Angioedema Involving the Larynx after Starting Apixaban

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Angioedema is characterized by subcutaneous nonpitting edema of the skin, mucosal membranes, or both. It is often anatomically limited to subsites of the head and neck, which can be life threatening because of its sudden onset and airway compromise.1 Although angioedema has many known causes, including medications and environmental exposures, the etiology of acquired angioedema is often difficult to ascertain. Angioedema can be unpredictable and must be recognized without delay by identifying the characteristic clinical presentation and history.

Apixaban is a direct factor Xa inhibitor used for venous thromboembolism and stroke prophylaxis in patients with atrial fibrillation. A single case report presented as an abstract at the International Academy of Cardiology Annual Science Session in 2014 discussed a patient with apixaban-associated angioedema and identified 6 other reported cases.2 However, these 6 other cases were described on a nonvalidated website. Angioedema has been reported to be associated with rivaroxaban, another factor Xa inhibitor.3 In this report, we present a rare case of acute angioedema and airway compromise without urticaria after starting apixaban for anticoagulation.

Case Report
A 73-year-old man presented to the emergency department with right-sided facial weakness and dysarthria. Computed tomography and subsequent magnetic resonance imaging (MRI) revealed a new left parietal cortex nonhemorrhagic cerebrovascular accident. The patient refused fibrinolytic therapy with tissue plasminogen activator. The following day, the patient developed new-onset left-sided weakness of the extremities, and the diagnostic MRI revealed infarction of the right insular cortex and right inferior frontal lobe. At this point, a flexible fiberoptic endoscopic evaluation of swallowing was performed for evaluation of dysphagia. This exam demonstrated pharyngeal pooling, laryngeal penetration, and aspiration with ineffective cough response. The true vocal folds were mobile bilaterally with no laryngeal lesions (Figure 1A). A nasogastric tube was placed for nutritional support. Anticoagulation therapy was initiated with apixaban 5 mg twice daily.

After starting apixaban, the patient developed shortness of breath. Otolaryngology performed flexible indirect laryngoscopy which demonstrated significant edema of the supraglottis, consistent with angioedema, along with impaired mobility of the left true vocal fold (TVF; Figure 1B). Apixaban was discontinued and the angioedema was treated with methylprednisolone intravenous (IV) taper, diphenhydramine IV twice daily, and famotidine IV twice daily.

Repeat flexible laryngoscopy 24 hours later displayed significant reduction in the supraglottic edema with persistent but improved left TVF hypomobility. Follow-up evaluation by speech pathology with a videofluoroscopic swallow study demonstrated profound aspiration. A percutaneous endoscopic gastrostomy tube was placed for long-term nutrition requirement. The patient returned to the laryngology clinic 2 weeks after discharge. Flexible laryngoscopy and stroboscopy confirmed normal TVF mobility and complete resolution of laryngeal edema and erythema (Figure 1C).

Discussion
According to the American Academy of Neurology, the American Association of Neurological Surgeons, and the Congress of Neurological Surgeons, intravenous fibrinolytic
therapy remains the standard treatment for patients with acute ischemic stroke who meet eligibility criteria. Without the reversal of ischemia, prevention of worsening or future thromboembolic events is the focus of stroke management.

While there are many potential causes of angioedema, apixaban was the most likely cause in this case because it was the only new medication this patient started before rapidly developing laryngeal edema clinically consistent with angioedema. Given the lack of urticaria or pruritus, the mechanism of angioedema in this patient is most likely related to the kallikrein-kinin cascade mediated by bradykinin considered drug-induced nonallergic angioedema. With the discontinuation of apixaban, this patient achieved a complete resolution of symptoms. During phase IV clinical trials, angioedema was cited as a possible adverse reaction for dabigatran and rivaroxaban but not apixaban. To our knowledge, this report is the first documented case of angioedema secondary to apixaban described in medical literature.

Drug-induced angioedema is an unpredictable adverse event that should be considered in patients starting new medications. This case highlights the morbidity of laryngeal angioedema in a patient after starting apixaban. With the increasing use of new target-specific anticoagulants, rare adverse events such as angioedema will become more common. Although infrequent and unpredictable, clinicians should be aware of this uncommon but possibly life-threatening adverse reaction to apixaban and other new oral anticoagulants when managing patients with atrial fibrillation at risk for thromboembolic stroke.

Disclaimer
The statements discussed are the result of previous evidence-based reports and do not necessarily reflect the view of the affiliated institution.

Author Contributions
Adrian Williamson, manuscript composition, acquisition of data, research; Cory A. Vaughn, research, manuscript preparation; Ozlem E. Tulunay-Ugur, project supervision, critical revision of manuscript.

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Figure 1. Views of larynx by flexible laryngoscopy. (A) Initial flexible laryngoscopy revealed no vocal fold lesions, edema, or evidence of impaired true vocal fold (TVF) mobility. (B) Laryngoscopy exhibited severe supraglottic edema and hypomobility of the left TVF, clinically consistent with angioedema. (C) Laryngoscopy at follow-up visit demonstrated resolution of edema, erythema, and no residual impairment of vocal fold mobility.