Case report

An unusual presentation of ACE inhibitor-induced visceral angioedema

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SUMMARY

ACE inhibitors (ACEi) are common anti-hypertensive drugs that can cause angioedema. Though classic, or facial angioedema is rare, visceral angioedema is even less common. When angioedema occurs, it typically presents early, within 30 days of initiating therapy. Visceral angioedema most commonly presents with nausea, emesis, abdominal pain and diarrhoea, and thus is often mistaken for an episode of gastroenteritis. When a CT scan is obtained, it typically shows characteristic findings, including ascetic fluid, mild mesenteric oedema and thickening of the small bowel. In this case report, we present a patient who did not experience her first episode of visceral angioedema until after she had been on ACEi therapy for 5–7 years. In addition, she experienced recurrent episodes of visceral angioedema that were separated by approximately 4 years at a time. Both of these features make for a particularly unique presentation.

BACKGROUND

ACE inhibitors (ACEi) are frequently used in treating hypertension, chronic kidney disease and heart failure. ACEi have been known to cause a variety of side effects, the most feared being angioedema and anaphylaxis. Angioedema is a relatively rare side effect of ACEi, but can be fatal in severe cases. Angioedema typically presents with swelling in the lips, tongue or face but rarely can manifest as episodic abdominal pain due to visceral angioedema. Angioedema can occur at any point in treatment. Most commonly, it presents within 30 days of initiating treatment; however, it can occur after being on therapy for years.¹ It can even happen up to 5 months after discontinuation of ACEi, and episodes can be isolated or continuous, making diagnosis challenging.²

CASE PRESENTATION

A 57-year-old African-American female patient with a medical history of heart failure with reduced ejection fraction, asthma, hypertension, chronic kidney disease and type 2 diabetes mellitus presented to the emergency department with acute onset of abdominal pain, nausea, emesis and 7 episodes of watery diarrhoea for 1 day. The patient denied any recent travel, sick contacts, new foods or fevers/chills. Review of systems was otherwise negative. Allergies included a cough with lisinopril, though she was currently taking this medication.

INVESTIGATIONS

Labs on admission were significant for a leucocytosis to $14.1 \times 10^9/L$ with $10.3 \times 10^9/L$ absolute neutrophils and creatinine elevation to 1.71 mg/dL (baseline 1.2 mg/dL). C4 level was normal at 23 mg/dL, lipase was normal at 40 U/L and lactate was normal at 1.6 mM/L.

Of note, the patient had been hospitalised on 2 prior occasions with similar presentations, approximately 4 and 9 years prior to presentation. Symptoms resolved with supportive treatment. A CT abdomen/pelvis during these 2 prior episodes (figure 1) showed multiple loops of small bowel with wall thickening and adjacent mesenteric oedema, no evidence of obstruction and some free fluid in the abdomen and pelvis. A CT abdomen/pelvis completed out of concern for nephrolithiasis in between these episodes showed no free fluid, small bowel wall thickening or mesenteric oedema.

A repeat CT during the patient's current admission (figure 2) again showed wall thickening, adjacent fat stranding and mesenteric oedema of the small bowel in the left hemiabdomen, and a small amount of upper abdominal and pelvic fluid, which was nearly identical in distribution to the 2 prior CTs mentioned.

DIFFERENTIAL DIAGNOSIS

The initial differential diagnosis was broad and included infectious, inflammatory, vasculitis or ischaemic aetiologies. However, our team was alerted by the attending radiologist who reported that the CT findings were highly characteristic of ACEi-induced small bowel angioedema, given the focality and recurrent distribution pattern when compared with prior CTs. Based on these imaging findings alone, other diagnoses considered included: Henoch-Schonlein purpura, intramural bleeding secondary to trauma, anticoagulation or haemophilia, neoplastic and acquired/hereditary C1 esterase deficiency.³ The patient's C4 was normal during the acute episode, making hereditary forms of angioedema unlikely. Her quick improvement in symptoms helped us to rule out most of our other differential diagnoses. Though gastroenteritis was still considered, we thought this much less likely as the patient had a mild leucocytosis, received only 1 dose of antibiotics on admission and continued to improve after cessation of antibiotics. Had gastroenteritis been the responsible aetiology, we would expect her to have other signs/symptoms of infection, such as fevers or chills and require a longer course of antibiotics in the setting of such significant

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Figure 1 CT scan from second episode of visceral angioedema demonstrating multiple loops of small bowel with wall thickening and adjacent mesenteric oedema.

findings on CT. Given the temporality and episodic nature of the patient's symptoms, her classic and recurrent CT findings and the resolution of her symptoms within 1 day of holding lisinopril, we were fairly certain that our diagnosis was consistent with ACEi visceral angioedema.

TREATMENT

During the patient's admission, supportive treatment was initiated. She initially received 1 dose of ceftriaxone and metronidazole. She also received ondansetron and morphine for symptomatic management. Her home lisinopril was also held

Figure 2 CT scan from most recent episode of visceral angioedema demonstrating wall thickening, adjacent fat stranding and mesenteric oedema involving a segment of small bowel in the left hemiabdomen.

due to an acute kidney injury (AKI). Given the CT findings and concern for ACEi-induced visceral angioedema, it was decided to stop antibiotics and to transition to prednisone 40 mg for a 5 day course. She also received 1 dose of benadryl and famotidine. In addition, lisinopril was discontinued and added to the patient's allergy list.

OUTCOME AND FOLLOW-UP

The patient's symptoms resolved the day after discontinuing lisinopril therapy. The patient was discharged in a stable condition. As of 5 months from the patient's discharge, she remains off lisinopril and symptom-free.

DISCUSSION

ACEi-induced angioedema is a rather rare side effect of ACEi. It typically involves the face, tongue and lips. In a retrospective, observational, cohort study, including 1 845 138 participants, 3301 patients had angioedema after a mean follow-up of 149 days.⁴ The cumulative incidence per 1000 persons was 1.79 (95% CI 1.73 to 1.85).⁴ In another retrospective study among 134 945 patients, 0.7% developed angioedema over a 5 year period.¹

Visceral angioedema is an even less common presentation of ACEi angioedema, though it likely goes unrecognised frequently. In a review by Palmquist and Mathews, the authors found 34 individual reports of ACEi-induced visceral angioedema.⁵ Interestingly, this study found some key characteristics of those with ACEi-induced visceral angioedema, namely women were more affected than men (85%), African Americans were more likely to be affected than other races, and lisinopril (56%) was most often the culprit ACEi.⁵ The average age of individuals affected was 49.5 years.⁵ Reported symptoms at presentation included abdominal pain in all patients, 77% with emesis and 47% with diarrhoea.⁵

In a review by Scheirey *et al* that included 20 patients, authors also found a high proportion of obese individuals (65%).⁶ In a review by Wilin *et al*, that included 25 unique cases, authors found similar findings as those mentioned previously, in addition, 52% (13/25) of cases included patients who presented on several different occasions, prior to obtaining an official diagnosis, likely secondary to decreased knowledge and awareness of ACEi-induced visceral angioedema.⁷ Interestingly, 42% (8/19) of patients presented within 1 week of initiation of an ACEi and 32% (6/19) presented at or after 1 year of ACEi initiation.⁷ In this review, the longest period an individual was on ACEi therapy prior to onset of visceral angioedema was 9 years.⁷ After being on ACEi therapy for 9 years, this patient had recurrent episodes of gastrointestinal symptoms, in addition to 2 episodes of facial angioedema.⁸ Her gastrointestinal symptoms were occurring as frequently as every 3 weeks.⁸ Her enalapril was discontinued after the second episode of facial angioedema, and at the time of the case report, she had been symptom-free, from a gastrointestinal perspective, for 2 years.⁸ Interestingly, in the review by Wilin *et al*, 16% of cases reported a prior history of facial swelling before being diagnosed with ACEi-induced visceral angioedema.⁷

Labs are relatively unhelpful in diagnosing visceral angioedema and it is mainly a clinical diagnosis though radiographical evidence can be useful. In the review by Wilin *et al*, of 25 patients, 48% had leucocytosis and 15 of 15 had normal complement 1 esterase levels.⁷ Normal complement levels (C4, C1i and C1q) help differentiate visceral angioedema caused by

ACEi from hereditary angioedema, as complement levels will typically be abnormal in hereditary forms of angioedema.^{5,7,9}

In addition to a classic clinical presentation, there have been common findings on imaging in ACEi-induced visceral angioedema. In the review by Scheirey *et al*, of 20 patients with 23 distinct episodes of ACEi-induced small bowel angioedema who underwent CT scans, findings included ascetic fluid, mild mesenteric oedema and abnormal small bowel with long-segment abnormalities, typically longer than 10 cm but less than 1/3 the entire length of the small bowel.⁶ All patient's small bowels were mildly dilated (mean diameter 2.9 cm) and wall thickening with a mean of 1.3 cm.⁶ A small bowel target sign was seen in 16 of 20 multidetector CT scans.⁶ The distribution most commonly involved the jejunum alone (10/23), ileum alone (7/23) and both the jejunum and ileum (6/23).⁶ Both cases in this article that had follow-up CT scans showed near complete resolution of previously mentioned abnormalities.⁶ Findings that are typically not present in visceral angioedema include mesenteric lymphadenopathy or bowel wall obstruction.¹⁰

Treatment of ACEi-induced visceral angioedema includes discontinuation of the offending agent and supportive care, including intravenous fluids, steroids and antiemetics.⁷ Resolution of symptoms typically occurs in about 1–2 days following cessation of the ACEi.⁵

Given the difficulty in diagnosing ACEi-induced visceral angioedema, a group of authors came up with diagnostic criteria. These include taking an ACEi, regardless of dose/duration of use, non-specific abdominal complaints with bowel oedema, resolution of symptoms and imaging findings after stopping the ACEi and lack of another diagnosis.¹¹

In this case report, we present a patient with recurrent episodes of visceral angioedema, separated by approximately 4 years of time. This patient had started lisinopril approximately 5–7 years prior to her initial episode of visceral angioedema. This case is significant because the long duration of ACEi therapy prior to her initial presentation is unusual. In addition, she remained symptom-free for relatively long periods of time in between episodes despite continuing an ACEi. Though the exact mechanism of ACEi-induced angioedema is unknown, it is suspected that at least one component is due to elevated bradykinin and substance p, which both cause increased plasma extravasation.¹² It is suspected that varying genetic profiles may predispose certain individuals to ACEi-induced angioedema.¹² In addition, certain environmental triggers have been associated with an increased risk of ACEi-induced angioedema, including smoking, food and other allergic triggers, trauma, certain medications, such as aspirin, non-steroidal anti-inflammatory medications (NSAIDs), immunosuppressive therapies and lidocaine.¹² Also, certain comorbidities, such as diabetes, can actually lower one's risk of ACEi-induced angioedema.¹² It is possible that each of her episodes were precipitated by a potential known trigger, which lowered her threshold for developing ACEi-induced visceral angioedema. Interestingly, the patient reported taking frequent NSAIDs prior to her first admission. Though lisinopril was not held during this admission, her NSAIDs were stopped and symptoms took 5 days to self-resolve. About 2 weeks before her second admission, she presented to clinic with diarrhoea and was found to have an AKI and so lisinopril was briefly held. She then restarted lisinopril a few days after her visit and the diarrhoea returned, which prompted her to go to the emergency room where she was admitted for an AKI. During this second admission, lisinopril was held and her symptoms resolved within 1 day. For

her most recent admission, it appears that the patient had been switched from losartan and then back to lisinopril approximately 1.5 months prior to presentation, which could have precipitated that episode. Though the patient has remained symptom-free for 5 months since discontinuing lisinopril, not enough time has passed to officially diagnose her with ACEi-induced visceral angioedema, as her 3 image-supported episodes of suspected visceral angioedema occurred approximately 4 years apart. However, given her risk factors (female, African American, obese, lisinopril-associated cough and age), recurrent presentations with suspected precipitating events, classic and recurrent imaging findings on 3 separate occasions, the normalisation of her CTs in between episodes, and the quick symptom resolution on discontinuing lisinopril, we are fairly confident in our diagnosis.

Patient's perspective

When discussing with the patient what she thought the cause of these recurring symptoms were she stated that 'I just thought I had some type of virus'. When she was told that lisinopril was the likely cause of her symptoms, she stated 'I felt confused because I had been on lisinopril for a long time and had never had a problem with it.'

Learning points

- ▶ Visceral angioedema is a very rare side effect of ACE inhibitors (ACEi).
- ▶ Visceral angioedema classically presents with abdominal pain, emesis and diarrhoea. Most commonly, it presents within 30 days of initiation of an ACEi.
- ▶ Labs are relatively unhelpful in diagnosing visceral angioedema; however, a thorough history and classic CT findings including ascetic fluid, mild mesenteric oedema and thickening of the small bowel, are highly suggestive.
- ▶ Suspect visceral angioedema in a patient who is on an ACEi and has recurrent episodes of abdominal pain, nausea and emesis even if episodes are few and far between.
- ▶ Treatment of visceral angioedema includes symptomatic support and discontinuing the offending ACEi.

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