Methotrexate-induced erythema multiforme

Miranda B. Kim, MD,† Christine Klimowicz White, DO, and John J. Stern, MD

Department of Internal Medicine, Division of Infectious Diseases, University of Pennsylvania Health Systems, Pennsylvania Hospital, Philadelphia

Methotrexate (MTX) is a drug that is commonly used to treat a range of diseases, including inflammatory conditions and malignancies. Although it is effective as a therapy, it is not a benign drug and can have serious adverse effects. In this article, we report and discuss a case of MTX-induced erythema multiforme (EM).

Case presentation

A 44-year-old man with acute T-cell lymphocytic leukemia was admitted for treatment with intrathecal and high-dose intravenous MTX. Immediately after treatment, the patient described a "warm rush" from his head to his toes, a reaction associated with nausea and vomiting and relieved with ondansetron. We drew labs and monitored his MTX levels on days 1 and 2 (Table 1). On day 3, the patient complained of feeling anxious and a "crawling" sensation on his skin. A physical examination revealed notable facial flushing. We relieved the patient's symptoms with lorazepam and discharged him later that day.

On the morning of day 4, the patient developed new skin lesions, this time worse than those that were treated on day 1. The patient went to his outpatient oncologist's office on day 5. An evaluation revealed normal cardiac, pulmonary, and abdominal results. However, the patient reported feeling a swollen throat and exhibited facial erythema (redness) associated with small, pustular lesions on his face, chest, and back that were nonpruritic and nontender (Figure 1). The patient was sent to the emergency department and admitted to the hospital, where an ear, nose, and throat evaluation using laryngoscopy revealed no airway involvement. He was treated with decadron, ondansetron, and diphenhydramine. Biopsies of a neck lesion revealed "skin with perivascular acute and chronic inflammation in dermis, mild lymphocytic epidermal infiltrate and predominantly basal apoptotic keratinocytes." A biopsy of an abdominal lesion also found "zonal full thickness epidermal necrosis, with focal underlying epidermal epithelialization and associated acute necrotizing folliculitis." These findings were consistent with EM, attributed to the MTX that had been administered a few days earlier.

Oral prednisone and triamcinolone 0.1% cream were recommended for treating the EM. During his hospitalization, the patient's lesions spread to his buttocks and groin and he developed severe oral mucositis. The patient's hospitalization course was also complicated by *Clostridium difficile* diarrhea, small-bowel obstruction, acute kidney injury, and delirium, all of which were treated appropriately and resolved. Over a 3-week period, the rash slowly began to crust and improve. The patient was feeling well and was stable enough to be discharged 43 days after initial admission.

Discussion

MTX is a folic acid analog interfering with DNA replication that has been used in cancer treatment for decades.[1,2] It works both systemically and in the central nervous system. Common side effects of MTX are acute hepatitis, stomatitis, nausea, vomiting, abdominal pain, diarrhea, myelosuppression, fever, and fatigue.[3]

Manuscript received September 5, 2012; accepted October 10, 2012.

Correspondence Miranda B. Kim, MD, Department of Radiation Oncology, Dana Farber Cancer Institute and Brigham and Women's Hospital, Level LL2, 75 Francis Street, Boston, Massachusetts (mbkim@partners.org).

Disclosures The authors have no disclosures to make. Drs Kim and White are co–first authors of this article.

†Dr. Kim is now in the Department of Radiation Oncology, Dana Farber Cancer Institute and Brigham and Women's Hospital, Boston, Massachusetts.

Commun Oncol 2013;10:88-91

Our patient first complained of a crawling sensation throughout his skin, or formication, in association with skin erythema the day of his first hospital discharge. Formication is associated with multiple entities, including anxiety, use of stimulates such as cocaine or methylphenidate, withdrawal from alcohol, renal impairment, hepatitis, and even parasitosis.[4] We ultimately attributed the patient's symptoms to anxiety, given his medication and social, travel, and medical history. Formication is not commonly induced by MTX, but itching is listed as a common side effect,[3] which may have been the patient's own verbalization of this reaction. The patient's facial erythema may have indicated a developing reaction to the medication, because flushing is a listed side effect to MTX. Nevertheless, administration of lorazepam improved the patient's symptoms. After about 12 hours of monitoring and no other serious complications, the patient and his treating physicians felt it was safe for him to be discharged. In retrospect, this likely was the early development of EM.

Although the Food and Drug Administration has included black box warnings about erythema multiforme secondary to treatment with MTX, we

TABLE 1 Laboratory values, including methotrexate levels

Variable	Value[a] Day 1	Value[a] Day 2	Reference range
Sodium, mmol/L	136	—	136 – 145
Potassium, mmol/L	4	—	3.5 – 5.1
Chloride, mmol/L	102	—	98 – 107
Carbon dioxide, mmol/L	26	—	22 – 32
BUN, mg/dL	9	—	6 – 20
Creatinine, mg/dL	1.06	—	0.70 – 1.30
Glucose, mg/dL	241	—	70 – 99
Calcium, mg/dL	9.2	—	8.6 – 10.3
Albumin, g/dL	3.6	—	3.4 – 4.8
Total protein, g/dL	6.3	—	6.0 – 8.0
Alkaline phosphatase, IU/L	38	—	38 – 126
AST, U/L	25	—	15 – 41
ALT, U/L	19	—	17 – 63
WBC, $10^3/\mu L$	7.1	—	4.0 – 11.0
Hemoglobin, g/dL	12	—	12.7 – 16.7
Hematocrit, %	34.3	—	38.0 – 50
Platelet, $10^3/\mu L$	216	—	150 – 450
Methotrexate level (μmol/L)	65.01	6.18, 3.14, 1.68	N/A

ALT, alanine amino transferase; AST, aspartate amino transferase; BUN, blood urea nitrogen; WBC, white blood cells.
[a] Indicates day after methotrexate.

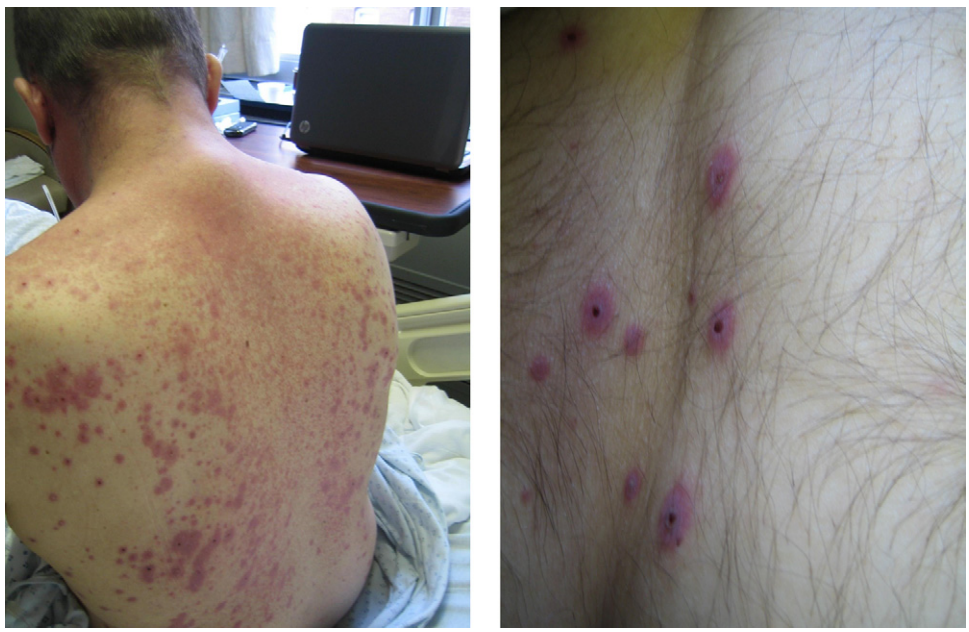

FIGURE 1 The small, pustular lesions on the patient's torso were nonpruritic and nontender.

TABLE 2 Summary of reported cases of methotrexate-induced erythema multiforme

Case	Year	Patient age, y	Sex, race	Diagnosis	Methotrexate dose	Time to develop EM symptoms with physical findings	Treatment
1[5]	1988	24	Female, white	Nonmetastatic gestational trophoblastic neoplasia	25 mg intramuscularly for 5 days, repeated at 14-day intervals	After 1st treatment course, oral mucosal ulcerations; after 2nd, pruritic rash on extensor surface of extremities; after 4th, skin lesions on abdomen	Symptomatic, spontaneous
2[6]	2005	74	Female, unknown	Seronegative polyarthritis	20 mg SC, weekly	About 1 month into treatment, erythematous macules and papules on torso, arms, and legs with progressive confluence of lesions and erosions on left arm	Oral and topical corticosteroids[a]
3[7]	2010	85	Female, white	Unknown	Unknown	Unknown	Topical and/or corticosteroids (not specified)
Present	2011	44	Male, white	T-cell acute lymphoblastic leukemia	15 mg intrathecally, followed by 1,000 mg IV, and 9,000 mg IV	After 5 days of therapy, see text	Oral and topical corticosteroids

EM, erythema multiforme; IV, intravenously; SC, subcutaneously; y, years.
[a] Symptoms reproduced by patch test study 6 months later.

found only 3 publications of such cases in our literature search (Table 2).[5-7]

EM affects men more commonly than it does women and is diagnosed mainly in adolescents and young adults. It is most commonly associated with infection – primarily with herpes simplex virus but also with mycoplasma pneumonia – and is recurrent in 30% of patients.[8] A predisposing gene, the HLA DBQB1-0301 allele, has been reported in patients with EM.[9] Clinically, the rash is acute in onset and is characterized by target lesions (not present on our patient) on the skin surface and in severe cases, in the mucosal membranes, especially those in the oral cavity. Because our patient exhibited severe symptoms, he required hospitalization and was started on total parenteral nutrition to maintain adequate sustenance. The rash is usually symmetric and located on the elbows, knees, palms, soles, and face; if severe, the rash may continue to spread diffusely and include mucosal surfaces.[10] The lesions can be numerous, with all typically appearing within 3 days and remaining for about 2 weeks.[8] The lesions tend to be asymptomatic, although in some cases itching and burning can be present, as was the case with our patient. Treatment includes systemic and topical steroids.

It is important to note the differential diagnosis of EM, which includes urticaria, fixed drug eruption, bullous pemphigoid, Sweet's syndrome, Rowell's syndrome, and polymorphous light eruption.[11] These various entities differ from EM clinically and pathologically. EM is typically mild and self-limited but it can progress in severe cases, leading to multiorgan failure and ultimately death.[12] It is important for clinicians to recognize this side effect of MTX in their patients. Early recognition will allow for better disease and symptom management, preventing extended hospitalizations for intractable reactions and decreasing morbidity and mortality.

References

1. Farber S, Diamond LK. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-a minopteroyl-glutamic acid. *N Engl J Med*. 1948;238(23):787-793.
2. Berlin NI, Rall D, Mead JA, et al. Folic acid antagonist. Effects on the cell and the patient. Combined clinical staff conference at the National Institutes of Health. *Ann Intern Med*. 1963; 59:931-956.
3. Methotrexate. Epocrates Web site. http://www.epocrates.com. Updated December 21, 2011. Accessed January 21, 2011.
4. Koh W, Liu T, Tay Y. Formication Due to True Parasitic Infestation: Bird Mites. *Arch Dermatol*. 2011;147:508-509.
5. Taylor SW, Barnhill DR, Burke TW, Linville WK, Yevich I. Methotrexate-induced erythema multiforme. *Gynecol Oncol*. 1989;33(3):376-378.
6. Sanchis JM, Bagan JV, Gavalda C, Murillo J, Diaz JM. Erythema multiforme: diagnosis, clinical manifestations, and treatment in a retrospective study of 22 patients. *J Oral Pathol Med*. 2010;39: 747-752.
7. Blanes M, Silvestre JF, Albares MP, Pascual JC, Pastor N. Erythema multiforme due to methotrexate reproduced with patch test. *Contact Dermatitis*. 2005;52(3):164-165.
8. Roujeau J. Chapter 39. Erythema Multiforme. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Dallas NA, eds. *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York:

McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=56032944. Accessed January 19, 2013.
9. Halli I, Lepage V, Douay C, et al. HLADQB1*0301 allele is involved in the susceptibility to erythema multiforme. *J Invest Dermatol*. 1991;97(4):697-700.
10. Kaye ET, Kaye KM. Chapter 17. Fever and Rash. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=9095654. Accessed January 19, 2013.
11. Sokumbi O, Wetter DA. Clinical features, diagnosis, and treatment of erythema multiforme: a review for the practicing dermatologist. *Int J Dermatol*. 2012;51(8):889-902.
12. Cameron AJ, Baron JH, Priestley BL. Erythema multiforme, drugs, and ulcerative colitis. *Br Med J*. 1966;2(5523):1174-1178.