Lymphocytic duodenitis or microscopic enteritis and gluten-related conditions: what needs to be explored?

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Abstract

Microscopic enteritis (ME) is characterized by abnormal infiltration of intraepithelial lymphocytes in intestinal mucosa. It was described as duodenal lymphocytosis or lymphocytic duodenitis until the dedicated Consensus Conference of 2015. ME represents a common feature of several gluten-mediated and non-gluten related diseases; therefore, it is an umbrella term embracing several conditions. The most frequent causes of ME are gluten-related disorders (celiac disease, non-celiac gluten sensitivity, wheat allergy), *Helicobacter pylori* infection and drug-related damages. Less frequently, ME may be secondary to inflammatory bowel disease, some autoimmune conditions, immunoglobulin deficiencies, blood malignancies, infections and irritable bowel syndrome. Therefore, the differential diagnosis of ME may be challenging. The diagnosis of ME needs to be driven by predominant symptoms and patient history. However, it is often difficult to achieve an immediate identification of the underlying condition, and a broad variety of diagnostic tests may be required. Ultimately, long-term surveillance is needed for a final diagnosis in many cases, since a hidden or quiescent condition may be disclosed after a period of latency. In any case, strict collaboration between the clinician and the pathologist is pivotal. The treatment of ME should be personalized, depending on the underlying disease. For gluten-related conditions (celiac disease, gluten sensitivity, wheat allergy, dermatitis herpetiformis), a gluten-free diet may be proposed. For other conditions, a targeted etiologic treatment is necessary. In conclusion, ME represents a novel entity that is attracting increasing interest. The growing epidemiologic trend confirms that it will become a common condition in clinical practice.

Keywords Microscopic enteritis, duodenal lymphocytosis, celiac disease, gluten sensitivity, gluten-free diet, intraepithelial lymphocytes

Ann Gastroenterol 2017; 30 (4): 380-392

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Conflict of Interest: None

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Introduction: Definition of microscopic enteritis (ME) and epidemiology

An abnormal infiltration of intraepithelial lymphocytes (IELs) in the gastrointestinal mucosa is a common feature of several diseases, both gluten-mediated and non-gluten-related [1]. It has been regarded as duodenal lymphocytosis or lymphocytic duodenitis in the past, but the recent Bucharest Consensus has proposed the new entity of ME as an umbrella term to describe this condition [2,3].

IELs are a usual element among the cells harvesting intestinal mucosa, and a number of 11-25 IELs per 100 enterocytes is considered normal [4-6]. However, a number exceeding 25 per 100 enterocytes (the so-called Marsh I stage) is regarded as a pathologic feature [7]. Nevertheless, this should not be considered as a strict cutoff value, since the distribution and the density of IEL infiltrate balance along the alimentary

tract is irregular. For this reason, the diagnosis of ME is often difficult and relies on the expertise of the pathologist.

As already stated, several diseases may imply ME. For this reason, it is viewed as a quite common condition with an increasing trend over time. Galli *et al* [8] found the prevalence of ME to be 6.2% in a retrospective database of 7000 duodenal biopsy samples and, interestingly, reported a fivefold increase from 2010 to 2013, especially for non-gluten related disorders. Another two studies reported a prevalence of ME of 1.3% and 2.2%, respectively [9,10]. Shmidt *et al* [11] described a prevalence of 4.3% in a pediatric population and, in another study, showed an increase from 3% to 10.9% over a 10-year period [12]. All these studies agree that the increasing prevalence of ME may be due mainly to conditions other than celiac disease and that females are more frequently affected than males.

Based on these reports, ME represents a novel entity that is attracting increasing interest. However, ME is a complex condition; therefore, the knowledge of the importance and the role that IELs play in mucosal immunity is fundamental before we analyze the individual conditions that may lead to ME.

The role of IELs in immune homeostasis

The intestinal mucosa is a pivotal contact barrier between the body and the environment. For this reason, it has continuous direct interaction with external antigens. As a consequence, the intestinal mucosa contains a huge population of immunity cells that regulate the interface between the human organism and germs and non-self antigens. In this context, IELs play a relevant role.

IELs are T-lymphocytes whose main function is to maintain immune surveillance. They are powerfully stimulated by several intraluminal factors, such as ingested antigens and gut microorganisms; therefore, their phenotype and function may vary along the intestinal tract [13]. Immunohistochemistry for CD3 is the most useful tool for detecting them in biopsy samples (Fig. 1). However, IELs often have a complex phenotype. Indeed, many subclasses have been described, according to clusters of differentiation and related T-cell receptor subtypes and specific functions [14]:

1. IELs CD4αβ are specifically expressed in the colon and produce interleukin (IL)-10, with anti-inflammatory properties
2. IELs CD8αβ CD94+ are able to cooperate with natural killer cells, activating them when IELs interact with some antigens
3. IELs CD8αβ CD94- are the main interferon-γ producers; therefore, they are able to mount an inflammatory response directly
4. IELs γδ represent a small percentage of IELs, but they play an important role in cell-mediated immunity.

The interaction between αβ and γδ IELs is essential to balance the immune tolerance and the response to antigens. When inflammatory stimuli occur, the αβ IELs upregulate the natural killer receptors, promote the production of proinflammatory cytokines, such as tumor necrosis factor-α and interferon-γ, and induce the lysis of infected enterocytes by releasing both perforin and granzyme B [15,16].

Therefore, IELs act as modulating cells in the process of antigen presentation. It is known that, in celiac disease, antigen-presenting cells pass gluten immunogenic peptides to T-lymphocytes in the *lamina propria* [17]. Following gluten stimulation, a marked proliferation of T-helper lymphocytes and an increased production of inflammatory cytokines, mainly interferon-γ, characterize the celiac intestinal mucosa. Remarkably, gluten-specific CD4+ T-cells can be isolated from the small intestinal biopsy samples of celiac disease patients and not from non-celiac controls, thus underlining their pathogenic relevance [18]. Despite the pivotal role played by CD4+ T-lymphocytes in the pathogenesis of celiac disease, recent evidence suggests that CD8+ T-cells are also involved in the inflammatory cascade elicited by the gluten. Therefore, IELs are both regulatory cells and main actors in the pathogenesis of celiac disease. Nevertheless, IELs are also agents of innate immunity; therefore, they are self-activated even if stimulated by antigens other than gliadin, such as bacteria, drugs and foods [19]. For this reason, they are involved in the development of all types of ME.

Figure 1 Histopathologic picture of microscopic enteritis. On the left, (A) a hematoxylin-eosin staining of a duodenal villus. Intraepithelial lymphocytes (IELs) are indicated by the arrow. On the right, (B) IELs are identified by immunohistochemistry for CD3 (brown staining)

Origin of ME

Celiac disease

Celiac disease is the most common autoimmune enteropathy, triggered by the ingestion of protein molecules (gliadin, secalin, hordein) contained in wheat and associated species of barley, rye and oats [20]. A genetic predisposition is frequent, with most subjects being carriers of human leukocyte antigen (HLA) DQ2 or DQ8. The mucosal damage is mediated by either innate or adaptive immunity. In this regard, Fig. 2 summarizes the pathogenesis of the different forms of ME.
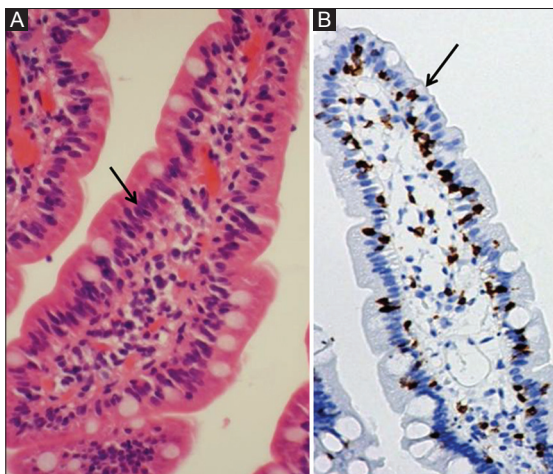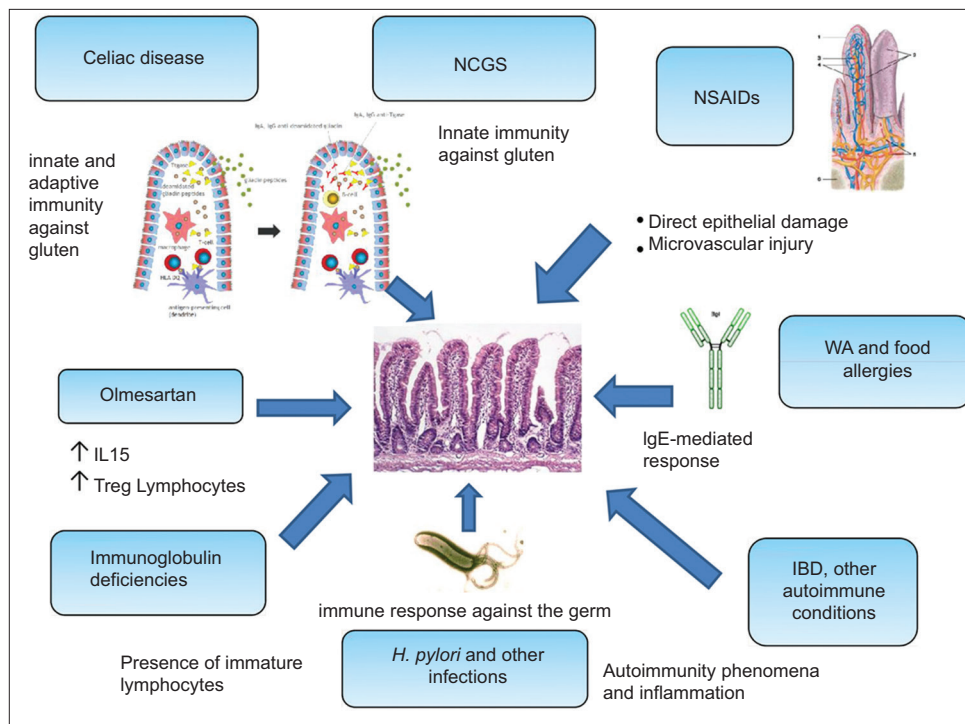
Figure 2 Different pathogenic mechanisms of microscopic enteritis.
NCGS, non-celiac gluten sensitivity; NSAIDs, non-steroidal anti-inflammatory drugs; IL, interleukin; WA, wheat allergy; IBD, inflammatory bowel disease; H. pylori, Helicobacter pylori

The degree of mucosal damage in celiac disease has been classified according to the Marsh staging. In this classification, a picture of duodenal lymphocytosis may be given a grade of 1, characterized by an infiltrate of more than 25 IELs/100 enterocytes. Although these subjects do not display a villous atrophy, they often show signs of malabsorption, such as anemia and osteopenia [21]. In contrast to non-gluten related causes of ME, they may reveal a clinical picture characterized by extraintestinal manifestations of celiac disease [22].

Notably, it has been reported that celiac patients with minimal mucosal alterations are less frequently positive for anti-transglutaminase and anti-endomysium antibodies than those with villous atrophy [23]. The condition marked by mild enteropathy, celiac disease and negative serology has been described as seronegative celiac disease [24,25]. A conflicting debate has arisen in this context, since some researchers do not acknowledge the need for a gluten-free diet and suggest a watch-and-see strategy until serology becomes positive [26]. Others recommend a gluten-free diet, since simultaneous mucosal inflammation and extraintestinal manifestations have been described in this condition [27,28].

Non-celiac gluten sensitivity

Non-celiac gluten sensitivity is a novel nosological entity in the panorama of gluten-related disorders. It is characterized by both gastrointestinal symptoms (abdominal pain, diarrhea, bloating) and extra-digestive manifestations, such as weakness, headache,

joint pain or sometimes depression [29]. This cohort of symptoms is linked to gluten ingestion, and it has been demonstrated that their onset shortly follows gluten exposure, in contrast to celiac disease, where a latency time of several weeks is usual [30]. Several experimental studies have shown a selective involvement of innate immunity in non-celiac gluten sensitivity, suggested by the elevation of Toll-like receptor expression (Fig. 2) [31,32]. This immune mechanism seems to be unbound from possible genetic susceptibility, since positivity of DQ2/8 haplotypes has been described in only 50% of cases. Auto-antibodies typical of celiac disease are usually absent, and only anti-native gliadin antibodies tested positive in half of populations with non-celiac gluten sensitivity [33]: this finding adds further support to the hypothesis of an exclusive involvement of innate immunity in non-celiac gluten sensitivity. Recently, some studies have suggested that the triggering factor might not be gliadin, but other components of wheat, such as amylase-trypsin inhibitors or fermentable oligosaccharides, disaccharides, and polyols [34,35]; for this reason, the alternative nomenclature of non-celiac wheat sensitivity has been proposed [36].

Given the absence of a specific marker or a characteristic clinical picture, the diagnosis of non-celiac gluten sensitivity is based solely on the exclusion of other possible diseases and the gluten-free diet represents the only effective treatment. Indeed, non-celiac gluten sensitivity is an emerging disease. While early studies identified a prevalence of up to 6% [37], nowadays the possibility of the nocebo effect biasing gluten-related symptoms has led to the emergence of rigorous criteria (Salerno consensus) to diagnose non-celiac gluten sensitivity.

This consensus advised a double-blind crossover gluten challenge [38]. The application of these criteria has proven that true non-celiac gluten sensitivity has been overestimated in the past years. Indeed, a recent study that started with a sample size of 140 patients with clinical suspicion of this condition reported that only 14% were recognized as true non-celiac gluten sensitivity after this diagnostic workup [39].

Non-celiac gluten sensitivity is commonly associated with ME. The histological analysis of duodenal biopsy samples usually finds a Marsh 0 or I grade enteropathy. Increased IEL infiltration is observed in up to 25% of patients [40,41]. The presence of a linear T-lymphocyte infiltration in the *lamina propria*, occurring in about 78.5% of patients, has been proposed as a distinct feature in a single-center experience, but at the moment there is only the single report [42]. Finally, an increase in eosinophils has also been described [43]. However, such histological pictures represent only case series reports, and the specific microscopic characteristics of non-celiac gluten sensitivity have not been yet established.

Wheat allergy

Wheat allergy is an allergic condition triggered by grain protein ingestion. The mechanism may be mediated by specific IgE or cellular immunoreaction (Fig. 2) [44]. It is often associated with other allergic manifestations, such as asthma (48-67%) or allergic rhinitis (34-62%) [45]. Symptoms occur from a few min to 2 h following wheat consumption. In young children, gastroenterological manifestations, such as vomiting, diarrhea or abdominal pain, are more common [46]. Cutaneous signs (urticaria, erythema, angioedema, itching) are observed in about 40%. In adults, wheat allergy is associated with respiratory disorders (wheeze, stridor, persistent cough, hoarse voice, respiratory distress, nasal congestion) and, in the most severe cases, anaphylaxis [47]. Wheat-dependent exercise-induced anaphylaxis is a rare form of IgE-mediated anaphylactic reaction occurring 10-60 min after physical exercise within 10 min to 4 h following wheat ingestion [48].

Wheat allergy diagnosis relies on allergy tests. First-line examinations are skin tests for wheat flour, such as skin prick tests, which investigate cellular-mediated reactions. A further step consists in the evaluation of serum concentrations of allergen-specific IgE to whole wheat extract. Finally, gluten-specific IgE can also be assessed [44].

ME may occur in the context of wheat allergy, but other microscopic characteristics are an increase in mucosal basophil and eosinophil granulocytes [49]. Unfortunately, studies investigating the duodenal histology of wheat allergy are rare; it is therefore impossible to establish a clear association between ME and wheat allergy.

Dermatitis herpetiformis

Dermatitis herpetiformis may be a skin manifestation of celiac disease, presenting with blistering rash and typical cutaneous IgA deposits [50]. In dermatitis herpetiformis, IgA are present in the skin, and inflammatory cells and cytokines are found in the lesions. Furthermore, anti-endomysium and anti-transglutaminase antibodies occur in the serum, and the rash is gluten-sensitive. Small erythematous macules are initially observed and rapidly develop into urticarial papules and small vesicles, which may split, dry, and form scabs. Predominant symptoms are itching and burning. The rash has a characteristic symmetrical distribution. Elbows and upper forearms are involved in more than 90%. Other common sites are buttocks, knees, shoulders, sacrum, face, scalp, neck and trunk. This characteristic rash undergoes a rapid improvement after a gluten-free diet. Moreover, antibodies to both tissue and epidermal transglutaminase are usually found in the serum of patients with dermatitis herpetiformis [51]. Only a minority of patients, about 10%, have mild gastrointestinal symptoms. Villous atrophy in the upper small intestinal mucosa is found in 65-75% of patients with dermatitis herpetiformis. Even in patients with apparently normal biopsies, subtle changes in the mucosa, such as an increased number of IELs, may suggest a gluten sensitization [52,53]. Reunala *et al* [54] reported a condition of ME in 61% of patients with dermatitis herpetiformis, irrespectively of the presence of gastrointestinal symptoms.

Allergy to alimentary proteins

Allergy to cows' milk, soy products, fish, rice, and chicken has been associated with ME. Variable degrees of villous alteration with crypt hyperplasia may be seen [55]. A patchy enteropathy was found in 60% of patients with cows' milk allergy, in all cases characterized by duodenal lymphocytosis [56]. A striking increase in γ/δ-positive T-cells has been reported in such patients [57,58]. Further diagnostic clues are increased eosinophils and the association with clinical manifestations of an allergic phenotype.

Autoimmune enteropathy

Autoimmune enteropathy is rare condition characterized by severe and prolonged diarrhea and malabsorption with weight loss. It is due to autoimmune phenomena targeting intestinal mucosa [59]. The production of autoantibodies against enterocytes or goblet cells is the main pathogenetic mechanism. Therefore, the detection of such autoantibodies in the serum is the main diagnostic tool. Autoimmune enteropathy usually develops in infants and young children, although some cases have been recorded in adults [60]. Small intestinal histopathology usually includes various degrees of villous atrophy, IEL infiltration in the enterocyte layer and *lamina propria*, apoptotic bodies and crypt hyperplasia. IELs are more plentiful in the crypts than in the surface and villous tips [61].

Inflammatory bowel disease and other autoimmune conditions

Inflammatory bowel diseases are chronic autoimmune disorders of the alimentary tract. They show a complex pathogenesis, which has not been completely elucidated so far. Ulcerative colitis and Crohn's disease are the two most common phenotypic manifestations of inflammatory bowel disease. In particular, Crohn's disease may involve the entire gastrointestinal system, and a duodenal localization has been reported in 28.2% of patients [62]. In this subset of patients, the macroscopic appearance of the mucosa shows ulcers or erythema. Microscopic examination of the duodenum usually reveals a picture mimicking celiac disease. For this reason, ME in Crohn's disease should prompt a differential diagnosis between concomitant celiac disease and a duodenal localization [63]. Although a transmural inflammation and granulomas are a rare finding in endoscopic biopsy samples, they could help in the differential diagnosis, being a particular feature of Crohn's disease. ME has been reported even in ulcerative colitis: Vidali *et al* [64] identified an abnormal IEL infiltrate in 26.6% of patients, with a significant increase in CD3- and CD8-positive cells.

Other autoimmune disorders associated with non-specific ME are rheumatoid arthritis, vasculitides, connective tissue disorders, autoimmune thyroiditis, psoriasis and multiple sclerosis [65-70].

Helicobacter pylori (H. pylori) **and other infections**

H. pylori is the major cause of chronic gastritis. However, it has been demonstrated that it is one of the most common causes of ME. In a group of patients with functional dyspepsia, a direct relationship was demonstrated between the presence of *H. pylori* and ME [71]. Furthermore, in a Spanish prospective study, *H. pylori* was considered as the starting point for 24.4% of ME cases [72], while 19% of subjects with ME had positivity for *H. pylori* in an Italian series [73]. Additionally, Memeo *et al* showed that duodenal IELs from patients with *H. pylori* gastritis ranged from 3-42 lymphocytes per 100 enterocytes (mean 18.5) compared to 3-18 lymphocytes/100 epithelial cells (mean 6.6) in the control group [74]. IEL elevation was seen in 44% of duodenal biopsies from patients with *H. pylori* gastritis, a significantly higher percentage than in the control group. Finally, a significant reduction in IELs was reported after successful eradication [75]. Conversely, one single study found no correlation between the density of IELs and concomitant *H. pylori* infection [75].

Since *H. pylori* selectively colonizes the gastric mucosa, possible mechanisms for ME occurrence have been hypothesized: i) ME could be a simple epiphenomenon of the infection; ii) a passive, perhaps transendothelial, migration and accumulation of IELs could occur; and iii) acid-induced injury may be a possible stimulation for intraepithelial lymphocytosis [77-79].

Among parasitic infections, *Giardia duodenalis* and *Criptosporidium* may cause both intraepithelial lymphocytosis and villous atrophy. The clinical manifestations (abdominal pain and watery diarrhea), along with the histological picture, often resemble celiac disease. In these cases eosinophilia may occur and a careful examination may identify the parasite in biopsy and fecal samples [80-82]. Elevated IELs count are also found in viral enteritis [83].

Tropical sprue [84] is a diarrheic disease that is common in patients living in tropical regions. It is believed to be caused by infective agents, but a single species has not yet been recognized: indeed, it has been hypothesized that enteric coliform organisms could underlie this disease. The histological picture is very similar to celiac disease, but concomitant eosinophilia is frequent and inflammatory changes are often seen along the whole small bowel [84].

Small intestinal bacterial overgrowth (SIBO), when related to gastric hypochlorhydria or intestinal dysmotility, has been associated with an increase in IELs (in the absence of villous atrophy) compared with healthy controls [85]. The prevalence of SIBO in ME was 4.5% according to Kakar *et al* [9] and 22% in a Spanish study [86]. In these cases, conditions causing stasis or recirculation of the intestinal contents are predisposing factors. Interestingly, SIBO was found to be associated with celiac disease that was not responsive to a gluten-free diet, thus suggesting a possible link between the two conditions [87].

Immunoglobulin deficiencies

The histologic aspects of the duodenum of patients affected by immunoglobulin deficiencies are often similar to those of celiac disease [88]. Moreover, patients with immunoglobulin deficiencies may report digestive symptoms in up to 50% of cases [89] and this may impede the differential diagnosis.

Selective IgA deficiency is the most widespread primary immunoglobulin deficiency, due to altered regulation of the final maturation of B lymphocytes into IgA-producing plasma cells [90]. Selective IgA deficiency implies an increased risk of concomitant celiac disease. Indeed, the prevalence of celiac disease in selective IgA deficiency is higher than in the general population, ranging from 6.7-20.6% [91,92]. On the other hand, selective IgA deficiency is more common in celiac patients, with a prevalence of 1-39% [93]. Common variable immunodeficiency is a heterogeneous group of primary immunoglobulin deficiencies characterized by low serum levels of immunoglobulins and a downregulated response to specific antigens, with a high risk of respiratory and gastrointestinal infections [94]. Although the estimated prevalence is 1:25-50,000, common variable immunodeficiency is considered to be the most frequent symptomatic immunoglobulin deficiency [94]. The diagnosis is based on reduced levels of IgG and IgA. Selective IgM deficiency is an extremely rare disorder, defined by low levels of IgM [95] in the absence of alterations of other immunoglobulin classes. In adults, the prevalence is about 1:15,000 [96]. Gastrointestinal phenomena are observed in 15.7% of patients with selective IgM deficiency, and some studies have demonstrated an association between celiac disease and selective IgM deficiency [97,98]. Interestingly, IgM levels return to normal in most pediatric and adult patients after a gluten-free diet [99].

The histopathological prototype of immunoglobulin deficiency has frequently been reported as a sprue-like picture, similar to celiac disease, with atrophy of villi and intraepithelial lymphocytosis. Some clues may help to distinguish between immunoglobulin deficiency and celiac disease. For instance, unlike celiac disease, common variable immunodeficiency should be suspected when plasma cells are reduced or absent in the *lamina propria* [100-102]. Biagi *et al* [103] stated that the histologic response to a gluten-free diet is the only reliable tool for establishing a diagnosis. Other authors suggested that HLA determination may be helpful [104]. Finally, a familial connection between celiac disease and common variable immunodeficiency has been hypothesized [105].

Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin are widespread drugs, given for various indications (pain control, osteoarthritis, rheumatologic and cardiovascular disorders). An association with ME has been observed in 14-29.5% of patients [9,12]. NSAIDs are a well-known risk factor for gastric ulcers and erosions, but they are also a cause of similar damage to the small bowel [106]. In a study of patients with ankylosing spondylitis under NSAID treatment, duodenal mucosal lymphocytic infiltration was found in 83.3% of patients compared to 48.6% of controls [107]. Epithelial loss may be the consequence of a direct drug effect, while enterohepatic recirculation may increase the damage. In a murine model, villous ischemia elicited by slowing of villous blood flow and breaks to microvasculature have been identified as a further pathogenic mechanism [108]. In addition, in a rat model, indomethacin showed a direct proliferative effect on IELs [109].

Olmesartan is an antihypertensive drug that has recently been implicated in several cases of sprue-like enteropathy, with villous atrophy mimicking celiac disease [110,111]. In all the reports in the literature, drug withdrawal was effective in both stopping diarrhea and reversing mucosal damage. Other drugs of the same class were not linked to this histopathologic and clinical condition [112]. The pathogenesis of olmesartan-induced enteropathy is unclear, but it shares many features with celiac disease, including symptoms and immune-pathogenic pathways, such as increased numbers of CD8+ cells and corresponding overexpression of IL15 by epithelial cells [113].

Hematological malignancies

The digestive system may be affected by several types of lymphomatous disorders. Both B- and T-cell lymphomas have been described. The most common B-cell hematological malignancies affecting the intestine are MALT lymphoma, follicular lymphoma, mantle cell lymphoma and diffuse large B-cell lymphoma [114-117]. These subsets of disorders express a monoclonal proliferation of B-lymphocytes that infiltrate the mucosal layer, thus conferring a picture of ME. Enteropathy-associated T-cell lymphoma is a monoclonal disorder due to malignant degeneration of IELs. Two subtypes have been described: type 1 and 2, according to the different immunohistochemical phenotype. Type 1 in particular may be a complication of refractory celiac disease and is characterized by CD30 expression and singular chromosomal anomalies, such as 9q31.3 duplication or 16q12.1 deletion [118,119].

Graft-versus-host disease is a common complication following allogeneic hematopoietic cell transplantation that typically exhibits skin, gastrointestinal and liver injury. An immune reaction of transplanted bone marrow cells against the recipient underlies this condition. In intestinal graft versus host disease, the histological pattern may mimic both celiac disease (IEL accumulation and villous atrophy) and inflammatory bowel disease (ulcerations, cryptitis, crypt abscesses), thus prompting a differential diagnosis [120-122].

Irritable bowel syndrome

Irritable bowel syndrome is a functional disorder characterized by a group of symptoms, including abdominal pain and changes in the pattern of bowel movements, without any evidence of underlying damage [123]. Despite this definition, several reports have evidenced that a local inflammatory status may underlie this form [124]. Barbara *et al*, for example, have shown a crowding of degranulating mast cells close to mucosal nerves [125].

On this basis, several studies have highlighted mild IEL infiltration in the duodenum of irritable bowel syndrome patients. Spiller *et al* first demonstrated that, in post-infective diarrheal irritable bowel syndrome, there was an increase in IELs compared to controls, paralleling an increase in gut permeability [126]. Sundin *et al* [127] observed an increase in aberrant CD4+/CD8+ mucosal lymphocytes in both colonic *lamina propria* and epithelium in subjects with post-infectious IBS. In a series of 100 cases of ME, Aziz *et al* [128] reported an irritable bowel syndrome prevalence of 18%. Remes Troche *et al* [129] reported a mean IEL count in irritable bowel syndrome of 16.7±6 per 100 enterocytes, significantly lower than in celiac disease. An increase in duodenal IELs was seen even in the constipation variant of irritable bowel syndrome [130], thus emphasizing that a microscopic inflammatory change may trigger this "functional" condition.

Causes of ME: a panorama

In conclusion, our overview of the etiology of ME emphasizes the heterogeneity of this "umbrella term". Studies [9-11,72,128,131,132] attempting to elucidate the prevalence of the different underlying factors are summarized in Table 1. It is evident that the most frequent causes of ME are common conditions, such as gluten-related disorders, *H. pylori* and drugs. However, some reports claim that an apparent cause of ME fails to be detected in a very high percentage of cases. However, in most cases long-term surveillance leads to

Table 1 Prevalence and conditions associated with microscopic enteritis

Conditions	Kakar [9] (n=43) (%)	Mahadeva [10] (n=14) (%)	Hammer [131] (n=100) (%)	Shmidt [11] (n=48) (%)	Aziz [128] (n=100) (%)	Losurdo [132] (n=85) (%)	Rosinach [72] (n=90) (%)
CD	9	21	18	19	16	27	70
NCGS	-	-		-	-	22	-
Tropical sprue	2	-	1	-	-	-	-
H. pylori	-	-	6	6	14	6	50
SIBO/other infections	5	-	3	-	-	-	6
Drugs	14	-	8	20	21	-	13
IBD	12	-	8	11	2	5	-
Autoimmune conditions	14	-	6	-	4	2	-
Unexplained	7	21	26	33	34	-	9
IBS	9	14	20	-	-	38	-
Other	28	43	4	11	9	-	-

In some studies, the sum of percentages is more than 100% when more than one cause of microscopic enteritis was detected

CD, celiac disease; NCGS, non-celiac gluten sensitivity; SIBO, small intestinal bacterial overgrowth; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; H. pylori, Helicobacter pylori

a final diagnosis, since a hidden or quiescent condition may be disclosed after a latency period.

Natural history, clinical features and diagnosis

As mentioned above, in about a third of patients a suitable cause is not found when ME is initially detected (Table 1). Therefore, the follow up of the "so-called" idiopathic ME often allows a final diagnosis to be achieved. In the previous experience of our group [132], after a 2-year period of surveillance, 49% of patients developed a gluten-related disease (27% celiac disease and 22% non-celiac gluten sensitivity) and a large proportion were diagnosed with irritable bowel syndrome (38%). In a series of patients with Marsh I lesions, 50% showed worsening of their histological picture (Marsh III) after a mean period of 25 months, and anti-transglutaminase positivity was strongly predictive of this event [133]. Aziz *et al* [134] demonstrated that the evolution of ME towards celiac disease may be predicted by a family history of this disorder (odds ratio 6.73), HLA DQ positive status and anti-transglutaminase levels more than 3 times the upper normal limit. Moreover, we have shown that the increased mucosal expression of some inflammatory mediators may predict the evolution towards a gluten-related disorder, in particular tissue transglutaminase, and interferon-γ could discriminate between the future development of celiac disease rather than non-celiac gluten sensitivity with a specificity of 87.1% and 96.77%, respectively despite a low sensitivity (about 50%) [135].

The clinical framework of ME is extremely heterogeneous, owing to the large variety of its etiology. Despite a macroscopically normal small bowel, microscopic and sub-

microscopic abnormalities consistent with ME may induce a malabsorption syndrome. This phenomenon may be linked to the activation of local and systemic cytokines that trigger the inhibition of nutrient uptake. Although the malabsorption is less evident than in the presence of severe mucosal atrophy, it has been demonstrated that the clinical presentation and the entity of nutrient deficiency do not correlate with the degree of villous atrophy, and a lack of micro and macronutrients may occur even in Marsh I lesions [21,22,136]. The most commonly described conditions are iron, folate, B12 vitamin and vitamin D deficiencies [21,22,132]. Diarrhea and abdominal pain are the most common symptoms in ME. Other clinical features are specific of the disease underlying ME: dyspepsia or epigastric pain may be associated with *H. pylori* infection, recurrent infections with immunoglobulin deficiencies, or the coexistence of rhinitis, asthma and/or urticaria with allergic diseases.

On this basis, the differential diagnosis of ME should be driven by predominant symptoms and patient history (Fig. 3). Exposure to drugs and improvement in the symptoms after their withdrawal may strongly suggest the diagnosis. Extra-intestinal manifestations fitting with celiac disease, anemia and diarrhea may be associated with gluten-related disorders, thus suggesting that specific serology should be determined. A gluten challenge according to the Salerno criteria is indicated for non-specific gluten sensitivity. Dyspeptic symptoms and/or iron deficiency anemia in young people should nudge the clinician in the direction of *H. pylori* gastritis. Bloody diarrhea, anemia and weight loss may raise the suspicion of inflammatory bowel disease; therefore, fecal calprotectin, colonoscopy and eventually small bowel magnetic resonance could be useful. A history of recurrent infections should prompt immunoglobulin profiling to investigate deficiencies.

The coexistence of urticaria with asthma or other respiratory symptoms may suggest wheat allergy or other allergies; therefore, allergy investigations such as a prick test, patch test or assay of IgE antigliadin may be indicated. Once further causes of ME have been ruled out, irritable bowel syndrome is plausible. In this context, HLA haplotype characterization may be very useful for ruling out gluten-related diseases, given the optimal negative predictive value of the test [137,138].
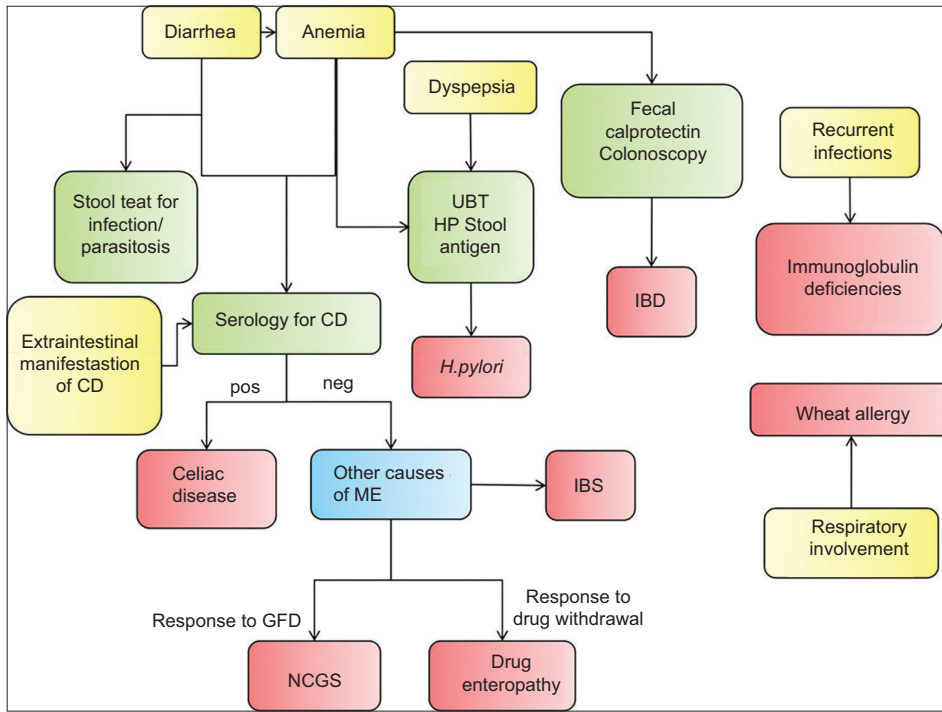

Figure 3 Proposal for a diagnostic algorithm for microscopic enteritis (ME)
CD, celiac disease; UBT, urea breath test; HP, Helicobacter pylori; IBD, inflammatory bowel disease; GFD, gluten-free diet; NCGS, non-celiac gluten sensitivity; IBS, irritable bowel syndrome
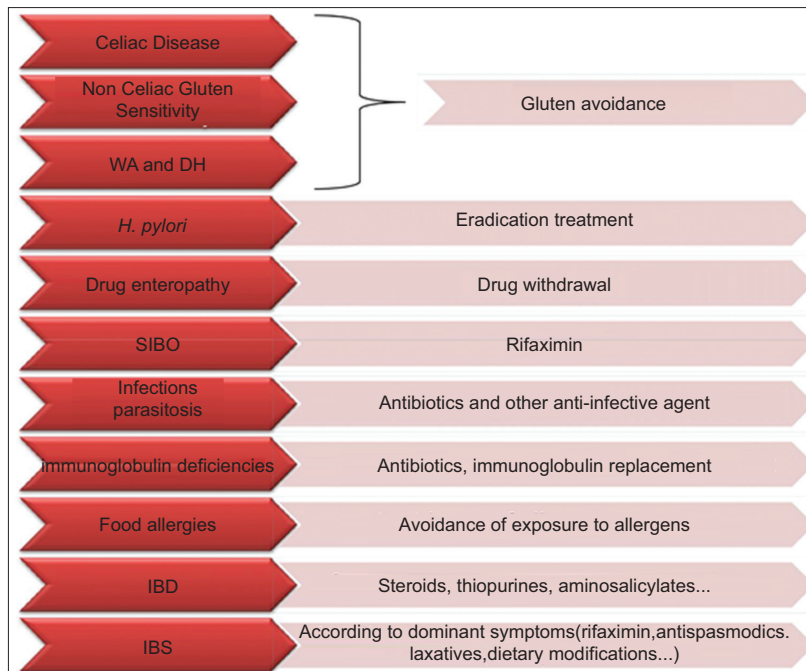

Figure 4 Figure summarizing possible treatments for microscopic enteritis according to the underlying disease
WA, wheat allergy; DH, dermatitis herpetiformis; SIBO, small intestinal bacterial overgrowth; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome

A possible diagnostic algorithm for ME is summarized in Fig. 3.

Treatment

The treatment of ME is personalized and depends on the underlying disease. For gluten-related conditions (celiac disease, non-celiac gluten sensitivity, wheat allergy, dermatitis herpetiformis), a gluten-free diet may be proposed, and it has demonstrated good effectiveness as regards symptom improvement and reversal of microscopic lesions [137]. For *H. pylori*-related duodenal lymphocytosis, eradication therapy should be proposed [139,140]. Antibiotics have shown effectiveness in both bacteria eradication and ME reversal [76]. Other intestinal infections require treatment that is targeted according to the etiologic agent, such as metronidazole for *Giardia spp*, rifaximin for SIBO, or fluoroquinolones for other bacterial species [141-143]. When the damage is sustained by drugs, withdrawal or switching to another class may be effective in curing ME [144]. For food allergies, avoidance of allergens is required [145]. As we know, the treatment of inflammatory bowel disease is based on several drug combinations, including aminosalicylates, steroids, antibiotics, thiopurines and biologic agents, according to the disease extension and severity, as recommended by guidelines [146,147]. Autoimmune enteropathy and other autoimmune conditions may require steroids and/or other immunosuppressive regimens [59]. Rare conditions, such as graft-versus-host disease, hematologic malignancies and immunoglobulin deficiencies, should be managed by a multidisciplinary dedicated team.

The therapy of irritable bowel syndrome is extremely varied, and needs to be personalized according to its subtype (diarrhea or constipation), following the Rome foundation report. The most currently used drugs encompass rifaximin, probiotics, prebiotics, fibers, antispasmodics, laxatives and dietary interventions [148-155].

In conclusion, the treatment of ME is complex and should be tailored for each patient, as reported in Fig. 4. A correct diagnosis, however, is necessary to guarantee the most indicated therapy and the best outcome.

Concluding remarks

ME is a heterogeneous condition, which thus represents a real challenge for the gastroenterologist. However, due to the complexity of the problem, the clinical approach needs interaction with other specialists, such as pathologists, immunologists, hematologists, allergists and laboratory medicine specialists. The challenge for the future will be the definition of novel methodologies to improve the diagnosis and treatment. At the moment, the state of the art requires an adequately skilled clinician.

Acknowledgment

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