CASE REPORT

'Epinephrine-resistant' angioedema

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SUMMARY

A man in his 60s was brought to the emergency department, with airway compromise and dysarthria due to a grossly enlarged tongue. As he was on a current course of antibiotics, he was treated for a likely antibiotic-associated allergic reaction. However, as he failed to improve with intramuscular and nebulised epinephrine, another cause of his symptoms was sought. Further discussion revealed a history of chronic lymphocytic leukaemia (CLL), which had recently relapsed. Investigations were ordered to confirm that the symptoms were due to acquired angioedema, and the patient was managed for this diagnosis based on the presence of an undetectable C4 level. This diagnosis was later confirmed when the results of specialist tests became available. The patient was treated for his relapsed CLL with good effect, and has had no further episodes of angioedema and an improvement in the level of his C1 esterase protein level and function.

BACKGROUND

Angioedema is a localised swelling in the dermis and subcutaneous tissues,¹ and it is most often seen together with urticaria due to mast cell degranulation. However, angioedema alone (without urticaria) can be due to a bradykinin-mediated angioedema. It is important to be aware of and to recognise this type of angioedema, as it is a condition that is unresponsive to epinephrine, corticosteroids and antihistamines,¹ and has in the past required intubation or a surgical airway to protect the airway until the swelling subsided. Recently, however, specific therapies have become more widely available to treat bradykinin-mediated angioedema,² and it is hoped that they will be able to decrease the use of intubation and surgical airway management. However, the condition needs to be recognised in the first instance to allow these specific therapies to be used.

CASE PRESENTATION

A man in his 60s presented to the emergency department, with a swollen tongue, dysarthria and dyspnoea. Four days before presentation, he had been prescribed prophylactic amoxicillin–clavulanic acid after excision of a skin lesion. He had no personal or family history of angioedema, but described a single episode of facial oedema 20 years earlier after taking an unknown antibiotic following a surgical procedure, which resolved after a single dose of antihistamine.

On examination, he was dysarthric but able to speak. He was tachycardic (100 bpm) but normotensive. He had a grossly swollen tongue protruding from his mouth and was sitting forward to try

to maintain an airway. He felt breathless when lying flat. He had no wheeze and no urticaria.

Empirical therapy for presumed angioedema secondary to penicillin allergy was instituted with three doses of 500 micrograms of intramuscular epinephrine, as well as nebulised epinephrine (5 mg×3), intravenous hydrocortisone and promethazine, all given in the first hour. Reassessment noted no improvement of the tongue swelling; an intravenous epinephrine infusion was started and surgeons from the otolaryngology team were contacted to discuss a possible surgical airway. Alternate diagnoses to an allergic reaction were also now considered.

The patient had a history of chronic lymphocytic leukaemia (CLL), hypertension, hypothyroidism, depression and anxiety, and was taking thyroxine and desvenlafaxine. The CLL had recently relapsed and he was due in the outpatient clinic the following week for a blood transfusion.

Examination revealed that he had cervical lymphadenopathy and hepatosplenomegaly consistent with CLL.

Owing to his known haematological malignancy, blood tests were performed to investigate for possible acquired C1 esterase deficiency (acquired angioedema, AAE) and his management changed based on these results, with discontinuation of the epinephrine infusion. Nasendoscopy showed a normal larynx, despite the gross swelling of the tongue and floor of the mouth, and a surgical airway was not required at this time. However, because of the continued threat to the patient's airway, he was admitted to the high dependency unit for monitoring and supportive care. The tongue oedema resolved slowly and had completely resolved by the following morning.

INVESTIGATIONS

Full blood analysis demonstrated anaemia (haemoglobin 75 g/L), thrombocytopenia (platelets $97 \times 10^9/L$) and leucocytosis (white cell count $72.8 \times 10^9/L$) with predominant lymphocytosis (lymphocytes $71.34 \times 10^9/L$) in keeping with a relapse of CLL.

To investigate for AAE, complement protein C3 and C4 levels, C1 esterase inhibitor (C1-INH) protein levels and function, as well as C1q levels, were ordered. A serum tryptase level was taken to exclude an anaphylactic reaction, however, this was unlikely due to the clinical features.

Complement levels, available after an hour, were: C3, 1.26 g/L (reference range (RR) 0.82–1.85); and C4, <0.03 g/L (RR 0.14–0.42). Undetectable C4 levels were suggestive of AAE resulting from the patient's known CLL, explaining

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the lack of response to epinephrine. The patient was managed for this diagnosis based on these results, as the results of the specific tests would not be available for a number of days.

Subsequently, decreased levels of C1-INH (28 mg/L; RR 195–440) and undetectable C1-INH function (<50 U/L; RR 477–923), as well as undetectable levels of C1q (<35 mg/L; RR 118–238), confirmed the diagnosis of type I AAE.

The patient's previously detected IgM κ was still present at a concentration of 1 g/L with associated suppression of normal immunoglobulin production with an IgG level of 3.1 g/L (RR 7–16), IgA 0.16 (RR 0.70–4.00) and IgM of 3.6 g/L (RR 0.4–2.3).

DIFFERENTIAL DIAGNOSIS

Given the patient's history of a prior antibiotic-related reaction, and the timeline relating to antibiotic use on this occasion, it was not unreasonable to consider an IgE-mediated allergic reaction in the first instance. However, the angioedema was unresponsive to epinephrine, raising the possibility that the expected action of epinephrine was blocked or that the symptoms were due to a bradykinin-associated angioedema. The presence of β -blockers must be considered when symptoms are not responsive to epinephrine, but in this case, this was excluded as the patient had not been taking β -blocking medications. The absence of urticaria would also be consistent with a bradykinin-associated angioedema. The most common cause of bradykinin-associated angioedema is the use (or recent cessation) of ACE inhibitors, neither of which applied in this case. There was no family history of angioedema and the age of presentation did not favour hereditary angioedema (HAE). In HAE, 50% of patients have onset of symptoms by 10 years of age, while in AAE, the majority of patients develop symptoms after 40 years of age.¹ Haematological malignancy is a common cause of AAE, in some cases episodes of AAE lead to the diagnosis of a previously undetected haematological malignancy.³

TREATMENT

Two days after presentation, the patient was started on combination immunochemotherapy (rituximab, fludarabine and cyclophosphamide) for progression of CLL. On discharge, he was given a medical alert bracelet stating his diagnosis, and was advised to avoid ACE inhibitors, which can worsen angioedema from any cause.

In this case, no specific treatment was required for the angioedema, although icatibant was considered in the first few hours. However, as the tongue angioedema slowly improved, it was not required. Bradykinin-induced angioedema should not improve with the medications given, however, we postulate that the tongue oedema may have improved due to the high doses of hydrocortisone given, causing lymphocyte lysis, slowing the 'vicious cycle' of complement consumption, as the lymphocyte count within a few hours of presentation had dropped from $71.34 \times 10^9/L$ to $57.1 \times 10^9/L$.

OUTCOME AND FOLLOW-UP

Now, 18 months later, the CLL is in remission and the patient has had no further episodes of angioedema. The levels and function of C1-INH have improved (level, 60 mg/L; function, 176 U/L) but have not normalised.

DISCUSSION

Angioedema is a localised, well demarcated, transient, asymmetric and often recurring swelling of the deeper dermal layers and/

or mucosal tissue.¹ It may be associated with urticaria.¹ As angioedema is predominantly seen in allergic reactions, it is usually treated with epinephrine (if there is airway compromise) steroids and antihistamines.

It is important, however, to be aware of the subset of patients in whom angioedema is caused by increased bradykinin levels as it will be unresponsive to epinephrine, steroids and antihistamines, and never associated with urticaria. Bradykinin-mediated angioedema can be due to HAE, ACE inhibitor angioedema, or AAE.²

HAE and AAE are due to a deficiency in either the level or function of C1-INH.¹ C1-INH inhibits, among other things, activated C1r and C1s, activated Hageman factor (XIIa) and activated kallikrein.^{2–4} Insufficient C1-INH results in uncontrolled activation of the kallikrein-kinin pathway, thus increasing bradykinin levels (causing vasodilation and increased endothelial permeability leading to angioedema) and uncontrolled activation of the classical complement cascade (leading to decreased levels of C4).^{2–4}

In HAE, this deficiency in the C1-INH protein (or its function) is due to mutations in the *SERPINC1* gene.¹ In AAE type I, the decreased C1-INH levels result from increased consumption of the protein, usually in the context of a lymphoproliferative disease, while AAE type II results from defective C1-INH function due to an autoantibody.⁴ The true incidence of AAE is not known, with 168 probable cases reported in the literature according to a 2010 review.⁵ It classically presents in or after the fourth decade, and most patients have an underlying disorder (eg, a low-grade lymphoproliferative disorder, monoclonal gammopathy of uncertain significance or autoimmune disease). It has also been associated with non-haematological malignant conditions, infections and vasculitis.³ It is vital that patients who present with AAE, and who do not already have a likely cause identified, are investigated for an underlying lymphoproliferative disorder.^{5–6}

Both HAE and AAE present with recurring angioedema, with each episode lasting for between 2 and 5 days.^{4–6} The angioedema can affect any part of the body, including potentially life-threatening oedema of the upper respiratory tract and tongue. Gastrointestinal attacks (oedema of the bowel wall presenting as severe abdominal pain) appear less frequently, or are less frequently reported, in AAE than in HAE.⁶

The diagnosis of both HAE and AAE is confirmed by laboratory tests. Blood tests reveal reduced levels of C4 in both conditions (due to the role C1-INH plays in control of the classical complement cascade) and either reduced C1-INH protein levels in HAE and AAE type I, or decreased C1-INH protein function (in HAE and AAE type II). With severe defects in C1-INH protein levels, the function is also affected. AAE is differentiated from HAE by C1q levels, which are normal in HAE but reduced in AAE.^{1–4}

The most common cause of bradykinin-induced angioedema is ACE inhibitor therapy, as ACE is one of the enzymes that break down bradykinin,² and in this condition there is no effect on levels of C1-INH or C4.

The treatment of AAE is usually directed at treating the underlying cause. There are no therapies specifically approved for the treatment of angioedema in these cases, however, case studies have described improvement in symptoms with the use of C1-INH concentrate, and in separate cases, icatibant, a B2-bradykinin receptor antagonist²—treatments that are approved and available for the treatment of HAE. These may be available to physicians for use in AAE but are expensive, and the patient should be aware that their use is 'off-label'. If

alternatives such as C1-INH and icatibant are available, fresh frozen plasma is no longer recommended as therapy for AAE;² although it contains C1-INH, it also contains kininogen, which can generate bradykinin and exacerbate angioedema.¹

Learning points

- ▶ Bradykinin-induced angioedema should be considered in patients with isolated angioedema unresponsive to epinephrine, corticosteroids and antihistamines.
- ▶ Bradykinin-induced angioedema is caused by the use of an ACE inhibitor, or by the presence of hereditary or acquired angioedema.
- ▶ Acquired angioedema should be considered in patients with a known haematological malignancy. Conversely, patients presenting with acquired angioedema should have a haematological malignancy excluded.
- ▶ Hereditary and acquired angioedema are both associated with decreased complement levels (particularly C4), which can be used as a relatively quick initial test while the formal studies are carried out.
- ▶ Specific therapies are now available to treat airway-threatening bradykinin-induced angioedema.

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