Methotrexate-induced nonhealing cutaneous ulcers in a nonpsoriatic patient without pancytopenia

Venkatesh Krishnamurthy Tekur

Department of Cardiology, Apollo Hospitals, Bengaluru, Karnataka, India

Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.190509

Quick Response Code:

Address for correspondence:
Dr. Venkatesh Krishnamurthy Tekur, Consultant Interventional Cardiologist, Apollo Hospitals, 154/11, Opposite IIM, Bannerghatta Road, Bengaluru - 560 007, Karnataka, India.
E-mail: venkateshtekur@yahoo.com

ABSTRACT

Methotrexate forms one of the main drugs in the pharmacological management of rheumatoid arthritis, psoriasis, and some neoplastic diseases. Methotrexate rarely causes cutaneous ulceration and most cases are reported in patients with psoriasis and have been accompanied by pancytopenia. The author here reports occurrence of multiple (two) cutaneous ulcers due to methotrexate in a nonpsoriatic patient. The patient was on methotrexate for seronegative rheumatoid arthritis for 10 years. To the best of the Author's knowledge, this is a rare case of cutaneous ulceration due to methotrexate in a nonpsoriatic patient reported in the literature so far, and probably one of its kind without pancytopenia or other hematological abnormalities. Stopping this medication led to complete healing of the ulcerated lesion in about four to six weeks.

Key words: Cutaneous ulcer, methotrexate, pancytopenia, psoriasis

INTRODUCTION

Methotrexate has been widely used in the treatment of rheumatoid arthritis. It has a number of adverse effects, and among the cutaneous effects, skin erosions and ulceration are rare. They have been mainly reported among patients with psoriasis. Cutaneous ulceration among nonpsoriatic patients are rare and only five cases have been reported in world literature so far to the best of our knowledge. Here, the author presents a rare case of two nonhealing cutaneous ulcers in a nonpsoriatic patient without pancytopenia, which showed almost complete recovery after six weeks after stopping methotrexate in a patient with seronegative rheumatoid arthritis.

CASE REPORT

A 78-year-old nondiabetic male, presented with two chronic nonhealing ulcers of six months duration, one on the posterior part of left lower leg, measuring 3.3 × 1.8 cm with a fibrinous base and a second cutaneous ulcer on the anterior part of right leg, measuring 3.0 × 2.0 cm with a fibrinous base [Figure 1]. The patient reported a sensation of tightness in and around the ulcer sites with increasing severity. Both ulcers had thick nonhealing edges with a punched out appearance. The patient had been administered previously with various medications, including various types of antibiotics for six months with no improvement in the healing of the ulcers. He was on Tab. methotrexate 15 mg once-a-week for seronegative rheumatoid arthritis from past 10 years. He had no history of psoriasis at any time. He underwent complete blood investigations, which showed no pancytopenia or any other significant hematological abnormality. Culture and sensitivity tests from ulcer sites were repeatedly sterile for bacteria and fungi. Venous and arterial doppler studies of both lower limbs were done to exclude peripheral vascular disease and were normal. In view of underlying rheumatoid arthritis, a biopsy of both the ulcers was performed. There was no histopathological evidence of vasculitis

Cite this article as: Tekur VK. Methotrexate-induced nonhealing cutaneous ulcers in a nonpsoriatic patient without pancytopenia. Indian Dermatol Online J 2016;7:418-20.

or granulomatous lesions [Figure 2]. After extensively reviewing the clinical and investigational findings, it was found that the appearance and characteristics of the ulcers resembled those of methotrexate-induced ulcer previously reported in the literature. After a detailed discussion with the patient, methotrexate was stopped and the ulcerated lesion was closely monitored. Also, the patient was monitored for any exacerbation of rheumatoid arthritis. Two weeks after withdrawal of methotrexate, the ulcer showed definite signs of healing and by six weeks it was almost complete healed [Figure 3]. No other significant adjunctive wound healing measures were given. There was no exacerbation of symptoms of rheumatoid arthritis. Subsequent to complete ulcer healing, the patient was started on Tab. hydroxychloroquin on the advice of the rheumatologist to prevent recurrence of arthritis. The patient is being followed up from the past three months and remains asymptomatic with no recurrence of ulcers or joint pains.

The dramatic healing of the chronic ulcer beginning within about two weeks after stopping methotrexate in the absence of any other adjunctive wound healing measures lends evidence to methotrexate being responsible for causation of the chronic ulcers.

DISCUSSION

Methotrexate is the mainstay of treatment for autoimmune conditions such as rheumatoid arthritis and psoriasis. Methotrexate has numerous side effects and, in rare circumstances, can lead to cutaneous ulceration. Stopping this medication can lead to complete healing of the ulcerated lesion. Cutaneous erosions are reported to herald impending pancytopenia in methotrexate toxicity.[1] Cutaneous ulceration has been reported as a sign of methotrexate toxicity.[2] Even low doses of methotrexate can cause early-onset pancytopenia and skin ulcers.[3] Majority of cases of cutaneous and noncutaneous ulcers due to methotrexate have been reported in patients with psoriasis.[4] The adverse effects of methotrexate may be classified as type A, dose dependent (methotrexate toxicity); type B, idiosyncratic (e.g., methotrexate pneumonitis); type C, resulting from long-term therapy but anticipated, based on overall drug exposure (e.g., methotrexate hepatotoxicity); and type D, delayed effects occurring even after discontinuation of the drug (e.g., methotrexate in the first trimester of pregnancy, inducing teratogenesis). Cutaneous ulceration due to methotrexate is considered to be a toxic adverse effect and is a rare occurrence-Type A.[2] Montero and colleagues reported cutaneous ulceration in a nonpsoriatic patient with rheumatoid arthritis treated with methotrexate for 19 months at a dosage of 15 mg/wk.[5] Adults with rheumatoid arthritis usually begin with a starting dose of 7.5–10 mg, once a week and it is increased to 20–25 mg a week over time if needed.[6] Delyon *et al.* have described the features of skin toxicity induced by low-dose

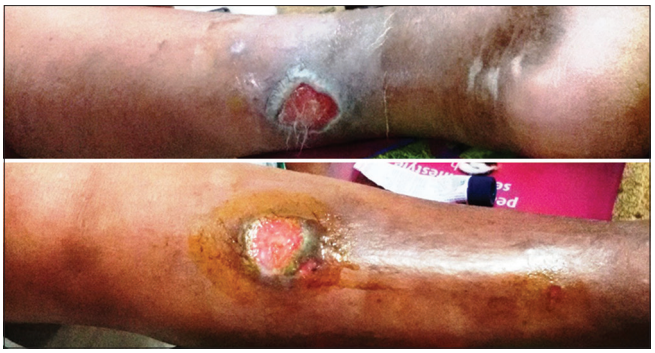

Figure 1: Two chronic nonhealing ulcers with fibrinous base—one on the posterior part of left lower leg (3.3 cm × 1.8 cm) and another on anterior part of right leg (3.0 cm × 2.0 cm) on initial presentation

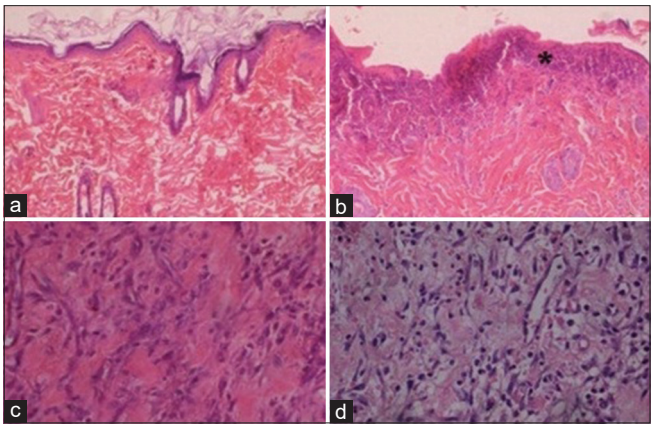

Figure 2: (a) Photograph from margin of ulcer showing epidermis and dermis with fibrosis (H and E, ×100). (b) Photograph showing ulcer area with loss of epidermis and dermis with fibrosis and granulation tissue (H and E, ×100). (c) Photograph shows granulation tissue having inflammatory cells and immature blood vessels (H and E, ×100). (d) Photograph shows no evidence of vasculitis or granulomas in sections studied (H and E, ×100)

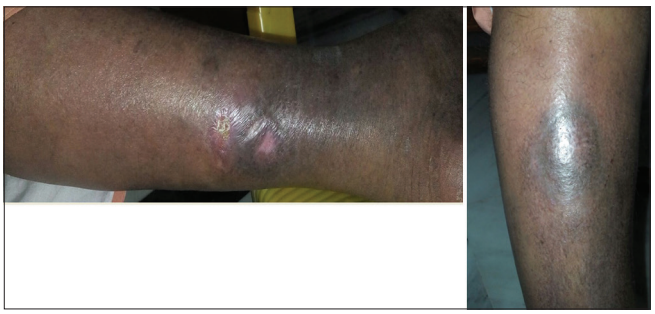

Figure 3: After 6 weeks of stopping methotrexate, ulcers showing almost complete healing

methotrexate.[7] Thus, there could be more mechanisms for cutaneous ulcerations other than the dose-dependent toxic adverse effect-Type A described. The first report of cutaneous ulceration as a sign of methotrexate toxicity in a patient without psoriasis was first reported by Ben-Amitai *et al.*[8] The fifth case in world literature of cutaneous ulcer induced by methotrexate in a nonpsoriatic patient accompanied by pancytopenia was reported by Kurien *et al.*[9] Treatment of cutaneous ulcer due to

methotrexate consists of stopping methotrexate and observing for ulcer healing. No other wound healing adjuvant measures are described to be useful in the literature to the best of the Author's knowledge.

The Author here reports occurrence of multiple (two) cutaneous ulcers due to methotrexate in a nonpsoriatic patient. To the best of the Author's knowledge, this is a rare case of cutaneous ulceration due to methotrexate in a nonpsoriatic patient and probably one of its kind without pancytopenia or other hematological abnormalities.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Shiver MB, Hall LA, Conner KB, Brown GE, Cheung WL, Wirges ML. Cutaneous erosions: A herald for impending pancytopenia in methotrexate toxicity. Dermatol Online J 2014;20. pii: 13030/qt46k975h8.
2. Del Pozo J, Martínez W, García-Silva J, Almagro M, Peña-Penabad C, Fonseca E. Cutaneous ulceration as a sign of methotrexate toxicity. Eur J Dermatol 2001;11:450-2.
3. Hocaoglu N, Atilla R, Onen F, Tuncok Y. Early-onset pancytopenia and skin ulcer following low-dose methotrexate therapy. Hum Exp Toxicol 2008;27:585-9.
4. Weidmann A, Foulkes AC, Kirkham N, Reynolds NJ. Methotrexate toxicity during treatment of chronic plaque psoriasis: A case report and review of the literature. Dermatol Ther (Heidelb) 2014;4:145-56.
5. Montero LC, Gómez RS, de Quirós JF. Cutaneous ulcerations in a patient with rheumatoid arthritis receiving treatment with methotrexate. J Rheumatol 2000;27:2290-1.
6. Luis M, Pacheco-Tena C, Cazarín-Barrientos J, Lino-Pérez L, Goycochea MV, Vazquez-Mellado J, *et al*. Comparison of two schedules for administering oral low-dose methotrexate (weekly versus every-other-week) in patients with rheumatoid arthritis in remission: A twenty-four week, single blind, randomized study. Arthritis Rheum 1999;42:2160-5.
7. Delyon J, Ortonne N, Benayoun E, Moroch J, Wolkenstein P, Sbidian E, *et al*. Low-dose methotrexate-induced skin toxicity: Keratinocyte dystrophy as a histologic marker. J Am Acad Dermatol 2015;73:484-90.
8. Ben-Amitai D, Hodak E, David M. Cutaneous ulceration: An unusual sign of methotrexate toxicity – First report in a patient without psoriasis. Ann Pharmacother 1998;32:651-3.
9. Kurian A, Haber R. Methotrexate-induced cutaneous ulcers in a nonpsoriatic patient: Case report and review of the literature. J Cutan Med Surg 2011;15:275-9.