## CLINICAL CASE OF THE MONTH

# An Extreme Presentation of Angiotensin Converting Enzyme Inhibitor-Induced Angioedema

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## INTRODUCTION

Angiotensin converting enzyme (ACE) inhibitor associated angioedema is an adverse drug reaction that can result in potentially life-threatening swelling of soft tissue including the lips, pharynx, and larynx. The patient presented in this case is an African American man with no prior history of angiotensin converting enzyme inhibitor usage. He was admitted to the hospital due to concerns that the edema involving his face would worsen to the point of airway compromise. The patient needed an emergent bedside intubation and remained in the hospital for six days. The intent of this report is to briefly explain the epidemiology, clinical presentation, method of diagnosis, and treatment of ACE inhibitor associated angioedema.

## CASE PRESENTATION

A 72 year-old African American man with a past medical history of hypertension, heart failure with reduced ejection fraction, and alcohol use presented to the emergency department (ED) with a chief complaint of a one day history of facial swelling (Figure 1). On the day prior to presentation, the patient noted that he took a dose of a friend's lisinopril in an attempt to relieve atraumatic left lower leg swelling. The swelling had been present for the past week and he believed it was caused by his previously diagnosed heart failure. Upon awakening the next morning, he noticed new onset lip swelling and took another tablet of lisinopril in an attempt to relieve the swelling. The swelling in his lips progressively worsened throughout the day, prompting him to seek medical attention at the hospital.

On presentation to the hospital, the patient denied difficulty breathing, throat swelling, and any previous history of allergic reactions. The patient was afebrile, normotensive, tachycardic, his oxygen saturation was 99% on ambient air, and he was in no apparent distress. He had significant non-pitting, non-erythematous edema of both his upper and lower lips, left cheek, left periorbital area, and mild edema of the right periorbital area. He did not show any signs of lingual or posterior pharyngeal swelling at this time. There was no appreciable urticaria or erythematous lesions on dermatologic examination. An examination of the patient's lungs revealed no wheezes or decreased breath sounds.

**Figure 1:** Patient upon presentation to the Emergency Department.

One and a half hours after admission, the edema continued to worsen and prompted concern regarding possible airway compromise due to evolving pharyngeal edema. The emergency medicine physician documented posterior pharyngeal wall edema (Figure 2) and recommended elective intubation to protect the patient's airway. However, the patient elected to refuse intubation in hopes that the swelling would resolve shortly.

While in the ED, a working diagnosis of ACEi-induced angioedema was established and the patient was treated with an immediate transfusion of two units of fresh frozen plasma (FFP). During this time, the hospital pharmacy was consulted about the availability of icatibant, a bradykinin B2-receptor antagonist used in the treatment of Hereditary Angiodema which has also been used off-label in management of ACEi-induced angioedema. To rule out hereditary angioedema and acquired angioedema, C1 inhibitor function and protein levels, C4 complement, and C1q levels were ordered. Results of all were within normal limits.

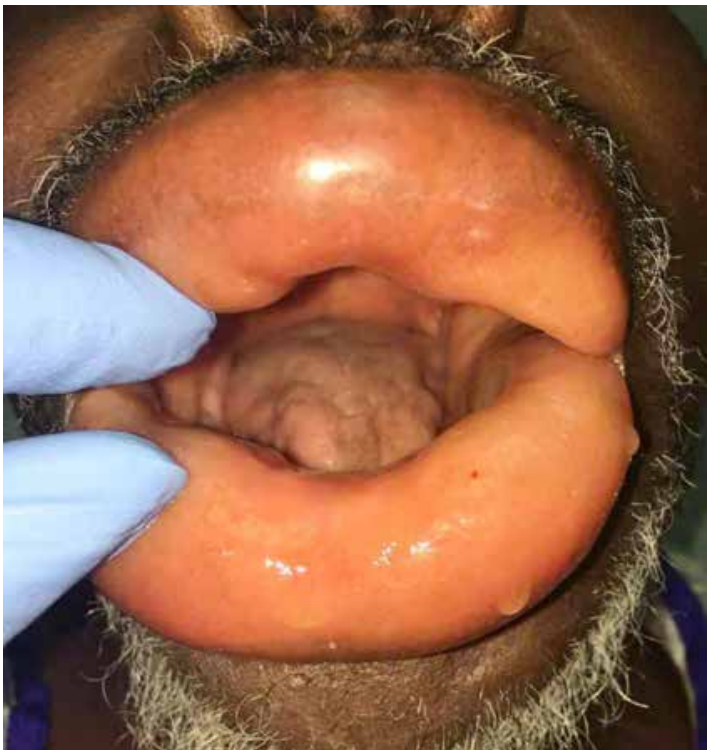

**Figure 2:** Pharyngeal Edema

Two hours after his initial presentation to the ED, the patient was admitted to the Intensive Care Unit (ICU) due to concern for impending airway compromise secondary to worsening facial and pharyngeal swelling. Five hours after admission to the ICU, the patient was emergently intubated (Figure 4).

On the day following his admission to the ICU, the patient's angioedema continued to progress and he was given another two units of FFP. During this time, the patient began exhibiting symptoms of alcohol withdrawal, most notably tachycardia

**Figure 2:** Prior to ICU admission

**Figure 4:** Post-intubation

and hypertension. These symptoms were well-controlled with clonidine patches and diazepam injections.

Approximately 36 hours after his initial presentation to the ED, the patient's facial swelling began to subside. On hospital day three, his airway was deemed stable and the patient was extubated. The patient was discharged to home on day six of his hospital stay and was instructed to follow up in clinic as an outpatient for management of his hypertension and heart failure. The patient was instructed not to take any angiotensin converting enzyme inhibitor or angiotensin II receptor blocker class medications in the future and was told to return to the ED if any of his symptoms returned.

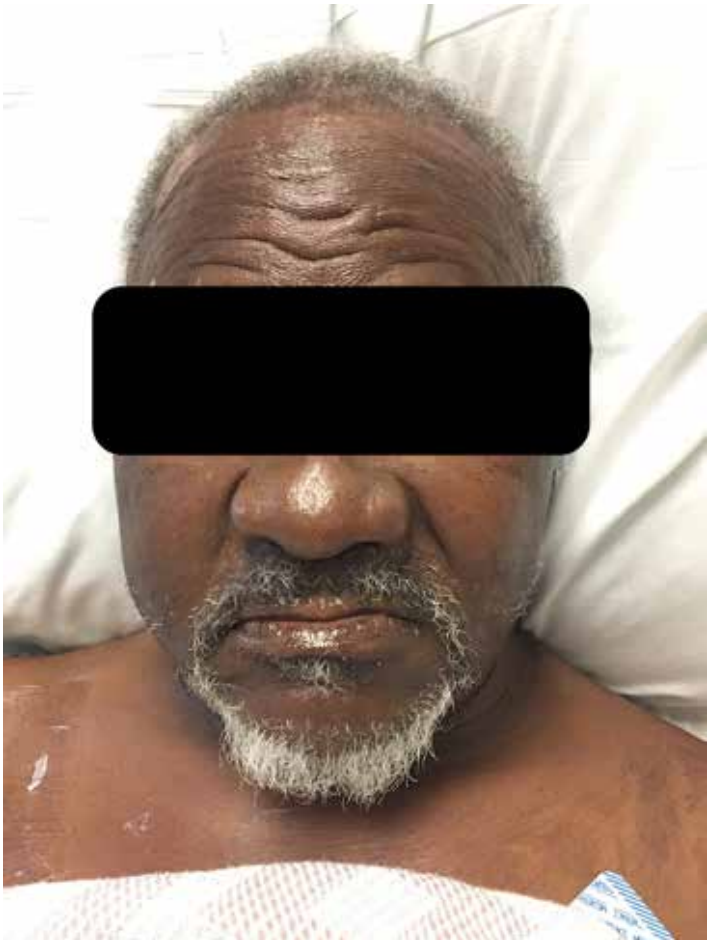

**Figure 4:** Patient on the day of discharge

## DISCUSSION

*Epidemiology*

Angioedema is a statistically uncommon adverse effect of ACEi's; the literature suggests an incidence rate of 0.1-0.7% in all comers.[1,2,3,4] African Americans have a relative risk of 4.5 compared to Caucasians, with some literature speculating that the presentation may even be more severe in this population due to, as of yet, unknown genetic components.[3,5] However, due to the number of patients currently prescribed ACEi's as an anti-hypertensive (i.e., approximately 30-40 million people), this "uncommon" adverse effect is encountered in the emergency room with astounding frequency and accounts for 17% of all ED visit complaints of angioedema.[3,6] This is not a benign disease. A staggering 50% of ACEi-induced angioedema cases who present to the ED are potentially life-threatening and may be deadly secondary to larynx or oropharynx swelling.[6] But, the overall fatality-rate associated with ACEi-induced angioedema is relatively low.[4]

## CLINICAL PRESENTATION

Angioedema is generally a benign, self-limiting condition characterized by swelling. Localized swelling occurs as plasma leaks from capillaries in deeper layers of subcutaneous and submucosal tissue.[7] This swelling occurs when vascular integrity decreases, in response to release or activation of vasoactive agents, and fluid is lost from local blood vessels.[4]

Angioedema can be classified as histamine or bradykinin-mediated. ACEi-induced angioedema is a type of bradykinin-mediated drug-induced angioedema which classically develops over a period of one to two days and resolves spontaneously by day five.[2] This is problematic because the delayed presentation makes identifying the trigger difficult. The majority of ACEI-angioedema cases, roughly 50%, occur within one week of initiating treatment.[8] However, there are reports of onset ranging from one day and ten years of starting ACEi therapy.[4]

The non-pitting, non-dependent edema associated with ACEi-induced angioedema is characteristically asymmetric, and generally involves the loose connective tissue of the face, lips, mouth, and larynx.[2] However, involvement of the extremities, genitalia, and bowel are not uncommon.[5] Unlike most hypersensitivity reactions associated with swelling, ACEi-induced angioedema is not associated with signs of anaphylaxis such as bronchospasm and urticaria, as these conditions are typically associated with mast cell degranulation and histamine release.[7]

## DIAGNOSIS

The diagnosis of angioedema is clinical, based primarily on the patient's history and physical exam findings. Some of the classic clinical features that distinguish angioedema from other swelling etiologies include association with ACE inhibitor ingestion, rapidity of onset, characteristic anatomic locations of involvement, absence of common associated hypersensitivity symptoms, and an acute, self-limiting course. In patients presenting with abdominal pain, abdominal imaging using either ultrasound or computed tomography (CT) will help support diagnosis as these imaging modalities can reveal signs of abdominal fluid accumulation, including dilated bowel loops, thickened mucosal folds, mesenteric edema and ascites. While there are no laboratory evaluations that definitively detect ACEi-induced angioedema, there are laboratory tests that can help

to rule out or confirm other etiologies of angioedema. Tests used to evaluate for hereditary (HEA) or acquired angioedema include serum C4 levels, C1 inhibitor serum levels and function tests and serum C1q levels.[9,10] While abnormal values of these tests may point to other causes of angioedema, results within normal ranges can help to rule out other etiologies and help to support the diagnosis of ACEi-induced angioedema.

## TREATMENT

The initial management of ACEi-induced angioedema is well defined and includes: 1) the immediate cessation of the offending medication and 2) assessment of the airway to evaluate for current or the possibility of future airway compromise. In the event of oropharyngeal swelling, emergent intubation and mechanical ventilation should undertaken to ensure airway patency. It is imperative to continuously monitor the patient's airway and respiratory status for signs of compromise. ACEi-induced angioedema is typically self-limited and resolves within 24-72 hours after cessation of the offending medication. However for cases of severe or refractory ACEi-induced angioedema, additional therapies may be initiated.

High concentrations of endogenous bradykinin pathway inhibitors, have shown significant efficacy in the treatment of ACEi-induced angioedema. Fresh frozen plasma (FFP), in addition to clotting factors and other plasma proteins, contains high levels of angiotensin converting enzyme (ACE). The ACE present in FFP inactivates bradykinin and thus is generally a very effective treatment in ACEi-induced angioedema, with typical symptom improvement beginning within two hours of infusion. Two units of FFP is the typical dose required for symptom improvement in adult patients with ACEi-induced angioedema. In addition, FFP has been shown to reduce symptom recurrence.[11,12,13] Purified concentrates of C1 inhibitor, a protein which functions to inhibit kallikrein, have also been reported as an effective therapy for ACEi-induced angioedema in several case reports.[14,15,16,17,18]

In addition to transfusions of endogenous bradykinin pathway inhibitors, there are synthetic medications that are FDA-approved for the use in Hereditary Angioedema (HAE) which have also shown efficacy in ACEi-induced angioedema. Icatibant, as was discussed in this case report, is a synthetic bradykinin B2-receptor antagonist. Icatibant is administered in a single dose subcutaneously and shows best results when administered within the first several hours of an ACEi-induced angioedema attack.[19,20] Additional doses can be administered if there is worsening of symptoms after six hours, but it is recommended that no more than three injections be given within a 24 hour period.[19]

Antihistamines, one of the mainstays of treatment in histamine-induced angioedema, have no biologic effect on bradykinin activity or metabolism. However, antihistamines administered in typical adult doses have been shown in a small number of studies to improve the clinical status in patient's suffering from ACEi-induced angioedema and were associated with earlier extubation.[21,22] Antihistamines should be administered in all cases of angioedema of unknown etiology due to their relatively benign safety profile and significant efficacy in histamine-induced angioedema and clinically similar allergic reactions.

## CONCLUSION

ACEi-induced angioedema is a potentially life-threatening adverse effect of ACEi medications. African Americans are disproportionally affected relative to Caucasians, however the percentage of patients that use these medications and develop angioedema remains low. A significant number of people use ACEi's, as such, angioedema is not an uncommon presentation to the ED. When these patients are identified early and treated appropriately, the outcome is generally favorable.

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