Vasculitis Associated with Dabigatran

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A 70-year-old woman arrived at the emergency department presenting a seven-day worsening pruritic and painful rash. No additional symptoms were present, including fever, arthralgia, anorexia, nausea, diarrhea, dyspnea, or other complaints. Besides initiating dabigatran therapy four days before its appearance, there was no other epidemiological context or personal or family history of similar dermatological conditions.

The patient had a medical history of heart failure and had recently been diagnosed with permanent atrial fibrillation. There was no history of allergies or drug reactions. Previous erythematous skin eruptions occurred in the past, affecting the trunk and back after taking apixaban and rivaroxaban. However, these were less severe and resolved only with drug withdrawal. Suspecting a cross-reaction between factor Xa inhibitors, her family doctor prescribed dabigatran (a thrombin inhibitor) as an alternative anticoagulant for atrial fibrillation.

The physical examination revealed a papular rash with geographic patterns, a pale center surrounded by violaceous lesions, and an erythematous annular pattern on the trunk, back, and proximal limbs (Fig. 1). The hands, feet, face, scalp, or mucosal membranes were not involved. No bullae or scaling was observed.

The patient's vital signs were within normal parameters. Both the chest X-ray and urine sediment examination were unremarkable; blood samples were collected for laboratory tests. The patient was admitted for further investigation and a skin biopsy was performed. Laboratory results revealed leucocytosis (17.90 x10^3 cells/uL) with neutrophilia of 13.75 x10^3 cells/uL and no changes in eosinophilic count (0.20 x10^3 cells/uL), ESR of 32 mm/h, CRP of 9.80 mg/dL, and ferritin of 378 ng/mL. Immunoglobulin E (IgE) was significantly elevated at 1600 UI/mL, with normal IgG subclasses. Anti-nuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA), and cryoglobulins were negative. Complement levels showed normal C3 and C4, but elevated C1q (24.7 mg/dL) and C1 esterase inhibitor (41.7 mg/dL), which suggested that a more severe condition such as hypocomplementemic urticarial vasculitis was less likely. There was no evidence of renal or hepatic involvement. Coagulation factors and platelets were within the normal range. Serological tests for syphilis, human immunodeficiency virus, hepatitis C and B virus, *Rickettsia conorii*, *Coxiella burnetii*, *Borrelia*, parvovirus and herpes virus (cytomegalovirus, Epstein-Barr and herpes simplex) yielded negative results. Additionally, the results of the blood cultures were also negative.

Given the patient's history of skin eruptions following anticoagulant therapy, the recent onset of severe skin lesions, elevated systemic inflammatory markers, and the recent initiation of dabigatran, a hypersensitivity reaction was deemed most likely. Dabigatran was suspended and treatment was adjusted to include immunosuppression and antihistamines, starting prednisolone at 1 mg/kg/day, hydroxychloroquine 400 mg daily, and hydroxyzine 25 mg three times daily.[1]

The patient was discharged after a four-day period, during which time there was a significant improvement in both pruritus management and the severity of the dermatological eruption. She was prescribed prednisolone 60 mg daily and hydroxychloroquine 400 mg daily for one month until her next outpatient follow-up. Additionally, dabigatran was replaced with warfarin due to adverse reactions to other direct anticoagulants. One month later, the dermatological lesions had almost disappeared, allowing the tapering of corticosteroid therapy with hydroxychloroquine maintenance.

Skin biopsy revealed the presence of infiltration of polymorphonuclear neutrophils around small vessels, accompanied by degranulation and apoptosis of neutrophils and damage to the vessels. These findings were consistent with the clinical picture of leukocytoclastic vasculitis. However, the immunofluorescence study yielded negative results. Consequently, the diagnosis of dabigatran-induced urticarial vasculitis was established. Five months later, the patient remained in remission, which allowed the discontinuation of hydroxychloroquine and the completion of prednisolone tapering. Additionally, the serological levels, including erythrocyte sedimentation rate, C-reactive protein, ferritin, and IgE levels, have normalized. One year later, the patient was asymptomatic, with no dermatological manifestations and no ongoing pharmacological treatment.

Urticarial vasculitis is a rare diagnosis. Medicines are a known trigger; however, there are just a few cases described in the literature related with direct anticoagulants.[2,3] To the best of our knowledge, this is the ninth reported case of leukocytoclastic vasculitis induced by dabigatran described in the literature.[4] Although bleeding is the most prevalent side effect of anticoagulants,[5] it is important to be aware of hypersensitivity reactions.

AUTHOR CONTRIBUTIONS

EMB: Writing of the manuscript.
RC: Literature review.

AP, NFS: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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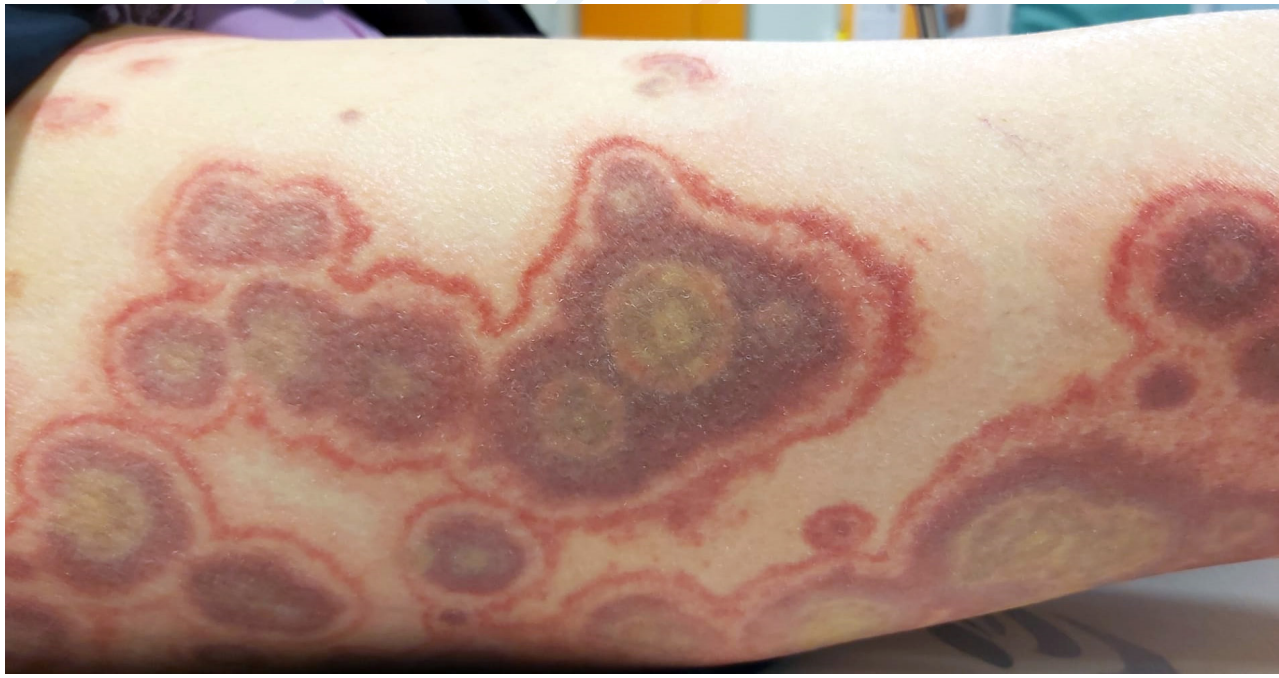

Figure 1 – Skin lesions on the right thigh at patient urgency department admission, seven days after starting dabigatran; presented as a papular rash with geographic patterns, featuring a pallid center surrounded by violaceous lesions and an erythematous annular pattern

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