Case Report

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Internal Medicine Section

Methotrexate Toxicity Masquerading as Systemic Lupus Erythematosus Flare: A Case Report

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ABSTRACT

A 36-year-old woman with Rheumatoid Arthritis (RA) and class V lupus nephritis presented with fever, dysphagia and oral mucosal bleeding. She had been prescribed Methotrexate (MTX) 15 mg weekly but used it irregularly-almost daily-for four months. On examination, she had oral ulcers, reduced mouth opening, diffuse hair thinning, and erythematous papules. Laboratory findings revealed severe pancytopenia, elevated liver enzymes, and an increased MTX level. Complement levels were normal and anti-dsDNA negative, making a Systemic Lupus Erythematosus (SLE) flare unlikely. The diagnosis of MTX toxicity was confirmed. She was managed with immediate MTX withdrawal, folinic acid rescue (15 mg i.v. every six hours for three days), blood transfusions, and supportive care. Her counts normalised, and mucositis resolved within two weeks. This case emphasises the diagnostic challenge in differentiating drug toxicity from disease flare in autoimmune patients and underscores the need for strict adherence to MTX monitoring guidelines.

Keywords: Drug monitoring, Lupus nephritis, Pancytopenia, Rheumatoid arthritis

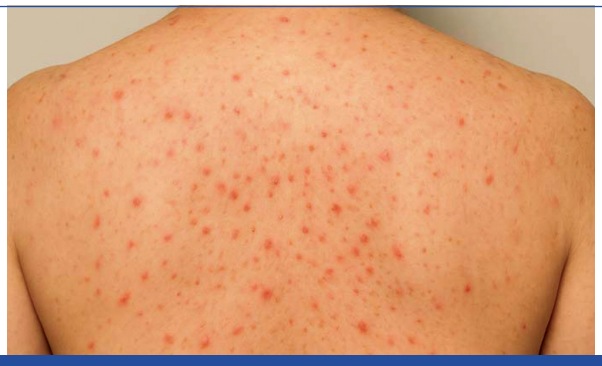
CASE REPORT

A 36-year-old woman presented to the emergency department with a three-day history of fever (up to 38.5°C), painful oral ulcers with spontaneous bleeding, difficulty swallowing solids, generalised weakness, and diffuse hair thinning. She reported poor oral intake due to pain and dysphagia.

The patient had a known diagnosis of RA and class V lupus nephritis, diagnosed five years prior to the current visit. She was prescribed MTX 15 mg weekly (oral), hydroxychloroquine 200 mg daily, and prednisolone 5 mg daily for the past four months. However, she admitted to irregular MTX use, taking 5-10 mg almost daily due to misunderstanding the weekly regimen, leading to a cumulative overdose. She had previously been managed with mycophenolate mofetil for lupus nephritis (discontinued one year prior to the current visit). No history of renal impairment, liver disease, alcohol use, or drug allergies was reported. No Non-steroidal Anti-Inflammatory Drugs (NSAIDs) or other interacting medications were used.

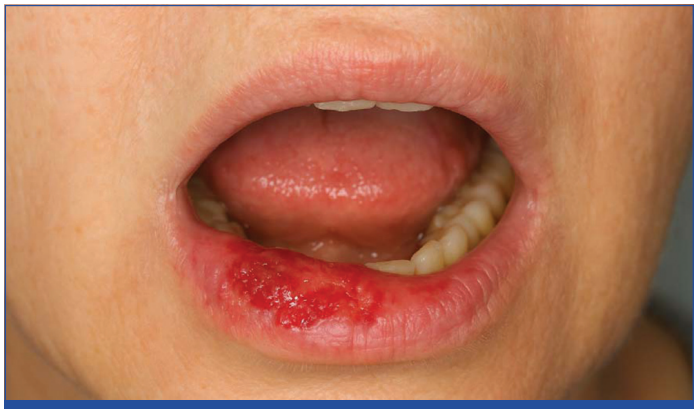
Examination findings: On admission, vital signs were stable: pulse 82/min, blood pressure 130/80 mmHg, respiratory rate 16/min, and SpO_2 98% on room air. Physical examination revealed:

- General: Pallor, diffuse hair thinning on the scalp, cheeks, and chin with reduced density .
- Skin: Multiple erythematous papules (3-5 mm) on the upper back and chest [Table/Fig-1].



[Table/Fig-1]: Clinical photograph showing multiple erythematous papules (3-5 mm) on the upper back, obtained on admission.

- Oral cavity: Multiple bleeding mucosal ulcers (2-5 mm) on the buccal mucosa and tongue, with reduced mouth opening (inter-incisal distance ~2.5 cm) [Table/Fig-2].



[Table/Fig-2]: Clinical photograph showing bleeding mucosal ulcers (2-5 mm) on the buccal mucosa, obtained on admission.

No joint swelling, rash, or lymphadenopathy was noted.

Laboratory findings: Laboratory findings on admission are summarised in [Table/Fig-3] [1].

Test	Result	Normal range [1]	Interpretation
Haemoglobin	6.6 g/dL	12-16 g/dL	Severe anaemia
Total leukocyte count	2000/µL	4000-11,000/µL	Leukopenia
Platelet count	25,000/µL	150,000-400,000/µL	Severe thrombocytopenia
PT-INR	1.8/1.3	INR <1.2	Prolonged PT
AST	120 U/L	<40 U/L	Elevated (liver dysfunction)
ALT	140 U/L	<40 U/L	Elevated (liver dysfunction)
Serum creatinine	1.8 mg/dL	0.6-1.2 mg/dL	Mild renal dysfunction
eGFR	48 mL/min/1.73m^2	>60 mL/min/1.73m^2	Reduced renal function
C3 Complement	110 mg/dL	90-180 mg/dL	Normal
C4 Complement	20 mg/dL	10-40 mg/dL	Normal

Anti-dsDNA	<2.6 IU/mL	<30 IU/mL	Negative
ANA profile	Positive	Negative	Autoimmune background
Methotrexate level	0.8 µmol/L	<0.1 µmol/L (therapeutic)	Suggestive of toxicity

[Table/Fig-3]: Laboratory investigations on admission [1].
PT-INR: Prothrombin time-International normalized ratio; AST: Aspartate transaminase; ALT: Alanine transaminase; eGFR: estimated glomerular filtration rate; ANA: Antinuclear antibodies

Diagnosis: The initial clinical suspicion was an SLE flare, given the patient's history of lupus nephritis, fever, oral ulcers, and positive Anti-nuclear Antibodies (ANA)/Extracting Nuclear Antigens (ENA) profiles (SS-A/Ro, SS-B/La) [Table/Fig-4] [2,3]. However, normal C3 (110 mg/dL) and C4 (20 mg/dL) levels, negative anti-dsDNA (<2.6 IU/mL), and absence of joint swelling or serositis argued against active SLE. Elevated MTX levels (0.8 µmol/L), severe pancytopenia, raised liver enzymes (AST 120 U/L, ALT 140 U/L), and mild renal dysfunction (eGFR 48 mL/min/1.73 m²) pointed to MTX toxicity. The history of daily MTX intake confirmed a cumulative overdose, leading to a diagnosis of MTX toxicity rather than an SLE flare.

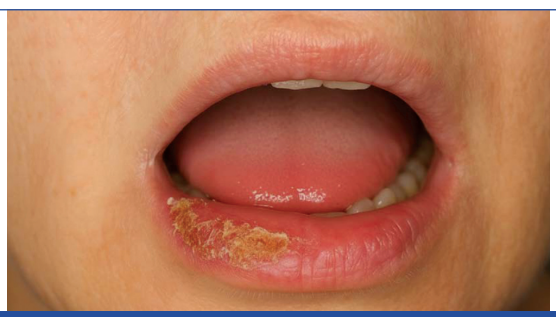
Autoantibody	Result	Clinical significance [2,3]
ANA	Positive	Indicates autoimmune activity
SS-A/Ro 60kD	+4	Seen in SLE, Sjögren's syndrome
SS-A/Ro 52kD	+4	Common in SLE/Sjögren's overlap
SS-B/La	+4	Associated with Sjögren's, SLE
Anti-dsDNA	Negative	Rules out active SLE flare

[Table/Fig-4]: ANA profile interpretation [2,3].

Management and Follow-up

- **MTX withdrawal:** Discontinued immediately on admission.
- **Folinic acid rescue:** Administered at 15 mg i.v. every six hours for five days, tapered based on declining MTX levels (0.3 µmol/L by day 5).
- **Supportive care:**
  - Packed red blood cell transfusion (2 units) for severe anaemia.
  - Platelet transfusion (1 unit) for thrombocytopenia.
  - Broad-spectrum antibiotics (ceftriaxone 1 g i.v. daily for seven days) to prevent sepsis.
  - For hydration, i.v. fluids (normal saline).
  - Topical lidocaine for oral ulcer pain.
- **Subsequent management:** Hydroxychloroquine (200 mg daily) and prednisolone (5 mg daily) continued. Mycophenolate mofetil (1 g twice daily) was reintroduced for lupus nephritis after renal function improved (eGFR 65 mL/min/1.73 m² by day 7).

By day 10, oral ulcers had healed significantly as shown in [Table/Fig-5], blood counts improved (haemoglobin 8.9 g/dL, leukocytes 3800/µL, platelets 90,000/µL), and liver enzymes decreased (AST 50 U/L, ALT 55 U/L). By day 14, all parameters normalised (haemoglobin 12.5 g/dL, leukocytes 6200/µL, platelets 200,000/µL, AST 35 U/L, ALT 38 U/L). At one-month follow-up, the patient was asymptomatic, with stable renal function (eGFR 68 mL/min/1.73 m²) and no recurrence of symptoms.



[Table/Fig-5]: Follow-up photograph at 1 month showing resolution of oral ulcers.

DISCUSSION

The MTX, a folate antagonist, is a cornerstone Disease-Modifying Antirheumatic Drug (DMARD) for RA and SLE, inhibiting dihydrofolate reductase and nucleotide synthesis to exert anti-inflammatory effects [4]. However, inappropriate dosing can lead to toxicity, affecting rapidly dividing tissues (bone marrow, mucosa, liver) and causing pancytopenia, mucositis, hepatotoxicity, and renal impairment [5]. In this case, the patient's daily MTX intake (5-10 mg instead of 15 mg weekly) led to cumulative toxicity, exacerbated by mild renal dysfunction (eGFR 48 mL/min/1.73 m²), which impairs MTX excretion [6].

The clinical presentation mimicked an SLE flare due to overlapping symptoms (fever, oral ulcers, and pancytopenia). Positive ANA and ENA (SS-A/Ro, SS-B/La) reflected the patient's autoimmune background but were non-specific in this context [2]. Normal complement levels and negative anti-dsDNA ruled out active SLE, while elevated MTX levels confirmed toxicity [7]. This diagnostic dilemma is well-documented, with case reports noting similar challenges in distinguishing MTX toxicity from SLE flares [7,8].

Current guidelines from the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommend monitoring complete blood counts, liver function, and renal function every 2-4 weeks during MTX initiation and every 8-12 weeks thereafter [9,10]. Folate supplementation (e.g., folic acid 5 mg weekly) reduces toxicity risk without compromising efficacy [11]. In this case, the absence of folate supplementation and irregular follow-up contributed to toxicity. Patient education on dosing schedules, using pill organisers, and regular monitoring could have prevented this outcome.

Strategies to improve adherence include clear verbal and written instructions, pharmacist counseling, and electronic reminders [8]. Differential diagnosis requires assessing complement levels, anti-dsDNA, and MTX levels, as SLE flares typically show hypocomplementemia and elevated anti-dsDNA, while toxicity presents with mucositis and elevated drug levels [2,7]. Patients with SLE and renal involvement face higher toxicity risks, necessitating tailored monitoring [12].

This case emphasises the need for vigilance in patients on MTX, particularly those with autoimmune diseases and renal impairment. Regular laboratory monitoring, patient education, and system-level safeguards (e.g., prescription alerts) are critical to prevent toxicity and ensure safe use of this valuable therapy.

CONCLUSION(S)

The MTX toxicity can closely mimic an SLE flare, posing a diagnostic challenge in patients with overlapping autoimmune disorders. This case illustrates the consequences of dosing errors and the importance of early recognition through regular monitoring of blood counts, liver, and renal function. Prompt MTX withdrawal, folinic acid rescue, and supportive care can be lifesaving. Clinicians must maintain a high index of suspicion for toxicity in patients with atypical symptoms, while health systems should implement safeguards to prevent dosing errors. Enhanced patient education and adherence to monitoring guidelines can optimise outcomes and preserve MTX's therapeutic benefits.

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