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Case report 2

Rivaroxaban induced leukocytoclastic vasculitis: an uncommon side effect of an emerging anticoagulant in Sri Lanka

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Key words: leukocytoclastic vasculitis, rivaroxaban, direct oral anticoagulant, skin biopsy, adverse drug reaction

Abstract

Rivaroxaban, a commonly used direct oral anticoagulant, is often preferred for venous thromboembolism due to its predictable anticoagulant effect and limited requirement for laboratory monitoring. However, rare adverse effects such as leukocytoclastic vasculitis (LCV) have occasionally been reported. We describe a 42-year-old woman with severe pulmonary hypertension and possible chronic thrombo-embolic pulmonary hypertension who developed a progressive petechial rash on both lower limbs two months after initiating rivaroxaban therapy. The clinical presentation was not associated with ulceration or bullae and examination revealed signs of right heart failure consistent with her underlying pulmonary hypertension. A skin biopsy confirmed the diagnosis of LCV, showing perivascular neutrophilic infiltration with focal vessel wall destruction, fibrinoid necrosis and extravasated red blood cells. Rivaroxaban was promptly discontinued, anticoagulation was switched to warfarin and the skin rash completely resolved following cessation of rivaroxaban. This case highlights the importance of maintaining a high index of suspicion for cutaneous vasculitis in patients on rivaroxaban who develop new skin lesions and underscores the role of timely diagnosis and drug withdrawal in ensuring clinical resolution.

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Introduction

Rivaroxaban is a direct oral anticoagulant (DOAC) increasingly used in the management of venous thromboembolism and other thrombotic conditions due to its ease of use and favorable pharmacokinetics. Despite its widespread use and safety profile, rivaroxaban is not without rare but clinically important adverse effects. Among them, LCV is an uncommon but potentially serious side effect[1].

LCV is characterized by inflammation of small dermal blood vessels[2] typically involving a neutrophil-predominant infiltrate and resulting in palpable purpura or petechiae[3,4]. We report a rare case of rivaroxaban-induced LCV in a woman with pulmonary hypertension, highlighting diagnostic challenges and management strategies.

Case report

A 42-year-old female with known severe pulmonary hypertension and suspected chronic thrombo-embolic pulmonary hypertension (CTEPH) was started on rivaroxaban 20 mg daily due to elevated D-dimer levels and concern for thromboembolic disease. Two months into treatment, she noticed a petechial rash on the dorsum of her left foot, which progressed to involve both lower limbs over the course of three days. She continued rivaroxaban for five additional days after the rash first appeared.

Her concurrent medications included sildenafil, frusemide, pantoprazole and calcium carbonate for her underlying pulmonary hypertension and renal

impairment. She reported no other recent medication changes, infections or systemic symptoms. On examination, she was pale with signs suggestive of right heart failure, including elevated jugular venous pressure and lower limb edema. A non-blanching petechial rash was observed on both lower limbs, without ulceration, necrosis or bullous lesions (Figure 1).

Figure 1. A non-blanching petechial rash on both lower limbs, without ulceration, necrosis or bullous lesions.

A skin biopsy was performed and histopathology revealed mild subepidermal fibrosis with dermal vessels lined by plump endothelium, perivascular neutrophilic infiltration, and focal destruction of vessel walls. There were also numerous apoptotic bodies, extravasated red blood cells and foci of fibrinoid necrosis, confirming a diagnosis of leukocytoclastic vasculitis.

Considering these findings, rivaroxaban was immediately withheld and warfarin was initiated for ongoing anticoagulation. The rash began to regress within days of stopping rivaroxaban (Figure 2). Topical corticosteroids and antihistamines were also prescribed.

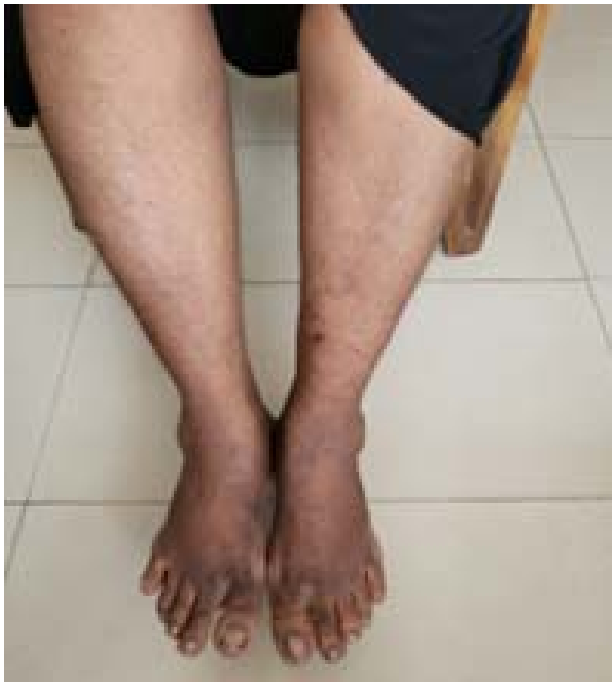

Figure 2. Disappearance of lesions 10 days after withholding rivaroxaban.

Discussion

LCV is a small-vessel vasculitis mostly confined to the skin, typically presenting as palpable purpura or petechiae[5]. It may arise idiopathically or secondary to infections, systemic autoimmune diseases or medications. In drug-induced LCV, the underlying mechanism is believed to be a type III hypersensitivity reaction[6]. Immune complexes formed between the drug (or its metabolites) and host antibodies deposit in postcapillary venules, activating the complement cascade. This leads to neutrophil recruitment, degranulation and release of proteolytic enzymes, resulting in endothelial injury, vessel wall necrosis and perivascular inflammation[7,8]. These processes give rise to the clinical and histopathological hallmarks of LCV.

The onset of drug-induced LCV typically occurs within 1 to 3 weeks of initiating the offending agent[5]. However, this case was notable for its delayed onset approximately eight weeks after rivaroxaban initiation. Although uncommon, delayed presentations have been documented. Tseng et al. reported onset within just two days[9], while El-Sabbagh et al. described LCV developing

one week after starting apixaban in a patient previously exposed to rivaroxaban, suggesting potential class sensitization or cumulative immune priming[5]. Hasbal et al. documented recurrence within three days upon drug rechallenge[10]. Furthermore, a case series by Mohamoud et al. reported LCV onset up to 120 days after starting anticoagulant therapy[11]. In our patient, prior exposure to immunosuppressive therapy, such as corticosteroids, may have delayed the immune response by transiently suppressing antibody production. Although systemic steroids were not being administered at the time of symptom onset, even intermittent use earlier in treatment could have contributed to a blunted or delayed hypersensitivity response.

Another challenge in this case was the timing of the skin biopsy. While the ideal diagnostic window for biopsy is within 24 to 48 hours of lesion appearance[8] before histological features begin to evolve, our patient underwent biopsy five days after rash onset. Typically, delayed biopsies may yield fewer specific results due to waning neutrophilic infiltration and increasing lymphocytic predominance. Nevertheless, the biopsy still demonstrated classical findings of LCV, including perivascular neutrophilic infiltrates, leuko-cytoclasia, fibrinoid necrosis and red blood cell extravasation. This highlights that even when performed outside the optimal time frame, a biopsy can remain diagnostically useful if the inflammatory process is still active.

No clear dose dependence or specific comorbidity profile has been consistently associated with rivaroxaban induced LCV[8]. Cases have occurred at standard therapeutic doses without links to renal dysfunction, autoimmune disease or other common risk factors. This suggests that individual immune susceptibility may play a greater role in pathogenesis than previously recognized.

In patients requiring continued anticoagulation, alternative agents must be carefully selected. Warfarin is frequently chosen due to its different mechanism of action and lower risk of cross-reactivity. Low molecular weight heparins (LMWHs) are also viable, particularly for short term management. While switching to another direct oral anticoagulant (DOAC) may be considered, caution is warranted, as LCV has been reported with both apixaban and dabigatran[12.13], raising the possibility of class-wide sensitivity. In this context, warfarin or LMWH may be safer alternatives.

Management of drug-induced LCV typically involves immediate withdrawal of the suspected agent. In most cases limited to the skin, this alone is sufficient for resolution. Systemic corticosteroids are reserved for more severe or systemic presentations[14]. According to Gota and Calabrese, fewer than 10% of patients require immunosuppressive therapy, with most showing improvement after drug cessation alone[4]. In our case, discontinuation of rivaroxaban and initiation of warfarin resulted in complete resolution of the rash without further recurrence.

This case underscores the need for clinical vigilance when evaluating new onset cutaneous vasculitis in patients on long-term anticoagulation, especially when there is a prolonged latency period. It also highlights the diagnostic value of skin biopsy even when delayed and the importance of considering patient specific immune factors and drug history when formulating a safe and effective anticoagulation plan.

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