CASE REPORT

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Asphyxia Due to Angiotensin Converting Enzyme (ACE) Inhibitor Mediated Angioedema of the Tongue During the Treatment of Hypertensive Heart Disease

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ABSTRACT: This report describes seven deaths caused by angioedema of the tongue related to angiotensin converting enzyme (ACE) inhibitors. These seven cases were received in our office between 1998 and 2000. In that time frame we performed approximately 2000 autopsies. The cases involved African-American men and women, aged 51 to 65 years, all of whom had been prescribed an ACE inhibitor for the treatment of hypertensive heart disease. In each case, the external examination revealed markedly swollen tongues. The autopsies confirmed massive tongue swelling due to angioedema, and some patients also had swelling of the lips, pharynx, and larynx. Toxicologic analyses on postmortem blood samples were negative for ethanol and drugs of abuse. Although oral and pharyngeal swelling related to angioedema is well known in the clinical literature, its fatal potential has rarely been described.

KEYWORDS: forensic science, angiotensin converting enzyme inhibitor, ACE inhibitor, airway obstruction

Angioedema of the tongue and oropharyngeal region can result in asphyxia as a consequence of swelling with resultant airway obstruction, and is a serious, potentially life-threatening complication of angiotensin converting enzyme (ACE) inhibitor therapy. ACE inhibitors (e.g., captopril, lisinopril, enalapril, etc.) are commonly prescribed as antihypertensive agents. Angioedema as a complication of therapy is well described in the clinical medical literature, and a warning is often prominently displayed in advertisements for these medications. The authors are aware of only two case reports of fatalities of this nature in the literature (1,2). We believe that the occurrence of this potentially lethal side effect may be underestimated because such patients are rarely referred to a coroner's or medical examiner's office. (Death is usually attributed to the underlying hypertensive heart disease and/or congestive heart failure.) Unless police, emergency medical personnel, or a death investigator at the scene notes the tongue swelling, these deaths may not be recognized as legitimate coroner/medical examiner cases and jurisdiction may be waived. In this report, we describe six cases of fatal airway obstruction caused by angioedema related to ACE inhibitor therapy and discuss our diagnostic approach to this condition.

Case 1

A 56-year-old, 66.5 in., 351 lb African-American woman was found collapsed on the floor of her residence by a neighbor. She was known to have essential hypertension (HTN), congestive heart failure (CHF), insulin dependent diabetes mellitus (IDDM), chronic obstructive pulmonary disease (COPD), and schizophrenia. Medications prescribed for her included monopril (for a five month period), insulin, furosemide, potassium, respirdal, and levaquin. No funeral arrangements had been made; therefore the body was brought to the coroner's office for storage. Our office policy specifies that at least an external examination be performed on all decedents received for storage. An autopsy was prompted by the observation of massive tongue swelling. Further investigation revealed a history of allergies to penicillin, aspirin, and ibuprofen (none of these agents were found at the scene). The autopsy confirmed a massively edematous tongue that tightly filled the oral cavity. The postmortem examination confirmed cardiomegaly (600 g), COPD, nephrosclerosis, and peptic ulcer disease. Microscopic examination of the tongue showed interstitial and submucosal edema with scattered scanty mixed submucosal inflammatory cells. Serum tryptase was mildly elevated at 16.8 ng/mL (reference range $<$ 11.5 ng/mL). Toxicologic screening tests for alcohol, ketones, and drugs of abuse were negative. The cause of death was determined to be airway obstruction due to angioedema of the tongue due to monopril therapy for treatment of hypertensive heart disease. Obesity was noted as a contributory cause. The manner was considered natural.

Case 2

A 51-year-old, 65 in., 147 lb African-American woman was found by her daughter collapsed alongside her bed. She was known to have HTN, CHF, IDDM, and hypothyroidism, with no history of allergies. Medications included benazepril (for the past 21

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months), furosemide, insulin, potassium, and Synthroid. No funeral arrangements had been made and the body was brought to the coroner's office for storage. Our external examination revealed massive swelling of the tongue and lips (Fig. 1) which prompted performance of an autopsy. The autopsy confirmed a massively swollen tongue tightly filling the oral cavity, and mild epiglottic edema. Cardiomegaly (heart weight 440 g, LV wall 1.5 cm) with left ventricular dilatation and mild nephrosclerosis was confirmed. The thyroid was unremarkable. Microscopic examination of the tongue and epiglottis showed interstitial edema and dilated lymphatic channels with no appreciable inflammation. Other microscopic sections were unremarkable. Blood screens for alcohols and drugs of abuse were negative. Vitreous acetone was 31 mg%, vitreous glucose was 1426 mg/dL, and vitreous electrolytes showed a uremic pattern (urea nitrogen 60 mg/dL and creatinine 3.7 mg/dL). Serum tryptase was not evaluated. The cause of death was determined to be diabetic ketoacidosis, with angioedema of the lips and tongue due to benazepril therapy for hypertensive heart disease noted as contributory. The manner was considered natural.

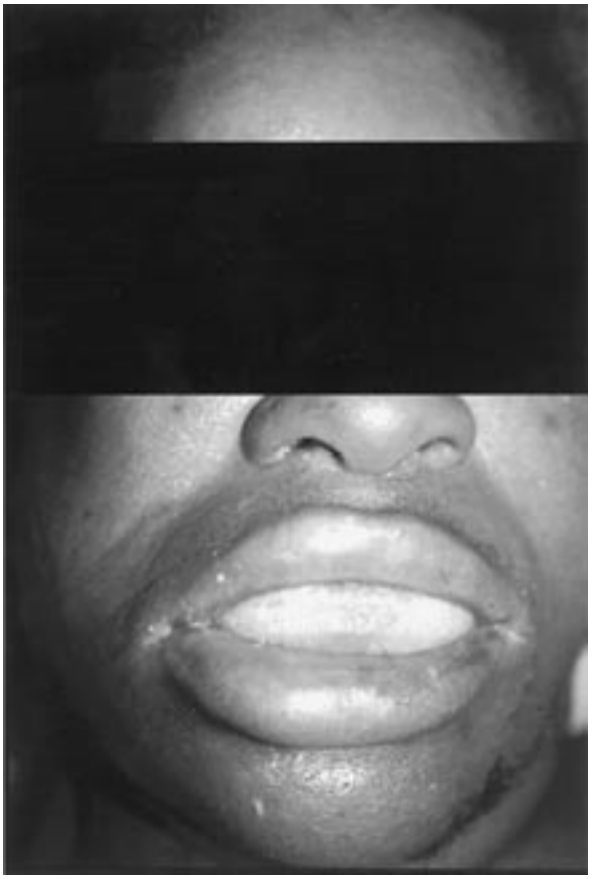

FIG. 1—*Angioedema of tongue.*

Case 3

A 63-year-old, 71 in., 163 lb African-American man was observed running from his house onto the front lawn waving a white towel and pointing toward his throat. He collapsed on the front lawn and was quickly attended to by neighbors witnessing the event. Emergency medical personnel arrived shortly and attempted intubation but failed as a consequence of a massively swollen tongue (Fig. 2). He was immediately transported to a hospital emergency room. A tracheostomy was performed in the emergency department, but was of no avail and the patient was pronounced dead shortly thereafter. Medical history included HTN treated with enalapril for at least eight months. According to a relative, the deceased had complained of tongue and mouth swelling intermittently during those months. Information from witnesses suggested that the deceased might have been stung by a bee prior to collapse. The body was brought to the coroner's office for an autopsy which disclosed a massively edematous tongue (12.5 cm by 7.5 cm by 5 cm thick) and minor edema of the epiglottis and larynx. No evidence of an insect sting was found. The heart was mildly enlarged (360 g) with respect to the body weight. No peripheral edema was noted. Microscopic examination of the tongue revealed submucosal and interstitial edema between myocytes with little or no inflammation. A micro-

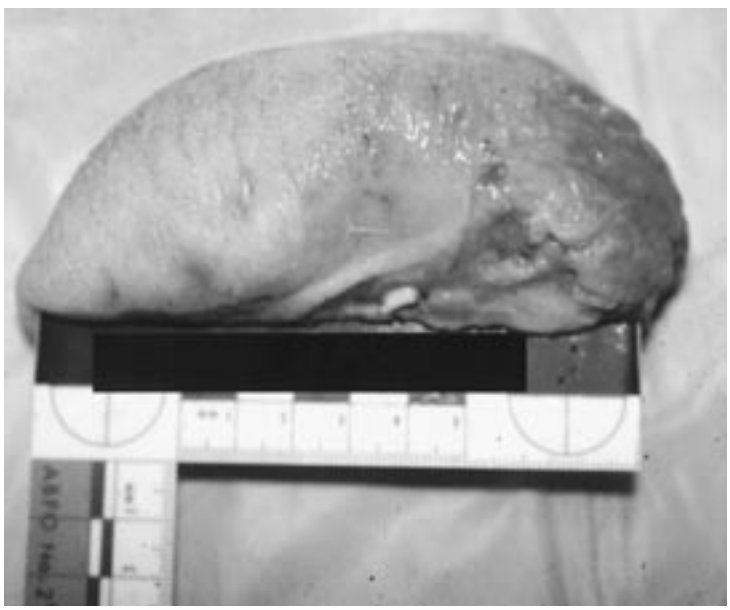

FIG. 2—*Angioedema of tongue.*

scopic section of the epiglottis showed submucosal edema and minor lymphocytic inflammation. Sections of other organs were unremarkable. Serum tryptase was within the reference range at 2.7 ng/mL. Screens for alcohol and drugs of abuse were negative. An IgE panel for insect stings was negative. The cause of death was determined to be upper airway obstruction related to angioedema of the tongue, oropharynx, hypopharynx and larynx due to enalapril therapy for hypertension. The manner was considered natural.

Case 4

A 54-year-old, 306 lb, 79 in. African-American man was transported by ambulance to a hospital with a 12 h history of tongue swelling, that had started about 10 h after beginning drug therapy with lisinopril, lasix, and prednisone. Past medical history was positive for hypertension, the nephrotic syndrome, and schizophrenia. The emergency department physician suspected an ACE inhibitor reaction, and had instructed the patient to stop taking the lisinopril and lasix. He provided the patient some Benadryl and sent him home. The patient was instructed to return to the hospital in a week or if symptoms recurred. Later that day, the deceased suffered a respiratory arrest and collapsed in front of family members. Emergency medical personnel attempted resuscitation and he was taken to a hospital emergency room where a tracheostomy was performed. He was pronounced dead soon after arrival and was brought to the coroner's office for an autopsy, which revealed a massively edematous tongue with moderate edema of the aryepiglottic fold (Fig. 3). The heart was markedly enlarged and dilated (685 g) and massive pulmonary edema was noted (right, 1125 g, left, 890 g). No peripheral edema was present. A microscopic section of the tongue (Fig. 4) and epiglottis showed submucosal and interstitial edema with scanty mononuclear inflammation. Sections of other organs were unremarkable. The serum tryptase level was moderately elevated at 24.4 ng/mL (reference range $<$11.5 ng/mL). Blood screening tests for alcohols, volatiles, and drugs of abuse were negative. The cause of death was determined to be obstruction of the airway with asphyxia due to angioedema of tongue and oropharynx related to lisinopril therapy for the treatment of hypertensive heart disease. The manner of death was considered natural.

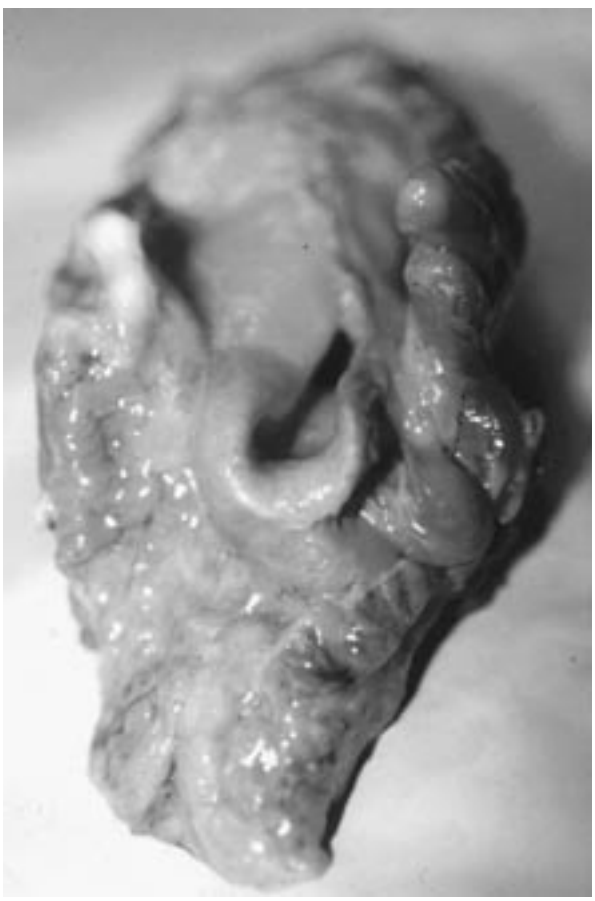

FIG. 3—*Angioedema of aryepiglottic fold of throat.*

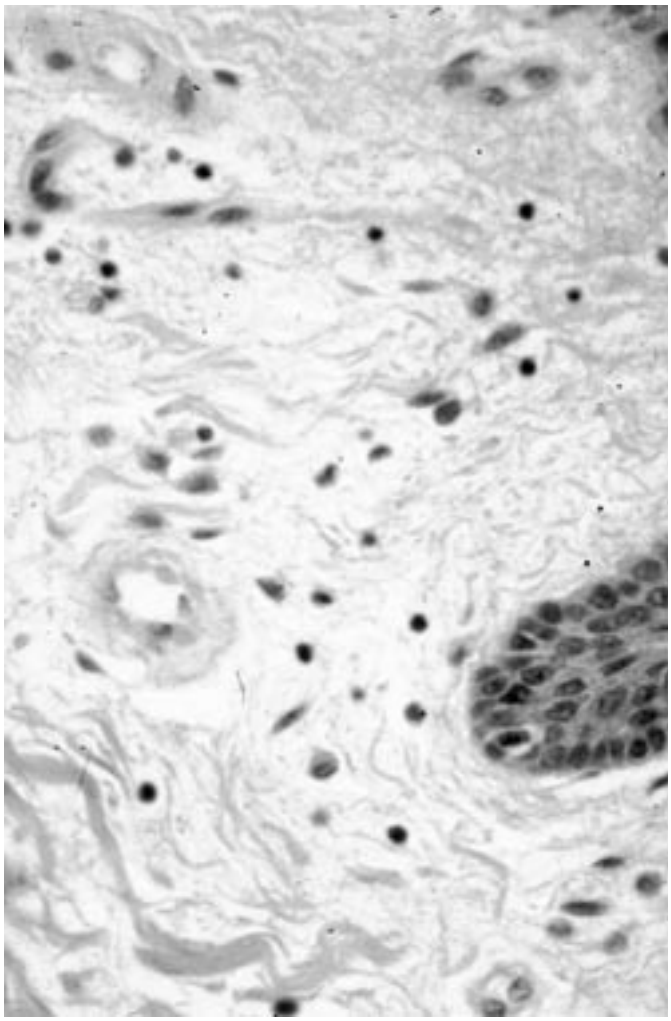

FIG. 4—*Microscopic view of angioedema of tongue.*

Case 5

A 65-year-old, 70 in., 257 lb African-American man became short of breath at home as his tongue started to swell. His family called the emergency squad and he was transported to a local hospital. He remained conscious and communicative in the emergency department, despite continued tongue swelling. Eventually he required airway protection, but endotracheal intubation was unsuccessful due to the swollen airway. He received an emergency tracheostomy, but died despite aggressive resuscitative efforts. His body was brought to the coroner's office for an autopsy. At au-

topsy, the tongue protruded between the teeth. Small erosions were noted on the tip of the tongue. The mucosa of the epiglottis and the upper larynx were moderately swollen. Cardiomegaly was confirmed (heart weight 565 g). Microscopic examination revealed focal ulceration of the tip of the tongue with local infiltration by lymphocytes and neutrophils with angioedema in the remainder of the tongue. The epiglottis was slightly edematous and chronic inflammatory cells were scattered in the tissue. There was no significant infiltration by eosinophils. Toxicologic screening tests for alcohol and drugs of abuse were negative. The cause of death was determined to be suffocation due to angioedema of the tongue and larynx due to enalapril therapy for essential hypertension. The manner of death was considered natural.

Case 6

A 70-year-old, 68 in., 223 lb African-American woman complained of respiratory distress caused by airway obstruction from angioedema and aspirated chewing gum. The patient told her daughter that she would take Benadryl as she had done in the past for similar swelling. Previously, the swelling subsided quickly. This time, however, the swelling continued. The patient's daughter had removed the gum from the airway by the time the emergency squad arrived. The emergency personnel attempted endotracheal intubation twice, but were unsuccessful, so they administered oxygen by bag and facemask. She was brought to a local hospital where oral intubation was established. Despite aggressive resuscitative efforts, she expired in the emergency department and was transported to the coroner's office. Medical history included essential hypertenstion and hypothyroidism. Medications included prinivil, Synthroid, premarin, prozac, furosemide, and lisinopril. It is unknown for how long she was prescribed lisinopril. At autopsy, her tongue, pharynx, and larynx were severely edematous and had a diffusely smooth, glistening, watery appearance. Cardiomegaly (heart weight 440 g) was confirmed. Microscopic examination revealed angioedema with scattered mononuclear inflammatory cells, but no significant infiltration by eosinophils. Toxicologic screening tests for alcohol and drugs of abuse were negative. The cause of death was determined to be asphyxia due to upper airway obstruction due to laryngeal and tongue edema due to lisinopril therapy for hypertension. The manner was considered to be natural.

Discussion

Angiotensin converting enzyme (ACE) inhibitors are used for the treatment of hypertension and congestive heart failure. They are sometimes used in combination with other agents and are generally considered safe and effective. Therapy with ACE inhibitors is contraindicated for patients with a prior history of idiopathic angioedema or for patients with hereditary or acquired C1 esterase inhibitor deficiency (usually associated with autoimmune or low-grade lymphoproliferative disorders) (3). Angiotensin converting enzyme has two major functions in circulation: inhibition of bradykinin and conversion of angiotensin I to the vasoconstrictor, angiotensin II. By combining with the zinc ion inherent in circulating ACE, ACE inhibitor drugs decrease the effectiveness of ACE mediated conversion of angiotensin I to angiotensin II resulting in increased local bradykinin levels. Bradykinin is a peripheral vasodilator and increases vascular permeability. The desired effect is a decrease in total peripheral resistance with a subsequent reduction in systemic blood pressure. (3) While overdoses with ACE inhibitors are infrequent, the toxic response is marked hypotension (4).

The incidence of angioedema of the tongue related to ACE inhibitor therapy is reported to be 0.1% (5). Compared with Caucasians, African-American patients are at a significantly increased risk of ACE inhibitor associated angioedema, independent of dose (6). Symptoms of angioedema usually occur within the first several doses of therapy (7), but can also occur much later (1). Treatment consists of withdrawing the drug plus some combination of epinepherine, steroids, antihistamines, and intubation (7). Recovery is complete by a few hours to a few days (7). Angioedema is not dose related or related to the length of time of treatment. In all but one of the cases presented in this paper, the ACE inhibitor had been used chronically.

To our knowledge, there have been only two reports of death due to ACE inhibitor related angioedema (1,2). The low incidence of ACE inhibitor related deaths reported to many coroner's/medical examiner's offices may be because these patients have a medical condition that predisposes them to sudden death. Therefore, jurisdiction may be waived and the body not examined by a forensic pathologist. Even if the body arrives at the morgue, the swelling may be missed if the pathologist does not remove or closely examine the tongue and neck organs. The gross impression of a swollen tongue might be minimized in favor of another pathologic finding. Unless an alternate anatomic cause of death is extremely compelling, the examination should include an investigation of a potential obstruction of the airway. During the external examination of two bodies who were received because of a lack of funeral arrangements, the swollen tongue seen on the external exam prompted an autopsy.

Measurements of the tongue provide little value as compared with the in situ impression of a tongue tightly packed in the oral cavity. The authors found it difficult to place a finger or two between the dorsum of the tongue and the palate (using an approach from the internal aspect of the neck) in all of the cases reported have angioedema. The tongue in all cases was diffusely soft, pale, and edematous. Microscopic examination of the affected tissues revealed interstitial and submucosal edema with scant to absent inflammation. The serum tryptase level was variable in the ACE inhibitor related deaths. When high, the serum tryptase level can distinguish angioedema from an anaphylactic reaction, especially in combination with a positive clinical history and elevated agent-specific IgE. The authors used this in the diagnosis of a fatal case of allergic reaction to amoxicillin in a hypertensive patient taking an ACE inhibitor.

As a function of the examination of bodies in which the cause of death was determined to be ACE inhibitor—related angioedema, our office practice has been slightly modified. After receiving a death report and learning that ACE inhibitors are included in the list of prescribed medications, we ask the police or first responders if there is a big, swollen tongue. If so, the decedent is brought to our facility for closer inspection and determination if an autopsy is warranted.

We considered the manner of death in these cases of ACE inhibitor angioedema to be natural. It is a known, albeit rare, adverse reaction to a medically necessary drug for the treatment of a medical disorder. However, we recognize that there is no uniformly accepted manner of death for every situation and that assignment is somewhat determined by convention and local tradition. Therefore, some forensic pathologists/coroners may consider these deaths to be accidents because ACE inhibitors are extrinsic and angioedema is not a common complication. It may be, therefore, considered a "therapeutic complication" in those jurisdictions that allow such a manner designation.

Conclusions

Angioedema due to ACE inhibitors is rare, but usually treatable if medical help is sought when symptoms first develop. Treatment consists of withdrawing the drug, protecting the airway, and instituting a different class of anti-hypertensive therapy. Fatalities are not common, but are characterized by a large, swollen tongue with variable swelling of the lips, oropharynx, and larynx. Swelling caused by ACE inhibitors and can mimic an anaphylactic reaction. Inflammation is minimal to absent. Serum tryptase may be slightly elevated or low. Angioedema related to ACE inhibitor therapy is more common in African-American patients than it is in Caucasians. Angioedema is probably related to elevated levels of circulating bradykinin, but may also be related to other circulating factors.

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