Olmesartan-associated enteropathy. A rare but easily treatable entity

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To the Editor,

A 76-year old woman, with a history of atrial fibrillation, hypertension and hypothyroidism, was referred to our clinic due to a 6-month history of severe diarrhea (7-8 watery stools per day and weight loss of about 30kg). She also complained of intense pruritus in the past 3 months. She reported an unsuccessful trial of empirical treatment for scabies and inadequate response to oral antihistamines. At presentation, a widespread maculopapular rash with scabs was noted. Previous evaluation included a colonoscopy and esophagogastroduodenoscopy (without biopsies), an abdominal CT and MRI and an endoscopic ultrasound without significant findings.

Laboratory tests at presentation revealed leukocytopenia, normocytic normochromic anemia, low serum protein and albumin, hypokalemia, and low Vitamin D. The rest of the lab tests were normal. Further workup during her hospital stay included : negative stool investigations (culture, parasitology and C. difficile toxin), negative HIV serology, normal blood smear examination and peripheral blood immunophenotyping, normal serum and urine protein electrophoresis and immunofixation, antinuclear antibodies titer 1:160, anti-smooth muscle antibodies titer 1:80, negative anti-mitochondrial antibodies, negative anti-parietal cell antibodies, normal IgG, IgA and IgM levels and negative celiac serology (anti-endomysial antibodies, and anti-tissue transglutaminase IgG and IgA).

A repeat upper endoscopy was performed this time with biopsies. Biopsies from the duodenum revealed moderate to severe villous atrophy (Fig. 1). Stomach biopsies demonstrated lymphocytic gastritis, a small tubular adenoma and H. Pylori. A skin biopsy is depicted in Figure 2.

Interestingly, the patient's diarrhea had already significantly improved at admission to our clinic without any intervention. Incidentally, a few days before, olmesartan/amlodipine (which the patient had been taking for about 2 years) was discontinued and switched to ramipril 2.5mg due to low blood pressure. At follow-up at 2 weeks, and while on an unrestricted diet, diarrhea had completely resolved and she had already gained 5 kg. A short course

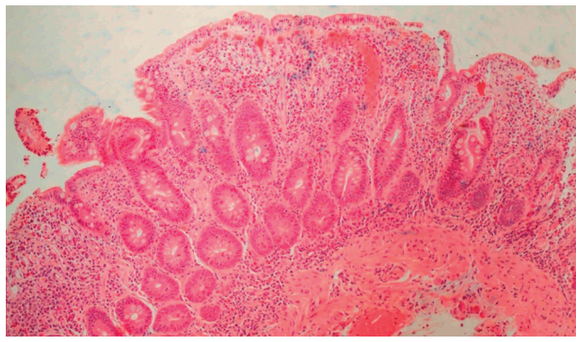

Fig. 1. — Microscopic view from duodenal biopsy showing moderate and severe villous blunting, a marked increase of intraepithelial lymphocytes, hypertrophic cysts and a moderate lymphoplasmacytic infiltrate in the lamina propria with eosinophils (H&E stain, x20).

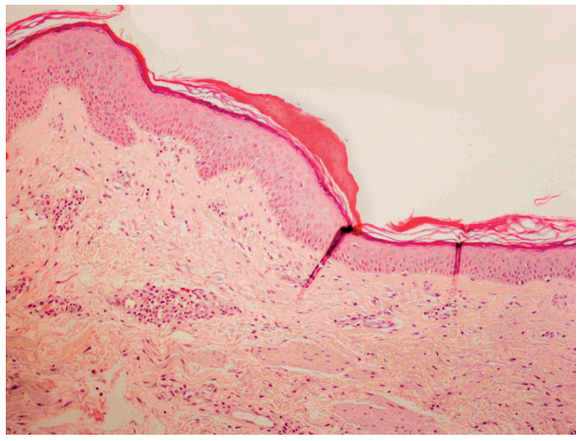

Fig. 2. — Microscopic view from a skin lesion biopsy, showing a moderate lymphohistiocytic, mostly perivascular infiltrate with eosinophils and focal parakeratosis and hyperkeratosis of the epidermis (H&E stain, x20).

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Table 1. — **Review of case series of olmesartan-associated enteropathy**

	Patient characteristics	Clinical characteristics	Olmesartan dose and duration	Lab tests	Treatment
Rubio-Tapia	22 patients,	median weight	Most common dose	Negative IgA TTG and IgA	Olmesartan cessation.
et al. (1)	13 women,	loss 18kg (2.5-	40mg/day	endomysial, anti-enterocyte	Multiple failed treatment
	median age	57kg), median	(range 10-40mg/day)	antibodies positive in 3 of 19,	trials: gluten free diet
	69.5 (47-81),	duration of	Mean duration 3.1	HLA-DQ2 (n=15),	(n=20), systemic
		symptoms	years before symptoms	HLA-DQ8 (n=2),	corticosteroids (n=20),
		19.2 months	onset (range. 0.5-7 years)	64% normocytic	opioid-derived antidiarrheal
		(3-53), median		anemia, 45%	agents (n=10), pancreatic
		of 6 evacuations		hypoalbuminemia,	enzymes (n=4), bile acid
		per day (3-42),		55% electrolyte abnormalities,	sequestrant (n=4),
		14 required			metronidazole (n=4),
		hospitalization			azathioprine (n=3),
					octreotide (n=3)
Marthey	36 patients,	Body weight	Median	Celiac serology	Olmesartan cessation
et al. (2)	20 women,	loss 18% (0-	dose 40mg/day	negative, 11 of 18	
	median age 70	48%), Median	(range 10-60),	HLA-DQ2 or DQ8	
	(46-91)	8 evacuations	Median duration	positive, ANA	
		per day (2-20)	28 months (2-139)	positive in 9 of 11,	
				anti-enterocyte	
				antibodies were negative	
DeGaetani	16 patients, 8	Not reported	Not reported	Negative celiac	Olmesartan cessation
et al. (3)	women,			serology, 12 of 16	resulted in cure.
	median age 67			HLA-DQ2 or DQ8	Symptomatic improvement
	(52-83)			positive	with immunossupressive
					treatment. Failed gluten-
					free diet (n=15).
Esteve *et al.* (4)	20 patients,	95% high	Most	All negative for	Olmesartan cessation.
	12 female,	volume non-bloody	common dose 40mg/day.	IgA TTG. 45%	Gluten-free diet
	median age 73	diarrhea, 90%	Median duration 22	positive for HLA-	unsuccessful in 5 patients.
	years (52-89),	significant	months (5-40)	DQ2, 20% for HLA-	
		weight loss, 87,5%		DQ8.	
		hospitalization			
Saez Gonzalez	12 patients, 9	Weight loss 4-22 kg	Dose 20-40mg/day,	All negative for	Omesartan cessation
et al. (5)	females,			IgA TTG, 1 positive	
	median age 67		duration 12 to 60 months	for HLA-DQ2, 3 for	
	(47-87)			HLA-DQ8	

ANA: anti-nuclear antibodies, TTG: tissue transglutaminase

of oral corticosteroids was necessary to induce remission of the rash. The patient was advised to avoid anti-hypertensive medication containing olmesartan. Three months later she had no recurrences and had regained a lot of the lost weight.

Olmesartan-associated enteropathy was first described in 2012 (1). Many case reports and series followed (e.g. (2-5)). It is a rare entity and the diagnosis is commonly delayed possibly due to lack of awareness of the disease among clinicians. Like our case, patients are often subjected to many investigations and empirical treatments without response. The diagnosis is often made "accidentally" after observing an unexpected resolution of symptoms following discontinuation of olmesartan due to low blood pressure. Cessation of olmesartan results in rapid symptomatic improvement (within days to 2 weeks) (1-5). Histologic recovery is noted within few months (1-5). If antihypertensive treatment is necessary, a medication from another class is usually preferred, although a class-effect has not been proven. Recurrence of symptoms has been described after re-exposure to olmesartan (e.g. (1)). Celiac serology is

Table 2. — **Histologic findings in case series olmesartan-associated enteropathy**

	Endoscopic-histologic findings
Rubio-Tapia *et al.* (1)	**Duodenal biopsies (n=22):** Total villous atrophy (n=15), partial villous atrophy n=7), thick band of subepithelial
	collagen deposition (n=7), mucosal inflammation (n=15), increased intraepithelial lymphocytes (n=14)
	Stomach biopsies (n=14): collagenous or lymphocytic gastritis in 7,
	Colon biopsies (n=13): microscopic colitis in 5
	Follow-up biopsies (n=18)(+6 of the 7 patients with gastritis): histologic recovery of the duodenum (n=18), focal
	partial villous atrophy (n=1), resolution of lymphocytic/collagenous gastritis (4 of 6), non-specific gastritis (2 of 6)
Martheyt *et al.* (2)	**Duodenal biopsies (n=36)**: villous atrophy (n-32), increased intraepithelial lymphocyte (n=19),
	crypt hypertrophy (n=9), collagen sprue (n=2)
	Colon biopsies: microscopic colitis (n=7)
DeGaetani *et al.* (3)	**Duodenal biopsies (n=16)**: Villous atrophy (n=16), total villous atrophy (n=8), subtotal villous atrophy (n=2), partial
	villous atrophy (n=3), increased subepithelial collagen (n=11), increased intraepithelial lymphocytes (n=11)
Esteve *et al.* (4)	**Duodenal biopsies (n=20)**: villous atrophy (n=19), microscopic enteritis (n=1)
	Gastric biopsies (n=10): lymphocytic gastritis (n=3)
	Colon biopsies (n=14): paucicellular colitis (n=2), lymphocytic colitis (n=3), collagenous colitis (n=1),
	active focal colitis (n=1), non-specific inflammation (n=3)
	Follow-up biopsies (n=19): complete histologic recovery (n=18), partial recovery (n=1, patient on candesartan)
Saez Gonzalez *et al.* (5)	**Duodenal biopsies (n=12)**: villous atrophy (n=12), intraepithelial lymphocytes (n=7), crypt hyperplasia (n=1),
	eosinophilic component (n=2)
	Colon biopsies (n=7): collagenous colitis (n=3), nonspecific colitis (n=2), colitis with eosinophilic component
	(n=2), melanosis coli (n=1)
	Follow-up biopsies (n=11): histologic recovery

almost always negative, anti-enterocyte antibodies are negative in most cases, and anti-nuclear antibodies may be positive. Many patients are positive for HLA-DQ2 or DQ8. Villous atrophy is almost always present in duodenal biopsies, and gastric and colon biopsies may demonstrate lymphocytic gastritis and microscopic colitis. Extra-intestinal manifestations have rarely been reported (2). We found only 3 cases with associated dermatitis (2,6). Hammoudi et al described a case of olmesartan enteropathy associated with pruritic papulo-erythematous lesions and scabs similar to our patient (6). Table 1 and 2 summarize the clinical, laboratory and histological findings from selected cases series (1-5).

In conclusion, although rare, olmesartan-associated enteropathy is associated with significant morbidity. Raising awareness of the disease may spare affected patients from months of unsuccessful investigations and treatments as response to olmesartan discontinuation is seen within days.

Conflict of Interest

The authors declare that they have no conflict of interest.

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