Microscopic Colitis (Lymphocytic and Collagenous), Eosinophilic Colitis, and Celiac Disease

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Clin Colon Rectal Surg 2015;28:118–126.

Abstract

Keywords

- microscopic colitis
- collagenous colitis
- lymphocytic colitis
- eosinophilic colitis
- celiac disease

Multiple tests are needed to diagnose a patient with noninfectious diarrhea. Some patients will be mistakenly labeled as diarrhea-predominant irritable bowel syndrome (IBS-D) because of nonspecific computed tomographic scans and grossly normal endoscopic findings. It is crucial to understand other less common pathologies to avoid these instances of misdiagnosis. This article focuses on microscopic colitis (MC), eosinophilic colitis (EC), and celiac disease. MC is an inflammatory condition of the colon that presents with two subtypes, only to be differentiated by histology. EC is a rare chronic inflammatory process. Depending on the extent of the disease, it can present with mild diarrhea, malabsorption, or at its worst, cause obstruction and perforation. Celiac disease affects the small bowel, but interestingly can present similarly to colitis. Both MC and EC respond to oral budesonide. Patients with celiac disease improve on gluten-free diets. These treatments are distinctly different from typical IBS-D care plans.

Patients with chronic noninfectious diarrhea often undergo multiple tests and studies so that a diagnosis can be made. Some of these patients will have nonspecific computed tomographic scans and grossly normal endoscopic findings. Because of their chronic symptoms, they may be mistakenly labeled as diarrhea predominant irritable bowel syndrome (IBS-D). Knowledge of the other less common but important differential diagnoses in these cases is crucial in recognizing the patient's underlying disorder.

Microscopic colitis (MC) is an inflammatory condition of the colon that presents with two subtypes: collagenous and lymphocytic colitis. Both types of MC present with watery diarrhea and normal endoscopic findings. Differentiation is made by histological examination but treatment is the same.

Eosinophilic colitis (EC) is a rare eosinophil predominant chronic inflammatory process that has a varied range of presentation depending on the extent of disease. It can present with mild diarrhea and malabsorption, but in severe cases can cause obstruction and perforation. Both MC and EC respond well to oral budesonide.

Celiac disease is an increasingly prevalent disease that causes diarrhea, abdominal pain, and bloating. Although this affects the small bowel, its presentation is very similar to other types of colitis. Treatment is discontinuing gluten in the diet.

In this article, we will delineate the distinguishing characteristics of these three entities to aid the colorectal surgeon in workup and management of patients with chronic diarrhea with subtle-to-no macroscopic endoscopic or imaging findings.

Microscopic Colitis

MC is an inflammatory bowel condition that presents with chronic watery diarrhea but with macroscopically normal colonoscopy findings. Histological evidence of pathology is only seen through biopsies of the colonic mucosa. This is a fairly recent disease entity that was first described in the 1970s; hence, information on incidences may be underreported. Epidemiological analyses of endoscopic biopsies performed for diarrhea in North America found an incidence of 8.6 per 100,000 from 1985 to 2001.¹ However, more recent studies based on the same population from 2002 to 2010

showed that incidences of MC more than doubled over that last decade with rates of 21.0 cases per 100,000 person-years.² This probably reflects increasing awareness of the disease among both endoscopists and pathologists, leading to higher rates of detection.

Collagenous colitis (CC) and lymphocytic colitis (LC) are two subtypes of MC that have similar presentations. Histologically, however, they have distinct characteristics. It is still a controversy whether CC and LC are just really one disease under MC, or if they should be considered as two distinct diseases that share some features. A review of 226 studies on CC and LC found little to no differences in epidemiology, clinical presentation, risk factors, and response to treatment.³

Epidemiology

The incidence of CC is 9.1 per 100,000 person-years and the incidence of LC is 12.0 per 100,000 person-years. The prevalence of MC was 219 cases per 100,000 persons (90.4 per 100,000 persons for CC and 128.6 per 100,000 persons for LC).¹ MC appears to be a disease of the older female population. The mean age for CC was 60 and for LC was 63. The proportion of women is slightly higher for CC than for LC (77 vs. 68%),⁴ and a higher female to male ratio is seen in CC versus LC (1.8 versus 1.6, respectively).⁵ Rarely, both types of MC can be seen in children.⁶

Clinical Presentation and Associated Conditions

CC and LC have similar presentations and there is really no distinct symptom that can differentiate one from another. The typical presentation is chronic watery, nonbloody diarrhea. Although it is a benign disease, it can be quite disabling. The average number of bowel movements experienced by these patients is around 6 to 7 times a day.⁴ Most follow a chronic intermittent course (85%), and 42% of the patients present with sudden onset of symptoms. Some patients experience nocturnal diarrhea (27%) as well. Other associated symptoms are abdominal pain (41%), weight loss (42%), and fecal urgency (29%).^{7,8} Prognosis is good with resolution of symptoms after medical therapy. As much as 38% of the patients achieve spontaneous remission with either no treatment or with simple anti-diarrheals.⁹ However, a retrospective study by Fernández-Banares in 2003 found that although 70% of the patients achieve clinical remission after treatment, 25% of the patients with LC and 30% of those with CC were found to have relapses after a mean follow-up of around 3 years.¹⁰ Diagnosis of MC before the age of 50 appears to be the highest risk factor for relapse.¹¹

Risk factors for MC are female gender, higher age, concomitant autoimmune disease, past and current diagnosis of malignancy of organ transplant.³

Although the exact etiology of MC is unknown, there are multiple studies in the literature that suggest that MC may be immunologically mediated, because of its strong association with other autoimmune diseases. Population studies reveal that approximately 30% of the patients with MC were found to have other concomitant autoimmune disorders⁹ such as celiac disease (12.9%) and autoimmune thyroid disease (10.3%), Sjögren syndrome (3.4%), diabetes mellitus (1.7%), and other autoimmune conditions of the skin and joints

(6.0%).¹² Among all autoimmune disorders, celiac disease appears to have the strongest association. Patients with MC have a 50 to 70 fold increased risk of having celiac disease as well compared with the general population.^{13,14}

There is also a strong association of MC with the use of certain medications (→ **Table 1**). Whether these medications triggered the inflammatory process is still an ongoing debate as all data available have been retrospective. The use of proton pump inhibitors (PPIs) (lansoprazole), low dose aspirin, β -blockers, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRI), statins, and bisphosphonates have all been associated with MC.^{9,15,16} Interestingly, there was a higher proportion of patients with CC who took NSAIDs and PPI on a chronic basis than what was noticed within the LC group. There was also a predominance of sertraline (SSRI) use by LC patients. Because of these strong associations, it is recommended that a key part of the evaluation should focus on identifying each medication taken by the patient and discontinuing medications that could potentially be worsening the disease.

Although there are some sparse data that show a high prevalence of smokers in both types of colitis, multivariate analysis studies have not shown any significant influence of smoking habits on clinical symptoms at diagnosis or clinical remission rate.¹¹

Diagnosis

The diagnosis of MC relies on adequate histological evaluation through lower endoscopy. Random sequential biopsies throughout the colon must be performed, as the gross appearance of the colon is usually unremarkable, though in some cases it can show mild edema (→ **Fig. 1**). Although there

Table 1 Medications which have been associated with microscopic colitis

Cardiovascular drugs
• Beta blockers
• Vinburnine (vasodilator)
• Lisinopril
• Simvastatin
• Angiotensin II receptor antagonist
Anti-platelet drugs
• Ticlopidine
• Aspirin
Gastrointestinal drugs
• Proton pump inhibitors
• Ranitidine
• Acarbose
Centrally-acting drugs
• Paroxetine
• Sertraline
• Carbamazepine
• Madopar
Miscellaneous
• NSAIDs
• Tardyferon (iron supplementation)
• Bisphosphonates
• Flutamide

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

is some belief that flexible sigmoidoscopy should be a first-line test and could provide a diagnosis in majority of the cases, 23% of the patients will have MC that is limited to the right side and the diagnosis can ultimately be missed with sigmoidoscopy alone.¹⁷ MC could present with a patchy distribution which can lead to misdiagnosis in 40% of the patients who have biopsies done only in the rectosigmoid area.¹⁸ Therefore, it is beneficial to perform a full colonoscopy to rule out other differential diagnoses, such as inflammatory bowel disease and malignancy. This thoroughness is especially important for patients who have not had a recent colonoscopy.

The histology found in MC (both CC and LC) demonstrates lymphocytic infiltration of the lamina propria and the epithelium. CC differs from LC in that there is marked thickening of the subepithelial layer (→**Fig. 2**). Intraepithelial lymphocytosis (IEL) can be found in both CC and LC, but is more pronounced in LC: ≥ 20 intraepithelial lymphocyte per 100 surface epithelial cells are needed to make the diagnosis (→**Table 2**).¹⁹

Fig. 1 Endoscopic photos of a pediatric patient with suspected microscopic colitis. (A) Ascending colon image demonstrates some mild mucosal edema, which might be associated with collagenous colitis. The edema is evident by the tiling and furrowing appearance of the mucosal surface versus (B) normal appearing cecum. (Photo credit Muhammad Khan, MD, Pediatric Gastroenterology, Children's National Medical Center.)

Management

Before initiating therapy for MC, it is important to get a thorough medication history first, and discontinue any potentially offending drug. Dietary modifications (avoiding caffeine and lactose) may also have some limited benefit.

Treatment should be customized depending on the patient's severity of symptoms. Patients with mild and

Fig. 2 (A) The normal colonic mucosa (hematoxylin and eosin [H&E], 200 $\times$) shows a single layer of surface epithelium overlying a thin basement membrane and uniformly arrayed crypts without many intraepithelial lymphocytes. (B) In contrast, in lymphocytic colitis (H&E, 400 $\times$), there is extensive infiltration of the colonic crypts by lymphocytes. (C) In collagenous colitis (H&E, 400 $\times$), the basement membrane zone is thickened and collagenous (arrows), with resultant disruption of the surface epithelial layer. (Photo credit Hareesh Mani, MD, Department of Pathology, Inova Fairfax Hospital.)

Table 2 Histological features of collagenous colitis and lymphocytic colitis

	Collagenous colitis	Lymphocytic colitis
Lamina propria	Lymphocytic infiltration of the lamina propria with little or no damage in mucosal architecture	
Subepithelial layer	Thickening of subepithelial layer > 10 µm	Subepithelial collagen layer not present or < 10 µm
Intraepithelial	Intraepithelial lymphocytosis could be present, but necessary for the diagnosis	Intraepithelial lymphocytosis (≥ 20 IEL per 100 surface epithelial cells)

intermittent symptoms can be treated with anti-diarrheal medication (loperamide). About one-third of the patients can have spontaneous resolution of symptoms and can be treated symptomatically. Specific treatments studied for MC are steroids (budesonide and prednisone), bismuth subsalicylate, 5-ASA, and bile-acid binding agent (cholestyramine) (► **Table 3**). Among all these therapies, only budesonide has strong supporting evidence and should be the first-line treatment for patients with moderate to severe symptoms. There are several randomized trials that show the effectivity of budesonide in inducing and maintaining clinical remission in both CC and LC.²⁰ It is a locally active corticosteroid that is well tolerated and has little systemic absorption. It is usually given at a dose of 9 mg/d for 1 month, and then tapered to 6 mg/d followed by 3 mg/d for the next 2 months. Tapering the dose of budesonide is believed to decrease the risk of remission. Prednisone is an alternative corticosteroid that has shown some efficacy in treating MC. However, studies have shown that patients treated with budesonide had a higher rate of complete response than those treated with prednisone (82.5 vs. 52.9%) with lesser recurrence rate.²¹ ► **Fig. 3** delineates an algorithm that may be useful in the workup and management of MC.

Eosinophilic Colitis

Epidemiology

EC is part of a family of disorders including eosinophilic gastroenteritis and eosinophilic esophagitis. Of the three entities, EC is the rarest form and mainly occurs in neonates and young adults.^{22,23} EC was first described in 1936, but did not surface in European/Western literature until 1959.²⁴ It has been documented as an equally distributed disease of the sexes, although in infants it has a slight predilection for males.²⁵ It is hard to quantify the true prevalence of EC as many secondary conditions can lead to a secondary eosinophilic inflammation in the colon, including IgE-mediated food allergy, gastroesophageal reflux disease (GERD), and inflammatory bowel disease. In the four decades preceding 2010, there were 196 cases documented, with a majority of case reports being more recently published since the year 2000. The paucity of information on EC is likely due to its vague definition and its status as a diagnosis of exclusion.^{26,27}

Pathogenesis

The exact etiology and pathogenesis of EC remains unclear. Genetic and environmental factors have been implicated in

the pathophysiology of the disease. Generally, 16% of those with eosinophilic gastrointestinal diseases have family members with a similar disorder. Interleukin-5 (IL-5) has been implicated in the development of EC. It has been reported that IL-5 supports terminal differentiation and proliferation of eosinophilic precursors and has the ability to maintain the viability of mature eosinophils. In general, eosinophils reside in the bone marrow but can naturally be found in the gastrointestinal system, excluding the esophagus. Eosinophils traffic to the submucosa gastrointestinal tract following a brief half-life in the peripheral circulation.^{27,28} Eosinophils harbor an array of cytotoxins which when released can cause tissue damage in the inflammatory and allergic states leading to chronic inflammation and fibrosis. They can acutely produce cytokines, leukotrienes, and lipid mediators of inflammation and trigger other immunogenic cells, including basophils and mast cells. It is via these mechanisms that they are implicated in the development of EC.

Atopy is a genetic predisposition to any excessive IgE-mediated reaction and is highly associated at all ages. The infantile form of EC in particular is often associated with allergy to cow's milk or soy protein,²⁹ which is mostly predominated by an IgE-mediated hypersensitivity.^{26,30} In infants, the connection with food allergy has been more frequently established. The adult form's direct pathogenesis remains largely unclear though it is thought that this variation is largely non-IgE mediated and likely acts through a CD4 Th2-mediated mechanism.^{26,27,30} In ► **Table 4**, the differences between the infantile and adult variant of EC are delineated.

Clinical Presentation

Clinical presentation can vary for the family of eosinophilic gastrointestinal disorders. It is however marked by three hallmark traits: peripheral eosinophilia (noted in up to 35% of the cases), segmental eosinophilic infiltration, and functional deficits. Generally, patients present with abdominal pain and varying degrees of diarrhea. Klein et al identified three subdivisions of disease for eosinophilic gastrointestinal diseases.²⁸ Clinical presentation is highly associated with the layer most extensively infiltrated by eosinophils. These subdivisions include mucosa-predominant, muscularis propria-predominant, and finally serosa-predominant disease. Mucosa-predominant disease is the most common form of EC. It is characterized by mucosal dysfunction including protein-losing enteropathy, malabsorption, and diarrhea. Transmural or muscularis propria-predominant disease is characterized by intestinal obstruction and bowel wall thickening on

Table 3 Medications for the treatment of microscopic colitis

Medication	Dose	Outcomes of randomized trials	Study limitations
Bismuth subsalicylate	8 to 9 262 mg tabs × 3 TID for 8 wk	Clinical response was shown after 8 wk of treatment versus placebo ⁴⁰	Study sample size was small
<i>Boswellia serrata</i>	400 mg tabs × 3 daily for 6 wk	No significant clinical response when compared with placebo ⁴¹	
Probiotic	<i>Lactobacillus acidophilus</i> and <i>Bifidobacterium animalis</i> 2 capsules BID × 12 wk	No significant clinical response when compared with placebo ⁴²	
Mesalamine	800 mg PO TID versus mesalamine 800 mg TID, plus cholestyramine	Clinical response was seen in both treatments after 6 mo. Slightly higher response rate in those treated with additional cholestyramine ⁴³	Study was randomized but not blinded
Budesonide	9 mg PO daily	All three randomized trials showed a high clinical response compared with placebo after 6 to 8 wk of treatment ^{44–46}	
Prednisolone	50 mg daily	Clinical response was seen after 2 wk of treatment ⁴⁷	Study sample size was small. Adverse effects were common.

Abbreviations: BID, twice daily; PO, per os (by mouth); TID, three times a day.

imaging. Intestinal obstruction has manifested as intussusception, perforation, or volvulus.^{23,31} Serosal involvement is characterized by eosinophilic ascites with as much as 80% eosinophils seen in fluid analysis, in up to 95% of the cases.

Diagnosis

Tissue eosinophilia in the colon can result from several conditions; therefore, EC remains a diagnosis of exclusion. Those conditions include parasitic colitis, drug-induced colitis, idiopathic hypereosinophilic syndrome (HES), inflammatory bowel disease, allogeneic bone marrow transplantation, and Tolosa–Hunt syndrome.²⁶

Fig. 3 Management algorithm for the workup and treatment of microscopic colitis.

EC itself is marked by peripheral eosinophilia, endoscopic and histological findings, with variable presence of eosinophilic ascites. As previously noted, EC can be subdivided into specific involvement of the layers of the gastrointestinal tract. Tissue diagnosis relies on eosinophilic predominance and aggregation in the lamina propria, generally extending into the muscularis mucosa, the submucosa, and sometimes into the muscularis propria. Multiple biopsies are needed as lesions can be patchy and normal eosinophil counts tend to increase from proximal to distal in the colon. Although there is no consensus for high power fields (HPF) to be seen for diagnosis, it is noted that normal eosinophil count in the colon ranges from the cecum at 35 eosinophils per HPF to the rectum with 8 to 10 per HPF.^{26,28,32,33} The presence of edema in the muscularis and submucosa, degranulation, involvement of the submucosa and muscularis mucosa, and the presence of eosinophils in the epithelium of the crypts are important factors for formulating a diagnosis of EC and distinguishing it from other colitides.³⁴ Serosal EC is characterized by eosinophilic ascites in addition to peripheral eosinophilia. The architecture of the mucosa is generally preserved, which can help in distinguishing this entity from other colitides.

HES can be differentiated from ES in that it has marked peripheral eosinophilia with associated end organ damage that is generally not limited to the colon, but includes the heart, skin, and other organs.²³

Endoscopic evaluation is rather modest and often not characteristic. Presentation can include patchy erythematous changes, loss of vascular pattern, nodularity, and/or

Table 4 Eosinophilic colitis in infantile and adult variant

Eosinophilic colitis	Infantile variant	Adult variant
Presentation	Bloody diarrhea	Nonbloody diarrhea, abdominal pain
Diagnosis	Endoscopy, pathology	Endoscopy, pathology
Treatment	Remove offending agent	Steroids, prednisone 1 to 2 mg/kg for 8 wk, then slow taper Budesonide 6 mg/day PO for maintenance therapy Alternatives: Immunomodulators—Azathioprine, 5-ASA
Prognosis	Usually self-limiting	Relapsing and remitting

Abbreviation: PO, per os.

superficial ulceration. Most endoscopic features predominate in the mucosal subtype.²⁶

Treatment

Steroid therapy has been the mainstay of therapy for EC.^{23,26,29} A majority of treatment methods have been compiled from the various case reports on the topic, as no randomized controlled trial or prospective study has taken place in regard to EC. The infant subtype of EC tends to be self-limiting, while the adult variety often requires medical intervention. In infants, removal of the causal agent tends to resolve symptoms. Diarrhea often resolves in less than 72 hours. Generally, infants may have foods reintroduced in 1 to 3 years, with no recurrence of symptoms. Up to 90% of the patients will respond to a 2-week long therapy of steroids in the presence of a slow taper.²³ Relapse occurs often, however, and requires recurrent courses of therapy or eventual dependence and requirement of maintenance steroid therapy.^{23,26,29} The efficacy of other therapies has been studied very little in EC, although there is increasing data in the other subtypes of eosinophilic gastrointestinal diseases. Budesonide daily for 1 to 2 weeks has also been shown to be efficacious. In patients who fail to respond to removing the offending agent in atopic variants, steroids (budesonide) or immunomodulator therapy (azathioprine) may be required.

Celiac Disease

Celiac disease is a well-described autoimmune disorder and food intolerance to dietary gluten, which is the major storage protein of wheat, barley, and rye. The disease primarily affects the proximal small bowel and induces a chronic inflammatory state that results in decreased digestion of food, decreased absorption of nutrients and net secretion of water and solutes.³⁵ As a consequence, the presenting symptoms are watery diarrhea, steatorrhea, abdominal pain, and weight loss. These symptoms are similar to the other colitides, and hence are important differential diagnoses to consider. There is, in fact, a strong association between MC and celiac disease as mentioned in the previous section and the two diseases can exist simultaneously in the same patient. Green's 2009 study of a database of 1,009 patients with celiac disease found that MC was present in 4.3% of the patients, and of these 25% of the patients were simultaneously diagnosed with both

diseases. The majority of the patients (64%) were diagnosed with celiac disease first. After further investigation, they were found to have MC as well.¹³

Epidemiology

It is generally accepted that the prevalence of celiac disease is 1%.³⁶ The rate of diagnosis is increasing and is well recognized in Europe and countries populated by persons of European ancestry, but is also recognized in North Africa, the Middle East, Asia, and South America.

Etiology

The development of the disease is a result of a unique interaction between gluten, immune, genetic, and environmental factors. Environmental factors that have been implicated include protective effects of breastfeeding, introduction of gluten into the diet before 4 months of age³⁷ is associated with an increased risk, and introduction of gluten into the diet at 7 months of age is a marginal risk.^{37,38} In addition, rotavirus in infancy has been described as an increased risk in the development of celiac disease in infancy. Genetic factors associated with celiac disease include the presence of the alleles that code for HLA-DQ2 or HLA-DQ8 proteins. These genes are necessitated to express the phenotype of celiac disease but are not solely sufficient. Studies in identical twins have implicated these alleles to having less than 50% contribution in the development of celiac disease. There are many other genes that have been implicated in the development of celiac disease but their influence on the disease is not as well substantiated as the two aforementioned proteins. Finally, the mucosal immune response is also integral to the pathogenesis of celiac disease. Immune responses to gliadin, which is the alcohol soluble fraction of gluten that contains the majority of the toxic components, promote an inflammatory reaction that is characterized by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy. This response is mitigated by both the innate and adaptive immune system.

Diagnosis

The diagnosis of celiac disease relies on serological test of small bowel intestinal biopsy. Immunoglobulin-A (IgA) anti-tissue transglutaminase antibody (TTG-IgA) is the preferred serological testing for the detection of celiac disease. The

Fig. 4 Endoscopic appearance of the duodenum of a pediatric patient with suspected celiac disease shows scalloping of the mucosa. (Photo credit Muhammad Khan, Pediatric Gastroenterology, Children's National Medical Center.)

Fig. 5 Histologically, biopsies from the duodenum of a patient with suspected celiac disease show a flattened mucosa and intraepithelial lymphocytes, up to 40 to 100 enterocytes. There is also focal acute inflammation. (Photo credit Dr. Scot Lewey, fooddoc.com.)

sensitivity and specificity of this test reaches 95%. There are, however, individuals with IgA deficiency, in which case IgG-based testing with IgG deaminated gliadin peptides (DGP) and IgG tissue transglutaminase should be performed. Anti-gliadin antibodies (AGA) were previously used for the diagnosis of the disease but are no longer recommended by the American College of Gastroenterology because of the variability in diagnostic accuracy.³⁹ The gold standard for establishing the diagnosis is biopsy of the proximal small intestinal mucosa. Grossly, the bowel mucosa appears to have a scalloped appearance (►Fig. 4). Histology reveals a range of findings depending on the severity of symptoms: increased intraepithelial lymphocytes, to enlarged hyperplastic crypts, to partial versus complete villous atrophy (►Fig. 5).³⁵

Treatment

The cornerstone in treatment is the adaptation of gluten-free diet. This has resulted in symptom improvement and prevention of complications. Cost and patient motivation has been a key factor in patient compliance with this treatment.

Conclusion

When a colorectal surgeon is referred a patient with chronic diarrhea in the absence of pathology identified in stool culture, endoscopy or imaging, the diagnosis of MC, EC, and celiac disease should be considered. Though rare, they compose an important aspect of the differential diagnoses and must be differentiated from IBS-D, which is a diagnosis of exclusion—after analysis of random biopsies of the colon as well as endoscopic evaluation of the proximal small bowel has been completed and deemed normal.

Acknowledgments

The authors gratefully acknowledge the editorial assistance of Anne Tretin and Allison Estep from Georgetown University School of Medicine. We also thank Muhammad Khan, MD, Pediatric Gastroenterology at Children's National Medical Center, Hareesh Mani, MD, Department of Pathology, Inova Fairfax Hospital, Elena Puscasiu, MD and D. Ashley Hill, MD, Division Chief, Department of Pathology, Children's National Medical Center for assistance with endoscopic and pathologic photos, as well as figure legends. The ASCRS CREST Committee has permitted us to share this work in this manner. Finally, we thank Anjali Kumar, MD, for editorial contributions, advice on collaborations, and overall mentorship of this work.

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