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Subacute methotrexate neurotoxicity in patients with oncohematological disease. A report of 3 cases

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ABSTRACT

Methotrexate is a folic acid analogue widely used in the treatment of autoimmune diseases, leukemias, and lymphomas. Methotrexate use may cause multiple adverse effects, including those related to the presence of neurological toxicity, which may be acute, subacute, or chronic. Subacute neurotoxicity typically occurs between 2 and 14 days after administration and may present as a wide range of neurological symptoms. In most cases, it does not recur with future exposures to the drug.

Here we describe 3 cases of subacute methotrexate neurotoxicity with different clinical manifestations in patients with oncohematological disease who were hospitalized between 2018 and 2020. Two of them showed recurrence with a new drug administration. Lesions were observed in the magnetic resonance imaging tests of all of them.

Key words: *methotrexate; neurotoxicity syndromes; leukemia; lymphoma.*

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INTRODUCTION

Methotrexate is a folic acid analogue drug that has been used in medical practice for more than 50 years. At present, it plays an important role in the treatment of certain malignancies, such as leukemias and lymphomas.[1]

Intravenous and intrathecal administration of methotrexate has replaced cranial irradiation, which had been used for the treatment and prophylaxis of central nervous system involvement. The direct adverse effects of irradiation are therefore avoided, as well as growth retardation and increased incidence of second malignancies.[2]

Methotrexate use may be associated with acute, subacute, and chronic neurotoxicity. Subacute toxicity typically occurs from 2 to 14 days after administration and may present with various symptoms, including episodes of neurological deficit (similar to ischemic stroke), encephalopathy, seizures, and aphasia; although rare, fatal cases have been described.[3] Most patients with subacute neurotoxicity can safely receive the drug again. A smaller percentage of patients may experience recurrence with subsequent methotrexate administration.[4,5]

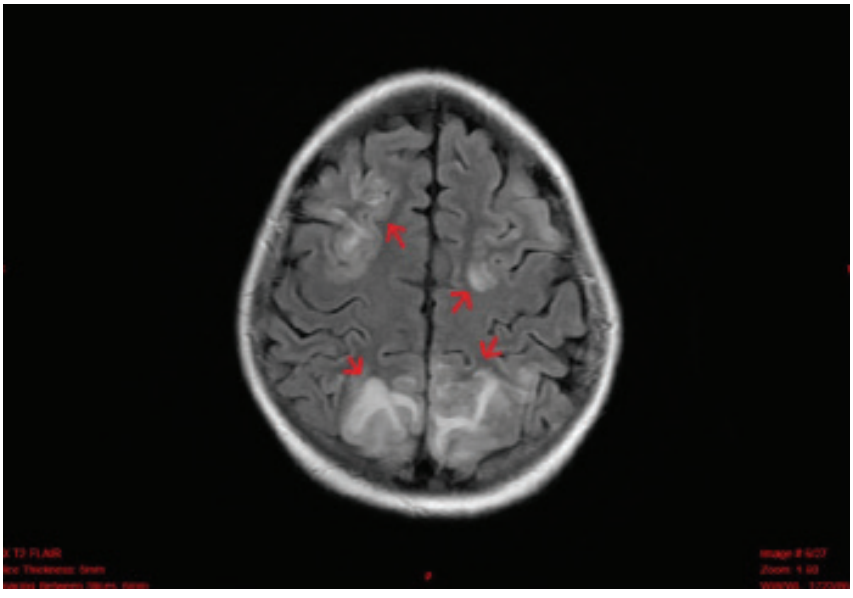
Here we describe 3 cases of subacute methotrexate neurotoxicity with different clinical presentations in patients with oncohematological disease who were hospitalized at Hospital Humberto Notti between 2018 and 2020.

CASE REPORT 1

This was a 13-year-old male patient diagnosed with B-cell lymphoma, R3 risk group according to the staging proposed by the German Berlin-Frankfurt-Münster (BFM) protocol. He started treatment according to the 2017 protocol proposed by the Argentine Group for Acute Leukemia Treatment (Grupo Argentino de Tratamiento de la Leucemia Aguda, GATLA) in the cytoreductive pre-phase (V) and, in the context of tumor lysis, he developed acute kidney failure requiring dialysis, which led to his admission to the pediatric intensive care unit (PICU). He remained in the PICU with hemodialysis requirement, where he continued his cancer treatment. He received RAA block with methotrexate administered intrathecally at an age-appropriate dose and intravenously at 2 g/m^2/infusion over 4 hours with 3 doses of leucovorin at 15 mg/m^2; 4 days later, he had 2 episodes of generalized tonic-clonic seizures. A computed tomography (CT) of the brain showed no lesions and, subsequently, a magnetic resonance imaging (MRI) showed hyperintense cortico-subcortical areas in the posterior region of the left parietal cingulate gyrus. He started anticonvulsant therapy with good clinical course and continued with chemotherapy without modifications in the administration of methotrexate.

Five months after diagnosis, the patient received his fifth chemotherapy course

Figure 1. Magnetic resonance imaging, axial slice in T2 and FLAIR sequences. Hyperintense cortico-subcortical lesions in the cingulate gyri of parietal and occipital lobes of both hemispheres. Case report 1



(RBB block) with intrathecal and intravenous methotrexate at 2 g/m²/infusion over 4 hours with 3 doses of leucovorin at 15 mg/m². Ten days later, he had 2 episodes of brief acute blindness which resolved to normal, inappropriate laughter, and generalized tonic-clonic seizure episode, which later focused on the left upper limb. A CT scan of the brain showed posterior, biparietal, and frontal parasagittal cortico-subcortical cellular edema in the left cerebral hemisphere with partial effacement of the subarachnoid spaces; these results were compared to a MRI of the brain, which showed multiple hyperintense cortico-subcortical lesions in the gyri of the frontal, parietal, and occipital lobes of both hemispheres, with slight vasogenic edema (*Figure 1*).

The patient had a favorable course with complete resolution of symptoms without neurological sequelae and was in cancer remission at the time of this publication.

CASE REPORT 2

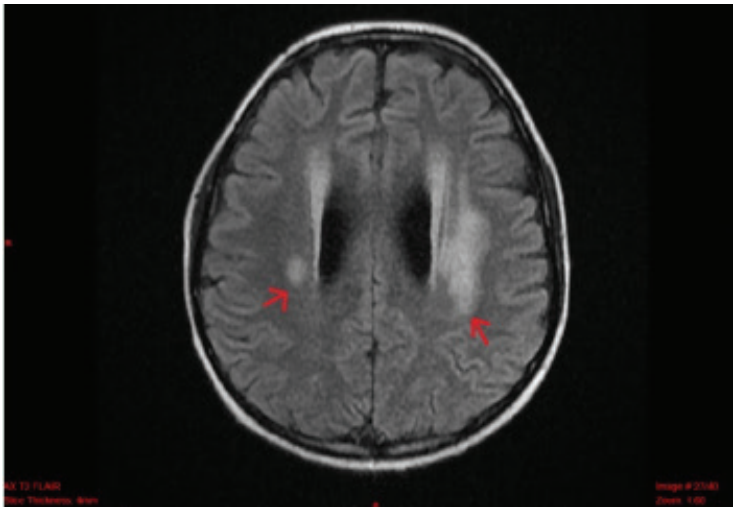
This was an 11-year-old male patient diagnosed with intermediate risk B-cell acute lymphoblastic leukemia (ALL) who was receiving chemotherapy according to the GATLA 2010 protocol in consolidation phase (M4), for which he received methotrexate intravenously at 2 g/m²/infusion over 24 hours and intrathecally in age-appropriate doses. He received 3 doses of leucovorin according to protocol at 15 mg/m². After 5 days, he had an event of deviation of the labial commissure with dysarthria and paresthesia of the left upper and lower limbs for approximately 30 minutes, which resolved completely. The following day, 6 days after methotrexate administration, he had a new episode of left facial-brachial-crural hemiparesis that resolved after 48 hours. The results of the brain CT and MRI were normal.

He had a favorable course with normal neurological examination and continued with chemotherapy without modifications. A follow-up brain MRI was performed 2 months after the event, which showed hyperintense areas in the periventricular white matter with posterior-superior predominance in the right hemisphere. He is currently in cancer remission without neurological sequelae.

CASE REPORT 3

This was an 11-year-old male patient diagnosed with intermediate risk B-cell ALL who was receiving chemotherapy according to the GATLA 2010 protocol in consolidation phase (M3), for which he received methotrexate intravenously at 2 g/m²/infusion over 24 hours and intrathecally in age-appropriate doses. He received 3 doses of leucovorin at 15 mg/m² according to protocol. Six days after administration, he developed Broca's (motor) aphasia, right facial-brachial-crural hemiparesis, and an altered state of consciousness. The brain CT and MRI showed no alterations and he had a favorable course over 24 hours with complete resolution.

Figure 2. Magnetic resonance imaging, axial slice in T2 and FLAIR sequences. Significant changes in signal intensity in the lentiform nucleus and periventricular white matter up to the centrum semiovale, predominantly in the left flank. Case report 3



Two weeks later, intravenous and intrathecal methotrexate was administered again (consolidation phase M4). Ten days later, the patient developed choreoathetosis in the left upper and lower limbs with paresthesias in the left side of the face for 2 hours, with complete resolution in 24 hours.

A follow-up MRI was performed 2 months after the event, which showed important changes in the signal intensity of T2 and FLAIR images in the lentiform nucleus and periventricular white matter up to the centrum semiovale, predominantly in the left flank (*Figure 2*). Due to event recurrence and the pathological MRI results, it was decided to discontinue the intrathecal treatment with methotrexate. The patient had bone marrow relapse 10 months after diagnosis (very early relapse) and was started on a high-risk relapse chemotherapy protocol; he died due to disease progression 2 months later.

DISCUSSION

The incidence of methotrexate neurotoxicity during treatment oncohematological disease is approximately 3%[4–6] and can be classified into acute, subacute, or chronic in relation to the time since administration. Acute neurotoxicity occurs within the first hours of administration (in most cases, 2 to 4 hours), and the most common clinical manifestations include drowsiness, confusion, fatigue, disorientation, and seizures. It may also present as acute arachnoiditis in cases of intrathecal administration. Chronic neurotoxicity develops over months to years following methotrexate exposure and may present as confusion, drowsiness or irritability, visual disturbances, language disorders, seizures, ataxia, and dementia.[7]

Subacute neurotoxicity occurs days to weeks after exposure to the drug; its clinical manifestations include hemiparesis, ataxia, aphasia, seizures, confusion, affective disorders, choreoathetosis.[8,9] Cases of severe myelopathy with impaired sensorium, lower limb pain, paraplegia, and neurogenic bladder have been reported secondary to intrathecal administration.[10] In subacute neurotoxicity, most patients have spontaneous improvement of symptoms within 48 to 72 hours, with complete clinical resolution.[8] Multiple publications have established that the risk for recurrence with future exposures is low and would not warrant methotrexate discontinuation.[5,6,8] When MRIs are performed, the radiological correlation corresponds to leukoencephalopathy consisting of hyperintense white matter images in T2 and FLAIR sequences.[9]

The mechanism by which methotrexate causes neurotoxicity has not been fully elucidated. A proposed theory is that, as a result of the inhibition of dihydrofolate reductase, which is necessary for the conversion of homocysteine to methionine, high levels of homocysteine are produced in both blood and cerebrospinal fluid. This may cause direct toxicity to the vascular endothelium and its metabolites are N-methyl-D-aspartate (NMDA) receptor agonists.[11,12]

Certain risk factors for the development of methotrexate neurotoxicity have been proposed. Recently, MK Mateos et al., published a study in patients with leukemia where age older than 10 years at diagnosis and high plasma aspartate aminotransferase (AST) levels 5 times the normal values (grade 3 toxicity) during induction/consolidation treatment, were risk factors.[13]

There is no consensus on the treatment of subacute methotrexate neurotoxicity, but there is some evidence regarding the use of dextromethorphan, an opioid derivate of morphine that acts as a non-competitive NMDA receptor antagonist and that has been shown to produce improvement of neurological symptoms attributed to subacute methotrexate toxicity when administered orally in doses of 1-2 mg/kg.[14,15]

REFERENCES

1. Vezmar S, Becker A, Bode U, Jaehde U. Biochemical and clinical aspects of methotrexate neurotoxicity. *Chemotherapy.* 2003; 49(1-2):92-104.
2. Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in pediatrics leukaemia. *Lancet Oncol.* 2008; 9(3):257-68.
3. García Hernández I, Rey Galán C, Concha Torre A, Los Arcos Solas M, Mayordomo Colunga J. Neurotoxicidad subaguda letal por metotrexato intratecal. *Bol Pediatr.* 2012; 52(219):37-42.
4. Rubnitz JE, Relling MV, Harrison PL, Sandlund JT, et al. Transient encephalopathy following high-dose methotrexate treatment in childhood acute lymphoblastic leukemia. *Leukemia.*1998; 12(8):1176-81.
5. Bhojwani D, Sabin N, Pei D, Yang JJ, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. *J Clin Oncol.* 2014; 32(9):949-59.
6. Millan N, Pastrana A, Guitter M, Zubizarreta PA, et al. Acute and subacute neurological toxicity in children treated for acute lymphoblastic leukemia. *Leuk Res.* 2018; 65:86-93.
7. Bleyer WA. Neurologic sequeale of methotrexate and ionizing radiation: a new classification. *Cancer Treat Rep.* 1981; 65(suppl 1):89-98.
8. Walker RW, Allen JC, Rosen G, Caparros B. Transient cerebral dysfunction secondary to high-dose methotrexate. *J Clin Oncol.* 1986; 4(12):1845-50.
9. Inaba H, Khan R, Laningham F, Crews KR, et al. Clinical and radiological characteristics of methotrexate-induced

acute encephalopathy in pediatric patients with cancer. *Ann Oncol*. 2008; 19(1):178-84.
10. Gagliano R, Costanzi J. Paraplegia following intrathecal methotrexate: Report of a case and review of the literature. *Cancer*. 1976; 37(4):1663-8.
11. Quinn CT, Greiner JC, Bottiglieri T, Arning E, Winick NJ. Effects of intraventricular methotrexate on folate, adenosine and homocysteine metabolism in cerebrospinal fluid. *J Peditr Hematol Oncol*. 2004; 26(6):386-8.
12. Quinn CT, Greiner JC, Bottiglieri T, Hyland K, et al. Elevation of homocysteine and excitatory amino acid neuotransmitters in the CSF of children who receive methotrexate for the treatment of cancer. *J Clin Oncol*. 1997; 15(8):2800-6.
13. Mateos MK, Marshall GM, Barbaro PM, Quinn MCJ, et al. Methotrexate- related central neurotoxicity: clinical characteristics, risk factors and genome-wide association study in children treated for acute lymphoblastic leukemia. *Haematologica*. 2022; 107(3):635-43.
14. Drachtman RA, Cole PD, Golden CB, James SJ, et al. Dextromethorphan is effective in the treatment of subacute methotrexate neurotoxicity. *Pediatr Hematol Oncol*. 2002; 19(5):319-27.
15. Vijayanathan V, Gulinello M, Ali N, Cole PD. Persistent cognitive deficits, induced by intrathecal methotrexate, are associated with elevated CSF concentrations of excitotoxic glutamate analogs and can be reversed by an NMDA antagonist. *Behav Brain Res*. 2001; 225(2):491-7.