

ACE inhibitor-induced angioedema: a case report and review of current management

Nina Kloth and Andrew S Lane

Clinical record

A 76-year-old woman presented to hospital with a 24-hour history of sore throat and left-sided facial pain. There was associated tongue swelling that had worsened over the previous 4 hours, causing an inability to speak, and drooling of saliva. She denied any pruritis or warmth around the area of swelling, and denied any recent contact with allergens. Relevant past medical history included acute myocardial infarction with subsequent coronary artery bypass surgery, hypertension, hypercholesterolaemia, depression and psoriasis. Her medications were ramipril, aspirin, atorvastatin, sertraline and glycerol trinitrate spray. She had no known drug allergies.

On examination, the patient's vital signs were as follows: temperature 38.2°C, blood pressure 161/75 mmHg, heart rate 108 beats/min, respiratory rate 16 breaths/min, and oxygen saturation 98% on 6 L oxygen/min. She had unilateral left-sided tongue swelling and palpable, tender left sublingual and submandibular glands. In view of these findings, an intra-oral abscess was diagnosed. Blood testing revealed raised levels of inflammatory markers (white cell count $16.5 \times 10^9/L$ with neutrophilia; C-reactive protein (CRP) 188 mg/L, and procalcitonin 10.45 ng/L), suggesting a bacterial infection. Antibiotic therapy with cefazolin, metronidazole and gentamicin was initiated, and intravenous hydrocortisone was given before the patient was transferred to a tertiary hospital for surgical review.

After transfer, the patient's respiratory function deteriorated and she required urgent intubation using fiberoptic guidance in the operating theatre. After successful nasotracheal intubation, she was then transferred to the intensive care unit. Antibiotic therapy was initially changed to clindamycin and benzyl penicillin, but after review of a subsequent computed tomography (CT) scan of her neck (Figure 1), which showed no evidence of an infective collection but revealed significant airway oedema, all antimicrobial therapy was ceased.

On Day 2, the tongue swelling increased so that it was now protruding out of her mouth, and she received two units of fresh frozen plasma. On Day 3, the swelling began to recede. A second CT scan once again did not suggest any infective collections, but showed a reasonable amount of space around the endotracheal tube (Figure 2). The patient was extubated on Day 4 and discharged from the ICU on Day 5. Autoimmune serology testing was negative, and

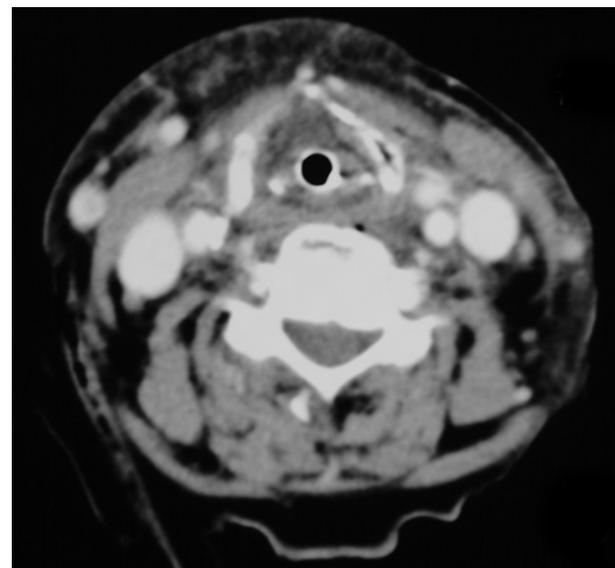
ABSTRACT

Angiotensin-converting enzyme inhibitors (ACEIs) have replaced diuretics and β -blockers as first-line agents for treating hypertension. Cough is a recognised side effect of ACEI treatment, and because of this, patients often have their medication changed to an angiotensin II receptor blocker (AIIIRB). Both ACEIs and AIIIRBs are associated with angioedema. We present a case of a late-onset angioedema associated with pyrexia and raised levels of inflammatory markers. We also discuss the causes and treatments of angioedema, and current controversies surrounding ACEIs and AIIIRBs and their relation to anaphylaxis and angioedema.

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levels of complement, C1 esterase inhibitor (C1EI) and tryptase were normal. There were no positive microbiological cultures.

Figure 1. Computed tomography scan of patient's neck, Day 1



The scan showed no evidence of an infective collection, but revealed significant airway oedema.

The patient remained in hospital for another 3 days and attended immunology outpatient follow-up. Her diagnosis was angioedema secondary to taking angiotensin-converting enzyme inhibitors (ACEIs). She was advised to discontinue any ACEI therapy, and her antihypertensive medication was changed to amlodipine and metoprolol.

Discussion

Angioedema is a non-inflammatory disease characterised by episodes of increased capillary permeability, with extravasation of intravascular fluid and subsequent oedema of the cutis or mucosa of the upper airways or gastrointestinal tract. Oedema of the mucous membranes of the mouth or throat may result in airway obstruction.

Classification of angioedema

Most forms of angioedema are considered idiopathic, and it is classified as occurring with or without urticaria. If urticaria is present on clinical examination, the reaction is considered a hypersensitivity reaction to an offending agent and the sequelae mast cell-mediated.¹ Histamine release and subsequent mast cell degranulation and tryptase release result in endothelial cell permeability, leading to angioedema and generalised urticaria. In severe cases, anaphylactic shock can occur.

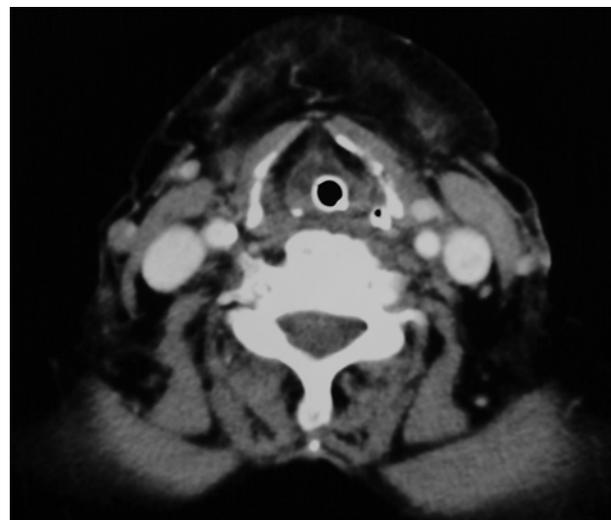
The 10% of angioedema cases that occur without urticaria are considered to be kinin-mediated rather than a hypersensitivity reaction.² This 10% can be classified into hereditary angioedema (HA) or acquired angioedema (AA), which are associated with insufficient or dysfunctional C1EI. Both types of angioedema may occur spontaneously or may be precipitated by stress or medications. It is the kinin-mediated type that is highly associated with ACEI treatment.³

HA can be classified into type 1 and type 2. Type 1 is characterised by C1EI deficiency, type 2 by C1EI dysfunction with normal to high circulating levels of C1EI. C1EI is a serine protease involved in the regulation of bradykinin. Low levels of C1EI result in activation of the kallikrein-kinin system, the complement cascade, and the fibrinolytic system, resulting in release of vasoactive peptides like bradykinin.^{4,5} These peptides cause vasodilation of endothelial cells, which ultimately manifests in the clinical presentation.³ AA is also classified as type 1 or type 2.¹ Type 1 is associated with B-cell proliferative disorders in which there is resulting hypercatabolism of C1EI, and type 2 is associated with autoantibodies directed against C1EI. Both these mechanisms result in low levels of C1EI.⁶

Differentiation of angioedema types

As HA, AA and ACEI-induced angioedema all present with the same clinical pattern, the cause is differentiated by the patient's history. In the case of ACEI angioedema, diagnosis

Figure 2. Computed tomography scan of patient's neck, Day 3



Once again, there was no evidence of an infective collection, but a reasonable amount of space around the endotracheal tube was now apparent.

is based on current ACEI use, absence of alternative diagnoses including other causes of angioedema, and the prompt resolution of symptoms on discontinuation of the ACEI.⁷ Examination is likely to yield little differentiating pathophysiology, apart from coexisting medical conditions that may also suggest the cause, but there are differences on biochemical analysis.

Specific biochemical investigation involves measuring the levels of complement components C4, C2, and C1 inhibitor, and is recommended in the diagnosis of suspected C1EI deficiency. The measurement of C1q level distinguishes between the acquired and hereditary form: the inherited form of C1EI deficiency is associated with normal levels of C1q, whereas the acquired form is confirmed by low levels of C1q and low C1EI activity.⁸ This latter condition is rare, and was excluded in our patient by normal C4 levels. The relationship between complement component levels and the different types of angioedema is summarised in Table 1.

Although ACEI angioedema has a different biochemical profile from HA and AA, it is classified with them because of the kinin-mediated mechanisms. In the setting of HA, AA and ACEI angioedema, serum bradykinin levels are elevated. As ACE is a natural inhibitor of bradykinin, patients receiving ACEIs have raised levels of bradykinin.

Clinical course of ACEI angioedema and predisposing factors

ACEI-induced angioedema has an incidence of 0.1%–0.7% among patients treated with ACEI. Between 47% and 72%

Table 1. Complement component levels and types of angioedema⁹

Angioedema syndrome	Complement component				
	C1q	C4	C2	C1 inhibitor function	C1 inhibitor level
ACEI/ARB	N	N	N	N	N
Inherited					
Type 1	N	L	L	L	L
Type 2	N	L	L	L	N or E
Acquired	L	L	L	L	N or E

ACEI = angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker. E = elevated. L = low. N = normal.

of patients with this condition present within the first week of commencing treatment,¹⁰ but symptom onset may be delayed by up to 7 years. ACEI angioedema has an unpredictable course, with variable severity and a transient appearance, and is often asymmetrical. The duration varies, but the condition is usually self-limiting to within 24–48 hours.¹⁰ African Americans, women, and patients with a previous history of angioedema are at greater risk of developing ACEI angioedema.^{10,11} It has also been reported that patients with pre-existing narrowing of the oesophageal space (due to obesity, previous surgery or trauma) and patients with obstructive sleep apnoea are more likely to develop ACEI angioedema.¹⁰ A history of ACEI-induced cough has been found to be a risk factor for developing angioedema,¹² and cough has been described in 5%–20% of patients treated with an ACEI.¹³

ACEI angioedema is not allergic in origin. Its aetiology is not completely understood and it may be viewed as a class effect of ACEIs. It is believed that polymorphism may lower the threshold for development of this complication, owing to an inherited lowering of bradykinin metabolism. ACEIs cause local increases in bradykinin levels by reducing the function of ACE, which inactivates bradykinin. If a predisposed individual starts taking an ACEI, angioedema may result, as ACEIs further reduce bradykinin clearance. With respect to the at-risk groups mentioned above, there is some evidence to suggest that African Americans may have an increased sensitivity to bradykinin,¹¹ and predominance of ACEI angioedema in women may reflect the interaction of oestradiol with the various pathways involved in pathophysiology of the condition.⁷

There is some evidence that predisposition to ACEI angioedema has a genetic component.¹⁴ Affected individuals often have affected family members. Another predisposing factor for ACEI angioedema is a previous history of angioedema. Patients who have experienced this condition before may also have relative deficiencies of other enzymes

involved in bradykinin degradation, such as aminopeptidase P or carboxypeptidase N.¹¹ A 2002 study by Adam et al of the plasma activities of both enzymes in hypertensive patients previously diagnosed with ACEI angioedema showed an association between a low plasma activity of aminopeptidase P (a metaboliser of bradykinin) and previous episodes of ACEI angioedema.¹⁵ It is therefore recommended that ACEIs not be used in patients with a history of angioedema.

Comparison of our case with other studies

Although thought to be a rare complication of ACEI use, the incidence of angioedema associated with ACEIs is well reported in the literature. The case reported here is interesting in that our patient presented with angioedema associated with raised inflammatory markers and pyrexia, pointing initially towards the diagnosis of a bacterial infection. There are a few case reports in the literature describing an association of ACEI angioedema with an elevated leukocyte count, raised body temperature or raised CRP level, but none describing a raised procalcitonin level. Our case was unique in that all three inflammatory markers were significantly raised, with associated fever.

In 1984, Gleich et al¹⁶ published a series of four case reports of recurrent attacks of angioedema, urticaria and fever, possibly due to hypereosinophilic syndrome. During the attack, leukocyte counts reached up to $108 \times 10^9/L$ (88% eosinophils). All four patients were below the age of 28 and did not take any regular medications.

In 2005, Bas et al¹⁷ designed a study to identify new factors contributing to ACEI angioedema. They measured inflammatory markers (CRP, fibrinogen, leukocyte count) and body temperature. Their findings demonstrated for the first time that ACEI-induced angioedema is associated with strongly increased plasma levels of CRP and fibrinogen, while leukocyte count and body temperature were normal.

Management of ACEI angioedema

The acute management of ACEI angioedema is not standardised. Antihistamines, corticosteroids and adrenaline are ineffective, both as acute and preventive treatment,¹⁸ in kinin-related angioedema, and there is no good evidence base for their use in this context.^{19,20} Fresh frozen plasma may be administered to a patient with life-threatening acute laryngeal oedema if C1EI is unavailable, and the efficacy of fresh frozen plasma has been suggested by several case reports.¹⁹ However, it is not generally recommended for use in patients with ACEI angioedema, as they already have normal circulating levels of C1EI. Most cases of ACEI angioedema are at the mild end of the spectrum. More severe forms causing upper respiratory tract obstruc-

tion are less common.¹⁹ The most important initial management step in these rare but life-threatening situations is airway assessment, securement if required, and discontinuation of the ACEI.⁷ A 2007 retrospective review of 228 patients with ACEI-induced angioedema showed that the oral cavity was the most common location of upper airway angioedema, with 10% of the patients requiring endotracheal intubation within the first 12 hours of presentation.²¹

Recommencing ACEI treatment after an episode of angioedema is contraindicated, and there is no rationale for trying different ACEIs, as this is a class effect. Some studies show an angioedema recurrence rate of up to 6%, with subsequent episodes being more severe.²² Changing the patient's medication to an angiotensin II receptor blocker (AIIIRB) is also controversial. In principle, AIIIRBs should provide a safe option, as they should not alter bradykinin metabolism, but animal data suggest that there may be a relationship between AIIIRB use and raised tissue bradykinin levels,^{23,24} and cases have been reported of patients having repeated episodes of angioedema after changing their medication to an AIIIRB.⁷ A meta-analysis by Haymoore et al in 2008 revealed a 2%–17% risk of recurring angioedema in patients changing from an ACEI to an AIIIRB after an episode of ACEI angioedema.²⁵ However, this may have been due to the patients' genetic predisposition and may have been an associative rather than causative relationship. Current data suggest that, although the incidence of AIIIRB-induced angioedema (0.1%) is lower than that of ACEI angioedema (0.3%), it can still occur and is potentially life-threatening, especially if the patient has had an episode of angioedema in the past.

In patients with pre-existing cardiovascular disease, their cardiovascular medications may significantly alter the outcome of severe anaphylaxis. Medications such as ACEIs and β -blockers may exaggerate the degree of shock and may make treatment refractory. β -blockers are also relatively contraindicated in patients with known severe anaphylaxis, due to the risk of extreme hypertension on treatment with adrenaline. This is due to unopposed α -adrenoreceptor stimulation.^{26,27}

It has now been suggested that ACEIs may predispose patients to the risk of developing anaphylaxis, as well as rendering treatment refractory.²⁸ For these reasons, ACEIs are also relatively contraindicated for patients with previous known severe anaphylaxis.

Conclusion

The aetiology and pathophysiology of ACEI-induced angioedema are still not well understood and not familiar to many physicians. Treatment of ACEI-induced angioedema is not standardised or well evidenced. We present a case of

late-onset ACEI-induced angioedema that was initially diagnosed as a bacterial infection of the oral cavity. The case demonstrates the difficulty that can surround the diagnosis and reinforces the principle that the priority of treatment in ACEI angioedema is securement of the patient's airway (if required), cessation of the offending medication, and then consideration of other measures.

Author details

Nina Kloth, Registrar in Intensive Care Medicine¹

Andrew S Lane, Staff Specialist in Intensive Care Medicine,¹ and Senior Lecturer in Critical Care²

¹ Nepean Hospital, Sydney, NSW, Australia.

² Sydney Medical School, University of Sydney, Sydney, NSW, Australia.

Correspondence: stuart.lane@sydney.edu.au

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