Apixaban-induced cutaneous hypersensitivity: a case series with evidence of cross-reactivity

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To the Editor:

Atrial fibrillation is the most common cardiac arrhythmia affecting more than 2.7 million patients in the US [1]. As the population ages, it is predicted to affect more than 6-12 million people by 2050 [1]. Patients with atrial fibrillation are at increased risk for thromboembolic events and require anticoagulation therapy to prevent thrombus formation and stroke. Apixaban, a novel oral anticoagulant that reversibly and directly inhibits factor Xa, was approved by the Food and Drug Administration in 2012 and has been widely used in the U.S. since [2]. Apixaban is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. According to the product monogram, hypersensitivity reactions (including drug hypersensitivity, such as skin rash and anaphylactic reactions, such as allergic edema) and syncope were reported in the Aristotle study to occur in less than 1% of patients on apixaban [2]. Very few cases of cutaneous reactions related to apixaban have been reported [5-8]. We describe four cases of apixaban induced hypersensitivity reaction and a potential cross-reactivity between apixaban and rivaroxaban.

Case 1

A 66-year-old woman with a history of venous thromboembolism presented with a pruritic rash. She was previously started on apixaban and within 1-2 weeks she developed low-grade fevers, chills, nausea, shortness of breath, headaches, and cough. She was admitted to the hospital where computed tomography of the chest demonstrated ground glass opacities located peripherally within her lungs. Laboratory results showed a decrease in hemoglobin, elevated dsDNA, positive rheumatoid factor, and elevated beta-2 glycoprotein concerning for drug-induced lupus. Her apixaban was held owing to concern for hemorrhage. A bronchoalveolar lavage was performed revealing eosinophilic predominance, suggestive of eosinophilic pneumonia secondary to a connective tissue disease versus drug reaction. After improving on prednisone 40mg daily, she was instructed to continue prednisone and to restart apixaban.

For the next two months while on apixaban, she continued to have slowly worsening malaise, arthralgias, and dyspnea. Examination revealed edematous pink ill-defined plaques on her legs, flanks, and abdomen. Three punch biopsies were performed, demonstrating a dermal hypersensitivity reaction with interstitial eosinophils, lymphocytes, and neutrophils. Apixaban was switched to warfarin and within two weeks her eruption had resolved, the rest of her symptoms had improved, and her antibody profile was negative when rechecked.

Case 2

A 67-year-old man presented with 2-3-day history of a rash on arms, legs, and abdomen after starting apixaban 2-3 weeks prior. He previously had a similar eruption when he had been on rivaroxaban. Examination revealed palpable purpura from the lower abdomen down to his feet. Given these

constellations of symptoms, IgA vasculitis was suspected and two punch biopsies were obtained which revealed a vasocentric neutrophilic infiltrate with leukocytoclasia; the direct immunofluorescence demonstrated vascular IgA deposition. The patient was switched to warfarin and started on a prednisone taper and dapsone 50mg daily that cleared his skin.

Case 3

A 65-year-old man was admitted for complications from a right common femoral artery cutdown who subsequently developed multiple pulmonary emboli and was then started on apixaban. Two weeks after starting apixaban, he developed abdominal pain, melena, and palpable purpura on his bilateral lower extremities and buttocks. Laboratory results showed an elevated creatinine of 5.69 from a baseline of 1.5mg/dL, necessitating dialysis. Apixaban was stopped and he did not develop additional new lesions during his hospital stay. The lesions resolved without treatment; he was transitioned to warfarin without further cutaneous manifestations. His renal function and cutaneous lesions slowly improved.

Case 4

A 48-year-old man developed complications after cardiac stent placement necessitating anticoagulation. He was initially started on low molecular weight heparin and later transitioned to apixaban for chronic anticoagulation. Five days after starting apixaban he developed palpable purpura on his lower legs. Over the next four days, he developed more lesions ascending onto his abdomen and upper extremities. Examination demonstrated the highest density at the lower legs, but with a significant component at the buttocks, abdomen, back, forearms, and upper arms. Biopsy demonstrated a perivascular neutrophilic infiltrate with leukocytoclasia, endothelial wall swelling and fibrin deposition; direct immunofluorescence was consistent with an IgA vasculitis. Laboratory workup was within normal limits. He was treated with topical corticosteroids with symptomatic relief. The patient was switched from apixaban to rivaroxaban and did not develop any further lesions. The remaining lesions resolved spontaneously.

Apixaban induced hypersensitivity reactions have rarely been described. Our literature review found only three case reports on apixaban induced cutaneous reactions even though several cases have been reported involving rivaroxaban [5-8].

Scores via the Naranjo Adverse Drug Reaction Probability Scale were assigned to each of our four cases (**Table 1**). For case 1, the Naranjo score, which demonstrated the likelihood of apixaban-skin induced reaction was definite (score 9). The skin biopsy results suggested dermal hypersensitivity with the presence of interstitial eosinophils, lymphocytes, and neutrophils; these findings are commonly seen in drug-induced skin hypersensitivities [4].

Case 2 demonstrates apixaban-induced cutaneous reaction, as well as cross-reactivity between factor Xa inhibitors. With a score of 8 on the Naranjo scale, the causality between apixaban and the patient's cutaneous reaction was probable. Our patient had cutaneous reactions to both rivaroxaban and apixaban indicating a possible cross-reactivity between different factor Xa inhibitors with similar structures. Cortellini et al. demonstrated a possible cross-reactivity between the factor Xa inhibitors, edoxaban and apixaban [8]. Because of the potential cross-reactivity between these agents, it is important to consider alternative anticoagulants from a different mechanistic group.

Case 3 was suspicious for apixaban induced cutaneous eruptions as the rash began 12-14 days after initiation of apixaban and improved with cessation. No other cause of vasculitis was found. The Naranjo nomogram scale of three supports a possible apixaban induced cutaneous hypersensitivity.

Case 4 developed a cutaneous rash five days after initiation of apixaban and it was suggestive of apixaban induced hypersensitivity reaction. With a Naranjo scale of 7, his cutaneous eruptions were probably related to apixaban. His eruption improved after cessation of apixaban and with topical corticosteroids.

We compiled four cases of apixaban induced hypersensitivity that resolved with medication discontinuation. All these cases had probable or

Table 1. *Naranjo Adverse Drug Reaction Probability Scale for Cases 1-4. The Naranjo nomogram is a questionnaire for determining the likelihood of whether adverse drug reaction is related to the drug instead of other factors. It classifies the reaction as doubtful (score ≤0), possible (1-4), probable (5-8), or definite (≥9). The table showcases Naranjo scores for Cases 1-4.*

Question	Yes	No	Do not Know	Score (Case 1)	Score (Case2)	Score (Case 3)	Score (Case 4)
Are there previous conclusive reports on this reaction?	+1	0	0	+1	+1	+1	+1
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2	+2	+2	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1	+1	+1	+1
Did the adverse event reappear when the drug was re-administered?	+2	-1	0	+2	0	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2	+2	-1	+2
Did the reaction reappear when a placebo was given?	-1	+1	0	0	0	0	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	0	+1	0	+1
Total Score				9= Definite	8= Probable	3= Possible	7= Probable

better Naranjo score, one demonstrating possible cross reactivity between apixaban and rivaroxaban. The use of novel oral anticoagulants have increased significantly in recent years because these agents have similar efficacy to heparin and warfarin and do not require laboratory monitoring. As this is a relatively new class of medications it is important for clinicians to recognize cutaneous reactions from these drugs. In addition, some patients might develop cross-reactivity among factor Xa inhibitors, thus switching to an anticoagulant from a different class should be considered.

Potential conflicts of interest

The authors declare no conflicts of interests.

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