Methotrexate Toxicity Induced by Ciprofloxacin Leading to Psoriatic Plaque Ulceration: A Case Report

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Practice Points

- Relatively low doses of methotrexate often are used in dermatology and toxicity is infrequent; however, it is important to consider that any insult, including common medications such as antibiotics, can result in toxicity in elderly patients.
- Early detection of the unique signs of toxicity, such as peripheral psoriatic plaque ulcerations, is important, as they could precede more catastrophic events, such as bone marrow suppression.

We present the case of a 90-year-old woman with psoriasis vulgaris who had been treated with methotrexate for many years. The patient presented with psoriatic plaque ulcerations uniquely limited to the active border as well as acute oral ulcerations and severe gastrointestinal upset after undergoing a course of ciprofloxacin for treatment of a bacterial infection.

Cutis. 2013;92:148-150.

Case Report

A 90-year-old woman with a history of severe psoriasis vulgaris developed psoriatic plaque ulcerations limited to the active border, acute oral ulcerations, and severe gastrointestinal upset following a course of ciprofloxacin. Her medical history was notable for type 2 diabetes mellitus, hypertension, hyperlipidemia, arthritis, and nephrolithiasis.

Her psoriasis had been treated with methotrexate for the last 4 years at doses ranging from 7.5 to 15 mg weekly. Six months earlier her psoriasis had remarkably improved and methotrexate was discontinued at the patient's request; however, psoriatic plaques recurred 2 months later and treatment with methotrexate (12.5 mg weekly) resumed. Two months later she developed two 5-mm superficial ulcerations with a yellowish base and mild tenderness on the dorsal aspect of the left foot that were suggestive of a bacterial infection A bacterial culture revealed *Pseudomonas aeruginosa*, and treatment with ciprofloxacin (500 mg twice daily) was initiated.

The patient returned after completing a 2-week course of ciprofloxacin. On presentation, the ulcerations on the dorsal aspect of the left foot demonstrated improvement; however, she complained of nausea, vomiting, and pain in her mouth as well as in her psoriatic plaques. On examination, 2 oral ulcerations were noted: 1 on the interior border of the lower lip (Figure 1) and another on the right buccal mucosa. Additionally, acutely developed peripheral ulcerations were observed in the psoriatic plaques on the trunk (Figure 2). This constellation of findings

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Drs. Kamangar, Berger, and Fazel report no conflict of interest.
Dr. Koo has been a clinical researcher, consultant, and speaker for Abbott Laboratories; Allergan, Inc; Amgen Inc; Astellas Pharma Inc; Galderma Laboratories, LP; Genentech, Inc; JSJ Pharmaceuticals, Inc; PhotoMedex, Inc; Roche USA; Teikoku Pharma USA, Inc; and Warner Chilcott.
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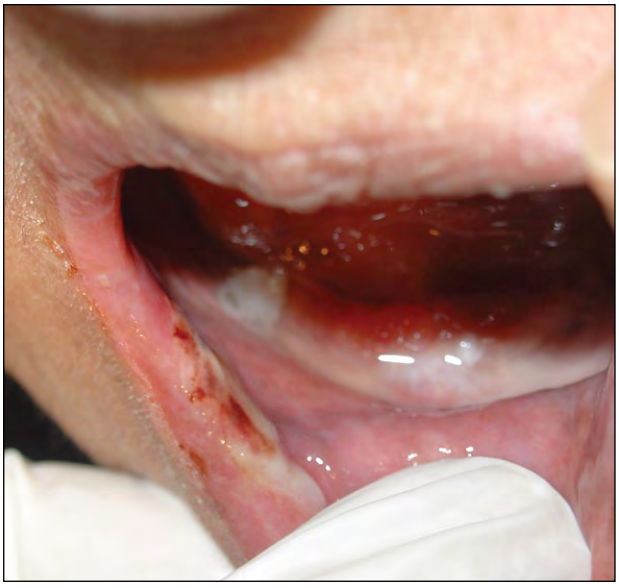

Figure 1. Mucosal ulceration of the right lower lip.

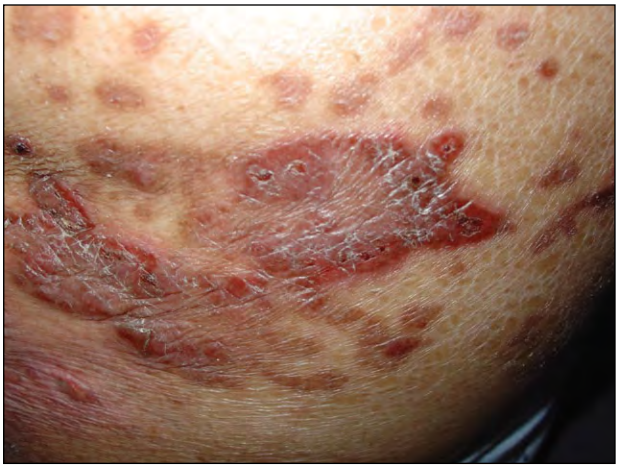

Figure 2. Psoriatic plaques on the trunk with active border ulceration.

suggested methotrexate toxicity. Subsequently, treatment with methotrexate was discontinued and the patient was advised to use clobetasol propionate ointment on psoriatic plaques. Laboratory test results demonstrated increased creatinine levels (from 0.9 mg/dL at baseline to 1.59 mg/dL [reference range, 0.6–1.2 mg/dL]), a white blood cell count of 5.3×10^9/L (reference range, $4.5-11.0\times10^9$/L), a platelet count of 123×10^9/L (reference range, $150-350\times10^9$/L), an aspartate aminotransferase level of 51 U/L (reference range, 10−30 U/L), and an alanine aminotransferase level of 53 U/L (reference range, 10−40 U/L). The serum methotrexate level was 0.05 μmol/L, which was below toxic level (reference range for toxic level, >0.10 μmol/L). The patient was started on prednisone 20 mg daily for 1 week, dexamethasone mouthwash, and oral clotrimazole solution 1%.

The patient returned 1 week later with the oral ulcerations and peripheral ulcerations on psoriatic plaques almost completely resolved. She reported no further episodes of gastrointestinal upset. Laboratory test results collected 2 weeks following the initial laboratory examination demonstrated a creatinine level of 1.11 mg/dL, a white blood cell count of 5.8×10^9/L, a platelet count of 179×10^9/L, an aspartate aminotransferase level of 92 U/L, and an alanine aminotransferase level of 47 U/L. The patient's psoriasis remained stable and treatment with methotrexate was not reinstituted.

Comment

Following treatment with ciprofloxacin, our patient presented with peripheral psoriatic plaque ulcerations uniquely limited to the active border, oral ulcerations, and gastrointestinal upset, as well as elevated creatinine levels, decreased platelet count, and increased liver function tests. The patient's serum methotrexate levels were below toxic levels; however, these levels were drawn 5 days after her last methotrexate dose, which may have been too late, as after a single dose of methotrexate, serum levels usually are not detectable after 18 to 24 hours.[1,2] Overall, the clinical and laboratory findings were highly suggestive of methotrexate toxicity.

The timing of the toxicity following the initiation of antibiotic therapy was suggestive of ciprofloxacin as the offending agent. Both methotrexate and ciprofloxacin can cause nephrotoxicity, and the combination of the 2 drugs can lead to increased methotrexate levels, which causes mucocutaneous, hematologic, and liver toxicity.[3]

Methotrexate toxicity can present with various signs, including gastrointestinal upset, abnormal liver function tests, decreased blood cell counts, stomatitis, oral ulcers, and headaches.[4] Rarely, methotrexate toxicity results in a unique pattern of cutaneous ulceration at the active peripheral border of psoriatic plaques. This peripheral rim of activity is where cell division is most robust, and methotrexate is thought to work prominently on these most actively dividing cells.[5] This phenomenon mainly has been reported in patients of advanced age; in previously reported cases, the majority of patients have been older than 60 years.[3,6-12] In elderly patients older than 80 years, toxicity has been reported in doses as low as 7.5 mg weekly.[13]

Methotrexate toxicity can be precipitated by numerous factors, including renal insufficiency, folate deficiency, hypoalbuminemia, excessive alcohol intake, drug interactions, and advanced age.[4] Medications that are known to increase methotrexate serum levels include antibiotics (eg, ciprofloxacin, trimethoprim-sulfamethoxazole, sulfonamide, penicillin, tetracycline), nonsteroidal anti-inflammatory drugs, barbiturates, colchicine, dipyridamole, ethanol, phenytoin, probenecid, sulfonylureas, thiazides, and furosemide.[4]

Relatively low doses of methotrexate often are used in dermatology and toxicity is infrequent; however, it is important to consider that any insult, including common medications such as antibiotics, can result in toxicity in elderly patients. Early detection of the unique signs of toxicity, such as peripheral psoriatic plaque ulcerations, is important, as they could precede more catastrophic events, such as bone marrow suppression.

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