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When a Routine Drug Turns Toxic: A Case of Methotrexate - Induced Multi-Organ Dysfunction

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Abstract

Background: Methotrexate (MTX), a folic acid antagonist used widely in oncology, rheumatology, and dermatology, carries significant risk for acute toxicity. This case report presents a middle-aged male with psoriatic arthritis who experienced severe, life-threatening multi-organ dysfunction following MTX exposure.

Case Presentation: The patient presented to the emergency department with acute-onset severe mucocutaneous ulcerations, erosive mucositis, respiratory distress (SpO_2 89%), and dysphagia. Laboratory investigations revealed profound pancytopenia (hemoglobin 7.6 g/dL, total leucocyte count 1,190/mm^3), acute kidney injury (urea 126 mg/dL, creatinine 1.5mg/dL), and markedly elevated inflammatory markers (ESR 62 mm/hr). Upper gastrointestinal endoscopy demonstrated diffuse erosive lesions extending from the oropharynx to the esophagus. Respiratory acidosis (pH 7.3, pCO_2 62.1 mmHg) developed, complicated by hospital-acquired pneumonia secondary to severe neutropenia.

Management and Outcome: Upon recognition of MTX toxicity, immediate interventions included drug discontinuation, leucovorin (folinic acid) rescue therapy at 100 mg three times daily, and granulocyte colony-stimulating factor (filgrastim) administration to support hematopoietic recovery. Broad-spectrum antimicrobial therapy with meropenem and tigecycline was initiated for nosocomial infection, and non invasive ventilation (BiPAP) was provided for respiratory support. At discharge, the patient demonstrated complete resolution of hematologic abnormalities and mucocutaneous lesions, with hemoglobin 13 g/dL, total leucocyte count 8,000/mm^3, platelets 3.5 × 10^5/mm^3, and oxygen saturation 99% on room air.

Clinical Significance: This case emphasizes the critical importance of early recognition of MTX toxicity through mucocutaneous manifestations and hematologic abnormalities, the role of prompt drug discontinuation and leucovorin rescue in improving outcomes, and the necessity for aggressive management of secondary complications including infection and respiratory.

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Introduction

Methotrexate (MTX) is a folic acid antagonist that functions as a potent antiproliferative and immunosuppressive agent, serving as a cornerstone medication in oncology, rheumatology, and dermatology for decades [1]. The drug exerts its therapeutic effects by inhibiting the enzyme dihydrofolate reductase (DHFR), thereby depleting intracellular reduced folate pools essential for purine and pyrimidine synthesis, leading to disruption of DNA and RNA synthesis and arrest of the cell cycle in the S phase [2]. While this mechanism accounts for methotrexate's efficacy in treating rapidly proliferating cells, it simultaneously underlies its potential for severe toxicity when applied to normal, rapidly dividing tissues such as the bone marrow, gastrointestinal mucosa, and skin [1].

MTX toxicity remains a serious concern despite its widespread clinical use and represents both dose-dependent and idiosyncratic adverse effects. Among the most devastating manifestations are hematologic toxicity—particularly myelosuppression manifesting as pancytopenia—mucocutaneous ulcerations, gastrointestinal erosive disease, hepatotoxicity, pulmonary complications, and acute renal dysfunction [2,3]. Risk factors include renal impairment, hypoalbuminemia, drug-drug interactions, advanced age, and crucially, medication dosing errors. Dosing errors remain a significant and preventable cause of acute MTX toxicity; inadvertent daily administration instead of the prescribed weekly dose can rapidly precipitate life-threatening complications [3,4]. Early recognition and prompt intervention with drug withdrawal, leucovorin (folinic acid) administration, hematopoietic growth factor support, and aggressive management of secondary complications are

critical to minimize morbidity and mortality.

Case Presentation

Clinical history and presentation

A middle-aged male with a long-standing history of psoriasis complicated by psoriatic arthritis presented to the emergency department with acute onset symptoms. He reported severe oral ulcers, crusting mucosal lesions, and erosive mucositis affecting the buccal mucosa, accompanied by marked edema of the lips. Associated symptoms included dysphagia, hoarseness of voice, and sudden-onset breathlessness. The patient had been receiving methotrexate as part of his long-term treatment regimen for his rheumatologic condition.

Vital parameters and initial assessment

On arrival at the emergency department, vital parameters were as follows: heart rate 85 bpm, blood pressure 110/75 mm hg at the time of admission, and SpO_2 89% on room air. The patient was alert and oriented but appeared restless and exhibited clear signs of respiratory distress, necessitating immediate evaluation and intervention.

Physical examination findings

Comprehensive physical examination revealed the following significant findings: multiple ulcerative and crusted mucocutaneous lesions distributed across the oral cavity, including erythema and erosions of the buccal mucosa. Characteristic psoriatic plaques and lesions were noted over the body surface. Oropharyngeal examination demonstrated marked involvement with edema and erosive changes. The cervical and thoracic regions showed signs consistent with methotrexate-induced cutaneous toxicity. Chest auscultation and abdominal examination were otherwise unremarkable at initial presentation (Figure 1).

Laboratory investigations at admission

Initial laboratory studies revealed severe pancytopenia with marked abnormalities:

The laboratory data revealed profound hematologic suppression with hemoglobin of 7.6 g/dL, a critically low total leucocyte count of 1,190/mm^3, and severe thrombocytopenia. The differential count showed relative lymphocytosis with neutropenia, consistent with severe myelosuppression. Additionally, renal parameters were deranged (urea 126 mg/dL, creatinine 1.5 mg/dL), indicating acute kidney injury, likely secondary to MTX accumulation and toxicity. Inflammatory markers including ESR were markedly elevated at 62 mm/hr. Notably, folic acid levels were elevated and vitamin B12 was within acceptable range.

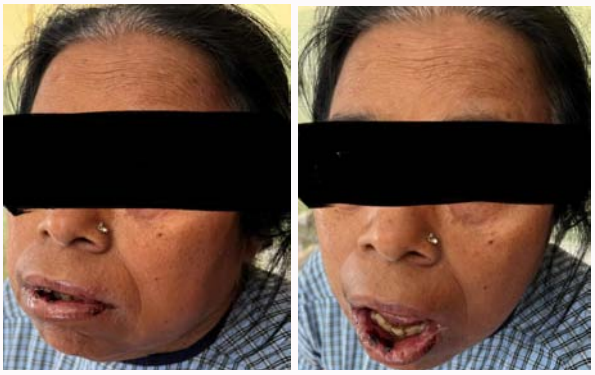

Figure 1: Physical examination findings.

Figure 2: Chest X-ray left lung.

Endoscopic findings

Upper gastrointestinal endoscopy (UGIE) was performed to evaluate the extent of mucosal involvement. Findings demonstrated diffuse erythema and multiple ulcerative lesions throughout the oropharynx and esophagus, confirming severe erosive mucositis extending from the oral cavity into the upper gastrointestinal tract. The stomach appeared relatively spared.

Clinical course and hospital-acquired complications

During hospitalization, the patient's condition evolved to include serious complications. Due to severe myelosuppression and neutropenia, the patient became susceptible to nosocomial infection and subsequently developed fever. Progressive respiratory compromise ensued, with the patient developing respiratory acidosis evidenced by arterial blood gas analysis: pH 7.3, HCO_3 30.7 mmol/L, pCO_2 62.1 mmHg. This prompted institution of noninvasive ventilation (NIV) with inspiratory pressure of 14 mmHg and expiratory pressure of 8 mmHg. Chest X-ray imaging revealed consolidation in the left lung, consistent with hospital-acquired pneumonia superimposed on respiratory compromise from mucositis and airway edema Figure 2.

Clinical Management and Therapeutic Interventions

Immediate interventions

Upon diagnosis of methotrexate toxicity, methotrexate was immediately discontinued. The patient was initiated on leucovorin (folinic acid) at a dose of 100 mg TDS (three times daily) and continued until serum methotrexate levels declined below 8 ng/mL, allowing rescue of normal cells from the folate antagonism induced by MTX [2].

Hematopoietic support

Due to persistent and severe pancytopenia unresponsive to initial supportive measures, granulocyte colony-stimulating factor (filgrastim) was administered to promote hematopoietic recovery. Filgrastim acts by stimulating the proliferation and maturation of neutrophil precursors in the bone marrow and enhanced mobilization of granulocytes from marrow stores [3]. The administration resulted in progressive and sustained recovery of all three hematopoietic cell lines—red blood cells, white blood cells, and platelets— over the course of hospitalization.

Table 1: Comprehensive laboratory results at presentation, showing severe pancytopenia, renal dysfunction, and elevated inflammatory markers.

Parameter	Value	Normal Range
Hematology		
Hemoglobin	7.6 g/dL	13.5-17.5 g/dL
Total Leucocyte Count	1,190 /mm^3	4,500-11,000 /mm^3
Neutrophils	42%	40-75%
Lymphocytes	50%	20-40%
Monocytes	2%	2-8%
Eosinophils	6%	1-4%
Basophils	0%	0-1%
ESR	62 mm/hr	<20 mm/hr
Renal Function		
Urea	126 mg/dL	7-20 mg/dL
Creatinine	1.5 mg/dL	0.7-1.3 mg/dL
Electrolytes		
Sodium	139 mmol/L	135-145 mmol/L
Potassium	3.9 mmol/L	3.5-5.0 mmol/L
Metabolic Markers		
HbA1c	6.40%	<5.7%
Liver Function		
Total Bilirubin	0.6 mg/dL	0.1-1.2 mg/dL
Albumin	3.9 g/dL	3.5-5.0 g/dL
Globulin	3.4 g/dL	2.3-3.5 g/dL
SGOT (AST)	11 U/L	<40 U/L
SGPT (ALT)	29 U/L	<41 U/L
ALP	107 U/L	30-120 U/L
Immunological Markers		
RA Factor	512 IU/mL	<14 IU/mL
Anti-CCP Antibodies	365.3 IU/mL	<20 IU/mL
Vitamin Status		
Folic Acid	>20 ng/mL	>5.38 ng/mL
Vitamin B12	291.1 pg/mL	200-900 pg/mL

Antimicrobial therapy

Given the development of hospital-acquired infection in the setting of profound neutropenia, broad-spectrum antimicrobial coverage was initiated. The regimen included meropenem (carbapenem) at 1 g intravenously as a stat dose, followed by 500 mg IV three times daily, and tigecycline at 100 mg as a loading dose followed by 50 mg intravenously twice daily. These agents provided comprehensive coverage against gram-positive, gram-negative, and atypical organisms likely involved in nosocomial respiratory infection. With antimicrobial therapy, the patient demonstrated gradual clinical improvement.

Respiratory support

Noninvasive ventilation with bilevel positive airway pressure (BiPAP) was instituted using inspiratory pressure of 14 mmHg and expiratory pressure of 8 mmHg, which effectively supported ventilation and oxygenation without requiring endotracheal intubation.

Clinical outcome and resolution

By discharge from the hospital, the patient demonstrated remarkable recovery and normalization of laboratory parameters:

- Hemoglobin: 13 g/dL (recovery from 7.6 g/dL)
- Total Leucocyte Count: 8,000/mm^3 (recovery from 1,190/mm^3)
- Platelets: 3.5 lakh/mm^3 (3.5 × 10^5/mm^3; recovery from severe thrombocytopenia)

All mucocutaneous lesions, including oral ulcerations and erosions, had completely healed. The patient regained the ability to swallow both liquid and solid foods without difficulty. Respiratory function improved substantially, with oxygen saturation at 99% on room air without supplemental oxygen or ventilatory support. The patient was discharged in stable clinical condition with resolution of the acute toxicity and recommendations for close outpatient follow-up.

Discussion

Pathophysiology of methotrexate toxicity

Methotrexate toxicity arises from the drug's mechanism of action: inhibition of dihydrofolate reductase (DHFR) leading to depletion of intracellular reduced folate pools [2]. These reduced folates serve as essential cofactors in one-carbon transfer reactions critical for the synthesis of purines, thymidylate, and methionine [1]. The non-selective nature of this mechanism means that MTX affects not only the target pathologic cells but also healthy, rapidly proliferating cells, particularly those in the bone marrow, gastrointestinal epithelium, and skin—tissues with high mitotic activity [2,4].

MTX accumulation occurs when renal clearance is impaired, and drug metabolites, particularly 7-hydroxymethotrexate and polyglutamated MTX forms, accumulate within cells, prolonging the duration and intensity of folate antagonism [8]. This is particularly relevant in the present case where creatinine was 1.5 mg/dL, indicating acute kidney injury. The polyglutamation of MTX within cells serves as a mechanism of cellular sequestration; while this can extend the duration of therapeutic effect, it also increases the risk of toxicity in the context of overdose or renal dysfunction [9].

Pancytopenia, as manifested in the present case, represents one of the most serious and potentially fatal complications of MTX toxicity. Myelosuppression occurs due to direct toxic effects on hematopoietic stem and progenitor cells, resulting in impaired production of red blood cells, white blood cells, and platelets. The risk of severe myelosuppression increases significantly in patients with renal impairment, as methotrexate is primarily eliminated through the kidneys; diminished renal clearance leads to drug accumulation and heightened cellular exposure to the toxic metabolite [3,4]. Studies have demonstrated that MTX-induced myelosuppression can progress rapidly from mild cytopenias to profound pancytopenia within 48-72 hours of overdose, with mortality rates ranging from 5-20% in severe cases managed without timely intervention [10,11].

Mucocutaneous manifestations and gastrointestinal toxicity

Oral mucositis and erosive mucosal lesions represent early and characteristic manifestations of MTX toxicity, serving as sentinel signs of systemic toxicity [1,3]. The gastrointestinal epithelium, with its rapid cellular turnover, is exquisitely sensitive to MTX's antiproliferative effects. The mechanism involves villous atrophy, epithelial necrosis, and inflammatory cell infiltration, accompanied by increased proteolytic enzyme activity and disrupted mucosal protein synthesis [2]. These changes result in loss of mucosal barrier integrity, pain, dysphagia, and potential for secondary infection [12]. In severe cases, erosive lesions may extend throughout the gastrointestinal tract, leading to diarrhea, malabsorption, and systemic complications.

The pathogenesis of MTX-induced mucositis involves dysregulation of pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β [13]. These cytokines, when elevated, promote increased mucosal inflammation and epithelial apoptosis. Additionally, MTX directly inhibits the proliferation of intestinal epithelial crypt cells, thereby reducing the rate of mucosal renewal and restoration of epithelial barriers [14]. Dysbiosis of the gut microbiota has also

been implicated as a contributing factor, with altered microbial composition potentially exacerbating mucosal inflammation [15].

Secondary infection and respiratory complications

The development of hospital-acquired infection in this patient was a direct consequence of profound neutropenia (TLC 1,190/ mm^3), which severely impaired the patient's ability to mount an effective innate immune response [3]. Neutropenic patients have altered barrier function, reduced microbicidal capacity, and impaired chemotaxis, rendering them susceptible to opportunistic and nosocomial pathogens. The resulting left lower lobe pneumonia and respiratory acidosis required aggressive antimicrobial therapy and respiratory support. This complication highlights the critical need for careful infection control measures and empirical broad-spectrum antimicrobial coverage in neutropenic patients [5]. Neutropenic fever in hospitalized patients has an infection documented in approximately 50-60% of cases and is associated with significant morbidity and mortality if empirical antibiotics are delayed [16].

The use of meropenem and tigecycline in this patient provided appropriate coverage for both common respiratory pathogens and potential resistant gram-negative organisms. Tigecycline, a broad-spectrum tetracycline derivative approved for hospital-acquired pneumonia and complicated intra-abdominal infections, was particularly valuable in this context given its activity against multidrug-resistant organisms [17]. The combination approach, along with supportive noninvasive ventilation, successfully mitigated the respiratory complication.

Role of leucovorin and growth factor support

Leucovorin (folinic acid) is the most specific and established antidote to MTX toxicity [2]. Unlike folic acid, which requires enzymatic conversion to its active form (a step blocked by MTX's inhibition of DHFR), leucovorin is a reduced folate that directly enters the folate cycle, thereby bypassing the metabolic blockade and rescuing normal cells from MTX-induced folate antagonism [2]. Initiation of leucovorin rescue within hours to a few days of MTX exposure significantly improves outcomes [18]. The standard leucovorin rescue regimen typically involves doses of 10-100 mg every 6-12 hours, continued until serum MTX concentrations decline below 0.1-1 μmol/L depending on the nomogram used [19]. High-dose leucovorin therapy (100 mg TDS as used in this patient) is particularly indicated in cases of severe MTX toxicity with pancytopenia and renal dysfunction.

Granulocyte colony-stimulating factor (G-CSF, filgrastim) accelerates recovery of neutrophil production and has been shown to significantly reduce the duration and severity of neutropenia and associated infectious complications in patients with chemotherapy-induced or drug-induced myelosuppression [3,4]. The mechanism of action of filgrastim involves binding to G-CSF receptors on hematopoietic progenitor cells, promoting proliferation, differentiation, and activation of neutrophil precursors [20]. In this patient, filgrastim administration resulted in recovery of absolute neutrophil count from 500/mm^3 to >2,000/mm^3 within 7-10 days, enabling resolution of neutropenic infection risk [21].

Risk factors and prevention

While MTX toxicity at standard therapeutic doses is relatively uncommon due to careful monitoring and leucovorin supplementation, the present case likely resulted from a dosing error or inadvertent overdose leading to acute toxicity. Dosing errors—such as daily administration instead of weekly dosing—remain a significant preventable cause of severe MTX toxicity [1,4]. A systematic review of medication errors involving MTX found that approximately 30-50% of severe MTX toxicity cases in non-oncology settings resulted from dosing errors, with daily ingestion instead of weekly dosing accounting for over 80% of these errors [22].

Other risk factors include renal impairment (present in this case with creatinine 1.5 mg/ dL), drug interactions, hypoalbuminemia, advanced age, and concurrent use of certain medications that impair MTX clearance or enhance toxicity [3,4]. Nonsteroidal anti-inflammatory drugs (NSAIDs), trimethoprim-sulfamethoxazole, loop diuretics, and probenecid all impair MTX renal clearance and increase toxicity risk [23]. The concurrent use of such agents with MTX necessitates careful patient monitoring and possible dose adjustment. Advanced age (>60 years) has been identified as an independent risk factor for MTX toxicity, partly due to age-associated decline in renal function and altered drug metabolism [24].

The elevated anti-CCP antibodies (365.3 IU/mL) and RA factor (512 IU/mL) in this patient confirm the diagnosis of rheumatoid arthritis or overlap rheumatologic condition with features of psoriatic arthritis, for which MTX is commonly prescribed. However, the patient's renal function impairment at baseline may have predisposed him to MTX accumulation and toxicity.

Clinical and therapeutic lessons

This case exemplifies the importance of:

1. Early Recognition: Mucocutaneous findings (oral ulcers, erosions) and hematologic abnormalities should raise immediate suspicion for MTX toxicity, prompting urgent evaluation and intervention [1].

2. Rapid Drug Discontinuation: Immediate cessation of MTX upon recognition of toxicity is paramount and likely contributed to this patient's favorable outcome.

3. Prompt Administration of Antidotes: Leucovorin rescue should be initiated as soon as MTX toxicity is suspected, particularly in patients with severe manifestations or renal impairment.

4. Aggressive Management of Complications: Supportive care including hematopoietic growth factor administration, management of secondary infections with appropriate antimicrobials, and respiratory support were essential to the patient's recovery [3].

5. Infection Control in Neutropenia: Careful monitoring for and empirical treatment of infections in neutropenic patients is critical, as neutropenic fever represents a medical emergency.

Learning Points for Clinical Practice

1. Methotrexate toxicity remains a serious, potentially fatal complication that can develop acutely, particularly with dosing errors or in patients with renal impairment. Early recognition based on mucocutaneous findings, hematologic abnormalities, and systemic manifestations is life-saving.

2. Pancytopenia with profound neutropenia, anemia, and thrombocytopenia may rapidly develop following MTX toxicity, necessitating hospitalization, close monitoring, and aggressive supportive care including blood product transfusions and hematopoietic growth factors.

3. Erosive mucositis affecting the oral cavity and esophagus is

a hallmark and early warning sign of MTX toxicity. Dysphagia, pain, and mucosal ulcerations should prompt immediate investigation for drug-related toxicity.

4. Leucovorin (folinic acid) is the definitive antidote for MTX toxicity and should be administered promptly at high doses (typically 100 mg every 6 hours) until serum MTX levels fall below the toxic threshold and clinical improvement is evident.

5. Granulocyte colony-stimulating factor (G-CSF, filgrastim) substantially accelerates neutrophil recovery in MTX-induced myelosuppression and reduces the incidence and severity of neutropenic infections and associated complications.

6. Hospital-acquired infections are common and life-threatening in neutropenic patients. Empirical broad-spectrum antimicrobial therapy should be initiated immediately in any neutropenic patient with fever or signs of infection, covering gram-positive, gram-negative, and atypical organisms.

7. Multidisciplinary management including close liaison between hematology, infectious diseases, pulmonology, and critical care specialists is essential in managing severe MTX toxicity with secondary complications.

8. Renal function monitoring is critical in patients receiving MTX, as renal impairment impairs drug clearance and significantly increases toxicity risk. Dose adjustment or discontinuation should be considered in patients with diminished renal function.

9. Patient education regarding medication dosing (particularly the weekly dosing schedule for MTX), adherence to prescribed regimens, and recognition of early warning signs of toxicity is essential for prevention of medication errors and improved safety.

10. Regular laboratory monitoring (complete blood counts, liver and renal function tests) should be performed routinely in patients receiving MTX to allow early detection of subclinical toxicity and enable intervention before progression to severe, life-threatening complications.

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