



CASE REPORT

Development of collagenous colitis in inflammatory bowel disease: two case reports and a review of the literature

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Abstract

The occurrence of collagenous colitis (CC) in patients with pre-existing inflammatory bowel diseases (IBD) is rare, with only seven cases reported in the past. Herein, we report two IBD cases who developed CC after successful treatment of their IBD with two different tumor necrosis factor (TNF)- α inhibitors, which have been previously reported to successfully treat refractory CC. This report highlights the need to do random biopsies of the colon for CC diagnosis in IBD patients with symptoms of diarrhea after complete mucosal healing. The report also reviews plausible mechanisms as to how CC may develop, including the role of multiple medications.

Key words: Collagenous colitis; inflammatory bowel disease; tumor necrosis factor- α inhibitors; infliximab; adalimumab

Introduction

Collagenous colitis (CC) and lymphocytic colitis (LC) represent the two main types of microscopic colitis (MC). Patients with CC mostly present with chronic intermittent watery diarrhea [1]. CC mainly affects middle-aged women at an age of approximately 55–63.8 years, with a female-to-male ratio of 3–6.8:1 [1,2]. Macroscopically, during colonoscopy, a patient with CC has normal-appearing colonic mucosa, although some abnormal changes have been reported in the literature, including edema, erythema, abnormal vasculature pattern and diffuse mucosal cloudiness [1,3]. CC is typically diagnosed after microscopic examination, showing a thickened sub-epithelial collagen band $\geq 10\ \mu\text{m}$ in colorectal biopsies [4]. Surface epithelial damage with inflammatory cell infiltration in both surface epithelium and lamina propria is also present [5].

The cause of CC and its association with other diseases are still unclear. Chutkan *et al.* in 2000 reported a family of mother, daughter and son who have CC, ulcerative colitis (UC) and Crohn's disease (CD), respectively, suggesting that CC and inflammatory bowel diseases (IBD) could be related or have a common genetic predisposition [6], but some studies have failed to find any significant association between CC and IBD [2], and yet others have reported the co-occurrence of CC and IBD. In most of the latter studies reporting co-occurrence of the two disease entities, CC was followed by the eventual development of clinical and pathological IBD [7–13]. There are also two reported cases of simultaneous occurrence of CC and IBD [14,15].

Here, we report two cases of IBD who have developed CC years after the onset of IBD in two patients who were in clinical remission. Interestingly, both cases had been successfully

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treated with tumor necrosis factor (TNF)- α inhibitors. In this report, we also review the seven published cases of CC that developed after pre-existing IBD [16–21]. Our report highlights two important issues: CC development occurs most often in patients who are clinically and endoscopically in remission necessitating random mucosal biopsies during endoscopy before symptoms can be attributed to irritable bowel syndrome (IBS); and CC can develop while the patient is in remission on TNF- α inhibitors, which have been used to treat refractory CC.

Case 1

A 49-year-old white female was diagnosed in 2004 with UC that involved her entire colon (i.e. pan-colitis) at the age of 39. Her symptoms of UC were intermittent bloody diarrhea, fecal urgency, fatigue and abdominal cramping with bowel movements. She was tried on mesalamine which did not control her symptoms; azathioprine and 6-mercaptopurine which gave her abdominal pain and resulted in pancreatitis; and infliximab to which she had a severe infusion reaction. She was then started on adalimumab in March 2008 (before the FDA approval of adalimumab for UC in the US) to which she clinically responded well. She had undergone multiple colonoscopies with surveillance biopsies in 2006, 2009 and 2010. None of these showed any evidence of CC. In 2011, colonoscopy showed minimal to no active disease, presence of multiple pseudo-polyps and no evidence of CC. Her past medical history included diabetes, Hashimoto's thyroiditis, anxiety, hyperlipidemia, gastroesophageal reflux disease and multiple drug allergies. Her medications at the time of CC diagnosis were adalimumab, rabeprazole, levothyroxine, pravastatin, glimepiride, metformin, ramipril, cetirizine, aspirin (81 mg daily) and multivitamins. She denied any history of smoking and she rarely drank any alcohol.

In 2013, the patient presented to the clinic with complaints of chronic intermittent diarrhea and abdominal pain for the past 3–4 months and she reported that this was very different from what she usually experiences with UC flares. Specifically, she denied any weight loss and blood in the stool. Her physical examination was unremarkable. Her laboratory studies revealed a normal complete blood count (CBC), CMP, erythrocyte sedimentation rate (ESR) and C-reaction protein (CRP). Her transglutaminase Ab (IgA), gliadin Ab (IgG and IgA) and endomysial Ab (IgA) were negative for celiac disease. Her anti-nuclear antibodies (ANA) were also normal. Stool for culture, ova and parasites, and *C. difficile* toxin were negative. A repeat colonoscopy showed a few 1–4 mm ulcerations around the ileocecal valve and in the sigmoid, and large pseudo-polyps in the left colon, as before. The rest of the colonic mucosa appeared normal, but was scarred and stiff. Histopathology of the surveillance colonic biopsies revealed a new-onset CC, with a thickened sub-epithelial collagen band of $>12\mu\text{m}$ to $>15\mu\text{m}$ (Figure 1). She was started on cholestyramine and budesonide

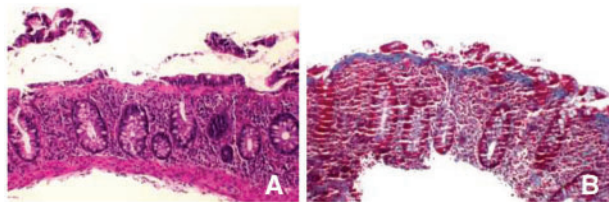


Figure 1. (A) Low-power microphotograph showing colonic mucosa with diffuse chronic colitis and thickened subsurface collagen band (H&E stain, $\times 100$). (B) Trichrome stain showing thickened collagen band ($>15\mu\text{m}$).

with resolution of her symptoms of CC. The patient was then maintained on cholestyramine long term to control her CC. A repeat colonoscopy was performed in 2015 for colon cancer surveillance and there was resolution of the histological changes of CC but mildly active patchy histological UC with mild erythema and granularity of the mucosa.

Case 2

A 61-year-old white Hispanic female with symptoms of CD for 10 years was diagnosed with CD (involving her esophagus, stomach, ileum and colon). She was started on infliximab with great improvement in her disease. She additionally had a past medical history of diabetes, hypothyroidism, diverticulosis and gastroesophageal reflux disease. In addition to infliximab, her medications included levothyroxine, sitagliptin phosphate, metformin, pravastatin, lansoprazole and vitamin D. She actively smoked cigarettes and rarely drank any alcohol. While she was on infliximab, the patient developed dysphagia and an esophagogastroduodenoscopy (EGD) was performed revealing candida esophagitis, which was successfully treated with fluconazole. A year after the start of infliximab in 2014, she presented with an unintentional weight loss of more than 2 kg, fatigue, abdominal pain and chronic intermittent diarrhea with some rectal bleeding. The patient's laboratory studies revealed a normal CBC, CMP, ESR and CRP. Stool for culture, ova and parasites, and *C. difficile* toxin PCR were negative for any evidence of infection. She had an EGD with small bowel biopsies that was also negative for celiac disease or other pathology. A surveillance colonoscopy was performed and showed few scattered aphthous ulcerations in the distal terminal ileum and complete mucosal healing of her colon. Histopathology of the colonic biopsies showed inactive CD and a diffuse mild chronic colitis with a thickened collagen band ($>25\mu\text{m}$) throughout the colon that is consistent with CC (Figure 2). She was started on cholestyramine and her symptoms of CC completely resolved. She was then maintained on cholestyramine long term to control her CC. Also, in the meantime, the dose of infliximab was reduced in the patient due to recurrent candida esophagitis. A repeat colonoscopy was performed in 2016 for colon cancer surveillance and there was resolution of the histological changes of CC and the CD was inactive in the terminal ileum and colon with complete mucosal healing and inactive colitis on random biopsies.

Discussion

CC has been linked with IBD, but development of CC after the IBD diagnosis is rare. CC has not been reported to occur in IBD patients in remission or those on TNF- α inhibitors. In fact, TNF- α inhibitors have been reported to successfully treat six out of seven cases of CC that were refractory to treatment [22–24].

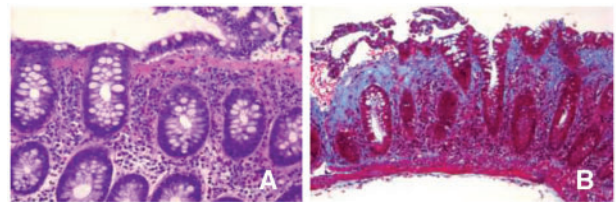


Figure 2. (A) Medium-power microphotograph showing diffuse chronic colitis, thickened collagen band and surface denudation (H&E stain, $\times 200$). (B) Trichrome stain showing thickened collagen band ($>25\mu\text{m}$).

Table 1. Cases in the literature reported to develop CC after an established diagnosis of IBD

Age at CC diagnosis (years)/gender	IBD type	Part of GI tract involved	Duration of IBD before diagnosis (years)	Duration of IBD before CC diagnosis (years)	IBD medication at CC diagnosis	Duration of TNF α inhibitor before onset of CC (months)	Active vs remission at CC diagnosis	Other medications	Associated diseases	Medications used to treat CC	Outcome of CC	Reference
Case 1 49/Female	UC	Entire colon	10	10	Adalimumab	66	Remission	Rabeprazole, levothyroxine, glimepiride, metformin, ramipril, cetrizine, aspirin	Diabetes, Hashimoto's thyroiditis, anxiety, GERD and multiple drug allergies	Cholestyramine and budesonide	Complete resolution	This report
Case 2 60/Female	CD	Esophagus, stomach, ileum and colon	2	2	Infliximab	12	Remission	Levothyroxine, sitagliptin phosphate/ metformin hydrochloride, pravastatin, lanzoprazole	Diabetes, hypothyroidism, diverticulosis and GERD	Cholestyramine	Complete resolution	This report
Case 3 35/Male	CD	Terminal ileum	NR	NR	No medications	NA	Active	Indomethacin, ACEI, ARB, IV antibiotics, steroids	Nephrotic syndrome, Amyloidosis	NR	NR	[17]
Case 4 79/Female	UC	NR	14	14	Mesalamine	NA	Remission	NR	NR	Mesalamine	Complete resolution	[16]
Case 5 59/Female	UC	Left side of the colon	13	13	Mesalamine	NA	Remission	ibuprofen (no association with CC symptoms)	NR	Bismuth	Complete resolution	[16]
Case 6 59/Female	CD	Perianal	NR	NR	Infliximab	NR	Active	Mood stabilizers (in the past)	Depression, h/o acute steroid psychosis	Bismuth subsalicylate and imodium	Complete resolution	[20]
Case 7 63/Male	UC	Left side of the colon	8	8	Mesalamine	NA	Remission	NR	NR	NR	NR	[18]
Case 8 57/Female	UC	Entire colon	5	5	Mesalamine and prednisolone	NA	Remission	ACEI, Adriamycin, Cyclophosphamide, Etoposide, Melphalan	Systemic Amyloidosis, autologous stem-cell transplantation	NR	NR	[19]
Case 9 70/Female	CD	Entire colon	5	5	No medications	NA	Remission	NR	IDDM, Grave's disease, atrophic gastritis	NR	NR	[21]

NR, not reported; NA, not applicable; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; CC, collagenous colitis; TNF α Is, tumor necrosis factor- α inhibitors; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; GERD, gastroesophageal reflux disease; IDDM, insulin-dependent diabetes mellitus.

Herein, we report two patients who developed CC following successful treatment of their IBD with TNF- α inhibitors, namely infliximab and adalimumab. This finding highlights the importance of taking random biopsies of the colon even if the mucosa appears normal endoscopically in IBD patients. We also highlight that CC in patients with existing IBD can be temporary.

There are seven IBD cases that have been previously reported to develop CC subsequently to their IBD diagnosis and these are shown in **Table 1** along with the features and characteristics related to each case, and the two cases from this report are also included in the table. It is important to note that seven out of the nine cases of CC emergence after IBD development occurred in the cases which were in remission. Of the two remaining active cases, one had active perianal disease and the left colon looked otherwise normal [20]. The other had active terminal ileitis and systemic amyloidosis, and the colon also looked normal [17]. These features highlight an important need to keep CC in the differential diagnosis of persistent diarrhea in IBD patients, and to take random mucosal biopsies of the normal-looking colon before symptoms are attributed to IBS or other causes, even after successful treatment. Other causes of diarrhea in IBD have been getting more notice in the context of clinical trials. Until recently, randomized clinical trials of IBD (and especially those in CD) enrolled subjects with persistent diarrhea and symptoms such as abdominal pain and general wellbeing used in composite symptom indices; yet, a significant portion of the patients in such clinical trials had no appreciable endoscopic evidence of inflammation, necessitating a recent recommendation to add objective measures such as CRP/colonoscopy/magnetic resonance elastography to the inclusion criteria of active IBD subjects [25]. This fact points out the importance of looking for additional causes of diarrhea in IBD patients other than the IBD itself, and implies how often the problem of diarrhea in IBD is misinterpreted as active disease. This also highlights a need for literature such as our case report documenting such additional causes of diarrhea in IBD patients and the need for random biopsies of the colon regardless of endoscopic appearances.

Why and how CC develops in existing IBD patients is not known. Two patients shown in **Table 1** had systemic amyloidosis, suggesting an aberrant immune response as an etiology. Interestingly, however, before the addition of the two cases in this report, six out of the seven previously reported patients were on minimal treatment with mesalamines or were on no medications. There is only one case of CC occurring in a patient with CD who had been successfully treated (also with a TNF- α inhibitor) [20]. This patient had colonic disease in remission, but had active perianal disease with a fistula, when CC developed. The noted collagen deposition in this case was most prominent distally and in the perianal area, which clinically and endoscopically looked abnormal, and this led to biopsies of the area and the CC diagnosis. Contrary to this previous case with active perianal disease, both of our cases were in complete clinical remission and had endoscopic colonic healing at the time of development of CC. The temporary occurrence of CC in our IBD patients could suggest some kind of aberrant or exaggerated healing response as a result of an imbalance between inflammatory pathways vs mucosal healing pathways, tipping the balance toward protracted healing. This conjecture fits with the clinical course of disease in our two cases. In Case 1 reported here, interestingly enough, we note disappearance of the CC after reappearance of mild UC. In Case 2, a dose reduction in infliximab treatment corresponds with the disappearance of CC.

Among the proposed theories that initiate the processes leading up to the altered collagen balance seen in CC are immune dysregulation/autoimmunity [2,26]; atypical responses to luminal toxins such as those from bacteria in susceptible patients [27–31] (which also is thought to account for improvement of CC with cholestyramine [32]); and drug idiosyncrasy. The two cases that we report here have preceding autoimmune thyroid disease and diabetes mellitus in addition to IBD, which could have contributed to CC development. In our two cases, despite a response to cholestyramine, we noted no evidence of infectious agents in stool studies. Among the previous medications that have been reported in association with CC and were used in both of our patients are non-steroidal anti-inflammatory drugs (NSAIDs) [33,34], proton pump inhibitors (PPIs) [3,35–37] and statins [34,38,39]. Even though we noted no temporal relationship between the use of these medications and CC onset in our patients, a careful medication history in IBD patients is needed, and it is certainly plausible that one or more of these agents could have led to the development of CC in our two IBD patients.

In conclusion, our cases highlight that CC development in IBD patients could occur despite successful treatment either due to an exaggerated healing response or due to the effects of multiple medications associated with CC; and highlight the need for random biopsies of the colon in IBD patients with new-onset diarrhea after successful treatment, especially in those cases with complete mucosal healing, before symptoms are attributed to IBS. The evidence presented herein is hypothesis-generating, proposing a need for further studies looking at the association between complete mucosal healing and subsequent CC development and its mechanisms.

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Conflict of interest

None declared.

References

- Bohr J, Tysk C, Eriksson S et al. Collagenous colitis: a retrospective study of clinical presentation and treatment in 163 patients. *Gut* 1996;**39**:846–51.
- Kao KT, Pedraza BA, McClune AC et al. Microscopic colitis: a large retrospective analysis from a health maintenance organization experience. *World J Gastroenterol* 2009;**15**:3122–7.
- Chiba M, Sugawara T, Tozawa H et al. Lansoprazole-associated collagenous colitis: diffuse mucosal cloudiness mimicking ulcerative colitis. *World J Gastroenterol* 2009;**15**:2166–9.
- Lee E, Schiller LR, Vendrell D et al. Subepithelial collagen table thickness in colon specimens from patients with microscopic colitis and collagenous colitis. *Gastroenterology* 1992;**103**:1790–6.
- Jessurun J, Yardley JH, Giardiello FM et al. Chronic colitis with thickening of the subepithelial collagen layer (collagenous

- colitis): histopathologic findings in 15 patients. *Hum Pathol* 1987;**18**:839–48.
6. Chutkan R, Sternthal M, Janowitz HD. A family with collagenous colitis, ulcerative colitis, and Crohn's disease. *Am J Gastroenterol* 2000;**95**:3640–1.
 7. Goldstein NS, Gyorfí T. Focal lymphocytic colitis and collagenous colitis: patterns of Crohn's colitis? *Am J Surg Pathol* 1999;**23**:1075–81.
 8. Pokorny CS, Kneale KL, Henderson CJ. Progression of collagenous colitis to ulcerative colitis. *J Clin Gastroenterol* 2001;**32**:435–8.
 9. Aqel B, Bishop M, Krishna M et al. Collagenous colitis evolving into ulcerative colitis: a case report and review of the literature. *Dig Dis Sci* 2003;**48**:2323–7.
 10. O'Beirne JP, Ireland A. Progression of collagenous colitis to Crohn's disease. *Eur J Gastroenterol Hepatol* 2005;**17**:573–5.
 11. Smith P, Bishop P, Whorwell PJ. Collagenous colitis, ulcerative colitis, coeliac disease and hyperparathyroidism in one patient: implications for the management of collagenous colitis. *Eur J Gastroenterol Hepatol* 2005;**17**:1239–42.
 12. Freeman HJ, Berean KW, Nimmo M. Evolution of collagenous colitis into severe and extensive ulcerative colitis. *Can J Gastroenterol* 2007;**21**:315–18.
 13. Giardiello FM, Jackson FW, Lazenby AJ. Metachronous occurrence of collagenous colitis and ulcerative colitis. *Gut* 1991;**32**:447–9.
 14. Chandratre S, Bramble MG, Cooke WM et al. Simultaneous occurrence of collagenous colitis and Crohn's disease. *Digestion* 1987;**36**:55–60.
 15. Nojgaard C, Nielsen PL, Rumessen JJ. Synchronous onset of collagenous colitis and Crohn disease. *Ugeskrift for laeger* 2002;**164**:2299–2300.
 16. Jegadeesan R, Liu X, Pagadala MR et al. Microscopic colitis: is it a spectrum of inflammatory bowel disease? *World J Gastroenterol* 2013;**19**:4252–6.
 17. Blackmur JP, Chapman FA, Bellamy CO et al. Anti-TNF-alpha therapy for renal amyloid as a complication of Crohn's disease. *QJM* 2014;**107**:57–9.
 18. Haque M, Florin T. Progression of ulcerative colitis to collagenous colitis: chance, evolution or association? *Inflamm Bowel Dis* 2007;**13**:1321.
 19. Janczewska I, Mejhert M, Hast R et al. Primary AL-amyloidosis, ulcerative colitis and collagenous colitis in a 57-year-old woman: a case study. *Scand J Gastroenterol* 2004;**39**:1306–9.
 20. Malik TA, Peter S, Jhala N et al. Crohn's colitis with perianal disease complicated by collagenous colitis: discourse on management options. *Digestion* 2010;**81**:142–4.
 21. Seguenot D, Marteau P, Lavergne A et al. [Collagen colitis after Crohn's disease: a fortuitous association?]. *Gastroenterol Clin Biol* 1990;**14**:891–2.
 22. Pola S, Fahmy M, Evans E et al. Successful use of infliximab in the treatment of corticosteroid dependent collagenous colitis. *Am J Gastroenterol* 2013;**108**:857–8.
 23. Munch A, Ignatova S, Strom M. Adalimumab in budesonide and methotrexate refractory collagenous colitis. *Scand J Gastroenterol* 2012;**47**:59–63.
 24. Esteve M, Mahadevan U, Sainz E et al. Efficacy of anti-TNF therapies in refractory severe microscopic colitis. *J Crohn Colitis* 2011;**5**:612–18.
 25. D'Haens G, Feagan B, Colombel JF et al. Challenges to the design, execution, and analysis of randomized controlled trials for inflammatory bowel disease. *Gastroenterology* 2012;**143**:1461–9.
 26. Vigren L, Tysk C, Strom M et al. Celiac disease and other autoimmune diseases in patients with collagenous colitis. *Scand J Gastroenterol* 2013;**48**:944–50.
 27. Jarnerot G, Tysk C, Bohr J et al. Collagenous colitis and fecal stream diversion. *Gastroenterology* 1995;**109**:449–55.
 28. Khan MA, Brunt EM, Longo WE et al. Persistent *Clostridium difficile* colitis: a possible etiology for the development of collagenous colitis. *Dig Dis Sci* 2000;**45**:998–1001.
 29. Vesoulis Z, Lozanski G, Lojudice T. Synchronous occurrence of collagenous colitis and pseudomembranous colitis. *Can J Gastroenterol* 2000;**14**:353–8.
 30. Bohr J, Nordfelth R, Jarnerot G et al. *Yersinia* species in collagenous colitis: a serologic study. *Scand J Gastroenterol* 2002;**37**:711–14.
 31. Makinen M, Niemela S, Lehtola J et al. Collagenous colitis and *Yersinia enterocolitica* infection. *Dig Dis Sci* 1998;**43**:1341–6.
 32. Andersen T, Andersen JR, Tvede M et al. Collagenous colitis: are bacterial cytotoxins responsible? *Am J Gastroenterol* 1993;**88**:375–7.
 33. Riddell RH, Tanaka M, Mazzoleni G. Non-steroidal anti-inflammatory drugs as a possible cause of collagenous colitis: a case-control study. *Gut* 1992;**33**:683–6.
 34. Fernandez-Banares F, Esteve M, Espinos JC et al. Drug consumption and the risk of microscopic colitis. *Am J Gastroenterol* 2007;**102**:324–30.
 35. Chande N, Driman DK. Microscopic colitis associated with lansoprazole: report of two cases and a review of the literature. *Scand J Gastroenterol* 2007;**42**:530–3.
 36. Kitagawa T, Sato K, Yokouchi Y et al. A case of lansoprazole-associated collagenous colitis with longitudinal ulcer. *J Gastrointest Liver Dis* 2013;**22**:9.
 37. Thomson RD, Lestina LS, Bensen SP et al. Lansoprazole-associated microscopic colitis: a case series. *Am J Gastroenterol* 2002;**97**:2908–13.
 38. Bonderup OK, Fenger-Gron M, Wigh T et al. Drug exposure and risk of microscopic colitis: a nationwide Danish case-control study with 5751 cases. *Inflamm Bowel Dis* 2014;**20**:1702–7.
 39. Pascua MF, Kedia P, Weiner MG et al. Microscopic colitis and medication use. *Clin Med Insights Gastroenterol* 2010;**2010**:11–19.