Diffuse Alveolar Hemorrhage Secondary to Apixaban Administration

To the Editor:
Atrial fibrillation carries a substantial risk of stroke. Various anticoagulant and antiplatelet agents are used to decrease this risk, but bleeding complications are natural to them.

A 79-year-old woman presented with syncope and hypoglycemia. Additional symptoms included black tarry stools in the weeks prior to admission and progressively worsening shortness of breath and dry cough in the previous 3 days. She denied chest pain, hemoptysis, orthopnea, peripheral edema, fever, nausea, and vomiting. Her medical history included atrial fibrillation, diabetes mellitus, chronic hypoxemia on continuous 3 L of oxygen, and a GI bleed on both warfarin and dabigatran therapy. The patient's cardiologist had recently placed her on treatment with apixaban 5 mg bid po. The patient had stopped taking all anticoagulation medication for 3 months prior to starting apixaban. On examination, she was borderline hypotensive, and there was no jugular vein distention. Chest imaging showed diffuse bilateral infiltrates (Fig 1) in the presence of a normal WBC count and hemoglobin level of 7.3 g/L, down from 10.3 g/L seen a month prior. Dyspnea did not improve with diuretic therapy; however, it did worsen renal function. The oxygen requirement escalated rapidly.

An esophagogastroduodenoscopy showed a pinpoint oozing vascular ectasia requiring cautery but no significant amount of blood in the upper GI tract. Immediately after that, bronchoscopy was performed. A large amount of dark blood was visualized in the trachea and lower airways, with each of four sequential 30-mL aliquots of BAL being bloodier than the previous. Cytologic examination revealed multiple hemosiderin-laden macrophages (Figs 2A, 2B). Subsequent workup was unremarkable, including negative antineutrophil cytoplasmic antibodies, antinuclear antibody, and antiglomerular basement membrane antibody, and all microbiologic study results. Echocardiogram showed normal left ventricle ejection fraction, mild valvular abnormalities, and mild pulmonary hypertension. Inpatient pulmonary function tests were not obtained. Given the clinical findings, a diagnosis of diffuse alveolar hemorrhage (DAH) secondary to apixaban was established.

The patient was treated with noninvasive CPAP, from which she was weaned gradually. Chest imaging improved slowly. Her oxygen requirement was weaned down to her home oxygen level. She was discharged to a rehabilitation facility with the plan of reinstituting low-dose aspirin therapy and evaluation for ablation modalities in the future. She was seen as an outpatient 2 months later with clearing of the chest radiograph and no new respiratory symptoms.

DAH is a rare complication of antithrombotic/antiplatelet therapy described previously with clopidogrel,
1 warfarin,2,3 and dabigatran.4 Apixaban, a novel direct factor Xa inhibitor, is associated with reduced risks of bleeding, stroke, and mortality, compared with warfarin.5 Typically, bleeding complications are related to the GI tract, with intracranial bleeding being the most feared complication. To our knowledge, DAH has never been reported with apixaban therapy.

In this case, the patient was started on apixaban 2 weeks prior to admission. Based on clinical and laboratory data, there was no evidence of cardiogenic pulmonary edema, infection, vasculitis, Goodpasture syndrome, or connective tissue disorder, nor was there any evidence of massive GI bleeding with significant aspiration. Visual characteristics and cytologic evaluation of BAL were also consistent with DAH. To our knowledge, this is the...
first report of DAH due to the factor Xa inhibitor drug class. Although rare and with potentially fatal complications, DAH should be incorporated into the differential diagnosis of diffuse pulmonary infiltrates for patients taking anticoagulants.

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Figure 2 – BAL cytology. A, ThinPrep slide with a cluster of alveolar macrophages demonstrating intracytoplasmic pigment (Papanicolaou, original magnification × 60). B, Cell block confirming pigment is hemosiderin (Prussian blue iron, original magnification × 60).

References