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Acute Methotrexate-Induced Neurotoxicity Mimicking Stroke in an Adult: A Case Report and Literature Review

Laalj Karim[1*], El Goubi Manal[1], Moussaoui Mohammed[2]

[1]Resident in Anesthesia and Intensive Care, Cheikh Khalifa University Hospital, Morocco
[2]Professor of Higher Education, Cheikh Khalifa University Hospital, Morocco

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***Corresponding author:** Laalj Karim
Resident in Anesthesia and Intensive Care, Cheikh Khalifa University Hospital, Morocco

Abstract | **Case Report**

Background: Methotrexate (MTX) is widely used in the treatment of malignancies and autoimmune diseases. Although generally well tolerated, neurotoxicity represents a rare but potentially serious adverse effect, with presentations ranging from mild encephalopathy to focal neurological deficits mimicking acute ischemic stroke. ***Case Presentation***: We report the case of a 67-year-old man with rheumatoid arthritis treated with methotrexate who presented with acute onset left-sided hemiplegia and dysarthria. Initial clinical suspicion was ischemic stroke. Brain magnetic resonance imaging (MRI) demonstrated findings consistent with toxic leukoencephalopathy. Methotrexate was discontinued, and folinic acid rescue with supportive intensive care management was initiated, resulting in progressive neurological recovery. ***Discussion***: Methotrexate-induced neurotoxicity remains poorly understood and is likely multifactorial, involving folate pathway disruption, homocysteine-mediated excitotoxicity, adenosine accumulation, and direct white matter injury. Advanced age, renal dysfunction, and impaired drug clearance are recognized risk factors. Diffusion-weighted MRI plays a central role in diagnosis by revealing characteristic reversible white matter lesions. Management is primarily supportive, with early drug withdrawal and folinic acid supplementation. Adjunctive therapies such as aminophylline and dextromethorphan have been described in selected cases. ***Conclusion***: Methotrexate-induced neurotoxicity should be considered in patients presenting with acute neurological deficits during methotrexate therapy. Early recognition, appropriate neuroimaging, and prompt supportive management are essential to prevent permanent neurological sequelae.

Keywords: Methotrexate, Neurotoxicity, Intensive care, Stroke mimic, Case report.

INTRODUCTION

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, thereby interfering with folate metabolism and DNA synthesis. It is extensively used in high doses for the treatment of hematological malignancies and in lower doses for chronic inflammatory diseases such as rheumatoid arthritis and psoriasis [1]. Common adverse effects include gastrointestinal toxicity, hepatotoxicity, and bone marrow suppression. Neurotoxicity, although rare, represents a potentially serious complication [2].

Methotrexate-induced neurotoxicity has been described following high-dose, intrathecal, and, more rarely, low-dose oral administration [3]. Clinical manifestations include acute encephalopathy, seizures, cognitive impairment, and focal neurological deficits, often resembling acute ischemic stroke [4]. This stroke-like presentation poses a major diagnostic challenge, particularly in emergency and intensive care settings, where rapid therapeutic decisions are required.

We report a case of acute methotrexate-induced neurotoxicity presenting with focal neurological deficits in an adult patient treated for rheumatoid arthritis and review the current literature regarding mechanisms, risk factors, imaging findings, and management.

CASE PRESENTATION

A 67-year-old man with a history of rheumatoid arthritis treated with methotrexate was admitted to the intensive care unit for acute onset of left-sided hemiplegia and dysarthria. There was no history of trauma, seizure activity, fever, or infectious symptoms. On neurological examination, the patient was conscious

and oriented but exhibited marked left-sided motor weakness and slurred speech.

Initial evaluation strongly suggested an acute ischemic stroke. Non-contrast brain CT performed at admission showed no evidence of intracranial hemorrhage or established ischemic infarction (Figure 1). Due to persistence of neurological deficits and the absence of radiological evidence of stroke, further neuroimaging was performed. Follow-up imaging revealed bilateral subcortical hypodensities involving the white matter, not corresponding to a specific vascular territory, consistent with toxic leukoencephalopathy (Figure 2).

During the intensive care stay, the patient developed respiratory symptoms requiring further evaluation. Chest radiography demonstrated bilateral diffuse pulmonary opacities (Figure 3). Methotrexate was immediately discontinued. Folinic acid rescue therapy and supportive intensive care management, including hydration and close neurological monitoring, were initiated. Progressive neurological improvement was observed over the following days, with partial recovery of motor function and speech.

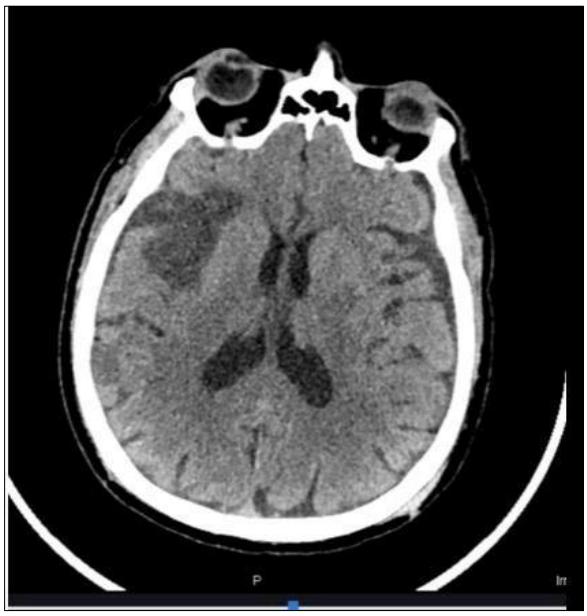

Figure 1: Initial brain CT scan (at presentation)

Non-contrast axial brain computed tomography demonstrating no acute intracranial hemorrhage or established territorial ischemic infarction.

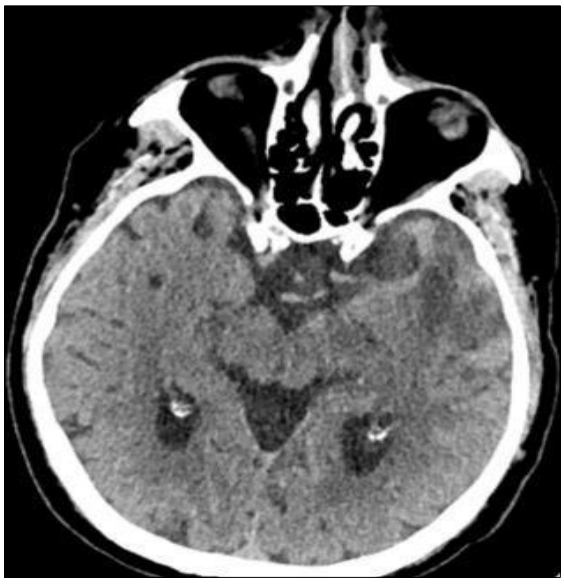

Figure 2: Follow-up brain CT scan

Axial brain computed tomography showing bilateral subcortical hypodensities involving the white matter, not conforming to a vascular territory, compatible with toxic leukoencephalopathy in the context of methotrexate-induced neurotoxicity.

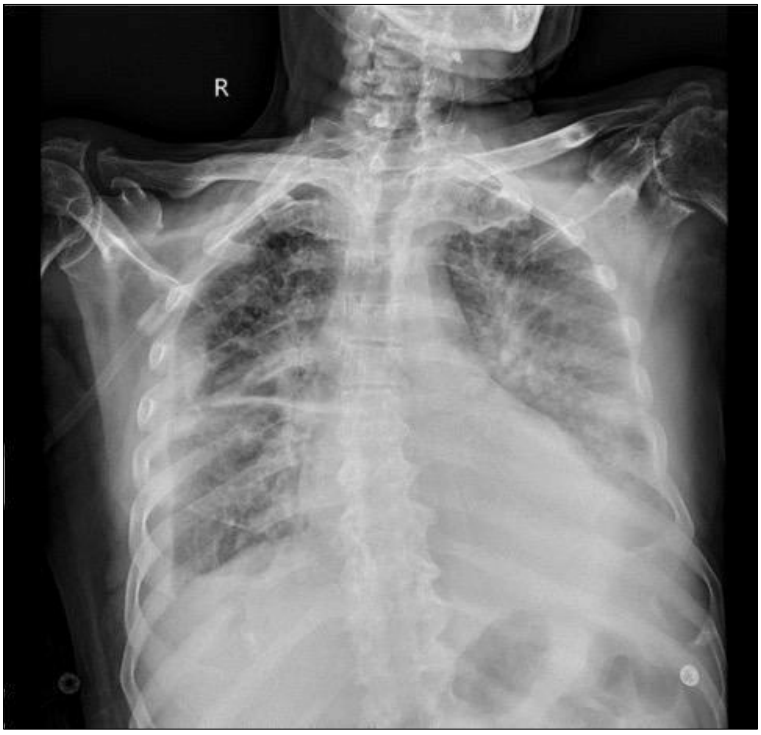

Figure 3: Chest X-ray during ICU stay

Anteroposterior chest radiograph demonstrating bilateral diffuse pulmonary opacities consistent with acute respiratory involvement during intensive care management.

DISCUSSION

Methotrexate-induced neurotoxicity is an uncommon but clinically significant adverse effect. It has been reported in approximately 3–10% of patients receiving high-dose or intrathecal methotrexate and more rarely in those treated with low-dose oral therapy for inflammatory diseases [3-5]. The clinical spectrum is wide and includes headache, confusion, seizures, cognitive disturbances, and focal neurological deficits [4].

Risk Factors

Several risk factors have been identified, including high cumulative or peak methotrexate dose, renal dysfunction, dehydration, folate deficiency, advanced age, and concomitant neurotoxic therapies [6]. In the present case, advanced age and possible impaired methotrexate clearance may have contributed to neurotoxicity despite conventional dosing. This observation highlights that methotrexate neurotoxicity is not restricted to oncological regimens and may occur in patients treated for autoimmune diseases.

Pathophysiology

The pathophysiological mechanisms underlying methotrexate-induced neurotoxicity remain incompletely understood and are likely multifactorial. Methotrexate inhibits folate metabolism, leading to elevated homocysteine levels in the cerebrospinal fluid. Homocysteine acts as an excitatory amino acid and may induce neuronal injury through N-methyl-D-aspartate (NMDA) receptor activation [7]. Additionally, methotrexate increases extracellular adenosine concentrations, which can alter cerebral blood flow and neurotransmission [8]. Direct toxic effects on oligodendrocytes and disruption of the blood–brain barrier have also been described, contributing to reversible white matter injury [9].

These mechanisms likely act synergistically, producing transient cytotoxic edema and demyelination, which explain both the acute neurological symptoms and the reversibility of imaging findings in many cases.

Neuroimaging Findings

Neuroimaging plays a crucial role in diagnosis. Magnetic resonance imaging, particularly diffusion-weighted imaging (DWI), is the most sensitive modality for detecting early changes. Typical findings include areas of restricted diffusion in the periventricular or subcortical white matter, often sparing the cortex and not conforming to a vascular distribution [4-10]. These radiological features help distinguish methotrexate-

induced leukoencephalopathy from acute ischemic stroke and avoid inappropriate thrombolytic therapy.

In our case, follow-up CT demonstrated bilateral white matter hypodensities, supporting the diagnosis in the appropriate clinical context.

Management

There is no standardized treatment for methotrexate-induced neurotoxicity. Immediate discontinuation of methotrexate is mandatory. Folinic acid (leucovorin) rescue therapy is commonly administered to counteract folate pathway inhibition [1-6]. Supportive care includes optimization of renal function, adequate hydration, and seizure management when necessary.

Adjunctive therapies have been proposed. Aminophylline, an adenosine receptor antagonist, has been used to reverse neurological symptoms by counteracting adenosine-mediated effects [11]. Dextromethorphan, an NMDA receptor antagonist, may reduce homocysteine-mediated excitotoxicity [7, 8]. However, evidence supporting these therapies remains limited to case reports and small case series.

Prognosis

The prognosis of methotrexate-induced neurotoxicity is generally favorable with early recognition and appropriate management. Most patients experience partial or complete neurological recovery within days to weeks [4-10]. Nevertheless, recurrent episodes and persistent neurological deficits have been reported, particularly when methotrexate is reintroduced or diagnosis is delayed [5]. Long-term cognitive impairment has also been described, especially following repeated exposures [12].

This case emphasizes the importance of including methotrexate-induced neurotoxicity in the differential diagnosis of acute focal neurological deficits in patients receiving methotrexate therapy.

Conclusion

Methotrexate-induced neurotoxicity is a rare but important cause of acute neurological deterioration in patients treated with methotrexate. Its presentation may closely mimic ischemic stroke, leading to diagnostic uncertainty. Awareness of this entity, early neuroimaging, and prompt withdrawal of the offending agent with supportive management are essential to optimize outcomes and prevent permanent neurological sequelae.

References

1. Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and managing toxicities of high-dose methotrexate. *Oncologist*. 2016;21(12):1471–1482.
2. Vezmar S, Becker A, Bode U, Jaehde U. Methotrexate-associated toxicity in patients with hematological malignancies. *Drug Saf*. 2003;26(5):367–384.
3. Bhojwani D, Sabin ND, Pei D, et al. Methotrexate-induced neurotoxicity in children with acute lymphoblastic leukemia. *J Clin Oncol*. 2014;32(9):949–959.
4. Rollins N, Winick N, Bash R, Booth T. Acute methotrexate neurotoxicity: findings on diffusion-weighted imaging and correlation with clinical outcome. *AJNR Am J Neuroradiol*. 2004;25(10):1688–1695.
5. Shuper A, Stark B, Kornreich L, et al. Methotrexate treatment protocols and the central nervous system: significant cure with significant neurotoxicity. *J Child Neurol*. 2000;15(9):573–580.
6. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. *Oncologist*. 2006;11(6):694–703.
7. Quinn CT, Griener JC, Bottiglieri T, Arning E, Winick NJ. Methotrexate increases homocysteine and excitatory amino acid neurotransmitters in cerebrospinal fluid. *J Clin Oncol*. 1997;15(8):2800–2806.
8. Drachtman RA, Cole PD, Golden CB, et al. Dextromethorphan is effective in the treatment of subacute methotrexate neurotoxicity. *J Clin Oncol*. 2002;20(6):1759–1764.
9. Gregorios JB, Gregorios AB, Winick N. Methotrexate-induced leukoencephalopathy: ultrastructural study of human brain. *J Neuropathol Exp Neurol*. 1989;48(3):207–219.
10. Fisher MJ, Khademian ZP, Simon EM, Zimmerman RA. Diffusion-weighted MRI in acute methotrexate neurotoxicity. *Neurology*. 2005;65(12):1869–1872.
11. Bernini JC, Fort DW, Griener JC, et al. Aminophylline for methotrexate-induced neurotoxicity. *Lancet*. 1995;345(8944):544–547.
12. Lautin EM, Apter S, Schneck MJ, et al. Methotrexate-induced encephalopathy: MRI patterns and clinical outcome. Neurology. 1999;52(9):1836–1839.