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A Rare Case of Synchronous Severe Duodenal Ulcers and Acute Colitis in Sartan-Induced Enteropathy: A Case Report and Review of Literature

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ABSTRACT

Sartan induced sprue-like enteropathy (SIE) was initially reported as a side effect of chronic Olmesartan use in 2012 and is characterized by chronic diarrhoea and weight loss. The diagnosis is often difficult and requires ruling out of other causes of enteropathy including infectious gastroenteritis, autoimmune enteropathy and celiac disease.

A 51 – year – old Caucasian male was admitted to our hospital because of chronic non-bloody diarrhoea associated with severe acute renal failure and electrolyte imbalances. His medical history was only positive for hypertension for which he was on Olmesartan Medoxomil and Lacidipine, both of which were discontinued due to hypotension at admittance. Stool cultures and search for C. Difficile toxin resulted negative, whilst a Colonscopy showed endoscopic and histological signs of aspecific acute colitis. After having responded to i.v. hydration with normalization of the renal function the patient was discharged home with the same medications he was on before admittance. His diarrhoea relapsed and he was readmitted shortly afterwards with acute renal failure and electrolyte imbalances; the anti-hypertensive medications were again discontinued. After having excluded all other causes of diarrohea, including celiac disease and HIV, Sartan – induced enteropathy (SIE) was suspected and then confirmed with an esophagogastroduodenoscopy which revealed a severe erosive duodenitis with multiple duodenal ulcers. The patient again responded to i.v. hydration with normalization of the renal function and Olmesartan was held also at discharge without further relapse of the symptoms.

SIE is a rare cause of chronic diarrhoea, weight loss and possible severe renal failure. It could affect the whole gastrointestinal tract and in cases of unexplained non-bloody diarrhea, suspecting SIE is fundamental and should be considered in the differential diagnosis. Discontinuation of the drug is generally sufficient for symptom resolution: in suspected cases with a positive medical history for chronic angiotensin receptor blocker (ARB) use, stopping the drug ex-juvantibus should be undertaken. Further research on the immunopathological mechanisms and how to recognize patients at higher risk of developing this condition is deemed necessary.

KEYWORDS: Olmesartan, Entheropathy, Chronic Diarrhoea.

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INTRODUCTION

Olmesartan is an antihypertensive angiotensin-receptor blocker belonging to the Sartan family (ARB) and originally approved by the U.S. Food and Drug Administration (FDA) in 2002. Sartan induced sprue-like enteropathy (SIE) was

Initially reported as a side effect of chronic Olmesartan use in 2012 and is characterized by chronic diarrhea and weight loss. The diagnosis is often difficult and requires ruling out of other causes of enteropathy including infectious gastroenteritis, autoimmune enteropathy and celiac disease. Therefore, a careful medical history could reduce unnecessary invasive tests and procedures.

CASE REPORT

A 51-year-old Caucasian male was admitted to our hospital because of severe diarrhoea associated with abdominal pain, both arisen 20 days prior to admittance, and weight loss (about 4Kg). He referred a maximum of 15 loose stool evacuations per day which were described as being liquid and greenish in colour; no macroscopic blood had ever been observed.

He was an active smoker of 1 pack/day of cigarettes and had a past medical history of hypertension for which he was on Lacidipine 4 mg/day and Olmesartan 20 mg/day. He had had neither nausea, vomiting, nor fever in the preceding days. He also denied any assumption of contaminated or raw food. He had empirically been treated with rifaximin from his family doctor with no improvement of symptoms.

At the emergency department, blood tests revealed severe volume depletion with acute renal failure (creatinine 7.36 mg/dL) and hypokalaemia (K+ 2.52mmol/L) associated with mild elevation of inflammatory markers. The antihypertensive drugs were discontinued because of hypotension and renal failure. The abdominal ultrasound (US) did not show any pathological alterations.

He was therefore admitted to our ward where he was initiated on metronidazole and i.v. hydration. Stool cultures and *Clostridium difficile* toxin search both resulted negative. The patient underwent a colonoscopy which revealed hyperaemia of the sigma; the latter was biopsied and the histologic specimen revealed a non-specific acute colitis.

The diarrhoea gradually resolved, the renal function normalized and the patient was discharged. The antihypertensive therapy was restored to that used before admittance: Lacidipine 4 mg/day and Olmesartan 20 mg/day.

Three days later, the patient was re-admitted to our ward because of a relapse of the diarrhoea, this time associated with nausea and vomiting. At admission, blood tests showed metabolic acidosis, acute renal failure, severe hypokalemia (and mild elevation of inflammatory markers.

The patient was empirically treated with piperacillin/tazobactam, metronidazole and cholestyramine in association with i.v. hydration and electrolyte supplementation. The patient again underwent an abdominal US which was normal. The cause of the diarrhoea was further studied: tissue transglutaminase IgA antibody testing was negative for celiac disease; HIV1/2 test and blood cultures were negative; bacterial stool cultures and stool *Clostridium difficile* toxin search were repeated and again resulted negative. Olmesartan-associated sprue was finally suspected so an esophagogastroduodenoscopy was undertaken and revealed reflux esophagitis and multiple fibrinous duodenal ulcers which were biopsied. The histologic finding was indicative of an acute erosive duodenitis with normal levels of intra-epithelial T-cell CD3 infiltrate, compatible with Olmesartan-induced enteropathy; collaterally also a mild non atrophic chronic gastritis (*H. Pylori* negative) was revealed.

With hydration the patient's renal function normalized again and the patient was discharged after complete resolution of symptoms. Olmesartan was held also at discharge and the calcium-channel blocker was confirmed as the only antihypertensive treatment; a proton-pump inhibitor was also prescribed and a follow-up gastroenterological visit was programmed

DISCUSSION

Sartan-induced enteropathy (SIE) is a rare drug-induced sprue-like enteropathy which has been mostly associated with the use of Olmesartan Medoxomil, an Angiotensin receptor Blocker, and seems to affect 3-147/100.000 patient-years (1); the actual incidence, though, might be underestimated due to the fact it goes easily unrecognized.

Most instances occur after years of chronic use of the drug, such as in our case. Indeed, differently from other Sartans, Olmesartan is a prodrug and is initially combined to the Medoxomil molecule. The selective role of Olmesartan could therefore be associated to the conversion to active drug in the intestine and its longer half-life (2). However, other sartans (Valsartan, Telmisartan, Irbesartan and Eprosartan) have sporadically been associated with cases of SIE, despite them being much rarer and only described in a few case reports (3; 4; 5). This suggests that SIE could be extended to the whole class of drugs rather than to Olmesartan alone. On the other hand, the only other Sartan combined with the Medoxomil molecule, Azilsartan (approved by the FDA in 2011), has not yet been associated with SIE even if this could be explained by the infrequent use of this specific drug (6). Moreover, many large observational cohort studies have not demonstrated and increased risk of intestinal malabsorption by the simple assumption of ARBs, including Olmesartan itself.

SIE was first described by Rubio-Tapia et al. in 2012 (7) and is characterized by non-bloody diarrhoea, nausea and weight loss; non typical symptoms such as severe dehydration, acute renal failure and acute hepatic injury have been described (8; 2). Having a clinical suspect is essential for diagnosis and SIE should be considered in all case of chronic unexplained diarrhoea. Differential diagnosis includes autoimmune enteropathy, common variable immune deficiency, bacterial overgrowth and celiac disease (9). Indeed, serologic testing for the latter condition is useful to distinguish the two entities. Though some patients with celiac disease may test seronegative, no patient with SIE has until now been tested seropositive (10).

Necessary for diagnosis is also the endoscopic evidence of enteropathy, with or without collagen deposition or intraepithelial lymphocytosis (11). Indeed, common endoscopic findings include villous atrophy, mucosal nodularity and ulceration. Microscopically duodenal biopsies

show villous blunting, increased intraepithelial lymphocytes and subepithelial collagen thickening (22% of cases). However other parts of the gastrointestinal tract may be involved and Colon biopsies may also show the same findings (9). Similarly to our example, there have been cases of severe duodenal ulcers associated with duodenitis and colitis. It is still unknown whether such findings could be found in patients on ARBs before the onset of diarrhoea (12).

Despite the fact the actual mechanism with which Olmesartan elicits the inflammatory response which causes SIE is still mostly unknown, it seems safe to say that the long period between the start of the ARB and the onset of diarrhea is probably due to cell-mediated immunity rather that to hypersensitivity (11). Moreover, a 2015 study by Marietta E.V. et al showed a series of interesting findings which could help better understand this disease. Firstly, the lymphocytic infiltration of the small bowel was characterized by a significant increase in T CD8+ cells with no change in the CD4+ cells; this was also associated with an increase in granzyme B+ cells, is very similar to what happens in celiac disease and is linked with the destruction of the epithelium. Similarly, upregulation in IL15R associated with a normal TGFβ signalling pathway suggest a loss of regulation of inflammation. Finally, direct treatment of Caco-2 cells (used as a model of the intestinal epithelium barrier) with Olmesartan acid show clear disruption of the zonula-occludens 1 in intestinal epithelial cells and independently increase IL15 expression; though this was not found when treated with Losartan or Telmisartan (6).

Discontinuation of the drug is generally the only needed therapeutic action; it is indicated that the complete regeneration of the intestinal mucosa should be expected between 3 and 12 months (5; 11). Nonetheless, since SIE is frequently diagnosed late some patients with severe symptoms may benefit from steroid treatment. Specifically, budesonide has been shown to have a rapid and positive effect on the healing of the mucosa due to its potent anti-inflammatory and immunosuppressive effects (13).

Finally, we support the provoking thought of Zimmer V. et al: despite the fact new European guidelines for microscopic colitis (MC) have been recently published (2020) and in which medication-induced MC has been amply discussed, no specific mention of SIE as relevant in the differential diagnosis of idiopathic MC has been made (14).

CONCLUSION

SIE is a rare cause of chronic diarrhoea, weight loss and possible severe renal failure. It could affect the whole gastrointestinal tract and in cases of unexplained non-bloody diarrhea, suspecting SIE is fundamental and should be considered in the differential diagnosis. Despite the fact the FDA had already added a gastrointestinal warning to Olmesartan in particular in 2013 (1), the newest guidelines still don't specifically acknowledge SIE, making it more difficult for physicians to be aware of this entity. Discontinuation of the drug is generally sufficient for symptom resolution: in suspected cases with a positive medical history for chronic ARB use, stopping the drug *ex-juvantibus* should be undertaken. Further research on the immunopathological mechanisms and how to recognize patients at higher risk of developing this condition is deemed necessary.

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