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Single Case

Mucocutaneous Ulcerations and Pancytopenia due to Methotrexate Overdose

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Keywords

Methotrexate toxicity · Cutaneous side effects · Cytotoxicity · Drug reaction · Erosive stomatitis · Immunosuppression · Mucocutaneous manifestation · Mucocutaneous symptoms · Poisoning · Side effects · Ulceration

Abstract

Methotrexate (MTX) is an antifolate drug used in the treatment of immune-mediated and neoplastic diseases. Initiation or dosage changes in MTX therapy can cause mucositis and bone marrow suppression. Skin lesions due to acute MTX toxicity are rare, but they serve as a herald for later-onset pancytopenia. Therefore, identification of those cutaneous lesions might help to initiate rescue strategies at an early stage. Here we describe a case with mucocutaneous ulcerations and pancytopenia due to overdosed MTX.

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Introduction

Methotrexate (MTX) is an antimetabolite drug used for a vast number of conditions. It is an analogue of folic acid and inhibits dihydrofolic acid reductase and thus the synthesis of folic acid. Folic acid is essential for DNA synthesis and repair. MTX reduces cell proliferation and inhibits proliferation of lymphocytes and cytokine synthesis in lower doses [1]. Due to its anti-inflammatory, antiproliferative and antineoplastic properties, MTX is used in the treatment of autoinflammatory and neoplastic diseases, such as rheumatoid arthritis, psori-

asis, choriocarcinoma or *meningeosis leucaemica*. It is also a component of chemotherapy regimens against breast and lung cancer, lymphomas or squamous cell cancer [1, 2].

MTX can induce side effects in several organ systems. Gastrointestinal leading symptoms are nausea, vomiting, ulcerative mucositis, stomatitis and secondary anorexia [3, 4], and sometimes pharyngitis or enteritis and diarrhea [3]. Moreover, it can lead to hepatitis and pneumonitis [2]. Headache, dizziness and fatigue occur as well. Immune dysregulation by MTX leads to fever and increased incidence of infections. In higher MTX doses, bone marrow toxicity causes pancytopenia. Lymphopenia results in an elevated infection risk, involvement of erythro- and thrombocytes produces anemia and risk of hemorrhage. Mucositis and bone marrow toxicity are dose dependent and occur at higher doses. These adverse effects are caused by the inhibitory effect of MTX on the folate synthesis and subsequently on the transmethylations reactions and purine synthesis. They primarily affect highly replicative cells, such as mucosal tissue and blood stem cells [3].

The side effects of MTX therapy on the skin are manifold. They include mild reactions such as pruritus, urticaria, ecchymosis and reversible alopecia, and severe ones, such as acute ulcerations of psoriatic plaques, erosions of the mucosa, reactivation of phototoxic responses and toxic epidermal necrolysis [3]. Mucositis and mucosal erosions are caused by the suppressive effect of MTX on cell proliferation. As highly replicative cells are affected more severely than cells of non-proliferative or weakly proliferative tissues [1], mucositis is one of the most common side effects of high-dose MTX therapy.

In patients with psoriasis, Lawrence and Dahl [5] described two manifestations of MTX toxicity: type 1 and type 2 ulcerations. Type 1 ulcerations are superficial erosions on pre-existing psoriatic plaques. Type 2 ulcerations are deeper ulcerations of non-psoriatic skin and are rare. In the original cohort, type 2 ulcerations appeared only on skin previously affected by other pathologies [5]. Recently, the development of MTX-induced type 2 ulcerations has also been described on healthy skin [4, 6]. Histological findings of both type 1 and type 2 ulcers suggest a direct toxic effect of MTX on the epidermis [4], probably through induction of apoptosis in keratinocytes [7]. After discontinuation of MTX, ulcerations heal rapidly. Previous publications report a complete recovery within 10 days of stopping MTX [4]. However, cases with a fatal outcome after MTX-induced ulcerations and pancytopenia have also been described [4, 8].

MTX can be administered orally or parenterally. In human plasma, over 50% of MTX is bound to albumin [2, 3]. It can be displaced by other medications with high plasma protein binding. For example, concomitant ingestion of NSARs, sulfonamides, retinoids, tetracyclines and salicylates raises serum levels of MTX [3, 8]. MTX is mainly excreted by glomerular filtration in the kidneys, only a minor portion is metabolized in the liver [2]. Consequently, renal impairment and low GFR may lead to accumulation, to higher blood levels and to toxicity [3]. Simultaneous administration of other medications that affect renal function may also interfere with MTX elimination. For example, NSAIDs, several antibiotics, sulfonamides and probenecid might lead to MTX accumulation in that way [8]. To detect MTX-induced organ toxicity at an early stage, monitoring of the blood cell count and of the liver enzymes is recommended at 1, 2, 3, 4, 5 and 12 weeks, and then every 3 months [9].

If MTX toxicity is suspected, its administration should be stopped at once and rescue measures must be initiated. Leucovorin, the biologically active S-form of racemate folic acid, should be administered intravenously every 6 h [1]. It replenishes the intracellular levels of reduced folate bypassing the dihydrofolic acid reductase and provides substrates needed for purine and thymidylate synthesis [2]. In order to increase MTX excretion, the patient should

be well hydrated and sodium-bicarbonate should be administered for urine alkalinization. MTX is poorly soluble in acidic solutions, so raising the urinary pH increases its excretion [2].

As MTX is retained in the cells in polyglutamated form, serum blood levels are not good indicators for its intracellular toxicity [4]. This intracellular retention allows administering MTX once weekly and still obtaining a constant effect. Therefore, rescue measures should be initiated independently of drug blood levels if the patient shows evident clinical symptoms of MTX toxicity.

Case Presentation

A 43-year-old unemployed man was referred to our clinic with multiform exanthema, stomatitis, balanitis and pancytopenia. Twelve months before presentation, the patient had noticed small red plaques of round shape covered by silvery scales on both knees. During the following months, the lesions progressed and spread to the elbows, arms, legs and the trunk. In January 2016, the patient visited his general practitioner due to the skin changes. The physician suspected psoriasis vulgaris and started topical treatment with clobetasol propionate, a urea-containing moisturizer, and oral treatment with MTX at an initial dosage of 5 mg for 3 days, then 10 mg daily.

Just 5 days later, the patient developed flu-like symptoms, painful productive cough and difficulty swallowing. His lips were painfully swollen, with crusts and fissures, causing him difficulties talking or brushing teeth. His genitals displayed painful redness and erosions. His left foot was erythematous and swollen, making walking impossible. The symptoms worsened gradually, involving different skin areas until presentation at our dermatologic emergency consultation 10 days after initiation of MTX. On admission, the patient had fever, night sweats and massive pain in all affected areas, especially when swallowing.

On examination, the patient was normotensive but febrile and in reduced general condition. Dermatological examination revealed multiple, ulcerated, erythematous to livid plaques of 1–2 cm in diameter (Fig. 1), distributed predominantly on the upper and lower extremities, including the palms and soles, with fewer lesions on the trunk. The lesions did not hurt or itch. Both feet and the area around the ulcerations were edematous and of livid color. On the knee and elbows, we noticed big, clearly demarcated, erythematous plaques with silvery scales. In the oral cavity and on the glans penis we detected extensive, clearly demarcated erosions. The submandibular lymph nodes were swollen, but there was no axillar or inguinal lymphadenopathy. The remaining review of systems was unremarkable.

The patient had no previous personal or family history of psoriasis or any other skin diseases. His past medical history revealed a metastasized testicular germ cell cancer, which had been treated surgically and with adjuvant chemotherapy. He was an ex-alcoholic and had a history of polysubstance abuse. He was still consuming different illicit drugs, amongst them 50 mg of methadone daily. His regular daily medication prior to admission was aspirin, mirtazapine and midazolam for depression, and MTX (10 mg daily). Once weekly, he took folic acid (5 mg). Based on the characteristic history and clinical presentation, we interpreted the clinical picture as a consequence of the excessive MTX intake. Due to the severe skin involvement, we immediately stopped MTX and hospitalized the patient. Laboratory testing on admission showed elevated CRP and pancytopenia. Skin swabs for bacteriological, viral and mycological testing and serological tests for HIV, hepatitis B and syphilis were all negative. Other laboratory findings were unremarkable except for elevated creatinine due to a pre-existing renal impairment. An ultrasound of the left ankle revealed diffuse edema of

the soft tissue structures without joint effusion, interpreted as secondary to the skin inflammation.

A biopsy of a representative skin lesion revealed orthohyperkeratosis, vacuolization of cells in the junction zone and apoptotic keratinocytes in the *stratum basale* and *suprabasale* of the epidermis on histological examination. Moreover, it showed scanty lymphocytic perivascular infiltrates in the upper dermis with neutrophils and discrete intradermal erythrocyte extravasation. There were signs of lichenoid dermatitis and interface dermatitis, but no evidence of vasculitis. Direct immunofluorescence showed no deposits of fibrinogen, complement (C3) or immunoglobulins.

We initiated topical therapy (triclosan and triamcinolone containing ointments on the body, halometasone and triclosan containing ointments on the hands) on the skin and mucosa (triamcinolone tincture and lidocaine spray), antiseptic baths (potassium permanganate) and adjusted analgesia (paracetamol 4 × 1 g, methadone 3 × 15 mg and oxycodone 5 mg). The first evening after admission, the patient developed fever. Blood cultures, urine cultures and X-ray imaging of the thorax did not detect a potential infectious focus, but due to fever and neutropenia, the decision was made to start broad-spectrum intravenous antibiotic therapy. A rescue therapy with leucovorin infusions 50 mg every 6 h was administered for 2 days (overall dose 600 mg) and stopped, as blood levels of MTX resulted below the detection level. To increase MTX excretion, hydration and urine alkalization was performed. The neutropenic fever persisted, and around both ulcer-ridden ankles sharply demarcated and warm erythematous patches potentially compatible with erysipela developed, thus antibiotics were continued.

Under intensive local and systemic therapy, the lesions all healed gradually, first on the trunk and the back of the hands, slowly also on the feet and the penis. Already after 6 days of treatment, there was a complete normalization of the blood count. After 8 days, most of the ulcerations were in re-epithelialized, with only a few open lesions left. The erysipela quickly regressed, but the antibiotic therapy was continued until day 9. Renal function improved as well and the patient was dismissed in good general condition and referred to a drug replacement therapy center. His previous medications apart from MTX were reinitiated and local therapy with sweet almond oil and zinc oxide cream was prescribed.

Discussion

We describe the clinical features and management of a rare case of acute MTX toxicity. The main cause for the development of acute toxic side effects of MTX in our patient was an incorrect prescription. He received 5 mg daily for 3 days and 10 mg daily for 8 days, which corresponds to a cumulative dose of 95 mg over 10 days.

The usual dosage of MTX prescribed in patients suffering from psoriasis ranges from 7.5 to 25 mg once weekly [3]. Normally, folic acid is administered 24 h after MTX in order to reduce side effects [3]. Our patient took folic acid once weekly as recommended, but due to the disproportioned amount of MTX, the antidote could not impede toxic effects of the drug. The most common causes leading to MTX intoxication are inappropriate dosage, impairment of renal function and thus decreased excretion, concomitant use of drugs, such as NSARs, antibiotics or salicylates, new initiation of MTX or re-instatement or increase of dosage and finally, uncontrolled self-medication [4].

In our patient, the reason for the excessive intake was a wrong prescription. Our patient took 100mg of aspirin daily, which can decrease renal MTX clearance by 35% [4]. The pa-

tient's renal impairment may have led to an additional increase of the MTX levels through reduced excretion. Additionally, his other medication could have affected the levels of MTX. Interestingly, the blood level of MTX in our patient was below the threshold of detection. As mentioned above, MTX can accumulate in the intercellular department and develop a toxic effect on the cells despite low serum levels. Therefore, this finding is well compatible with our diagnosis.

The histological findings in the biopsy were concordant with those of patients suffering from MTX intoxication previously prescribed in the literature. Cell vacuolization in the junction zone and apoptotic keratinocytes in the epidermis, which were present in our patient, are commonly interpreted as a sign of direct MTX toxicity. Hyperkeratosis, interstitial dermatitis and perivascular infiltrates of lymphocytes detected in our patient are characteristic too [1, 4]. In our patient, the biopsy revealed no eosinophilic infiltrate, which is detectable in some but not all patients with MTX-induced skin ulcerations [4]. Direct immunofluorescence enables exclusion of differential diagnoses and should be performed if a biopsy is taken.

As previously described in other cases [4], our patient suffered from both pancytopenia and ulcerations in previously healthy skin. It has been suggested that cutaneous erosions may be a herald for later-onset pancytopenia [4]. The nadir of peripheral blood cells normally occurs about 1 week to 10 days after the last MTX intake. Accordingly, the lowest cell count was registered 4 days after our patient's admission, even though MTX had been immediately stopped and rescue therapy started the same day. However, perhaps due to the rapid initiation of rescue therapy, our patient experienced a quick and complete recovery.

Taken together, our patient experienced severe MTX toxicity after administration of an inappropriate dose. He developed both ulcerated livid plaques on previously healthy skin as well as ulceration of pre-existing psoriatic plaques, oral mucositis and genital erosions. The skin lesions preceded a severe pancytopenia. Under rescue therapy, both skin lesions and pancytopenia resolved within 10 days. Mucocutaneous ulceration on psoriatic plaques or previously healthy skin due to inappropriate MTX administration may precociously indicate the development of other severe organ damage such as bone marrow suppression. Physicians should be aware of the existence and morphology of MTX-induced skin lesions in order to take appropriate therapeutic action at an early stage and prevent the development of further complications.

Statement of Ethics

The patient's consent to publish this case was obtained.

Disclosure Statement

The authors report no conflict of interests. The authors alone are responsible for the content and writing of this article.

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Fig. 1. **a** Cutaneous ulcerations (type 1 ulcers) of the back of the hands. **b** Mucosal erosion on the palate. **c, d** Cutaneous ulcerations of the elbows and legs (type 1 ulcers).