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Collagenous colitis development occurs after long standing mucosal healing in IBD with TNF-α inhibitors, and could be due to exaggerated healing response from excess TNF-α inhibition

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A B S T R A C T

Collagenous colitis is a relatively rare disorder affecting mainly middle-aged women where they present with chronic non-bloody diarrhea. Both with lymphocytic colitis they compose microscopic colitis. The exact cause of collagenous colitis is still unknown however; many potential pathophysiologic mechanisms have been proposed but no convincing mechanism has been identified. Collagenous colitis has been linked to medications mainly NSAIDs, SSRIs, and PPIs. It is also believed that collagenous colitis is autoimmune disease and there are weak believe it could have some genetic inheritance. We reported before two cases of collagenous colitis developed in patients with Crohn's disease and ulcerative colitis while they were in complete mucosal remission after being treated with tumor necrosis factors-α inhibitors. In this article we will try to explain how collagenous colitis can develop in patients with inflammatory bowel disease especially those on tumor necrosis factors-α inhibitors.

Background

Collagenous colitis is a rare disease, with little information on its molecular mechanisms

Collagenous colitis (CC) is a chronic inflammatory process of the colon that typically presents with chronic non-bloody watery diarrhea. CC incidence and prevalence in the US estimated to be 3.1 and 103 respectively, per 100,000 [1]. CC is a relatively newer gastrointestinal disorder, and it was first reported in 1976 [2]. It mainly occurs in middle age, with a female predominance and the reasons for this are unclear [3,4]. Macroscopic and radiological findings are unremarkable and diagnosis can only be made microscopically by taking colonic biopsy samples at the time of colonoscopy that typically show thickened subepithelial collagen band ≥ 10 μm in the mucosa [5].

CC occurs more frequently in those with other autoimmune diseases

Among the proposed etiologies for CC is autoimmunity as shown in previous studies and eluded to by the frequent co-occurrence of CC and other autoimmune diseases such as celiac disease (CeD), autoimmune thyroid disease (AITD), rheumatoid arthritis (RA), Sjogren's disease, Raynaud/CREST syndrome, and diabetes mellitus (DM) [4,6]. Female preponderance and noticeable improvement on steroids also increase the likelihood that CC could be an autoimmune disorder [7].

Luminal toxins may be contributory to CC

Another theory that could possibly contribute to development of CC is loss of immune tolerance toward the resident gut flora, yeast, and food antigens, which may be factors for initiation of CC. Evidence for the role of luminal toxins in the development of CC has been suggested through the noted clinical and histological remission of CC after diversion of the fecal stream by surgery; and subsequent clinical and histological recurrence of CC with re-establishment of the fecal stream after re-anastomosis [8]. Specifically, bacterial toxins related to C. *difficile* and Yersinia infection have been associated with CC [9–12]. The improvement in CC symptoms in response to the toxin binding resin, cholestyramine, also supports the role of luminal toxins in disease pathogenesis [13].

Medications implicated in CC development affect fibrosis through direct and indirect mechanisms

Other environmental factors such as medications, specifically non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), statins, and selective serotonin reuptake inhibitors (SSRIs) have been completely or partially implicated in CC development [14–21].

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The mechanism by how these medications are shown to affect fibrosis and cause CC is still not clear. However, it has been postulated that NSAIDs inhibit prostaglandin synthesis, which would increase intestinal permeability and allows access of the luminal contents to the lamina propria. This causes inflammation and activation of the pericryptal fibroblasts, leading to thickening of the collagen layer [22]. PPIs can cause growth inhibition and oxidative stress in CT26 cells through alkalinazing the growth media. CT26 cells express Na + H exchanger genes, affecting salt and water transport. Treatment with PPIs also increases expression of fibrosis inducing factors such as transforming growth factor β (TGF-β) and fibroblast growth factor 2. PPI treatment also decreases expression of a negative regulator of collagen production, replication factor C1, resulting in increased expression of collagen type III and IV in association with lipid peroxide [23].

There may be a genetic predisposition to CC, similar to other inflammatory diseases of the bowel; and this may suggest a common mechanism as to how CC develops

The exact etiology of CC remains unclear; however, among etiologies that have been brought up is a genetic predilection, which seems common with other traditional inflammatory diseases of the bowel, such as ulcerative colitis (UC) and Crohn's disease (CD). In support of this hypothesis, in 2000, Chutkan et al. reported a family of a mother, daughter, and son with CC, UC, and CD, respectively [24]. In contrast to CC, both UC and CD have a much broader presentation that goes beyond diarrhea. Specifically, both UC and CD are typically associated with blood in the stool, abdominal pain, urgency, tenesmus, weight loss, and fever [25,26]. Diagnosis of UC and CD can be established radiologically through abdominal x-ray, barium studies, and CT scans. Endoscopic examination and biopsies of inflamed GI parts is mandatory to diagnose UC and CD, which usually do not demonstrate the subepithelial fibrosis seen in CC, but show ulcerations.

The co-occurrence of CC and IBD has been reported: In most of the studies, CC was followed by the eventual development of clinical and pathological UC or CD [27–33]. The co-occurrence of CC with UC or CD, suggests that there has to be dysregulation in a common mechanism that leads to the development of both. In our practice, we observed 2 unusual cases of UC and CD: Both had colonic involvement and both were successfully treated with TNF-α inhibitors; and surprisingly, both developed CC when their UC and CD was in complete remission and when they had mucosal healing. Considering that TNF-α inhibitors can be used to treat CC [34,35], it can be considered highly unusual to develop CC after IBD is fully treated with a TNF-α inhibitor.

Preclinical data about TNF-α inhibition and fibrosis suggests long term TNF-α/TGF-β imbalance may play a role in CC development after IBD onset

Our cases has lead us to pose the question of whether the development of CC in our patients is related to some kind of aberrant or exaggerated healing response to TNF-α inhibitors due to an unknown predisposition. There are very plausible mechanisms as to how this may occur with TNF-α inhibition: In all cases of CC, regardless of the cause, there is excess subepithelial collagen that can be explained by either overproduction or reduced degradation of collagen or both. TNF-α inhibitors can plausibly lead to the development of CC in the healing IBD mucosa through two mechanisms; either by enhancing overproduction of collagen in the extra-cellular matrix (ECM) or by reducing collagen degradation.

ECM overproduction as a genesis of CC is supported by the finding of an increase in the number of subepithelial myofibroblasts and their activity in CC patients that was demonstrated by increased expression of α-smooth muscle actin and tenascin [36]. TNF-α inhibitors have been suggested to promote fibrosis and strictures in patients with CD [37], although this is clinically controversial. Beddy et al. [38] found that fibroblasts isolated from CD strictures had significantly higher level of connective tissue growth factor (CTGF) expression than fibroblasts isolated from normal colon. Another mechanism through which collagen deposition is controlled is TGF-β, which enhances collagen deposition [39]. In fact, CC patients have been shown to have an increased expression of the TGF-β gene compared with controls which could either be mediated through eosinophils [40], or through Foxp3 + regulatory T cells, which can secrete TGF-β and are increased in the lamina propria of CC patients compared to LC patients and controls [41]. TNF-α has been shown to oppose the effect of TGF-β in terms of collagen synthesis [39]. Therefore, theoretically, TNF-α inhibitors can also potentially increase collagen production in the healing colonic mucosa by altering the balance between TNF-α and TGF-β, through shutting down the effect of TNF-α, and thereby indirectly enhancing the effect of TGF-β. Beddy et al. also found that (TGF-β) increases the expression of CTGF in fibroblasts isolated from both control (normal colon) and CD strictures, and that the addition of TNF-α suppresses TGF-β-stimulated-CTGF-expression in both the normal and diseased states, but the effect was lesser on the fibroblasts isolated from CD strictures. Therefore, it is plausible that treatment with TNF-α inhibitors could up-regulate TGF-β-mediated-CTGF, which would promote fibroblast proliferation, at least in some patients. Moreover, exposure of fibroblasts to TNF-α can lead to decreases in collagen mRNA and net collagen production (especially collagen type I) through inhibition at the transcriptional level shown in both human and animal studies [42,43]. Therefore, inhibition of TNF-α could be also detrimental by removing the checks and balances of TNF-α on collagen synthesis, plausibly in some IBD patients. Furthermore, in animal studies by Rapala et al., the down-regulatory effect of TNF-α in terms of collagen synthesis (at both the mRNA and protein levels) in granulation tissues in rats occurred with daily applications of TNF-α and a onetime application of TNF-α did not cause any reduction in collagen synthesis [44]. This data suggests that long-term suppression of TNF-α and disease control may be required before collagen synthesis is adequately affected by TNF-α inhibitors.

The second mechanism by which collagen could be increased in colonic tissues by TNF-α inhibitors is by reduced matrix degradation. Matrix-metalloproteinases (MMPs) have a central role in collagen remodeling and degradation; and reduced effective MMP activity could be one mediator playing a role in CC development. This mechanism has been supported by prominent staining of the collagen bands (type VI collagen and tenascin) with no significant increase in collagen type VI messenger RNA expression in CC [45]. Further support for locally impaired fibrolysis comes from the finding of restricted MMP-1 RNA expression, counteracted by increased endogenous tissue inhibitors of metalloproteinase (TIMP)-1 expression in CC patients [46]. Additionally, allelic variations of the MMP-9 gene have been reported to be associated with CC [47]. This suggests that familial occurrences of CC [48,49] could be explained in some instances by MMP-9 gene polymorphisms. MMP enzyme activity is regulated by TIMPs. TIMPs can be released from different connective tissue cells in response to pro-inflammatory mediators such as TNF-α and IL-1. In fact, TNF-α is a main inducer of MMPs [50], and inflamed intestinal tissues of IBD patients have increased levels of MMPs [51]. Theoretically, it is therefore also plausible that long-term inhibition of TNF-α in IBD patients could prevent induction of MMPs to degrade and remodel collagen in the ECM, resulting in excess collagen seen in CC.

Based on the above data, it appears that mucosal healing with excessive TNF-α inhibition in IBD can potentially come at a cost of an adverse event as CC.

Hypotheses

1. CC development after IBD while on TNF-α inhibitors occurs only in those patients who achieve mucosal healing for extended periods of time.
2. During long standing mucosal healing in IBD patients on TNF-α inhibitors, CC may develop in susceptible cases due to excessive

suppression of TNF-α and resultant unopposed TGF-β pathway action.

Evaluation of the hypothesis

To evaluate our hypotheses, we have looked for other cases of CC associated with IBD, beyond our two cases, who developed the disease after long standing remission with TNF-α inhibitors. We have found seven previously reported IBD cases in which CC developed after IBD treatment [52–57]. Befitting our hypothesis, five out of the seven cases were in patients who were in remission, but they were not on a TNF-α inhibitor. Of the other two, one had some perianal disease but a normal looking colon while on a TNF-α inhibitor [56]. The other had ileal disease with systemic amyloidosis and also a normal looking colon [53]. We reported our cases together with those in the literature [58]. After publication, we were also contacted by an additional female patient who read our report. She had Crohn's disease and was on a TNF-α inhibitor, enjoyed long-standing remission over 3 years and then developed CC (personal communication with EAM). Therefore, the two cases we have seen appear not to be in isolation.

Because CC is a rare disease and development of CC after IBD is even rarer, it is difficult to prove or disprove the above hypothesis for any one single investigator or any one single center treating IBD patients. Furthermore, majority of the time TNF-α inhibition in the mucosa is incomplete and most patients with IBD do not achieve complete mucosal healing or lose response to the TNF-α inhibiting drugs over time through antibody formation against the drug [59,60]. This may actually be considered a saving grace in a subgroup of IBD patients in whom an exaggerated response of healing and unopposed TGF-β action could occur with excessive TNF-α suppression, causing CC. Lastly, it is very unlikely to detect CC development as an undesired effect of TNF-α inhibition with short-term studies that last a year, which is typical of the clinical studies that have led to approval of this class of medications for treatment of IBD. It is also not possible to detect a CC related effect at an average post-marketing phase 4 trial limited to a few thousand patients, half of whom are on other drugs (since they represent controls), and most of which do not achieve long term mucosal healing with the TNF-α inhibitors.

However, considering the future in which we expect major developments in large-scale data generation and analysis through use of electronic medical records, evaluating our hypotheses may be possible. In fact there is a current movement toward shared health records and coalescence of such records to a handful of electronic systems in the next 10–20 years, making our hypotheses testable, if the cases are tracked and reported either in the electronic record or reported in another database. This is one of the major motivations for us to write this article, to alert other health providers (doctors, nurses, physician assistants, etc.) treating IBD to report such cases to federal or industry sponsored databases and make note of it in their electronic records; so that cases with CC development in those with pre-existing IBD can be carefully tracked. Since our observations and thus our hypothesis suggests this occurs in IBD patients who achieve mucosal healing for extended periods of time, we also suggest collection of clinically relevant data such as duration of treatment after mucosal healing; concomitant medications; therapeutic drug level of the TNF-α inhibitor used by the patient; and other clinically relevant variables to look for patterns especially in those patients who have unexplained non-bloody diarrhea who are in endoscopic or radiological remission, and whose symptoms are attributed to irritable bowel syndrome.

Lastly, we suggest that TNF-α levels and TGF-β levels in tissue be measured in cases in which there is complete mucosal healing to further investigate the pathogenesis of CC development with TNF-α inhibitors. This could be done with previously published techniques such as Real time PCR or enzyme-linked immunosorbent assay [61–63].

Clinical implications of the hypothesis

There can be large clinical implications of this hypothesis, if the hypothesis is proven to be correct. First and simplest of these implications pertains to the management of patients who have IBD and who develop CC during long-term and successful treatment with a TNF-α inhibitor achieving mucosal healing. If our hypothesis is correct, these types of CC-IBD patients could benefit significantly from a careful dose reduction of the TNF-α inhibitor they are taking, in an effort to find the minimum effective dose for maintaining remission of their IBD and also achieving remission of their CC. Alternatively, switching to another mechanism of treatment of the IBD can also be considered if CC related symptoms are not able to be controlled despite dose reductions.

The second implication of our hypothesis is for those IBD patients, who are doing well and have achieved mucosal healing on their current dose of TNF-α inhibitors and who do not have CC. There is now an emphasis on measuring anti-TNF-α trough levels and anti-drug antibodies in responders and non-responders, however, there are still limited and conflicting data regarding the role of these measurements in guiding treatment [64]. Current IBD guidelines suggest monitoring therapeutic drug levels in IBD patients in order to improve IBD related outcomes [65]; and most experts agree that therapeutic drug monitoring (TDM) of TNF-α inhibitors should be done in all IBD patients with symptomatic disease [66]. However, there is considerable debate whether TDM should also be done for all patients with IBD regardless of their remission status and some IBD experts promote dose increases of medications even for those IBD patients who are in remission to raise blood concentrations of the drugs to average recommended levels [66]. Proponents of dose increases typically state and cite evidence that TNF-α inhibitors have decreased short term rates of surgery related to strictures in Crohn's disease, which occur as a result of bowel fibrosis [67]; and therefore claim that there is no excess fibrosis risk. However, if our hypothesis is correct, this statement may not be true for all IBD patients. In fact, for IBD patients who have achieved mucosal healing with their current dose of TNF-α inhibitor, increasing doses of medication based on TDM could lead to overtreatment and CC development or fibrosis development elsewhere in the body. As such, TDM guidelines may need to emphasize not to increase doses of TNF-α inhibitors in patients who are doing clinically well and have achieved mucosal healing, regardless of the drug level seen with TDM.

Lastly, there has been a push for endoscopic mucosal healing in all IBD patients with higher and higher doses being used of all drugs. This is because IBD patients who achieved mucosal healing after treatment with TNF-α inhibitors have reduced endoscopic disease activity, lower surgery rates, fewer hospitalizations, higher steroid-free remission rates, and less need for colectomy [68]. This push is expected to result in increases in average recommended "therapeutic drug levels". Some experts now go on even further than that, and studies are now looking to examine the effects of histological healing on IBD outcomes. Indeed, there is some evidence that histological healing may predict risk of complications in ulcerative colitis beyond what is achievable with endoscopic mucosal healing, although data are limited in Crohn's disease [69]. If our hypothesis is correct, level of fibrosis or CC development could be a tracked as outcome in those who are using increasing dose of medications or combination of medications in order to achieve endoscopic mucosal healing or histological healing.

Conclusion

With this hypothesis we highlight that CC development in IBD patients could occur despite successful treatment with immunosuppressives such as TNF-α inhibitors, especially after long-standing and effective treatment with them. TNF-α inhibitors could directly play a role in CC development by creating an imbalance in the mucosa with unopposed TGF-β action.

Authors' contribution

Saad R E and Shobar R acquired and analyzed the data and reviewed the literature and wrote the manuscript; Mutlu E A conceived the report, wrote and revised the manuscript.

Competing interests

The authors have no conflicts of interest to disclose related to the work being submitted.

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