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Abstract

Angiotensin-converting enzyme inhibitors (ACE-Is) are the primary medication class implicated in drug-associated angioedema. Angioedema is most common early in ACE-I therapy, yet episodes can occur late in therapy and have been reported even as late as 10 years after single treatment initiation. We present a case of a 65-year-old African American woman who experienced 2 episodes of angioedema, with the second being life threatening after receiving several concomitant agents known to cause angioedema, most notably lisinopril for 11 years.

Keywords

cardiology, emergency medicine, internal medicine

Introduction

Drug-associated or drug-induced angioedema has been reported among numerous drugs, including estrogens, fibrinolytics, antihypertensives, immunomodulators, psychotropics, and biologics. However, angiotensin-converting enzyme inhibitors (ACE-Is) are the primary drug class implicated. Angioedema can be mediated by bradykinin, mast-cell degradation, or of unknown etiology and results in localized swelling of subcutaneous or submucosal tissue that can be life threatening. Upon presentation of angioedema, a careful medication review is essential so that potential drug causes can be identified. Symptoms can resolve within 24 to 48 hours after discontinuation of the offending agent, but supportive measures may be necessary until symptoms resolve.

Case

We present the case of a 65-year-old African American woman who experienced 2 episodes of angioedema, with the second being life threatening after receiving multiple concomitant medications carrying the risk of angioedema. The patient's medical history was significant for heart failure, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, diabetes mellitus, obesity, depression, anxiety, and obstructive sleep apnea. Her outpatient medications included lisinopril 40 mg daily (taken for 11 years), aspirin (ASA) 81 mg daily, amlodipine 5 mg daily, metoprolol tartrate 12.5 mg twice daily, hydrochlorothiazide 25 mg daily, simvastatin 40 mg daily, glipizide 5 mg before breakfast, bupropion 150 mg daily, alprazolam 0.25 mg twice daily, methocarbamol 500 mg daily, calcium with vitamin D daily, ibuprofen 600 mg three times

daily as needed, and albuterol 2 puffs every 6 hours as needed. She reported smoking 1 pack of cigarettes per day for the past 20 years and occasional ethyl alcohol use with a history of abuse. She denied the use of any illicit drugs. Her only known allergy was self-reported anxiety secondary to guaifenesin, but her mother and daughter both had a self-reported history of allergic reactions to penicillin, which could suggest some hereditary risk of angioedema.

The patient presented to the emergency department with an upper respiratory infection, and she was discharged with a prescription for moxifloxacin and prednisone. Approximately 5 hours after taking the second dose of moxifloxacin, her throat began to swell and she had difficulty in breathing. She returned to the emergency department and was diagnosed with an allergic reaction to moxifloxacin and treated with intravenous (IV) methylprednisolone, diphenhydramine, and ranitidine. Her symptoms resolved, and she was discharged later that day with prescriptions for prednisone, diphenhydramine, ranitidine, and amoxicillin-clavulanate (Figure 2).

Approximately 7 weeks later, the patient again presented to the emergency department complaining of an episode of aphasia, inability to swallow, and shortness of breath that lasted

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Figure 1. Life-threatening angioedema episode requiring emergency cricothyrotomy.

3 to 4 minutes. Her initial diagnosis was a benzodiazepine overdose because she was very somnolent and had altered mental status. She received naloxone and 2 doses of flumazenil, after which she became more alert. Despite an outpatient prescription for alprazolam, her urine drug screen returned negative for benzodiazepines. Neurology was consulted to evaluate the patient, and she was admitted for observation. Due to concern that she had experienced a transient ischemic attack, she was started on 325 mg of ASA daily. It was documented in the medical record that she had stopped taking her 81 mg ASA home dose 1 week earlier due to prolonged bleeding following minor injuries. Since she had experienced shortness of breath, computed tomography examinations with contrast were performed on hospital day 2 to rule out a pulmonary embolism. The patient received a total dose of 140 mL of iodixanol and had also received contrast dye in the past without any apparent reactions.

On hospital day 3, a magnetic resonance imaging (MRI) was scheduled with plans to discharge the patient home following the test. She had a neurology examination that morning and no facial anomalies were noted. She received a dose of lorazepam before the MRI to prevent claustrophobia and was kept following the procedure due to persistent somnolence.

Early in the morning on hospital day 4 (Figure 3), the patient reported to the nurse's station with right-sided swelling of her tongue and difficulty swallowing. She was treated with IV diphenhydramine, ranitidine, and methylprednisolone, and then transferred to the intensive care unit after her tongue continued to swell and she went into respiratory distress. Fiberoptic intubation attempts were unsuccessful due to severe epiglottic swelling so an emergency cricothyrotomy was performed at the bedside (Figure 1). She was also given dexamethasone, midazolam, propofol, and normal saline and started on continuous infusions of fentanyl and midazolam. She experienced severe hypotension that was treated with epinephrine and fluid resuscitation.

The episode of angioedema was believed to be drug-induced so both her lisinopril and ASA were discontinued. The patient

remained on mechanical ventilation for 1 day and received IV histamine blockers and dexamethasone for 3 days. Follow-up studies were done to rule out other causes of shock, hereditary angioedema, or autoimmune disorders (Table 1). All blood cultures remained negative. The tracheostomy was decannulated 6 days after the onset of angioedema, and the patient was discharged home the following day. Approximately 1 month later during a subsequent admission for community-acquired pneumonia, she received the same volume of iodixanol without any complications, which would indicate her angioedema was not due to contrast. At that time, she also received vancomycin, piperacillin-tazobactam, and metronidazole without known reactions to any of those antibiotics.

Discussion

Drug-associated or drug-induced angioedema has been reported with numerous drugs, and this patient received several medications within a relatively short time span, which could have contributed to her presentation, including lisinopril, moxifloxacin, ASA, ibuprofen, and contrast media. When ruling out drug-induced causes for angioedema in cases such as this, the clinician needs to be aware of potential medication causes and their mechanisms for hypersensitivity so that the appropriate offending agent can be discontinued.

Angioedema can be mediated by bradykinin, mast-cell degradation, or of unknown etiology. Bradykinin-mediated angioedema is normally associated with ACE-I therapy or complement abnormalities. When triggered by mast cells, angioedema is more common in atopic individuals. It develops when mast cells are activated, releasing inflammatory mediators that affect the integrity of the vasculature. It often presents as part of a type I hypersensitivity reaction, and urticaria, anaphylaxis, or hypotension may occur.¹ Certain medications trigger mast cell release that is not immunoglobulin E (IgE)-mediated, including opiates and contrast media.² Nonsteroidal anti-inflammatory drugs (NSAIDs) can induce reactions with urticaria and angioedema, that is normally attributed to increased production of leukotrienes.³ Antibiotics, particularly beta-lactams and cephalosporins, also cause hypersensitivity reactions that may involve angioedema as part of an anaphylactic or anaphylactoid reaction.

ACE-I-Induced Angioedema

ACE-Is are one of the most frequently prescribed drug classes, and angioedema is a well known, but rare side effect.⁴ The reported incidence of ACE-I-associated angioedema is 0.1% to 6%, with a higher rate of occurrence in certain patient populations.⁵ Multiple studies have shown an increased incidence in black patients.⁶⁻¹¹ Other reported risk factors include smoking, female sex, seasonal allergies, prior drug rash, and age greater than 65 years.^{5,6,10,11} Genetic factors may also impart an increased risk of angioedema.¹² Our patient had multiple concomitant risk factors for ACE-I-induced angioedema including age, race, female sex, and smoking.

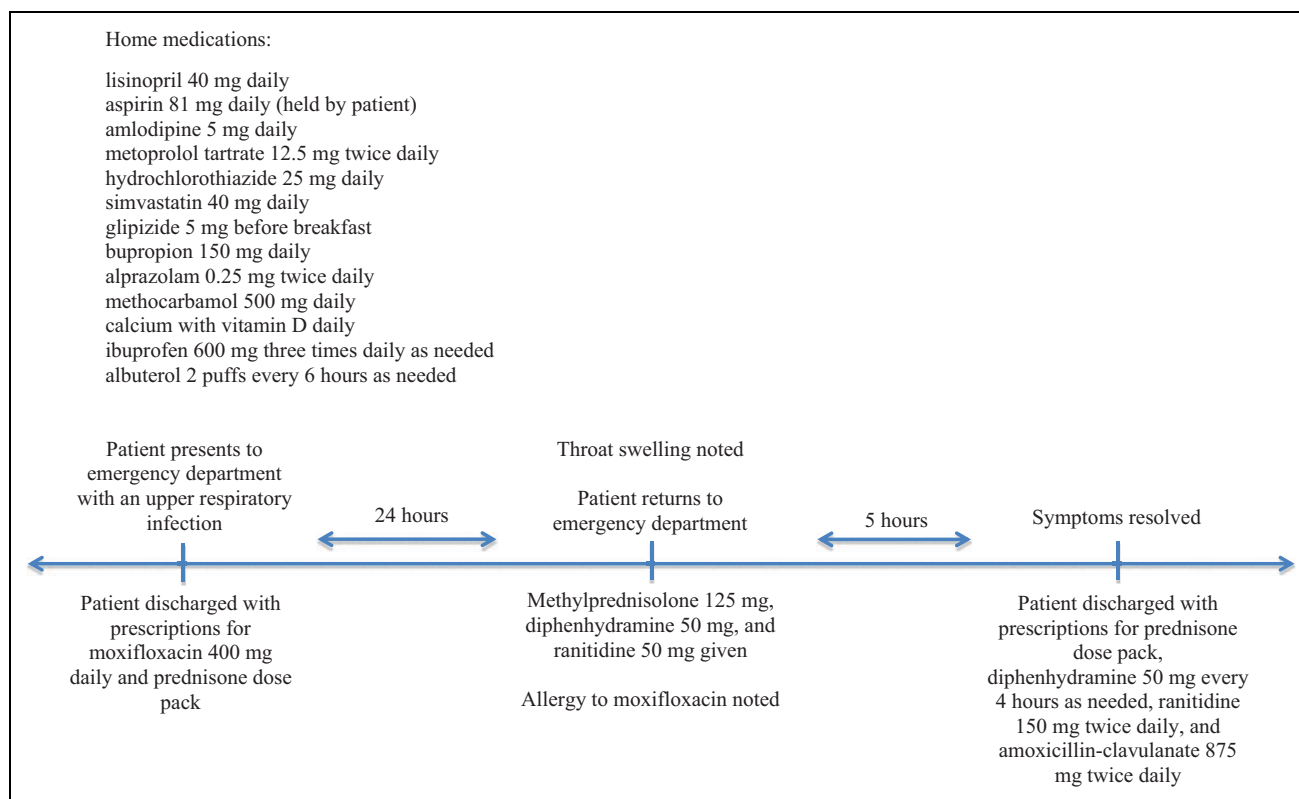


Figure 2. Time line of drug exposure and symptoms related to first episode of angioedema.

The highest incidence of angioedema from ACE-I has been reported within the first month of treatment and particularly during the first week of treatment, with up to a 14-fold increase.^{11,13,14} While it is more likely for angioedema to occur early on, angioedema can occur at any time after initiation of therapy, even as late as 10 years.¹⁵ This patient had been taking an ACE-I, lisinopril, for 11 years. To the authors' knowledge, this is the longest time frame reported in the literature for development of ACE-I-induced angioedema after continuous therapy with 1 ACE-I.

The mechanism of ACE-I-associated angioedema is normally attributed to the accumulation of vasoactive bradykinin secondary to the inhibition of ACE, one of the enzymes that degrades it. The excess bradykinin can then act on bradykinin B2 receptors, leading to a change in vascular integrity and subsequent edema. There is evidence from animal models that substance P may also be affected by ACE-I and consequently affect vascular permeability.^{5,16,17} Angioedema that results from bradykinin-mediated pathways usually does not involve urticaria or pruritis.^{1,5} Given that the patient did not have urticaria or any other symptoms commonly associated with a mast-cell-mediated etiology, it is more probable that her reaction was bradykinin mediated and potentially caused by an ACE-I.

ACE-I associated angioedema can range from mild to life threatening, and it normally resolves after the ACE-I is discontinued^{13,14,18}; however, severe cases may necessitate intubation or cricothyroidotomy.⁵ Unfortunately, lack of identification of the drug as the causative agent may delay its

discontinuation. In a study by Agostoni et al, the ACE-I was not withdrawn for a median of 10 months after the onset of angioedema.¹⁹ There is no definitive treatment, and treatment with antihistamines or corticosteroids has not been shown to be effective. Case reports have described successful treatment with icatibant, a bradykinin receptor antagonist approved for the treatment of hereditary angioedema.²⁰ It is not currently recommended to rechallenge a patient with an ACE-I after the development of angioedema due to an increased incidence of angioedema upon continued exposure to an ACE-I,²¹ and our patient was not rechallenged with lisinopril due to the severity of her presentation.

Several studies have evaluated the risk of treating patients who have experienced ACE-I-associated angioedema with an angiotensin receptor blocker (ARB). Although there are reports of angioedema to ARBs through an unknown mechanism, it occurs less often. In a direct comparison of telmisartan to ramipril in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), the rate was much lower with telmisartan (0.1% vs 0.3%, respectively).²² In the Candesartan in Heart Failure Assessment of Mortality and Morbidity (CHARM) Alternative trial, 83 patients with a previous history of angioedema to an ACE-I were treated with candesartan or placebo. Of the 39 patients randomized to candesartan, 3 developed subsequent angioedema compared to none of the 44 patients on placebo.²³ There is also evidence that patients are still at an increased risk of angioedema for months after the discontinuation of an ACE-I

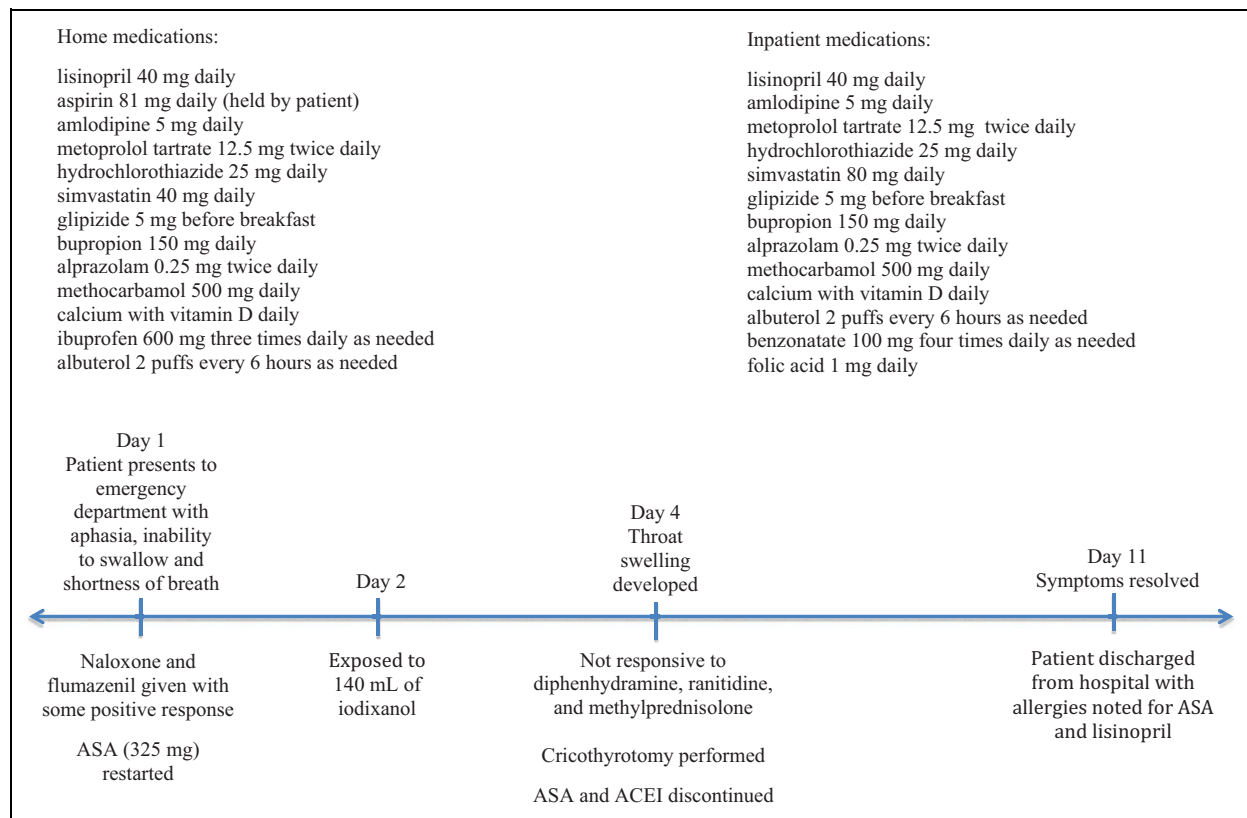


Figure 3. Time line of drug exposure and symptoms related to second episode of angioedema.

Table 1. Laboratory Results for Patient Case

Laboratory test	Result	Reference range	Interpretation
Serum IgE	24	0-100 IU/mL	Equivocal for atopic allergy
Serum tryptase	5.7	1-11.5 mcg/L	Drawn too late to interpret
Complement C4	30	9-36 mg/dL	Normal
Complement C3	163	90-180 mg/dL	Normal
Complement C1 esterase inhibitor	103%	>67% mean	Normal
Complement C1q	13	7.9-25.1 mg/dL	Normal
ANA	Negative	0-99	Negative
Anti-smooth muscle Ab	7	0-19 units	Negative
Anti-DNA (ds) antibodies	<1	0-9 IU/mL	Normal
Anti-mitochondrial anti (LC)	3.7	0-20 Units	Normal

Abbreviations: Ab, antibody; ANA, anti-nuclear antibody; ds, double stranded; Ig, immunoglobulin; LC, long chain.

due to persistently elevated bradykinin levels, which could be a confounding factor in reports of angioedema when a patient is switched from an ACE-I to an ARB. Due to the life-threatening severity of this patient's angioedema, it was decided not to prescribe ARB therapy.

ASA- and NSAID-Induced Angioedema

ASA and NSAIDs have also been implicated in angioedema and particularly in patients of female sex or with atopy.^{24,25} Patients who have a history of an allergic reaction to an antimicrobial drug may also be at increased risk of reaction,

even to drugs such as acetaminophen.²⁶ This patient's recent angioedema episode after moxifloxacin exposure (7 weeks prior) may have contributed to her increased risk of subsequent reaction.

Angioedema may be a component of anaphylactic reactions associated with antigen-specific IgE.²⁷ In this type of reaction, the patient must have previously been exposed and sensitized to the drug acting as a hapten, and this type of reaction can occur with NSAIDs that affect cyclooxygenase (COX) I or II.²⁸ It is theorized that there is an increased risk of hypersensitivity reactions with NSAIDs that are used for acute pain episodes because the intermittent use leads to multiple

Table 2. Naranjo's Algorithm for the Offending Agents Suspected in Causing or Contributing to Case of Angioedema

Question:	Yes	No	Do not know	Moxifloxacin	Lisinopril	Contrast	Aspirin
1. Are there previous conclusive reports of this reaction?	+1	0	0	+1	+1	+1	+1
2. Did the adverse event appear after the suspect drug was administered?	+2	-1	0	+2	+2	+2	+2
3. Did the adverse reaction improve when the drug was discontinued?	+1	0	0	+1	+1	+1	+1
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0	0	-1	+2
5. Are there alternate causes that on their own could have caused the reaction?	-1	+2	0	-1	-1	-1	-1
6. Did the reaction appear when a placebo was given?	-1	+1	0	0	0	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when decreased?	+1	0	0	0	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0	0	0	0
Total score ^a				3	3	2	5

^a The total score defines the probability that the adverse event was caused by a particular agent. Total score >8 = *definite (certain)*, total score 5 to 8 = *probable*, total score 1 to 4 = *possible*, and total score <1 = *doubtful (unlikely)*.

exposures and opportunities for allergic sensitization to the drug.^{27,29}

NSAIDs may also trigger angioedema as part of an anaphylactoid reaction that does not involve IgE. This type of reaction is attributed to COX-1 inhibition that shunts arachidonic acid metabolism toward the 5-lipoxygenase pathway, resulting in the formation of inflammatory mediators, cysteinyl leukotrienes.^{27,30} With anaphylactoid reactions, there could be cross-reactivity with any NSAID that also inhibits COX-1, even if the drugs are structurally dissimilar. In patients with chronic idiopathic urticaria, drugs that inhibit COX-1 may lead to reactions involving urticaria or angioedema with the reaction occurring within an average of 1 to 4 hours after taking the drug.³¹ In a retrospective review by Banerji et al, patients who had been receiving an ACE-I, ASA, or an NSAID had an increased incidence of angioedema when another drug associated with angioedema was added to the patient's therapy.³² Interestingly, 25% of the patients who developed angioedema and 40% of those who required intubation were on an ACE-I combined with ASA or an NSAID as was our patient. Given that ASA and NSAIDs can be associated with angioedema, this patient's ASA was also held. She had not received ibuprofen or any other NSAID as an inpatient. The Naranjo Algorithm (Table 2) indicates that ASA was a probable cause of or contributor to this patient's adverse event. This patient had received ASA for more than 11 years in variable doses without any previous hypersensitivity or event. Because of this extended time frame, ASA was not considered as the main cause. However, it is probable that ASA increased her risk of event as described by mechanisms above. Both ASA and lisinopril were added as allergies in this woman's medical record. While NSAIDs were not documented as an allergy at the time of this admission, it is noteworthy that she has received multiple scheduled NSAIDs at therapeutic doses before and after her life-threatening event without

sequelae. This further implicates lisinopril as the primary causative agent in this case.

Florquinolone-Associated Angioedema

The fluoroquinolones are widely used as antimicrobial agents, and the newer quinolones have a broader spectrum of activity that has expanded their use. Immune-mediated hypersensitivity reactions have been estimated to occur in less than 1 in 50 000 treatments based on postmarketing surveillance.³³ Of these reports, immediate IgE-mediated reactions, including urticaria, angioedema, and anaphylaxis, occur most frequently.^{33,34} Anaphylactic reactions, which may involve angioedema, have been estimated at 0.46 to 1.2 cases per 100 000 patients.³⁵ The time frame for the reaction varies, with some reports following the first dose.^{36,37} Some studies have shown an increased incidence of anaphylaxis with moxifloxacin versus other fluoroquinolones,^{36,38} but other studies have found a similar incidence.³⁹ In a large, retrospective review looking at allergic events associated with 4 fluoroquinolones, cephalosporins, and penicillin, the lowest incidence of any allergic reaction was seen with moxifloxacin and penicillin.³⁹ Our patient's symptoms occurred after the second dose of moxifloxacin, were mild, and resolved after treatment with a steroid and antihistamines. Moxifloxacin was noted as an allergy in the patient record.

Complement Proteins and Angioedema

Though irregularities of the complement protein C1 inhibitor can also lead to increased levels of bradykinin and subsequent angioedema, ACE-I-induced angioedema is a diagnosis of exclusion. In an effort to determine whether anaphylaxis was the cause of shock and to rule out other causes of angioedema, an extensive laboratory workup was ordered for this patient.

Serum IgE and tryptase are used to diagnose anaphylaxis or allergic angioedema; complement C1q, C3, C4, and complement C1 esterase inhibitor can identify other causes of angioedema; and anti-nuclear antibody, anti-smooth muscle antibody (Ab), anti-double-stranded DNA, and anti-mitochondrial (long chain) Ab can be used to exclude systemic lupus erythematosus (SLE).^{40,41} Neither the eosinophil sedimentation rate nor the C-reactive protein was checked for 48 hours after the initial event, therefore, the degree of inflammation was not evaluated. The results of the laboratory workup (Table 1) were negative for SLE and hereditary angioedema and were indeterminate for anaphylaxis or allergic angioedema due to timing. It is recommended that serum tryptase be checked as soon as possible (15 minutes to 3 hours) after the onset of anaphylaxis because it peaks near the onset of anaphylaxis and has a half-life of 2 hours.⁴² A tryptase level greater than 12 mcg/L is indicative of anaphylaxis, thus the observed level of 5.7 mcg/L drawn 16 hours after initial symptoms and 7 hours after the onset of shock cannot be interpreted. Serum IgE levels, also drawn 17 hours after symptom onset, were not markedly elevated as would be expected in anaphylaxis, but IgE levels were mildly elevated as seen in atopic allergy. These negative results are compatible with ACE-I-induced angioedema and do not clearly support other causes of angioedema.

Conclusion

With ACE-I-induced angioedema, the close temporal relationship that is normally associated with drug reactions may not be present, causing the drug to be overlooked as the causative agent and delaying its discontinuation. This experience highlights the importance of ruling out drug-induced causes for angioedema and maintaining suspicion for ACE-I, even after long periods of treatment.

Declaration of Conflicting Interests

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