

Angiotensin-Converting Enzyme Inhibitor–Induced Small-Bowel Angioedema: Clinical and Imaging Findings in 20 Patients

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OBJECTIVE. The purpose of this article is to retrospectively review the radiologic and clinical findings in patients with angiotensin-converting enzyme inhibitor (ACEI)–induced small-bowel angioedema, with an emphasis on CT findings.

MATERIALS AND METHODS. Imaging findings, with an emphasis on CT, and clinical characteristics of 20 patients (23 presentations) presenting to two institutions' emergency departments from 1996 through 2010 with ACEI-induced small-bowel angioedema were retrospectively reviewed by two abdominal radiologists who were aware of the diagnosis. Examinations were reviewed in consensus to determine common radiographic findings.

RESULTS. Patient age range was 23–83 years (mean, 56 years). Sixteen of the 20 patients were women, and 15 of 20 were obese. All had acute onset of severe abdominal pain. The date of the initial episode prompting CT evaluation ranged from 2 days to 10 years after the start of ACEI therapy (average, 3.3 years). All patients underwent abdominal CT examinations while symptomatic; five patients also underwent a small-bowel series. Three patients underwent urgent surgery for presumed small-bowel ischemia. All patients had resolution of symptoms within 4 days of hospitalization. CT findings included ascites in all patients, small-bowel wall thickening (mean, 1.3 cm), mild dilatation (mean, 2.9 cm), and straightening. There was no small-bowel obstruction.

CONCLUSION. ACEI-induced small-bowel angioedema should be included in the differential diagnosis when patients receiving ACEI therapy present with abdominal complaints and the following combination of findings on CT examination: ascites, small-bowel wall thickening, dilatation without obstruction, and straightening.

Keywords: angioedema, angiotensin-converting enzyme inhibitor, intestinal, small bowel

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Angiotensin-converting enzyme inhibitors (ACEIs) are a widely used pharmacotherapy to control hypertension. Angioedema is the vascular leakage of serum from small vessels and is the process that induces cutaneous hives. Angioedema induced by ACEI therapy is a well-known entity. Many clinicians and radiologists are aware that drug-induced angioedema affects the tongue, throat, face, and other cutaneous sites. Reports of death from laryngeal edema exist [1]. However, many clinicians and, we think, radiologists fail to recognize the causal relationship between ACEI therapy and angioedema, especially in the small bowel [2].

Despite articles in the medical and gastrointestinal literature, ACEI-induced small-bowel angioedema is rarely reported in the imaging literature; to our knowledge, there are only two individual case reports in the radiographic literature [3, 4]. The CT description of these cas-

es overlaps with those of other causes of small-bowel angioedema, including hereditary and idiopathic small-bowel angioedema. Findings described previously of small-bowel angioedema, either related to ACEI or not, include segmental bowel-wall thickening with submucosal edema and ascites [3–6]. Abdominal presentations include complaints of abdominal pain, diarrhea, nausea, and vomiting [7]. Symptoms are generally self-limited and will resolve with or without cessation of the ACEI therapy [8]. If the diagnosis of ACEI-induced small-bowel angioedema is not established, recurrences may occur [8, 9]; episodic abdominal pain may result in unnecessary emergency department visits, hospital admissions, radiologic examinations, or even surgical exploration.

To increase radiologists' awareness of this underrecognized condition and assist in its radiologic detection, we report the clinical and imaging findings of 20 patients (with 23 presentations) with a diagnosis of ACEI-induced

small-bowel angioedema, with an emphasis on the CT findings.

Materials and Methods

A retrospective analysis of patients with at least one abdominal and pelvic CT examination and with a diagnosis of ACEI-induced small-bowel angioedema was performed. Patient records were from radiology teaching file cases accumulated at two institutions between 1996 and 2010. The diagnosis had been made by CT or by clinical or surgical exclusion of other disease processes, in combination with rapid resolution of symptoms. Institutional review board approval was obtained, with waiver of informed consent for retrospective analysis. All examinations were reviewed by two abdominal radiologists, with an average of 17 years of experience, who were aware of the diagnosis. Three examinations were reviewed on printed film; the rest were reviewed on a PACS workstation. CT scans were reviewed by consensus to determine vascular patency and to subjectively rate the degree of mesenteric edema (i.e., absent, mild, moderate, or severe). The abdominal and pelvic CT images were also reviewed for the presence or absence of ascites. The small bowel was evaluated to determine the location (i.e., duodenal, jejunal, or ileal) of the involved segment, the length of abnormal bowel, and the length of contrast luminal transit. In addition, the luminal caliber and the wall thickness were measured at the most dilated and most thickened segments of small bowel, respectively. The presence or absence of straightening, which we defined as a loop of small bowel that lengthened to occupy greater than either half of the transverse diameter or half of the anteroposterior diameter of the peritoneal cavity, was also evaluated. All abnormal segments of bowel were also assessed for the presence or absence of the target sign. The small-bowel series, which were performed in five patients, were reviewed for the presence or absence of wall thickening, length of bowel involvement, and the presence or absence of obstruction.

One of the two radiologists who examined the radiographic studies also reviewed the patients' medical records. Clinical histories and chart notes were reviewed to determine age at initial CT examination, comorbidities, prior angioedema presentations, and initiation and duration of ACEI therapy before the development of abdominal symptoms. In addition, chart notes were reviewed to exclude patients with a known diagnosis of Crohn disease, previous radiation therapy, or ongoing infectious gastroenteritis. Emergency department notes were reviewed to determine patient complaints and physical examination findings, as well as concurrent laboratory abnormalities. Hospital notes were reviewed to determine duration of symptoms and hospital course.

Results

Patients

Twenty patients with 23 distinct episodes were identified. Patients ranged in age from 23 to 83 years (mean, 56 years). Thirteen of 20 patients were obese women, two were obese men, and there were five nonobese patients (two men and three women). All patients had hypertension, 10 had hyperlipidemia, and eight had diabetes.

ACEI Therapy

All patients were receiving ACEI therapy for the treatment of hypertension. Nineteen patients were receiving oral lisinopril therapy at the time of initial presentation (dose range, 5 mg/day to 40 mg twice/day), and one patient was receiving oral enalapril (5 mg/day). Induction of ACEI therapy could be documented for a specific time for 14 of 20 patients (for five patients, the start date of therapy was not listed in the chart notes, and for the other patient, chart notes indicated "years" of lisinopril therapy). In these 14 patients, the date of initial episode prompting CT evaluation ranged from 2 days to 10 years after the start of therapy, with an average of 3.3 years. Three patients presented to the emergency department twice. In one patient who presented twice, we could not document the start date of ACEI therapy, but the patient's symptoms resolved while therapy was withheld in the hospital during initial admission, and she presented again 1 week after reinitiation of therapy as an outpatient. The second patient who presented twice had been receiving lisinopril for 1 month, but presented 24 hours after an increase in dose from 5 to 10 mg. The association with the ACEI was not recognized, and this patient continued taking her medication until she represented 5 months later; this occurred 24 hours after an additional increase in lisinopril from 10 to 20 mg. In the third patient with two presentations to the emergency department, the initiation of therapy was not indicated. This patient had two different admissions to an outside institution for abdominal pain within 3 months. In seven patients, therapy duration was longer than 1 year, whereas in seven others, therapy duration was less than 1 year.

Signs and Symptoms

Abdominal pain was present in all patients; 17 complained of nausea, 12 of vomiting, and eight of diarrhea. No patient had gastrointestinal bleeding. Of the 23 total episodes, 21 began with abrupt onset of symptoms (duration, 6–72 hours; mean, 29 hours) prompting pre-

sentation to the emergency department. One patient had symptoms for 1 week, and another had symptoms for 4 days. Seven of 20 patients reported previous similar abdominal episodes. One had an episode of facial edema 6 months before admission.

Physical findings included abdominal tenderness and normoactive bowel sounds in all patients. Fifteen of the patients at presentation had normal vital signs, four had mild systolic hypotension (102–108 mm Hg), and four had mild systolic hypertension (170–182 mm Hg). All patients were afebrile. At presentation fourteen of the patients had elevated WBC counts ($> 10,800$ cells/mL), with an overall range of 4800–26,000 cells/mL (mean, 12,795 cells/mL). No other common laboratory abnormalities were found. All patients were admitted to the hospital, and with the exception of the four patients who underwent surgery, all the others were treated conservatively with pain management and IV hydration. Thirteen patients were also given antibiotics because of uncertainty regarding the initial diagnosis.

Radiology

All patients underwent IV contrast-enhanced CT scans at presentation. Three CT scans were performed on single-slice scanners, and the remaining 20 were performed on MDCT scanners (8–64 detector rows). Nineteen of the 23 CT examinations were performed with standard positive oral contrast agent (for three of the examinations, the patients were unable to tolerate oral contrast agent), and one patient was given water as an oral contrast agent. One patient was given rectal contrast agent in addition to positive oral contrast agent.

Ascitic fluid was present in all patients, with a spectrum in the amount of ascitic fluid encountered (Fig. 1). Twenty CT examinations revealed mild mesenteric edema (Fig. 2), whereas three showed no evidence of mesenteric edema. The visceral vasculature was patent on all examinations. All CT examinations showed abnormal small bowel with long-segment abnormalities; the involved segment was estimated to be longer than 10 cm, but less than one third the entire length of the small bowel on 21 of the 23 CT examinations. In two patients, more than half of the entire small bowel was involved. Three patients had skip lesions. All patients had mildly dilated small bowel, with a mean diameter of 2.9 cm (normal, < 2.5 cm) [10] and wall thickening with a mean of 1.3 cm (normal, < 4 mm) [11]. Sixteen of the 20 MDCT scans showed a small-bowel tar-

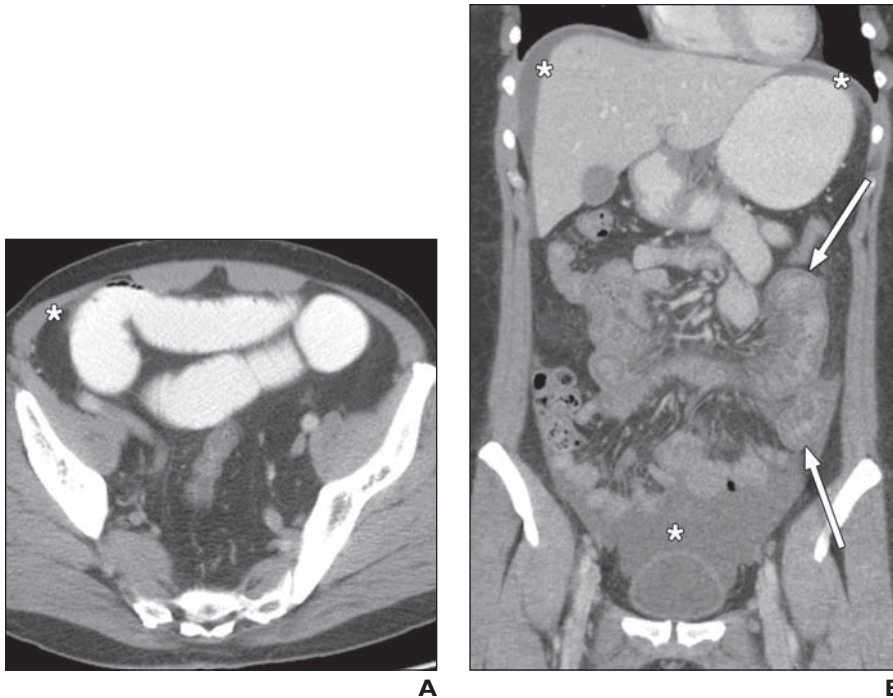


Fig. 1—Spectrum of ascites encountered in patient series.

A, Image is of 57-year-old man receiving 10 mg lisinopril who presented with abdominal pain, nausea, and vomiting. Oral and IV contrast-enhanced pelvic CT scan shows least amount of ascites encountered in patient series, with trace ascites (*asterisk*) adjacent to small bowel in right lower quadrant. Note small-bowel dilatation and relatively mild fold thickening.

B, Image is of 43-year-old woman receiving 5 mg lisinopril who presented with abdominal pain, nausea, and vomiting. Oral and IV contrast-enhanced coronal abdominal and pelvic CT reformation shows four-quadrant ascites (*asterisks*) and long-segment jejunal wall thickening (*arrows*) with target sign.

get sign with fluid density submucosa (Fig. 3). Distribution of involvement was jejunal only (10/23), ileal only (7/23), and combined jejuno-ileal (6/23). Straightening of the involved segment was present on 10 of the CT examinations (Fig. 4). No other acute viscer-

al organ involvement was present. No patient had evidence of a small-bowel obstruction. In 16 of 19 patients who tolerated oral contrast agent, it extended into the cecum.

Follow-up CT scans were performed for two patients. One follow-up CT examination

was performed within a day for a 46-year-old man and revealed nearly complete resolution of small-bowel abnormalities, although some ascitic fluid remained (Fig. 5). The other follow-up CT examination was performed for a 49-year-old woman, 4 days after initial CT and discontinuation of ACEI therapy, and revealed complete resolution of small-bowel thickening and ascites.

Five small-bowel follow-through examinations were performed within 72 hours of presentation because of uncertainty regarding the initial diagnosis; two patients had small-bowel series within 24 hours of presentation, one had a small-bowel series 36 hours after presentation, another at 48 hours, and the last at 72 hours after presentation. There was no difference in the appearance of the CT scans in those patients who underwent a barium small-bowel examination, and those patients for whom no small-bowel series was performed. All five barium examinations revealed long-segment small-bowel involvement with fold thickening and submucosal edema, but without obstruction (Fig. 6).

In all patients, clinical symptoms improved within 4 days of hospitalization. In eight of the pain episodes, the diagnosis of ACEI-induced small-bowel angioedema was suggested prospectively by the radiologist; in the remaining 15 pain episodes, the association was not made until retrospective review by an abdominal radiologist. Four patients underwent surgical exploration; there was no significant difference in the CT findings of these four patients compared with those who did not undergo surgery. Three patients underwent surgery, in part because the initial interpreting radiologist was



Fig. 2—65-year-old woman receiving 20 mg lisinopril who presented with abdominal pain and nausea. Oral and IV contrast-enhanced pelvic CT scan shows most pronounced mesenteric edema (*arrowhead*) encountered in patient series and long-segment jejuno-ileal wall thickening (*arrows*) with target sign. Subsequent diagnostic laparoscopy 72 hours after admission was normal.

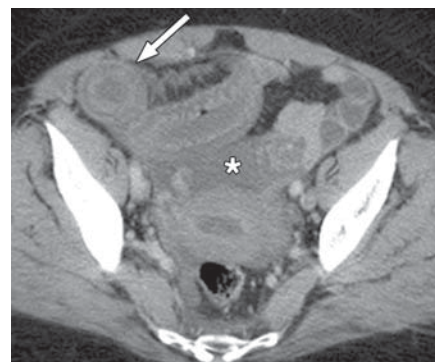


Fig. 3—63-year-old woman receiving 40 mg lisinopril who presented with abdominal pain and vomiting. IV contrast-enhanced pelvic CT scan shows typical target sign (*arrow*) affecting long segment of ileum, with four-quadrant ascites (*asterisk*).



Fig. 4—77-year-old woman receiving 5 mg lisinopril who presented with abdominal pain and nausea. Oral and IV contrast-enhanced pelvic CT scan depicts typical long-segment small-bowel edema (*arrow*) with straightening of small bowel.

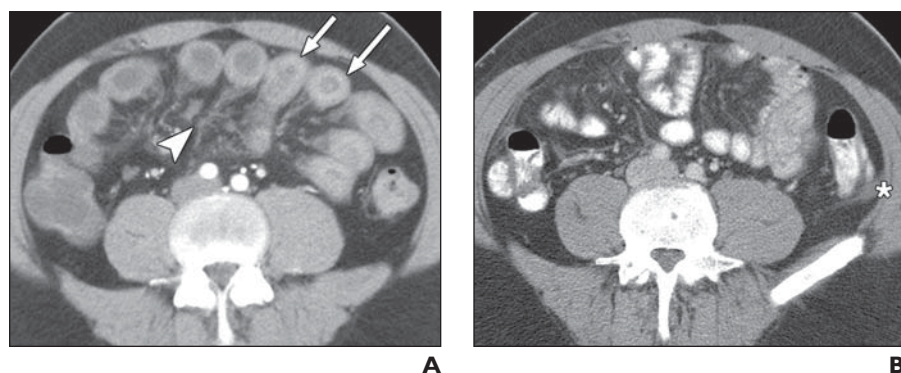


Fig. 5—46-year-old man receiving 5 mg lisinopril who presented with nausea, diarrhea, and abdominal pain. **A**, IV contrast-enhanced abdominal CT scan shows long-segment jejunal thickening (arrows) with target sign and mild mesenteric edema (arrowhead). **B**, Follow-up oral and IV contrast-enhanced CT scan performed within 24 hours shows nearly complete resolution of small-bowel thickening and mesenteric edema, although trace ascites persists (asterisk).

unsure of the diagnosis and raised the question of small-bowel ischemia on the basis of the small-bowel wall thickening and ascites; the initial CT interpretation combined with the clinical presentation of severe abdominal pain therefore prompted surgical exploration in these three patients. Two patients, 46- and 83-year-old women, despite CT findings of small-bowel edema and associated ascites, had only mild erythema of the distal ileum at surgery within 24 hours of CT examination. Another 65-year-old woman had a normal laparoscopy approximately 72 after presentation. The fourth patient was taken to surgery despite an initial interpretation suggesting ACEI-induced angioedema. This 60-year-old man had atypical increasing pain after admission, which prompted exploration to exclude ischemia, but only mild erythema of the small bowel was seen. None of the patients had a small-bowel biopsy. None of the three patients who presented twice underwent surgery.

Discussion

Angioedema occurs in the skin and mucous membranes [8] and is due to vasodilatation, which leads to serum accumulation in interstitial tissue spaces. Although the mechanism is not entirely understood, one theory is that ACEI-induced angioedema is related to elevated levels of bradykinin, a potent vasodilator and cause of vascular permeability [12]. ACEI therapy causes delayed breakdown of bradykinin [13], with intermittent peaks of bradykinin at random time intervals, resulting in angioedema.

In 2001, one study estimated that nearly 40 million people worldwide are receiving ACEI therapy [14]. ACEI-induced angioedema is estimated to occur in approximately 0.1–0.5% of patients receiving these medications [13], al-

though many researchers think that this entity may be underrecognized [9, 13, 15]. One confounding variable is the time lag between the initiation of therapy and the initial angioedema episode, which may be years [16, 17]. A prior retrospective review of all types of angioedema cases documented a median length of 12 months from initiation of ACEI therapy before the initial angioedema episode [8]. This is similar to our experience with small-bowel angioedema, with 10 patients presenting at least 8 months after initiation of therapy.

Clinical symptoms of intestinal angioedema include abdominal pain, nausea, vomiting, and diarrhea. Pain can be severe and may be mistaken for small-bowel ischemia. Two of our first three patients underwent

surgical exploration to exclude small-bowel ischemia because of severe abdominal pain in the setting of an abnormal CT examination and the lack of a definitive diagnosis. In retrospect, if the association between the ACEI therapy and the abnormal CT findings had been recognized, surgery could have been averted.

Of interest was the number of obese women in our patient population (65%). Research suggests that estrogen may play a role in some forms of hereditary angioedema [13]. Although evaluation of all types of ACEI-induced angioedema shows no sex predilection [8, 18], for unknown reasons, most reported cases of ACEI-induced small-bowel angioedema have occurred in women, possibly underscoring the interaction of estrogens in the pathogenesis of the disease [4].

Initial descriptions of the radiologic appearance of small-bowel angioedema were based on barium studies and included thickened mucosal folds, spiculation, thumbprinting, and separation of adjacent bowel loops [19, 20]. Scattered descriptions of the CT appearance of small-bowel angioedema then appeared in the radiology literature. CT findings included small-bowel wall thickening and ascites [21, 22]. More recently, two case reports of the CT appearance related to ACEI-induced angioedema were published; CT findings included ascites and circumferential bowel wall thickening with submucosal edema [3, 4]. Although these isolated radiology case reports exist, we strongly believe that radiologists should be more attuned

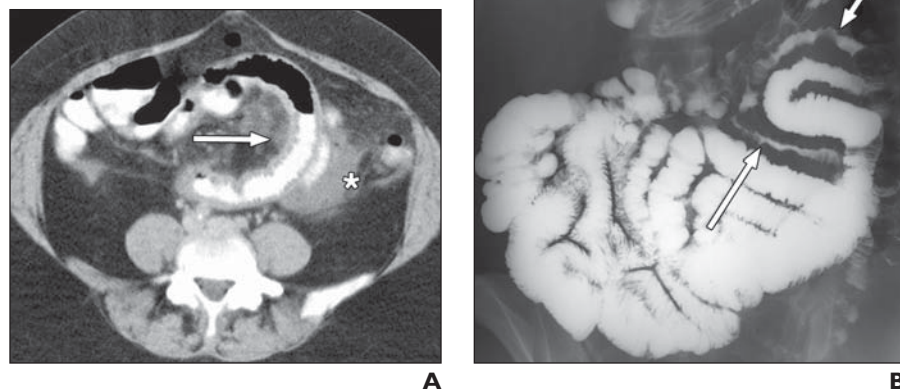


Fig. 6—46-year-old woman receiving 5 mg enalapril who presented with nausea, vomiting, and left upper quadrant pain. **A**, Oral and IV contrast-enhanced abdominal CT scan depicts marked straightening (arrow) of edematous loop of jejunum, with adjacent ascites (asterisk). **B**, Small-bowel series performed next morning reveals persistent abnormal segment of jejunum (arrows) with fold thickening, spiculation, and fold separation. Note lack of small-bowel obstruction. Subsequent laparoscopy was negative.

to the association of ACEI therapy with small-bowel angioedema. In light of the widespread use of ACEI therapy, and the increasing number of CT scans being performed throughout the United States and elsewhere, the scarcity of case reports in the radiology literature suggests that ACEI-induced small-bowel angioedema may be underappreciated.

Radiologists should recognize the main CT findings in our series, which should prompt radiologists to include small-bowel angioedema related to ACEI in the differential diagnosis, in the correct clinical setting: ascites and preservation of luminal transit (i.e., no small-bowel obstruction, including contrast transit to the colon) despite thickening, dilatation, and straightening of the small bowel. There is long-segment involvement of small bowel, with a tendency to affect the jejunum. The majority of cases will have continuous segments of small bowel involved. The affected small bowel typically has marked submucosal edema with the associated target sign [3, 23]. The target sign is produced by alternating enhancement of the mucosa, relatively hypodense submucosa (related to edema), and enhancing serosa [24]. This has previously been described as the "hallmark of a benign lesion" [6], although there is radiologic overlap with other causes of small-bowel thickening, such as small-bowel ischemia, superior mesenteric and portal vein thrombosis, radiation, vasculitides, Crohn disease, hemorrhage, and infection [6, 24]. However, these other causes often involve tissue damage; the presence of pneumatosis, ulceration, or pronounced mesenteric edema should prompt a search for alternate diagnoses. In our retrospective series, the small-bowel wall was thought to be straightened because it was elongated, as seen in obstruction, but without significant distention. Also, the wall was not as thickened as in severe ischemia or intramural hemorrhage. In ischemia, straightening is accompanied by wall thickening because of intramural blood and edema. In small-bowel obstruction, straightening is related to increased intraluminal pressure. The elongation in ACEI-induced small-bowel angioedema is therefore believed to be related to a primary increase in tissue turgor (i.e., stiffening) of the small-bowel wall. We liken this phenomenon to long-segment urticaria of the small-bowel—that is, interstitial edema producing adjacent thickening and wall tension, effacing the adjacent wrinkles or folds, and lengthening the affected segment of bowel.

On contrast-enhanced CT examinations, the presence of vascular patency will exclude cen-

tral arterial or venous thrombosis. Crohn disease, vasculitides, and radiation injuries will typically have a longer time course and, often (particularly with radiation enteritis), a characteristic history. In the appropriate clinical setting, the combination of radiographic findings is suggestive of ACEI-induced small-bowel angioedema. These patients have abrupt onset as well as quick resolution of symptoms, and all have vascular patency and preservation of bowel motility. However, according to our series, the CT appearance can vary from patient to patient and within each patient, on the basis of the timing of their presentation. The clinical onset and resolution of symptoms can be abrupt, and we think that patients who are not imaged when most symptomatic may have a less pronounced radiographic appearance, which may account for the variability in CT appearance.

We wondered whether we could have misdiagnosed gastroenteritis or mild mesenteric ischemia as ACEI-induced small-bowel angioedema because 13 patients were given precautionary IV antibiotics at admission. In particular, elevated WBC counts noted in some patients could suggest infectious enteritis. However, we think that the lack of fever in patients with severe pain, prominent ascites, and bowel-wall thickening makes an infectious cause less likely. Similar to our findings, others have documented elevated WBC counts in patients with angioedema [25, 26]. We also believe that the degree of abdominal pain, in some cases prompting surgical exploration, is greater than that encountered with infectious enteritis. Mild mesenteric ischemia was thought to be unlikely, particularly because all visceral vessels were patent and no patient had risk factors for or other clinical features of nonocclusive mesenteric ischemia.

There are some limitations to our study. The major limitation is the lack of pathologic proof for any of the cases and the lack of a specific laboratory finding to pinpoint the diagnosis. However, this does not preclude the diagnosis of ACEI-induced small-bowel angioedema. Although ACEI-induced small-bowel angioedema remains a diagnosis of exclusion, the constellation of clinical, laboratory, and radiographic findings should direct both radiologists and clinicians to the correct diagnosis. Another limitation is that this is a retrospective evaluation of collected cases, but a prospective study would be very difficult to conduct, given the relatively rare occurrence of ACEI-induced small-bowel angioedema. Also, we did not compare our findings to other causes of angioedema, in-

cluding hereditary or other drug-related angioedema cases. Other case reports have suggested that long-segment wall thickening and ascites may occur in those specific diagnoses [3, 5, 25, 26], although the degree of straightening of small bowel has not been previously described, to our knowledge. Although we have only discussed the involvement of the small bowel, radiologists should also recognize that both hereditary angioedema and ACEI-induced angioedema may involve other portions of the gastrointestinal tract, including the stomach and colon, although no other gastrointestinal tract involvement was encountered in our patients [4, 27–29].

In conclusion, ACEI-induced small-bowel angioedema is primarily seen in women and causes severe abdominal pain, mild leukocytosis, and CT findings that may potentially be mistaken for small-bowel ischemia or other diagnoses. Radiologists should be aware of this diagnosis and its radiographic appearance. The findings of ascites, preserved luminal transit, with small-bowel wall thickening, dilatation, and straightening, should prompt radiologists to include ACEI-induced small-bowel angioedema in the differential diagnosis. Because the CT findings of bowel edema and symptoms resolve quickly, close clinical follow-up will avert unnecessary surgery or other diagnostic and therapeutic procedures. Early diagnosis should initiate a prompt change in antihypertensive medication.

Addendum

As this article was going to press, an article was published in the March 2011 issue of *AJR*, briefly describing six MDCT cases of ACEI-induced small-bowel angioedema from one institution. The authors noted similar descriptions of the small-bowel appearance as in our cases, with individual small-bowel wall thickness ranging from 4 to 9 mm and lengths of involvement estimated from 20 to 60 cm, without associated lymphadenopathy or bowel obstruction [30].

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