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TOPIC HIGHLIGHT

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Distinct colonoscopy findings of microscopic colitis: Not so microscopic after all?

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Abstract

Microscopic colitis (MC) is considered an "umbrella term", comprising two subtypes, i.e., collagenous colitis (CC) and lymphocytic colitis (LC). They are classically associated with normal or unremarkable colonoscopy. In the last few years, reports have been published revealing findings that are thought to be characteristic or pathognomonic of MC, especially CC. A systematic electronic and manual search of PubMed and EMBASE (to December 2010), for publications on distinct endoscopic findings in MC, resulted in 42 relevant reports for inclusion in this review. Eighty eight patients with collagenous colitis were presented. Only one publication describing a distinct endoscopic pattern in LC was found. Typical findings in CC are alteration of the vascular mucosal pattern, mucosal nodularity, a sequence of change from mucosal defects to mucosal cicatricial lesions, and perhaps (although of doubtful relevance) mucosal pseudomembranes. A causal connection of mucosal defects with the use of lansoprazole seems to exist. Adoption of the proposed lesion description herein is recommended in order to improve homogeneity of future reports.

Key words: Collagenous colitis; Microscopic colitis; Endoscopy; Mucosa; Lesion

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INTRODUCTION

Microscopic colitis (MC), regarded as a rare entity in the early 80s (and certainly overlooked), has now emerged as an increasingly common cause of chronic, non-bloody/watery diarrhea[1].

MC is an "umbrella term", comprising two entities/subtypes, i.e., collagenous colitis (CC) and lymphocytic colitis (LC)[2]. The two entities are characterized by a variable, yet apparently benign, clinical course of protracted, non-bloody diarrhea and classically normal or unremarkable colonic mucosa on endoscopy[3]. In 1984, Gledhill[4] established that thickening of the colonic acellular basement membrane by > 15 μm is invariably associated with diarrhea.

The histological abnormalities in MC are discontinuous, subtle and often unequally located in the colon, making it necessary to take multiple biopsies from various

colonic regions for identification of the pathognomonic microscopy, i.e., thickened sub-epithelial collagen band and increased intraepithelial lymphocytes[5] (Figure 1).

However, there are occasions where endoscopy reveals findings that are thought to be characteristic or pathognomonic of MC, and especially CC. Although the estimated prevalence of MC is up to 10% in patients with chronic diarrhea[5], there are few reports of macroscopic findings in MC. This review attempts to describe the known characteristic endoscopy findings in MC and to categorize them in different types.

PATHOPHYSIOLOGICAL BACKGROUND

CC was first described in 1976, independently in Sweden by Lindström[6] and in Canada by Freeman[7], while LC was first described by Lazenby *et al*[8] in 1989. An increase in their incidence has been recently reported, but this is most likely an artifact secondary to increased awareness and prompt diagnosis[9]. In the absence of persistent endoscopic findings, diagnosis is based mainly on specific histological criteria[9].

It is not clear whether CC and LC are separate entities or part of the spectrum of a single disease[2]. With regard to pathogenesis, several hypotheses have been suggested, including inflammation secondary to medication, smoking, immune dysfunction, autoimmunity, and/or infection.

Studies of collagen typing in patients with CC have produced conflicting results. Electron microscopy findings have suggested that the collagen in CC appears similar to that found in granulation tissue, supporting the hypothesis that its presence would suggest a reparative response to injury[10]. In fact, it is plausible to assume that overproduced, multiple, and different collagen types may deposit in the sub-epithelial layer of the colon and manifest clinically as CC[11]. Günther *et al*[12] showed that increased connective tissue growth factor expression might be the final mediator of local fibrosis in CC.

Non-steroidal anti-inflammatory drugs (NSAIDs) have been implicated as causative factors, through their ability to inhibit prostaglandin synthesis from the colonic mucosa. More recently, several reports have been published incriminating proton pump inhibitors (PPIs), especially lansoprazole, in the induction of CC. Most of the findings to support this came from the temporal relationship of resolution of symptoms with cessation of NSAID or PPI therapy. PPI-induced conformational changes in the cytoskeleton of epithelial cells may result in alterations in the function of the tight junction, leading to increased paracellular permeability. Keszthelyi *et al*[13] postulated that this could allow the luminal contents to easily penetrate the lamina propria causing an immune and/or inflammatory reaction. On this basis, and in light of some recent reports[14], which incriminate lansoprazole as the main cause of linear mucosal defects in CC, it may be plausible to suggest that CC is a syndrome with various causes and perhaps graded histopathology.

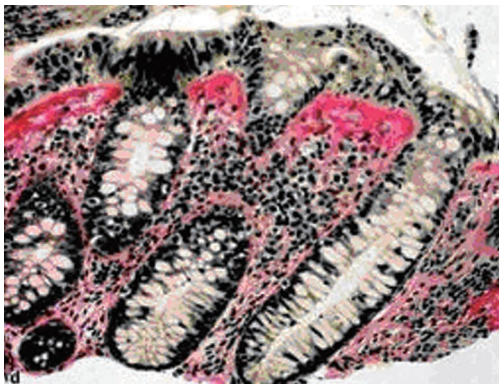

Figure 1 Van Gieson Stain, sub-epithelial collagen table.

The purpose of this review is to present the published experience on distinct endoscopic findings in MC and suggest a unifying lexicon for the reported lesions.

SEARCH STRATEGY

We conducted a PubMed and EMBASE computer search (to December 2010) in order to identify articles on microscopic colitis and endoscopic findings. Our search strategy for PubMed was ["Colitis, Microscopic" (MeSH) or "Colitis, Collagenous" (MeSH) or "Colitis, Lymphocytic" (MeSH)] and ["Endoscopy" (MeSH) or "colonoscopy" (MeSH) or "intestinal mucosa" (MeSH)]. We confined our search to articles in humans but we did not apply any language restriction. In order to search EMBASE we used the following key words: "collagenous colitis", "microscopic colitis" or "lymphocytic colitis", "endoscopy" or "colonoscopy". A further search of electronic journals was undertaken.

Duplicate articles identified in PubMed or EMBASE were manually deleted. The first selection, based on the title and/or abstract was carried out by one of the authors (AK). From the outset, we agreed not to include for further review reports or studies on endoscopic technology, e.g., confocal laser endomicroscopy, which is not yet widely available or restricted to a small number of tertiary institutions. The full paper of each potentially relevant report was then obtained. Thereafter, the two authors independently assessed publications for inclusion in the review. In addition, the reference lists of relevant reports and review papers were cross-searched, in order to identify papers that our initial computer search may have missed.

The following data were extracted from each included publication: year of publication and first author, country of origin, number of cases reported, gender and age of the cases, described endoscopic findings, histopathological diagnosis, post-endoscopy/clinical complications and any important clinical associations (Table 1).

SEARCH FINDINGS

Our initial computational search returned 89 articles in

Table 1 Overview of reports of endoscopic findings/appearance of collagenous colitis

Year	Ref.	No. of cases, gender, age	Endoscopic findings	Lesion location collagen table thickness	Clinical associations	Complications
1990	Giardiello *et al*[15]	1, M, 60	Pseudomembranes	S colon 50-70 μm	Watery diarrhea, received NSAIDs/antibiotics	None
1993	Richieri *et al*[16]	1, F, 43	Linear mucosal tears/lacerations	R colon	Watery diarrhea, abdominal pain	None
			Absent vascular mucosal pattern	30-40 μm	Successful therapy with steroids, some bloody stools	
			6 mo later; many linear cicatricial lesions			
1993	Smiley *et al*[17]	1, F, 53	Carpet-like patch with nodularity (5 cm)	R colon	Watery diarrhea	None
			Similar to sessile villous adenoma	20-40 μm	Therapy with bulking agents	
1995	Katanuma *et al*[18]	1, F, 72	Diminished vascular pattern	Pancolonic	RA on sulindac, diarrhea and wt loss	None
			Edematous/red mucosa	n/s	Treated by discontinuation of NSAID and salazosulphopyridine	
1997	Katsinelos *et al*[19]	1, M, 65	Multiple red mucosal spots	R colon	Watery diarrhea,	None
			Diminished vascular pattern	n/s	Successful therapy with steroids	
1997	Yabe *et al*[20]	1, F, 47	Multiple red mucosal spots	Pancolonic	6 F/U colonoscopies	None
			Diminished vascular pattern	n/s	showed no improvement	
1998	Sato *et al*[21]	1, F, 78	Crowded/tortuous vascular pattern	R + T colon	Watery diarrhea	None
			I/C spray: coarse/nodular surface	n/s		
1999	Bermejo *et al*[22]	1, F, n/s	Pseudomembranes and aphthae	n/s	Watery diarrhea, received	None
				n/s	NSAIDs/antibiotics	
2001	Freeman *et al*[23]	1, F, 37	Deep, elliptical mucosal defect/ulcer	S colon	Watery diarrhea, acute abdomen	Perforation
				n/s	Diagnostic laparotomy + IV antibiotics	
2001	Yagi *et al*[24]	1, F, 77	Mucous-covered lesions in R colon	R + T colon	Watery diarrhea, 4	None
			Ulcer in descending colon	30-60 μm	colonoscopy linear lesions in rectum, ASA-associated	
			2nd look: rectal pseudomembranes			
2002	Cruz-Correa *et al*[25]	2, F, (73/61)	Deep lacerations/tears	R and T colon	All had hypothyroidism	None
		1, M, 62	0.5-4 cm long (to muscularis mucosa)	n/s	Therapy with tetracycline/5-ASA	
2003	Kakar *et al*[26]	8, F, (a. r: 37-91)	Linear ulcers or lacerations (5)	R colon (5)	Aspirin and NSAID-associated CC	None
		1, M, 27	Diminished vascular pattern (2)	S colon (3)	Treated with discontinuation, bismuth	
			Aphthae (2), pseudomembranes (1)	n/s	Mesalamine or azathioprine/6-MP	
2003	Sato *et al*[27]	1, F, 78	1st colonoscopy: 3 mm nodule	Pancolonic	Watery diarrhea, wt loss	None
			2nd look: crowded/tortuous vascular pattern	R: 40-70 μm	ASA-associated	
			I/C spray: coarse and nodular, uneven surface	L: 20 μm		
2003	Byrne *et al*[28]	1, F, 27	Erythematous mucosa	S colon	Watery diarrhea,	None
			Multiple pseudomembranes	n/s	common variable immunodeficiency (CVID)	
2003	Yuan *et al*[29]	6, F, (a. r: 54-81)	Linear ulcers (1), R colon ulcers (2), inflamed rectum (1)	T colon n/s	Pseudomembranes in CC, only endoscopic cases included	None
2004	Buchman *et al*[30]	1, F, 58	Hemorrhagic mucosal spots and	R colon	Prednisolone, antibiotics,	None
		1, F, 46	erythema, granularity/ pseudomembranes		TPN, PPI, hypoalbuminemia	
2004	Sherman *et al*[31]	3, F, (a. r: 66-73)	Mucosal tears and fractures	R + T colon	Watery diarrhea, wt loss,	Perforation
		1, M, 69	Granularity of mucosa at places	40-50 μm	hypoalbuminemia	in 3/4 cases
2006	Wickbom *et al*[32]	3, F, (a. r: 73-86)	Mucosal tears and fractures (4-5 cm long)	R + T colon	All on aspirin	None
			Mucosal scars on repeat colonoscopy	14-40 μm	ACE/lansoprazole-induced (1 case)	
2006	Koulaouzidis *et al*[33]	1, F, 83	Mucosal tears	Cecum n/s	Iron deficiency anemia	None
2007	Poupardin-Moulin *et al*[34]	1, F, 80	Longitudinal mucosal fractures	R + T colon n/s	No significant clinical associations, diagnosis missed	None

2007	Smith *et al*[35]	1, F, 43	Long, linear mucosal fractures	R colon n/s	Treated with sulfasalazine	Perforation Hemicolectomy
2007	McDonnell *et al*[36]	3, n/s, n/s	Bright linear marks/parallel corkscrew lesions: "cat scratch" colon	R colon n/s	n/s	none
2008	Allende *et al*[37]	9, F, (a. r: 44-80)	Mucosal fractures to muscularis propria (7)	R colon (6)	2/12 underwent barium enema	Perforation all cases
		1, M, 71	Ragged mucosal defect (1)	T colon (3)		2 during colonoscopy
			Wall induration (1), constriction (1)	L colon (1)		
2008	Umeno *et al*[38]	7, n/s, (a. r: 37-92)	Longitudinal mucosal defects (ulcers/tears)	L colon	Only in the lansoprazole treated group	None
			Longitudinal scar in one case	12.5-50 μm		
2008	Hashimoto *et al*[39]	1, F, 66	Whirling/circling mucosal vessel network	Pancolonic	SLE, treated with mesalamine	None
			Linear (20 cm) ulcer/scar in the descending	n/s	2nd look: normal vessels, smaller scar	
2009	Watanabe *et al*[40]	1, F, 68	Multiple, longitudinal thin ulcers	L colon 30 μm	Lansoprazole, discontinued and healed	None
2009	Yusuke *et al*[41]	1, F, 78	Ragged and linear, long mucosal tear	S colon	Abrupt abdominal pain, PR blood	None
			Hypertrophic scar	n/s	Lansoprazole, discontinued	
2009	Cuoco *et al*[42]	1, F, 68	Deep linear ulcer-type defects	R + L colon	Watery diarrhea, abdominal pain	None
			7 cm long in ascending	n/s	4 L PEG for cleansing	
2009	Dunzendorfer *et al*[43]	1, F, 60	3 cm hypertrophic mucosal scar	S colon n/s	Long history of constipation Wt loss, combination therapy	None
2009	Chiba *et al*[44]	1, F, 70	Distinct diffuse mucosal cloudiness	Pancolonic	On lansoprazole and loxoprofen,	Reoccurred on a further Lansoprazole course
			Indistinct vascular pattern (UC-like pattern)	n/s	treated with sulfasalazine	
2009	Sekioka *et al*[45]	1, F, 82	2 longitudinal mucosal fractures	T colon	Lansoprazole-associated (6 mo)	Peritonitis, pre-endoscopy
			2nd look: A ridge-type cicatricial lesion	n/s	Treated by discontinuation	
2010	Couto *et al*[46]	1, F, 48	Hemorrhagic mucosal tears Longitudinal white ridges/lines	T + L colon n/s	OA on nimesulide and lansoprazole, abdominal pain, wt loss (10%)	None Colonoscopy halted at T colon
2010	Sawada *et al*[47]	1, M, 77	Disappearance of vascular network,	L colon	Lansoprazole-associated (6 years)	None
			Red (numerous) mucosal spots	25 μm	Wt loss, treated by discontinuation collagen table reduced on 2nd look	
2010	Koulaouzidis *et al*[48]	1, M, 83	Fine cicatricial line	L colon	n/s	None
		1, F, 45	Hypertrophic mucosal scar	n/s		
2010	van Velden *et al*[49]	1, F, 63	Linear tears Diminished vascular pattern and edema 2nd look colonoscopy: multiple linear scars	R + S colon 20 μm	Instrumentation-induced and insufflation-induced mucosal tears	Perforation Treated conservatively
2010	Nomura *et al*[50]	1, F, 67	Linear mucosal defect x 2, Linear scar in sigmoid, I/C spray	L colon n/s	Lansoprazole-associated Improved on discontinuation	None Painful left abdomen
2010	Miyagawa *et al*[51]	1, M, 81	Longitudinal mucosal defect	L colon n/s	Lansoprazole and hemodialysis	None
2010	Milestone *et al*[52]	3, F; 1, M (a. r: 57-75)	Long (5-20 cm) linear ulcers, non-hemorrhagic with evidence of healing	S colon n/s	Treated with budesonide and/or bismuth subsalicylate	None
2010	Kawamura *et al*[53]	3, n/s, n/s	Longitudinal mucosal ulcers	L + S colon n/s	Lansoprazole induced	None
2010	Fasoulas *et al*[54]	1, F , 68	"Cat scratch" colon	R colon n/s	n/s	None
2010	Cimmino *et al*[55]	4, F, (a. r: 24-77)	Mosaic pattern (honeycomb image), I/C spray: for delineation of pattern	Rectum+ S colon n/s	Case control study Mosaic pattern had high LR+/spec	None

n/s: Not stated; M: Male; F: Female; a. r: Age range; I/C spray: Indigo carmine spray; R colon: Right colon; T colon: Transverse colon; L colon: Left colon; S colon: Sigmoid colon; LR: Likelihood ratio; spec: Specificity; UC: Ulcerative colitis; TPN: Total parenteral nutrition; OA: Osteoarthritis; ASA: Acetyl salicylic acid; wt: Weight; PPI: Proton pump inhibitor; 6-MP: 6-mercaptopurine; PEG: Polyethylene glycol; ACE: Angiotensin converting enzyme; NSAIDS: Nonsteroidal antiinflammatory drugs; CC: Collagenous colitis; SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis.

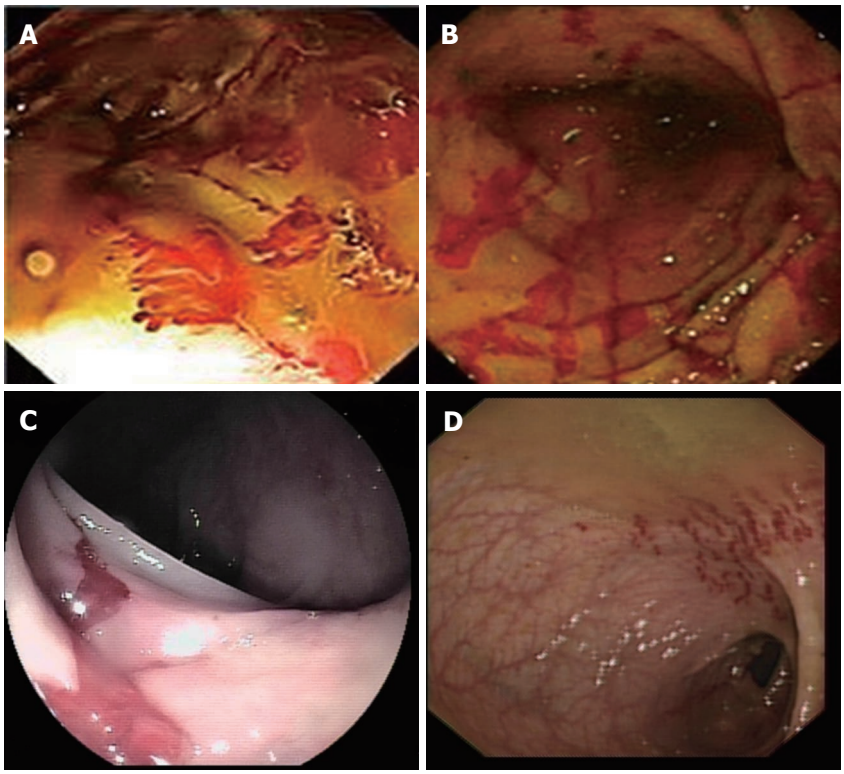

Figure 2 Colon lacerations/mucosal breaks in collagenous colitis. A, B and C: Colon lacerations/mucosal breaks; D: Cat-scratch colon.

PubMed and 499 in EMBASE. Nineteen and 50 articles, from PubMed and EMBASE respectively, were included for further review. After obtaining the full papers, 35 papers were selected. Another seven publications were identified from references lists and included in the final analysis.

The terms mucosal break, defect, tear, fracture or laceration were used indiscriminately. For the purpose of this review and in order to standardize the terminology, we agreed to use the term "mucosal defect" as a collective one, under which there are two subtypes of lesions: (1) mucosal lacerations/tears which are the longitudinal (superficial or deep) and mainly fresh/hemorrhagic in appearance mucosal breaks (Figure 2); and (2) mucosal fractures describing the deeper (with occasional exposure of the muscularis mucosa) and white-based or more chronic looking mucosal defects (Figure 3).

Although to an extent arbitrary, we believe that this terminology will aid the introduction of a universal lexicon for future reports of similar lesions. It is obvious that in accordance with the above, the "cat scratch colon" belongs to the first category, i.e., mucosal lacerations or tears.

Eighty eight cases [65 females, 10 males, 13 not stated (n/s); median age: 67 years] were reported in 41 publications. Of these, 14 publications were from Japan[18,20,24,27,37-41,44,45,47,50,51], 12 from the United States[15,17,25,26,28-31,35-37,43], three from the United Kingdom[33,48,52], two each from France[16,34], Sweden[21,32], and Greece[19,54], and one each from Argentina[55], Canada[23], Italy[42], the Netherlands[49], Portugal[46], and Spain[22]. Where reported, the submucosal collagen table thickness ranged from 14-70 μm. The only publication reporting endoscopic findings in LC described the presence of a subtle mucosal change in an 85-year-old female[56].

Gardiello *et al*[15] were the first to report distinct endoscopic findings in CC (i.e., pseudomembranes), but in fact it was Richieri *et al*[16] who first described the presence of multiple linear mucosal lacerations with sharp edges in the right colon of a 43-year-old female, with subepithelial collagen table thickness of 30-40 μm. Eventually, on repeat colonoscopy 6 mo later the lesions had healed, resulting in fine cicatricial lines on an otherwise unremarkable colonic mucosa. Therefore, Richieri *et al*[16] had effectively pointed to a pattern seen in some of the reports that followed, i.e., the continuum of laceration to cicatricial healing of the mucosa.

Since this report, 53 cases (34 females/6 males/13 n/s; median age: 69 years) of linear, long or shorter and finer (cat-scratch type) mucosal tears, fractures and ulcers have been reported[25,26,29,31-42,45,46,49-54]. Sixteen patients with mucosal defects were on lansoprazole, and in the majority, discontinuation of the medication resulted in symptomatic, endoscopic and histopathological improvement.

On the other hand, only 11 (10 females/1 male) cases of mucosal cicatricial lesions have been reported to date, identified either during the index colonoscopy that revealed the mucosal defects, or at follow-up colonoscopic examinations[16,32,38,41,43,45,46,48-50]. The lesions ranged from hypertrophic (celoid-type mucosal scars)[32,38,41,43,45,46,48-50] to fine, cicatricial lines[16,48] (Figure 4).

We did not manage to establish an association of any

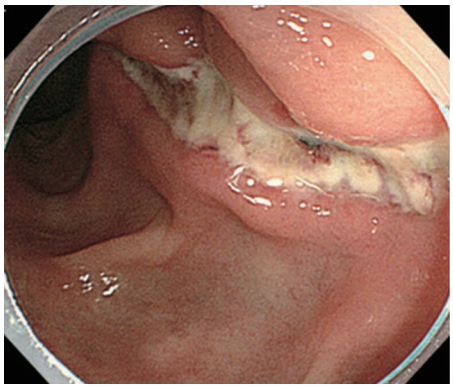

Figure 3 Colon mucosal fractures in collagenous colitis.

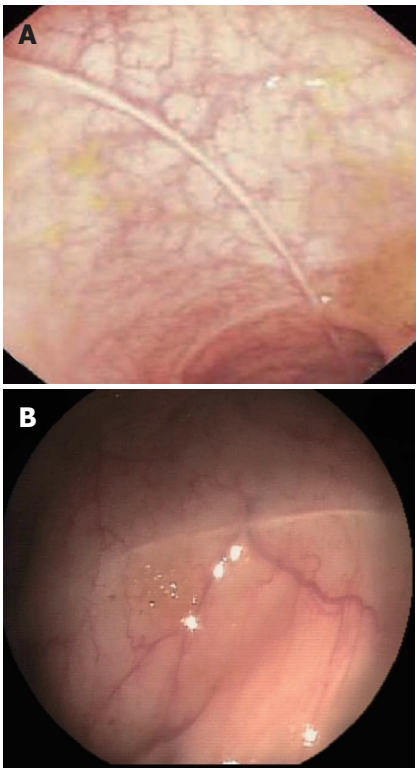

Figure 4 Cicatricial mucosal lesions in collagenous colitis (A and B).

of these lesions either with the collagen table thickness or with symptom severity in the review cohort.

The right colon (for the purpose of this review defined as the area from the cecum to the hepatic flexure), irrespective of the type of findings, was affected in 32 cases, the transverse colon in 16 and the left (descending, sigmoid and rectum) colon in 32. Five reports presented cases with pancolonic mucosal involvement[18,20,27,39,44].

Although the sign of a mosaic pattern or mucosa nodularity ("honeycomb mucosa") was noted first by Smiley *et al*[17] in 1993 in the ascending colon of a 53-year-old woman, a retrospective case-control study was only published in 2010[55]. In the appropriate clinical context of watery diarrhea, the "honeycomb pattern" had an odds ratio of 19.4 with a specificity of > 99% for diagnosis of CC. The authors though pointed out that, due to both the retrospective nature of the study and the high possibility of under-reporting, this may be an overestimation.

Dye spray (indigocarmine), for improved delineation of the identified lesions, was utilized in four reports[21,27,50,55], and seems helpful in the context of subtle mucosal changes and/or disturbed vascular architecture. However, this should be balanced against the greater resource implications and procedure time.

With regard to complications, there were 17 recorded perforations/peritonitis in the review cohort[23,31,35,37,45,49]. As expected, these were all associated with cases where mucosal defects (tears or fractures) were evident on colonoscopy[52,57].

WHAT IS CURRENTLY KNOWN

We found four broad categories of distinct endoscopic findings in CC: (1) pseudomembranes[15,22,24,26,28,30]; (2) mucosal vascular pattern alteration which includes an indistinct appearance of the blood vessels and a variable degree of pruning of the mucosal vasculature, or a crowded, dilated and tortuous capillary network[16,18-21,26,27,39,44,47]; (3) mucosal abnormalities such as red spots and some mucosal nodularity or textural alteration, evident with or without chromoendoscopy[17,19-21,27,30,31,55]; and (4) a continuum of mucosal breaks/defects, i.e., mucosal lacerations/tears, including the so-called "cat scratch colon" pattern, or fractures usually along the long axis of the colonic wall[16,25,26,29,31-42,45,46,49-54]to the fine linear cicatricial lines or thick scar-like ridges of the mucosal surface (effects of the mucosal healing process of mucosal defects)[16,32,38,41,43,45,46,48-50]. There was only one publication describing a characteristic endoscopic pattern in LC[56].

Hemorrhagic mucosal breaks have an appearance that could be liberally described as "colon craquelé"[16]. The term mucosal fracture was introduced by Sherman *et al*[31] in 2004 and it is admittedly a successful descriptive one. Thickened and abnormal sub-epithelial collagen table leads, at some areas, to loss of attachment with the epithelial component, and this in turn causes stretching of the mucosa over the deeper wall layers, and eventually tearing of the detached mucosal surface (in a "zip" fashion, hence the longitudinal lesions). The sharply demarcated margin of these mucosal defects, as if the mucosa has been slashed with a sharp knife, helps to differentiate them from ischemic colitis[50].

Mucosal defects are more likely to be found in the right colon as a result of a colonic insult, i.e., instrumentation or air insufflation due to the abundant presence of a thicker and denser (hence dysfunctional) collagen type Ⅲ table, in association with increased colon diameter on that side[25,37,58]. The right colon thinner wall and its expansion to a greater diameter during fecal storage and transit, produce greater relative wall tension (Laplace's law, i.e., tension on the wall of a cylinder is proportional to the radius). Therefore, a competent ileocecal valve and a deformed sigmoid are sufficient to cause colonic air

entrapment in a closed space[59], and eventually "cracking" of the brittle colonic mucosa[11,25,31,32,48,58]. Although the colon can not be seen as a simple cylinder[37], we suggest that these breaks can occur spontaneously, and postulate that increased intra-colonic pressure during peristalsis and defecation leads to mucosal stretching and defects that will heal with time leaving behind various types of cicatricial lesions[33,48].

McDonnell *et al*[36] coined the term "cat scratch colon" to describe the red linear marks in the cecum or ascending colon seen in 21 of 8277 patients undergoing colonoscopy. They reported a 14% prevalence of CC of in their cohort. They also postulated that these marks were due to barotrauma from insufflation[36,59-61]. However, it is unclear whether biopsies were taken in all patients undergoing the test for diarrhea, other than in those that had the "cat scratch" appearance. Furthermore, endoscopic findings are non-specific for CC and have been described in the normal colon (attributed to barotrauma from excessive insufflation during colonoscopy), in diversion colitis, and even in chronic cholestasis[54,61,62].

The true prevalence of mucosal tears is unknown due to the rarity of reported cases, but it is estimated to be around 1%. Under the assumption that not all of the relevant cases have been reported, the true prevalence may be much higher. However, based on the type of publications included in this review, i.e., case reports or series, it is not possible to estimate prevalence. In addition, practices vary worldwide and up until recently flexible sigmoidoscopy was considered sufficient to diagnose MC (it is believed that left-sided biopsies probably miss less that 5% of MC cases, due to its patchy nature), and as lesion awareness rises, the incidence of macroscopic findings will increase[63]. On the other hand, the increased frequency of reports published during the last decade show that there is an increased awareness of the distinct endoscopic appearances in MC, and perhaps endoscopist enthusiasm may result in over-diagnosis (as mucosal tears/scratches have been described in the normal colon, diversion colitis and in lansoprazole colitis[36,64,65]) of an entity whose main hallmark remains histological confirmation.

It is also now known that mucosal defects in CC represent a marker of increased risk of colonic perforation[52,54]. A recent review found 21 cases of perforation in CC. The majority of these were either colonoscopy-associated (15 cases) or barium enema-associated (four cases), while the rest seem to have occurred spontaneously[57].

There are several reports of remission, including disappearance of the collagen layer on follow-up. This would indicate that an environmental factor such as medication may be responsible in susceptible individuals. NSAIDs or PPIs have been implicated. It has also been suggested that collagen plate thickness is greater with lansoprazole[38]. The pathophysiologic mechanism by which lansoprazole induces microscopic colitis and mucosal defects is not well understood. Although a clear temporal correlation exists, it should be remembered that, due to the fluctuating nature of CC[66], it might simply represent a coincidence, as PPIs are one of the most commonly prescribed drug categories worldwide.

It has been postulated that this may be due to higher concentrations of drugs such as NSAIDs in the right colon[26]. However, it is possible that more right sided biopsies are taken because of endoscopic abnormalities, more likely to be observed in the right colon, as mentioned above. More case control studies and multivariate analysis may provide the answer[14].

In conclusion, the endoscopic appearances of CC are becoming more familiar amongst the endoscopic community. We recommend adoption of the proposed lesion description herein in order to improve homogeneity of future reports.

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REFERENCES

1 **Tysk C**, Bohr J, Nyhlin N, Wickbom A, Eriksson S. Diagnosis and management of microscopic colitis. *World J Gastroenterol* 2008; **14**: 7280-7288
2 **Pardi DS**. Microscopic colitis: an update. *Inflamm Bowel Dis* 2004; **10**: 860-870
3 **Bohr J**. A review of collagenous colitis. *Scand J Gastroenterol* 1998; **33**: 2-9
4 **Gledhill A**, Cole FM. Significance of basement membrane thickening in the human colon. *Gut* 1984; **25**: 1085-1088
5 **van der Wouden EJ**, Karrenbeld A, Kleibeuker JH, Dijkstra G. Microscopic colitis: an unfamiliar but treatable disease. *Neth J Med* 2009; **67**: 41-45
6 **Lindström CG**. 'Collagenous colitis' with watery diarrhoea--a new entity? *Pathol Eur* 1976; **11**: 87-89
7 **Freeman HJ**, Weinstein WM, Shnitka TK, Wensel RH, Sartor VE. Watery diarrhoea syndrome associated with a lesion of the colonic basement membrane-lamina propria interface. *Ann R Coll Phys Surg Can* 1976; **9**: 45
8 **Lazenby AJ**, Yardley JH, Giardiello FM, Jessurun J, Bayless TM. Lymphocytic ("microscopic") colitis: a comparative histopathologic study with particular reference to collagenous colitis. *Hum Pathol* 1989; **20**: 18-28
9 **Olesen M**, Eriksson S, Bohr J, Järnerot G, Tysk C. Microscopic colitis: a common diarrhoeal disease. An epidemiological study in Orebro, Sweden, 1993-1998. *Gut* 2004; **53**: 346-350
10 **Stampfl DA**, Friedman LS. Collagenous colitis: pathophysiologic considerations. *Dig Dis Sci* 1991; **36**: 705-711
11 **Chopra A**, Kola H, Thornton J. Collagenous colitis and osteogenesis imperfecta: is defective collagen to be blamed? *Am J Gastroenterol* 2009; **104**: 2866
12 **Günther U**, Bateman AC, Beattie RM, Bauer M, MacDonald TT, Kaskas BA. Connective tissue growth factor expression is increased in collagenous colitis and coeliac disease. *Histopathology* 2010; **57**: 427-435

13 **Keszthelyi D**, Jansen SV, Schouten GA, de Kort S, Scholtes B, Engels LG, Masclee AA. Proton pump inhibitor use is associated with an increased risk for microscopic colitis: a case-control study. *Aliment Pharmacol Ther* 2010; **32**: 1124-1128
14 **Capurso G**, Marignani M, Attilia F, Milione M, Colarossi C, Zampaletta C, Di Giulio E, Delle Fave G. Lansoprazole-induced microscopic colitis: an increasing problem? Results of a prospecive case-series and systematic review of the literature. *Dig Liver Dis* 2011; **43**: 380-385
15 **Giardiello FM**, Hansen FC, Lazenby AJ, Hellman DB, Milligan FD, Bayless TM, Yardley JH. Collagenous colitis in setting of nonsteroidal antiinflammatory drugs and antibiotics. *Dig Dis Sci* 1990; **35**: 257-260
16 **Richieri JP,** Bonneau HP, Cano N, Di Costanzo J, Martin J. Collagenous colitis: an unusual endoscopic appearance. *Gastrointest Endosc* 1993; **39**: 192-194
17 **Smiley DN**, Barkin J. Unusual endoscopic appearance of collagenous colitis. *J Clin Gastroenterol* 1993; **17**: 84-85
18 **Katanuma A**, Kodama T, Tamaki T, Katabami S, Yamashita K, Itoh J, Imai K. Collagenous colitis. *Intern Med* 1995; **34**: 195-198
19 **Katsinelos P**, Katsos I, Patsiaoura K, Xiarchos P, Goulis I, Eugenidis N. A new endoscopic appearance of collagenous colitis. *Endoscopy* 1997; **29**: 135
20 **Yabe M,** Igarashi k, Hata K, Ho N, Tsukioka S, Shibuya H. A case of collagenous colitis with a unique endoscopic appearance. *Gastroenterol Endosc* 1997; **39**: 1099-1104
21 **Sato S**, Benoni C, Tóth E, Veress B, Fork FT. Chromoendoscopic appearance of collagenous colitis--a case report using indigo carmine. *Endoscopy* 1998; **30**: S80-S81
22 **Bermejo F**, Moreira V, Redondo C, Martín Scapa MA, Gisbert JP, Defarges V, Aller R. Collagenous colitis in Spain: a report of nine new cases. *Rev Esp Enferm Dig* 1999; **91**: 93-104
23 **Freeman HJ**, James D, Mahoney CJ. Spontaneous peritonitis from perforation of the colon in collagenous colitis. *Can J Gastroenterol* 2001; **15**: 265-267
24 **Yagi K**, Nakamura A, Sekine A, Watanabe H. Nonsteroidal anti-inflammatory drug-associated colitis with a histology of collagenous colitis. *Endoscopy* 2001; **33**: 629-632
25 **Cruz-Correa M**, Milligan F, Giardiello FM, Bayless TM, Torbenson M, Yardley JH, Jackson FW, Wilson Jackson F. Collagenous colitis with mucosal tears on endoscopic insufflation: a unique presentation. *Gut* 2002; **51**: 600
26 **Kakar S**, Pardi DS, Burgart LJ. Colonic ulcers accompanying collagenous colitis: implication of nonsteroidal anti-inflammatory drugs. *Am J Gastroenterol* 2003; **98**: 1834-1837
27 **Sato S**, Matsui T, Tsuda S, Yao T, Iwashita A, Takagi Y, Nishida T. Endosocopic abnormalities in a Japanese patient with collagenous colitis. *J Gastroenterol* 2003; **38**: 812-813
28 **Byrne MF**, Royston D, Patchett SE. Association of common variable immunodeficiency with atypical collagenous colitis. *Eur J Gastroenterol Hepatol* 2003; **15**: 1051-1053
29 **Yuan S**, Reyes V, Bronner MP. Pseudomembranous collagenous colitis. *Am J Surg Pathol* 2003; **27**: 1375-1379
30 **Buchman AL**, Rao S. Pseudomembranous collagenous colitis. *Dig Dis Sci* 2004; **49**: 1763-1767
31 **Sherman A**, Ackert JJ, Rajapaksa R, West AB, Oweity T. Fractured colon: an endoscopically distinctive lesion associated with colonic perforation following colonoscopy in patients with collagenous colitis. *J Clin Gastroenterol* 2004; **38**: 341-345
32 **Wickbom A**, Lindqvist M, Bohr J, Ung KA, Bergman J, Eriksson S, Tysk C. Colonic mucosal tears in collagenous colitis. *Scand J Gastroenterol* 2006; **41**: 726-729
33 **Koulaouzidis A**, Henry JA, Saeed AA. Mucosal tears can occur spontaneously in collagenous colitis. *Endoscopy* 2006; **38**: 549
34 **Poupardin-Moulin C,** Atlani M, Sabate JM, Coffin B. [Mucosal tears in a patient with collagenous colitis]. *Gastroenterol Clin Biol* 2004; **28**: 310-311
35 **Smith RR**, Ragput A. Mucosal tears on endoscopic insufflation resulting in perforation: an interesting presentation of collagenous colitis. *J Am Coll Surg* 2007; **205**: 725
36 **McDonnell WM**, Loura F, Pointon MJ, Greenson JK. Cat scratch colon. *Endoscopy* 2007; **39**: 459-461
37 **Allende DS**, Taylor SL, Bronner MP. Colonic perforation as a complication of collagenous colitis in a series of 12 patients. *Am J Gastroenterol* 2008; **103**: 2598-2604
38 **Umeno J**, Matsumoto T, Nakamura S, Jo Y, Yada S, Hirakawa K, Yoshimura R, Yamagata H, Kudo T, Hirano A, Gushima M, Yao T, Nakashima Y, Iida M. Linear mucosal defect may be characteristic of lansoprazole-associated collagenous colitis. *Gastrointest Endosc* 2008; **67**: 1185-1191
39 **Hashimoto Y**, Endo Y, Kuroki Y, Yoshikumi H, Yoshiba M. Collagenous colitis with unique colonoscopic findings. *Endoscopy* 2008; **40** Suppl 2: E162
40 **Watanabe T,** Hirakawa K, Sato S, Kochi S, Nakajima Y, Aoyagi K, Matsumoto T, Iida M. A case with collagenous colitis and multiple longitudinal ulcers. *Gastroenterol Endosc* 2008; **50**: 27-33
41 **Yusuke H**, Jun T, Naotaka M, Yuichi T, Yutaka E, Kazuaki I. Lansoprazole-associated collagenous colitis: unique presentation, similar to ischemic colitis. *Endoscopy* 2009; **41** Suppl 2: E281-E282
42 **Cuoco L**, Bertoncello V, Salvagnini M. Colonic perforation after colonoscopy in patients with collagenous colitis. *Am J Gastroenterol* 2009; **104**: 1846-1847; author reply 1847
43 **Dunzendorfer T**, Wilkins S, Johnson R. Mucosal tear in collagenous colitis. *Clin Gastroenterol Hepatol* 2009; **7**: e57
44 **Chiba M**, Sugawara T, Tozawa H, Tsuda H, Abe T, Tokairin T, Ono I, Ushiyama E. Lansoprazole-associated collagenous colitis: diffuse mucosal cloudiness mimicking ulcerative colitis. *World J Gastroenterol* 2009; **15**: 2166-2169
45 **Sekioka T,** Saitou M, Tanaka T, Takeda S, Kumamoto S, Kajiwara M, Nakai O, Yamada T. A Case of Lansoprazole-associated Collagenous Colitis with Peritonitis Accompanying Endoscopically Fractured Colon. *Nippon Daicho Komonbyo Gakkai Zasshi* 2009; **62**: 527-533
46 **Couto G**, Bispo M, Barreiro P, Monteiro L, Matos L. Unique endoscopy findings in collagenous colitis. *Gastrointest Endosc* 2009; **69**: 1186-1188
47 **Sawada K,** Fujiya M, Itabashi K, Suzuki M, Kubo K, Nata T, Ueno N, Inaba Y, Moriichi K, Okamoto K, Ikuta K, Tanabe H, Mizukami Y, Takagi Y, Kohgo Y. Collagenous colitis appeared after 6-year administration of lansoprazole. *Clin J Gastroenterol* 2010; **3**: 18–21
48 **Koulaouzidis A**. Mucosal scars in collagenous colitis. *Gastrointest Endosc* 2010; **71**: 221-222; author reply 222
49 **van Velden R**, Snieders I, Quispel R. Image of the month. Tearing of the colon in a patient with collagenous colitis during colonoscopy. *Clin Gastroenterol Hepatol* 2010; **8**: A28
50 **Nomura E**, Kagaya H, Uchimi K, Noguchi T, Suzuki S, Suzuki M, Onodera H, Tateno H. Linear mucosal defects: a characteristic endoscopic finding of lansoprazole-associated collagenous colitis. *Endoscopy* 2010; **42** Suppl 2: E9-E10
51 **Miyagawa T,** Ueda T. A case of Lansoprazole-associated collagenous colitis in a hemodialysis patient. *Nihon Toseki Igakkai Zasshi* 2010; **43**: 843-846
52 **Milestone AN,** Teare JP, Goldin RD. W1498: Linear Ulceration in Collagenous Colitis. A Case Series and Literature Review. *Gastrointestinal Endoscopy* 2011; **71**: AB343
53 **Kawamura T,** Yasuda K, Mochizuki N, Tanaka K, Uno K, Ueda M, Kawabata H, Katsura K. Three cases of collagenous colitis with longitudinal ulcers. *Gastroenterological Endoscopy* 2010; **52**: 1261-1266
54 **Fasoulas K,** Terzoudis S, Lazaraki G, Atmatzidis S, Beltsis A, Pilpilidis I, Chatzimavroudis G, Katsinelos P. *Annals of Gastroenterology* 2010; **23**: 311-313
55 **Cimmino DG**, Mella JM, Pereyra L, Luna PA, Casas G, Caldo I, Popoff F, Pedreira S, Boerr LA. A colorectal mosaic

pattern might be an endoscopic feature of collagenous colitis. *J Crohns Colitis* 2010; **4**: 139-143
56 **Maroy A.** A case of drug-induced lymphocytic colitis with a peculiar colonoscopic mucosal feature. *ACEN* 2001; **31**: 301-302
57 **Hussain Z**, Kelly S, Clarke A, Adams S, Miller G. Colonic perforation in collagenous colitis: a systematic review of a rare complication and guidance on management. *Surg Endosc* 2010; **24**: 2930-2934
58 **Yarze JC**. Finding mucosal tears in collagenous colitis during colonoscopic insufflation. *Gut* 2003; **52**: 613-614; author reply 614
59 **Woltjen JA**. A retrospective analysis of cecal barotrauma caused by colonoscope air flow and pressure. *Gastrointest Endosc* 2005; **61**: 37-45
60 **Tominaga K**, Shigiyama F, Ito S, Iida T, Fujinuma S, Maetani I. Emergence of "cat scratch colon" during a colonoscopy. *Endoscopy* 2008; **40**: 353; author reply 353
61 **Baudet JS**, Diaz-Bethencourt D, Arguiñarena X, Soler M, Morales S, Avilés J. Cat scratch colon is caused by barotrauma secondary to insufflation during colonoscopy. *Endoscopy* 2008; **40**: 878; author reply 878-879
62 **Purnak T**, Ozaslan E, Yildiz A, Efe C. The cat scratch colon sign in a patient with chronic cholestasis. *Endoscopy* 2010; **42** Suppl 2: E117
63 **Pardi DS**. Microscopic colitis. *Mayo Clin Proc* 2003; **78**: 614-616; quiz 616-617
64 **Hata K**, Watanabe T, Kanazawa T, Kazama S, Shida D, Nagawa H. Mucosal tears on endoscopic insufflation. *Gut* 2003; **52**: 613; author reply 613
65 **Hashimoto Y,** Takano Y, Sakiyama A, Takashaki H. W1469: Lansoprazole Associated Colitis Is a New Drug Induced Enteropathy Presenting Unique Clinical Manifestations and Endoscopic Findings. *Gastrointestinal Endoscopy* 2010; **71**: AB336
66 **Chande N**, Driman DK. Microscopic colitis associated with lansoprazole: report of two cases and a review of the literature. *Scand J Gastroenterol* 2007; **42**: 530-533

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