

## **Case Studies in Chronic Gastrointestinal Inflammation**

*E Ihara MD PhD, JL Wallace PhD and PL Beck MD, PhD*

In a case based format, the goal of this chapter is to introduce some new emerging chronic inflammatory conditions of the gastrointestinal tract. We present how a patient presents, clinical features, epidemiology, treatment approaches and the current knowledge on the pathogenesis of these disease states. We compare and contrast these new emerging disease states with more commonly known entities including gastroesophageal reflux disease (GERD), ulcerative colitis and Crohn's disease. It is hoped that this chapter will increase the awareness of these emerging common chronic inflammatory conditions of the gastrointestinal tract and stimulate research ultimately enhance patient care.

### **Case Presentation 1**

A 32 year man was doing some grocery shopping when he decided he would "sample" a few grapes. Immediately after quickly swallowing some grapes he developed some mild chest discomfort and a sense that some thing was stuck. Over the next hour he was unable to swallow his saliva and presented to the emergency department. His only pertinent medical history is that he had a life long history of asthma and allergies to shell fish. A few year ago he had to had a piece of meat removed from his esophagus via endoscopy. Over the last year he had noticed some a sticking sensation when swallowing solids requiring him to have to drink ample fluids with every meal. He

denied symptoms of gastro-esophageal reflux. His family history was negative except that his father also had swallowing problems which required several episodes of “stretching” of his esophagus with a balloon. His physical exam was normal. He underwent an upper endoscopy and was found to have three grapes stuck in his distal esophagus (Figure 1A), these were removed and he was found to a dominant stricture in the distal esophagus (Figure 1B). He also had prominent rings in his esophagus and linear furrows (Figure 1C). These endoscopic features were recognized as classic features associated with eosinophilic esophagitis (EE). Biopsies from the mid-esophagus revealed a prominent eosinophilic infiltrate (Figures 1E-F) which confirmed the diagnosis of EE. Skin testing confirmed a shell fish allergy but was negative for all other antigens tested. He was treated with fluticasone propionate 250 µg orally 3 times per day. Within two weeks he had complete resolution of his swallowing difficulties and 3 months later an upper endoscopy showed a reduction in the esophageal rings but some linear furrows were still present (Figure 1D) and biopsies showed a reduction in the eosinophilic infiltrate. Interestingly, upon review of his previous upper endoscopy done 3 years earlier for meat bolus impaction, there was also a dominant stricture as well as the rings and furrows classic of EE. At that time these features were not recognized by the endoscopist and no biopsies were taken but the stricture was dilated without complications.

EE was first described in the pediatric population but has been increasingly recognized as a common cause of dysphagia in adults. This case highlights the fact that EE does occur in adults and

was often missed by endoscopist even a few years ago. Since EE has now been recognized as common cause of dysphagia in adults and indeed represents a new emerging chronic inflammatory disease state we review the diagnosis, epidemiology, treatment and what is known about the pathogenesis of EE. With this review we hope to increase the awareness of this disease entity with hopes that it will stimulate research in EE and ultimately enhance patient care.

## **Diagnosis**

Eosinophilic esophagitis (EE) is defined as a clinicopathologic disease characterized by esophageal symptoms associated with eosinophilic infiltration of esophageal mucosa. Since eosinophils can be present with gastroesophageal reflux disease (GERD) the diagnosis of GERD should be excluded (often via a trial of a proton pump inhibitor) before making the diagnosis of EE. The guidelines for the diagnosis of EE has been recently proposed by the First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees as follows; (i) Clinical symptoms of esophageal dysfunction (ii) more than 15 eosinophils in 1 high-power field (iii) Lack of responsiveness to high-dose proton pump inhibition (up to 2 mg/kg/day) or normal pH monitoring of the distal esophagus. The diagnostic criteria for children are the same as for adults. Endoscopic features including white exudates, white specks, linear furrowing, circular rings and stricture are associated with EE. The presence of the rings in EE is also referred to as feline esophagus (cats have similar such esophageal rings) or trachealization (the esophagus has the

appearance of the trachea which normal has concentric rings). Although none of these features can be pathognomonic for EE, the presence of more than 1 of these features is strongly suggestive of the diagnosis of EE. Increased peripheral eosinophil counts are observed in some patients, but not in all patients. Before making a final diagnosis of EE, Crohn's disease, connective tissue diseases and eosinophilic gastroenteritis as well as GERD should be excluded.

## **Epidemiology**

EE occurs in all age groups. Males are more commonly affected than females. EE patients seem to have a variety of ethnic backgrounds, including white, African-American, Latin and Asian. The prevalence and incidence of EE have been increased especially last a few years both in adult and children. This increase does not seem to be due entirely to the increased recognition of EE by clinicians and pathologists. Often patients have a history of atopy including; asthma, food allergies and rhinitis. Indeed our patient had a history of asthma and food allergies. In the pediatric literature food allergies appear to be more commonly associated with EE and skin testing is commonly done. As reviewed below, there has been some success in the pediatric population with treating patients with a restrictive diet that specifically avoids common food allergens and any known allergens noted on history or skin testing.

## **Pathogenesis**

EE represents an immune-mediated disease of undetermined pathogenesis. The substantial

proportion of the patients have associated food, inhalant and seasonal allergies, indicating that allergy responses are strongly implicated in the etiology of EE. Alternatively, there also appears to be a yet to be discovered genetic link since EE patients have a family history of dysphagia and EE. Several cases reports describe several family members (most commonly male) that have EE across several generations. Recent studies have suggested that the eosinophil-specific chemoattractant eotaxin-3 plays a role in pathogenesis of EE. Accumulated evidence have also shown that EE is associated with T helper cell ( $T_H$ ) 2 type immune responses specially with elevation of interleukin (IL)-4, IL-5, and IL-13. It is generally accepted that inflammatory responses affects underlying smooth muscle and induce smooth muscle dysfunction. Since  $T_H2$  cytokines, such as IL-4 and IL-13, are associated with intestinal smooth muscle hypercontractility, they probably lead to esophageal dysmotility accompanied by smooth muscle hypercontractility and spasm observed in patients with EE.

### **Clinical manifestations**

The symptoms of EE are associated with esophageal dysmotility. The symptoms of EE seen in adults are different from those in children. The most common symptoms in adults are dysphasia and food impaction whereas food refusal, emesis, abdominal pain are more common in children with EE. GERD-like symptoms are also common both to adults and children with EE. The disease does not appear to limit life expectancy however limited long-term data exist. Although natural history of

EE is unclear, esophageal metaplasia (Barrett's esophagus) and esophageal adenocarcinoma does not appear to be more common in patients with EE. Since EE often causes strictures and generally narrowing of the esophagus significant dysphagia is common. Often, prior to the increased awareness of EE, these patients underwent esophageal dilation. EE can cause the esophagus to become more rigid and fragile making them more susceptible to both spontaneous and iatrogenic tears and perforation (as likely occurred in our patient's father). Recent studies suggest that dilation of strictures in EE is associated with markedly increased risk of esophageal perforation (which has a high mortality rate). Most suggest that dilation should only be considered after a significant trial of medical therapy and if performed it should be done cautiously and preferably in an institution that has significant experience with esophageal dilation and can manage any complications.

## **Treatment**

Consistent with the postulated pathogenesis of EE described above, dietary therapy with dietary antigen elimination is reasonably highly effective in inducing and maintaining remission of EE especially in the pediatric population. The dietary therapy usually involves either the elimination of specific food antigens based on allergy testing, via clinical history or removal of all potential common food allergens by using an amino acid-based formula. Medical therapy with administration of corticosteroids is another effective treatment for EE. Dosage of systemic corticosteroids are similar to those used for inflammatory bowel disease (1-2 mg/kg/day of prednisolone).

Interestingly, it has recently reported that the swallowed topical corticosteroids (fluticasone propionate or beclomethasone which are effectively cleared on first pass through the liver, limiting systemic exposure), are extremely effective and fewer side effects than classical systemic corticosteroids. Disappointingly, many if not all patients have relapse of symptoms and esophageal eosinophilia following discontinuation of the dietary and medical therapy. It has yet to be determined what the appropriate maintenance therapy is or what is the appropriate treatment end point. Although dietary and medical therapies should be the initial choice for treatment of EE, endoscopic esophageal dilatation procedure is useful for the patients who present with symptomatic esophageal narrowing secondary to fixed strictures. In addition, therapies based on what little is known on the pathogenesis of EE agents such as leukotriene receptor antagonists and biologic treatment including anti-IL-5 represent potential novel therapies for EE.

### **Eosinophils in Chronic Gastrointestinal Inflammation**

Interestingly, although eosinophils have been documented in many disease processes their role in disease pathogenesis and host defense remains unclear. Normally, in non-inflamed normal gastrointestinal tissue eosinophils are present in small numbers. Increased tissue eosinophils have been classically described with parasitic infections and in allergic conditions but can also be increased with malignancy and certain drugs. In general there are broad categories of intestinal eosinophilia. The first is primary intestinal eosinophilia that includes; EE, eosinophilic enteritis,

eosinophilic gastritis and eosinophilic colitis. Apart from EE, these are rare conditions but can be associated with abdominal pain, diarrhea and malabsorption. Up to 75% of patients with primary GI eosinophilia have a history of atopy. The second category is GI eosinophilia resulting from hypereosinophilic syndrome (HES). HES is a rare disorder that includes; persistent eosinophilia of at least 1500 cells/mm<sup>2</sup> for a minimum of 6 months, lack of known causes for eosinophilia and features of organ system involvement. One of the biggest advances in HES is the remarkable clinical efficacy of the tyrosine kinase inhibitor imatinib mesylate, an agent that was previously used for chronic myelogenous leukemia. The third category is GI eosinophilia triggered by known causes including, parasitic infections, drugs, and malignancy or connective tissue diseases.

The mechanism by which eosinophils are recruited to GI tissues is unclear but in many settings it appears that eotaxin-1 is involved. Once in the tissue eosinophils can express numerous cytokines depending on the disease state involved. In EE and parasitic infections the cytokine profile is generally Th2 in nature (IL-1, IL-3, IL-4, IL-5, IL-13, specifically) but can also release TNF, TGF- $\beta$ , granulocyte macrophage colony stimulating factor (GM-CSF), RANTES, VEGF and eotaxin-1. Eosinophils also can release products from their granules which can cause tissue injury and inflammation including major basic protein (MBP-1 and MBP-2) and eosinophil peroxidase. Eosinophils can also secrete an array of cytokines, including IL-2, IL-4, IL-6, IL-10 and IL-12, that are involved in lymphocyte proliferation, activation, and Th1 or Th2 polarization. Eosinophils also



produce large amounts of leukotrienes (LTC<sub>4</sub> and LTD<sub>4</sub>) that can induce tissue injury, increase vascular permeability and smooth muscle contractions. As noted above blockade of leukotrienes has been used with success in EE.

Other settings that are associated with increased GI eosinophils include NSAID-induced enteritis/colitis, IBD, connective tissue disease and GERD. However, it has yet to be determined what pathological roles eosinophilia plays under these conditions. Clearly it can be debated that in these settings eosinophils may be involved in disease pathogenesis and conversely maybe involved in wound repair and intestinal homeostasis.

### **Concluding Statement**

The eosinophil appears to play a prominent role in several forms of chronic gastrointestinal inflammation. The mechanisms involved in the pathogenesis of eosinophilia associated GI disease states are poorly understood but appear to differ depending on the disease entity. For example, the eosinophilia in EE appears to be driven by IL-5 and eotaxin-3 where as in eosinophilic enteritis eotaxin-1 appears to be a more critical mediator. The case of EE was chosen to highlight this new emerging entity. Clearly more research is required on the both role of the eosinophil in chronic gastrointestinal inflammation and in the areas of epidemiology and pathogenesis of EE and other chronic GI inflammatory states associated with eosinophilia for these conditions are becoming more common and are associated with significant morbidity.

## **Case Presentation;**

59 year old woman presented with an 8 month history of diarrhea. Generally she has 6-8 liquid, stools per day. Occasionally she has noted bright red blood on the toilet paper with wiping and is not sure if the blood is mixed into the stool. She has also noted increased abdominal pain and bloating over the last few months. She denies fevers, weight loss or other gastrointestinal symptoms. She underwent a colonoscopy 4 months ago at an outlying center that reported a normal appearing colon and thus no biopsies were performed. Her blood work showed a normal complete blood count and normal celiac serological screen (normal TTG, normal IgA). Her past history is significant for longstanding reflux (treated effectively with the proton pump inhibitor lansoprazole. She has longstanding hypothyroidism treated with Synthroid (normal thyroid stimulating hormone (TSH)). She takes both the non-steroid anti-inflammatory (NSAIDs) agents diclofenac and ibuprofen (> 5 years) for osteoarthritis. She smokes 1 pack per day (x 40 years). Four weeks ago she received a course of antibiotics for a tooth abscess. Family history, mother has celiac disease and her sister was diagnosed with Crohn's disease (CD) at the age of 42 years. Her physical exam was grossly normal.

The differential diagnosis in such a patient is broad. The presentation of celiac disease at this age is not common but can occur. Serological testing for celiac disease is a good screen but false negatives even in the setting of a normal IgA can occur. She is at increased risk for celiac

disease since her mother has celiac disease. Although celiac disease does not have a clear autosomal recessive or dominant inheritance pattern those with an affected first degree relative are at increased risk. She has recently had antibiotics and thus one must consider the possibility of *Clostridium difficile* (C dif) infection. Such a prolonged course is not common for C dif and stool studies for culture and sensitivity, ova and parasites and C Dif toxin should be sent. Again these studies can be falsely negative. The normal TSH suggests appropriate thyroid replacement but should be rechecked if not done recently. NSAIDs can cause not only gastric and duodenal injury but can also cause damage throughout the small bowel and colon. The family history of inflammatory bowel disease (IBD) in her sister again increases her risk for IBD. Studies such as a small bowel follow through (a barium swallow study or a capsule endoscopy could be performed to rule out small bowel CD. The colonoscopy report did not mention intubation of the terminal ileum. The blood upon wiping is concerning. It would be unlikely that a colon cancer or significant polyp was missed on colonoscopy however miss rates for such lesions are in the range of 2-5%. The other disease state that was not mentioned on her assessment by the physician that performed the colonoscopy is microscopic colitis (MC).

She underwent a second colonoscopy was performed with ileal intubation and multiple random biopsies were taken. There was no endoscopic evidence of Crohn's disease that can appear as small aphthous ulcers, diffuse nonspecific inflammation or deep linear ulcers (Fig 2A).

Classically CD affects the colon and/or terminal ileum but can involve the entire gastrointestinal tract (GI) in a skip segment pattern where affected mucosa is interspersed with normal mucosa that can give rise to a cobblestone appearance. Perianal disease, which is common in CD, was not present. There was no evidence of ulcerative colitis (UC) which commonly affects the distal colon but can involve the entire colon. Deep ulcers are less common in UC versus CD and a diffuse (non-skip segment) superficial inflammatory response is more common (Fig 2B). Bleeding can occur with both UC and CD but is generally more common in UC. The terminal ileum appeared normal. Although the terminal ileum is common involved in CD it can be inflamed in UC with what is termed as backwash ileitis. There was also no evidence of Crohn's colitis which has a classic appearance of pseudomembranes (Fig 2C) that are generally more common in the distal colon but can be limited to the right colon and rarely can also involve the terminal ileum in very severe cases.

The colon and terminal ileum had a completely normal endoscopic appearance (Fig 2D) except that large internal hemorrhoids were present and felt to be the cause of the fresh blood with wiping. Biopsies that were randomly taken from the terminal ileum and throughout the colon showed inflammatory changes. Ileal biopsies showed mild non-specific inflammation and the colonic biopsies revealed a marked inflammatory infiltrate with a thickening of the sub-epithelial collagen band (Fig 2E). These findings are classic for collagenous colitis (CC) a form of MC (Fig 2E). There are two forms of MC; CC and lymphocytic colitis (LC). LC characteristically has a

marked lymphocytic infiltration on the lamina propria and submucosa but does not have thickening of the sub-epithelial band that is diagnostic of CC (Fig 2F). Although it was initially thought that the terminal ileum is not involved, Sapp and colleagues (Am J Surg Pathol; 2002) found that patients with either LC or CC had markedly increased intra-epithelial lymphocytes (IELs) (5 fold increase) compared to normal controls and those with UC.

Our patient was thus diagnosed with CC a form of MC. Why was this diagnosis not made on the initial colonoscopy? MC is an emerging entity that was only first described approximately 30 years ago by Freeman and Lazenby. It was initially thought to be a rare entity and thus was not even discussed in most medical schools or training programs up until the last 10 years. We have recently completed a study that colonoscopists that have completed a formal training program in gastroenterology are much more likely to make the diagnosis of MC. In Canada, especially in smaller centers, colonoscopy and sigmoidoscopy are commonly performed by individuals that have not completed a formal gastroenterology training program.

The patient failed to respond to anti-diarrheal therapy and Pepto bismol but had a complete response to a three month course of Entocort (budesonide) a topical corticosteroid with minimal systemic effects. Since MC can be lifelong it was not surprising that she had a relapse of her symptom 2 months after stopping Entocort. This milder flare was treated effectively with a 2 week course of Pepto bismol. An upper endoscopy done at a later date for reflux failed to show any

histological features of celiac disease.

Since MC, both CC and LC are increasingly recognized as common causes of chronic diarrhea and chronic colonic inflammation we will review the epidemiology, pathogenesis, disease course and management. The MC is clearly an important emerging entity it is hope this review will enhance the reader knowledge of these disease states and stimulate research in this area with hopes of better understanding pathways of chronic gastrointestinal inflammation and ultimately improving patient care.

### **Microscopic Colitis**

MC is a group of diseases representing an inflammatory condition of the colon in which the colonic mucosa appears endoscopically normal, but histologic examination reveals specific pathological features. The two forms of MC can be differentiated by histological analysis (Figure 2E,F and Table 1). MC is increasingly recognized as a common cause of diarrhea in middle-aged and older patients. In some countries the incidence of MC approaches that of ulcerative colitis or Crohn's disease. The incidence of LC and CC have been reported to range from 1.1 to 12.6 per 100,000, with a point prevalence of MC of 103.0 (39.3 for collagenous and 63.7 for lymphocytic colitis per 100,000) (Table 2).

The some of the identified risk factors for MC include; increasing age, female sex,

autoimmune diseases (such as thyroid diseases and celiac disease), past or current diagnosis of malignancy and solid organ transplantation. Smoking and the use of several medications also increased the risk of MC. The incidence of MC increases markedly with advancing age and is rarely encountered in children. We recently reported that patients greater than age 65 years were more than five times as likely to have developed MC and females were four times as likely to develop MC. The cause for the increased risk in these individuals is unclear except that drug use (including those associated with MC) is more common in the elderly and autoimmune diseases are more common in females. Remarkably, one study found that 53% of CC patients and 43% of LC had a co-existing autoimmune disease. More specifically, one study found that 40% of patients with Hashimoto's thyroiditis had histological findings compatible with LC. The main medications that have been found to be associated with MC include; NSAIDs, SSRIs beta-blockers, statins, biphosphonates, some PPIs, ticlopidine, and flutamide. Anecdotally, patients often get better following discontinuation of the medication but some also require MC-specific therapy (reviewed below) (see tables 3,4).

The etiology of MC is unknown, but it is likely multi-factorial. Although there are reports of familial clusters of MC, evidence for a strong genetic contribution is lacking. Some studies have found differential expression of some HLA types including HLA DQ2 that is also commonly associated with celiac disease. Interestingly, MC does appear to be associated with other chronic

inflammatory condition including a study that found that up to 12% of patients with microscopic colitis have a family history of inflammatory bowel disease or celiac disease. Cases of co-existing celiac disease and MC are common and there are reports of overlap syndrome where patients with MC have some features consistent with classical IBD (UC or CD). There have also been reports of patient that initially are diagnosed with MC go on to develop classical IBD. For a review of the clinical, endoscopic and pathological differences between IBD and MC see Tables 1a-c and 5).

Similar to IBS, an infectious etiology for MC has been proposed but remains elusive. The evidence to support this comes from reports of patients improving with antibiotic therapy and of a documented intestinal infection (including; *Clostridium difficile*, *Yersinia* and *Campylobacter jejuni*) preceding the diagnosis of MC. Bile acid malabsorption has been implicated in the pathogenesis of MC in that some studies report rates of bile acid malabsorption ranging from 9-60%. Bile acid-binding therapy is also effective therapy in a proportion of MC patients but efficacy seems to vary greatly between studies. Although there are case reports suggesting that cholecystectomy increases the risk of developing MC a recent well designed study failed to find such an association.

There have only been a few studies that have addressed the mechanisms involved the inflammatory response and/or diarrhea in MC. Some have suggested that the thickened collagen band in CC represents a barrier to fluid absorption and other studies have documented increases in



chloride excretion and decreases in net sodium absorption. Altered barrier function has also been described with marked decreases in tight junctional protein expression including E-cadherin and ZO-1. We have recently reported that MC is associated with increases in expression of prostaglandin receptors EP-2 and EP-4 and that these changes correlate with tissue levels TNF- $\alpha$  expression. Such altered prostaglandin (PG) signaling would intuitively make sense in view of the fact that NSAIDs are a dominant risk factor in MC and that PG therapy commonly causes diarrhea and abdominal cramping. Altered PG levels have been noted in a case reports in MC and it is possible that NSAID exposure may alter PG receptor expression and impact PG signaling events.

In summary, the etiology of MC remains elusive but the documented changes in bile salt absorption, reduced tight junctional protein expression, altered PG signaling and changes in cytokine expression coupled with the known risk factors are the focus of most studies addressing the pathogenesis of MC.

## **Diagnosis**

The diagnosis of microscopic colitis is dependent on: 1) a convincing clinical history that rules out etiologies (see Table 5; clinical features of MC versus IBD), 2) normal or near normal endoscopic and/or radiographic findings, with no endoscopic evidence suggestive of infectious colitis of IBD (Figure 2, Tables 1a-c) and 3) endoscopic biopsies (via sigmoidoscopy or colonoscopy, the latter having the highest pick up rate) with histopathological findings consistent

with MC (Table 1, Figure 2). The first step in the diagnostic process is a thorough history with attention to risk factors and disease associations. A complete history may help to rule out other etiologies that may cause a similar clinical picture such as IBD, celiac disease, diarrhea predominant irritable bowel syndrome or infectious colitis (see Table 5. Laboratory and radiographic investigations can be employed to help rule out other entities on the differential diagnosis list (i.e. hyperthyroidism, celiac disease, IBD (in some settings), infectious colitis) but there are no specific laboratory/radiological investigations that can confirm the diagnosis of MC.

## **Treatment**

Treatment recommendations for microscopic colitis are largely based on case reports and uncontrolled studies. The agents tried include anti-diarrheal agents, 5-ASA, corticosteroids (including prednisone and budesonide a corticosteroid with more topical actions and reduced systemic side effects), other immunomodulators (including azathioprine, and methotrexate), bismuth,( Pepto-Bismol) and some reports of probiotics. Small controlled trials support the use of budesonide, Pepto-Bismol and more recently there has been a study showing efficacy of 5-ASA therapy. It should be noted that in some patients the disease is self-limiting and resolves without therapy and in others resolution follows withdrawal of medications associated with MC. The first step in managing a patient with microscopic colitis is to complete an in depth medication history to rule

out the use of any medications that may be associated with MC (Table XX). Associated conditions such as celiac disease and thyroid disease (hyperthyroidism classically is associated with diarrhea) should be ruled out or appropriately managed. In patients with mild symptoms, dietary restrictions like avoiding caffeine and lactose may be beneficial. The initial therapy often depends on disease severity. If mild and not associated with significant abdominal cramping and bloating often anti-diarrheal agents like loperimide, Pepto-Bismol or bile salt binding resins are effective. If these approaches fail and/or the patient presents with more severe symptoms (including marked diarrhea, incontinence, significant abdominal pain or cramping, weight loss) often more specific therapy is required.

A recent randomized controlled trial of 41 patients with LC and 23 patients with CC showed that the 5-ASA preparation mesalamine induced complete resolution of diarrhea in 84% of patients within 2 weeks. In those that continued the 5-ASA therapy for over 6 months, clinical and histological remission was achieved in 85% of LC and 91% of CC. Other previous smaller studies reported more variable success rate with 5-ASA. Budesonide is currently the most promising treatment for CC. Three trials involving 94 CC patients given either budesonide therapy (9 mg daily for 6-8 weeks) or placebo have all reported significant improvements in clinical symptoms and quality of life. A recent Cochrane database meta-analysis reported pooled odds ratio of 12.3 for clinical response with budesonide and a number needed to treat of 2. All three trials documented

significant a reduction in histopathological inflammatory changes following budesonide therapy. Although effective in the short-term, all trials showed a high rate (61-80%) of relapse within about 2 weeks after budesonide cessation. Although, there are no studies to support a tapering course of budesonide, many clinicians employ this approach with anecdotal reports that it reduces the rates of relapse. There is only one randomized controlled trial of budesonide in LC and it to showed significant clinical efficacy. Remarkably, budesonide is effective in both CC and LC and has minimal corticosteroid side effects. The main issue with this agent is that patients find the therapy expensive and often revert to more inexpensive therapy such as Pepto-Bismol and loperimide. Interestingly, those that have failed therapy agents such as Pepto-Bismol and loperimide often respond to these agents once their symptom are brought under control with budesonide, that is these agents can used for subsequent relapses following budesonide even if they failed to initially respond to them prior to budesonide. Not surprisingly, the systemic corticosteroids prednisone and prednisolone also have been shown to have efficacy in case reports but are rarely used due to the systemic side effects.

Other immunosuppressive therapy, including azathioprine or methotrexate has been utilized in patients with refractory disease but there are no randomized controlled trials to guide therapy with these medications. Generally these agents are only used in patients with significant symptoms that either fail budesonide therapy or relapse after withdrawal of budesonide.

A small study does support the use of bismuth containing compounds such as Pepto-Bismol and many patients find it effective in more mild disease. Often patients have trouble tolerating it for longer than a few weeks thus necessitating other therapy. Case reports suggest that pentoxifylline, verapamil and subcutaneous octreotide might be treatment options, but their use cannot be recommended at this time. Rarely, in severe refractory cases surgical intervention is required and usually involved colonic resection and colostomy/ileostomy.

Microscopic colitis has a variable course, but overall the long-term prognosis is good. Symptoms of diarrhea and abdominal pain may precede diagnosis for months to years. Unfortunately, as occurred with our patient, the diagnosis of MC will be missed on colonoscopy and sigmoidoscopy if biopsies are not taken. Often these patients are given the incorrect diagnosis of irritable bowel syndrome and often struggle with their symptoms. The clinical course is highly variable; some patients have self limiting mild disease, while others have severe disease that relapse following therapy. More studies are required to determine if this variability in disease course can be predicted.

## **Conclusion:**

Microscopic colitis is a common cause of diarrhea and chronic intestinal inflammation in older patients. Clearly, there are few studies on the mechanisms involved in the pathogenesis of

MC and although the incidence and prevalence of MC is similar to that of IBD, few basic science researchers are aware of MC. With an aging population, increasing incidence of many auto-immune diseases and the increased use of many of the medications associated with MC we will be seeing more and more of these patient in or clinics. This case report will have served to introduce some (and furthered the knowledge of others!) to the entity of MC. By detailing how a patient presents, the epidemiology of MC, associated risk factors, the limited information on the mechanisms involved in disease pathogenesis, approach to management as well as how MC differs from other chronic inflammatory GI conditions we hope that this stimulates further research in MC with the ultimate goal of curing MC and/or enhancing patient care.

## **Chapter Synopsis;**

**... still to do**

## **Figure Legends**

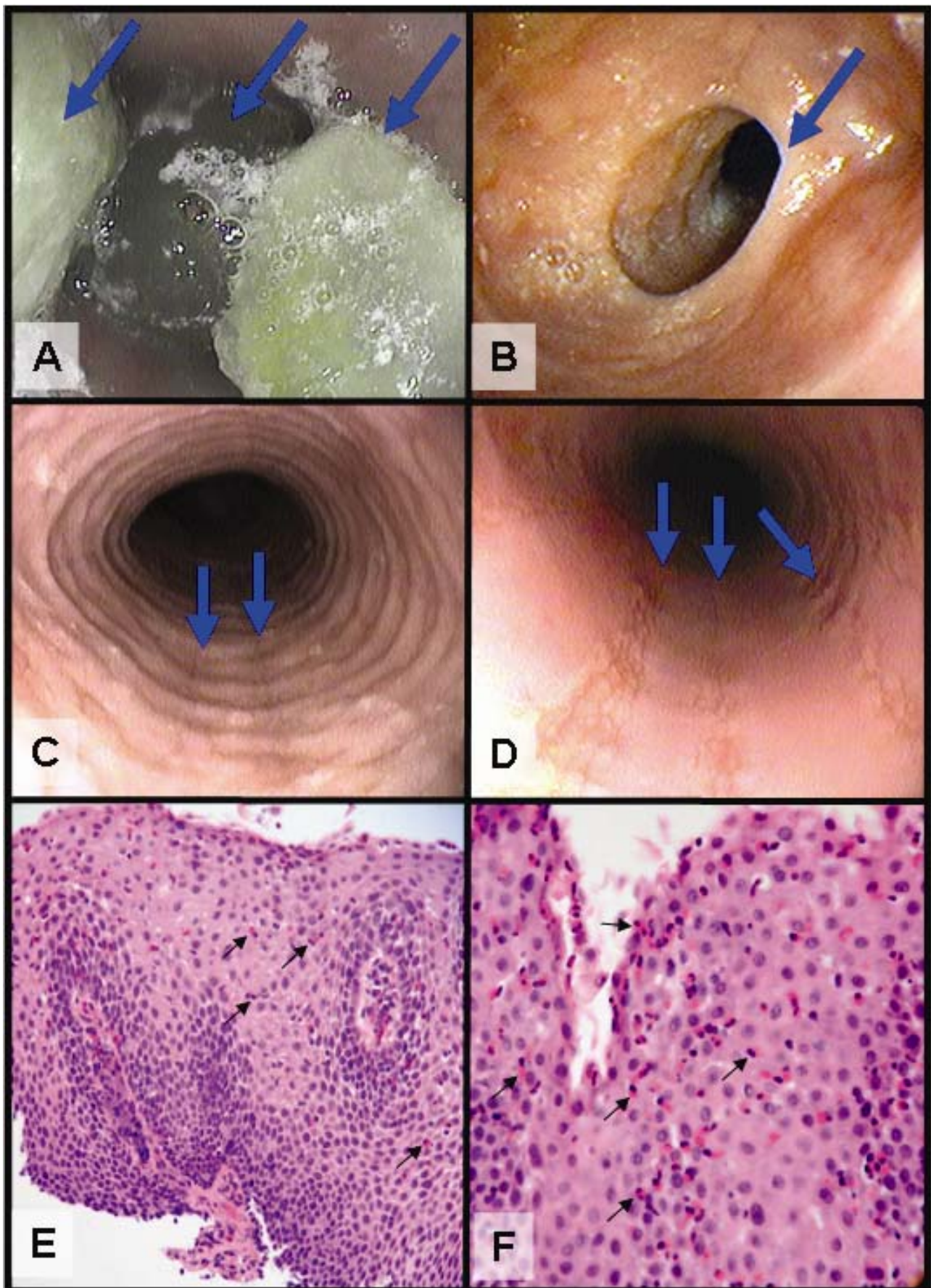
### **Figure 1: Case #1**

Case presentation. 1A; endoscopy revealed 3 grapes (arrows) in the distal esophagus. Following removal of the grapes a significant distal esophageal stricture was noted (1B). Classic features of EE were also noted and include concentric rings (feline esophagus) and linear furrows (arrows) (1C). With topical corticosteroid therapy the patient had complete resolution on his symptoms an upper endoscopy done 3 months later showed overall improvement but linear furrows (arrows) were still present (1D). A prominent eosinophilic infiltrate (arrows) was noted in biopsies take at the initial endoscopy (1E-F).

### **Figure 2: Case #2**

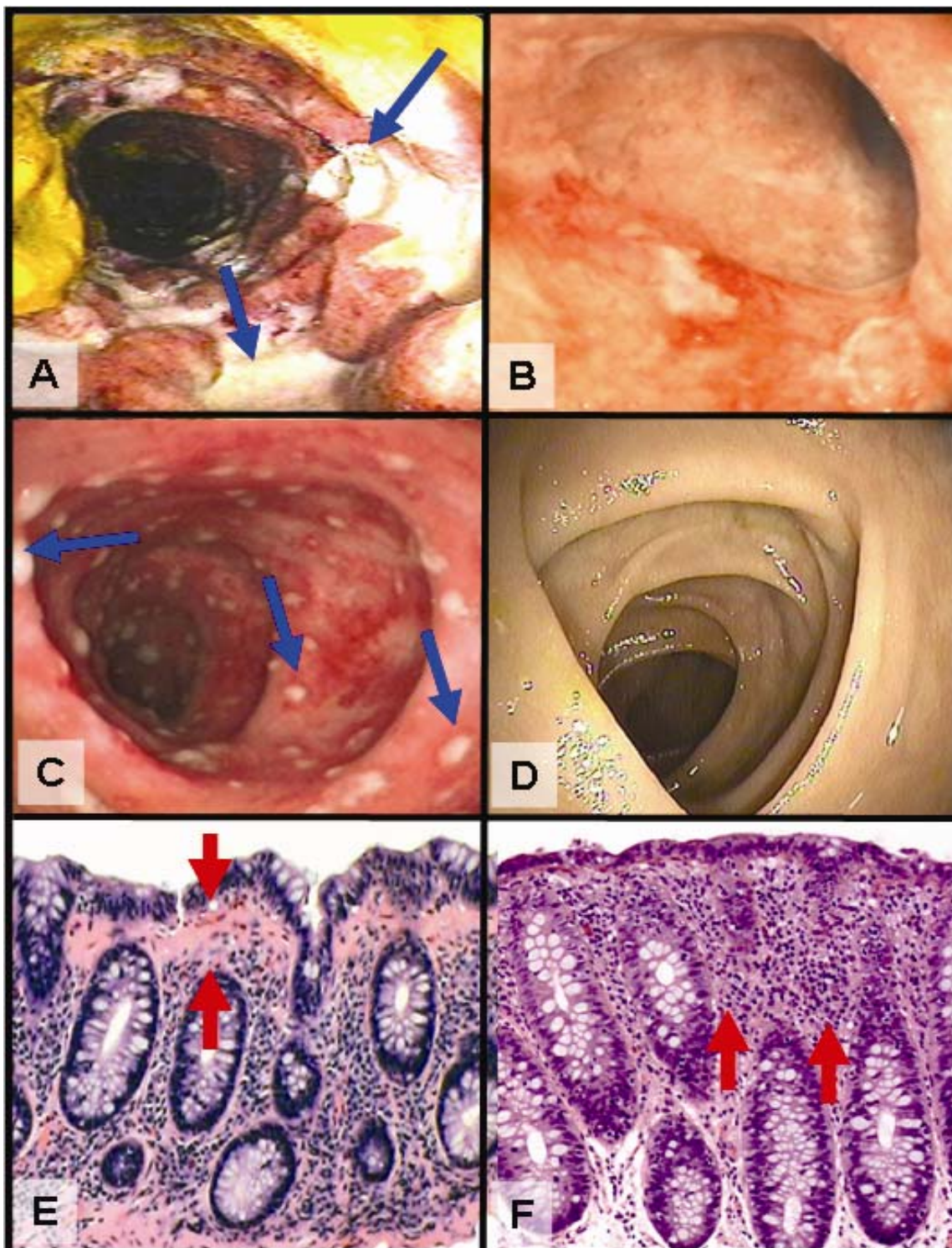
Endoscopic features of Crohn's disease (A), ulcerative colitis (B), *Clostridium difficile* colitis (C) and microscopic colitis (D). Unlike the significant ulceration and inflammation that is seen upon endoscopic evaluation of active CD (arrows so deep linear ulcers), UC and *Clostridium difficile*-associated colitis (arrows show pseudomembranes) the endoscopic appearance of MC is often normal (D). Histology features of CC reveals a thicken sub-epithelial band (arrows) (E) and a marked lymphocytic infiltrate in LC (arrows) (F).

**Figure 1; Case #1**





**Figure 2: Case #2.**



**Table 1a: Histological Features of MC**

| <b>Lymphocytic Colitis</b>  | <b>Collagenous Colitis</b>   |
|---|--|
| 1) intraepithelial lymphocytosis ( $\geq 20$ IELs/100 epithelial cells)                 | 1) thickening of a subepithelial collagen layer of more than 10 $\mu$ m  |
| 2) inflammation in the lamina propria consisting of mainly lymphocytes and plasma cells | 2) inflammation in the lamina propria consisting of mainly lymphocytes and plasma cells; and   |
| 3) epithelial damage, such as flattening and detachment and                             | 3) epithelial damage, such as flattening and detachment. Increased IELs may be present, but is not necessary for the diagnosis of CC |
| 4) subepithelial collagen layer not present or less than < 10 $\mu$ m                   |  |

**Table 1b: Endoscopic Features of IBD**

| <b>Endoscopic Lesions</b> | <b>ULCERATIVE COLITIS</b> | <b>CROHN'S DISEASE</b> |
|---------------------------|---------------------------|------------------------|
| <b>Colon</b>              |                           |                        |
| Contiguous                | +++                       | +                      |
| Symmetric                 | +++                       | +                      |
| <b>Rectum</b>             | +++                       | ++                     |
| Friability                | +++                       | +                      |
| Granularity               | +++                       | +                      |
| Cobblestone               | +                         | +++                    |
| <b>Ulceration</b>         |                           |                        |
| Ileum                     | -                         | +++++                  |
| Discrete lesion           | +                         | +++                    |
| Size >1 cm                | +                         | +++                    |
| Deep                      | +                         | ++                     |
| Linear                    | +                         | +++                    |
| Aphthoid                  | +/-                       | +++++                  |

**Table 1c: Pathological Features of IBD**

| <b>Pathological Features</b>            | <b>ULCERATIVE COLITIS</b> | <b>CROHN'S DISEASE</b>                  |
|---|---------------------------|---|
| <b>Segmental</b>                        | -                         | ++                                      |
| <b>Transmural</b>                       | +/-                       | +++                                     |
| <b>Fibrosis</b>                         | +                         | +++                                     |
| <b>Fissuring/Fistula</b>                | +/-                       | ++                                      |
| <b>Mesenteric fat, node involvement</b> | -                         | ++                                      |
| <b>Granuloma</b>                        | -<br>(very rare)          | +<br>(≈ 20% depending on specimen type) |

**Table 1d: Clinical features of ulcerative colitis (UC), Crohn's disease (CD) and microscopic colitis (MC)**

| <b>Clinical Features</b>                                    | <b>UC</b>                         | <b>CD</b>       | <b>MC</b>   |
|---|-----------------------------------|-----------------|---|
| Diarrhea  | ++                                | ++              | ++  |
| Rectal Bleeding   | ++                                | +               | +   |
| Abdominal Pain  | +                                 | ++              | +/-   |
| Palpable Mass   | -                                 | ++              | -   |
| Small Bowel involvement                                     | +/-<br>(rare backwash<br>ileitis) | ++              | +/-<br>some have mild<br>inflammatory changes<br>(see text)   |
| Rectal involvement  | ++<br>(90%)                       | + / ++<br>(50%) | ?<br>(rectum/sigmoid/desc.<br>colon involvement in<br>60-80%) |
| Strictures  | +/-                               | ++              | -   |
| Fissures/fistula/perianal disease.                          | +/-                               | ++              | -   |
| Extraintestinal Manifestations<br>(eye, skin, joint, liver) | ++                                | ++              | +/-<br>(arthralgias are more<br>common)                       |

**Table 2: Epidemiology of microscopic colitis**

| <b>Study</b>        | <b>Patients (n)</b> | <b>Incidence<br/>CC/10<sup>5</sup></b> | <b>Incidence<br/>LC/ 10<sup>5</sup></b> |
|---------------------|---------------------|--|---|
| Sweden (1984-1993)  | 30                  | 1.8                                    | N/A                                     |
| Spain (1993-1997)   | 60                  | 1.1                                    | 3.1                                     |
| Sweden (1993-1998)  | 97                  | 4.9                                    | 4.4                                     |
| Iceland (1995-1999) | 125                 | 5.2                                    | 4.0                                     |
| USA (1985-2001)     | 130                 | 3.1                                    | 5.5                                     |
| Sweden (1984-2004)  | 115                 | 5.2                                    | 5.5                                     |
| Canada (2002-2004)  | 164                 | 4.6                                    | 5.4                                     |

**Table 3 Epidemiology of microscopic colitis versus ulcerative colitis and Crohn's disease.**

| <b>FACTOR</b>                  | <b>UC</b>           | <b>CD</b>           | <b>MC</b>   |
|--------------------------------|---------------------|---------------------|-------------|
| Incidence/100,000              | 3–10                | 3–10                | 3-12        |
| Prevalence/100,000             | 45–140              | 40–110              | 10-103      |
| Westernized Countries          | ++                  | ++                  | ?           |
| Racial/Ethnic incidence        | ↑Caucasians, Jewish | ↑Caucasians, Jewish |             |
| Gender                         | Female=Male         | Female=Male         | Female>Male |
| Frequent age at onset          | 15–35y              | 15–35y              | 50-70y      |
| Smoking                        | ↓                   | ↑                   | ↑           |
| Drug associations              | Nil                 | Nil                 | ++          |
| Associate autoimmune diseases  | +                   | +                   | ++          |
| Increased risk of colon cancer | +                   | +                   | Nil         |

**Table 4: Microscopic colitis- Risk Factors and Disease Associations**

| <b>MC Risk Factors and Disease Associations</b> |
|---|
| Increasing age                                  |
| Female sex                                      |
| Autoimmune Disease                              |
| Celiac Disease                                  |
| Thyroid Disease                                 |
| Past or Current history of Malignancy           |
| Solid Organ Transplantation                     |
| Medications                                     |
| Smoking   |

**Table 5: Drugs Associated with Microscopic Colitis**

| <b>Drugs Associated with Microscopic Colitis</b> |
|--|
| NSAIDs   |
| Lansoprazole (a PPI)                             |
| ASA  |
| Flutamide  |
| Sertraline                                       |
| Ticlopidine                                      |
| Ranitidine                                       |
| Acarbose   |
| Simvastatin                                      |

**Table 6: Suggested Treatment Algorithm for Microscopic Colitis**

| <b>Treatment Algorithm for Microscopic Colitis</b>   |
|--|
| Confirm Diagnosis/Rule out Other Disorders   |
| Dietary changes (avoid caffeine, lactose)  |
| Trial of Anti-diarrheal therapy including Pepto-Bismol   |
| Trial of Budesonide or 5-ASA   |
| Consider prednisone/azathioprine/methotrexate at discretion of an experienced gastroenterologist |

## **Suggested reading**<sup>1-10</sup>

1. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133(4):1342-63.
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8. Tagkalidis PP, Gibson PR, Bhathal PS. Microscopic colitis demonstrates a T helper cell type 1 mucosal cytokine profile. *Journal of clinical pathology* 2007;60(4):382-7.



9. Beaugerie L, Pardi DS. Review article: drug-induced microscopic colitis - proposal for a scoring system and review of the literature. *Alimentary pharmacology & therapeutics* 2005;22(4):277-84.
10. Loftus EV, Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004;126(6):1504-17.