



Case Reports

Isolated Intestinal Angioedema Induced by an ACE-inhibitor

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ABSTRACT

INTRODUCTION: We report a case of isolated angioedema in a patient who presented with severe abdominal pain shortly after starting Lisinopril for treatment of hypertension. **CASE DESCRIPTION:** A 26 year old female presented with diffuse abdominal pain with onset and relief associated with Angiotensin-converting enzyme inhibitor (ACE-I) initiation and discontinuation, respectively. Additional history was not overly concerning for an infectious cause and no personal or family history suggestive of inflammatory bowel disease (IBD) was present. Physical examination revealed non-peritoneal abdominal pain, no associated IBD findings, and no apparent angioedema. Initial labs were unremarkable. Computed tomography (CT) imaging showed diffuse small bowel inflammation and was followed with direct visualization and biopsy via push enteroscopy. The small bowel appeared grossly normal, and biopsies confirmed normal mucosa. Her ACE-I was held upon admission; nausea and pain were treated symptomatically. The patient achieved complete resolution of her symptoms with no known recurrence. **DISCUSSION:** This case highlights an important diagnosis to consider in the differential of abdominal pain in a patient on an ACE-I in order to avoid expensive and invasive testing.

Key words: Intestinal angioedema; ACE-Inhibitor; Lisinopril; Isolated angioedema

INTRODUCTION

Angioedema (AE) is described as localized, non-pitting edema involving the dermis as well as the subcutaneous layers, and most commonly involves the tongue, lips, face, and throat.¹ In rarer circumstances, angioedema may also involve the viscera, as well as other areas of the body.¹ Reported overall lifetime incidence varies, with percentages as high as 15% (Lewis). Furthermore, AE may be allergic or non-allergic, which includes hereditary, acquired, or idiopathic forms. Signs and symptoms vary depending on the area of involvement and include dyspnea, drooling, stridor, difficulty swallowing or speaking, abdominal pain and diarrhea.¹ Urticaria is present in about half of cases, and is typically accompanied by pruritus.² Noteworthy is that in ACE-I induced AE,

urticarial and pruritus are rarely present.³ Treatment varies with causes, symptoms, and location of involvement, and ranges from observation to intubation and vasopressors; specific treatments are beyond the scope of this report.

Various forms (i.e., hereditary, acquired) of AE share a common pathways through which clinical effects are mediated, including the kallikrein-kinin system.¹ Angiotensin-converting enzyme inhibitors (ACE-I) and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most important causes of drug-induced AE.⁴ ACE-I used in the management of hypertension, chronic heart failure and renal insufficiency, work by altering the balance between angiotensin II and bradykinin.⁵ Although generally well-tolerated, side effects of these drugs include persistent dry cough, renal failure, and angioedema.⁶ ACE-I are responsible for 20-30% of all AE cases seen in emergency departments in the United States.⁷ The range of reported incidence of ACE-I related peripheral angioedema is 0.1% to 0.2%, with visceral AE occurring more rarely.⁸ As of 2010, only twenty-one cases of ACE-I induced intestinal angioedema had been reported in English medical literature³. Cases have involved multiple members of the ACE-I family, with the first Lisinopril-induced case reported in 1997.⁹ No dose related effect has been described.³

CASE REPORT

The patient is a 26 year old white female with past medical history significant for arthritis related to athletic training and idiopathic hypertension diagnosed by her primary care physician three weeks prior to presentation to the hospital. She was started on Lisinopril 10 mg daily and subsequently developed mild, diffuse abdominal pain described as “stomach in knots” in character. This persisted until one week prior to admission when she developed constipation and stopped the Lisinopril. Her constipation and abdominal pain resolved. She restarted Lisinopril two days prior to admission and subsequently her pain returned on the night before admission and was intensified. She had associated nausea and vomiting and presented to the emergency department in the morning. She denied any fevers, chills, painful defecation. No oral ulcers, rashes, changes in vision or genitourinary symptoms. She has baseline arthritis secondary to athletics, with no recent change. She is sexually active, on oral contraceptives, and reports no vaginal discharge or history of sexually transmitted infections. No surgical history. No family history of inflammatory bowel disease. Physical examination confirmed historical points and was otherwise unremarkable with the exception of diffuse tenderness to palpation of her abdomen, worst in the left lower quadrant, without peritoneal signs. No swelling of lips or tongue was present. Initial CBC, CMP, and urinalysis were within normal limits and a pregnancy test was negative. Stool studies were negative. CT abdomen showed diffuse small bowel inflammation involving the jejunum and possible gastric outlet obstruction. Ascites is also present. Please see images **Figure 1** and **Figure 2**. She was admitted for further evaluation and a push enteroscopy was performed. This study revealed normal esophageal, gastric, and small bowel mucosa. Biopsies were taken and confirmed normal mucosa. Her ACE-I was held upon admission and her pain and nausea were treated symptomatically. She had complete resolution of her symptoms by hospital day three and was discharged not on any medications. Outpatient follow-up was scheduled with a gastroenterologist, with option of cancellation if she had no recurring symptoms. She did not keep the appointment.

Figure 1. Coronal view of the patient’s abdominal CT showing small bowel inflammation and ascites.



Figure 2. Axial view from patient's abdominal CT showing small bowel inflammation with jejunal thickening.



DISCUSSION

This case illustrates the potential for isolated intestinal angioedema with use of ACE-I, and the importance of its early consideration to avoid invasive testing and procedures in patients presenting with a common chief complaint of acute abdominal pain. Acute abdominal pain has been reported as the reason for 5% to 10% of all visits to the emergency room.¹⁰ Furthermore, data from the National Hospital Ambulatory Medical Care Survey showed that abdominal pain was the primary reason for visit in 7 million noninjury ED visits in 2007-2008, representing a 31.8% increase from the start of the survey in 1999-2000.¹¹ With over 42 million prescriptions, Lisinopril is the fourth most prescribed medication in the US.¹² At the cross-section of these commonalities lies case at hand and the opportunity to provide more patient-centered care.

Our patient had two epidemiologic factors associated with ACE-inhibitor angioedema, including female gender (RR 1.6) and cigarette smoking (RR 2.7).¹³ In addition to cough, the relationship between ACE-inhibitors and peripheral angioedema of the face, lips, and upper airway is well known and often easily recognized. However, the rarer presentation of visceral involvement in the absence of other involvement, as seen in this patient, can mimic an acute abdomen and result in unnecessary invasive diagnostic investigations and interventions, such as surgery for presumed bowel-wall ischemia.⁸ Any part of the gastrointestinal tract may be affected by AE, resulting in nausea, vomiting, abdominal pain, and even obstruction.² The angioedema may be confined to only one part of the intestine, most commonly the small bowel.¹⁴ Typical signs of visceral AE include leukocytosis, ascites, and small bowel changes seen on CT.¹⁵ The CT findings in this case prompt a differential including inflammatory bowel disease, vasculitis, and lymphoma among other causes, which would not be expected to improve in the short time frame seen here. A previous case series suggested CT findings of ascites, small bowel wall thickening, dilation without obstruction, and straightening should prompt inclusion of the diagnosis in the differential, if not already considered, in patients presenting with abdominal pain while taking an ACE-inhibitor.¹⁶ The diagnosis of ACE-I induced visceral angioedema is multifactorial, including a temporal relationship between medication intake and symptoms, as well as resolution following discontinuation of the ACE-I; other causes must also be excluded.⁸ Although the majority of cases have a temporal presentation within the first few weeks as seen in our patient, delayed onset of years has been reported as well.³ Cessation of the medication is often sufficient management to completely reverse ACE-I induced intestinal AE, typically leading to symptom resolution in 24-48 hours.³ Although earlier diagnostic algorithms for analysis of different types of AE had listed drug-induced AE as a last explanation, others have suggested the diagnosis be considered at an early stage since simply stopping the medication can prevent possible complications and unnecessary surgery.⁴

The exact mechanism of action of ACE-I induced visceral angioedema is not completely known. Bradykinin-associated vasodilation and altered vascular permeability have been suggested as the cause of the edema seen with ACE-I.⁸ This class of drugs have also been found to induce tissue-specific and anti-nuclear antibodies, which some submit may cause AE through immunological reactions.¹⁷ Hormonal etiologies for ACE-I induced intestinal AE have also been theorized based on the predilection for women and the average age of 48 years.³

SUMMARY

A 26 year old woman presented with diffuse abdominal pain associated with initiation of an angiotensin-converting enzyme inhibitor. Work-up revealed characteristic findings of ACE-I induced intestinal angioedema on CT abdomen. Other causes were excluded and the pain subsided within three days of discontinuation of the ACE-I. Although rare, this diagnosis must be considered in patients with consistent history (e.g., use of an ACE-I and abdominal pain) and CT findings (e.g., intestinal edema and ascites) to prevent unnecessary patient morbidity. A quick and accurate diagnosis can lead to reversal of the symptoms with nothing more than discontinuation of the offending drug and supportive care. Misdiagnosis can result in expensive and invasive testing and procedures for the patient, as well as the potential for repeat episodes if the drug is continued. The patient presented in this report was fortunate in that she did not have to experience recurrent episodes or undergo

unnecessary surgical intervention prior to resolution of her symptoms with discontinuation of Lisinopril. Clinicians should aspire to increased awareness that more patients may achieve similar outcomes.

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