SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Gastrointestinal diseases of immune-mediated inflammatory pathogenesis – immunologic and clinical perspectives

by Istvan Fedor, MD

Supervisor:
Eva Zold, MD, PhD

UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF GYULA PETRÁNYI CLINICAL IMMUNOLOGY AND ALLERGOLOGY

DEBRECEN, 2026

Gastrointestinal diseases of immune-mediated inflammatory pathogenesis – immunologic and clinical perspectives

By Istvan Fedor, MD

Supervisor: Eva Zold, MD, PhD

Doctoral School of Clinical Immunology and Allergology, University of Debrecen

Reviewers:

Prof. Dr. László Majoros, PhD
Dr. István Takács, PhD

Head of the Defense Committee:

Prof. Dr. Attila Bácsi, DSc

Members of the Defense Committee:

Dr. Bíborka Nádró, PhD
Dr. Renáta Erika Laczik, PhD

The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, at 13:00, on 5th of February, 2026.

INTRODUCTION

Inflammatory Bowel Disease (IBD)

Inflammatory bowel diseases (IBD) are chronic, immune-mediated conditions, including Crohn's disease (CD) and ulcerative colitis (UC). In addition to genetic predisposition, environmental factors and the interaction between the gut microbiome and the immune system play a significant role. Although IBD primarily affects the gastrointestinal tract, extraintestinal manifestations can also occur.

CD and UC share similar clinical symptoms (e.g., diarrhea, abdominal pain), but they differ in their genetic and inflammatory patterns. While CD can affect any part of the gastrointestinal tract, UC is confined to the colon. In CD, the inflammation is segmented ("skip lesions"), whereas in UC the inflammation is continuous. The inflammation in CD is transmural, affecting deeper layers of the intestine, while UC involves more superficial inflammation.

The genetic background of IBD is complex. Crohn's disease is associated with mutations in the NOD2/CARD15 gene, while ulcerative colitis is linked to mutations in the IL23R and HLA-DRA genes. Genetic research is helping to better understand these diseases and identify new therapeutic targets.

The gut microbiome is increasingly recognized as a key player in the pathogenesis and disease course of IBD. Changes in gut flora composition (dysbiosis) may contribute to maintaining the inflammatory state of the gut. Restoring the microbiome, for example, through probiotics, could be a promising therapeutic approach for IBD management.

The prevalence of IBD is similar in men and women, although Crohn's disease is slightly more common in women, whereas UC shows a male predominance, especially in older age groups. IBD is typically diagnosed in young adulthood, though some cases emerge as early as childhood or adolescence. Geographically, the highest incidence of IBD is observed in North America and Europe, with lower rates reported in Asia and the Middle East. In developed countries, the incidence of new cases has stabilized, while in developing regions, the incidence is rising, likely due to lifestyle changes – adopting a "Westernized lifestyle". In recent decades, the burden of disease, such as disability-adjusted life years (DALYs) and years of life lost (YLL), has improved due to advancements in treatment.

The treatment of IBD requires a multidisciplinary approach, including drug therapies (e.g., aminosalicylates, corticosteroids, immunomodulators, biological agents) and surgical interventions when necessary. The available therapies have made it possible to adopt a treat-to-target (T2T) strategy. Significant advances have been made with biological therapeutics, which have enabled better disease control and maintenance of remission, thus reducing the need for surgical interventions such as bowel resection.

Present and future research aims to develop precision medicine and personalized treatment strategies. Genetic and biomarker research, along with the development of new therapies, can contribute to a better understanding and treatment of the disease. Investigating the role of environmental and lifestyle factors is also a priority for both disease prevention and treatment.

Microscopic colitis

Microscopic colitis (MC) is a chronic inflammatory disease of the colon that can be divided into two types: lymphocytic colitis (LC) and collagenous colitis (CC). Due to the nature of the disease, a definitive diagnosis is made through colonoscopy and histopathological examination. Macroscopically, the mucosa appears intact, but histopathologically, characteristic inflammatory abnormalities are observed. Lymphocytic colitis is dominated by the presence of increased intraepithelial lymphocytes, whereas in collagenous colitis, thickening of the subepithelial collagen bundle is observed. Although there is overlap in their clinical manifestations and treatments, LC and CC are considered distinct diseases.

Microscopic colitis – as opposed to IBD - affects only the intestinal tract, occurs mainly in older age, and is usually associated with fewer complications. It does not increase the risk of developing colorectal cancer.

The prevalence of microscopic colitis varies geographically, similar to inflammatory bowel diseases. In Western societies, the incidence has stabilized in recent years, while in developing countries, it is increasing.

Objectives

Our studies aimed to compare the clinical features of microscopic colitis (MC) and inflammatory bowel disease (IBD), with particular attention to the age at diagnosis, affected bowel segments, and associated autoimmune and allergic diseases. We also aimed to identify

the similarities and differences in the incidence and clinical presentation of MC and IBD, thus contributing to improved diagnostic and therapeutic approaches.

- Description of autoimmune and allergic-atopic diseases associated with microscopic colitis in our patients.
- Description of the Montreal classification in patients with inflammatory bowel disease (IBD), the affected and inflamed bowel segments, and the relationship between these and clinical presentation.
- Description of extraintestinal manifestations (EIM) in our IBD patients and associated immunoinflammatory diseases, with particular focus on the timeline of these conditions, the co-occurrence of specific EIMs, and their relationship with the affected bowel segments.

PATIENTS AND METHODS

Patients Participating in the Study

All patients included in the study were under the care of a single specialist at the Clinical Center of the University of Debrecen. We reviewed the patient's medical records from the period between 2008 and 2022. Only patients with a definitive – confirmed - diagnosis of IBD or MC, as noted in their medical history, were considered.

In total, we analyzed data from 103 patients with microscopic colitis and 508 patients with inflammatory bowel disease (IBD). In the MC group, there were 28 patients with lymphocytic colitis (5 men, 23 women) and 75 patients with collagenous colitis (31 men, 44 women). Among the 508 IBD patients, there were 303 with Crohn's disease (133 men, 170 women) and 205 with ulcerative colitis (89 men, 116 women), meaning the IBD group included 222 men and 286 women overall.

Methods

We conducted a retrospective data collection based on previous medical records. MC diagnosis was confirmed in all cases by biopsy and histopathological sampling, reviewed independently by two pathologists. Immun-mediated inflammatory and allergic diseases associated with MC were diagnosed by the respective specialist. During data collection, we considered the age at diagnosis, the presence of autoimmune and allergic diseases, and the most frequent bowel

symptoms (constipation, diarrhea).

For IBD patients, we assessed the Montreal classification, the temporal appearance of extraintestinal manifestations (EIM), the age at diagnosis, and the presence of associated autoimmune diseases. The IBD diagnosis was confirmed by intestinal biopsy and imaging studies. We did not include a healthy control group, as it would not have been relevant to the research objectives and would not have added scientific value to the study.

Statistical Analysis

Patient data were recorded in Microsoft Excel (2019), and statistical analysis was conducted using Excel and Medcalc Software based on descriptive statistics. Group proportions were compared using the chi-square test, taking into account the specific characteristics of small sample sizes. In cases involving multiple groups, an ANOVA test was applied, while independent t-tests were used for comparing ages. Data visualization was performed using R-Studio.

Our data were compared with previously published results in the literature, prioritizing more recent publications from the NCBI PubMed database. When interpreting the results, the limiting factors associated with the small sample size were considered.

RESULTS

Microscopic Colitis: Controversies in Clinical Symptoms and Autoimmune Comorbidities

General Characteristics of Patients with Microscopic Colitis

In our study, we analyzed the medical histories of 103 patients with microscopic colitis (28 diagnosed with lymphocytic colitis and 75 with collagenous colitis). The average age at diagnosis differed: patients with lymphocytic colitis were significantly younger at the time of diagnosis (44.5 years) compared to those with collagenous colitis (51.9 years). Gender distribution also differed: in collagenous colitis, the male-to-female ratio was more balanced (1:1.6), while in lymphocytic colitis, there was a greater female predominance (1:4.6). The prevalence of autoimmune comorbidities was similar in both groups: 36% in the lymphocytic colitis group and 40% in the collagenous colitis group. Constipation was observed in 39% of patients with collagenous colitis, while it was less common in lymphocytic colitis, occurring in only 18% of the patients. Conversely, diarrhea was present in the vast majority of lymphocytic

colitis patients (82%).

Differences in bowel habits were often observed between lymphocytic colitis (LC) and collagenous colitis (CC). While patients with lymphocytic colitis primarily experienced diarrhea, those with collagenous colitis had a higher incidence of constipation.

Autoimmune Comorbidities in Microscopic Colitis

A significant portion of our patients with microscopic colitis also had associated autoimmune diseases. The difference between LC and CC patients was not significant, with similar rates of autoimmune comorbidities in both groups. Autoimmune diseases were present in 36% of those with lymphocytic colitis and 40% of those with collagenous colitis. The most common associated autoimmune diseases included Hashimoto's thyroiditis, rheumatoid arthritis, Sjögren's syndrome, and gluten-sensitive enteropathy (coeliac disease).

Allergic-Atopic Diseases in Microscopic Colitis

In lymphocytic colitis, the prevalence of allergic and atopic diseases was 21% (6 patients), while in collagenous colitis, this rate was 28% (21 patients). Asthma bronchiale and allergic rhinitis were the most common associated diseases. Asthma was present in 50% of lymphocytic colitis patients (3 patients) and 43% of collagenous colitis patients (9 patients). Allergic rhinitis also occurred at significant rates in both groups: 48% in collagenous colitis (10 patients) and 17% in lymphocytic colitis (1 patient).

Based on the examination of specific IgE antibodies for nutritional antigens, no such antibodies were detected in 80% of cases. A positive test was observed in 18 cases (22.2%). The most commonly detected antibodies were against peanuts, soy, and tomatoes, present in 33-44% of those who had a positive IgE test.

Temporal Relationship of Extraintestinal Manifestations in Inflammatory Bowel Disease - Results

General Characteristics of Our Patients and Affected Bowel Segments

In this study, we included 303 patients with Crohn’s disease (133 men, 170 women) and 205 patients with ulcerative colitis (89 men, 116 women). Crohn’s patients were diagnosed at a younger average age (32.4 years) compared to UC patients (35.0 years), and the difference was

statistically significant (2.63 years, p = 0.0313). Most Crohn's patients were in the Montréal A2 (age) category, with diagnoses between 17 and 40 years of age. The most common site of Crohn's disease involvement was the ileum and colon combined (Montréal L3), present in 42.2% of cases, while inflammation confined to the ileum (Montréal L1) occurred in 23.1% of cases.

In ulcerative colitis, inflammation localized to the distal colon (E1, proctitis) was most common: in 99 UC patients, the inflammation did not extend beyond the distal colon. In a smaller proportion of cases, left-sided colonic involvement (E2) was observed in 68 patients, while total colonic involvement (pancolitis – E3) occurred in 37 patients.

There was no significant difference in the age at diagnosis between the different groups of ulcerative colitis patients. The average age at diagnosis in the E1 (proctitis ulcerosa) group (99 patients) was 36.1 ± 14.55 years, while in the E3 (pancolitis, 37 patients) group, it was 32.7 ± 12.2 years. (95% CI: -8.7192 – 1.9192, p = 0.2084).

Extraintestinal Manifestations in Our CD and UC Patients

We compared the prevalence of extraintestinal manifestations (EIM) in patients with Crohn's disease and ulcerative colitis. EIMs were present in 41.91% of Crohn's patients, while their occurrence in ulcerative colitis was 39.51%. The difference between the two groups was not statistically significant. Extraintestinal symptoms were more common in our female patients, particularly involving the musculoskeletal system and ocular diseases (iridocyclitis, episcleritis). Skin conditions associated with Crohn's disease, such as erythema nodosum (EN), were also frequent.

We also found that EIMs occurred significantly more often in patients with ileocolonic Crohn's disease, whereas in ulcerative colitis, the occurrence of EIMs was particularly higher in those with pancolitis.

Relationship Between Affected Bowel Segments and EIMs

In our patients with Crohn's disease and ulcerative colitis, the overall presence of extraintestinal manifestations (EIM) showed similar rates, although there were some differences based on the affected bowel segments. Among Crohn's patients, the highest prevalence of EIMs was observed in those with ileo-colonic (L3) involvement, with a rate of 44.53%. There was

minimal variation in EIM occurrence across the different Montréal L categories for our Crohn's patients. In ulcerative colitis, pancolitis (E3) and left-sided colitis (E2) showed similar EIM rates (43.24% and 42.65%, respectively), while the rate was lower in patients with proctitis (E1), at 36.3%. Overall, EIMs were more frequently observed in our IBD patients with colonic involvement (Crohn's L2, L3, and ulcerative colitis). Typically, EIMs develop after the diagnosis of IBD.

EIMs Affecting Different Organ Systems in IBD

The most common extraintestinal manifestations (EIMs) were affecting the musculoskeletal system. Sacroiliitis occurred in 51 patients, with nearly equal distribution between those with Crohn's disease (32 patients: 20 women, 12 men) and ulcerative colitis (19 patients: 14 women, 5 men). Ankylosing spondylitis (SpA) occurred in 25 patients, with a higher prevalence in Crohn's patients (14 cases, 4.62%).

Among dermatological extraintestinal manifestations, erythema nodosum (EN) and pyoderma gangrenosum (PG) were the most common. EN was observed in 22 Crohn's patients (7.26%) and 5 ulcerative colitis patients (2.44%), often presenting before the diagnosis of IBD.

Gallstones were present in both groups (8.58% in Crohn's patients and 6.83% in ulcerative colitis patients), but gallstones are not classified as EIMs. There was no significant difference between the two groups in the prevalence of gallstones.

Timing of IBD and EIM Diagnoses

EIMs typically develop after the diagnosis of IBD. In our Crohn's patients, 9.45% developed EIMs before the diagnosis of IBD, whereas in UC patients, this figure was 17.28%. Multiple EIMs could also appear before bowel symptoms: in 4 Crohn's and 2 UC patients, more than one EIM developed before the diagnosis of IBD. There was no significant difference in the timing of EIM onset between the groups.

In Crohn's disease, 15% of our patients with ileo-colonic (Montréal L3) involvement first presented with extraintestinal diseases. This rate was 8% in the L1 (ileal) and L2 (colonic) Crohn's groups. In ulcerative colitis, the extent of disease (E) and the earlier onset of EIMs showed similar patterns: 16 pancolitis (E3) patients had EIMs in their medical history, and in 5 of them, EIMs developed before the onset of IBD symptoms. Inflammation of the descending

colon (left-sided colitis, E2) was associated with the development of EIMs prior to IBD in 6 out of 24 patients (25%). In proctitis ulcerosa (E1), EIMs were registered in 30 cases during the course of the disease, with 3 patients presenting EIMs before the diagnosis of IBD (10%).

Patients with multiple EIMs in IBD: Order and Associations

Due to the small sample size, no significant "pattern" was observed in the sequence of specific EIMs. The most common EIMs to develop first were joint-related, particularly peripheral joint inflammations. Clustering of joint inflammations was observed in 27 Crohn's patients and 15 UC patients. Dermatological manifestations often accompanied the presence of multiple EIMs, particularly in Crohn's disease.

Contrasting Autoimmune Comorbidities in Microscopic Colitis and Inflammatory Bowel Diseases - Results

General Characteristics of Our MC and IBD Patients

The age at diagnosis of our patients with microscopic colitis was younger than expected. In lymphocytic colitis, a significant female predominance was observed, while in collagenous colitis and IBD (Crohn's and UC), the male-to-female ratio was more balanced. There was a notable difference in the prevalence of associated autoimmune diseases between our IBD and MC patients. There was also a variation in the average age at diagnosis, showing different patterns across the four patient groups (LC, CC, CD, UC).

Autoimmune Diseases in IBD and MC: The Role of Colonic Involvement

In our patients, the prevalence of autoimmune conditions was twice as high in microscopic colitis compared to IBD (MC: 38.8% [40 patients out of 103], IBD: 19.1% [97 IBD patients out of 508]). The 19.7% difference was statistically significant (95% CI: 10.1324–29.8622; $p < 0.0001$).

In Crohn's disease restricted to the colon (L2), associated autoimmune diseases were more common in the medical histories of our patients. Inflammation predominantly affecting the small intestine (L1, L3, L4) was associated with autoimmune diseases in 29 patients (14.21% of 204 patients), while in Crohn's disease limited to the colon (L2), autoimmune diseases were diagnosed in 22 patients (24.7% of 89 patients). The 10.49% difference was statistically significant ($p = 0.0297$).

Including the data from the UC group, it was observed that 23.13% of IBD patients with purely colonic involvement had associated autoimmune diseases (68 patients out of 294 CD L2 and UC patients). This significantly differed from the 14.21% seen in small bowel-predominant Crohn's disease, where autoimmune diseases were diagnosed (8.92% difference; $p = 0.0135$).

In UC, the prevalence of associated autoimmune diseases was nearly the same as in Crohn's disease limited to the colon (L2 Crohn: 22 patients, 24.7%, vs. UC: 46 patients, 22.4%). The small 2.3% difference was not statistically significant ($p = 0.6678$).

We also compared the rates of autoimmune comorbidities in IBD patients with predominant colonic involvement to those in our MC patients. Autoimmune diseases were significantly more frequent in MC than in IBD cases involving the colon. The 15.67% difference was significant (95% CI: 5.4351–26.2999; $p = 0.0021$).

In Crohn's disease, the prevalence of autoimmune diseases was not significantly lower than in UC. In Crohn's patients, 16.8% had a history of associated autoimmune disease, while in ulcerative colitis, the rate was 22.4% (51 patients out of 303 Crohn's patients and 46 patients out of 205 UC patients). The 5.6% difference was not statistically significant given the small sample size ($p = 0.1153$).

Autoimmune Diseases of the Hepatobiliary System in IBD

There was no significant difference in the occurrence of liver and biliary autoimmune diseases between IBD and MC patients. Among the IBD patients, autoimmune hepatitis (AIH) occurred in 3 cases (0.6%, out of 508 patients). In our microscopic colitis patients, AIH was diagnosed in 1 case (0.97%, out of 103 patients), but no cases of primary biliary cholangitis (PBC) were observed.

Autoimmune Diseases of the Thyroid Gland in IBD

Autoimmune thyroid diseases were common across all patient groups, including both IBD and MC patients. Among our microscopic colitis patients, 14 cases of autoimmune thyroid disease (13.6%) were recorded. In the Crohn's disease group, 13 patients (4.29%) had a history of autoimmune thyroiditis, while in ulcerative colitis, this was observed in 10 patients (4.88%)—primarily in the form of Hashimoto's thyroiditis. The difference between the IBD groups was

not statistically significant (difference: 0.59%, p = 0.7539).

DISCUSSION

Microscopic Colitis: Controversies in Clinical Symptoms and Autoimmune Comorbidities - Discussion

Microscopic colitis and inflammatory bowel diseases share several common features, as both are characterized by chronic inflammatory processes in the gastrointestinal tract, primarily based on interactions between the immune system and the gut.

One of the methodological limitations of our study is the relatively small sample size (103 MC and 508 IBD patients), which reduces the generalizability of the results. Additionally, since the data were collected retrospectively, our study is primarily descriptive and not suitable for identifying causal relationships. However, it provides a basis for generating important hypotheses and defining new research directions, particularly for better understanding the clinical manifestations and comorbidities of these diseases.

Instead of involving a control group, we focused on comparing the patient groups, which allowed us to highlight disease-specific differences and similarities. The results may assist clinical practice, particularly in fine-tuning diagnostic and therapeutic decisions, by taking into account the distinct clinical characteristics of the patient groups.

In the case of microscopic colitis (MC), previous studies have generally found lymphocytic colitis (LC) to be more common, whereas our findings showed a marked predominance of collagenous colitis (CC). It is not surprising that the proportion of women is higher in both LC and CC, especially pronounced in LC. Additionally, constipation and the presence of IgE antibodies against dietary antigens were more frequent in collagenous colitis.

An established risk factor for the earlier diagnosis of MC at a younger age is smoking, which can bring forth the onset of the disease by one or two decades. Since this phenomenon is already well-known, we chose not to record detailed information regarding smoking status and habits.

The pathomechanism of microscopic colitis is closely related to immune-mediated alterations in the colonic mucosa, including increased intraepithelial lymphocyte count and thickening of the subepithelial collagen layer. These alterations may be bi-directionally linked to microbial dysbiosis, which also plays a role in the disease processes. The disruption of gut flora balance,

often observed in MC, may contribute to the persistence of the inflammatory state. The histological differences between LC and CC suggest that distinct immunological and microbial factors may contribute to the maintenance of these diseases.

The prevalence of autoimmune diseases was significantly higher in female MC patients (47.8%) compared to males (22.2%). Autoimmune diseases usually precede the diagnosis of microscopic colitis. These comorbidities often appear first in young adulthood, while MC is typically diagnosed in older age.

There is a well-established link between gluten-sensitive enteropathy (GSE, coeliac disease) and microscopic colitis (MC). In our cohort, four patients (3.86%) had coeliac disease, which is significantly higher than the estimated global prevalence of 0.7-1% (biopsy-confirmed). While the results may not be fully generalizable, they suggest that patients with MC may have a higher risk of developing coeliac disease, and vice versa. Further studies are needed to better understand the relationship between MC and coeliac disease, as well as the risk factors that promote their association.

The co-occurrence of microscopic colitis with other inflammatory bowel diseases (Crohn's disease and ulcerative colitis) is also known. However, we did not observe this association in our patients. It is important to note that MC cannot be considered a precursor to IBD, as the two diseases have distinct genetic backgrounds and processes.

We analyzed IgE antibodies to food antigens in 78 microscopic colitis patients. While 80% of patients did not have detectable IgE antibodies, the remaining 20% showed responses to one or more antigens. The most common reactions were to peanuts, soy, and tomatoes. This proportion is significant, as most patients with MC do not typically show high levels of IgE antibodies. This may suggest that a disruption in the gut barrier function plays a role in the development of allergic reactions.

Asthma and microscopic colitis, though distinct conditions, show some histological similarities. Both asthma and collagenous colitis can involve connective tissue proliferation (collagen fiber thickening) and lymphocytosis. A direct connection between lung fibrosis and collagenous colitis is rare. However, they share similarities with progressive systemic sclerosis (PSS, CREST syndrome), which points to a collagen metabolism disorder. These cases are rare in the literature, and none of our MC patients had such a diagnosis.

Clinically, younger patients with microscopic colitis often present with constipation or abdominal discomfort, which differs from the typical, prolonged diarrhea symptoms. Neither age nor the presence or absence of certain symptoms should be used as exclusion criteria during diagnosis.

A key element of the remission criteria proposed by Hjortswang is that the patient should pass normal stool no more than three times per day. This reflects an essential indicator of microscopic colitis remission, as active MC typically involves more frequent, watery stools. However, in "atypical" cases where constipation dominates, this criterion is not as easily applicable, making disease monitoring more challenging. In such cases, budesonide, a locally acting steroid, can be effective in relieving symptoms and restoring normal bowel function.

The dynamic change in symptoms, such as alternating constipation and diarrhea, can make disease monitoring more difficult, as histological remission criteria may not always be met. In older age, colorectal cancer screenings may help detect hidden cases that have not yet produced clinical symptoms. These screenings can also aid in the early detection of MC and IBD.

Regardless of whether the patient presents with constipation or diarrhea, associated autoimmune diseases were found at similar rates in their medical history. In Sjögren's syndrome, slow peristalsis often leads to constipation. Enteric nervous system neuropathy and digestive disorders are also common in Sjögren's, along with reduced saliva and digestive enzyme production due to damage to the salivary and pancreatic glands. Esophageal motility disorders and delayed gastric emptying are also frequent in Sjögren's syndrome.

In our small sample, we found that autoimmune diseases in the medical history were associated with constipation and alternating symptoms. Nearly half (44%) of patients with chronic constipation had a known autoimmune disease, compared to 37% of patients with diarrhea. This suggests that pre-existing immune-mediated inflammatory diseases may be slightly linked to atypical symptoms, although there was no significant difference between the two groups. The 7% difference ($p = 0.4972$) was not statistically significant, but it raises the possibility that, in a larger sample, constipation may be more common in connection with autoimmune diseases.

As seen with intestinal complications in IBD, inflammatory cytokines and environmental factors play an important role in maintaining the structural homeostasis of the extracellular

matrix (ECM).

The role of the ECM is significant in IBD, as it is closely linked to the structural integrity of the intestinal wall and the inflammatory response. ECM components, such as collagen and elastin, are crucial for regulating the mechanical properties of the intestines and the inflammatory responses. Damage to the ECM caused by inflammation, followed by fibrotic transformations, influences the progression of IBD.

Temporal Relationship of Extraintestinal Manifestations in Inflammatory Bowel Disease - Discussion

Extraintestinal manifestations (EIMs) in IBD patients can develop at any time, with no specific temporal relationship between the diagnosis of the primary disease and the appearance of EIMs. Visible – by the eye - EIMs may predict the later onset of IBD. In seven of our patients, noticeable EIMs appeared before intestinal symptoms, usually in the form of ophthalmologic and dermatologic conditions. Dermatologic manifestations were more frequent in Crohn's disease, and in all cases where skin symptoms preceded IBD, Crohn's disease was diagnosed. In contrast, ophthalmologic manifestations were more often followed by a diagnosis of ulcerative colitis, though the low number of cases prevents drawing general conclusions.

When examining the relationship between affected bowel segments and the appearance of EIMs, we found no significant differences between the various Montréal L groups in Crohn's disease. In cases where the colon was involved (L2 and L3), EIMs were recorded slightly earlier.

In ulcerative colitis, we observed that extraintestinal manifestations (EIMs) often develop earlier when the entire colon is affected (pancolitis, E3), sometimes even before the IBD diagnosis. In our pancolitis patients, about one-third of EIMs occurred before the IBD diagnosis, while in proctitis (E1) cases, this was true for only about one-tenth of patients.

We defined extraintestinal manifestations (EIMs) based on ECCO guidelines. Previous publications did not uniformly record EIMs, and the literature is heterogeneous with little consensus. For example, our data showed that sacroileitis occurred in 10% of patients, while higher rates have been reported in other regions. Underdiagnosis is possible, as sacroileitis is often asymptomatic and may only be identified incidentally during imaging studies.

In both IBD groups, the first EIM typically appeared as peripheral arthritis, while axial involvement, such as sacroileitis, rarely preceded peripheral joint inflammation. The clinical significance of this is uncertain, as axial arthropathies often progress independently of IBD activity and require specialized rheumatological care.

A patient with IBD may develop multiple EIMs over the course of their disease, which can appear at different times. No specific sequence can be established for the appearance of these manifestations. We emphasize the importance of lifetime prevalence when discussing EIMs. The appearance and order of EIMs show significant individual variation and are often not closely related to IBD activity, meaning they can occur independently of the primary disease's progression.

In addition to skin manifestations like erythema nodosum (EN) and pyoderma gangrenosum (PG), metastatic Crohn's disease occurs less frequently. This is an extraintestinal form of Crohn's disease that manifests as granulomatous skin lesions. Among our more than 300 Crohn's patients, metastatic Crohn's disease was observed in only two cases during the course of the illness.

Psoriasis is not considered an EIM of IBD but a distinct comorbid autoimmune disease. Patients with psoriasis often have mild, non-specific intestinal inflammation and altered gut microbiome. Beyond the skin, psoriasis predisposes individuals to cardiovascular, metabolic diseases, and joint inflammations, making it a more complex, multi-systemic condition.

Psoriasiform rashes can rarely occur when using TNF-α inhibitors (e.g., adalimumab), posing differential diagnostic challenges. Among our patients, two with psoriasis were treated with biological therapies, and no psoriasiform rashes were observed as a side effect.

The treatments for IBD and psoriasis overlap to some extent, as IL-12/23 and TNF-α inhibitors are effective for both conditions. However, immune system interventions may also lead to unexpected side effects. For example, IL-17 inhibitors like secukinumab or ixekizumab can, in rare cases, increase the risk of developing IBD.

The most common eye-related symptoms in our patients were conjunctivitis and dry eye. However, these can also be caused by other conditions. For example, associated Sjögren’s syndrome was present in four Crohn’s patients and three ulcerative colitis patients. Additionally, lifestyle factors can contribute to these conditions. Since these symptoms are not

always immunologically based and are not considered classic EIMs, we did not include them in our papers.

Dry eye disease (DED), which results from lacrimal gland dysfunction, is also known in IBD, primarily associated with Crohn's disease. DED is characterized by the absence of autoantibodies linked to Sjögren's syndrome, and the cases do not meet other clinical criteria for Sjögren's syndrome. Joint involvement and pancreatitis can also occur in Sjögren's syndrome, complicating the etiological assessment of these conditions. Pancreatitis, which is not considered an EIM of IBD, was observed in our patients: 10 Crohn's patients (3.3%) and 21 ulcerative colitis patients (10.2%) had a history of pancreatitis. This was significantly more frequent in the latter group (difference: 6.9%, 95% CI: 2.5492%-12.0253%, p = 0.0014).

The hepatobiliary immune diseases associated with IBD include primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). The prevalence of PSC in the medical history was similar in both the CD and UC groups. According to the literature, PSC is about four times more common in association with UC than with CD. However, our patient data did not confirm this. The number of cases in our cohort (CD: 4 patients – 1.32%, UC: 4 patients – 1.95%, difference: 0.63%, p = 0.5761) showed no significant difference. Although few of our patients developed these diseases, we observed differences compared to earlier publications. Both patients with AIH also had PSC, presenting with "PSC-AIH overlap" syndrome. Additionally, both patients were male, even though autoimmune hepatitis usually shows female predominance. This may be explained by the fact that PSC primarily affects males, and in overlap syndrome, consistent gender differences are not always evident. PSC was not observed in any of our microscopic colitis patients and was only associated with IBD as an EIM.

Many extraintestinal manifestations (EIMs) are inflammatory in origin and can be well controlled with proper IBD treatment. However, certain EIMs, such as axial arthropathies and pyoderma gangrenosum, progress independently of the underlying disease, requiring separate attention and treatment. This highlights the need for close collaboration across multiple specialties in managing IBD.

It is traditionally believed that thromboembolic events are more frequent in IBD, though they were rarely observed in our patients. We only encountered isolated cases of deep vein thrombosis and peripheral circulatory disorders. While the presence of IBD slightly increases the risk of thrombosis, the absolute risk remains low. However, acute disease flares,

hospitalizations, and abdominal surgeries significantly increase the likelihood of thrombotic complications.

Oral mucosal inflammation and lesions can also occur in IBD. Among our patients, five cases of oral mucosal abnormalities were documented in their medical history. The relationship between IBD, the oral microbiome, and periodontal tissue inflammation is complex and not fully understood. Previous research has shown conflicting results but has demonstrated that the oral bacterial communities in IBD patients differ from those of healthy controls, and increased inflammation is observed in periodontal tissues.

Although proper oral hygiene may contribute to better disease control, it has no direct effect on the development of IBD. Periodontal diseases are multifactorial, and it is difficult to assess the isolated role of IBD in these processes. It remains unclear whether there is a bi-directional relationship between IBD and oral inflammation.

Contrasting Autoimmune Comorbidities in Microscopic Colitis and Inflammatory Bowel Diseases - Discussion

Our study aimed to provide a detailed comparison of patients with microscopic colitis (MC) and inflammatory bowel diseases (IBD). Although our research has certain limitations—such as the relatively small sample size and the retrospective, descriptive nature of the data collection—our results still offer valuable insights. From these data, certain conclusions can be drawn, particularly regarding colonic involvement, and they raise further questions for future research.

The prevalence of autoimmune comorbidities is significantly less common in IBD than in microscopic colitis, yet it is still higher compared to the healthy population. International estimates suggest that the prevalence of autoimmune diseases in the general population is around 3-4%, while in IBD patients, this figure can reach up to 15%. In our microscopic colitis patients, the prevalence of associated autoimmune diseases was nearly twice as common as in IBD. It is important to note that the average age at diagnosis was significantly higher in MC patients than in IBD patients, making it more difficult to determine the lifetime prevalence of autoimmune comorbidities in both disease groups.

In cases of undifferentiated connective tissue disease (UCTD), although the full diagnostic criteria for autoimmune disease are not met, serological abnormalities are already present. This

entity was observed with similar frequency in our UC patients and in those with microscopic colitis. Among our MC patients, UCTD was diagnosed in 5 cases (4.95%). Some cases of UCTD never progress to systemic autoimmune disease, though in 30-40% of cases, progression can occur, typically within two years after the disease onset.

Our study focused on the prevalence of classic autoimmune diseases and did not cover all immune-inflammatory conditions. Conway and colleagues (Boston, USA) conducted a comprehensive survey of immune-mediated inflammatory diseases, including asthma and allergic-atopic conditions. In their study, the prevalence of psoriasis was higher than in our IBD patients. According to international data, such as the systematic review and meta-analysis by Alinaghi et al., psoriasis is more common among IBD patients than in the general population. In addition to inflammatory bowel diseases, these patients may also be more prone to developing psoriatic arthritis.

An interesting observation is that Secukinumab (monoclonal antibody targeting IL-17), used in psoriasis therapy, can rarely trigger IBD with prolonged use. Among our patients, no psoriatic patient received Secukinumab treatment. Though incident IBD cases are rarely reported during treatment, the medication is generally considered safe (as confirmed by a meta-analysis by Schreiber et al.). None of our microscopic colitis patient groups showed signs of psoriasis during the course of their disease.

In IBD patient groups, especially those with colonic inflammation, associated autoimmune diseases were more common. Crohn's patients with colonic involvement (L2) showed a similar prevalence of autoimmune comorbidities as UC patients. Clinically, Crohn's disease with predominantly colonic involvement (L2) can differ from other types – mainly affecting the small bowels. Patients with predominantly colonic Crohn's disease are more likely to develop a poor or waning response to TNF inhibitor therapies, which can lead to reduced treatment efficacy.

The prevalence of rheumatoid arthritis (RA) showed significant differences between Crohn's disease and ulcerative colitis. In a systematic review and meta-analysis by Chen and colleagues, which included eight studies, a stronger association was found between Crohn's disease and the co-occurrence of RA. However, it is important to note that not all previous studies confirmed an increased risk of RA in Crohn's disease. Rheumatoid arthritis appeared at similar rates in ulcerative colitis and microscopic colitis, although it was slightly more frequent in the

latter.

Gluten-related diseases were more frequently observed in Crohn's disease than in ulcerative colitis. Recently, gluten- and casein-free diets are increasingly being considered as complementary treatments for immune-mediated inflammatory diseases. Although there is no reliable scientific evidence that the consumption of gluten-containing grains triggers relapses in IBD, the popularity of gluten-free diets continues to grow. Current evidence, however, does not support the general recommendation of a gluten-free diet for IBD patients.

Celiac disease and dermatitis herpetiformis (DH) are well-defined, conditional autoimmune diseases associated with specific immunoserological abnormalities. In contrast, the pathogenesis of non-celiac gluten sensitivity (NCGS) is not known, and it usually does not show immunoserological markers. We did not diagnose NCGS in our patients, as the diagnostic criteria and etiology are heterogeneous and not standardized. An interesting observation was that two-thirds of our patients with L4 CD (upper gastrointestinal Crohn's disease) had associated autoimmune diseases (4 out of 6 cases), three of which involved celiac disease (GSE). Histological examinations in all cases revealed changes characteristic of Crohn's disease, although the two conditions are histologically distinct. However, due to the small number of patients, it is not advisable to draw far-reaching conclusions about the associated autoimmune diseases.

There were few cases of liver and biliary autoimmune diseases (autoimmune hepatitis – AIH and primary biliary cholangitis – PBC) in the study groups. Nevertheless, we believe that IBD and MC increase the risk of these rare diseases compared to the general population. Out of 611 patients, AIH or PBC was diagnosed in four cases. Although AIH and PBC are less common in immune-inflammatory gastrointestinal diseases in absolute terms, the risk may be higher compared to the control population.

Primary sclerosing cholangitis (PSC) was not classified as an associated autoimmune disease and was recorded exclusively in our IBD cohort (as an extraintestinal manifestation, EIM); it did not occur among our microscopic colitis patients. PSC was observed in 4 patients from both the CD and UC groups. The concurrent presence of PSC and MC is also rarely reported in the literature. Some authors presume, that IBD with associated PSC could represent a distinct phenotype. These patients may have a higher risk of "backwash ileitis" and right-sided colonic inflammation, may require less steroid use, and surgical intervention may be needed less

frequently.

In our IBD patients, the prevalence of Hashimoto's thyroiditis was slightly higher compared to the general population (the estimated prevalence of Hashimoto’s thyroiditis is 0.8-1%). Inflammation of the thyroid gland, primarily Hashimoto's thyroiditis, is not uncommon in the control population either, and its prevalence is increasing.

The so-called "leaky gut" (increased intestinal permeability) may be a predisposing factor for the development of other immune-mediated inflammatory conditions. Glutamine is a crucial amino acid for the cells of the intestinal mucosa and for tissues with intense cell division and renewal, such as the immune system. Glutamine plays a role in the division of intestinal epithelial cells, contributes to the restoration of the damaged intestinal barrier, enhances the integrity of tight junctions, and can affect certain inflammatory signaling pathways. Although there are currently no official recommendations for the use of glutamine or other dietary supplements in IBD, experience suggests that it may improve patients' well-being and reduce gastrointestinal symptoms. Due to its biological plausibility and positive practical outcomes, glutamine supplementation might be worth considering for IBD patients. Supplements that support the intestinal lining may also reduce the risk of associated autoimmune diseases during the course of the disease. However, a 2021 meta-analysis by Severo and colleagues and a 2016 Cochrane review by Akobeng found insufficient evidence that glutamine supplementation provides a benefit in the course of IBD.

Among popular dietary supplements, not only glutamine but also zinc ions contribute to maintaining proper barrier function and supporting cell regeneration. Zinc plays a crucial role in inflammatory and immune-regulatory processes. Zinc deficiency—particularly in Crohn’s disease and celiac disease—is common among patients. Zinc supplementation should be considered if necessary, as zinc deficiency is not uncommon even in the healthy population. Damage to the intestinal mucosal barrier and intestinal dysbiosis are risk factors for the development of immune-inflammatory diseases. Factors that disrupt the homeostasis of the intestinal lining and microbial communities may contribute to an increased risk of autoimmune diseases and a decline in intestinal barrier function.

In summary, we believe that despite the limited number of patients and resources, our research has contributed to the growing knowledge base on IBD, its extraintestinal manifestations, and associated autoimmune comorbidities. Previous publications have rarely addressed the

temporal relationships or specific characteristics of the involvement of different intestinal segments. Furthermore, there is limited literature on the sequential appearance of EIMs. Although no consistent patterns were observed in our sample due to the small number of cases, we believe that a larger, multi-regional prospective study could provide valuable new insights into extraintestinal manifestations. The occurrence of primary sclerosing cholangitis (PSC) in other gastrointestinal diseases (unrelated to IBD) is also an under-researched area. Additionally, we would like to emphasize the importance of socio-economic factors, living conditions, and environmental influences in the pathogenesis of IBD and other immune-mediated inflammatory diseases. These factors can impact disease development and progression, playing an important role in both prevention and optimizing treatment.

SUMMARY

Microscopic colitis (MC) and inflammatory bowel diseases (IBD) are immune-mediated inflammatory conditions affecting the gastrointestinal tract. There are notable differences in the age of onset between these diseases. Crohn's disease typically develops earlier in life, while ulcerative colitis (UC) and MC tend to appear later, with MC cases rising in older adults.

In Hungary, patients with MC are diagnosed at a younger age compared to global data. Collagenous colitis (CC) is more common than lymphocytic colitis (LC), with a gender imbalance between the subtypes. Chronic constipation, or the absence of diarrhea, is often the dominant symptom in CC, particularly when associated with Sjögren's syndrome.

Autoimmune diseases are more common in patients with MC, but there is no significant difference between CC and LC. These comorbidities are twice as frequent in MC as in IBD.

In MC, autoimmune comorbidities and gastrointestinal symptoms are key features, whereas IBD presents as a multisystem condition with frequent extraintestinal manifestations (EIMs) and a higher risk of other immune diseases. EIMs occur similarly in Crohn’s disease and UC and are more frequent in women. These manifestations can appear at any point, often years after diagnosis, but sometimes decades before IBD symptoms.

Joints, skin, and eyes are the most affected extraintestinal organ systems. Gallstones, once mainly linked to Crohn’s disease, occurred with similar frequency in both IBD groups in our cohort, while pancreatitis was significantly more common in UC.

Colon involvement increases the risk of autoimmune comorbidities and EIMs. In Crohn's disease, EIMs tend to develop earlier with colon involvement. Undifferentiated connective tissue disease (UCTD) is more frequent in UC. No clear bimodal pattern in the age of diagnosis or consistent sequence of disease manifestations was observed in our cohort. We consider lifetime prevalence of disease features more significant than their timing.

SUMMARY OF NEW FINDINGS

Microscopic colitis: Controversies in clinical symptoms and autoimmune comorbidities

Due to the limitations of retrospective observational studies, the results should be interpreted with caution, and no causal relationships can be drawn. Some of our observations raise new hypotheses.

- Microscopic colitis (MC) is diagnosed 10-15 years earlier in the studied population compared to international data, likely due to environmental and lifestyle factors.
- Certain dietary antigens and IgE antibodies may be linked to MC, with associations observed with other allergic and atopic diseases.
- MC, particularly forms associated with autoimmune diseases, does not always present with profuse, watery diarrhea. In many cases, chronic constipation was the main gastrointestinal symptom and responded well to budesonide treatment.
- Collagenous colitis (CC) shows less female predominance than lymphocytic colitis (LC).

Temporal Relationship of Extraintestinal Manifestations in Inflammatory Bowel Disease

- There is no significant difference in the occurrence of extraintestinal manifestations (EIMs) between Crohn's disease and ulcerative colitis. EIMs can develop at any point during the disease course, sometimes even years before IBD symptoms. Earlier onset of EIMs is more commonly associated with colonic inflammation, which was more frequent than expected.
- The most common EIMs in IBD are peripheral and axial joint inflammations. Peripheral joint inflammation usually precedes axial joint involvement. Hip arthritis was less common than anticipated. Eye and skin-related manifestations were also frequent but less common.

- Undifferentiated connective tissue disease (UCTD) is more likely to develop in ulcerative colitis than in Crohn's disease. Gluten-related diseases are more common in Crohn's disease.
- Younger age at diagnosis is mildly associated with more extensive inflammation (Crohn L3, UC E3).

Microscopic Colitis: Controversies in Clinical Symptoms and Autoimmune Comorbidities

- Autoimmune diseases are twice as common in microscopic colitis (MC) as in IBD. In IBD, autoimmune comorbidities are more frequent in predominantly colonic subtypes (Crohn L2, UC). Extraintestinal manifestations associated with IBD do not occur in microscopic colitis.
- The age of diagnosis follows distinct patterns for each disease subtype.

ACKNOWLEDGMENTS:

I would like to express my gratitude and appreciation to my supervisor, Dr. Éva Zöld, for her patience, guidance, and support throughout the publication process and the preparation of this dissertation. I am also deeply thankful to Dr. Zsolt Barta, whose invaluable expertise greatly contributed to the publication process and played a crucial role in the completion of this dissertation.

DEBRECENI EGYETEM
EGYETEMI ÉS NEMZETI KÖNYVTÁR
H-4002 Debrecen, Egyetem tér 1, Pf.: 400
Tel.: 52/410-443, e-mail: publikaciok@lib.unideb.hu

Nyilvántartási szám: DEENK/16/2024.PL
Tárgy: PhD Publikációs Lista

Jelölt: Fedor István
Doktori Iskola: Petrányi Gyula Klinikai Immunológiai és Allergológiai Doktori Iskola

A PhD értekezés alapjául szolgáló közlemények

1. **Fedor, I.**, Zöld, É., Barta, Z.: Contrasting Autoimmune Comorbidities in Microscopic Colitis and Inflammatory Bowel Diseases.
   Life (Basel). 13 (3), 1-12, 2023.
   DOI: http://dx.doi.org/10.3390/life13030652
   IF: 3.2 (2022)
2. **Fedor, I.**, Zöld, É., Barta, Z.: Microscopic colitis in older adults: impact, diagnosis, and management.
   Ther. Adv. Chronic Dis. 13, 1-15, 2022.
   DOI: http://dx.doi.org/10.1177/20406223221102821
   IF: 3.5
3. **Fedor, I.**, Zöld, É., Barta, Z.: Microscopic colitis: controversies in clinical symptoms and autoimmune comorbidities.
   Ann. Med. 53 (1), 1279-1284, 2021.
   DOI: http://dx.doi.org/10.1080/07853890.2021.1962965
   IF: 5.348
4. **Fedor, I.**, Zöld, É., Barta, Z.: Temporal Relationship of Extraintestinal Manifestations in Inflammatory Bowel Disease.
   J Clin Med. 10 (24), 1-13, 2021.
   DOI: http://dx.doi.org/10.3390/jcm10245984
   IF: 4.964

DEBRECENI EGYETEM
EGYETEMI ÉS NEMZETI KÖNYVTÁR
H-4002 Debrecen, Egyetem tér 1, Pf.: 400
Tel.: 52/410-443, e-mail: publikaciok@lib.unideb.hu

További közlemények

5. **Fedor, I.**, Gyarmati, É., Zöld, É., Barta, Z.: Gondolatok a cink szerepéről az immunrendszerünkben.
   Orvostovábbk. szle. 29 (10), 83-89, 2022.
6. **Fedor, I.**, Zöld, É., Barta, Z.: Liver Abnormalities in Turner Syndrome: the Importance of Estrogen Replacement.
   J. Endocr. Soc. 6 (10), 1-7, 2022.
   DOI: http://dx.doi.org/10.1210/jendso/bvac124
   IF: 4.1
7. **Fedor, I.**, Zöld, É., Barta, Z.: A gluténérzékenység extraintestinalis spektruma.
   Orv. hetil. 160 (34), 1327-1334, 2019.
   DOI: http://dx.doi.org/10.1556/650.2019.31493
   IF: 0.497

A közlő folyóiratok összesített impakt faktora: 21,609
A közlő folyóiratok összesített impakt faktora (az értekezés alapjául szolgáló közleményekre): 17,012

A DEENK a Jelölt által az iDEa Tudóstérbe feltöltött adatok bibliográfiai és tudománymetriai ellenőrzését a tudományos adatbázisok és a Journal Citation Reports Impact Factor lista alapján elvégezte.

Debrecen, 2024.01.18.

DEBRECENI EGYETEM * Egyetemi és Nemzeti Könyvtár *