Acute abdomen due to intestinal angioedema induced by ACE inhibitors : not so rare ?

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Abstract

During the last 5 years we identified 7 patients with a history of episodic acute abdominal pain and subobstruction due to intestinal angioedema secondary to the use of Angiotensin Converting Enzyme (ACE) inhibitors. These cases were all diagnosed in one gastroenterology department. This is thereby the largest single centre case series of ACE inhibitor-induced angioedema that has been published until now. Our findings suggest that this syndrome is far more frequent than international literature would let us believe. We also describe one of the first male cases diagnosed with this entity for which there is a significant female predominance. In the presence of an appropriate history and suggestive findings on CT scan, this diagnosis can relatively easily be made if one is sufficiently intent on it. An appropriate diagnosis can save these patients a lot of unnecessary diagnostic procedures and discomfort. (Acta gastroenterol. belg., **2009**, 72, **455-457**).

Introduction

Angiotensin Converting Enzyme (ACE) inhibitors are increasingly used not only as antihypertensive drugs but also for their general cardiovascular protective effects. Angioedema is a well known side effect of these drugs reported to occur in 0.1 to 0.7 percent of patients treated (1,2,3), typically involving the mouth, lips, tongue, larynx, pharynx and subglottis. Intestinal angioedema may also develop but is considered to occur very infrequently. Although we could find only few case reports in the international literature on this subject, we identified 7 cases of ACE inhibitor induced angioedema diagnosed in a period of 5 years in our gastroenterology department (Table 1). Two cases are presented more in detail. Our experience suggests that the incidence of ACE inhibitor-induced intestinal angioedema is probably more common than is usually believed.

Case series

In a period of 5 years we found 7 patients presenting on our gastroenterology unit with episodes of abdominal pain caused by ACE inhibitor induced angioedema. Referring to table 1 for the general characteristics of all 7 cases, the two most remarkable cases will be described in detail below.

The first case is a 42 years old woman with a medical history of arterial hypertension and an ovarian resection. In a period of 1 year and 2 months she presented 3l times to the emergency unit with acute abdominal pain, nausea

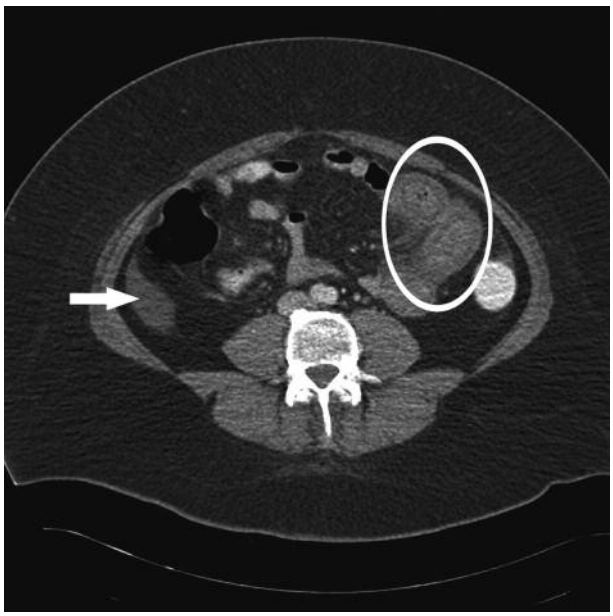

Fig. 1. — CT-scan of the abdomen in the acute phase with a small amount of free abdominal fluid (arrow), wall thickening of a long ileal segment and local edema of the mesenterium.

en diarrhea. Blood tests showed a raised leucocytosis (15,100/mm³) and CRP level (28.4 mg/L). CT scan (Fig. 1) showed an aspecific swelling of the small intestinal wall for which she underwent 3 laparoscopic interventions, each remaining inconclusive. Even an atypical presentation of Crohns ileitis was suggested. With a normal C1 esterase inhibitor and complement level an abdominal attack of hereditary angioedema was excluded. Finally, after 1 year and 2 months of unexplained episodic abdominal pain and diarrhea, the diagnosis of ACE inhibitor-induced angioedema was suggested. After stopping the ACE inhibitor, in this case lisinopril, all complaints disappeared.

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Table 1. — **Summary of all 7 cases collected in our department in a period of 5 years**

	Age	Sex	ACE inhibitor	Symptomatic period before diagnosis	Time lag between first presentation in our department and diagnosis
Patient 1	42	female	Lisinopril	1 year 2 months	1 year and 2 months
Patient 2	51	female	Ramipril	4 years	1 day
Patient 3	67	female	Lisinopril	2 years 6 months	2 days
Patient 4	53	male	Perindopril	1 week	1 day
Patient 5	69	female	Perindopril	1 week	2 days
Patient 6	49	female	Lisinopril	1 year	1 day
Patient 7	39	female	Lisinopril	1 year	1 day

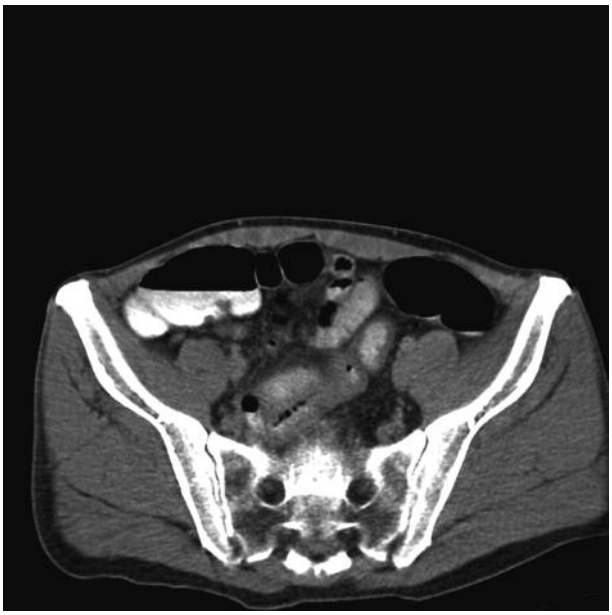

Fig. 2. — CT-scan of the abdomen (with intravenous and oral contrast). During an acute attack of ACE inhibitor induced intestinal angioedema, CT-scan shows circumferential transmural thickening of ileal loops producing a target-like lesion typical of intestinal edema.

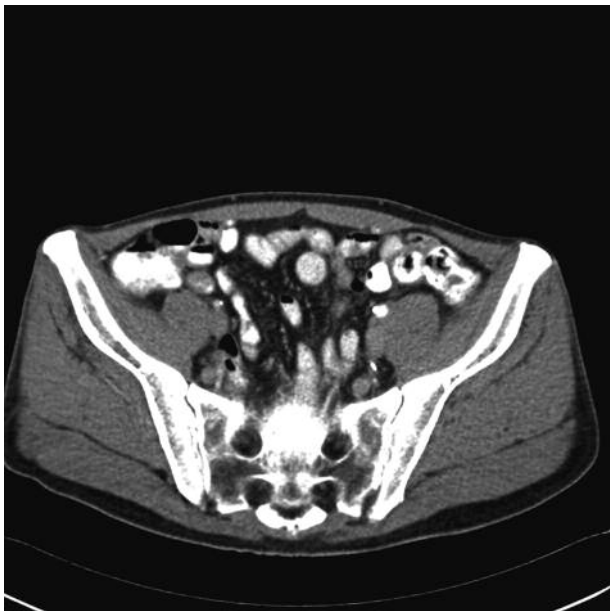

Fig. 3. — CT-scan of the abdomen (with intravenous and oral contrast). Five days after cessation of the ACE inhibitor, CT-scan shows a total resolution of the previous abnormal findings.

The fourth patient is a 53 years old man with a history of arterial hypertension, a knee operation, lactase deficiency and COPD (GOLD III), who presented to our emergency unit with an episodic mesogastric abdominal pain since a few weeks. Abdominal pain was accompanied by episodes of nausea and vomiting. He was on a therapy with bisoprolol-hydrochloorthiazide, cloxazolam, butylhyoscinebromide and was started on perindopril since one month. On clinical examination he had a normal blood pressure, heart rate and temperature, normal cardiopulmonary auscultation and mesogastric tenderness without signs of peritonitis. On abdominal auscultation vivid peristaltic murmurs were heard.

Blood analysis showed a white blood cell count of 11,700/mm³, CRP level being normal as well as plasma lactate. Abdominal X-ray showed some prominent small intestinal loops with unspecific air-fluid levels. An abdominal CT scan was made and showed sub mucosal edema of a long intrapelvic segment of the ileum (Figs. 2 and 3). Because of the temporal link between the start of his complaints and the start of the ACE inhibitor (perindopril) treatment, ACE inhibitor induced angioedema was included in our differential diagnosis. Perindopril was immediately stopped and abdominal pain disappeared. A new CT scan 5 days later showed a total resolution of the ileal wall changes.

Discussion

We present here the largest published single centre case series on ACE inhibitor-induced intestinal angioedema. We presume therefore that this entity is not so rare and that it often remains undiagnosed. Lack of familiarity with the entity can lead to misdiagnosis but also to repeated invasive procedures and unnecessary diagnostic testing in patients with recurrent severe symptoms as is demonstrated by the first case.

ACE inhibitor-induced angioedema is not caused by a mast cell mediated allergic reaction to ACE inhibitors but by an ACE inhibitor induced decrease in vasoconstrictive angiotensin II and an increase in bradykinin causing vasodilatation and increased vascular permeability (1,2,4). This entity appears independently of which ACE inhibitor is taken (Table 1). The time lag between the start of the ACE inhibitor treatment and the start of ACE inhibitor-induced angioedema symptoms is variable. Even though none of our patients had facial or oropharyngeal symptoms, the presence of intestinal angioedema does not preclude other clinical manifestations of angioedema as was illustrated by other case reports (5).

Very remarkable also is the fact that up to now only case reports on female patients have been reported. Although 6 out of 7 of our patients are female, our fourth case describes one of the first male cases of ACE inhibitor induced intestinal angioedema that have been published. Although some authors presume an interaction of oestradiol in the pathogenesis of this disease, the reason for the remarkable female predominance still remains unclear (5). Intestinal angioedema causes quite unspecific episodic periods of diffuse acute abdominal pain or other symptoms such as diarrhea and vomiting (6,7,8). Since there is no specific diagnostic test for ACE-inhibitor induced intestinal angioedema, it is important to think about this entity in all cases of unexplained acute abdominal pain in patients taking ACE inhibitors. Thereby a lot of unnecessary testing can be avoided. This is also illustrated in Table 1 by the striking difference in diagnostic lag between the first case and the more recent ones. The best diagnostic tool is a CT scan of the abdomen in the acute phase with both oral and intravenous contrast. It typically shows marked segmental small bowel wall thickening (target like pattern due to submucosal edema) along with peritoneal fluid, edema and vascular engorgement of the local mesenterium. The list of possible diagnoses based on these radiological findings is rather limited because of the transient and segmental nature of the small bowel edema (9). It includes ischemia, Henoch-Schönlein purpura, intramural bleeding or hereditary angioedema caused by C1-esterase inhibitor deficiency (9,10).

Therapy is very simple and cheap since it only consists of discontinuing the ACE inhibitor treatment and changing it for an adequate alternative. In case of ACE inhibitor-induced cough these drugs can easily be switched to angiotensin receptor blockers. However some data suggest that patients with previous ACE inhibitor induced angioedema (in general) are more prone to develop angioedema on angiotensin receptor blockers too (11). So the latter should only be used if there is no other alternative.

Conclusion

Although the use of ACE inhibitors has been increasing over the last years, ACE inhibitor-induced intestinal angioedema still is rarely diagnosed and probably is underdiagnosed. By reporting on the largest single center case series of this entity, we wanted to illustrate its clinical importance. The diagnosis of intestinal angioedema should be considered in every case of acute abdominal pain of unknown origin in a patient on ACE-inhibitors. A CT-scan in the acute phase is very useful to provide arguments for or against. A timely diagnosis can save these patients a lot of unnecessary discomfort and diagnostic procedures. Although the entity is much more common in women, the diagnosis of ACE inhibitor induced angioedema should also be considered in men.

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