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### Permalink

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### Journal

Dermatology Online Journal, 20(7)

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### Publication Date

2014

### DOI

10.5070/D3207023133

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## Case Report

### Cutaneous erosions: a herald for impending pancytopenia in methotrexate toxicity

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*Dermatology Online Journal* 20 (7): 5

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## Abstract

Psoriatic plaque erosion is a rare toxic side effect of low-dose methotrexate (LDMTX) that has been reported during the treatment of psoriasis and described as a herald for impending pancytopenia. Fatalities from this have rarely been reported. Even rarer is methotrexate (MTX)-induced erosions of clinically normal skin in patients without a history of psoriasis. We report 3 rare presentations of MTX-induced cutaneous erosions, 2 fatalities occurring with MTX-induced psoriatic plaque erosions, and the sixth reported case of MTX-induced erosions with no prior history of psoriasis. Each were elderly patients on proton pump inhibitors with a history of chronic non-steroidal anti-inflammatory drug (NSAID) use. They all presented with acute onset of erosions after a recent change in their MTX dose. Pancytopenia followed in each case. Physicians' awareness of the sequelae in MTX-induced cutaneous erosions is imperative so MTX can be discontinued and treatment instituted to prevent fatal bone marrow suppression.

## Introduction

Methotrexate (MTX) is a mainstay of treatment for psoriasis and rheumatoid arthritis (RA), selected for its efficacy and long track record of safety [1,2]. The most common minor adverse events with low-dose methotrexate (LDMTX) use are stomatitis, fatigue, headaches, nausea, and anorexia [3,4]. Whereas hepatotoxicity has historically been the most feared side effect, pancytopenia is now emphasized as the most serious adverse event and has been reportedly observed in approximately 1.5% of patients taking LDMTX [1,4,5]. Psoriatic plaque erosion is a rare cutaneous manifestation of LDMTX toxicity with unknown prevalence and has been described as a herald for impending pancytopenia [6]. Fatality resulting from pancytopenia that occurred secondarily to MTX-induced psoriatic plaque erosion has rarely been reported. Even rarer are reports of MTX-induced cutaneous erosions in patients with no history of psoriasis. We describe 2 fatal cases of MTX-induced psoriatic plaque erosions as well as a case of a non-psoriatic patient who developed widespread, MTX-induced cutaneous erosions confined within areas of clinically normal skin previously affected by multiple bouts of candidiasis. We highlight the risk factors, histopathologic findings, and mechanisms of toxicity underlying these unusual cases in an effort to raise physician awareness of this infrequent and potentially fatal adverse event.

# Case synopsis

## Case 1:

A 62-year-old woman with a long-standing history of plaque psoriasis and rheumatoid arthritis presented with a 1-week history of painful psoriatic plaque erosions immediately after she resumed her regular weekly MTX dose (12.5 mg) following a drug hiatus. Other home medications included ibuprofen, aspirin, and a proton pump inhibitor (PPI). (See Table 1 for full list of all patient's home medications)

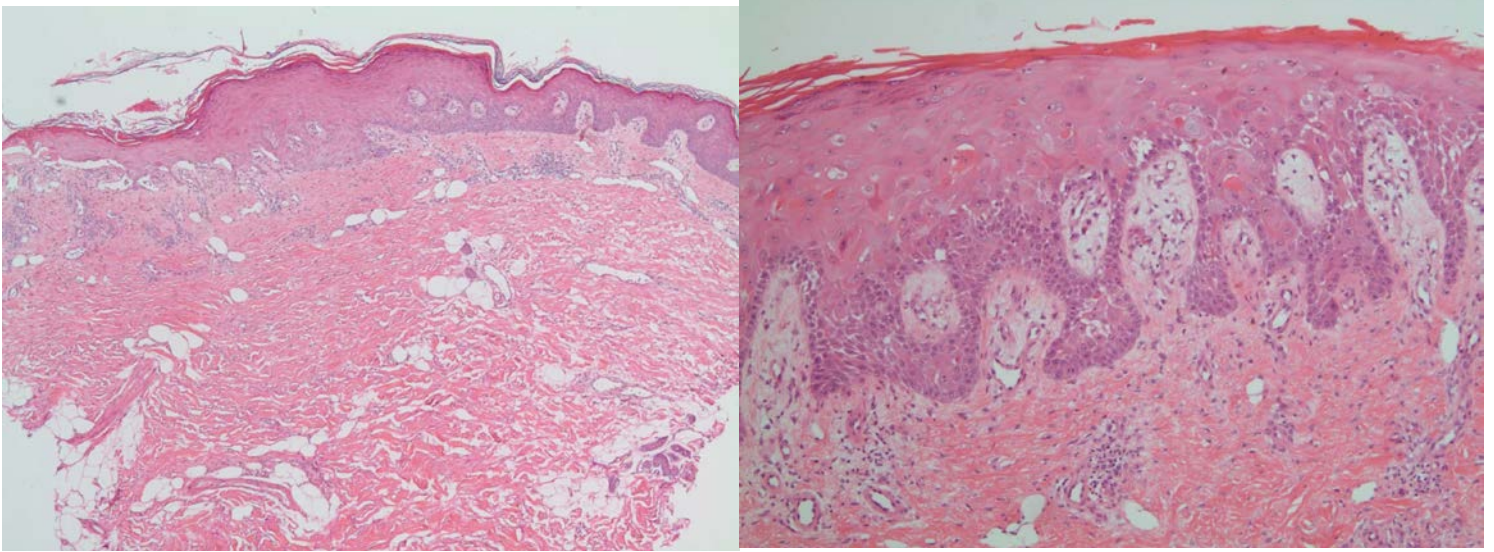
Examination of the skin revealed eroded, erythematous papules and plaques on the elbows, dorsal hands, and lower extremities. The groin, buttocks, and posterior thighs were the most severely affected, demonstrating a confluence of marked, bright red, moist erosions (Figure 1). On her feet, tense bullae were still intact. The face and mucous membranes were spared.



**Figure 1.** MTX-induced cutaneous erosions/ulcerations: Erosion of psoriatic plaques of the buttocks and posterior thighs of patient 1

Initial laboratory studies revealed values within the normal range for WBC count, platelet count, and absolute neutrophil count. Mean corpuscular volume (MCV) was 99 fL. Hemoglobin (Hb) and hematocrit (Hct) were 9.8 g/dL and 30.8%, respectively. Serum studies showed a blood urea nitrogen (BUN) of 36 mg/dL, creatinine (Cr) of 1.6 mg/dL (baseline of 1 mg/dL), mildly elevated liver enzymes, and a low serum albumin of 1.9 g/dL. She was started on empiric vancomycin and piperacillin/tazobactam for possible infection. MTX was held. The patient's hospital course was complicated by respiratory failure requiring intubation and an unexplained progressive decline in renal function with the development of acute tubular necrosis (ATN) refractory to aggressive fluid hydration. By day 4, laboratory studies revealed pancytopenia with a WBC count of 2.44 K/ $\mu$ L, platelet count of 125 K/ $\mu$ L, Hb of 8.1 g/dL, Hct value of 26.2%, and absolute neutrophil count of 1.4 K/ $\mu$ L. Her MCV was 102 fL. Treatment was supportive. The patient's skin erosions progressed without healing prior to her death on day 7.

A skin biopsy revealed focal subepidermal blisters with a mild perivascular and interstitial inflammatory infiltrate as well as an acanthotic epidermis with reactive atypia, spongiosis, and necrotic keratinocytes. Focal parakeratosis and papillary dermal edema were noted (Figure 2A,B). The presence of squamous atypia was consistent with a toxic drug effect and a diagnosis of MTX toxicity was made.



**Figure 2 A, B.** Histopathological features of MTX-induced psoriatic plaque erosions in patient 1: **A**, Punch biopsy of an erosive lesion demonstrates focal subepidermal separation. **B**, Magnification reveals an acanthotic epidermis with keratinocyte dysmaturity and dyskeratosis, focal parakeratosis, papillary dermal edema, and a mild interstitial and perivascular inflammatory infiltrate (hematoxylin and eosin stain; **A**, low power; **B**, high power).

*Case 2:*

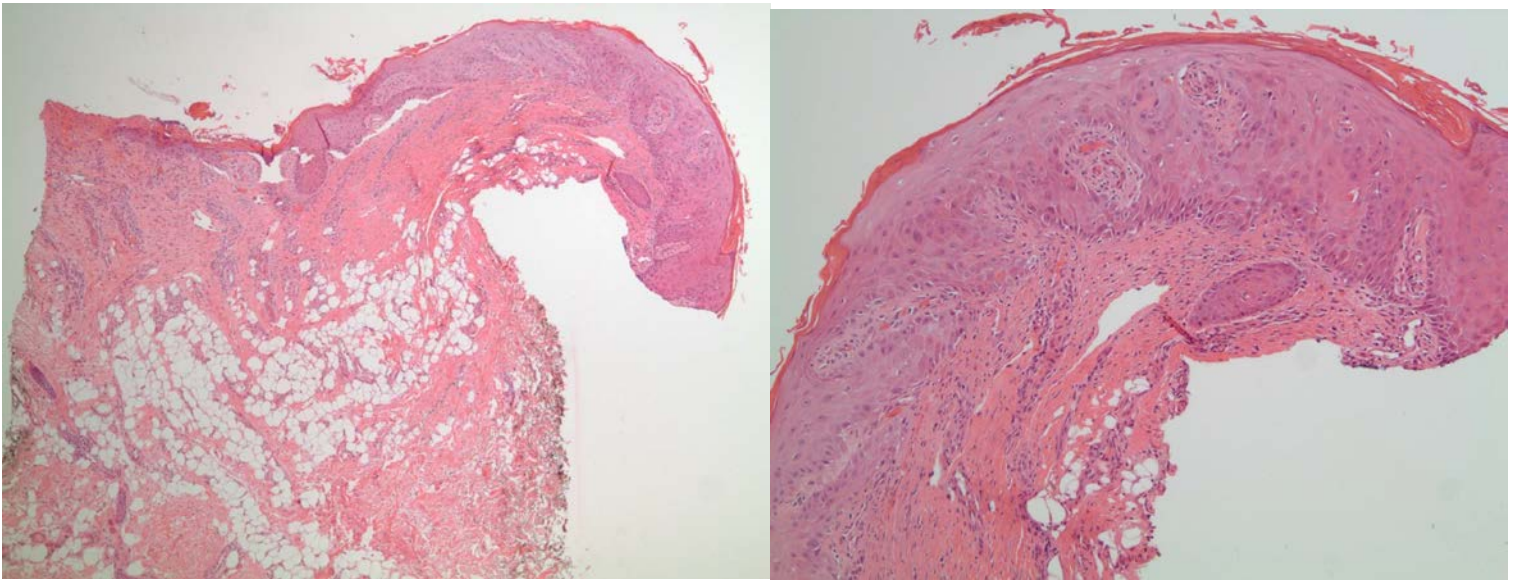
A 65-year-old man with a 10-year history of severe psoriasis and psoriatic arthritis presented with eroding psoriatic plaques that began immediately after the patient increased his weekly MTX injection of an unknown dose 3 days prior. Other home medications included meloxicam and a PPI.



**Figure 3.** Erosion of psoriatic plaques of the back of patient 2

Examination of the skin revealed extensive psoriatic plaques covering nearly the entire skin surface with erosions on the back, buttocks, and pannus exuding serous and bloody fluid (Figure 3). There was no mucosal involvement.

A skin biopsy demonstrated epidermal acanthosis with dysmaturity and cytologic atypia. Parakeratosis, subepidermal blisters, and metaplasia of the eccrine gland were seen. Also present was a mixed interstitial inflammatory infiltrate including patchy collections of eosinophils (Figure 4A,B). These changes were consistent with a diagnosis of MTX toxicity.



**Figure 4 A, B.** Histopathological features of MTX-induced psoriatic plaque erosions in patient 2. **A,** Punch biopsy from an erosive lesion demonstrates focal subepidermal separation and focal epidermal loss. **B,** Magnification reveals keratinocyte dysmaturation and dyskeratosis, focal parakeratosis, mixed interstitial inflammatory infiltrate and eccrine gland metaplasia (hematoxylin and eosin stain; **A,** low power; **B,** high power).

Initial laboratory studies revealed a WBC count of 9.02 K/ $\mu$ L, platelet count of 135 K/ $\mu$ L, Hb of 8.8 g/dL, Hct value of 28%, ANC of 7.8 K/ $\mu$ L, and MCV of 98 fL. Serum studies showed a BUN of 68 mg/dL, Cr of 3.5 mg/dL (baseline 0.5 mg/dL), mildly elevated liver enzymes, and serum albumin of 1.2 g/dL. His condition quickly deteriorated with a progressive decline in renal function refractory to fluids and hemodialysis; he became markedly pancytopenic. He received platelet transfusions without response and was transferred to end of life care on day 7. Prior to transfer, laboratory studies revealed a WBC count of 0.69 K/ $\mu$ L, absolute neutrophil count of 0 K/ $\mu$ L, platelet count of 14 K/ $\mu$ L, Hb of 7 g/dL, and Hct value of 23.9%. BUN and Cr were still elevated at 43 mg/dL and 2.2 mg/dL, respectively. His cutaneous erosions failed to re-epithelialize. Treatment was supportive.

### Case 3:

A 66-year-old woman with severe rheumatoid arthritis (RA) presented with a 2-week history of oral mucositis and painful erosions affecting normal skin previously affected by multiple bouts of candidiasis. The patient reported having doubled her weekly MTX of unknown dose prior to symptom onset owing to a recent flare in her RA. She had no history of psoriasis. Other home medications included hydroxychloroquine sulfate, aspirin, and a PPI.

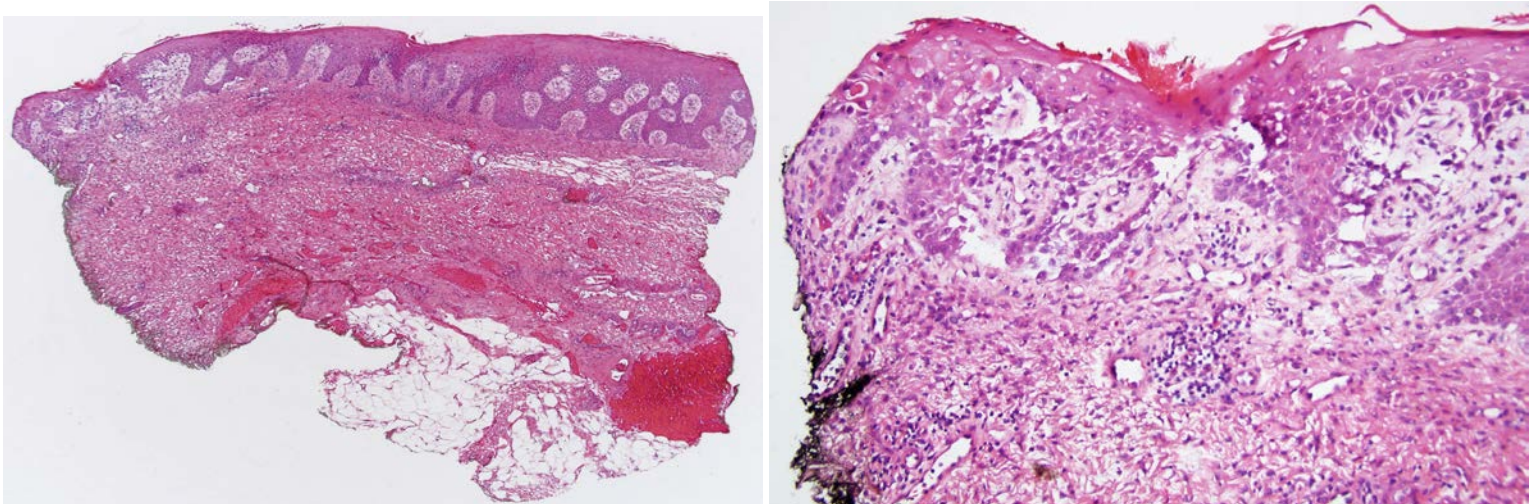


**Figure 5.** Ulceration of clinically normal skin of abdominal skin folds of patient 3

Examination of the skin revealed confluent, shallow ulcerations surrounded by non-indurated erythema along the lower abdomen, pannus folds, and bilateral inner thighs (Figure 5). Numerous scars from previous ulcers were observed on her anterior abdomen. The buccal mucosa demonstrated a telangiectatic, erythematous pattern with intact bulla on her central upper gingiva.

Initial laboratory studies revealed a WBC count of 1.1 K/ $\mu$ L, absolute neutrophil count of 0 K/ $\mu$ L, platelet count of 172 K/ $\mu$ L, Hb of 10.9 g/dL, Hct of 37%, and MCV of 99 fL. Serum studies showed a BUN of 50 mg/dL, Cr of 1.9 mg/dL (baseline of 1.4), normal liver enzymes, and a low serum albumin of 2 g/dL. The patient was started on intravenous fluids and both MTX and hydroxychloroquine were held. By day 2, pancytopenia was evidenced by the addition of a sudden drop in platelets to 111 K/ $\mu$ L. Her renal function returned to baseline after receiving fluids and her skin began to quickly re-epithelialize. Blood counts began to normalize on day 5. Treatment was supportive.

A skin biopsy revealed changes consistent with MTX toxicity, including an acanthotic and spongiotic epidermis with overlying parakeratosis and scattered dyskeratotic keratinocytes. Within the dermis underlying the ulcer was a mild superficial and perivascular lymphocytic infiltrate. Dermal vessels were ectatic and congested, characteristic of an inflammatory reaction, with rare eosinophils. Dermal edema and fibrosis with fibroblast proliferation extended all the way into the subcutaneous septae (Figure 6 A,B). No evidence of vasculitis or infectious process was seen. PAS was negative for fungi.



**Figure 6.** Histopathological features of MTX-induced ulcerations of clinically normal skin in patient 3; **A**, Punch biopsy adjacent to an ulcerated lesion demonstrates focal epidermal sloughing. **B**, Magnification reveals an acanthotic and spongiotic epidermis with scattered dyskeratotic keratinocytes, overlying parakeratosis, dermal edema, and a mild superficial and perivascular lymphocytic infiltrate (hematoxylin and eosin stain; **A**, low power; **B**, high power).

**Table 1.** List of all patient's home medications

| Study               | Age (yrs) / Sex | MTX dose       | Relevant Drugs   | Risk Factors   | Bone Marrow Suppression | Histopathology   | Rescue therapy                          | Outcome  |
|---------------------|-----------------|----------------|--|--|-------------------------|--|---|--|
| Primka and Camisa   | 78 M            | 25 mg IM       | bumetanide   | Age, flare of pustular psoriasis, increase in dose, ARF  | Yes                     | atrophic necrotic epidermis, dermal lichenoid infiltrate of lymphocytes and eosinophils  | Leucovorin, urine alkalinization, G-CSF | Death ~1 mo.   |
| Arevalo-Lopez       | 71 M            | 10 mg daily    | NA   | Age, inappropriate self-medication   | Yes                     | NA   | NA                                      | NA   |
| Kazlow et. al       | 58 M            | 15 mg weekly   | NA   | Age, renal impairment  | No                      | NA   | No                                      | Resolution of skin ulcers and blood counts after d/c of MTX                    |
| Agarwal et. al      | 57 M            | 7.5 mg daily   | NA   | Age, inappropriate self-medication   | Yes                     | NA   | Leucovorin, G-CSF, plt transfusions     | Blood counts normalized by day 7, complete healing of plaques by day 14        |
| Agarwal et. al      | 68 M            | 15 mg daily    | NA   | Age, inappropriate self-medication   | Yes                     | NA   | G-CSF                                   | NA   |
| Sanz-Sánchez et. al | 71 W            | 20 mg daily    | NSAIDs   | Age, inappropriate self-medication, DDI  | Yes                     | Suprabasilar blister, acantholysis, dermal mixed inflammatory infiltrate, focal apoptotic keratinocytes  | No                                      | Blood counts returned to normal and skin completely re-epithelialized by day 6 |
| Bookstaver et. al   | 59 W            | 2.5 mg daily   | NSAIDs<br>Furosemide<br>Colchicine<br>Spironolactone<br>Metolazone<br>Lisinopril   | Age, inappropriate self-medication, ARF, DDI, increased NSAID use, folate deficiency             | Yes                     | Consistent with adverse drug reaction  | Leucovorin                              | Significant re-epithelialization and normalization of blood counts by day 5    |
| Bilaç C et. al      | 62 W            | 25 mg weekly   | Meloxicam  | Age  | No                      | Acanthotic epidermis with focal ulceration and dermal perivascular lymphocytic infiltration  | NA                                      | NA   |
| Fridlington et. al  | 37 M            | NA             | Azithromycin<br>TMP/SMX  | Inappropriate self-medication 3 days prior, ARF, DDI   | Yes                     | Interface dermatitis with acanthotic epidermis, dyskeratotic keratinocytes, dermal perivascular and interstitial inflammatory infiltrate with eosinophils  | Leucovorin, alkalinization of urine     | Death on day 9   |
| Wong et. al         | 52 M            | 11.2 mg weekly | NA   | Age, Hep B, CKD, renal impairment  | Yes                     | NA   | Leucovorin, G-CSF                       | White cell and plt counts normalized and the ulcers healed after 10 days       |
| Wong et. al         | 50 M            | 15 mg weekly   | NA   | Recently increased MTX dose  | No                      | NA   | Oral folic acid                         | White counts normalized by day 2, plts by day 10, ulcers healed within 2 weeks |
| Shiver et. al       | 62 W            | 12.5 mg weekly | Ibuprofen<br>Aspirin<br>Metolazone<br>Furosemide<br>Esomeprazol<br>Solumedrol<br>Vancomycin<br>Piperillin/tazobactam<br>Insulin<br>Glipizide | Age, recently resumed MTX dose after drug hiatus, ARF, folate deficiency, low serum albumin, DDI | Yes                     | Focal subepidermal blisters, mild perivascular and interstitial inflammatory infiltrate, acanthotic epidermis with reactive squamous atypia, spongiosis, and necrotic keratinocytes, focal parakeratosis, papillary dermal edema | No                                      | Death on day 7   |
| Shiver et. al       | 65 M            | NA             | Meloxicam<br>Furosemide<br>Omeprazole  | Age, recent increase in MTX dose, ARF, folate deficiency, low serum albumin,                     | Yes                     | epidermal acanthosis with dysmaturation and cytologic atypia. parakeratosis, subepidermal blisters, metaplasia of the eccrine gland, mixed inflammatory infiltrate including patchy collections of eosinophils                   | No                                      | Death after day 7  |

Table 1: Summary of reported cases of MTX-induced psoriatic plaque erosions since 1996; MTX, methotrexate; ARF, acute renal failure; G-CSF, granulocyte colony stimulating factor; NA, not available; d/c, discontinue; plt, platelet(s); NSAIDs, non-steroidal inflammatory drugs; DDI, drug-drug interactions; Hep B, hepatitis B; CKD, chronic kidney disease

## Discussion

From 1967 to 1996, Pearce and Wilson found 17 patients who experienced cutaneous erosions secondary to MTX toxicity [7]. A review of the literature since 1996 along with 2 of our cases reveals at least 13 patients who developed erosions confined to areas of pre-existing psoriatic plaques while being treated with LDMTX (Table 1) [3,5,6,8-13]. Ulceration of clinically uninvolved skin as well as cutaneous ulceration in non-psoriatic patients has also rarely been reported [2,14,15]. Even rarer is a fatal outcome because healing typically begins rapidly with complete re-epithelialization of lesions occurring by day 10 after the discontinuation of MTX [3,7,16]. Our case series is unique in that it represents 3 unusual cases. Neither patient 1 nor 2 demonstrated the rapid healing and re-epithelialization of lesions that is classically described after the cessation of MTX in psoriatic patients, and instead experienced a fatal outcome. Patient 3 had no psoriatic history and developed cutaneous erosions within areas of clinically normal skin previously affected by multiple bouts of candidiasis. In contrast, previous cases in non-psoriasis patients have described ulcerations as occurring in oral mucosa or clinically normal skin with no primary site pathology, specifically the skin of the feet, hands, and extensor surfaces overlying the joints [2].

Table 2 describes risk factors for psoriatic plaque erosion with the most common being the initiation or reinstatement of MTX after a drug hiatus, an increase in the MTX dose, renal impairment, and the use of NSAIDs or aspirin. Age >55, folate deficiency, low serum albumin, and drug-drug interactions are also common. Concomitant infection, psoriatic flare, and alcohol ingestion will also increase the risk of an adverse reaction. As evidenced by our case series, myelosuppression is a common later sequela, and a rise in MCV can serve as a useful indicator of early bone marrow dysfunction. Recognition of these risk factors is crucial because this toxicity initially manifests as pain and erythema followed by development of erosions and ulcerations and can easily be mistaken for a psoriatic exacerbation [3,5,7,10,17].

**Table 2.** Risk factors for MTX toxicity

| Risk factors for MTX toxicity  |   |   |
|--|---|---|
| Alteration in MTX dose   | Drug-Drug Interactions  |   |
| <ul style="list-style-type: none"> <li>• initiation</li> <li>• re-initiation after hiatus</li> <li>• recent escalation in dose</li> <li>• inappropriate self-medication</li> </ul> | <ul style="list-style-type: none"> <li>• NSAIDs</li> <li>• Aspirin (salicylates)</li> <li>• Sulfonamides<br/>i.e. Probenecid,<br/>TMP-SMX</li> <li>• Penicillins</li> <li>• Colchicine</li> <li>• Ciprofloxacin</li> <li>• Barbiturates</li> <li>• Nitrofurantoin</li> <li>• Triamterene</li> </ul> | <ul style="list-style-type: none"> <li>• Pyrimethamine</li> <li>• Ethanol</li> <li>• Phenytoin</li> <li>• Tetracycline</li> <li>• Chloramphenicol</li> <li>• Sulfonylureas</li> <li>• Diuretics</li> <li>• Proton Pump Inhibitors (PPIs)</li> </ul> |
| Renal Impairment   |   |   |
| Age >55  |   |   |
| Folate deficiency  |   |   |
| <ul style="list-style-type: none"> <li>• as indicated by borderline/elevated MCV</li> </ul>  |   |   |
| Low serum albumin  |   |   |
| Infection  |   |   |
| Psoriatic flare  |   |   |
| MTX, methotrexate; TMP-SMX, trimethoprim- sulfamethoxazole   |   |   |

MTX is a synthetic folic acid analogue that halts cell division in rapidly proliferating cells via competitive and irreversible inhibition of dihydrofolate reductase (DHFR) in the S-phase of cell division [1]. Sprecher *et al.* concluded that MTX's selective activity in psoriatic plaques is related to MTX's cellular uptake via the reduced folate carrier (RFC-1) protein, whose gene is up-regulated by a localized folate deficiency as a result of hyperproliferative activity [18]. This can explain why MTX selectively affects psoriatic plaques and areas of previous tissue damage undergoing increased cell turnover. This can also explain the acral predilection of MTX toxicity in non-psoriatic patients because mitotic index is directly proportional to epidermal thickness and epidermal turnover occurs at increased rates in areas such as acral skin [19].

Histopathology of erosions from our cases demonstrate the classic changes previously described in the literature and parallel the histopathologic changes described by Comaish and Juhlin following intralesional MTX injection of psoriatic plaques, providing evidence for an etiological direct toxic effect [20]. Focal dermal-epidermal separation with keratinocyte dysmaturation and necrosis are classic features and consistent with a maturation defect related to a direct toxic antimetabolite effect on the epidermis. Epidermal acanthosis, spongiosis, and focal parakeratosis as well as a mild superficial perivascular and interstitial mixed inflammatory infiltrate consisting of lymphocytes, histiocytes, and neutrophils within the dermis are common. The papillary dermis is often edematous with ectatic vessels. Dermal eosinophils may or may not be seen. Not previously reported is the squamous metaplasia of the eccrine gland seen in case 2, supporting a toxic drug effect.

Drug-drug interactions are key contributors to toxicity (Table 2). The main route of MTX elimination is via glomerular filtration, which results in almost 90% being excreted within 24 hours [3]. A small amount occurs via active tubular secretion in the renal proximal tubules [1,7]. NSAIDs decrease blood flow and GFR by inhibiting prostaglandin synthesis and compete with MTX at the renal tubules, resulting in drug retention. Aspirin in particular has been shown to have a greater effect on exposure of the renal tubules to MTX and decreases MTX clearance by 35% [5]. Other competitors of secretion include sulfonamides, penicillins, and colchicine [1].

Folic acid deficiency allows uninhibited MTX activity. Thus, drugs that impair folate absorption (barbiturates, nitrofurantoin) or inhibit DHFR (trimethoprim-sulfamethoxazole (TMP-SMX), triamterene, pyrimethamine, ethanol) can precipitate toxicity [3,10]. Once in the circulation, albumin binds 35-50% of MTX and 90-95% of its primary active metabolite, hydroxymethotrexate [1]. Medications that displace MTX from albumin (phenytoin, probenecid, salicylates, barbiturates, sulfonamides, tetracycline, chloramphenicol, sulfonylureas) may potentiate toxicity [1,3].

TMP-SMX has been previously recognized as the most common offending drug in MTX toxicity and a fatal case of psoriatic erosions following TMP-SMX usage has been reported [4,6]. In addition to displacement from albumin and impairment of renal elimination, TMP-SMX has a synergistic toxicity with MTX. Thus, concomitant use of TMP-SMX and MTX should be avoided.

Recently, the FDA updated the MTX label to include the possible drug-drug interaction that may exist between high-dose methotrexate (HDMTX) and proton pump inhibitors (PPIs) [21]. PPIs seem to exhibit inhibitory effects on the transporters involved in the renal excretion of MTX, particularly the breast cancer resistance protein (BCRP), leading to elevated serum levels of both the drug and its metabolite. In a study by Suzuki *et al.*, co-administration with PPIs had a greater effect on delayed plasma



HDMTX elimination than co-administration with NSAIDs [22]. Because all 3 of our patients were taking PPIs, it is plausible that this drug-drug interaction existed. To our knowledge, our case series is the first to suggest that concomitant PPI use may play a role in the development of the cutaneous erosions and ulcerations seen in LDMTX toxicity.

Bone marrow toxicity is rare with dermatologic use of MTX [3]. In a review of the published case reports since 1996, 11 of 13 cases described pancytopenia developing in the setting of psoriatic plaque erosion [3,5,6,8-13]. The maximum depression of leukocytes and platelet count has been estimated to occur approximately 7-10 days after the last dose of MTX, a time frame consistent with those in our cases [4]. Unlike the majority of cases, the blood counts of our first 2 patients failed to quickly normalize. Thus, our interest in cases 1 and 2 stems from the lack of clinical improvement that is classically described after the cessation of MTX, which ultimately resulted in death for both of our patients. We feel this is largely related to their refractory renal failure; renal impairment has been recognized as the most common risk factor for LDMTX-induced pancytopenia [5].

Treatment includes prompt initiation of high-dose leucovorin (leucovorin rescue), aggressive hydration, and urinary alkalization with sodium bicarbonate [6]. Leucovorin supplies the active form of folic acid, bypassing DHFR inhibition. Except in renal insufficiency, leucovorin's efficacy requires administration within 24 hours of the last MTX dose [3]. We advise against basing rescue treatment off of serum MTX levels because the serum blood level of MTX can be a poor indicator of intracellular toxicity [6,13]. Leucovorin should be given intravenously at a dose equivalent to or higher than the last MTX dose, every 6 hours until a significant clinical improvement is observed; a bolus dose is recommended in renal impairment [3,5,6,10,13]. Removal via dialysis is likely ineffective because MTX is retained in toxic amounts in the polyglutamated form within the cells [23]. Granulocyte colony stimulating factor (G-CSF) institution has previously been recommended as soon as bone marrow suppression is observed, though its utility has not been established [3]. Owing to the lack of prompt recognition, treatment in cases such as ours is usually supportive. Additionally, lesions typically heal rapidly and blood counts normalize without any treatment after cessation of MTX [7]. Thus, the efficacy of rescue therapies in LDMTX toxicity is unclear.

In conclusion, we describe 3 rare presentations of LDMTX toxicity, 2 fatalities with early-onset MTX-induced psoriatic erosions and the 6<sup>th</sup> reported case of LDMTX-induced cutaneous erosions in a non-psoriatic patient [2]. All were elderly patients with a history of chronic NSAID and concomitant PPI use who presented with the acute onset of cutaneous erosions after a recent change in their MTX dose. Cutaneous erosions with renal insufficiency were an early sign of MTX toxicity in all cases and served as a herald for impending pancytopenia, regardless of psoriatic history. Histopathology is classic and can confirm diagnosis. Physician awareness of this rare ominous presentation is imperative so that MTX can be immediately discontinued and rescue therapy can be initiated without delay.

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