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Case Report

Lisinopril Induced Visceral Angioedema

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Angiotensin-Converting Enzyme inhibitors (ACE-i) is now recommended to be one of the four medications for initial therapy for Hypertension (HT) (Herman, Padala, Annamaraju, et al., 2020; Page, 2014). Various trials have shown better patient outcomes (Yusuf, Sleigh, Pogue, Bosch, Davies, & Dagenais, 2000; Fox, 2003). However, ACE-i is one of the leading causes of drug-induced angioedema. Peripheral angioedema has been reported in 0.1-0.2% of patients taking lisinopril. However, visceral angioedema is extremely rare. Here we present a case of a 58-year-old male presenting with acute abdominal pain seven days after starting lisinopril and was found to have visceral angioedema on CT scan.

A 58-year-old male with a medical history of hypertension, GERD, generalized anxiety disorder, and sigmoid diverticulitis requiring a sigmoid resection with diverting ileostomy (11 years back) presented with acute onset, generalized abdominal pain. He had one episode of non-bloody, non-bilious vomiting. He had been passing flatus and denied fever, melena, or hematochezia. His home medications were aspirin, simvastatin, sumatriptan, and lisinopril. Lisinopril was started one week before the presentation. He denied any family history of IBD and never had a colonoscopy. There were no recent changes in his diet, and he denied any recent travel history. His abdomen was soft and mildly distended with mild

tenderness to palpation, generalized, without guarding, rigidity, or rebound tenderness. Bowel sounds were normoactive.

Laboratory investigations revealed WBC of 12, CRP of 29 and an ESR of 37. LFTs, lipase, serum electrolytes, troponin, procalcitonin and lactate were within normal limits. Abdominal CT revealed thickened loops of small bowel in the mid-abdomen without definite evidence for obstruction (Figure 1). Gastroenterology was consulted. Based on imaging, inflammatory etiologies including Crohn's or Ulcerative Colitis were less likely. Infectious workup including procalcitonin as well as cultures were negative. His bowel thickening was diagnosed as visceral edema secondary to lisinopril. His Naranjo score for adverse drug reaction was four which indicated Possible adverse drug reactions. Lisinopril was stopped, and we transitioned him to Amlodipine. His symptoms resolved before discharge.

ACE-I inhibits ACE competitively to prevent the formation of Angiotensin II (Ang II) from Angiotensin I, resulting in a decreased production of both Ang II and Aldosterone, resulting in the desired cardioprotective effects by limiting vasoconstriction and free water retention, respectively (Herman, Padala, Annamaraju, et al., 2020; Page, 2014). Inhibition of ACE also leads to the accumulation of bradykinin and Substance P, locally acting hormones that promote vasodilation and increased vascular permeability (Brown & Vaughan, 1998; Ana, Inês, Rita, Alexandra, & Jorge, 2016). Under normal circumstances, these hormones have only transient effects, and they are quickly degraded to their inactive forms. However, ACE-I fosters an environment whereby these molecules have a prolonged effect, resulting in localized fluid extravasation, the proposed mechanism behind ACE-I Angioedema (Brown & Vaughan, 1998; Ana, Inês, Rita, Alexandra, & Jorge, 2016).

Angioedema typically affects the head and neck region, resulting in potential airway compromise and the need for urgent intubation (Krause, Patel, & Morgan, 2019; Palmquist & Mathews, 2017). Visceral ACE-I angioedema is far less common; 34 cases had been reported in a recent literature review, most common presenting symptoms were episodic abdominal pain, nausea, and non-bloody emesis (Palmquist & Mathews, 2017). Although the degree of small bowel involvement may vary, most patients who underwent a CT were found to have small bowel involvement greater than 10 cm with associated mesenteric edema and ascites (Scheirey, Scholz, Shortsleeve, et al., 2011) (13). The timeline for developing symptoms from the initiation of ACE-I can vary from 1 week up to 9 years after stable treatment (Krause, Patel, & Morgan, 2019; Palmquist & Mathews, 2017). The combination of nonspecific abdominal symptoms with variable onset of occurrence from treatment initiation often leads to missed or delayed diagnosis, a failure to remove the culprit medication, and unfortunately, a rate of recurrence of greater than 50% in 5 years (Hoover, Lippmann, Grouzmann, Marceau, & Herscu, 2010). This temporal variability also helps support the notion that the cause of ACE-I angioedema is multifactorial with multiple environmental and genetic components (Hoover, Lippmann, Grouzmann, Marceau, & Herscu, 2010). In addition to ACE, several other hormones, including Aminopeptidase P (APP), neutral endopeptidase (NEP), and dipeptidyl peptidase IV (DPPIV), are responsible for Kinin degradation, and mutations in these hormones may leave a limited reserve once ACE-I therapy is begun.

Other risk factors include African American race, female gender, and smoking (Hoover, Lippmann, Grouzmann, Marceau, & Herscu, 2010).

Interestingly, diabetic patients seem to have a lower incidence of AE, possibly due to an overactive DPPIV enzyme associated with hyperglycemia (Mannucci, Pala, Ciani, et al., 2005). This is further supported by the fact that the concomitant use of ACE-I with DPPIV inhibitors such as sitagliptin was associated with a higher incidence of AE. In addition, other medications, including aspirin, have been found to have higher rates of AE when combined with ACE-I (Hoover, Lippmann, Grouzmann, Marceau, & Herscu, 2010). In our patient, the short duration from ACE inhibitor exposure to the development of abdominal symptoms suggests other factors may be involved, possibly aspirin intake (Brown & Vaughan, 1998; Ana, Inês, Rita, Alexandra, & Jorge, 2016). The mildly elevated inflammatory markers did raise suspicion for an infectious etiology initially. However, the absence of other infectious sequelae, classic radiographic findings, and the rapid improvement following discontinuation of the lisinopril without antibiotics helped solidify our diagnosis.

Regarding management, discontinuation of the offending agent is the mainstay of treatment, and symptoms should resolve within 24-72 hours (Beltrami, Zanichelli, Zingale, Vacchini, Carugo, & Cicardi, 2011). Medications used to manage Hereditary Angioedema, including C1 inhibitor concentrate, have been trialed in ACE-I induced AE; however, the benefit of these regimens remains unclear (Beltrami, Zanichelli, Zingale, Vacchini, Carugo, & Cicardi, 2011). Although repeat episodes of AE may still occur following ACE-I removal, most cases occurred within the following 30 days; repeat episodes outside that time frame may be secondary to a separate entity (Beltrami, Zanichelli, Zingale, Vacchini, Carugo, & Cicardi, 2011). The data regarding alternative antihypertensive regimens is also not entirely clear. Angiotensin Receptor Blockers (ARB's) and Beta Blockers (BB) have been reported to precipitate AE, although less likely (Toh, Reichman, Houstoun, et al., 2012). Current recommendations argue that using these regimens, provided their intended benefit, outweighs future AE episodes' risk (Toh, Reichman, Houstoun, et al., 2012).

Although very rare, ACE inhibitor-induced angioedema should be considered in patients presenting with acute abdomen after careful exclusion of other causes. Unfortunately, because of the variability in symptom onset, the diagnosis is missed, failing to remove the culprit medication and a high rate of symptom recurrence. Following ACE-I discontinuation, a rapid improvement of symptoms should be observed, the absence of which should prompt consideration towards an alternate diagnosis. If indicated, risks and benefits should be carefully considered before resuming any ACE inhibitor or ARB group of medications in these patients.

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Abbreviations:

ACE-i: Angiotensin Converting Enzyme

AE: Angio-Edema

APP: Aminopeptidase P

ARB: Angiotensin Receptor Blocker

BB: Beta- Blocker

DPPIV: Dipeptidyl Peptidase IV

GERD: Gastro Enteric Reflux Disease

HT: Hypertension

NEP: Neutral Endopeptidase

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Consent: Written informed consent was obtained from the patient to publish this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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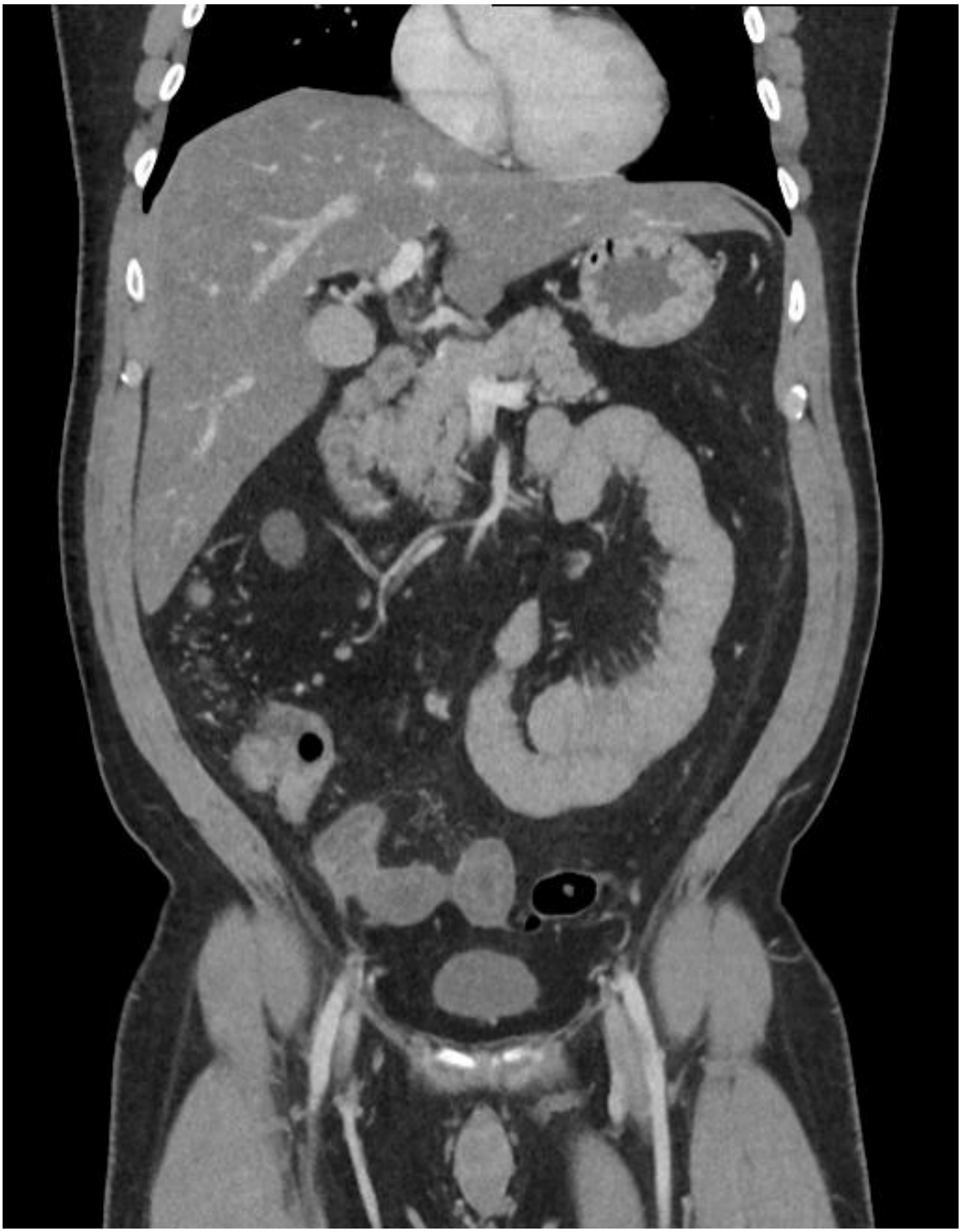

Figure 1. CT Scan of Abdomen and Pelvis. (Thickened Loops of Small Bowel in the Mid Abdomen)