

Angioedema From Recombinant TPA Administration: Case Report and Pathophysiology Review

Alison Foster-Goldman, MD* and Danielle McCarthy, MD, MPH

Angioedema is an uncommon, yet morbid, adverse reaction to recombinant tissue plasminogen activator (rtPA) administration for ischemic stroke. Orolingual edema may preclude completion of rtPA therapy and cause potential airway compromise. Few case reports and case series have examined the incidence of angioedema and anaphylaxis related to this common stroke therapy. We report a case of orolingual edema and bleeding in a patient who received rtPA for acute ischemic stroke who was concurrently on an angiotension-converting enzyme inhibitor and discuss the pathophysiology of this reaction.

Keywords: angioedema, rt-PA adverse reaction, orolingual edema, ACE-inhibitors and rt-PA interaction

INTRODUCTION

The typical concern when administering recombinant tissue plasminogen activator (rtPA) for ischemic stroke is the risk of cerebral hemorrhage. Orolingual angioedema is an uncommon, yet potentially morbid, side effect from rtPA infusion. There have been few case reports and case series examining the incidence of angioedema and anaphylaxis during rtPA administration.^{1–3} The authors of these case series have preliminary evidence that patients concurrently taking an angiotensin-converting enzyme (ACE) inhibitors showed preponderance toward developing orolingual angioedema and anaphylaxis when receiving rtPA. Additionally, some have suggested that there is a relationship between the location of the cerebral infarct and the incidence and location of oral swelling when given rtPA.^{1,4} However, as with many rare conditions, the low incidence of these cases has limited prospective investigation. This case report adds to the existing literature on this topic by describing an uncommon and potentially life-

threatening complication of rtPA administration during a patient's stay in the emergency department (ED).

CASE REPORT

A 75-year-old woman presented to the ED with right-sided facial weakness, dysarthria, and right-sided extremity weakness for 40 minutes. The patient was last seen at her baseline approximately 2 hours before arrival when she was eating lunch with a friend. Her past medical history was significant for hypertension, hyperlipidemia, diabetes, pulmonary embolism, and a prior stroke without any residual deficit. Her current medications included hydrochlorothiazide, lisinopril, atenolol, amlodipine, darifenacin, atorvastatin, and plavix. Physical examination at the time of arrival to the ED revealed decreased motor function of the right lower face, dysarthria without word finding difficulties, right upper and lower extremities with 4 of 5 strength (left upper and lower 5 of 5), mild right pronator drift, and decreased sensation of the right upper and lower face. These deficits correlated with a National Institutes of Health stroke scale score of 9. Pertinent laboratory results included a hemoglobin 14.9 g/dL, platelets 221,000/mL, international normalized ratio 1.0 IU, partial thromboplastin time 24.6 seconds. The computed tomography scan of the brain was significant for a new small area of hypoattenuation extending from

Department of Emergency Medicine, Northwestern University, Chicago, IL.

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*Address for correspondence: Department of Emergency Medicine, Northwestern University, 211 E. Ontario Street, Suite 200, Chicago, IL 60611. E-mail: alif27@gmail.com

the medial aspect of the left postcentral gyrus into the posterior left centrum semiovale. The age of the infarct could not be determined from these imaging findings, but there was no evidence of intracranial bleed.

The patient's presentation and imaging findings were consistent with an acute ischemic stroke. The emergency physicians and consulting neurology stroke service agreed that the patient was a candidate for rtPA treatment. Exactly 0.9 mg/kg of rtPA was administered per protocol (0.1 mg/kg over a minute and 0.8 mg/kg for 1 hour infusion thereafter) without any immediately apparent complications. Approximately 20 minutes after the hour-long rtPA infusion, the patient started to report swelling of her tongue and mild increased work of breathing. On physical exam, she was noted to have angioedema which was more pronounced on the right side of her tongue and lip without any evidence of posterior pharyngeal swelling or intolerance of secretions. She had no evidence of rash, wheeze or decreased aeration on pulmonary exam, and no gastrointestinal distress.

The patient received diphenhydramine and methylprednisolone, and the ED team prepared for a possible fiberoptic intubation if the patient's condition deteriorated. Approximately 10 minutes later, epistaxis was noted with oozing in both nares and posterior pharynx. Pressure was applied intermittently to each nare and suction was provided to posterior pharynx to help clear bloody secretions. Cryoprecipitate, fresh frozen plasma, and packed red blood cells were available at the bedside. Throughout the next 2 hours, the patient's oral swelling markedly improved and her epistaxis slowed. The patient was transferred to the neurologic intensive care unit. A subsequent magnetic resonance imaging/magnetic resonance angiography confirmed a left middle cerebral artery stroke. The patient had an uncomplicated course in the intensive care unit during which her facial weakness and dysarthria improved significantly and she was discharged home with outpatient rehabilitation.

DISCUSSION AND PATHOPHYSIOLOGY REVIEW

The patient described in this case manifested 2 potentially dangerous side effects of rtPA—nasopharyngeal bleeding and angioedema. Fortunately, neither of these complications caused the patient significant morbidity; however, the presence of either 1 of these side effects could impact the airway. Experiencing both bleeding and angioedema concurrently presents a potentially disastrous airway scenario because the presence of blood in the airway limits the use of not only direct

laryngoscopy but also advanced airway rescue techniques often needed with angioedema, such as fiberoptic intubation.

The most feared complication of rtPA administration is intracerebral hemorrhage although other reactions including minor bleeding, anaphylaxis, and orolingual edema have been reported. Although the incidence of intracerebral hemorrhage in patients receiving rtPA (5.8%) is close to the incidence of angioedema or anaphylaxis (range from 1.9% to 5.1%), bleeding complications have received more attention in the literature.^{2,4} According to a prospective study by Hill et al,² 9 of 176 patients treated with intravenous rtPA for acute ischemic stroke were found to have orolingual angioedema [5.1%; 95% confidence interval (CI): 2.3–9.5]. Additionally, patients had a 13.6 relative risk (95% CI: 3.0–62.7) of angioedema when concurrently taking ACE inhibitors and a relative risk of 9.1 (95% CI: 1.4–30.0) when suffering with ischemia in the insula or anterior frontal cortex on initial computed tomography of brain.² Hill et al^{2,4} also reported that the majority of reactions were transient, mild, and contralateral to the ischemic hemisphere. Changes in autonomic control on the ischemic side of the brain is likely responsible for the lateralization of tongue swelling seen in many patients.^{1,4}

Engelter et al¹ conducted an observational study of 120 patients consecutively treated with alteplase infusion for ischemic stroke. Two of the 120 patients had evidence of orolingual edema. Additionally, 1 of 19 patients concurrently taking an ACE inhibitor experienced angioedema.

Most emergency physicians have seen cases of angioedema related to both anaphylaxis and to ACE inhibitors. In contrast to angioedema related to anaphylaxis, the majority of the cases of angioedema from rtPA are not thought to be immunoglobulin mediated. Vasodilation, urticaria, orolingual edema, and/or hypotension seen with rtPA administration are due to anaphylactoid-like responses and not increased expression of IgE antibodies. Alteplase is structurally identical to endogenous tissue plasminogen activator, and single infusion of rtPA does not result in antibody formation.³

Angioedema related to rtPA is thought to be involved in the same pathway that causes spontaneous angioedema related to ACE inhibitor use.⁵ rtPA is a serum protease that hydrolyzes plasminogen to plasmin causing the desired fibrinolytic effect after an ischemic event. This pathway can activate the complement cascade and kinin pathway, which can have a potent vasodilatory effect contributing to angioedema.^{2,5} Normally, bradykinin is partly degraded by kinase enzymes, but in a patient taking an ACE inhibitor, this pathway is blocked leading to increased vasodilation.

The bradykinin cascade also activates the complement cascade causing an increase in C4a and C5a for approximately 90 minutes after administration. C4a and C5a encourage mast cells and basophils to release vasoactive substances contributing to the angioedema.⁵

In the majority of cases reported in the literature, patients who experience orolingual edema, hypotension, or anaphylaxis are responsive to conventional anaphylaxis treatment such as corticosteroids, antihistamines, epinephrine, and cessation of causative agent.

Although the outcome of our case was favorable, it nonetheless demonstrates the need to prepare, recognize, and assess symptoms consistent with angioedema and prepare for airway protection in patients who receive rtPA. Other authors have recommended routinely checking patients 30–60 minutes after rtPA administration for evidence of orolingual edema.² Additionally, when preparing to intubate a patient with rtPA-induced orolingual edema, anticipating

the potential for blood obscuring the airway is also critical.

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