Intestinal Angioedema: An Often Misdiagnosed Entity

Most clinicians are familiar with angioedema involving the face and the upper respiratory airways. Bradykinin mediated angioedema may sometimes present with gastrointestinal symptoms alone. Such uncommon presentations are easily misdiagnosed, bearing serious consequences for the patient and the hospital system through unnecessary extensive workups. We include a typical example of the situation where a 60 year old woman presented multiple times to the hospital with gastrointestinal (GI) symptoms due to ACE inhibitor associated angioedema superimposed on hereditary angioedema. Her unusual presentation was initially treated symptomatically and this led to a late diagnosis and intervention consequently prolonging her hospital stay. In addition, we review the pertinent literature and provide guidelines for gastroenterologists encountering this challenging entity which could assist in the timely diagnosis and treatment of this condition.

CASE REPORT

A 60 year old Hispanic female presented with generalized crampy abdominal pain of 24 hours duration. Pain was acute in onset and associated with nausea, nonbilious emesis, and several bouts of watery, nonbloody diarrhea. She denied fever, chills, dysuria or sick contacts. Medical history was significant for multiple admissions in the past for similar episodes as well as hypertension, diabetes mellitus type 2, chronic deep venous thrombosis and dyslipidemia. Family history is positive for hereditary angioedema in four family members. Social history was negative for alcohol, tobacco or illicit drug use and she had no known allergies. Home medications included warfarin, metformin, Lisinopril, Lantus, and simvastatin.

On physical examination, she was lethargic. Vital signs were BP 68/39mmHg; heart rate 130beats/min; Respiratory rate 16/min; temperature 36.4°C; Mean arterial pressure 49mmHg. Oxygen saturation was 93% at room air. Other pertinent findings included dry skin and mucous membranes, generalized abdominal tenderness with voluntary guarding but without rebound tenderness. Bowel sounds were hyperactive. Rectal examination was unremarkable and a stool guaiac done was negative.
(continued from page 32)

Laboratory investigations showed: increased White Blood Cell (WBC) count of 15060/mcl and bands of 7%; potassium 3.1mEq/l; chloride 107mEq/l; bicarbonate 17mEq/l with an anion gap of 17; lactate 7.5mEq/l; BUN 17mg/dl and creatinine 1.4mg/dl; plasma glucose 256mg/dl. Her hemoglobin of 15.4 and hematocrit of 46.6 was explained by her severe dehydration and hemoconcentration which also explained the low potassium and borderline changes in renal function.

CT scan of the abdomen and pelvis without contrast showed a small amount of ascites with a ventral wall hernia containing small bowel without any evidence of obstruction or strangulation. The wall of the bowel could not be commented on as contrast was not used due to concerns about the renal function.

Resuscitative management was instituted upon presentation including central line placement, several boluses of intravenous normal saline and norepinephrine drip to address her severe hypotensive state. While being managed as a case of recurrent gastroenteritis, she underwent an extensive work up including antibodies for celiac disease, clostridium difficile stool studies, adrenal insufficiency, and hyperthyroidism which all came out negative. Eventually, C1 inhibitor, functional level was done which showed a low level. This new finding together with her strong family history of angioedema and her recurrent episodes while on Lisinopril led to the diagnosis of ACE inhibitor associated angioedema superimposed on hereditary angioedema.

The patient was properly educated about her condition, including medications to avoid. Her symptoms resolved after four days of symptomatic therapy for nausea, vomiting, abdominal pain and dehydration and she was discharged home in stable condition after her Lisinopril was permanently discontinued and a safer antihypertensive agent of a different class prescribed.

INTRODUCTION

There are two main categories of angioedema: the mast-cell mediated and the bradykinin mediated angioedema.1 Bradykinin mediated angioedema, unlike the mast-cell mediated angioedema is usually without symptoms of pruritus and urticaria and includes 3 major categories. The hereditary form is known as hereditary angioedema (HAE) which is an autosomal dominant condition typically presenting as recurrent attacks of angioedema with a variable age of onset.2,3

Another category is termed acquired C1 inhibitor (C1 INH) deficiency which is a rare syndrome of recurrent episodes of angioedema, without urticaria and is associated with B cell lymphoproliferative disorders in some patients.4 A third presentation is the drug induced angioedema of which the most commonly recognized medication has been Angiotensin Converting Enzyme inhibitor (ACEi). Angioedema has also been reported as a rare event with Angiotensin Receptor Blockers (ARBs), fibrinolytic agents, estrogens, antihypertensive drugs other than ACE inhibitors, psychotropic drugs and nonsteroidal anti-inflammatory drugs.5 Angioedema from ACEi accounts for approximately 30% of all cases of angioedema; however, only 0.1% to 0.5% of patients taking ACEi develop angioedema.6,7 Considering that 35 to 40 million patients are treated worldwide with ACE inhibitors, this drug class could theoretically account for several hundred deaths per year from laryngeal oedema.5 However, ACEi induced angioedema of the gastrointestinal tract is very rare and its incidence is not well described.7-9

C1 esterase inhibitor is a serine protease inhibitor that works directly on complement and contact plasma cascades to reduce bradykinin release, which is the primary pathologic mechanism in HAE and acquired C1 inhibitor (see Figure 1). Hereditary angioedema (HAE) involves quantitative deficiency (type 1) or qualitative dysfunction (type 2) of C1 esterase inhibitor protein (HAE). A third type of familial angioedema is characterized by normal C1INH levels and is called HAE with normal C1INH. The drug-induced angioedema (mostly ACE inhibitors) is as a result of enhanced

(continued on page 36)
activity of bradykinin, a potent vasodilating peptide
due to inhibition of ACE, an enzyme responsible for
its breakdown (see Figure 1 below). Pharmacological
inhibition of ACE leads to increased plasma levels of
bradykinin and high levels have been demonstrated
in plasma during an acute episode of angioedema.\textsuperscript{10,11}
Notably, although degradation of bradykinin is
blocked in all patients treated with ACE inhibitors,
angioedema only occurs in a small percentage of
such patients. Therefore it is likely that factors, other
than impaired bradykinin degradation, are involved
in the development of angioedema.\textsuperscript{5} In our patient,
the background biochemical profile for HAE could
be considered as a predisposing factor when an ACE
inhibitor is introduced.

Classically, bradykinin mediated angioedema is
located in the pharynx, extremities, or face. However,
the bowel wall may be involved concomitantly in up
to 75\% of cases.\textsuperscript{12} Rarely, as we present in this case,
angioedema of the bowel mucosa may be the only site
of angioedema.\textsuperscript{13,14} The initial clinical presentation in
patients with isolated gastrointestinal involvement
may include colicky abdominal pain accompanied by
nausea and vomiting that may easily be mistaken for
other etiologies.\textsuperscript{13} About a day into an acute attack,
the patient may experience watery diarrhea secondary
to extravasation of fluid into the intraluminal space.\textsuperscript{13}

Discussion
Abdominal pain is one of the most common conditions
in clinical practice and yet a challenging complaint to
accurately diagnose due to the vast number of possible
etiologies.\textsuperscript{15} Intestinal angioedema is an uncommon but
well described cause of abdominal pain and diarrhea
easily misdiagnosed, leading to unnecessary surgical
procedures and the possibility of a mortality rate.\textsuperscript{1} In a
series of 235 patients with HAE up to a third of these
patients had undergone exploratory laparotomies,
appendectomies, or both, during their abdominal
attacks.\textsuperscript{16}

Considering the infrequent occurrence of intestinal
angioedema, a high index of suspicion with a detailed
history and physical examination are paramount for a
diagnosis to be made. A detailed history should include
the following: appropriate characterization of the attack;
history of previous attacks; age at first attack; intervals
between attacks; presence or absence of inciting factors
or medications; complete medication history; presence
or absence of respiratory system involvement, and
whether there is a family history of similar attacks.\textsuperscript{17}
Physical examination is most relevant during an acute
attack and it will include a proper examination of the
skin as well as the face and eyelids and upper airways,
the commonly involved areas. For episodes with acute
abdominal involvement, the abdominal examination
findings are very nonspecific. Palpation of the abdomen
may reveal diffuse abdominal tenderness with or
without rebound.\textsuperscript{17} Usually there is no distension to
suggest an obstructive picture. Bowel sounds may be
hypoactive or hyperactive and the patient may have
signs of dehydration from diarrhea depending on the
presentation.

Radiologic tests may help confirm a diagnosis of
intestinal angioedema. In severe cases, plain abdominal
radiographs may show dilated loops of bowel along
with “thumbprinting,” which describes an area of
mucosal edema (see Figure 2).\textsuperscript{1} Ultrasonography often
reveals mucosal thickening and free peritoneal fluid in
dependent areas of the abdomen.\textsuperscript{18}

There may also be a detectable compressible but
edematous bowel wall with increased intraluminal
fluid and decreased motility.\textsuperscript{19} The most sensitive
diagnostic imaging study is a contrast-enhanced CT
scan of the abdomen. CT is more useful for identifying
milder degrees of intestinal edema, dilated loops of
small or large bowel, and ascites than ultrasound and
plain radiographs.\textsuperscript{20} CT findings typically include
massive edema of the small bowel or colon, prominent
mesenteric vessels, thickened omentum, moderate
ascites, and a normal appearance of the pericolic fat.
Normal appearance of pericolic fat is useful for ruling
out inflammatory changes seen in other diseases, such
as appendicitis or diverticulitis.\textsuperscript{21,22} If imaging is delayed
until after recovery, then radiologic imaging may only
show normal results.\textsuperscript{1} As in the patient described,
subtle or mild intestinal edema of any cause may
be overlooked by interpreting radiologists even in
symptomatic patients.\textsuperscript{17}

Worsening abdominal pain severity after an earlier
negative CT scan should not necessarily preclude
consideration of intestinal angioedema diagnosis or a
repeat imaging study.\textsuperscript{17} Sometimes these CT findings
involving the bowel lead to a Gastroenterology
consultation and if colonoscopy is performed, massive
edema of the the bowel wall can be documented
(see Figure 3).
Intestinal Angioedema: An Often Misdiagnosed Entity

GASTROINTESTINAL MOTILITY AND FUNCTIONAL BOWEL DISORDERS, SERIES #17

(continued from page 36)

Laboratory tests are necessary to confirm a diagnosis of angioedema. However there may be no need to do a further laboratory test in a patient with drug (ACE inhibitor) induced angioedema whose diagnosis can easily be made from history and confirmed with radiologic studies. If HAE is suspected, 4 laboratory tests should be obtained: C1 INH level, C1 INH activity, serum C4 level, and serum C1q, which is a byproduct of C1 INH degradation. Low C4 is always present in HAE. In addition to low C4, a low C1 INH level and activity along with a normal C1q level is consistent with type I HAE. A normal C1 INH level with low functional activity and a normal C1q are consistent with type II HAE.

Management

Acute management will involve airway protection, hemodynamic stability and symptomatic therapy (antinausea and pain medications) depending on presentation and initial assessment. There are currently three FDA-approved intravenous pharmacologic agents available in the United States for the targeted acute treatment of HAE: plasma-derived C1 INH replacement protein (C1 INHRP), icatibant, and ecallantide (see Figure 4 below). Plasma-derived C1 INHRP obtained from pooled human plasma is the best studied first-line therapy for an acute HAE attack and it acts by repleting plasma C1 INH to exert inhibitory effects on the angioedema-causing pathways. Icatibant, marketed as Firazyr, is a synthetic B2 receptor antagonist that blocks the effects of bradykinin during an acute angioedema attack by competitively binding to B2 receptors resulting in resolution of swelling and pain. Note that bradykinin, generated during HAE attacks, interacts with bradykinin-1 and B2 receptors to cause angioedema. Ecallantide is a novel plasma kallikrein inhibitor (thereby blocking the production of bradykinin) approved in the United States in December 2009 for the treatment of acute attacks of HAE. Data from 2 randomized double-blind, placebo-controlled phase 3 trials of ecallantide in 143 patients with HAE to examine the speed of efficacy of ecallantide vs placebo showed that its beneficial effect was demonstrated earliest for abdominal attacks, followed by laryngeal and peripheral attacks. Most patients given any of the first line therapies take 15 minutes to 2 hours before experiencing onset of relief, and major swelling may take up to 24 hours to completely resolve after drug therapy. A second line agent Fresh frozen plasma may be used when the first line agents are not available or have not shown efficacy.

Following acute management, adequate patient education as well as prophylactic therapy is usually given as patients are prone to having recurrence of attacks. Prophylaxis may be administered short term in anticipation of a procedure or period of stress, or long term for the reduction of attack rates. Two agents are currently FDA approved for both long term and short term prophylaxis in the United States: oral attenuated androgens (mainly, danazol) and Cinryze, a nanofiltered C1 INH concentrate. Antifibrinolytics (eg, tranexamic acid) currently being used in Europe is not recommended in the United States due to concerns

(continued on page 40)
Intestinal angioedema can be well managed if diagnosed early. Due to the debilitating nature of this condition, and the risk of complications from misdiagnosis (such as surgery) there is need for a high index of suspicion among clinicians. Clinicians should be cognizant of medications that can induce this condition particularly ACEi in order to immediately discontinue its use. The treatment guideline we have provided will also facilitate management decisions.

This case report and literature review serve to heighten the awareness of intestinal angioedema among gastroenterologists as well as help differentiate the condition from other more common gastrointestinal conditions. Intestinal angioedema should feature in the differential diagnosis when CT and other imaging modalities or colonoscopy identify bowel wall edema.

Clinical Pearls for Gastroenterologists

Recurrent admissions for presentations of abdominal pain with no unifying diagnosis being made but sometimes accompanied by surgical intervention should prompt consideration of the diagnosis of intestinal angioedema. Even without involvement of any other part of the body like the eyes or the upper airways, this should not be ruled out when there is a high index of suspicion based on the history, physical exam or radiological findings.

Intestinal angioedema should feature in the differential diagnosis when CT and other imaging modalities or colonoscopy identify bowel wall edema.

References

(continued from page 40)


