A Rare Case of Lisinopril-Induced Small Bowel Angioedema: An Important Differential Diagnosis

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Background

Angiotensin-converting enzyme inhibitors (ACEi) are common medications used for the treatment of hypertension (HTN), diabetes-related kidney disease, heart failure, stroke, and more.[1] In 2019, a Medicare report showed 12.9 million people had been prescribed an ACEi.[2] With the widespread use of ACEi, it is important to understand some of the adverse effects that patients can present with. Angioedema is a rare side effect that typically presents with oropharyngeal or facial swelling. Less commonly and less known, is the rarer side effect of small bowel angioedema. This edema is the result of excess bradykinin due to ACE inhibition which ultimately leads to increased vascular permeability.[3] The incidence of angioedema has been studied to be approximately 0.10 - 0.12% yearly.[1] Because of the lack of awareness and non-specific symptoms that can mimic other general surgery emergencies, angioedema of the small bowel is underrecognized.[4] **Overall, failure to keep ACEi-induced angioedema on the list of differential diagnoses can lead to unnecessary interventions and increased patient morbidity.**

Case Presentation

Our patient was a 40-year-old female with a history of uterine fibroids, ovarian cysts, and newly diagnosed HTN, for which she had just started Lisinopril. She stated she had only taken Lisinopril twice since being prescribed. Her surgical history was significant for a right ovarian cystectomy and cesarean section. She reported occasional alcohol use but denied any recreational drugs or smoking. She had no known drug allergies. She denied any family history of colon cancer, Crohn's, ulcerative colitis, or irritable bowel. She presented to the ED with complaints of acute and severe abdominal pain that started earlier that day. She reported nausea and one episode of emesis. Her last bowel movement was earlier that day and she was passing minimal flatus. Her vitals on presentation were stable. Physical exam revealed a soft abdomen that was diffusely tender to palpation, moderately distended, and without guarding or rebound. She had no facial swelling or signs of airway edema. Laboratory findings were significant for elevated white blood cell count of 22.7 x10 3/uL, C-reactive protein level of 2.5 mg/dl, and a normal lactic acid level of 1.7 mmol/L. CT abd/pelvis demonstrated multifocal areas of severe bowel wall thickening involving the entire small bowel and duodenum suggestive of nonspecific infectious/inflammatory enteritis (Figures 1,2). Given her history of previous abdominal surgeries and acute abdominal pain, initial concern was for a bowel obstruction; however, after examining the images, discussing with radiology, and reviewing literature on ACEi side effects, angioedema of the bowel became a plausible differential diagnosis along with infectious enteritis. As there was no transition point seen on CT and she had been passing flatus, surgery opted to treat the patient conservatively versus an exploratory laparoscopy. Patient was admitted, lisinopril was stopped, she was made NPO, started on fluids & broad-spectrum antibiotics. She was monitored overnight with repeat abdominal exams to ensure no worsening of symptoms. The following day, an abdominal MRI was performed for further assessment. Results supported our suspicion as the radiologist stated the intestinal angioedema was either hereditary or medication-induced, as seen with ACEi therapy.

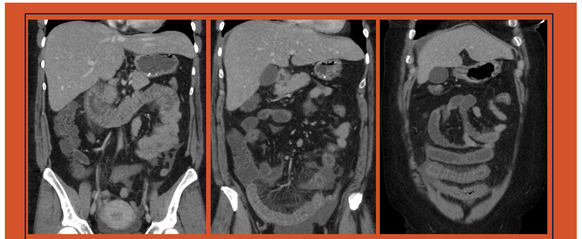
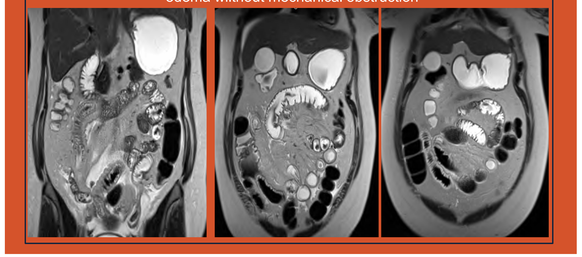


Figure 1 (above): CT abdomen/pelvis

Figure 2 (below): MRI abdomen/pelvis. Both showing diffuse small bowel edema wilthout mechanical obstruction



Case Presentation Cont.

In an attempt to rule out a possible allergic etiology or hereditary angioedema- tryptase, IgE, & C4 were all ordered and within normal limits. C1 esterase inhibitor never resulted, though this was ruled out given there was no family hx of it. ESR was within normal limits while CRP was slightly elevated. Blood cultures had no growth, and stool PCR never resulted, although lack of diarrhea, recent travel or antibiotic use decreased the likelihood this was an infectious etiology. The diagnosis of ACEi induced angioedema mainly relied on the patient's history, exam findings, and the radiologist's interpretation of the MRI. This has been documented in multiple case reports to typically involve ascites, preserved luminal transit, small bowel wall thickening of long segment, dilatation, and straightening of small bowel.[5] These findings should prompt radiologists to include ACEi induced small bowel angioedema in the differential diagnosis and aid in the decision-making of surgeons on whether to take a patient to the operating room or not. In 2023, Li et al demonstrated elevated bradykinin levels can be assessed using liquid chromatography with tandem mass spectrometry; however, this test is not feasible in most hospitals providing another barrier toward a definitive diagnosis.[6]

Over the course of 4 days, our patient's symptoms gradually improved, she was having normal bowel movements and was tolerating a diet. This timeline of improvement was similar to others diagnosed with ACEi-induced angioedema based on prior case reports.[5] Our patient was cleared for discharge with instructions to stop Lisinopril and avoid all ACEi.

Discussion

Intestinal angioedema secondary to ACE-i is a phenomenon that is currently diagnosed based on history and radiographic findings at the exclusion of obstruction, ischemic, inflammatory or infectious etiologies. The proposed mechanism of this rare phenomenon is the same mechanism as upper airway angioedema from ACE-i use. Theoretically, accumulation of bradykinin with the inhibition of ACE leads to increased vasodilation and vascular permeability of post capillary venules allowing for submucosal edema. Upper airway angioedema incidence is well studied with a 5-year incidence of 0.7% after starting an ACE-i.[2] On the other hand, the incidence of intestinal angioedema is not well studied and appears less in the literature. Lack of awareness of this side effect can lead to challenges with diagnosis. Similar to our patient who presented with an acute abdomen, case reports have shown patient's with ACE-i induced bowel angioedema have undergone unnecessary surgery when simple discontinuation of the ACE-i would have been curative.[7,8] After diagnosing a patient correctly with angioedema, further treatment can be challenging given the literature that is available on different types of angioedema. Upper airway allergic angioedema typically requires glucocorticoids along with H1 antihistamine treatment, while ACEi induced angioedema primarily involves discontinuing the medication along with ensuring a patent airway. Hereditary angioedema due to C1 inhibitor deficiency is treated with purified C1 inhibitor concentrate, FFP, Kallikrein inhibitor (ecallamtide), or bradykinin & B2 receptor antagonist (icatibant). Studies are inconclusive on whether treatment with C1 esterase inhibitor concentrate improves ACEi induced angioedema, while Bas et al demonstrated a significant decrease in time for complete resolution of angioedema following treatment with icatibant versus prednisolone with clemastine (H1 antagonist). [9,10] Although the typical treatment for bowel angioedema secondary to ACEi use is with bowel rest, IV fluids and discontinuation of the drug, these studies point to possible treatment options that may be beneficial in the future.

Conclusion

Small bowel angioedema is a rare, underdiagnosed phenomenon of ACEi treatment, yet very important to know about. Recognizing this side effect and distinguishing it from other similar illnesses can help prevent unnecessary workups, consults, and procedures such as surgery. Thorough history taking including a detailed medication list, symptoms, PE, and imaging can help correctly make the diagnosis**. Supportive care and stopping the ACEi leads to resolution of symptoms as seen in this case and in the literature.**

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