

Olmesartan-Induced Gastropathy: An Important Cause to Think about in Refractory Peptic Ulcer Disease

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Keywords

Angiotensin receptor blockers · Refractory peptic ulcer disease · Drug-induced gastropathy

Abstract

Background: Angiotensin receptor blockers are a pharmacological class widely used as antihypertensive therapy. Recently, a relationship between these agents and gastrointestinal disease has been described, namely, enteropathy, gastropathy, and microscopic colitis. The mechanism is unknown, but it is thought that a cell-mediated immune reaction is involved and does not appear to be a class effect. Treatment consists of stopping the drug and rechallenge can confirm the diagnosis. **Case Presentation:** An 85-year-old man with a history of hypertension treated with olmesartan/hydrochlorothiazide for 12 years presented to the emergency department with months of epigastric pain, without vomiting, blood loss, diarrhea, or weight loss. A recent upper gastrointestinal endoscopy (UGE) showed congested mucosa, irregular erosions, and friability in the distal body, notch, and antrum. Histology revealed moderate chronic

gastritis, severe inflammatory activity, abundant eosinophils, intestinal metaplasia with low-grade dysplasia, and marked atrophy, with no signs of malignancy or *Helicobacter pylori* (Hp). The patient had previously been treated by his family doctor with lansoprazole and sucralfate, without improvement, and was subsequently discharged on esomeprazole with a referral for a gastroenterology consultation. Three months later, a follow-up UGE showed persistent erosions despite good adherence to esomeprazole. Hp serology was positive, and the patient was started on bismuth-based quadruple therapy. A post-treatment urea breath test confirmed Hp eradication. Six months later, UGE still showed multiple ulcers in the distal body and antrum. Olmesartan was switched to lisinopril, and after another 6 months, a follow-up UGE showed no ulcers or erosions. Biopsies revealed reduced inflammation and no dysplasia, indicating histological improvement. Olmesartan-induced gastropathy was diagnosed. **Conclusions:** This case report illustrates olmesartan-induced gastropathy, an important diagnosis to consider in cases of non-Hp gastritis and refractory peptic ulcer disease.

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Gastropatia induzida por olmesartan: uma causa importante a pensar na doença ulcerosa péptica refratária

Palavras Chave

Antagonistas dos recetores da angiotensina · Doença ulcerosa péptica refratária · Gastropatia induzida por medicamentos

Resumo

Introdução: Os antagonistas dos recetores da angiotensina são uma classe farmacológica amplamente utilizada como terapêutica anti-hipertensiva. Recentemente, foi descrita uma relação entre estes agentes e doenças gastrointestinais, nomeadamente enteropatia, gastropatia e colite microscópica. O mecanismo é desconhecido, mas acredita-se que envolva uma reação imune mediada por células e não parece ser um efeito de classe. O tratamento consiste na suspensão do fármaco, e a reexposição pode confirmar o diagnóstico.

Apresentação do Caso: Um homem de 85 anos, com antecedentes de hipertensão arterial tratada com olmesartan/hidroclorotiazida há 12 anos, recorreu ao serviço de urgência por dor epigástrica persistente com vários meses de evolução, sem episódios de vômitos, perdas de sangue, diarreia ou perda de peso. Uma endoscopia digestiva alta (EDA) recente revelou mucosa congestiva, erosões irregulares e friabilidade no corpo distal, incisura e antro gástrico. A histologia mostrou uma gastrite crónica moderada, com elevada atividade inflamatória, eosinófilos abundantes, metaplasia intestinal com displasia de baixo grau e atrofia acentuada, sem sinais de malignidade ou de *Hp*. O doente já tinha previamente sido medicado pelo seu médico de família com lansoprazol e sucralfato, sem melhoria, e acabou por ter alta com esomeprazol e um pedido de consulta de gastroenterologia. Três meses depois, uma nova EDA revelou erosões persistentes, apesar da boa adesão ao esomeprazol. A serologia para *Hp* foi positiva, e foi iniciada erradicação com terapêutica quádrupla com bismuto. Um teste de respiração de ureia pós-tratamento confirmou a erradicação do *Hp*. Seis meses depois, a EDA ainda mostrou múltiplas úlceras no corpo distal e no antro gástrico. O olmesartan foi substituído pelo lisinopril, e após mais seis meses, uma nova EDA não demonstrou úlceras nem erosões. As biópsias mostraram uma redução da inflamação e ausência de displasia, indicando uma melhoria histológica. Assumiu-se o diagnóstico de gas-

tropatia induzida por olmesartan. **Conclusões:** Este relato de caso ilustra a gastropatia induzida por olmesartan, um diagnóstico importante a considerar em casos de gastrite não associada a *Hp* e doença ulcerosa péptica refratária.

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Introduction

Gastric pathologies, including gastritis and peptic ulcer disease, are frequently encountered in clinical practice, with well-established causes such as *Hp* infection and nonsteroidal anti-inflammatory drug (NSAID) use. However, there is growing recognition of drug-induced gastrointestinal diseases related to medications not traditionally associated with such effects, including angiotensin receptor blocker (ARB). ARBs are a widely used class of antihypertensives known for their cardiovascular benefits, but recent reports have highlighted potential links between their use and gastrointestinal complications.

Olmesartan, a commonly prescribed ARB, has been implicated in causing conditions such as enteropathy and gastropathy. The clinical presentation of ARB-induced gastropathy can be subtle and nonspecific, often delaying diagnosis. Symptoms may persist despite conventional treatment for gastritis or peptic ulcers, and standard etiological investigations, including *Hp* testing, may be negative. In such cases, medication-related causes should be considered.

Case Presentation

An 85-year-old man with arterial hypertension, treated with olmesartan/hydrochlorothiazide for the past 12 years, presented to the emergency department with epigastric pain that had developed gradually over several months. He reported no associated symptoms such as vomiting, blood loss, diarrhea, or weight loss. There was no history of NSAID use, and he had no family history of gastric cancer.

Physical examination was unremarkable. Laboratory studies and computed tomography revealed no changes. The patient's family doctor had previously ordered an UGE, which showed congested mucosa in the distal body, gastric notch, and antrum, with a firm consistency, irregular erosions, and friable areas that appeared suspicious. There were no other findings of

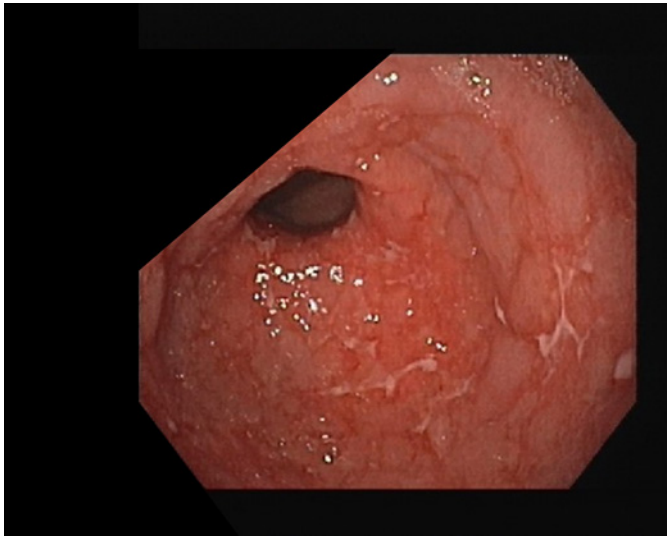


Fig. 1. Gastric antrum with ulcers on upper gastrointestinal endoscopy, before stopping olmesartan.

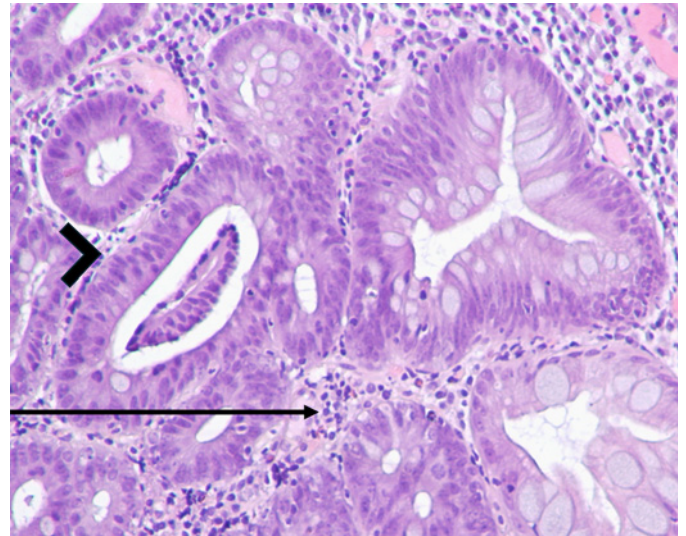


Fig. 2. Histopathological findings of gastric mucosa prior to discontinuing olmesartan, stained with hematoxylin and eosin (H&E), at $\times 100$ magnification. Inflammatory infiltrate in the lamina propria (arrow), indicative of gastritis, and low-grade dysplasia (arrowhead) were present.

note. The patient was treated with lansoprazole and sucralfate. Histology showed severe intestinal metaplasia with low-grade dysplasia in the gastric antrum, chronic gastritis with moderate inflammation, and severe atrophy. No signs of Hp or granulomas were found. He was discharged with twice-daily 40 mg esomeprazole, and a gastroenterology consultation was requested.

Three months later, a follow-up UGE showed persistent erosions and ulcers in the gastric antrum (shown in Fig. 1), despite good adherence to esomeprazole. Histology revealed moderate chronic gastritis with severe inflammation and abundant eosinophils (20 eosinophils per high power field), severe intestinal metaplasia with low-grade dysplasia, and marked atrophy (shown in Fig. 2). No granulomas, giant cells, or signs of malignancy were found, and Hp was not detected. Hp serology was performed, and it was positive, so quadruple therapy with bismuth was prescribed. Post-eradication urea breath test was negative.

Six months later, a repeat UGE still showed multiple superficial ulcers in the distal body and antrum. Histology revealed diffuse chronic gastritis without active inflammation, along with intestinal metaplasia, but no dysplasia, giant cells, or granulomas. At this point, the possibility of olmesartan-induced gastropathy was considered, and olmesartan was replaced with lisinopril.

Another UGE, performed 6 months after changing antihypertensive therapy, showed areas of atrophy and metaplasia in the antrum and notch but no ulcers or

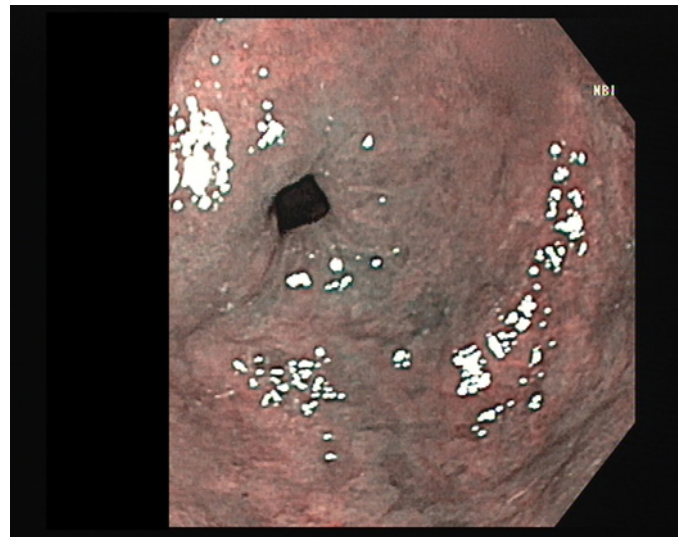


Fig. 3. Gastric antrum visualized using narrow band imaging (NBI) during upper gastrointestinal endoscopy, after stopping olmesartan.

erosions (shown in Fig. 3). Biopsies demonstrated a reduction in inflammatory infiltrate and an absence of dysplasia, indicating histological improvement (shown in Fig. 4). Olmesartan-induced gastropathy was assumed to be the cause of the initial symptoms.

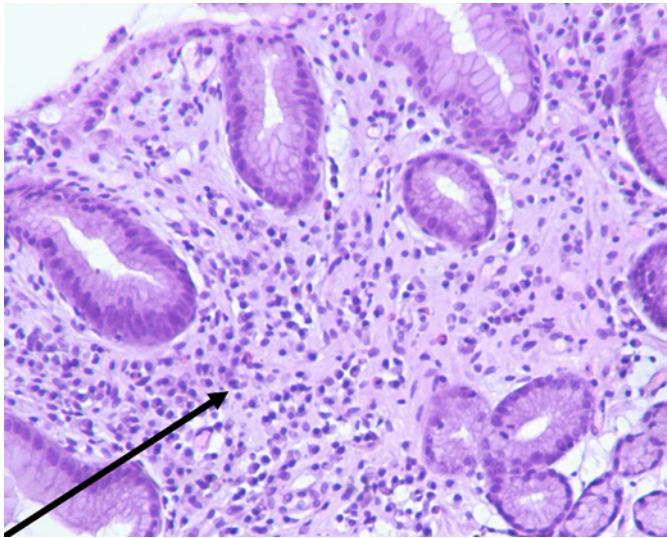


Fig. 4. Histopathological findings of gastric mucosa after discontinuation of olmesartan, stained with hematoxylin and eosin (H&E), at $\times 100$ magnification. A reduction in the inflammatory infiltrate (arrow) was observed, indicating histological improvement.

Duodenal biopsies were not performed as there was no clinical suspicion of malabsorption syndrome. The patient's condition improved following the change in antihypertensive therapy, with a resolution of symptoms and stabilization of gastric histopathology.

Discussion

This case involved an 85-year-old man with a 12-year history of olmesartan/hydrochlorothiazide therapy for hypertension, who presented with progressive epigastric pain over several months. Despite treatment with proton pump inhibitor and successful eradication of *Hp* infection, UGE revealed persistent gastric erosions and ulcers. Histological findings included severe chronic gastritis, intestinal metaplasia, dysplasia, and abundant eosinophilic infiltration. After olmesartan was discontinued and replaced with lisinopril, follow-up endoscopy and histology showed significant improvement, with resolution of ulcers and reduced inflammation. This suggested that olmesartan-induced gastropathy was a probable diagnosis, although it remained non-definitive, as there are no pathognomonic features specific to this condition.

In this case, the differential diagnosis of refractory peptic ulcer disease must consider several possibilities. Initially, *Hp* infection was a likely cause, especially given

the patient's histological findings of chronic gastritis and intestinal metaplasia. Although the initial biopsies were negative for *Hp*, the positive serology warranted a trial of eradication therapy. Post-eradication urea breath test confirmed successful *Hp* eradication. Despite this, the persistence of ulcers on follow-up endoscopy suggested a non-*Hp*-related cause of the refractory disease. The absence of NSAID use ruled out one of the most common causes of drug-induced peptic ulcers. Other less common conditions that could be considered include Zollinger-Ellison syndrome, although this was unlikely given the absence of significant weight loss or diarrhea. Autoimmune gastritis was also considered in the differential diagnosis; however, it typically affects the gastric body, where parietal cells and intrinsic factor are produced, rather than the antrum, which appears to be the predominant site of gastritis in this case. Crohn's disease was another possibility, but there were no accompanying symptoms such as diarrhea, and multiple biopsies revealed no typical pathology findings. The resolution of the patient's ulcers following the discontinuation of olmesartan strongly supports olmesartan-induced gastropathy as the most likely diagnosis.

ARBs are a pharmacological class widely used as antihypertensive therapy. By inhibiting angiotensin II activity in type 1 angiotensin receptors, ARBs decrease vasoconstriction and aldosterone production and consequently reduce blood pressure. Recently, a relationship between these agents and gastrointestinal disease has been described, namely, enteropathy, gastropathy, and microscopic colitis [1, 2].

The most common symptoms associated with the disease are abdominal pain, weight loss, and diarrhea [3]. However, weight loss and diarrhea are likely more closely related to ARB enteropathy, given the high co-occurrence of both conditions. That said, some patients with probable ARB gastropathy and normal duodenal histology have also experienced weight loss [3].

Few studies have been conducted on the gastric involvement of ARB. The most common endoscopic findings in the stomach are nonspecific and include erythema, mucosal nodularity, friability, and erosions/ulcers, both in the antrum and on the body [3]. Histological findings are often heterogeneous and nonspecific, including lymphoplasmacytic infiltrate with eosinophils, as seen in this case, and other features such as glandular atrophy, occasional intestinal metaplasia, intraepithelial lymphocytes, subepithelial collagen deposition, and epithelial surface lesions [1, 3]. These findings may involve the entire mucosa or the intermediate region (unlike *Hp* gastritis, where inflammation predominantly affects the

surface of the mucosa). The presence of dysplasia has not been reported in other cases of ARB-induced gastropathy in the literature.

Olmesartan is the most frequently involved ARB [3], but there are also cases described with telmisartan and irbesartan. The mechanism is unknown, but it is thought that a cell-mediated immune reaction is involved and does not appear to be a class effect [3]. There may be gastric disease without duodenal disease [3, 4], but the co-occurrence of both varies between 15 and 50% [3]. The latency period between the initiation of the drug and the onset of symptoms can range from 6 months, as reported in the literature [3], to several years, as observed in this case. For other ARB-related conditions, such as enteropathy, the time between starting ARB treatment and the onset of symptoms can also span several years [3, 5]. Symptoms are variable with weight loss, diarrhea, abdominal pain, nausea, and vomiting being the most common. Treatment consists of stopping the drug and rechallenge can confirm the diagnosis.

It is important to note that the initial two UGE did not report clear margins for any lesions, and the severity of the endoscopic findings appeared inconsistent with low-grade dysplasia. This raised the possibility that the findings could have been a misinterpretation of severe inflammation or as a sampling error indicative of diffuse gastric cancer. Consequently, a strategy of close surveillance was adopted, considering both low-grade dysplasia and diffuse gastric cancer as potential diagnoses.

In this specific case, the observed low-grade dysplasia could have been associated with a concurrent inflammatory process resulting from a long-standing chronic Hp infection. Furthermore, distinguishing between low-grade dysplasia and inflammation can be particularly challenging in the context of severe inflammation, especially given that only one pathologist examined the histological results in this instance.

Importantly, the UGE conducted after the discontinuation of olmesartan revealed improvements in the endoscopic appearance of the gastric mucosa, alongside a

reduction in histological inflammation and no evidence of dysplasia. This strongly suggests that the initial findings were likely misinterpreted as inflammatory changes. This case emphasizes the need for heightened clinical awareness of drug-induced gastrointestinal disorders, particularly when standard treatments fail to resolve symptoms, and highlights the importance of considering ARB-related gastropathy as part of the differential diagnosis.

Statement of Ethics

Written informed consent of the patient was obtained for publication of his medical case and accompanying images. Ethical Committee approval was not required for this case report as it involves the retrospective review of a single patient's medical records and no experimental interventions were performed.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Diogo Simas wrote the case report. André Ruge Gonçalves, Plácido Gomes, Pedro Russo, and Helena Vasconcelos critically reviewed the manuscript. Cristina Amado provided the histology images and their descriptions. All the authors approved the final manuscript.

Data Availability Statement

All the details about this clinical case are included in this article. Further inquiries can be directed to the corresponding author.

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