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Olmesartan-associated sprue-like enteropathy: a systematic review with emphasis on histopathology☆

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Summary Sprue-like enteropathy associated with the angiotensin II receptor blocker (ARB) olmesartan was first described in 2012, and a number of cases have since been reported. This syndrome is characterized by severe diarrhea and sprue-like histopathologic findings in the intestine, often with increased subepithelial collagen. The incidence of this adverse drug reaction is not entirely clear, although it is thought to be rare. It is also not well established if other ARBs cause such a syndrome, although case reports suggest they can. The histopathologic features of olmesartan-related injury have only been described in a limited number of cases, and there are no guidelines regarding the histopathologic distinction of olmesartan-associated enteropathy from other causes of sprue (eg, celiac disease, tropical sprue). Herein, we review the histopathologic changes and clinical observations described in recent reports of olmesartan-associated sprue-like enteropathy comprising case series and isolated reports, other relevant literature, and our experience at a referral center specializing in small intestinal disorders. We will review recent literature suggesting other ARBs can be associated with a similar phenotype. Lastly, we will discuss the histopathologic differential diagnosis and provide clues to distinguish this entity from other entities which can cause sprue-like histopathology.

1. Introduction

Olmesartan medoxomil is an antihypertensive drug, which acts by blocking the angiotensin II receptor. An association between olmesartan use and a severe sprue-like enteropathy was first described by Rubio-Tapia et al in 2012 [1]. A recent study has suggested that olmesartan use may also be associated with less severe histopathologic findings

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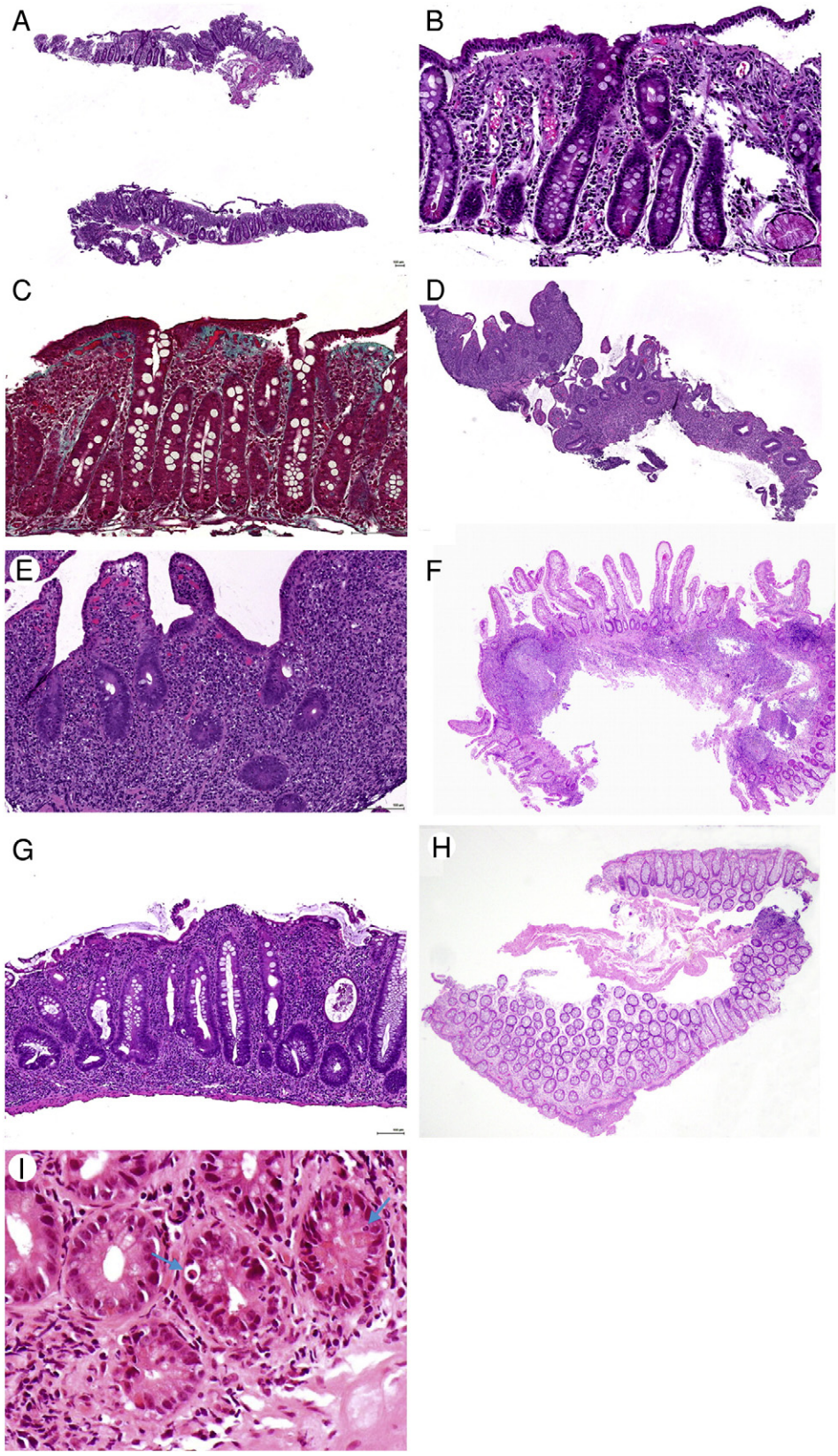
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in patients presenting with abdominal pain [2]. Case reports of patients taking other angiotensin receptor blockers and demonstrating a profound sprue-like enteropathy also exist [3-6]. The pathophysiology of olmesartan-associated enteropathy is somewhat unclear. However, a recent study proposed roles for IL-15 signaling and disruption of the tight junction protein ZO-1 in disease pathogenesis and showed an overlap between the changes observed in olmesartan enteropathy patients and active and refractory celiac disease patients [7]. Another study demonstrated similar clinical and histologic phenotypes between olmesartan enteropathy patients and autoimmune enteropathy (AIE) patients, suggesting immune dysregulation in the pathogenesis of this entity [8]. Awareness of the spectrum of clinical and histopathologic changes associated with olmesartan use is of great importance to practicing pathologists, as it will avoid misclassification of patients with other disorders and allow for a very simple but powerful intervention (namely, switching antihypertensive medication). This review examines case series, case reports, and other literature relevant to this topic and offers useful clues that may be helpful to pathologists considering olmesartan-associated injury as the etiology of small intestinal mucosal histopathology.

Rubio-Tapia et al [1] reported a series of 22 patients from the Mayo Clinic who presented with severe diarrhea and profound weight loss and uncovered the association between olmesartan exposure and a severe enteropathy. The time of symptom onset varied from several months to several years after commencement of the antihypertensive medication. Serologic testing for celiac disease was negative in all cases, and no patient responded to a gluten-free diet. Small intestinal biopsies showed villous atrophy, with 15 showing total villous atrophy. Fourteen also had a concomitant increase in intraepithelial lymphocytes (IELs), whereas 8 had a normal density of IELs. Of note, 7 patients had features of collagenous sprue (Fig. A-C). In 2010, the same group had noted that olmesartan use was present in one-third of a cohort of patients with collagenous sprue [9]. Of the 14 patients who also had gastric biopsies performed, 5 (36%) exhibited lymphocytic gastritis, and 2 (14%) displayed features of collagenous gastritis. Colon biopsies of 5 (38%) of the 13 patients showed microscopic colitis (2 lymphocytic, 3 collagenous). Clinical symptoms resolved quickly after cessation of the medications in all cases, and the histologic changes disappeared in the vast majority (17 of 18 patients with follow-up biopsy) [1]. These findings along with those from the case series discussed below are summarized in Table 1. A study performed at our institution evaluated a series of 72 patients with seronegative villous atrophy who had been referred for management of poorly responsive celiac disease. Although 20 patients (28%) had celiac disease–associated genotypes and responded to a gluten-free diet (seronegative celiac disease), 16 patients (22%) were found to be taking olmesartan, and these patients had similar clinical and histologic findings as described in the Mayo Clinic study, making olmesartan enteropathy the second most common etiology of seronegative villous atrophy. Of these 16 patients, 11 (69%) had collagenous sprue [10]. A study of nonceliac villous atrophy cases published before the description of olmesartan-associated enteropathy described unclassifiable immune mediated enteropathy as the etiology of 10 (33%) of 30 patients with nonceliac villous atrophy, with 3 (10%) considered to have "primary" collagenous sprue [11]. It is unclear whether a proportion of these cases were receiving or were exposed to olmesartan.

A smaller series (5 cases) of suspected olmesartan-related enteropathy was reported by a group in France. These patients had similar clinical and pathologic findings as described by Rubio-Tapia et al [1]. Two of the patients were rechallenged with olmesartan, and diarrhea recurred in both. The authors noted that theirs is a small gastroenterology service (4 gastroenterologists), so they wondered if this may be more common than currently thought [12]. Another study from France discussed 7 patients with severe enteropathy refractory to a gluten-free diet. Discontinuation of olmesartan did not lead to clinical resolution in 2 patients. However, remission was achieved with anti–tumor necrosis factor α therapy, suggesting that olmesartan may provoke an immune-mediated enteropathy [8]. A study from India described 7 patients who presented with watery diarrhea after taking olmesartan. The symptoms were severe enough to necessitate hospitalization of 3 patients. Duodenal biopsy showed total villous atrophy in 3 patients and partial villous atrophy in the remaining 4. Increased IELs were noted in all cases. Within a few days of discontinuing olmesartan, all 7 patients showed a marked improvement of their clinical symptoms. Repeat duodenal biopsies performed in 2 patients

Fig. Characteristic and unusual changes seen in ARB enteropathy. A, Two well-oriented duodenal biopsy pieces from an olmesartan-exposed patient show total villous atrophy and crypt hyperplasia (hematoxylin and eosin, original magnification ×4). B, Higher power view shows no significant intraepithelial lymphocytosis and suggests increased subepithelial collagen (hematoxylin and eosin, ×20). C, Trichrome stain confirms the increase in subepithelial collagen (Masson trichrome, ×20). D, Low-power view of an ileal biopsy from another ARB-exposed patient shows distorted villi, significant inflammation in lamina propria, and extensive crypt dropout (hematoxylin and eosin, ×4). E, Higher power view shows loss of both goblet and Paneth cells (hematoxylin and eosin, ×20). This biopsy was taken before the association between ARB and enteropathy was described, and the working diagnosis was autoimmune enteropathy. F, However, after several months off ARB, the ileum had reverted to normal histology (hematoxylin and eosin, ×4). G, Colonic biopsies from the above patient show crypt architectural distortion and a crypt abscess, consistent with chronic active colitis and suggestive of inflammatory bowel disease (hematoxylin and eosin, ×10). H, Follow-up colonic biopsies taken after cessation of the medication show normal histology (hematoxylin and eosin, ×4). In our experience, this is a rare presentation in the colon, microscopic colitis being more frequent. I, This ARB-exposed patient had prominent crypt apoptosis (arrows), a finding which could be confused with mycophenolate toxicity (hematoxylin and eosin, ×60).

Table 1 Summary of case series and case reports

	No. of patients	Length of olmesartan use before symptoms	HLA DQ2/DR8	Small bowel villous atrophy	IEL	Collagenous sprue	Microscopic colitis	Lymphocytic or collagenous gastritis	Clinical resolution after drug cessation
Rubio-Tapia et al 2012 [1]	22	0.5-7 y (14)[a]	81% (21)	68% TVA 32% PVA	64%	32%	38% (13)	50% (14)	100%
DeGaetani et al 2013 [10]	16	NA	92% (13)	50% TVA 12% STVA 19% PVA 19% NSVA	69%	69%	NA	NA	100% (15)
Theophile et al 2014 [11]	5	NA	NA	40% STVA 40% PVA 20% No VA	40%	NA	NA	NA	100%
Bhat et al 2014 [12]	7	0.5-5 y	NA	29% TVA 14% STVA 57% PVA	100%	NA	100% (1)	NA	100%
Ianiro et al 2014 [13]	3	3 y (1)	0%	67% TVA 33% PVA	0%	NA	NA	NA	100%
Scialom et al 2015 [8]	7	2-10 y	67% (6)	57% TVA 43% STVA	100%	14%	0%	14%	67% (6)
Marthey et al 2014 [6]	36	<1 mo-11.5 y	63% (19)	72% TVA/STVA 17% PVA 11% No VA	68% (28)	8% (26)	19%	NA	92%
Single cases[b]	8	0.5-7 y (5)	43% (7)	63% TVA 12% PVA 25% NSVA	88%	50% (2)	80% (5)	100% (1)	100%
Total	104	<1 mo-11.5 y (70)	70% (69)	67% TVA/STVA 23% PVA 5% NSVA 5% No VA	70% (96)	30% (73)	27% (62)	41% (22)	95% (102)

Abbreviations: IEL, intraepithelial lymphocytosis; NA, not available; NSVA, nonspecified villous atrophy; PVA, partial villous atrophy; STVA, subtotal villous atrophy; TVA, total villous atrophy; VA, villous atrophy.

[a]Values in parenthesis indicate the number of patients evaluated for a given characteristic.

[b]Includes results from Nielsen et al, Stanich et al, Dreifuss et al, Khan et al, Fiorucci et al, de Fonseka et al, Gaur et al, and Heerasing et al [14-21].

3 months after drug cessation showed villous recovery and a decrease in IELs [13]. A series of 3 patients reported from Italy as part of a review manifested typical clinical findings, and all responded dramatically to cessation of olmesartan. Interestingly, the index biopsies had severe villous atrophy, but they lacked significant intraepithelial lymphocytosis [14]. This was also noted in a sizable minority of the patients described by Rubio-Tapia et al [1].

Several isolated case reports of olmesartan-associated enteropathy have been published. Nielsen et al [15] reported a case of collagenous sprue in an individual taking olmesartan who experienced a 20-lb weight loss over a few weeks. Discontinuation of olmesartan because of resolution of hypertension resulted in complete symptomatic and pathologic recovery [15]. The case of a patient requiring total parenteral nutrition with sprue-like histology and lymphocytic colitis was reported by a group from Ohio State University. Total resolution of symptoms was noted just 7 days after cessation of olmesartan [16]. These observations are consistent with our experience, where patients typically start to notice great improvement just days after medication cessation. Other groups from the United States, Australia, and Italy have reported similar cases [17-22]. The latter described lymphocytic gastritis and lymphocytic colitis in addition to the characteristic duodenal findings. Interestingly in this case, lymphocytic colitis had been overlooked at the time of original histopathology review and was only recognized on re-reviewing the case [19]. A suspected case of olmesartan enteropathy has been reported in which the patient had chronic diarrhea but presented in an emergent setting with a colon perforation, which was managed with antibiotics and cessation of olmesartan therapy, after which the patient had a profound recovery. Unfortunately, adequate histologic findings were not provided (reported as "inflammatory changes in the stomach and colon") [23].

2. Epidemiological studies

The incidence of sprue-like enteropathy among olmesartan users has yet to be quantified. However, a group in France recently made efforts toward this end by collecting case reports of angiotensin receptor blocker (ARB)–associated enteropathy from gastroenterologists across the country. In total, 27 medical centers submitted 48 reports. Of these, 40 (83%) had complete data available, and 36 (75%) included biopsies confirming abnormal intestinal histology associated with olmesartan use. Although this study provides some information regarding prevalence, its scope is somewhat limited, as only gastroenterologists were contacted, and it remains likely that due to low awareness of this condition, patients are still being misclassified as having celiac disease or an inflammatory disorder [6]. Another French study used the hospitalization records of 4 546 680 ARB and angiotensin-converting enzyme inhibitor (ACEI) users to assess the risk of enteropathy associated with olmesartan use. The authors determined the incidence of hospitalization for intestinal malabsorption among olmesartan users, ACEI users, and nonolmesartan ARB users. The incidence of hospitalizations for olmesartan users was 2.49 times that of ACEI users and 3.17 times that of other ARB users. The incidence of hospitalizations for other ARB users was 0.78 times that of ACEI users, suggesting that, among ARBs, olmesartan is more likely to be associated with enteropathy. Hospitalizations with a discharge diagnosis of celiac disease were also considered. The incidence of hospitalizations for celiac disease for olmesartan users was 4.39 times that of ACEI users and 4.82 times that of other ARB users. The rate of hospitalizations for other ARB users was 0.91 times that of ACEI users [24]. A recent study at our institution reviewed medication records for patients undergoing endoscopy or colonoscopy for chronic diarrhea and compared the medications to a control group of patients for whom the indication was either heartburn (for endoscopy) or colon cancer screening (for colonoscopy). No significant association between olmesartan use and chronic diarrhea was observed; however, this study was underpowered, as only a small percentage (0.7%-1%) of the study population was taking olmesartan [25]. Further studies are necessary to get a more accurate sense of the frequency of olmesartan-associated enteropathy, particularly in the United States.

3. Disease spectrum

Future studies should also clarify the spectrum of gastrointestinal symptoms and histologic changes associated with olmesartan use, as recent works have introduced the possibility of milder presentations. A report from 2012 described a suspected case of sprue-like enteropathy in a patient taking olmesartan for 3 years [26]. Duodenal biopsy revealed mild villous blunting, increased IELs, and negative celiac serology. However, the patient did not exhibit symptoms typical of enteropathy, such as diarrhea. This suggests that, in addition to severe sprue-like enteropathy, olmesartan use may be associated with a broader range of gastrointestinal pathology [26]. Our recent study suggested that olmesartan can induce more subtle intestinal damage in patients who lack the severe diarrhea characteristic of sprue-like enteropathy. In this study, intestinal biopsies from both olmesartan users and control patients experiencing abdominal pain (but not diarrhea) were retrospectively examined for sprue-like features including architectural abnormalities, increased IELs, and chronic inflammation. Although no single feature was statistically more frequent in either group, the results taken as a whole suggested a trend of sprue-like histologic changes in olmesartan users; specifically, 50% of patients taking olmesartan had 1 characteristic as compared to only 20% of control patients. Whether this milder presentation represents a stage in the ultimate development of severe sprue-like enteropathy or a limited injury remains to be determined [2]. Notably, in the aforementioned French study of ACEI and ARB users, the incidence of hospitalization was also determined with respect to treatment duration. Within the ACEI and olmesartan groups, patients were divided into 3 groups of treatment duration: less than 1 year, 1 to 2 years, and 2+ years. The rate ratio of hospitalization for intestinal malabsorption for olmesartan compared with ACEI was 0.76 for the less than 1 year group, 3.66 for the 1 to 2 years group and 10.65 for the 2+ years group. The rate ratio of hospitalization for celiac disease for olmesartan compared with ACEI was 1.98 for the less than 1 year group, 4.36 for the 1 to 2 years group, and 10.21 for the 2+ years group. Thus, the incidence of enteropathy-related hospitalizations increases markedly as time of exposure to olmesartan increases, suggesting that olmesartan-induced enteropathy may develop slowly [24]. Therefore, future studies are awaited to determine whether olmesartan can induce varying degrees of gastrointestinal damage and, if so, the resultant spectrum of symptoms and histologic findings. The role of olmesartan in the etiology of microscopic colitis also needs to be established.

4. Nonolmesartan ARBs

Other drugs in the class of ARBs have a similar intended mechanism, but it is uncertain to what degree they may be associated with a clinical syndrome or histopathologic changes similar to those observed for olmesartan. A few recent reports have implicated several nonolmesartan ARBs in sprue-like enteropathy. For instance, a case report in which a patient had symptoms and histologic findings quite similar to what has been described above for olmesartan and was found to be taking valsartan. Cessation of valsartan coincided with a complete resolution of symptoms following years of debilitating diarrhea [3]. Two cases of irbesartan-associated enteropathy have also been reported. One patient, a 54-year-old woman, experienced abdominal pain and significant weight loss after taking irbesartan for less than 1 year. Duodenal biopsies demonstrated total villous atrophy, and antibody testing confirmed negative celiac serology. Withdrawal of irbesartan resulted in clinical

remission [6]. A second similar case has also been reported [5]. The possibility of a class effect is further suggested by a case report describing telmisartan-associated enteropathy in a 71-year-old woman who presented with diarrhea and weight loss after 2 months of telmisartan use. Histologic findings revealed villous atrophy, subepithelial collagen deposition, lamina propria inflammation, and intraepithelial lymphocytosis in the terminal ileum. Normal histology and relief of symptoms were achieved within 7 months after drug cessation [4]. Clinical trials of the more recently released ARB, azilsartan, are also worth considering. Although no histopathologic changes have been described, the manufacturer reported that diarrhea was the most common side effect (2% versus 0.5% placebo) observed during clinical trials of 4184 patients [27]. Another trial of the drug also found diarrhea to be an adverse effect (4.2% for 80 mg dose versus 1.3% placebo) [28]. Further studies could elucidate whether diarrhea experienced by patients taking azilsartan is associated with sprue-like histologic changes.

5. Histopathologic differential diagnosis

Based on the histologic features described above, it is clear that the histopathology of ARB enteropathy overlaps with both common and rare etiologies of small intestinal mucosal injury. Although not discussed in the literature thus far, we have observed that most ARB-enteropathy cases exhibit varying degrees of granulocytic infiltration (both neutrophils and eosinophils) and increased crypt apoptosis. This broadens the differential even further, and there is no cardinal finding which can establish the diagnosis of olmesartan-induced injury based solely on histopathology. On the other hand, if one is aware that this entity exists and obtains the relevant history, then the diagnosis is fairly straightforward in most cases. The entities with overlapping histopathologic features are discussed below, and where possible, distinctions are noted (Table 2).

5.1. Celiac disease

For most pathologists, the first consideration when encountering a flat duodenal biopsy is celiac disease, and indeed, up to 15% of patients will carry a diagnosis of seronegative celiac disease [10,29]. Based on personal experience and the published literature, there are some subtle histologic differences which can be observed. It is unusual to see a flat lesion in celiac disease and not be able to detect an appreciable increase in IELs. On the other hand, studies have shown that a sizable proportion of ARB enteropathy patients do not display this feature [1,14]. In addition, ARB enteropathy cases are very frequently associated with increased subepithelial collagen, which is a rare complication of celiac disease [1,10]. Ultimately, seronegativity and ARB use are the most meaningful discriminators between celiac disease and ARB enteropathy.

5.2. Tropical sprue

Tropical sprue is notable for severe intraepithelial lymphocytosis usually without profound villous atrophy, and flat lesions are rare [30]. Collagenous sprue is not generally associated with otherwise typical tropical sprue. As many cases of ARB enteropathy are associated with microscopic colitis, it is not likely that comparison of duodenal and ileal biopsies (often

Table 2 Possible histopathologic differences between ARB enteropathy and other entities

Entity	Histopathologic features	Distinguishing features of ARB-enteropathy
Celiac disease	Intraepithelial lymphocytosis Crypt hyperplasia Villous atrophy	IEL sometimes within, or close to, normal limits Collagen deposition frequent
Tropical sprue	Intraepithelial lymphocytosis, often worse in terminal ileum than duodenum Often preserved architecture	Villi often flat IEL sometimes within, or close to, normal limits Collagen deposition frequent
Autoimmune enteropathy	Variable features—villous atrophy, possible intraepithelial lymphocytosis, loss of goblet cells,loss of Paneth cells	No known histopathologic distinguishing features
Crohn disease	Patchy active inflammation Intraepithelial lymphocytosis Granulomas Variable architectural distortion	Granulomas not characteristic Diffuse involvement Collagen deposition frequent
Mycophenolate toxicity	Typically shows only increased crypt apoptosis; however, some cases may show intraepithelial lymphocytosis and/or villous atrophy	More diffuse and severe villous atrophy More chronic and active inflammation Collagen deposition frequent

Abbreviations: ARB, angiotensin receptor blocker; IEL, intraepithelial lymphocytosis.

helpful in the differential of tropical sprue and celiac disease) would be particularly useful in the distinction of tropical sprue and ARB enteropathy.

5.3. Autoimmune enteropathy

AIE is an autoimmune disorder which causes intractable diarrhea in both children and adults and is, at least in some instances, associated with autoantibodies to intestinal epithelial cells [31]. Histopathologically, it demonstrates villous atrophy, intraepithelial lymphocytosis, chronic and active (acute) inflammation, increased crypt apoptosis (resembling graft-versus-host disease), and sometimes loss of goblet and Paneth cells (which are the target of the autoantibodies) [31]. All of these findings have been described in ARB enteropathy and observed in such cases in our clinical practice [8]. Therefore, the distinction of AIE and ARB enteropathy seems practically impossible without the relevant history (Fig. D-F).

5.4. Inflammatory bowel disease

Both Crohn disease and ulcerative colitis can affect the duodenum in approximately 1/4 to 1/3 of cases [32,33]. We are unaware of granulomas being identified in ARB enteritis, whereas they are seen in variable numbers of Crohn patients (although some studies report finding them only rarely) [32,33]. Thus, if a granuloma is encountered in the duodenum, Crohn disease or an infectious etiology is much more likely than ARB enteritis. Furthermore, although this has not been formally studied, while Crohn disease demonstrates a patchy distribution, ARB enteropathy seems to affect the duodenum more diffusely. Duodenal involvement by ulcerative colitis may be more difficult to distinguish, although, again, collagenous sprue is not typically a feature of upper gastrointestinal involvement by ulcerative colitis. See Fig. G and H.

5.5. Other medications

Other types and classes of drugs can have protean manifestations in the gastrointestinal tract. Medications derived from mycophenolic acid can cause sprue-like changes in the duodenum [10,34]. The most characteristic finding in most cases of mycophenolate toxicity is increased crypt apoptosis (Fig. I). However, intraepithelial lymphocytosis and villous atrophy can also be seen in such cases [34,35].

6. Conclusions

Olmesartan-associated enteropathy is a recently described entity with clinical features including severe diarrhea and weight loss. The mechanism of injury is not well established, but the phenotypic similarity to the entities described above suggests an immune-mediated inflammatory disorder in susceptible individuals. Histopathologic findings include severe (total) intestinal villous atrophy with more variable intraepithelial lymphocytosis, frequently increased subepithelial collagen, and inflammation of lamina propria. Cessation of olmesartan results in complete resolution of both clinical and histologic features. Less frequently, other drugs of the same class have been reported to cause this syndrome. It is also possible that less severe forms of intestinal injury are also associated with olmesartan use. Although we have attempted to provide histopathologic features which may aid in the differential diagnosis, definitive diagnosis requires clinico-pathological correlation, highlighting the importance of effective 2-way communication between pathologists and gastroenterologists. Very rarely can such a small intervention (switching antihypertensive medications) have such a drastic impact on a patient's health, thus, it is important for pathologists, as well as other physicians, gastroenterologists, cardiologists, and primary care, among others, to be aware of the histopathologic changes associated with ARB enteropathy.

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