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CASE REPORT

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Massive mesenteric edema in a patient with type I hereditary angioedema

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Abstract We report a patient with hereditary angioedema (HAE) presenting with skin edema and abdominal pain. Laboratory examination showed reduced levels of CH50, C2, C4, and C1 inhibitor (C1-INH). Abdominal computed tomography (CT) showed marked mesenteric edema and wall thickening of the duodenum and transverse colon. Acute abdominal pain is common in HAE and is difficult to distinguish from surgical emergency. Massive mesenteric edema on CT is a rare, but specific, sign suggesting HAE.

Key words Abdominal pain · C1 inhibitor (C1-INH) · Computed tomography (CT) · Hereditary angioedema (HAE) · Mesenteric edema

Introduction

Hereditary angioedema (HAE) is an autosomal dominant hereditary disease characterized by recurrent episodes of potentially life-threatening angioedema.[1–4] HAE is caused by mutations of the C1 inhibitor (C1-INH) gene, resulting in loss of function of plasma C1-INH.[5,6] To date, nearly 100 different mutations in the C1-INH gene have been reported.[7] C1-INH is a serine protease inhibitor whose major role is to control activation of the classical pathway of the complement cascade, the intrinsic coagulation cascade, and the kinin cascade.[8] Two types of HAE have been recognized according to the plasma level of C1-INH:[9,10] Type I HAE is evident in 85% of HAE patients and is characterized by low antigenic and functional plasma levels of the C1-INH protein, while type II HAE is evident in 15% of HAE patients and is characterized by normal or elevated C1-INH antigenic levels with low functional activity. The clinical features of the disease are recurrent angioedema of subcutaneous tissue, larynx, soft palate, and gastrointestinal mucosa.[1–4] Acute abdominal pain is common in HAE and can mimic surgical emergencies, particularly in patients with no other symptoms.[2,11–13] Here we report a patient with recurrent abdominal attacks of HAE presenting marked mesenteric edema on computed tomography (CT).

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Case report

The patient was a 62-year-old Japanese man.[14] At the age of 57 years he began experiencing swelling in the extremities. He was diagnosed as having HAE based on recurrent episodes of subcutaneous tissue edema in the face (Fig. 1A), upper airway (Fig. 1B), and extremities, and low plasma levels of C4 (2.4 mg/dl; normal, 17–45 mg/dl), C1-INH (7.0 mg/dl; normal, 10–25 mg/dl), and C1-INH activity (<25%; normal, 80–125%), with normal C1q (9.8 mg/dl; normal, 8.8–15.3 mg/dl) and C3 (101 mg/dl; normal, 86–160 mg/dl) levels. Routine blood tests including carcinoembryonic antigen and carbohydrate antigen 19-9 were normal. Chest and abdominal CT, upper and lower endoscopy, gallium scintigram, and bone marrow aspiration showed no signs of malignancy. Genetic diagnosis for HAE revealed a single base change (G→A) at nucleotide 8722, which changed the 3′ acceptor splice site AG to AA at the end of intron 5. This mutation may abolish the correct splicing of intron 5 and create an unstable mRNA.[14] Treatment was started with a small of dose of danazol (12.5 mg/day), because of the development of adverse effects, such as nausea, headache, and myalgia. The dose was slowly increased up to 200 mg/day. Although danazol decreased the frequency of angioedema attacks and slightly increased C1-INH activity to 27%, the patient still had a few attacks per month.

He was admitted to our hospital with an acute episode of diffuse abdominal pain. Enhanced CT of the abdomen, performed during an acute episode, showed marked diffuse

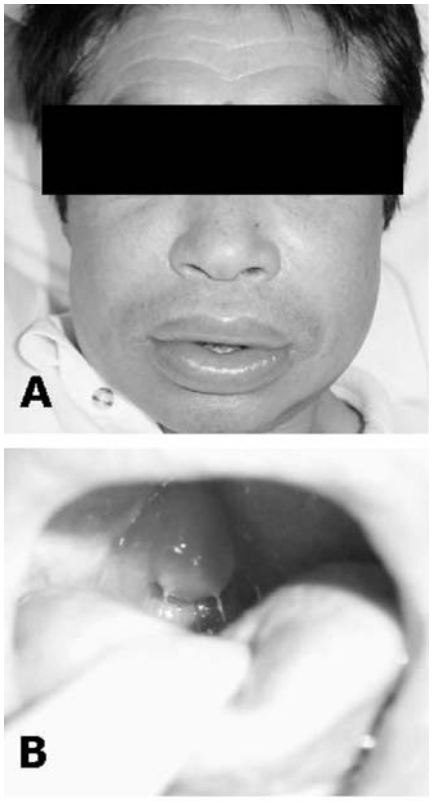

Fig. 1A,B. Angioedema of the patient. Marked swelling of the face (**A**), soft palate, and uvula (**B**) were observed

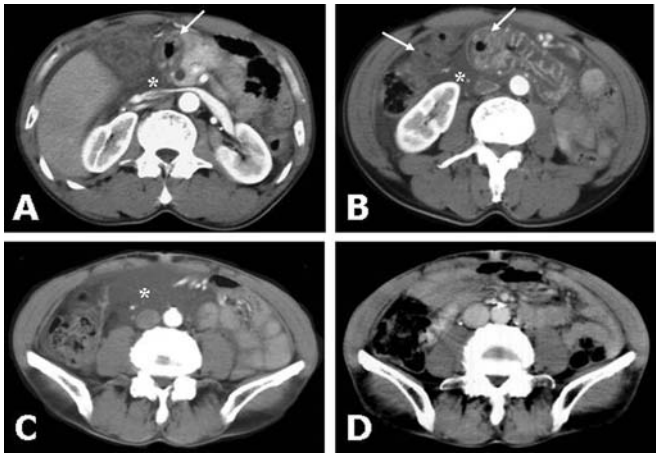

Fig. 2A–D. Abdominal computed tomography (CT) of the patient. **A–C** Abdominal CT performed during an episode of abdominal pain. Enhanced CT of the upper (**A**), middle (**B**), and lower (**C**) abdomen showed marked mesenteric edema (*asterisk*), and circumferential and symmetrical wall thickening of the duodenum and transverse colon (*arrows*). The small intestine was translocated to the lateral side in the peritoneal cavity by massive mesenteric edema, and the pancreas was compressed by the edematous duodenum. **D** Abdominal CT performed 11 days later. Enhanced CT of the lower abdomen showed almost complete resolution of the abnormalities

mesenteric edema and circumferential wall thickening of the duodenum and transverse colon (Fig. 2A–C). A small amount of ascites was also observed around the liver. Mesenteric edema occupied the central part of the peritoneal cavity and translocated the small intestine to the lateral side. The results of routine blood laboratory tests were not remarkable except for leukocytosis (14060/mm^3). The history of subcutaneous tissue edema and CT findings suggested an abdominal attack of HAE. The patient was treated with intravenous injection of C1-INH concentrates and the abdominal symptoms subsided within 72 h. A follow-up abdominal CT performed 11 days later showed almost complete resolution of the abnormalities (Fig. 2D).

Discussion

There are two forms of C1 inhibitor deficiency: the inherited form (HAE) is usually detected in the first or second decade of life and shows a typical autosomal dominant inheritance,[1–4] while the acquired form (acquired angioedema, AAE) primarily affects adult or elderly patients with no family history of the disease.[15,16] These two forms can be distinguished by measurement of serum C1q: Levels of C1q are normal in HAE and are decreased in AAE.[16] Initially, the present patient was suspected as having AAE, because of his late age of onset (57 years old) and negative family history. However, his normal serum C1q level prompted us to perform genetic tests for HAE. He was diagnosed as having HAE based on the presence of a pathogenic mutation in his C1-INH gene.[14] Although the mutation observed in the present patient should cause a marked change to the protein, he developed HAE late in life. Environmental and genetic factors other than C1-INH gene mutation may influence the phenotype in HAE.

Hereditary angioedema is manifested by episodic attacks of painless nonpruritic edema of the face and extremities, and submucosal edema of the upper airway and gastrointestinal tract. The attacks may occur spontaneously or may be precipitated by trauma, anxiety, or emotion. The present patient had recurrent episodes of subcutaneous edema and abdominal pain, which are the most common symptoms of HAE occurring in 91%–96% and 73%–93% of cases, respectively.[2,4] Severe abdominal pain due to intestinal involvement is frequently seen during an HAE attack, sometimes being the sole manifestation of HAE.[2,11–13] Episodes of bowel angioedema are self-limited and usually resolve without complications in 72 h; however, more than 30% of patients with HAE undergo inadequate appendectomy or exploratory laparotomy,[4] because the characteristics of the abdominal attacks are not pathognomonic and are difficult to distinguish from surgical emergency.

Computed tomography scans are useful in suggesting the diagnosis;[12,13,17,18] a circumferential thickened intestine wall during the acute phase is thought to be characteristic, and moderate to large amounts of ascites are also observed in some patients.[19–21] Remarkable mesenteric edema was one of the striking findings on CT in our patient. Mesenteric edema has occasionally been reported as a minor feature contributing to thickening of the small-bowel wall and mu-

cosa in HAE.[12,17] To our knowledge, this is the first presentation of massive mesenteric edema on CT in an HAE patient. Other disorders have been shown to present mesenteric edema, such as small bowel ischemia,[22] sclerosing mesenteritis,[23] and mesenteric venous thrombosis,[24] but diffuse edema without a sclerosing soft-tissue mass or vascular abnormality distinguishes HAE from other diseases. Diffuse mesenteric edema on CT is a rare, but specific, sign suggesting HAE. When clinical or radiological evidence suggests a diagnosis of HAE, complement levels should be measured. The C4 level is the best screening test for the diagnosis of HAE. Greater awareness of the clinical and radiological features of this disease may prevent unnecessary testing and treatments, leading to more effective therapies, such as danazol and C1-INH concentrates.

Danazol is the most effective drug in preventing angioedema attacks.[25] The mechanism of its action seems to be related to increases in expression of C1-INH mRNA and protein.[26] Hosea et al.[25] reported that all patients showed a clinical response to the administration of danazol, with decreases in both the frequency and severity of attacks. They started danazol therapy at a dose of 600 mg/day in three divided doses, and decreased the dosage to a level that consistently controlled the symptoms of the disease. The appropriate maintenance dose of danazol was ascertained individually depending on the clinical responses and adverse effects. Alternatively, antifibrinolytic agents (ε-aminocaproic acid[27] and tranexamic acid[28]) were also reported to decrease the frequency of attacks in the majority of patients. In the present patient, the effects of danazol (200 mg/day) were limited. Therefore, we are planning to treat him with antifibrinolytic agents in combination with danazol.

References

1. Donaldson VH, Rosen FS. Hereditary angioneurotic edema: a clinical survey. Pediatrics 1996;37:1017–27.
2. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. Ann Intern Med 1976;84: 580–93.
3. Sim TC, Grant JA. Hereditary angioedema: its diagnostic and management perspectives. Am J Med 1990;88:656–64.
4. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. Medicine (Baltimore) 1992;71:206–15.
5. Stoppa-Lyonnet D, Tosi M, Laurent J, Sobel A, Lagrue G, Meo T. Altered C1 inhibitor genes in type I hereditary angioedema. N Engl J Med 1987;317:1–6.
6. Carter PE, Duponchel C, Tosi M, Fothergill JE. Complete nucleotide sequence of the gene for human C1 inhibitor with an unusually high density of Alu elements. Eur J Biochem 1991;197: 301–8.
7. Bowen B, Hawk JJ, Sibunka S, Hovick S, Weiler JM. A review of the reported defects in the human C1 esterase inhibitor gene producing hereditary angioedema including four new mutations. Clin Immunol 2001;98:157–63.
8. Davis AE III. C1 inhibitor and hereditary angioneurotic edema. Annu Rev Immunol 1998;6:595–628.
9. Rosen FS, Alper CA, Pensky J, Klemperer MR, Donaldson VH. Genetically determined heterogeneity of the C1 esterase inhibitor in patients with hereditary angioneurotic edema. J Clin Invest 1971;50:2143–9.
10. Gadek JE, Hosea SW, Gelfand JA, Frank MM. Response of variant hereditary angioedema phenotypes to danazol therapy. Genetic implications. J Clin Invest 1979;64:280–6.
11. Weinstock LB, Kothari T, Sharma RN, Rosenfeld SI. Recurrent abdominal pain as the sole manifestation of hereditary angioedema in multiple family members. Gastroenterology 1987;93:1116–8.
12. Ciaccia D, Brazer SR, Baker ME. Acquired C1 esterase inhibitor deficiency causing intestinal angioedema: CT appearance. AJR 1993;161:1215–6.
13. Sadeghi N, Van Daele D, Hainaux B, Engelholm L, Michel O. Hereditary angio-edema involving the gastrointestinal tract: CT findings. Eur Radiol 2001;11:99–101.
14. Sekijima Y, Hashimoto T, Kawachi Y, Koshihara H, Otsuka F, Ikeda S. A novel RNA splice site mutation in the C1 inhibitor gene of a patient with type I hereditary angioedema. Intern Med 2004; 43:253–5.
15. Cicardi M, Bergamaschini L, Cugno M, Beretta A, Zingale LC, Colombo M, et al. Pathogenetic and clinical aspects of C1 inhibitor deficiency. Immunobiology 1998;199:366–76.
16. Markovic SN, Inwards DJ, Frigas EA, Phyliky RP. Acquired C1 esterase inhibitor deficiency. Ann Intern Med 2000;132:144–50.
17. Kim SH, Cho JY, Lim HK. CT findings of isolated small bowel angioedema due to iodinated radiographic contrast medium reaction. Abdom Imaging 1999;24:117–9.
18. De Backer AI, De Schepper AM, Vandevenne JE, Schoeters P, Michielsen P, Stevens WJ. CT of angioedema of the small bowel. AJR 2001;176:649–52.
19. Shah TJ, Knowles WO, McGeady SJ. Hereditary angioedema with recurrent abdominal pain and ascites. J Allergy Clin Immunol 1995;96:259–61.
20. Talavera A, Larraona JL, Ramos JL, Lopez T, Maraver A, Arias J, et al. Hereditary angioedema: an infrequent cause of abdominal pain with ascites. Am J Gastroenterol 1995;90:471–4.
21. Branco-Ferreira M, Pedro E, Barbosa MA, Carlos AG. Ascites in hereditary angioedema. Allergy 1998;53:543–5.
22. Chou CK, Mak CW, Tzeng WS, Chang JM. CT of small bowel ischemia. Abdom Imaging 2003;29:18–22.
23. Horton KM, Lawler LP, Fishman EK. CT findings in sclerosing mesenteritis (panniculitis): spectrum of disease. Radiographics 2003;23:1561–7.
24. Matsushita I, Hanai H, Sato Y, Arai H, Iida T, Hosoda Y, et al. Protein-losing enteropathy caused by mesenteric venous thrombosis with protein C deficiency. J Clin Gastroenterol 2000;30:94–7.
25. Hosea SW, Santaella ML, Brown EJ, Berger M, Katusha K, Frank MM. Long-term therapy of hereditary angioedema with danazol. Ann Intern Med 1980;93:809–12.
26. Pappalardo E, Zingale LC, Cicardi M. Increased expression of C1-inhibitor mRNA in patients with hereditary angioedema treated with Danazol. Immunol Lett 2003;86:271–6.
27. Frank MM, Sergent JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema. A double-blind study. N Engl J Med 1972;286:808–12.
28. Sheffer AL, Austen KF, Rosen FS. Tranexamic acid therapy in hereditary angioneurotic edema. N Engl J Med 1972;287:452–4.