CASE REPORT

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Fatal Angioedema Associated with Captopril

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ABSTRACT: A markedly hypertensive, 70-year-old, black man had been on captopril for 2 years when he rapidly developed obstructive angioedema. The initial sign of difficulty in understanding his speech progressed to severe laryngeal and glossal edema over a 3½ h period. His airway became obstructed less than a minute after arrival at the emergency room. Oral intubation was unsuccessful, and a difficult tracheostomy was too late to save the patient. The death was reported to the medical examiner because of its sudden and unusual nature. The risk of angioedema while on angiotensin converting enzyme inhibitor therapy has been noted previously in the clinical literature. Because of the sudden onset and possible confusion with an allergic reaction, this entity is brought to the attention of the forensic medical community.

KEYWORDS: pathology and biology, angioedema, captopril, hypertension

Sudden, unusual deaths are regularly reported to medical examiners. When confronted by a fatal case of rapid onset of angioedema of the upper airway, allergic response to bee or wasp sting immediately comes to mind. After this is reasonably ruled out, in a victim with no previous history of urticaria or angioedema, the diagnosis becomes more difficult. This report describes a rare cause of angioedema of the tongue and epiglottis, as a side effect of angiotensin-converting enzyme (ACE) inhibitor therapy, which may be confused with death due to an allergic reaction to hymenoptera venom. The ACE inhibitor captopril has been available since the mid 1970s for the treatment of hypertension and congestive heart failure. This class of drugs, which also includes enalapril, lisinopril, and saralasin acetate, is generally well tolerated, but there are well-described side effects. The more common, with incidence of 1 to 5%, include headache, dizziness, fatigue, diarrhea, skin rash, hypotension, cough and nausea. Less frequent side effects, with less than 1% incidence, are renal insufficiency, pancytopenia and angioedema [*1*].

Angioedema induced by ACE inhibitors has an estimated incidence of 0.1%. The condition is much more common in the first week of therapy, affecting about one in 3000 patients. Thereafter, it becomes more rare, with an incidence of about one in 42 000 patients [*2*]. No temporal trend has been noted after the first week. The problem is usually mild to moderate, but if severe requires prompt and effective treatment to maintain an airway [*3*].

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Case Report

The victim was a 70-year-old black man who had been treated with furosemide, labetalol, minoxidil, atenolol, colbenemid, and captopril 50 mg three times per day, for a little more than 2 years prior to his death. His medical diagnoses were chronic obstructive pulmonary disease and hypertension. The only change in his medications had been a substitution of a generic form of labetalol for the brand-name product he had been taking, 3 days before his death.

He had awakened at 9 A.M. and the change in his speech was noted by his wife. He went about his usual routine, including driving a family member to work, but was unable to take his medications due to difficulty in swallowing. His tongue became progressively more swollen during the morning, until an ambulance was called at 12:20 P.M. The paramedics who responded recorded respirations of 22/min, pulse of 100/min, and blood pressure of 200/106 mmHg. He denied any chest pain, dizziness, itchiness, or swelling elsewhere. No hives or urticaria were observed. His lungs were clear to auscultation. He was placed on oxygen by mask and given 50 mg benadryl intravenously while en route to the hospital. The victim indicated that his tongue swelling had decreased somewhat while in the ambulance, but within 30 s of his entry to the emergency room, his airway became completely obstructed. His tongue was markedly enlarged, and protruding from his mouth at this time. Intubation by direct laryngoscopy was unsuccessful, as was an attempt at #14 gauge needle cricothyroidotomy. Surgical tracheostomy was finally performed, but pulse had been lost by that time, and could not be brought back with further resuscitative attempts. The victim was pronounced dead 41 min after his arrival at the emergency room.

Autopsy

This case was reported to and accepted by the medical examiner, and an autopsy was performed. The body was that of an obese, elderly appearing, black man, 6′0″ tall. His lower face and neck were swollen, and his tongue protruded to the anterior aspect of his lips from his edentulous mouth. Although the family assured the authorities that there had been no insect bite a careful examination of the body was also made, and indeed, failed to show any lesion with the appearance of such a bite.

Internal examination showed the endotracheal tube was present in the tracheostomy, with its tip 10 cm above the carina. The neck organs were removed as a block. There was severe edema about the epiglottis, largely confined to its superior surface, and extending over the base of the tongue, proximally, for a distance of 7 cm. The tongue was markedly edematous on sectioning, with yellow glistening cut surface, somewhat more so on the left than on the right. The lining of the larynx was somewhat roughened about the vocal cords, but glistening and not edematous below the cords. The remainder of the autopsy showed extreme enlargement of the heart, which weighed 940 g. Although the coronary arteries were thick-walled, there were no significant arteriosclerotic occlusions. Myocardium showed no scars. Lungs were congested and edematous, right and left weighing 675 and 465 g, respectively. The liver was markedly enlarged, weighing 2910 g. Section showed acutely congested parenchyma. Kidneys showed finely nodular surfaces, a few retention cysts, and a 1 by 1.5 cm tan cortical tumor of the right kidney. Prostate was moderately enlarged. Other organs were grossly unremarkable.

Microscopic examination of the edematous tongue and epiglottis showed separation of microscopic structures by wide areas of unstained space, representing edema fluid. Giemsa stain showed between three and six cells with basophilic granules in their cytoplasm, consistent with mast cells, in the immediate vicinity of arterioles of the tongue and epiglottis, within their edematous zones. Many of these cells showed partial to almost

complete degranulation. Also present in these regions were up to a dozen small lymphocytes. No other cellular infiltrate was present in the affected regions. Sections of the lungs did not show basophilic granule containing cells. A test of blood obtained at autopsy for immunoglobin E gave a result of 42 μ/L with the normal reported as less than 100 μ/L. Toxicology screen was completely negative.

Discussion

This complication was first described by Jett in 1984 [*4*]. A review article by Roberts and Wuerz in 1991 cites 227 reports of this reaction [*5*]. This article goes on to note that there is no clinical profile that identifies patients at increased risk. It describes the unique clinical characteristics of this idiosyncratic reaction: angioedema may suddenly occur even though the drug has been well tolerated for months or years; symptoms may regress spontaneously while the patient continues the medication, erroneously prompting an alternative diagnosis; the lesion has a special predilection for the tongue, a circumstance that renders orotracheal and nasotracheal intubation difficult; symptoms may progress rapidly despite aggressive medical therapy, necessitating emergency airway procedures; there may be a rebound phenomenon following successful medical therapy, a situation this patient did not live to experience. Many of these features were found in the case described. The differential diagnosis includes hereditary deficiency of the first component of compliment. Although this condition was not tested for in this individual after death, the lack of any similar reaction in his past or in his family would tend to rule out this diagnosis.

Three deaths resulting from angioedema associated with ACE inhibitor therapy have been reported previously in the literature [*1*,*2*,*6*]. None of the reports include an autopsy examination. This case is therefore the first published autopsy description of the condition.

The substrates of ACE are angiotensin I, the kinins, in particular bradykinin, and sensory neuropeptides, such as substance P. The mechanism by which ACE inhibitors produce angioedema is thought to be by the decreased metabolism of bradykinin [*7*,*8*]. The autopsy microscopic finding of an apparently increased number of degranulating mast cells adjacent to arterioles in the affected, edematous tissue is consistent with this proposed cause, as is the normal level of immunoglobulin E.

Medical examiners must be sensitive to the possibility of ACE inhibitor therapy causing obstructive angioedema in cases, which may look on the outset to be typical bee or wasp sting reactions. Only the taking of a thorough history and careful investigation can lead to the correct cause of the condition.

Acknowledgments

Just prior to investigating this case, the Atlantic County Medical Examiner's Office obtained the use of the National Library of Medicine's Medical Literature Analysis and Retrieval System (MEDLARS), using their computer program Grateful Med. Use of that system led to a rapid diagnosis in this case, and has allowed efficient searching of the medical literature for this case report. Without MEDLARS and Grateful Med, the solution of this mystery would have been difficult to impossible in the semirural setting of Atlantic County, New Jersey, which hosts no medical schools and only limited medical libraries. I would also like to thank the Pathology Department of Shore Memorial Hospital, Somers Point, New Jersey, for preparing the microscopic slides and special stains needs for this case, and the medical library at Shore Memorial Hospital for obtaining copies of pertinent articles.

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