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LARGE INTESTINE (B CASH AND R CHOKSHI, SECTION EDITORS)

Colonic and Anorectal Manifestations of Systemic Sclerosis

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Abstract

Purpose of Review Systemic sclerosis is a chronic autoimmune disorder commonly involving the gastrointestinal tract, including the colon and anorectum. In this review, we summarize major clinical manifestations and highlight recent developments in physiology, diagnostics, and treatment.

Recent Findings The exact pathophysiology of systemic sclerosis is unclear and likely multifactorial. The role of the microbiome on gastrointestinal manifestations has led to a better understanding of potential pathogenic gut flora. Carbohydrate malabsorption is common. Evaluation using fecal calprotectin and high-resolution anorectal manometry may broaden our understanding of the etiologies of diarrhea and fecal incontinence and help with early recognition of pathology. Prucalopride, a high-affinity $5HT_4$ agonist, and pyridostigmine, an acetylcholinesterase inhibitor, may help improve colonic transit in patients with constipation. Intravenous immunoglobulins have been used to target muscarinic receptor antibodies that are believed to contribute to gastrointestinal dysmotility.

Summary Colonic and anorectal manifestations of systemic sclerosis include constipation, diarrhea, and fecal incontinence, and can diminish quality of life for these patients. Recent studies regarding pathophysiology as well as diagnostic and treatment options are promising. Further targeted studies to facilitate early intervention and better management of refractory symptoms are still needed.

Keywords Constipation · Diarrhea · Fecal incontinence · Anorectal · Scleroderma · Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease with gastrointestinal (GI) involvement reported in up to 90% of patients [1]. Any part of the gastrointestinal tract may be affected from the mouth to the anus, but the esophagus is most frequently involved, followed by the anorectum and small bowel. Colonic and anorectal complications of SSc may present in various ways and are known to impair health-related quality of life, often assessed by the University of California, Los Angeles; Scleroderma Clinical Trials Consortium Gastrointestinal Scale (UCLA SCTC GIT 2.0); and Patient Reported Outcome Measurement Information System (PROMIS) [2, 3]. Such tools have played an important role in advancing clinical practice by assessing disease burden and guiding treatment.

Most affected individuals require a multidisciplinary approach to management between the gastroenterologist, rheumatologist, and often a dietician. Early monitoring and intervention are necessary to minimize complications and improve quality of life.

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Pathophysiology

The underlying pathogenesis of SSc is not clearly understood, but suggested theories implicate a complex interplay between vasculopathy, autoimmunity and inflammation, and fibrosis [4–6]. Vascular abnormalities include endothelial cell damage, increased expression of adhesion molecules, reperfusion injury, intimal proliferation, and proteoglycan deposition leading to fibrosis [6, 7•]. Immune system activation, including production of growth factors, cytokines, and autoantibodies, has a known role in skin and lung involvement and likely affects the gastrointestinal tract as well [6–8]. Both neuropathic and myopathic processes are involved in the immune-related development of gastrointestinal manifestations. Autoantibodies against muscarinic receptors interfere with cholinergic nerve stimulation and reduce smooth muscle contractility [9]. Altered neural function has been noted in early stages of the disease, during which the smooth muscle continues to respond to prokinetics. Type 2 helper CD4+ T cells play a role in fibroblast activation, which can lead to interstitial and perivascular fibrosis [6, 7•]. The fibrosis and atrophy of the smooth muscle often portends increased morbidity and mortality related to GI disease, usually related to profound gut dysmotility and subsequent malnutrition. These severe complications of gut involvement occur in approximately 8% of SSc patients [10]. Multiple recent studies also highlight the role of oxidative stress at various levels of pathogenesis, acting on all cellular targets [11–13].

Given that gut microbiota have been found to affect both the pathogenesis and severity of various autoimmune diseases, recent studies have sought to explore their exact role in SSc. The severity of SSc gastrointestinal involvement has been associated with alterations in fecal microbiota composition. Patients with SSc demonstrate decreased levels of beneficial flora, such as *Clostridium* and *Bacteroides*, as well as increased levels of pathogenic flora, such as *Fusobacterium* and *Prevotella* [14•]. Further, Patrone et al. showed that fecal testing in patients with SSc and gastrointestinal symptoms demonstrated a higher proportion of *Lactobacillus*, *Eubacterium*, and *Acinetobacter*, and lower proportion of *Roseburia*, *Clostridium*, and *Ruminococcus* than healthy controls. The fecal microbiota of SSc patients without gastrointestinal symptoms, however, was similar to that seen in healthy controls [15]. This new understanding of the possible role of the microbiome suggests that future management of SSc could include more targeted drug and dietary options and even potentially fecal transplantation.

Clinical Manifestations and Management

Colon

Colonic involvement of systemic sclerosis can be seen in an estimated 20–50% of patients [1]. The primary clinical manifestations include constipation and diarrhea, but other complaints may include bloating, malabsorption, malnutrition, and gastrointestinal bleeding [4].

Constipation

Constipation in SSc is related to multiple factors including decreased or absent contractions of the colon and an impaired gastrocolic reflex leading to delayed transit time [16]. Both neuropathy and smooth muscle atrophy likely contribute to diminished peristalsis, which can also cause patients to feel abdominal pain and bloating. More severe cases of constipation may be associated with pseudo-obstruction, colonic dilation or megacolon, impaction, stercoral ulceration, or even volvulus. Diverticular disease can also result from smooth muscle atrophy and loss of haustra [7•]. The thin muscle wall of the colon is prone to developing wide-mouthed diverticula along the anti-mesenteric border (Fig. 1a).

Patients with SSc and constipation are often managed in a similar fashion to those without SSc. A careful history, including medications that can impair gastrointestinal motility, is essential, along with a digital rectal examination. Radiographic films may demonstrate loss of haustrations (Fig. 1b), diverticula, or colonic dilation. Colonoscopy can help exclude structural causes, especially when red flag symptoms are present. Transit studies, such as wireless motility capsule or radio-opaque marker imaging, may also be performed to assess for delayed transit, though this is not often necessary.

An aggressive bowel regimen can help maintain adequate bowel habits for the patient with SSc. Bulking agents, such as fiber, are often not well tolerated, causing bloating and flatulence. Laxatives are first-line therapy. The newer agents for constipation, including lubiprostone, linaclotide, and plecanatide, may be used, but studies ensuring their safety and efficacy in this population are lacking.

Prucalopride is a high-affinity 5-HT_4 receptor agonist with no major cardiac toxicity that exhibits gastrointestinal prokinetic activity. A recent Italian study of 40 SSc patients with constipation showed increased complete spontaneous bowel movements ($p = 0.014$) and overall improved constipation symptoms as measured by both Likert and UCLA GIT 2.0 scales [17•]. The observed improvement in colonic function was attributed partially to accelerated colonic transit time, measured by lactulose breath testing. Of note, 17.5% of the initial cohort were unable to complete the study due to adverse effects, including abdominal pain and headache. Pyridostigmine, an acetylcholinesterase inhibitor, has also been found to improve constipation symptoms in one study [18•]. Of the 19 SSc patients who reported constipation, 31.6% reported improvement after at least 4 weeks of use. Previous studies have also noted the benefit of pyridostigmine on colonic transit time in patients with autonomic neuropathy

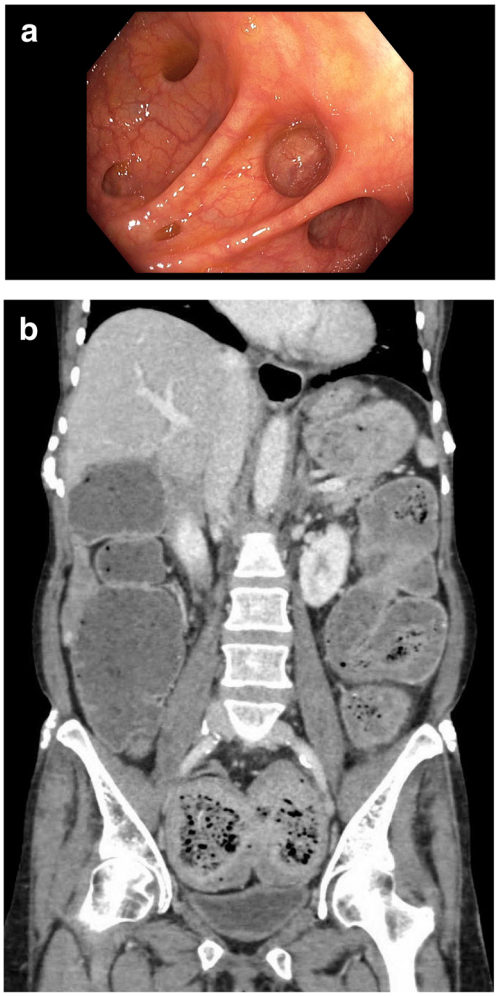

Fig. 1 Colonic alterations seen in systemic sclerosis. **a** Diverticulosis. **b** Loss of haustrations (reprinted with permission from: McFarlane IM, Bhamra MS, Kreps A, et al. Gastrointestinal manifestations of systemic sclerosis. Rheumatology (Sunnyvale) 2018;8(1). pii:235.). Used with permission from the author who holds copyright

[19]. Small sample sizes preclude generalizing these results, but both medications show potential and may provide an alternative in refractory cases.

Diarrhea

Diarrhea in SSc is often multifactorial in etiology, and the various causes help dictate the diagnostic approach. Small intestinal causes are more common than colonic ones and include bacterial overgrowth and carbohydrate malabsorption [4]. Luminal food stasis due to hypomotility can lead to small intestinal bacterial overgrowth (SIBO), an important cause of diarrhea and malnutrition in SSc. Traditionally, hydrogen/methane breath testing using either glucose or lactulose has been used to diagnose SIBO. However, recent evidence suggests a correlation between high levels of fecal calprotectin and positive glucose breath testing. Marie et al. [20] showed a strong correlation between fecal calprotectin levels ≥ 275 μg/g and positive glucose breath testing in SSc patients, with sensitivity up to 0.93 and specificity of 0.95. Eradication of SIBO after 3 months of rotating antibiotics resulted in significantly decreased calprotectin levels. Considering that breath testing is not available at all centers and that repeat breath testing can be a laborious way to assess treatment response, these findings provide a potential alternative for SIBO diagnosis and monitoring. Evidence of the utility of probiotic use to reduce risk of SIBO in SSc is lacking [21]. However, some studies do report benefit of probiotics for overall gastrointestinal symptoms [22, 23•].

Both lactose and fructose malabsorption have been described in approximately 40% of SSc patients [24, 25]. Lactose-free diets can be helpful. In addition, a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) decreased diarrhea symptoms from 31.3 to 6.3% ($p = 0.022$) in patients with fructose malabsorption [25]. Overall, however, the data for dietary modification in SSc are limited [23•].

Other possible causes of diarrhea include bile acid malabsorption, which has been postulated but not formally studied in this population, as well as overflow from constipation and pseudo-obstruction. Plain abdominal radiography may help diagnose the latter.

One potential new therapy for gastrointestinal symptoms in SSc patients is intravenous immunoglobulin (IVIG). Used for multiple autoimmune disorders, IVIG is thought to be a safe and effective immunomodulator that acts via neutralization of autoantibodies and inhibition of inflammatory mediators [26•]. Gastrointestinal dysmotility in SSc has been linked with autoantibodies against the muscarinic-3 receptor (M3-R) of the myenteric cholinergic neurons and smooth muscle, inhibiting intestinal contractions [9]. IVIG significantly decreases binding at these receptors. A recent French study demonstrated a trend toward improved bowel symptoms with use of IVIG, with 42% reporting abnormal bowel movements prior to therapy versus 27% at the end of therapy ($p = 0.06$) [27]. Also noted were lower corticosteroid doses at the end of treatment, indicating a possible steroid-sparing effect of IVIG. Raja et al. [28] demonstrated a significant decrease in diarrhea (0.73 to 0.36, $p = 0.026$) and distension (1.86 to 1.08, $p = 0.003$) scores after IVIG as measured by the UCLA SCTC GIT 2.0. Results should be repeated before recommending regular use, but these findings suggest immunotherapy may be an option in severe cases.

Malnutrition

Malnutrition in SSc is reported in the range of 8–58% and can lead to increased morbidity and mortality as well as impaired

quality of life [10, 29, 30]. Either constipation or diarrhea may be present, often related to underlying dysmotility, SIBO, and/or intestinal pseudo-obstruction. Traditional assessment of malnutrition, such as body mass index and/or serum prealbumin, may not by themselves be good correlates in SSc. The Canadian Scleroderma Research Group utilized the Malnutrition Universal Screening Tool (MUST) in their database study of 586 SSc patients, concluding that nearly 18% were at high risk for malnutrition and that disease severity increases that risk [31]. Early screening using the MUST may help expedite referrals to the gastroenterologist and dietician. Enteral and/or parenteral nutrition are indicated in severe cases.

Gastrointestinal Bleeding

Vascular mucosal disease is common in SSc and can present as GI bleeding and/or iron deficiency anemia. Gastrointestinal bleeding is seen in an estimated 15% of SSc, with mucosal telangiectasias being the most common source [32]. These telangiectasias can occur throughout the GI tract, including the colon, and may be treated with argon plasma coagulation or bipolar cautery. Diffuse presence may be treated with iron therapy [33]. Other colonic manifestations that can present with bleeding include diverticular disease and stercoral ulcers. Investigation should include assessment of iron stores and endoscopic evaluation.

Pneumatosis Cystoides Intestinalis

Pneumatosis cystoides intestinalis (PCI) is a rare complication of SSc characterized by gas-filled cysts in the submucosa and subserosa of the small or large bowel. Symptomatic patients commonly report abdominal pain or distention, bowel habit changes, or weight loss. Diagnosis is primarily radiographic, with linear or circular gas bubbles seen on commuted tomography. Endoscopy is not needed but can show grape-like, beaded, or cobblestone forms [34]. Endoscopic ultrasound with a miniprobe may be helpful for those with colonic involvement, demonstrating multiple hyperechoic air pockets in the colonic submucosa [35]. Medical management is the rule and can include bowel rest, supplemental nutrition, antimicrobials, and even hyperbaric oxygen therapy [36]. Surgical exploration may be necessary for peritoneal irritation or refractory bowel obstruction.

Anorectum

The anorectum may be affected in about 50–70% of SSc patients, second in prevalence only to the esophagus, with major complaints including fecal incontinence, rectal prolapse, pain, and tenesmus (l). Anorectal dysfunction has been closely linked to esophageal involvement, and both can present early in the disease course [37]. Screening for anorectal symptoms is essential as patients may be too embarrassed to report symptoms.

Fecal Incontinence

Reported in 27–38% of the SSc population, fecal incontinence (FI) can often be severe [38, 39] and is known to impair quality of life [40, 41]. Physiologically, lower resting pressures of the anorectum may be seen. Atrophy and fibrosis of the internal anal sphincter (IAS) have been implicated, though both symptomatic and asymptomatic SSc patients have been noted to have IAS atrophy [42]. Rather, neurogenic mechanisms may have more clinical significance, at least early on. Heyt et al. [43] demonstrated impaired or absent rectoanal inhibitory reflex (RAIR) in 71.4% of scleroderma patients as well as a significant relationship between FI in SSc and impaired RAIR. The RAIR represents a local neural reflex most commonly discussed in relation to Hirschsprung's disease. Why its absence leads to constipation in that disease and FI here is unclear. Another 2012 study that compared symptomatic and asymptomatic SSc patients to incontinent controls showed that FI was related more to anal sensory threshold and absent RAIR versus resting and squeeze pressures or rectal compliance [44]. The authors thus concluded that FI in SSc was more related to neuropathy than to sphincter atrophy and fibrosis.

Diarrhea or constipation with overflow can precipitate FI. Fecal impaction and pelvic floor dysfunction may exacerbate symptoms. Increased severity of symptoms has been associated with loose stools, SIBO, constipation, and urinary incontinence [38].

The functional evaluation of FI is performed using high-resolution anorectal manometry. Commonly cited manometric abnormalities include low resting anal pressure, predominantly supplied by the IAS (Fig. 2), and impaired or absent RAIR (Fig. 3). Function of the external anal sphincter may be normal [44, 45]. Other potential findings include diminished squeeze pressures and decreased rectal capacity and compliance. Of note, 11% of patients with an abnormal anorectal manometry are still asymptomatic, suggesting that early manometric evaluation may be useful in delaying the morbidity of anorectal symptoms [45]. Less frequently used diagnostics include magnetic resonance imaging (MRI) with defecography and endoanal ultrasound. MRI may show forward buckling of the anterior rectal wall, air in the upper part of the anal sphincter, or atrophy and fibrosis of the sphincters [46]. Endoanal ultrasound can also be used to evaluate for structural sphincteric defects or IAS thinning [47].

Fecal incontinence treatment requires a multifaceted approach. Dietary and behavioral modifications and pharmacotherapy to bulk stools or slow transit typically mirror those used in patients without SSc and are considered first-line therapy. Collins et al. [48•] demonstrated the efficacy of biofeedback in SSc patients to be similar to those without SSc. After

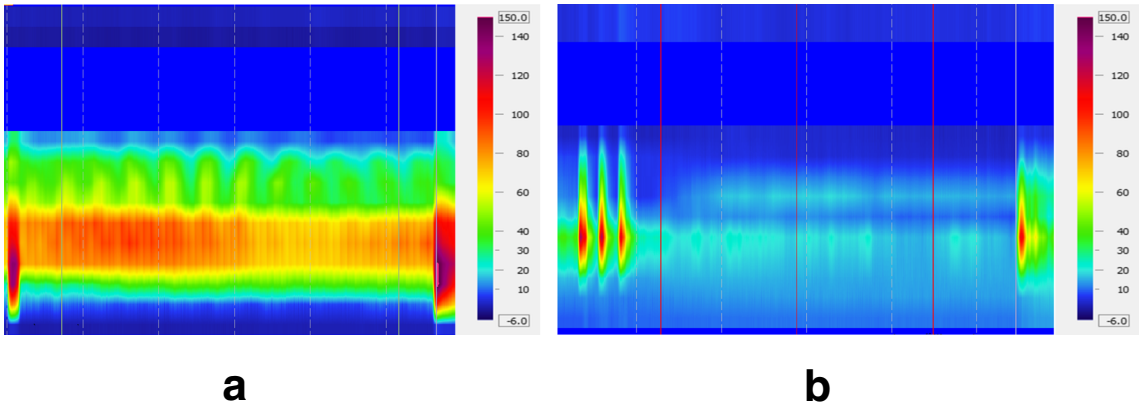

Fig. 2 Normal (a) versus low (b) resting pressures on high-resolution anorectal manometry (image obtained from copyright holder Darren M. Brenner, MD, Northwestern Medicine, Chicago, IL, with permission)

6 weeks of therapy, the 13 SSc patients in the study showed a similar significant benefit in Fecal Incontinence Severity Index scores and quality of life measures, and the impact was sustained after 6 months. Further studies should be performed to corroborate this benefit. In more severe cases of FI, treatment with sacral nerve stimulation has been described with mixed results [49, 50]. Surgical intervention can be considered in refractory cases.

Rectal Prolapse

Rectal prolapse can arise from constipation and straining, reduced rectal compliance, and anorectal weakness. Prolapse worsens anal sphincter dysfunction and can be responsible for exacerbating FI and even causing intussusception. Ventral involvement has been described [51], and defecography can help with diagnosis. On anorectal manometry, prolapse can contribute to reduced rectal capacity and compliance and low anal canal pressures, as the prolapsing mucosa keeps the sphincter open [52]. Rectal prolapse can be treated surgically, though this is reserved for more severe cases given the high risk of recurrence [51, 52]. Recurrent FI may occur due to the progression of anorectal disease.

Summary

Systemic sclerosis commonly presents with potentially disabling colonic and anorectal symptoms. Recent advances in

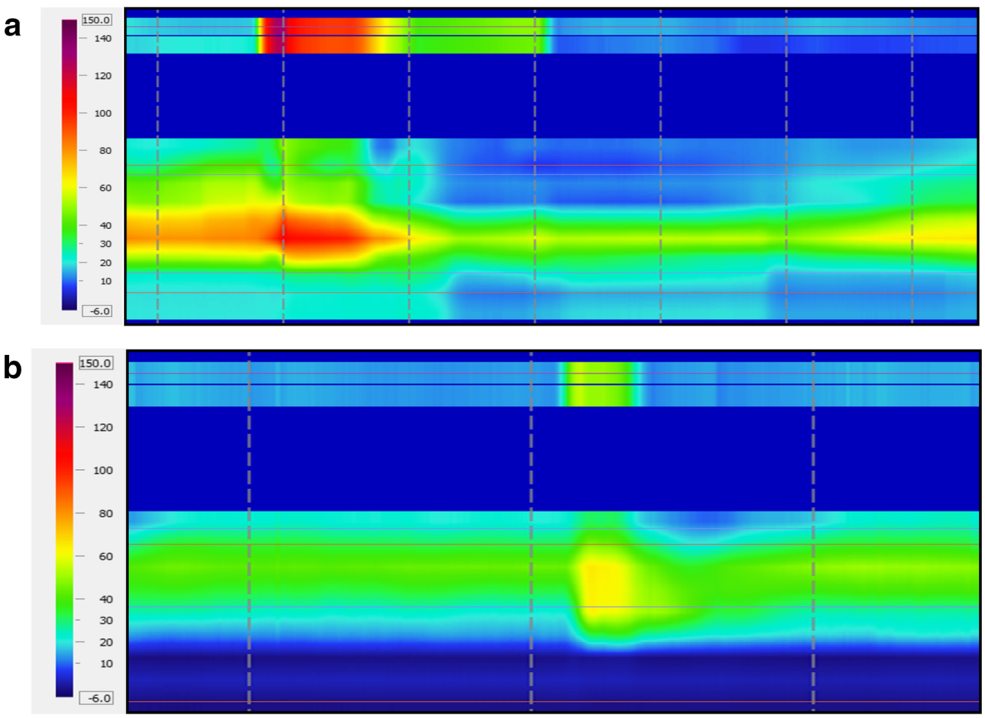

Fig. 3 Normal (a) versus abnormal (b) RAIR on high-resolution anorectal manometry (image obtained from copyright holder Darren M. Brenner, MD, Northwestern Medicine, Chicago, IL, with permission)

Table 1 Summary of recent advances in the study of colonic and anorectal manifestations of SSc

Pathogenesis and etiology of GI symptoms
- Role of oxidative stress at all levels of pathogenesis
- Microbiome effects: discovery of specific pathogenic flora
- Lactose and fructose intolerance described in a high number of SSc patients

Diagnostic testing
- Fecal calprotectin as a potential marker of small intestinal bacterial overgrowth

Treatment
- Prucalopride for constipation
- Pyridostigmine for constipation
- Intravenous immunoglobulins (IVIG) for bowel symptoms
- Dietary therapy in the setting of carbohydrate intolerances (e.g., lactose free diet or low FODMAP diet)
- Biofeedback for anorectal dysfunction, fecal incontinence

microbiome research have advanced our understanding of the complex etiologies of this important disease. Early screening of individuals for bowel symptoms, and even evaluation using such tools as fecal calprotectin measurement and high-resolution anorectal manometry, may hasten interventions and improve quality of life. Medical management continues to be the mainstay of treatment. Studies of targeted options for refractory symptoms, such as the recent investigation of specific diets, prucalopride, pyridostigmine, and IVIG, will likely continue as we gain a better understanding of the underlying pathogenesis of gastrointestinal manifestations of SSc (Table 1).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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