CASE REPORT

Acute mucocutaneous methotrexate toxicity with marked tissue eosinophilia

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SUMMARY

Methotrexate toxicity in mucocutaneous areas is usually not associated with tissue eosinophilia. We describe a case of acute methotrexate-induced mucocutaneous erosions with interface dermatitis and eosinophils. A 76-year-old African-American woman with a history of bullous pemphigoid on methotrexate therapy presented with lower extremity cellulitis, developing oral and cutaneous erosions during hospitalization after daily dosage of methotrexate. Shallow circular cutaneous erosions were found on chest, abdomen and limbs. Laboratory results showed pancytopenia and elevated liver function tests. Skin biopsy revealed irregular acanthotic epidermis with interface dermatitis, individual dyskeratotic cells and superficial perivascular lymphocytic infiltrate with numerous eosinophils. Methotrexate was stopped and leucovorin was administered, leading to improvement. The histopathological changes in acute mucocutaneous toxicity range from pauci-inflammatory erosions with dyskeratotic keratinocytes to interface dermatitis and infrequently seen eosinophils. This case exemplifies that interface dermatitis with a marked eosinophilic infiltrate can be found in the setting of acute mucocutaneous methotrexate toxicity.

BACKGROUND

Bullous pemphigoid (BP) is an autoantibody-mediated blistering skin disease that usually affects the elderly, for which immunosuppressive medications are effective. The standard therapy for extensive cutaneous disease includes systemic corticosteroids and steroid-sparing agents such as azathioprine, mycophenolate mofetil and cyclophosphamide.^{1 2} In elderly patients, low-dose course (2.5–10 mg/week) of methotrexate can be effective.³ A rare skin finding of methotrexate toxicity is painful erosions, where histological examination contributes to the diagnosis. The pathological changes related to acute mucocutaneous methotrexate toxicity (AMMT) range from pauci-inflammatory erosions with dyskeratotic keratinocytes to interface dermatitis and rarely eosinophils.⁴ Tissue eosinophilia is not a classic finding in AMMT. Thus, we describe a case of AMMT accompanied with pancytopenia and mucocutaneous erosions with interface dermatitis and numerous eosinophils. Recognition of these rare pathological features is pivotal in expeditious therapy initiation.

CASE PRESENTATION

A 76-year-old African-American woman with a history of BP presented to the emergency room complaining of pain to the right foot associated with blisters on the dorsal aspect for the past month. The patient stated that the previous week she went to a nearby hospital and was discharged with trimethoprim-sulfamethoxazole; however, she had continued having pain for which she came to our hospital for further evaluation and management. Her BP had been controlled (with no active symptoms and signs) with methotrexate for approximately 4 months, 10 mg weekly. The initial physical examination showed erosions on the dorsal aspect of right foot with mild suppuration, erythema and warm skin. Patient was admitted to the hospital with the diagnosis of cellulitis of the right foot and treated with vancomycin 1 g intravenously two times a day and piperacillin/tazobactam 3.375 g intravenously three times a day. During hospitalization and at the fourth day of antibiotic treatment, the patient developed painful oral erosions located at the soft palate and buccinators mucosa that inhibited oral intake, thrombocytopenia, leucopenia and worsening of possible chronic anaemia. She subsequently became stuporous with respiratory failure that required intubation. Patient was transferred to medical intensive care unit. Although the patient had not been taking folic acid supplementation, she initially reported continued compliance with her once-weekly dosing of methotrexate. However, further questioning revealed that she was taking methotrexate daily within the last week. Additional medical history included type 2 diabetes mellitus, hypertension, hyperlipidaemia, chronic kidney disease (baseline serum creatinine of 4.5 mg/dL, reference range 0.52–1.04 mg/dL) and status postcolectomy due to colon cancer. Her medication list included nifedipine, glipizide, furosemide, clonidine, prednisone, gabapentin, methotrexate and triamcinolone 0.1% cream.

Physical examination revealed multiple oral erosions with stigmata of bleeding; haemorrhagic crusts were visualised on oropharynx. There were numerous 2–5 cm round erosions in various phases of healing with crusting and foci of yellowish exudates that tended to be confluent in the neck, back, chest, inframammary area, abdomen, both thighs, anterior legs and dorsum of the right foot (figure 1).

Laboratory evaluation showed white cell count of $0.7 \times 10^9/L$ (reference range $4\text{--}10.5 \times 10^9/L$), haemoglobin 8.2 g/dL (reference range 11.1–14.6 g/

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Figure 1 Cutaneous erosions in AMMT. Erosion left after blistering associated with fissure (see close-up) on the inframammary area. Patient also had similar lesions on the neck, back, chest, abdomen, thighs and legs. AMMT, acute mucocutaneous methotrexate toxicity.

dL), haematocrit 25.3% (reference range 37%–50%) and platelet count $13 \times 10^9/L$ (reference range $140\text{--}400 \times 10^9/L$); indicating pancytopenia. The mean corpuscular volume was within normal limits. Liver function tests were increased with aspartate aminotransferase 97 U/L (reference range 15–46 U/L) and alanine transferase 127 U/L (reference range 9–52 U/L). Renal function was altered with serum creatinine of 4.92 mg/dL (reference range 0.52–1.04 mg/dL) and blood urea nitrogen 84 mg/dL (reference range 7–17 mg/dL). Her methotrexate levels were in normal range of 0.08 mM/L (reference range <1 mM/L).

A biopsy of a cutaneous erosion revealed psoriasiform epidermal hyperplasia with vacuolar interface dermatitis and individual dyskeratotic cells. Other histopathological features included focal confluent dyskeratosis, pigment incontinence, focal acantholysis and perivascular lympho eosinophilic infiltrate (figure 2). Direct immunofluorescence studies were negative for deposition of immune reactants such as IgA, IgG, IgM and complement factor C3.

The development of cutaneous erosions and mucositis associated with pancytopenia in the setting of the patient's intake of daily methotrexate dosing was consistent with methotrexate toxicity; however, drug reaction with eosinophilia and systemic symptoms (DRESS) was also suspected. The diagnosis of methotrexate toxicity was confirmed histologically by the presence of interface dermatitis associated with dyskeratosis. The usually reported mean values for elimination half-life of methotrexate are 5 to 8 hours, which are increased in our patient due to Chronic Kidney Disease. The fact that the normal methotrexate level of 0.08 mM/L around 5 days after last dose is indicative that the methotrexate titre was supratherapeutic when the patient presented to our clinic. Methotrexate was discontinued and leucovorin 1000 mg orally two times a day with filgrastim (granulocyte colony-stimulating factor) were administered. All erosions and ulcerations healed progressively after withdrawal of methotrexate.

DISCUSSION

Methotrexate was first reported as a treatment for BP in 1969.⁵ Methotrexate is a folic acid antagonist that inhibits synthesis of nucleic acids via binding to dihydrofolate reductase. Its antiproliferative, antineoplastic and anti-inflammatory properties make it suitable for BP treatment, as well as other rheumatological, oncological and dermatological conditions.^{4,6} Acute toxicity in low-dose oral treatment (7.5–15 mg weekly) mostly presents as oral and gastrointestinal ulceration (3%–10% of patients) and bone marrow suppression (1%–3%);⁶ but it can also cause cutaneous side effects in up to 5% of patients. Cutaneous reactions in patients taking high

Figure 2 Interface dermatitis with numerous interstitial eosinophils. Irregular acanthosis with focal acantholysis and dyskeratosis. Interface dermatitis associated with numerous interstitial and perivascular eosinophils in the superficial dermis. Dermal melanophages, consistent with pigment incontinence (H&E, $\times 100$).

doses of methotrexate include skin blistering, desquamation, folliculitis and acral erythema.^{6,7} In low-dose therapies, as used in this patient, reported cutaneous findings vary from urticarial to toxic epidermal necrolysis. Minor side effects such as reduced appetite, nausea, fatigue, stomatitis and malaise can be cleared by folic acid therapy.⁸ More severe toxicity associated with methotrexate use presents as hepatotoxicity and pulmonary fibrosis, which are uncommonly seen at low doses.⁴

Mucocutaneous ulcerations have been seen with acute and less frequently, after chronic treatment with methotrexate.^{4,9} Methotrexate toxicity may arise within the start of methotrexate therapy, methotrexate dose adjustments (as seen in our patient with inadvertent overdosage), concurrent non-steroidal anti-inflammatory medication use and restart of methotrexate after dose interruption.^{4,10} High-dose regimens produce drug levels that are between 0.1 to 1 mM/L 1–3 days after drug infusion; while the toxic levels at low-dose therapy (eg, rheumatoid arthritis, psoriatic arthritis, BP) is >0.2 mM/L and at high-dose therapy (eg, leukaemia) is >1 mM/L.

Other contributing factors include renal insufficiency, folic acid deficiency, infection and other concomitant use of medications, such as cyclosporine, penicillin, trimethoprim-sulfamethoxazole and phenytoin.⁴ In our patient, two possible mechanisms can be proposed for the development of erosions and ulcerations: first, the methotrexate overdosage, evidenced by the accidental daily intake and second, renal dysfunction which results in elevated methotrexate levels due to reduced renal clearance.

The classic histopathological findings seen in AMMT, such as acanthosis, epidermal necrolysis, interface dermatitis and dyskeratosis, corroborate with the clinical manifestations of a direct methotrexate toxicity. These features are characteristically associated with mild perivascular lymphocytic infiltrate without eosinophils.^{4,11} Our case is distinguished by the occurrence of perivascular and interstitial lymphocytic infiltrate with numerous eosinophils. This finding was also reported by Ferguson *et al*⁴ and Fridlington *et al*.¹² Pathologists must be aware of these histopathological changes since they can mislead the diagnosis towards an inflammatory condition rather than a toxic skin reaction, deferring treatment.

These unusual skin changes are deemed important clues for clinicians and pathologists to identify, since cutaneous features frequently precede bone marrow suppression.^{4,6,12} In relation to the differential diagnosis in the current case, the cutaneous ulcerations and oral involvement could also have suggested immune-bullous disease, such as paraneoplastic pemphigus possibly due to an underlying lymphoma that could explain the cytopenias. An idiosyncratic drug reaction such as DRESS, characterised by skin eruption, eosinophilia, lymphadenopathy and internal organ involvement, such as liver, kidney or lungs,¹³ could have also caused clinical findings similar to those seen in our patient. However, in DRESS the latency period between the drug exposure and disease onset is between 2 to 8 weeks, and the patient was under methotrexate regimen for 4 months. BP can also show eosinophilic infiltration with the same pattern as shown in figure 2; but this diagnosis is less likely because it was under control without any symptoms for the entire methotrexate regime before the clinical presentation. Drug skin reaction could have also explained the skin erosions; however, patient stated that she had these antibiotics in the past for previous cellulitis due to secondary infection of the blisters without any evidence of skin eruptions. These diagnoses were also eventually excluded because of the histopathology, the negative direct immunofluorescence and the improvement of symptoms after withdrawal of methotrexate.

This case highlights that interface dermatitis with marked eosinophilic infiltrate can be found in the setting of AMMT, and rapid recognition of toxicity may lead to methotrexate cessation and lifesaving initiation of leucovorin rescue that should be received within the first 24 hours of the last dose of methotrexate.¹⁴

Learning points

- Methotrexate toxicity may arise within the start of methotrexate therapy, methotrexate dose adjustments, concurrent non-steroidal anti-inflammatory medication use and restart of methotrexate after dose interruption.
- Methotrexate should not be prescribed in patients with renal dysfunction, preferably when glomerular filtration rate <30 mL/min/1.73 m².
- Patients should be educated about the adequate dosing of methotrexate before starting or adjusting treatment to avoid these possible adverse effects.
- Patients also should be encouraged to take folic acid supplementation along with methotrexate therapy.

Contributors LJB wrote this article as first author. AR is a senior resident of the Department of Dermatology, who took care of the patient. GV worked on the pathology slides pictures and made suggestions for this article. CM was the pathologist that made the diagnosis and made suggestions to the manuscript.

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REFERENCES

- 1 Patton T, Korman N. Role of methotrexate in the treatment of bullous pemphigoid in the elderly. *Drugs Aging* 2008;25:623–9.
- 2 Hammers CM, Stanley JR. Mechanisms of disease: pemphigus and bullous pemphigoid. *Annu Rev Pathol* 2016;11:175–97.
- 3 Bologna J, Duncan KO, Ko CJ, *et al*. Mucous membrane pemphigoid, and epidermolysis bullosa acquisita. In: Bologna J, Duncan KO, Ko CJ. *Dermatology essentials*. London: Elsevier, 2014.
- 4 Ferguson NN, Asarch A, VanBeek M, *et al*. Acute mucocutaneous methotrexate toxicity associated with interface dermatitis and numerous eosinophils. *Am J Dermatopathol* 2013;35:e63–6.
- 5 Kwatra SG, Jorizzo JL. Bullous pemphigoid: a case series with emphasis on long-term remission off therapy. *J Dermatolog Treat* 2013;24:327–31.
- 6 Warner J, Brown A, Whitmore SE, *et al*. Mucocutaneous ulcerations secondary to methotrexate. *Cutis* 2008;81:413–6.
- 7 Hani N, Casper C, Groth W, *et al*. Stevens-Johnson syndrome-like exanthema secondary to methotrexate histologically simulating acute graft-versus-host disease. *Eur J Dermatol* 2000;10:548–50.
- 8 Kalb RE, Strober B, Weinstein G, *et al*. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol* 2009;60:824–37.
- 9 Wong S-ming, Chong YT, Thevarajah S, *et al*. Methotrexate toxicity presenting as ulcerated psoriatic plaques. *Australas J Dermatol* 2012;53:81–3.
- 10 Kaplan DL, Olsen EA. Erosion of psoriatic plaques after chronic methotrexate administration. *Int J Dermatol* 1988;27:59–62.
- 11 Primka EJ, Camisa C. Methotrexate-induced toxic epidermal necrolysis in a patient with psoriasis. *J Am Acad Dermatol* 1997;36(5 Pt 2):815–8.
- 12 Fridlington JL, Tripple JW, Reichenberg JS, *et al*. Acute methotrexate toxicity seen as plaque psoriasis ulceration and necrosis: A diagnostic clue. *Dermatol Online J* 2011;17:2.
- 13 Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. *J Am Acad Dermatol* 2013;68:693 e1–14.
- 14 Roenigk HH, Auerbach R, Maibach HI, *et al*. Methotrexate guidelines-revised. *J Am Acad Dermatol* 1982;6:145–55.

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