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Methotrexate-Induced Mucositis as a Sign of Bone Marrow Toxicity: A Retrospective Study of Clinical and Epidemiological Characteristics☆

La mucositis por metotrexato como marcador de toxicidad medular. Estudio retrospectivo de las características clínicas y epidemiológicas

To the Editor:

Methotrexate (MTX) is an antimetabolite that inhibits folic acid synthesis. It is widely used in dermatology, rheumatology, and oncology.[1] Although MTX has a good safety profile, serious adverse effects such as pneumonitis, hepatic fibrosis, and bone marrow aplasia can occur.[1–3] Previous studies have suggested that MTX-induced mucositis may be a sign of bone marrow toxicity.[2,3] The aim of this study was to analyze clinical, laboratory, and epidemiological characteristics of patients with MTX-induced mucositis.

We performed a retrospective study of patients with a diagnosis of MTX-induced mucositis or mouth ulcers evaluated by the dermatology department at our hospital between January 2013 and July 2018. The patients' medical records were reviewed to collect epidemiological, clinical, and pictorial information. Five patients (1 man and 4 women) with a median age of 72 years (range, 50–90 years) were included. The epidemiological and clinical characteristics are summarized in Table 1. The median MTX dose was 15 mg/wk (range, 10–35 mg/wk). The route of administration was subcutaneous in 3/5 patients and oral in 2/5 patients. Two of the patients were taking MTX for psoriasis and 3 were taking it for rheumatoid arthritis. All the patients had erosions and necrotic crusts in the oral cavity (Fig. 1A–D). Additional conditions included pancytopenia or bicytopenia in 4/4 patients, fever in 2/5, and skin ulcers in 2/5 (one had ulcerated psoriatic plaques and the other had an ulcerated basal cell carcinoma on the leg (Fig. 2A and B). Median peripheral blood leukocyte count was 2475×10^6 (range, $330–4200 \times 10^6$). Additional laboratory values (median [range]) were hemoglobin 73.5 g/L (range, 53–92 g/L), mean corpuscular volume 98.5 fL (range, 93–105 fL), and platelets $92\,500 \times 10^6$ (range, $37\,000–128\,000 \times 10^6$). Serum creatinine levels were elevated in 2/4 patients (median, 2.42 mg/dL [range, 0.44–5 mg/dL]). Only 1 patient had impaired liver function reflected by elevated gamma-glutamyl transferase (156 mg/dL [reference value < 40 mg/dL]) and prothrombin time (international normalized ratio, 1.4). Bone marrow aspiration was performed in 3/5 patients and showed marked hypocellularity, which is consistent with MTX toxicity. The most common trigger was use of a nonsteroidal anti-inflammatory drug (NSAID) (2/5), followed by an administration error (1/5), infection (1/5), and a lack of folic acid intake (1/5). Plasma MTX levels were normal (<0.3 mol/L) in 3/3 patients. Treatment included MTX withdrawal in 5/5 patients, intravenous folic acid in 4/5, and granulocyte colony stimulating factor in 1/5. All the patients achieved complete recovery and just 1 was restarted on MTX.

The most common serious adverse effect of MTX is bone marrow toxicity, which has been observed in 2.5% to 10% of patients and is potentially fatal.[4] Mucocutaneous ulceration is a characteristic finding in patients with acute MTX toxicity.[3,5] MTX inhibits cells with a fast turnover and therefore hematopoietic and skin cells are more likely to be affected by its antiproliferative action.[6] MTX is mainly eliminated by glomerular filtration, and just a small fraction is metabolized in the liver. Decreased glomerular filtration rate due to dehydration, infection, and use of drugs such as NSAIDs can therefore lead to MTX accumulation and subsequent toxicity.[3,7] In our study, 3/4 patients had impaired kidney function and 3/5 were taking NSAIDs. These associations are consistent with previous reports describing dosing errors, kidney failure, drug-drug interactions (NSAIDs, antibiotics, or salicylates), and MTX reintroduction or dose increments as the main causes of MTX toxicity.[2,3,5,7]

All the patients in our study with blood test results (4/4) had pancytopenia or bicytopenia, and 2 required empirical antibiotic therapy due to febrile neutropenia. These findings highlight the complex management of MTX-induced toxicity, the potential complications, and the need for a high index of clinical suspicion in patients who develop mucocutaneous ulcers while on MTX, particularly if they have risk factors for decreased glomerular filtration rate.[2,3] Elevated mean corpuscular volume (present in 2 of our

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Table 1 Epidemiological and Clinical Characteristics of Patients With MTX-induced Toxicity and Mucocutaneous Lesions.

Patient	Age, y/Sex	Comorbidities	MTX Dose	Route of Administration	Time on MTX	Trigger	Clinical Presentation	Kidney Failure	Clinical Course	Treatment	Reinitiation of MTX
1	90/F	Rheumatoid arthritis Hypertension Breast cancer	5 mg/wk	Oral	5 y	Administration error 5 mg/d	Fever, mucositis, pancytopenia	No	CR	Withdrawal of MTX Folic acid 15 mg/d IV	No
2	61/F	Rheumatoid arthritis DM2 Hypertension CRF (CrCl)	10 mg/wk	Subcutaneous	9 y	Folic acid not administered	Fever, mucositis, pancytopenia	Yes Clcr 25 mL/min	CR	Withdrawal of MTX Folic acid 15 mg/d IV	Yes 10 mg/wk
3	50/F	Psoriasis ID-DM2 Hypertension CRF	25 mg/wk	Subcutaneous	25 y	Impaired renal function due to NSAID	Mucositis, skin ulcers, pancytopenia	Yes Clcr 9.8 mL/min	CR	Withdrawal of MTX Folic acid 140 mg IV followed by 50 mg IV every 6 h GCSF	No
4	72/F	Psoriasis DM2	15 mg/wk	Subcutaneous	1 mo	Use of NSAIDs	Mucositis	Unknown	CR	Withdrawal of MTX	No Etanercept
5	81/F	Rheumatoid arthritis Chronic lung disease CRF	10 mg/wk	Oral	Unknown	Skin infection and NSAID	Mucositis, skin ulcers, bicytopenia	Yes Clcr 22 mL/min	CR	Withdrawal of MTX Folic acid IV (nonspecified dose)	Not known

Abbreviations: CR, complete response; CRF, chronic renal failure; DM2, diabetes mellitus type 2; F, female; ID, insulin-dependent; M, male; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug.

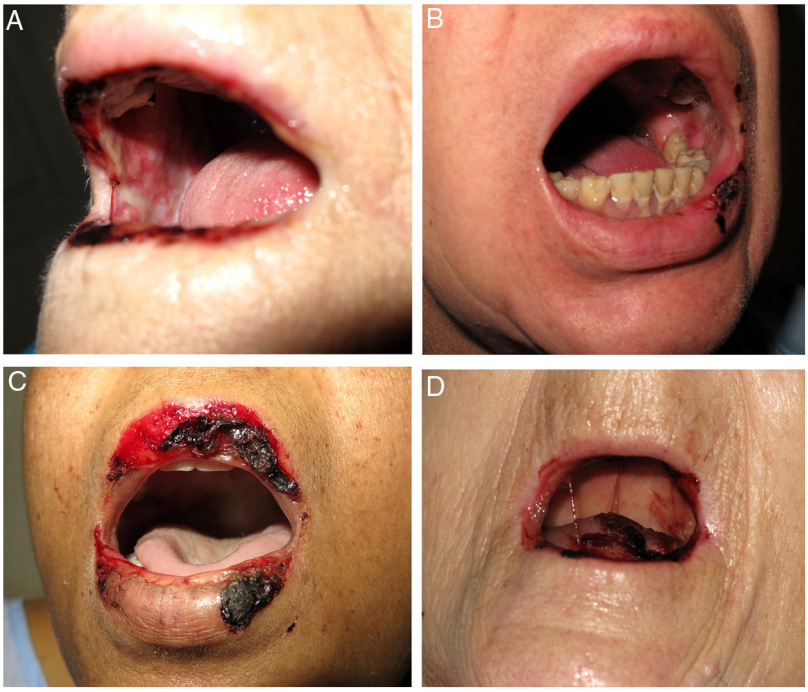

Figure 1 Methotrexate-induced mucositis. Erosions and necrotic crusts. A, Patient 1. B, Patient 2. C, Patient 3. D, Patient 4.

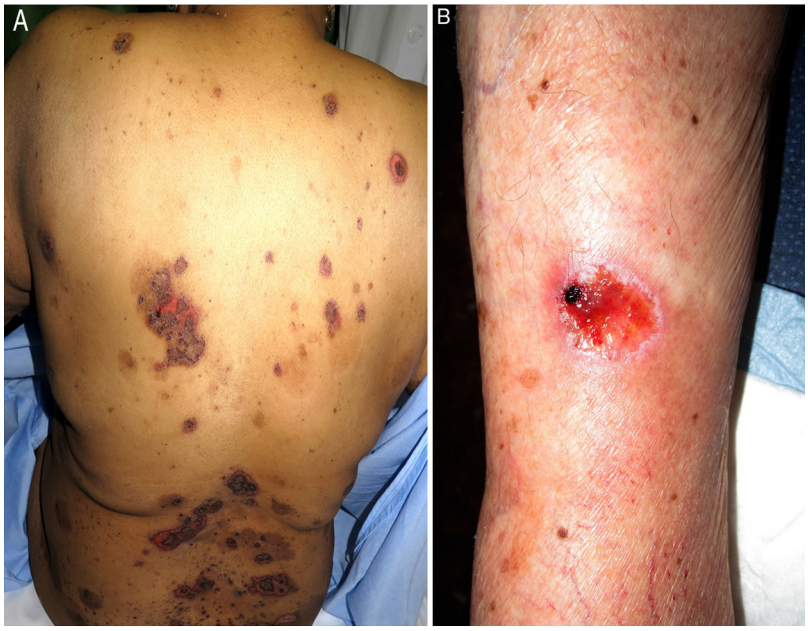

Figure 2 Cutaneous ulcers due to methotrexate. A, Ulcerated psoriasis plaques on the back (patient 3). B, Ulcerated basal cell carcinoma on the leg (patient 5).

patients) could be an early sign of bone marrow toxicity due to folic acid deficiency. Serum MTX levels were low in 3 of the 4 patients with mucositis and pancytopenia tested. These low levels can be explained by the cellular accumulation of the drug. Plasma concentrations are typically 0.01 M 24 hours after withdrawal of MTX, and serum levels do not correlate well with toxicity.[7]

Skin ulcers due to MTX have mostly been described in association with psoriasis or previous injury.[2,5] In our series, ulcers were observed in psoriatic plaques in 1 patient and in a basal cell carcinoma in the other. Ulcers can, however, also affect healthy skin.

MTX toxicity can cause high morbidity and mortality.[3] Detection of mucocutaneous ulcers in a patient on MTX should raise suspicion of pancytopenia and kidney failure, even in patients on low MTX doses and with normal serum concentrations. These patients must be hospitalized and treated by a multidisciplinary team.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Foreign-Body Reaction to Dermal Filler: Good Response to Treatment With Allopurinol☆

Respuesta favorable al tratamiento con alopurinol de reacción granulomatosa a relleno

Dear Editor:

Procedures involving dermal filler for cosmetic purposes are carried out every day. However, this practice is not risk-free. One reported complication is that of foreign-body granulomatous reaction to a component of the filler.[1,2] One of the initial treatment options is infiltration with corticosteroids, although the condition can also be managed with oral allopurinol.[3–5]

An 83-year-old woman was referred for a lesion on her left cheek that had been treated for 3 weeks with oral antibiotic therapy (amoxicillin clavulanate, 875/125 mg/8 h), surgical drainage, and a 2-week tapering course of oral corticosteroids (starting with prednisone 30 mg/d), albeit with minimal improvement. The patient's history was remarkable only for the fact that she reported undergoing surgery in this area some years previously. Similarly, she denied having received infiltrations or fillers. Physical examination revealed a fistulous tract with purulent discharge, depressed areas of scarring, and, adjacent to these areas, a reddish exudative papular lesion. The lesions were surrounded by an edematous area with a doughy consistency, occupying almost the whole cheek (Fig. 1A). Ultrasound revealed several nodular hypoechoic lesions that differed in size, the largest being 1 cm in diameter. These were mainly superficial, with vascularization in the interior and slightly increased echogenicity of the underlying subcutaneous tissue. A histopathology study was recommended. Biopsy revealed a foreign-body granulomatous reaction in the dermis and subcutaneous tissue, with the presence of 2 different materials in the histology sections: a superficial eosinophilic material with no associated granulomatous reaction and a deeper basophilic amorphous material accompanied by a moderate inflammatory infiltrate composed of macrophages with granular cytoplasm (Fig. 2). Given the diagnosis of a foreign-body granulomatous reaction and the uselessness of previous treatments, we offered the patient the possibility of treatment with allopurinol under a compassionate use regimen (300 mg/d, po) combined with mometasone furoate in blocks of 15 days every month. This treatment led to a slow but gradual improvement with fluctuations until the lesions were totally controlled 8 months later (Fig. 1B), with resolution of the initial soft tissue edema and atrophic scarring. Treatment was well tolerated, and no adverse effects were reported during follow-up.

Comment

While relatively harmless, infiltration of dermal filler is not free of complications, which can be classed as short-term, such as hematomas and infections, and long-term, such as migration of material or foreign-body granulomatous reactions, as in the present case. Granulomatous reactions are

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