Considerations and Changes in the Evaluation, Management, and Outcomes in the Management of Diverticular Disease: The Diagnosis, Pathology, and Treatment of Diverticular Colitis

Robert J. Kucejko, MD, MS, MBA¹ Juan L. Poggio, MD, MS¹

¹ Department of Surgery, Division of Colon and Rectal Surgery, Drexel University College of Medicine, Philadelphia, Pennsylvania

Clin Colon Rectal Surg 2018;31:221–225.

Address for correspondence Robert J. Kucejko, MD, MS, MBA, Department of Surgery, Division of Colon and Rectal Surgery, Drexel University College of Medicine, 245 N Broad Street, MS 413, Philadelphia, PA 19107 (e-mail: robert.kucejko@gmail.com).

Abstract

Keywords

- ▶ diverticular
- ▶ segmental
- ▶ sigmoid
- ▶ diverticulosis
- ▶ colitis

Diverticular colitis, also known as segmental colitis associated with diverticulosis, is a colonic inflammatory disorder on the spectrum of inflammatory bowel disease (IBD). The disease consists of macroscopic and microscopic inflammation affecting inter-diverticular mucosa, sparing peri-diverticular mucosa, with inflammation confined to the descending and sigmoid colon. The disease likely arises from the altered immune response of an individual, genetically susceptible to the IBD spectrum of diseases. Patients with segmental colitis associated with diverticulosis (SCAD) are typically older, and likely represent a subgroup of IBD—susceptible patients who lacked an environmental trigger until that point in their life. Most patients remain in remission with initial treatments of mesalamine or topical steroids, and maintenance mesalamine afterwards. Only the most severe form of the disease necessitates immunomodulatory therapy and the consideration of surgery.

Diverticulitis is the pathologic triad of a thickened muscularis propria of the colon, penetration of the diverticulum, including the mucosa and muscularis mucosa, through the muscle where it is weakest, and the redundancy of surface mucosal folds, which characterizes the diverticular disease. Diverticular colitis, or the inflammation of the colonic mucosa between the diverticula, but not within the diverticula, was once thought to be a complication of diverticulitis. This complication was thought to be secondary to the disordered intestinal motility leading to localized bacterial stasis, overgrowth, and inflammation. While these factors contribute to the pathology of diverticular colitis,¹ it is now considered to be a distinct pathophysiologic response, within the spectrum of inflammatory bowel disease.²

The first likely appearance of diverticular colitis in the literature stemmed from case studies describing Crohn's inflammation related to the diverticula. These studies date back to 1968, with symptoms strikingly familiar to those now

considered standard to diverticular colitis.³ The first literature on a distinct entity of diverticular colitis appeared in 1983, and was thought to be a new complication of diverticular disease.⁴ The symptoms of two of the three patients discussed in this communication improved with salazopyrin, a drug with sulfasalazine as the active metabolite, more commonly used for inflammatory bowel disease. A year later the entity gained the nomenclature of diverticular colitis.⁵ Since then, other terms have been used to describe the disease including crescentic fold disease,⁶ diverticular disease-associated colitis (DAC),⁷ or segmental colitis associated with diverticulosis (SCAD).⁸ The latter definition has been most prevalent in the recent journal articles and these authors believe it to be the most specific nomenclature.

Segmental colitis associated with diverticulosis is a colonic inflammatory disorder that may mimic clinical, endoscopic features defined in other forms of inflammatory bowel disease, including Crohn's disease and ulcerative colitis. There is

macroscopic and microscopic inflammation affecting inter-diverticular mucosa, sparing peri-diverticular mucosa. This inflammation is non-specific, non-granulomatous, and localized in nature.⁹ By definition, this inflammation is limited to the left colon, sparing the right colon and the rectum.² These inflammatory manifestations are different from those in conventional colonic diverticulitis, which is essentially a pericolic inflammatory process that originates within the diverticula and extends into the surrounding tissues, but spares the non-diverticular colonic mucosa.¹⁰

Epidemiology

Epidemiology data are sparse concerning SCAD. Endoscopic incidence of the disease is expected every 300 to 400 colonoscopies of symptomatic patients.² These data are limited to a small number of retrospective and prospective studies, confined to a handful of centers in the same region. The prevalence range was 0.26% to 1.48% of patients undergoing endoscopy, with a mean age at diagnosis of 61.7 years to 66.5 years. When examining the epidemiology in patients with SCAD through the primary care setting, the incidence was 4/100,000, the median age was 68, and the mean time between onset of symptoms to diagnosis was 36 months.¹¹ The prevalence of SCAD in patients with diverticulosis was seen to be over 11% in prospective endoscopic studies.¹²

As previously mentioned, SCAD primarily occurs in the elderly, and it coincides with the second peak of incidence of IBD in the elderly.^{13,14} When there is concern for SCAD in this population, the differential diagnosis should include ischemic colitis (vasculitis, sclerosing mesenteritis, venous congestion), drug-induced colitis (NSAIDs), infective colitis (C-Diff, CMV) especially in the immunosuppressed patient, and the spectrum of IBD. While ischemic colitis is thought to present with acute onset abdominal pain and bloody diarrhea, some presentations mimic that of chronic colitis.¹³

The exact pathogenesis of SCAD is unknown, but many have postulated that it is related to the diverticula. The mucosal prolapse, fecal stasis, and microbial dysbiosis can lead to mucosal ischemia through mass-effect by subserosal peridiverticulitis.¹⁵ Diverticulosis predisposes a patient to dysbiosis through stasis, which can trigger an immune response. Host genetics may determine the difference between a localized inflammatory response versus a condition on the spectrum of IBD.¹⁶

Diagnosis and Findings

The overlap of inflammatory bowel disease (IBD) and diverticular disease can be difficult to distinguish both clinically and histologically from severe SCAD. Most studies cite the initial symptoms at onset as diarrhea and hematochezia.^{9,17} Others noted tenesmus.¹⁶ Abdominal pain was present, but is cited as a less common symptom of SCAD in most studies.

To definitively diagnose SCAD, one must first rule out other inflammatory bowel conditions. Negative seromarkers, specifically anti-neutrophil cytoplasmic antibodies (ANCA) and anti-saccharomyces cerevisiae antibodies (ASCA) should be

Table 1 Treatment response of SCAD based on endoscopic grading

Type A (11 patients)	Type B (8 patients)
All in remission after induction	All in remission after induction
1 of 6 on maintenance therapy relapsed	3 patients relapsed (37.5%)
Type C (4 patients)	Type D (4 patients)
All in remission after induction	No patients in remission at follow-up
3 of 4 patients never relapsed (1 lost to follow-up)	2 patients requiring 2 further induction treatments to obtain remission
	2 other patients requiring prednisone for remission and azathioprine thereafter

Abbreviation: SCAD, segmental colitis associated with diverticulosis.

included in the workup.⁹ Endoscopically, the inflammation in SCAD is confined to the mucosa between the diverticula, sparing the orifice itself. This may be difficult to determine by gross examination alone; therefore rectal biopsies negative for inflammation are required for the diagnosis. Endoscopically, when SCAD presents without concurrent diverticulitis, it can be divided into four categories of presentation, and their response to treatment is described in ►Table 1. These categories have shown to be predictive of severity in small studies, and can be used to determine treatment.^{12,18}

Histologic findings were related to endoscopic patterns in all patients in the study. Type A histology showed a range of inflammatory changes consistent with acute and chronic inflammation without architectural changes of the crypts. There was some incidence of intraepithelial micro-abscess. Type B histology demonstrated changes correlating with active chronic ulcerative colitis (UC), with most patients showing active inflammation with crypt architectural changes, and diffuse intraepithelial abscesses. Type C showed the most diverse histopathology with a wide spectrum of inflammatory infiltration with florid lymphoid follicles transmucosally and within the lamina propria. Also seen were micro-fissures, but no significant cryptic architectural changes. Abdominal pain at presentation was associated with this type of SCAD. Type D histopathology mimicked that of active severe chronic UC with massive active inflammation, architectural changes of crypts, diffuse cryptitis and crypt abscesses, and goblet cell depletion. Distinction between SCAD and IBD was most difficult upon gross inspection with this type.

Recent studies have evaluated the histopathology of SCAD as compared with UC. This study confirmed that all inflammatory bowel disease parameters may be detected in samples of SCAD. Multiple parameters were assessed among both samples, and all parameters were found to be altered in both conditions. These parameters included epithelium destruction, mucin depletion, intraepithelial lymphocytes, inflammatory, blood vessel dilation, edema, fibrosis, and hemorrhage. Significant differences were seen in mucin depletion, erosion,

and inflammatory infiltrate with histoid cells, lymphocytes, and plasma cells. Cytoarchitectural structure was severely altered in all of the UC samples, with no significant alteration seen in SCAD samples.¹⁹

Treatment and Prevention

Initial treatment case studies were based on small numbers of patients who often had concomitant diverticulitis as well as colitis. Early studies were divided, with some patients responding well to treatment directed toward diverticular disease, including antibiotics and dietary fiber.^{20–22} Other studies at the same time showed patients responding to sulfasalazine and steroids as one would treat colitis.^{21,23}

In a 2006 study, 15 patients were followed-up for over 7 years. These patients had SCAD without active diverticulitis. Mesalamine enemas for 6 weeks provided a complete clinical response within 6 weeks in all patients enrolled in the study. Out of 15 patients, 10 remained in endoscopic remission after 1 year, though the 5 with endoscopic evidence were asymptomatic. A total of seven patients relapsed in the 7-year study period, four of whom were the initial five with persistent endoscopic evidence. The relapsing patients were treated again with 6 weeks of mesalamine enemas and all achieved clinical remission. Two patients required surgery for critical colonic stenosis, though it was possible to make a firm diagnosis of Crohn's disease in both patients. Of the two patients diagnosed with Crohn's, their primary initial symptoms were abdominal pain and fever.¹⁷

In 2008, a similar study following 24 patients over a 20-year period, found similar findings. Two patients who were not treated had spontaneous remission within 1 month. 17 of the patients treated with oral 5-ASA had remission within 6 months, without the need for steroids or surgery. In the first systematic review to date, a total of 227 patients were selected from 18 studies. More than half of the patients were managed medically, and one quarter of the patients developed recurrent symptoms after treatment. Most studies managed patients with 5-ASA derivatives. Six of the 18 studies reported progression to overt IBD, but many times the authors postulated IBD as the initial diagnosis.¹⁶ One other meta-analysis has been published since, which showed similar results.²⁴

Once an endoscopic spectrum of disease was developed, treatment protocols became more specific to the extent of disease. One such protocol is illustrated in **Fig. 1**. In this study, all patients suffering from type A, B, or C SCAD obtained remission after induction. Induction was done with either mesalamine, or local steroid with probiotics. Beclomethasone dipropionate (BDP) was used as the steroid because it has a high "first-pass" metabolism, with little left in systemic circulation after metabolism. It was originally used to treat ulcerative colitis, and has since been successfully used in treating diverticular colitis.²⁵ VSL#3 is a probiotic mixture containing lactobacilli, Bifidobacterium, and streptococcus salivarius initially used in small prospective studies in SCAD.²⁶ Five type A patients (45%) refused maintenance treatment, two of which relapsed, one was lost to follow-up, and two remained disease free after

Fig. 1 Treatment algorithm for segmental colitis associated with diverticulosis.

5 years with no maintenance therapy. All patients who relapsed successfully remained in remission after re-treatment except those with type D. Remission rates were adequate in all but type D with the maintenance use of mesalamine. Type D, albeit the least prevalent type in the study population, necessitated the use of immunosuppressants to control symptoms.¹⁸

There is a sparsity of data determining the best treatment for patients with complicated disease, considering the strong response with previously discussed treatments. Earlier studies proceeded to surgery soon after initial treatment failures, but much less was known about SCAD, and in IBD in general. Failure of treatment before was attributed to a missed diagnosis of IBD. Now, with a stronger endoscopic classification of SCAD, and more experience with IBD, failure of treatment may be far and few between. The authors believe that if the condition is truly resistant to treatment, and is truly restricted to the sigmoid colon without evidence of IBD, it is reasonable to offer the patient the choice of surgical removal. The other option under investigation is the use of biologics to abate symptoms.

In attempts to generalize the successful use of TNF- α inhibitors in UC, Hassan et al showed successful application of infliximab to treat steroid dependent SCAD.²⁷ Ierardi et al later demonstrated the overexpression of TNF- α in SCAD patients when compared with similarly matched patients with IBD.²⁸ Tursi et al then showed that after successful response to BPD/VSL#3, TNF- α levels were significantly reduced in histologic samples after successful treatment.¹⁰

Discussion/Conclusion

Systematic reviews and meta-analyses on the subject suffer from patient heterogeneity.^{16,24} Diagnostic specificity has improved dramatically over the past 20 years in the treatment of IBD, which allows these patients to be removed from those being considered for SCAD.

What Causes SCAD, Diverticulitis or IBD?

Initially SCAD was thought to be a complication of diverticulitis. Other authors thought it to be a precursor to inflammatory bowel disease. Recently, authors have made the argument to consider it an entity of its own.

Initial hypotheses of the etiology of SCAD was that it was a minor epiphenomenon of diverticulitis, with resultant colitis secondary to active inflammation.²³ Later data support SCAD resulting from individuals who are genetically susceptible to the IBD. A retrospective review compared 100 patients with IBD and diverticular disease matched to 100 patients with IBD without diverticular disease. It was found that macroscopic inflammatory activity is more common in the sigmoid mucosa in those patients with both IBD and diverticulosis, which led the authors to conclude that mucosal disease in the areas of the diverticula is unlikely to be coincidental. There were also increased extra-intestinal manifestations of the disease in patients with both, as well as a later age of onset of IBD. Both of these observations suggest that these individuals may have been genetically susceptible, and the diverticular disease provided the environmental trigger of fecal stasis and bacterial overgrowth to begin the pathologic process.²⁹

Histopathologic results suggest SCAD is a form of chronic intestinal inflammation occurring in a colon harboring the diverticula, rather than a complication of diverticular disease, given the similarities between patient samples.¹⁹ Further evidence against the likelihood of the condition being caused by episodes of diverticulitis is the constant absence of peritonism, leukocytosis, and fever.¹⁷

Does SCAD Progress to IBD?

Early studies have documented the progression of SCAD to IBD, and some studies showed as many as 10% of patients diagnosed with SCAD progressed to having rectal involvement.^{7,30,31} Other studies were able to show that patients thought to have progressed from SCAD to inflammatory bowel disease actually had the diagnosis of inflammatory bowel disease from the beginning.⁷ With a more precise endoscopic definition, and a well-defined treatment algorithm, the initial distinction may be less important. SCAD is a chronic disease, as evidenced by patients with mild forms have a high rate of relapse without maintenance therapy.¹⁸

Conclusion

Segmental colitis associated with diverticulosis should be considered a chronic colitis on the spectrum of inflammatory bowel disease, and treated as a mild form of IBD as outlined above. It is secondary to an altered immune response of an individual genetically susceptible to the IBD spectrum of

diseases. Patients with SCAD are typically older, and likely represent a subgroup of IBD-susceptible patients who lacked an environmental trigger at until that point in their life. Most often, the colitis in a SCAD patient will be well-controlled with minimal medication, and well-maintained on well-tolerated medication, though this is dependent on initial presentation of the disease. It is unlikely that the patient will progress to UC or Crohn's, but this is dependent on the initial severity of the disease. If a patient does progress further along the spectrum to IBD, then they should be treated according to their revised diagnosis of IBD.

References

- Matrana MR, Margolin DA. Epidemiology and pathophysiology of diverticular disease. *Clin Colon Rectal Surg* 2009;22(03):141–146
- Tursi A. Segmental colitis associated with diverticulosis: complication of diverticular disease or autonomous entity? *Dig Dis Sci* 2011;56(01):27–34
- Schmidt GT, Lennard-Jones JE, Morson BC, Young AC. Crohn's disease of the colon and its distinction from diverticulitis. *Gut* 1968;9(01):7–16
- Cawthorn SJ, Gibbs NM, Marks GG. Segmental colitis: a new complication of diverticular disease. *Gut* 1983;24(05):A500
- Sladen GE, Filipe MI. Is segmental colitis a complication of diverticular disease? *Dis Colon Rectum* 1984;27(08):513–514
- Gore S, Shepherd NA, Wilkinson SP. Endoscopic crescentic fold disease of the sigmoid colon: the clinical and histopathological spectrum of a distinctive endoscopic appearance. *Int J Colorectal Dis* 1992;7(02):76–81
- Pereira MC. Diverticular disease-associated colitis: progression to severe chronic ulcerative colitis after sigmoid surgery. *Gastrointest Endosc* 1998;48(05):520–523
- Jani N, Finkelstein S, Blumberg D, Regueiro M. Segmental colitis associated with diverticulosis. *Dig Dis Sci* 2002;47(05):1175–1181
- Freeman HJ. Natural history and long-term clinical behavior of segmental colitis associated with diverticulosis (SCAD syndrome). *Dig Dis Sci* 2008;53(09):2452–2457
- Tursi A, Elisei W, Brandimarte G, et al. Tumour necrosis factor-alpha expression in segmental colitis associated with diverticulosis down-regulates after treatment. *J Gastrointest Liver Dis* 2011;20(04):365–370
- Tursi A, Elisei W, Picchio M. Incidence and prevalence of inflammatory bowel diseases in gastroenterology primary care setting. *Eur J Intern Med* 2013;24(08):852–856
- Tursi A, Elisei W, Brandimarte G, et al. The endoscopic spectrum of segmental colitis associated with diverticulosis. *Colorectal Dis* 2010;12(05):464–470
- Taleban S, Colombel JF, Mohler MJ, Fain MJ. Inflammatory bowel disease and the elderly: a review. *J Crohn's Colitis* 2015;9(06):507–515
- Heresbach D, Alexandre JL, Bretagne JF, et al; ABERMAD. Crohn's disease in the over-60 age group: a population based study. *Eur J Gastroenterol Hepatol* 2004;16(07):657–664
- Ludeman L, Shepherd NA. What is diverticular colitis? *Pathology* 2002;34(06):568–572
- Mulhall AM, Mahid SS, Petras RE, Galandiuk S. Diverticular disease associated with inflammatory bowel disease-like colitis: a systematic review. *Dis Colon Rectum* 2009;52(06):1072–1079
- Imperiali G, Terpin MM, Meucci G, Ferrara A, Minoli G. Segmental colitis associated with diverticula: a 7-year follow-up study. *Endoscopy* 2006;38(06):610–612
- Tursi A, Elisei W, Giorgetti GM, et al. Segmental colitis associated with diverticulosis: a 5-year follow-up. *Int J Colorectal Dis* 2012;27(02):179–185
- Tursi A, Inchigolo CD, Picchio M, Elisei W, Mangiola F, Gasbarrini G. Histopathology of segmental colitis associated with diverticulosis

- resembles inflammatory bowel diseases. *J Clin Gastroenterol* 2015; 49(04):350–351
- 20 Lamps LW, Knapple WL. Diverticular disease-associated segmental colitis. *Clin Gastroenterol Hepatol* 2007;5(01):27–31
 - 21 Makapugay LM, Dean PJ. Diverticular disease-associated chronic colitis. *Am J Surg Pathol* 1996;20(01):94–102
 - 22 Koutroubakis IE, Antoniou P, Tzardi M, Kouroumalis EA. The spectrum of segmental colitis associated with diverticulosis. *Int J Colorectal Dis* 2005;20(01):28–32
 - 23 Evans JP, Cooper J, Roediger WE. Diverticular colitis - therapeutic and aetiological considerations. *Colorectal Dis* 2002;4(03):208–212
 - 24 Mann NS, Hoda KK. Segmental colitis associated with diverticulosis: systematic evaluation of 486 cases with meta-analysis. *Hepatogastroenterology* 2012;59(119):2119–2121
 - 25 Rizzello F, Gionchetti P, D'Arienzo A, et al. Oral beclomethasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2002;16(06):1109–1116
 - 26 Tursi A, Brandimarte G, Giorgetti GM, Elisei W. Beclomethasone dipropionate plus VSL#3 for the treatment of mild to moderate diverticular colitis: an open, pilot study. *J Clin Gastroenterol* 2005;39(07):644–645
 - 27 Hassan C, Zullo A, Ierardi E, Burattini O, De Francesco V, Morini S. Tumour necrosis factor alpha downregulation and therapeutic response to infliximab in a case of segmental colitis associated with diverticula. *Gut* 2006;55(04):589–590
 - 28 Ierardi E, Meucci G, Hassan C, et al. Tumour necrosis factor alpha in segmental colitis associated with diverticula. *Dig Dis Sci* 2008; 53(07):1865–1868
 - 29 Sultan K, Fields S, Panagopoulos G, Korelitz BI. The nature of inflammatory bowel disease in patients with coexistent colonic diverticulosis. *J Clin Gastroenterol* 2006;40(04):317–321
 - 30 Rampton DS. Diverticular colitis: diagnosis and management. *Colorectal Dis* 2001;3(03):149–153
 - 31 Hokama A, Kinjo F, Tomiyama R, Maeda K, Saito A, Matayoshi M. Progression of diverticular colitis to ulcerative colitis. *Inflamm Bowel Dis* 2005;11(06):618