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REVIEW ARTICLE

Collagenous colitis associated with novel sprue-like intestinal diseases

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ABSTRACT

Almost a half-century ago, an unusual and distinct form of colitis was first recognized, collagenous colitis, characterized by sub-epithelial trichrome-positive deposits having the ultrastructural features of collagen. Later, other reports documented more extensive collagenous dis-ease in these patients, sometimes in the stomach and small bowel, a close linkage with other forms of microscopic colitis and its association with celiac and other immune-mediated diseases. Moreover, emerging genetic methods permitted large studies of collagenous colitis to complement these intriguing clinical and pathological studies. Finally, recent and related studies have further demonstrated these immune-based forms of colitis, with new sprue-like intestinal diseases caused by novel medications, recently detected viral infections and vaccinations.

Keywords: Celiac disease, Colitis, collagenous sprue, Collagenous colitis, Colon cancer, Sprue-like intestinal disease.

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Diagnostic aspects

In January 1976, 2 independent reports described a new colonic mucosal inflammatory disorder in three patients, labeled collagenous colitis (1, 2). Two were from Canada (1) and one from Sweden (2). In one, long-standing celiac disease was present leading to investigations focused on refractory diarrhea, despite a gluten-free diet. Extensive fecal and blood studies in search of an infectious cause were negative. Serum endocrine peptide measurements (e.g. gastrin, vasoactive intestinal polypeptide, VIP) along with extensive radiographic imaging were nor-mal. Colonoscopic evaluations revealed a normal-appearing mucosa, but biopsies showed very distinctive histopathologic features, reminiscent of changes described in collagenous sprue (3). Changes included an inflammatory process with an unusual sub-epithelial band of eosinophilic-staining hyaline deposits. These deposits were trichrome-positive, typical of collagen. Increased numbers of intra-epithelial lymphocytes were also evident with increased lamina propria immune cells (lymphocytes, plasma cells). Sloughing or shedding of surface epithelial cells were often seen, sometimes leaving behind only remnant sub-epithelial collagen deposits in the superficial lamina propria in contact with the intestinal lumen. Ultrastructural studies with electron microscopy confirmed that these deposits contained typical collagen fibers, later confirmed by other investigators (4). Subsequent studies showed that biopsies from the recto-sigmoid alone were often inadequate in detection of these collagen deposits (5). Over the ensuing decades, numerous clinical and fundamental research studies con-firmed the nature of an intriguing and more extensive family of collagenous inflammatory mucosal disorders involving other sites in the stomach and intestinal tract (i.e., collagenous gastritis and enterocolitis) as well as their association with celiac disease and other sprue-like intestinal diseases (6). These histopathologic changes in the colon, stomach and small intestine have been extensively illustrated elsewhere (6).

Epidemiological aspects

Larger clinical series, mainly from Scandinavian hospitals, detailed that most affected patients with collagenous colitis were middle-aged to elderly females (7, 8). In addition, children were also described (9, 10).

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Moreover, the disorder was also recorded in other primate species, specifically in baboons (11), and, finally, marine mammals, melon-headed whales in Florida, USA (12). Interestingly, in the latter, identical pathological changes were described after a mass stranding event implying that these disorders, particularly collagenous colitis, may have a very heterogenous etiology and pathogenesis.

Associations with celiac disease

Subsequently, collagenous colitis was recorded in wide variety of clinical settings, in particular, celiac disease and other immune-mediated disorders. Based on sequential biopsy studies, it was suggested that some cases may evolve from one type of microscopic colitis to another, particularly lymphocytic colitis into collagenous colitis (13). In retrospect, this may reflect the typically patchy nature of collagen deposits in the colon (leaving intervening areas of residual inflammatory change without deposits). Regardless, both had already been well recorded as independent entities in celiac disease. In a very early study (14), for example, 12 of 39 celiac patients, or 31%, had features of increased numbers of intra-epithelial lymphocytes in colonic biopsies, i.e., lymphocytic colitis. We also noted similar histopathological changes in the gastric mucosa of patients with celiac disease, defined as lymphocytic gastritis (15). In both gastric and colonic biopsies, intra-epithelial lymphocytes were positive for a T-cell marker (MT-1). Others later recommended exclusion of celiac disease if lymphocytic colitis was initially detected (16). Subsequently, in a prospective study of a series of 36 patients with already established collagenous colitis (17), 8 were subsequently shown to have biopsy-defined celiac disease. Interestingly, in all 8 celiac patients treated with a gluten-free diet, diarrhea improved and small intestinal biopsies normalized. However, in 5 of these 8 patients, repeated biopsies of the colon showed persistent sub-epithelial deposits. Later, a meta-analysis of 26 studies with a total of 22,802 patients from different countries further emphasized this important association between celiac disease and microscopic colitis, including collagenous colitis (18). In addition, intra-epithethial lymphocytosis alone in the ileum led to later detection of unsuspected celiac disease (19). This finding suggested an important clinical and pathological clue to later detection of unsuspected adult celiac disease.

Familial and genetic risk

Familial forms of microscopic colitis have also been documented. In 1990, collagenous colitis was recorded in two sisters and a father and his adult son (20) and, in 2001, in a mother and her daughter (21). In another report of familial disease, a mother and her 2 adult daughters were noted with lymphocytic colitis (22). In addition, a Swedish database search in 2001 uncovered 5 families with microscopic colitis (23), and finally, a mother and her 6 year old daughter were later reported with collagenous colitis (24). All of these clinical reports in adults and children, although uncommon, suggested a genetic risk for development of colitis.

Although explored in many studies, moderna molecular genetic methods have been applied to potentially important heritable interactions between celiac disease and microscopic colitis, specifically collagenous colitis, and furthered our comprehension of risk for these disorders. A large multi-center study explored HLA signatures in formalin-fixed and paraffin-embedded tissue samples from 804 histologically-confirmed collagenous colitis cases. Altogether, a total of three HLA alleles (i.e., HLA-B*08:01, HLA-DRB1*03:01, HLA-DQB1*02:01), all related to the ancestral haplotype 8.1, were significantly associated with increased collagenous colitis risk and shared genetic risks for other immune-mediated diseases, including celiac disease (25). The likely evolution of these methods for exploring the role of genetics in future will permit even more detailed evaluation of these disorders.

Medication-related factors

In addition to definition of genetic risks, a number of reports have added specific, even novel, environmental factors as potentially causative for both microscopic forms of colitis (i.e., lymphocytic colitis, collagenous colitis) as well as sprue-like intestinal diseases. These medications are structurally unrelated and employed for a diverse group of different clinical disorders. However, some are currently in popular use including: proton pump inhibitors, particularly lansoprazole, non-steroidal anti-inflammatory drugs (NSAIDS) and selected serotonin re-uptake inhibitors (26-28).

Others have only been developed or used in recent decades including olmesartan, mycophenolate mofetil and different immune checkpoint inhibitors.

Inevitably, this list will likely lengthen as more and more novel medications are developed and marketed by the pharmaceutical industry for different disorders.

Olmesartan is an angiotensin II receptor antagonist used for about 20 years in the treatment of hypertension (29). The drug was designed to block AT1-receptors and modulate the renin-angiotensin system. Blockade of AT1 receptors causes vasodilation as well as reduced vasopressin and aldosterone secretion leading to reduced blood pressure. Although drug-associated diarrhea was initially described in early clinical studies, but similar to placebo (30), later, severe and more persistent diarrhea with weight loss along with sprue-like intestinal pathology was noted (31-33). Patients using the medications for extended periods were most at risk. In some, gastric and colonic histopathological changes were also noted. If recognized, the disorder was often reversible, but in others, further intestinal complications were noted, including collagenous sprue and collagenous colitis (34-36).

Another commonly used agent, particularly in solid organ transplantation, has been mycophenolate. This drug frequently led to gastrointestinal toxicity in up to 45% of renal transplant recipients (37). An immune-mediated colitis and, less often, changes in the colonic mucosa typical of graft-versus-host disease were seen (37). A sprue-like small intestinal disease was also recognized (37) shown to rarely evolve into collagenous sprue (38). Celiac serological studies have been negative and the disorder was refractory to a gluten-free diet, sometimes with a fatal outcome.

Finally, another group of agents, checkpoint inhibitors, may cause an immune-related enteritis, colitis or both has been used to treat advanced or extensive malignancies, including malignant melanoma (39). These agents promote survival of cytotoxic T-cells that exhibit immune checkpoint cell surface proteins. They include anti-CTLA-4 (cytotoxic T lymphocyte-associated protein 4) and anti-PD-1 (programmed cell death protein 1).

Anti-CTLA-4 agents include ipilimumab and tremelimumab that block tumor growth and prolong survival. Anti-PD-I agents are represented by nivolumab and pembrolizumab. Others include atezolizumab, durvalumab and avelumab. Each may have a multitude of adverse effects, dependent on the agent utilized. Toxicities, such as colitis (40), particularly after anti-CTLA-4 treatment seemed to be relatively common, but less so with anti-PD-1 forms of treatment. Enteritis or sprue-like small intestinal disease mimicking celiac disease as well as microscopic forms of colitis, including collagenous colitis, were also reported after both checkpoint inhibitor types, anti-CTLA-4 and anti-PD-1 (41-43). Interestingly, persistent collagenous colitis was also documented (42).

Microbiome and infectious factors

Early studies raised the possibility of an infectious agent being responsible. Specific agents thought to be historically important included Yersinia species (43-46) and, possibly, a bacterial toxin. In recent years, others have speculated on the potential role of the microbiome in the development of immune-mediated forms of colitis (47). Most intriguing are recent reports related to SARS-Cov-2 infection in the gastrointestinal tract (48, 49) causing diarrhea, nausea and vomiting, weight loss, anorexia and loss of taste. Early endoscopic biopsy studies revealed only limited pathological changes in the upper gastrointestinal tract and colon, mainly increased numbers of lymphocytes and plasma cells (50). Additional studies showed positive staining of the viral host receptor ACE2 in the cytoplasm of epithelial cells along with positive staining in gastric and intestinal cells for viral nucleocapsid protein (50). Later reports noted an association between severe coronavirus disease 2019 and collagenous colitis, but

Table1. Possible underlying causes of collagenous colitis

Idiopathic
Familial forms
Possible evolution/relationship with lymphocytic colitis
Celiac disease (prospective and retrospective studies)
Associated with ulcerative colitis, Crohn's disease, toxic colitis/megacolon
Associated with collagenous gastritis or collagenous enteritis (sprue)
Medications (lansoprazole, NSAIDs, serotonin uptake inhibitors, olmesartan, mycophenolate, immune checkpoint inhibitors)
Bacterial infections (i.e., *Yersinia* species) or toxins
Coronavirus - 19 infection or vaccination for COVID-19

not lymphocytic colitis (51, 52). In a related report (53), transient lymphocytic colitis after SARS-CoV2 mRNA vaccine was described in an elderly female after a second dose of the SARS-CoV2 mRNA vaccine from Pfizer (53). In the same report, note was made of 5 earlier cases recorded in the Vaccine Adverse Event Reporting system, including 2 post-Pfizer and 3 post-modern related cases, all after the second vaccine dose (53). Further studies are needed to elucidate the pathogenesis of these post-vaccination intestinal changes.

Long-term natural history and treatment

To date, only a limited information is available on the long-term natural history of collagenous colitis. Indeed, due to increased recognition of a heterogeneous list of possible causes in recent years, singular definition of an anticipated natural history seems more remote (Table 1). Most earlier studies suggested a benign clinical course in follow-up studies for a decade or more, at least for the colitis (54). Although different medications have been used for treatment, changes may resolve with no treatment or minimal treatment. In some, however, persistent diarrhea or periods of recurrent diarrhea may lead to medication use. Even here, however, the clinical response to treatment may be difficult to assess since spontaneous resolution may occur. Even the pathological features may be difficult to define with treatment. As noted earlier, collagen deposits, tend to be patchy within the colon, variable in depth, and not always diffuse and continuous in its mucosal distribution (6). Some have required steroids, often in delayed release forms (such as budesonide). In persistently refractory patients, immunosuppressive agents or biological agents have also been used.

Surgical forms of treatment for collagenous colitis have also been historically recorded, including total proctocolectomy with ileal pouch anal anastomosis (55). Interestingly, in a patient treated with ileostomy and sigmoidostomy with clinical and histological remission, stomal closures led to recurrent diarrhea and re-development of the collagen de-posits raising the possible importance of a luminal factor in disease pathogenesis (56). Collagenous pouchitis (57) and collagenous cuffitis (58) have also been reported after protocolectomy and staged reconstruction for colitis.

Collagen deposits have been recorded in gastric (i.e., collagenous gastritis) and small intestinal biopsies (i.e., collagenous enteritis or collagenous sprue) of some patients (59) suggesting that some patients with collagenous colitis may have far more extensive disease (6). Even in extensive collagenous disease, however, complete resolution has been recorded (60).

Disease complications

In collagenous colitis, other complications, including persistent severe disease, even fatal, may occur (61). Mucosal sloughing, with shed surface epithelial cells, may cause protein loss. Ulceration may occur, especially with concomitant use of non-steroidal anti-inflammatory drugs (62). Toxic colitis, sometimes with megacolon, may develop. Rare cases of Crohn's disease and ulcerative colitis have been recorded (63-65) including collagenous colitis evolving into ulcerative colitis (65). Perforation and spontaneous peritonitis may occur (66). Colonic micro-fractures have been recorded as "colonic cat scratch disease", possibly related to instrumentation and air insufflation (67, 68). Most intriguing, as in celiac disease (69), colonic cancer has been rarely noted in collagenous colitis (70-72), and yet, other celiac-related malignancies develop, such as lymphoma (73, 74).

Final perspective

Following initial reports of collagenous colitis, a greater appreciation for this unusual and distinctive inflammatory process has emerged. Not only has there been an evolution in genetic definition, and relation to celiac disease and other immune-mediated diseases better defined, but increased recognition of intriguing sprue-like intestinal diseases with colitis due to novel medications and infectious agents.

Conflict of interests

All authors declare that they have no conflict of interest.

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