Transient recurrent ascites

Nsinire L. Kahegeshe[1], Anna Pestiaux[2], Jean-Paul Henry[2], Jacques van Cauter[2]

(1) Department of Gastroenterology and Hepaticopancreatology, Erasme Hospital, University Clinics of Brussels, Free University of Brussels, Brussels, Belgium ; (2) Department of Gastroenterology, CHU de Charleroi, Free University of Brussels, Brussels, Belgium.

Abstract

Angiotensin-converting enzyme (ACE) inhibitors are widely used in heart diseases.

We describe a case of a young woman treated with fosinopril. She started experiencing abdominal pain, vomiting and diarrhoea with peritoneal signs on physical examination three years after her treatment has been initiated. She presented ascites and signs of ileitis on imaging studies. She even underwent surgery. The diagnosis of ACE inhibitor-induced angiooedema of the small bowel was made after the fourth episode. Fosinopril was stopped and the symptoms never recurred. The case we describe illustrates clinical presentation, radiological findings and difficulty of making an accurate diagnosis in such a patient. (Acta gastroenterol. belg., **2006**, 69, **381-383**).

Clinical case

A 31 years old woman presented to the emergency department in August 2000 with a two day history of severe crampy abdominal pain, nausea, vomiting and diarrhoea. She denied fever. There was no recent travel. She had a past history of hypertension, hyperlipemia, gastric ulcer, gastrooesophageal reflux and urticaria attributed to benzoate after allergic cutaneous tests in 1997. She was at that time treated with metoprolol which was changed to fosinopril. Her treatment at the time of admission was fosinopril and fenofibrate.

On physical examination, her vital signs were normal ; she was afebrile (36.8°C). Tenderness to palpation was localised to the right lower quadrant without guarding. Rebound was present. Blood test revealed mild inflammation with upper limit white cell count (9900/mm^3, normal : 4500-10 000/mm^3) and CRP 4.4 mg/dl (normal less than 1). Liver function tests, renal function and pancreatic enzymes were normal. Antinuclear factor was negative. There were no circulant anticoagulants. Ascites was found on abdominal ultrasound. Abdominal CT scanner showed ascites and thickening of the terminal ileum. The appendix was inflamed.

Appendicectomy was performed. Histology revealed early inflamed appendix. She was free of symptoms four days after surgery.

She presented two similar transient episodes lasting for 3 to 4 days and resolving without any specific treatment.

In June 2001, she had a new attack. Laboratory tests were unremarkable except for CRP of 12.7 mg/dl. Serum complement levels (C1-esterase inhibitor, functional C1-esterase inhibitor, C3, C4) were normal.

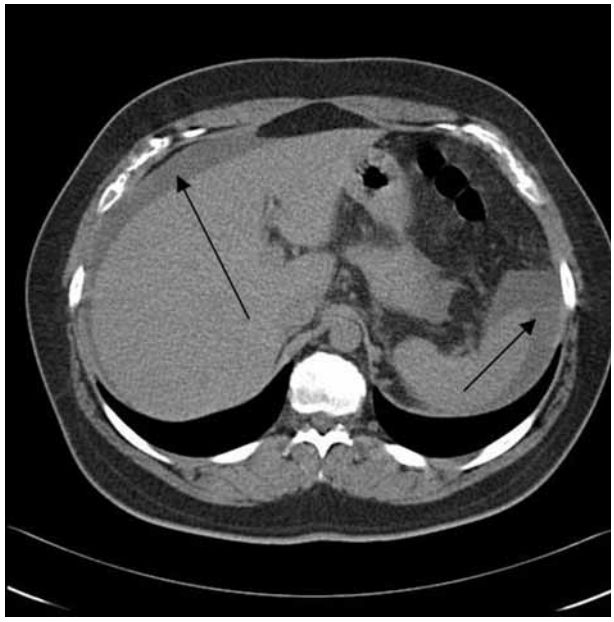

Fig. 1. — Computerized tomography scan of the abdomen demonstrating ascites (arrow).

Abdominal CT scanner was similar to the previous performed before (Fig. 1). Ascites was tapped and was exudates. Cultures were negative. Barium follow through diagnosed ileitis affecting the terminal ileum (Fig. 2). Stool studies for faecal leukocytes, bacterial and viral organisms were negative. Yersinia serology was negative. Upper gastrointestinal endoscopy and colonoscopy were normal. Diagnosis of angiotensin-converting enzyme inhibitor inducing angiooedema of the small bowel was made. Fosinopril was stopped. She was put on a calcium channel blocker (isradipine). The symptoms never recurred again. A small bowel series was performed a few months later and was normal.

Corresponding author : N.L. Kahegeshe, Department of Gastroenterology and Hepaticopancreatology, Erasme Hospital, University Clinics of Brussels, 808 Route de Lennik, 1070 Brussels, Belgium.
E-mail : nkahegeshe@hotmail.com.

Submission date : 04.07.2006
Acceptance date : 21.08.2006

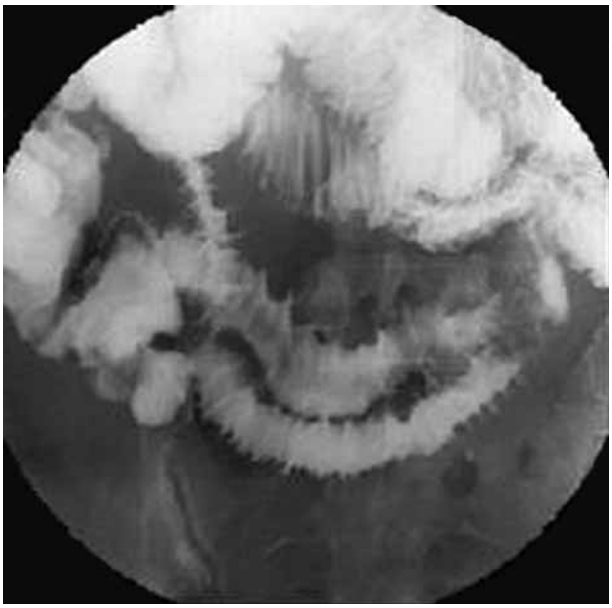

Fig. 2. — Small bowel follow-through demonstrating typical submucosal oedeme narrowing the bowel lumen affecting the terminal ileum.

Discussion

Angiooedema is a non inflammatory disease characterised by capillary permeability with extravasation of intravascular fluid and subsequent oedema of the cutis or mucosa of the upper airways or gastrointestinal tract (1).

Angiooedema is usually due to a defect of the C1 inhibitor (C1 INH) which is either hereditary or acquired. Hereditary angiooedema (HAE) is a genetic disease resulting from a quantitative or functional defect of the C1 inhibitor (C1 INH) (2). It is transmitted in a dominant autosomic manner (2). In 85% of cases, the defect is quantitative (type I) whereas in 15% the level of C1 INH is normal but the mutated protein is not functional (type II) (2).

Acquired C1 INH deficiency is characterised by a normal level in C1-INH but antibodies are synthesized against C1 INH. This type is associated with cryoglobulinemia, lymphoproliferative syndromes and myeloma.

Angiooedema can also be induced by drugs. It may be caused by an immunoglobulin E-mediated allergic reaction, but for the majority of the reactions the pathogenesis remains unclear (3). Those involved are angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin-receptor antagonists, oestrogens, non steroid anti-inflammatory drugs, aspirin (acetylsalicylic acid), bupropion hydrochloride and fibrinolytic agents. Those less involved are calcium channel blockers, amiodarone, metoprolol, psychotropes (risperdone, paroxetine) (3). Among drugs, ACE inhibitors are widely used to treat hypertension and congestive heart failure. It is also use to delay or to prevent the onset of diabetic nephropathy in patients with microalbuminuria. Angiooedema is one of the rare side effects of ACE inhibitors. Its incidence is around 0.1-0.2% (4-6). Patients with inherited or acquired dysfunctional C1 esterase inactivator, lymphoproliferative, neoplastic, and auto-immune diseases may be at increased risk of spontaneous angiooedema from the use of ACE inhibitors (7). Female predominance has been documented in the incidence of ACE inhibitor-induced cough and angiooedema (4,8).

The two major gastrointestinal manifestations of ACE inhibitor adverse effects are angiooedema of the intestine and acute pancreatitis (8). Angiooedema most commonly develops in the first 4 weeks of treatment, but it can be observed later, after several months or even years (9,10). It can recur irregularly while under treatment and some cases of late onset of angiooedema have also been observed weeks after discontinuation of the ACE inhibitors (3).

Clinical manifestations are swelling of the subcutaneous tissues and upper respiratory tract. Pruritus is uncommon. The most commonly reported symptoms of visceral angiooedema include abdominal pain, emesis, and watery diarrhoea (4). Pain does not occur unless the gastrointestinal tract is involved. Leucocytosis is usually present. ACE inhibitor-induced angiooedema is associated with strongly increased plasma levels of CRP (11).

The extravasation of intravascular fluid into peritoneal cavity due to oedema of the intestinal wall could originate ascites (2). Ascites almost always occur and it is usually an exudate.

Recurrent episodes can occur one to twelve times a year. Usually the episode last for 4 days. Sometimes the abdominal complains are given an alternative diagnosis with occasional surgical interventions. The diagnosis is usually delayed. A correct diagnosis depends on a high index of suspicion in patients taking ACE inhibitors (6). Clinicians should be aware of these symptoms to avoid patients undergoing an extensive and expensive negative evaluation. Skin tests and antibody determinations are typically unreliable for the diagnosis (3). Diagnostic criteria are listed in Table 1 (8).

Radiological studies (contrast-enhanced CT and/or ultrasonography) are instrumental in documenting the location and the extend of bowel oedema and ascites and their resolution.

The characteristic radiological findings include segmental thickened bowel wall (small and/or large intestine), narrowed lumen, and prominent and thickened valvulae, often with the presence of ascites (8).

The differential diagnosis includes inflammatory bowel disease, ischemia, vasculitis, infection, mechanical obstruction, lymphoproliferative disease and acquired or hereditary C1 esterase deficiency (4).

The treatment is usually the discontinuation of the offending drug. The symptoms usually resolve without any intervention within 24 to 48 hours after discontinuation (7). The radiological abnormalities also resolve

Table 1. — **Diagnostic criteria for angiotensin-converting enzyme (ACE) inhibitor-induced angiooedema of the intestine**

Use of an ACE inhibitor (irrespective of dose and duration of use)
Non specific abdominal complaint(s) with the presence of bowel oedema (with or without ascites)
Resolution of symptoms and radiological changes following discontinuation of ACE inhibitor
Absence of alternative diagnoses

completely. There is no role for antihistamine or corticosteroids during the acute symptomatic period (3,8).

The case we have illustrated is similar to those previously described in the literature. Our patient had transient severe abdominal pain associated with vomiting and diarrhoea. Laboratory tests showed raised CRP. On imaging she had ascites and signs of extensive ileitis. She was once operated for appendicitis. Her symptoms recurred irregularly while she was on fosinopril. The symptoms only completely resolved once fosinopril was stopped. She is up to now free of symptoms, more than five years later. This case emphasises the fact that clinicians should think about angiooedema of the small bowel in a patient on ACE inhibitor presenting abdominal symptoms such as described above ; the treatment being quite simple by discontinuation of the offending drug.

References

1. DE BACKER A.I., DE SCHEPPER A.M., VANDEVENNE J.E. *et al.* CT of angiooedema of the small bowel. *Am. J. Roet.*, 2001, **176** : 649-652.
2. TALAVERA A., RAMOS J.L., LOPEZ T. *et al.* Hereditary angioedema : an infrequent cause of abdominal pain with ascites. *Am. J. Gastroenterol.*, 1995, **90** : 471-474.
3. AGOSTONI A., CICARDI M. Drug-induced angioedema without urticaria. Incidence, prevention and management. *Drug safety*, 2001, **24** : 599-606.
4. SCHMIDT T.D., MC GRATH K.M. Angiotensin-converting enzyme inhibitor angiooedema of the intestine : a case report and review of the literature. *Am. J. Med. Sci.*, 2002, **324** : 106-108.
5. MATSUMURA M., HARUKI K., KAJINAMI K. Angiooedema likely related of angiotensin converting enzyme inhibitors. *Internal Medicine*, 1993, **32** : 424-426.
6. BYRNE T.J., DOUGLAS D.D., LANDIS M.E. *et al.* Isolated visceral angiooedema : an underdiagnosed complication of ACE inhibitors ? *Mayo Clin. Proc.*, 2000, **75** : 1201-1204.
7. ROSENBERG E.I., MISHRA G., ABDELMALEK M.F. Angiotensin-converting enzyme inhibitor-induced isolated visceral angiooedema in a liver transplant recipient. *Transplantation*, 2003, **75** : 730-732.
8. OUDIT G., GIRGRAH N., ALLARD J. ACE inhibitor-induced angiooedema of the intestine : case report, incidence, pathophysiology, diagnosis and management. *Can. J. Gastroenterol.*, 2001, **15** : 827-832.
9. EROS N., KAROLYI Z., KOZMA L. Angioneurotic edema induced by angiotensin converting enzyme inhibitors. *Orv. Hetil.*, 2001, **142** : 2731-2735.
10. HELLEBRAND M.C., KOJDA G., HOFFMANN T.K. *et al.* Angiooedema due to ACE inhibitors and AT(1)-receptor antagonists. Hautarzt, 2005.
11. BAS M., HOFFMANN T.K., BIER H. *et al.* Increased C-reactive protein in ACE-inhibitor-induced angiooedema. *Br. J. Clin. Pharmacol.*, 2005, **59** : 233-238.