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Case report

Case of both rivaroxaban- and dabigatran-induced leukocytoclastic vasculitis, during management of pulmonary thromboembolism

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ABSTRACT

Leukocytoclastic vasculitis is a disorder characterized by neutrophilic inflammation that is predominantly limited to the superficial cutaneous postcapillary venules. This condition may be idiopathic or may have a defined cause. Rivaroxaban and dabigatran have been widely used as warfarin alternatives, because of their efficacy and safety. In this case report, we describe a case of leukocytoclastic vasculitis induced by both rivaroxaban- and dabigatran-, which developed during the management of pulmonary thromboembolism.

1. Introduction

Leukocytoclastic vasculitis (LCV) is defined histologically as a predominantly neutrophilic perivascular infiltrate affecting the cutaneous postcapillary venules. The condition is most commonly idiopathic, but can be associated with drugs, malignancies, infections, or connective tissue disorders [1]. Rivaroxaban and dabigatran, which belong to the non-vitamin K antagonist oral anticoagulant (NOAC) family, are more convenient therapeutic options than warfarin and have demonstrated at least equivalent efficacy in comparison with warfarin [2]. In this report, we describe a case of LCV induced by both rivaroxaban- and dabigatran-, which was confirmed by skin punch biopsy and had developed during the treatment of pulmonary thromboembolism (PTE). To our knowledge, this is the first case of both NOAC-associated LCV occurring in a single patient and also the first report that presents direct immunofluorescence (DIF) findings.

2. Case report

A 75-year-old female patient was admitted with sudden-onset dizziness on April 8, 2017. She had a medical history of hypertension, diabetes mellitus, pulmonary tuberculosis and chronic obstructive pulmonary disease with an FEV1 of 62% of normal predicted (1.39 L). This patient did not report any allergies from the past. Brain magnetic resonance imaging indicated an infarction in the posterior inferior cerebellar artery territory. Atrial fibrillation was also found. Edoxaban and bisoprolol were administered together with amlodipine, gliclazide, metformin, and atorvastatin.

The patient became drowsy and dyspneic on May 4, 2017. Her body temperature was 37.6 °C with a white blood cell (WBC) count of 7530/mm^3 and D-dimer level of 0.89 μg/ml. *Enterobacter cloacae* was grown on blood and urine cultures. She received ertapenem for 15 days. However, she continued to experience dyspnea until May 18 and the D-dimer level increased to 5.52 μg/ml. Multiple PTEs were found at the segmental pulmonary arteries of the right lower lobe and left lung with focal deep vein thromboses at the infrarenal inferior vena cava, left popliteal vein and calf vein on three-dimensional angiography computed tomography scans. The activated partial thromboplastin time was 38.4 s (29.0–44.0 s); the prothrombin time, 14.5 s (international normalized ratio, 1.17) and WBC count, 7440/mm^3. We stopped edoxaban and started intravenous heparin injection.

Rivaroxaban 15 mg twice a day was started from May 30. Non-blanching erythematous palpable petechiae and purpura (Fig. 1) were found on both thighs, both arms, and the lower abdomen on June 16. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), and the biochemical profile with liver and renal function, coagulation studies, and urine analysis were within normal limits. Chest X-ray (CXR) showed no active parenchymal lesion. Further studies, including antinuclear antibody (ANA), rheumatoid factor (RF), antineutrophil cytoplasmic antibodies (ANCA) (cytoplasmic and perinuclear), complement levels (C3, C4), serum cryoglobulins, hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus test, yielded

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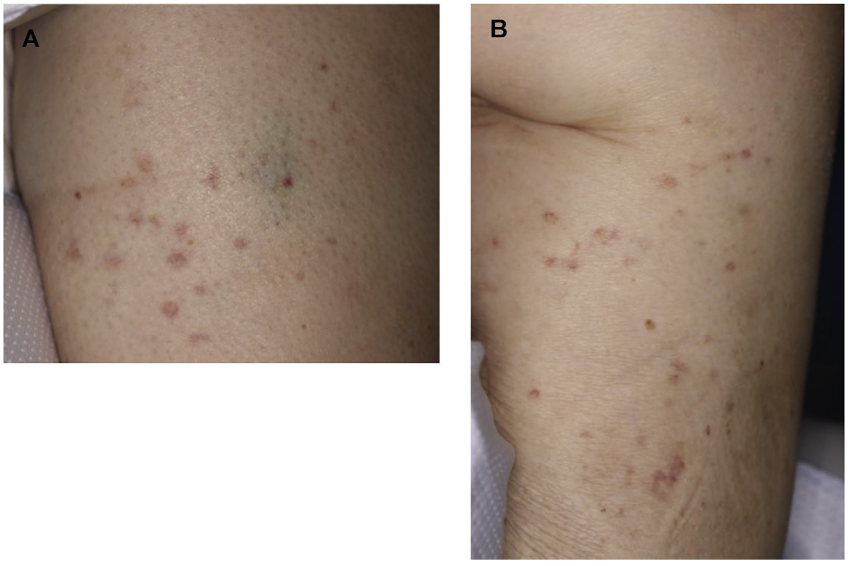

Fig. 1. Non-blanching erythematous palpable petechiae and purpura on the right thigh (A) and left arm (B).

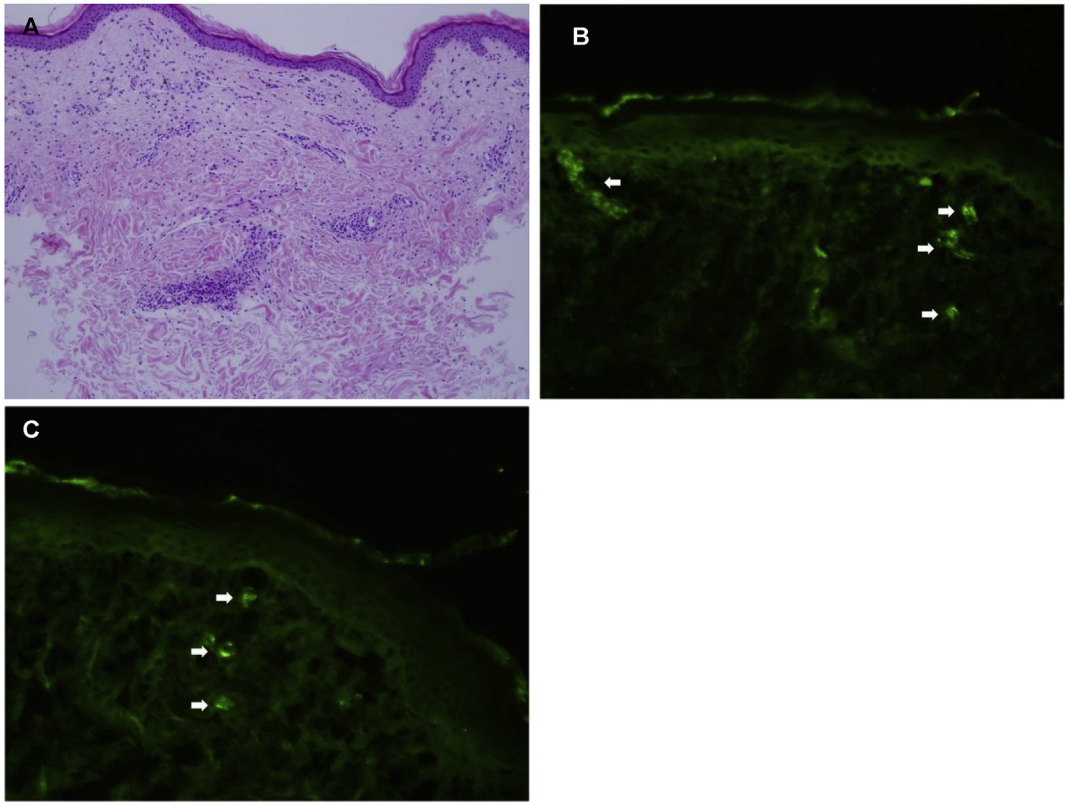

Fig. 2. Perivascular neutrophilic infiltration with leukocytoclastic debris is seen in the deep dermis (Hematoxylin and eosin stain, X 100) (A). Direct immunofluorescence staining demonstrates granular deposition of immunoglobulin A (B) and complement 3 (C) in dermal blood vessels. Arrows indicate the deposited immunoglobulin A and complement 3, respectively.

normal results. We performed punch biopsies on the abdomen on June 20. The biopsy specimen showed superficial perivascular neutrophilic infiltration with leukocytoclastic debris, and interstitial infiltration of a few eosinophils and melanophages, consistent with LCV. Direct immunofluorescence (DIF) staining demonstrated granular deposition of immunoglobulin A and C3 in dermal blood vessels (Fig. 2).

We stopped rivaroxaban on July 12 and started dabigatran 110 mg twice a day instead. The skin lesions improved within 2–3 days. We administered rivaroxaban 20 mg daily again from July 19 to confirm that the skin lesions were caused by it. Similar skin lesions developed again on July 29, and rivaroxaban was stopped on July 31. We started dabigatran 110 mg daily again from August 1. The skin lesions improved within 2–3 days again but they began to reappear on August 13. Dermatological assessment performed at that time indicated that this was the same disease. Since the patient was not receiving any concomitant medication that could be suspected as the cause of LCV, we stopped dabigatran on August 15, and started edoxaban 15 mg daily from August 16. The skin lesions improved over several days. We did

not administer rivaroxaban and dabigatran anymore, and the skin lesions also did not develop again subsequently. However, the patient developed hospital-acquired pneumonia and died of it on September 11, 2017.

3. Discussion

The most common presentation of LCV involves nonblanching palpable purpuric lesions that occur predominantly on dependent areas [3]. Cutaneous LCV is associated with various conditions [1,3]. A single acute simultaneous appearance of vasculitic lesions is often associated with a drug or infection [3]. Drug-induced LCV accounts for up to 10%–15% of the cases, and many medications can cause LCV [1,3]. In cases in which an unknown medication was used shortly before the onset of the rash, no other apparent factor contributed to the etiology. Because the lesions regressed upon discontinuation of the medication, the vasculitis was deemed to be associated with the use of the medication [4]. In this case, the skin lesion improved on discontinuation of rivaroxaban but recurred after its re-use. The subsequent disappearance of the lesions after rivaroxaban was discontinued again indicates that this was a case of rivaroxaban-induced LCV. However, the patient showed similar skin lesions after dabigatran, and the lesion improved again after dabigatran was stopped. Therefore, we believe that these findings also indicate dabigatran-induced LCV.

There was a report in which temporal association of skin and ocular lesions with Enterobacter epididymo-orchitis suggested an etiologic link between these conditions, but it was not substantiated because DIF was not performed [5]. Infection-induced LCV was diagnosed if the patients had concurrent or preceding infections [6]. In our case, *E. cloacae* was observed only once in early May, which was eradicated with antibiotics. No more pathogens were isolated from then on until mid-August during which LCV developed. Hence, we could exclude the infection as the cause of LCV in this case.

The diagnosis of LCV should be confirmed with a skin biopsy. The preferred technique is a deep punch biopsy to include the deep dermis and part of subcutis as well as the epidermis and superficial dermis [3]. This usually includes separate specimens for light microscopy (hematoxylin and eosin [H&E]) and DIF [1,3]. Because vessel wall injury in LCV is antibody-mediated and characterized by deposition of immune complexes, determination of these immune complexes by DIF therefore may aid in diagnosis as well as etiological classification of LCV [7]. A DIF study should be performed, whenever possible, due to the immunologic nature of the pathophysiology of LCV [7,8]. Notably the timing and location of the biopsy are critical for an accurate diagnosis. For H&E staining, a lesion that has been present for only 18–48 h is ideal. Immune complexes can be seen in the early stages of lesion formation, but may disappear as soon as 48 h after appearance [1]. However, a high positivity rate was noted for both histopathology (80%) and DIF (100%) even on 3–7 day lesions [6]. In this case, we performed biopsy on the fourth day after the skin lesions were observed initially and we were able to confirm a diagnosis of LCV on the basis of the typical findings in both in H&E and DIF staining. However, we did not need to perform skin biopsy again when the skin lesions developed after dabigatran.

Nevertheless, identification of vasculitis on biopsy is not the end of the road in the diagnostic algorithm, as it needs to be combined with a careful history, a detailed physical examination, and laboratory and imaging studies to establish whether the cutaneous manifestations are isolated to the skin or are a part of a systemic vasculitic process. Laboratory examinations should initially include any pertinent infectious serologies and cultures, CBC, creatinine, urine analysis, ESR, CXR, liver function test, cutaneous biopsy for H&E and DIF staining. The following additional studies can be added as indicated: ANCA including proteinase-3 and myeloperoxidase, ANA, complement (CH50, C3, C4), RF and cryoglobulins, renal biopsy, or bone marrow biopsy [1,3]. In patients with cutaneous LCV, IgA is the most common immunoglobulin found by DIF. If IgA deposition in LCV is observed, the clinician should consider the patient to have a systemic vasculitis, and screen for renal and gastrointestinal involvement [9]. However, there is evidence that IgA does not appear to be pathognomonic of Henoch–Schonlein purpura (HSP) [10]. One study found that in an adult population with LCV, IgA deposition within dermal vessels was most often secondary to drug-induced hypersensitivity vasculitis rather than HSP [11]. In this case, HSP was excluded there was no evidence of any features suggestive of HSP or other systemic causes of LCV.

Once the clinician has established that the LCV is limited to the skin the clinical approach should be directed at eliminating the cause if possible. Stepwise treatment approach should include: leg elevation, compression stockings, and medications [1,3]. In this case, to stop both NOAC was sufficient.

4. Conclusions

NOACs, including rivaroxaban and dabigatran, have been widely used as warfarin alternatives, because of their efficacy and safety. Rivaroxaban- and dabigatran-associated LCV have previously separately been reported in some patients each [12–19]. They emphasize that clinicians should be aware of this rare but important adverse effect because of the increased use of these NOACs. To our knowledge, this is the first case of rivaroxaban- and dabigatran-associated LCV occurring in a single patient and also the first report that presents DIF findings.

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Conflicts of interest

None.

Informed consent

Yes.

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