing lower limb weakness, inability to stand, unilateral weakness and aphasia. Her condition worsened rapidly over the next 24 hours leading to paraplegia and ultimately quadriplegia. Within 48 hours from onset of symptoms, she had lost all her motor functions, potentially leading to impending apnoea. We placed her on mechanical ventilation. MRI brain showed drug (MTX)-induced leukoencephalopathy (LE).

In most cases, recovery starts within 5-7 days and by the 3rd week, majority have usually recovered. However, cases of irreversible neurologic damage and late-onset chronic toxicities have been reported.

Key Words: *Methotrexate, Leukoencephalopathy, Chemotherapy, Leukemias.*

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INTRODUCTION

Methotrexate is an anti-metabolite with anti-inflammatory and anti-leukemic activity. It makes an integral part of chemotherapeutic regimens in acute lymphoblastic leukemia (ALL) and certain non-Hodgkin's lymphomas (NHLs). Myelotoxicity, pulmonary fibrosis and hepatic derangement are its well-known adverse effects. Neurotoxicity, in the form of acute leukoencephalopathy (LE) or chronic neurotoxicity, is a less understood but established complication of high-dose intravenous MTX and intrathecal MTX.[1]

The reported incidence of MTX-induced leukoencephalopathy (LE) varies from 0.5% to 3%. Common clinical presentations include transient stroke-like symptoms, visual disturbances, and aphasia. These symptoms frequently follow a waxing and waning pattern. Characteristic radiologic findings include a diffuse high signal in centrum semiovale and deep white matter on MRI T2 and FLAIR sequences. Treatments with folinic acid, dextromethorphan, aminophylline, and methylprednisolone are effective in the management of MTX-induced LE.[2]

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Here, we present a case of an adolescent girl who had potentially life-threatening experience owing to MTX-induced LE, followed by a curated literature review of the clinical features, diagnosis and treatment of MTX-induced LE, and its implications for further chemotherapy.

CASE REPORT

A 19-year female presented with a 2-week history of menorrhagia, fever and easy fatigability. Apart from mild pallor, her physical examination was unremarkable. Initial investigations revealed pancytopenia with few atypical lymphoid cells on peripheral smear. With the suspicion of acute leukemia, we did a bone marrow examination, which showed 55% lymphoid blast cells. Immunophenotyping confirmed the diagnosis of T-cell ALL. The cerebrospinal fluid (CSF) analysis did not show evidence of central nervous system (CNS) involvement. We started induction chemotherapy as per the UK ALL 2011 recommendations. Three weeks into induction chemotherapy, there was a change in her behaviour. There were episodes of low mood, crying spells, and emotional apathy alternating with agitated behaviour, anxiety, and low-frequency fine tremors of upper limbs. However, she did not lose consciousness or develop any focal neurological deficit. We documented no seizure activity. Considering the high doses of steroids administered in induction chemotherapy, steroid-induced psychosis was suspected. She was placed on anti-psychotic and anxiolytics by psychiatrists and neurologists. The patient responded to treatment with an improvement of symptoms. Her post-induc-

tion bone marrow examination showed successful remission induction.

The Berlin, Frankfurt, Muenster (BFM) consolidation protocol was started on schedule. On day-13 of consolidation chemotherapy, she started complaining of headache with no associated vomiting, visual disturbance, or other focal deficit. Since the patient had received asparaginase as part of induction chemotherapy, we did CT brain to rule out thrombotic complications associated with asparaginase. However, CT brain was normal. Over the next 24 hours, left-sided body weakness developed with the power of 2/5 as per MRC grading in the upper limb and upgoing planters with a Glasgow coma scale (GCS) of 15/15. Consolidation chemotherapy was discontinued, and we performed an urgent magnetic resonance imaging (MRI) brain. She regained power in her left limbs to 5/5 in the next 12 hours and could ambulate without support. However, she redeveloped neurological deficit over the next 12 hours affecting all the four limbs, leaving patient-quadriplegic, with power below 2/5. CSF examination showed normal chemistry and cytology. MRI brain showed abnormal non-enhancing subtle T2W hyperintense areas involving bilateral centrum semiovale regions and showing restricted diffusion on diffusion-weighted images (DWI)/ADC mapping, findings consistent with the diagnosis of MTX-induced LE. The patient had received five doses of intrathecal MTX and the last intrathecal dose was given 13 days before the onset of the symptoms.

We managed her with intravenous folinic acid, methylprednisolone and oral dextromethorphan. Her condition worsened with GCS dropping to 7/15, requiring mechanical ventilation. She was placed on mechanical ventilation and successfully weaned off after 15 days. The patient experienced multiple episodes of tonic-clonic seizures during that time. Her condition improved gradually over the next one week and she was discharged subsequently. At her discharge from the hospital, she was fully alert and oriented. Power in both the upper limbs was 4/5, and 3/5 in lower limbs. Administration of intrathecal MTX was withheld. She is on maintenance chemotherapy with 6-mercaptopurine and vincristine, and is tolerating chemotherapy well.

DISCUSSION

LE is a structural alteration of cerebral white matter affecting the myelin sheath, which can result from infections, toxins and cranial irradiation. Combination of high dose intravenous with intrathecal MTX is a known cause of toxic LE. Rarely, LE is reported with long-term intake of low-dose oral MTX for rheumatoid arthritis.[2] Symptomatic toxic LE because of MTX has been reported in up to 3% of the patients receiving high dose MTX or intrathecal MTX.[3] The incidence varies with the dose, route and frequency of drug administration; risk factors being high dose treatment, intrathecal route, age over 10 years or less than 60 years, and concomitant or prior cranial irradiation.[4,5] Germline polymorphisms in variants of certain genes including GSTP1, 17 MTHFR, and SHMT1 may contribute to the development of MTX-induced neurotoxicity.[5] Neurotoxic manifestations of MTX may be acute, sub-acute or chronic. Acute LE mostly occurs within 2-14 days of drug administration. Initial symptoms may be non-specific like headache, nausea and vomiting, which are followed by transient stroke-like symptoms including hemiparesis or paraparesis, visual disturbances and aphasia. Inaba *et al*. described a series of cases in which emotional lability ranging from inappropriate laughter to unprovoked crying, anxiety, and unresponsiveness was the presenting clinical feature.[6] Our patient had developed similar mood changes during induction chemotherapy, which were mistaken for steroid-induced mood changes. Though, no radiographic evidence is available from that time, it is plausible to assume these too may have been due to LE. An interesting feature of MTX-induced LE is the waxing and waning nature of symptoms. As in our patient, hemiplegia recovered in 12 hours but recurred in the next 24 hours. This resolves completely or partially ranging from few hours to days, only to recur on the same side or opposite side of the body.[7] Recovery frequently occurs in 5-7 days.[8]

In a relevant clinical setting, the above-mentioned clinical presentations coupled with characteristic radiologic findings should suffice to make a confident diagnosis. While findings on CT scan are non-specific, MRI provides vital information. Diffuse high signal in centrum semiovale and deep white matter are commonly seen on T2 and FLAIR sequences. Findings on DWI are more specific, which show restricted diffusion across multiple vascular territories in the centrum semiovale, either unilateral, bilateral, or alternating, that eventually disappear after symptom resolution.[6,9] The radiologic findings in our case were straightforward. Doan *et al*., however, have described a case where MRI failed to show typical DWI signals; and they confirmed the diagnosis on magnetic resonance spectroscopy (MRS).[10]

Regarding prognosis of acute LE, many case reports and small case series have shown clinical recovery of LE ranging from 1 to 21 days after onset of the symptoms. However, long-term follow-up studies to monitor for resolution and study the impact of LE on long-term adverse effects, especially neurocognitive functioning, are lacking. Chronic neurotoxicity is reported, ranging from several months to years after MTX therapy, characterised by a slow progressive cognitive deterioration, seizure, ataxia, spasticity or coma. These neurologic deficits are irreversible.[5] Another observation has been the appearance of typical radiologic features in a significant proportion (20-70%) of asymptomatic patients who have received four or more doses of intrathecal MTX.[5] The clinical significance of this asymptomatic LE and the tendency to progression to symptomatic LE is unclear.

Whether patients who have recovered from MTX-induced LE should be given intrathecal MTX re-challenge in further chemotherapy cycles is debated. Balancing the risk of primary disease relapse *versus* the potential recurrence of neurologic symptoms with further therapy is probably best decided on case-to-case basis. The rate of recurrence has been reported

between 10-56%.[5] Many authors have reported successful resumption of MTX therapy after resolution of LE, with few reporting using a lower MTX to leucovorin (folinic acid) ratio and/or aminophylline as prophylaxis.[5] Our patient has not received further doses of intrathecal MTX so far, as she is still having a residual neurologic impairment and the family's unwillingness for intrathecal MTX.

We should keep MTX-induced LE in the differential diagnosis of a patient who has received high dose MTX or intrathecal MTX, and presents with neurologic symptoms mimicking stroke. MRI with DWI provides valuable information regarding diagnosis and early management. LE is reversible and frequently resolves within one to three weeks. Continuation of MTX therapy after resolution of symptoms may cause recurrence, but has been done successfully in some reported cases.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
FH, JR: Manuscript writing.
QUC, SKM, TG: Senior supervisors in overall case management.

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