Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2016;25:79-81
doi: 10.15570/actaapa.2016.23

Methotrexate-induced panniculitis in a patient with rheumatoid arthritis

Raghda Al Maashari[1] ✉, Mowafak M. Hamodat[2]

Abstract

Methotrexate-induced accelerated nodulosis (MIAN) is not an uncommon adverse effect associated with the use of the methotrexate in rheumatoid arthritis. Limited case reports describe panniculitis as a pathological finding in this setting. A 31-year-old female with seropositive rheumatoid arthritis on methotrexate therapy presented with a 2-week history of sudden onset of painful infiltrated subcutaneous nodules on both forearms. Based on clinical and histological findings, a diagnosis of methotrexate-induced panniculitis was made. The majority of MIAN case reports that we reviewed showed characteristic pathological findings of classic rheumatoid nodules; few reported panniculitis as a finding. This case illustrates the importance of recognizing this phenomenon as methotrexate-induced panniculitis should be considered in the differential diagnosis of any patient receiving methotrexate presenting with a recent history of accelerated nodulosis. Discontinuation of methotrexate remains controversial.

Keywords: panniculitis, methotrexate, rheumatoid arthritis, nodulosis

Received: 19 July 2016 | **Returned for modification:** 18 August 2016 | **Accepted:** 29 August 2016

Introduction

Methotrexate is one of the most widely used anti-rheumatic drugs in the management of rheumatoid arthritis. Methotrexate-induced accelerated nodulosis (MIAN) is not an uncommon adverse effect associated with the use of methotrexate in rheumatoid arthritis. There are limited case reports that describe panniculitis as a pathological finding in this setting. We report a case of panniculitis in a patient with rheumatoid arthritis on methotrexate therapy.

Case history

A 31-year-old female developed symmetric arthritis in her hands, ankles, knees, and lower back and was initially diagnosed as a case of seropositive rheumatoid arthritis in 2009. Her arthritis was poorly responsive to treatment with several agents including azathioprine and sulfasalazine. In October 2011, she was started on methotrexate at a dosage of 20 mg per week. During the course of the treatment, other agents used in combination with methotrexate included adalimumab and tocilizumab, which were both discontinued at the patient's personal preference. Since October 2013, methotrexate has been used as monotherapy and it achieved partial control of her symptoms.

In January 2014, the patient presented to the clinic with a 2-week history of sudden onset of painful infiltrated subcutaneous nodules that developed on both forearms. Physical examination revealed well-circumscribed, indurated, tender, subcutaneous nodules localized over the lateral proximal aspect of the forearms bilaterally.

At that time, the laboratory data were as follows: white blood cell count 8.4 × 10^9/l (normal range 4.5–11 × 10^9/l) , hemoglobin 127 g/l (117–155 g/l) , platelet count 406 × 10^9 (normal range 140–450 × 10^9/l), erythrocyte sedimentation rate 10 mm/hr (normal range 0–20 mm/hr), and a positive antinuclear antibody titer 1:80 speckled pattern. Rheumatoid factor, cyclic citrullinated peptide, and extractable nuclear antigen were all negative.

A 5 mm punch biopsy taken from the left forearm showed septal panniculitis and fibrosis (Fig. 1). The septa were infiltrated by lymphocytes and histiocytes, with areas of hemorrhage (Fig. 2), microcyst formation, membranous fat necrosis, and lipophages (Fig. 3). A few eosinophils were seen (Fig. 4). High-power magnification showed lipophages and membranous fat necrosis. Focally, a small vein was noted cuffed by lymphocytes (Fig. 5). No definite granuloma was identified, nor leukocytoclastic vasculitis (Fig. 6). High-power magnification showed microcyst formation. Based on the clinical and histological findings, methotrexate was stopped with no additional drugs started.

Within one month of methotrexate cessation, the lesion completely resolved, although clinically her peripheral arthritis worsened. Tofacitinib was later introduced and helped in controlling the patient's arthritis.

Discussion

Rheumatoid arthritis is a chronic inflammatory disease affecting about one percent of the general population (1). Methotrexate is an anti-metabolite that inhibits dihydrofolate reductase and is considered one of the most frequently used drugs for rheumatoid arthritis and many other immune diseases due to its beneficial anti-inflammatory and immunosuppressive effects (2).

One to 10 percent of patients on methotrexate may develop cutaneous lesions, which may include cutaneous ulcerations, photosensitivity, alopecia, macular punctate rash, hypersensitivity vasculitis, and lower leg ulcers. Adverse effects associated with the use of methotrexate also include the development of accelerated nodulosis, also known as methotrexate-induced accelerated nodulosis (MIAN).

The first report that documented the occurrence of MIAN was published in 1986 (3) and since then a number of case reports and systematic studies have reported this phenomenon, which describes the development or acceleration of nodulosis in patients receiving methotrexate therapy for autoimmune conditions. This phenomenon is thought to occur in eight to 10 percent of rheumatoid arthritis patients (1). The time period between the beginning

[1]Dermatology Department, Sheikh Khalifa Medical City (SKMC), Abu Dhabi, UAE. [2]Pathology and Laboratory Medicine Department Sheikh Khalifa Medical City (SKMC), Abu Dhabi, UAE. ✉ **Corresponding author: raalmaashari@seha.ae**

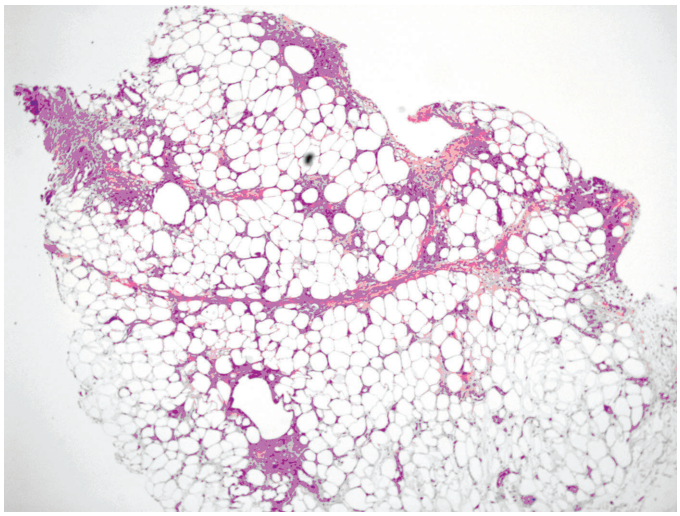

Figure 1 | Septal panniculitis and fibrosis.

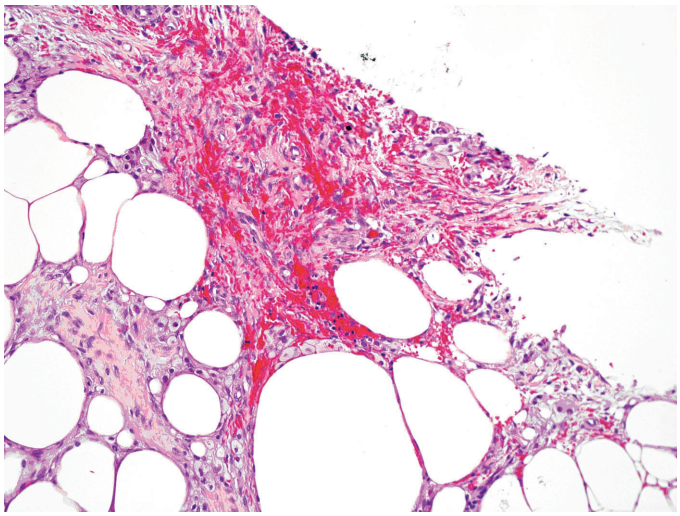

Figure 2 | Infiltration of the septa by lymphocytes and histiocytes, with areas of hemorrhage.

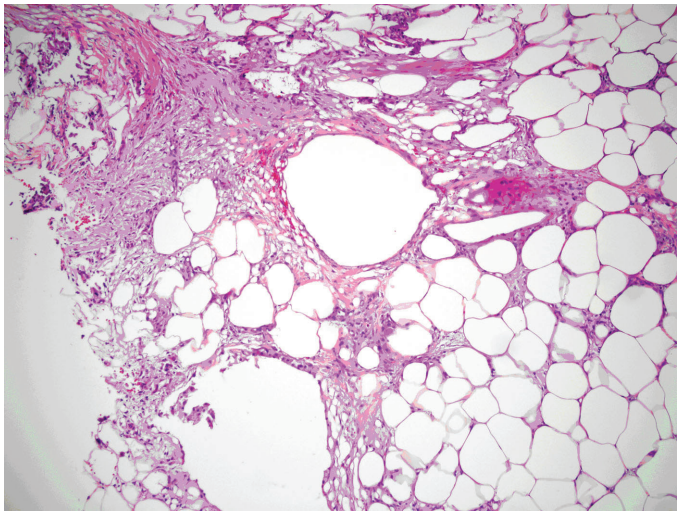

Figure 3 | Lipophages, microcyst formation, and membranous fat necrosis.

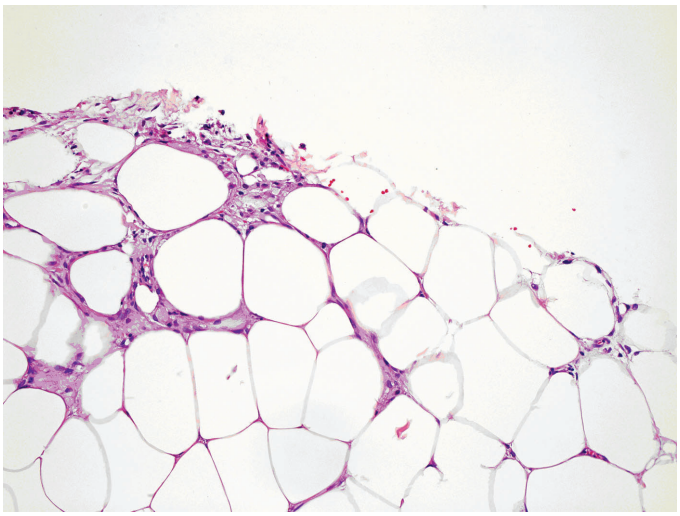

Figure 4 | A few eosinophils identified in this image.

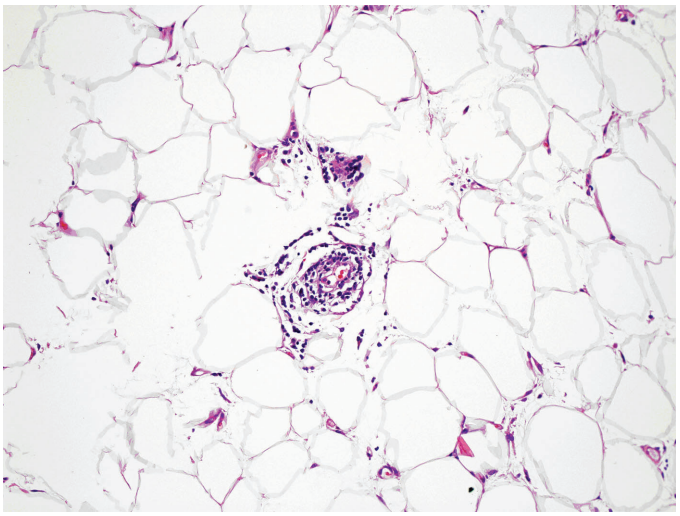

Figure 5 | High-power image of lipophages and membranous fat necrosis. Focally, a small vein was noted cuffed by lymphocytes.

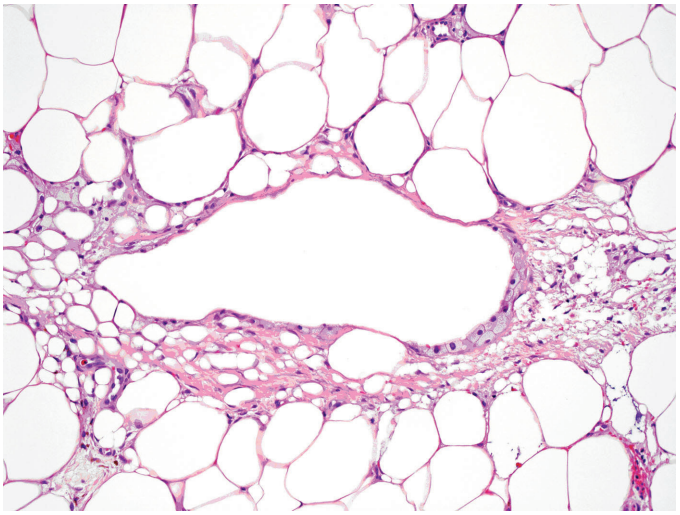

Figure 6 | Leukocytoclastic vasculitis and a definite granuloma are absent.

of methotrexate administration and the development of the nodules is variable (weeks to years) (4).

Panniculitis has several causes, including various infections, malignancies, and connective tissue disease, and drugs such as steroids, sulfonamides, and oral contraceptives, as well as MINE chemotherapy in rare cases (5). Methotrexate was listed by Brissaud in 2000 among one of the possible causes (6). The pathogenesis of methotrexate-induced panniculitis remains obscure.

The pathological findings in the majority of the MIAN case reports that we reviewed showed the classic findings of the classic rheumatoid nodule. However, a few reported panniculitis as a finding, as in the case of our patient.

To date, autoimmune conditions that have been reported to be associated with methotrexate-induced panniculitis include rheumatoid arthritis, dermatomyositis (2), and MCTD (7). Interestingly, there has been a report of MAIN in a patient with psoriatic arthri-

tis in which the histopathological findings were consistent with septal panniculitis (8).

It is unclear what factors determine predisposition of a certain category of rheumatoid arthritis patient to develop accelerated nodulosis because many reports of its occurrence are limited to case reports or are inconclusive due to a small sample size (3). Both the HLA-DRB1*0401 allele (3) and MTR 2756GG genotype (9) have been proposed to be associated with MIAN. Moreover, cumulative methotrexate dosage (3) and treatment efficacy (6) do not appear to affect the occurrence of methotrexate-induced nodulosis.
Methotrexate-induced nodules can present as an isolated finding or associated with systemic symptoms. They are commonly seen in the fingers and are usually smaller in size (< 5 mm in diameter) than rheumatoid nodules, though they may be clinically indistinguishable. Histologically, some methotrexate-induced nodules are characterized by septal panniculitis (7).

Clues that favor the diagnosis of MIAN involve the occurrence of skin lesions simultaneously with methotrexate use and its disappearance upon drug withdrawal. In some cases, methotrexate rechallenge can be performed to confirm the diagnosis. However, the absence of nodule recurrence with methotrexate re-challenge cannot rule out the role of methotrexate as an inciting agent (6). In the case of our patient, it was not performed.

Histological findings associated with drug-induced panniculitis can range from septal panniculitis with a lympho-histiocytic infiltrate to lobular panniculitis with a mixed or mostly neutrophilic infiltrate particularly with tyrosine kinase inhibitors (10).

The management of panniculitis depends on the cause. In methotrexate-induced panniculitis, controversy remains regarding whether methotrexate should be discontinued or not. In the case of our patient, the nodules resolved within 1 month of methotrexate cessation without the use of any additional drugs. Clearance of nodules remains variable, although it has been reported that nodules may clear after 6 months (3) of methotrexate discontinuation but sometimes recur when the drug is restarted. In cases in which methotrexate needs to be continued, additional drugs such as (11) hydroxychloroquine, colchicine, sulfasalazine, azathioprine, or D-penicillamine should be started because nodulosis can persist for 3.5 years if methotrexate is continued (3).

References

1. Pugner KM, Scott DI, Holmes JW, Hieke K. The costs of rheumatoid arthritis: an international long-term view. Semin Arthritis Rheum. 2000;29:305-20.
2. Jang KA, Choi JH, Moon KC, Yoo B, Sung KJ, Koh JK. Methotrexate nodulosis. J Dermatol. 1999;26:460-4.
3. Ahmed SS, Arnett FC, Smith CA, Ahn C, Reveille JD. The HLA-DRB1*0401 allele and the development of methotrexate-induced accelerated rheumatoid nodulosis: a follow-up study of 79 Caucasian patients with rheumatoid arthritis. Medicine. 2001 Jul;80:271-8.
4. Patatanian E, Thompson DF. A review of methotrexate-induced accelerated nodulosis. Pharmacotherapy. 2002;22:1157-62.
5. Saint-Cyr I, Vezon G, Boisseau-Garsaud AM, Calès-Quist D, Panelatti G, Ossondo M. Panniculitis induced by MINE chemotherapy. Ann Dermatol Venereol. 2001;128:756-8.
6. de Sèze S, Ryckewaert A, Kahn MF, Kuntz D, Meyer O, Bardin T, Orcel P, editors. Actualité Rhumatologique. Paris (France): Expansion Scientifique Française; c2000. Brissaud P, Grossin M. Panniculites systémiques; p. 80-106. French.
7. Nezondet-Chetaille AL, Brondino-Riquier R, Villani P, Bouvenot G. Panniculitis in a patient on methotrexate for mixed connective tissue disease. Joint Bone Spine. 2002;69:324-6.
8. Berris B, Houpt JB, Tenenbaum J. Accelerated nodulosis in a patient with psoriasis and arthritis during treatment with methotrexate. J Rheumatol. 1995;22:2359-60.
9. Berkun Y, Atta IA, Rubinow A, Orbach H, Levartovsky D, Suhail A, et al. 2756GG genotype of methionine synthase reductase gene is more prevalent in rheumatoid arthritis patients treated with methotrexate and is associated with methotrexate-induced nodulosis. J Rheumatol. 2007;34:1664-9.
10. Kerl K. Histopathological patterns indicative of distinct adverse drug reactions. Chem Immunol Allergy. 2012;97:61-78
11. Patatanian E, Thompson DF. A review of methotrexate-induced accelerated nodulosis. Pharmacotherapy. 2002;22:1157-62.