What do we know today about drug-induced microscopic colitis? A case of lymphocytic colitis on olmesartan

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Abstract

Microscopic colitis is part of the differential diagnosis of chronic watery diarrhea. Colonoscopy discloses a normal looking mucosa, therefore its diagnosis is based on histology of colonic biopsies. Two main phenotypes are distinguished: collagenous colitis and lymphocytic colitis. A third entity, incomplete microscopic colitis or unspecified microscopic colitis has been reported in the literature. It affects preferentially women over 60 years of age and its association with certain drugs is increasingly established. In case of suspected drug-induced microscopic colitis, identification of the responsible drug is a key to management. After discontinuation of the suspected drug, the gold standard of treatment is budesonide both for induction and for maintenance in case of clinical relapse, as is often the case after discontinuation. Therapy with immunomodulators, biologics, or surgery is reserved for refractory forms of microscopic colitis after multidisciplinary consultation. Through the clinical case of colitis on olmesartan, we will review the latest recommendations on drug-induced microscopic colitis. (Acta gastroenterol. belg., **2023,** 86, **474-480**).

Keywords: microscopic colitis, collagenous colitis, lymphocytic colitis, olmesartan.

Introduction

It is now accepted by scientific experts that microscopic colitis belongs to the group of chronic inflammatory bowel diseases (IBD). Unlike Crohn's disease and ulcerative colitis, microscopic colitis is distinguished from these by the presence of histological abnormalities despite normal looking mucosa at colonoscopy.

The first cases of microscopic colitis were described in the late 1970s, whereas the term microscopic colitis was first used by Read et al (1) in 1980. Patients with chronic watery diarrhea and normal colonoscopy, underwent colon biopsies revealing an increased inflammatory infiltrate of the colonic mucosal chorion. Indeed, from a histological point of view, microscopic colitis includes two entities, namely collagenous colitis and lymphocytic colitis.

Collagenous colitis, defined by the presence of collagenous deposits thicker than 10 µm under the basement membrane of the colonic surface epithelium, was described by Lindstrom in 1976 (2). Lymphocytic colitis on the other hand was individualized in 1989 by Lazenby et al (3). It is defined by an increase in the number of intraepithelial lymphocytes above 20 per 100 epithelial cells, without collagenous deposition under the basement membrane. In recent decades, microscopic colitis, which was previously less well known, has been the subject of numerous studies due to the increasing number of reported cases. Its incidence is now comparable to that of other chronic inflammatory bowel diseases (4,5). A French population-based study of the EPIMAD registry conducted between 2005 and 2007 revealed an incidence of 7.9 cases/100,000 person-years of microscopic colitis (collagenous colitis 5.3 cases/100,000 person-years and lymphocytic colitis 2.6 cases/100,000 person-years) compared to 7.4 cases/100,000 person-years for Crohn's disease (6). Studies report an incidence of 4.1/100,000 person-years for collagenous colitis and 4.9/100,000 person-years for lymphocytic colitis (7): it is therefore no longer a rare disease.

Starting with a case report, we will review the history of microscopic colitis, particularly of drug origin, from its physiopathogenesis to its management.

Case report

This is the story of a 49-year-old patient who was followed in 2019 for chronic watery diarrhea, often accompanied by abdominal pain, with a loss of 18 Kg over 2 months. As history she had arterial hypertension, hypothyroidism and OSAS. Her medication included levothyroxine 50µg/d, bisoprolol 10 mg 1co/d, olmesartan 40 mg 1co/d and pantoprazole 40 mg 1co/d.

Two months earlier she presented to our department with watery diarrhea 2 to 3 times a day, accompanied by diffuse abdominal pain and an episode of vomiting, without fever, for one week. She had not had any recent travel or dietary changes. There was no known addiction or allergy. At the onset of symptoms, she was treated with domperidone, butylhyoscine and loperamide without success. After performing a stool analysis, her general physician started her on ciprofloxacin 500 mg 1co 2x/d without response. The stool analysis showed a moderate amount of white and red blood

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Submission date: 30/11/2022
Acceptance date: 26/07/2023

cells, without microorganisms. Blood workup showed hypokalemia (at 3 mmol/L), grade 3 acute renal failure, moderate inflammatory syndrome (White blood cell count: 13360/ µL, C-reactive protein: 9.6 mg/L), moderate cytocholestasis with total bilirubin at 2.99 mg/dL, lipasemia at 99 U/L. Repeated bacteriological and parasitological stool examinations were negative. Abdominal ultrasound showed vesicular sludge without wall thickening. Abdominal CT scan was normal.

After one week of hospitalization under treatment with ciprofloxacin of unfavorable evolution, the workup was completed by endoscopic examinations. Gastroscopy showed macroscopically a grade A esophagitis and biopsies were taken from the duodenum and the stomach (duodenum D2 (2x), angular arch (1x), antrum (2x at the greater and lesser curvature) and body (2x at the greater and lesser curvature). Colonoscopy showed macroscopically a non-specific left colitis, dolichocolon and hemorrhoidal congestion; biopsies were taken from the right colon to the left colon. She was put on piperacillin/tazobactam 4 g 4X/d and methylprednisolone 40 mg/d for 5 days: in the hypothesis of a more severe digestive infection with a secondary colitis, despite negative stool cultures. The evolution seemed favorable after treatment initiation. The patient was seen in the out-patient clinic two weeks after discharge with methylprednisolone 32 mg/d; she presented with worsening of diarrhea to more than 6 stools per day and a loss of 17 kg since the beginning of the symptoms. Biopsies revealed the presence of mild chronic gastritis with moderate inflammatory activity and moderate chronic duodenitis. At the ileal level there was acute non-specific ileitis (villous shortening, associated with an increase in the inflammatory infiltrate of polynuclears in the lamina propria) and in the colon, image of microscopic colitis without sign of malignancy (increase of the inflammatory infiltrate of polynuclears in the lamina propria, associated with some lesions of focal cryptitis. Increase of intraepithelial lymphocytes confirmed by anti-CD3 and CD8 immunostaining). In view of these results, methylprednisolone was stopped, and budesonide 9 mg/d was started with a planned outpatient follow-up. She was hospitalized again one week later for clinical deterioration (8 stools/day, not mucous or bloody). She also had worsening of acute renal failure, hypokalemia and persistent cholestasis. A more extensive blood test was performed with viral and autoimmune hepatitis serologies, a search for overload hepatopathies, an autoimmune workup (including dysthyroidism, diabetes, celiac disease, rheumatological and inflammatory diseases). These blood tests were mostly negative except for: hypokalemia at 2.6 mmol/l, renal failure, cyto-cholestasis and immunization against CMV, and positive ANCA.

At this point, the patient was asked about her medication history. She said she had started olmesartan 1 month before the onset of diarrhea. Indeed, colitis on olmesartan and olmesartan-related enteropathy with chronic diarrhea has already been decribed (8,9,10,11). The first cases were described in 2012 at the Mayo Clinic by Rubio-Tapia et al (12). Olmesartan was stopped from her treatment without the need for substitution. Three days after discontinuation, the patient reported a reduction in diarrhea to 4 times per day, and after 6 days she had only 2 loose stools per day. She returned home one week after stopping olmesartan, while maintaining budesonide 9 mg/d. Her clinical course was favorable at follow-up visits. Budesonide was stopped after 2 months of treatment. Clinical evolution at one year was always favorable, without the need for resuming therapy.

Etiology and risk factors for microscopic colitis

To date, the etiology of microscopic colic is not clearly established. However, numerous studies have identified some of the risk factors potentially involved and have developed hypotheses for its pathophysiology (13,14,15,16,17). Although a multifactorial origin is retained, the concept of an abnormal immune response of the colonic mucosa to an intraluminal antigen, in a genetically predisposed terrain, is generally emphasized (17,18).

- The association of certain drugs with an increased risk of microscopic colitis is increasingly established, but this does not imply a causal relationship (14): sustained pathophysiological evidence is still lacking. In drug-induced microscopic colitis, the drug is the intraluminal antigen. Criteria suggesting causality include the onset of symptoms 4 to 8 weeks after the introduction of the drug. On the other hand, the discontinuation of the drug leads to a clinical response in a few days and a histological response in a few weeks (less than 6 months) (17). A review published in 2005 (19) proposed a system for evaluating drug-induced microscopic colitis by adapting existing drug causality criteria. On the basis of this review, several drugs are identified as having an intermediate or high probability of inducing microscopic colitis (19) (Table 1). Diarrhea is known as a side effect for most of these drugs (20). Nonsteroidal anti-inflammatory drugs (NSAIDs) were the first treatments described as potentially responsible for triggering microscopic colitis (21). Other drugs identified as potentially inducing microscopic colitis include proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), venotonics, angiotensin II receptor antagonists (ATII-receptor antagonists), and some cancer immunotherapies (12,8,10,14,20,22).

- An autoimmune terrain is observed in 18 to 24% of patients with microscopic colitis, explaining its association with some autoimmune and inflammatory diseases. Frequently associated conditions include celiac disease, dysthyroidism, type I diabetes, psoriasis, inflammatory rheumatologic conditions, autoimmune liver disease, and autoimmune gastritis (13,17) (Table 2). One study showed that both collagenous colitis and lymphocytic colitis were associated with the human leukocyte antigen haplotype HLA-DR3-DQ2, as was

Table 1. — **Level of likelihood that a specific drug can trigger microscopic colitis (10,12,14,19)**

Drug or therapeutic class	Likehood that the drug can cause MC
Acarbose	High
Aspirin	High
Carbamazepine	Intermediate
Cimetidine	Low
Vegetable extract from Ruscus	High
Diosmine and flavonoïde	Low
Flutamide	Intermediate
Gold salts	Low
PPIs	High
Lisinopril	Intermediate
Levodopa and benserazide	Intermediate
NSAIDs	High
ATII-receptor antagonists	Intermediate
Nocertone	Intermediate
Ranitidine	High
SSRIs	High
Simvastatin	Intermediate
Iron sulphate	Intermediate
Ticlopidine	High

PPIs: proton pump inhibitors; TII-receptor antagonists: angiotensin II receptor antagonists; NSAIDs: nonsteroidal anti-inflammatory drugs; SSRIs: selective serotonin reuptake inhibitors.

Table 2. — **Autoimmune and inflammatory diseases associated with microscopic colitis (17)**

Diseases Prevalence
Celiac disease 15 to 20 %
Dysthyroidism 8 to 19 %
Insulin-dependent diabetes 5 to 9%
Inflammatory rheumatological conditions 3 to 10%
Psoriasis 2 to 3%
Autoimmune hepatopathies 2 to 3%
Autoimmune gastritis 2 to 3 %

celiac disease: suggesting some similarities in their pathogenesis (18).

- From an epidemiological point of view, **high age and female gender are** identified as risk factors for microscopic colitis. Its incidence is higher in the elderly, with a median age of at least 60 years at diagnosis. Similarly, its incidence is higher in women with a female-to-male ratio of 2.5:1 (7,13,14).

- Smoking is an important risk factor for microscopic colitis. The risk of microscopic colitis is further increased by current smoking: this is as true in collagenous colitis as in lymphocytic colitis, regardless of gender (15,16).

Pathophysiology of microscopic colitis

The pathophysiology of microscopic colitis is not clearly established to date: most studies in the literature have involved small cohorts, with often conflicting results. Although several hypotheses have been reported, researchers agree that the primary mechanism involves an inappropriate immune response to luminal antigens in a genetically predisposed individual (14,18,22).

- Genetic susceptibility. Several studies have been conducted on human leukocyte antigen (HLA) associations, but the extent to which a genetic predisposition is involved in the development of microscopic colitis is unknown. A few familial cases have been described, as well as cases of concomitant MC in patients with IBD (23). Studies have reported an association between the HLA-DQ2 haplotype of microscopic colitis and the HLA-DR3-DQ2 haplotype that predisposes to celiac sprue or celiac disease (12,18,24).

- Abnormal collagen metabolism. In collagenous colitis, the extensive collagenous deposition in the subepithelial layer observed may be due to increased expression of key fibrogenic genes and tissue inhibitor of metalloproteinase (TIMP-1). These metalloproteinases are involved in collagenous degradation and regulation of transforming growth factor (TGF-b) (25). TGF-b and vascular endothelial growth factor can influence the balance of local fibrogenesis and fibrinolysis, leading to a net accumulation of immature subepithelial matrix (26).

- Impaired epithelial barrier function. An increase in transcellular permeability of antigens and bacteria has been observed in collagenous colitis, after histological analysis: testifying to a dysfunction of the mucosal barrier, with downregulation of epithelial tight junction proteins (27).

The observation of synchronous collagenous and pseudomembranous colitis in some patients has suggested a possible etiological role of Clostriduim difficile in the occurrence of microscopic colitis (28). Cases of association have also been described with Yersinia enterolytica and Campylobacter jejuni, where histological features of microscopic colitis have been found in colonic biopsies of patients with these infectious diarrheas (17,24).

- Bile acid malabsorption. It has been suggested that bile acid malabsorption may play a potential role in the pathogenesis of microscopic colitis (29), but the results of different studies have been contradictory: this requires further study, given the implication this would have for treatment.

Clinical presentation

The cardinal symptom of microscopic colitis is the presence of chronic watery, non-bloody diarrhea (14,30,31), reported by 84% to 100% of patients in 22 studies (14). An average of 6 to 7 watery stools per day is reported, but in rare cases it may exceed 15 stools (31,32). These diarrheas are very often of abrupt onset and intermittent evolution, with periods of spontaneous remission, without any identified trigger (30,31). This symptom is associated with concomitant symptoms,

notably: fecal urgency (55%), nocturnal stools (35.3%) and fecal incontinence (26.3%) (32).

Less frequent symptoms with variable prevalence according to studies are abdominal pain, weight loss (in 15 to 20% of cases) and bloating (14,33).

The diagnosis of microscopic colitis should be excluded in any patient with functional bowel disease, presenting the diagnostic criteria for irritable bowel syndrome (IBS) with diarrhea predominance, in the absence of response to treatment of IBS and/or particularly in the presence of risk factors for microscopic colitis.

Diagnostic approaches

Studies have shown that the delay between the onset of symptoms of microscopic colitis and its diagnosis can be as long as 6 months in 43% of cases (14). When microscopic colitis is suspected, the diagnosis will only be made based on histological features demonstrated on mucosal biopsies obtained during endoscopy.

Before referring for colonoscopy, a complete evaluation is important to exclude other causes of diarrhea. Laboratory tests are often normal in many cases, or slightly disturbed in patients with microscopic colitis. Mild anemia is reported in 50% of cases, with a small inflammatory syndrome in 15-20% of cases. Autoantibodies may be present in 20-40% of cases, in association with autoimmune pathologies (30,17). Celiac serologies should be performed to exclude celiac disease. Hypokalemia is rare and occurs in 10% of cases (17).

Fecal calprotectin is not a reliable indicator for the diagnosis of microscopic colitis, as its elevation remains minimal between 48 and 80 µg/g, not allowing for confirmation or not of the diagnosis, or for monitoring microscopic colitis (14,34). A stool analysis with parasitological examinations on three samples should be performed, to exclude causes of diarrhea such as Giardia.

Colonoscopy with biopsies is necessary to establish the diagnosis of microscopic colitis. The first endoscopic feature in microscopic colitis is that the macroscopic appearance of the colon is usually normal. Macroscopically visible lesions or alterations have been reported in 38.8% of patients in various parts of the colon, including: mild oedema, erythema, friability, isolated linear ulcerations, pseudomembranes, irregular vascular patterns, and mucosal lacerations (14). Biopsies are recommended from the right to the left colon, as the diagnosis may be missed in up to 40% of cases if biopsies are taken only on the left (35): this is due to the decrease in histological burden from the proximal to the distal colon (36).

Table 3. — **Histopathological changes in microscopic colitis (CC and CL) (37)**

Collagenous colitis	**Lymphocytic colitis**
Lymphocytic infiltration of the epithelium without neutrophils	Lymphocytic infiltration of the epithelium without neutrophils
Distinct pattern of fibrosis	
Subepithelial collagen strips located in the right and transverse colon	No collagen thickening
No distortion of the crypt	Little or no distortion
Chronic inflammation of the lamina propria	Chronic inflammation of the lamina propria

The inflammatory cellular response is similar in lymphocytic and collagenous colitis, consisting primarily of lymphocytic infiltrates of the epithelium without neutrophils (37). However, certain key histologic features are used to diagnose collagenous colitis and lymphocytic colitis (Table 3).

Collagenous colitis is characterized by the presence of collagenous deposits greater than 10 µm thick beneath the basement membrane of the colonic surface epithelium (2). This collagenous deposition forms a band that is most evident between crypts.

Lymphocytic colitis is characterized by an increased number of intraepithelial lymphocytes greater than 20 lymphocytes per 100 epithelial cells, without collagenous deposition beneath the basement membrane (3). The crypt architecture is usually not distorted, but focal cryptitis may be present.

A third entity of microscopic colitis is reported in the literature, it is **incomplete microscopic colitis or unspecified microscopic colitis**. This entity involves a cohort of patients with chronic watery diarrhea but whose histologic features do not meet the diagnostic criteria for collagenous and lymphocytic colitis (38). These patients have responded to standard microscopic colitis therapies (30,32).

Treatment

The primary goal of management of patients with microscopic colitis, both drug-induced and otherwise, is to achieve clinical remission (i.e. fewer than three stools per day and no watery stools for a period of one week) and to improve their quality of life. Active disease is defined by the presence of at least three stools per day or at least one watery stool per day (39).

The general approach is to stop the potentially offending drugs first. Withdrawal alone is usually insufficient to achieve clinical remission when drugs are implicated in moderate to severe microscopic colitis (30).

In cases of mild microscopic colitis (i.e. patients with less than 3 bowel movements per day), treatment may be limited to symptomatic treatment with antidiarrheal agents such as loperamide or cholestyramine in cases of proven concomitant bile acid malabsorption (30,14). Loperamide is the most used antidiarrheal, especially at night to reduce the frequency of episodes.

In moderate to severe microscopic colitis, budesonide is the effective reference treatment for inducing clinical

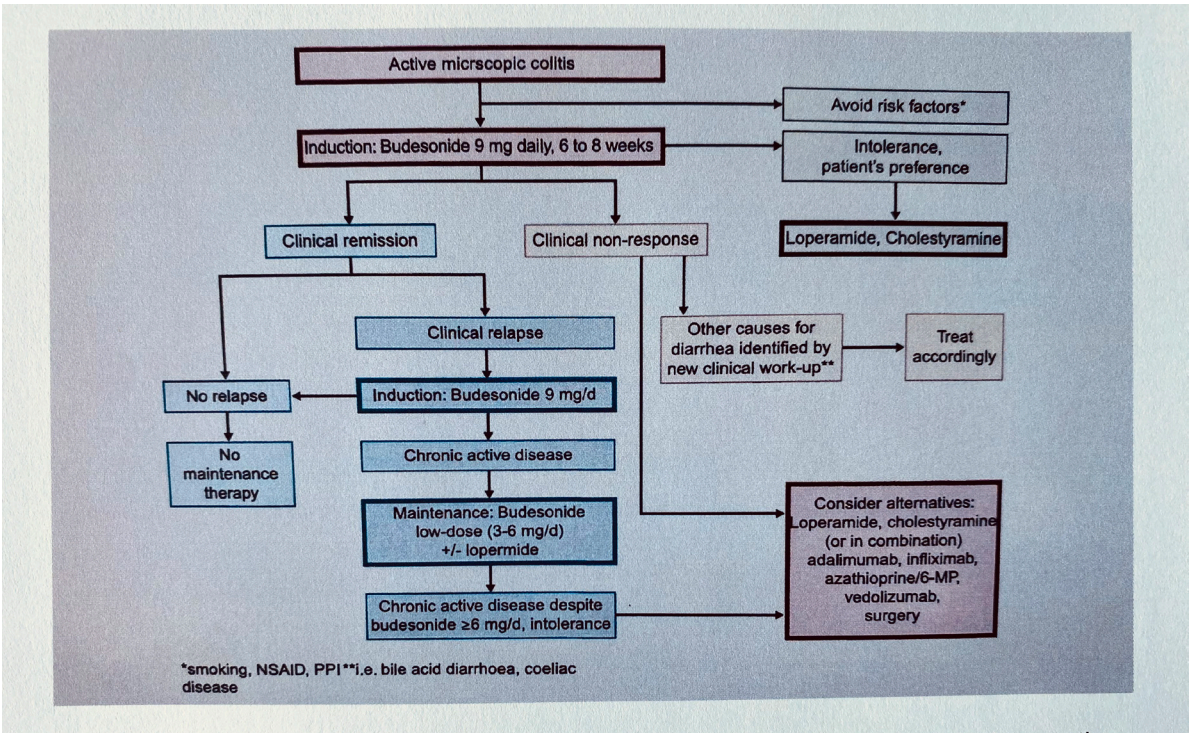

Figure 1. — Treatment algorithm for microscopic colitis in clinical practice. Based on United European Gastroenterology (UEG) and European Microscopic Colitis Group (EMCG) statements and recommendations.

remission in both collagenous and lymphocytic colitis (13,14,31). It appears that a histological response is also achieved with budesonide in as shown in a pooled analysis of four studies (14,40), where a histological response is achieved in 78% of patients receiving budesonide versus 32% of those receiving placebo. Unlike other corticosteroids such as prednisolone, budesonide has the advantage of acting locally with 90% degradation during the first hepatic passage: it therefore induces fewer systemic effects and consequently few side effects. The recommended dose of budesonide for induction in active microscopic colitis is 9 mg daily for 6 to 8 weeks to achieve clinical remission (Figure 1) (37,14,40,41). Studies have shown that a clinical response can be achieved after 2 to 4 weeks, and that quality of life is normalized within 6 weeks (42,14). It is therefore an effective, inexpensive, and well-tolerated treatment.

However, clinical relapse is common upon discontinuation of budesonide therapy in 60-80% of cases. Predictors of this relapse are older age (>60 years) at diagnosis, longer duration of disease (>12 months) before budesonide therapy, and more severe diarrhea at baseline (>5 stools per day) (30,22). Oral maintenance therapy with budesonide is therefore recommended to maintain clinical remission (14) at the minimum effective dose. Results from two randomized clinical trials showed that maintenance therapy with 6 mg budesonide daily for 6 months resulted in a lower risk of clinical relapse (RR: 0.34, 95% CI: 0.19-0.6). A lower dose of budesonide (3 mg per day alternating with 6 mg per day) over 12 months showed similar efficacy in maintaining clinical response (14,40).

In patients with symptomatic microscopic colitis, the American Gastroenterological Association (AGA) recommends treatment with budesonide rather than mesalamine for induction of clinical remission (41). In contrast, for patients with symptomatic microscopic colitis in whom budesonide therapy is not feasible, the AGA suggests mesalamine rather than no therapy for induction of clinical remission. Of note, only one randomized clinical trial suggested moderate evidence that mesalamine treatment was associated with a lower likelihood of achieving a clinical response compared with no treatment (OR: 0.74; 95% confidence interval, 0.44-1.24), although this was not statistically significant (41). Other clinical trials have not found this evidence for the efficacy of mesalamine versus placebo (22,43). For these reasons, United European gastroenterology (UEG) advises against the use of mesalazine in patients with MC for the induction of remission (14). Similarly, the use of Bismuth Salicylate is not recommended in the treatment of microscopic colitis, due to lack of sufficient evidence (14).

If there is no response to budesonide therapy, other etiologies that may be associated with diarrhea should be excluded, including celiac disease, unrecognized hyperthyroidism, carcinoid syndrome, drug-induced enteropathy and many others. If these etiologies are excluded, then the diagnosis is refractory microscopic colitis.

In refractory microscopic colitis, treatment with immunomodulators (such as azathioprine and 6-mer-

captopurine) or biologics such as anti-tumor necrosis factors (such as infliximab or adalimumab) and an anti-integrin (vedolizumab) can be used to induce and maintain clinical remission (30,8,14). The use of methotrexate in patients with microscopic colitis is discouraged because of modest responses in retrospective studies and failure to achieve clinical remission in a prospective study of nine patients (14,44).

Surgery is to be considered in some patients as a last option if all medical treatments fail. Surgical treatments include ileostomy, sigmoidostomy, or colectomy with or without ileoanal anastomosis (14,45).

In the case of refractory microscopic colitis, which should involve either immunomodulatory treatment, biological treatment or surgical treatment, a multidisciplinary medical-surgical discussion is crucial, given the significant implications and consequences of these treatments.

Conclusion

Microscopic colitis has an increasing incidence and should be included in the diagnosis of chronic watery diarrhea. This disease must be suspected especially in elderly patients (> 60 years), women even more if there is a history of autoimmune diseases. Thorough history taking along with complete investigation of medications are crucial. Since the first case series of Olmesartan-related enteropathy described by Rubio at the Mayo Clinic in 2012 (12), several other cases that have been reported in the literature, as well as olmesartan-related microscopic (lymphocytic) colitis (8,9,10,11). Current medications taken by the patient should be explored as an underlying cause.

Conflict to interest statement

The authors certify that they have no conflict of interest.

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