Clinical, Cosmetic and Investigational Dermatology

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CASE REPORT

Methotrexate-Induced Leukocytoclastic Vasculitis: A Case Report and Literature Review

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Abstract: Methotrexate (MTX) is widely utilized for the management of autoimmune diseases and neoplasms. It may cause several adverse effects, including myelosuppression, hepatitis, and mucositis, and in rare cases, can result in cutaneous vasculitis. We present a case involving a 60-year-old female patient receiving 5 milligrams (mg) of MTX weekly for the treatment of systemic lupus erythematosus (SLE). Her underlying condition was end-stage renal disease (ESRD), requiring hemodialysis (HD). Ten weeks after MTX treatment, she developed oral ulcers, pancytopenia, and hepatitis, followed by multiple non-blanchable erythematous papules, along with a few vesicles and pustules on the neck, trunk and arms. Laboratory results indicated elevated serum MTX levels, and skin biopsy demonstrated dense superficial perivascular and interstitial lymphocytic, eosinophilic, and neutrophilic infiltration, along with nuclear debris and extravasated erythrocytes, indicative of early leukocytoclastic vasculitis (LCV). Direct immunofluorescence (DIF) identified C3 deposits at the dermo-epidermal junction and superficial blood vessels, indicating possible immune complex-mediated vascular disease. The patient was diagnosed with MTX toxicity and histologically confirmed LCV secondary to MTX. MTX toxicity was effectively treated with intravenous folinic acid and cessation of MTX, alongside prescriptions of oral prednisolone and emollients for LCV management. Serum MTX levels became undetectable after a five-day treatment regimen. Skin lesion resolution occurred within one week. Additionally, a review of existing literatures on MTX-induced LCV was conducted.

Keywords: cutaneous small vessel vasculitis, methotrexate, type III hypersensitivity reaction, toxicity

Introduction

Methotrexate (MTX) is an anti-metabolite drug which is extensively used for immunosuppressive and chemotherapeutic treatments, particularly for autoinflammatory disorders and hematologic malignancies. It is a folate antagonist, which competitively inhibits the activity of folate-dependent enzymes and synthesis of purine and pyrimidine required for DNA and RNA production in rapidly multiplying cells.[1,2] Despite its therapeutic benefits, MTX is associated with several adverse effects, which are categorized into dose-dependent and dose-independent. Dose-dependent adverse effects are typically associated with higher concentrations of the drug in the body, leading to a reduction in DNA synthesis and cellular proliferation. Rapidly dividing cells, notably in the bone marrow, gastrointestinal (GI) tract, mucosa and liver, are particularly affected. Common dose-dependent side effects of MTX include pancytopenia, nausea, vomiting, mucositis, and liver toxicity.[3] Conversely, dose-independent side effects are unpredictable and may occur at lower doses of MTX. These reactions are not directly related to the drug's concentration but rather with patient-specific factors, including genetic variations, pre-existing conditions, or immune responses. Examples include hypersensitivity reactions, such as rashes and pneumonitis. Leukocytoclastic vasculitis (LCV) also arises from a dose-independent mechanism.[4–6]

The term LCV refers to a histopathological description of a common form of small vessel vasculitis (SVV), which can be found on the skin and internal organs. The pathogenesis of LCV involves immune complex deposition in small vessel walls in addition to activation of the complement system.[7] The histopathological findings are characterized by evidence of neutrophilic infiltration within and around the vessel wall with signs of leukocytoclasia or nuclear dust, as well as

Received: 17 March 2025
Accepted: 18 August 2025
Published: 24 August 2025

fibrinoid necrosis and extravasated erythrocytes.[8] The clinical presentation of cutaneous SVV (CSVV) including palpable purpura, petechia, macular purpura, urticarial papules, vesicles, pustules, targetoid papules or plaques and ulcers.[7,9]

While maculopapular eruptions and urticaria are the most common cutaneous drug reactions.[10] It has been estimated that 10–20% of dermal reactions are vasculitic in nature.[4] The etiologies of CSVV include autoimmune disorder, infectious agents, as well as drug exposures, with drugs accounted for 10–15% of cases. In the case of MTX, in addition to its systemic adverse effects, common cutaneous side effects include oral ulcers, alopecia, photosensitivity. Less commonly, it has been associated with necrosis of psoriatic plaques and accelerated rheumatoid nodulosis.[11] MTX-associated LCV, however, is relatively rare. Moreover, the idiosyncratic nature makes it unpredictable and difficult to recognize. Currently, reports of MTX-induced LCV are scarce and lack systematic review. Nonetheless, the aforementioned clinical features and history of MTX administration should include MTX-induced LCV in differential diagnosis. Therefore, we present a case of a female patient with underlying end-stage renal disease (ESRD) requiring hemodialysis (HD), who developed histologically confirmed LCV after ten weeks of oral MTX for systemic lupus erythematosus (SLE). A literature review is also provided.

Case Presentation

A 60-year-old female has been diagnosed with SLE for 30 years. She presented with fever, malar rash, leg edema, proteinuria and a high antinuclear antibody (ANA) titer of 1:320 with fine-speckled pattern. Four years later, she developed ESRD due to lupus nephritis class VI and regularly required HD. There is no family history of autoimmune diseases. Current medications for SLE included oral MTX 5 milligrams (mg) weekly, prednisolone 5 mg every other day and hydroxychloroquine (HCQ) 600 mg weekly. MTX was initiated 10 weeks ago due to newly developed arthritis. Afterwards, she presented with a one-week history of oral ulcers preceding hospitalization. Physical examination revealed multiple ulcers on the buccal mucosa (Figure 1A). Laboratory findings showed pancytopenia including hemoglobin at 8.2 grams/deciliter (g/dL), hematocrit at 24.6%, white blood count at 1,330 cell/dL, platelet count at 27,000/mm^3 and elevated liver enzymes with aspartate aminotransferase (AST) 368 units per liter (U/L), alanine transaminase (ALT) 438 U/L. There was no MTX concentrations measured prior to these signs and symptoms, however, at the current admission MTX level was high (0.03 micromoles per liter). Therefore, she was initially diagnosed with MTX toxicity and was hospitalized for MTX antidote, folinic acid 150 mg intravenously (IV) every 4 hours (100 mg/m^2), GCSF 300 mg IV once daily and blood component transfusion. Simultaneously, MTX was discontinued. The last dose was administrated one week ago. The risk factors that contributed to MTX toxicity were thought to be the underlying ESRD and advanced age.

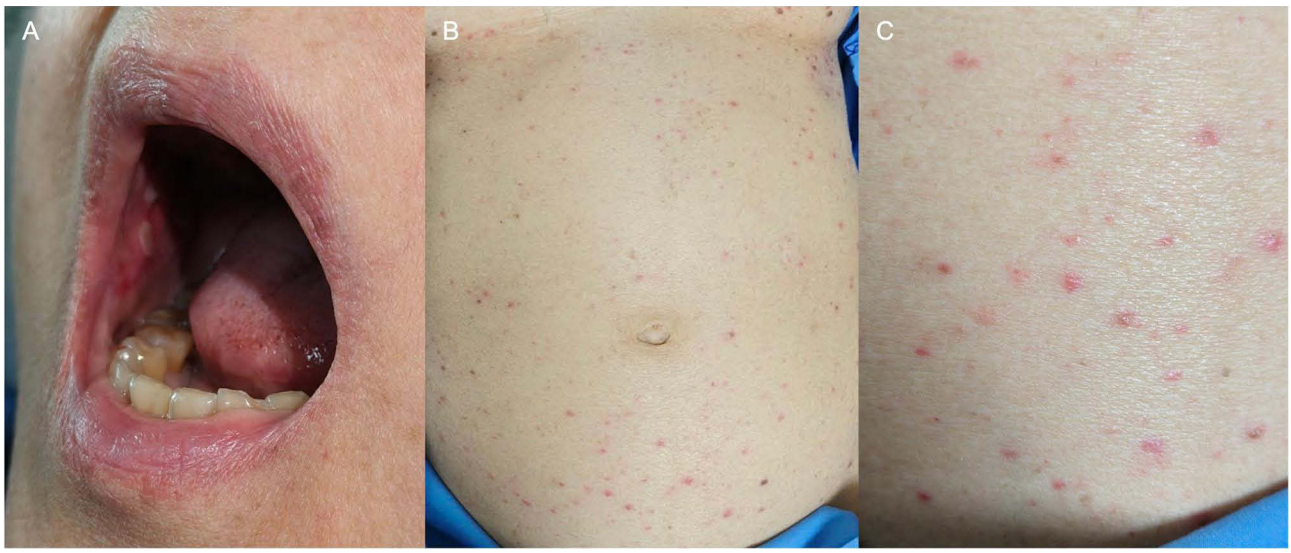

Figure 1 Oral ulcers at right buccal mucosa resulting from MTX toxicity (**A**), multiple non-blanchable erythematous papules located on abdomen (**B**) with few pustules, and vesicles (**C**).

Two days after admission, she developed multiple non-blanchable erythematous papules on the neck, trunk, and both arms, along with a few vesicles and pustules on the abdomen (Figure 1B and C) without fever, malaise, arthritis, or malar rash. Differential diagnoses were infections including varicella zoster virus (VZV) infection, disseminated herpes simplex virus (HSV) infection, CSSV due to infectious agents such as hepatitis viral, human immunodeficiency virus (HIV), bacterial infections and non-infection causes including MTX-induced LCV and CSVV secondary to SLE. Laboratory findings were assessed. Tzanck's smear and polymerase chain reaction (PCR) for VZV, HSV1, HSV2 from base of vesicle yielded negative results. Blood for anti-HIV and viral hepatitis profile including hepatitis A, B, and C were negative. Blood culture for aerobe was undetectable, urinalysis showed no leukocyte, and chest x-ray showed no abnormal opacity. Serum complement levels (C3 and C4) were within normal limits, while erythrocyte sedimentation rate (ESR) was mildly elevated at 24 millimeters per hour. C-reactive protein was also elevated at 7.99 mg/L. Serum cryoglobulin was not tested due to the absence of history of cold-induced skin lesions.

A skin punch biopsy was performed at an erythematous papule on abdomen, revealing dense superficial perivascular and interstitial infiltration of lymphocytes, eosinophils, few neutrophils, few nuclear dusts and extravasate erythrocytes, suggestive of early leukocytoclastic vasculitis (Figure 2A–C). Lesional direct immunofluorescence (DIF) studies demonstrated focal deposits of C3 at the dermo-epidermal junction and at superficial blood vessels, immunoglobulin (Ig)G showed a few cytoid bodies, while IgM and IgA revealed no deposits. These DIF findings suggest a possible immune complex-mediated vascular disease (Figure 2D). Given the temporal relationship with the history of MTX toxicity and the exclusion of other potential causes including infection and SLE condition, which was inactive due to the absence of fever, photodistributed rash, alopecia, arthritis as well as normal complement levels and only mildly elevated ESR, a diagnosis of MTX-induced LCV was made. She was administered oral prednisolone at 10 mg/day for immunosuppression and HCQ 600 at mg/day. No additional immunosuppressants were prescribed. Some of the lesions progressed to palpable purpuric macules, and overall, the lesions began to subside by day 4 as the serum MTX level became undetectable, and all erythematous papules on the trunk and extremities turned to brownish macules within 7 days; oral mucositis also healed during this timeframe (Figure 3). The same dosage of the drugs was maintained for the management of underlying SLE.

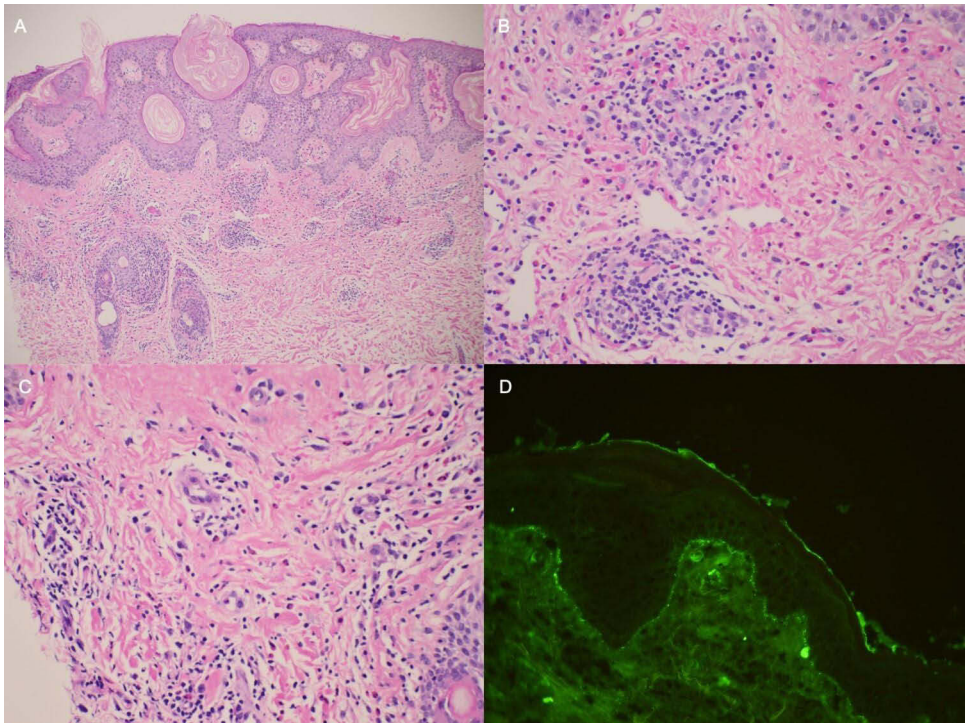

Figure 2 Hematoxylin and Eosin (100x, 400x) showing dense superficial perivascular and interstitial infiltration of lymphocytes, eosinophils, few neutrophils, few nuclear dusts and extravasate erythrocytes, suggestive of early leukocytoclastic vasculitis (**A**–**C**). Direct immunofluorescence studies demonstrated focal deposits of C3 at dermo-epidermal junction and at superficial blood vessels, consistent with possible immune-complex vascular disease (**D**).

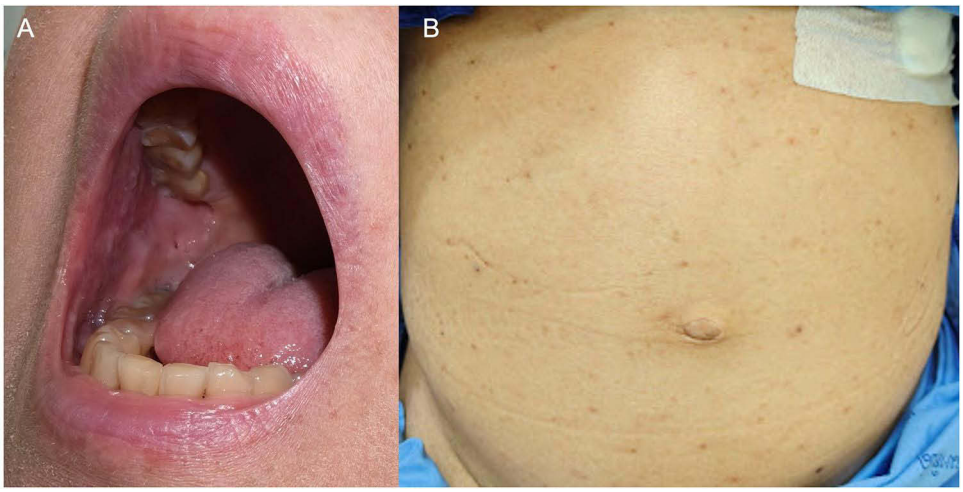

Figure 3 Resolution of the lesions within one week: right buccal ulcers (**A**), and erythematous papules on the trunk resolving into brownish macules (**B**).

Discussion

In our case, the patient presented with multiple non-blanchable erythematous papules on the trunk, and extremities, along with a few vesicles, and pustules on the abdomen. The morphology of the lesions was suggestive of CSVV, which can present with non-blanchable erythematous papules, vesicles and pustules. However, due to the appearance of vesicles and pustules, infection such as VZV and HSV were included in the differential diagnoses. Laboratory investigations excluded these infections, Histopathology revealed superficial perivascular lymphocytic and neutrophilic infiltration, nuclear dust, eosinophils and extravasated erythrocytes. Although fibrinoid necrosis was not observed, early LCV was suggested. Furthermore, DIF also supported the diagnosis of LCV, indicating a possible immune complex-mediated vascular disease. Moreover, during the subsequent observation, the lesions progressed to macular and palpable purpura. Take all findings into account, the skin lesions were diagnosed as cutaneous LCV.

The etiologies of cutaneous LCV include infectious agents, inflammatory disorders, drug exposure and idiopathic cause. In our case, the patient had no fever or specific symptoms such as respiratory tract symptoms or diarrhea. Furthermore, we have excluded bacteremia, viral hepatitis and HIV infection. Regarding inflammatory disorders, LCV secondary to the underlying SLE was considered in the differential diagnosis. However, the SLE condition was inactive due to the absence of fever, photo-distributed rash, alopecia, arthritis as well as normal complement levels and only mildly elevated ESR, Thus, SLE-associated LCV was excluded. Therefore, LCV secondary to MTX is the most likely explanation for the skin lesions, given the temporal relationship, concomitant diagnosis of MTX toxicity, elevated serum MTX level, and the absence of other identifiable causative agents. Consistently, the presence of tissue eosinophil infiltration suggests that the vasculitis may be drug-induced.[8]

According to the Naranjo causality scale[12] for adverse drug reactions of probable case. The score was 8, which included the previous reports on the reaction, temporal relationship between MTX administration and onset of LCV, evidence of toxic level of MTX in serum, consistency of histological and direct immunofluorescence studies, resolution after drug discontinuation or antidote and exclusion of differential diagnoses. The risk factors of our patient that contributed to MTX toxicity were advanced age and ESRD, as MTX is predominantly excreted by the kidneys (70%–90%).[1] Previous study showed that even a low dosage of 2.5 mg/week could lead to elevated plasma concentrations and prolonged half-life in HD patients, with the drug levels remaining elevated after 3 weeks.[13] Consequently, the prescription of MTX in patients with compromised renal function must be approached with caution. Furthermore, drug interactions between MTX and other agents such as aspirin, nonsteroidal anti-inflammatory drugs, furosemide and trimethoprim-sulfonamide should be aware since these drugs can exacerbate the toxicity of MTX.[14]

MTX-induced LCV is a rare but well-documented adverse effect. The exact pathogenesis is not fully understood but is presumed to involve a type III hypersensitivity reaction, in which immune complexes deposit in wall of small blood vessel. This deposition triggers the recruitment of inflammatory cells, which in turn leads to the vessel wall damage. In contrast,

Table 1 Review of the Literature of Patients with Histologically Proven MTX-Induced Leukocytoclastic Vasculitis

Author/Year (Number of Cases)	Age (Years), Sex	Underlying Disease for MTX Therapy	MTX Dosage, Duration, and Onset	Clinical Presentation of Cutaneous Vasculitis	Histological Findings	Systemic Symptoms/ Involvement	Resolution of Skin Lesions
Our case (1)	60, F	SLE	5 mg/week PO, 10 weeks	Non-blanchable erythematous papules on neck, trunk, upper arms with few pustules, and vesicles	Dense superficial perivascular and interstitial infiltration of lymphocytes, eosinophils, few neutrophils, few nuclear dusts and extravasate erythrocytes	None/ pancytopenia, hepatoxicity, mucositis	1 week
Diab et al 2022[16] (2)	50, F	RA	15 mg/week PO, 12 years	Erythematous pruritic papules and plaques on trunk and lower extremities	Moderately dense cells infiltration around superficial and mid-dermal small vessels composed of neutrophils, lymphocytes, and few eosinophils, with endothelial cells swelling, leukocytoclasis, focal fibrinoid necrosis of vessel walls and extravasation of RBCs	N/A / leukopenia and thrombocytopenia	3 months
	73, F	RA	N/A, 15 years	Non- blanching palpable purpura, blisters on both legs, with a large ulcerative plaque with focal necrosis on the buttock, and crusty necrotic plaque on the nose	Perivascular neutrophilic infiltration, vascular wall damage, occasional intraluminal thrombi and marked extravasation of RBCs, with intraepidermal blister, intranuclear inclusions and some multinucleated giant cells	Fever, cough/ pancytopenia, pulmonary fibrosis	6 days
Markham et al 2021[17] (1)	10, M	JIA	10–20 mg/week SC, 5 months	Painful, confluent and violaceous rash on face, legs, trunk and erythematous desquamating rash on plantar feet	Medium vessel vasculitis with fibrinoid necrosis and thrombus occluding vessel	Malaise, nausea, and joint pains/ anemia	1 week, completely resolved at 4 weeks
Dewan et al 2021[5] (1)	10, F	Acute biphenotypic leukemia	Intrathecal MTX, 20 weeks following by maintenance oral MTX 15 mg/ m^2/week, 4 weeks	Pruritic violaceous macules and papules on all extremities	Mild perivascular inflammatory infiltrate composed of neutrophils, lymphocytes at places invading into the vessel wall along with focal RBC extravasation	None/ pancytopenia, hepatoxicity	2 weeks
Henna et al 2018[18] (1)	56, M	Primary CNS lymphoma	3 g/m^2 infused over 24 hours for 1 dose, rash onset 14 days	Violaceous plaques at lower extremities and penis	Reactive small vessels in the upper dermis with a mild perivascular lymphocytic infiltrate and mildly hyperplastic epidermis with a few apoptotic bodies	Fever/neutropenia, thrombocytopenia, acute kidney injury	3 weeks, completely resolved at 4 weeks
Moreno et al 2003[19] (2)	27, M	Erythrodermic psoriasis	10 mg/week PO, 6 months	Multiple petechiae and pustules	Pustular psoriasis with a marked presence of leukocytoclastic vasculitis	Joint pain/IgA nephropathy	Improvement

(*Continued*)

https://doi.org/10.2147/CCID.S528734

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Table 1 (Continued).

Author/Year (Number of Cases)	Age (Years), Sex	Underlying Disease for MTX Therapy	MTX Dosage, Duration, and Onset	Clinical Presentation of Cutaneous Vasculitis	Histological Findings	Systemic Symptoms/ Involvement	Resolution of Skin Lesions
	70, M	Psoriasis	7.5 mg/week PO, 3 weeks	Necrosis in psoriatic plaques and apparently healthy skin	Presence of necrotizing angiitis in the early stages	N/A / pancytopenia, advanced chronic renal impairment	Improvement
Borman et al 2000[20] (1)	27, F	AS	7.5 mg/week PO, 6 months	Painful erythematopurpuric, nonpalpable, confluent skin rash on lower legs, arms	Dermal vessel with swollen endothelium, heavy mononuclear inflammatory cell infiltration around the superficial dermal capillaries, and nuclear dust in the vascular wall	N/A / mild anemia	Completely resolved in a couples of weeks
Halevy et al 1998[21] (1)	68, F	RA	7.5 mg/week PO, 2 weeks	Pruritic erythematous papules on trunk and extremities	Inflammatory cell infiltrate composed of mononuclear cells, polymorphonuclear cells and numerous eosinophils around blood vessels, thickened blood vessel walls and fibrin deposits	N/A / none	Completely resolved at 3 weeks
Simonart et al 1997[22] (1)	50, F	RA	5 mg/week IM, 2 weeks	Painful erythematous to purpuric, symmetrical patches on thighs, following by blisters and large necrotic patches	Intense polymorphonuclear infiltration around small vessels. The vessels were dilated and thrombosed, with endothelial swelling and fibrinoid changes	None/none	Improved 3 weeks after radical necrotic tissue excision and corticosteroid
Carlos et al 1989[23] (1)	19, M	Acute lymphoblastic leukemia	500 mg/m^2 infused in 24 hours weekly, 2 weeks, rash onset 5 days after second dose	Diffuse erythematopurpuric palpable skin rash on the face, trunk, limbs and scrotum	Mononuclear vasculitis	Fever/ N/A	Spontaneously resolved within a few days
Navarro et al 1986[24] (1)	45, M	Osteogenic sarcoma	8 g/m^2/week IV, 2 weeks, rash onset 24 hours after second dose	Extensive erythematopurpuric skin rash on the trunk and all extremities	Leukocytoclastic vasculitis	Fever, N/A	A few days
Marks et al 1984[6] (8)	N/A	RA, psoriatic arthritis	15 mg/week PO or less, cumulative dose 7.5–1250 mg	Discrete, small, purpuric rash and confluent area of erythema	Reported 2 out of 8 cases, one patient showed leukocytoclastic angiitis, while the other revealed finding suggestive of monoclonal Ig deposition	N/A	All patients recovered after MTX discontinuation

Abbreviations: AS, ankylosing spondylitis; CNS, central nervous system; F, female; g, grams; Ig, immunoglobulin; IM, intramuscular; IV, intravenous JIA, juvenile idiopathic arthritis; m, meters; mg, milligrams; MTX, methotrexate; N/A, not applicable; PO, per oral; RBC, red blood cell; RA, Rheumatoid arthritis; SC, subcutaneous; SLE, systemic lupus erythematosus.

common side effects of MTX such as nausea and vomiting, cytopenia and hepatotoxicity are more likely caused by the drug direct toxic effects on tissues.[7,8] The clinical presentations consist of petechia, palpable purpura, non-blanchable discrete erythematous to violaceous papules, confluent erythema to blister and necrotic patches on trunk, extremities, and face. The lesions may exhibit pruritus, discomfort and extensive distribution.[15] The diagnosis is established based on clinical, histological, DIF studies and temporal relation between MTX administration and onset, exclusion of other potential causes, resolution after drug withdrawal and reappearance following re-challenge (if appropriate). The treatment of LCV depends on two major factors: the underlying etiology and the extent of disease. First, eliminating or treating the triggers; and second, evaluating the extent of involvement, if the lesions are limited to the skin, the treatment should primarily focus on symptomatic relief, as the lesions are typically self-limited and resolve over 3–4 weeks. In cases of severe CSVV, systemic corticosteroid may be prescribed with or without the adjunctive therapies, such as colchicine, dapsone, HCQ. In systemic vasculitis, steroid-sparing immunosuppressive agents such as methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, and intravenous immunoglobulin (IVIG) may be needed.[7,8]

The Table 1 presents a total of 14 cases from 11 previous reports[5,6,16–24] involving histologically proven LCV, which was strongly suspected to be associated with MTX. The patients' age ranges from 10 to 73 years with MTX treatment for RA, psoriasis, JIA, ankylosing spondylitis, acute lymphoblastic leukemia, primary central nervous system lymphoma and osteogenic sarcoma. The dosage varies including a high dosage for chemotherapy and a low dosage for autoinflammatory disorders (5–20 mg/week). The onset of cutaneous vasculitis may manifest following the initial or subsequent high dose-MTX and within 2 weeks to 6 months following low dose-MTX. Additionally, there is a report showing 2 cases of cutaneous vasculitis in patients receiving MTX more than 10 years after triggering by viral infection in the preceding 5–6 months' duration.[18] The clinical presentations comprise petechia, palpable purpura, non-blanchable discrete erythematous to violaceous papules, confluent erythema to blister and necrotic patches on trunk, extremities, and face. The lesions may be pruritic, painful, and extensive. Systemic symptoms such as fever, malaise, nausea, and arthralgia may be present. Myelosuppression, hepatoxicity, renal impairment, pulmonary fibrosis and mucositis may coexist with the cutaneous vasculitis. The lesions predominantly subsided within 1 week and completely resolved within 3–4 weeks.[17,18,21,23,]

A limitation of our study is that it is a single case report. However, we presented a rare case of MTX-induced LCV, which occurred concurrently with MTX toxicity, and highlighted that such adverse events can arise even at very low doses (5 mg/week). This case underscores the need for caution when prescribing MTX to patients with underlying ESRD, as they may be more susceptible to both direct toxicity and immune complex–mediated reactions, which are thought to contribute to the pathogenesis of MTX-induced LCV. Additionally, we conducted a literature review to summarize the existing clinical data and provide further context for our findings.

Conclusion

MTX-induced LCV is a rare but well-documented complication which may unpredictably occur after either high or low-dose MTX regimen and may occur alongside concurrent MTX toxicity. The diagnosis depends on the temporal relationship of drug usage and the exclusion of other potential etiologies. We report a case of histologically confirmed MTX-induced LCV and summarize the clinical presentations and MTX dosing of the prior MTX-induced LCV reports.

Ethics Approval and Consent to Participate

This article was performed in accordance with the principles of Declaration of Helsinki. Ethical review was approved to publish the case details in accordance with the local legislation and institutional requirements (MURA2025/233). Written informed consent was obtained from the patient for publication of this case report and any accompanying images as per our standard institutional rules.

Disclosure

The authors report no conflicts of interest in this work.

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