Intermittent Inflammatory Bowel Disease and Microscopic Colitis: Variant or Epiphenomenon?

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Abstract

Background: Idiopathic inflammatory bowel disease and microscopic colitis are distinct entities; however, some clinical features overlap.

Aims: To identify if these alternative diagnoses may direct clinical therapy more effectively.

Methods: We describe seven patients who had intermittent phases of either inflammatory bowel disease or microscopic colitis in at least two separate occasions with matching clinical and endoscopic pictures.

Results: Diarrhea was the presenting symptom in all cases. In two of seven cases, the initial diagnosis was microscopic colitis, and in five cases it was inflammatory bowel disease. Addition of medication specific to diagnosis had resulted in improvement in six out of seven cases. Among the seven patients we reported, three had used nonsteroidal antiinflammatory drugs, a well-known trigger, before the onset of microscopic colitis.

Conclusions: Inflammatory bowel disease and microscopic colitis are distinct clinicopathologic entities that may coexist in the same patient. Triggering factors for microscopic colitis in the general population can also be the culprit in inflammatory bowel disease patients. Microscopic colitis may present as an epiphenomenon which is superimposed on predisposing inflammatory bowel disease patients. A thorough synthesis of all clinical, medication, endoscopic, radiology, and pathological data is crucial in these patients.

INTRODUCTION

Idiopathic inflammatory bowel disease (IBD) mainly includes ulcerative colitis and Crohns disease, with unique clinical, endoscopic, and histologic features. Microscopic colitis (MC) consists of two entities, collagenous colitis and lymphocytic colitis, which are clinically characterized by nonbloody, watery diarrhea and an essentially normal endoscopy. IBD and MC are distinct entities; however, some clinical features overlap. Interestingly, a small number of cases with co-occurrence of IBD and MC at different periods in the same patient during the clinical course of disease have been reported.[4, 6, 8, 12]To date, the relationship between IBD and MC in this patient group is largely unclear. Some authors suggested that MC might be part of the spectrum of IBD, given the lack of other compounding factors (infection or other autoimmune condition) in their IBD patients with MC episodes.[8] In this paper we present a case series that includes seven patients who had either IBD or MC at different stages of their disease progression. The occurrence of MC and IBD with regard to the clinical and endoscopic context was fully analyzed to address their relationship.

MATERIALS AND METHODS

A retrospective search of the Laboratory Information Systems at Indiana University Health and Washington

University was performed for the period between January 2000 and September 2013. This study was approved by the Institutional Review Boards. Patients who had distinct diagnoses of both IBD and MC in at least two separate occasions were identified. The relevant clinical history, endoscopy reports, and surgical pathology slides for these patients were retrieved and reviewed. Cases were included if a patient had biopsy or resection specimens that showed histologic features of either MC or IBD at two distinct time points. Cases with inadequate clinical or endoscopic history or questionable histologic diagnoses were eliminated. A total of seven cases met the study criteria and were included.

The pathology specimens were evaluated by each pathologist (HO, JL, RW, and IN) without knowing the clinical history or prior diagnosis. The histological features, including architectural distortion, intraepithelial lymphocytosis, subepithelial collagen table thickening, increased inflammatory cells within the lamina propria, presence of epithelial injury, cryptitis, and crypt abscesses, were evaluated in each individual case by each pathologist. The histopathological changes were then correlated with the clinical and endoscopic findings. The diagnoses of IBD and MC were made only on occasions in which the clinical symptoms and endoscopic and histologic findings were compatible with the respective disease stage. Disagreements among investigators were resolved by consensus opinion.

In all cases in which a diagnosis of MC was made, the endoscopic picture was normal or near normal, and nonbloody diarrhea or worsening of diarrhea was the main presenting symptom. Ulcerative colitis and Crohns disease were accompanied by varying degrees of gross endoscopic changes that included increased vascular pattern, erythema of the mucosa and ulceration, and clinical intestinal and/or extraintestinal symptoms.

CASE REPORT

Patient 1

A 40-year-old female presented with diarrhea alternating with constipation for one year at an outside facility. Her endoscopy was reported to show aphthous ulcers and the pathology revealed chronic inflammatory changes (slides not available for review). An initial diagnosis of Crohns disease was suspected. The patient did improve on donnatal. A followup colonoscopy one month later did not reveal any endoscopic abnormalities. However, the biopsies from the colon revealed lymphocytic colitis (Figure 1A and 1B; Table 1), with no evidence of chronic or active colitis or architectural disarray. An upper endoscopy was performed at the same time that revealed longitudinal ulcers in the gastric body and several small erosions in the stomach and duodenum, confirmed microscopically to be consistent with acute inflammation

and ulceration. The patient was started on asacol with only partial improvement.

She experienced worsened diarrhea and an anal fissure one year later; a colonoscopy revealed congested granular mucosa suggestive of IBD. The biopsies showed chronic active colitis with cryptitis and crypt abscesses consistent with IBD (Figure 1C and 1D). Budesonide and entocort were added to asacol at this point which proved effective in controlling the symptoms. Three years later, the patient had more or less controlled diarrhea, but experienced intermittent epigastric pain, nausea, and vomiting. A colonoscopy was performed and showed granular mucosa in the left colon. Interestingly, a diagnosis of collagenous colitis was rendered on microscopic examination (Figure 1E and 1F). The mucosal architecture appeared to be preserved; however, thickened subepithelial collagen table was found with increased intraepithelial lymphocytes. The patient resumed asacol and entocort with improved response to diarrhea. Nexium was added to control the recent upper gastric symptoms.
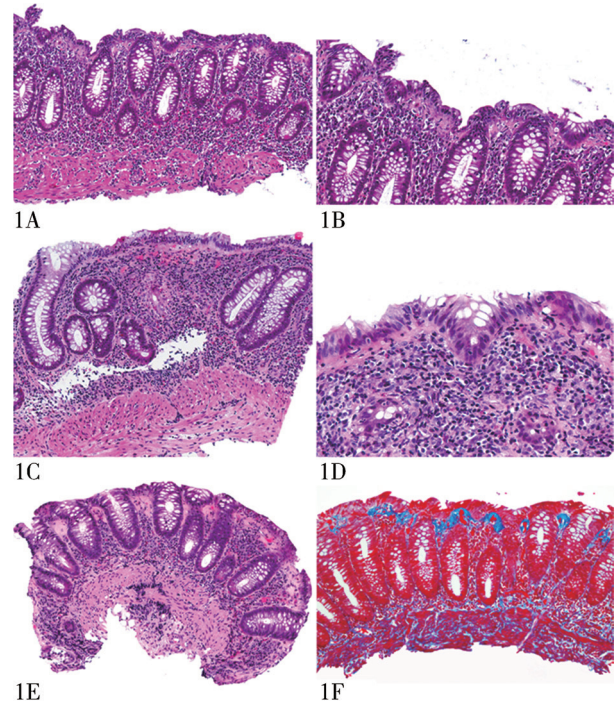

Figure 1
Episodes of Inflammatory Bowel Disease and Microscopic Colitis in Patient 1.

A (low power) and **B** (high power), Phase 1: Lymphocytic colitis. Biopsy showing intraepithelial lymphocytosis, epithelial injury, and increased inflammatory infiltrate in the lamina propria without mucosal architectural distortion. **C** and **D**, Phase 2: Inflammatory bowel disease. Biopsy showing chronic active colitis with architectural distortion and cryptitis. **E** and **F**, Phase 3: Collagenous colitis. Biopsy showing preserved colonic architecture with intraepithelial lymphocytosis, epithelial injury, and thickened subepithelial collagen table deposition highlighted in trichrome stain **(F)**.

Table 1
Clinical Characteristic of Patients

	Case	1	2	3	4	5	6	7
	Age at the time of first Phase (y)	40	67	50	60	39	49	58
	Gender	F	F	F	M	F	F	F
	Other history	chronic back pain	meralgia parasthesia, ischemic heart disease	none	hypertension, seasonal allergy, gastroesophageal reflux, bronchospasm	choledocho-lithiasis	squamous cell carcinoma of anal canal	enteropathic arthritis, breast cancer, depression
	History of smoking	no	no	no	yes, 25-pack/year	no	no	yes, 8-pack/y
First Phase	Phase	**microscopic colitis**	**microscopic colitis**	**IBD (UC)**	**IBD (UC)**	**IBD (CD)**	**IBD (CD)**	**IBD (CD)**
	Pathology	lymphocytic colitis	lymphocytic colitis	CAC	CAC	patchy CAC	normal	focal/patchy CAC
	Duration	1 years	2 years	2 years	13 years	10 years	18 years	15 years
	Endoscopic	normal colon	normal colon	chronic colitis	chronic colitis	chronic colitis	remission	patchy colitis
	Clinical	diarrhea	acute nonbloody diarrhea	diarrhea	episodes of diarrhea	episodes of diarrhea	episodes of diarrhea	remission
	Effective Medication	none	none	asacol	asacol	imuran / entocort / azathioprine	remicade / cymbalta	humira / 6MP / MTX / sulfasalazine
	Noneffective medication	asacol	imodium	none	remicade/prednisone	none	imuran	none
Second Phase	Phase	**IBD (UC)**	**IBD (UC)**	**microscopic colitis**	**microscopic colitis**	**microscopic colitis**	**microscopic colitis**	**microscopic colitis**
	Pathology	CAC	patchy CAC	collagenous colitis	collagenous colitis	collagenous colitis	collagenous colitis	lymphocytic colitis
	Duration	3 years	2 years	4 years	6 months	2 years	1 year	4 weeks
	Endoscopic	N/A	suggestive left sided UC	normal colon	colitis	Patchy erythema	remission	normal colon
	Clinical	worsened diarrhea, anal fissure	bright red blood per rectum	cramping and diarrhea	refractory diarrhea	increasing diarrhea	weight loss, loose stools	watery diarrhea
	Effective Medication	asacol / budesonide / entocort	asacol	asacol	none	entocort	entocort	none
	Noneffective medication	N/A	N/A	N/A	prednisone / remicade / asacol	N/A	N/A	humira / 6MP / MTX / sulfasalazine
Third Phase	Phase	**microscopic colitis**	N/A	N/A	N/A	**IBD (CD)**	N/A	N/A
	Pathology	collagenous colitis				CAC with granuloma		
	Duration	5 years				1 year		
	Endoscopic	granular mucosa in left colon				extensive mild colitis		
	Clinical	intermittent epigastric pain, N&V				diarrhea		
	Effective Medication	asacol / entocort / nexium				Imuran / entocort / azathiprine		
	Noneffective medication	none				none		

Note. CAC, chronic active colitis; CC, collagenous colitis; CD, Crohns disease; IBD, inflammatory bowel disease; LC, lymphocytic colitis; N/A, not applicable; N&V, nausea and vomiting; UC, ulcerative colitis; 6MP, mercaptopurine; MTX, methotrexate .

Patient 2

A 67-year-old female presented with lower quadrant pain for 3 months. Her medication history was significant for norvasc for hypertension, lexapro and xanax for depression and anxiety, and gabapentin for meralgia paresthetica. A colonoscopy showed an essentially normal colonic mucosa with no evidence of polyps or diverticulosis. Moderate sized internal hemorrhoids were noted on retroflexion of the endoscope in the rectum. No biopsy was performed. She developed acute nonbloody diarrhea 5 months later and colonoscopy was still normal despite poor colonoscopy prep. At this time biopsies showed lymphocytic colitis with no evidence of chronic active colitis. Imodium was tried without satisfactory response. Approximately two years later, the patient presented with bloody diarrhea and a colonoscopy showed changes consistent with ulcerative colitis characterized by congested erythematous mucosa with a prominent vascular pattern. Histologically, there was a dense chronic inflammatory cell infiltrate in the lamina propria including numerous eosinophils with minimal architectural disarray. Patchy crypt abscesses were identified. There was mild increase in intraepithelial lymphocytes within the crypts but relatively sparing the surface epithelium. The subepithelial collagen band was normal. No granulomas or dysplasia were seen. These findings were those of IBD rather than lymphocytic colitis. Asacol was started with remission of symptoms.

Patient 3

A 50-year-old female presented with a chief complaint of nonbloody chronic diarrhea for approximately two years. She did not have any other significant medical issues. She associated the onset of the diarrhea with her dietary switch to a vegetarian diet. Her bowel movements changed to more frequent movements of about twice a day; however, for the last 6 months she developed approximately ten movements per day without mucous, blood, or oil. These were accompanied by lower quadrant cramping and pressure. A colonoscopy was performed and revealed diffuse areas of congested, erythematous, and vascular pattern–decreased mucosa from rectum to descend colon. The biopsy revealed patchy chronic active colitis with architectural disarray consistent with IBD. No granulomas or other abnormalities were seen. She was started on asacol 400mg, TID, with significant improvement.

Three years later, the patient relapsed with cramping and increased diarrhea. Another colonoscopy was scheduled which revealed an essentially normal colon. Biopsy revealed preserved architecture with no evidence of active inflammation. There was focally thickened subepithelial collagen table deposition, increased intraepithelial lymphocytosis, associated epithelial damage, and lymphocytic infiltration of the lamina propria. Given these findings, a diagnosis of collagenous colitis was rendered. The patient continued asacol therapy for four years with occasional bouts of cramping and diarrhea.

Patient 4

A 60-year-old man presented for a 13-year history of ulcerative colitis. He was unable to wean from prednisone with persistent diarrhea consisting of five to ten bowel movements per day and decreased rectal tone. His other medical problems included hypertension, seasonal allergies, gastroesophageal reflux disease, bronchospasm, and a previous 25-pack per year smoking history. He initially had a diagnosis of ulcerative proctitis and was treated with asacol with good response for 10 years. Three years later, he had worsening clinical symptoms, thus remicade in addition to the prednisone was given with no response. A trial of azathioprine followed which resulted in transaminitis. Canasa and hydrocodone suppositories were also not successful. He continued to use 40 mg of oral prednisone daily. A flexible sigmoidoscopy performed at that time showed continuous disease from proximal colon to the rectum. Biopsies showed chronic active inflammation with foci of cryptitis, crypt abscesses, basal plasmacytosis, and prominent architectural disarray compatible with ulcerative colitis. No granulomas or dysplasia were identified.

The most recent colonoscopy, performed a year before colectomy, showed diffuse inflammation involving the descending colon to the rectum. The inflammation was mild in the distal descending colon and moderate in the sigmoid colon and rectum. Biopsies performed at an outside facility were reported to show diffuse chronic inactive colitis with architectural disarray and a patchy thickened subepithelial collagen band only in the ascending and sigmoid colon. No change in his medical treatment was made during this period.

In light of his persistent refractory symptoms and decreased rectal tone, definitive treatment by total colectomy and ileostomy were undertaken. Histologic sections showed increased intraepithelial lymphocytes as well as a markedly thickened subepithelial collagen band throughout the entire specimen. No architectural disarray, cryptitis, or crypt abscesses were seen. Thus, a diagnosis of collagenous colitis was rendered. His postoperative period was complicated by bowel evisceration and stomal prolapse that required surgical intervention. One year after surgery, he continues to do well with his stoma.

Patient 5

A 39-year-old female has a history of Crohns disease that was somewhat stable on medications. During a period of 10 years she appeared to have a more or less stable disease with episodes of increasing symptoms occurring every several months. Her main medication was imuran 200 mg a day; however, remicade, azathioprine, and entocort had been added at various times. She seemed to respond best to steroids during her worsened episodes. She did not

have any extraintestinal symptoms. Both her endoscopic and pathologic pictures were consistent throughout the 10-year period. Her colonoscopies were consistent with Crohns disease in remission with localized erythematous areas and vascular pattern noted in the sigmoid colon and rectum. Scarring of the sigmoid colon was more prominent at approximately 7 years post-presentation. The pathology consistently showed a varying degree of architectural distortion with occasional minimal to mild activity that corresponded to clinical presentations.

She then developed increased bowel movements of nonbloody diarrhea with cramping and was unable to stay in remission despite steroids. *Clostridium difficile* was suspected, although no evidence was found. The colonoscopy appeared normal with only a few patches of erythema but no granularity. Histologically, the subepithelial collagen layer was increased in thickness and was accompanied by a mild intraepithelial lymphocytosis with increased inflammatory cells in the lamina propria. These findings were most consistent with collagenous colitis. She started entocort and responded dramatically for 2 years.

Unfortunately, she developed bloody diarrhea 2 years later that required steroids. The diarrhea would remit every time she was tapered off the steroids. Azathoprine was added and she was able to eventually go back in remission. Colonoscopy performed after remission showed patchy inflammation in the bowel. The biopsies confirmed the colonoscopic findings and showed chronic minimally active colitis and proctitis with no granulomata. There was no thickening of the subepithelial collagen table noted.

Patient 6

A 49-year-old female presented an extensive history of Crohns disease for more than 18 years. She suffered extraintestinal manifestations, such as aphthous stomatitis, persistent chronic sinusitis, and eye symptoms, which presented approximately 10 years after initial diagnosis and was responsive to remicade. Her gastrointestinal disease was initially controlled with remicade and cymbalta with good response and only rare episodes of increased diarrhea, which was successfully treated with titration of remicade.

Colonoscopies done during that period revealed extensive colitis in remission. Throughout the entire period of 18 years, colonoscopies consistently showed scattered pseudopolyps with scarred vascular pattern–decreased mucosa throughout the entire colon. She developed an anal fissure almost 17 years since her diagnosis. Pathologically, chronic inactive colitis was the predominant histologic diagnosis throughout that fits the endoscopic and clinical pictures. Occasionally, focal activity was noted, and scattered tubular adenomas were also found.

She most recently presented with a complaint of weight loss and a painful digital exam. This was attributed to the history of an anal fissure. A colonoscopy procedure was performed and a mass was found in the rectum. The remainder of the colon had the usual appearance of scarred vascular pattern–decreased mucosa with scattered pseudopolyps. Pathology revealed two unexpected diagnoses for this patient: an anal poorly differentiated squamous cell carcinoma and collagenous colitis. Biopsies from the rectal mass revealed poorly differentiated basaloid-type squamous cell carcinoma that was positive for p63 and negative for synaptophysin and chromogranin A by immunostaining. The remainder of the colon showed preserved villous architecture with thickened subepithelial collagen layer, increased intraepithelial and lamina propria lymphocytes, and some endothelial damage. There was no evidence of chronic or active colitis, and there was no evidence of granuloma. She received chemoradiation for the anal carcinoma that was determined clinically to be a T2N0M0 with excellent response. There was no evidence of residual disease on subsequent PET scan. Her diagnosis of collagenous colitis was accompanied by diarrhea that did not respond to remicade infusions. Subsequently, entocort was added to her therapy providing appropriate relief.

Patient 7

A 58-year-old woman with a more than 15-year history of Crohn disease, whose clinical course was complicated by enteropathic arthritis, presented with a 4-week history of watery diarrhea occurring up to six to seven times per day. Many years prior, she had a diagnosis of ulcerative colitis, which was revised to Crohns disease. Her other medical problems included a history of breast cancer treated with a mastectomy and adjuvant chemotherapy as well as depression. She is a current eight-pack per year smoker. Her bowel disease had been in full remission on humira, 6-mercaptopurine, methotrexate, and sulfasalazine prior to this present episode. The patient did not report any melena or hematochezia. Stool studies, including an examination for ova and parasites, *Clostridium difficile* toxin, and culture were negative. Colonoscopy was performed and showed an ulcer in the ascending colon and 4–6mm polyps in the descending colon. Biopsies demonstrated severe chronic active colitis in the right colon and focal activity in the left colon. Both biopsies had evidence of chronic mucosal injury with architectural disarray, including focal Paneth cell metaplasia on the left sided biopsies. No dysplasia or granulomas were seen.

Two years later, another colonoscopy was performed which showed two sessile polyps in the rectum and normal colonic mucosa throughout. Biopsies from the right and left colon as well as the rectosigmoid colon showed increased intraepithelial lymphocytes with some surface damage. Paneth cell metaplasia was again noted in the left colon but no active inflammation, granulomas, or architectural disarray was identified. A diagnosis of lymphocytic colitis was rendered. In an effort to eliminate a possible medication-related effect, the patient was asked

to taper sertraline that was previously prescribed. At followup, she continues to be symptomatic.

DISCUSSION

IBD and MC are two well recognized clinicopathologic entities. However, the etiology and the pathogenesis of either IBD or microscopic colitis remain incompletely understood. Recent studies suggest that a complex interplay between the gut microbiome and genetic susceptibility play a role in IBD.[9] More than 160 loci have been associated with the susceptibility to IBD.[9] This genetic susceptibility may be due to an altered immune response to the gut flora, allowing the host to be susceptible to specific gut bacteria and increasing the risk of IBD. Other factors that may contribute to the pathogenesis of IBD include genetic, infectious, physiological, dietary, and immunological factors.[10, 15] The etiology of MC is also multifactorial. Lymphocytic colitis has a known association with autoimmune disorders including celiac disease, rheumatoid arthritis, thyroiditis, and type I diabetes mellitus.[3] A wide variety of drugs, including nonsteroidal antiinflammatory drugs and proton pump inhibitors, selective serotonin reuptake inhibitors, and statins, are considered possible triggers.[3, 11, 14]

Interestingly, more evidence supports shared risk factors between both IBD and MC. For example, smoking is a risk for collagenous colitis as well as Crohns disease.[1, 3, 13] Like IBD, there is evidence that the pathogenesis of MC may be secondary to genetic and immunological predisposition to mucosal insults by bacteria, although only a limited number of "family clusters" in MC have been reported. Some family members of MC patients have been reported to have Crohns disease, ulcerative colitis, and microscopic colitis within the family, emphasizing the genetic relationship between these diseases.[5] Interestingly, in a study by Olesen et al, 7% of patients with lymphocytic colitis have a family history of either ulcerative colitis or Crohns disease.[7]

However, the incidence of both MC and IBD in the same patient is rare, generally puzzling clinicians and pathologists. Goldstein et al described focal and patchy lymphocytic colitis and collagenous colitis in biopsies from four patients of Crohns disease, suggesting a temporal precedence of MC before the presentation of Crohns disease.[7] On the contrary, another study by Jegadeesan et al demonstrated six patients with IBD who later developed MC.[8] A few other papers addressed the metachronous occurrence of collagenous colitis and IBD. In two papers, collagenous colitis succeeded ulcerative colitis or Crohns disease, while others reported precedence of collagenous colitis.[2, 4, 6, 12] These papers are summarized in Table 2. Although these studies emphasized on the occurrence of MC either before or after IBD, a detailed correlation among pathologic, endoscopic,

and clinical course regardless of the order between IBD and MC has not been closely studied. In this paper, we focus on the occurrence of MC and IBD at various timeframes and with regard to the clinical and endoscopic context to fully evaluate this relationship. It appears that lymphocytic colitis occurrence likely preceded that of IBD (Cases 1 and 2), while collagenous colitis succeeded it (Cases 1, 3, 4, 5, and 7). In one case, the patient was initially diagnosed with lymphocytic colitis, then Crohns disease, and finally collagenous colitis (Case 1), highlighting the complex relationship between these entities. This is the first time, to our knowledge, that multifaceted compound transition between IBD and MC has been reported. The transition from one phase to the other was often accompanied clinically by worsening diarrhea or by resistance to the treatment that was used in the former phase. The appropriate switch in therapy often resulted in improvement of symptoms, suggesting that these alternative diagnoses (particularly those of MC) are real co-occurrences rather than nonspecific pathomorphologic findings.

Table 2
Reported Cases of Intermittent Inflammatory Bowel Disease and Microscopic Colitis

Reports	Case number	Initial episode	Second episode	Third episode
Osman (current)	7	2 LC 3 CD 2 UC	2UC 2 CC and 1 LC 2 CC	1 CC 1 CD
Chandratre[4]	1	CC	CD	
Bohr[2]	3	CD	CC	
Pokorny[12]	2	CC	UC	
Giardiello[6]	1	CC	UC	
Jegadssen[8]	6	UC	MC	
Goldstein[7]	4	CD	MC	

Note. IBD, inflammatory bowel disease; MC, microscopic colitis; UC, ulcerative colitis; CC, collagenous colitis.

Taken together all cases we reported here along with a few other prior reports, it appears that MC may be accompanying the diagnosis of IBD either before or after. Are the episodes of IBD and MC in one patient unrelated? Or do these two events belong to the same pathologic process? Previous reports suggested that MC might be a part of the spectrum of IBD, given the lack of other compounding factors (infection or other autoimmune condition) in their IBD patients with MC episodes.[8] However, the etiology of MC in these IBD patients could be equally complex. Among the seven patients we reported, three (Cases 1–3) had used nonsteroidal antiinflammatory drugs (NSAID, asacol), a well-known trigger, before the onset of MC. NSAID usage was also reported in two of six patients with IBD who subsequently developed MC in a previous study.[8] MC may, therefore, present as an epiphenomenon which is superimposed on predisposed individual with other

well-established disease processes including IBD. MC might be associated with a certain drug in susceptible IBD patients due to an idiosyncratic reaction. Thus, the co-occurrence of IBD and MC may or may not belong to the same disease. The etiology of each patient may be different depending on the variable genetic background, treatment regimen, and peculiar reaction.

In practice, information of drugs is frequently overlooked. In addition, it is not a surprise that other related information, including autoimmune disease and infection, is not well documented or available for pathologists before making a diagnosis of MC. Therefore, we recommend, for each patient with intermittent episodes of IBD and MC, a thorough synthesis of all data including clinical symptoms, medication, endoscopy, radiology, and pathology. A close collaboration between the clinicians and pathologists is of paramount importance to reach an accurate diagnosis.

In summary, IBD and MC are two distinct clinical entities that may coexist in the same patient. Identification of these alternative diagnoses may direct clinical therapy more effectively. MC may present as an epiphenomenon which is superimposed on susceptible IBD patients. Triggering factors for MC in the general population can also be the culprit in IBD patients. A thorough synthesis of all clinical, medication, endoscopic, radiology, and pathological data is crucial in these patients.

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