Angioedema Likely Related to Angiotensin Converting Enzyme Inhibitors

Masami MATSUMURA, Katsuo HARUKI, Kouji KAJINAMI and Takashi TAKADA

Angioedema associated with angiotensin converting enzyme inhibitors is a rare adverse reaction. It commonly involves the face, oropharyngeal and laryngeal tissues. To our knowledge, angioedema of the abdominal viscera related to angiotensin converting enzyme inhibitors has not been reported previously. We present a rare case of a patient who had episodes of angioedema and abdominal pain with ascites probably related to the ACE inhibitor captopril.
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Key words: angioedema of the abdominal viscera, abdominal pain, ascites

Introduction

Angiotensin-converting enzyme (ACE) inhibitors have been available as antihypertensive agents since 1980. Dry cough, excessive hypotension, hyperkalemia and angioedema have been described as adverse reactions (1, 2). Angioedema associated with ACE inhibitors has an estimated incidence of 0.1–0.2% in the general population (3, 4). It usually occurs in the oropharyngeal or laryngeal tissues and may result in fatal acute airway obstruction. To our knowledge, there has been no previous report on abdominal viscera angioedema related to ACE inhibitors.

We present a patient who had episodes of angioedema and abdominal pain with ascites probably related to ACE inhibitor.

Case Report

A 48-year-old Japanese woman with essential hypertension was started on captopril 12.5 mg three times daily in March 1990. The second day of medication, the patient complained of mild abdominal pain. Gastroendoscopy and abdominal ultrasound imaging disclosed no definite abnormality. The patient's complaint subsided within a few days. For four months, the patient achieved excellent control of her hypertension. In July 1990, remarkable lip swelling suddenly developed (Fig. 1) but disappeared the next day. The captopril was continued. Six days later, the patient was admitted to our hospital because of crampy abdominal pain, nausea and vomiting. Scout film of the abdomen and abdominal ultrasound imaging revealed no abnormality. After the patient fasted, with captopril also withheld, the symptoms subsided within a day. Seven days later, the patient was well and could be discharged. Medication of captopril was resumed. One month later, she was again admitted to our hospital because of lower abdominal pain, nausea, and vomiting.

On admission, her vital signs were as follows: temperature 36.6°C, pulse 78/minutes, and blood pressure 120/90 mmHg.

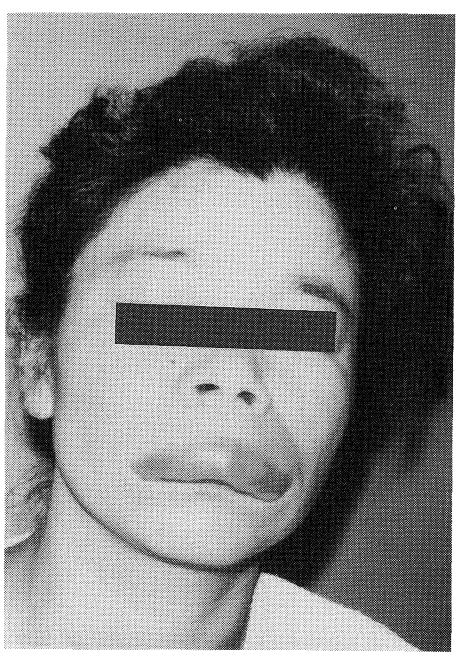

Fig. 1. Remarkable swelling of the upper lip.

From the Department of Internal Medicine of Tsurugi General Hospital, Ishikawa
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Reprint requests should be addressed to Dr. Masami Matsumura, the Second Department of Internal Medicine, School of Medicine, Kanazawa University, Takara-machi 13-1, Kanazawa-city 920, Japan

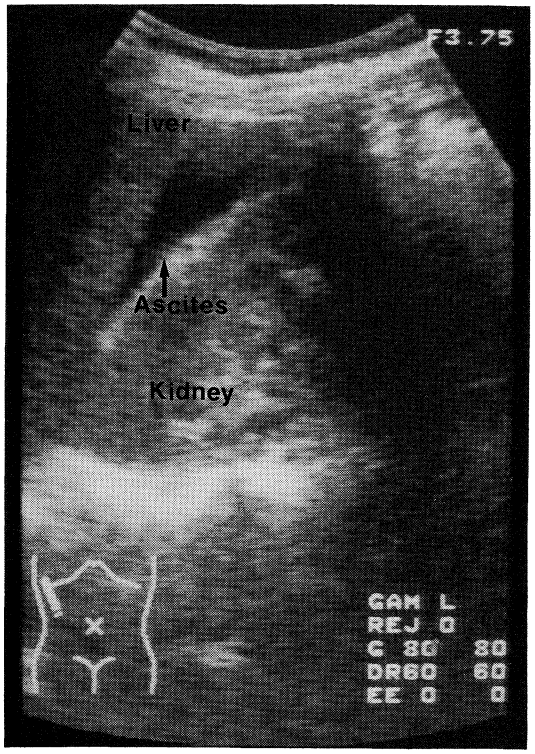

Fig. 2. Abdominal ultrasound imaging showing a fluid into the peritoneal cavity.

Table 1. Analysis of the Ascites

Appearance	Slight turbid, yellow
Specific gravity	1.035
Protein content	5.3g/dl
Red blood cell count	112/mm^3
White cell count	1,216/mm^3
Amylase	94U/dl
LDH	256IU/l
Glucose	95mg/dl

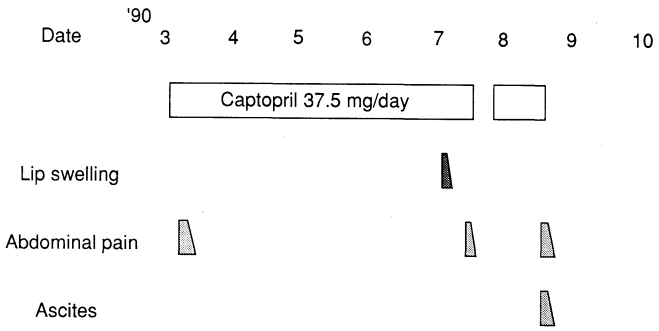

Fig. 3. Clinical course.

On physical examination, no rash or swelling was observed. The abdomen was moderately distended and the right lower quadrant tender, but there was no muscular rigidity.

Urinalysis was negative. The hematocrit was 36.9%. The white-cell count was 6,100, with 68% neutrophils, 22% lymphocytes, 8% monocytes and 2% eosinophils. Liver function was normal: GOT 14 IU/l and GPT 11 IU/l. The urea nitrogen, creatinine, sodium, chloride, potassium, amylase, C3, C4, and CH50 were all normal. Serum IgE was normal at 6.8 IU/ml. Scout film of the abdomen showed no abnormality. Abdominal ultrasound imaging revealed an excess of fluid distributed in the upper, lower abdomen and pelvic areas (Fig. 2). An edematous gastrointestinal wall was not apparent. The ascites collected from the peritoneal cavity appeared exudative (Table 1). Because of the episodes of lip swelling and recurrent abdominal pain, we suspected angioedema of the abdominal viscera caused by idiopathic form, hereditary form, or ACE inhibitors.

After admission, captopril was stopped. We treated the patient with nafamostat mesilate (50 mg i.v.), a serine protease inhibitory agent. The symptoms had almost disappeared the next day. Three days later, the ascites had completely disappeared on the abdominal ultrasound imaging. On admission, serum C1 esterase inhibitor (C1 INH) was normal at 16.5 mg/dl (normal, 15 to 35 mg/dl) and its activity was normal at 86% (normal, 80 to 130%). Hereditary angioedema was excluded. Liver diseases, pancreas diseases, infectious diseases, collagen diseases, and malignancies were ruled out by further examinations. Gynecological examinations showed no abnormal findings except for myoma of the uterus. Her past history showed no significant allergies, angioedema, or recurrent abdominal pain. But her father, a 74-year-old Japanese male, had a history of swelling of the throat, face and lip, unrelated to food or medication, 5–6 times per year, from his youth. He did not develop recurrent abdominal pain. His angioedema was thought to be an idiopathic form (his C1 INH and its activity were normal). No further angioedema or abdominal pain occurred after discontinuation of captopril. Considering the clinical course (Fig. 3), laboratory data, and other examinations, angioedema of the digestive organs related to ACE inhibitor was strongly suspected as the cause of the abdominal pain with ascites in our case, while we could not detect apparent edema of the abdominal viscera.

Discussion

The mechanism of angioedema associated with ACE inhibitors has not been established, but is likely related to kinin metabolism. ACE is identical to kininase II and degrades bradykinin (5). Ferner et al (6) reported that ACE inhibitors potentiate the effects of intradermal bradykinin in vivo. Bradykinin causes vasodilatation, increases vascular permeability and the release of other vasoactive peptides, and therefore participates in the inflammatory process.

Orfan et al (7) reported cases of angioedema related to ACE inhibitors in patients with a history of idiopathic angioedema. The present case showed no history of angioedema before administration of captopril, but her father had a history of idiopathic angioedema. It was suggested that there might be

another hereditary basis different from C1 INH deficiency. The patients with a history of idiopathic angioedema may be at increased risk for the development of angioedema associated with ACE inhibitors.

Angioedema induced by ACE inhibitors has an estimated incidence of 0.1–0.2% (3,4). It has been reported that angioedema occurs without gender preference or dose-response relationship (3). To our knowledge, angioedema associated with ACE inhibitors has not been reported in Japan, despite the widespread use of ACE inhibitors in this country. This low incidence in Japan may be attributable to racial differences. The angioedema usually occurs with the start of medication (3, 8). Chin and Buchan (9) reported a case that had two separate episodes of angioedema occurring many months apart after long-term use of the ACE inhibitor enarapril. Our case also had episodes of angioedema and abdominal pain with ascites after several months use of captopril. Thus it is important to be aware that angioedema may occur even after the long-term use of an ACE inhibitor.

The common locations of angioedema associated with ACE inhibitors include the lip, tongue, oropharyngeal, and laryngeal tissues (8). Although angioedema of the abdominal viscera commonly occurs in the hereditary form (10), it rarely occurs in association with ACE inhibitors. To our knowledge, angioedema of the abdominal viscera related to ACE inhibitors has not been reported previously. Polger et al (11) reported a rare case of small bowel edema and ascites during the infusion of an iodiated contrast medium. Burghardt and Wernze (12) emphasized the value of abdominal ultrasound imaging for the early diagnosis of hereditary angioedema. Significant findings were fluid distribution on the peritoneal cavity and edematous gastrointestinal wall.

Nafamostat mesilate is a protease-inhibiting agent developed by Fujii and Hitomi (13) in 1981. The biological effect of nafamostat mesilate is inhibition of kinin-kallikrein system activation. Nomura et al (14) reported that the infusion of nafamostat mesilate into a patient with a hereditary angioedema increased the high molecular kininogen level and improved the angioedema. Although the effect of nafamostat mesilate in our case was uncertain, in view of the speculated mechanism of angioedema associated with ACE inhibitors, nafamostat mesilate may be effective in its treatment.

In summary, we report a rare case of angioedema and abdominal pain with ascites probably related to the ACE inhibitor captopril. Angioedema of the abdominal viscera related to ACE inhibitor was suspected as the cause of the abdominal pain with ascites. Recognition of angioedema and abdominal pain occurring after long-term use of an ACE inhibitor is important.

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