

## CASE REPORT

# Angioedema after thrombolysis with tissue plasminogen activator: an airway emergency

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## Abstract

Recombinant tissue plasminogen activator (rtPA), an enzyme that catalyzes the conversion of plasminogen to plasmin resulting in fibrinolysis, is used for the treatment of acute ischemic strokes. The use of this medication is not without complication. One complication of this therapy is angioedema. This complication can be life-threatening if not recognized quickly. However, the potential for the development of angioedema after rtPA administration is not widely known. This is a case of a 60-year-old man who suffered an acute ischemic stroke and was given rtPA. The patient subsequently developed rapidly progressing angioedema leading to airway compromise. The patient was intubated with some difficulty and the angioedema improved and the patient was able to be extubated the next day. Angioedema secondary to administration of rtPA is thought to be bradykinin mediated, but the exact mechanism is unknown. Treatment with FFP, Icatibant, Ecallantide or a C1-esterase inhibitor can be considered.

## INTRODUCTION

Since 1958, thrombolysis has been used to treat acute ischemic strokes [1]. The currently recommended fibrinolytic is recombinant tissue plasminogen activator (rtPA), an enzyme that catalyzes the conversion of plasminogen to plasmin resulting in fibrinolysis [2, 3]. The major complication of rtPA therapy is intracranial hemorrhage, which occurs in 2–9% of patients [2–4]. A lesser-known, but also potentially life-threatening complication is orolingual angioedema, occurring in 1.3–5.1% of patients [5–8]. Patients with concomitant angiotensin converting enzyme (ACE) inhibitor use are at an increased risk of angioedema following rtPA [7–10], but the complication can be seen in patients not on ACE inhibitor therapy [11–13].

Angioedema is caused by fluid moving into interstitial tissues as a result of increased vascular permeability due to inflammatory mediators. There are three major causes of angioedema: mast cell mediated, such as allergic reactions and non-steroidal anti-inflammatory drugs; bradykinin mediated,

such as ACE inhibitors and C1 inhibitor deficiency; and unknown mechanisms, such as idiopathic angioedema and fibrinolytic agents. ACE inhibitors are the leading cause of drug-induced angioedema in the USA with 0.1–0.7% of patients taking the drug developing angioedema [14–16].

Awareness of the possibility of angioedema development following rtPA administration among physicians using this drug is critically important. Although most cases require only supportive care, we present a case of a patient with rapidly progressive angioedema requiring emergent intubation.

## CASE REPORT

A 60-year old man with a history of hypertension and Crohn's disease was at home with his wife when he suddenly developed right sided weakness and right facial droop. The patient's only home medication was an ACE-inhibitor and he had no known allergies to medications. The patient presented to the

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emergency department (ED) ~1 h after the onset of symptoms. The patient was evaluated on arrival and given a National Institutes of Health Stroke Scale (NIHSS) of 8 [17]. He was taken immediately for a noncontrast head computed tomography (CT) scan which showed several old infarcts, but no acute hemorrhage or hypodensities. The patient and his wife were offered treatment with rtPA and chose to go forward with treatment. Within 10 min of initiation of rtPA therapy per National Institute of Neurological Disorders and Stroke (NINDS) protocol, the patient's symptoms resolved completely [2]. Approximately 50 min after rtPA was started, the patient noted significant edema of the right side of his tongue. There was no hemodynamic instability and the patient was not having any difficulty breathing. The patient was immediately evaluated by the emergency physician and neurologist and was given intravenous diphenhydramine (50 mg) and solumedrol (125 mg). Fifteen minutes later, the edema had progressed to involve the entire tongue and the decision was made to intubate the patient for airway protection. The rtPA infusion was stopped with <1 mL remaining to infuse. The patient was given 10 mg etomidate for sedation and awake fiberoptic intubation was attempted. On the first attempt at intubation, the vocal cords were visualized and the entire larynx was normal in appearance. However, the patient was not successfully intubated on this attempt due to secretions and the patient coughing/gagging. The patient's oxygen saturation was beginning to decline, so the initial attempt was aborted. A nasal airway was placed and a jaw thrust/chin lift maneuver was done which immediately improved the patient's oxygen saturation. On a second attempt at intubation, marked edema of the entire larynx was noted and ability to discern to vocal cords was decreased, but the patient was successfully intubated. After successful intubation, the patient was noted to have edema of the right submandibular area and anterior neck down to approximately the level of the cricoid cartilage. The edema quickly progressed to involve the left submandibular area and the left side of the neck. The patient was admitted to the Neurology Intensive Care Unit for monitoring.

While in the ICU, the patient received scheduled doses of diphenhydramine, famotidine and prednisone. The following day, the edema had improved and the patient was evaluated by respiratory therapy and found to have a cuff leak. He was successfully extubated ~15 h after intubation and the angioedema completely resolved after 3 days. The patient remained hospitalized for 6 more days and was discharged to a rehabilitation facility. On discharge, the patient's neurological deficits were unchanged from initial presentation.

## DISCUSSION

This case describes the development of angioedema requiring emergent intubation subsequent to infusion of rtPA. Orolingual angioedema develops after treatment with rtPA in 1.3–5.1% of patients, with most cases beginning hemilingually and within an hour of completion of rtPA infusion [6–13]. The main risk factors for developing angioedema after rtPA administration include ACE-inhibitor use (this patient was taking an ACE inhibitor for his hypertension) (relative risk 13.6) and early signs of infarction in the territory of the middle cerebral artery (relative risk 6.4) [7]. Most cases of post-rtPA angioedema begin hemilingually, usually contralateral to the area of infarct, which may be due to autonomic dysfunction resulting from infarction of the insular cortex [7, 8]. While most cases of rtPA associated angioedema are mild and self-limiting, there is a

risk of rapidly progressing edema that could potentially lead to asphyxia.

Angioedema following rtPA infusion is thought to be bradykinin mediated [18]. RtPA generates plasmin, which cleaves kininogen into bradykinin. Bradykinin is a vasodilator and increases vascular permeability, allowing fluid to move into interstitial tissues. Bradykinin-mediated angioedema is also seen with ACE inhibitors and C1-esterase deficiency [19]. As such, patients who are taking ACE inhibitors are more susceptible to rtPA-induced angioedema due to higher levels of circulating bradykinin.

When angioedema is caused by bradykinin, treatment with antihistamines, corticosteroids and epinephrine is generally ineffective and is not recommended [20]. However, initial and maintenance doses of these medications are often administered. Many cases will resolve with only supportive care. Fresh frozen plasma (FFP), Icatibant (a bradykinin B2 receptor antagonist) and Ecallantide (a recombinant protein that inhibits Kallikrein) have been used in ACE-inhibitor induced angioedema and may be helpful in rtPA associated angioedema given that both processes are bradykinin mediated [21–23]. Because administration of rtPA activates the complement cascade, C1-esterase inhibitor may improve angioedema associated with rtPA administration and allow avoidance of airway maneuvers [24]. Although often unnecessary, intubation should be considered as soon as angioedema develops as symptoms can progress rapidly. Patients with symptoms limited to the lips and anterior tongue generally do not require intubation, but angioedema progressing to the floor of the mouth, palate, hypopharynx or larynx increases the likelihood that patient will require intubation. Awake fiberoptic intubation either nasally or orally is likely the best choice for intubation. Direct laryngoscopy is likely to be difficult due to edema and carries the risk of bleeding secondary to trauma. Supraglottic devices may be temporizing in the event that a definitive airway cannot be secured. A surgical airway is likely to be exceptionally difficult due to excessive bleeding in a patient that just received rtPA.

Although a fairly uncommon occurrence, angioedema is a potentially life-threatening complication of rtPA administration. Physicians who administer rtPA must be aware of this risk, particularly in patients who are also taking an ACE inhibitor. Treatment with FFP, Icatibant, Ecallantide or a C1-esterase inhibitor can be considered and a potential intubation approach should be considered as soon as angioedema is suspected.

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## CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

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## ETHICAL APPROVAL

No ethical approval required.

## CONSENT

Case report sufficiently anonymized.

**GUARANTOR**

Kimberly M. Rathbun.

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