

# Delayed Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema

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**A**ngiotensin-converting enzyme (ACE) inhibitors have emerged as important therapeutic agents for the treatment of many medical conditions, such as heart failure, hypertension, and diabetic nephropathy. Like most other medications, ACE inhibitors are associated with adverse reactions. Angioedema is a side effect of ACE inhibitors that is potentially fatal but is treatable in the majority of cases. We describe a case of ACE inhibitor-induced angioedema that occurred in a patient who had been using ACE inhibitors for more than 10 years.

## CASE PRESENTATION

### Initial Presentation and History

A 93-year-old white man presented to the emergency department with a complaint of swelling that started on the right upper lip several hours prior to presentation. The onset was gradual, but the patient's lip became increasingly swollen and the area of involvement increased to include the whole upper lip and minimally the lower lip over the next several hours, prompting the patient to seek medical attention. The patient went to the emergency department after first calling his primary care provider. He denied any itchiness or warmth around the area of swelling but reported some swelling and numbness in the anterior aspect of his tongue. He also noted transient antecubital and groin pruritus. The patient denied having chest pain, dyspnea, difficulty swallowing, or other discomfort. He denied having had any similar past episodes. He had no recent history of contact with allergens, insect bites, dietary changes or ingestion of soy, wheat, sulfites, or seafood, or trauma.

The patient's past medical history was significant for hypertension, diet-controlled type 2 diabetes mellitus, critical aortic stenosis, multiple transient ischemic attacks, trigeminal neuralgia, glaucoma, benign prostatic hypertrophy status post-transurethral resection of prostate, spinal stenosis, hiatal hernia, and atypical myco-

bacteriosis. The patient's home medications were amlodipine, aspirin, clonidine (dose recently increased from 0.3 mg once daily to twice daily), clopidogrel, enalapril, metoprolol XL, finasteride, lansoprazole, fentanyl patch, paroxetine, timolol eyedrops, latanoprost eyedrops, acetaminophen, and psyllium. Of note, the patient had been taking captopril for about 11 years without any problem before he was switched to enalapril approximately 1.5 years before his presentation, presumably to change the medication regimen from 3 times a day to once daily. The patient denied taking any over-the-counter medications or herbal supplements. He reported having experienced hallucinations secondary to morphine and meperidine, rash secondary to phenytoin, weakness secondary to carbamazepine, and confusion secondary to amitriptyline. The patient denied any previous problem with ACE inhibitors.

Family history was significant for diabetes, cerebrovascular accident, and hypertension. One of patient's children had a history of spinal tumor. No family history of angioedema was noted. The patient lived with his wife. He denied any tobacco, alcohol, or other medication use.

### Physical Examination

On evaluation, blood pressure was 154/80 mm Hg, heart rate was regular at 76 bpm, respiration rate was 22 breaths/min, temperature was 37.8°C (100°F), and weight was 55 kg (121 lb). Physical examination was remarkable for edema of the upper lip. There was a

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moderate amount of tongue and uvula swelling, but the airway appeared patent. Examination of the heart revealed a 2/6 crescendo decrescendo murmur at the left sternal border, which had been documented previously. No lesion or rash was found in the antecubital or groin region. The patient had decreased sensation on his right cheek and jaw. He had 4/5 strength in his lower extremities, an assessment unchanged from previous documentation.

### **Hospital Course**

Drugs were considered as the possible cause of this patient's episode of angioedema given the lack of history or other evidence suggesting other causes, such as exposure to allergens, C1 esterase inhibitor deficiency, or recurrent angioedema with eosinophilia syndrome. The patient was diagnosed with presumed ACE inhibitor-induced angioedema in the emergency department and given prednisone 60 mg orally. He was admitted overnight because the swelling continued to increase. No laboratory tests were performed. Given the patient's history of benign prostatic hyperplasia, diphenhydramine was not started by the medical team. The swelling gradually improved overnight, and the patient's stay in the hospital was generally unremarkable. He was discharged the following day on a short course of prednisone (10 mg once daily for 2 days) and with the instruction to discontinue the ACE inhibitor. At the follow-up visit with his primary care provider approximately 7 days after discharge, the patient did not have continuation of the angioedema.

### **DISCUSSION**

Angioedema occurs when release of inflammatory mediators, such as histamine, leukotrienes, prostaglandins, heparin, and bradykinins, increase vascular permeability, resulting in tissue edema. Among the medications that the patient was taking, the ACE inhibitor enalapril is most commonly associated with angioedema<sup>1</sup>; this effect is believed to be mediated, at least in part, by potentiation of the bradykinins. Approximately 0.1% to 0.7% of patients on ACE inhibitors develop angioedema.<sup>2</sup> The incidence of ACE inhibitor-induced angioedema has increased in parallel with increases in the indications and the number of prescriptions for ACE inhibitors.<sup>3</sup> Although most events occur within weeks of starting this medication, some may occur a few years after initiation of therapy;<sup>4</sup> in 1 case, angioedema was reported 7 years after therapy was started.<sup>5</sup> The case patient had been on an ACE inhibitor for many years, albeit of a different kind. As noted, he had been on captopril for approximately 11 years before being switched to enalapril 1.5 years before he presented with angioedema. Captopril and

enalapril are structurally different, and it is possible that the change in ACE inhibitor might have triggered the event; however, there are no clear data to support this conjecture.

The sudden onset of symptoms and the asymmetry of the lesion seen in this patient is typical for angioedema, but the antecubital and groin pruritus is not. However, pruritus has been reported as a cutaneous adverse effect of ACE inhibitors, along with photosensitivity, exfoliative dermatitis, onycholysis, pemphigus, erythematous, and macular, papular, lichenoid, and pityriasis rosea-like rashes.<sup>2</sup>

Intestinal angioedema has been reported in patients taking ACE inhibitors. A review article that evaluated 15 case reports noted that this condition typically affects middle-aged women who recently started the medication; these patients typically presented with abdominal pain, vomiting, and diarrhea.<sup>6</sup> Findings of leucocytosis and ascites and abdominal computed tomography scan showing edematous small bowel<sup>7</sup> can help to make the diagnosis, but more invasive procedures such as surgery are frequently needed to confirm the diagnosis. Although intestinal angioedema is rare, this diagnosis should be considered in patients on ACE inhibitors who present with abdominal symptoms.

### **Risk Factors**

A recent retrospective cohort study by Morimoto et al<sup>8</sup> suggested that patients who smoke and have a history of ACE inhibitor-induced cough are at increased risk of developing ACE inhibitor-induced angioedema (hazard ratio, 2.7 [95% confidence interval {CI}, 1.1-7.0] and 9.1 [95% CI, 2.1-39.9], respectively). This condition is also more common in African Americans.<sup>9</sup> Patients with a history of angioedema unrelated to administration of ACE inhibitors may also be at increased risk of developing ACE inhibitor-induced angioedema. ACE inhibitors are contraindicated in patients with hereditary or acquired C1 esterase inhibitor deficiency.

### **Therapies for Angioedema**

Corticosteroids, such as prednisone or hydrocortisone, and histamine blockers (both H<sub>1</sub> and H<sub>2</sub>),<sup>10</sup> such as diphenhydramine and cimetidine, are often used to control ACE inhibitor-induced angioedema. In mild cases in which the patient is stable and when there is no contraindication, some patients may require only the histamine blockers and may be managed on an outpatient basis. Although most cases can be managed with medical therapy, some cases can quickly progress to airway compromise and become life-threatening.<sup>11</sup> Therefore, airway patency needs to be closely monitored. If

the patient has symptoms suggesting anaphylaxis, such as chest tightness or hypotension, epinephrine 0.5 to 1 mg 1:10,000 intravenously or 0.5 to 1 mg 1:1000 subcutaneously should be administered. It is important to note that corticosteroids and antihistamines do not have immediate onset of action in this situation, and some patients might require epinephrine infusion. Close observation for potential biphasic anaphylactic reaction is also needed. If the reason for anaphylaxis is unclear and if there is no contraindication, the patient should be discharged with an epinephrine auto-injector and proper instruction on how to use this device.

Some reports have suggested that administering fresh frozen plasma (FFP) confers a benefit in cases of resistant angioedema.<sup>12,13</sup> In the case reported by Warrior et al,<sup>12</sup> FFP was used in a 43-year-old woman who had continuous and worsening tongue swelling for 4 days despite being treated with antihistamines, corticosteroids, epinephrine, antileukotrienes, cyclosporine, and intravenous immunoglobulin. Her symptoms improved after 2 units of FFP were administered. The authors suggested that the benefit of FFP might be due to the effect of kininase II in breaking down accumulated bradykinin.

#### Follow-up of Patients

The case patient was taking enalapril for hypertension. Although angiotensin-receptor blockers do not cause an increase in bradykinins, recurrent angioedema has been reported in patients with a history of ACE inhibitor-induced angioedema who have been switched to these agents.<sup>14</sup> For blood pressure control, the patient might benefit from an increase in his  $\beta$ -blocker dose or addition of a thiazide diuretic.

In a retrospective analysis, Cicardi et al<sup>15</sup> determined the outcome in 64 consecutive patients diagnosed with ACE inhibitor-induced angioedema whose medication was discontinued without additional work-up to evaluate the etiology. Fifty-four patients were available for a median follow-up of 11 months (range, 1-80 months). Angioedema was drastically reduced in 85% of these patients upon stopping the medication,<sup>15</sup> which suggests that extensive evaluation is not needed for the first episode of angioedema if the patient is on an ACE inhibitor. However, newly emerging evidence shows that some inflammatory markers, such as C-reactive protein and fibrinogen, might help to determine if the angioedema is indeed due to ACE inhibitors. Bas et al<sup>16</sup> performed a retrospective cohort study involving 25 patients who developed angioedema while on ACE inhibitors, 18 patients with idiopathic angioedema, and 21 patients on ACE inhibitors without angioedema. During the angioedema episode, patients who were taking ACE inhibitors

had significantly increased mean plasma concentrations of C-reactive protein and fibrinogen (by 7.3-fold and 1.5-fold, respectively), while leukocyte count and body temperature remained normal. These changes disappeared after successful treatment of angioedema and were not found in patients with idiopathic angioedema and those receiving ACE inhibitor without having experienced angioedema.<sup>16</sup>

If the patient had experienced recurrent symptoms despite the discontinuation of the ACE inhibitor, it would have been necessary to discontinue other medications that can cause angioedema, such as aspirin,<sup>17</sup> amlodipine (rare), and acetaminophen<sup>18</sup> (rare), preferably in a step-wise manner, to determine which is the offending agent. In such cases, it may be beneficial to evaluate the patient for possible acquired C1 esterase deficiency<sup>19</sup> and eosinophilia.<sup>20</sup>

#### CONCLUSION

With increasing use of ACE inhibitors and other medications in clinical practice, the incidence of drug-induced angioedema has also increased. It is prudent for practitioners to become familiar with the basic pathophysiology and management of this condition. This case highlights the fact that angioedema can occur many years after the initiation of ACE inhibitor therapy. Based on currently available evidence, extensive work-up is usually not needed and discontinuation of medication and observation is sufficient in most cases. **HP**

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