

Angioedema After tPA: What Neurointensivists Should Know

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Abstract

Background Angioedema is an underappreciated and potentially life-threatening complication of intravenous (IV) recombinant tissue plasminogen activator (rt-PA). Patients taking angiotensin converting enzyme (ACE) inhibitors are at increased risk of this rare complication.

Methods Case report.

Results A 74 year-old woman taking lisinopril for hypertension was treated with IV rt-PA for right hemispheric acute ischemic stroke. Shortly after completion of the rt-PA infusion, she developed asymmetric angioedema involving the tongue and left lower lip. No emergent airway intervention was needed. Following treatment with epinephrine, antihistamines, and corticosteroids, the edema resolved within 24 h. The patient made an excellent recovery from the ischemic stroke.

Conclusions Orolingual angioedema can complicate rt-PA treatment of acute stroke and is often ipsilateral to the side of hemiparesis. Neurointensivists should be aware of this possibility, which is increased in patients taking ACE inhibitors. Epinephrine can be given safely in this scenario. Identification of high risk features may help guide decisions regarding early definitive airway management.

Keywords Angioedema · Tissue plasminogen activator · TPA · Thrombolytic therapy · Angiotensin converting enzyme inhibitors · Airway management

Introduction

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) not only improves outcomes in acute ischemic stroke but is a relatively safe drug [1, 2]. Even the most feared complication of IV rt-PA, symptomatic intracranial hemorrhage, occurs in only 2–9% of treated patients [1–3]. An even less frequent—but most life-threatening—complication is orolingual angioedema, which is reported in 1.3–5% of stroke patients treated with IV rt-PA [4, 5]. Though usually it manifests as a transient, self-limited swelling of the lips and tongue, occasionally its severity or rapid progression may necessitate emergent intubation or cricothyrotomy [4, 6]. Patients taking angiotensin converting enzyme (ACE) inhibitors are at increased risk of developing angioedema after rt-PA [5], but it has been reported in patients not taking these medications [7]. Neurointensivists should be aware of this complication after rt-PA and the practical treatment and monitoring implications if it occurs.

Case Report

A 74 year-old woman with a history of hypertension was evaluated in a local emergency department for acute left sided weakness. Her outpatient antihypertensive medications included lisinopril, atenolol, and hydrochlorothiazide. On initial evaluation her blood pressure was 131/71 mmHg and heart rate 65 beats per minute. She was awake and alert

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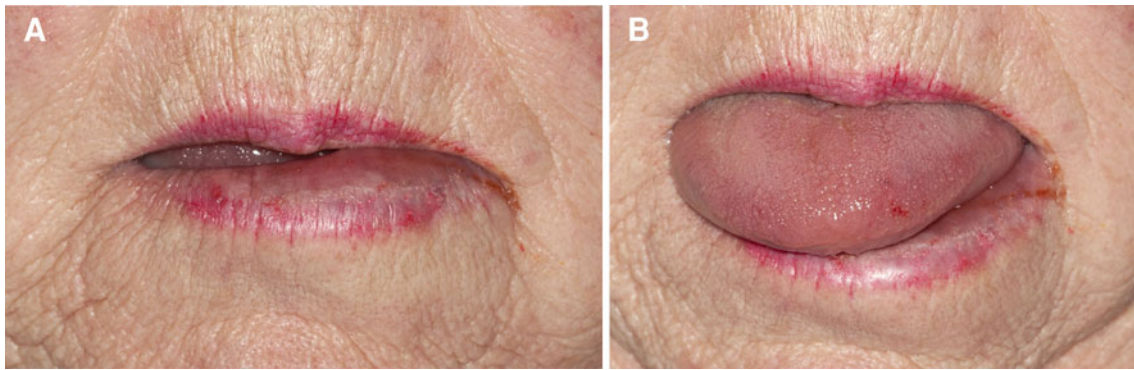


Fig. 1 Photographs taken about 30 min after completion of rt-PA infusion shows angioedema asymmetrically involving the left lower lip (**a**) and the tongue (**b**)

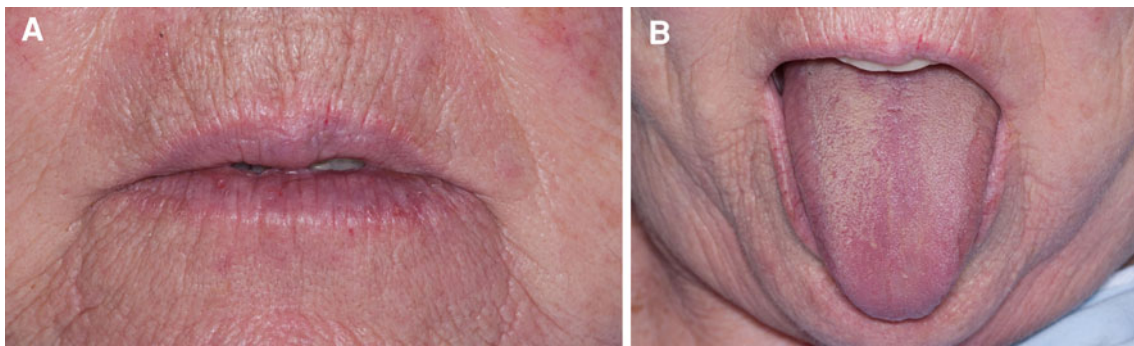


Fig. 2 Photographs taken approximately 20 h after administration of rt-PA shows resolution of angioedema in both the lips (**a**) and tongue (**b**)

with a right gaze preference, left homonymous hemianopia, dense left hemiplegia, and neglect. National Institutes of Health stroke scale (NIHSS) was 17. A noncontrast head computed tomography (CT) scan showed no hemorrhage, no early ischemic changes, and no hyperdense vessel signs. She received 90 mg total of IV rt-PA with 10% given as a bolus approximately 1 h after symptom onset and was transferred to our hospital. Within minutes after completing the rt-PA infusion, she developed left lower lip and tongue swelling and hives on her upper extremities. Examination revealed an edematous tongue without ecchymosis and asymmetric left lower lip edema (Fig. 1). Stridor, wheezing, and drooling were absent. No significant uvular, soft palate, or sublingual involvement was noted. She was treated with 0.3 mg intramuscular epinephrine, 10 mg IV dexamethasone, and 50 mg IV diphenhydramine. The edema began to improve within 10 min of treatment and was resolved within 24 h (Fig. 2). Her neurologic deficits improved dramatically; NIHSS was two within an hour of completing the rt-PA infusion. The serum levels of C1 esterase inhibitor antigen, C3 complement, and C4 complement were normal. Complete blood count with differential, comprehensive metabolic panel, erythrocyte sedimentation rate, and thyroid stimulating hormone assay were all within normal limits. Brain magnetic resonance

imaging showed a right middle cerebral artery territory infarction (Fig. 3).

Discussion

Orolingual angioedema can appear unexpectedly after administration of IV rt-PA for acute stroke. A sudden enlargement of the tongue should invoke this consideration, keeping in mind that a lingual hematoma is another possibility [8]. Angioedema is a rare complication of rt-PA. In a large series of 1,135 patients seen over 2.5 years at 60 centers in Canada, only 1.3% of patients developed angioedema [4]. Angioedema can be rapidly progressive and dangerous necessitating emergent airway management with intubation or cricothyrotomy [6]. However, these interventions are not necessary in most because the majority of patients have self-limited, benign clinical courses [4, 5, 7, 9].

The mechanism by which angioedema is produced by rt-PA is related to increased plasma kinins. IV rt-PA generates plasmin, which is a protease that cleaves bradykinin from high-molecular-weight kininogen. An increase in bradykinin, which has vasodilatory properties and increases vascular permeability, is the primary cause of angioedema associated with rt-PA [10]. Plasmin also activates the

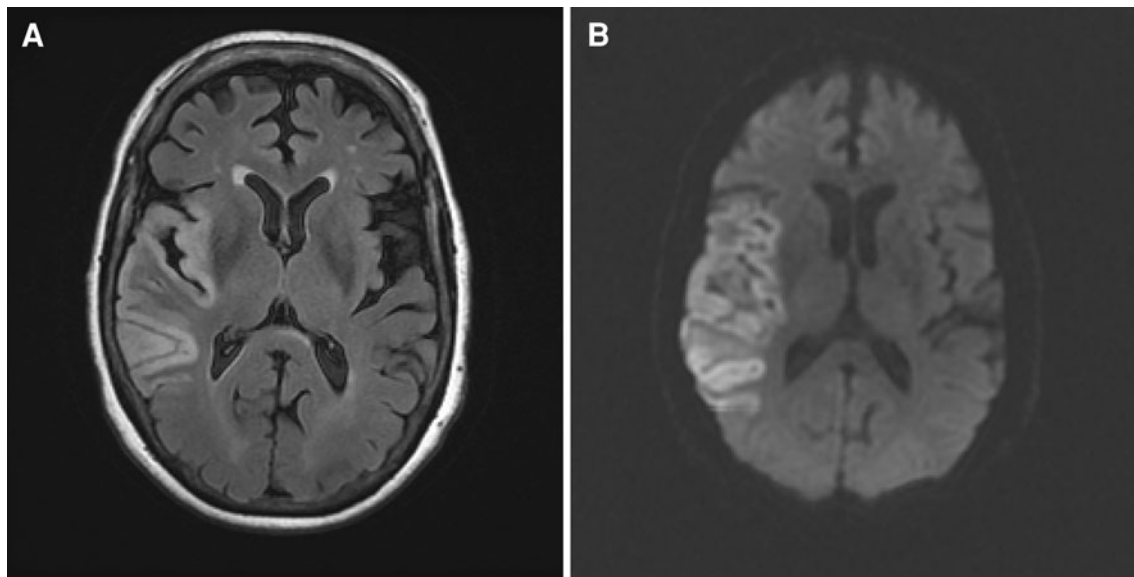


Fig. 3 Axial FLAIR (a) and diffusion weighted (b) brain magnetic resonance imaging shows acute right middle cerebral artery infarction with T2 hyperintensity involving the right insula, frontal, temporal, and parietal lobes

complement cascade by activating C1. This subsequently triggers the activation of C3a and C5a, potent anaphylotoxins that cause mast cell degranulation and histamine release [11]. The concomitant use of ACE inhibitors makes patients more susceptible to angioedema because of baseline higher accumulation of bradykinin levels (ACE normally inactivates bradykinin) [12].

The commonly asymmetric appearance of angioedema is more difficult to explain. Our case, similar to prior reported cases, had involvement of the lips that affected primarily the hemiparetic side [5]. One proposed theory for this is that infarction of the contralateral insular cortex leads to autonomic dysfunction and vasomotor changes in the hemiparetic side [11]. Although our case also had involvement of the insular cortex, this theory may not be entirely sufficient because several cases without insular involvement have been described [5].

The decision of when (and if) to intubate patients with angioedema is difficult, but can be guided by several clinical factors. First, the anatomical location of edema should be considered. In one retrospective review of 228 patients with ACE inhibitor induced angioedema, the location of edema was significantly predictive of the need for intubation. Of 145 patients who had edema involving only the anterior tongue and lips, none required intubation. In contrast, 34% of patients with laryngeal or hypopharyngeal involvement and 18% of patients with involvement of the palate, floor of the mouth, or oropharynx required intubation [12]. Second, the rapidity of edema progression could factor into the decision. Rapid may be arbitrarily defined as progressive swelling in 30 min. Third, early involvement of a skilled intubator for symptomatic patients

or those with edema not limited to the lips and/or anterior tongue is prudent. Fourth, flexible fiberoptic airway inspection with nasotracheal intubation may be needed in those with high risk features: supraglottic edema obscuring the glottic view, drooling, or respiratory distress [13]. If time and resources allow, an awake fiberoptic technique is likely optimal given the ability to both inspect and secure the airway. Direct laryngoscopy in this setting may be highly difficult and carries the risks of failed intubation, airway bleeding due to traumatic laryngoscopy, and labile blood pressures due to stimulation and sedation use.

Hypotension, hypertension, and airway bleeding may pose particular challenges in the acute stroke patient recently treated with rt-PA. Awake fiberoptic intubation will require judicious titration of local anesthetics, relatively cardiostable sedatives, and/or short-acting opioids in order to facilitate intubation while maintaining stable hemodynamics and preserving adequate spontaneous respiratory activity [14–16]. In those recently given rt-PA, use of the nasal approach for fiberoptic intubation requires assessment of attendant epistaxis risk in the context of the likelihood of success with an oral approach. Preparatory thermosoftening of the endotracheal tube and application of topical vasoconstrictors and anesthetics to the nasal mucosa may be useful [17]. In the event of a failed airway, use of a supraglottic airway as a temporizing measure has been described [18]. However, surgical airway management via cricothyrotomy or tracheostomy fortunately is rarely needed and may be quite problematic in a patient with recent rt-PA administration [4, 19].

Medical treatments have varied in reported cases, with some spontaneously resolving with only supportive care [7]

and others receiving antihistamines and corticosteroids [6, 9, 11, 18]. We administered epinephrine (EpiPen Autoinjector) in addition to antihistamines and corticosteroids in our case. Although this has been avoided in other cases for fear of precipitating intracerebral hemorrhage [5], our case demonstrates that this can be safe. If severe angioedema develops while rt-PA is still being given, it would be most prudent to stop the infusion. Maintenance doses of corticosteroids and antihistamines are reasonable to continue for the short-term in patients who need to be intubated or who have extensive edema that does not quickly respond to first doses of medications. In addition, a bradykinin B2 receptor antagonist, icatibant, has been recently approved for the indication of hereditary angioedema and was efficacious in a very small case series of patients with ACE-inhibitor induced angioedema [20]. Give the relatively brief duration of angioedema, extubation timing can be guided by serial examination and flexible laryngoscopy [13].

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