Rude Awakening: Acute Abdominal Pain with Spontaneous Resolution

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PRESENTATION
Correct and timely diagnosis of acute abdominal pain, a common presentation in emergency departments, is essential to avoid unnecessary surgery. We report the puzzling case of a previously healthy 54-year-old woman who presented to the emergency department after severe acute-onset generalized abdominal pain woke her from sleep. Cramp-like and nonradiating, the pain also was associated with bloating, nausea, and vomiting. Her vital signs were stable, and a physical examination was notable for mild abdominal distention, tenderness on palpation, and reduced bowel sounds. She did not have urticaria.

The pain decreased in intensity in approximately 10 hours with administration of morphine, and it completely resolved in 24 hours after an episode of diarrhea. The patient recalled 2 similar but milder episodes of abdominal pain that had occurred 2 and 10 years previously. These also woke her from sleep and were associated with reduced appetite. Both earlier episodes resolved in 12 hours.

ASSESSMENT
Results from a comprehensive metabolic profile, serum amylase level, serum lipase level, erythrocyte sedimentation rate, and urinalysis were normal. The patient’s emergency department workup included an abdominal computed tomography (CT) scan without contrast, which revealed bowel wall edema (Figure A and C). A CT scan with contrast obtained the following day showed complete resolution of the edema (Figure B and D). The rapid resolution of edema is consistent with angioedema, which is an intense, temporary, tissue swelling in a localized area of the body.1 Typically, such swelling lasts 1-5 days, and the tissue returns to normal in between episodes.2 Swelling may affect the face, oropharynx, larynx, extremities, trunk, genitalia and gastrointestinal tract.3-4

Angioedema can be classified as allergic, acquired, hereditary, drug-induced, or idiopathic. The patient had no acute exposure to known allergens, no urticaria during her acute episode, and no history of autoimmune disorders or lymphoma, all making allergic and acquired angioedema less likely. No family history of angioedema existed, reducing the probability of hereditary angioedema but not excluding the diagnosis, since 25% of cases are the result of a spontaneous mutation.5 A complement C4 level, the screening test for inherited and acquired angioedema, indicated a reduced concentration at 12.6 mg/dL (normal range, 16-47 mg/dL). Because hereditary angioedema and acquired angioedema are due to abnormalities in C1 inhibitor (C1-INH), we checked the antigenic level and functional activity of C1-INH and the level of C1q, the measurable component of C1 complex that is reduced in some patients with acquired angioedema. These were within normal limits (see Table).

DIAGNOSIS
The patient’s clinical presentation was typical for acute, localized, gastrointestinal angioedema. Idiopathic angioedema was highly unlikely, since idiopathic disease almost never includes laryngeal or gastrointestinal involvement. She was not taking any angiotensin-converting enzyme (ACE) inhibitors, which have rarely been reported to cause angioedema of the bowel wall.6 Allergic angioedema is usually associated with urticaria and temporally associated with a trigger; neither of these factors applied to our patient. This left the possibility of hereditary or acquired angioedema.
With an incidence of approximately 1 per 50,000 people, hereditary angioedema is a rare, life-threatening, swelling disorder characterized by recurrent episodes of edema of the skin or the oropharyngeal, laryngeal, or gastrointestinal mucosa; the cause is a mutation of 1 allele of the C1-INH gene.7-8 Patients with type I hereditary angioedema have a very low serum level of the C1-INH protein, resulting in inadequate C1-INH function.9 Type II hereditary angioedema is characterized by normal levels of C1-INH protein, but the protein is inactive, hence functional activity is reduced.10 Acquired angioedema is due to the formation of an antibody against C1-INH, which results in reduced functional activity of C1-INH and low amounts of C1q protein. In our patient’s case, the normal C1-INH level and function

### Table: Laboratory abnormalities in hereditary vs acquired vs idiopathic angioedema

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<th>C4</th>
<th>C1 Inhibitor Level</th>
<th>C1 Inhibitor Function</th>
<th>C1q</th>
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<tbody>
<tr>
<td>HAE, type I</td>
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<td>↓</td>
<td>↓</td>
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<td>Acquired angioedema</td>
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<td>Idiopathic angioedema</td>
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<td>Patient's results</td>
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<td>Normal</td>
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HAE = hereditary angioedema.
ruled out types I and II hereditary angioedema. Also, acquired angioedema was ruled out since her C1-INH level and function and her C1q level were normal (See Table).

In recent years, a third form of familial angioedema, type III hereditary angioedema, has been characterized by swelling that is strikingly similar to types I and II hereditary angioedema, but patients have normal C1-INH levels and function. As with types I and II hereditary angioedema, the inheritance of type III is dominant. However, it almost exclusively affects women, and clearly, estrogen plays a role, as attacks can be initiated by hormone replacement therapy, menarche, and pregnancy.11 Although the patient did not have a family history of angioedema, a de novo mutation can cause type III hereditary angioedema; similarly, this can occur in types I and II. Therefore, the patient with no family history may represent the first case in a family. Our patient was given a diagnosis of type III hereditary angioedema.

We do not have an explanation for the patient’s low C4 level, although mild deficiency of C4 is not uncommon. Her complement C3 and antinuclear antibody levels were normal, making systemic lupus erythematosus unlikely.

**MANAGEMENT**

Bradykinin, a powerful vasodilator, mediates the distinctive swelling in hereditary, acquired, and ACE-inhibitor-induced angioedema. Hereditary angioedema is characterized by over-production of bradykinin, and ACE, also known as kininase II, is the major enzyme responsible for bradykinin degradation, so treatment with ACE inhibitors leads to defective degradation. Edema, including laryngeal edema, associated with the release of bradykinin does not respond well to antihistamines, epinephrine, and corticosteroids. In contrast, histamine is the mediator in idiopathic and allergic angioedema, making these forms typically responsive to antihistamines, epinephrine, and corticosteroids.

Various treatment options have recently become available for management of types I and II hereditary angioedema. These include recombinant or plasma-derived C1-INH, plasma kallikrein inhibitors (ecallantide), and icatibant, which is a bradykinin receptor antagonist.12-14 Theoretically, these treatments also could be used for acquired and ACE-inhibitor-induced angioedema, but no clinical trials have been performed.

C1-INH concentrate may be used for both prophylaxis and management of acute episodes of angioedema. However, prophylaxis should be administered intravenously 3 times a week, and our patient’s episodes were so infrequent that prophylactic therapy was not recommended. Ecallantide and icatibant are approved for the treatment of acute episodes. Given the rare nature of her attacks, we decided to prescribe ecallantide, to be used as needed.

In conclusion, angioedema should be included in the differential diagnosis in a patient presenting with acute abdomen. Unnecessary surgery may be performed if diagnosis is delayed.

**References**