CASE REPORT

Methotrexate injection site reactions: Case report and literature review

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Key words: eosinophilic fasciitis; injection site reaction; subcutaneous methotrexate.

INTRODUCTION
Methotrexate (MTX) can be administered either orally or subcutaneously. Subcutaneous MTX is generally well tolerated and has fewer side effects compared to orally administered MTX.1 Injection site reactions associated with the subcutaneous use of MTX are rare but have been previously reported in patients with seronegative knee arthritis, psoriasis, psoriatic arthritis, and dermatomyositis.2-5 Although MTX is a mainstay of treatment for eosinophilic fasciitis, injection site reactions in this patient population have not been previously described. Here, we report a case of MTX injection site reactions in a patient with eosinophilic fasciitis and review prior reports of similar reactions.

CASE REPORT
A 77-year-old woman with a past medical history significant for hypothyroidism presented with a 1-year history of diffusely hardening skin with associated reduced mobility and flexibility (Fig 1, A and B). The patient reported fatigue and muscle weakness but denied difficulty swallowing, shortness of breath, oral tightness, fevers, chills, and weight loss. A physical examination revealed subcutaneous induration of the right forearm with groove sign; diffuse, patchy induration of the chest, abdomen, lower back, and thighs; and firm, well-defined peau d'orange plaques on the lower legs. No sclerodactyly, facial sclerosis, or decreased oral aperture was noted. Her eosinophil count was markedly elevated (1500/µL). Rheumatoid factor and antinuclear, anti-dsDNA, anticientromere, anti-Scl70, and anti-RNA polymerase III antibody levels were normal. Punch biopsies showed pandermal fibrosis, atrophy of the entrapped eccrine glands, and a superficial and deep perivascular lymphohistiocytic infiltrate with eosinophils and rare plasma cells consistent with morphea or eosinophilic fasciitis. The patient declined a fascial biopsy, and magnetic resonance imaging to evaluate for fascial involvement was denied by insurance. Abdominal ultrasound and computed tomography were within normal limits. Given the history of marked eosinophilia, eosinophils on skin biopsy, and focally indurated lesions, a diagnosis of eosinophilic fasciitis was made.

The patient was initially treated with 40 mg of prednisone daily, 25 mg of MTX by mouth once weekly, and 1 mg of folic acid daily. Topical steroids were used intermittently, as needed. The patient reported gastrointestinal symptoms, fatigue, and alopecia with MTX use. Routine laboratory monitoring did not indicate MTX toxicity. Hair and nail thinning improved after increasing folic acid to 2 mg once daily and starting biotin supplementation. Systemic steroids were tapered slowly, and the indurated plaques softened. After 7 months, MTX was changed from oral to subcutaneous administration due to continued poor tolerance and increased skin inflammation.

The patient presented at her next appointment with a new red, inflamed lesion on the right medial thigh of unknown etiology, suspicious for an injection site reaction (Fig 2, A). At subsequent visits, red, nonscaly patches at recent injection sites and multiple scattered hyperpigmented patches at sites of previous injections on the bilateral anterior thighs

Abbreviation used:
MTX: methotrexate

JAAD Case Reports 2022;23:79-82.
2352-5126
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https://doi.org/10.1016/j.jdcr.2022.02.030

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Funding sources: None.
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79
confirmed the diagnosis (Fig 2, B and C). The application of ice and topical steroids to the injection sites had only modest symptomatic benefits. No new lesions developed after switching injection sites to the abdomen (Fig 2, D). At 21 months of treatment, the patient is off of systemic steroids and continues to improve slowly while tapering MTX (currently, 15 mg weekly).

DISCUSSION
We present a case of injection site reactions associated with subcutaneous MTX administration in a 77-year-old woman with eosinophilic fasciitis. MTX is a first-line, corticosteroid-sparing agent utilized in the treatment of eosinophilic fasciitis and can be administered orally, subcutaneously, or intravascularly. Subcutaneous MTX is typically well tolerated and has greater bioavailability and efficacy than orally administered MTX in the treatment of rheumatoid arthritis and psoriasis. Rare adverse events reported with the subcutaneous administration of MTX have included hypocellular marrow, cutaneous ulcers, dermatitis, and lichenoid skin reactions, none of which were specific to injection sites.

Injection site reactions are extremely rare among patients utilizing subcutaneous MTX. Among 101 patients with rheumatoid arthritis utilizing MTX autoinjectors for subcutaneous administration, no injection site reactions were reported. A literature search yielded only 5 cases of MTX injection site reactions, a summary of which is included in Table I. Injection site reactions have been reported in patients with seronegative knee arthritis, psoriasis, psoriatic arthritis, and dermatomyositis. To our knowledge, the lesions in our patient are the first reported in a patient with eosinophilic fasciitis. The lesions included diffuse induration, erythema, and hyperpigmentation of the chest, lower back, lower legs, abdomen (A), thighs, and forearms (B), including groove sign.

Fig 1. Initial clinical presentation included diffuse induration, erythema, and hyperpigmentation of the chest, lower back, lower legs, abdomen (A), thighs, and forearms (B), including groove sign.
### Table I. Reported cases of methotrexate injection site reactions

| Reference                | Age | Sex | Indication                        | Dose  | Reaction                                           | Location | Histology                                                                 | Clinical course                                                                                     |
|--------------------------|-----|-----|-----------------------------------|-------|---------------------------------------------------|----------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Sadoghi et al⁴ 2021      | 50  | M   | Psoriasis and psoriatic arthritis | 15 mg/wk | Asymptomatic, erythematous to livid annular patches | Abdomen  | Superficial inflammatory infiltrate with eosinophils, necrotic keratinocytes, pigment incontinence | Slight decrease in size and color intensity with topical mometasone furoate for ~ 10 d               |
| Sadoghi et al⁴ 2021      | 52  | M   | Psoriasis and psoriatic arthritis | 15 mg/wk | Reddish annular patches                           | Abdomen  | Lichenoid dermatitis, necrotic keratinocytes, lymphohistiocytic infiltrate mixed with melanophages | Faded within ~ 3 d, topical treatment with mometasone furoate for 5 d                                 |
| Fusta et al² 2017        | 66  | M   | Seronegative knee arthritis       | 15 mg/wk | Asymptomatic erythematous plaque with crusting and scaling | Abdomen  | Acanthosis, hyperkeratosis, minimal spongiosis, moderate lymphocytic perivascular infiltrate, little erythrocyte extravasation in superficial dermis | Change to oral MTX administration, 1 wk later lesion was almost healed without scarring              |
| Priego-Recio et al⁶ 2014 | 37  | M   | Psoriasis                         | 15 mg/wk | Edematous and erythematous papules with crust and laminar scaling | Abdomen  | Not reported                                                              | Change to oral MTX administration, lesions healed with topical fusidic acid and betamethasone treatment |
| Giard et al³ 2010        | 71  | F   | Dermatomyositis                   | 20 mg/wk | Extensive necrotic patch that evolved into a 10 cm ulceration with indurated borders | Buttock  | Dermal infiltrate of CD30+ B-cells, presence of Epstein-Barr virus         | Diagnosis of EBV-associated B-cell lymphoma, ulceration regressed 15 d following MTX discontinuation and healed 4 mo later |

*MTX, Methotrexate.*
subcutaneous administration of MTX has been found to be an effective alternative to oral administration. The initiation of subcutaneous MTX should be considered in patients intolerant of or unresponsive to oral MTX therapy. Although rare, injection site reactions can occur. Topical steroid treatment and/or alterations in MTX regimens may improve the lesions. Providers should consider close monitoring for injection site reactions following the initiation of subcutaneous MTX.

Conflicts of interest
None disclosed.

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