An unusual cause of severe, persistent diarrhoea

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Abstract

We present two cases of patients with severe persistent diarrhoea, in whom duodenal biopsies revealed villous atrophy that could be attributed to the use of olmesartan. The differential diagnosis of villous atrophy without serological markers of celiac disease should include drugs as possible cause, with olmesartan as a recently discovered culprit. Gastroenterologist should be aware of this entity. (Acta gastroenterol. belg., **2017**, 80, **416-418**).

Keywords : diarrhea, coeliac disease, and olmesartan

Introduction

Diarrhoea is a common adverse effect of many drugs, but mostly the underlying mechanism is not understood and damage of the intestinal mucosa is rarely seen. In contrast, spruelike enteropathy is characterised by villous involvement (intestinal villous atrophy, VA), malabsorption and causes severe diarrhoea. Reports of damage to the intestinal villi by drugs have been described with azathioprine, mycophenolate mofetil, methotrexate, neomycin and colchicine (1,2). Recently olmesartan was found to be associated with severe spruelike enteropathy too (3). Olmesartan is an angiotensin-II-receptor antagonist (ARB). Sartans are frequently used as an anti-hypertensive drug, especially when patients suffer from an angiotensin-converting enzyme (ACE)-inhibitor.

Case descriptions

A 72 year old man with a past medical history of acute myocardial infarction and arterial hypertension was admitted with persistent diarrhoea for more than one year. Diarrhoea was worsening the last weeks (up to 15 watery stools daily, neither blood nor mucus) with dehydration and significant weight loss (40 kilos in 15 months). At presentation the patient suffered from orthostatic hypotension and dizziness for which olmesartan (40mg/day) was disrupted. Biochemical analyses revealed a normochromic normocytic anaemia with a slightly reduced renal function (MDRD 79 ml/min/1.73m^2) without electrolyte disturbances. There were no inflammatory parameters. Total protein was 55.7 g/L with normal albumin level. A normal thyroid function was found. No iron-deficiency was observed. Extensive investigations in the past revealed an ulcerative duodenitis with histologically proven

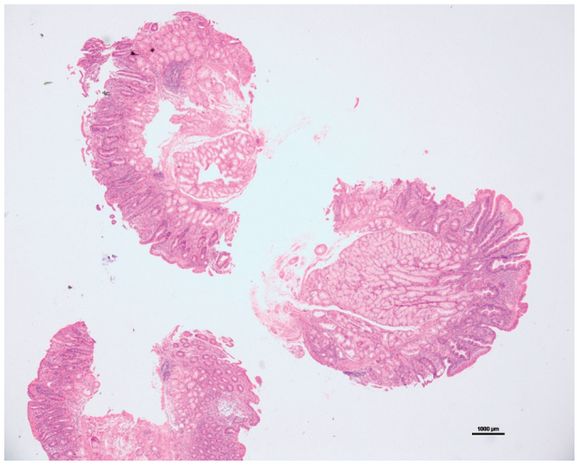

Figure 1. — Villous atrophy while taking olmesartan.

moderate VA and intra-epithelial lymphocytosis (Marsh IIIB), suggesting an underlying celiac disease, however without serological confirmation (normal anti-tissue transglutaminase and anti-endomysium antibodies; no underlying Ig-A deficiency) (Fig. 1). As a lactose-breathing test was positive too, an empiric gluten- and lactose-free diet was started, unfortunately with clinical improvement only temporarily. Reconstruction of the history disclosed that within this period of improvement, therapy with olmesartan was simultaneously dicontinued due to hypotension. Complementary investigations (CT-graphic evaluation of the abdomen, colonoscopy with blind biopsies, empiric therapy with Saccharomyces Boulardii and pancreatic enzymes and dosage of 5-hydroxyindoleacetic acid on a 24hours urine collection) were all negative. Chromogranin-level was raised but the patient took proton-pump inhibitors. Furthermore, endoscopic and radiologic tests showed no signs of a neuroendocrine tumour.

After interrupting antihypertensive therapy with olmesartan during hospitalisation, diarrhoea disappeared within a few days. Macro- and microscopic re-evaluation

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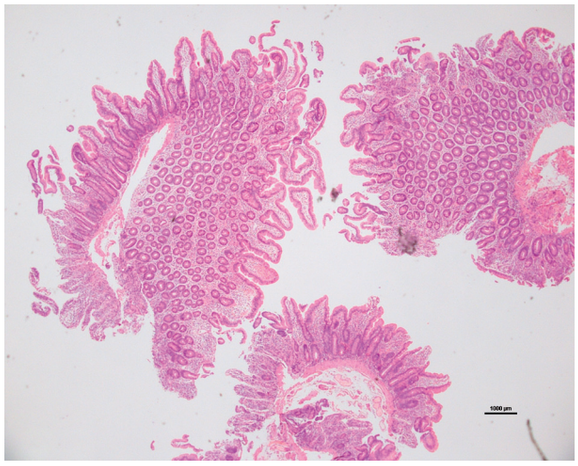

Figure 2. Regenerating villous pattern, 4 weeks after disrupting olmesartan.

four weeks later revealed a regenerating villous pattern (Fig. 2). Four months later the patient gained almost 16 kilos of weight. No diarrhoea was seen anymore, although gluten and lactose were reintroduced into the patients diet. The patient denied any use of olmesartan since the discontinuation during hospitalisation.

The second case involves *a 77 year old woman* who was admitted at the intensive care unit, due to a severe acute renal insufficiency (creatinine 5,61 mg/dl at admission; baseline 1,00mg/dl), because of severe diarrhoea since more than one month. Dialysis was not necessary as renal function recovered soon after aggressive intravenously rehydration. Owing to her renal impairment, the antihypertensive therapy (olmesartan) was interrupted. Biochemical analyses revealed, besides the acute renal insufficiency, severe electrolyte disturbances (Sodium 124.6 mmol/L, Potassium 2.10 mmol/L) and metabolic acidosis ($HCO3^-$ 13,8 mmol/l). There were no inflammatory parameters. Total protein was 60.3 g/L with a normal albumin level. Furthermore a normal thyroid function was found. As the patient made a trip to South Africa five months before, multiple faeces cultures and microscopic analyses for parasites were performed, all were negative. Additional endoscopic investigations were reassuring. Although, the histological examination of the blind duodenal biopsies suggested coeliac disease: the pathologist described VA and intra-epithelial lymphocytosis (Marsh IIIA), however without serological confirmation (normal anti-tissue transglutaminase and anti-endomysium antibodies without IgA-deficiency). Anti-enterocyte and anti-goblet antibodies were not determined. Complementary investigations (CT-graphic evaluation of the abdomen, colonoscopy with blind biopsies) were all negative. Though this patient was taken olmesartan for a couple of years, after interrupting this drug, diarrhoea disappeared almost immediately and all microscopic findings (suggesting coeliac disease) vanished even without following a glutenfree diet.

Discussion

A variety of pathologies can explain a VA in the absence of a positive celiac serology : common variable immunodeficiency, autoimmune enteropathy, small intestinal bacterial overgrowth, infection, intestinal lymphoma, collagenous sprue, Crohn's disease, tropical sprue and drugs. In an observational study of a tertiary centre with patients with VA on biopsy with negative celiac serologies, 26% of the patients suffered from a drug-related VA (2).

Although the causality between the intake of olmesartan and development of spruelike enteropathy has not been proven so far, growing evidence – based on observational studies and case reports – supports a clear association (3,6). Since the publication by Rubio-Tapia *et al.* of a series of 22 patients suffering from unexplained chronic diarrhoea and enteropathy while taking olmesartan, many other reports have been published (2,3,6-13).

The long delay – mean duration in the series of the Mayo Clinic was 3.1 years (3) – between the initiation of olmesartan and the onset of diarrhoea (and enteropathy), makes a type I hypersensitivity reaction less likely. Presumably a cell-mediated immunity process is involved. VA in the olmesartan enteropathy might be the result of a pro-apoptotic effect of angiotensin II on intestinal epithelial cells. Angiotensin II binds to two receptor forms, called AT1 and AT2. AT1 is expressed throughout the whole gastrointestinal tract, while the AT2 is expressed only in the duodenum and jejunum (13,14). Angiotensin II promotes apoptosis of enterocytes through binding to AT2 (13,16). Olmesartan shows high affinity for AT1. In case of AT1 receptor saturation by olmesartan, circulating angiotensin II could bind only AT2, with a consequently pro-apoptotic effect. Apoptosis of enterocytes may ultimately lead to VA without inflammatory reaction and increase intra-epithelial lymphocytes (13).

Recent observations by Marietta et al. might explain the shared features between coeliac disease and olmesartan induced enteropathy. They observed that many of the mechanistic pathways (an increased number of CD8+ lymphocytes and corresponding overexpression of interleukin 15 (IL-15)) in the innate immune responses to gliadin in coeliac disease are similar to those present in the olmesartan enteropathy pathogenesis. On hypothesis is that these patients in certain circumstances are unable to down-regulate the IL-15 expression induced by olmesartan and therefore later developed enteropathy (17).

In our cases the recovery of the duodenal mucosa (both endo- and microscopic) took place quite soon (i.e. one month) after discontinuation of olmesartan. Other groups reported the same observation, unlike series of patients with celiac disease in which it may take years before recovery of duodenal mucosa is seen despite adherence to a gluten-free diet (3).

Olmesartan associated enteropathy is a very serious, possibly life-threatening phenomenon but the incidence is fortunately very rare. In a large randomized controlled trial comparing olmesartan and placebo in diabetic patients (the Randomized Olmesartan Medoxomil And Diabetes Microalbuminuria Prevention, ROADMAP) no association between olmesartan and gastrointestinal side effects could be noticed (18, 19). Furthermore, a retrospective analysis at the Mayo Clinic concluded that neither olmesartan nor other ARBs were associated with diarrhoea among patients undergoing endoscopy (20). Although, a recent French nationwide observational cohort study demonstrated that olmesartan is associated with an increased risk of hospitalisation for coeliac disease and intestinal malabsorption (6).

So far there is only one case report about other ARBs associated with villous enteropathy (1,21). Therefore the United States Food and Drug Administration (FDA) changed the label of olmesartan alone and not for the whole group of ARBs. The FDA warned that olmesartan can cause intestinal problems including severe, chronic diarrhoea with substantial weight loss, months to years after starting olmesartan (22).

Conclusion

We present two cases of patients with severe persistent diarrhoea, in whom duodenal biopsies revealed villous atrophy that could be attributed to the use of olmesartan. The differential diagnosis of villous atrophy without serological markers of celiac disease should include drugs as possible cause, with olmesartan as a recently discovered culprit. Gastroenterologist should be aware of this entity.

Conflicts of interest

The authors declare to have no conflict of interests.

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