CASE REPORT

Delayed presentation of ACE inhibitor-induced angio-oedema

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SUMMARY

We report two probable cases of delayed presentation of ACE inhibitor (ACEi)-induced angio-oedema. The first patient was on ACEi for more than 10 years while the second one was on it for 7 years. Both the patients presented with initial unilateral swelling of the tongue which progressed further to involve the soft tissues of the oropharynx, head and neck leading to a compromised airway needing awake fiberoptic intubation and were managed successfully in the intensive care unit (ICU). C1 esterase inhibitor and mast cell tryptase level was normal for both patients. Both were treated with intravenous antihistamines and corticosteroids in the ICU. Both patients were successfully extubated within 72 h and transferred to a medical ward. Age above 65 years, atopy and non-steroidal anti-inflammatory drug use may have been the predisposing factors. Both patients made a full recovery with no complications and the ACEi was ceased.

BACKGROUND

ACE inhibitors (ACEis) are among the most common medicines prescribed in the world. They are recognised as first-line treatment for patients with hypertension and cardiac failure. The majority of cases of ACEi-related angio-oedema occur soon after initiation of treatment, with almost half of patients experiencing their symptoms within 1 week of treatment and over three quarters of patients within 3 weeks after treatment is initiated.¹ However, the duration of time on therapy before symptoms present is unpredictably variable with an average duration of 6–7 months.^{1 2} This delay between initiation of the ACEi therapy and symptom onset often makes identifying the association between the two more difficult, leading to clinicians incorrectly misattributing the presentation to other causes, most commonly food or other drug allergies. This in turn leads to recurrent presentations before the association is recognised and the ACEi is ceased. There are only a few cases reported in literature where similar presentations have happened as late as more than 5 years and hence the report.^{3 4}

CASE PRESENTATION**Patient 1**

A 76-year-old man presented to the emergency department (ED) with a swollen tongue and dysphonia, having woken up from his sleep with an uncomfortable feeling in the mouth. The swelling had started at one half of the tongue and progressed through the entire tongue over an hour

with no response to antihistamines. There was no respiratory distress and he was haemodynamically stable on room air on presentation. There was no urticaria, rhinorrhoea or wheeze.

He had a history of allergic rhinitis, hypertension and ischaemic heart disease (IHD) for which he had undergone two percutaneous coronary interventions. He had no history of asthma or eczema.

His medications included perindopril, clopidogrel, aspirin, pravastatin and diclofenac for a rotator cuff injury. He had no recent additions or dose changes to his medication. He had been on the ACEi for 10 years with no side-effects till then.

Patient 2

A 78-year-old man presented to the ED with progressive swelling of the tongue associated with drooling of saliva. The swelling was initially unilateral when he noticed it in the morning and by evening had become bilateral and symptomatic. There was no urticaria, rhinorrhoea or wheeze. He was normotensive on presentation and was treated with epinephrine nebulisations, steroids and antihistamines. He was transferred to intensive care unit (ICU) for further monitoring.

The patient had a history of asthma with moderate airflow obstruction and was on regular bronchodilators. He had a history of percutaneous coronary interventions performed 7 years previously and was on clopidogrel, atorvastatin, perindopril since then. He was also a known epileptic and was on phenytoin as well.

INVESTIGATIONS

In the case of both patients the complete blood count at time of presentation did not show any leucocytosis to suggest an underlying infection. The C1 esterase inhibitor level was normal which suggest hereditary and acquired C1 esterase inhibitor deficiency was unlikely to be the cause of angio-oedema. Mast cell tryptase levels were also normal which suggested that type 1 hypersensitivity was unlikely.

DIFFERENTIAL DIAGNOSIS

ACEi-induced angio-oedema (ACEiA), type 1 hypersensitivity, infection and other causes of angio-oedema such as hereditary and acquired C1 inhibitor deficiency were the main differential diagnoses. All can present with soft tissue swelling; however, the pathological process is different and so is the management.

Anaphylaxis is driven by mast cell degranulation releasing histamines and cytokines that lead to

To cite: Amey G, Waidyasekara P, Kollengode R. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-010453

smooth muscle spasm, vasodilation and increased capillary leakage of blood vessels. Clinically presentation includes wheezing due to bronchospasm, urticaria and hypotension due to capillary leakage and vasodilation and pruritus due to mast cell tryptase. Our patients did not have any of these signs thus anaphylaxis was unlikely.

Pollen food allergy or oral allergy syndrome is more common among people with allergic rhinitis due to increased likelihood of cross reactivity of allergens in food such as raw fruit and vegetables. These patients usually present with non-dependent area and upper airway swelling with no systemic symptoms.⁵ Patient 1 had allergic rhinitis but no indication in history of ingestion of such foods.

Infection was unlikely due to no fever and no septic changes on complete blood count. Ludwig's angina can present with the swelling of the submandibular region and neck and can be life-threatening due to airway blockage. Neither patient had a history of recent dental abscess or mouth trauma to make this diagnosis likely. Further there was no associated fever trismus, stridor, redness or heat at site of swelling, and no septic changes on complete blood count.

In both patients ACEiiA was the most probable clinical diagnosis base on the presentation of angio-oedema of the characteristic head and neck region, absence of urticaria, wheeze and hypotension. Normal mast cell tryptase and C1 inhibitor level further supported this diagnosis.

These patients had numerous risk factors for the development of ACEiiA, including concomitant non-steroidal anti-inflammatory drug (NSAID) use, age >65 and an atopic predisposition.⁶ Based on the clinical presentations of patient 1, it appears that the use of two kinds of NSAIDs was an independent risk factor for ACEiiA rather than the sole causative agent, as NSAID-induced angio-oedema usually presents with urticaria and occurs soon after taking the medication.⁷ It has been noted that the concurrent use of NSAID can precipitate or worsen ACEiiA.

TREATMENT

Patient 1

The patient was unable to speak and in view of the worsening swelling of the tongue it was decided that he would be for a semi-elective awake nasal fiberoptic intubation. A successful intubation was achieved with a size 8 endotracheal tube. The patient was subsequently transferred to the ICU for further management. He was given intravenous steroids and antihistamines.

Patient 2

The swelling continued to increase in size in the ICU and the patient grew more apprehensive. The patient was hence nasally intubated under awake conditions with a fiberoptic bronchoscope as a semiemergent procedure. A size 7 endotracheal tube snugly fitted into the trachea with no cuff leak.

OUTCOME AND FOLLOW-UP

Tongue swelling in patient 1 subsided gradually over the next 48 h and he was successfully extubated on the third day. He was discharged home having educated on ACEiiA and his perindopril ceased. His general practitioner and cardiologist were notified and the adverse effect to ACEi was documented in his medical record.

Patient 2 was extubated in 24 h after confirmation of cuff leak and was discharged to the medical ward after ceasing the perindopril. He was discharged home with education and notification to his general practitioner.

Neither patient had any complications. Both had achieved normal function of their pharynx with respect to breathing and feeding. Neither have presented to the ED or their general practitioner with similar symptoms to date.

DISCUSSION

Despite ACEi being relatively well tolerated by patients, angio-oedema is recognised as an infrequent but potentially life-threatening complication of their use. ACEi exert their effect on the cardiovascular system by manipulating the renin-angiotensin-aldosterone (RAA) pathway. This pathway is utilised by the body to regulate systemic blood pressure and renal perfusion. ACEi block the ACE, preventing the conversion of angiotensin I to angiotensin II, and thus avoiding the potent vasopressor action of angiotensin II. ACE also catalyses the breakdown of serum bradykinin and substance P. Both these mediators cause vasodilation and increased capillary permeability leading to oedema. It is the increase in serum bradykinin primarily, as well as substance P, which is postulated to be the major contributor to ACEiiA.⁸

The incidence of this reaction has been steadily increasing due in part to increasing usage of ACEi, and also possibly due to the increased recognition by clinicians of this phenomenon. The reported incidence of ACEiiA is 0.1–0.2% accounting for 0.7 of every 10 000 ED consultations. However, these figures may be somewhat underestimated, due to its often delayed presentation after start of ACEi therapy and subsequent under recognition of the condition.⁸ The spectrum of presentations of ACEiiA reaction is significantly varied, and can range from a localised mild swelling to potentially fatal airway obstruction. It most commonly affects the floor of the mouth, lips, tongue, larynx, neck and face.¹ Less commonly, it can affect the bowel walls, presenting with nausea, diarrhoea and diffuse abdominal pain. Case reports have also been documented on cerebral oedema attributed to ACEi use, presenting as generalised seizures, as well as ACEi-induced genital angio-oedema.^{9–10} As the pathophysiological basis of the reaction is believed to be primarily due to bradykinin imbalance and not mast-cell degranulation, there is typically no associated itching or urticaria with ACEiiA. Unlike the oedema seen in the anaphylactic reaction, ACEiiA is slowly progressive over a number of hours, with ED presentation typically 4–6 h after symptom onset and complete resolution of symptoms after an average of 30 h.¹

While predicting those who will develop ACEiiA remains difficult, various risk factors have been identified. The incidence of angio-oedema has been reported to be high in the African American population, and the risk is higher in patients who have obesity, trauma, head and neck surgery, recent airway instrumentation and organ transplantation.¹¹ Drug interactions have also been recognised as a possible factor in the development of ACEiiA. The most commonly reported of these is the concurrent use an ACEi with aspirin, NSAIDs or opiates. The addition of one of these drugs to patients previously 'stable' on ACEi therapy led to an increased incidence of angio-oedema.¹²

Treatment strategies for ACEiiA commonly utilised in the ED include corticosteroids, antihistamines and epinephrine. However, the use of these drugs remains largely unproven and is unlikely to be of significant benefit given that the presumed aetiology is elevated bradykinin rather than histamine-release. Without strong evidence for any other medical treatment modalities, the mainstay of treatment of ACEiiA involves recognition of its aetiology and discontinuing the offending agent while ensuring the patency of the patient's airway. Often this will

require substituting the ACEi with a medication of similar effect once the acute episode has resolved. Of consideration when choosing an alternate agent are case reports of angio-oedema occurring with the use of angiotensin II receptor blockers (A2RB). Similar to ACEi, A2RBs act on the RAA pathway, specifically by acting as competitive antagonists at the angiotensin II receptors sites. They differ from ACEi in that they do not affect bradykinin degradation, therefore should theoretically not pose the same risks of angio-oedema. However, cases of A2RB angio-oedema have been described in the literature, with a meta-analysis suggesting that for those patients who previously developed ACEiiA, the risk of developing angio-oedema with an A2RB is up to 9%.¹³

Similarly, direct renin inhibitors should theoretically not confer a risk of bradykinin-mediated angio-oedema. However, a recent meta-analysis of over 12 000 patients treated with aliskiren found the incidence of angio-oedema to be similar to that of patients on ACEi.¹⁴ Less commonly, angio-oedema has also been linked to calcium channel blocker use.¹⁵ Clinicians should be aware of these antihypertensive drugs that can cause angio-oedema so as to make safe medication alterations. However, risk increase in patients with ACEiiA who use calcium channel blockers and A2RB have not been reported.

There are various treatment options showing promise in small clinical trials and case reports. Most notable of these is the use of icatibant, a selective bradykinin B2-receptor antagonist that is licensed for use in the treatment of hereditary angio-oedema.¹⁶ Another encouraging treatment option is the use of fresh frozen plasma (FFP). FFP contains ACE within its formulation, which is postulated to lead to the breakdown of accumulated bradykinin and subsequent resolution of angio-oedema, reducing the need for intubation and ventilation.¹¹

Our two case reports highlight the importance of educating clinicians about how ACEiiA is not uncommon and is a potentially fatal adverse reaction to a common class of drugs prescribed in Australia. We presume that ACEi therapy is the most likely cause of angio-oedema here as there are no definite means to make a diagnosis. The interesting feature of the two patients in this case report is the delay in time from initiation of ACEi therapy to the onset of symptoms of angio-oedema. Both these patients had an atopic condition and were on antiplatelet drugs and statins, which increase the risk of developing this complication. The first patient described had been taking ACEi for IHD for 10 years before his presentation to the ED while the second patient was on ACEi for 7 years. Both these patients presented with severe angio-oedema requiring urgent awake intranasal intubation for airway protection. Similarly, symptoms of both patients resolved completely within 72 h following treatment with steroids and antihistamines. While there have been a few reports published describing promising future treatment options, these are largely untested and their efficacy is yet to be verified by randomised controlled trials.

Learning points

- ▶ ACE inhibitors (ACEi) are the most commonly used antihypertensives; thus clinicians need to be aware of the clinical presentation of ACEi-induced angio-oedema.
- ▶ Time of onset of angio-oedema can be as late as 10 years from start of ACEi.
- ▶ Early recognition and management of the condition can reduce the need for a lengthy admission in the intensive care unit.

Contributors GA, RK and PW were involved in writing the manuscript. GA and RK were involved in treating the patients as well as obtaining consent. RK was involved in compiling and editing the report as necessary to meet the publication standards of BMJ case reports.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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