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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Another Crohn's Disease Mimicker: A Case of Angiotensin-Converting Enzyme Inhibitor-Induced Intestinal Angioedema

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ABSTRACT

Angiotensin-converting enzyme inhibitors are a common cause of drug-induced angioedema, which rarely affects the gut. We present a 32-year-old White woman with Crohn's disease on lisinopril experiencing 1 year of episodic abdominal pain, nausea, and vomiting, prompting multiple steroid tapers and a switch in biologic therapy. She was hospitalized and was profoundly hypotensive on arrival. Initial imaging showed marked small bowel wall thickening and free fluid in the abdomen. She had rapid symptomatic and radiographic improvement after only 24 hours and was diagnosed with angiotensin-converting enzyme inhibitor-induced intestinal angioedema, an important Crohn's disease mimicker that may lead to unwanted management if unrecognized.

KEYWORDS: Crohn's disease; angiotensin-converting enzyme inhibitors; angioedema; adverse drug reaction; enteritis

INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEIs) are commonly used medications with well-known adverse effects, including drug-induced angioedema, and are responsible for about one-third of angioedema-related hospitalizations in the United States.[1–4] Pathophysiology is mediated through the bradykinin pathway and leads to increased vascular permeability and extravasation of fluid into the interstitium, resulting in tissue edema.[5] ACEI-induced angioedema usually affects the mouth, face, and upper airway but may also affect the gut. Isolated intestinal angioedema is an extremely rare manifestation and often represents a diagnostic dilemma for clinicians, especially if it manifests in the background of other chronic abdominal diseases such as inflammatory bowel disease (IBD).[6–10]

CASE REPORT

A 32-year-old White woman with hypertension and stricturing ileocolonic Crohn's disease presented to the emergency department with 2 days of progressively worsening abdominal pain, nausea, and vomiting. Her Crohn's disease was complicated by small bowel obstruction with perforation requiring small bowel resection 6 years ago. She had been well maintained on infliximab plus azathioprine for 5 years until 1 year ago, when she developed recurrent symptomatic episodes requiring 12 emergency department visits within 1 year and several rounds of steroid therapy. Repeat upper endoscopy and colonoscopy appeared normal, and random duodenal, ileal, and colon biopsies were unrevealing. Computed tomography (CT) imaging during these evaluations showed enteritis, but follow-up CT enterography was normal, attributed to clinical improvement from steroids. She was deemed to have primary failure of infliximab and was switched to risankizumab, but the episodes continued.

In the emergency department, she was afebrile, tachycardic, and significantly hypotensive with an initial blood pressure of 76/50 mm Hg and nadir of 53/40 mm Hg, associated with a syncopal episode. Abdominal examination showed generalized tenderness without peritoneal signs. There was no orofacial swelling, skin rash, or respiratory symptoms. Laboratory tests were significant for white blood cell count 18.8×10^3/cmm with neutrophil predominance, eosinophil count 0.10×10^3/cmm, C-reactive protein 32.7 mg/L,

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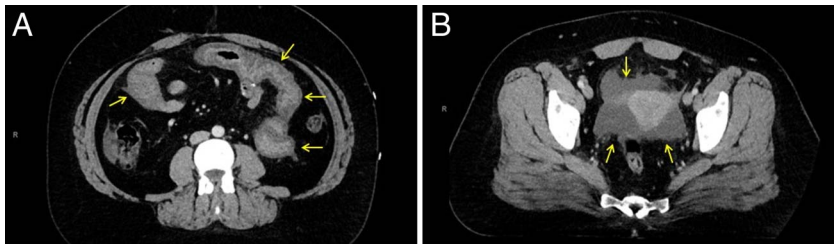

Figure 1. Initial computed tomography imaging of the abdomen and pelvis with intravenous contrast. (A) Extensive small bowel enteritis with marked wall thickening. (B) Free fluid in the pelvis. The arrows represent the presence of bowel angioedema.

and lactic acid 4 mmol/L. She had a normal fecal calprotectin of 112 mcg/g and a negative gastrointestinal pathogen panel. Abdominal/pelvic CT with intravenous contrast showed extensive marked small bowel wall thickening (Figure 1) with free fluid adjacent to the cecum and in the pelvis (Figure 1).

She was admitted and started on intravenous methylprednisolone for presumed exacerbation of her Crohn's disease. Her home lisinopril was held due to hypotension. Over the next 24 hours, her symptoms completely resolved. CT enterography obtained 29 hours after the initial CT showed substantial improvement with only mild bowel wall thickening and mural hyperenhancement involving a short segment of small bowel (Figure 2). The previously seen abdominal free fluid had resolved (Figure 2). Given her atypical presentation, other diagnoses were considered including intestinal angioedema. Further history revealed that the patient was started on lisinopril 1 year ago, just a few weeks before the onset of her symptomatic episodes. C1 esterase inhibitor level was normal at 33 mg/dL and serum IgE was <25.0 IU/mL. Given her relapsing symptoms, new therapy failures, and unusual presentation with unexplained hypotension, ascites, and rapid symptomatic and radiographic improvement 24 hours after holding lisinopril, it was assumed that ACEI-induced intestinal angioedema was the most likely diagnosis. Lisinopril was stopped, and she was discharged with a prednisone taper. Five days later, she underwent push enteroscopy showing a long segment of chronic-appearing mucosal edema, flattened villi, and pseudopolyps in the proximal jejunum (Figure 3). Multiple biopsies from this area showed normal small intestinal mucosa, and endoscopic findings were attributed to residual healing from previously inflamed small bowel. Same-day ileocolonoscopy was otherwise normal. At her clinic visits 2 and 8 months later, she reported no recurrent symptoms and resumed risankizumab therapy. Repeat CT enterography is pending.

DISCUSSION

ACEI-induced intestinal angioedema affects <1% of medicated patients; the majority are female patients in their 40s.[11] It mainly presents with acute abdominal pain and sometimes nausea, vomiting, or diarrhea.[2] It is more easily recognized in the setting of other angioedema manifestations but is challenging to diagnose if isolated. Cross-sectional imaging may reveal bowel wall edema, thickening, and ascites.[12] Jejunal involvement is most common, followed by the ileum and duodenum.[3,8,12] Biopsies are usually normal, but often done to evaluate for active IBD, cytomegalovirus, and other IBD mimickers.[13] Serum complement factor 4 and C1 esterase levels may evaluate for hereditary or acquired angioedema. Timing is variable, as onset can occur from weeks to years after the initial prescription. Symptoms typically improve in 24–48 hours after stopping the ACEI, which remains the primary treatment. Other therapies used in hereditary angioedema, such as icabitant and C1 esterase inhibitor, have been investigated with no proven benefit in ACEI-induced angioedema.[14]

Three case reports of intestinal angioedema in the setting of Crohn's disease demonstrate the clinical heterogeneity and diagnostic challenges of these patients. Malcolm et al described a patient with abdominal pain who underwent 2 laparotomies, oral corticosteroids, and olsalazine for presumed appendicitis and Crohn's disease before being diagnosed with acquired

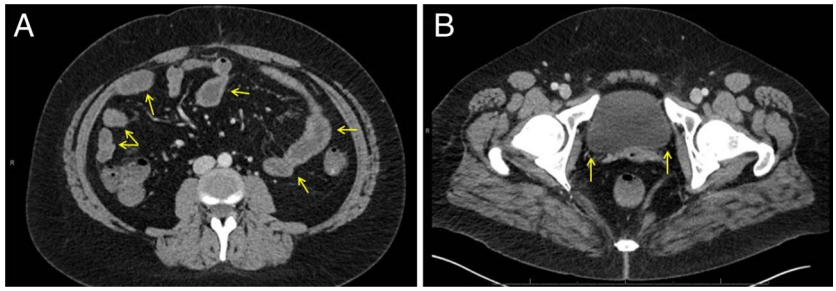

Figure 2. Subsequent CT enterography with intravenous and oral contrast performed 29 hours after initial CT scan. (A) Significantly improved wall thickening of the small bowel. (B) Previously seen free fluid in the pelvis has resolved. CT, computed tomography. The arrows represent the resolution of bowel angioedema.

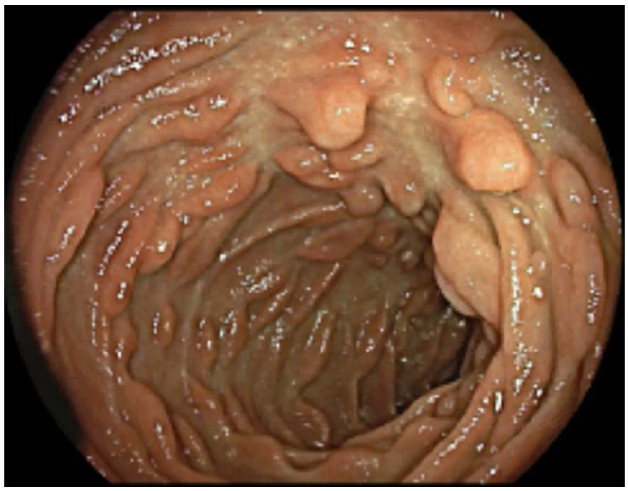

Figure 3. Follow-up push enteroscopy showing a long segment of chronic-appearing mucosal edema, flattened villi, and pseudopolyps in the proximal jejunum.

intestinal angioedema.[15] Freeman et al linked Crohn's to hereditary angioedema, describing 2 family members with both conditions and deficient serum C1 esterase levels. Shahani reported a similar case of isolated lisinopril-induced intestinal angioedema managed by switching to amlodipine.[16]

ACEI-induced intestinal angioedema is a rare condition that clinicians should consider when managing patients with IBD not responding to multiple therapies or present with unusual findings. Other IBD mimickers should also be explored, including infectious (e.g., cytomegalovirus, *Clostridioides difficile*, histoplasmosis, tuberculosis) and noninfectious causes (e.g., eosinophilic gastroenteritis, vasculitides, common variable immunodeficiency, sarcoidosis).[17,18] For example, although circulating IgE and eosinophil levels were normal in our patient, eosinophilic gastroenteritis may present similarly with glucocorticoid responsiveness, ascites, pseudopolyps, and normal biopsies.[19] Additional tissue sampling, imaging, and further history is often necessary in these difficult cases.[17] A comprehensive review of medications should always be performed to identify those associated with drug-induced colitis such as nonsteroidal anti-inflammatory drugs, hormonal therapy, rituximab, mycophenolate, or supplements such as kratom, bitter orange, and ma huang.[17,20] After identification and removal of the offending agent, patients should be reassessed to ensure ongoing clinical improvement and evaluate for alternative etiologies if diagnostic uncertainty remains.

DISCLOSURES

Author contributions: M. Adam was responsible for the original draft and literature review. All authors contributed to manuscript revisions. A. Evans supervised and critically reviewed the manuscript. All authors made substantial contributions to the conception of the work. All authors approve the final submitted manuscript. M. Adam is the article guarantor.

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