Enalapril-induced angioedema: A forgotten adverse event

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Abstract
Angioedema is an edema of skin, mucosa, respiratory, and gastrointestinal tract, due to vascular permeability increase, resulting in plasma extravasation, which has been associated with multiple causes. We describe a case of a patient who was prescribed with enalapril and presented with symptoms suggestive of angioedema.

KEYWORDS
ACE inhibitors, adverse event, angioedema, enalapril

1 INTRODUCTION: WHAT IS KNOWN AND OBJECTIVES?
Angiotensin-converting enzyme (ACE) inhibitors are widely used and effective antihypertensive agents.1 The most common side effects of ACE inhibitors are vertigo (4%), cough (3%), headache (2.5%), hypotension (2%), dysgeusia, and worsening of renal function in patients with renal artery stenosis.2 Its safety profile is well established; however, one of its feared adverse events is angioedema with a reported incidence of 0.1%–0.7%.3,4

Angioedema is characterized by asymmetric edema of the skin and mucous membranes (including the gastrointestinal and respiratory tracts), secondary to increased vascular permeability extravasation plasma.5 Is an entity of multifactorial etiology and non-specific symptomatology, for which clinical suspicion and exploration of differential diagnoses are of great importance.

We describe a patient with heart failure with reduced ejection fraction (LVEF), of unknown cause, who received treatment with enalapril as a drug to optimize ventricular function and as a mortality modifier and developed symptoms suggestive of angioedema. Angioedema associated with the use of ACEIs is a forgotten adverse event. There is no frequent report of this manifestation, and the available studies show the underreporting of this association.

2 DETAILS OF THE CASE
An 82-year-old female patient with heart failure with depressed LVEF, dilated cardiomyopathy of unknown cause,
and hyperthyroidism was under pharmacological management (enalapril 5 mg/12 h, propranolol 40 mg/12 h, spironolactone 25 mg/day, atorvastatin 40 mg/day and methimazole 5 mg/8 h). She consults with sensation of marked generalized xerosis (Figure 1A), edema, and facial erythema with greater bipoalpebral, oral, and lingual involvement (Figure 1B), denying pruritus in face, dyspnea, dysphonia, or other associated symptoms. Vital signs and physical examination were unremarkable. She reported symptoms began 45 days ago, coinciding with the start of the ACE inhibitors.

Laboratory tests revealed eosinophilia (2600/µL–Normal Value (NV) 0–800), increased IgE (>3000 IU/ml–VN 1.5–378 IU/ml) and CRP (17.4 mg/L–VN<6 mg/L). Angioedema due to ACE inhibitors was diagnosed.

She was hospitalized, ACE inhibitors were withdrawn, steroids and oral antihistamines were started. She was assessed by dermatology who performed a biopsy in the area of erythema and xerosis for diagnostic confirmation (Figure 2). After 6 days, she presented symptom resolution (Figure 1C), and hospital discharge was indicated. She is currently asymptomatic in follow-up and without new episodes of angioedema.

3 | DISCUSSION: WHAT IS NEW AND CONCLUSION?

Angioedema is observed more frequently in treatments lasting more than 3 months, especially with long-acting ACE inhibitors. Usually occurs within the first year of exposure, although there are reports of late-onset cases. The latency period between taking the drug and the onset of symptoms is highly variable: ranging from the first weeks of treatment in 42%–72% of cases with descriptions up to 23 years later.

Several types of angioedema are known histaminergic, hereditary, associated with acquired C1 inhibitor deficiency, associated with angiotensin-converting enzyme inhibitors, bradykinin-mediated, and idiopathic non-histaminergic angioedema. The development of angioedema will depend on the release of histamine, bradykinins, or a stimulus unknown as in idiopathic. In this case, it was an ACE-associated angioedema. ACE inhibitors act on the renin–angiotensin–aldosterone axis, blocking the angiotensin-converting enzyme, which converts angiotensin I to angiotensin II. Additionally, this is responsible for the degradation of bradykinin, which binds to receptors, increasing vascular permeability and stimulating the release of substance P, which in turn has a vasodilator effect, resulting in extravasation into the tissues and ultimately to the manifestation of angioedema. Other theories have been established in the development of ACE-associated angioedema, suggesting that in those that occur there is a slowdown in the degradation of bradykinins, producing vasodilation, and stimulation of substance P.

Multiple publications have shown underreporting of this adverse event. In France, a registry was carried out from 1994 to 2013 of angioedema associated with ACE inhibitors or angiotensin II receptor blockers (ARB), finding 112 cases of which 77% were related to ACE inhibitors and 21% to ARB. The average duration for the appearance of the first crisis was 720 days, being of greater presentation in the first week with an incidence of 1:1000. A median duration of symptoms of 36.5 h has been reported. 41% of patients had recurrences despite discontinuation of medication.

Regarding the characteristics of angioedema crises, airway involvement is reported in 89% of cases, 48.2% lingual involvement, 23.2% laryngeal involvement, and to a lesser extent at the abdominal level. Other cutaneous locations are less frequent, and it is inferred that in some cases epigastric and abdominal discomfort could be due to angioedema of the gastrointestinal tract. Infection of the palms, soles, or genitalia is rarer.

Several risk factors have been described for the development of this adverse event, such as age >65 years, female gender, black race, coronary heart disease, heart

![Figure 1](image-url)
failure, previous history of seasonal allergies, smoking, or concomitant use with DPP4 inhibitors. Other risk factors include airway narrowing, obesity, and interruption of treatment, as well as hemodialysis, because the membranes used activate bradykinins and potentiate the effect of ACE inhibitors.

To achieve an adequate diagnosis, this requires the exclusion of other causes of angioedema without urticaria, mainly hereditary angioedema or caused by other drugs. There are useful screening methods, such as skin tests and measurement of specific IgE in blood; however, the gold standard for diagnosis is the double-blind placebo-controlled challenge test. It is recommended to measure C4 levels, since there is a predisposition to develop hereditary angioedema in response to ACE inhibitors.

Treatment is generally based on discontinuation of the drug, the use of antihistamines, corticosteroids, and adrenaline, although the use of the former is controversial since this reaction is not mediated by histamine. Corticosteroids have an effect by expressing the angiotensin-converting enzyme, which accelerates the metabolism of bradykinin, reducing mucosal and skin compromise. The efficacy of molecules for hereditary angioedema is being evaluated.

In severe cases with airway compromise, icatibant, a bradykinin B2 receptor inhibitor, can be administered 30mg subcutaneously, which is usually effective in most patients. The use of human plasma derived C1 inhibitor concentrates could also be effective.

The gold-standard management is drug suspension. After discontinuation of ACE inhibitors treatment, the condition usually reverts spontaneously in a matter of days; however, some works mention that it could even last for months.

Angiotensin-converting enzyme inhibitors play a very important role in the treatment of high blood pressure and heart failure. With increasing use, a greater number of side effects have been observed and an increase in the frequency of angioneurotic edema is expected. Risk factors have been established to consider for early recognition, since it can have a potentially fatal outcome. Unfortunately, there is not a frequent report of this manifestation. The reporting culture will return the due importance to this reaction to take timely measures and reduce the associated morbidity and mortality.

AUTHOR CONTRIBUTIONS
All authors contributed to preparing this article. MCMB, AMMS, and BEOS were involved in data preparation and data interpretation. MCMA was involved in the draft writing. FMJ and JCGD critically revised the report, commented on drafts of the manuscript. All authors approved the final report.

ACKNOWLEDGMENTS
None.

CONFLICT OF INTEREST
There is no conflict of interest.

DATA AVAILABILITY STATEMENT
Data are available on request.

ETHICAL APPROVAL
This study has been reviewed and approved by Universidad del Norte and Centro Hospitalario Serena del Mar. We confirm that all authors have read the Journal’s position
on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Manzur-Barbur MC, Mejia-Sanjuanelo AM, Martínez-Ávila MC, Manzur-Jattin F, García-Dominguez JC, Orozco-Sebá B. Enalapril-induced angioedema: A forgotten adverse event. Clin Case Rep. 2022;10:e05944. doi:10.1002/ccr3.5944