

Can a test-dose of methotrexate cause methotrexate-induced epidermal necrosis?

Sir,

The development of methotrexate-induced epidermal necrosis is a rare adverse reaction to this drug, usually associated with chronic kidney disease and high initial dosage.¹ However, in this report, we highlight that methotrexate-induced epidermal necrosis may occur only after a test-dose, even in the absence of a significant renal impairment.

A 54-year-old hypertensive and diabetic woman was referred to our Department with palmoplantar pustular psoriasis. She had been using furosemide, propranolol, metformin, and acetylsalicylic acid regularly for 2 years. The patient failed to respond to several previous psoriasis treatments, including topical preparations (potent steroids and coal tar), colchicine, and dapsone. A new treatment attempt with methotrexate was suggested, as soon as a thorough pre-evaluation was performed and showed no contraindication. Pretreatment routine biochemistry was unremarkable except for mild renal dysfunction [creatinine: 0.9 mg/dL and estimated glomerular filtration rate (eGFR): 73 mL/

min]. Thus, a test-dose of subcutaneous methotrexate was administered (7.5 mg/week) [day 0] followed by oral folic acid (5 mg) 2 days later. On day 4 the patient presented with a bullous eruption. Examination revealed hemorrhagic bullae on the palms and soles [Figure 1], along with few scattered lesions on the lower extremities and thorax. Mucosal involvement of the upper and lower lips could be observed, showing extensive irregular ulcerations, cracking, and fissuring with blood encrustation [Figure 2]. Intraoral and genital ulcerations were also visualized. Immediately after the first assessment, methotrexate was suspended. Histopathological examination of a lesion on the leg revealed a vacuolar interface dermatitis with epidermal necrosis, dyskeratosis, and moderate inflammatory infiltrate with eosinophils [Figure 3]. Laboratory investigations detected neutropenia ($0.42 \times 10^9/L$; normal value: $1.50\text{--}7.00 \times 10^9/L$), leukopenia ($2.51 \times 10^9/L$; normal value: $3.60\text{--}11.00 \times 10^9/L$), thrombocytopenia ($69 \times 10^9/L$; normal value: $150\text{--}400 \times 10^9/L$), and elevated aminotransferases [alanine aminotransferase (ALT): 219 U/L; normal value 10–34 U/L

and aspartate aminotransferase (AST): 136 U/L; normal value: 10–49 U/L]. Based on the history, clinical examination, and histopathologic findings, a final diagnosis of methotrexate-induced epidermal necrosis was established, associated with myelosuppression and hepatic injury. After 10 days of drug withdrawal, cutaneous lesions resolved with re-epithelization, along with progressive normalization of laboratory parameters.

Methotrexate-induced epidermal necrosis is a rare acute idiosyncratic reaction that may be life-threatening.² It is characterized clinically by skin detachment and mucosal erosions, which mimics Stevens–Johnsons syndrome and toxic epidermal necrolysis. Therefore, reports have previously described cases as “methotrexate-induced necrolysis”² or “pseudo-toxic epidermal necrolysis”.³ Recently, a case series of 24 patients has established the term methotrexate-induced epidermal necrosis.¹ This study compared cases with a control group of 150 patients who were also using methotrexate. The most important risk factors for methotrexate-induced epidermal necrosis included older age (>60 years), chronic renal disease (eGFR < 60 mL/min), and a high initial dosage (>10 mg/week) without folic acid supplementation. Interestingly, our patient did not present any of the risk factors: she was younger than the cutoff age, she did not present with a significant decrease in renal function, the initial dose of methotrexate was very low (test-dose), and it was followed by supplementation with folic acid.

In the same case-series variable degree of skin detachment was observed, ranging from 8% to 80% of total body surface area.¹ In addition, approximately half of the patients had leukopenia and thrombocytopenia, while significant hepatic impairment was present in only 1 case (AST 184 U/L and ALT 183 U/L). The median duration of methotrexate exposure was 34 days (ranging from 3 to 90 days), with a median initial dose of 12.4 mg. Additional findings included concomitant nonsteroidal anti-inflammatory drug use [20.8% (n = 5)] and hypoalbuminemia (<3.5 g/dL) [85.7% (n = 18)] in methotrexate-induced epidermal necrosis cases. Our patient presented with a small area of skin detachment (8%), along with leukopenia and thrombocytopenia. Although uncommon, our case also presented with elevated hepatic enzymes, adding to the single case described by Chen *et al.*¹ Remarkably, our patient developed symptoms within 4 days of a test-dose of 7.5 mg; however, she was using concomitant acetylsalicylic acid, which may have increased free active methotrexate in the serum, as both drugs compete for albumin-binding sites.^{4,5} Furthermore, our patient had a borderline albumin level (3.5 g/dL).

Since methotrexate is used in a wide spectrum of dermatologic diseases, we believe it is important to report a significant cutaneous reaction to this drug, to raise awareness about this possible event.



Figure 1: Hemorrhagic bullae on the palmar region



Figure 2: Extensive irregular ulcerations, cracking, and fissuring with hemorrhagic crusting of the mucosal upper and lower lips

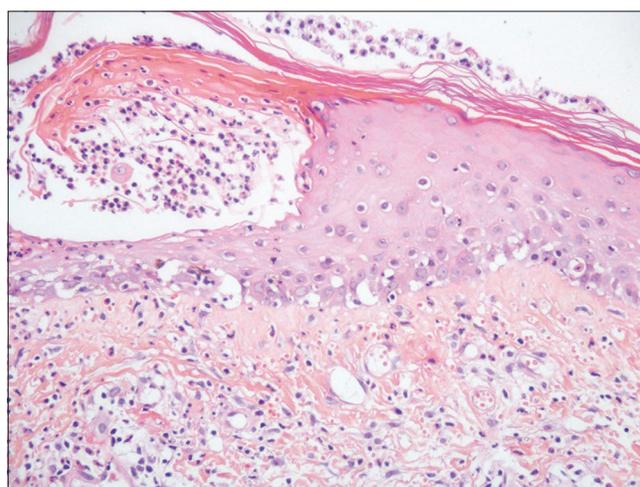


Figure 3: Vacuolar interface dermatitis with epidermal necrosis, dyskeratosis, and chronic inflammatory infiltrate with eosinophils (H and E, ×200)

Declaration of patient consent

The authors certify that they have obtained all appropriate

patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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