Low-dose methotrexate-induced skin toxicity: Keratinocyte dystrophy as a histologic marker

Julie Delyon, MD,[a] Nicolas Ortonne, MD, PhD,[b] Emmanuel Benayoun, MD,[c] Julien Moroch, MD,[b] Pierre Wolkenstein, MD, PhD,[a,e,f] Emilie Sbidian, MD, PhD,[a,d,e,f] and Olivier Chosidow, MD, PhD[a,e,f]
Créteil, France

Background: Skin toxicity during low-dose methotrexate therapy is rare, ill described, and reported to have nonspecific histologic characteristics. Thus, misdiagnosis is common in patients with mucosal ulcers and/or skin erosions related to low-dose methotrexate.

Objective: We sought to describe the features of skin toxicity induced by low-dose methotrexate.

Methods: We evaluated the clinical and histologic features in 5 patients who experienced skin toxicity induced by low-dose methotrexate between 2011 and 2013.

Results: All 5 patients had acute mucosal ulcers, 4 had moderately abnormal blood cell counts, and 3 had skin erosions. In 3 patients, methotrexate dosage or dosing-schedule errors were identified. No other contributing factors (eg, renal dysfunction or interacting drugs) were identified. Mucocutaneous biopsy specimens consistently showed multiple dystrophic keratinocytes.

Limitations: We studied only 5 patients and obtained no sensitivity or specificity data on the diagnostic value of keratinocyte dystrophy.

Conclusion: Keratinocyte dystrophy may help to diagnose skin toxicity of low-dose methotrexate, even in the absence of known risk factors or methotrexate administration errors. Studies of the diagnostic performance of this histologic sign are needed. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.06.015.)

Key words: keratinocyte dystrophy; methotrexate; pancytopenia; psoriasis; skin toxicity; ulcers.

Low-dose methotrexate is among the first-line treatments for numerous inflammatory diseases such as moderate to severe psoriasis and rheumatoid arthritis. Methotrexate decreases cell proliferation by inhibiting dihydrofolate reductase, which is required for purine synthesis.[1] The most common side effects of low- and high-dose methotrexate therapy are acute myelosuppression, gastrointestinal disorders, hepatotoxicity, and acute renal failure.[2] Among patients receiving high-dose methotrexate for malignant diseases, 17% experience mucosal ulcers and 5% skin erosions. These mucocutaneous manifestations are believed to be rare during low-dose methotrexate therapy,[3] as only a few anecdotal cases have been published.[4,5] However, their frequency may be underestimated, as their clinical features are ill described[6] and their histologic pattern reported to be nonspecific.[7,8] Thus, cases may be misdiagnosed by both dermatologists and pathologists.

Here, we describe the features of mucocutaneous toxicity induced by low-dose methotrexate therapy in 5 patients. Keratinocyte dystrophy was a consistent histologic finding reminiscent of the epidermal

From the Département de Dermatologie,[a] Pathologie,[b] and Hématologie Biologique,[c] and Pôle Recherche Clinique Santé Publique,[d] Assistance Publique-Hôpitaux de Paris (AP-HP) Hôpitaux universitaires Henri Mondor; Inserm, Centre d'Investigation Clinique 1430[e]; and Equipe d'Accueil (EA) EpiDermE, Université Paris-Est Créteil.[f]

Drs Delyon and Ortonne contributed equally to this article. Drs Sbidian and Chosidow contributed equally to this article.

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Correspondence to: Emilie Sbidian, MD, PhD, Département de Dermatologie, AP-HP, Hôpitaux universitaires Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny Créteil, F-94010, France.

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dysmaturation described in patients receiving chemotherapies.

METHODS

We conducted a retrospective case series study of consecutive patients admitted to our department over a 3-year period (2011-2013) with mucosal ulcers and/or cutaneous erosions during low-dose methotrexate therapy. Demographic and clinical characteristics were collected from the medical records. A 4-mm punch biopsy specimen from the skin or mucosa adjacent to an erosion or ulcer was obtained in 4 patients; the general health of the remaining patient (patient 5) was deemed too poor to allow a biopsy. The specimens were processed for standard histology. The presence of herpes simplex virus (HSV)1/2 in biopsy specimens was assessed by immunohistochemical staining and polymerase chain reaction (PCR). Immunohistochemical staining for Ki-67 was performed for 2 of the 4 patients with biopsy specimens (patients 3 and 4).

CAPSULE SUMMARY

- Low-dose methotrexate can induce mucocutaneous erosions that remain ill described, particularly regarding their histologic features.
- Keratinocyte dystrophy was found in 5 patients with mucocutaneous toxicity of low-dose methotrexate.
- Keratinocyte dystrophy in mucocutaneous lesions may serve as a warning sign of potentially life-threatening methotrexate toxicity.

RESULTS

Table I lists the main clinical features in the 5 patients. Briefly, all patients were prescribed methotrexate in dosages of 10 to 20 mg weekly, for psoriasis (patients 1 and 2), rheumatoid arthritis (patients 3 and 4), or bullous pemphigoid (patient 5). The oral cavity was consistently involved. Mucosal ulcers were present on the oral mucosa (n = 5), palate (n = 2), gingiva (n = 1), and/or nasal mucosa (n = 3) (Fig 1, *E*). In addition, 3 patients had skin erosions, including 2 patients with psoriasis (patients 1 and 2) who had extensive erosions on their psoriatic plaques (Fig 1, *A-C*); the remaining patient (patient 4) had small shallow erosions on her arms and trunk (Fig 1, *D*). Of the 5 patients, 3 had taken more than prescribed methotrexate dose, either unintentionally (patients 1 and 5) or intentionally (patient 2): before symptom onset, patient 1 had taken twice the weekly dosage and patients 2 and 5 had taken methotrexate daily instead of weekly. The other 2 patients correctly had taken methotrexate as prescribed. All patients denied using interacting drugs such as nonsteroidal anti-inflammatory drugs.

Laboratory tests showed moderate and transient blood cell count abnormalities in 4 patients, consisting of anemia (n = 4), neutropenia (n = 2), and/or thrombocytopenia (n = 2). Anemia was accompanied with an increased mean corpuscular volume in 3 patients, compared with previous complete blood cell counts, including 1 patient with macrocytosis (patient 5). Examination of a bone-marrow aspirate performed to evaluate pancytopenia in patient 3 revealed qualitative abnormalities in the myeloid cell lines, with enlarged precursor cells, segmented nuclei, agranular cells, and pseudo–Pelger-Huët anomaly, which were not related to myelodysplastic syndrome. Liver and renal function test results were normal in all patients. Folate deficiency was diagnosed in a single patient (patient 5), who had taken appropriate supplementation. Serum methotrexate levels measured on the day of admission were below the detection threshold in all 5 patients.

Biopsies were performed in 4 patients (Table II). In the 2 patients with psoriasis (patients 1 and 2), biopsy specimens of eroded plaques exhibited the usual features of psoriasis, and unevenly arranged, dystrophic keratinocytes of variable size, containing clear cytoplasm and variably enlarged nuclei, some of which had irregular contours (Fig 2, *A* and *D*). Mucosal biopsy specimens from the 2 patients with rheumatoid arthritis (patients 3 and 4) showed multiple dystrophic keratinocytes including giant multinucleate keratinocytes in 1 case (Fig 2, *B* and *C*). Similar cells were found in biopsy specimens of cutaneous erosions from 1 of these patients (patient 4). Direct immunofluorescence (IgA, IgG, IgM, and C3) identified nonspecific deposits in all 4 cases. Of the 4 patients with biopsy specimens, 1 had equivocal HSV1/2 immunohistochemical staining at both oral cavity and skin sites (patient 4). Only the oral cavity sample was positive with HSV1/2 by PCR. Two other patients had positive PCR assays for HSV1/2 DNA in only 1 of 2 sampled sites (ie, in the oral cavity or skin) (patients 1 and 2). A single PCR-positive patient (patient 4) received valacyclovir.

In 1 patient (patient 4), in addition to methotrexate toxicity, pemphigus vulgaris was considered a possible diagnosis. This patient had taken methotrexate as prescribed and had no major blood cell count abnormalities. Therefore, we continued methotrexate therapy until the biopsy specimen results