World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(CASE REPORT)

Rivaroxaban-induced cutaneous leukocytoclastic vasculitis with necrotic ulcerations: A case report

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World Journal of Advanced Research and Reviews, 2026, 29(03), 278-283

Publication history: Received on 28 January 2026; revised on 03 March 2026; accepted on 05 March 2026

Article DOI: https://doi.org/10.30574/wjarr.2026.29.3.0545

Abstract

Since their introduction in the early 2000s, direct oral anticoagulants (DOACs), including rivaroxaban, a factor Xa inhibitor, have been widely used for managing atrial fibrillation and venous thromboembolism. Hypersensitivity reactions associated with rivaroxaban are rarely reported, as the drug's mechanism of action draws significant attention to hemorrhagic adverse effects. Consequently, non-hemorrhagic adverse effects, such as cutaneous reactions, often remain underrecognized. Here, we report the case of a 70-year-old woman with a history of atrial fibrillation and transient ischemic attack (TIA), treated with rivaroxaban, who developed a diffuse petechial rash and a palpable purpura, mainly on her lower extremities, blisters, and ulcerations with necrotic surface after 7 days of therapy diagnosed as leukocytoclastic vasculitis (LCV) via skin biopsy with negative serum anti-neutrophil cytoplasmic antibody (ANCA). Rivaroxaban was identified as the causative agent and discontinued, leading to symptom resolution. This case highlights the importance of recognizing rare cutaneous adverse effects of rivaroxaban to ensure timely diagnosis and management.

Keywords: Anticoagulant; Hypersensitivity; Leukocytoclastic; Rash; Rivaroxaban; Vasculitis

1. Introduction

Leukocytoclastic vasculitis(LCV) is a small vessel vasculitis characterized clinically by palpable purpura and histologically by neutrophilic infiltration with fibrinoid necrosis of dermal vessels[1]. While often idiopathic, it can be triggered by infections, autoimmune conditions, malignancies, or medications[2].Rivaroxaban, a direct oral anticoagulant (DOAC) and factor Xa inhibitor approved since 2011, is commonly prescribed for stroke prevention in non-valvular atrial fibrillation and for the treatment and prevention of venous thromboembolism[3]. Although generally well tolerated, it has been rarely associated with hypersensitivity reactions such as leukocytoclastic vasculitis (LCV), with only a few cases reported[4–7]. We describe here a patient with atrial fibrillation and ischemic stroke who developed LCV shortly after starting rivaroxaban.

2. Case presentation

A 70-year-old woman with morbid obesity, insulin-dependent diabetes mellitus, hypertension, and atrial fibrillation presented with painful purpuric and necrotic skin lesions on the extremities. Her chronic medications included angiotensin-converting enzyme inhibitors, antiplatelet agents, diuretics, and atorvastatin. Rivaroxaban was initiated

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one week prior to symptom onset for secondary prevention following a transient ischemic attack (TIA). The rash emerged shortly thereafter, approximately 10 days before presentation and progressed rapidly. On examination, she was alert, oriented, and appeared non-toxic. Vital signs included blood pressure 132/87 mmHg, heart rate 100 bpm, temperature 36.8°C, and respiratory rate 18 breaths/min. The rash involved all four limbs with confluent infiltrated purpura **(Figure 1)**; occasional hemorrhagic bullae on a purpuric base, some with a pseudo-target-like appearance; and multiple well-demarcated ulcerations of varying sizes with irregular borders and necrotic surfaces, predominantly on the lower limbs **(Figure 2)**. Bilateral second toes showed ulcerations with necrotic, purulent, and macerated bases. Infiltrated purpura was also present on the lower abdomen. Mucosal surfaces were spared, and the patient denied fever, arthralgias, abdominal pain, or other systemic complaints. Laboratory studies revealed anemia (hemoglobin 9.1 g/dL), with otherwise normal complete blood cell count, comprehensive metabolic panel, and urinalysis. Inflammatory markers were elevated (raised erythrocyte sedimentation rate and C-reactive protein). Extensive workup to exclude systemic or alternative causes was negative, including serologies for HIV and hepatitis B/C, antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA, including PR3 and MPO), cryoglobulins, and normal serum complement levels (C3, C4, CH50). A punch biopsy from the affected skin confirmed cutaneous leukocytoclastic vasculitis, showing an inflammatory infiltrate in the dermis predominantly composed of altered neutrophils with pyknotic nuclei and eosinophils surrounding congested vascular structures, with prominent leukocytoclasia and fibrinoid necrosis of vessel walls; extravasation of red blood cells was present **(Figure 3)**. Direct immunofluorescence (DIF) was negative. Given the clear temporal relationship, the absence of other identifiable triggers, and a negative workup for infectious, autoimmune, or immune-complex mediated disease, rivaroxaban was considered the most plausible culprit. Rivaroxaban was immediately discontinued. The patient was transitioned to heparin with subsequent bridging to warfarin. Topical corticosteroids were initiated for symptomatic management of the vasculitis. Fortunately, the skin lesions showed progressive clinical improvement and complete regression over the following weeks, with no recurrence observed during follow-up visits. The Naranjo score was 7, indicating probable causality for rivaroxaban-induced cutaneous hypersensitivity.

Figure 1 Clinical features of severe purpuric eruption on the extremities.

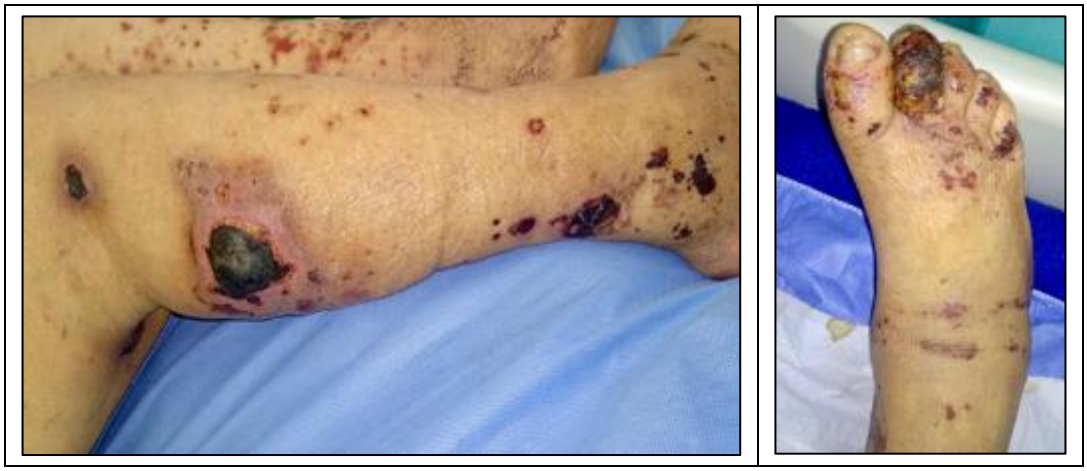

Figure 2 Numerous coalescent purpuric patches with areas of necrosis and bullous detachment on the lower extremities

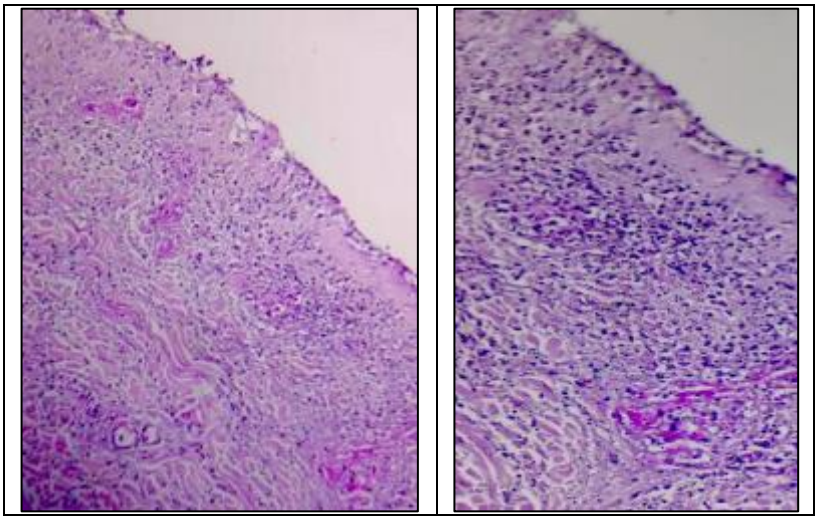

Figure 3 Punch biopsy from the right lower limb showing dense perivascular neutrophils with pyknotic debris and hyalinized small vessel endothelium; eosinophils are also present with extravasated erythrocytes. H and E, 100×, 200×

3. Discussion

Leukocytoclastic vasculitis, also known as hypersensitivity vasculitis, is the most frequent form of vasculitis affecting the skin[8]. It can present at any age, although it typically occurs in adults. [9] Clinically, it manifests as red patches with raised palpable purpura, most often appearing symmetrically on the lower parts of the body (legs and buttocks). Still, it can also affect the trunk or upper extremities in some cases[6]. Less common skin findings include hemorrhagic vesicles and bullae, pustules, nodules, crusted ulcers, or livedo reticularis [1]. Extracutaneous manifestations such as low-grade fever, malaise, weight loss, myalgias, and arthralgias can rarely develop [9]. The pathogenesis of leukocytoclastic vasculitis involves both cell-mediated and humoral immune responses, leading to small vessel inflammation with early neutrophilic infiltration and leukocytoclasia within the first 48 hours, followed by lymphocytic infiltration and fibrinoid necrosis of the vessel walls [1]. The etiology of LCV is unknown in almost half of the cases, but it can be triggered by infections, neoplasms, autoimmune diseases, and drugs, with which it is associated in 10 to 20% of cases, with onset typically 1 to 3 weeks after initiation[1,8]. Among drug-induced forms, several medications have been associated with LCV, including anti-inflammatory drugs, antibiotics (e.g., beta-lactams, vancomycin, sulfonamides), antiepileptics (e.g., phenytoin), allopurinol, furosemide, and others [10]. Diagnosing drug-induced LCV is often challenging due to a broad differential diagnosis, which includes infectious emboli (e.g., from endocarditis), cellulitis, viral rashes, warfarin-induced skin necrosis, antiphospholipid syndrome, and more[11].

Table 1 Reported cases of leukocytoclastic vasculitis associated with rivaroxaban

Authors / Year	Patient (Age/ Sex)	Indication	Onset Time	Clinic	Location	Management and Outcome	Rivaroxaban Alone / Mixed
Chaaya et al., 2016[4]	68/M	DVT	7 days	Palpable purpura + urticarial lesions	Extremities + abdomen + lumbar area	Discontinuation + IV methylprednisolone → resolution	Alone
Dean et al., 2017[6]	38/F	DVT	7 days	Palpable purpura + urticarial lesions	Extremities	Discontinuation + antibiotics + heparin and warfarin → resolution	Alone
Hasbal et al., 2017[5]	28/M	DVT	10 days	Palpable purpura	Lower extremities	Discontinuation + heparin → resolution	Alone
Sainz-Gaspar et al., 2018[7]	81/M	Atrial fibrillation	3 months	Palpable purpura	Lower extremities	Discontinuation + oral prednisone + heparin → resolution	Alone
Lee et al., 2019 [13]	75/F	Pulmonary thromboembolism + DVT	17 days	Non-blanching erythematous palpable petechiae and purpura	Both thighs, both arms, lower abdomen	Discontinuation of rivaroxaban → improvement; rechallenge → recurrence; dabigatran → recurrence; final discontinuation → resolution	Mixed (dabigatran cross-reactivity)
El-Sabbagh et al., 2023 [14]	45/M	Hypercoagulability	1 week after apixaban, and persisted despite the discontinuation of apixaban	Petechial rash, palpable purpura, bullae, ulceration	Lower extremities	Discontinuation of both apixaban and rivaroxaban + warfarin + short-course prednisone → resolution	Mixed (apixaban)
Isaq et al., 2020 [15]	67/M	Not specified	2–3 days after apixaban	Palpable purpura from the lower abdomen to the feet	Lower abdomen to feet	Switch to warfarin + prednisone taper + dapsone → clearance	Mixed (apixaban)
Present case (2026)	70/F	Atrial fibrillation +TIA	7 days	Confluent infiltrated purpura, hemorrhagic bullae, pseudo-targetoid lesions, necrotic ulcerations on extremities and toes, and lower abdomen involvement	All four limbs, lower abdomen, bilateral toes	Discontinuation + warfarin + corticosteroids → resolution	Alone

DVT: deep vein thrombosis; TIA: transient ischemic attack; IV: intravenous.

A detailed history, meticulous physical exam, appropriate investigations(complete blood count, complete metabolic panel, urinalysis, blood cultures, and immunologic screening), skin biopsy from a recent lesion, and direct immunofluorescence testing are therefore essential for timely and accurate diagnosis [9]. Despite its favorable pharmacokinetic profile, widespread use in thromboembolic disorders, and lack of routine monitoring, rivaroxaban has only rarely been associated with leukocytoclastic vasculitis[12]. A comprehensive review of existing literature revealed seven cases of anticoagulant-induced LCV, including four attributed to rivaroxaban use alone **(Table 1).** The first reported case of rivaroxaban-induced LCV was described in 2016 by Chaaya et al.[4], where a patient developed palpable purpura shortly after starting the drug, with biopsy confirmation and resolution after discontinuation. Since then, only three additional cases of isolated rivaroxaban-induced LCV have been published in the literature [5–7], making the present case the fifth reported instance of rivaroxaban-associated LCV. Three further cases have involved rivaroxaban in association with other direct oral anticoagulants, Lee et al. [13], with dabigatran cross-reactivity, El-Sabbagh et al.[14], with apixaban after switching from rivaroxaban to apixaban, and one additional mixed report by Nasro et al., where the patient had cutaneous reactions to both rivaroxaban and apixaban, suggesting possible cross-reactivity within DOACs with similar structures[15]. Additionally, a single case of ANCA-positive systemic vasculitis with pulmonary involvement (hemoptysis) has been attributed to rivaroxaban by Agarwal et al. [16], illustrating a more severe pauci-immune presentation distinct from the cutaneous-limited pattern observed in our patient. Initial management of leukocytoclastic vasculitis begins with immediate discontinuation of any suspected offending medication (in this case, rivaroxaban). For mild or limited cutaneous involvement, symptomatic treatment is usually sufficient[1]. In cases with more severe skin manifestations, systemic corticosteroids, immunosuppressive agents, or rituximab may be considered depending on the clinical severity and response to initial therapy[9].

4. Conclusion

This report adds to the limited but growing evidence of rivaroxaban as a rare trigger of reversible cutaneous LCV and underscores the need for clinicians to consider this possibility in patients presenting with acute palpable purpura shortly after DOAC initiation.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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