CASE REPORT

THE PATIENT
67-year-old man

SIGNS & SYMPTOMS
– Upper extremity pain
– Upper extremity edema
– Recent diagnosis of heart failure

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THE CASE

A 67-year-old man with a history of gout, tobacco use, hypertension, hyperlipidemia, prediabetes, and newly diagnosed heart failure with reduced ejection fraction presented with a new concern for sudden-onset, atraumatic right upper extremity pain and swelling. The patient had awakened with these symptoms and on the following day went to the emergency department (ED) for evaluation. Review of the ED documentation highlighted that the patient was afebrile and was found to have a slight leukocytosis (11.7 x 10^3/μL) and an elevated C-reactive protein level (4 mg/dL; normal range, 0.3 to 1 mg/dL). A right upper extremity x-ray was unremarkable. The patient was treated with cephalexin and colchicine for cellulitis and possible acute gout.

Three days after the ED visit, the patient presented to his primary care clinic, reporting adherence to the prescribed therapies (cephalexin and colchicine) but no improvement in symptoms. He was again afebrile, and his blood pressure was controlled to goal (118/80 mm Hg). On exam, he had significant nonpitting, unilateral edema extending from the elbow through the fingers without erythema, warmth, or rash (**FIGURE**). A right upper extremity ultrasound was obtained; results were negative for deep vein thrombosis.

Medication reconciliation completed during the clinic visit revealed that the patient had started and continued to take newly prescribed medications for the treatment of heart failure, including metoprolol succinate, lisinopril, and furosemide. The patient confirmed that these were started 7 days prior to symptom onset.

FIGURE
Edema in a patient starting a new heart failure regimen

PHOTO COURTESY OF HALEY STEWART, DO

Physical exam revealed significant nonpitting, unilateral edema extending from the elbow through the fingers without erythema, warmth, or rash.

THE DIAGNOSIS

Given the clinical resemblance to angioedema and the recent initiation of lisinopril, the patient was asked to hold this medication. He was also advised to discontinue the cephalexin and colchicine, given low suspicion for cellulitis and gout. Six days later, he returned to clinic

and reported significantly improved pain and swelling.

DISCUSSION

Angioedema is a common condition in the United States, affecting approximately 15% of the general population.[1] When associated with hypotension, respiratory compromise, and other end-organ dysfunction, it is treated as anaphylaxis. Angioedema without anaphylaxis can be categorized as either histaminergic or nonhistaminergic; the former is more common.[2]

Certain patient and disease characteristics are more prevalent in select subsets of angioedema, although there are no features that automatically identify an etiology. Here are some factors to consider:

Recent exposures. Within the histaminergic category, allergic angioedema has the longest list of potential causes, including medications (notably, antibiotics, nonsteroidal anti-inflammatory drugs, opiates, and perioperative medications), foods, latex, and insect stings and/or bites.[2] Nonhistaminergic subtypes, which include hereditary and acquired angioedema, are caused by deficiencies or mutations in complement or coagulation pathways, which can be more challenging to diagnose.

Acquired angioedema may also be associated with the use of angiotensin-converting enzyme (ACE) inhibitors. Risk factors for ACE inhibitor–induced angioedema include history of smoking, increasing age, and female gender.[3] African-American race has been correlated with increased incidence of angioedema, with rates 4 to 5 times that of Whites,[1] but race is now identified as a social and not a biological construct and should not be relied on to make medical decisions about prescribing.

The rate of occurrence for ACE inhibitor–induced angioedema is highest within the first 30 days of medication use[2]; however, it can occur anytime. The absolute risk has been estimated as 0.3% per year.[4]

Patient age. Histaminergic angioedema can occur at any age. The hereditary subtype of nonhistaminergic angioedema is more common in younger individuals, typically occurring in infancy to the second decade of life, and tends to run in families, while the acquired subtype often manifests in adults older than 40.[2]

Physical exam findings. The typical manifestation of nonhistaminergic angioedema is firm, nonpitting, nonpruritic swelling resulting from fluid shifts to the reticular dermis and subcutaneous or submucosal tissue. In comparison, histaminergic reactions commonly involve deeper dermal tissue.

Commonly affected anatomic sites also vary by angioedema type but do not directly distinguish a cause. Allergic and ACE inhibitor–induced subtypes more commonly involve the lips, tongue, larynx, and face, whereas hereditary and other acquired etiologies are more likely to affect the periphery, abdomen, face, larynx, and genitourinary systems.[2] So the way that this patient presented was a bit unusual.

Symptom history. Allergic angioedema often has a rapid onset and resolution, whereas hereditary and acquired subtypes appear more gradually.[2] While the presence of urticaria distinguishes a histaminergic reaction, both histaminergic and nonhistaminergic angioedema may manifest without this symptom.

In our patient, the timeline of gradual symptom manifestation and the physical exam findings, as well as the patient's age, tobacco history, and recent initiation of an ACE inhibitor, made acquired angioedema a more likely etiology.

Treatment for ACE inhibitor–induced angioedema, in addition to airway support, entails drug discontinuation. This typically leads to symptom resolution within 24 to 48 hours.[2] Treatment with corticosteroids, antihistamines, and epinephrine is usually ineffective. Switching to an alternative ACE inhibitor is not recommended, as other members of the class carry the same risk. Instead, angiotensin receptor blockers (ARBs) are an appropriate substitute, as the incidence of cross-reactivity in ACE inhibitor–intolerant patients is estimated to be 10% or less,[5] and the risk for recurrence has been shown to be no different than with placebo.[3,4]

Our patient was transitioned to losar-

The patient's age, tobacco history, and recent initiation of an ACE inhibitor made acquired angioedema a more likely etiology.

tan 25 mg/d without recurrence of his symptoms and with continued blood pressure control (125/60 mm Hg).

THE TAKEAWAY

Angioedema is a common condition. While many medications are associated with histaminergic angioedema, ACE inhibitors are a common cause of the acquired subtype of nonhistaminergic angioedema. Commonly affected sites include the lips, tongue, and face; however, this diagnosis is not dependent on location and may manifest at other sites, as seen in this case. Treatment involves medication discontinuation. When switching the patient's medication, other members of the ACE inhibitor class should be avoided. ARBs are an appropriate alternative without increased risk for recurrence. JFP

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