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Methotrexate-Induced Subacute Neurotoxicity Surrounding an Ommaya Reservoir in a Patient with Lymphoma

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 21
Final Diagnosis: Methotrexate induced neurotoxicity
Symptoms: Dysarthria • hemiparesis
Medication: Methotrexate
Clinical Procedure: —
Specialty: Hematology

Objective: Challenging differential diagnosis

Background: Intraventricular administration of methotrexate (MTX) using an Ommaya reservoir is a useful therapeutic maneuver for malignant CNS involvement in patients with hematological malignancies. MTX-induced subacute neurotoxicity is a rare complication that typically progresses with involvement of the basal ganglia. Local toxicity due to misplaced catheters has been described, although the impact of normally positioned catheters on toxicity is not clear.

Case Report: We report the case of a 21-year-old man diagnosed with stage IV diffuse large B-cell lymphoma who experienced a central nervous system relapse. While receiving intraventricular MTX using an Ommaya reservoir and systemic MTX, he experienced sudden left-side hemiparesis. All diagnostic tests were negative except for altered MRI findings with FLAIR hyperintensity in the basal ganglia and restricted diffusion in the same location that followed the track of the Ommaya catheter. The syndrome resolved after administration of high-dose steroids, and the patient received subsequent MTX courses without recurrence.

Conclusions: MTX-induced neurotoxicity is a rare adverse event related to systemic and intrathecal administration of the drug. Many cases of Ommaya-related CNS symptoms have been described, although most were related to misplaced or malfunctioning catheters. Here we present a case of subacute MTX toxicity affecting the area around a correctly positioned catheter, suggesting that the catheter track could be more susceptible to MTX-induced toxicity.

MeSH Keywords: Keywords: Lymphoma, B-Cell • Lymphoma, Large B-Cell, Diffuse • Methotrexate • Paralysis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/915632

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Background

Intraventricular administration of methotrexate (MTX) using an Ommaya reservoir is a useful therapeutic maneuver for malignant CNS involvement in patients with hematological malignancies. MTX-induced subacute neurotoxicity is a rare complication that typically progresses with involvement of the basal ganglia. Local toxicity due to misplaced catheters has been described, although the impact of normally positioned catheters on toxicity remains unclear. Here, we report a rare presentation of MTX-induced neurotoxicity affecting the area around a correctly placed Ommaya reservoir.

Case Report

A 21-year-old man was diagnosed with ABC-type diffuse large B cell lymphoma (DLBCL) with involvement of the bone marrow, spleen, and skin and a poor Revised International Prognostic Index score (4 points). Immunohistochemistry showed that the lymphoma cells expressed BCL-2 and BCL-6, and FISH revealed BCL-6 rearrangement.

The patient received 4 R-Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone plus rituximab) with 3 alternating courses of rituximab plus MTX/Ara-Ca. The PET-CT performed at the end of treatment revealed a complete metabolic response. Three months later, the patient presented with III left cranial nerve palsy, isolated leptomeningeal relapse, and cerebrospinal fluid (CSF) involvement. He received a course of high-dose (HD) MTX (3 g/m^2 on day 1) and 1 course of intrathecal chemotherapy (MTX 12 mg, Ara-C 30 mg, hydrocortisone 20 mg). An Ommaya reservoir was placed for further chemotherapy on day 5, and a further 2 intraventricular chemotherapy courses were administered on days 6 and 9. CSF was successfully cleared (negative flow cytometry) after the first course of chemotherapy. Symptoms resolved during the first 48 hours after chemotherapy started, and the patient was successfully discharged on day 9. On day 20 after the relapse, he received a course of R-ICE (ifosfamide, carboplatin, and etoposide plus rituximab) for stem cell chemomobilization with granulocyte colony stimulating factor, which resulted in failure of mobilization. He continued receiving weekly intraventricular chemotherapy on days 16 and 23.

On day 25 after diagnosis, he developed vague symptoms such as general malaise and drowsiness. Forty-eight hours after the onset of symptoms, he presented left hand clumsiness that quickly progressed to complete left-side hemiparesis of the upper and lower extremities and left side of the face accompanied by dysarthric speech. He remained temporally and spatially oriented. CSF analysis revealed no malignant infiltration, normal glucose and protein levels, and 5 leukocytes/HPF in the setting of pancytopenia. The patient started broad-spectrum antibiotics, although these discontinued early after an extensive work-up for infectious processes proved negative. Urgent cranial CT and angio-CT revealed no pathological findings.

Conventional MRI the following day showed new lesions with mild hyperintensity on FLAIR sequences in the white matter at the right *centrum semiovale* and *corona radiata*, with marked restricted diffusion at the same site in the apparent diffusion coefficient (ADC) map and extension to juxtacortical frontal white matter and the cingulate gyrus (Figures 1–3). The T1 sequence revealed no lesions. These findings were more intense along the track of the Ommaya reservoir without contrast enhancement. The catheter was correctly placed, and there was no liquid reflux surrounding it. HD dexamethasone was initiated owing to an initial suspicion of disease progression. Symptoms resolved during the following 24 hours with no neurological sequelae. He continued his scheduled MTX-containing intraventricular and systemic chemotherapy without further recurrence of symptoms. A control MRI performed 15 days after resolution showed normalization of the restricted diffusion in the ADC map, with more prominent white substance lesions and hyperintensity in FLAIR and T2 and hypointensity in T1. Finally, the patient underwent haploidentical stem cell transplantation with post-transplant myeloablative cyclophosphamide as prophylaxis for GvHD. One year after the onset of symptoms, engraftment has proven successful, and the patient is asymptomatic and in complete remission.

Discussion

MTX is an antimetabolite drug that inhibits the enzyme dihydrofolate reductase, thus preventing conversion of folic acid to tetrahydrofolic acid and impairing DNA synthesis. MTX is widely used for the treatment of multiple hematologic malignancies and constitutes the hallmark of prophylaxis and treatment of acute lymphoblastic leukemia and aggressive lymphomas at risk of CNS involvement [1] thanks to its ability to cross the blood-brain barrier [2]. It can be administered intrathecally, orally, or intravenously. Doses >500–1000 mg/m^2 are usually defined as HDMTX [2,3].

Myelosuppression, mucositis (especially oral mucositis), nephrotoxicity, hepatotoxicity, and neurotoxicity [2,4] are well-known side effects of MTX.

Neurotoxicity has been described in up to 15% of HDMTX courses [4]. Clinical manifestations are various, and patients frequently report transient CNS disturbances that can be significant in some cases. Significant MTX-induced neurotoxicity is rare (only 2-3.8% of patients) [4–7]. Intrathecal administration, and Ommaya reservoirs in particular [8], are often described

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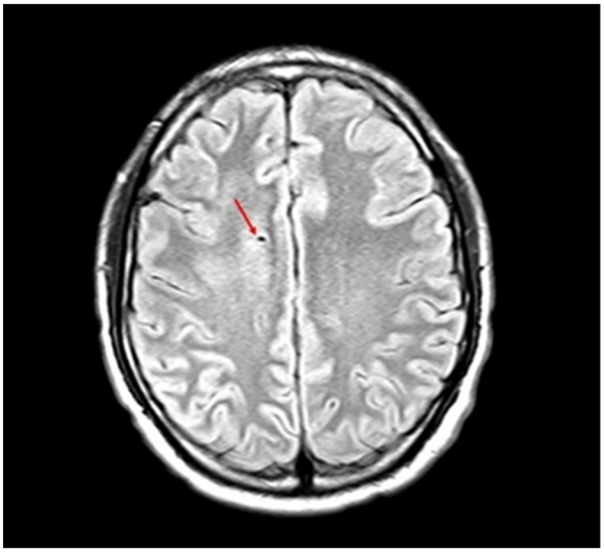

Figure 1. FLAIR sequence showing mild hyperintensity in the *corona radiata* (area surrounding the track of the intraventricular catheter).

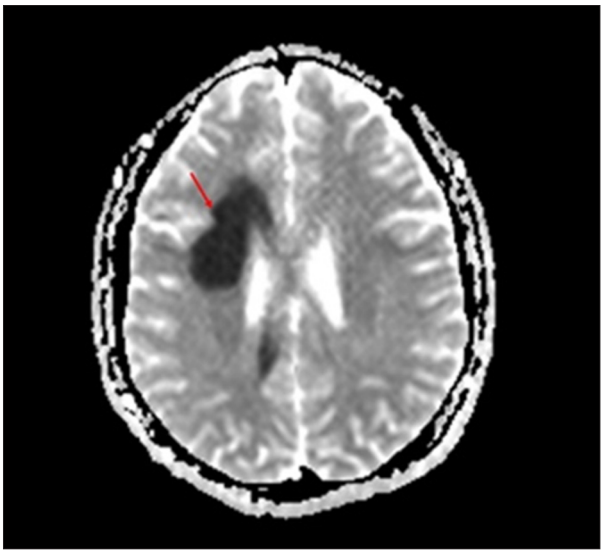

Figure 2. Diffusion ADC map showing intense restricted diffusion (black) in the *corona radiata*.

as risk factors for MTX-induced neurotoxicity. It is noteworthy that the patient we report developed the radiological lesion in the area surrounding the Ommaya catheter (Figures 1–3). Two main patterns of CNS symptoms have been described: acute-subacute MTX neurotoxicity with symptoms mimicking strokes, and chronic MTX leukoencephalopathy. Headache, seizures, and acute stroke-like symptoms are the most frequent subacute clinical manifestations of MTX-induced toxicity, with the clinical course ranging from hours to a few days (48–72 hours) and spontaneous resolution without significant sequelae [4,9]. The hypotheses to explain this clinical behavior include release of adenosine (which impacts vasodilatation

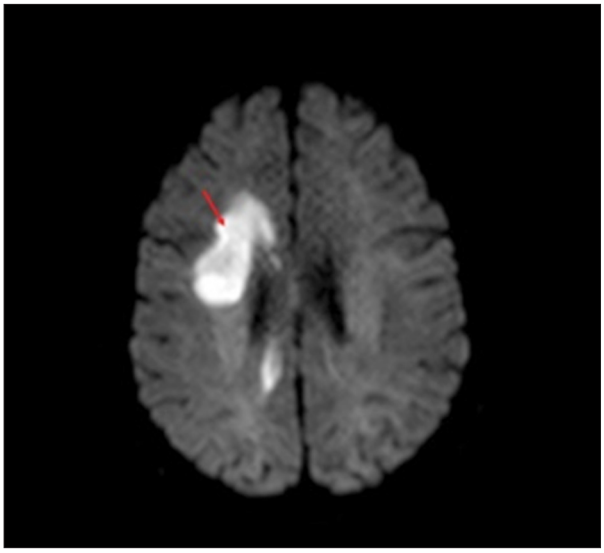

Figure 3. Diffusion-weighted image showing intense restricted diffusion (white) in the *corona radiata*.

with impaired release of neurotransmitters [10]), metabolic derangements associated with folate and homocysteine levels [11], and cytotoxic edema. Nevertheless, in patients with acute/subacute MTX-induced neurotoxicity, repeated doses of MTX do not seem to worsen the symptoms. In the present case, symptoms improved quickly after administration of dexamethasone and did not reappear with subsequent administration of intraventricular chemotherapy. Chronic MTX-related leukoencephalopathy is more common, with series reporting incidences of up to 23% [4]. The disease usually has an asymptomatic course, although the characteristic clinical feature is gradual impairment of cognitive function months after MTX treatment. In many cases, withdrawal of MTX helps to stabilize or improve symptoms, although in some cases it can lead to severe disability [12].

MRI has become the main diagnostic imaging technique in MTX-induced toxicity. While conventional MRI (T1, T2, or FLAIR sequences) is often normal, at least at the beginning of the process, diffusion-weighted imaging is much more sensitive at the onset of MTX-induced neurotoxicity, showing restricted diffusion in the white matter and low ADC values, typically in the periventricular white matter and *centrum semiovale*. In addition, the finding is commonly congruent with the neurologic event [13]. The patient we report developed similar lesions surrounding a well-placed catheter. The often complete resolution of the patient's clinical manifestations contrasts with this finding, as restricted diffusion is usually related to irreversible injury (acute ischemia, neoplasia), thus suggesting some level of cytotoxic edema. Subsequent MRI scans tend to show hyperintense abnormalities in the FLAIR sequence, with normal ADC values, thus suggesting demyelinization and/or gliosis [14].

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There is no established or successful treatment for this event, although it is often treated with aminophylline (a competitive adenosine antagonist) or a single leucovorin rescue dose 24 hours after MTX outcome is poor [9]. Since most patients receive subsequent HDMTX or intrathecal MTX without recurrence of neurotoxicity, discontinuation is not frequently required [4]. Adequate supportive care with folinic acid rescue remains crucial for prevention of MTX-induced toxicity. The patient received 2 subsequent intraventricular doses of MTX with chemotherapy and another high-dose MTX course without recurrence of symptoms, although systemic chemotherapy had to be discontinued owing to prolonged pancytopenia. He subsequently underwent myeloablative stem cell transplantation and is now in complete remission.

Conclusions

Acute/subacute neurotoxicity is a rare complication in patients receiving MTX. MRI with highly restricted diffusion is almost diagnostic and should be performed in any patient presenting with neurological disturbances during treatment with MTX. Local factors such as intraventricular catheters, even when correctly placed and functioning normally, should be taken into account as possible predisposing factors in this condition. The process usually resolves spontaneously, and subsequent administration of MTX is generally safe.

Department and Institution where work was done

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Conflicts of interest

None.

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