

Recognizing a Rare Phenomenon of Angiotensin-Converting Enzyme Inhibitors: Visceral Angioedema Presenting with Chronic Diarrhea—A Case Report

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ABSTRACT

Introduction: Peripheral angioedema of the face and upper airways is a well-known phenomenon of angiotensin-converting enzyme inhibitors occurring in only 0.1% to 0.7% of patients. We describe a case of the even less-common manifestation of visceral angioedema, which causes symptoms of chronic and intractable diarrhea.

Case Presentation: A 68-year-old white woman presented with large-volume diarrhea, caused by visceral angioedema secondary to lisinopril therapy. Initial imaging studies were significant for distended small bowel loops, with subsequent unremarkable findings on colonoscopy and biopsy studies. After an exhaustive laboratory work-up, her diarrhea resolved only after the discontinuation of lisinopril.

Discussion: Use of angiotensin-converting enzyme inhibitors is increasing, making the recognition of visceral angioedema important in preventing significant morbidity and avoiding invasive and costly studies.

INTRODUCTION

The combination of abdominal pain, nausea, and vomiting is the most common manifestation of isolated angioedema of the gastrointestinal tract secondary to treatment with angiotensin-converting enzyme (ACE) inhibitors.^{1,2} This condition is a rare phenomenon with unknown prevalence, probably because of the paucity of clinical suspicion. Further complicating the diagnosis is the initial presentation of an even less common symptom: Isolated chronic diarrhea.^{1,2} The following report describes the case of a 68-year-old woman with chronic intractable diarrhea that was misdiagnosed as caused by irritable bowel syndrome. It was only after the discontinuation of our patient's ACE inhibitor that her symptoms resolved.

CASE PRESENTATION

Presenting Concerns

A 68-year-old white woman with a 1-month history of large-volume chronic nonbloody diarrhea, presumed initially to be irritable bowel syndrome, presented to our hospital with hypotension and acute kidney injury. Her symptoms were associated with urgency, fecal incontinence, decreased food intake,

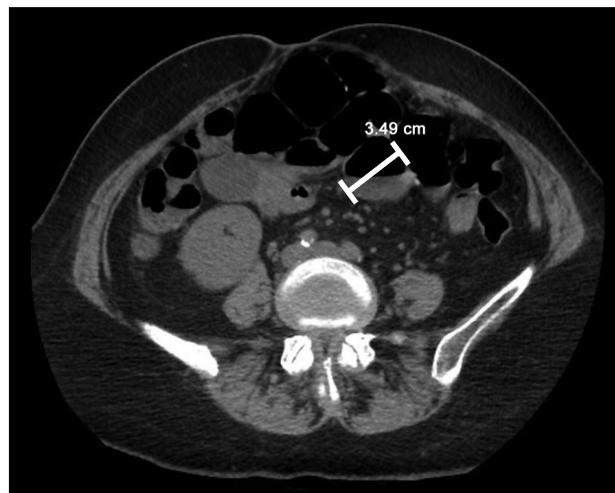


Figure 1. Noncontrast computed tomography scan of the abdomen showing diffuse distention of the small bowel, up to 3.49 cm in diameter (white marker), without a transition point to suggest an obstruction.

and weight loss of 11 lbs, with failed initial outpatient treatment with loperamide and metronidazole. Her medical history included mesenteric ischemia and partial small bowel resection, chronic obstructive pulmonary disease, and hypertension treated with lisinopril (40 mg daily) for the previous 23 months. Her physical examination was positive only for left lower quadrant abdominal tenderness without peritoneal signs. Laboratory test values were pertinent for a creatinine of 1.79 mg/dL (baseline 1.2 mg/dL), nonanion gap metabolic acidosis (bicarbonate 18 mmol/L, reference range [RR], 22-32 mmol/L), and anion gap 14 mmol/L (RR, 5-15 mmol/L). Stool studies were negative for *Clostridium difficile* toxin AB, lactoferrin, occult blood, *Giardia/Cryptosporidium* antigens, ova/parasites, Shiga toxin, *Salmonella*, *Shigella*, and *Campylobacter* species. Noncontrast computed tomography showed diffuse nonobstructive distention of the small bowel (Figure 1), which was later confirmed by computed tomography enterography (Figure 2). Ultimately, a colonoscopy was performed, which showed normal-appearing ileal and colonic mucosa with biopsies confirming these findings.

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Figure 2. Computed tomography enterography scan of the abdomen showing distended, fluid-filled small bowel loops (white arrow).

Therapeutic Intervention and Treatment

Considering all the negative diagnostic studies with the diagnostic findings of dilated bowel loops without a clear transition point, ACE inhibitor-induced visceral angioedema was suspected and a 7-day trial of drug discontinuation was initiated by our patient’s primary care physician. We expected resolution of diarrhea within 24 to 72 hours after lisinopril was discontinued. Our patient was to follow-up with her primary care physician within 7 days.

Follow-up and Outcomes

At clinical follow-up both one week and three weeks after discontinuation of our patient’s ACE inhibitor, our patient reported symptom resolution back to her baseline. Of note, she remained symptom-free for three years, until lisinopril was restarted by a physician consultant for treatment of diastolic dysfunction. However, her symptoms resolved once again when the drug was ultimately switched to losartan by her primary care physician. With the exclusion of other causes, negative colonoscopy findings, imaging supportive of dilated small bowel loops, a positive drug challenge, and the prompt resolution of the diarrhea upon discontinuation of the ACE inhibitor, we could definitively make the diagnosis of ACE inhibitor-induced visceral angioedema. See Table 1 for a timeline of the case.

DISCUSSION

ACE inhibitors are some of the most widely prescribed drugs with proven efficacy in the management of hypertension, congestive heart failure, and diabetic nephropathy.^{1,2} In 2014, there were 115 million prescriptions for lisinopril in the US alone, and this number is expected to increase.¹⁻³ It is widely accepted that this class of drugs raises bradykinin metabolites by almost 12-fold and is thought to be responsible for causing the dry cough and peripheral angioedema of the face and upper airways in 0.1% to 0.7% of individuals.^{1,2} Visceral angioedema, on the other hand, is an under-recognized side effect most commonly affecting the jejunum, ileum, duodenum, and rarely the stomach and liver.^{1,2,4,5} Although the pathophysiology has yet to be elucidated, the higher levels of bradykinin similar to

the peripheral form is the most recognized mechanism.^{6,7} The result is increased vascular permeability within the bowel’s mucous membranes, causing the symptoms (abdominal pain, emesis) and objective findings of dilated bowel loops and wall thickening seen on imaging.

In their literature review, Korniyenko et al⁴ found that from 1980 to 2010, there were only 27 reported cases of visceral angioedema secondary to ACE inhibitor therapy.⁴ Since then, there have been 12 additional reports, the majority of which involve lisinopril as the offending agent. It was found to occur predominantly in women with approximately 82% of the cases at a mean age of 49.5 years and a predilection to African Americans. Notably, even though most cases presented within the first 72 hours of starting therapy (51.2% of patients), up to 23.1% had a delayed reaction ranging from 2 weeks to 18 months. It was found, however, that a significant number were kept on ACE inhibitors for up to 9 years after initial presentation, probably because of misdiagnosis. In addition, 57% were subjected to unnecessary surgery or gastrointestinal biopsy. Many underwent extensive workup for diarrhea including, but not limited to, colonoscopy and laparotomy, and most were diagnosed with a psychosomatic etiology or irritable bowel syndrome.⁴

A strong clinical suspicion with exclusion of other causes is the chief modality of diagnosis for ACE inhibitor-induced visceral angioedema.^{1,4} This can be complemented by findings on contrast-enhanced computed tomography, showing circumferential small bowel thickening, dilation of intestinal loops without obstruction, and/or ascites with an unremarkable colonoscopy.^{1,2,4,5} Treatment involves the discontinuation of the

Table 1. Case timeline	
Timeframe	Events and interventions
Day 1	Initiation of lisinopril for hypertension
Month 23	Start of symptoms: Large nonbloody bowel movements associated with urgency, fecal incontinence, weight loss
Year 1	Presentation at the hospital
Hospital day 1	Discontinuation of lisinopril because of acute kidney injury; fluid resuscitation
Hospital day 2	Negative stool studies and noncontrast computed tomography scan of the abdomen showing diffuse small bowel distention
Hospital day 5	Computed tomography enterography confirming small bowel distention without a transition point
Hospital day 7	Negative colonoscopy on gross visualization and histopathology; signs of irritable bowel disease or microscopic colitis
Hospital day 8	Improving symptoms; trial of angiotensin-converting enzyme inhibitor discontinuation and discharge to home
Outpatient days 7 and 14	Sustained resolution of symptoms
Outpatient year 3	Recurrence when lisinopril was restarted by a consultant and sustained resolution once ultimate change to losartan was made

offending drug with expected symptom resolution within 24 to 72 hours. This improvement of the clinical picture is mandatory for final diagnosis, and the resolution of radiologic findings will often follow afterwards if repeated. Clinicians should also be aware that cross-reactivity for angioedema between ACE inhibitors and angiotensin receptor blockers, albeit low, could cause similar gastrointestinal effects, which have been reported with losartan and valsartan.^{1,7}

CONCLUSION

Even though ACE inhibitor-induced visceral angioedema is a well-described phenomenon in some literature, it remains underdiagnosed owing to the lack of clinical suspicion. It results in considerable morbidity and aggressive diagnostic approaches. With careful review of medications and proper suspicion, significant improvement in patient outcome can be achieved earlier, especially given the increasing use of ACE inhibitors. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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