A Gut Feeling: Isolated Small Bowel Angioedema due to Angiotensin-Converting Enzyme Inhibitor

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ABSTRACT

Isolated angioedema of the small intestine is a rare adverse event in patients taking angiotensin-converting enzyme inhibitors. Here, we present a case of visceral angioedema in a 32-year-old woman who presented with left upper quadrant pain, nausea, vomiting, diarrhea, and characteristic radiographic signs of small bowel angio-edema, six months after starting lisinopril. Her symptoms improved within 48 hours of withholding the offending agent and with supportive care. We discuss the epidemiology, pathophysiology, diagnosis, and management of angiotensin-converting enzyme inhibitor-induced angioedema.

KEYWORDS: ACE inhibitor, visceral angioedema, abdominal pain

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEi) are commonly prescribed for the management of hypertension, kidney disease, and heart failure. Although this class of medications is typically well tolerated, they are associated with distinctive adverse effects, including dry cough, hyperkalemia, and angioedema. ACEi-induced angioedema commonly affects the lips, tongue, face, and upper airway, which poses an increased risk of life-threatening airway obstruction. However, isolated visceral angioedema rarely occurs, and a limited number of cases have been reported. These patients typically present with diffuse abdominal pain, diarrhea, vomiting, and ascites. Symptoms are often non-specific and may mimic an acute abdomen. ACEi-induced angioedema is currently under-recognized, which could lead to increased morbidity as well as unnecessary testing and interventions. We discuss the epidemiology, pathophysiology, diagnosis, and management of ACEi-induced intestinal angioedema.

CASE PRESENTATION

A 32-year-old woman with essential hypertension presented to the emergency department with five days of worsening left upper quadrant pain and subjective lip swelling. The patient reported nausea, vomiting, diarrhea, and poor oral intake. New medications included lisinopril within six months of presentation and an oral estrogen and progesterone contraceptive pill three days before the onset of her symptoms. Her vital signs were notable for tachycardia to 100 beats per minute and a blood pressure of 156/94 but were otherwise within normal limits (**Table 1**). She was uncomfortable

Table 1. Vital Signs on Presentation

Temperature	98 °F
Blood Pressure	156/94 mmHg
Heart Rate	100
Respiratory Rate	20
O2 Saturation	99% (ambient air)

Table 2. Clinical Laboratory Data on Admission

	Admission	Reference Range
Sodium (mmol/L)	141	135–145
Potassium (mmol/L)	3.9	3.6–5.1
Chloride (mmol/L)	101	98–110
Bicarbonate (mmol/L)	27	22–32
BUN (mg/dL)	14	6–24
Creatinine (mg/dL)	0.78	0.44–1.03
Glucose (mg/dL)	86	67–99
Aspartate Aminotransferase (IU/L)	14	10–42
Alanine Aminotransferase (IU/L)	11	6–45
Alkaline Phosphatase (IU/L)	53	34–104
Total Bilirubin (mg/dL)	0.7	0.2–1.3
Lipase (IU/L)	7	10–60
White Blood Cells (x 10^3/mm^3)	10.9	3.5–11.0
Red Blood Cells	4.76	3.70–5.00
Hemoglobin (g/dL)	14.7	11.0–15.0
Hematocrit	45.1	32.0–45.0
Platelets (x 10^3/mm^3)	327	150–400
C-Reactive Protein (mg/L)	33	0–10
Erythrocyte Sedimentation Rate (mm/hr)	27	0–20
Complement factor 3 (mg/dL)	137	83–193
Complement factor 4 (mg/dL)	26	15–57
C1 Esterase Inhibitor (mg/dL)	32	21–38

Figure 1. Axial view of computed tomography of the abdomen and pelvis with contrast demonstrating loops of dilated, thickened small bowel, most prominent in the left upper quadrant (labeled with red arrows).

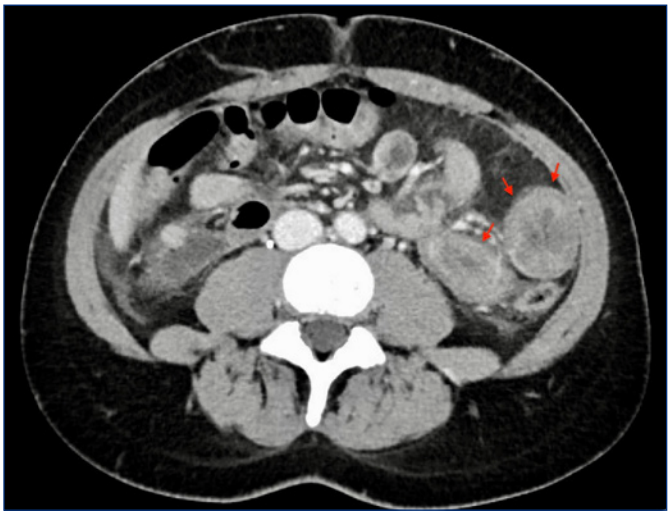
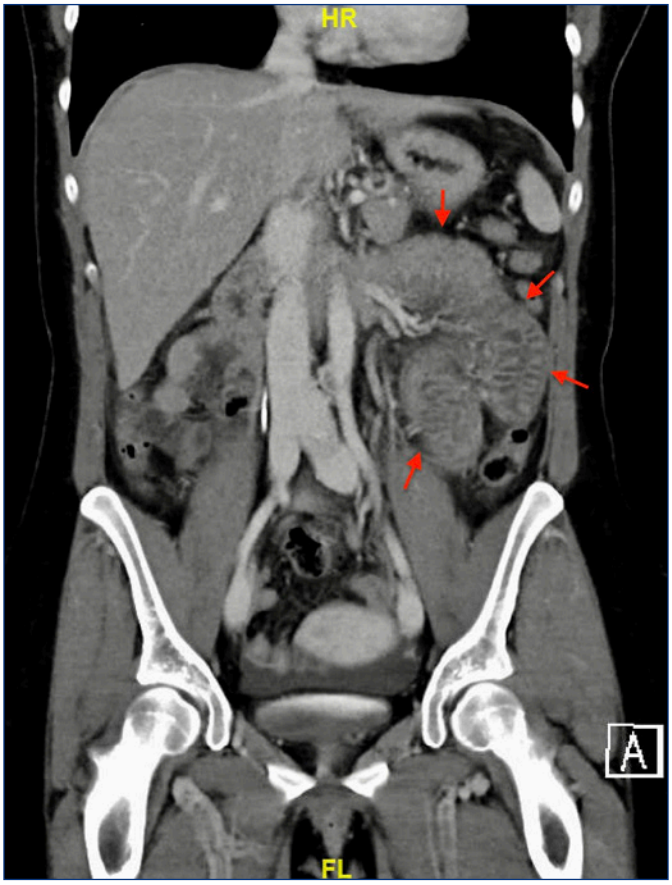


Figure 2. Coronal view of computed tomography of the abdomen and pelvis with contrast demonstrating loops of dilated, thickened small bowel (labeled with red arrows) as well as a small amount of free fluid in the paracolic gutters and pelvis.



appearing, with mild lower-lip edema, and an abdominal exam revealing left upper quadrant tenderness to palpation without rebound tenderness or guarding. She had no peripheral edema or rash on extremity and skin exam. Laboratory studies, including a complete metabolic panel, complete blood count with differential, and lipase, were within normal limits. C-reactive protein and erythrocyte sedimentation rate were mildly elevated. Complement factor 3 (C3), complement factor 4 (C4), and C1 esterase inhibitor were all within normal limits (**Table 2**).

Abdominal computed tomography with intravenous contrast showed dilated, thickened small bowel loops with a small amount of free fluid in the paracolic gutters and pelvis (**Figures 1 & 2**). There was no pneumatosis, enteric vessel pathology, or abscess. Given the patient's history of lisinopril use, intestinal angioedema was determined to be the most likely culprit. Following discontinuation of lisinopril and the administration of intravenous corticosteroids with antihistamines, her symptoms improved. She returned twice to the emergency room in the subsequent two weeks after discharge with similar symptoms that resolved with supportive care.

DISCUSSION

Angioedema is a well established, albeit infrequent, complication of ACEi therapy with an estimated incidence between 0.1% and 0.7%.[1,2] A vast majority of ACEi-induced angioedema cases present with non-pitting edema of the lips, tongue, face, upper airway, and larynx, requiring ventilatory support in up to 7% of cases.[3] Rarely, patients develop predominantly visceral angioedema instead. These patients typically present with a diffuse abdominal pain, vomiting, diarrhea, and ascites. In one review of 34 cases of ACEi-induced angioedema, 100% of patients reported vomiting, 76% emesis and 47% diarrhea.[4] Simultaneous orofacial involvement is uncommon, but has been reported.[5] Up to 54% of reported cases of ACEi-induced intestinal angioedema present within three days of initiation of an ACEi,[6] but patients have also been diagnosed after up to nine years of ACEi treatment.[7] Because symptoms are non-specific and typically resolve within 24–48 hours, many patients have multiple, recurrent episodes before a diagnosis is made.[7] While most cases of angioedema have been reported in patients taking lisinopril, other ACEi have been implicated, including enalapril, captopril, and benazepril.[8] In a study of 111 patients with ACEi-induced angioedema, 46% were found to have recurrence of angioedema after discontinuing the ACEi, typically within the first month.[9] Female sex has been reported as a risk factor for ACEi-induced angioedema broadly,[10] and 85% of patients with ACEi-induced angioedema of the small bowel have been female.[4]

Given its non-specific presentation, there is a broad differential diagnosis for patients presenting with intestinal

angioedema relating to ACEi treatment. The acute onset of abdominal pain, nausea, vomiting, and diarrhea can mimic many causes of a surgical abdomen, including appendicitis, cholecystitis, small-bowel obstruction, and acute mesenteric ischemia. Symptoms can also resemble gastrointestinal infections, inflammatory bowel disease, vasculitis, and obstructing lymphomas. Many cases of intestinal angioedema have undergone surgical exploration or endoscopic biopsy prior to reaching the final diagnosis.[11-13] Beyond ACEi, there are a number of other causes of angioedema including allergic angioedema, hereditary angioedema with C1 deficiency, hereditary angioedema with normal C1, acquired angioedema, and NSAIDs.[14]

Work-up includes a complete blood count, complete metabolic panel, stool antigen and infectious assays, and complement studies (C3, C4, and C1 esterase inhibitor) to rule out hereditary or acquired angioedema.[4,8] Ultrasound and computed tomography (CT) are non-invasive, useful tools to investigate ACEi-induced angioedema, as they can demonstrate supportive findings and rule out other etiologies. Characteristic CT findings include dilated bowel loops, thickened mucosal folds, ascites, and mesenteric edema resembling a "stacked coin" or "doughnut."[11,15] Ascites has been reported in 59% of cases.[8] The jejunum followed by the ileum and duodenum are most commonly affected,[11] but involvement of the distal antrum and pylorus of the stomach have been reported as well.[16] Proposed diagnostic criteria for ACEi-induced intestinal angioedema include the following: 1) Use of an ACEi (regardless of dose or duration), 2) Non-specific abdominal complaints with the presence of bowel edema, 3) Resolution of symptoms upon discontinuation of the ACEi, and 4) Absence of alternative diagnoses for abdominal symptoms.[17]

There is no standardized treatment of ACEi-induced intestinal angioedema. Once a diagnosis has been established, the most important intervention for the resolution of symptoms is cessation of the ACEi. Additional supportive care measures include intravenous fluids, bowel rest, pain management, and anti-emetics. Most cases resolve within 48 to 72 hours with conservative measures. Corticosteroids, antihistamines, and epinephrine are the mainstays of treatment in histamine-mediated angioedema and anaphylaxis, and, as in our patient, are often administered empirically in cases of ACEi-induced angioedema. Unfortunately, these interventions have shown minimal efficacy in bradykinin-driven cases of angioedema.[14,18,19] Symptoms are typically isolated to the small bowel, although simultaneous small bowel and orofacial involvement has been reported, and physicians should also monitor for signs of facial edema and impending airway collapse.[5] Several agents used in the treatment of hereditary angioedema have been investigated for ACEi-induced angioedema, including tranexamic acid, icatibant (bradykinin B2 receptor antagonist), ecallantide (kallikrein inhibitor), berinert (C1 inhibitor concentrate), and fresh frozen plasma. Although these agents should theoretically be effective in the treatment in bradykinin-mediated angioedema, they have shown conflicting efficacy in ACEi-induced angioedema and remain under investigation. Currently, their use is mainly recommended in severe cases with worsening angioedema threatening the airway, particularly when the etiology has not been definitively established.[14,19] Following an episode of ACEi-induced angioedema, patients should be switched to other agents. Of note, although previous studies had linked angiotensin II receptor blockers (ARBs) to an increased risk of angioedema,[20] more recent large-scale meta-analyses and cohort studies have found these agents to be safe alternatives.[21,22] Angioedema has also been reported with direct renin inhibitors (i.e., aliskiren).[23]

CONCLUSIONS

Given its rarity and non-specific symptoms, there are no studies characterizing the incidence of ACEi-induced intestinal angioedema and therefore it is likely underdiagnosed.[24] A careful history and physical examination as well as laboratory studies and imaging can help establish this diagnosis while ruling out other similarly presenting etiologies. This condition typically resolves with supportive care within 48-72 hours of discontinuation of the offending ACEi; however, symptoms frequently recur. Increased awareness is essential to prevent repeated occurrences of gastrointestinal symptoms, rehospitalizations, and potentially unnecessary endoscopic or surgical interventions.

References

1. Banerji A, Blumenthal KG, Lai KH, Zhou L. Epidemiology of ACE Inhibitor Angioedema Utilizing a Large Electronic Health Record. J Allergy Clin Immunol Pract 2017;5(3):744-749. DOI: 10.1016/j.jaip.2017.02.018.
2. Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. Hypertension 2008;51(6):1624-30. DOI: 10.1161/HYPERTENSIONAHA.108.110270.
3. Banerji A, Clark S, Blanda M, LoVecchio F, Snyder B, Camargo CA, Jr. Multicenter study of patients with angiotensin-converting enzyme inhibitor-induced angioedema who present to the emergency department. Ann Allergy Asthma Immunol 2008;100(4):327-32. DOI: 10.1016/S1081-1206(10)60594-7.
4. Palmquist S, Mathews B. Isolated intestinal type angioedema due to ACE-inhibitor therapy. Clin Case Rep 2017;5(5):707-710. DOI: 10.1002/ccr3.925.
5. Smoger SH, Sayed MA. Simultaneous mucosal and small bowel angioedema due to captopril. South Med J 1998;91(11):1060-3. DOI: 10.1097/00007611-199811000-00015.
6. Korniyenko A, Alviar CL, Cordova JP, Messerli FH. Visceral angioedema due to angiotensin-converting enzyme inhibitor therapy. Cleve Clin J Med 2011;78(5):297-304. DOI: 10.3949/ccjm.78a.10102.
7. Orr KK, Myers JR. Intermittent visceral edema induced by long-term enalapril administration. Ann Pharmacother 2004;38(5):825-7. DOI: 10.1345/aph.1D458.

8. Benson BC, Smith C, Laczek JT. Angiotensin converting enzyme inhibitor-induced gastrointestinal angioedema: a case series and literature review. J Clin Gastroenterol 2013;47(10):844-9. DOI: 10.1097/MCG.0b013e318299c69d.
9. Beltrami L, Zanichelli A, Zingale L, Vacchini R, Carugo S, Cicardi M. Long-term follow-up of 111 patients with angiotensin-converting enzyme inhibitor-related angioedema. J Hypertens 2011;29(11):2273-7. DOI: 10.1097/HJH.0b013e32834b4b9b.
10. Morimoto T, Gandhi TK, Fiskio JM, et al. An evaluation of risk factors for adverse drug events associated with angiotensin-converting enzyme inhibitors. J Eval Clin Pract 2004;10(4):499-509. DOI: 10.1111/j.1365-2753.2003.00484.x.
11. Scheirey CD, Scholz FJ, Shortsleeve MJ, Katz DS. Angiotensin-converting enzyme inhibitor-induced small-bowel angioedema: clinical and imaging findings in 20 patients. AJR Am J Roentgenol 2011;197(2):393-8. DOI: 10.2214/AJR.10.4451.
12. de Graaff LC, van Essen M, Schipper EM, Boom H, Duschek EJ. Unnecessary surgery for acute abdomen secondary to angiotensin-converting enzyme inhibitor use. Am J Emerg Med 2012;30(8):1607-12. DOI: 10.1016/j.ajem.2011.10.028.
13. Parreira R, Amaral R, Amaral L, Eloi T, Leite MI, Medeiros A. ACE inhibitor-induced small bowel angioedema, mimicking an acute abdomen. J Surg Case Rep 2020;2020(10):rjaa348. DOI: 10.1093/jscr/rjaa348.
14. Nzeako UC. Diagnosis and management of angioedema with abdominal involvement: a gastroenterology perspective. World J Gastroenterol 2010;16(39):4913-21. DOI: 10.3748/wjg.v16.i39.4913.
15. Marmery H, Mirvis SE. Angiotensin-converting enzyme inhibitor-induced visceral angioedema. Clin Radiol 2006;61(11):979-82. DOI: 10.1016/j.crad.2006.06.010.
16. Shahzad G, Korsten MA, Blatt C, Motwani P. Angiotensin-converting enzyme (ACE) inhibitor-associated angioedema of the stomach and small intestine: a case report. Mt Sinai J Med 2006;73(8):1123-5. (https://www.ncbi.nlm.nih.gov/pubmed/17285209).
17. Oudit G, Girgrah N, Allard J. ACE inhibitor-induced angioedema of the intestine: Case report, incidence, pathophysiology, diagnosis and management. Can J Gastroenterol 2001;15(12):827-32. DOI: 10.1155/2001/247816.
18. Long BJ, Koyfman A, Gottlieb M. Evaluation and Management of Angioedema in the Emergency Department. West J Emerg Med 2019;20(4):587-600. DOI: 10.5811/westjem.2019.5.42650.
19. Montinaro V, Cicardi M. ACE inhibitor-mediated angioedema. Int Immunopharmacol 2020;78:106081. DOI: 10.1016/j.intimp.2019.106081.
20. Haymore BR, Yoon J, Mikita CP, Klote MM, DeZee KJ. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. Ann Allergy Asthma Immunol 2008;101(5):495-9. DOI: 10.1016/S1081-1206(10)60288-8.
21. Rasmussen ER, Pottegard A, Bygum A, von Buchwald C, Homoe P, Hallas J. Angiotensin II receptor blockers are safe in patients with prior angioedema related to angiotensin-converting enzyme inhibitors - a nationwide registry-based cohort study. J Intern Med 2019;285(5):553-561. DOI: 10.1111/joim.12867.
22. Makani H, Messerli FH, Romero J, et al. Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. Am J Cardiol 2012;110(3):383-91. DOI: 10.1016/j.amjcard.2012.03.034.
23. White WB, Bresalier R, Kaplan AP, et al. Safety and tolerability of the direct renin inhibitor aliskiren: a pooled analysis of clinical experience in more than 12,000 patients with hypertension. J Clin Hypertens (Greenwich) 2010;12(10):765-75. DOI: 10.1111/j.1751-7176.2010.00352.x.
24. Byrne TJ, Douglas DD, Landis ME, Heppell JP. Isolated visceral angioedema: an underdiagnosed complication of ACE inhibitors? Mayo Clin Proc 2000;75(11):1201-4. DOI: 10.4065/75.11.1201.

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