

Migrating Angioedema Possibly Related to Angiotensin-Converting Enzyme Inhibitor

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Angioedema is a well-demarcated swelling that occurs in the deeper layers of the skin and subcutaneous tissue.^{1,2} It occurs in approximately 0.1% to 0.2% of patients receiving angiotensin-converting enzyme (ACE) inhibitors.³ The actual prevalence is likely higher because the presentation is poorly recognized and the symptoms occurring late in therapy are difficult to diagnose.^{2,3} This report describes a case of suspected ACE-inhibitor-induced angioedema with an unusual presentation.

CASE REPORT

A 42-year-old white man was admitted to hospital on June 21, 2000, with chest and epigastric pain. He was not taking any medications regularly and had no known allergies or history of angioedema. He had experienced an intermittent urticarial rash in the past, but no associated diagnosis had been made and no allergens identified. Urticaria was not observed during the current admission. Electrocardiography and cardiac enzyme testing demonstrated evidence of acute inferior myocardial infarction. The patient was given alteplase and was started on a heparin protocol, acetylsalicylic acid (ASA) 325 mg daily, captopril 12.5 mg tid, metoprolol 50 mg bid, nitroglycerin 0.4 mg/h patch applied during the day, simvastatin 10 mg at bedtime, and docusate 100 mg bid. The patient's chest pain resolved, and the electrocardiographic results returned to normal. Forty-eight hours after admission, coronary angiography and rescue percutaneous transluminal coronary angioplasty (PTCA) were required, as the patient was experiencing chest pain similar to the initial presentation. Repeat electrocardiography revealed

ongoing myocardial ischemia. A glycoprotein IIb/IIIa inhibitor was not administered. After insertion of a stent, the patient was started on clopidogrel 75 mg daily, ranitidine 150 mg bid, and ramipril 5 mg daily. The ASA and the captopril were discontinued. No further chest pain or discomfort was reported.

Four days after admission, approximately 48 h after the PTCA, the patient experienced sudden onset of swelling of the palmar surface of the left hand and right foot. He was given furosemide 40 mg, but it had no effect on the swelling. A few hours later there was a profound increase in the swelling, which involved both dorsal and palmar surfaces of the affected hand and foot. The swelling was asymmetric, nonerythematous, and well demarcated. At that time the patient described the swelling as somewhat pruritic but not painful. There was no involvement of the tongue or lips, and the patient did not experience any difficulty breathing. ACE-inhibitor-induced angioedema was suspected, and the ramipril was discontinued. The patient was given diphenhydramine 50 mg IV and methylprednisolone 80 mg daily for 3 days. On day 5 after admission, as swelling of the left hand and right foot resolved, the opposite hand and foot started to swell. This swelling was described as nontender edema without pruritus. The edema was so extensive that the patient could not make a fist. The following day the swelling of the hand and foot decreased markedly; however, the patient experienced numbness and profound swelling of the lower lip, with no tongue or laryngeal involvement. On day 7 after admission, approximately 72 h after discontinuation of the ramipril, the lip swelling had completely resolved, and there was no further swelling of any area of the patient's body.



DISCUSSION

Angioedema is a vascular reaction that involves swelling of the deep dermal and subcutaneous tissues.³ This condition is often characterized by asymmetric, well-demarcated, nonpitting edema.^{1,4,5} Any area of the body may be involved, yet it most commonly affects the face, lips, tongue, and throat.^{1,3-5} Some of the less commonly reported sites of angioedema associated with the use of ACE inhibitors include the small bowel and the genitals^{6,7} (Table 1). The patient described here experienced a migrating angioedema, which started with swelling of a single hand and foot, progressed to the opposite hand and foot, and finally involved the lower lip. The swelling was asymmetric, well demarcated, nonerythematous, and nonpainful, with minimal pruritis.

In this case several medications previously associated with angioedema had been started during the patient's hospital stay. The agents that might have been involved in the reaction observed in this patient include ramipril, captopril, alteplase, contrast dye, and ASA. However, reports of angioedema with presentations similar to this patient's reaction have not been identified for alteplase, contrast dye, or ASA. These latter medications tend to cause angioedema soon after or during drug administration.¹⁴⁻¹⁷ Given the temporal relationship between administration of medication and the onset of swelling, alteplase, contrast dye, and ASA were considered less likely to have caused the angioedema in this patient.

ACE-inhibitor-induced angioedema may account for 35% to 40% of cases of angioedema.^{2,18} According to the Naranjo adverse drug reaction scale,¹⁹ the risk of angioedema induced by ACE inhibitors was rated as "possible" for this patient.

Angioedema is a known adverse effect of ACE inhibitors. The exact mechanism has not been determined, although several have been proposed. One suggestion is that accumulation of bradykinin leads to vasodilatation, fluid extravasation, and ultimately angioedema.^{9,20} Other possibilities include an immune-mediated effect, complement 1 esterase inhibitor deficiency, histamine-related or substance-P-related effects, and deficiencies of certain enzymes.^{3,9,21} Angiotensin II receptor antagonists are thought to be a suitable alternative for patients who do not tolerate ACE inhibitors, although there have been reports of patients experiencing angioedema from both ACE inhibitors and angiotensin II receptor antagonists.^{22,23}

The patient described here experienced a migrating

Table 1. Infrequently Reported Presentations of Angioedema Associated with Angiotensin-Converting Enzyme Inhibitors⁶⁻¹³

Single Site	Multiple Sites
Penis	Face, hands, feet
Small bowel	Face, arms, legs
Subglottic stenosis	Lips, scrotum, feet
Transient myocardial dysfunction	Face, legs
Pancreatitis	Lips, scrotum
	Face, arms
	Tongue, lips, eyes

localized angioedema affecting 3 distinct areas of his body, each area being affected for about 24 h. The initial diagnosis was complicated by the patient's unusual presentation. Patients experiencing angioedema involving more than one body site have been described previously.^{8,13} However, no previous reports of migrating angioedema were identified, and published reports of extremity involvement have been limited.⁸

Angioedema resulting from administration of ACE inhibitors occurs most often during the first week of drug therapy, although it may occur years after initiation of therapy.^{5,8,24} In this case the first stages of angioedema developed approximately 4 days after the ACE inhibitor was started. Treatment includes discontinuing the drug, even when the angioedema is not severe, and providing supportive therapy.^{3,5} Angioedema tends to resolve without medications within hours of discontinuation of the ACE inhibitor.^{21,24} Methylprednisolone and diphenhydramine may have a role in treating allergic angioedema, but their efficacy has not been proven for ACE-inhibitor-induced angioedema.^{4,24} These 2 agents afforded only minimal benefit for the patient described here, as new angioedema sites continued to develop. For this patient the angioedema resolved approximately 72 h after ramipril was discontinued. This time frame correlates with the anticipated rate of drug elimination (the half-life in the therapeutic range of ramiprilat, the active metabolite of ramipril, is approximately 11 to 17 h²⁵).

The patient has not experienced any further episodes of angioedema since the ACE inhibitor was discontinued. Because of the potential risk of recurrent and possibly life-threatening angioedema the patient has not been re-challenged with an ACE inhibitor or angiotensin II receptor antagonist since his hospital admission. The medications he is currently taking include metoprolol 50 mg bid, ASA 325 mg daily, and microcoated fenofibrate 160 mg daily.



In summary, this patient experienced angioedema migrating from the left hand and right foot to the contralateral limbs and finally to the lower lip. This case is reported here to increase the awareness of potential unusual presentations of ACE-inhibitor-associated angioedema.

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