Development of leukocytoclastic vasculitis during long-term methotrexate therapy in patients with rheumatoid arthritis: description of two clinical cases

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Leukocytoclastic vasculitis (LCV) is a small vessel vasculitis characterized by immune complex depositions involving dermal post-capillary venules. Cutaneous small vessel vasculitis is most often idiopathic but may be aggravated by secondary causes, such as inflammatory conditions, infections, neoplasms, and drugs exposure.
Herein, we describe two patients with a long history of rheumatoid arthritis (RA) treated with methotrexate (MTX) for more than ten years, who later developed generalized LCV with pancytopenia after a viral infection, one with herpes simplex virus, and the other with SARS-CoV-2 virus. Because of the worldwide use of MTX in treatment of RA, strict follow-up and preventive measures are needed nowadays, especially during COVID-19 pandemic, in order to avoid any infection which may provoke LCV with or without systemic manifestations. So, using MTX for treating RA or other similar disorders may be considered a double-edged sword, especially during COVID-19 pandemic.

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Introduction

Leukocytoclastic vasculitis (LCV) is the inflammation of blood vessels caused by precipitation of immune complexes in capillaries and venules [1]. Many autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus, Sjogren syndrome, Henoch–Schцnlein purpura, lead to deposition of these immune-mediated complexes in vessels leading to hypersensitivity vasculitis [1]. Additional causes of acute LCV include medications, infections, and malignancies which cause generation of antigens that bind to antibodies leading to immune complex depositions in dermal vessels [2].

We present two female RA patients with cutaneous LCV and pancytopenia who were treated with methotrexate (MTX) for a long time. The first patient was infected with COVID-19, and the second one was infected with herpes simplex virus (HSV). Both patients recovered after MTX discontinuation, and there was no recurrence of skin lesions in the follow-up months.

Case 1

A 50-year-old female patient with a history of RA and hypothyroidism presented with a few-month history of generalized erythematous pruritic papules (Figure 1, a–c). The patient was taking MTX (15 mg weekly, started twelve years before), sulfasalazine which was started four years before, and levothyroxine. Five months before, the patient was infected with COVID-19 virus. Because of COVID-19 infection, MTX and sulfasalazine were discontinued for one month and then initiated again. Three months later, she started complaining of erythematous pruritic papules and plaques on her abdomen that gradually spread to her trunk and lower extremities (Figure 1, b). Laboratory evaluations revealed low white blood cell count – 2,6·10³/uL, Hb – 14,3 g/dl, and low platelet count – 127·10³/ul. She had normal C3, C4, CH 50, c-ANCA, and p-ANCA titer with ANA 1/640 (normal up to 1/80), and a high level of anti-CCP u/ml. After a rheumatologist's consultation, MTX and sulfasalazine were discontinued.

A skin biopsy from a lesion was performed with differential diagnoses of urticarial vasculitis, prodromal stage of bullous pemphigoid, and Wells syndrome. Microscopic examination revealed a moderately dense inflammatory cells infiltration around superficial and mid-dermal small vessels composed of neutrophils, lymphocytes and few eosinophils accompanied by endothelial cells swelling, leukocytoclasis, focal fibrinoid necrosis of vessel walls and extravasation of red blood cells – RBCs (Figure 2, a, b). The result was compatible with acute leukocytoclastic vasculitis. She started treatment with prednisolone 20 mg daily, and cetirizine 20 mg daily, for about two weeks with mild improvement. Oral tacrolimus 2 mg daily was then initiated. During the next three months, prednisolone was tapered gradually to reach 5 mg daily. Lab test after 3 months showed an improvement in white blood cell count – 4,48·10³/uL, Hb – 12,9 g/dl, and platelet count – 155·10³/ul. Despite using prednisolone, the improvement was slow and accelerated only after stopping MTX. Rituximab was suggested for treatment of RA.

Case 2

A 73-year-old female patient presented with a 3-week history of a pruritic eruption which started on her lower extremities and was associated with fever and mild cough. On examination, she had non-blanching palpable purpura and multiple blisters on both legs, with a large ulcerative plaque with focal necrosis on the buttock, and crusty necrotic plaque on the nose (Figure 3, a–c). There were also multiple painful oral ulcers. The patient had no lymphadenopathies, nor

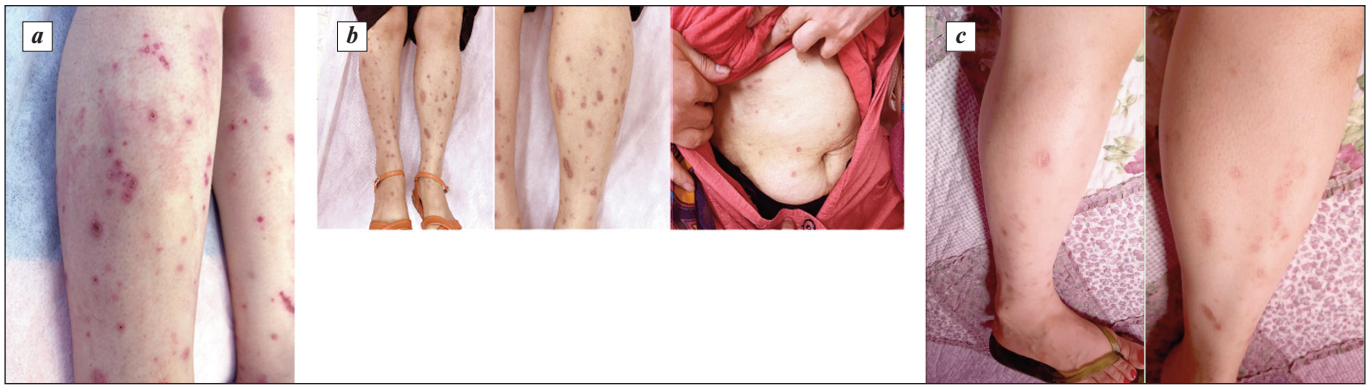

Figure 1. *Skin lesions in patient 1: a — The patient's first presentation three months after COVID-19 infection; b — Follow-up after one month; c — Great improvement in skin lesions after four months following treatment*[1]

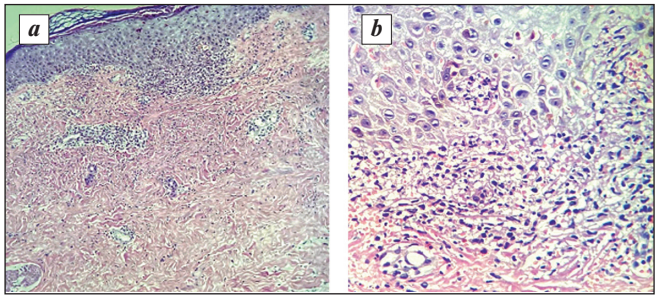

Figure 2. *Microscopic examination of patient 1 skin biopsy material: a — LCV. Neutrophil-rich perivascular infiltrate involving superficial and mid-dermal small vessels (H&E ×10 objective); b — Note vascular wall damage characterized by narrowing of vascular lumen, leukocytoclasis, focal fibrinoid necrosis in vessel wall and marked extravasation of RBCs (H&E ×40 objective)*

organomegaly.

The patient's medical history revealed RA which debuted 15 years ago and was treated with several anti-rheumatic drugs, including MTX, hydroxychloroquine, and prednisolone. The patient also had a history of hypertension and osteoporosis. The patient had a history of Herpes zoster five months before which was treated successfully.

Chest computed tomography scan showed bibasilar ground glass opacity with multiple bilateral nodules and peribronchial thickening which suggested fibrosis caused by MTX. (Figure 4). Direct immunofluorescence (DIF) result showed anti-IgG, anti-IgM, and anti-C3 with granular deposits along superficial dermal vessels. Two skin biopsies were taken from the abdomen and buttock skin with differential diagnoses of vasculitis and linear IgA bullous dermatosis. The histopathologic findings were compatible with acute LCV of small dermal vessels with overlying intraepidermal blister

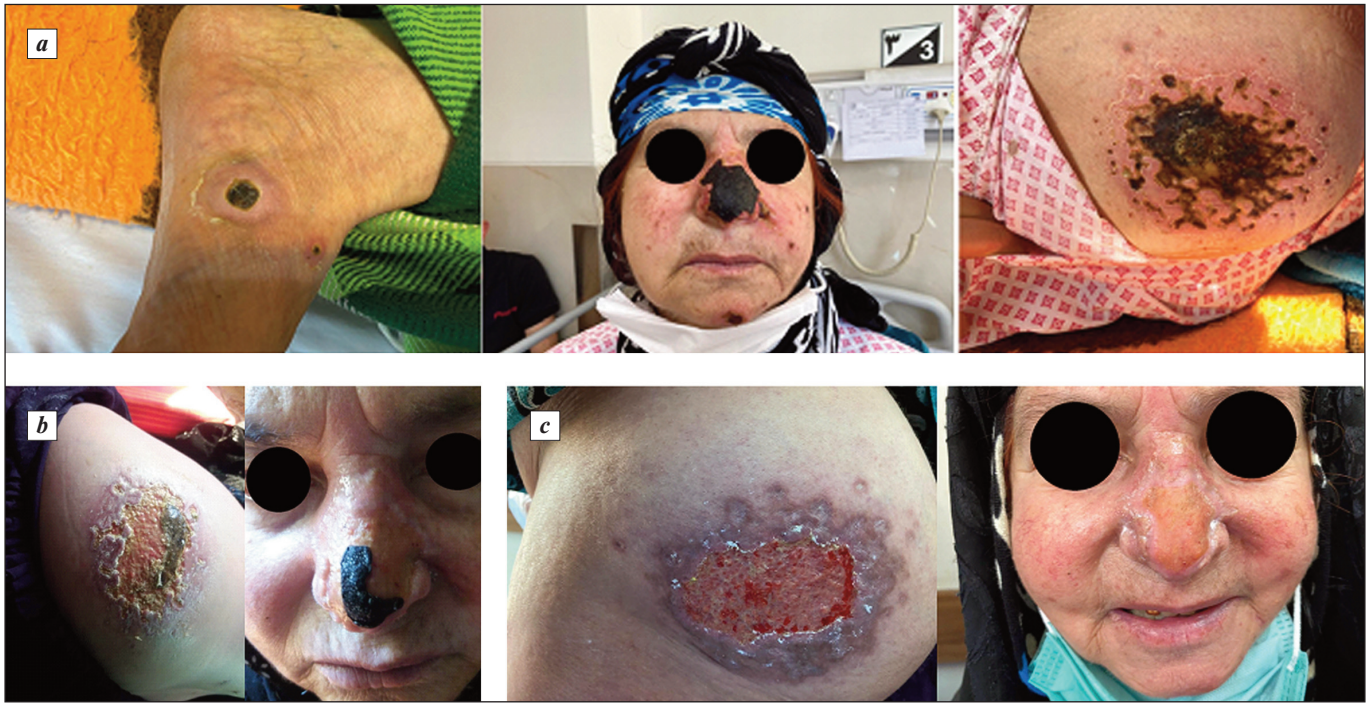

Figure 3. *Skin lesions in patient 2: a — At the time of presentation; b — Two weeks after treatment; c — 1 month later*

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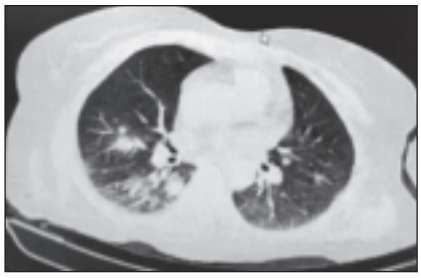

Figure 4. *Chest computed tomography of patient 2*

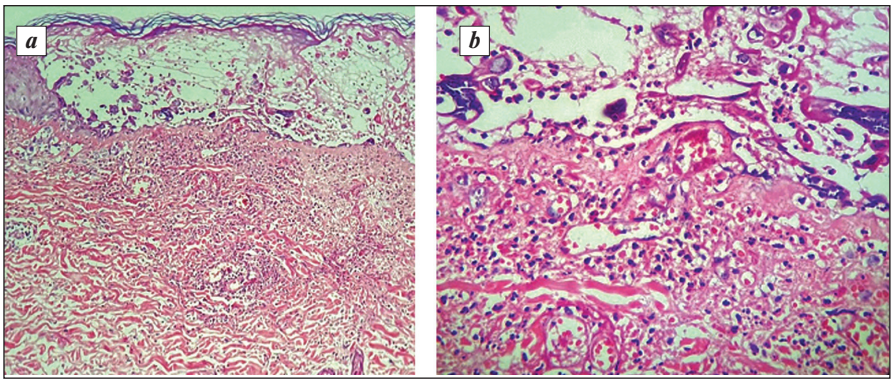

Figure 5. *Biopsies from the abdomen and buttock lesions show similar features with HSV intraepidermal blister and underlying acute LCV in patient 2: a – Low power view of the intraepidermal blisters and underlying dermal vasculitis; b – High power view shows keratinocytes with intranuclear inclusions and some multinucleated giant cells with nuclear molding. The dermis shows perivascular neutrophilic infiltration, vascular wall damage, occasional intraluminal thrombi and marked extravasation of RBCs*

showing HSV cytopathic effects (Figure 5, a, b).

Laboratory evaluations revealed pancytopenia with low white blood cell count – 3,4·10³/uL, Hb – 8,3 g/dl, and platelet count – 140·10³/uL. There was an elevation in the erythrocyte sedimentation rate – 45 mm/h; serum ferritin level – 800 ng/mL; LDH – 511 (normal range, 220–500U/L); anti-CCP – 45 (normal range <12), and C-reactive protein – 12mg/dL (normal range, 0–10). She had normal C3, C4, ANA, anti-ds DNA, c-ANCA, and p-ANCA with negative RF.

Bone marrow biopsy was also performed and showed cellularity of 40%, with the ratio of myeloid cells to nucleated erythroid cells – 1,5:1. There was an adequate number of megakaryocytes. Bone marrow iron status according to Gale's method was grade II; no ring sideroblasts. Blasts constituted less than 5% of nucleated bone marrow cells. Plasma cells accounted for less than 5% of nucleated bone marrow cells. Lymphocytes accounted for less than 10% of nucleated bone marrow cells. Neoplastic infiltration or infection were not detected. Bone marrow biopsy and aspiration showed cellular marrow with mild hematopoietic dyspoiesis, most likely to be drug-induced.

Based on the consultations of a rheumatologist and a hematologist, bone marrow biopsy, clinical presentation and histological findings, it was suggested that the most likely triggering factor for this vasculitis was an adverse reaction to MTX.

MTX was discontinued, and the patient started oral prednisone 60 mg daily, cyclosporine 100 mg daily, and acyclovir 400 mg tds. Six days later white blood cell count increased to 7,2·10⁹/L, Hb – 8,6 g/dl and platelet count – 340·10⁹/L. The results showed significant improvement and regression of the patient's lesions and pancytopenia with MTX withdrawal, and later the dose of prednisone was gradually tapered. No recurrence was reported after 3 months of the follow-up. After complete remission, a low dose of MTX was again initiated, and during a few months of maintenance therapy, the patient didn't develop any new skin lesions (Figure 3, c).

Discussion

Cutaneous vasculitis can be drug-induced or triggered by infections; it usually resolves with stopping the medication and treating the implicated infection [2]. When vasculitis is suspected in a patient who is using multiple medications, several considerations should be included in order to attribute the side effect to one drug, including the overall clinical picture, the time period of using the medication and its cumulative dose, in addition to resolution of the symptoms after the drug discontinuation [3]. In these two cases, there was more than ten-year history of RA treated with MTX. Both patients were immunosuppressed, and the triggers of these vasculitic presentations were viral infections, including HSV and COVID-19 infection. An additional finding which suggested that MTX was the main factor responsible for these presentations was pancytopenia.

MTX is one of the important medications used for treatment of autoimmune diseases, and because of immunosuppression, especially when used for a long time, it can predispose to viral infections which, together can lead to vasculitis [4]. Although, MTX is used to treat recalcitrant cutaneous small-vessel vasculitis (CSVV), these two cases show that it can be considered a triggering factor for CSVV [5]. In patients with RA presenting with CSVV, biopsy-established cases showed LCV, and a possible suggested mechanism was a hypersensitivity reaction [6].

The treatment of these LCVs included stopping the offending factor, which was MTX, and starting prednisolone. After four months of follow-up there was a significant improvement in skin lesions, resolution of pancytopenia, and no recurrence was recorded. This also confirms that the offending and main triggering factor was MTX. So, for a patient with a long history of RA treated with MTX who presents with LCV in multiple body sites (not limited to lower extremities like in usual vasculitis) and pancytopenia, it is recommended to stop MTX until the resolution of lesions and to start corticosteroids.

Nowadays, with the emergence of the COVID-19 pandemic, and because of the high prevalence of using MTX for treatment of RA, we suggest close follow-up of these patients, especially those who are treated with multiple drugs, and especially MTX, because of possible side effects and interactions. According to literature, death was recorded in 10% of patients especially with multiple organ involvement [7]. So, early diagnosis and discontinuation of the culprit drug can be tremendously important in decreasing unfavorable outcomes.

While waiting for new recommendations about RA treatments during the COVID-19 pandemic, strict preventive measures should be taken to avoid any infection – whether with coronavirus or other common viruses like HSV – in order to prevent undesirable manifestations [8].

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Conflict of Interest Statement

Contributors

Mohammad Shahidi Dadras and Hamideh Moravvej were involved in the diagnosis and management of the patients, and were responsible for the clinical part of the manuscript. Azadeh Rakhshan reported the result of the histopathological evaluation. Fahimeh Abdollahimajd, Reem Diab, and Ali Kaddah did the literature review and drafted the manuscript. Fahimeh Abdollahimajd and Hamideh Moravvej were responsible for final editing of the manuscript, and coordinated the study. All authors have read and approved the final manuscript.

Patient consent for publication

Written informed consent was obtained from the patients' families for publication of these case reports and any accompanying images.

Competing interests

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