Methotrexate injection site reactions: Case report and literature review

Japsimran Kaur, BS,[a] Jeanette Zambito, MD,[b] and Christopher T. Richardson, MD, PhD[b]
Rochester, New York

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.

Abbreviation used:

MTX: methotrexate

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, anticentromere, 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

From the University of Rochester School of Medicine and Dentistry[a] and the Department of Dermatology, University of Rochester Medical Center.[b]

Funding sources: None.

Correspondence to: Christopher T. Richardson, MD, PhD, Department of Dermatology, University of Rochester Medical Center, 601 Elmwood Ave, Box 697, Rochester, NY 14642. E-mail: crichardson@urmc.rochester.edu.

JAAD Case Reports 2022;23:79-82.
2352-5126

https://doi.org/10.1016/j.jdcr.2022.02.030

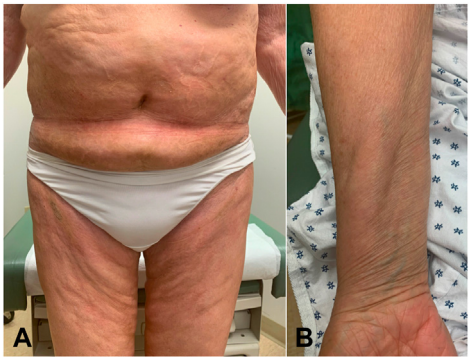

Fig 1. Initial clinical presentation included diffuse induration, erythema, and hyperpigmentation of the chest, lower back, lower legs, abdomen (**A**), thighs, and forearms (**B**), including groove sign.

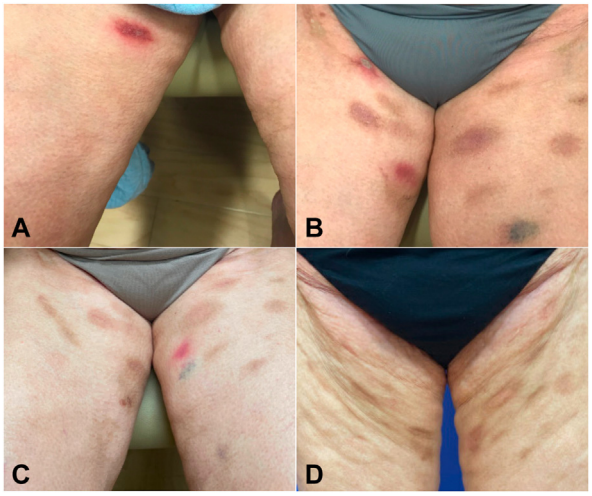

Fig 2. Injection site reactions on anterior thighs with initial bright red erythema, postinflammatory hyperpigmentation, and rare ulceration. **A**, First injection site reaction. **B** and **C**, Subsequent injection site reactions 4 and 7 months later, respectively. **D**, Anterior thighs after switching injection sites to abdomen.

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.[1,6,7] 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.[8,9]

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.[10] 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.[2-5] To our knowledge, reactions in patients with eosinophilic fasciitis have not been previously described. Lesion characteristics and histologic findings have varied among patients, including the rare finding in one report of an associated B-cell lymphoma.[5] Most patients with injection site lesions have developed red patches or papules similar to those observed in our patient. Three patients, including ours, have had scaling associated with their lesions.[2,4] Most reported reactions have occurred in the abdomen, likely given that patients typically prefer this location for injections. In contrast, our patient injected her thighs to avoid the diffuse abdominal skin induration. She switched to abdominal injections after her skin had significantly softened, which coincided with the tapering of the MTX dose. It is possible that the lack of injection site reactions in the abdominal skin was due to the lower dose.

In most previously reported cases of MTX injection site reactions, the lesions have improved significantly with MTX discontinuation and/or the application of topical steroids. Three cases have reported the discontinuation of subcutaneous MTX.[2,4,5] Two of these 3 patients initiated oral MTX administration, and one concomitantly utilized topical antibiotics and steroids.[2,4] Two additional patients noted improvement with topical steroid use.[3] For our patient, however, topical steroids only resulted in mild improvements in the lesions. A consistent treatment regimen has not been identified, and further research is necessary to determine the best practices for addressing MTX injection site reactions.

To our knowledge, this is only the sixth report of an injection site reaction associated with the subcutaneous administration of MTX and the first reported in a patient with eosinophilic fasciitis. The

Table I. Reported cases of methotrexate injection site reactions

Reference	Age	Sex	Indication	Dose	Reaction	Location	Histology	Clinical course
Sadoghi et al[3] 2021	50 y	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 al[3] 2021	52 y	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 al[2] 2017	66 y	M	Seronegative knee arthritis	15 mg/wk	Asymptomatic erythematous plaque with crusting and scaling	Abdomen	Acanthosis, hyperkeratosis, minimal spongiosis, moderate lymphocytic perivascular infiltrate, little erythrocytic extravasation in superficial dermis	Change to oral MTX administration, 1 wk later lesion was almost healed without scarring
Priego-Recio et al[4] 2014	37 y	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 al[5] 2010	71 y	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.

REFERENCES

1. Hameed B, Jones H. Subcutaneous methotrexate is well tolerated and superior to oral methotrexate in the treatment of rheumatoid arthritis. *Int J Rheum Dis*. 2010;13(4):e83-e84. https://doi.org/10.1111/j.1756-185X.2010.01482.x
2. Fustà X, Combalia A, Guañabens N, Iranzo P. Uncommon local reaction at the injection site of subcutaneous methotrexate. *Rheumatology*. 2018;57(1):27. https://doi.org/10.1093/rheumatology/kex264
3. Sadoghi B, Kränke B, Cerroni L, Weger W. Unusual cutaneous reaction at site of methotrexate injection in two patients with psoriasis and psoriatic arthritis. *Acta Derm Venereol*. 2021;101(11):adv00593. https://doi.org/10.2340/actadv.v101.352
4. Priego-Recio CM, Camacho-Martínez FM. Local reaction after subcutaneous injection of methotrexate: uncommon side effect. *J Eur Acad Dermatol Venereol*. 2016;30(3):523-524. https://doi.org/10.1111/jdv.12920
5. Giard C, Avenel-Audran M, Croué A, Verret JL, Martin L. Primary cutaneous Epstein-Barr virus—associated B-cell lymphoma arising at the site of subcutaneous injections of methotrexate. *J Clin Oncol*. 2010;28(34):e717-e718. https://doi.org/10.1200/JCO.2010.28.3796
6. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M. Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. *J Rheumatol*. 2004;31(4):645-648.
7. Reich K, Sorbe C, Griese L, Reich JLK, Augustin M. The value of subcutaneous vs. oral methotrexate: real-world data from the German psoriasis registry PsoBest. *Br J Dermatol*. 2021;184(4):765-767. https://doi.org/10.1111/bjd.19690
8. Kurian A, Haber R. Methotrexate-induced cutaneous ulcers in a nonpsoriatic patient: case report and review of the literature. *J Cutan Med Surg*. 2011;15(5):275-279. https://doi.org/10.2310/7750.2011.10078
9. Gridneva G, Muraviev Y. AB0486 Subcutaneous methotrexate discontinuation in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2018;77:1404.
10. Freundlich B, Kivitz A, Jaffe JS. Nearly pain-free self-administration of subcutaneous methotrexate with an autoinjector: results of a phase 2 clinical trial in patients with rheumatoid arthritis who have functional limitations. *J Clin Rheumatol*. 2014;20(5):256-260. https://doi.org/10.1097/RHU.0000000000000117