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Case Report

Rivaroxaban-Associated Bullous Pemphigoid in a Patient With Atrial Fibrillation

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ABSTRACT

Rivaroxaban is commonly used for prevention of thromboembolic diseases in patients with atrial fibrillation. We report a case of an 86-year-old man with hypertension, chronic kidney disease, type 2 diabetes mellitus, dyslipidemia, and atrial fibrillation who developed bullous eruptions 1 week after a rivaroxaban dose increase. He was subsequently hospitalized, and direct immunofluorescence confirmed bullous pemphigoid (BP). After switching to apixaban, the patient's skin eruptions stabilized and improved. This is the first reported case of immunofluorescence-confirmed BP associated with rivaroxaban use. Prompt discontinuation of rivaroxaban and a switch to other anticoagulants is important for patients with suspected drug-associated BP.

RÉSUMÉ

Le rivaroxaban est couramment utilisé pour la prévention des maladies thromboemboliques chez les patients atteints de fibrillation auriculaire. Nous rapportons le cas d'un homme de 86 ans atteint d'hypertension, de néphropathie chronique, de diabète de type 2, de dyslipidémie et de fibrillation auriculaire, qui a présenté des éruptions bulleuses une semaine après l'augmentation de sa dose de rivaroxaban. Il a par la suite été hospitalisé, et une analyse par immunofluorescence directe a permis de confirmer le diagnostic de pemphigoïde bulleuse. Après le passage à l'apixaban, les éruptions cutanées du patient se sont stabilisées et atténuées. Il s'agit du premier cas rapporté de pemphigoïde bulleuse confirmée par immunofluorescence associé à l'utilisation du rivaroxaban. Chez les patients présentant une pemphigoïde bulleuse possiblement associée au rivaroxaban, il est important d'arrêter rapidement l'administration du médicament et de le remplacer par d'autres anticoagulants.

Rivaroxaban is a direct oral anticoagulant (DOAC) with common indications, including treatment of venous thromboembolism and anticoagulation in atrial fibrillation.[1] However, cutaneous skin eruptions may occur with use of rivaroxaban.[1]

Bullous pemphigoid (BP) is an autoimmune process classically characterized by diffuse truncal and limb tense blisters, urticarial plaques, intense pruritus, and sparing of mucosal membranes.[2] patients with BP have increased mortality, ranging from 10% to 40% in the first year.[3] Although the temporal relationship with drug ingestion is crucial when drug-associated BP is suspected, a combination of clinical assessment and histologic examination of perilesional biopsies all further support a diagnosis. For conclusive diagnosis, the gold-standard test remains the direct immunofluorescence (DIF) detection of autoantibodies and/or complement component c3 at the dermal–epidermal basement membrane.[4] For DIF, the biopsy specimen must be stored in Zeus medium and not formalin.

We found 2 suspected cases of rivaroxaban-associated BP-like reaction supported by either clinical judgement and/or hematoxylin and eosin histopathology in the English-language literature.[1,5] However, to our knowledge, there were no reports with confirmatory immunofluorescence establishing a definitive diagnosis of BP secondary to rivaroxaban exposure, as presented in this report.

Case

Our patient is an 86-year-old Chinese man with a medical history of hypertension, type 2 diabetes mellitus, chronic kidney disease (baseline estimated glomerular filtration rate: 45-50), dyslipidemia, and paroxysmal atrial fibrillation (AF) with a CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category) score of 4.

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See page 1319 for disclosure information.

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Novel Teaching Points

- BP is a rare but serious adverse event that can be associated with initiation of medications, and the gold-standard diagnostic test for BP is immunofluorescence testing, which requires a separate perilesional punch biopsy with a sample stored in Zeus medium and not formalin.
- In suspected rivaroxaban-associated BP, rivaroxaban needs to be promptly discontinued, and switching to apixaban may be safe
- If BP persists or is severe, dermatology consultation and corticosteroid therapy should be considered.

On July 4, 2019 he was diagnosed with AF and was prescribed rivaroxaban at 15 mg daily and bisoprolol at 1.25 mg daily.

In December 2019, the patient began to develop progressive generalized pruritus. As the pruritus persisted after discontinuing beta-blockers, the patient was switched to apixaban on January 22 when his family physician suspected that rivaroxaban was the culprit. However, he was noncompliant with the twice daily dosing of apixaban, and therefore his cardiologist restarted his rivaroxaban at 20 mg once daily on February 4th, 2020.

At the time, the patient was taking a baseline regimen of ramipril at 5 mg daily, metformin at 500 mg 3 times daily, atorvastatin at 10 mg daily, gliclazide at 60 mg daily, diltiazem at 360 mg daily, and digoxin at 0.125 mg daily. The patient had not been taking other nonprescription medications. We were able to verify the dosage and medication dispensation date on PharmaNet, a province-wide database that records every prescription dispensed in pharmacies. However, adherence to daily medications is not recorded on PharmaNet and was obtained via interview with the patient.

A week later, the patient developed tense bullae on his abdomen that eventually ruptured and formed crusted erosions prior to healing. He continued to suffer from urticaria and tense bullae formation on his upper and lower extremities and was eventually admitted to the hospital on March 2, 2020.

On physical examination, he appeared well, with normal vital signs, and was not in AF. On visual inspection, there were healed well-demarcated violaceous plaques with hemorrhagic crusts on his central abdomen (Fig. 1A). There were multiple intact bullae in his upper and lower extremities, with serous content (Fig. 1B–F). There was no evidence of mucosal involvement. His bloodwork was unremarkable compared to his baseline.

He was switched to apixaban at 5 mg twice daily, and we performed 2 lesional and perilesional punch biopsies taken

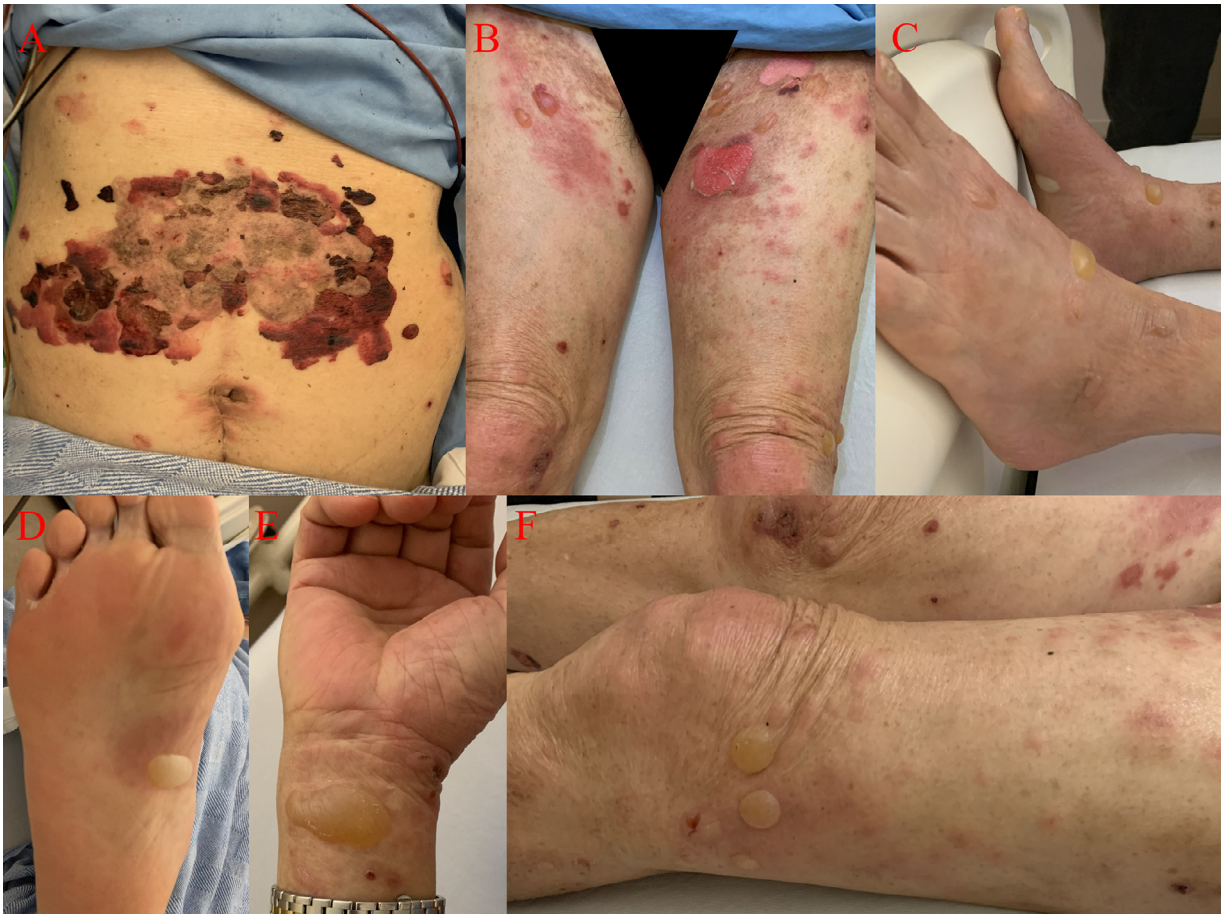

Figure 1. Photographs of the patient's cutaneous lesions on March 2, 2020: (**A**) abdomen; (**B**) anterior aspect of upper legs; (**C**) feet; (**D**) right foot; (**E**) right wrist; (**F**) lateral aspect of upper legs.

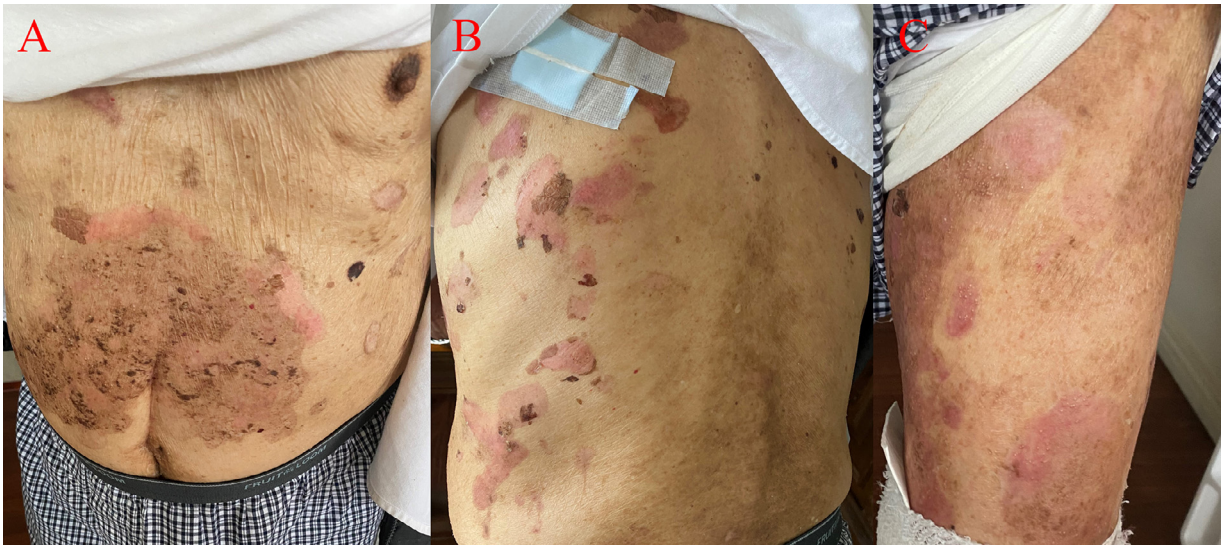

Figure 2. Photographs of the patient's cutaneous lesions on May 25, 2020: (**A**) abdomen; (**B**) back; (**C**) anterior aspect of upper left leg.

around the intact bullae on his right leg, for light microscopy and direct immunofluorescence.

The patient was discharged in stable condition on March 4 but was readmitted 4 days later as he was unable to manage his wound care at home. Later, results of the biopsies showed a subepidermal blister with prominent eosinophils on routine histology, and DIF demonstrated strong fluorescence for C3 along the dermal−epidermal junction. The pathology report concluded that both biopsy specimens showed features consistent with BP.

The patient was then put on a course of oral prednisone at 50 mg daily, tapering to 16 mg daily for treatment of BP. After an uneventful hospital stay, he was discharged on March 17 with scheduled at-home wound care. On follow-up visit with the dermatologist on May 28, his bullous lesions had largely resolved (Fig. 2). His BP medications at this follow-up were prednisone at 16 mg daily, zzathioprine at 100 mg daily, and doxycycline at 100 mg daily, to be gradually tapered over the following months. At his most recent cardiology follow-up on March 25, 2021, he continued to report no issues after being switched to apixaban more than 1 year earlier. Lastly, this adverse reaction has now been reported to the Canada Vigilance Program for adverse drug reactions.

Discussion

Rivaroxaban-associated BP is a rare occurrence, and this is the first case, to our knowledge, of DIF-confirmed BP associated with rivaroxaban use.

In our case, as well as in previous case reports,[1,5] distinguishing between drug-associated BP and idiopathic BP was difficult. Many cases of drug-associated BP, including the two previous case reports for rivaroxaban-associated BP, present as acute, self-limiting diseases with quick onset and rapid resolution after drug withdrawal.[1,2,5] However, there have been documented cases of drug-associated BP with more chronic presentations. Specifically, drug eruptions can occur for up to months after the first introduction, and remission can be achieved after weeks to months of oral corticosteroid treatment, similar to the pattern in our case.[2,6]

The Naranjo algorithm for adverse drug reaction probability was previously employed by Chohan et al. and revealed a "probable" association between rivaroxaban use and BP.[5] In our case, we obtained a score of +5, which indicates a "probable" adverse drug reaction due to rivaroxaban (Supplemental Table S1). An important point to note is that, unlike Chohan et al., we have not attributed points to items 1 and 5, as we do not believe there has been a conclusive prior report of rivaroxaban-induced BP, nor can we exclude idiopathic BP from the differential.

Here, suspension of rivaroxaban after recognition of BP was a logical step, but choosing an alternative agent for anticoagulation was not straightforward. In the previously mentioned case reports, there was only one report documenting one patient who safely switched from rivaroxaban to warfarin.[1] In our case, the patient was switched from rivaroxaban to apixaban, without recurrence of BP for at least 1 year. This provides some evidence for the safety of apixaban in that it did not trigger another episode of BP. Overall, the evidence is lacking in terms of the best approach for anticoagulation in patients who develop BP associated with anticoagulant use but need long-term anticoagulation. In the future, more reports and studies would be helpful to assess the best approach for switching anticoagulant type when drug-associated BP is suspected.

Lastly, BP is associated with a significant morbidity and mortality risk of up to 40% in 1 year, especially for frail elderly patients.[3] Specifically, the medical comorbidities in elderly patients requiring anticoagulation make them even more susceptible to the consequences of developing BP.

In conclusion, rivaroxaban-associated BP is a rare but serious adverse event that may be diagnosed from clinical features, as well as histology and immunofluorescence testing. Rivaroxaban should be discontinued immediately, and corticosteroid therapy should be considered for those with more-severe presentations, to promote healing and improve quality of life. Apixaban may be considered as an alternative to rivaroxaban in these cases.

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at doi:10.1016/j.cjco.2021.06.003.