Case Letter

Orolingual angioedema during thrombolysis in acute ischemic stroke: A case report

Yao Wang, Hao Sun, Gan-nan Wang, Xiao-min Zhang, Jin-song Zhang

Department of Emergency Medicine, Jiangsu Province Hospital, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China

Corresponding Author: *Jin-song Zhang, Email: zhangjso@njmu.edu.cn*

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Dear editor,

According to the World Health Organization, ischemic heart disease and stroke were the top 2 leading causes of death in 2019.[1] In the past few years, intravenous recombinant tissue-type plasminogen activator (rt-PA) has been a significantly effective treatment to increase survival and reduce mortality in acute ischemic stroke.[2,3] However, as the number of patients who receive alteplase is increasing, a rare but potentially life-threatening adverse complication of alteplase administration is becoming more common—orolingual angioedema (OA).[4-6] OA is acute swelling of the tongue, lips or face and may be life-threatening, as it can increase the risk of upper airway obstruction. Some studies have found that angiotensin-converting enzyme (ACE) inhibitors could increase the risk of OA caused by rt-PA intravenous thrombolysis, which is related to an anaphylactoid reaction.[5-7] However, it has also presented in acute stroke patients not taking these medications. The rt-PA-related OA has rarely been reported in Asian countries, especially in China. Herein, we report a case of an elderly Chinese man who experienced OA after thrombolysis in emergency conditions, which might have been caused both by acute hypersensitivity and anaphylactoid reactions. We suggest that increased attention should be given during or after alteplase therapy.

CASE

A 77-year-old Chinese man with known hypertension and a previous transient ischemic attack presented to the emergency department of our hospital at 2 hours after the acute onset of dysarthria and right-sided weakness. He was only taking irbesartan. On arrival at the hospital, his blood pressure was 120/70 mmHg (1 mmHg=0.133 kPa), heart rate was 92 beats per minute, and the National Institutes of Health Stroke Scale (NIHSS) score was 3. His complete blood count, serum glucose, coagulation parameters, and electrocardiography were normal. A brain computed tomography (CT) scan was negative for any acute hemorrhage. A brain CT angiography indicated no evidence of artery embolism. This patient met the criteria to treat acute ischemic stroke with intravenous alteplase. He was given 0.9 mg/kg alteplase, including a 10% bolus initially, and the remaining drug was infused over 60 minutes. Treatment with intravenous alteplase was initiated at 144 minutes after stroke onset.

At 37 minutes after treatment initiation, the patient presented some discomfort and itching. An urticarial rash was noted in areas of his abdomen and arms. Then, his tongue, lips, and periorbital region developed extensive bilateral swelling (Figures 1 and 2), and his blood pressure dropped to 89/62 mmHg. Alteplase infusion was discontinued after he received a total of 37 mg of alteplase. He was immediately administered intravenous methylprednisolone (40 mg), crystalloid, and oral loratadine (8.8 mg). The patient's blood pressure rose to 103/78 mmHg 15 minutes later. No dyspnea or bronchospasm was observed. We tested his blood and found that his serum levels of IgE were elevated to 103.65 U/mL (normal level ≤60 U/mL) after 6 hours. Magnetic resonance imaging/angiography demonstrated mild intracranial atherosclerosis of the cerebral arteries. His OA and urticarial rash resolved completely within 24 hours (Figures 1 and 2). His neurologic deficits improved, and the NIHSS score dropped to 0. After two weeks, the patient was discharged without sequelae.

DISCUSSION

Apart from intracranial hemorrhage, allergic reactions and other adverse effects of rt-PA have gradually received increasing attention from clinicians. The incidence of rt-PA-related OA has been reported to be 0.89%–7.90% in acute ischemic stroke patients. However, in Asians, the rt-PA-related OA incidence is only 0.89%.[8-10] There is only one large sample size report in China that recruited 1,223 patients at one center over one year and found that 1.14% of patients developed rt-PA-related OA.[7] Most OA is mild and reversible within 24 hours; however, in a few severe cases, it can rapidly progress and become life-threatening. Patients need rapid establishment of emergent airway management with intubation or cricothyrotomy and to be transferred to the ICU.

Currently, the underlying pathophysiology and influential factors for rt-PA-related OA are unclear. Although alteplase is an endogenous protein and relatively safe, it may also provoke immunogenic reactions, which have been found to be anti-alteplase IgE antibodies in one case of rt-PA-related OA. We also found that serum IgE levels in this patient were significantly elevated 6 hours later without ischemic lesions in the insula and frontal lobe. Compared with previous reports of similar cases, the interval between the patient's symptom onset and alteplase infusion was within the typical range of allergic-type I reactions.[11] Although anaphylactic-type reactions to alteplase seem to be extremely rare, we hypothesize that our patient suffered an anaphylactic reaction.

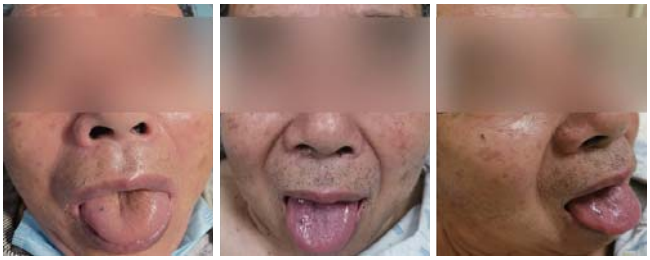

Figure 1. Orolingual angioedema following thrombolysis for ischemic stroke after 37 minutes (left) and the vanishing of the symptoms of angioedema after 24 hours (middle, right).

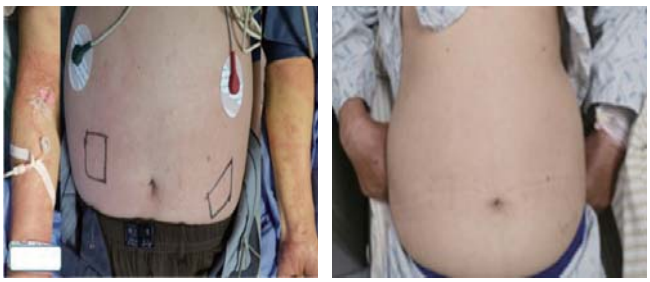

Figure 2. Urticarial rash following thrombolysis for ischemic stroke after 37 minutes (left) and the vanishing after 24 hours (right).

Furthermore, rt-PA-related OA might be an anaphylactoid reaction, which is attributed to the activation of the vasoactive mediators histamine and plasmin of the bradykinin and complement pathways.[11] Concurrent use of an ACE inhibitor and rt-PA is proposed to cause further bradykinin accumulation by blocking plasma kininases, which may increase the risk of OA. In fact, angiotensin receptor blockers (ARBs) could also increase bradykinin levels.[12] According to the empirical clinical evidence, our treatment with antihistamines and corticosteroids is based on the treatment of angioedema and anaphylactic shock. We avoided to use epinephrine, which could increase the risk of intracerebral hemorrhage and a sudden increase in blood pressure.

CONCLUSIONS

OA should be considered a possible life-threatening anaphylactoid reaction after rt-PA treatment despite a little-known adverse event in China. Although the incidence of anaphylactic reactions of rt-PA is extremely rare, the occurrence cannot be ruled out. The prompt and appropriate management of our ischemic stroke patient improved the neurological outcome. Emergency physicians should be aware of the risk that rt-PA-related OA may occur in intravenous thrombolysis patients who use ARBs.

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Conflicts of interests: The authors have no competing interests relevant to the present study.

Contributors: YW wrote the study. All authors read and approved the final manuscript.

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