The use of thrombolytic medications for the treatment of acute ischemic cerebral infarctions has dynamically altered stroke care. However, there are both major and minor side effects associated with its use—most notably major bleeding, which led to strict inclusion and exclusion criteria governing the administration of this medication class. One less recognized but potentially serious complication is angioedema secondary to tissue plasminogen activator (tPA). Our case emphasizes the importance of early recognition of this clinical syndrome as it relates to airway compromise and potential respiratory failure in patients who are treated with tPA.

Case
A 70-year-old woman with a history of diabetes and hypertension and a remote history of breast cancer, nonhemiplegic migraines, and hypothyroidism presented to the ED with complaints of aphasia and right-sided paralysis, with onset 2 hours prior. Regarding the patient’s medication history, she had been taking lisinopril for hypertension.

Upon assessment, the patient was awake and alert and her vital signs were normal and stable, but she was aphasic, unable to accurately phonate, and was not able to move her right arm or leg against gravity. Her sensation appeared intact, and she had mild facial asymmetry with inability to raise the right corner of her mouth; her tongue had midline protrusion.

An emergent computed tomography (CT) scan of the head demonstrated mild brain atrophy and minimal low attenuation within the cerebral hemispheric white matter—most noticeably within the subcortical region of the left frontal lobe, consistent with small vessel ischemia. There was no evidence of acute intracranial hemorrhage, midline shift, or focal mass ef-
Studies have shown the risk of developing angioedema is significantly increased in the setting of concomitant use of an angiotensin converting enzyme inhibitor (ACE-I). Factors include the development of early signs of ischemia in the frontal lobe on initial CT scan, which likely increased her risk for angioedema.

**How tPA Can Trigger Angioedema**

The development of angioedema after administration of tPA has a well-described biochemical basis. Angioedema has been linked to the local vasodilatory effects of bradykinin, mast cell degranulation, and histamine release from activation of the complement pathway. Tissue plasminogen activator may trigger both of these pathways. It is a serine protease that cleaves plasminogen to plasmin; the plasmin in turn cleaves fibrin, resulting in the desired thrombolytic effects. Plasmin can cause mast cell degranulation through conversion of C3 to C3a and through activation of the complement pathway through conversion of C1 to C1a.

Studies have shown tPA to have low antigenicity, and activation of this pathway is most likely secondary to direct proteolytic effects as opposed to antibody complexes. In a study by Bennett et al., tPA was shown to significantly increase C3a, C4a, and C5a serum levels when given in the setting of myocardial infarction (MI). It has also been shown to activate and increase serum kallikrein, which cleaves high-molecular weight kininogen to bradykinin, a potent vasodilator.

Since bradykinin is broken down by several enzymes, including ACE, degradation is therefore delayed in patients on ACE-I. The alternate pathway for bradykinin degradation in the absence of ACE may also result in formation of des-Arg bradykinin, another similar active metabolite that mimics the effects of bradykinins. The formation of bradykinin through the proteolytic effects of tPA, in combination with the delayed breakdown in patient’s taking an ACE-I, likely plays a significant role in the development of angioedema.

In addition to the direct proteolytic effect of tPA resulting in angioedema, the underlying ischemic insult may also predispose patients to angioedema. As was the case with our patient, angioedema preferentially affects the ipsilateral side of the patient’s deficit. Theories suggest this is due to the lack of autonomic compensatory responses in the setting of ischemic insult. Interestingly, the development of angioedema in relation to the use of recombi-
nant-tPA (eg, alteplase) in the setting of MI has not been as well described and may be related to the effect of central nervous system insult.3

Treatment
Although hemorrhagic complications of tPA therapy for cerebrovascular accident are well known, the risk for angioedema as a complication is less recognized. In most cases, angioedema is transient, and very few patients require aggressive support.3,12 Treatments that have previously been described include antihistamines and steroids.1,11,13 Epinephrine has been reported in one case study as an adjunct treatment of tPA-induced angioedema; however, it was given in combination with steroids and antihistamines.14 Therefore, caution should be taken regarding the use of epinephrine in this setting as there may be a theoretical precipitation of intracranial hypertension or hemorrhage.2

Given the likely significant role of the bradykinin-mediated pathway in tPA-induced angioedema, the true efficacy of these agents is unknown. Our patient had significant laryngeal and lingual involvement, and given the concern for impending airway compromise, fiber optic intubation was performed. The decision to intubate and the technique employed must be carefully considered as a failed airway and need for a surgical airway is a concerning prospect in the setting of fibrinolysis. Successful cricothyroidotomy without significant complications has been described in the setting of streptokinase-induced angioedema when given for MI.15

Conclusion
The use of tPA for the treatment of ischemic stroke has been increasing over the last decade.16,17 Given the high prevalence of ACE-I use in patients who are also at risk for ischemic stroke, physicians administering tPA must be aware of the risk of tPA-associated angioedema. Patients with a known history of angioedema or anaphylaxis to tPA should be counseled on these risks and should not be given this medication, but rather considered for potential endovascular or mechanical clot retrieval therapy if they meet inclusion criteria for its use.

References