Received: 24 April 2024 | Revised: 1 July 2024 | Accepted: 6 July 2024

DOI: 10.1002/ccr3.9244

CASE REPORT

Clinical Case Reports Open Access WILEY

Adalimumab-induced leukocytoclastic vasculitis in a patient with ankylosing spondylitis: A case report

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Clinical Key Message

In patients receiving anti-TNF-α drugs for ankylosing spondylitis, monitoring purpuric and ischemic skin lesions is crucial. This case underscores the significance of identifying and addressing drug-induced vasculitis while stressing the necessity for prompt evaluation and exploration of alternative treatment options to safeguard patient well-being.

Abstract

The case discusses a 38-year-old female with a history of ankylosing spondylitis (AS) who presented with skin lesions, including purpuric skin lesions and ischemia of her right foot digits, after initiating treatment with adalimumab. After excluding other potential causes, such as infections and malignancies, the patient received a diagnosis of moderate-sized vascular vasculitis associated with adalimumab use. Discontinuation of adalimumab and treatment with high dose glucocorticoids and intravenous pulse of cyclophosphamide resulted in the resolution of her ischemic lesions. This case underscores the importance of considering drug-related side effects in patients with new skin lesions, particularly in the context of rheumatic diseases such as AS.

KEYWORDS

adalimumab, ankylosing spondylitis, anti-TNF-α related vasculitis, leukocytoclastic vasculitis, necrotizing vasculitis, polyarteritis nodosa

1 | INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease that affects the axial skeleton and presents by inflammatory low back pain and sacroiliitis.[1] Although AS mainly affects the musculoskeletal system, involvement of other organs can also occur, the most common being anterior uveitis, colitis, aortitis, and interstitial lung disease.[1] However, research has shown that vasculitis, such as IgA vasculitis, leukocytoclastic vasculitis (LCV), obstructive retinal vasculitis, Takayasu's arthritis, and polyarteritis nodosa (PAN), can rarely be associated with AS.[2–8]

LCV is a small-vessel vasculitis characterized by the inflammation and damage of blood vessel walls, primarily involving post capillary venules. The etiology of LCV is multifactorial, with both primary and secondary causes

contributing to its pathogenesis. Primary LCV often occurs in the absence of an identifiable underlying systemic disease and is classified as idiopathic. Secondary LCV, on the other hand, can be associated with a wide range of conditions, including infections (such as viral or bacterial), medications (such as nonsteroidal anti-inflammatory drugs or antibiotics), autoimmune diseases (such as rheumatoid arthritis or systemic lupus erythematosus), malignancies (such as lymphoproliferative disorders or solid tumors), and systemic vasculitides (such as PAN or granulomatosis with polyangiitis). The exact mechanisms by which these primary and secondary factors trigger LCV are not fully understood, but immune complex deposition, complement activation, cytokine dysregulation, and endothelial cell injury are believed to play significant roles in the development and perpetuation of the vasculitic process. Understanding the diverse etiologies of LCV is crucial for accurate diagnosis, appropriate management, and optimal outcomes for affected patients.

Anti-TNF-α agents are extensively utilized in the treatment of seronegative spondyloarthritis, rheumatoid arthritis, and other immune-mediated diseases.[9] Various side effects have been reported for anti-TNF-α agents, including infection, anemia, pancytopenia, demyelinating disorders, neuropathy, and skin reactions.[10] Cutaneous side effects of anti-TNF-α agents encompass infusion and injection site reactions, psoriasiform eruptions, lupus-like disorders, LCV, eczematous dermatitis, cutaneous infections, melanoma, and non-melanoma skin malignancies.[10,11]

2 | CASE HISTORY AND EXAMINATION

A 38-year-old woman was admitted to the hospital complaining of purpuric skin lesions and ischemia in her fingers, presenting with pain, coldness, and bruising of the third toe of her right foot. The patient was diagnosed with AS 18 months ago, based on symptoms including inflammatory back pain, asymmetric oligoarthritis, and sacroiliitis observed on magnetic resonance imaging (MRI) (see Figure 1). Her medical history revealed no indications of bowel disease or psoriasis.

The patient was treated with various NSAIDs, sulfasalazine and methotrexate. However, due to treatment resistant arthritis of the knee and ankle joints the patient was treated with adalimumab, 40 mg subcutaneously, once every 2 weeks for 4 months.

Eight weeks after initiating treatment with adalimumab, the patient's symptoms improved. However, 2 months post-commencement of adalimumab therapy, the patient developed pruritic, diffuse, purpuric skin lesions, approximately 1 cm in size. These lesions, unresponsive to pressure, initially manifested in the periumbilical region before extending to the anterior and posterior aspects of the right leg and the posterior aspect of the right thigh (Figure 2). One month subsequent to the onset of these skin lesions, the patient presented with pain and gangrene affecting the third toe of the right foot, accompanied by pain and necrotic lesions on the plantar aspect of the first to fourth toes of the right foot. Vascular examination revealed 2+ symmetrical pulses of the radial artery and 1+ pulses of the dorsal pedis artery. The patient's vital signs were as follows: blood pressure, 130/80 mmHg; heart rate, 83 beats per minute; respiratory rate, 19 breaths per minute; body temperature, 37.1°C. The patient denied experiencing back pain, morning stiffness, and peripheral joint abnormalities. Disease activity assessment using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) indicated remission of the disease (BASDAI = 2.2).

Laboratory investigations yielded the following results: White blood cell count (WBC) of 5100 cells/mm^3 (4000–12,000), red blood cell count (RBC) of 4.26×10^6 cells/mm^3 (4.1–6.1), Hemoglobin level of 11.5 g/dL,[12–16] mean

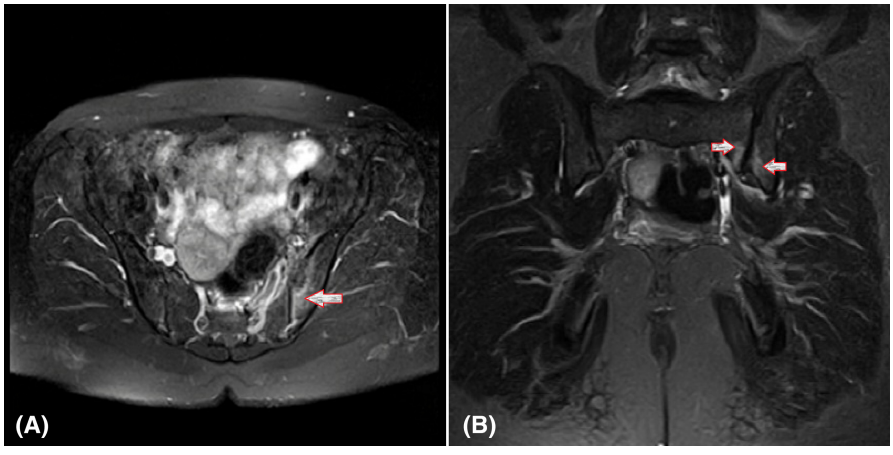

FIGURE 1 Increased signal intensity on T2-weighted images within and around the left SIJ (A, B) in favor of confirmingthe sacroiliitis (arrow).

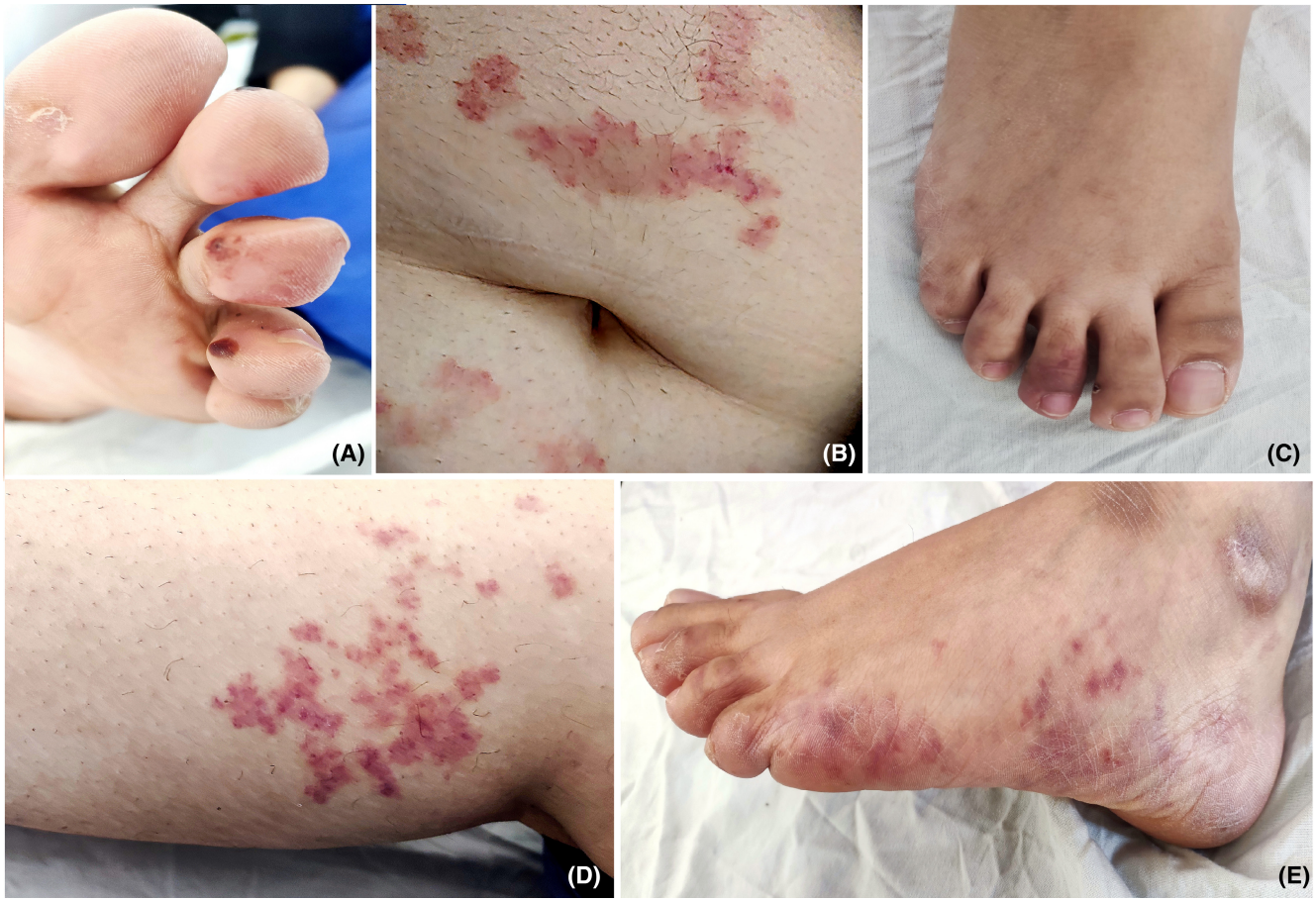

FIGURE 2 Necrotic lesions on the plantar side of fingers 1–4of the right foot (A), diffuse, purpuric skin lesions located in periumbilical, calf, feet (B, D, E), third digit gangrene right foot (C).

corpuscular volume (MCV) of 87 fl (80–90), platelet count of 208,000 cells/mm^3 (130000–440,000), urea level of 31 mg/dL (12.8–45), creatinine level of 0.90 mg/dL (0.7–1.4), serum glutamic-oxaloacetic transaminase (SGOT) level of 17 IU/L (5–37), serum glutamic-pyruvic transaminase (SGPT) level of 16 IU/L (5–56), alkaline phosphatase level of 196 IU/L (80–306), total bilirubin level of 0.3 mg/dL (0.3–1.4), direct bilirubin level of 0.1 mg/dL (<0.3), International normalized ratio (INR) of 1.06 (0.9–1.1), prothrombin time (PT) of 14.5 s[11–15] partial thromboplastin time (PTT) of 30 s (25–45), erythrocyte sedimentation rate (ESR) of 49 mm/L at the first hour (<20), and C-reactive protein (CRP) level of 8 mg/L (with a reference range up to 7 mg/L). Wright and Coombs Wright tests were negative (Table 1).

3 | METHODS (DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS AND TREATMENT)

HLA-B27 tested positive. Antinuclear antibody (ANA) level was 0.31 (with positivity defined as >1.2), anti-double stranded DNA (anti-dsDNA) was 4 U/mL (with positivity defined as >24), P-antineutrophil cytoplasmic antibodies (P-ANCA) was 3 U/mL (with positivity defined as >20), and central-antineutrophil cytoplasmic antibodies (C-ANCA) was 2.4 U/mL (with positivity defined as >18). Tests for Hbs Ag, HCV Ab, HIV Ab, serum IgA, IgG, rheumatoid factor (RF), and anti-CCP all returned negative results. Cryoglobulins were within the normal range. C3 and C4 levels were at the lower limit of normal: 0.87 g/L (normal range: 0.89–1.87 g/L) and 0.29 g/L (normal range: 0.165–0.380 g/L), respectively (Table 2).

Malignancy workup yielded normal results. Nerve conduction velocity (NCV) study showed normal results with no evidence of mononeuritis multiplex or polyneuropathy. Arterial color duplex sonography of the lower limbs revealed triphasic blood flow in the femoral artery, external iliac artery, popliteal artery, and distal parts of the tibialis and peroneal arteries. Additionally, a punch biopsy was performed on purpuric lesions on the truncal skin and thigh. Microscopic evaluation revealed orthokeratosis, spongiosis with neutrophils, erythrocytic and eosinophils with fibrinoid necrosis of the vessel walls, fibrin extravasation with prominent endothelial

TABLE 1 Patient laboratory data.

Test	Result	Unit	Normal range
WBC	5100	cells/mm^3	4000–12,000
RBC	4.26×10^6	cells/mm^3	4.1–6.1
Hemoglobin	11.5	g/dL	12–16
MCV	87	fl	80–90
Platelet	208,000	cells/mm^3	130,000–440,000
Urea	31	mg/dL	12.8–45
Creatinine	0.90	mg/dL	0.7–1.4
SGOT	17	IU/L	5–37
SGPT	16	IU/L	5–56
ALP	196	IU/L	80–306
Total bilirubin	0.3	mg/dL	0.3–1.4
Direct bilirubin	0.1	mg/dL	<0.3
INR	1.06	–	0.9–1.1
PT	14.5	s	11–15
PTT	30	s	25–45
ESR 1 hr	49	mm/L	<20
CRP	8	mg/L	<7 mg/L
Wright test	Negative	–	<1/20
Coombs Wright test	Negative	–	<1/20

Abbreviations: ALP, alkaline phosphatase; CRP, C-reactive protein; INR, International normalized ratio; MCV, mean corpuscular volume; PT, prothrombin time; PTT, partial thromboplastin time, ESR, erythrocyte sedimentation rate; RBC, red blood cell count; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; WBC, white blood cell count.

swelling, and neutrophilic nucleoclasis of the vessel walls. Marked RBC extravasations were also observed in the dermis (refer to Figure 3). The microscopic diagnosis was LCV.

A diagnosis of medium vessel vasculitis of the PAN type was made for the following reasons: purpuric lesions of the skin and ischemia of the right toes, along with the increase of ESR and LCV in the skin biopsy, the negativity of autoantibodies and the rejection of infections and malignancies. Given that vasculitis manifested 2 months after initiating adalimumab therapy and the underlying disease was in remission, the ultimate diagnosis was secondary vasculitis attributed to anti-TNF treatment. The patient received three consecutive days of pulse therapy with 1 g of methylprednisolone, followed by discharge after receiving a pulse of cyclophosphamide (CYC) at 1 g and symptom management with prednisolone at 60 mg per day.

TABLE 2 patient immunologic laboratory tests result.

Test	Result	Unit	Normal range
HLA-B27	Positive	–	Negative
ANA	0.31	Index	<1 Negative, >1.2 positive
Anti-dsDNA	4	U/mL	Positive if >24
P-ANCA(MPO)	3	U/mL	Positive if >20
C-ANCA(PR-3)	2.4	U/mL	Positive if >18
Serum IgA	1.2	g/L	1–3
Serum IgG	9.3	g/L	7–16
RF	4	IU/mL	<25
Anti-CCP	3.78	–	>30
C3	0.87	g/l	0.89–1.87 g/L
C4	0.29	g/l	0.165–0.380

Abbreviations: ANA, anti-nuclear antibody; anti-CCP, Anti–cyclic citrullinated peptide; anti-dsDNA, anti-double-stranded DNA; C-ANCA(PR-3), antineutrophil cytoplasmic autoantibody, cytoplasmic (proteinase 3); HLA-B27, human leukocyte antigen B27; P-ANCA(MPO), perinuclear anti-neutrophil cytoplasmic antibodies; RF, rheumatoid factor.

4 | CONCLUSION AND RESULTS (OUTCOME AND FOLLOW-UP)

Considering the most probable diagnosis, which includes anti-TNF associated vasculitis, it was decided to discontinue adalimumab. The patient received monthly pulses of cyclophosphamide (1 g) for six consecutive months, along with a gradual tapering of the glucocorticoid dose. Two months after initiating treatment, the patient's skin lesions completely healed. However, after 8 months, due to severe inflammatory back pain and a high activity score for AS, the treatment strategy for AS was changed to etanercept. During the 6-month follow-up with this alternative anti-TNF agent, no vasculitis-like skin lesions occurred.

5 | DISCUSSION

LCV is a vasculitis affecting skin capillaries and venules, characterized by immune complex deposition and neutrophil infiltration around these vessels.[1] It can be triggered by various factors including medications, chemicals, neoplasms, and infections such as HIV, bacterial, and fungal infections, as well as rheumatic diseases like systemic lupus erythematosus, Sjogren's syndrome, and primary vasculitis. While LCV is uncommon in AS, there have been only two reported cases of LCV in AS patients without a history of drug use, infections, or neoplasms.[1,12] Medications implicated in LCV development include penicillins, sulfonamides, NSAIDs, thiazides, retinoids, and antibiotics of the

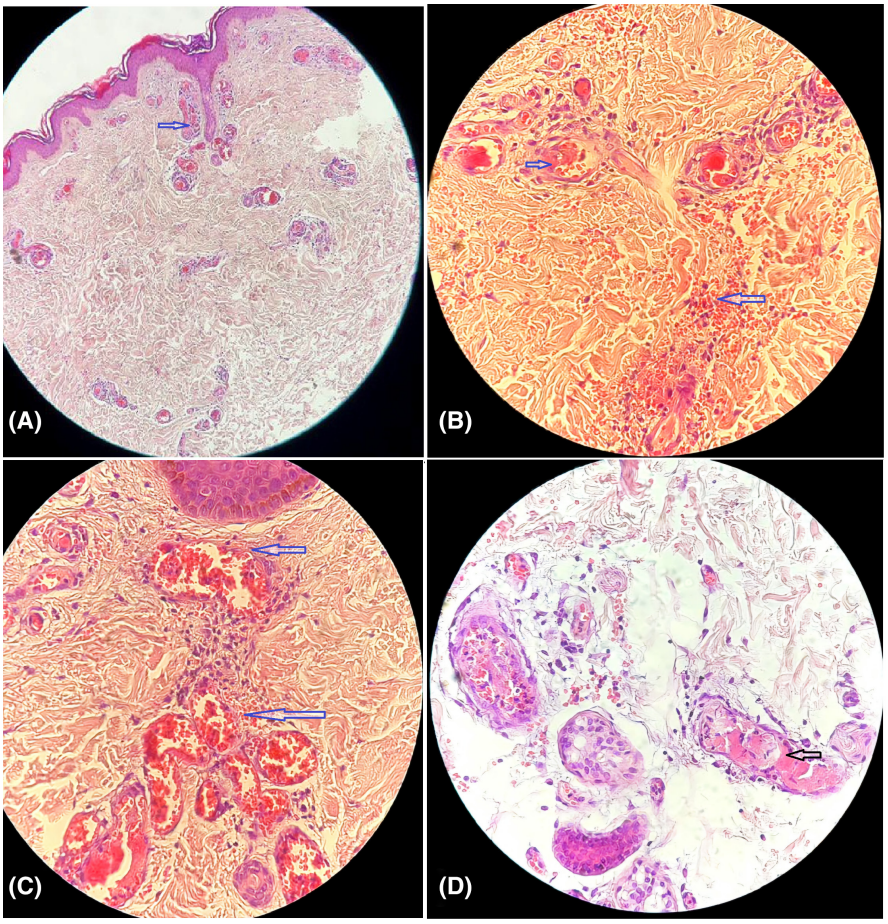

FIGURE 3 Spongiosis with neutrophils, erythrocytic and eosinophils with fibrinoidnecrosis of the vessel walls (A, B, D), fibrin extravasation with prominentendothelial swelling, and neutrophilic nucleoclasis of the vessel walls (B, C) inpathology from skin punch biopsy suggestive LCV (arrow).

quinolone group.[1] Several case reports suggest a potential association between LCV and anti-TNF-α agents in inflammatory bowel disease (IBD),[13–17] with LCV induced by adalimumab reported in two patients with rheumatoid arthritis (RA).[18,19]

The exact pathogenic mechanisms underlying anti-TNF-related LCV remain unclear. It is hypothesized that auto-antibodies against anti-TNF-α agents may contribute to this adverse effect by forming immune complexes that deposit within small vessel walls, triggering a type III hypersensitivity reaction. Another proposed mechanism suggests that anti-TNF agents disrupt cytokine balance in the body, leading to a predominance of the Th2 pattern.

In our presented case, after ruling out potential mimickers of vasculitis such as infections, malignancies, and other connective tissue diseases, and considering the remission status of AS activity, the onset of petechiae and purpura skin lesions 2 months after initiating adalimumab, elevated erythrocyte sedimentation rate (ESR), and pathology findings supportive of LCV, the likelihood of underlying vasculitis in the context of AS diminishes. Instead, the improvement of skin symptoms following discontinuation of anti-TNF therapy, along with immunosuppressive treatment, strengthens the possibility of anti-TNF-related vasculitis. This case potentially represents the first documented instance of LCV attributed to adalimumab in Ankylosing Spondylitis thus far.

AUTHOR CONTRIBUTIONS

Alireza Khabbazi: Supervision; visualization; writing – review and editing. **Mehrzad Hajialilo:** Supervision; writing – original draft; writing – review and editing. **Sepideh Tahsini Tekantapeh:** Conceptualization; data curation; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Sahar Farshchi Tabrizi:** Data curation; writing – original draft. **Alireza Salehi:** Investigation; writing – review and editing.

ACKNOWLEDGMENTS

None.

FUNDING INFORMATION

We did not receive funding for this article.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The patient details are available in the electronic medical records and can be made available from the authors on request.

ETHICS STATEMENT

The research followed the tenets of the Declaration of Helsinki.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Khabbazi A, Hajialilo M, Tahsini Tekantapeh S, Farshchi Tabrizi S, Salehi A. Adalimumab-induced leukocytoclastic vasculitis in a patient with ankylosing spondylitis: A case report. *Clin Case Rep*. 2024;12:e9244. doi:10.1002/ccr3.9244