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A Rare Case of ACEi-associated Angioedema of the Small Bowel

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Abstract

A middle-aged female presented with abdominal pain, vomiting, and watery non-bloody diarrhea shortly after her lisinopril dose was increased. Extensive workup did not reveal a definite pathology however CT of the abdomen showed bowel wall thickening of the proximal jejunum. Her lisinopril was held at the start of the admission due to an acute kidney injury and hypotension. A colonoscopy was done and biopsies revealed increased intraepithelial lymphocytes at every site which is characteristic of medication induced enteropathy. She was instructed to not restart lisinopril and symptoms completely resolved. She was diagnosed with ACEi-angioedema of small bowel.

Keywords: Angioedema; Angiotensin converting enzyme inhibitors; ACEi associated angioedema; Small bowel angioedema

Introduction

ACEi-angioedema is a well-documented adverse effect with a clearly defined pathophysiological pathway. Angiotensin converting enzyme (ACE) degrades the vasodilators bradykinin and substance P. By inhibiting ACE, both bradykinin and substance P cannot be degraded which leads to plasma extravasation into the submucosal tissue resulting in angioedema. This form of angioedema most commonly affects the face and neck. ACEi-angioedema of the gastrointestinal tract is a particularly rare manifestation with non-specific symptoms and radiographical findings.

Case Presentation

A 56-year-old female with a past medical history of hypertension (HTN), post-traumatic stress disorder (PTSD), and depression presented to the emergency department (ED) with 4 weeks of cramping lower abdominal pain, nausea, vomiting, and watery non-bloody diarrhea. Computed tomography (CT) of the abdomen and pelvis showed bowel wall thickening of the proximal jejunum. A GI PCR and Clostridium difficile (C. diff) toxin PCR were both negative. Gastroenterology was consulted and at that time the differential diagnosis included irritable bowel syndrome with diarrhea (IBS-D), microscopic colitis, functional diarrhea, viral gastroenteritis, and malabsorption. Her symptoms improved but did not resolve and she was discharged after a 2-day hospitalization with plans for outpatient colonoscopy and enteroscopy.

She presented back to the ED 2 weeks later with recurrence of these same symptoms. She was hypotensive and had an acute kidney injury (AKI). She was fluid resuscitated and started on ceftriaxone and metronidazole to empirically cover an infectious bacterial colitis. On this admission her lisinopril was held due to the AKI and hypotension. On physical exam

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she had lower abdominal tenderness on palpation without rigidity, guarding, or rebound. She had no swelling of the lips, tongue, or neck. CT of the abdomen and pelvis at this admission was unremarkable without any edema of the small bowel. Blood cultures did not yield any growth. Gastroenterology was consulted and did an enteroscopy and colonoscopy inpatient. Enteroscopy found a few small non-bleeding erosions in gastric antrum without stigmata of recent bleeding. There was no significant pathology in entire duodenum, and proximal to mid jejunum. The entire colon appeared normal on colonoscopy. The stomach and jejunum biopsies were normal without any diagnostic alteration. There was no histologic evidence of helicobacter pylori. The colon biopsy showed colonic mucosa with increased intraepithelial lymphocytes at every biopsy site. Increased intraepithelial lymphocytes on colon biopsy was a non-specific finding with most cases being idiopathic. However, it can also be seen in medication induced enteropathy from non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin re-uptake inhibitors (SSRI), ACEi, angiotensin receptor blockers (ARB), and anti-body based immune checkpoint inhibitors. Of note her lisinopril dose had been increased approximately 1 month prior to initial hospitalization. She was treated with supportive care, hospitalized for total of 5 days, and discharged with instruction to completely stop lisinopril.

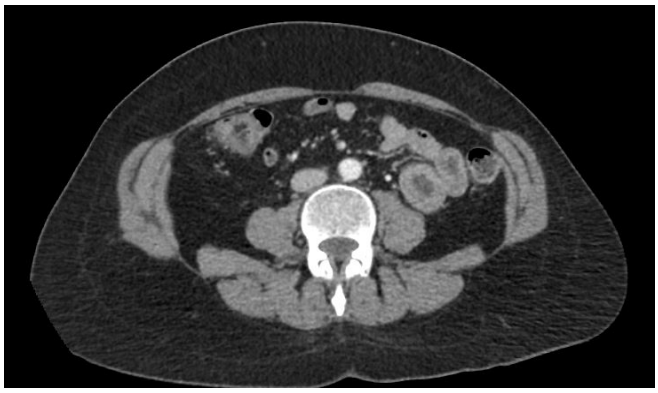

Image 1:

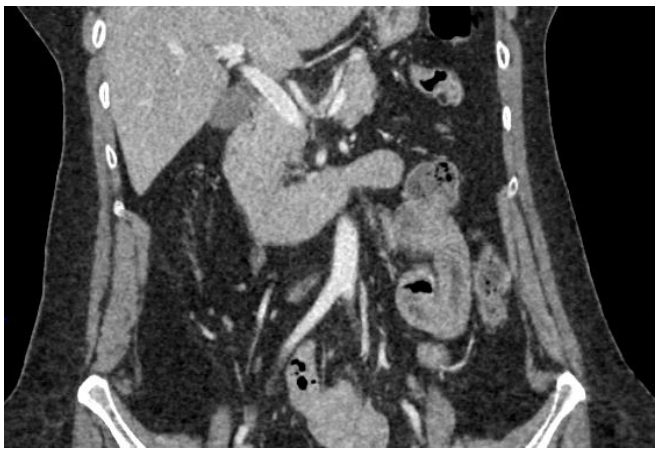

Image 2:

When she followed up in clinic 1 month after discharge all her symptoms had resolved with cessation of lisinopril. She was diagnosed with ACEi-induced angioedema of the bowel.

Discussion

ACEi are one of the main causes of angioedema and responsible for around 27% to 57% of all angioedema cases [1,2] and account for 1/3rd of ED visits for angioedema [9]. The prevalence of angioedema amongst patients on ACEi is between 0.1 to 0.7% [3-7]. ACEi-AE can occur at any time during the course of ACEi use with cases being seen up to 5 years from initiation of therapy [3]. If a patient develops ACEi-AE, the agent must be stopped immediately and the patient cannot take any other ACEi indefinitely. If a patient is continued on an ACEi despite an initial bout of angioedema there was a 10-fold increase risk of developing angioedema again [10]. Certain ACEi are more strongly associated with angioedema than others. The OCTAVE trial found that the incidence of angioedema was markedly higher with omapatrilat (2.2%) than enalapril (0.7%) [11].

Most individuals do not develop angioedema despite inhibition of ACE thus other factors must be involved in the pathogenesis, such as an intrinsic defect in the degradation of bradykinin, des-Arg9-BK, and substance P [12]. Several risk factors have been identified for ACEi-AE. The OCTAVE trial identified that age >65, African American patients, and history of drug rash or seasonal allergies were risk factors [11]. The increase in risk of angioedema for patients age >65 is likely related to decreased levels of dipeptidyl peptidase IV (DPP-IV) in the elderly, an enzyme involved in degradation of bradykinin [13]. Women are at higher risk of developing angioedema, likely due to the role of estrogen in inducing expression of prekallikrein and bradykinin type 2 receptor while also suppressing ACE gene expression [14,15]. Smokers were found to be at increased risk of ACEi-AE due to significantly lower levels of DPP-IV, while diabetics appeared to have lower rates of angioedema in relation to higher levels of DPP-IV [12].

Although epinephrine, corticosteroids, and antihistamines are commonly used for ACEi-AE there is weak evidence for their efficacy for this particular form of angioedema. Supportive care, immediate cessation of ACEi, and close airway monitoring with intubation if necessary are the standard of care.

ACEi induced angioedema of the bowel is an exceedingly rare complication. One retrospective study of 20 patients with this complication found that all had acute onset of severe abdominal pain, date of initiation of ACEi ranged from 2 days to 10 years, all had resolution of symptoms within 4 days of hospitalization, and CT findings included ascites, small-bowel wall thickening, mild dilatation, and straightening without small bowel obstruction [16].

Our patient had an increase in the dose of lisinopril shortly prior to presentation which likely triggered the angioedema. Given the widespread use of ACEi in conjunction with non-specific symptoms and radiographic findings, ACEI-AE of the bowel may be an under-recognized and under-diagnosed. Even biopsy findings of increased intraepithelial lymphocytes lack specificity since these can also be idiopathic in etiology. A more granular review of radiology, careful attention to medication history and dosage changes, and trial of cessation of ACEi should be considered in patients with idiopathic abdominal pain. Confirmation of the diagnosis requires cessation of the ACEi and close follow-up to monitor for a response in symptoms.

Ethical Approval and Consent to participate

Not applicable

Consent for publication

Informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflicts of interest

None

Declaration of funding

None

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None

Author contributions

Case report was chiefly written by Michael Ladna, with contributions and editing by Naueen Chaudhry, Vanessa Rodriguez, and Angela Pham

Abbreviation List

ACE	Angiotensin-converting enzyme inhibitor
ACEi	Angiotensin-converting enzyme inhibitors
ACEi-AE angioedema	Angiotensin-converting enzyme inhibitors
AKI	Acute Kidney Injury
ARB	Angiotensin receptor blockers
C. Diff	Clostridium Difficile
DPP-IV	dipeptidyl peptidase IV
ED	Emergency Department
HTN	hypertension
IBS	Irritable bowel syndrome
IBS-D	irritable bowel syndrome with diarrhea
IBD	Inflammatory bowel disease
NSAIDs	Non-steroidal anti-inflammatory drugs
PTSD	Post-traumatic stress disorder
PCR	polymerase chain reaction
RR	Relative Ricks
SSRI	selective serotonin receptor inhibitors

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