RESEARCH ARTICLE

Clinical Approach to Gastrointestinal Involvement in Patients with Systemic Sclerosis

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Abstract

Systemic sclerosis (SSc) is an autoimmune connective tissue disease that negatively impacts the function of the skin and internal organs. The gastrointestinal (GI) tract is the most commonly affected internal organ in SSc, though GI complications may also arise indirectly when infections occur in the setting of immunosuppression or concurrent disease processes arise for which patients with SSc are found to be at higher risk. In this review, we provide a systematic approach for the clinical assessment of GI complications in SSc from the oropharynx to the anorectum to guide both general internists and rheumatologists caring for this complex patient population. It is organized so that each component of the luminal GI tract has its own specified section, beginning with a review of a clinical approach to diagnosis, followed by a more detailed discussion of the literature surrounding approaches for an objective GI evaluation. A focused discussion early in the manuscript addressing what is known about pathogenesis, and later about in the manuscript about the assessment for GI bleeding are also included.

Key indexing terms: systemic sclerosis, scleroderma, clinical, gastrointestinal

1.0 INTRODUCTION

The evaluation of gastrointestinal (GI) complaints in patients with systemic sclerosis (SSc) can be a daunting task for both the general internist and the rheumatologist. A targeted and thorough assessment is essential, as the majority of complaints are often non-specific and can have a wide variety of potential therapies, depending on their etiology. Upwards of 90% of patients with SSc report some form of GI symptoms, with a significant subgroup of this population endorsing a noticeable reduced quality of life (65% of patients in this group meeting clinical criteria for depression).[1] Additionally, GI manifestations of SSc are associated with significant morbidity and mortality, cited as the third leading cause of death following pulmonary arterial hypertension and interstitial lung disease.[2] These factors reveal the importance of a thorough clinical evaluation and strategic approach to diagnostic testing to minimize the risk of poor outcomes in this patient population. The goal of this review is to provide a succinct, anatomically-focused, systematic approach to the clinical assessment and evaluation of common GI symptoms in patients with SSc for clinicians. The scope will remain mostly on the luminal issues of the GI tract, with an additional focused discussion for GI bleeds. Manifestations within the hepatobiliary system are not in the scope of this review. The management options for these manifestations are also not in the scope of this review: reference materials for this may include the 2017 EULAR updated recommendation guidelines,[3] as well as excellent reviews by Shreiner et al.[4] and Gyger and Baron.[5]

1.1 Brief overview of pathogenesis

The proposed general mechanism of SSc involves structural and functional endothelial cell abnormalities, ultimately leading to the release of reactive species (cytokines, chemokines, and growth factors) and the recruitment of fibrocytes. These factors result in fibroproliferative vasculopathy and progressive tissue fibrosis.[6] However, the response of the GI tissue to the SSc disease milieu appears to be somewhat distinct from that of other organ systems, as smooth muscle atrophy, rather than fibrosis, is often the most prominent feature.[7] Numerous mechanistic processes for the development of GI dysfunction in SSc have been proposed, including a progressive vasculopathy, diffuse fibrosis, dysbiosis, and an autoantibody-driven neuropathic process.[8,9] More recently many investigators have invoked a neuropathy as the initial pathologic event in SSc. For example, comparative studies of the lower esophageal sphincter in patients with SSc against control groups exhibited an abnormal muscular response to cholinergic neural stimulation, whereas direct muscle stimulation through gastrin and methacholine demonstrated a normal response.[10-12] Preservation of muscle function was also suggested by the reversal of esophageal motility in select patients with SSc when challenged with intraarterial reserpine.[13] This hypothesis is further supported by the discovery of functional autoantibodies in these patients that interfere with cholinergic-mediated contraction via the M3R receptor, causing inhibition myopathy at the level of the smooth muscle within the GI tract. The extent and intensity of this binding appears to be associated with the duration of disease.[6] In a cohort of patients with SSc and GI symptoms, ultrastructural studies of rectal biopsies revealed axonal and smooth muscle cell degeneration. Biopsies throughout the GI tract demonstrated patchy atrophy with progression to diffuse muscularis propria atrophy.[11,14,15] Histologic examinations of autopsy specimens from esophageal tissue of patients with SSc have demonstrated a non-vascular distribution of muscular atrophy with an absence of inflammatory infiltrates, significant fibrosis, or ischemic necrosis.[7] Therefore this “neurogenic hypothesis” suggests that a reduced neural

stimulation of smooth muscle via autoantibodies ultimately leads to neural and muscle atrophy with varying degrees of fibrosis.[11] These processes are thought to frame the pathophysiology behind many GI complaints.

2.0 THE ORAL CAVITY

2.1 Clinical approach to screening for oral complications in SSc

Symptoms involving the oral cavity are a result of both primary GI-SSc disease as well as secondary complications of cutaneous manifestations. Common presenting complaints include microstomia, xerostomia, periodontal disease, and fibrosis of the base of the tongue manifesting as tongue stiffness.[2,16] Microstomia is a common, often disfiguring, and functionally impactful complication of SSc. Patients may report peri-oral vertical creasing, as well as difficulty with fully opening the mouth when attempting daily dental hygiene or when biting a large sandwich. Such limitations may ultimately lead to poor nutrition and perioral care.[2,14] Acquired microcheilia is reported is 50-80% of patients, and is reported to occur in the context of perioral cutaneous thickening.[2,17]

Xerostomia, or dry mouth, has been reported in 30-70% of patients with SSc.[14,17,18] The majority of patients with SSc, however, do not meet criteria for Sjogren's Syndrome (SS): one study[19] of 133 patients with SSc found that 68% could be diagnosed with Sicca syndrome based on clinical symptoms and/or a Schirmer I test, yet only 20% fit diagnostic criteria for SS as defined by the American-European Consensus Group criteria. Interestingly this study did find an association between SS and the limited cutaneous subtype of SSc, with 18 of the 19 patients diagnosed with SS falling under this SSc subtype. Xerostomia may lead to lingual and buccal mucosal crenations, and an increased incidence of periodontal disease.[18,20] This has been attributed to a reduction in salivary volume and enzymes which are essential in controlling oral bacterial populations.[21,22] A case-control study[23] of 109 patients (54 with SSc, 55 control) in Italy found that patients with SSc had a significant 2.95 increased risk (95% CI 1.26-6.84) for periodontal disease as defined by clinical attachment loss. Another case-control study[24] of 394 patients (163 with SSc, 231 control) in Canada found a significant increase in the number of decayed teeth as well as periodontal disease defined by clinical attachment loss. However it should be noted there is conflicting data on the correlation between SSc and decayed teeth, as other studies have not found significant differences when comparing SSc patients to controls.[18,25]

2.2 Objective evaluation

The examiner should take care to assess for facial changes such as a decreased oral aperture, thinning and retraction of the lips (leading to a puckered or grimaced appearance), vertical wrinkling around the mouth, and a thickened sublingular frenulum.[2,14] Diagnosis of microstomia is primarily a clinical diagnosis, with a review of systems positive for decreased mouth opening or limited range of motion of the mandible. Panoramic dental imaging can be utilized to confirm this diagnosis, however this is unlikely to impact management from the standpoint of a generalist or rheumatologist.[17] Physical limitations related to microstomia and microcheilia may preclude an effective routine examination, and therefore a referral for a focused dental exam may be warranted.[26] The value of mouth stretching exercises for microstomia is still a subject of debate, as studies to date are limited by a number of factors including poor adherence to oral exercise regimens, parallel systemic therapy changes, and small study group sizes.[27,28] The general consensus is that any benefit that may exist is quickly lost with non-adherence.[28]

Patients should be counseled with the knowledge that the true benefit is still ill-defined, yet it remains an intervention with minimal potential harm.

While a formal evaluation for SS (i.e. serologies, salivary gland functional testing, and biopsies) could be completed if there is concern for SSc-SS overlap, the history is likely to be sufficient for a diagnosis of xerostomia and more invasive studies are unlikely to change symptomatic management. One study[29] compared the salivary gland biopsies of 202 patients with primary SS disease and 27 patients with SSc-SS overlap and noted that these processes appeared histologically identical. In addition, the presence of anti-Ro/SSA and anti-La/SSB dual antibody positivity (prevalence: 35% in primary SS vs 18.5% in SSc-SS overlap) was not associated with Sicca severity as measured by complications, adverse prognosis factors, and activity markers (levels of erythrocyte sedimentation rate, C-reactive protein, beta-2 glycoprotein, C4 serum complement, gammaglobulin, and cryoglobulin). Interestingly, the study did find that patients with SSc-SS overlap were less likely to have severe pulmonary fibrosis and peripheral neuropathy than patients with SSc alone.[29] A dentist who has experience in the management of patients with SSc is an essential partner to optimize patient care.[26] Additionally, identifying and limiting the use of medications which may further aggravate these problems is another important consideration for clinicians.

3.0 THE PHARYNX

3.1 Clinical approach to screening for pharyngeal complications in SSc

Pharyngeal involvement in SSc often presents as hoarseness, cough, and/or micro-aspirations. Pharyngeal complications in SSc are most frequently caused by uncontrolled gastroesophageal reflux disease (GERD) which is discussed below, or an overlapping inflammatory myositis leading to weakness of the pharyngeal muscles. Notably 42.6% of overlap myositis syndromes are associated with SSc (the most commonly associated connective tissue disease), and thus myositis is an important and relevant diagnosis to remain on any clinician's differential.[30]

3.2 Objective evaluation

A history evaluating for symptoms of uncontrolled GERD, proximal muscle weakness, and other systemic manifestations of myositis should be performed to screen for pharyngeal involvement. Unfortunately little data exists on the workup of pharyngeal myositis specifically in the setting of SSc, and thus this topic warrants further investigation. However, for the general population any patient that describes new symptoms concerning for pharyngeal myopathy should also be screened for symptoms of respiratory muscle involvement. Some causes of proximal myopathy (particularly involving the pharyngeal or respiratory musculature) such as myasthenia gravis may overlap with SSc and should be quickly eliminated from the differential.[31] One case report literature review[32] identified 14 patients with observed myasthenia gravis-SSc overlap. Laboratory values that may be useful as screening for an inflammatory myositis include serum creatine kinase (CK), aldolase, and antibodies associated with myasthenia gravis such as anti-acetylcholine receptor antibodies.[32,33] Swallow videofluoroscopy (modified barium swallow study) may also be useful in determining whether pharyngeal muscle involvement is contributing to dysphagia given the significant overlap of symptoms.[34] Clinical suspicion for this diagnosis must remain high as it may guide the addition of certain therapeutics and provide opportunities to minimize aspiration risks.

4.0 THE ESOPHAGUS AND STOMACH

4.1 Clinical approach to screening for gastroesophageal complications in SSc

It is estimated that approximately 90% of patients with SSc have some form of esophageal involvement, whether it be symptomatic or subclinical, making the esophagus the most commonly involved region of the GI tract.[2,11] Symptoms typically arise from GERD or esophageal dysmotility (which can be seen at any level: the pharynx, upper esophageal sphincter, lower two thirds of the esophagus, or lower esophageal sphincter).[14,17] The most common presenting complaint is that of heartburn, though additional complaints may include dysphagia, odynophagia, regurgitation, chronic cough, and hoarseness.[17] Early diagnosis and treatment of esophageal involvement is important as chronic regurgitation and micro-aspiration are associated with the presence of interstitial lung disease, which is a leading cause of mortality in SSc.[35,36] Chronic untreated/undertreated GERD or dysmotility may also contribute to other complications, including esophagitis, ulcers, strictures, intestinal metaplasia, or esophageal adenocarcinoma.[2,17] Many of these complications can present with reflux or dysphagia as well, therefore it is imperative for the clinician to maintain a wide differential when evaluating these patients. An additional diagnosis that presents similarly is eosinophilic esophagitis (EoE), with recent data supporting a connection between EoE and connective tissue diseases.[37] A Utah population analysis in 2016 reported 11 patients with SSc-EoE overlap, and when matched with controls for age and gender, a 6-fold increased risk for SSc in patients diagnosed with EoE was identified.[38]

Approximately half of patients with SSc will present with symptoms suggestive of co-existing gastric involvement and report symptoms such as postprandial fullness, early satiety, bloating, nausea/vomiting, or epigastric pain.[39] This has been attributed to delayed gastric emptying and/or abnormalities in gastric accommodation.[40-42] In addition, as with the esophagus, it is suspected that there is a substantial subgroup of patients who have subclinical gastric disease. Studies have found that 80-90% of patients with SSc studied showed signs of gastric slow wave disturbances, although the clinical significance of this data is uncertain.[40,43] Impaired gastric motility can also present more insidiously with weight loss secondary to decreased nutritional intake from early satiety, and thus should remain on a clinician's differential when evaluated for malnutrition (discussed in more detail below).[41]

Gastric *Helicobacter pylori* infection is also an important consideration in patients with SSc. Presenting complaints include abdominal pain and dyspepsia, however some infections may present more insidiously with iron or vitamin B12 deficiency.[44-46] A meta-analysis of articles studying the relationship between this bacterium and SSc[47] found an increased incidence of *H. pylori* exposure in patients with SSc by ELISA testing (although notably an insignificant increase in cases detected by urea breath testing, which would indicate an active infection). Preliminary data comparing SSc patients with active *H. pylori* infection (diagnosed by urea breath testing and histology) to those SSc patients with negative testing demonstrated increased modified Rodnan skin scoring in the infected group.[48] This data has been extrapolated to suggest eradication therapy may be beneficial in mitigating disease activity, however more research in this area is needed to support this hypothesis.[49]

4.2 Objective evaluation

Given the significant symptom overlap with many of these manifestations, it is important to think broadly when planning the work-up. In patients with solitary reflux symptoms without

dysphagia, empiric acid suppression therapy is a reasonable first step of management in clinics not equipped with direct endoscopy, as outlined by the Evidence-based Clinical Practice Guidelines for GERD 2015.[50] In patients with dysphagia, or heartburn that is recurrent or unresponsive to high doses of proton pump inhibitors (PPIs) and/or H2 receptor blockers, the guidelines recommend esophagogastroduodenoscopy (EGD) as an important diagnostic and potentially therapeutic intervention (e.g. screening for erosive esophagitis and Barrett's esophagus, ruling out EoE, management of esophageal strictures).[37,50,51] One retrospective analysis of 13 SSc patients naïve to acid suppressant medications[52] found that low grade esophagitis had a prevalence of 77%. Another study evaluated 133 SSc patients on long-term PPI therapy[53] (median treatment of 6 years, total range 1-38 years) and demonstrated a lower prevalence of esophagitis at 32.3% compared to the previously mentioned acid suppressant-naïve study. In both studies a variety of complications aside from esophagitis were identified, including dysmotility, gastritis, *H. pylori* infection, esophageal candidiasis, and hyperplastic gastric polyps. The noted lower prevalence of visible esophagitis following PPI/H2 blocker therapy and the presence of these other abnormalities further reinforces the importance of acid suppression therapy.[51-53] In the setting of a confirmed case of Barrett's esophagus, routine follow up screening with EGD is typically recommended: every 3-5 years in Barrett's without dysplasia, every 6-12 months for low-grade dysplasia, and every 3 months for high-grade dysplasia (based on 2008 *American Journal of Gastroenterology* guidelines).[54] pH monitoring has been shown to be a useful subsequent study to diagnose non-erosive reflux disease in cases with normal mucosal findings on EGD.[36,55] A retrospective study of 10 SSc patients with reflux referred for lung transplant[56] found that abnormal pH was predictive for lower 1-year survival rates.

Numerous expert consensus guidelines have identified high-resolution esophageal manometry (HREM) as the appropriate test to screen for aperistalsis, decreased amplitude of smooth muscle contractions within the esophageal body, or dysfunction within the lower esophageal sphincter.[2,51,57-61] This is typically conducted following the exclusion of mechanical obstruction or mucosal disease via EGD, and can be done in conjunction with pH monitoring.[62,63] HREM can also be utilized in combination with esophageal pressure topography (a space-time pressure plot) and a functional luminal imaging probe (measuring distensibility of the esophageal body) to isolate a dysfunctional component of the esophagus that is contributing to symptoms for diagnostic purposes.[35,51,64] The accurate diagnosis of esophageal dysmotility may also have systemic implications, as one study of 79 SSc patients noted that abnormal contractility diagnosed by HREM was associated with increased severity of skin and lung disease.[65] While multiple small studies have confirmed the utility of HREM for esophageal dysmotility diagnosis in the SSc patient population, additional research is needed to understand its implications.[66-70]

As discussed above, in patients who report symptoms suggestive of gastric involvement, such as early satiety, postprandial fullness, bloating, or nausea/vomiting that is unresponsive to medical management, further evaluation of gastric function should be pursued in conjunction with an esophageal workup. The *American Journal of Gastroenterology* in 2013 published guidelines[71] on the diagnosis and management of gastroparesis provides examples of three separate tests useful in the detection of gastric dysmotility: four-hour gastric emptying scintigraphy, the wireless motility capsule, and

C-octanoate or -spirulina breath testing. However, it should be noted that these same guidelines acknowledge that the latter two tests still require additional validation studies, and therefore scintigraphy still ultimately remains the most reliable test.[71] For this reason, a four-hour technetium-99 sulfur colloid gastric emptying study should be pursued when considering the diagnosis of impaired gastric transit in patients with SSc.[2,72,73] Ideally, this should be a combined solid-liquid study, as the inclusion of liquids increases the overall sensitivity of the test by an estimated 25-36%.[71]

While there is no gold standard test, an assessment for *H. pylori* infection could include urea breath testing, as it has been studied in the SSc patient population and is proven to have high sensitivity and specificity in general (96 and 93%, respectively) while remaining noninvasive.[74,75] While not specifically studied for SSc, stool antigen testing has also been proven to have high sensitivity and specificity for active infection (94 and 97%, respectively) and may also be a useful diagnostic tool given its ease of collection.[75]

5.0 THE SMALL BOWEL

5.1 Clinical approach to screening for small bowel complications in SSc

Many patients with SSc may also present with symptoms of small bowel involvement, including diarrhea, unintentional weight loss, distention, bloating, and malnutrition.[2,17] The prevalence of small bowel dysmotility is estimated to be between 40-88% based on manometry studies. There is also increasing evidence that small bowel involvement precedes symptoms. For example, one landmark study[76] of 17 SSc patients noted that 65% of patients with small bowel involvement by manometry were asymptomatic at the time of the study. A common complication of the small bowel in patients with SSc is small intestinal bacterial overgrowth (SIBO). While this is often attributed to small bowel dysmotility, it may also be a consequence of large bowel dysmotility with a weakened ileocecal valve and/or chronic gastric acid suppression.[77] It is reported that the prevalence of SIBO in symptomatic patients is 30-62.5%, however these figures may be a high estimate due to inconsistencies in outcome measures both in terms of diagnostic modalities and symptom presentation.[2,78] All of these complications may contribute to chronic malnutrition leading to long-term morbidity, such as dependence on total parenteral nutrition for adequate caloric intake.[79] Therefore, the early identification of small bowel dysfunction and correction of malnutrition, SIBO, and/or dysmotility is essential.[80]

5.2 Objective evaluation

Prior to attributing these symptoms to SSc, it is important for clinicians to rule-out other causes of GI symptoms which are prevalent in the general population. Important considerations include infection, inflammatory or infiltrative bowel diseases, overlapping autoimmune bowel complications, and GI malignancies.

Diagnostic modalities for the assessment of small bowel dysmotility are limited. An abdominal x-ray may identify extensive disease, demonstrating the classic "hide-bound" appearance indicative of tightly packed valvulae conniventes in the duodenum and jejunum, with dilated bowel loops.[2,79] Small intestinal manometry has been used to demonstrate the presence of dysmotility in SSc, as evidenced by low-amplitude contractions with either absent or prolonged migrating motor complexes.[81] Unfortunately this procedure has several clinical limitations, as it takes multiple hours to perform and is only able to assess the upper portions of the small

bowel.[2,79] Other types of studies that are increasingly utilized include scintigraphy, wireless motility capsules, and computed tomography/magnetic resonance enterography.[82] Clinicians should note that wireless motility capsules are to be avoided in patients with known, severe gastroparesis or bowel strictures.[79]

The gold standard for diagnosis of SIBO is jejunal culture, where >10^5 organisms/mL constitutes a positive test; however this test is limited in the SSc patient population as it is invasive and not infrequently the cardiopulmonary complications of SSc prohibit routine anesthesia.[78] The only diagnostic tests for SIBO that are specifically validated in this patient population are the hydrogen and methane breath tests after an oral glucose or lactulose bolus. While these tests have been shown to have reasonable specificity ranging from 78-100%, their sensitivities range from 62-93%, which make their use as screening tests sub-optimal.[79] Clinicians can attempt to improve the sensitivity by preferentially ordering lactulose over glucose boluses (82 versus 62.5%, respectively).[78] Ultimately diagnosis and treatment of SIBO may come down to strong clinical suspicion in the setting of a broad negative workup. Although not infrequently used, there is mixed data to support the practice of prescribing empiric antibiotic therapy; one meta-analysis of 10 studies found that while antibiotics were more effective than placebo to induce clinical improvement (as demonstrated by a normalized breath test), analysis of these studies was complicated by overall study heterogeneity and varying antibiotic choices.[83,84] The most recent American Gastroenterological Association practice guidelines for SIBO,[85] based on expert consensus, recommend the identification and correction of underlying causes and nutritional deficiencies with adjunct antibiotic use, taking note of the potential risk-benefit of empiric treatment. These guidelines similarly acknowledge the need for additional randomized control trials to further support specific antibiotic strategies.[85]

Concurrently with this workup, patients should be regularly screened for overall malnutrition, as this is indicative of worsened disease.[79] The Malnutrition Universal Screening Tool (MUST) has been frequently utilized for preliminary screening in the SSc patient population for its ease of use, correlation with other screening tools, and validation in both the inpatient and outpatient setting.[86-88] Positive screening with this tool has been shown to correlate with worsened outcomes.[89] The prevalence of malnutrition in SSc has been variably described due to inconsistencies in the diagnostic criteria utilized, ranging from 5.3-55.6%.[86,90,91] For this reason, the use of the ESPEN (European Society for Clinical Nutrition and Metabolism) criteria for malnutrition diagnosis following a positive screening should be highly considered, as these criteria were developed with a goal to define malnutrition terminology on a global level in line with the World Health Organization's ICD system.[86,92] A suggested initial evaluation for malabsorption or malnutrition in patients with SSc, based on expert consensus, should include hemoglobin, vitamin A, vitamin B12, folate, albumin, iron panel, carotene, and selenium.[93-95]

6.0 THE COLON

6.1 Clinical approach to screening for colonic complications in SSc

The prevalence of colonic manifestations in SSc is hypothesized to be up to 50% of all patients, but data is limited as these findings are often under-reported in the literature.[40,96] The typical presentation of colonic involvement in SSc includes pain, distention, constipation, and tenesmus, with less common manifestations including fecal impaction and

recurrent intestinal pseudoobstruction.[2] Related long-term complications of constipation and colonic dysmotility may include pseudodiverticula, ulcerations, volvulus, and very rarely perforation or infarction.[5]

One additional GI tract complication to consider is pneumatosis cystoides intestinalis (PCI). This can present with abdominal pain, distention, nausea, or vomiting. PCI is a rare diagnosis that is felt to be indicative of end-stage disease when associated with SSc, and is therefore considered a poor prognostic sign.[97] Most literature surrounding this diagnosis exists in the form of case reports with limited population data.[5,98] A generalized review[99] of a population with this diagnosis, not specific to SSc, found that the colon was the most commonly affected at 46% of cases, followed by small bowel (27%) and simultaneous small and large bowel disease (7%). Pneumoperitoneum is a frequent complication, with one case report series review[100] of 37 patients finding an incidence rate of 87%.

6.2 Objective evaluation

As with the upper portions of the GI tract, complications of the large bowel can be evaluated by direct visualization through sigmoidoscopy/colonoscopy and manometry.[5] Abdominal radiographs or computed tomography are beneficial in quickly identifying complications of dysmotility, pseudoobstruction, or fecal impaction such as colonic dilation and perforation. [97,101] Manometry of the large bowel comes with similar complications and limitations as small bowel manometry, including length of procedure time and cardiopulmonary limitations with anesthesia.[78] Sitz markers (radiopaque markers that are used to assess colonic transit times) enable the assessment of colonic transit over several days, though concerns exist regarding pellet retention and risk of bowel perforation in patients with severe delays.[102] One caveat to all available assessments of colonic dysmotility is that while multiple testing modalities exist, these are only able to identify the presence of dysmotility and their data does not consistently correlate with symptom severity.[101,103] Both abdominal imaging and endoscopy also have the potential to visualize PCI and/or pneumoperitoneum, with direct visualization by endoscopy showing beaded, grape-like, or cobblestone abnormalities within the bowel wall.[2,104]

7.0 THE ANORECTUM

7.1 Clinical approach to screening anorectal complications in SSc

Following the esophagus, the anorectum is the second most commonly involved portion of the GI tract in patients with SSc. Up to 50-70% of patients report symptoms of dysfunction, with one survey reporting the most common symptom as fecal incontinence (38%), and a need for regular digital stimulation or evacuation of the rectum in 18% of patients.[40,105] A case-control study[106] found that 71.4% of patients within the SSc group had an impaired recto-anal inhibitory response (RAIR), which correlated with fecal incontinence symptoms. Notably there was no correlation found between various SSc subtypes, the duration of disease, or other GI symptoms. Another study[107] of 44 SSc patients found that patients reporting fecal incontinence symptoms exhibited a lower mean resting pressure of the internal anal sphincter compared to patients who were asymptomatic, suggesting hypotonia is a major contributor to symptoms; however, other studies did not confirm these findings.[106] A differential for abnormal RAIR diagnosed in adulthood should also include Chagas' disease, dermatomyositis, peripheral neuropathy (such as in diabetes), neurovascular insult, and post-surgical complication.[107-110]

7.2 Objective evaluation

History and physical exam is important in the diagnosis of anorectal SSc involvement. A digital rectal exam may be used to identify fecal impaction and evaluate anal sphincter tone, which is essential in differentiating anorectal from colonic involvement.[14] Beyond the physical exam, anorectal manometry has also been utilized to assess the resting tone of the internal and external anal sphincters. An important distinction found on manometry in SSc is that the internal anal sphincter is preferentially affected, and the external sphincter is typically spared.[2,111] This finding has been further supported by endoanal ultrasound, which typically shows a thin or atrophic internal anal sphincter – however this additional imaging beyond manometry is not typically needed for patient care.[2,107]

8.0 GASTROINTESTINAL BLEEDING

GI bleeding is a symptom that is relatively common in the general population, but warrants the consideration of a broader differential diagnosis when seen in the SSc population. As discussed above, many patients with SSc experience chronic GERD which can lead to esophagitis, and ulcers of the esophagus Barrett's esophagus, and progression to esophageal adenocarcinoma, seen in 1.9% of patients.[2,17] The presence of persistent reflux should also warrant consideration of peptic ulcer disease as a source of GI bleeding. In patients with SSc who utilize antibiotics frequently for SIBO or digital ulcers, *H. pylori* infection must be considered as well.[112]

An additional cause of bleeding that is more common in SSc patients relative to the general population is gastric antral vascular ectasia (GAVE). GAVE, also known as "watermelon stomach" given its appearance on endoscopy, is defined as vascular ectasia of the mucosal capillaries of the stomach, with focal thrombosis, spindle cell proliferation, and fibrohyalinosis seen histologically.[2,113] While traditionally considered a rare diagnosis, its true prevalence is up for debate: a large retrospective study[114] had previously defined the incidence of clinically significant gastric antral vascular ectasia as 5.7%, however a more recent study of asymptomatic patients (the SCOT trial)[115] reported a much higher prevalence of 22.3%.[116] An association between GAVE and anti-RNA polymerase-III antibodies is reported in several studies, though not all studies confirmed this association.[115,117]

Patients with SSc are also found to have a greater incidence of telangiectasias and angiodysplasia throughout the GI tract, from the oropharynx and throughout the bowel. As these vascular abnormalities, particularly those in the small bowel, can be difficult to diagnose and treat, they are frequently the culprit of recurrent bleeds.[2,118,119] One capsule endoscopy study of 50 patients with SSc[119] found that patients with GI vascular lesions were more likely to have the limited cutaneous subtype of SSc (73.3% limited cutaneous subtype vs. 26.7% diffuse cutaneous subtype, n=15). A standard GI bleeding workup should be pursued in all symptomatic patients or those with signs of iron deficiency anemia, starting with a bidirectional endoscopy, followed by consideration for capsule study, computed tomography or magnetic resonance enterography, and then push or balloon endoscopy.[116,120,121] Given the complexities of using general anesthesia in SSc, patients should be referred to an experienced center for these latter studies.

9.0 CONCLUSIONS

Clinicians should maintain a wide differential in the evaluation of GI symptoms in patients with SSc (see Figure 1), taking care to rule out diagnoses most prevalent in the general population prior to pursuing a workup more specific to SSc-linked processes. The possibility of multi-level disease throughout

the GI tract must be entertained. As mentioned previously, GI involvement in SSc not only has a significant impact on quality of life, but, when severe, is associated with increased mortality. While the treatments for these specific complications are outside the scope of this review, successful identification of the underlying process of symptoms is imperative to allow for appropriate targeted therapies. As a mechanistic understanding of SSc and its impact on the GI tract is further established and risk stratification improves, this may potentially allow for more targeted assessments in the future.

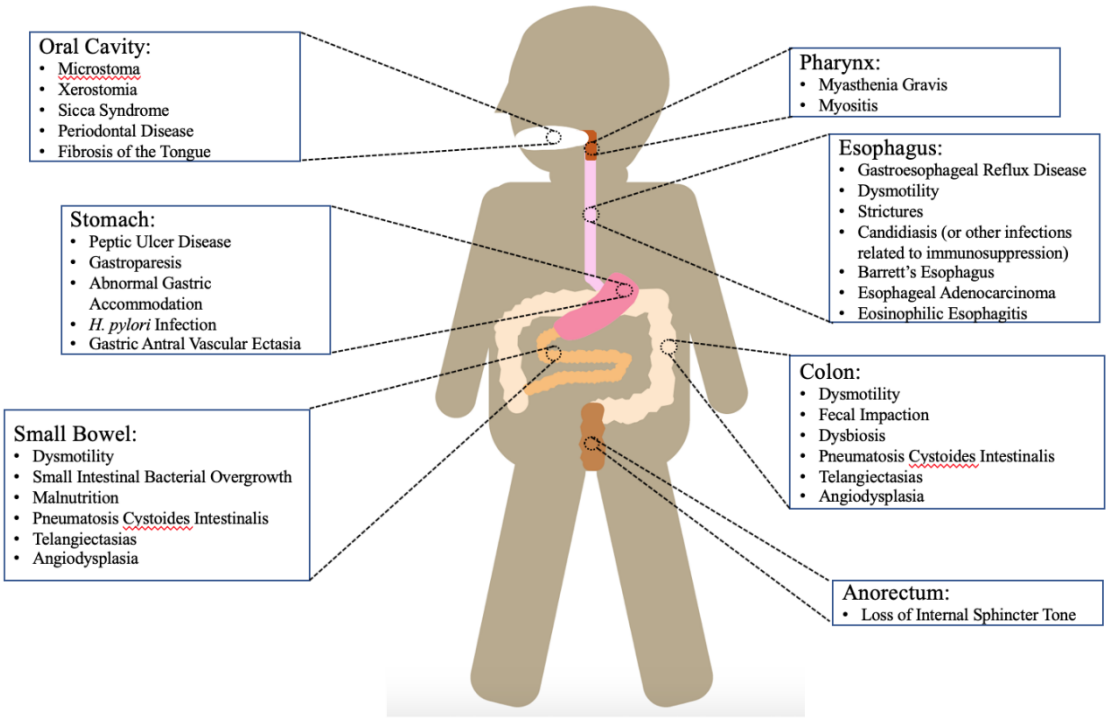

Figure 1. Differential for GI manifestations of SSc

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