Alteplase-Induced Hemi-Orolingual Angioedema

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A 63-year-old White man with a medical history significant for Bell palsy, non-ST-elevation myocardial infarction, coronary artery disease, hypertension, hyperlipidemia, type 2 diabetes, and hepatitis C virus infection presented to the community hospital emergency department after his wife noted he had right-sided weakness, facial droop, and slurred speech.

He immediately received a computed tomography (CT) scan of the head without contrast, which confirmed suspicions of an acute ischemic stroke. The neurologist on-call was present and, upon confirmation with imaging, prescribed alteplase. Shortly after administration, the patient was found to have hemi-orolingual swelling, increased secretions, and subsequent difficulty breathing. He was given a loading dose of methylprednisolone and an antihistamine (diphenhydramine), which resulted in mild improvement of the angioedema. He was given oxygen via nasal cannula for both supplementary and comfort measures and placed into the critical care unit for close monitoring of his airways.

Overnight, a medical emergency was called on the patient who was noted to have increased difficulty breathing with secretions, and additional methylprednisolone and antihistamine were provided. A chest radiography scan was also performed because of concern for aspiration; however, intubation was withheld as normal oxygen saturations were able to be regained.

The patient had significant neurologic improvement with mild neurologic deficits when the medical team on-call had been notified of the admission. His history was limited because of his inability to articulate given the hemi-orolingual angioedema. On examination, he had muscle strength 5/5 in all 4 extremities, although his right extremities had mild weakness compared with his left extremities. Sensation was intact, reflexes were normal (2+), and his central nervous system was grossly intact.

During his hospital admission, he received an ischemic stroke workup consisting of a 24-hour post-alteplase injection CT head, CT scan of the brain and neck, and brain magnetic resonance imaging (Figure), all of which were consistent with an acute lacunar infarct in the region of the left putamen/posterior limb of the internal capsule. An echocardiogram showed normal ejection fraction, impaired left-ventricular diastolic filling, mild aortic root dilation, and bicuspid aortic valve, with probable moderate to severe aortic stenosis.

With improvement of the angioedema, it was noted that the patient had residual Broca aphasia. He had impaired verbal expression and difficulty writing with his dominant right hand. Despite the neurologic deficits, he had no functional impairments, and so he was cleared by the physical and occupational therapy team for home discharge with home physical therapy. He will continue to be followed by a neurologist and his primary care physician in the outpatient setting.

Discussion

About 5% to 10% of adverse drug reactions are drug allergies, the most common symptoms of which include rash, hives, and raised bumps.[1] Severe reactions may result in angioedema or anaphylaxis. Some medications, such as angiotensin-converting enzyme inhibitors (ACEIs), may be more commonly associated with certain adverse effects, including angioedema.[2] ACEIs, which inhibit the enzyme kininase II, impact the renin-angiotensin-aldosterone pathway and impede the degradation of bradykinin. The increased bradykinin, which is a peptide involved in the vasodilation and permeability of capillaries, results in the extravasation of plasma into submucosal tissue, thus, resulting in the clinical manifestation known as angioedema.[3]

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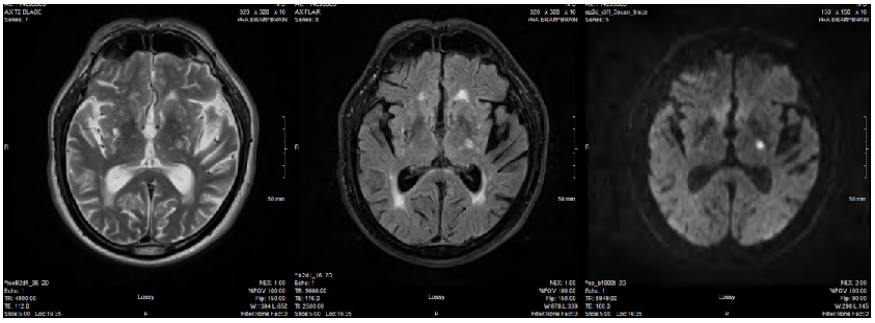

Figure. A brain MRI was consistent with acute lacunar infarct.

Angioedema, in particular hemi-orolingual angioedema, is an uncommon adverse reaction to alteplase use.[3] In the same way that ACEIs are known to contribute to angioedema, alteplase is believed to have a bradykinin-mediated reaction.[4,5] As the activated plasmin from alteplase use breaks fibrin clots in the fibrinolytic pathway, it simultaneously activates factor XII in the coagulation pathway (also known as the plasma kallikrein-kinin system) and, in doing so, leads to the bradykinin-mediated inflammation.[4] Interestingly, hemi-orolingual angioedema has a higher prevalence among patients who use ACEIs or have experienced insular infarcts.[6] This case discusses the management of this particular patient, who presented with an insular stroke and developed hemi-orolingual angioedema after alteplase use.

While angioedema in response to an ACEI occurs in only 0.1% to 0.7% of patients, it is responsible for up to 40% of annual emergency department visits for angioedema.[2] In this case report, our patient had no known prior adverse reactions to his daily use of an ACEI: lisinopril, 10 mg. While hemorrhagic conversion of an ischemic stroke after alteplase use still remains the greatest concern, angioedema is becoming a more recognizable adverse reaction. It has been documented that alteplase can cause angioedema in about 1.3% to 5.0% of cases with factors such as ACEI and insular infarcts contributing to higher percentages.[7] It has been reported that about 10% of patients with insular infarcts[4] and 17% of patients with concurrent ACEI use are susceptible to orolingual angioedema.[3]

There is still much to be learned about the pathophysiology and mechanism of angioedema in the setting of alteplase use. Why does it often present as hemi-orolingual angioedema? What makes patients more susceptible, and what are the predisposing factors? Can repeated alteplase use make patients more susceptible? As there are still many unknowns, the management, too, remains fluid. Corticosteroids and antihistamines remain the staple of treatment; however, there have been reports of concurrent epinephrine use with success.[2] In addition, targeted therapy such as fresh frozen plasma, icatibant, ecallantide, or a C1-esterase inhibitor have also been considered.[2]

Conclusions

Our patient presented with an uncommon adverse reaction of alteplase use for his initial presentation of acute ischemic stroke. His course was managed with a loading dose of solumedrol and an antihistamine and required additional doses when there was concern for airway protection. Fortunately, this patient did not require any invasive intervention; however, this led to the question of standardized care in such cases. As this patient required additional doses of corticosteroids, it may have been prudent to administer epinephrine in the acute setting to combat the allergic reaction. We present this case report in the hopes of better understanding this adverse reaction in the setting of alteplase use and to contribute to existing literature to guide others in the management of their patients.

References

1. Drug allergies. UCLA Health. Accessed March 25, 2022. www.uclahealth.org/allergy/drug-allergies#:~:text=Only%20 5%2D10%20percent%20of%20adverse%20 drug%20reactions%20are%20drug%20 allergies
2. Guyer AC Banerji A. ACE inhibitor-induced angioedema. UpToDate. Updated June 1, 2020. Accessed March 25, 2022. www.uptodate.com/contents/ace-inhibitor-induced-angioedema
3. Kim C, Hladik A. Angioedema secondary to tPA use in acute ischemic stroke patient with hypertension: a case report. Clin Pract Cases Emerg Med.2021;5(2): 159-162. doi.10.5811/cpcem.2021.1.49582
4. Napolitano F, Montuori N. The role of the plasminogen activation system in angioedema: novel insights on the pathogenesis. J Clin Med. 2021;10(3):518. doi.10.3390/jcm10030518
5. Rathbun KM. Angioedema after thrombolysis with tissue plasminogen activator: an airway emergency. Oxford Medical Case Rep. 2019;2019(1):omy112. doi.10.1093/omcr/omy112
6. Myslimi F, Caparros F, Dequatre-Ponchelle N, et al. Orolingual angioedema during or after thrombolysis for cerebral ischemia. Stroke. 2016;47(7):1825-1830. doi.10.1161/STROKEAHA.116.013334
7. Harris D, Harter D. A case report of unilateral orolingual angioedema secondary to alteplase administration. Cureus. 2018;10(6):e2869. doi.10.7759/cureus.2869