Unilateral Tongue Angioedema Induced by Angiotensin Converting Enzyme Inhibitor: A Case Report

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ABSTRACT

Tongue angioedema is a well-recognized side effect of angiotensin-converting enzyme inhibitor particularly during the first few months of initiation. Unilateral tongue involvement is rarely encountered. We report the case of a 78-year-old woman who presented with unilateral right side tongue angioedema, which occurred after two years of lisinopril use. She did not have any respiratory distress and her symptoms had completely resolved after twelve hours of observation. Lisinopril was discontinued and no recurrence of angioedema was reported.

Worldwide, angiotensin-converting enzyme (ACE) inhibitor is a widely used class of drugs for treating hypertension and heart failure. Although its safety is well-recognized, serious and life-threatening side effects such as angioedema rarely occur. Angioedema due to ACE-inhibitor is mediated by the accumulation of bradykinins and is usually slower in onset than histamine-mediated angioedema. Swelling may involve different body organs, but the tongue is particularly vulnerable.[1] Around 0.7% of patients who commence ACE-inhibitors develop angioedema.[2] Moreover, the majority of cases occur within the first three months of its initiation.[3] Unilateral tongue angioedema is a rare side effect of ACE-inhibitors and few case reports have been published to document its occurrence.

CASE REPORT

A 78-year-old woman, who was known to have hypertension, hyperlipidemia, ischemic heart disease, bilateral knee osteoarthritis, and urinary incontinence presented to the emergency department with a four-hour history of unilateral right side tongue swelling for the first time. She described it as painless tongue heaviness associated with an inability to swallow solid food initially, but this swallowing difficulty then progressed to include liquids. She reported mild dysarthria but denied any history of facial asymmetry or limb weakness. She did not notice any itching, skin rash, difficulty in breathing, stridor, wheezing, hoarseness of voice, rhinorrhea, difficulty in controlling oral secretions, or fever. She denied having skin contact with any products such as soap and facial creams. The patient denied history of ingestion of any new type of food and she was not known to have any history of allergy. There was no history of tongue trauma or any dental problems.

She was taking the following medications regularly: amlodipine 10 mg, rosuvastatin 20 mg, aspirin 100 mg, lisinopril 5 mg, calcium with vitamin D, bisoprolol 5 mg, diclofenac sodium, and a multivitamin. She has been taking lisinopril 5 mg once a day for the last two years without any side effects.

On examination, the patient looked comfortable and had no respiratory distress. She had no stridor. Her blood pressure was 160/96 mmHg, pulse rate 87 beats per minute, and oxygen saturation of 99%

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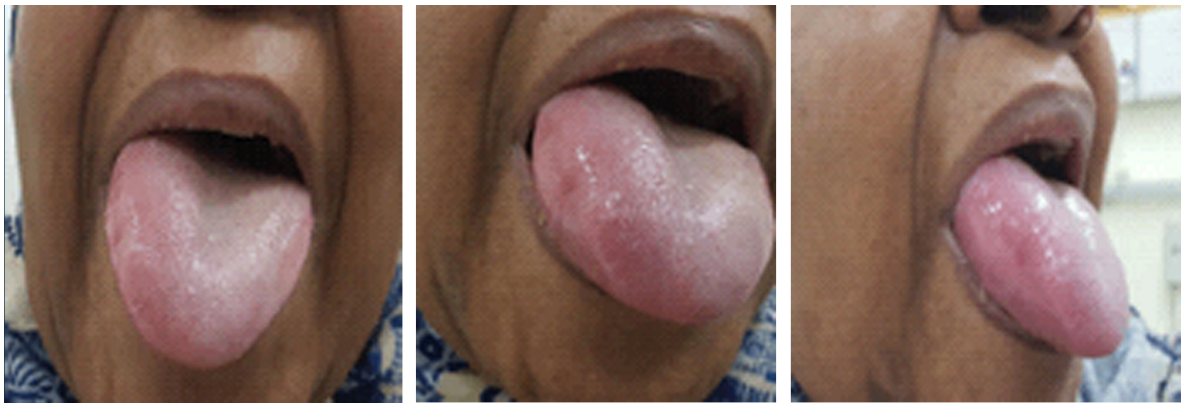

Figure 1: The patient's tongue showed unilateral tongue swelling.

in room air. Tongue examination revealed a soft and non-tender enlargement of the right side only with no involvement of the left side, which looked normal [Figure 1]. There was no mandibular tenderness or cervical lymphadenopathy. The rest of the physical examination was unremarkable. Routine blood tests were within normal limits. Her white blood cell count was 6.3×10^9/L.

The patient was given chlorpheniramine maleate 10 mg intramuscularly, and she was kept for observation for 12 hours. Airway evaluation was not required as she was not in respiratory distress. During the observation period, she remained stable and had a complete resolution of her symptoms after about 12 hours. Lisinopril was stopped and was replaced with indapamide. She reported no recurrence of her symptoms when she was seen two-months later during a follow-up visit.

DISCUSSION

While ACE-inhibitors are safe and well-tolerated by the majority of patients, angioedema is a rare side effect that requires early detection and timely management. It occurs due to the effects of ACE-inhibitors on the renin-angiotensin-aldosterone system, which results in increased levels of angiotensin I and bradykinin. Bradykinin is considered the main contributor to the development of angioedema by causing vasodilation and swelling.[4]

The first task for the clinician in this situation is to distinguish between histamine- and bradykinin-mediated angioedema. The main distinguishing features which make bradykinin-mediated angioedema more likely are the slower onset, absence of urticaria, and lack of history of a known or suspected trigger for allergy.[5] Other causes of angioedema, such as pollen-food allergy syndrome, infection, and hereditary and acquired C1 inhibitor deficiency should also be considered.

Pollen-food allergy syndrome is a type I immunoglobulin E mediated cross-reaction to a plant-derived antigen causing pruritus in the mouth. People with allergic rhinitis or asthma are more prone to pollen-food allergy syndrome.[6] Our patient had no history of allergic rhinitis or asthma and she denied any raw fruit or vegetable ingestion before her presentation.

Infection is unlikely in this patient as she had no fever. Moreover, a white blood cell count was within normal limits.

The diagnosis of ACE-inhibitor angioedema is usually made based on the clinical presentation. The typical symptoms are angioedema localized to the face, erythema with no pruritus which lasts for 24–72 hours, followed by spontaneous remission.[5]

Since the patient did not have any previous episodes of angioedema and had no family history of hereditary angioedema, further laboratory tests such as C1 esterase inhibitor and C4 levels were not considered necessary.

Unilateral tongue involvement is rare and only a few case reports have been published to document this condition. A summary of previous case reports is shown in Table 1.[7–12] Of note, all cases occurred in people over 60 years old. Three out of seven cases were due to perindopril, and two were caused by lisinopril. The duration of ACE-inhibitor use until unilateral tongue edema developed ranged from two days to 10 years. Angioedema resolved within two days in the majority of cases.

Table 1: A summary of previously published case reports of unilateral tongue angioedema.

Author and year of publication	Patient's age, years and sex	Type of ACE-inhibitor and duration of use	Other medications	Treatment received for angioedema	Time to resolution of symptoms	Follow-up
Amey et al.[7] 2013	76, M	Perindopril, 10 years.	Clopidogrel, aspirin, pravastatin, and diclofenac for a rotator cuff injury. Clopidogrel and atorvastatin.	Intravenous steroids and antihistamine. Intubation. Perindopril was stopped. Intubation. Perindopril was stopped.	48 hours	No recurrence of symptoms.
	78, M	Perindopril, seven years.			24 hours	No recurrence of symptoms.
Mlynarek et al.[8] 2003	73, F	Enalapril, three years.	Nifedipine, lorazepam, clonidine, levothyroxine, aspirin, and hydrochlorothiazide.	Methylprednisolone, diphenhydramine, and penicillin. Enalapril was not stopped initially.	Overnight	Symptoms recurred after three weeks. Then enalapril was stopped. No further recurrence at one, three, and 12 months follow-up.
Chan et al.[9] 2005	68, F	Benazepril, several months.	Humulin 70/30, norvasc, and chlorthalidone.	Intravenous benadryl, solumedrol, and famotidine.	Within 24 hours	No recurrence of symptoms at two month follow-up.
Ee et al.[10] 2010	71, M	Perindopril, three months.	Pantoprazole (40 mg once daily), one dose of intravenous ceftriaxone (2 g), and pre-operative prophylaxis (evacuation of subdural hematoma).	Intravenous dexamethasone.	48 hours	No recurrence of symptoms at two weeks follow-up.
Kuhlen et al.[11] 2012	62, M	Lisinopril, recently.	Other medications were not mentioned. He had a kidney transplant.	Diphenhydramine, famotidine, and solu-medrol. Intubation.	48 hours	Not mentioned.
Leung et al.[12] 2012	64, F	Lisinopril, two days.	Mammalian target of rapamycin inhibitor for the liver transplant.	Intravenous steroids and antihistamine. Lisinopril was stopped.	Within hours	No recurrence of symptoms at four weeks follow-up.

ACE: angiotensin-converting enzyme; M: male; F: female.

The reason for unilateral tongue edema is not well understood, but it could be the initial sign of bilateral and progressive angioedema.[12]

Although ACE-inhibitor angioedema is triggered by excessive bradykinin activity rather than histamine release, corticosteroid and antihistamine medications are widely used as part of the management of such cases. Table 1 shows that the majority of patients who were reported in previous case reports had indeed received corticosteroids and anti-histamines. The mainstay treatment of ACE-inhibitor angioedema is securing the upper airway and preparing for mechanical intervention whenever it is required. In addition, it is essential to discontinue the offending drug and substitute it with another medication from a different class. Patients should be informed that angioedema may occur or recur several weeks after cessation of ACE-inhibitor therapy. Although not yet approved by the US Food and Drug Administration, fresh frozen plasma (FFP) has been effectively used in some patients. FFP contains ACE and some patients reported marked improvement after administration of two units.[5,13] Moreover, research is still ongoing

to determine the usefulness of targeted treatment such as C1-inhibitor replacement products, which are currently used for the management of acute hereditary angioedema, in this type of angioedema.[5] Follow-up of these patients is important to ensure the absence of recurrence of angioedema.

Several risk factors associated with the development of ACE-inhibitor angioedema have been identified. These are black race, history of drug rash, age over 65 years, seasonal allergies, and concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs).[14,15]

The concomitant use of NSAIDs in our patient might be the precipitant for her angioedema.

While the incidence of angiotensin receptor blocker (ARB) angioedema is much less than that induced by ACE-inhibitor therapy, cross-reactivity might occur in less than 10%.[13] Thus, initiating ARB in patients who experienced ACE-inhibitor angioedema should be cautiously determined based on benefit-risk assessment.

CONCLUSION

Although ACE-inhibitor induced angioedema is a well-recognized side effect of ACE-inhibitors, unilateral tongue involvement is rare. This condition should be considered as one of the differential diagnosis regardless of the duration of therapy with ACE-inhibitors. Once the diagnosis of ACE-inhibitor angioedema is made, great attention should be given to secure the upper airway, followed by discontinuation of the offending drug, and initiation of a suitable alternative medication from a different class.

Disclosure
The authors declared no conflicts of interest.

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