
Case report

Acute pancreatitis due to hereditary angioedema

Damir Matesic, MD†; Evans R. Fernández Pérez, MD*; Nicholas E. Vlahakis, MD‡; and John B. Hagan, MD§

Background: Hereditary angioedema (HAE) is an infrequent disorder characterized by abnormalities in the levels and/or function of complement C1 esterase inhibitor. Clinical manifestations of HAE are due to recurrent episodic swelling of the subcutaneous or submucosal tissue. When swelling involves the gastrointestinal mucosa, patients may present with nausea, vomiting, diarrhea, and severe abdominal pain. However, HAE is almost never suspected as a potential cause of acute pancreatitis.

Objective: To describe a patient with HAE-associated pancreatitis requiring intensive medical care that responded favorably to conservative and supportive measures.

Methods: Various tests were performed, including abdominal imaging, measurement of pancreatic enzymes levels, liver function tests, measurement of complement levels, and endoscopic retrograde cholangiopancreatography.

Results: The results of these tests confirmed the diagnosis of HAE-associated acute pancreatitis. No other obvious origin, such as gallstones or alcohol use, was identified.

Conclusion: This case illustrates the need for a high clinical suspicion of acute pancreatitis when caring for patients with HAE who present with abdominal symptoms. There continues to be an urgent need for better and additional therapeutic options for HAE patients, including those to prevent and abort ongoing attacks.

Ann Allergy Asthma Immunol. 2006;97:611–614.

INTRODUCTION

Hereditary angioedema (HAE) is an infrequent disorder characterized by abnormalities in the levels and/or function of complement C1 esterase inhibitor. Clinical manifestations of HAE are due to recurrent episodic swelling of the subcutaneous or submucosal tissue. When swelling involves the gastrointestinal mucosa, patients may present with nausea, vomiting, diarrhea, and severe abdominal pain. However, HAE is almost never suspected as a potential cause of acute pancreatitis. Herein, we describe a patient with HAE-associated pancreatitis requiring intensive medical care that responded favorably to conservative and supportive measures.

REPORT OF A CASE

A 40-year-old man presented with a 1-day history of nausea, emesis, and severe intermittent abdominal pain radiating to his back. He had a 10-year history of HAE-associated abdominal attacks. He was first seen at Mayo Clinic at the age of 20 years, where the diagnosis of HAE was confirmed after a review of his clinical history and reduced C1 esterase

inhibitor antigen level. At the time he was taking aminocaproic acid, 10 g/d, and was having 1 to 2 attacks per week.

The patient was then temporally switched to methyltestosterone, 10 mg twice daily. The dose was increased to 3 times daily and eventually to 4 times daily. Because of the lack of improvement, he was then switched to stanozolol, 8 mg/d, which decreased the frequency and severity of the attacks significantly. Over the years, he experienced mild attacks less than once every 4 months on average. However, at the age of 37 years the patient was hospitalized in an outside medical center with an acute severe abdominal attack. During this time, review of outside records revealed an abdominal computed tomogram that demonstrated either mucosal herniation or intussusception in the region of the second portion of the duodenum. He had no gallstones or other abdominal abnormalities, and laboratory testing revealed normal lipase and amylase levels. Unfortunately, complement levels were not measured at the time. Nevertheless, several days after this episode, while the patient was in remission, the C1 esterase inhibitor antigen was low at 8 mg/dL (reference range, 19–37 mg/dL), and the C4 level was 9 mg/dL (reference range, 14–40 mg/dL).

When the patient was 39 years old, stanozolol became unavailable and he started taking danazol. However, the frequency and severity of attacks increased. Symptoms occurred almost monthly, starting usually as a dull lower back pain, which spread to the abdomen within hours.

His medical history included coronary artery disease and peptic ulcer disease. His only medications included

* Department of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, Minnesota.

† Department of Allergy and Clinical Immunology, Mayo Clinic, Rochester, Minnesota.

‡ Department of Pulmonary and Critical Care, Mayo Clinic, Rochester, Minnesota.

§ Department of Allergic Diseases, Mayo Clinic, Rochester, Minnesota.

Received for publication April 9, 2006.

Accepted for publication in revised form June 4, 2006.

ezetimibe, 10 mg orally once daily; esomeprazole, 40 mg orally once daily; and danazol, 200 mg orally twice daily. He denied smoking, alcohol use, illicit drug use, or any history of abdominal surgery or trauma. Family history was significant for HAE in the patient's father and paternal uncle but an absence of familial pancreatitis and/or collagen vascular diseases.

Physical examination revealed a healthy-appearing young man severely dehydrated and in acute distress. The patient was afebrile (temperature, 98°F) with an initial blood pressure of 149/96 mm Hg, a regular pulse rate of 110/min, and a respiratory rate of 22/min. The results of examination of the head and neck were unremarkable, with normal-appearing tongue and uvula and no evidence of scleral icterus or lymphadenopathy. He had no evidence of any external cutaneous angioedema or urticaria. Cardiovascular examination revealed regular first and second heart sounds and no murmurs. Decreased breath sounds in the bilateral lower lung fields were appreciated. The abdomen was noted to have hyperactive bowel sounds, yet it was soft and mildly diffusely tender without guarding or rebound tenderness and no evidence of Gray-Turner or Cullen sign. There was no edema in the extremities, and findings of the neurologic examination were unremarkable.

The patient's laboratory results showed leukocytosis, hemoconcentration, azotemia, and elevated liver and pancreatic enzyme levels (Table 1). Serum total bilirubin, electrolytes, creatinine, and triglycerides levels were within the reference range. The C1 esterase inhibitor antigen was low at 7 mg/dL (reference range, 19–37 mg/dL) and the C4 level was 4 mg/dL (reference range, 14–40 mg/dL). The C1 esterase inhibitor functional assay (75%; reference range, >67%), C1q level (17 mg/dL; reference range, 12–22 mg/dL), and C2 level (1.9 mg/dL; reference range, 1.1–3 mg/dL) were within the reference range. Abdominal ultrasound showed no cholelithiasis. A contrast-enhanced computed tomogram of the abdomen demonstrated patchy areas of pancreatic necrosis and marked duodenal swelling (Fig 1). No bile duct dilation or pancreatic calcification was detected. Oral intake was withheld, and the patient was treated with intravenous fluids, antibiotic prophylaxis, patient-controlled analgesia, and nasogastric decompression and continued on proton pump inhibitor treatment. Danazol therapy was continued at the same dose. By hospital day 3, he had marked improvement in clinical status and normalization of pancreatic enzymes. Upper esophagogastroduodenoscopy results were normal, and subsequent endoscopic retrograde cholangiopancreatography (ERCP) demonstrated normal sphincter of Oddi manometry and a patent pancreatic duct of normal caliber. The results of analysis of bile for microlithiasis were entirely normal. The patient was released from the hospital without complications after 7 days.

DISCUSSION

HAE is an autosomal dominant disorder that affects 1 in 10,000 to 1 in 150,000 persons with a clinical course char-

Table 1. Serum Laboratory Results for the Case Patient

Component	Result	Reference range
White blood cell count, $\times 10^9/L$	19,300	3.5–10.5
Hemoglobin, g/dL	18.6	13.5–17.5
Hematocrit, %	55.1	38.8–50
Sodium, mEq/L	143	134–145
Potassium, mEq/L	4.1	3.5–5.0
Magnesium, mg/dL	1.9	1.5–2.4
Ionized calcium, mg/dL	4.7	4.65–5.30
Bicarbonate, mEq/L	23	23–28
Creatinine, mg/dL	0.9	0.7–1.3
Blood urea nitrogen, mg/dL	55	8–20
Glucose, mg/dL	101	70–105
Aspartate aminotransferase, IU/L	68	0–35
Alanine aminotransferase, IU/L	105	0–35
Alkaline phosphatase, IU/L	333	98–251
Lactate dehydrogenase, IU/L	744	122–222
Total bilirubin, mg/dL	0.5	0.3–1.2
Amylase, IU/L	1,176	0–130
Lipase, IU/L	11,485	0–95
Triglyceride, mg/dL	249	<150
Pao ₂ /Fio ₂ ratio	457	>300

Abbreviation: Pao₂/Fio₂, partial pressure of oxygen, arterial/fraction of inspired oxygen.

acterized by recurrent episodes of angioedema, affecting a variety of organ systems and manifesting with numerous clinical syndromes.^{1,2} HAE occurs because of a quantitative (type 1, most common) or qualitative (type 2) abnormality of C1 esterase inhibitor, which may result from more than 100 gene mutations on chromosome 11q12-q13.1 described to date.³ An additional variant was recently described as an estrogen-dependent inherited form of angioedema that affects only women with normal C1 esterase inhibitor (and normal C4) complement levels, and the mechanism remains unknown.⁴

Although previous data have suggested that symptoms in HAE might be mediated via complement system activation, recent data indicate that the major mediator is bradykinin.^{3,5,6} Clinical presentations can be severe and even fatal, particularly with the symptoms of upper airway edema. The gastrointestinal tract is frequently affected, at an early age, and usually presents with recurrent abdominal pain and nausea.^{7,8} Interestingly, this is a distinguishing feature of HAE, because abdominal involvement is rarely seen in other types of angioedema.⁹ Recently, Bork et al¹⁰ reported the clinical and time course of untreated abdominal attacks in patients with HAE. They retrospectively documented a total lifetime history of 33,671 abdominal attacks in 153 patients with HAE. However, the frequency of pancreatitis as a potential cause was not described. This is, to our knowledge, only the third

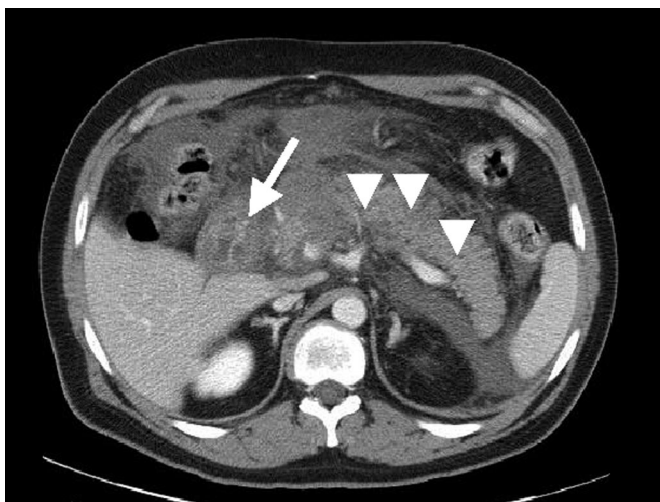


Figure 1. Computed tomography of the abdomen with intravenous contrast demonstrating findings consistent with acute pancreatitis. There is mild pancreatic enlargement, inflammation, and indistinctness of the anterior body of the pancreas with stranding of the adjacent mesentery (arrowheads). Areas of the pancreatic body are nonenhancing, consistent with complicated pancreatitis and partial pancreatic necrosis. Also note the remarkably swollen duodenum (arrow).

report of pancreatitis associated with HAE to be reported in the literature.^{11,12}

Gallstones and excess alcohol consumption are the 2 most common precipitating origins of acute pancreatitis. Less common causes included severe hypertriglyceridemia, hypercalcemia, post-ERCP, blunt or penetrating abdominal trauma, congenital abnormalities, infections, and autoimmune and medication-induced pancreatitis. Ezetimibe and danazol have been associated with the occurrence of acute pancreatitis.^{13,14} However, our patient's pancreatitis resolved spontaneously despite the fact that he had been taking these 2 medications. In the present case, complement studies from the outside hospitalization for abdominal pain were not available. Yet our patient's episode of acute pancreatitis was not characterized by any of the typical predisposing or causative origins, suggesting HAE as the most likely cause. However, it is possible that an unidentified predisposition to pancreatitis may have triggered an HAE flare such as genetic mutations in the cystic fibrosis transmembrane regulator gene and cationic trypsinogen genes (hereditary pancreatitis autosomal dominant disorder).¹⁵ However, the patient had no features typical of cystic fibrosis or a family history of pancreatitis in a first-degree or second-degree relative. Of note is that ERCP failed to detect pancreatic duct swelling or narrowing, which most likely reflects the delay in performing this procedure. Taken together, the weight of evidence in this case strongly supports a diagnosis of an HAE attack causing pancreatitis. The reason exaggerated angioedema localized to the pancreas and peripancreatic tissues occurs so infrequently remains unclear.

A significant problem faced in the daily care of patients with HAE is the lack of a C1 esterase inhibitor concentrate approved for use in the United States. For more than 30 years this product has been repeatedly proven to be safe and effective in Europe in the treatment of HAE flares, including those involving gastrointestinal symptoms.^{16,17} Fresh frozen plasma (FFP) has been used as a prophylactic agent in efforts to prevent angioedema in high-risk patients with documented but asymptomatic HAE before surgery.¹⁸ The effectiveness of this therapy remains controversial, and as a result there is reluctance to use FFP in patients who have active disease. Two reports from 1969 that questioned the safety of FFP use in symptomatic HAE patients suggested that there could be a paradoxical worsening of symptoms.^{19,20} However, further studies in 1972, as well as some recent publications, suggested that the use of FFP may be not only effective but also safe in the treatment of HAE.^{21–24} The treatment of acute HAE with FFP remains controversial. Because of this and the patient's progressive and steady clinical improvement documented during his hospitalization, FFP was not given.

Antifibrinolytic agents (aminocaproic acid or tranexamic acid) and attenuated androgens (danazol and stanozolol off-market) have proved useful in reducing the frequency and severity of HAE attacks and in the short-term prophylaxis of surgical procedures. Uses of attenuated androgens are associated with virilization and liver abnormalities. This kind of treatment is not appropriate for all patients, and those who are treated have to be monitored carefully. Antifibrinolytics are not as effective as the attenuated androgens, and the most significant adverse effects include nausea, vertigo, diarrhea, postural hypotension, fatigue, myopathy, and increased risk of venous thromboembolism. Currently, several promising agents, such as recombinant human C1 esterase inhibitor, kallikrein inhibitor (DX-88), and bradykinin 2 inhibitor (Icibant), are undergoing phase 3 evaluation and may offer safer and more effective treatment options.

CONCLUSION

Patients with HAE may present with a variety of clinical manifestations. In this report, we document the rare occurrence of acute pancreatitis in association with a flare of HAE. Based on the clinical presentation, laboratory testing, and radiologic studies, we speculate that HAE was associated with primary angioedema and obstruction of the ampulla of Vater and/or ductal edema interfering with normal pancreatic drainage. There continues to be an urgent need for better and additional therapeutic options for HAE patients, including those to prevent and abort ongoing attacks.

REFERENCES

1. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med.* 2001;161: 2417–2429.
2. Frigas E, Nzeako UC. Angioedema: pathogenesis, differential diagnosis, and treatment. *Clin Rev Allergy Immunol.* 2002;23: 217–231.

3. Davis AE III. The pathophysiology of hereditary angioedema. *Clin Immunol*. 2005;114:3–9.
4. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1- inhibitor activity in women. *Lancet*. 2000;356:213–217.
5. Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE III. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest*. 2002;109:1057–1063.
6. Nussberger J, Cugno M, Cicardi M, Agostoni A. Local bradykinin generation in hereditary angioedema. *J Allergy Clin Immunol*. 1999;104:1321–1322.
7. Sadeghi N, Van Daele D, Hainaux B, Engelholm L, Michel O. Hereditary angioedema involving the gastrointestinal tract: CT findings. *Eur Radiol*. 2001;11:99–101.
8. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema as a cause of transient abdominal pain. *J Clin Gastroenterol*. 2002;34:57–61.
9. Agostoni A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114:S51–131.
10. Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am J Gastroenterol*. 2006;101:619–627.
11. Cutler AF, Yousif EA, Blumenkehl ML. Hereditary angioedema associated with pancreatitis. *South Med J*. 1992;85:1149–1150.
12. Brickman CM, Tsokos GC, Balow JE, et al. Immunoregulatory disorders associated with hereditary angioedema. *J Allergy Clin Immunol*. 1986;77:749–757.
13. Association of Ezetrol (ezetimibide) with myalgia, rhabdomyolysis, hepatitis, pancreatitis, and thrombocytopenia. Public Advisory Health Canada and Merck Frosst/Schering Pharmaceuticals, 1 Feb 2005. Available at: http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/ezetrol_hpc_e.html. Accessed April 29, 2006.
14. Balasch J, Martinez-Roman S, Carreras J, Vanrell JA. Acute pancreatitis associated with danazol treatment for endometriosis. *Hum Reprod*. 1994;9:1163–1165.
15. Grigorescu M, Grigorescu MD. Genetic factors in pancreatitis. *Rom J Gastroenterol*. 2005;14:53–61.
16. Bork K, Meng G, Staubach P, Hardt J. Treatment with C1 inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema. *Transfusion*. 2005;45:1774–1784.
17. Agostoni A, Bergamaschini L, Martignoni G, Cicardi M, Marasini B. Treatment of acute attacks of hereditary angioedema with C1-inhibitor concentrate. *Ann Allergy*. 1980;44:299–301.
18. Pickering RJ, Good RA, Kelly JR, Gewurz H. Replacement therapy in hereditary angioedema: successful treatment of two patients with fresh frozen plasma. *Lancet*. 1969;1:326–330.
19. Rosen FS, Austen KF. The “neurotic edema” (hereditary angioedema). *N Engl J Med*. 1969;280:1356–1357.
20. Donaldson VH. Therapy of “the neurotic edema”. *N Engl J Med*. 1972;286:835–836.
21. Jaffe CJ, Atkinson JP, Gelfand JA, Frank MM. Hereditary angioedema: the use of fresh frozen plasma for prophylaxis in patients undergoing oral surgery. *J Allergy Clin Immunol*. 1975;55:386–393.
22. Longhurst HJ. Emergency treatment of acute attacks in hereditary angioedema due to C1 inhibitor deficiency: what is the evidence? *Int J Clin Pract*. 2005;59:594–599.
23. Fine SR, Fogarty M, Linz A. Fresh frozen plasma for prophylaxis in hereditary angioedema [letter]. *J Allergy Clin Immunol*. 1976;57:624–625.
24. Hill BJ, Thomas SH, McCabe C. Fresh frozen plasma for acute exacerbations of hereditary angioedema. *Am J Emerg Med*. 2000;22:633.

Requests for reprints should be addressed to:
 Evans Fernández Pérez, MD
 Department of Pulmonary and Critical Care Medicine
 Mayo Clinic College of Medicine
 Mayo Clinic E 18
 200 First St SW
 Rochester, MN 55901
 E-mail: fernandez.evans@mayo.edu