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IM - CASE RECORD

A simple treatment for a potentially life-threatening cause of malabsorption

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Case presentation

Dr. Solbiati: a 60 year-old man presented to our emergency department (ED) for abdominal pain, diarrhea, and vomiting. He reported a 1-year history of multiple bowel movements per day without evacuation of blood or mucous. Symptoms were not exacerbated by meals nor associated with abdominal pain. He had no fever and had a negative travel history. Since the onset of symptoms, he reported significant weight loss (about 25 kg). In the past few days, the number of daily liquid stools progressively worsened (up to 5–6 per day), and he started experiencing vomiting.

He had been repeatedly evaluated by his primary care physician and had undergone some investigations as an outpatient. Laboratory tests showed negative stool cultures, slightly elevated fecal calprotectin and subclinical hypothyroidism with positive thyroid peroxidase and thyroglobulin antibodies. An abdominal ultrasound revealed gallstones, while a colonoscopy was positive for diffuse colonic diverticulosis without mucosal abnormalities. An ex-adjuvantibus therapy with rifaximin was attempted, without benefit.

A few days before admission, an esophagogastroduodenoscopy (EGD) was performed showing petechial gastritis and chronic duodenitis. The histopathology was remarkable for chronic moderate gastritis, severe atrophic duodenal mucosa with a slight increase of the intraepithelial lymphocytes (IELs), and chronic active inflammation of the lamina propria.

He was advised to start proton-pump inhibitor treatment, and to obtain a gastrin level measurement, that was normal.

His past medical history was positive for arterial hypertension, for which he was on chronic treatment with an angiotensin II receptor blocker (ARB) and calcium channel blockers for the past several years. His family history was unremarkable.

Dr. Bonzi: while waiting to be evaluated in the ED, he experienced a syncopal episode in orthostatic position. On admission, he was hypotensive and tachycardic (BP 75/40 mmHg and HR 110 beats per min). Except for signs of dehydration, his physical examination was unremarkable. The electrocardiogram showed sinus tachycardia without other abnormalities. Blood tests revealed renal insufficiency (creatinine 3.5 mg/dl, urea 176 mg/dl), mild hypokalemia, hypocalcemia, and hypomagnesemia, while C-reactive protein was only slightly elevated. Venous blood gas analysis showed severe metabolic acidosis without hyperlactacidemia (pH 7.12, HCO3− 9.8 mmol/l, lactate 0.6 mmol/l). Abdominal X-ray findings were unremarkable. Focused abdominal ultrasound revealed a completely collapsing inferior vena cava suggesting low central venous pressure without adjunctive pathological findings.

He was started on parenteral hydration with crystalloids, electrolyte, and bicarbonate supplementation, and was admitted to our internal medicine ward after vitals stabilization.

Further investigations and differential diagnoses

Dr. Bonzi: on the ward, admission vital signs were normal, blood tests revealed an initial improvement of renal function, normal electrolytes and acid–base balance, severe hypoalbuminemia, folate and vitamin D deficiency, spontaneous increase in prothrombin time (international normalized ratio 2.4), and mild normochromic normocytic anemia.

Dr. Solbiati: the clinical picture was suggestive of severe intestinal malabsorption. Considering EGD findings (severe

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atrophic duodenal mucosa with slight increase of IELs), a diagnosis of celiac disease (CD) was considered.

Dr. Bonzi: both serology for tissue transglutaminase (both IgA and IgG) and total IgA level were normal. Screening for human leukocyte antigen (HLA)-DQ2 was positive, while HLA-DQ8 was negative.

Dr. Fiorelli: considering the assessments' results, a diagnosis of seronegative CD may be hypothesized. Histopathologic findings are also compatible with tropical sprue, but the negative travel history makes this hypothesis very unlikely. An intestinal lymphoma may be reasonably excluded due to the absence of aberrant or clonal expansion of intraepithelial lymphocytes. HIV enteropathy is excluded by negative serology (Table 1).

Dr. Montanelli: another uncommon cause of severe villous atrophy with negative CD serology is medication-associated enteropathy (i.e., olmesartan, mycophenolate mofetil, methotrexate, and azathioprine).

Dr. Furlan: after reassessing the medical history, it emerged that there had been a long-time (several years) therapy with a combination of olmesartan/amlodipine 40/5 mg once daily, which was interrupted at time of hospital admission due to severe hypotension and acute kidney injury.

Dr. Solbiati: considering the aforementioned tests' results, the most probable diagnoses are, at this point, seronegative CD or an olmesartan-associated sprue-like enteropathy. Nevertheless, these conditions share common clinical, histopathologic, and laboratory features, and can be differentiated only evaluating the response to a gluten-free diet (GFD). The absence of HLA DQ2/DQ8 is a further element which reasonably excludes CD.

Dr. Bonzi: considering the severity of initial presentation, we should start an ex-adjuvantibus therapy for both conditions: GFD and olmesartan definitive withholding.

The patient was discharged home after 7 days with a great improvement in bowel movements (two bowel movements per day, Bristol type 6) and normal blood tests.

At 30-day ambulatory follow-up, the patient reported a complete normalization of the stools, and weight gain. Therefore, GFD was interrupted and a free diet was suggested. After 2 months of free diet, the patient was still doing well, bowel movements were normal, and a further weight gain was observed. An EGD was repeated showing a normal mucosal macroscopic aspect, and a significant regression of histopathologic abnormalities.

A conclusive diagnosis of olmesartan-associated sprue-like enteropathy was made.

Discussion

Dr. Bonzi: olmesartan-associated sprue-like enteropathy is a rare but potentially serious complication of an extensively used drug, even though the incidence is still unclear. This complication appears to be an olmesartan-specific rather than a drug-class effect; isolated cases of enteropathy associated with other ARBs (i.e., valsartan, irbesartan, telmisartan and losartan) have been reported [1–3]. In 2012, Rubio-Tapia et al. published a case series of 22 patients with olmesartan-associated enteropathy [4]. This led the FDA to release a warning in July 2013 to underline the correlation between olmesartan use and gastrointestinal symptoms such as chronic diarrhea and weight loss [5]. Since then, many case reports, case series, and two systematic reviews have been published [6–11]. The most reported symptoms are diarrhea and weight loss. Other common symptoms are fatigue, nausea and vomiting, abdominal pain, and bloating. Normocytic normochromic anemia and hypoalbuminemia are the most frequent laboratory abnormalities; CD serology is completely negative. The prevalence of HLA DQ2/DQ8, commonly associated with CD, is higher among patients with olmesartan-associated sprue-like enteropathy than in the general population (68% vs. 25–30%) [4, 12].

Dr. Fiorelli: the most common macroscopic characteristic at upper endoscopy is a variable degree of mucosal atrophy [4, 11]. There are no pathognomonic histopathologic features of olmesartan-associated enteropathy, since most of them are in common with other clinical conditions. Variable degrees of villous atrophy are the most common finding, followed by increased IELs. Some patients may have an increased subepithelial collagen layer, a feature typical of collagenous sprue, and a rare complication of CD [4, 13]. The severity of histopathologic presentation is extremely variable, and this may determine a heterogeneous clinical spectrum (ranging from isolated histopathological finding to severe malabsorption syndrome).

Dr. Montanelli: olmesartan-associated sprue-like enteropathy's mechanism is not well understood; however, a cell-mediated immunity damage seems to be involved. Indeed, Marietta et al. observed an overexpression of CD8+ cells in duodenal biopsies of patients with olmesartan-associated enteropathy [14]. The hypothesis that olmesartan-associated enteropathy may be mediated by a cell-mediated immunity damage rather than type I hypersensitivity is also supported by the long latency before the onset of symptoms (generally years) [15]. Epithelium destruction might also be regulated by angiotensin II; indeed, angiotensin II binds to two different receptors, AT1 receptors, which are expressed throughout the entire alimentary tract, and AT2 receptors, which are

Table 1 Differential diagnoses of malabsorption with endoscopic and histological findings of villous atrophy

	Prevalence	Clinical presentation	Genetic test	Laboratory abnormalities	Endoscopic appearance	Histopathology	Treatment
Celiac disease	1:70–1:300	Diarrhea Weight loss Malabsorption	HLA-DQ2/DQ8 (> 99%)	Anemia Findings of malabsorption Typical serology	Flattening of duodenal folds and "scalloping" Nodular mucosa	Villous atrophy Increased IEL Enhanced epithelial apoptosis Crypt hyperplasia	Gluten-free diet
Olmesartan-associated enteropathy	NA	Diarrhea Weight loss Nausea/vomiting Abdominal pain Malabsorption	HLA-DQ2/DQ8 (68%)	Normocytic normochromic anemia Hypoalbuminemia Negative CD serology	Mucosal atrophy	Villous atrophy Increased IEL Enhanced epithelial apoptosis Crypt hyperplasia Increased sub epithelial collagen layer	Olmesartan withholding Rarely: steroids, immunosuppressive drugs
Zollinger–Ellison	1–9:100,000	Abdominal pain Diarrhea Malabsorption Nausea/vomiting Weight loss	MEN1 11q13 (when MEN1-associated)	Increased serum gastrin level Positive secretive stimulating test	Peptic ulcer Prominent gastric folds	Hyperplasia of parietal cells in fundic glands Normal antral glands	Proton-pump inhibitors Surgery (not in MEN 1) Radiotherapy for non-surgical candidates
Tropical sprue	NA	Not defined Endemic in tropical areas (narrow band north and south of the equator to 30° latitude) Visitors of tropical areas for more than 1 month	HLA DQ2/DQ8 negative	Megaloblastic anemia Severe folate and vitamin B12 deficiency Negative CD serology	Flattening of duodenal folds and "scalloping"	Shortened or blunted villi Mild lymphocytic and eosinophils infiltration Elongated crypts	Spontaneous recovery Tetracycline and folate supplementation (outstanding response to folate therapy)
Intestinal lymphoma	NA	Abdominal pain Diarrhea Weight loss	NA	Findings of malabsorption Positive CD serology in CD-associated intestinal lymphoma	Small nodular mucosa Polypoid tumours Large circumferential ulcers Adjacent mucosa: numerous IEL, eosinophils, macrophages; villous and crypt atrophy	Villous atrophy Anaplastic cells Clonal abnormalities	Chemotherapy
Eosinophilic gastroenteritis	22–28:100,000	Abdominal pain Nausea/vomiting Diarrhea Early satiety Allergic manifestations: asthma, eczema, rhinitis	NA	Findings of malabsorption Eosinophilia (80%)	Nodular mucosa Polypoid gastric mucosa Erythema, erosions	Increased number of eosinophils (no defined cutoff)	Elemental diet Glucocorticoids

Table 1 (continued)

	Prevalence	Clinical presentation	Genetic test	Laboratory abnormalities	Endoscopic appearance	Histopathology	Treatment
Whipple disease	NA	Arthralgia Weight loss Diarrhea Abdominal pain Fever Possible cardiac, neurological, mucocutaneous and lymph nodal involvement	NA	Findings of malabsorption	Pale, yellow, shaggy mucosa alternating with eroded erythematous or mildly friable mucosa of duodenum and jejunum	Villous atrophy Extensive PAS positive material in the lamina propria Positive PCR for *Tropheryma whipplei* on histologic specimen	Ceftriaxone followed by trimethoprim-sulfamethoxazole for 1 year

MEN-1 multiple endocrine neoplasia type 1 characterized by parathyroid tumours, pituitary adenomas, and pancreatic islet cell/gastrointestinal tumours (i.e., gastrinoma), *IEL* intraepithelial lymphocytes, *CD* celiac disease, *NA* not applicable

more expressed in the duodenum and jejunum. These two receptors mediate different effects, and intestinal epithelium apoptosis seems to be promoted by AT2 receptors through an up-regulation of pro-apoptotic proteins and down-regulation of anti-apoptotic proteins [16]. It is well known that ARBs have a higher affinity for AT1 receptors, and drug-induced AT1 receptors saturation may favor the binding of angiotensin II to AT2 receptors, thus promoting apoptosis.

Dr. Furlan: patients with olmesartan-associated enteropathy do not benefit from GFD, but generally have an outstanding response to drug suspension both in terms of clinical improvement and histopathologic abnormalities regression [17]. There are only rare cases in which immunosuppressive therapy with steroid or other immunosuppressive agents are necessary [4, 6, 7].

There are also a few cases in which a re-challenge test determined symptoms exacerbation [6]. Considering the severity of presentation, we decided not to perform an olmesartan re-challenge test, while a free-diet re-challenge did not determine new symptoms onset, supporting the hypothesis that seronegative CD does not seem to be a plausible diagnosis.

Conclusions

Dr. Solbiati: olmesartan-associated enteropathy is a rare but potentially severe disease caused by a commonly used drug. Its presentation resembles a much more common condition: celiac disease. There are no clinical, laboratories nor histopathologic features that allow the distinction of these entities, but their treatment is extremely different. This highlights the importance of anamnesis in the diagnostic and therapeutic work-up.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with human and animals performed by any of the authors.

Informed consent None.

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