CLINICAL CASE

ABORDAJE MULTIDISCIPLINARIO DE LA INTOXICACIÓN POR METOTREXATO EN PEDIATRÍA

MULTIDISCIPLONARY APPROACH TO METHOTREXATE INTOXICATION IN PEDIATRICS

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RESUMEN.

El Metotrexato (MTX) es un fármaco inmunosupresor e inhibidor del ácido fólico que disminuye los niveles de tetrahidrofolato en las células, cuyo mecanismo de acción se basa en el bloqueo de las enzimas dihidrofolato reductasa y timidilato sintetasa, las cuales, desempeñan un papel clave en la síntesis de ácidos nucleicos. Sin embargo, el uso crónico de este medicamento trae consigo la probabilidad de desarrollar una toxicidad sistémica severa, principalmente pulmonar y hepática, concomitante con procesos infecciosos. El presente artículo, reporta el caso de una paciente que se encontraba en tratamiento con MTX por diagnóstico de Artritis Reumatoidea Juvenil, que presentó signos de toxicidad severa y fue tratada en el Hospital Universitario Erasmo Meoz con respuesta favorable. Es importante el reconocimiento temprano de los efectos adversos del medicamento y su caracterización clínica, por lo que, se estima que la suspensión inmediata del fármaco y un tratamiento adecuado, son factores que contribuyen al manejo integral y a la reducción de la morbilidad.

PALABRAS CLAVE: Metotrexato, ácido fólico, toxicidad sistémica, infección, artritis reumatoidea.

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ABSTRACT

Methotrexate (MTX) is an immunosuppressive drug and folic acid inhibitor that decreases the levels of tetrahydrofolate in cells, whose mechanism of action is based on blocking the enzymes dihydrofolate reductase and thymidylate synthetase, which play a key role in the synthesis of nucleic acids. However, chronic use of this medication brings with it the probability of developing severe systemic toxicity, mostly pulmonary and hepatic, concomitant with infectious processes. This article reports the case of a patient who was being treated with Methotrexate due to a diagnosis of Juvenile Rheumatoid Arthritis, who presented signs of severe toxicity and was treated at the Erasmo Meoz University Hospital with a response. favorable. Early recognition of the adverse effects of the drug and its clinical characterization is important, therefore, it is estimated that the immediate suspension of medication and adequate treatment are factors that contribute to comprehensive management and reduction of morbidity.

KEYWORDS: Methotrexate, folic acid, systemic toxicity, infection, rheumatoid arthritis.

INTRODUCTION.

Poisonings from chemical products—including medications, pesticides, and household cleaning agents—are a public health concern and have been monitored in Colombia for over a decade. The national incidence rate is 15.5 cases per 100,000 people, with 17.5% of reported deaths due to drug poisoning. Around 10% of pediatric emergency consultations are due to this type of intoxication. [1].

MTX is a therapeutic agent with immunomodulatory and anti-inflammatory properties, indicated for the treatment of severe psoriasis, rheumatoid arthritis, malignant neoplasms (such as childhood acute lymphoblastic leukemia and lymphoproliferative disorders), Crohn's disease, and systemic lupus erythematosus. In the case of rheumatoid arthritis, it should be administered in low doses—between 5 and 20 milligrams weekly—due to its favorable activity-to-toxicity ratio [2]. However, this drug has a high incidence of adverse effects—up to 50%—which leads to treatment discontinuation in 35% of cases, including in pediatric patients [3].

These effects may manifest systemically: cutaneous (erythema, rash, and pruritus), gastrointestinal tract (stomatitis, abdominal pain, mouth ulcers, nausea, and vomiting), respiratory tract (interstitial pneumonitis and pulmonary fibrosis), Central Nervous System (weakness, dizziness, and headache) y alteration in laboratory results or laboratory abnormalities (elevated transaminases and hyperbilirubinemia). Regarding pulmonary injury, the mechanisms are multifactorial and not clearly defined; they may include hypersensitivity or host vulnerability due to impaired

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resistance to infection—both caused by direct toxic effects. Additionally, pulmonary toxicity can develop within the first year and recur repeatedly [4].

Ultimately, the severity of these adverse effects necessitates serious consideration of the substantial negative potential of chronic MTX use. Therefore, its clinical justification and implications for public health contribute to analyzing the natural course of MTX drug intoxication and its impact on the patient's homeostatic balance. The development of this case report, documented at the Erasmo Meoz University Hospital, may offer new insights for establishing guiding criteria for comprehensive management that clarify its pathophysiology and define specific differential diagnostic criteria for its treatment. Without awareness that MTX toxicity causes pulmonary and hepatic complications, it would be impossible to make accurate differential diagnoses between clinically similar conditions such as hepatitis virus and infectious pneumonia.

CLINICAL CASE.

The case concerns a 12-year-old female adolescent who presented with a clinical condition of approximately four days' duration, characterized by chest pain accompanied by unquantified fever and abdominal pain. Relevant medical history includes: *juvenile rheumatoid arthritis*, diagnosed nine years ago and under treatment with methotrexate (oral tablets, 2.5 mg – 12.5 mg per week), along with folic acid (oral tablets, 5 mg), prednisolone (oral tablets, 5 mg every 48 hours), and adalimumab (subcutaneous injectable solution, 40 mg – 20 mg every two weeks); as well as *recurrent respiratory infections* (fungal pneumonia – March 2022 and pneumonia of unspecified etiology – October 2022), with the last episode of mild respiratory symptoms occurring two months earlier, without complications.

On physical examination, the patient appeared feverish and pale, with signs of dyspnea and oxygen desaturation. *Admission vital signs* were: BP 104/68 mmHg, HR 95 bpm, SpO_2 84%, RR 28 bpm, with a weight of 26 kg and a height of 143 cm. *Segmental examination* revealed a symmetrical thorax with a prominent chest wall deformity, identified as pectus carinatum, along with pronounced intercostal, subcostal, and supraclavicular retractions. Painful hepatomegaly was noted on palpation.

Admission lab tests showed: mild leukopenia, elevated transaminases, and direct hyperbilirubinemia, with elevated CRP. Imaging studies were ordered to correlate the patient's clinical condition with a possible infectious focus: chest X-ray showed reticular opacities in both lung fields. Abdominal ultrasound revealed a liver of normal shape, size, and echogenicity, with no focal lesions. Intra- and extrahepatic bile ducts appeared normal. The common bile duct was unremarkable. The gallbladder was distended with thin walls and anechoic content. The pancreas and spleen appeared normal

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in shape, size, and echogenicity. Kidneys were also of normal shape, size, and echogenicity, with no evidence of parenchymal lesions. Corticomedullary differentiation was preserved. The central pyelocaliceal system showed no signs of dilatation, and no free fluid was seen in the abdomen. A transthoracic echocardiogram was also performed and revealed a structurally and functionally normal heart, with adequate systolic and diastolic function.

To make a differential diagnosis and determine the course of treatment, a comprehensive and multidisciplinary approach was necessary:

Pediatrics: Given the patient's tendency toward leukopenia and immunosuppressed status with multiple comorbidities, broad-spectrum antibiotics were started before cultures were taken. FilmArray and acute phase reactants were also requested.

Pediatric Pulmonology: Considered that immunosuppressive drugs could be responsible for pulmonary fibrosis and drug-induced pneumonitis. However, the possibility of an infectious focus could not be ruled out, so a high-resolution chest CT was requested (Figures 1 and 2).

Pediatric Gastroenterology: The diagnostic impression was acute hepatopathy, likely of toxic-drug or viral origin, which needed to be ruled out first.

Toxicology: Concluded that MTX used for the underlying condition was causing pulmonary, hepatic, and hematopoietic issues. The recommended antidote was folinic acid.

Pediatric Infectious Diseases: Recommended outpatient testing for hepatitis A antibodies, HBsAg, HSV 1–2 serology, and complementary vaccinations including 13-valent pneumococcus, meningococcus ACYW135, DPTa, and annual influenza.

Finally, the patient was hospitalized for ten days, during which immunomodulatory therapy was discontinued. Oxygen was administered via nasal cannula at 1–2 liters per minute to maintain optimal saturation above 94%. Broad-spectrum antibiotic therapy was initiated with ceftriaxone (intravenous, 1.3 grams every 12 hours for five days). Additionally, the specific antidote—folinic acid (50 mg/5 mL ampoules)—was administered at a dose of 10 mg/m² every six hours.

The patient's clinical course was favorable, with significant reduction of respiratory symptoms. Adequate oxygen saturation was observed under ambient conditions, with no signs of respiratory distress and normal values in arterial blood gases and transaminases. These favorable findings enabled discharge on the tenth day of hospitalization. During discharge, detailed instructions were given regarding the precise dosing of the prescribed medications (excluding MTX, continuing only with corticosteroids), along with guidance for home self-care. Warning signs were highlighted, and information was

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provided on the risks of outpatient management and potential complications, emphasizing the importance of attending follow-up appointments.

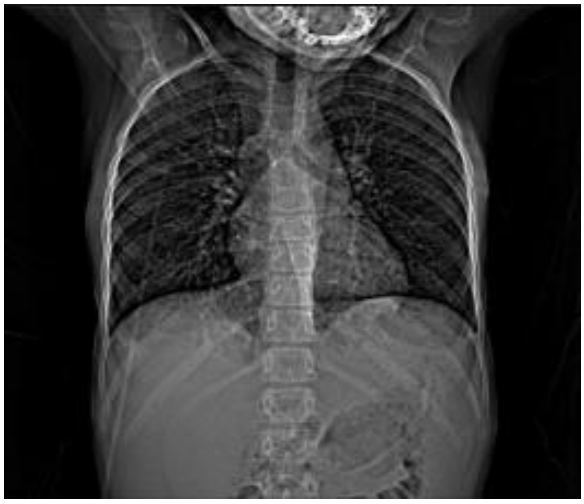
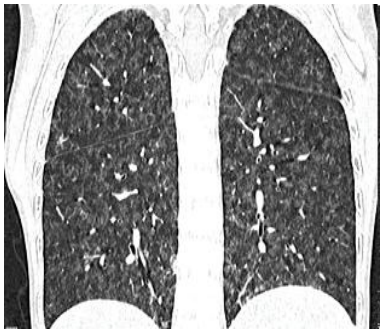


Figure 1. Frosted glass pattern.



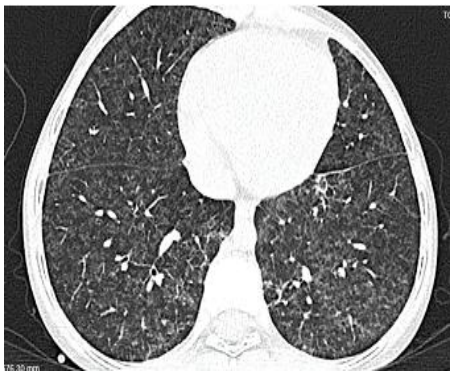


Figure 2. TCAR. Changes in the pneumatization of the pulmonary parenchyma due to diffuse multiple infiltrate.

DISCUSSION.

In the present case, the suspicion of methotrexate (MTX) intoxication was based on four important parameters: a history of chronic MTX use; clinical symptoms (vomiting, thoracoabdominal pain, febrile episodes, skin rash, and mucositis); laboratory findings (direct hyperbilirubinemia, elevated transaminases, and pancytopenia); and imaging results (ground-glass pattern and changes in lung parenchyma aeration due to multiple diffuse infiltrates).

A toxicologically severe case related to chronic MTX use—such as the one described here, involving a teenage patient with systemic, pulmonary, hepatic, and bone marrow involvement—must be thoroughly analyzed to understand the differential diagnostic protocol and appropriate treatment.

PHARMACODYNAMICS.

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MTX is a type of antimetabolite that performs a dual function, acting as both an antiproliferative and immunosuppressive agent. Its action is based on the competitive inhibition of the enzyme dihydrofolate reductase (DHFR). This enzyme plays a crucial role in folic acid metabolism, regulating the availability of folate within cells for the synthesis of proteins and nucleic acids. By preventing the formation of tetrahydrofolate—essential for nucleic acid synthesis—MTX disrupts this vital process. DHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, the active form of endogenous folate, which donates methyl groups essential for protein synthesis.

Primarily, MTX blocks the cell division cycle by targeting thymidylate synthase, leading to the inhibition of pyrimidine synthesis. Unlike folic acid, MTX contains structural modifications that allow it to block this process due to its higher affinity for DHFR. Since DHFR is responsible for converting dihydrofolic acid into tetrahydrofolate, and MTX preferentially binds to this enzyme, it reduces the synthesis of tetrahydrofolate [5,6].

PHARMACOKINETICS.

Once administered (either as tablets or injectable solution), MTX is absorbed in the gastrointestinal tract through carrier proteins—i.e., active transport. At high doses, its bioavailability (rate and amount absorbed) decreases significantly due to variations in first-pass metabolism.

The next parameter is distribution, which is influenced by the drug's binding to plasma proteins—approximately 50%. It's worth noting that the unbound fraction of the drug plays a key role in determining its pharmacological effect, a concept known as "fractional equilibrium."

Additionally, genetic polymorphisms have been described that alter the pharmacological response to MTX. These variations may facilitate MTX absorption, meaning greater intracellular entry via the RFC1 transport system, which in turn may enhance its therapeutic effect—or its adverse effects [5,6].

MTX undergoes hepatic metabolism at a rate of about 10%, producing an active metabolite—7-hydroxyMTX—which prolongs the drug's therapeutic effect. In terms of excretion, most of the drug is eliminated via glomerular filtration and active secretion in the proximal tubule. Around 20% of both MTX and its metabolite are excreted through the biliary system [5,6].

Returning to the main argument, in rheumatoid arthritis, the addition of MTX to biological therapy has been evaluated for its benefits via two pathways: Primarily, maintaining therapeutic efficacy by reducing the formation of anti-tumor necrosis factor (TNF) antibodies. Secondly, Enzymatic inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide

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transformylase, resulting in increased release of adenosine, an anti-inflammatory mediator [5,6].

PULMONARY TOXICITY.

Various pulmonary complications have been recorded in patients receiving this antifolate, with a range of clinical presentations, radiographic findings, and histological characteristics. Pneumonitis is the most recognized pulmonary toxic effect of methotrexate (MTX); it is usually an acute and serious complication that requires discontinuation of the drug for recovery. According to research, more than 25% of patients treated with MTX experience cough, wheezing, shortness of breath, or other respiratory symptoms, likely due to unique or individual immune responses. Forms of associated pulmonary toxicity include acute pneumonitis (the most frequent, which can occur at any stage of treatment, though more common during the first year), interstitial fibrosis, pulmonary nodulosis, lymphoma, and non-cardiogenic pulmonary edema [7,8,9].

Due to the toxicity related to this drug, it is appropriate to include Diffuse Interstitial Lung Disease (DILD), which involves lung parenchyma changes that lead to fibrosis. This results from a failed repair process, where the alveolar wall undergoes remodeling due to inflammatory cell infiltration. It is important to highlight the cascade of reactions: the first step occurs during treatment at therapeutic doses (5–15 mg weekly, increasing gradually every 4 weeks without exceeding 25 mg) [6,8]. During this repair process, pneumocytes become active and promote the production of fibrosis mediators such as TNF-alpha. Physiologically, TNF-alpha binds to its receptor and activates COX-2, which induces prostaglandins that regulate the production of this factor, limiting its function. Specifically, in DILD, this regulation fails, resulting in continuous adhesion of inflammatory and mesenchymal cells and an imbalance in fibroblastic activity, driven by the platelet-derived growth factor pathway [10].

The most common symptoms include cough, shortness of breath (82%), and fever (76%). On examination, crackling sounds, tachypnea, and cyanosis may be detected. Sudden onset of respiratory failure is not uncommon and tends to occur in patients with diffuse alveolar damage, which is often associated with a worse prognosis [8].

Multiple scoring systems have emerged to diagnose MTX-related pneumonitis, although none are globally standardized. Nonetheless, they offer diagnostic guidance. Among them, the criteria proposed by Searles and McKendry (1987) are commonly used in clinical practice and include nine items. A score of six or higher confirms the diagnosis, five suggests a probable diagnosis, and four indicates a possible diagnosis [11]. In this case, the patient had a score of six, confirming the diagnosis of MTX-related pneumonitis.

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Dyspnea less than eight weeks old.
Tachypnea and non-productive cough.
Fever.
Oxygen saturation less than 90% breathing room air.
Blood leukocytes levels <15,000/mm3.
Histopathologic report of hypersensitivity pneumonitis without evidence of additional infection.
Negative blood and sputum cultures.
Restrictive pattern in pulmonary function tests.
Alveolar or interstitial infiltrates on chest X-ray.

Table 2. Diagnostic criteria for MTX pneumonitis

TREATMENT.

In cases where MTX toxicity is suspected or confirmed, the first step is immediate discontinuation of the medication [6]. However, initiating prophylactic antibiotic therapy is recommended in case of potential infectious complications. Respiratory support should be provided, such as oxygen therapy or, if needed, mechanical ventilation, along with the systemic use of glucocorticoids [6,10].

ANTIDOTE.

Monitoring plasma concentrations of MTX is essential as a predictive tool to assess the patient's condition and evaluate drug toxicity and efficacy. Once the levels are known, the initial management involves administering the specific antidote, folinic acid, which antagonizes MTX. It should be continued until blood cell counts and mucosal lesions return to normal [9]. Folinic acid acts via two mechanisms [5,6]: Competing with MTX for cellular entry, and Displacing MTX from its binding site by directly competing for dihydrofolate reductase (DHFR).

The dosage of folinic acid ranges from 10 to 25 mg/m² IV every 6 hours for 72 hours. In the present case, the patient received a total of 120 mg IV (10 mg/m² every 6 hours for 72 hours).

According to the Academic Drug Compendium, the starting dose of MTX in children over 3 years and adolescents is 10–15 mg orally, once per week. In refractory cases, this can be increased to 15–20 mg [13].

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In acute intoxication, if the patient presents within the 1-hour window, MTX absorption in the gastrointestinal tract can be delayed using bile salts and activated charcoal. To enhance elimination, urinary alkalinization with sodium bicarbonate may be performed. In addition to folinic acid, carboxypeptidase G2 (not available in Colombia) can be used to hydrolyze MTX into non-toxic metabolites [5,6].

CONCLUSIONS.

The analysis and comprehensive understanding of factors associated with MTX intoxication—evaluating its clinical manifestations, toxicity mechanisms, risk factors, and potential prevention and treatment strategies at the Erasmo Meoz University Hospital—proved to be highly effective. This was achieved through thorough documentation of clinical manifestations, including both acute and chronic symptoms, to provide a detailed description of associated adverse effects.

Specific risk factors were identified, including the administered dose, treatment duration, presence of comorbidities, and other individual variables that may increase susceptibility. As part of ongoing learning, it is essential to consider the effectiveness of various therapeutic approaches to MTX intoxication, including evaluating the efficacy of specific antidotes, supportive therapies, and other medical strategies to improve the clinical management of intoxication cases.

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DAY IN THE LABORATORY		1 DÍA INGRESO	2 DÍA EVOLUCIÓN	4 DÍA EVOLUCIÓN	5 DÍA EVOLUCIÓN	7 DÍA EVOLUCIÓN
HEMATOLOGY PANEL	WBC	3.71 10^3/uL				6.26 10^3/uL
	RBC	5.52 10^6/uL				5.04 10^6/uL
	HGB	14.40 gr/dL				12.9 gr/dl
	PLT	248.000				449.000
	LIN%	34%				15.4%
	NEU%	49.5%				81.6%
	PT	13.5 s		11.80 s		12 s
	PTT	35.7 s		26.7 s		24.5 s
	INR	1.18		1.04		1.05
	PROCAL	0.42 ng/mL				
	PCR	45.31 mg/L				
LIVER FUNCTION	BT	3.23 mg/dL				0.6 mg/dL
	BD	2.16 mg/dL				0.39 mg/dL
	BI	1.07 mg/dL				0.21 mg/dL
	LDH	563.77 U/L				
	TGO	113.5 U/L		31.44 U/L		8.51 U/L
	TGP	153.23 U/L		64.82 U/L		26.87 U/L
	ALKAKINE PHOSPHATASE		1718.60 U/L			
RENAL FUNCTION	BUN	13.7 mg/dL		21.73 mg/dL		18.43 mg/dL
	UREA	29.32 mg/dL		46.5 mg/dL		39.43 mg/dL
	CREATININE	0.51 mg/dL		0.39 mg/dL		0.51 mg/dL
URINALYSIS	COLOR	YELLOW			YELLOW	
	APPEARANCE	SLIGHTLY TURBULENT			TRANSPARENT	
	Ph	1.025			1.025	
	DENSITY	6.5			6.5	
	LEUKOS	NEGATIVE			NEGATIVE	
	NITRITES	NEGATIVE			NEGATIVE	
	GLUCOSE	NEGATIVE			NEGATIVE	
	SEDIMENT	HEMATIES 15-20XC			NORMAL	
	PH		7.38			
	PO2		80 mmHg			

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ARTERIAL BLOOD GASES	PCO2		40 mmHg			
	FIO2		28%			
	HCO3		23.70 mmol/L			
OTHERS	Urine culture	NEGATIVE				
	Blood culture	NEGATIVE				
	Filmarra and respiratory	NEGATIVE				
	HBSAG		NEGATIVE			
	Antibodies HCV		NEGATIVE			
	Epstein Barr IGM		NEGATIVE			
	Hepatitis A IGM		NEGATIVE			
	CMV		NEGATIVE			
	Toxoplasma (IGM, IGG)		NEGATIVE			
	HIV		NEGATIVE			
	NA+	138 mmol/L	138 mmol/L			
	K+	4.2 mmol/L	3.4 mmol/L			
	CL-	104 mmol/L	104 mmol/L			

Table 1. Paraclinical follow-up according to the clinical evolution of the patient.

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