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SHORT REPORT

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Critical angioedema induced by a renin angiotensin system blocker in the contemporary era of increasing heart failure: A case report and commentary

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Abstract

Bradykinin-mediated angioedema, a nonallergic reaction most commonly caused by renin angiotensin system (RAS) blockers, has the potential to lead to a critical condition. RAS blockers are important for treating heart failure and are widely used in clinical settings. We present the case of an 85-year-old man who was administered enalapril after percutaneous coronary intervention for an acute myocardial infarction and developed severe angioedema requiring a tracheostomy. He had multiple risks for angioedema including advanced age, smoking history, renal dysfunction, and longstanding use of an angiotensin receptor blocker. The prompt diagnosis of drug-induced angioedema is critical and depends on physicians' recognition of risk factors and knowledge of pathophysiology. In the present era of increasingly prevalent heart failure, it is imperative that the possibility of angioedema receives attention, especially given the continuing reliance on RAS blockers and the advent of angiotensin receptor neprilysin inhibitors, a new type of heart failure drug.

1 | CASE REPORT

An 85-year-old man with a history of hypertension treated with candesartan was admitted to our hospital at midnight due to chest discomfort. His blood pressure was 93/47 mmHg, and his pulse rate was 61 bpm without heart murmurs or leg pitting edema. Electrocardiography revealed a complete atrioventricular block and ST elevations in II, III, aVF, and V3R–V5R lead with reciprocal changes. Transthoracic echocardiography detected akinesis of the inferior wall with an ejection fraction of 40%. Blood tests showed an elevated white blood cell count and creatinine level, but no elevation of creatine phosphokinase or the troponin T level. Under the diagnosis of acute inferior myocardial infarction, an emergency coronary angiography revealed 99% stenosis in the proximal right coronary artery, and an ad hoc percutaneous coronary intervention (PCI) was successfully performed.

On the day following the PCI, we discontinued the patient's candesartan 4 mg and introduced enalapril 2.5 mg. His blood pressure was 149/60 mmHg at the time of the introduction of enalapril. About 6 h later, slight swelling was noted on the patient's tongue and neck (Figure 1A). The amount of sputum increased, and his tongue turned a dark-red color. Twenty hr after the patient took the first dose of enalapril, the tongue and neck swelling worsened, and the patient began to experience dyspnea. Tracheal intubation failed due to the edematous tongue and neck, necessitating an emergent tracheostomy (Figure 1B).

Computed tomography showed marked edema of the tongue and soft tissue of the neck compressing the trachea (Figure 1D–F). We suspected the presence of angiotensin-converting enzyme

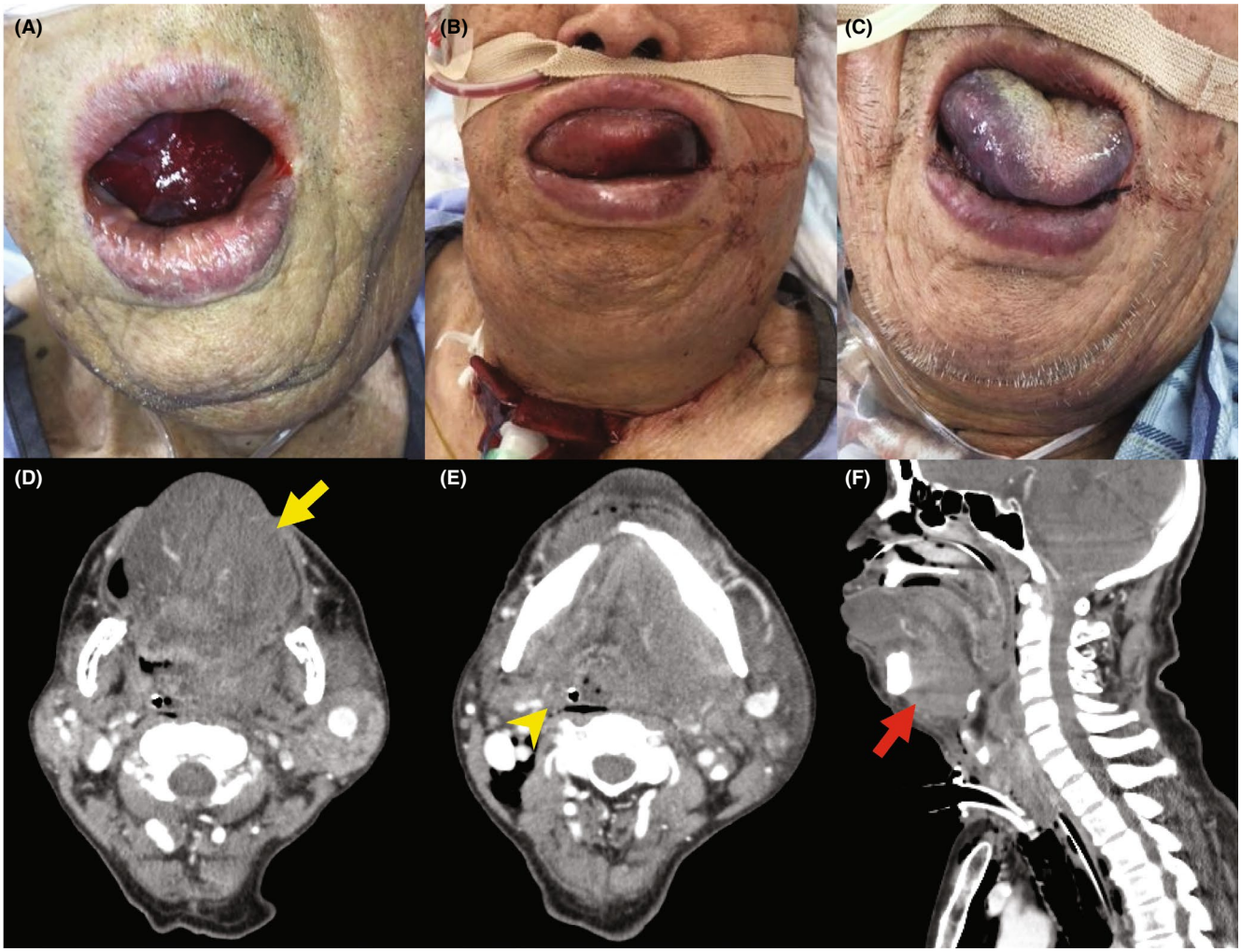

FIGURE 1 Time-series changes in the patient's tongue and neck findings. A, About 6 h after the patient took enalapril, mild swelling was observed in the tongue and neck. B, At the 20 h after taking enalapril, the swelling of the patient's tongue and neck worsened. Because of the patient's dyspnea and the inability to intubate the patient, a tracheostomy was performed. C, Angioedema improved ~72 h after the discontinuation of enalapril. D–F, CT images showing the marked edema of the tongue and soft tissue of the neck (*yellow and red arrow*), resulting in compression of the trachea (*yellow arrowhead*)

inhibitor-induced angioedema (ACEI-AE) based on the clinical presentation and sequence of events. We discontinued the enalapril, and the edema improved in about 72 h (Figure 1C). The patient's laboratory data showed no decrease in the levels of C4 or C1 esterase inhibitors (C1-INH); therefore, hereditary angioedema and acquired C1-INH deficiency could be ruled out with a presumptive diagnosis of ACEI-AE. We carefully re-introduced candesartan, which the patient had taken before, and there was no recurrence of angioedema. Fiberoptic laryngoscopy revealed improvement in the pharyngeal and laryngeal edema, and the tracheotomy was surgically closed on the 26th hospital day. The patient was discharged on the 36th day of illness.

2 | DISCUSSION

We have presented a typical but potentially fatal case of ACEI-AE. Fortunately, careful follow-up and intensive care with early detection and proper airway management saved the patient's life. Bradykinin-mediated angioedema is classified into three groups: hereditary C1-inhibitor deficiency, acquired C1-inhibitor deficiency, and drug-related angioedema (including ACEI-AE).[1] ACEI-AE presents with nonpitting subcutaneous edema and without urticaria and has a longer onset, whereas histamine-mediated angioedema causes flushing, pruritus, and urticaria, and generally presents within 60 min of antigen exposure.[1] The incidence of ACEI-AE among patients taking ACE inhibitors is reported to be 0.1%–0.7%,[2–4] which is the highest incidence among drug-induced angioedema cases.[5] ACEI-AE mainly affects the lips, face, neck, tongue, and sometimes bowels and is life-threatening when it extends to the larynx and compresses the airway.[6]

It was reported that angioedema occurred in 86 (0.68%) of 12 577 enalapril-treated patients, but only two patients (0.01%) required hospitalization and none required mechanical airway management.[6] On the other hand, there are cases of ACEI-AE requiring tracheal intubation or tracheostomy, and leading to death.[5] Angioedema often

develops within the first week of taking an angiotensin-converting enzyme inhibitor (ACEI), and symptoms resolve spontaneously in 48–72 h with discontinuation of the causative agent.[7] In clinical settings, antihistamines, steroids, and adrenaline are often used for bradykinin-mediated angioedema, but the efficacy of these drugs has not been proven.[2] Considering our patient's clinical course, we did not use glucocorticoids, antihistamines, or epinephrine because we diagnosed bradykinin-mediated angioedema due to the ACE inhibitor (ie, enalapril).

In recent years, the efficacy of fresh frozen plasma and C1-INH for ACEI-AE has been reported,[2] and these drugs may be considered for the treatment of severe angioedema such as that experienced by our patient. ACEIs reduce bradykinin degradation, which causes vasodilation and vascular hyperpermeability, resulting in angioedema.[2] ACEI-AE is rare but can be fatal in clinical practice[1]; thus, recognizing the risk factors for angioedema is important. We reviewed the literature and summarize the risk factors for ACEI-AE in the Table 1 with the relevant past cases and our patient's case.[1–4,6,8–14] We could find many background risks and triggers of ACEI-AE, whereas drugs can also be background risks or triggers of ACEI-AE by their nature. For this reason, the drugs are displayed separately in the Table 1.

Hoover et al noted that tissue injury has been linked to an upregulation of B1 receptors and an increased level of des-Arg9-BK (which acts at the B1 receptors); this link provides a potential mechanism underlying the development angioedema under the above-described circumstances.[1] Homma et al reported that 7 days after receiving a PCI for a myocardial infarction, a patient developed angioedema after brushing his teeth.[11] Based on these reports, a local tissue injury such as that caused by a myocardial infarction or PCI may be a risk for angioedema. Our patient also developed angioedema after the PCI for myocardial infarction, although this situation seems to be rare in clinical practice. The accepted understanding is that angioedema develops when certain triggers are added to certain patient backgrounds (see the Table 1).[12]

Our patient had been taking candesartan for a long time. Campbell et al reported that losartan increases bradykinin levels, and the cause of the increase in bradykinin levels can be a change in metabolism mediated by neprilysin (NEP) and angiotensin-converting enzyme (ACE) due to a chronic administration of losartan. They also noted that decreased lung NEP activity has a greater effect on elevated bradykinin levels than decreased lung ACE activity.[13] The established guideline recommends that an ACEI should be induced within 24 h to patients at high risk of left ventricular dysfunction (ie, with an ejection fraction ≤40%) or heart failure after the onset of acute coronary syndrome.[15] Following this guideline, we stopped our patient's candesartan and started enalapril the next day without a washout period. Therefore, the patient's long-term oral candesartan regimen may have increased his bradykinin level to such an extent that the new administration of enalapril led to a further increase in the bradykinin level that provoked the severe angioedema.

Angiotensin receptor neprilysin inhibitors (ARNIs) are a newly approved class of drugs for the treatment of heart failure. The first commercial drug in this class, sacubitril/valsartan (trade names Entresto®, Azmarda, Neparvis, and others), is a combination of sacubitril (an NEP inhibitor) and valsartan. This combination drug can also cause angioedema. NEP inhibitors block the conversion of natriuretic peptides to inactive metabolites and activate natriuretic

TABLE 1 Risk factors for ACEI-AE classified by patient backgrounds and triggers

Background	Trigger	Drug
Hereditary angioedema[2]	Trauma[1]	ACEI[1,8]
C1-INH deficiency[1]	Cardiac catheterization[1]	NSAID[1]
African American[1,2,4,6,8]	Anesthesia[1,12]	Aspirin[1,4]
Female gender[1,2,4,8]	Intubation procedure[1]	DPP IV inhibitor[2,4]
Elderly patient[1,2,4,8]	Transplant[1]	Statin [4]
Smoking[1,2,4]	Ischemic stroke thrombosis[9,10]	Lidocaine[1,12]
History of angioedema[1]	ACS[11] (our patient)	Immunosuppressive agent[1]
History of ACEI-induced cough[1]		Tissue-plasminogen activator[10]
Food/contact allergies[1]		ARB[13] (our patient)
Seasonal allergies[1,2,4,6]		ARNI[3,14]
Absence of diabetic mellitus[1,2,4,6,8]		
Coronary artery disease[1,8]		
Chronic heart failure[1,8]		
Renal dysfunction[1,6]		

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; C1-INH, C1 esterase inhibitor; DPP IV, dipeptidyl peptidase IV; NSAID, non-steroidal anti-inflammatory drug.

peptide receptor A for vasodilatory, natriuretic, and cardio-protective effects.

Neprilysin is an enzyme that inactivates bradykinin and kallidin; thus, NEP inhibitors increase blood levels of bradykinin and kallidin.[14] In the OCTAVE trial, angioedema appeared more frequently in the patients treated with omapatrilat (2.17%), which inhibits both NEP and ACE, compared to the patients treated with enalapril (0.68%). As a result, the US Food and Drug Administration withheld its approval for omapatrilat.[3]

The results of the PARADIGM-HF study demonstrated that the use of ARNIs reduced the risks of cardiovascular death and hospitalization for heart failure compared to enalapril in patients with heart failure with reduced ejection fraction.[14] There was no significant difference in angioedema causation, with 19 cases (0.45%) caused by an ARNI and 10 cases (0.24%) by enalapril; however, there was a suspicion that the diagnosis of angioedema may have been underestimated due to selection bias.[4] Therefore, the incidence of angioedema due to ARNI treatment in clinical practice may be higher than that previously reported. In today's era of increasingly prevalent heart failure, ARNIs are expected to be used more frequently, and physicians should be aware that ARNIs can cause angioedema because of its active mechanism. It is crucial to understand the risk factors when prescribing ARNIs or the RAS inhibitors for the first time, and early recognition of signs such as swelling of the neck or tongue, pharyngeal discomfort, and dyspnea will contribute to a timely diagnosis of angioedema.

3 | CONCLUSIONS

We treated a patient with severe angioedema due to administration of an ACEI after an emergency PCI. The prompt and early diagnosis of angioedema due to an RAS blocker's administration is important because angioedema can be fatal, and since the use of RAS blockers continues to increase.

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CONFLICT OF INTEREST

All authors report no potential conflicts of interest in relation to this article.

AUTHOR CONTRIBUTION

Takahashi M takes primary responsibility for this paper. Sato M wrote the manuscript. Sato M, Takahashi M, and Kario K reviewed/edited the manuscript.

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REFERENCES

1. Hoover T, Lippmann M, Grouzmann E, et al. Angiotensin converting enzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors. *Clin Exp Allergy*. 2010;40:50-61.
2. Brown T, Gonzalez J, Monteleone C. Angiotensin-converting enzyme inhibitor–induced angioedema: a review of the literature. *J Clin Hypertens*. 2017;19:1377-1382.
3. Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: the omapatrilat cardiovascular treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens*. 2004;17:103-111.
4. Kostis WJ, Shetty M, Chowdhury YS, et al. ACE inhibitor-induced angioedema: a review. *Curr Hypertens Rep*. 2018;20:55.
5. Weisman DS, Arnouk N, Asghar MB, et al. ACE inhibitor angioedema: characterization and treatment versus non-ACE angioedema in acute hospitalized patients. *J Community Hosp Intern Med Perspect*. 2020;10:16-18.
6. Kostis JB, Kim HJ, Rusnak J, et al. Incidence and characteristics of angioedema associated with enalapril. *Arch Intern Med*. 2005;165:1637-1642.
7. Bezalel S, Mahlab-Guri K, Asher I, et al. Angiotensin-converting enzyme inhibitor-induced angioedema. *Am J Med*. 2015;128:120-125.
8. Miller DR, Oliveria SA, Berlowitz DR, et al. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension*. 2008;51:1624-1630.
9. Fröhlich K, Macha K, Gerner ST, et al. Angioedema in stroke patients with thrombolysis: a lesion mapping study. *Stroke*. 2019;50:1682-1687.
10. Lekoubou A, Philippeau F, Derex L, et al. Audit report and systematic review of orolingual angioedema in post-acute stroke thrombolysis. *Neurol Res*. 2014;36:687-694.
11. Homma H, Aoki J, Tanabe K. Life-threatening angioedema after primary percutaneous coronary intervention. *Intern Med*. 2015;54:999-1000.
12. Schiller P, Messmer SL, Haefeli W, et al. Angiotensin-converting enzyme inhibitor-induced angioedema: late onset, irregular course, and potential role of triggers. *Allergy*. 1997;52:432-435.
13. Campbell DJ, Krum H, Esler MD. Losartan increases bradykinin levels in hypertensive humans. *Circulation*. 2005;111:315-320.
14. McMurray JJ, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.
15. Kimura K, Kimura T, Ishihara M, et al. JCS 2018 guideline on diagnosis and treatment of acute coronary syndrome. *Circ J*. 2019;83:1085-1196.

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