A 78-Year-Old Man with a Pulmonary Embolism Who Developed Skin Necrosis 7 Days After Treatment with the Direct Oral Anticoagulant Factor Xa Inhibitor Apixaban

Tusharkumar Pansuriya
Trung Nguyen
Mir Ali Sadat
Syed A. Raza
Siva T. Sarva

Corresponding Author: Siva T. Sarva, e-mail: sivatej.sarva@gmail.com

Conflict of interest: None declared

Patient: Male, 78-year-old
Final Diagnosis: Skin necrosis
Symptoms: Cough • SOB
Medication: —
Clinical Procedure: N/A
Specialty: Cardiology • Critical Care Medicine • Dermatology • Hematology • General and Internal Medicine • Pharmacology and Pharmacy • Pulmonology

Objective: Unusual clinical course
Background: Apixaban is one of the newer direct oral anticoagulants (DOACs) being used to manage venous thrombosis. Skin toxicities are recognized adverse effects of the new DOACs, but are rare and usually associated with vasculitis. This report is of a 78-year-old man admitted to the hospital with pulmonary thromboembolism, who developed severe and extensive skin necrosis of both forearms 7 days after treatment with apixaban.

Case Report: A 78-year-old man was admitted for pulmonary embolism and congestive heart failure exacerbation. He was started on therapeutic enoxaparin and diuresis. Later on, enoxaparin was substituted with apixaban. Seven days after starting apixaban, he suddenly developed skin changes that developed into skin necrosis on both forearms and the abdominal wall. A skin biopsy was not performed due to the high risk of bleeding. Skin necrosis was diagnosed based on clinical findings. A review of clinical data and the patient's medication profile did not reveal any other possible etiology or culprit medication. Clinical presentation and lab values were not consistent with infections or autoimmune etiologies. Apixaban was discontinued as it was perceived to be the likely cause of skin necrosis. The skin changes gradually improved within 1 week with supportive wound care, and the patient did not require a skin graft. The patient was discharged safely with subcutaneous low-molecular-weight heparin therapy.

Conclusions: This report shows that skin toxicity can be associated with apixaban and that with the increasing use of these newer DOACs, clinicians should be aware of these potential adverse effects.

MeSH Keywords: Anticoagulants • Drug-Related Side Effects and Adverse Reactions • Skin Abnormalities

Abbreviations: DOACs – direct oral anticoagulants; COPD – chronic obstructive pulmonary disease; CAD – coronary artery disease; CABG – coronary artery bypass graft; CKD – chronic kidney disease; ProBNP – pro brain natriuretic peptide; V/Q scan – ventilation-perfusion scan; AISN – apixaban-induced skin necrosis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/929002
Background

In late 2010, a new class of anticoagulants known as direct oral anticoagulants (DOAC) was introduced as an alternative to conventional anticoagulation therapy [1]. DOACs have proven to be equal or superior to conventional therapy for preventing stroke in nonvalvular atrial fibrillation, with similar efficacy for prevention and treatment of venous thromboembolism [1,2]. This new class has clear advantages over warfarin, with better pharmacodynamics and pharmacokinetic properties, less drug-drug interactions, and no requirement for frequent coagulation test monitoring [2,3]. Bleeding risk is a significant concern for all anticoagulant therapies, but trials showed that compared to warfarin, DOACs have similar or less risk of major bleeding [4,5]. DOACs include direct thrombin inhibitors (Dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban).

There are reported data available for non-hemorrhagic adverse events caused by DOACs, such as leukocytoclastic vasculitis, psoriatic-like skin reaction, and lichenoid reaction [6–9]. Although skin toxicities are recognized adverse effects of the new DOACs, including apixaban, they are rare and are usually associated with vasculitis. This report is of a 78-year-old man admitted to the hospital with pulmonary thromboembolism, who developed severe and extensive skin necrosis of both forearms 7 days after treatment with apixaban.

Case Report

A 78-year-old man with a history of hypertension, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), coronary artery bypass graft (CABG), diastolic heart failure, and stage 3 chronic kidney disease (CKD) presented with worsening dyspnea, swelling of the left leg, and pain for the last 2 days. On physical examination, he had bilateral basilar crackles with expiratory wheezing and bilateral lower-extremity edema. Troponin was 0.02 ng/ml, pro brain natriuretic peptide (ProBNP) was 1140 pg/ml, and D-dimer was elevated to 1066 ng/ml FEU. A chest X-ray showed right basilar lung infiltrate. Initially, he was started on bronchodilators for his COPD, diuretics for his congestive heart failure (CHF), and intravenous antibiotics for possible pneumonia. Pulmonary embolism was also considered in the differential diagnosis due to his increased oxygen requirement. CT angiography of the chest was not performed due to his elevated creatinine. The clinical presentation was not consistent with any autoimmune process. Apixaban was discontinued immediately. After reviewing all the patient’s medications during that interval, the clinical conclusion was a diagnosis of apixaban-induced skin necrosis. The skin changes gradually improved within 7 days with wound care and dressing.

enoxaparin was initiated based on the creatinine clearance, as recommended by the pharmacy.

During the hospital stay, his condition was stabilized with bronchodilators and systemic glucocorticoids for advanced COPD, piperacillin/tazobactam for pneumonia, and diuresis for chronic diastolic congestive heart failure. His respiration was supported with a continued nasal cannula and BiPAP as needed. After 2 days of enoxaparin, he was switched to oral apixaban for his pulmonary embolism. His shortness of breath was improving slowly due to his underlying advanced COPD and CHF. During this time, he was waiting for a skilled nursing home placement.

After the seventh day of initiating apixaban, he developed a painful small ecchymosis on the left forearm, which quickly progressed to skin necrosis across the left forearm within 2 days (see Figure 1). He also developed skin necrosis on the right arm and the abdominal wall area. Surgery and Dermatology services were consulted. A skin biopsy was not performed due to the high risk of bleeding. The clinical presentation was not consistent with any autoimmune process. Apixaban was discontinued immediately. After reviewing all the patient’s medications during that interval, the clinical conclusion was a diagnosis of apixaban-induced skin necrosis. The skin changes gradually improved within 7 days with wound care and dressing. The

Figure 1. The left forearm shows a confluent and extensive area of skin necrosis with no raised skin lesions, no vesicles, and no purulent exudate.
patient did not require skin grafting, and he was discharged with therapeutic subcutaneous enoxaparin. Two weeks after discharge, he was readmitted for anemia, at which time his skin lesion had improved significantly.

**Discussion**

Apixaban is reported to cause non-hemorrhagic adverse effects [6–9]. In leukocytoclastic vasculitis cases, lower-extremity skin purpura developed after 9 days of apixaban therapy [6,7]. It was managed with systemic steroid with complete resolution of skin changes within a few weeks [6,7]. In one case, the patient was successfully switched to rivaroxaban without any adverse events [7]. Veliyev et al. described a case of palmoplantar psoriasiform drug eruption in which cutaneous drug eruption developed after 3 days of apixaban therapy; it was managed with topical steroids, and skin changes resolved entirely within a few weeks [8]. Patil et al. reported a case of apixaban-induced delayed drug reaction-lichenoid reaction in which the patient was managed with topical steroids [9]. Similar to apixaban, rivaroxaban, another DOAC, has also been reported to cause skin toxicity. Soliman et al. reported a case of rivaroxaban-induced skin necrosis in which skin changes developed after 3 days of therapy; it was managed with a topical steroid, and the patient was successfully switched to low-molecular-weight heparin [10].

The pathophysiology behind DOAC-induced skin toxicity is unclear. Possible mechanisms include microvascular thrombosis, an imbalance between anticoagulant and procoagulant factors, autoimmune response, and direct medication toxicity [10]. The pathophysiology of warfarin-induced skin necrosis is well explained. Warfarin inactivates vitamin K-dependent coagulation factors II, VII, IX, and X. However, it also inactivates the vitamin K-dependent anticoagulants protein C and S. This may generate an imbalance between pro-coagulation and anticoagulation, which can lead to microvascular thrombi and skin necrosis [11,12]. It is unknown at this time if warfarin-induced skin necrosis and DOAC-induced skin toxicity share a similar pathophysiology.

There are some limitations to this case report. An autoimmune workup for drug-induced vasculitis was not performed. Protein C and Protein S levels could not be obtained because of inpatient restrictions as per hospital policy. A skin biopsy was not performed as the patient was on aspirin and Plavix as a home medication due to his significant coronary artery disease, and he was at high risk for bleeding and post-biopsy skin infections.

Our experience and literature review suggest that treatment of this condition with prompt discontinuation of the offending DOAC and conservative management with wound care is sufficient to manage the skin necrosis.

**Conclusions**

Although skin toxicities are recognized adverse effects of the new DOACs, including apixaban, they are rare and are usually associated with vasculitis. To the best of our knowledge, apixaban-induced skin necrosis has not been reported. This report has shown that skin toxicity can be associated with apixaban and that with the increasing use of these newer DOACs, clinicians should be aware of these potential adverse effects. In this case, the mainstay of treatment was the discontinuation of the causative agent and supportive treatment.

**Disclaimer**

This whole case report was supported by HCA Health Care-Kingwood Medical Center. The views expressed in this publication represent those of the authors and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

**Conflict of interest**

None
References:

1. Chen A, Stecker E, A Warden B: Direct oral anticoagulant use: A practical guide to common clinical challenges. J Am Heart Assoc, 2020; 9(13): e017559

2. Ortel TL, Neumann I, Ageno W et al: American Society of Hematology 2020 guidelines for management of venous thromboembolism: Treatment of deep vein thrombosis and pulmonary embolism. Blood Adv, 2020; 4(19): 4693–38

3. Byon W, Garonzik S, Boyd RA, Frost CE: Apixaban: A clinical pharmacokinetic and pharmacodynamic review. Clin Pharmacokinet, 2019; 58(10): 1265–79

4. van der Hulle T, Kooiman J, den Exter PL et al: Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: A systematic review and meta-analysis. J Thromb Haemost, 2014; 12(3): 320–28

5. Agnelli G, Becattini C, Meyer G et al., Caravaggio Investigators: Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med, 2020; 382(17): 1599–607

6. Spears J, Chetrit DA, Manthey S et al: Apixaban as a rare cause of leukocytoclastic vasculitis. Case Rep Rheumatol, 2020; 2020: 7234069

7. Nasir UB, Kumar A, Easwar A: Apixaban causing leukocytoclastic vasculitis. J Allergy Clin Immunol Pract, 2018; 6(5): 1744–45

8. Veliyev V, Özmén İ, Yaşar S et al: A rare side effect seen due to the use of apixaban: Palmoplantar psoriasiform drug eruption. Anatol J Cardiol, 2016; 16(3): 213–15

9. Patil T, Hanna S, Torre W: A rare case report of apixaban-induced lichenoid eruption. Ther Adv Drug Saf, 2020; 11: 2042098620937884

10. Soliman M, Mowafy K, Elsaadany N, Awad S: Rivaroxaban-induced skin necrosis: A case report. European Journal of Medical Case Reports, 2019; 173-1555632293

11. Kakagia DD, Papanas N, Karadimas E, Polychronidis A: Warfarin-induced skin necrosis. Ann Dermatol, 2014; 26(1): 96–98

12. Vu TT, Goorharn M: Adverse drug reactions and cutaneous manifestations associated with anticoagulation. J Cutan Med Surg, 2017; 21(6): 540–50

This work is licensed under Creative Common Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)