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A case of leukocytoclastic vasculitis caused by novel anticoagulant rivaroxaban.

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Abstract

Cutaneous leukocytoclastic vasculitis (LCV) is type of small vessel vasculitis that commonly presents as palpable purpura involving the lower extremities and buttocks. Approximately half of cases are idiopathic, but the disease may be triggered by infection, drug reaction, inflammatory disease, or other causes. We report a case of leukocytoclastic vasculitis secondary to the novel anticoagulant rivaroxaban (Xarelto®).

Keywords: leukocytoclastic vasculitis, rash, novel anticoagulant, rivaroxaban, Xarelto

Introduction

Leeukocytoclastic vasculitis (LCV) is type of small vessel vasculitis characterized histologically by neutrophilic infiltration through small-sized vessels with hyalinization of the vessels and fibrinoid necrosis [1]. The type of endothelium targeted in LCV is usually the postcapillary venule within the dermis. The disorder frequently presents as palpable purpura involving dependent areas including lower legs and buttocks, but can also involve skin at the trunk and upper extremity [2]. Less common skin manifestations include urticarial plaques, bullae, nodules, or ulceration [2, 3]. Approximately half of LCV cases are idiopathic, but the disease can be triggered by infections (e.g., hepatitis B or C, HIV, Streptococcus), reactions to certain medications (e.g., NSAIDs, beta-lactams, sulfa drugs), connective tissue disease, or malignancy [1, 3]. In cases of medication-induced LCV, symptoms typically present between 7-10 days after initial medication exposure, but can occur sooner [4, 5]. Definitive diagnosis of LCV requires biopsy of affected skin, though classic histological findings may be lacking in specimens obtained after 48 hours [2]. In the absence of systemic organ involvement, LCV is a self-limited disease with an excellent prognosis and low recurrence rate [2]. The mainstay of therapy for acute LCV is treatment or removal of the etiologic trigger, if one can be found. Systemic corticosteroids are reserved for more severe cases or those with internal organ involvement [2, 3].

Case Synopsis: A 38-year-old woman with a history of chronic right lower extremity lymphedema from a thermal injury sustained in childhood presented to the emergency department for right lower extremity pain and swelling after a prolonged automobile trip. Laboratory and imaging findings revealed a deep venous thrombosis of the right lower extremity and type II diabetes mellitus, for which she was prescribed rivaroxaban, 15mg twice daily, and metformin, 500mg once daily. Twelve days later, the patient returned to the emergency department with a diffuse purpuric skin eruption that started four days after initiating the new medication regimen. Per examining physician, the skin lesions appeared sterile and were not accompanied by systemic symptoms of infection or internal organ dysfunction. The patient was instructed to discontinue rivaroxaban therapy and was discharged home.

The patient was admitted to the hospital one week later, after arriving to the hospital with complaints of foul-smelling discharge, erythema, and edema consistent with a secondary infection of the existing skin lesions on her right lower extremity. Otherwise,

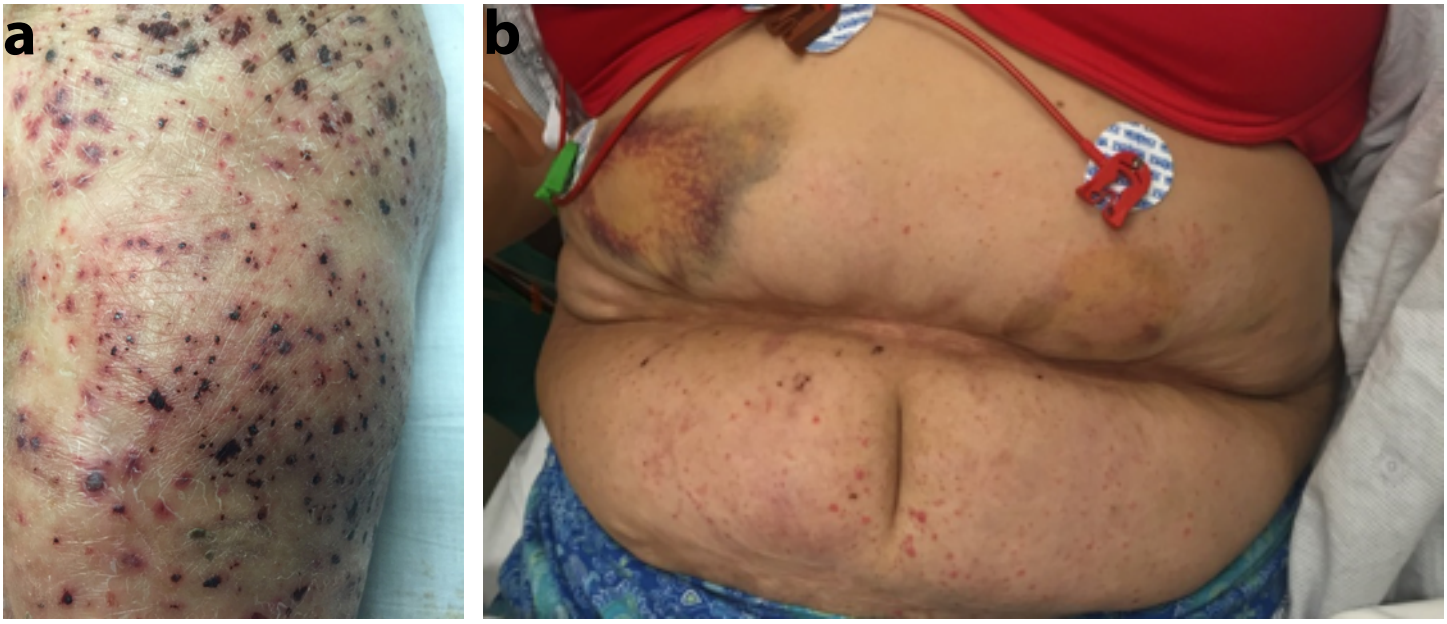


Figure 1. *A) Hemorrhagic crusted papules and petechial with the erythematous papules representing newer lesions as compared to the darker crusted papules. B) Purpuric papules scattered along abdomen with background ecchymoses secondary to low-molecular weight heparin injections.*

the patient stated that her rash had started to improve in all other affected areas. She confirmed that her only current home medication was metformin and denied any known allergies to medications or foods, recent fever, chills, cough, hematuria, or sick contacts. Physical exam findings noted the presence of purpuric papules (**Figure 1**A) distributed primarily from the patient's waist downward, somewhat mirroring the distribution of her prior thermal injuries (**Figure 1**B). Over the patient's chronically lymphedematous right lower extremity were multiple large coalescent hemorrhagic papules and plaques with foul-smelling purulent drainage (**Figure 2**A). Examination of the patient's upper extremities revealed multiple pink urticarial-appearing plaques (**Figure 2**B). There was no mucous membrane involvement and the

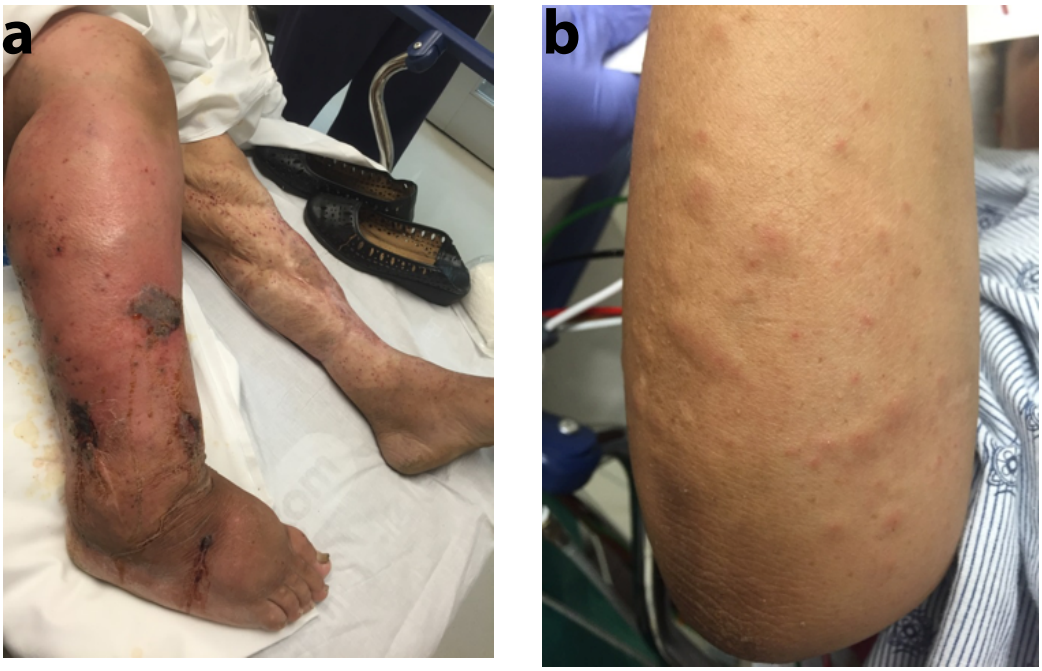


Figure 2. *A) Right lower extremity with chronic lymphedema and multiple hemorrhagic plaques with foul-smelling purulent drainage. B) Right forearm with indurated papules and plaques, some with early wheal.*

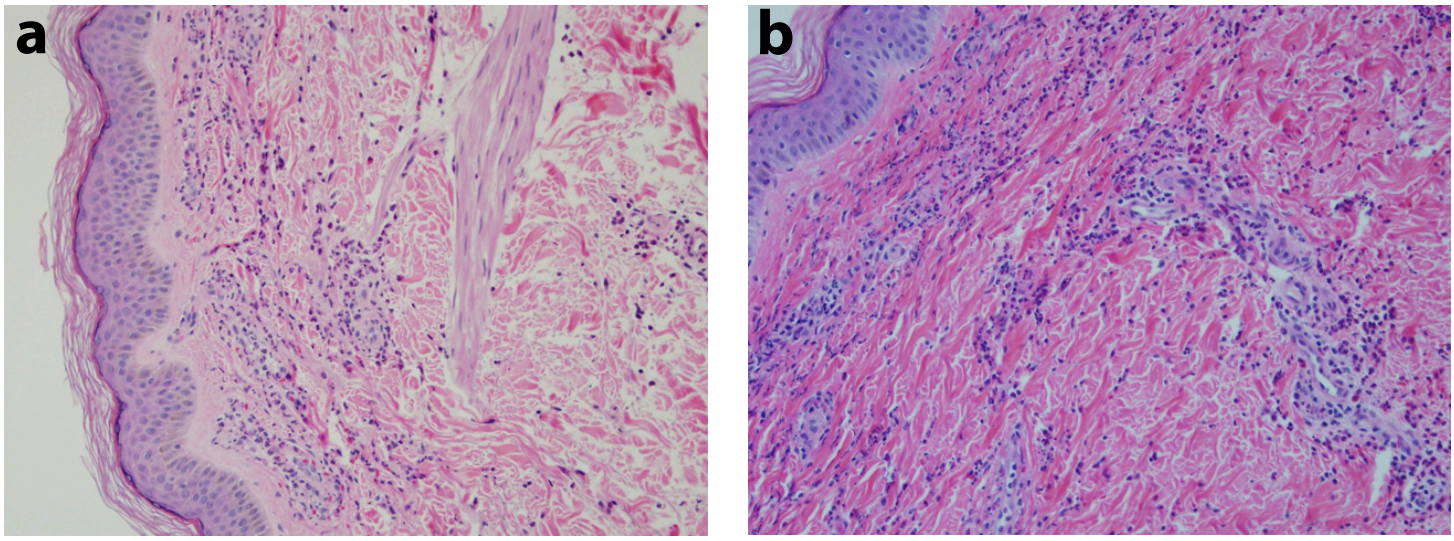


Figure 3. *A) Punch biopsy from right upper arm showing dense superficial perivascular neutrophils with pyknotic debris and hyalanized small vessel endothelium, H&E, 20%. Multiple eosinophils also present. B) Neutrophilic perivascular and transendothelial infiltrate with extravasated erythrocytes. Eosinophils are present in the background inflammation, H&E 10%.*

remainder of the physical exam was otherwise unremarkable. Complete blood cell count, comprehensive metabolic panel, and urinalysis were within normal limits. ESR and CRP were elevated (60 mm/hr and 3.91 mg/dL, respectively). HIV, Hepatitis Panel, ANA, ANCAs, cryoglobulins, urine drug screen, and serum complements were all negative or within normal limits.

Punch biopsies performed at the right upper arm (**Figure 3**A) and left lateral upper thigh (**Figure 3**B) showed a diffuse predominantly neutrophilic inflammatory infiltrate in the papillary and upper reticular dermis with extravasated erythrocytes and scattered increased eosinophils. The small-caliber vessels showed transmural migration of neutrophils with destruction of the vessel wall as evidenced by the fibrinoid degeneration consistent with leukocytoclastic vasculitis. Direct immunofluorescence was not performed. Over the course of the patient's hospital stay, the palpable purpura of the lower extremities and urticarial lesions of the forearms continued to show improvement. Right lower extremity pain, edema, and purulent drainage quickly resolved with empiric antibiotics as well as heparin therapy with bridging to warfarin in place of rivaroxaban. Upon discharge, she restarted metformin without recurrence of skin lesions and continued warfarin therapy for the deep venous thrombosis. At her follow-up appointment 12 weeks post-discharge, she reported compliance with her medications and had not displayed signs or symptoms of recurrent LCV.

Case Discussion

The temporal relationship between rivaroxaban administration in our patient and initial symptomatic onset, lack of other known etiologic triggers, and resolution of symptoms following discontinuation of the medication implicates rivaroxaban as the trigger for her LCV. Although the patient presented with a cutaneous infection, another potential cause of LCV, before a final dermatopathologic diagnosis was made, the symptomatic timeline indicates that her infection was the consequence of LCV rather than the cause.

Drug-induced LCV can be a challenging diagnosis to make as the differential diagnosis for LCV is broad and timing or quality of symptoms can vary by case [4]. Careful history-taking to establish a precise timeline of symptoms and to eliminate other possible etiologic triggers is paramount. Rivaroxaban (Xarelto®) is a novel anticoagulation drug, which acts by direct inhibition of factor Xa of the coagulation cascade [6]. It is part of a drug class becoming increasingly prescribed over traditional forms of anticoagulation such as warfarin or low-molecular weight heparins owing to its oral bioavailability, lack of requirement for INR monitoring, and efficacy for patients with contraindications to other anticoagulant classes [7]. The upturn in popularity of rivaroxaban and other

Anticoagulant Name	Mechanism of Action	Number of reported cases	Symptomatic Onset	References
Dabigatran	Direct inhibition of thrombin	3	3 days <1 week 1 week	An et al. [8] Potolidis et al. [9] Cakmak et al. [10]
Argatroban		0	N/A	N/A
Lepirudin		1	3 weeks	Jappe et al. [11]
Heparins	Increased activity of antithrombin III	2	7 days Within hours	Kearsley et al. [12] de Bats et al. [13]
Fondaparinux	Factor Xa inhibition via anithrombin III	0	N/A	N/A
Warfarin	Inhibition of vitamin K-dependent synthesis of factors II, VII, IX, X, proteins C and S	11	10 days 4 days 4 weeks 10 years 2 years 10 years 3 years 12 years 2 months 4 years 4 weeks	Tanay et al. [14] Howitt et al. [15] Tamir et al. [16] Yaghoubain et al. [17] Yaghoubain et al. [17] Yaghoubain et al. [17] Yaghoubain et al. [17] Kurt et al. [18] Kapoor et al. [19] Hsu et al. [20] Jumean et al. [21]
Acenocoumarol		4	3 weeks 3 weeks 2 months 3 days	Susano et al. [22] Jimenez-Gonzalo et al. [23] Borras-Blasco et al. [24] Aouam et al. [25]
Rivaroxiban	Direct inhibition of Factor Xa	3	7 days 10 days 7 days	Chaaya et al. [26] Hasbal et al. [27] Present case
Apixiban		0	N/A	N/A

Table 1 *Summary of anticoagulant-induced leukocytoclastic vasculitis.*

factor Xa inhibitors can be expected to coincide with emergence of rare side effects attributed to their use.

A comprehensive review of existing literature revealed twenty-three cases of anticoagulant-induced LCV, including two attributed to rivaroxaban use (**Table 1**), [8-27]. It is worth noting that along with our patient, one of the two reported patients with rivaroxaban-induced LCV was prescribed metformin, another drug rarely implicated as a cause of LCV, prior to the development of symptoms [26, 28]. Our patient, however, was documented at long-term follow-up to have restarted metformin therapy without recurrence of the LCV. The pathophysiologic mechanism of rivaroxaban-induced LCV is currently unknown, but may be a form of type III hypersensitivity reaction if the mechanism parallels other causes of LCV [29].

To our knowledge, the reported case represents only the third rivaroxaban-induced LCV described. This rare but serious side effect may be more common than the current body of literature suggests because of underreporting. Publication of similar findings is encouraged to assess true prevalence and identify possible risk factors of patients susceptible to this adverse drug reaction.

References

1. Fiorentino DF. Cutaneous vasculitis. *J Am Acad Dermatol.* 2003;48(3):311-40. [PMID: 12637912].
2. Russell JP, Gibson LE. Primary cutaneous small vessel vasculitis: approach to diagnosis and treatment. *Int. J. Dermatol.* 2006;45(1):3-13. [PMID: 16426368].
3. Goeser MR, Laniosz V, Wetter DA. A practical approach to the diagnosis, evaluation, and management of cutaneous small-vessel vasculitis. *Am J Clin Dermatol.* 2014;15(4):299-306. [PMID: 24756249].
4. Carlson JA, Chen KR. Cutaneous vasculitis update: small vessel

neutrophilic vasculitis syndromes. *The Am J Dermatopathol.* 2006;28(6):486-506. [PMID: 17122493].
5. Shinkai K, Fox LP. Cutaneous Vasculitis. In: Bolognia, editor. *Dermatology.* 3 ed. Philadelphia, PA: Elsevier; 2012. p. 385-410.
6. Samama MM. The mechanism of action of rivaroxaban--an oral, direct Factor Xa inhibitor--compared with other anticoagulants. *Thromb Res.* 2011;127(6):497-504. [PMID: 20888031].
7. Yeh CH, Hogg K, Weitz JI. Overview of the new oral anticoagulants: opportunities and challenges. *Arterioscler Thromb Vasc Biol.* 2015;35(5):1056-65. [PMID: 25792448].
8. An J, Garje R, Wanat KA, Leone JP. Dabigatran-related leukocytoclastic vasculitis. *BMJ Case Rep.* 2017;2017. Epub 2017/01/06. [PMID: 28052946].
9. Potolidis E, Mandros C, Kotsa K, Mitsiou E, Potolidis D, Fanourgiakis P. Dabigatran Associated Leukocytoclastic Vasculitis. *Case Rep Med.* 2015;2015:616109. Epub 2016/02/05. [PMID: 26843867].
10. Cakmak MA, Sahin S, Cinar N, Karsidag S. Adverse skin reaction caused by dabigatran. *Eur Rev Med Pharmacol Sci.* 2014;18(18):2595. Epub 2014/10/16. [PMID: 25317789].
11. Jappe U, Reinhold D, Bonnekoh B. Arthus reaction to lepirudin, a new recombinant hirudin, and delayed-type hypersensitivity to several heparins and heparinoids, with tolerance to its intravenous administration. *Contact Dermatitis.* 2002;46(1):29-32. Epub 2002/03/29. [PMID: 11918584].
12. Kearsley JH, Jeremy RW, Coates AS. Leucocytoclastic vasculitis and skin necrosis following subcutaneous heparin calcium. *Aust N Z J Med.* 1982;12(3):288-9. Epub 1982/06/01. [PMID: 6956298].
13. de Bats B, Rivard L, Bellemin B, Duflo F, Allaouchiche B, Chassard D. [Leukocytoclastic vasculitis after injection of low-molecular-weight heparin (letter)]. *Presse Med.* 2000;29(29):1604. Epub 2000/11/10. [PMID: 11072362].
14. Tanay A, Yust I, Brenner S, Koffler M, Abramov AL. Dermal vasculitis due to coumadin hypersensitivity. *Dermatologica.* 1982;165(3):178-85. Epub 1982/09/01. [PMID: 6751887].
15. Howitt AJ, Williams AJ, Skinner C. Warfarin-induced vasculitis: a dose-related phenomenon in susceptible individuals? *Postgrad Med J.* 1982;58(678):233-4. Epub 1982/04/01. [PMID: 6213948].
16. Tamir A, Wolf R, Brenner S. Leukocytoclastic vasculitis: another coumarin-induced hemorrhagic reaction. *Acta Derm Venereol.* 1994;74(2):138-9. Epub 1994/03/01. [PMID: 7911622].
17. Yaghoubian B, Ngo B, Mak M, Ostrzega E, Tesoro J, Mitani GH. Warfarin-induced leukocytoclastic vasculitis. *Cutis*. 2005;75(6):329-38. Epub 2005/07/29. [PMID: 16047871].
18. Kurt M, Shorbagi A, Aksu S, Haznedaroglu I, Altundag K, Erkin G. Warfarin-induced skin necrosis and leukocytoclastic vasculitis in a patient with acquired protein C and protein S deficiency. *Blood Coagul Fibrinolysis.* 2007;18(8):805-6. Epub 2007/11/06. [PMID: 17982324].
19. Kapoor KG, Bekaii-Saab T. Warfarin-induced allergic interstitial nephritis and leucocytoclastic vasculitis. *Intern Med J.* 2008;38(4):281-3. Epub 2008/04/03. [PMID: 18380703].
20. Hsu CY, Chen WS, Sung SH. Warfarin-induced leukocytoclastic vasculitis: a case report and review of literature. *Intern Med.* 2012;51(6):601-6. Epub 2012/03/28. [PMID: 22449668].
21. Jumean K, Arqoub AA, Hawatmeh A, Qaqa F, Bataineh A, Shaaban H. Warfarin-induced leukocytoclastic vasculitis and proteinuria. *J Family Med Prim Care.* 2016;5(1):160-2. Epub 2016/07/28. [PMID: 27453863].
22. Susano R, Garcia A, Altadill A, Ferro J. Hypersensitivity vasculitis related to nicoumalone. *BMJ.* 1993;306(6883):973. Epub 1993/04/10. [PMID: 8490477].
23. Jimenez-Gonzalo FJ, Medina-Perez M, Marin-Martin J. Acenocoumarol-induced leukocytoclastic vasculitis. *Haematologica.* 1999;84(5):462-3. Epub 1999/05/18. [PMID: 10329927].
24. Borras-Blasco J, Girona E, Navarro-Ruiz A, Matarredona J, Gimenez ME, Gutierrez A, Enriquez R, Martinez A. Acenocoumarol-induced Henoch-Schonlein purpura. *Ann Pharmacother.* 2004;38(2):261-4. Epub 2004/01/27. [PMID: 14742763].
25. Aouam K, Gassab A, Khorchani H, Bel Hadj Ali H, Amri M, Boughattas NA, Zili JE. Acenocoumarol and vasculitis: a case report. *Pharmacoepidemiol Drug Saf.* 2007;16(1):113-4. Epub 2006/09/19. [PMID: 16981216].
26. Chaaya G, Jaller-Char J, Ghaffar E, Castiglioni A. Rivaroxaban-induced leukocytoclastic vasculitis: A challenging rash. *Ann Allergy Asthma.* 2016;116(6):577-8. [PMID: 27017562].
27. Hasbal NB, Basturk T, Koc Y, Sahutoglu T, Bayrakdar Caglayan F, Unsal A. Leukocytoclastic Vasculitis Associated with a New Anticoagulant: Rivaroxaban. *Turk J Haematol.* 2017;34(1):116-7. Epub 2016/11/01. [PMID: 27796264].
28. Czarnowicki T, Ramot Y, Ingber A, Maly A, Horev L. Metformin-induced leukocytoclastic vasculitis: a case report. *Am J Clin Dermatol.* 2012;13(1):61-3. [PMID: 21846159].
29. Carlson JA, Cavaliere LF, Grant-Kels JM. Cutaneous vasculitis: diagnosis and management. *Clin Dermatol.* 2006;24(5):414-29. [PMID: 16966021].