Systemic Sclerosis

Gastrointestinal Disease and Its Management

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KEYWORDS

• Systemic sclerosis • Gastroesophageal reflux • Dysmotility • Gastroparesis
• Pseudo-obstruction • Constipation • Fecal incontinence • Esophagus

KEY POINTS

- A multidisciplinary approach with a gastroenterologist, nutritionist, and often a speech therapist is mandatory in all patients with severe gastrointestinal involvement.
- Oral cavity abnormalities are common in systemic sclerosis and can be severe.
- Gastroesophageal reflux may trigger or worsen interstitial lung disease.
- All patients with scleroderma should be screened for malnutrition.
- Treatment of fecal incontinence starts with optimization of the constipation treatment.
- Probiotics may be useful in patients with bloating and distension and small intestinal bacterial overgrowth.
- Well-powered prospective studies are needed to determine the effect of immunosuppressive treatment on the onset of gastrointestinal tract disease, especially in early systemic sclerosis.

INTRODUCTION

The gastrointestinal (GI) tract is the most frequently involved internal organ in systemic sclerosis (SSc), affecting more than 90% of patients.[1] The most frequent GI involvement is the esophagus, followed by the ano-rectum and small bowel, but any part of the GI tract can be affected, from the mouth to the anus.

This article reviews the pathophysiology of GI tract involvement in SSc and discusses the investigations and management of the disease. **Table 1** shows the most commonly used investigations to assess the GI tract in SSc, and treatments are listed in **Table 2**.

The authors have no relevant financial disclosures to make.
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Rheum Dis Clin N Am ■ (2015) ■–■
http://dx.doi.org/10.1016/j.rdc.2015.04.007 **rheumatic.theclinics.com**
0889-857X/15/$ – see front matter

Table 1
Common investigation for gastrointestinal involvement in SSC

Organ	Abnormality	Investigations
Esophagus	Esophagitis, stricture, Barrett esophagus	EGD
	Dysmotility, GER	Esophageal transit (nuclear medicine)
	Stricture, dysmotility	Barium swallow
	Dysmotility	Manometry
Stomach	Dysmotility	Gastric emptying study (nuclear medicine)
	GAVE, gastritis, ulcers, adenocarcinoma	EGD
Small bowel	Pseudo-obstruction	Plain abdominal radiography and CT scan
	Pneumatosis intestinalis and perforation	
	SIBO	Lactulose and glucose
	—	Hydrogen breath test
Colon	Dilatation, volvulus, perforation	Plain radiography and CT scan
	Large wide mouth diverticula	—
	Telangiectasis	Colonoscopy
Anorectum	Incontinence	Anorectal manometry
	—	Endosonography
	—	Defecography

PATHOPHYSIOLOGY OVERVIEW

Sjogren[2] has proposed an interesting hypothesis of the pathophysiology of the GI tract in SSc that includes 4 stages: vasculopathy, neural dysfunction, smooth muscle atrophy, and tissue fibrosis.[2] The earliest lesion may be vascular with mild changes in intestinal

Table 2
Treatment options

Organ	Problem	Treatment
Oral cavity	Dry mouth	Artificial saliva, sugar free gum and candies
		Secretagogues pilocarpine, cevimeline
Esophagus	GER	Lifestyle changes
		Proton-pump inhibitors
		H2 receptor antagonist
		Sucralfate
		Antacid
	Dysmotility	Prokinetic agents: Domperidone
		Cisapride
Small bowel	Small intestinal bacterial overgrowth	Antibiotics, probiotics
	Pseudo-obstruction	Treat SIBO, domperidone, metoclopramide
		Octreotide ± erythromycin, cisapride
	Pneumatosis intestinalis	Antibiotics, nasal oxygen or elementary diet or parenteral nutrition
Colon	Constipation	Diet rich in fiber, stool softener, polyethylene glycol, Probiotics, possibly prucalopride
Anorectum	Fecal incontinence	Treat constipation, sphincter muscle training
		Sacral nerve stimulation

permeability, transport, and absorption. This stage is followed by neural dysfunction, in which the patient starts to have clinical symptoms such as dysphagia, gastroesophageal reflux (GER), and bloating. At that phase, prokinetic drugs may largely reverse the functional abnormalities. The vasculopathy and neural dysfunction then lead to the third stage of smooth muscle atrophy. This stage is marked by only partial response to drugs. Finally, the end stage is muscle fibrosis, when drugs are no longer useful.

Recent detection of circulating autoantibodies to myenteric neurons in a substantial number of SSc patients suggests an autoimmune etiology of the neural dysfunction in the GI tract.[3,4] The muscarinic 3 receptor (M3R) is the principal receptor of acetylcholine, which is the main excitatory neurotransmitter regulating GI tract motility. Antibodies to the M3R receptor have been found in SSc and may inhibit this excitatory effect of acetylcholine and cause dysmotility.[3–5] Intravenous infusion of immunoglobulin could neutralize SSc antibodies against M3R, and this was suggested in a recent study.[5]

ORAL CAVITY

Oral cavity abnormalities are common in SSc and can be severe but are frequently disregarded. SSc patients have significantly more missing teeth and periodontal disease, less saliva production, and a smaller interincisal distance compared with controls.[6] The number of missing teeth is associated with worse hand function, the presence of GER, and decreased saliva production.[7] Oral health-related quality of life of SSc patients is significantly impaired and is not captured well by physician assessment of disease severity.[8] Use of adaptive devices such as flossers, powered oscillating-rotating toothbrushes, and orofacial exercise to improve oral health should be considered.

ESOPHAGUS

The esophagus is the most common internal organ involvement in SSc, affecting 70% to 90% of the patients. The distal two-thirds of the esophagus is affected, with smooth muscle atrophy, fibrosis, and dilatation. There is a weakened lower esophageal sphincter with profound loss of peristaltic action and dysmotility.[1] A dilated esophagus on a computed tomography (CT) of the chest is common in SSc.[9] As many as 50% of patients will be completely asymptomatic. Investigations with esophagealgastroduodenoscopy (EGD) in 13 patients with early SSc without GI tract symptoms found reflux esophagitis in 77% of patients, dysmotility of the distal esophagus in 85%, gastritis in 95% (31% erosive gastritis) and *Helicobacter pylori* in 38% of the patients.[10] Some pathologic conditions of the upper GI tract were found in all the patients.

Symptoms of esophageal dysfunction range from asymptomatic to dysphagia, GER, nausea, or vomiting with poor eating and severe weight loss.[1] Damage from GER includes peptic esophagitis that can progress to erosive esophagitis, bleeding, and frank ulceration if untreated. Peptic stricture, fistulae, and an achalasialike syndrome may also occur as well as candida esophagitis owing to poor emptying of the esophagus and immunosuppressive treatment. Barrett's esophagus with ultimate adenocarcinoma is also increased in SSc patients.[11] Moreover, GER is suggested to be a risk factor for the development of interstitial lung disease (ILD).[12]

Diagnosis of Esophageal Involvement

Diagnosis of dysmotility is made with esophageal manometry, barium swallow, or esophageal transit (scintigraphy). Other possible tests used include impedance monitoring.[13] Although manometry is the gold standard, it is an invasive test and is not convenient. A study on the comparison of esophageal scintigraphy with manometry showed that esophageal scintigraphy is nearly as accurate as manometry in detecting

esophageal hypomotility.[14] It can also detect GER. In contrast, barium contrast studies lack sensitivity and specificity, and interpretation is largely subjective, but it gives qualitative information about structure (eg, diverticula, strictures, masses). Esophageal transit is, therefore, a good examination to assess esophageal involvement. However, if there is any doubt about the results on clinical grounds, one should pursue the investigation with manometry. They are no clear recommendations, however, concerning what test should be used, and choice depends largely on the center where the tests are performed.

EGD allows evaluation of ulcers, esophagitis, stricture, Barret's disease, and adenocarcinoma.

Treatment of Esophageal Involvement

First-line management of symptomatic esophageal involvement implies lifestyle changes such as smoking cessation, eating smaller portions more often, eating the last meal of the day earlier, and elevation of the head of the bed. Dietary interventions include modifying the texture of food, such as purees or scrambled eggs. Yogurt may be recommended and avoidance of exacerbating food groups, such as spicy food. Despite the lack of specific randomized, controlled trials, some experts feel that all SSc patients should be treated with proton-pump inhibitor (PPI), for the prevention of GER, GER-related ILD, esophageal ulcers, and strictures.[15] Some patients require twice-daily PPI administration with addition of H2 blockers at night. Sucralfate, a sucrose sulfate-aluminium complex that binds to the mucosa, thus creating a physical barrier that impairs diffusion of hydrochloric acid in the gastrointestinal tract and prevents degradation of mucus by acid, may also be added as a cytoprotector. Although there may be concern that suppression of gastric acid could alter the bacterial flora of the upper gastrointestinal tract and lead to complications such as cancer and enteric or other infections and malabsorption, the current evidence indicates that this suppression rarely leads to clinical disease.[16] Because it is suggested that GER may be responsible for some of the interstitial lung disease in SSc, it may be especially important to prevent GER although it is not yet clear if gastric acid or other components of gastric juices might be responsible for lung damage.[17–19] The use of PPI in patients with idiopathic ILD showed a stabilization of the disease in a case series of 4 patients followed up for 3 to 6 years.[20] Moreover, in a prospective study of 6 SSc patients with ILD possibly attributed to GER, intensive treatment with antireflux therapy showed stability of their lung disease after 1 year.[21] More studies are needed to assess the role of aggressive dysmotility treatment and prevention of ILD in SSc.

Treatment of symptomatic esophageal dysmotility, such as dysphagia and severe GER not well controlled on PPI, includes prokinetic drugs. Cisapride, a serotonin 5-HT_4 receptor agonist, was found to have a beneficial effect on gastric emptying and lowering esophageal pressure in a small, randomized, controlled study.[22] However, because of concerns about long QT syndrome and severe arrhythmias, the medication was withdrawn from the market in some countries. Domperidone, a dopamine D2 receptor antagonist, increases the tonus of the inferior esophagus and the peristalsis of the antrum and is a safer drug than cisapride. Domperidone can be used in patients with dysphagia. A dose of 10 to 20 mg up to 4 times a day 30 minutes before meals can be tried. However, the risk of sudden death and severe arrhythmia has been a recent concern and may be increased in patients taking doses higher than 30 mg/d or in patients older than 60 years. It should be used with caution in patients with heart failure or arrhythmia and if used concomitantly with another QT-prolonging drugs. Because it is usually helpful in SSc patients, a reasonable approach is to monitor the QT with electrocardiogram when the dose is increased.

Strictures are most often treated with dilatation via endoscopic balloon dilatators or bougies. Barrett esophagus can be treated by radiofrequency ablation, endoscopic thermal therapy, photodynamic therapy, cryotherapy, or endoscopic mucosal resection.[23]

STOMACH

Gastric dysfunction has been reported in up to 50% of patients, and manifestations include early satiety, bloating, nausea, and abdominal discomfort. However, it is not rare to have normal gastric function with severe esophageal and small bowel dysmotility. Patients with gastroparesis symptoms must be referred to a gastroenterologist to rule out gastric outlet obstruction. Gastric dysfunction also increases severity of GER.[1] Normally, liquids distribute throughout the stomach and empty after a pressure gradient from the proximal stomach to the duodenum. Solids, in contrast, are pushed toward the antrum by smooth muscle contraction. Reduced frequency of the slow waves by the gastric pacemaker (bradygastria), which initiates contraction to crush food against a closed pylorus, combined with decreased muscle activity and increased compliance in the fundus, can result in significant dysfunction.[24] Assessment of delayed emptying is done with gastric emptying studies in nuclear medicine, but a motility capsule can also be used as well as gastric emptying breath test, antroduodenal manometry, and electrogastrography.[13]

Treatment to increase gastric motility includes prokinetic drugs such as metoclopramide, domperidone, erythromycin, and cisapride.[13,24,25] Metoclopramide, a central and peripheral dopamine receptor antagonist, has been found to augment antral, duodenal, and jejuna motor activity.[24] A dose of 10 to 15 mg 4 times a day is the maximum dose. However, concern about long-term use and extrapyramidal side effects limits its use. A long-term dose of 10 mg hs (every night at bed time) is reasonable if symptoms persist despite domperidone and erythromycin. Domperidone, (10–20 mg daily, up to 4 times a day) does not cross the brain barrier and is therefore safer. Erythromycin at low dose (100–150 mg daily, up to 4 times a day) imitates the effect of motilin on the gastrointestinal motility and acts directly on smooth muscle. One must be careful about the combination of domperidone and erythromycin, as both increase QT. Mosapride, a selective 5-HT_4 agonist, has been found to accelerate gastric emptying but was not studied in SSc.[15]

Iron deficiency or, less commonly, severe bleeding, can occur secondary to gastric vascular ectasia (GAVE), know as *watermelon stomach*.[1] In one study, the prevalence was 5.6%, and it was more prevalent in early diffuse cutaneous SSc and late-onset limited SSc.[26] A second in early severe diffuse SSc found a prevalence of 22.3%.[27] Anemia is present in most patients affected by GAVE. Histologic studies show mucosal capillary dilatations containing fibrin thrombi, fibromuscular hyperplasia, and reactive foveal epithelial changes.[28] GAVE has also been recently linked to the presence of anti-RNA pol III antibodies and renal crisis and the absence of antitopoisomerase I antibodies.[27,29] Patients with chronic gastrointestinal bleeding can be treated with laser or argon plasma coagulation.

EGD can evaluate isolated telangiectasis or GAVE and gastric ulcer. Capsule endoscopy can also be used.

SMALL BOWEL

Patients with small bowel involvement have alterations of peristalsis, which can lead to stasis of the intestinal contents with small intestine bacterial overgrowth (SIBO). This can lead to bloating, abdominal discomfort, steatorrhea, and diarrhea. More severe

cases can present with pseudo-obstruction, pneumatosis intestinalis, malabsorption, weight loss, and ultimately malnutrition, although some patients remain asymptomatic.

Small Intestine Bacterial Overgrowth

SIBO is common in SSc, affecting 33% to 43% of the patients.[30] Microorganisms increase in number or there is a change in the balance of the flora, which leads to competition for essential nutrients (such as vitamin B12), deconjugation of bile acids leading to fat malabsorption, reduced food intake, and diarrhea. Malabsorption has been found in 10% to 25% of patients and is a poor prognostic factor, with a 50% mortality rate at 8.5 years.[31,32] Although SIBO is the main cause of malabsorption, other causes include exchange disturbances, dysfunction of adsorptive epithelial cells, lymphatic drainage disturbance, and reduced intestinal permeability secondary to fibrosis of the mucosa and submucosa. Finally, chronic intestinal ischemia, pancreatic dysfunction, and primary biliary cirrhosis are other causes of malabsorption.[30]

Method of diagnosis of SIBO includes jejunal culture, breath tests, and Schilling tests. None of these methods has been validated, but the hydrogen breath test (often glucose or lactulose) is the most widely used and is noninvasive. However, this method is not available in all centers. Therefore, irrespective of the result of the breath test, a trial of antibiotic can be prescribed in a patient with high suspicion of SIBO. If the patient responds to the treatment, SIBO is likely.

Treatment of SIBO includes antibiotics that are usually prescribed initially for 10 or 21 days and then a 10- to 14-day course can be repeated if diarrhea recurs.[25] Patients who quickly relapse could need a 10-day course of antibiotic every month. Moreover, some patients who relapse whenever the antibiotics are discontinued need continuous treatment, with alternating antibiotics every 2 weeks. The choices of antibiotics are listed in **Table 3**.[25] For the treatment of diarrhea, opioid analogues such as loperamide can also be used but with caution to prevent pseudo-obstruction. In cases of fat malabsorption caused by SIBO, cholestyramine or other bile salt sequestrant may be helpful.

A few small studies have found very good results in patients with SIBO (not SSc patients) treated with probiotics.[33,34] One study in SSc patients complaining of bloating and distension showed significant improvement in bloating or distension after 2 months of daily probiotic use.[35] Probiotics exert various beneficial effects including strengthening the barrier function of the gut, inhibiting several pathogens, modifying

Table 3
Oral antibiotics for small intestinal bacterial overgrowth

Agent	Dose
Tetracycline	250 mg qid
Doxycycline	100 mg bid
Minocycline	100 mg bid
Amoxicillin-clavulanic acid	875 mg bid
Cephalexin+ Metronidazole	250 mg qid 250 mg tid
Ciprofloxacin	500 mg bid
Norfloxacin	400 mg bid
Chloramphenicol	250 mg qid

the inflammatory response of the bowel, reducing visceral hypersensitivity, and having immunomodulatory activities.[36,37] Moreover, they are generally regarded as safe. Align (bifidobacterium infantis; Procter and Gambles, USA), Culturelle (lactobacillus; i-Health Inc, USA), or yogurt with probiotics can be used. There is no consensus regarding how and when to use probiotics, but daily use without antibiotics[35] or use after an antibiotic course has been suggested.[25,34]

Pseudo-Obstruction

In severe cases, small bowel motility disturbance can manifest by obstipation, which can progress to pseudo-obstruction.[1] Pseudo-obstruction is characterized by signs and symptoms of intestinal obstruction in the absence of an occluding lesion of the intestinal lumen (**Fig. 1**). An abdominal CT scan should be performed to exclude a mechanical cause. Pseudo-obstruction can be of various degrees of severity, may be either acute or chronic, and may be present in up to 40% of patients.[31] Scintigraphy, MRI and dynamic MRI are other tests that can be used to diagnose pseudo-obstruction.

Treatment of pseudo-obstruction includes promotility agents and, in severe cases, small bowel rest with nasogastric tube. Promotility agents include domperidone, metoclopramide, and erythromycin. In refractory cases, treatment with octreotide, 50 to 100 μg subcutaneously at bedtime is prescribed with good results.[38–40] Long-acting–release octreotide, 20 mg intramuscularly every month may be needed if relapse occurs and may limit the short relapses.[41] It is safer to start with a monthly intramuscular dose equivalent to the total daily dose per month and then increase slowly. Addition of erythromycin to octreotide could also be beneficial.[42] Octreotide has some disadvantages, including inhibitory effects on gastric emptying, pancreatic secretions, gallbladder contractions, and increased incidence of cholelithiasis. Surgical intervention in pseudo-obstruction is often complicated by prolonged ileus and is, therefore, discouraged.

Pneumatosis Cystoid Intestinalis

Pneumatosis cystoid intestinalis is a rare condition and a poor prognostic sign. It is characterized by air cysts in the mucosa and submucosa of the small bowel wall,

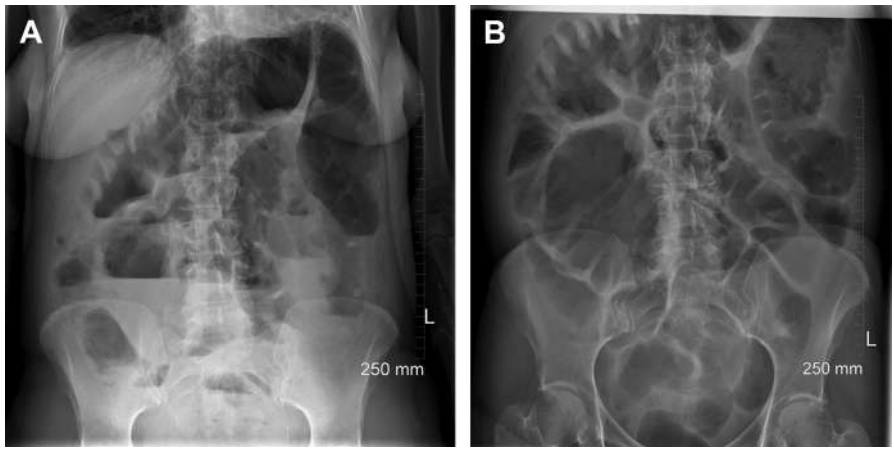

Fig. 1. Pseudo-obstruction. (*A*) There are multiple air fluid levels and dilatation of bowel in keeping with pseudo-obstruction. (*B*) Important dilatation of the colon secondary to pseudo-obstruction in scleroderma.

probably secondary to increased luminal pressure in the context of excessive gas production. It can be seen on plain radiography, but CT of the abdomen is a more sensitive test (Fig. 2). Pneumatosis cystoid intestinalis can present with nausea, abdominal pain, weight loss, vomiting, or diarrhea although often is asymptomatic. A picture of spontaneous benign pneumoperitoneum occurs if cysts rupture. The condition is usually sterile and is not an intra-abdominal catastrophe in which surgery is indicated. The lack of leukocytosis, fever, or rebound tenderness favors the benign etiology. Conservative treatment is mandatory, with antibiotics, nasal oxygen or elementary diet, or total parenteral nutrition.

Vascular Ectasias in the Small Intestine

Vascular ectasias in the small intestine may be the source of bleeding and can be diagnosed with capsule endoscopy or enteroscopy.[13]

Malabsorption

Malabsorption is unfortunately a common manifestation of gastrointestinal involvement and has to be recognized to prevent further deterioration with malnutrition. Malabsorption affects 10% to 25% of patients and is a poor prognostic factor, with a 50% mortality rate at 8.5 years. Patients present with diarrhea and weight loss, and it can be confirmed with the following tests: serum methylmalonic acid, zinc, 25-OH vitamin D levels, vitamin K level, or prothombin time and hydrogen breath test, as malabsorption is mainly caused by SIBO. Malabsorption can ultimately lead to malnutrition.

Malnutrition

The risk of malnutrition is high in SSc, with more than 28% of patients at medium or high risk of malnutrition in a Canadian study.[43] Experts agree that all patients with SSc should be screened for malnutrition.[25] Weight loss is the most sensitive indicator of malnutrition and should be performed at regular intervals. Experts agree that a weight loss of 1% to 2% in the previous week, greater than 5% in the previous month, greater than 7.5% in the previous 3 months, or greater than 10% in the previous year is a significant weight loss. A body mass index less than 18.5 kg/m^2 is also suggestive of protein-energy malnutrition.[25]

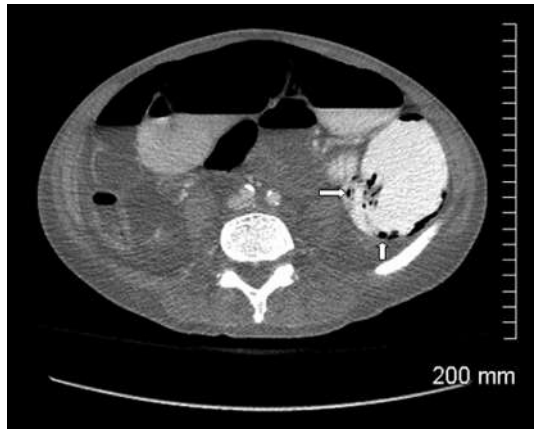

Fig. 2. Air in the wall of the intestine (*arrows*) in keeping with pneumatosis intestinalis.

Malnutrition is usually attributed to SIBO[44] or to dysmotility disorder of the GI tract leading to early satiety, nausea, and vomiting. However, malnutrition was also associated with the physician assessment of global disease severity, suggesting that malnutrition could also be secondary to causes other than GI tract involvement.[43]

An easy screening tool such as the Malnutrition Universal Screening Tool may be helpful. This tool was developed by the British Association for Parenteral and Enteral Nutrition and combines body mass index and weight measures.[25,30]

Tests should be obtained to confirm malnutrition. These tests include those performed to rule out malabsorption (previous discussion) and prealbumin (transthyretin). Albumin is not a sensitive or specific marker of protein energy malnutrition but more a negative acute phase reactant.[30]

Patients with a positive malnutrition screening result must be seen by a team including a rheumatologist, gastroenterologist, and nutritionist. A referral to a mental health worker may also be necessary if symptoms of depression are present. Referral to a speech pathologist to assess swallowing and protection of the airway should be considered as well as a consultation with a dentist.[25]

Specific treatment for all possible causes should be initiated. These include treatment of dysmotility of the esophagus, stomach, and small bowel and SIBO. In refractory cases, enteral nutrition via a jejunostomy (preferable to a gastrostomy) or parenteral nutrition must be started. Because of increased risk of infections with parenteral nutrition and vascular thrombosis and liver failure, enteral nutrition should first be tried.[25] However, some patients with severe gastric and small bowel dysmotility will not tolerate enteral nutrition.

Unusual Specific Radiologic Findings

CT scan may also show abnormalities that are specific for SSc, such as “hide-bound” small bowel, characterized by diffuse dilatation of the small bowel with closely packed valvulae conniventes, affecting more frequently the duodenum and jejunum.[45]

COLON

Colonic involvement can affect 20% to 50% of the patients.[15] Reduced colonic motility and prolonged transit cause constipation. Rectorrhagia can occur secondary to telangiectasias in the colon or rectum (watermelon rectum) causing iron deficiency anemia. Other potential complications of colonic involvement include ulcerations, perforations, stricture, volvulus, and infarct.[30] Pseudodiverticula are common, with secondary rectal prolapse.[30] Although surgery is avoided as much as possible because of fear of prolonged ileus postoperation, occasionally it is mandatory, with successful results. Colonic involvement can be evaluated with sigmoidoscopy and colonoscopy, manometry, sitz markers (opaque markers that when swallowed can be used to measure transit time in the large intestine), and radiologic imaging, such as plain radiography and CT scan.[13,14]

Treatment of constipation includes a diet rich in fiber, stool softener, and polyethylene Glycol (Lax-A-Day, Pendopharm, Canada). Osmotic laxatives can aggravate bloating and discomfort. Treatment of concomitant SIBO with antibiotics and use of probiotics can be useful. Prucalopride, a selective high-affinity 5-HT_4 receptor agonist, is safe and useful in patients with opiod-induced constipation.[46] Preclinical studies show that prucalopride induces giant migrating contractions, stimulates proximal colonic motility, enhances gastro-pyloro-duodenal motility, and accelerates delayed gastric emptying.[46] It was also studied in patients with chronic intestinal pseudo-obstruction with good results, improving pain, nausea, vomiting, and bloating.[47]

However, only case reports are published in SSc.[48] It is a promising drug in SSc. Studies are needed before drawing recommendations. Sacral nerve stimulation in constipation is useful in chronic idiopathic constipation, but there is no study in SSc, and it is expensive.[15]

Investigations to assess colon involvement include colonoscopy, radiologic imaging, manometry, barium enema, and scintigraphy.[13]

ANORECTAL INVOLVEMENT

The anorectal involvement affects 50% to 70% of the patients. More than 20% of patients will suffer from fecal incontinence.[49] Patients can also suffer from rectal prolapse. Tenesmus and pain during defecation can also occur in SSc patients. SSc patients, regardless of their symptoms of fecal incontinence, have thin and atrophic sphincters.[49] Patients with fecal incontinence, however, had a higher anal sensory threshold compared with asymptomatic patients, suggesting a neuropathic cause to fecal incontinence.[50] Diagnostic tests include manometry, defecography, and endoscopy. Treatment of fecal incontinence starts with optimization of the constipation treatment, sphincter muscle training, and, in more severe cases, sacral nerve stimulation.[1,13,51]

Tests performed to assess anorectal involvement include anorectal manometry, sigmoidoscopy and colonoscopy, defecography, endosonography, and surface electromyography.[13]

LIVER

The most frequent associated disease is primary biliary cirrhosis (PBC).[13] PBC is associated with antimitochondrial antibodies (AMAs) in 80% to 96.5% of the cases and is also associated with CENP-B antibodies.[52] PBC occurs in 2% to 18% of SSc patients.[52] Diagnosis is suspected in patients with an elevation of alkaline phosphatase, increased immunoglobulin M levels, and positive AMAs. At least half of the patients are asymptomatic at diagnosis. The utilization of AMA (MIT3) and sp100 antibodies as a combined marker of PBC improved detection of PBC in patients with SSc.[52] Patients with suspected PBC should be referred to the gastroenterologist or hepatologist, as it is a treatable disease. It seems that PBC associated with SSc has a slower progression, with increased time to death by liver disease or time to liver transplant compared with PBC-alone patients.[53]

Subclinical elevation of transaminases can be present in the context of anti-inflammatory or analgesic use or other immunosuppressive therapy potentially affecting the liver.

PANCREAS

Although rare, pancreatic involvement in SSc has been reported and should be suspected in patients with steatorrhea not improving on antibiotics. Fat malabsorption can be investigated with a qualitative test of the stool and then confirmed by a 72-hour fecal fat collection. Treatment with specific enzymes might be needed.[13]

GASTROINTESTINAL INVOLVEMENT, DEPRESSION, AND QUALITY OF LIFE

Between 36% and 65% of patients with SSc have clinically significant symptoms of depression.[54] The number of gastrointestinal symptoms was significantly associated with depression, after controlling for sociodemographic factors and global estimates of SSc severity and duration.[55] Another study found that depression was highly and independently associated with worse functioning of the upper gastrointestinal tract.[56]

Depressed patients had worse GI scale scores and reflux and constipation scales were independently associated with worse depression score.[57]

Patients with SSc GI involvement also suffer from reduced quality of life.[58,59] A recent study from a population-based cohort of patients with SSc found that patients with lower bowel symptoms had reduced quality of life compared with the general population. Moreover, GI complaints and especially abdominal pain and bloating affects patients' social lives.[58]

IMMUNOSUPPRESSIVE THERAPY FOR GASTROINTESTINAL INVOLVEMENT

There is no evidence suggesting that immunosuppressive therapy prevents GI disease in SSc. Our own data from a longitudinal cohort study of early SSc subjects (<3 years of disease since onset of first non-Raynaud's symptom) without severe GI disease found that exposure to immunosuppressive therapy (for other disease manifestations) did not protect against the onset of severe GI disease (Canadian Scleroderma Research Group data, unpublished, 2013). Unfortunately, data from trials of immunosuppression for SSc rarely report GI outcomes and, therefore, provide little insight on this question. Well-powered prospective studies are needed to determine the effect of immunosuppressive treatment on the onset of GI tract disease, especially in early SSc.

ALTERNATIVE AND FUTURE TREATMENTS

Although studies on complementary and alternative treatments are small and scarce, modalities such as acupressure and transcutaneous electroacupuncture may improve GI functioning or symptoms in SSc patients.[60] Recent publications highlight the nonnutritional effects of food that could have a therapeutic role in chronic gastrointestinal diseases.[61] Studies on a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) in patients suffering from irritable bowel syndrome (IBS) suggest a potential role of this diet in patients with this condition.[62] Given a potential role of SIBO in the pathophysiology of IBS and that ingestion of FODMAPs increases the delivery of readily fermentable substrates and water to the distal small intestine and colon resulting in luminal distension and gas,[62] there might be a role for this diet in SSc. Studies in SSc, however, are needed.

SUMMARY

Gastrointestinal involvement is common and appears early in SSc, and the esophagus is the first internal organ affected in most patients. We cannot rely on patients' symptoms for early diagnosis, as 50% of them are asymptomatic. Therefore, treatment of all SSc patients with a PPI to prevent GI and lung complications might be considered. Physicians must also appropriately question their patients regarding possible GI involvement and start therapy early, before irreversible damage occurs. A multidisciplinary approach with a gastroenterologist, nutritionist, and often a speech therapist is mandatory in all patients with severe GI involvement. Finally, patients with GI disease often suffer from depression and have a reduced quality of life; therefore, referral to a psychiatrist or psychologist should be considered.

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