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Case report

Tenecteplase-Associated Delayed Orolingual Angioedema in ACE inhibitor-Naive Hypertensive Stroke: A Case Report

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Abstract

Tenecteplase is a modified form of tissue plasminogen activator that has been gaining traction as a thrombolytic option in acute ischemic stroke, largely because it can be given as a single bolus and has a more predictable pharmacokinetic behaviour compared to older agents. Orolingual angioedema, though uncommon, is one of the more serious complications that can arise. Most of what has been reported concerns alteplase, and reports on tenecteplase remain few. A 77-year-old female presented with sudden onset right-sided body weakness and slurred speech. She is diagnosed with hypertension that has not been well controlled on amlodipine alone. Her National Institutes of Health Stroke Scale (NIHSS) was 10. Non-contrast CT head ruled out haemorrhage, and she received tenecteplase within the treatment window and remained stable for the first hour. Around ninety minutes post-infusion, however, she developed tongue and lip swelling without any rash or hemodynamic compromise. Tenecteplase-associated orolingual angioedema can occur in the absence of recognised pharmacological risk factors. Given this, keeping a close eye on these patients well after the initial monitoring period seems worthwhile, and any early signs of airway involvement should be acted on without hesitation. This case adds to the limited experience with tenecteplase-associated angioedema and notably occurred in the absence of recognised predisposing factors.

Keywords: Orolingual angioedema, ACE (angiotensin-converting enzyme inhibitors), tenecteplase, thrombolysis, ischemic stroke, bradykinin

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Introduction

Intravenous thrombolysis remains the mainstay of treatment for acute ischemic stroke when given within the appropriate time window. Tenecteplase has been gaining attention as the preferred thrombolytic agent, offering greater fibrin specificity, a longer half-life, and the practical advantage of a single bolus dose. Several trials have supported its non-inferiority to alteplase, and its use in stroke centres has grown accordingly [1,2]. Orolingual angioedema is a recognised though uncommon complication of thrombolytic therapy, reported in roughly 1.3% to 5.1% of patients receiving alteplase for acute ischemic stroke [3,4]. The condition involves rapid-onset non-pitting swelling of the lips, tongue, floor of the mouth, and oropharynx, which can

progress to life-threatening upper airway obstruction if not recognised and treated promptly [7]. Two principal pathophysiological mechanisms have been described: bradykinin-mediated angioedema, in which plasmin activates the kallikrein–kinin cascade, generating excess bradykinin that increases vascular permeability; and mast-cell-mediated (histaminergic) angioedema, which involves immunoglobulin E-dependent degranulation, releasing histamine and other vasoactive mediators, typically accompanied by urticaria and pruritus [8]. The bradykinin pathway is considered the predominant mechanism in thrombolysis-associated angioedema, which explains why the concomitant use of angiotensin-converting enzyme inhibitors, which inhibit bradykinin degradation via kininase II, substantially increases the risk [3,5].

Although the evidence base for tenecteplase-associated angioedema is growing, published case reports remain relatively few compared with the alteplase literature [5,6]. This report describes a case of acute orolingual angioedema following tenecteplase administration in an elderly hypertensive patient who was not receiving any medication known to predispose to angioedema, and in whom the reaction was delayed beyond the immediate observation period. The case adds to the limited literature on this adverse event with tenecteplase and highlights the importance of extended monitoring, particularly as tenecteplase use continues to expand in clinical practice.

Case Presentation

A 77-year-old woman presented to the emergency department after her family noticed she had developed slurred speech and weakness of the right side of her body about an hour before they brought her in. She was known to have hypertension, though it had been difficult to control, and she was on amlodipine 5 mg daily for this. She was not receiving angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dipeptidyl peptidase-4 inhibitors, or non-steroidal anti-inflammatory drugs. She had no known history of allergic reactions, previous angioedema, urticaria, or atopy. She was a non-smoker and had no history of diabetes mellitus, dyslipidemia, or ischemic heart disease.

On examination, she was alert and oriented. Her blood pressure was 180/90 mmHg in the right arm, heart rate was 82 beats per minute and regular, respiratory rate was 18 breaths per minute, oxygen saturation was 97% on room air, and temperature was 36.8°C. Cardiovascular examination revealed normal heart sounds with no murmurs; the chest was clear to auscultation bilaterally. Abdominal examination was unremarkable. Neurological examination demonstrated right-sided hemiplegia with muscle power of 0/5 in the right upper and lower limbs, left upper motor neuron facial weakness, dysarthria, and right-sided sensory inattention. The National Institutes of Health Stroke Scale (NIHSS) score was 10. Examination of the oropharynx at the time of admission was normal, with no evidence of swelling or obstruction.

An urgent non-contrast computed tomography scan of the brain showed no evidence of intracranial haemorrhage or established infarction. Routine blood investigations, including full blood count, renal function, hepatic function, coagulation profile, and random blood glucose, were within normal limits. The patient met the criteria for intravenous thrombolysis and received tenecteplase (0.25 mg/kg as a single intravenous bolus) 2.5 hours after the onset of neurological symptoms (Table 1). No other medications were administered between the tenecteplase bolus and the onset of angioedema.

Table 1: Timeline of events

Time	Event
T=0 (approximately 10:00)	Onset of slurred speech and right-sided weakness
T + 1 hour	Arrival at emergency department;
T + 1.5 hours	Non-contrast CT brain: no hemorrhage or infarction
T + 2.5 hours	Intravenous tenecteplase administered
T + 2.5 to T + 4 h	Post-thrombolysis observation: uneventful; no new medications given
T + 4 hours (90 min post-dose)	Acute onset of tongue and lip swelling, worsening dysarthria, dyspnea
T + 4 hours (immediately)	Treatment initiated: oxygen, adrenaline, dexamethasone, chlorpheniramine
T + 4.5 hours	Transfer to intensive care unit for monitoring
T + 10 hours (6 h post-onset)	Complete resolution of angioedema
Next day	No recurrence; transferred to high-dependency unit

The initial ninety-minute post-thrombolysis observation period was uneventful. Subsequently, the patient developed sudden swelling of the tongue and lips, accompanied by worsening dysarthria and new-onset dyspnea. Notably, there was no stridor, urticaria, pruritus, cutaneous rash, hypotension, tachycardia, or

bronchospasm. Oxygen saturation remained stable at 96% on room air.

A clinical diagnosis of acute orolingual angioedema secondary to tenecteplase was made. The patient was immediately managed with high-flow supplemental oxygen, repeated nebulised with adrenaline, and intravenous dexamethasone (16 mg) and chlorpheniramine (10 mg). An airway management trolley was positioned at the bedside, and the anaesthesia team was alerted. The airway remained patent throughout, and invasive airway intervention was not required. She was transferred to the intensive care unit for close cardiorespiratory monitoring.

The angioedema gradually subsided and had resolved completely within six hours of onset. There were no recurrences during the remainder of the hospital admission.

Complement studies and C1 esterase inhibitor levels were measured to exclude hereditary and acquired forms of angioedema and were within normal limits (Table 2). Routine haematological and biochemical investigations were unremarkable (Table 3).

Table 2: Complement and C1 esterase inhibitor levels

Investigation	Result	Reference range
C1 esterase inhibitor	32	23-41 mg/dL
Complement C3	168	83-177 mg/dL
Complement C4	24	12-36 mg/dL

Table 3: Basic investigation with reference range

Investigation	Result	Reference Range
Hemoglobin	13.0	11.5-15.5 g/dL
Total leucocyte count	7.0	4.0-11.0 × 10^9/L
Platelets	250	150-400 × 10^9/L
Sodium	140	135-145 mmol/L
Potassium	4.0	3.5-5.0 mmol/L
Creatinine	70	46-92 µmol/L
Fasting glucose	5.0	3.9-5.6 mmol/L
HbA1c	38	< 48 mmol/mol (< 6.5%)
Alanine transaminase	28	7-56 U/L
Aspartate transaminase	25	10-40 U/L
Prothrombin time	13	11-14 seconds
INR	1.0	0.8-1.2
APTT	32	26-38 seconds
Total cholesterol	4.5	< 5.0 mmol/L
LDL cholesterol	2.5	< 3.0 mmol/L
HDL cholesterol	1.5	> 1.2 mmol/L
Triglycerides (fasting)	1.2	< 1.7 mmol/L
C-reactive protein	< 5	< 5 mg/L
Erythrocyte sedimentation rate	< 20	< (Age+10)/2 mm/hour

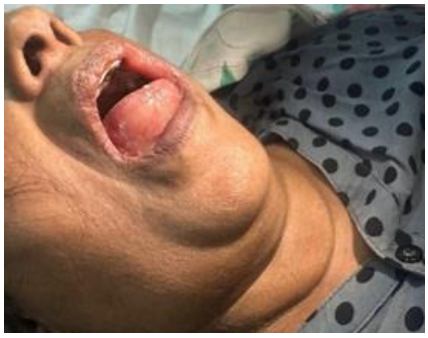

Figure 1: Orolingual angioedema involving the tongue and lips observed approximately 90 minutes after intravenous tenecteplase administration for acute ischemic stroke

Figure 2: Complete resolution of orolingual angioedema approximately two hours after initiation of medical management with nebulised adrenaline, corticosteroid, and antihistamine

The patient was monitored in the intensive care unit, and as the angioedema completely settled, she was transferred to the high-dependency unit in the ward the following day. The next day, she underwent a repeat NCCT brain, and after excluding haemorrhage, she was started on aspirin 300 mg with a high-intensity statin as secondary stroke prevention therapy. She was discharged the next day, clearly documenting her anaphylaxis.

Discussion

The angioedema seen in this case is best explained through the bradykinin pathway. Plasmin generated during thrombolysis cleaves high-molecular-weight kininogen, releasing bradykinin, which binds to vascular endothelial receptors and causes localised submucosal swelling [8]. The orolingual region is particularly vulnerable given its high density of bradykinin receptors [8]. The absence of urticaria, rash, or hemodynamic instability in this patient argues against a histamine-mediated allergic reaction, and this distinction matters clinically, as bradykinin-mediated angioedema responds poorly to antihistamines alone and may require agents such as icatibant or C1 esterase inhibitor concentrate in refractory cases [9].

Most published experience with thrombolysis-associated angioedema involves alteplase, with reported incidence ranging from 1.3% to 5.1%, and many events occurring within the first 60 minutes [3,4]. Reports involving tenecteplase remain few [5,6]. Newman and colleagues described a similar case of delayed orolingual swelling following tenecteplase, and the present case follows the same pattern, with onset occurring after an initially uneventful post-infusion period [5]. Since the underlying mechanism is a consequence of fibrinolysis itself rather than specific to any one agent, this risk should be assumed to exist with all thrombolytics [8].

Notably, this patient had no recognised predisposing factors. She was not on ACE inhibitors, angiotensin receptor blockers, or gliptins, all of which impair bradykinin degradation [3,8]. This reinforces that the thrombolytic agent alone is sufficient to trigger the reaction, and the absence should not falsely reassure clinicians of high-risk medications. The delayed onset in this case also raises questions about current monitoring practices. Usually, standard protocols focus on observation of parameters following thrombolysis for the first 60 minutes, but this and similar cases [5-7] suggest that observation should extend to at least two hours, to detect delayed expected or rare complications, including severe anaphylaxis with airway equipment readily available and staff alert to early warning signs such as tongue swelling, drooling, or worsening dysarthria.

Conclusion

Orolingual angioedema is an uncommon but potentially life-threatening complication of thrombolysis with tenecteplase in the setting of acute ischemic stroke [5,6]. This case demonstrates that angioedema can occur in the absence of recognised pharmacological risk factors and beyond the immediate post-infusion observation window. As the use of tenecteplase in stroke care continues to expand [1,2], clinicians should remain vigilant for this adverse event during an extended post-treatment monitoring period and have appropriate airway management resources readily available. Early recognition and prompt treatment remain the most important determinants of outcome.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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