REVIEW

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Visceral angioedema due to angiotensin-converting enzyme inhibitor therapy

ABSTRACT

Visceral angioedema is an uncommon but serious complication of therapy with angiotensin-converting enzyme (ACE) inhibitors. We report a case, review the literature, and discuss the incidence, features, and clinical recognition of this condition.

KEY POINTS

Visceral angioedema due to ACE-inhibitor therapy can easily be diagnosed by clinical suspicion and abdominal computed tomography (CT).

Many physicians are not aware of this condition and so may subject patients to unnecessary invasive procedures, including surgery and endoscopy.

If a middle-aged woman taking an ACE inhibitor presents with abdominal pain and emesis, the differential diagnosis should include visceral angioedema, and CT should be strongly considered.

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A 57-year-old black woman presented to the emergency department with severe, dull abdominal pain associated with nonbilious vomiting and nausea. She had diabetes mellitus and hypertension, for which she had been taking metformin (Glucophage) 500 mg twice a day and lisinopril (available as Prinivil and Zestril) 20 mg daily for the last 4 years.

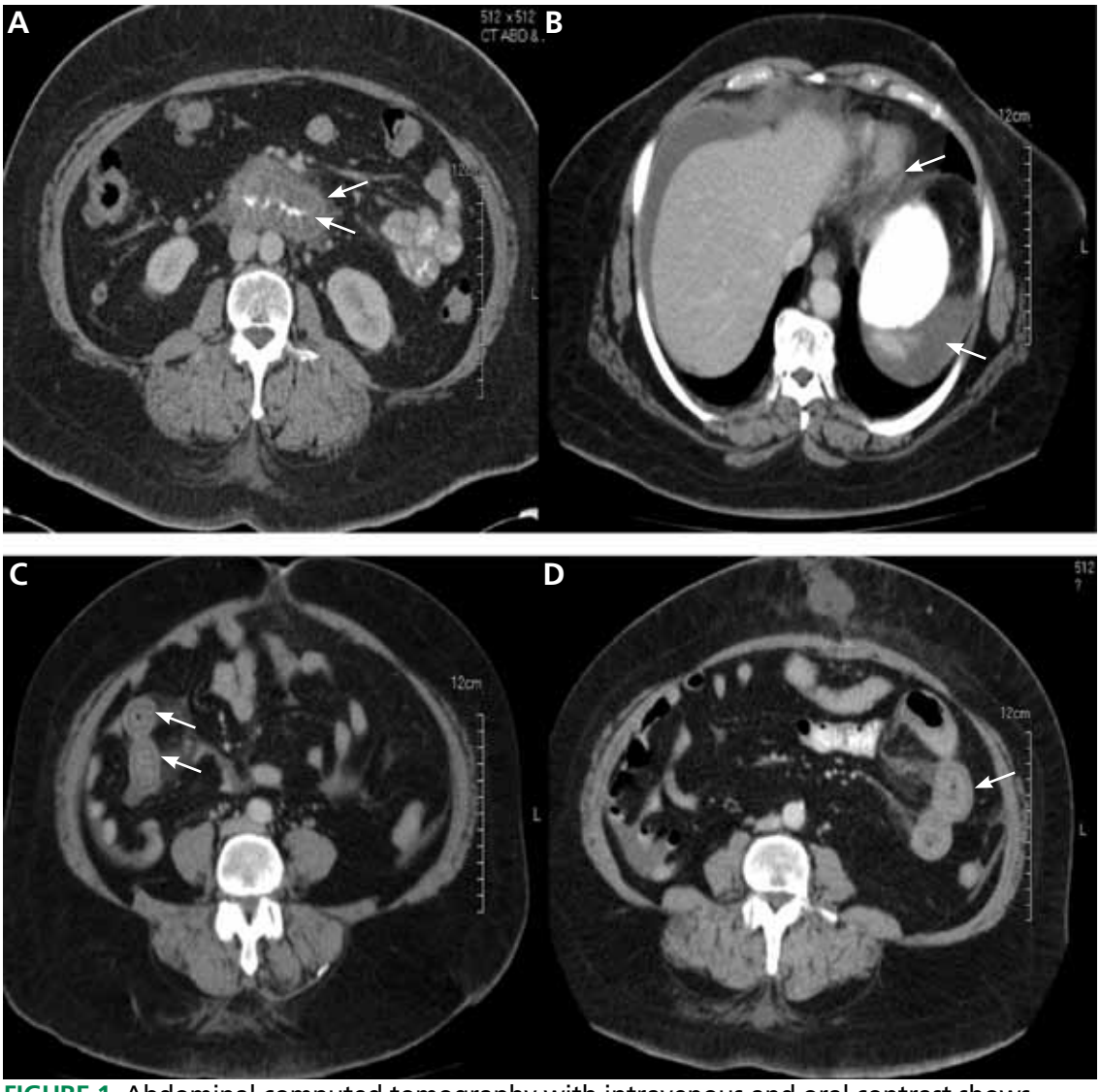
Multiple admissions in the past 4 years

The patient started taking lisinopril 10 mg daily in 2005, and she presented to her medical provider 2 weeks later with abdominal discomfort. Colonoscopy was performed, which revealed a benign polyp. She continued taking her medications, including lisinopril.

She continued to occasionally have abdominal pain of variable severity, but it was tolerable until 6 months later, when she presented to the emergency department with severe recurrent abdominal pain.

In view of the clinical picture, her physicians decided to treat her for small bowel obstruction, and an exploratory laparotomy was performed. The surgeons noted that she had moderate ascites, adhesions on the omentum, and a thickened high loop of the small bowel that was unequivocally viable and hyperemic, with thickening of the mesentery. Ascitic fluid was evacuated, adhesions were lysed, and the abdomen was closed. She was discharged with the same medications, including lisinopril; the dose was subsequently increased for better control of her hypertension.

The woman was admitted three more times within the same year for the same symptoms



Physicians need to be aware of this potential complication

FIGURE 1. Abdominal computed tomography with intravenous and oral contrast shows oral contrast in the middle of the lumen, giving it a "target-sign" appearance (image A). On the last two images (C and D), the contrast did not reach the lumen, but thickening of the intestinal wall is visible (arrows). Image A shows impressive thickening of the duodenal wall (arrows). The submucosa can be differentiated from the serosa in all intestinal images because of the thickening of the mucosal wall with multiple dilated loops. Image B shows some ascites and thickening of the stomach wall (arrows).

and underwent multiple workups for pancreatitis, gastritis, small-bowel obstruction, and other common gastrointestinal diseases.

Present admission

On review of systems, she denied any dry cough, weight loss or gain, food allergies, new medications, or hematochezia.

On physical examination, she had hypoactive bowel sounds and diffuse tenderness with guarding around the epigastric area.

Laboratory tests did not reveal any abnormalities; in particular, her C1 esterase concentration was normal. Stool studies were negative for infectious diseases.

Plain radiography of the abdomen showed a nonobstructive bowel-gas pattern.

Computed tomography (CT) of the abdomen and pelvis showed diffuse thickening of the duodenal wall, jejunum, and areas of the

stomach. The duodenal wall was almost four times as thick as normal, with differentiation of the mucosa and submucosa due to the degree of edema (FIGURE 1). There was a trace of ascites around the liver and small intestine. Previous CT of the abdomen showed perihepatic fluid collection but no evidence of small-bowel obstruction or pancreatic pathology. However, that study did show multiple areas of wall-thickening with resolution at the jejunum and distal antrum-pylorus of the stomach.

She was diagnosed with gastrointestinal angioedema secondary to angiotensin-converting enzyme (ACE) inhibitor therapy. Her lisinopril was discontinued, and the symptoms resolved completely in 24 hours. On follow-up 8 weeks and 16 months later, her symptoms had not returned.

A RARE COMPLICATION OF ACE-INHIBITOR THERAPY

Angioedema occurs in 0.1% to 0.7% of patients taking ACE inhibitors, and it can affect about 1 of 2,500 patients during the first week of exposure.[1–3] It usually manifests as swelling of the face, tongue, and lips, and in rare cases, the gastrointestinal wall. Thus, visceral angioedema is a rare complication of ACE-inhibitor therapy.

Because angioedema is less obvious when it involves abdominal organs, it presents a diagnostic challenge. It is placed lower in the differential diagnosis, as other, more common, and occasionally more high-risk medical conditions are generally considered first. Most of the time, the diagnosis is missed. Some physicians may not be aware of this problem, since only a few case reports have been published. Nevertheless, this potential complication needs to be considered when any patient receiving ACE inhibitors for treatment of hypertension, myocardial infarction, heart failure, or diabetic nephropathy presents with diffuse abdominal pain, diarrhea, or edema of the upper airways.[4–8]

If a high level of suspicion is applied along with good clinical judgment, then hospitalizations, unnecessary procedures, patient discomfort, and unnecessary health care costs can be prevented.

A MEDLINE SEARCH

To investigate the characteristics associated with this unusual presentation, including the time of symptom onset, the types of symptoms, and the diagnostic studies performed on the patients with visceral angioedema, we performed a MEDLINE search to identify case reports and case series published in English from 1980 to 2010 on the topic of abdominal or visceral angioedema. The search terms used were "visceral," "intestinal angioedema," "ACE-inhibitor side effects," and the names of various ACE inhibitors.

Pertinent articles were identified, and clinical characteristics were collected, including demographics, onset of symptoms, the drug's name, and others. In our summary below, data are presented as the mean and standard deviation for continuous variables and percentages for categorical variables.

SUMMARY OF REPORTED CASES

Our search revealed 27 reported cases of visceral angioedema associated with ACE inhibitors (a table summarizing our findings is available at WWW.CCJM.ORG/CONTENT/78/5.TOC).[9–34] The drug most often involved was lisinopril (11 cases), followed by enalapril (Vasotec) (8 cases).

Angioedema can recur in up to a third of patients who switch from an ACE inhibitor to an ARB

Twenty-three (82%) of the cases were in women. The mean age of the patients was 49.5 ± 12.2 years (range 29–77 years); the mean age was 46.7 ± 11.7 years in women and 57 ± 13 years in men. Unfortunately, the race and ethnicity of the patients was documented in only some cases.

In 15 (54%) of the cases, the patient presented to a physician or emergency department within 72 hours (41.1 ± 17.4) of starting therapy, and in 8 cases the patient presented between 2 weeks and 18 months.

In 10 cases (including the case we are reporting here), the patients were kept on ACE inhibitors from 2 to 9 years after the initial presentation, as the diagnosis was missed.[9,12,14,18,20,31,32] In 2 cases, the dose of the ACE inhibitor had been increased after the patient presented with the abdominal pain.

All of the patients were hospitalized for further diagnostic workup.

As for the presenting symptoms, all the patients had abdominal pain, 24 (86%) had emesis, 14 (50%) had diarrhea, and 20 (71%) had ascites. Laboratory results were mostly nonspecific. Twelve (44%) of the patients had leukocytosis. The C1 esterase inhibitor concentration was measured in 18 patients, and the results were normal in all of them.

Twenty-four (86%) of the patients underwent abdominal and pelvic CT or ultrasonography as part of the initial diagnostic evaluation, and intestinal wall-thickening was found in 21 (87.5%) of them.

Either surgery or gastrointestinal biopsy was performed in 16 (57%) of the patients; the surgical procedures included 2 cholecystectomies and 1 bone marrow biopsy. Only 1 case was diagnosed on the basis of clinical suspicion and abdominal radiographs alone.

The combination of intestinal and stomach angioedema was found in only 2 cases.

Two patients were kept on an ACE inhibitor in spite of symptoms and intestinal wall edema that showed a migratory pattern on imaging after chronic exposure.

The thickening involved the jejunum in 14 patients (50%), the ileum in 8 (29%), the duodenum in 5 (18%), the stomach in 2, and the sigmoid colon in 1.

In 12 cases (43%), visceral angioedema and its symptoms resolved within 48 hours of stopping the ACE inhibitor.

In most patients, symptoms resolved within 48 hours of stopping the ACE inhibitor

A DIAGNOSIS TO KEEP IN MIND

As we have seen, the diagnosis of visceral angioedema needs to be kept in mind when a patient—especially a middle-aged woman—taking an ACE inhibitor presents with abdominal pain, vomiting, diarrhea, leukocytosis, ascites, and wall-thickening of the small bowel on imaging studies.[9,35,36]

The diagnosis is hard to establish, and in the interim the patient may undergo invasive and unnecessary procedures, which can be avoided by a heightened awareness of this complication. In all of the reported cases, the patients required hospitalization because of the severity of symptoms and attempts to exclude other possible diseases.[36]

POSSIBLY DUE TO BRADYKININ

Several theories have been proposed to explain how visceral angioedema is induced by ACE inhibitors. The possible mechanisms that have been described include the following:

- The accumulation of bradykinin and substance P secondary to the effect of the ACE inhibitor, which may lead to the inflammatory response, therefore increasing permeability of the vascular compartment
- Deficiency of complement and the enzymes carboxypeptidase N and alpha-1 antitrypsin
- An antibody-antigen reaction[37]
- Hormones such as estrogen and progesterone (suggested by the greater number of women represented[38])
- Contrast media used for imaging[39]
- Genetic predisposition
- Inflammation due to acute-phase proteins
- C1-inhibitor deficiency or dysfunction (however, the levels of C1/C4 and the C1-esterase inhibitor functional activity usually are normal[2,10,40]).

Many other theories are being explored.[11,12,38,41–53]

The most plausible mechanism is an increase in the levels of bradykinin and its metabolites.[45] The absence of ACE can lead to breakdown of bradykinin to des-Arg bradykinin via the minor pathway, which can lead to more pronounced vasodilation and vascular permeability.[54,55] During an acute attack of angioedema secondary to ACE inhibition, the bradykinin concentration can increase to more than 10 times the normal level.[56]

Moreover, C-reactive protein levels were higher (mean 4.42 mg/dL ± 0.15 mg/dL) in patients with ACE-inhibitor-induced angioedema than in those with other causes of angioedema ($P < .0001$).[52] The patients taking ACE inhibitors without any previous angioedema had normal C-reactive protein levels (0.39 mg/dL ± 0.1 mg/dL).[52]

INCIDENCE RATES

In our review of the literature, all of the patients were taking an ACE inhibitor, and some were taking both an ACE inhibitor and

an angiotensin-receptor blocker (ARB).

Initially, the incidence rate of angioedema was thought to be 0.1% to 0.2%, but recently the Omapatrilat Cardiovascular Treatment Assessment vs Enalapril (OCTAVE) trial had more than 12,000 patients on enalapril and reported the incidence of angioedema to be 0.68%,[57] with a higher risk in women than in men (0.84% vs 0.54%)[58] and a relative risk of 3.03 for blacks compared with whites.[59]

Even though ARBs seem to be safer, angioedema can recur in up to one-third of patients who switch from an ACE inhibitor to an ARB.[60–63]

Moreover, one study in the United States found that the frequency of hospital admission of patients with angioedema increased from 8,839 per year in 1998 to 11,925 in 2005, and the cost was estimated to be close to $123 million in 2005.[64]

Interestingly, when angioedema involved the face, it developed within the first week in 60% of cases,[65] whereas when visceral angioedema developed, it did so within the first week in 59% of cases. Therefore, the timing of the onset is similar regardless of the body area involved.

Smokers who developed ACE-inhibitor-induced cough had a higher risk of ACE-inhibitor-induced angioedema in a retrospective cohort study by Morimoto,[66] but no relationship to the area of involvement was made.

ON IMAGING, A THICKENED BOWEL WALL

Computed tomography can reveal bowel edema and ascites more reliably than plain radiography or barium studies. Edema thickens the bowel wall, with increased contrast enhancement that makes mesenteric vessels show up on the study. In some instances edema is so significant that edematous submucosa can be differentiated from the serosa due to impressive thickening of the mucosal wall.[15,16] Oral contrast can be seen in the middle of the lumen, giving it a target-sign appearance. Edema of the small bowel and ascites can lead to fluid sequestration in the abdomen, resulting in a presentation with shock.[67]

Magnetic resonance imaging can be even more useful in identifying gastrointestinal angioedema, but it would not be cost-effective, and based on our study, CT and ultrasonography of the abdomen were diagnostic in most cases.

AVOIDING UNNECESSARY TESTING

Hemodynamic instability and abdominal pain usually trigger a surgical consult and a more extensive workup, but with a good clinical approach, unnecessary testing and invasive diagnostic procedures can be avoided under the right circumstances.

Numerous surgical procedures have been reported in patients presenting with visceral angioedema secondary to ACE inhibitors.[67] Although a thorough history and physical examination can give us a clue in the diagnosis of drug-induced gastrointestinal angioedema, CT is extremely helpful, as it shows dilated loops, thickened mucosal folds, perihepatic fluid, ascites, mesenteric edema, and a "doughnut" or "stacked coin" appearance.[17,68]

So far, there have been only two reports of angioedema of the stomach (the case reported by Shahzad et al[10] and the current report). Angioedema can affect any visceral organ, but we usually see involvement of the jejunum followed by the ileum and duodenum.[40]

FINDINGS ON ENDOSCOPY

Usually, endoscopic examination of the upper and lower gastrointestinal tract does not reveal any specific pathology, but endoscopy and biopsy can rule out other causes of abdominal pain, such as Crohn disease, ulcerative colitis, infection, malignancy, granuloma, and vasculitis. Also, hereditary or acquired C1-esterase deficiency and other autoimmune disorders should be considered in the workup.[18,69] In the reported cases, endoscopy revealed petechial bleeding with generalized edema.[19]

Biopsy often demonstrates an expanded edematous submucosal layer with inflammatory cell infiltration and protrusion of the proper muscular layer into the submucosal layer.[15] A proper muscular layer and an edematous submucosal layer can produce edema so severe as to obstruct the intestine.[15]

Ultrasonography or CT provides essential information as to location, structure, and size, and it rules out other diagnoses. Therefore, consid-

A median of 10 months elapsed between the onset of angioedema and withdrawal of the ACE inhibitor

TABLE 1

Red flags for visceral angioedema due to an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker

Current use of an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker
Female sex
Abdominal pain with or without other gastrointestinal symptoms (eg, nausea, vomiting, diarrhea)
Computed tomography or ultrasonography of the abdomen and pelvis showing bowel-wall thickening, with or without ascites
Resolution of symptoms and edema with cessation of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker
Normal C1-esterase inhibitor level

eration should be given to noninvasive imaging studies and laboratory testing (C1-esterase inhibitor, complement, antinuclear antibody, complete metabolic panel, complete blood cell count) before resorting to endoscopy or exploratory laparotomy.[20,70] In three case reports,[29,30,32] abdominal ultrasonography did not show any thickening of the small-bowel wall. Several cases have been diagnosed with the help of endoscopy.

Symptoms usually resolve when the ACE inhibitor is stopped

There is no standard treatment for ACE-inhibitor-induced visceral angioedema. In most patients, stopping the drug, giving nothing by mouth, and giving intravenous fluids to prevent dehydration are sufficient. Symptoms usually resolve within 48 hours.

In several case reports, fresh-frozen plasma was used to increase the levels of kininase II, which can degrade high levels of bradykinin.[51,71,72] However, no randomized controlled trial of fresh-frozen plasma for ACE-inhibitor-induced angioedema has been published.

Drugs for hereditary angioedema—eg, recombinant C1-INH, the kallikrein inhibitor ecallantide (Kalbitor), and the BKR-2-antagonist icatibant (Firazyr)[73]—have not been prospectively studied in gastrointestinal angioedema associated with ACE inhibitors. Icatibant has been shown to be effective in the treatment of hereditary angioedema and could be promising in treating angioedema secondary to ACE inhibitors.[8] Rosenberg et al[21] described a patient who was on prednisone when she developed intestinal angioedema, thus calling into question the efficacy of steroids in the treatment of visceral angioedema.

RAISING AWARENESS

Identifying the red flags (TABLE 1) can promote early recognition of ACE inhibitor-induced visceral angioedema. In previous reports, a median of 10 months elapsed between the onset of angioedema and withdrawal of the ACE inhibitor (range 1 day to 10 years).[74] In our review of the literature, we found several patients with visceral angioedema who took ACE inhibitors for years before the cause of their symptoms was recognized.[9,12,14,18,20,31,32]

More than 40 million patients are currently taking ACE inhibitors or ARBs.[9] Therefore, we suggest that patients with a known history of angioedema in response to these drugs should wear an identification bracelet to increase awareness and to prevent recurrence of angioedema.

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