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EPISODIC MACROGLOSSIA AS THE SOLE MANIFESTATION OF ANGIOTENSIN-CONVERTING ENZYME INHIBITOR-INDUCED ANGIOEDEMA

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We describe a patient who had recurrent life-threatening episodes of isolated macroglossia due to the use of an angiotensin-converting enzyme (ACE) inhibitor. No associated facial, labial, pharyngeal, or laryngeal edema was noted. Aggressive treatment with epinephrine, steroids, and antihistamines resulted in rapid resolution of the tongue swelling and respiratory distress. Recurrent isolated angioedema of the tongue is an extremely rare variant of ACE inhibitor-related angioneurotic edema. The widespread use of ACE inhibitors mandates a special awareness by physicians of this potentially life-threatening yet treatable side effect.

KEY WORDS — angioedema, angiotensin-converting enzyme inhibitor, macroglossia, tongue.

INTRODUCTION

Angioedema is a well-described complication of angiotensin-converting enzyme (ACE) inhibitor therapy. Isolated angioedema of the tongue is an extremely rare variant of this side effect, and can result in lethal upper airway obstruction unless promptly diagnosed and treated. We describe a patient who suffered recurrent, near-fatal, isolated macroglossia of the tongue secondary to the use of an ACE inhibitor, with emphasis on the diagnostic and treatment approaches.

CASE REPORT

A 71-year-old man was hospitalized for severe swelling of the tongue that caused acute obstruction of the upper respiratory tract. His past medical history was significant for long-standing non-insulin-dependent diabetes mellitus that was treated with metformin hydrochloride and sulfonyleurea and for essential hypertension that had been tightly controlled over the previous 2 years with the ACE inhibitor enalapril.

The patient denied the use of all other medications, including prescription drugs, over-the-counter drugs, and natural and herbal medications, as well as the abuse of drugs or alcohol. He presented with no risk factors for the human immunodeficiency virus and had no known food or drug allergies.

Upon further questioning, the patient noted several prior acute episodes of isolated tongue enlargement, all of which occurred during the 2 years of enalapril treatment. None of the episodes featured any facial

swelling other than that of the tongue, although some did cause mild respiratory distress. The episodes resolved spontaneously without requiring medical help. There was no known familial history of angioneurotic edema.

Physical examination revealed a severely dyspneic patient with a huge, edematous tongue occupying the entire oral cavity and causing acute severe obstruction of the upper airway. The remainder of the physical examination findings were unremarkable. The absence of a skin rash was noted, including lack of any additional form of swelling or edema of the face, lips, neck, or extremities, other than the tongue. Routine laboratory tests, including a complete blood count, kidney and liver function tests, and chest radiography yielded normal findings.

The patient was immediately transferred to the operating room and was nasally intubated under direct fiberoptic vision. Laryngoscopy, performed by an otolaryngologist, revealed a severely edematous tongue with no evidence of pharyngeal, epiglottic, or laryngeal edema. The patient was transferred to a respiratory intensive care unit and was treated with repeated subcutaneous doses of epinephrine and intravenous administration of hydrocortisone and antihistamines. After 3 days of treatment, the patient's tongue began to return to its normal size; he was gradually weaned off mechanical ventilation and was successfully extubated.

Further workup, including measurement of C1 esterase inhibitor and early components of the comple-

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ment system, yielded unremarkable findings. The recurrent episodes of isolated macroglossia were concluded to be a rare, unique, life-threatening variant of ACE inhibitor-induced angioedema.

Upon discharge, the patient was instructed to avoid the use of any member of the ACE inhibitor or angiotensin receptor II antagonist family of medications. Over 2 years of follow-up, the patient was free of any recurrent episodes of angioedema or tongue swelling.

DISCUSSION

Angiotensin-converting enzyme inhibitors are a frequent cause of angioedema, causing up to 25% of all angioedema cases seen in the emergency room.¹ Most cases present within weeks of ACE inhibitor onset, but some develop even years after institution of treatment.

Cases of ACE inhibitor-induced angioedema are clinically indistinguishable from hypersensitivity-related angioedema, differing only with absence of an allergy history and by the increased average age of the patients. Diagnosis is often delayed by physicians' erroneous attribution of the angioedema to other causes. After the first episode of angioedema, continued treatment with an ACE inhibitor leads to a substantially increased risk for recurrence of angioedema.²

Traditionally, the accepted mechanism of angioedema secondary to ACE inhibitors was based upon its inhibition of the breakdown of bradykinin, a potent vasodilator. Several reports in recent years have linked the use of angiotensin II receptor antagonists to the development of angioedema.³ Therefore, other kinin-independent mechanisms are probably involved in the formation of ACE inhibitor-induced angioedema.

Treatment is aimed at the maintenance of a patent upper airway. Repeated doses of subcutaneous epinephrine and intravenous corticosteroids and antihistamines are administered to alleviate tissue swelling,

although their efficacy has never been proven. Inhalation of nebulized racemic epinephrine may provide an added therapeutic benefit, but some patients require airway protection in the form of intubation, cricothyroidotomy, or tracheotomy. Because many patients who use ACE inhibitors have hypertension, ischemic heart disease, or congestive heart failure, close monitoring is required in order to avoid potentially life-threatening epinephrine-related side effects.

Ten previous cases of patients who suffered massive, life-threatening tongue swelling during treatment with an ACE inhibitor have been published in the English-language literature.⁴⁻⁶ One patient, similar to ours, had recurrent episodes of isolated tongue swelling. Six patients had only a single episode of massive tongue swelling during their prolonged use of the medication, in contrast to our patient, who had recurrent episodes. Three patients had recurrent episodes of massive tongue swelling, but it is unclear whether they had isolated tongue swelling or angioedema of other facial structures, such as the pharynx and larynx.

The recurrent episodes of macroglossia observed in the patient we present are an extremely rare manifestation of long-term ACE inhibitor use. In the one life-threatening episode that necessitated our urgent medical intervention, it was demonstrated both clinically and endoscopically that the tongue was the only edematous organ, and that its enormous size was, in fact, responsible for the patient's severe upper airway obstruction.

This variant of ACE inhibitor-induced angioedema appears to be a rare clinical phenomenon, but is important because of the common use of ACE inhibitors and angiotensin II receptor antagonists by the general public. Physicians must be aware that an acutely enlarged tongue may represent an episode of ACE inhibitor-induced angioedema. Otherwise, they might erroneously attribute the enlarged tongue to other causes, possibly endangering patients' health.

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