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Case report

Losartan-induced sprue-like enteropathy: A case report

Siomara Aransuzú Chávez-Sánchez,[1*] Jorge Luis Espinoza-Ríos,[1] José Luis Pinto-Valdivia,[1] Julissa Mirella Guevara-Miranda,[1] Jaime Augusto Cáceres-Pizarro.[2]

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[1] Gastroenterologist, Clínica San Felipe, Lima, Peru.
[2] Pathologist, Hospital Nacional Cayetano Heredia, Lima, Peru.

***Correspondence:** Siomara Aransuzú Chávez.
siomara.chavez@upch.pe

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Abstract

Introduction: Sprue-like enteropathy induced by angiotensin II receptor antagonists (ARBs) is an uncommon entity, initially described with olmesartan and later with other drugs in the same class. It is characterized by chronic diarrhea, weight loss, and histological changes similar to celiac disease, but with negative serology. **Case presentation:** We present the case of a 75-year-old woman receiving long-term treatment with losartan who developed diarrhea and progressive weight loss. Duodenal biopsies showed villous atrophy and chronic inflammation. After discontinuing the drug, the patient achieved complete clinical resolution. **Discussion:** The differential diagnosis includes refractory celiac disease, inflammatory bowel disease, and infectious enteropathies. The key finding is the temporal relationship with drug use, the absence of positive serology for celiac disease, and resolution of symptoms after withdrawing the ARB. **Conclusion:** This case reinforces the importance of considering ARB-induced enteropathy in the differential diagnosis of chronic diarrhea, especially in the presence of negative celiac serology.

Keywords

Losartan, angiotensin II receptor antagonists, diarrhea.

INTRODUCTION

Drug-induced sprue-like enteropathy belongs to the group of seronegative enteropathies with villous atrophy. Its primary differential diagnosis is celiac disease. Celiac disease is an immune-mediated enteropathy triggered by gluten in genetically susceptible individuals. It is usually associated with positive anti-tissue transglutaminase or anti-endomysial antibodies and improves with a gluten-free diet[(1)]. In contrast, drug-induced sprue-like enteropathy may exhibit similar histologic findings, including villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis, but with negative celiac serology and no response to gluten exclusion. These features suggest alternative etiologies, including drug-induced enteropathies[(2-4)].

Enteropathy associated with angiotensin II receptor blockers (ARBs) is an uncommon but potentially reversible condition. It was initially described in association with olmesartan,[(1)] but cases involving other drugs in the same class, including valsartan, irbesartan, and losartan, have subsequently been reported. Recognizing this association is clinically relevant because ARBs are widely prescribed, and discontinuation of the offending drug leads to resolution of the condition in most cases.

CASE PRESENTATION

We present the case of a 75-year-old woman with a history of hypertension who had been treated with losartan 50 mg/day and atenolol 50 mg/day for 10 years. Four years

earlier, she had developed intermittent episodes of watery diarrhea, with three to four bowel movements per day. The stools were not accompanied by mucus or blood. She also reported mild left flank abdominal pain. During the same period, she experienced progressive weight loss of approximately 25 kg.

Initial testing was negative for infectious causes, including serial stool parasite examinations and stool cultures. Hemoglobin was 10.8 g/dL, and anti-tissue transglutaminase antibodies were negative. Thyroid function, ferritin levels, and vitamin B12 levels were normal. Upper gastrointestinal endoscopy revealed duodenal villous atrophy and nodularity, whereas colonoscopy showed an edematous distal ileum. Video capsule endoscopy demonstrated villous atrophy (**Figures 1A** and **1B**). Histopathologic examination showed villous atrophy, crypt elongation, intraepithelial lymphocytosis, and patchy eosinophilia. These findings were consistent with sprue-like enteropathy.

Based on these findings and the chronicity of the diarrhea, weight loss, negative serologic markers for celiac disease, and lack of response to conventional measures, losartan-associated enteropathy was considered. The drug was discontinued, resulting in complete resolution of the diarrhea within a few days and progressive nutritional recovery. No gluten-free diet or other additional treatment was required.

Notably, a focused medical history revealed no chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), mycophenolate, immunosuppressants, herbal supplements, or homeopathic preparations potentially associated with enteropathy. In addition to atenolol and losartan, the patient was taking only levothyroxine, with no exposure to other medications associated with intestinal mucosal injury.

DISCUSSION

This case is consistent with previous reports in the literature. In 2015, Negro and Blanco[5] described the first case of severe losartan-induced enteropathy, with a similar clinical and histologic pattern and complete recovery following drug discontinuation. Subsequently, Mazhar and Arnautovic[6] reported another case at the American College of Gastroenterology meeting, further supporting the possibility that losartan can also induce sprue-like enteropathy. In a systematic review by Kamal et al.[2] that included 248 cases of ARB-associated enteropathy, the vast majority were associated with olmesartan. However, losartan accounted for approximately 0.8% of reported cases. In that review, the latency between treatment initiation and symptom onset ranged from 2 weeks to 13 years. Villous atrophy was present in 92% of patients, and clinical remission after ARB withdrawal occurred in 97%.

Regarding pathophysiology, Marietta et al.[7] demonstrated that olmesartan can induce interleukin-15 and its receptor overexpression in *in vitro* models, as well as disruption of the tight junction protein ZO-1. These findings are similar to those observed in celiac disease. However, these changes were not reproduced with losartan or telmisartan. This has raised the question of whether the condition represents a class effect or a more selective pharmacologic phenomenon. Despite this controversy, clinical

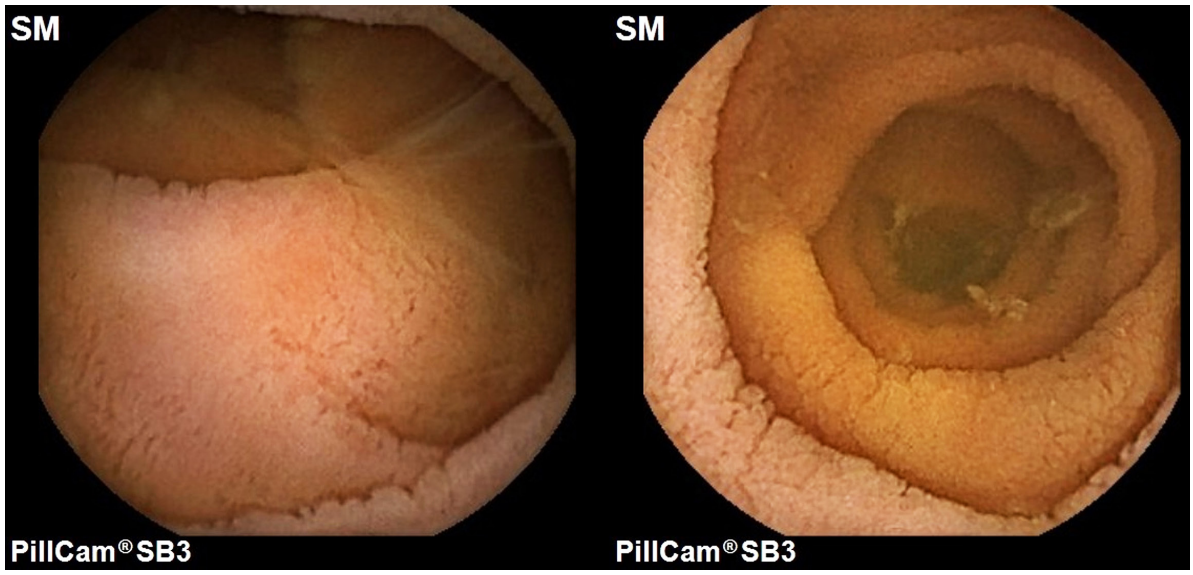


Figure 1. Video capsule endoscopy. **A.** Villous atrophy in the duodenum. **B.** Villous atrophy in the jejunum.

evidence indicates that more than one ARB can trigger the condition. The long latency to symptom onset, reported by Kamal et al. to be as long as 13 years, makes recognition of the causal association particularly challenging.

In 2013, the U.S. Food and Drug Administration (FDA)[8] issued a safety alert concerning olmesartan and the risk of sprue-like enteropathy. Although the warning did not include the other ARBs at that time, subsequent reports[3,9-11] suggest that surveillance should extend to the entire drug class.

In patients with seronegative villous atrophy, several differential diagnoses should be considered in addition to celiac disease. These include autoimmune enteropathy, small intestinal bacterial overgrowth, giardiasis, common variable immunodeficiency, small bowel Crohn's disease, collagenous enteropathy, and drug-induced enteropathies. The latter group includes olmesartan, mycophenolate, azathioprine, methotrexate, colchicine, immune checkpoint inhibitors, and NSAIDs[2-4,12].

In our patient, the diagnosis of losartan-induced enteropathy was supported by seronegative villous atrophy; exclusion of infectious, inflammatory, and other drug-induced enteropathies; and clinical resolution following drug discontinuation, consistent with a positive *dechallenge*.

The key findings were the temporal relationship with drug use, the absence of positive celiac serology, and resolution of the condition after ARB withdrawal. In persistent or severe cases, some authors have reported the use of oral corticosteroids, particularly budesonide, as adjunctive therapy. However, most patients have a favorable clinical course with drug discontinuation alone.

CONCLUSIONS

We present a case of losartan-induced sprue-like enteropathy that underscores the need to include this condition in the differential diagnosis of patients with chronic diarrhea, weight loss, and villous atrophy with negative celiac serology. Despite its low frequency, early recognition of this association allows discontinuation of the offending drug and clinical resolution, thereby avoiding unnecessary diagnostic and therapeutic interventions.

Ethical considerations

This case report was prepared in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of the clinical information and images related to the case. Her anonymity and data confidentiality were preserved at all times.

Informed consent

The patient consented to the use of her data and images for publication of this case report.

Conflicts of interest

The authors declare no conflicts of interest.

Use of artificial intelligence

The authors declare that they did not use artificial intelligence-assisted technologies during the preparation of this manuscript.

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Author contribution

- Study design and conception: Siomara Aransuzú Chávez-Sánchez, Jorge Luis Espinoza-Ríos, José Luis Pinto-Valdivia, Julissa Mirella Guevara-Miranda, and Jaime Augusto Cáceres-Pizarro.
- Data acquisition: Siomara Aransuzú Chávez-Sánchez, Jorge Luis Espinoza-Ríos, José Luis Pinto-Valdivia, Julissa Mirella Guevara-Miranda, and Jaime Augusto Cáceres-Pizarro.
- Data analysis and interpretation: Siomara Aransuzú Chávez-Sánchez, Jorge Luis Espinoza-Ríos, José Luis Pinto-Valdivia, Julissa Mirella Guevara-Miranda, and Jaime Augusto Cáceres-Pizarro.
- Manuscript drafting: Siomara Aransuzú Chávez-Sánchez, Jorge Luis Espinoza-Ríos, José Luis Pinto-Valdivia, Julissa Mirella Guevara-Miranda, and Jaime Augusto Cáceres-Pizarro.
- Critical revision of the manuscript: Siomara Aransuzú Chávez-Sánchez, Jorge Luis Espinoza-Ríos, José Luis Pinto-Valdivia, Julissa Mirella Guevara-Miranda, and Jaime Augusto Cáceres-Pizarro.
- Approval of the final version for publication: Siomara Aransuzú Chávez-Sánchez, Jorge Luis Espinoza-Ríos, José Luis Pinto-Valdivia, Julissa Mirella Guevara-Miranda, and Jaime Augusto Cáceres-Pizarro.

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