

Unusual Cutaneous Reaction at Site of Methotrexate Injection in Two Patients with Psoriasis and Psoriatic Arthritis

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Psoriasis is a chronic immune-mediated inflammatory disease with a prevalence of approximately 2% in the overall population worldwide (1–3). Therapy for psoriasis is based on an inter-individual regime, and systemic therapeutics are widely used. One first-line systemic therapeutic is the antimetabolite methotrexate (MTX) (2, 4–6).

Several biologics have been developed and approved for treating psoriasis and psoriatic arthritis and seem to have a favourable safety profile (1, 3). However, a well-known side-effect is injection site reactions (ISR), which are reported in up to 20% of treated patients, especially in the first weeks of treatment (7, 8). The aetiology of ISR is still not fully elucidated; it appears to be multifactorial and may be based on various factors, such as the injection volume, the temperature of the administered drug, the needle used, and various immunological features (8).

To our knowledge this is the first report of ISR in patients with psoriasis treated with subcutaneously (s.c.) administered MTX.

CASE REPORTS

Case 1. In a 50-year-old male patient who suffered from psoriasis and psoriatic arthritis, treatment with s.c. administered 15 mg MTX was initiated due to worsening of the patient's dactylitis. Initially he presented with a PASI of 3.4 and DLQI of 6. The patient had no complaints directly after the injection. At the third injection the patient noticed an asymptomatic, erythematous to livid annular patch at the most recent injection site, approximately 3 cm in diameter on the abdomen (**Fig. 1A**). An identical lesion appeared at the site of the fourth injection on the contralateral abdomen. Histology of the punch biopsy revealed a superficial inflam-

matory infiltrate, mixed with eosinophils, necrotic keratinocytes and pigment incontinence (**Fig. 1B**). The histological finding was consistent with a hypersensitivity reaction. The diagnosis of an ISR was made and the lesion was treated topically with mometasone furoate for approximately 10 days, resulting in a slight decrease in size and intensity of colour (**Fig. 1C**). At the subsequent injection no new onset of plaque was reported.

Case 2. A 52-year-old male patient who suffered from psoriasis vulgaris and psoriatic arthritis, was otherwise healthy. Treatment with 15 mg MTX s.c. was started. The patient had no complaints directly after the injection. However, 1 month after initiation of MTX the patient reported a reddish annular patch (**Fig. 2**) appearing immediately after the injection, which faded within approximately 3 days. Histological analysis revealed signs of a lichenoid dermatitis with necrotic keratinocytes. Furthermore, a moderate lymphohistiocytic infiltrate mixed with melanophages was present. The histological finding was consistent with a fixed drug eruption (FDE). The lesions were treated topically with mometasone furoate for 5 days. After another month of therapy, no further cutaneous side-effects were observed, despite re-injection of MTX, and the dose of MTX was increased up to 25 mg s.c. once a week with no other cutaneous adverse events.

DISCUSSION

MTX is an antimetabolite and synthetic folic acid inhibitor, which blocks dihydrofolate reductase during cell division (2, 4). It inhibits DNA synthesis and provides anti-inflammatory, immunomodulatory and immunosuppressive effects (2, 5).

Side-effects are mainly related to the gastrointestinal system or the blood, and display a broad range of severity (2, 4). Cutaneous adverse events have also been described (2, 4). Cutaneous erosion is a rare and toxic side-effect and has been considered to be a promoter for pancyto-

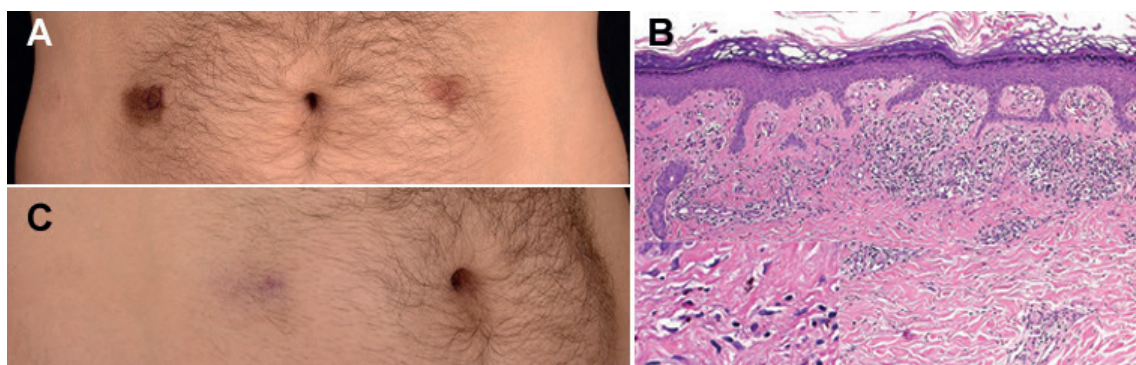


Fig. 1. Case 1. (A) Clinical presentation mimics a fixed drug eruption-injection site reaction due to subcutaneously (s.c.) administered methotrexate (MTX). (B) Histological analysis of injection site reactions (ISR), hematoxylin-eosin stain; original magnification 100/400. (C) ISR faded within days after application of topical mometasone furoate.



Fig. 2. Case 2. Injection site reaction due to subcutaneous (s.c.) methotrexate: reddish annular patches visible at the site of injection

paenia (4). Skin erosions, as well as mucosal ulcers and keratinocyte dystrophy as a histological marker have been mentioned in the literature as warning signs for potentially threatening toxicity of MTX (6). High-dose administrations of MTX may lead to direct toxic effects and the most feared complication is myelosuppression (5). To date, injection site reactions due to MTX have not been reported in the literature.

Hypersensitivity reactions to biological drugs were extensively elucidated in a review by Corominas et al. (9) in 2014. ISR are described to occur within the first 2 months of treatment induction as itching, erythematous, oedematous lesions at the site of drug administration that appear and resolve within a few days (7–9) after administration of the drug. Numerous reports about ISR were noticed in a remarkable amount in patients treated with TNF-alpha inhibitors (10, 11). The majority of ISR was reported within the first 2 weeks of treatment (8). Immediate, as well as delayed-type, allergic reactions have been suspected, as Benucci et al. (10) performed prick-, intradermal- and patch-testing in 4 subjects who experienced ISR and were treated either with etanercept or adalimumab. Prick- and patch-tests were negative in all subjects. Two patients who were treated with etanercept showed positivity at immediate reading of intradermal testing only; whereas in the 2 patients who received adalimumab positivity was found at the late reading. Therefore, immediate and cell-mediated reactions would both be possible. However, the phenomenon is still not fully elucidated and further research is necessary to elucidate the pathogenesis of the ISR.

In the current cases the ISR showed clinical similarities to a FDE. A FDE is defined as a sharply demarcated red or livid plaque, appearing on a regular basis depending on the repeated intake of the causative drug (12). This type of adverse drug reaction is induced mainly by the intake of non-steroidal anti-inflammatory drugs (NSAIDs), anti-depressive or antibiotics, but reports regarding various triggers have emerged in the literature. FDE have a distinct histopathological pattern, comprising lichenoid or erythema multiforme similar lesions (12). However, the pathogenesis of FDE seems to be based on type IV (delayed reaction via cytotoxic T cells) immune reactions (12) and it is notable that FDE re-appear on the same side on every uptake of the causative drug, favouring the hands, feet, genitalia, and face. In both of

the cases reported here the clinical presentation did not match the diagnosis of a typical FDE, as re-injection of the medication did not result in further hyperpigmentation at the same prior injection sites.

MTX can cause a variety of adverse events, including some well-known cutaneous side-effects. To date, ISR have not been noticed in patients treated with MTX. Therefore, one must consider ISR a rare, but potential, new adverse reaction in patients treated with s.c. administered MTX.

The authors have no conflicts of interest to declare.

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