

Probable apixaban-induced purpura

Giuseppe Famularo¹, Francesco Casorati²

¹Internal Medicine San Camillo Hospital, Rome, Italy

²Otorinolaryngology, San Camillo Hospital, Rome, Italy

Key words

Apixaban, purpura, cutaneous leukocytoclastic vasculitis, direct oral anticoagulants

To the Editor,

The factor X inhibitor apixaban is used in atrial fibrillation and venous thromboembolism with an acceptable safety profile.

A 59-year-old woman was started on apixaban (10 mg bid) because of pulmonary embolism.

The patient reported a history of hypertension, vocal cord paralysis, chronic respiratory failure, and hypothyroidism for which ramipril, amlodipine, and levothyroxine had been prescribed. She had no known drug allergies and there was no family history notable for autoimmune, allergic, and cutaneous diseases.

After 2 days of treatment with apixaban, she complained of painful, swollen, and warm knees and we noted palpable and painful purpura involving both the lower limbs below the knees. The patient had no other symptoms, vital signs were normal, and physical examination was otherwise unremarkable.

Laboratory investigations, including complement levels, an autoimmunity screening, cryoglobulins, and search for hepatitis B and C viruses, revealed no atypical findings. C-reactive protein was elevated at 19.7 mg/dl. A duplex ultrasound showed no thrombosis or obstruction.

The patient denied permission for a skin biopsy. Apixaban was discontinued and enoxaparin and prednisone were initiated. Arthritis quickly resolved and the purpura progressively faded and disappeared at the 24th day. Prednisone was tapered off and the anticoagulant treatment was continued with the factor II inhibitor dabigatran due to the ongoing embolic risk. At the time, the patient had no relapse of arthritis or purpura and did not experience any other adverse events. At follow-up 2 months later, she was doing well while still on dabigatran. The cause of pulmonary embolism remained undetermined.

The clinical diagnosis was apixaban-induced purpura. Taken together, however, findings in this case were most consistent with cutaneous leukocytoclastic vasculitis (CLV) even though this was not confirmed by pathology examination because the patient refused to undergo a skin biopsy.¹ Presentation, clinical features, laboratory findings, and the resolution of purpura with glucocorticoids support our view that leukocytoclastic vasculitis was the underlying immunopathologic process.

The temporal clustering and scoring on the Naranjo Scale, that standardizes causality assessment for adverse drug reactions, indicated a probable causal relationship between apixaban and the adverse event.² We ruled out other causes upon history, clinical examination, laboratory and imaging investigations. The patient had no systemic manifestations and did not relapse during treatment with dabigatran.

There are reports of purpura and CLV associated with the direct oral anticoagulants (DOACs) apixaban, rivaroxaban, and dabigatran.³⁻⁶ The key dimensions of the problem are unknown and findings of the post-marketing surveillance suggest that rivaroxaban might be associated with a greater risk of CLV as compared to other DOACs.⁷ Available data do not support the hypothesis of CLV as a class-specific side-effect of DOACs.⁸ It is unclear if older patients with comorbidities could have a worse clinical outcome with prolonged disease course and complications.

The pathogenesis of apixaban-induced CLV is poorly understood. Molecular mimicry between apixaban and vascular endothelium antigens, endothelial injury due to immune activation and release of proinflammatory cytokines triggered by apixaban, and hypersensitivity to circulating immune complexes that contain apixaban on the vessel wall may be at play.

Our patient had no flare-up of purpura during treatment with dabigatran. This suggests that patients with apixaban-induced purpura may be safely treated with an alternative DOAC. However, cross-reactivity between DOACs has been reported based upon clinical findings and results of patch testing.^{9,10}

Clinicians should be aware of the potential risk of purpura in patients treated with apixaban.

References

1. Fraticelli P, Benfaremo D, Gabrielli A. Diagnosis and management of leukocytoclastic vasculitis. *Intern Emerg Med* 2021; 16:831-841. doi: 10.1007/s11739-021-02688-x
2. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30:239-245.

3. Carli G, Farsi A, Chiarini F, et al. Hypersensitivity reactions to non-vitamin K oral anticoagulants. A review of literature and diagnostic work-up proposal. *Eur Ann Allergy Clin Immunol* 2019; 51:7-14. doi: 10.23822/EurAnnACI.1764-1489.80
4. Liedke C, Nomani H, Lozeau D, Yao Q. Apixaban-induced leukocytoclastic vasculitis. *J Clin Rheumatol* 2021; 27: e172-e173. doi: 10.1097/RHU.0000000000001310.
5. Sainz-Gaspar L, Pita da Veiga G, Suárez-Peñaranda JM, Vázquez-Veiga H, Sánchez-Aguilar D. Leukocytoclastic vasculitis associated with rivaroxaban. *Int J Dermatol* 2018; 57:622-624. doi: 10.1111/ijd.13952.
6. An J, Garje R, Wanat KA, Leone JP. Dabigatran-related leukocytoclastic vasculitis. *BMJ Case Rep* 2017; doi:10.1136/bcr-2016-217423
7. Mohamoud M, Horgan C, Eworuke E et al. Complementary use of U.S. FDA's Adverse Event Reporting System and Sentinel System to characterize direct oral anticoagulants-associated cutaneous small-vessel vasculitis. *Pharmacotherapy* 2020; 40:1099-1107. doi: 10.1002/phar.2468.
8. Ajao A, Cosgrove A, Eworuke E et al. A cohort study to assess risk of cutaneous small vessel vasculitis among users of different oral anticoagulants. *Pharmacoepidemiol Drug Saf* 2022; 31:1164-1173. doi: 10.1002/pds.5514.
9. Lee HL, Kim L, Kim CW et al. Case of both rivaroxaban- and dabigatran-induced leukocytoclastic vasculitis, during management of pulmonary thromboembolism. *Respir Med Case Rep* 2019; 26:219-222. doi: 10.1016/j.rmcr.2019.01.017.
10. Cortellini G, Carli G, Franceschini L, et al. Evaluating nonimmediate cutaneous reactions to non-vitamin K antagonist oral anticoagulants via patch testing. *J Allergy Clin Immunol Pract* 2020; 8:3190-3193. doi: 10.1016/j.jaip.2020.04.055