An encounter with enalapril-induced resistant, life-threatening angioedema at rural health center in Botswana

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Abstract
Angioedema, a rare, potentially fatal and usually self-limiting adverse effect of therapy with enalapril, is always a challenging encounter for an intensive care specialist at a rural setup. Here, we present a 74-year-old female, who presented to the Emergency Department of Sekgoma Memorial Hospital, Serowe village, Botswana, with progressive swelling of her face, tongue and breathing difficulty just 2 days after starting tablet enalapril. She failed to respond to usual treatment with adrenaline, steroids, and H1-antihistaminic agent, but she responded well with intravenous fresh-frozen plasma infusion. This helped us manage a difficult airway situation in a less equipped rural health center.

Keywords: Angioedema, angiotensin-converting enzyme inhibitor, difficult airway, enalapril, fresh-frozen plasma

Introduction
A rare, potentially fatal and usually self-limiting adverse effect of therapy with enalapril, the angioedema, is always a challenging encounter for an intensive care specialist. The unpredictability of clinical course and the risk of airway compromise with not so high end airway management gears at hand make it more challenging in a rural health setup. Incidence of enalapril-induced angioedema is three times more common in population of African origin.[1] Botswana is a country in Southern Africa and black race constitutes 96% of population. Botswana provides universal health care to its citizens, and health sector is almost completely under government management. Enalapril is one of the most commonly used antihypertensive agents. All these factors make enalapril-induced angioedema a frequent encounter at emergency department. We came across two cases in a very short window of about a month at a rural health center.

Case Report
A 74-year-old female was admitted to the Emergency Department of Sekgoma Memorial Hospital, Serowe village, Botswana, past midnight with progressive swelling of her face, tongue and breathing difficulty for about 8 h. The family gave a history of change of antihypertensive medication recently. She has been started on tablet enalapril, 20 mg, once daily, orally, 2 days back. On examination, she was conscious, coherent but very anxious. Her heart rate was 123/min, regular. Blood pressures were high and reading was 180/96 mmHg. Her room air oxygen saturation was 91% (SpO2). There was no stridor. On auscultation of...
chest, air entry was good bilaterally and there were some conducted sounds from pharynx due to excessive secretions. The tongue was grossly swollen, hard in consistency, it was wedged between the teeth and she was not able to close her mouth [Figure 1]. Lot of secretions were pooling in and dribbling from the mouth. There was no space in oral cavity for oral intubation. Only possible airway managements were a blind nasal intubation or surgical airway. It was not possible to transfer this case to a tertiary care hospital by helicopter as there were landing issues in darkness. Transfer by road was risky for patient as it would have taken 5 hours. It was decided to go ahead with management locally. The patient was started on oxygen support at the rate of 5 l/min by facemask for building up her oxygen reserves in case of airway emergency. Lateral view X-ray of neck was done which showed airway patency as fine [Figure 3]. Elective blind nasal intubation as a proactive airway management was risky due to less chances of success and more risk of further airway compromise. There were no ear, nose, and throat (ENT) specialists available for either evaluation or surgical airway management. She was injected with 100 mg of hydrocortisone, intravenously and 0.5 ml of injection adrenaline (1:1000) subcutaneously. Injection pheniramine maleate, 45.5 mg, was injected intravenously. She was positioned in sitting position. Intermittent atraumatic oral suction was advised. She was observed for about 30 min in which she gradually became worse and swelling of face and tongue increased. Blood pressures were shooting up. Provisional diagnosis was enalapril-induced angioedema. We decided to go ahead with fresh-frozen plasma infusion under intravenous beta-blocker antihypertensive coverage. Her blood group was O-positive and hospital being a peripheral center; we had only blood storage facility where O-positive fresh-frozen plasma was not available. Blood bank was 3 h away. We decided to go ahead with transfusion of the only pint of O-negative fresh-frozen plasma available at our storage facility. Injection metoprolol, 5 mg, intravenously was instituted and then we started with O-negative fresh-frozen plasma infusion intravenously, 220 ml over next 30 min. On post-fresh-frozen plasma infusion, patient’s condition started improving [Figure 2]. Blood pressures remained stable around 150/90 mmHg after metoprolol injection. Over next 2½ hours, she recovered grossly and after 6 h she was able to close her mouth completely. We shifted her to wards after counseling about ACEI and ARB. We explained in detail the need to avoid enalapril.[2]

**Discussion**

ACE inhibitors are one from the most widely used antihypertensive worldwide, particularly for the diabetics to prevent nephropathy[3] and in cases of left ventricular dysfunction or heart failure.[4] Soon after the development of ACE inhibitors, Wilkin et al.[5] reported angioedema and proposed enhanced kinin effects from inhibition of kininase II as the underlying mechanism.
Later, reports of ACE inhibitor-related angioedema estimated an incidence between 1/1000 and 3/1000.[6]

Kostis et al.[3] reported following about enalapril-induced angioedema. Angioedema was about three times more likely to occur among black patients (1.62% vs. 0.55% for white patients) and slightly more likely in women (0.84% vs. 0.54% for men). The incidence of angioedema was lower in diabetic patients (0.43%) and higher in patients with renal disease (1.63%) or a history of rash (2.48%). The most common sites of angioedema were the lips (49%) and the face (52%). Swelling of the tongue, neck, or eyelids occurred in approximately 1 of 5 patients with angioedema. The incidence of angioedema was not affected by prior or current use of ACE inhibitors at randomization. They identified black race, history of drug rash, age >65 years, and seasonal allergies as independent risk factors for angioedema related to enalapril. This case being reported had two of these risk factors.

Angioedema is more likely to occur early after initiation of ACE inhibitor therapy. Slater et al.[8] reported a 14-fold higher incidence of angioedema in the 1st week compared with later time intervals. Hedner et al.[9] reported that about half of the cases occurred in the 1st week of therapy. This case under discussion also presented in the 1st week of therapy.

The management of angioedema should be prompt and aggressive. Discontinuation of the initiating agent and supportive care are the keys to therapy. Careful management of the airway is crucial as well. On presentation, these patients should be carefully examined for any evidence of respiratory compromise such as stridor, a markedly enlarged tongue, symptoms of dyspnea, acutely presenting dysphagia, and drooling of saliva. Lateral view X-ray of neck may be an important tool to decide about intubation. Airway shadow can give a status of laryngeal edema. The decision of when to intubate should be made early based on standard physiologic criteria, recognizing that intubation may be difficult secondary to edema of the airway. Cricothyrotomy or emergency tracheostomy is required for maintenance of the airway if oropharyngeal and nasopharyngeal intubation fails. A careful ENT examination is recommended in all cases.

Fluid resuscitation and therapy with vasopressors may be required if the patient is hemodynamically unstable. Hypotension can be seen in severe cases secondary to the extravasation of large amounts of fluid into the extravascular space. Patients presenting with respiratory symptoms should immediately receive 0.5 ml epinephrine (1:1000) subcutaneously.[10] The dose can be repeated in 15–20 min. Therapy with antihistamines and steroids should be started initially in all patients, as a true allergic reaction cannot be excluded. Although the role of epinephrine, antihistamines, and corticosteroids is controversial in nonmast cell-mediated angioedema, i.e. ACE inhibitor-related angioedema,[11] in our case, we used all the three above-mentioned agents but there was no clinical improvement. Fresh-frozen plasma has been used successfully for the treatment of resistant, life-threatening angioedema induced by ACE inhibitor.[12,13] The benefit of fresh-frozen plasma in this condition may be due to the effect of kininase II in breaking down accumulated bradykinin.[14,15] In this case, we used fresh-frozen plasma, and the clinical improvement was observed. We recommend that in case of life-threatening enalapril-induced angioedema in rural setup, where advanced airway management procedures may be difficult, we must give an early thought about starting fresh-frozen plasma.

These therapies can be safely used until the etiologic agent is identified and discontinued. Supportive management should continue until upper airway swelling has resolved. Once angioedema has resolved, patients can be safely discharged to home.

Declaration of Patient Consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

References