Gastrointestinal manifestations of systemic sclerosis (scleroderma)

AUTHORS: Stephanie A Kaye-Barrett, MD, Christopher P Denton, MD
SECTION EDITORS: John S Axford, DSc, MD, FRCP, FRCPCH, Nicholas J Talley, MD, PhD
DEPUTY EDITORS: Philip Seo, MD, MHS, Shilpa Grover, MD, MPH, AGAF

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Apr 15, 2022.**

INTRODUCTION

The systemic manifestations of systemic sclerosis (SSc, scleroderma) are diverse. Most prominent are abnormalities of the circulation (most notably Raynaud phenomenon) and involvement of multiple organ systems, including the musculoskeletal, renal, pulmonary, cardiac, and gastrointestinal (GI) systems, with fibrotic and/or vascular complications. GI symptoms can cause significant morbidity [1,2].

This topic will review the pathogenesis, clinical manifestations, and diagnosis of GI disease in SSc. Management of GI disease in SSc is discussed separately. (See "Treatment of gastrointestinal disease in systemic sclerosis (scleroderma)".)

EPIDEMIOLOGY

Nearly 90 percent of patients with systemic sclerosis (SSc) have some degree of gastrointestinal (GI) involvement, and approximately one-half are symptomatic [3,4]. Involvement of the gut occurs with equal frequency among patients with the diffuse and limited subtypes of SSc (dcSSc and lcSSc, respectively) [5]. It is rare in localized scleroderma syndromes [6]. (See "Clinical manifestations and diagnosis of systemic sclerosis (scleroderma) in adults".)

Although the esophagus is the most frequently affected part of the GI tract, any part of the GI tract may be involved. The presence of malabsorption and esophageal dysfunction among patients with SSc is associated with an unfavorable prognosis because they can exacerbate other manifestations of the disease, notably lung fibrosis due to microaspiration and cardiac manifestations due to poor nutrition and electrolyte abnormalities [7-9]. Studies consistently identify GI involvement as a risk factor for early death in diffuse cutaneous SSc, particularly those with poor nutrition or severe midgut disease [9]. In one study that included 264 patients with dcSSc, GI involvement was associated with poor survival. Among 131 deaths related to SSc during a mean follow-up of 5.2 years, 13 deaths were due to GI complications [10].

As for other major complications of SSc, there are emerging associations with the hallmark diagnostic autoantibodies, especially anticentromere antibodies (ACA) and antibodies directed against ribonucleic acid (RNA) polymerase III (ARA) reactivity for higher GI symptom scores, which can help identify patients at higher risk early in the course of disease [11]. This is notable as the skin severity of these two subgroups is markedly different, supporting the observation that severity of GI complications crosses traditional skin-based disease subsets. This may reflect distinct pathogenic processes linked to antinuclear antibody (ANA) subtype [12].

PATHOGENESIS

Systemic sclerosis (SSc) is associated with alterations of the microvasculature, the autonomic nervous system, and the immune system, leading to fibrosis [13-15]. Sjögren advanced the theory that SSc affects the gastrointestinal (GI) tract by an orderly series of steps that result in progressive dysfunction [16]. According to this hypothesis, the disease begins with an initial neural disorder, progresses to muscle dysfunction, and ends with fibrosis. Early neural dysfunction may be a consequence of collagen deposits causing vascular derangement, compression of the nerves, or autoimmune-mediated injury [17-24]. Several studies have highlighted a potential role for autoantibodies targeting acetylcholine muscarinic receptors [25] or directed against vinculin [26]. The second stage of small bowel disease occurs with smooth muscle atrophy. Most patients present with symptoms at this stage. This is followed by the final stage of muscle fibrosis. At this point, the muscle is incapable of responding to stimuli and pharmacologic restoration of function is no longer possible. This hypothesis has been extended to include more data concerning potential genetic differences that may explain patterns of GI involvement across different populations and also incorporating emerging evidence for abnormalities in the adaptive or innate immune system [27]. However, the central concept of microvasculopathy, neural damage, and increased gut wall fibrosis remains valid and reflects emerging concepts of dysregulated tissue repair within the GI tract [27]. Interplay with the gut

microbiome is also emerging as a potentially relevant factor, including evidence of dysbiosis early in the disease course [28], that may influence clinical impact, but the precise role in pathogenesis remains uncertain [29]. (See "Pathogenesis of systemic sclerosis (scleroderma)", section on 'Summary'.)

Another possible mechanism underlying GI disease in SSc is related to altered transforming growth factor (TGF)-beta signaling. A mouse model of SSc that replicates lung and vascular fibrosis with altered TGF-beta signaling has also demonstrated spontaneous bowel wall fibrosis and dysmotility, suggesting that this may be a unifying mechanism for GI disease in scleroderma [23]. Several studies have highlighted delayed GI transit as a major contributor to the symptom burden in SSc GI disease [30].

Gastrointestinal histopathology — The principal pathologic abnormalities of the GI tract consist of smooth muscle atrophy and gut wall fibrosis. Other histopathologic findings include:

- Mild infiltration of the lamina propria with chronic inflammatory cells [31]. Villous architecture is generally normal, although there have been individual case reports of partial villous flattening in association with pseudo-obstruction or concurrent celiac disease [32-34]. Epithelial cell morphology is also normal [32,35].
- Collagenous encapsulation of Brunner's glands, periglandular sclerosis, and fibrous replacement of the muscularis may be found in the submucosa (picture 1) [36]. Atrophic changes and fibrosis are more marked in the circular than in the longitudinal layers, and muscle atrophy appears to exceed fibrosis [37,38].
- Axonal degeneration and neuronal collagen cuffing (picture 2).
- Vascular abnormalities include myointimal proliferation, luminal narrowing and obliteration, disruption of the internal elastic lamina, and capillary basement membrane thickening.

OROPHARYNGEAL INVOLVEMENT

Oropharyngeal involvement in patients with systemic sclerosis (SSc) includes reduced oral aperture from skin thickening, xerostomia, and swallowing difficulties.

Oropharyngeal dysphagia — Oropharyngeal deglutition abnormalities occur in up to 25 percent of patients with SSc and may lead to oral leakage, retention, and aspiration [7,39]. Patients may complain of difficulty initiating a swallow, a sensation of residual food remaining in the pharynx, nasal regurgitation, and coughing after swallowing. (See "Oropharyngeal

dysphagia: Clinical features, diagnosis, and management" and "Oropharyngeal dysphagia: Etiology and pathogenesis".)

Oropharyngeal dysphagia in SSc results from involvement of the oral and perioral tissues. Patients develop narrowing of the oral aperture, as well as rigidity and thinning of the soft palate, larynx, and oral mucosa (which may also become tender). Extrinsic pressure from skin changes may cause resorption of alveolar bone and malalignment of teeth. This can lead to rigidity of the facial skin and tongue and can result in impaired mastication and deglutition. These functions can be further compromised when sicca syndrome and SSc coexist, since saliva production is severely reduced with sicca syndrome. In addition to inflammatory pathology in the salivary glands, analogous to Sjögren's disease, there is also often fibrosis and loss of minor salivary gland structure in the oral mucosa in SSc. Sicca symptoms have appeared to improve after autologous lipotransfer procedures, which may reflect regrowth or recovery of salivary structures [40]. Mechanistic studies are ongoing. (See "Clinical manifestations of Sjögren's disease: Exocrine gland disease", section on 'Dry mouth'.)

ESOPHAGEAL INVOLVEMENT

Esophageal dysfunction is present in 50 to 80 percent of patients with systemic sclerosis (SSc) [41,42].

Pathophysiology — SSc leads to atrophy of the smooth muscle in the lower two-thirds of the tubular esophagus and the lower esophageal sphincter. On pathologic examination, the muscle of the lower esophagus may be partly replaced by fibrous tissue. The lamina propria and submucosa often contain increased quantities of collagen, and the mucosa frequently shows the inflammatory changes of esophagitis. However, esophageal muscle dysfunction in SSc may be secondary to a neuronal abnormality rather than excessive collagen deposition [17,38,43,44].

The incompetent lower esophageal sphincter leads to gastroesophageal reflux. Hypotensive peristaltic contractions in the esophagus are associated with ineffective esophageal transit and prolonged esophageal exposure to gastric acid. Acid reflux may result in reflux esophagitis and subsequent stricture formation. Patients with longstanding reflux may develop Barrett's esophagus; however, esophageal adenocarcinoma appears to be rare in SSc [45]. The upper skeletal muscle portion of the esophagus is rarely involved, although thickening of the pharyngoesophageal muscles with collagenous tissue has been reported [39].

Esophageal motility disorder and gastroesophageal reflux — Abnormal esophageal motility as detected by esophageal manometry is present in 70 to 96 percent of patients of SSc.

However, up to 30 percent of these patients are asymptomatic [46]. Symptomatic patients may complain of heartburn, dysphagia or odynophagia. Patients with advanced dysphagia may regurgitate food and fluids. Dysphagia in SSc can result from reduced peristalsis, esophageal candidiasis, gastroesophageal reflux, or an esophageal stricture when the luminal diameter is ≤13 mm [47,48]. Development of an esophageal stricture markedly decreases gastroesophageal reflux and the symptoms of heartburn. Esophagitis may be found in up to 60 percent of patients with scleroderma reflux, and Barrett's metaplasia is found in more than one-third of patients [49]. (See "Pathophysiology of reflux esophagitis".)

Evaluation for esophageal involvement is guided by the patient's symptoms. Where symptoms are abolished or very well controlled with standard treatment such as proton pump inhibitor (PPI), then further evaluation may not be needed. However, upper endoscopy is indicated for evaluation in patients with refractory heartburn, dysphagia, or odynophagia and to screen for Barrett's esophagus in patients with risk factors. Direct measurement of esophageal motility with manometry is usually only necessary in patients with symptoms refractory to empiric trial of proton pump therapy. We do not routinely perform barium esophagram or esophageal scintigraphy to evaluate patients with SSc due to their low sensitivity and specificity, respectively. Our management is generally consistent with expert consensus guidelines [50]. (See "Barrett's esophagus: Surveillance and management", section on 'Screening for Barrett's esophagus' and "Approach to the evaluation of dysphagia in adults", section on 'Acute dysphagia'.)

Findings of SSc on esophageal testing include:

- **Upper endoscopy** – Upper endoscopy findings in patients with SSc include reflux esophagitis, infectious esophagitis (eg, candidiasis), Barrett's esophagus, and esophageal stricture. In addition, upper endoscopy allows for mechanical dilatation of strictures or mucosal rings. (See "Endoscopic interventions for nonmalignant esophageal strictures in adults".)

- **Esophageal manometry** – Manometric findings in patients with SSc include a hypotensive lower esophageal sphincter with a low resting sphincter pressure (<10 mm Hg) and low-amplitude (<30 mmHg) contractions in the distal smooth muscle portion of the esophagus, or aperistalsis. Hypotensive peristaltic contractions are associated with ineffective esophageal transit. Patients with advanced disease may have diminished peristalsis in the upper skeletal muscle portion.

- Barium **esophagram** – Findings on barium esophagram in patients with SSc include an air-filled esophagus on plain radiograph, impaired or absent peristalsis with dilation of the

esophagus, and a rapid flow of contrast medium in upright position ("waterfall esophagus") [42].

- **Esophageal transit scintigraphy** – Transit scintigraphy demonstrates prolonged esophageal clearance time in patients with SSc and is of little diagnostic value.

GASTRIC INVOLVEMENT

The most common gastric manifestation of systemic sclerosis (SSc) is gastroparesis [51]. Gastric antral venous ectasia (GAVE; "watermelon stomach") can also be seen in a small subset of patients.

Pathophysiology — Histological abnormalities of the stomach consist of submucosal collagen deposition and replacement of smooth muscle with fibrous tissue. These pathologic changes are less marked than those of the esophagus or small intestine.

Symptoms in patients with gastroparesis are due to delayed gastric emptying. The cause of GAVE is unclear. It is hypothesized that GAVE may result from a loose connection between the distal gastric mucosa and the adjacent muscularis externa [52]. This loosening can cause prolapse of the antral mucosa in the pylorus and the development of GAVE. An alternative hypothesis is that GAVE results from cross-reacting antibodies to specific proteins in the gastric mucosa and submucosa. It has also been suggested that GAVE is a vascular manifestation of SSc, as histopathologic findings in skin biopsies of patients with SSc and in gastric mucosal biopsies from are similar [53]. Both demonstrate capillary dilation, fibrin deposits, and platelet thrombosis.

Gastroparesis — The stomach is not usually the primary source of gastrointestinal (GI) symptoms in SSc, but it may contribute to reflux when gastric emptying is delayed [54]. Gastroparesis is rare, but if severe can cause abdominal pain, nausea, and vomiting, which may cause weight loss and nutritional deficiencies. The symptoms are intermittent, with remissions lasting several months. Barium swallow may reveal a dilated atonic stomach. In the absence of gastric outlet obstruction, the diagnosis of gastroparesis is established by the presence of delayed gastric emptying on scintigraphy [55]. (See "Gastroparesis: Etiology, clinical manifestations, and diagnosis", section on 'Diagnosis'.)

Gastric antral vascular ectasia — GAVE is an increasingly recognized complication of SSc [53,56]. A large retrospective study including 264 patients with SSc reported a prevalence of 5.7 percent of GAVE [56]. It is likely that the actual prevalence of GAVE is higher, as diagnostic studies are usually performed only when patients are symptomatic or an anemia is detected.

While acute bleeding may occur, low-grade GI bleeding is more common in GAVE, and most patients present with iron deficiency anemia.

The diagnosis of GAVE is made by upper endoscopy. GAVE has a characteristic endoscopic appearance of longitudinal rows of flat, reddish stripes radiating from the pylorus into the antrum that resemble the stripes on a watermelon. The red stripes represent ectatic and sacculated mucosal vessels. Histopathologically, GAVE is characterized by vascular ectasia, spindle cell proliferation, and fibrohyalinosis. Rarely, massive upper GI bleeding secondary to mucosal telangiectasia (as part of the CREST [**c**alcinosis, **R**aynaud phenomenon, **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasia] syndrome) can also occur [57]. (See "Clinical manifestations and diagnosis of systemic sclerosis (scleroderma) in adults".)

GAVE can be observed in both the limited and diffuse cutaneous subsets of SSc. Limited data also suggest that GAVE is more prevalent among patients with early diffuse cutaneous SSc (dcSSc) [58]. There may also be an association with the presence of anti-RNA polymerase III antibodies and the absence of anti-topoisomerase I (anti-Scl-70) antibodies [58]. Although the data are conflicting, it seems that severe GAVE is more commonly seen in early diffuse SSc and may improve after treatment with immunosuppression despite its vascular basis [52]. (See "Causes of upper gastrointestinal bleeding in adults", section on 'Gastric antral vascular ectasia'.)

SMALL INTESTINAL INVOLVEMENT

After the esophagus, the small intestine is the most common gastrointestinal (GI) target in systemic sclerosis (SSc) patients [59]. Abnormal small bowel function has been reported in 20 to 60 percent of patients [38]. Severe GI problems, such as malabsorption and intestinal pseudo-obstruction, are much less common, affecting less than 10 percent of patients during the first nine years of illness [60].

Pathophysiology — The major manifestations of small intestinal involvement are due to reduced peristalsis with resulting stasis and intestinal dilatation [61]. This results in abdominal distension and pain arising from dilated bowel loops. Small intestinal bacterial overgrowth (SIBO) subsequently emerges due to intestinal stasis and pooling. Impaired absorption of nutrients in SIBO results from either maldigestion in the intestinal lumen, or from malabsorption at the level of the intestinal microvillus membrane due to enterocyte damage. However, it is notable that malabsorption is usually seen in only severe cases of SIBO. (See "Small intestinal bacterial overgrowth: Etiology and pathogenesis", section on 'Pathophysiology'.)

The results of studies on the small intestine point toward an underlying neuromuscular disorder similar to that in the esophagus [62-64]. Light microscopy reveals few clues to the evolution of the pathology of small intestinal involvement in SSc. Villous structure is normal, but there may be collagen deposition around Brunner's glands, leading to periglandular sclerosis. This feature is said to be pathognomonic of intestinal SSc and may occur in the absence of radiologic changes [36]. Unfortunately, this finding is of limited clinical value, since small intestinal biopsies rarely include the submucosal layer. Full thickness biopsies may reveal a marked increase in submucosal and serosal collagen and elastin as well as atrophy of the smooth muscle layers.

Electron microscopy has shown reduced numbers of smooth muscle cells in the external muscle layers and a marked paucity of junctional complexes between muscle cells [65]. In addition, there may be perineuronal collagen cuffing, neuronal degeneration in the absence of collagen cuffing, and perivascular fibrosis.

Small intestinal bacterial overgrowth — Approximately 10 to 30 percent of patients with SSc have evidence of SIBO [66,67]. The majority of patients with SIBO present with nonspecific symptoms of bloating, flatulence, or abdominal discomfort. Many patients diagnosed with severe SIBO have diarrhea. SIBO plays a major role in the pathogenesis of malabsorption and subsequent malnutrition (see 'Malnutrition' below). The diagnosis of SIBO is made by a positive breath test or jejunal aspirate cultures. (See "Small intestinal bacterial overgrowth: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

Hypomotility and intestinal pseudo-obstruction — Patients with hypomotility and ineffective peristalsis may present with recurrent or chronic abdominal pain and bloating. Patients with intestinal pseudo-obstruction present with more acute symptoms of abdominal pain, nausea, and vomiting with marked abdominal distension. (See "Chronic intestinal pseudo-obstruction: Etiology, clinical manifestations, and diagnosis", section on 'Clinical manifestations'.)

Dilatation of intestinal loops is the most prominent radiographic feature in SSc when absence of peristalsis affects the duodenum and proximal jejunum. A characteristic sign of small bowel SSc is an "accordion" or "wire-spring" appearance produced by closely packed valvulae in a dilated bowel (image 1) [68]. In patients with intestinal pseudo-obstruction, duodenal and jejunal loops become markedly dilated and air-fluid levels [69].

Scintigraphy or wireless motility capsule can detect delayed small bowel transit. The diagnosis of chronic intestinal pseudoobstruction is based on the presence of longstanding symptoms of obstruction in the absence of an anatomic cause of obstruction despite endoscopy and/or

contrast imaging (computed tomographic [CT]/magnetic resonance [MR] enterography) and confirmation of impaired motility with scintigraphy.

Malnutrition — Weight loss in SSc is common and often multifactorial. It is especially seen in early diffuse SSc but requires careful and systematic assessment at all stages of the disease. The reported prevalence of malnutrition in SSc patients is approximately 15 to 20 percent, and it is a significant cause of morbidity and mortality [8,70]. Malnutrition in SSc patients may be due to loss of appetite, physical challenges of eating, oral symptoms, drug side effects, gastroparesis, and malabsorption secondary to bacterial overgrowth, and it is associated with higher disease activity rather than nutritional intake [70,71]. The Malnutrition Universal Screening Tool (MUST) questionnaire provides a simple bedside tool for screening patients for malnutrition risk [70,72]. This tool has limitations due to it being more focused on acute weight loss but complements other measures such as the University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract (GIT) 2.0 instrument, which also assesses GI symptoms [8,73,74]. In clinical practice, regular monitoring of weight and body mass index as part of routine follow-up is important, and any patients who are losing weight will benefit from individualized advice and guidance about nutrition to maintain weight and reduce the severity and frequency of gastrointestinal symptoms [75,76].

Other — Other rare complications include bleeding from small bowel telangiectasias, pneumatosis cystoides intestinalis, small bowel diverticula, and small bowel volvulus [51,77-80]. (See "Treatment of gastrointestinal disease in systemic sclerosis (scleroderma)".)

COLON AND ANORECTAL INVOLVEMENT

Colonic disease occurs in 10 to 50 percent of patients with systemic sclerosis (SSc), with the anorectum as the most frequently affected area [81]. In one study, the colon was almost as frequently involved as the esophagus; in addition, patients with abnormal esophageal manometry almost always had abnormal anorectal motility [82]. Constipation and fecal incontinence are the common manifestations of colon and anorectal involvement of SSc and negatively impact quality of life among patients with SSc [83-85].

Pathophysiology — Physiologic studies show that the gastrocolic reflex, in which ingested food leads to significant spike and contractile activity in the colon, is absent early in the course of SSc [78]. SSc involvement of the large intestine is similar pathologically to that of the small intestine. Collagen is deposited in the mucosa and submucosa, while the muscularis externa undergoes atrophy. Thinning of the muscular wall leads to the development of wide-mouthed diverticula on the antimesenteric border that can be detected on barium enema (image 2).

Disordered anorectal function is also an early finding in SSc and is a major factor in the development of fecal incontinence. Studies of anorectal involvement in SSc suggest that neurologic abnormalities may be more influential in determining the severity of complications than the structural changes in the anal sphincters [86,87]. The later stages of the disease are characterized by reductions in resting pressures of the internal and external sphincters, in the length of the anal canal, and in compliance due to collagen deposition [82,88].

Colonic inertia — Patients with colonic involvement of SSc have slow transit and have symptoms of constipation, bloating, and abdominal pain. Fecal impaction may produce stercoral ulceration resulting in lower gastrointestinal (GI) bleeding and iron deficiency anemia.

Characteristic radiologic findings include wide-mouthed diverticula or sacculations (usually along the antimesenteric border), colonic dilation, and loss of haustration resulting in a smooth colon in outline [89]. Colonic transit is delayed as demonstrated with radiopaque markers. (See "Etiology and evaluation of chronic constipation in adults", section on 'Radiopaque marker study'.)

Diarrhea and fecal incontinence — Diarrhea is commonly reported in patients with SSc and many patients describe diarrhea that may alternate with constipation [2]. Diarrhea in SSc is often multifactorial and may be due to small intestinal bacterial overgrowth, pancreatic exocrine insufficiency, or overflow from constipation. Fecal incontinence may result from involvement of the anal sphincter, which is common in SSc and usually associated with atrophic change of both internal and external sphincters when assessed by endoanal ultrasound [87]. Patients may also have an associated rectal prolapse. Diarrhea may also contribute to fecal incontinence in these patients. The most common manometric abnormality is an absent or diminished rectoanal inhibitory reflex and decrease in internal anal resting pressure [82]. These neurologic abnormalities are especially associated with symptoms of incontinence and appear more important than structural abnormalities [86]. The response of the external sphincter is either normal or increased. These findings are similar to those seen in Hirschsprung disease and are consistent with a neuronal abnormality in the myenteric plexus. (See "Approach to the adult with chronic diarrhea in resource-abundant settings", section on 'Initial evaluation' and 'Small intestinal bacterial overgrowth' above and 'Pancreatic exocrine insufficiency' below and "Treatment of gastrointestinal disease in systemic sclerosis (scleroderma)", section on 'Small intestinal bacterial overgrowth' and "Treatment of gastrointestinal disease in systemic sclerosis (scleroderma)", section on 'Pancreatic disease'.)

Magnetic resonance imaging (MRI) abnormalities in such patients include forward buckling of the anterior rectal wall, air in the upper portion of the anal sphincter, and atrophy of fibrotic appearing sphincteric muscle [90]. Defecography is particularly useful for the evaluation of

rectal prolapse. The evaluation of fecal incontinence and rectal prolapse are discussed separately. Our approach in SSc patients is generally consistent with expert consensus recommendations [73]. (See "Fecal incontinence in adults: Etiology and evaluation", section on 'Evaluation' and "Overview of rectal procidentia (rectal prolapse)", section on 'Radiographic studies'.)

Other — Other less frequent complications of colonic disease include rectal prolapse, spontaneous perforation, stercoral ulcerations, colonic perforation, diverticulosis, pneumatosis coli, colon volvulus, colonic telangiectasias, or colonic infarction. GI bleeding in patients with SSc may be from diverticulosis, stercoral ulcerations, and telangiectasias. Vascular ectasia may also occur in the rectum.

LIVER AND BILIARY TREE INVOLVEMENT

Hepatic disease is rare in systemic sclerosis (SSc) but can occur in association with primary biliary cholangitis (PBC; previously referred to as primary biliary cirrhosis). A significant elevation in transaminases should therefore first prompt consideration of coincident inflammatory muscle disease or drug induced hepatotoxicity.

Primary biliary cholangitis overlap — PBC occurs in 2 to 18 percent of patients with SSc [91,92]. Most patients with both SSc and PBC have limited cutaneous SSc (lcSSc) or scleroderma overlap syndromes; diffuse skin involvement is much less common [92-94]. (See "Pathogenesis of primary biliary cholangitis (primary biliary cirrhosis)".)

Patients with PBC may be asymptomatic, or they may present with symptoms such as fatigue and pruritus. Other clinical manifestations include jaundice, cholestatic liver enzymes, antimitochondrial antibodies, and signs and symptoms of cirrhosis.

Patients with PBC and SSC are often positive for antimitochondrial antibodies (AMA) [93,94]. SP100 has also been detected in AMA-negative PBC patients and is a useful marker for serological diagnosis of PBC [92,95,96]. Anticentromere B autoantibodies (CENP-B) are strongly associated with PBC in SSc, while antitopoisomerase I and anti-RNA polymerase III antibodies are not [92]. (See "Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis".)f

Patients with lcSSc tend to have slower progression of hepatic disease compared with patients with PBC but without SSc. This was illustrated in a study of 580 patients with PBC, 43 of whom had SSc (40 with lcSSc) [94]. There was a significantly slower increase in bilirubin and a lower rate of liver transplantation in those with SSc-associated PBC versus PBC alone. Overall

mortality rates were similar in those with and without SSc. By comparison, cirrhosis is very rare, as is idiopathic noncirrhotic portal hypertension (including nodular regenerative hyperplasia).

PANCREATIC INVOLVEMENT

Pancreatic involvement in patients with systemic sclerosis (SSc) is uncommon but can occur [97,98].

Pancreatic exocrine insufficiency — Advanced pancreatic exocrine insufficiency (PEI) results in maldigestion of fat and protein leading to steatorrhea and weight loss. Although subtle changes in exocrine function can be detected in patients with early pancreatic disease, overt steatorrhea does not occur until approximately 90 percent of glandular function has been lost. Other symptoms include bloating, cramping, increased flatulence, and diarrhea. Patients with mild PEI may have subclinical maldigestion and normal-appearing bowel movements.

There does not appear to be a correlation between the severity of SSc and the degree of pancreatic insufficiency. Histologic studies of the pancreas show a fibrotic process; hemorrhagic pancreatitis has rarely been described, but may reflect overlap syndromes or potential drug effects [99]. (See "Exocrine pancreatic insufficiency", section on 'Clinical manifestations' and "Undifferentiated systemic rheumatic (connective tissue) diseases and overlap syndromes".)

SUMMARY AND RECOMMENDATIONS

- Nearly 90 percent of patients with systemic sclerosis (SSc, scleroderma), including both diffuse and limited forms, have gastrointestinal (GI) involvement; about half are symptomatic. Although the esophagus is the most frequently affected part of the GI tract, any part of the GI tract may be involved. Alterations of the microvasculature, the autonomic nervous system, and the immune system, leading to fibrosis, appear important in the pathogenesis of SSc in general and in GI involvement. The principal pathologic abnormalities throughout the GI tract are of smooth muscle atrophy and gut wall fibrosis, which may result from an initial neural disorder. (See 'Epidemiology' above and 'Pathogenesis' above.)

- Oropharyngeal involvement in patients with SSc includes reduced oral aperture from skin thickening, xerostomia, and swallowing difficulties. Oropharyngeal deglutition abnormalities occur in up to 25 percent of patients with SSc and may lead to oral leakage, retention, and aspiration. Patients may complain of difficulty initiating a swallow, a sensation of residual food remaining in the pharynx, nasal regurgitation, and coughing

after swallowing. (See 'Oropharyngeal involvement' above and 'Oropharyngeal dysphagia' above.)

- Abnormal esophageal motility is present in almost all patients with SSc. However, approximately 30 percent of patients are asymptomatic. Symptoms result from gastroesophageal reflux and its complications. Symptomatic patients may complain of heartburn, dysphagia, or odynophagia. Evaluation for esophageal involvement is guided by the patient's symptoms. Patients with heartburn, dysphagia, or odynophagia should undergo upper endoscopy. Upper endoscopy findings in patients with SSc include reflux esophagitis, infectious esophagitis (eg, candidiasis), Barrett's esophagus, and esophageal stricture. Direct measurement of esophageal motility with manometry is usually only necessary in patients with symptoms refractory to empiric trial of proton pump therapy. (See 'Esophageal involvement' above and 'Esophageal motility disorder and gastroesophageal reflux' above.)

- The stomach is not usually the primary source of symptoms in GI SSc, but it may contribute to gastroesophageal reflux when gastric emptying is delayed. Gastroparesis can also cause abdominal pain, nausea, and vomiting, and weight loss. Upper GI bleeding may result from mucosal telangiectasia (as part of the CREST [**c**alcinosis, **R**aynaud phenomenon, **e**sophageal dysmotility, **s**clerodactyly, and **t**elangiectasia] syndrome) or from gastric antral venous ectasia (GAVE). GAVE should be suspected in patients with unexplained iron deficiency anemia. (See 'Gastric involvement' above.)

- Abnormal small bowel function is present in 20 to 60 percent of patients with SSc. The major clinical manifestations are due to reduced peristalsis with resulting stasis and intestinal dilatation, causing abdominal distension and pain arising from dilated bowel loops. Bacterial overgrowth occurs due to the intestinal stasis and pooling, resulting in malabsorption (in approximately 10 to 30 percent of patients with SSc) and the development of diarrhea, steatorrhea, and weight loss. Intestinal pseudo-obstruction, small bowel perforation, pneumatosis cystoides intestinalis, and small bowel volvulus each occur rarely. (See 'Small intestinal involvement' above and 'Hypomotility and intestinal pseudo-obstruction' above and 'Malnutrition' above.)

- Colonic disease occurs in 10 to 50 percent of patients with SSc, with the anorectum as the most frequently affected area. Constipation and fecal incontinence are common problems in SSc; less frequent symptoms of colonic disease include rectal prolapse, spontaneous perforation, and colonic infarction. (See 'Colon and anorectal involvement' above.)

- Hepatic or pancreatic involvement is rare in SSc. However, hepatic disease due to primary biliary cholangitis (PBC; previously referred to as primary biliary cirrhosis) can occur in patients with SSc, particularly the limited cutaneous form. (See 'Liver and biliary tree involvement' above and 'Pancreatic involvement' above.)

REFERENCES

1. Khanna D, Hays RD, Maranian P, et al. Reliability and validity of the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument. Arthritis Rheum 2009; 61:1257.
2. Thoua NM, Bunce C, Brough G, et al. Assessment of gastrointestinal symptoms in patients with systemic sclerosis in a UK tertiary referral centre. Rheumatology (Oxford) 2010; 49:1770.
3. Turner R, Lipshutz W, Miller W, et al. Esophageal dysfunction in collagen disease. Am J Med Sci 1973; 265:191.
4. Akesson A, Wollheim FA. Organ manifestations in 100 patients with progressive systemic sclerosis: a comparison between the CREST syndrome and diffuse scleroderma. Br J Rheumatol 1989; 28:281.
5. Furst DE, Clements PJ, Saab M, et al. Clinical and serological comparison of 17 chronic progressive systemic sclerosis (PSS) and 17 CREST syndrome patients matched for sex, age, and disease duration. Ann Rheum Dis 1984; 43:794.
6. Zaninotto G, Peserico A, Costantini M, et al. Oesophageal motility and lower oesophageal sphincter competence in progressive systemic sclerosis and localized scleroderma. Scand J Gastroenterol 1989; 24:95.
7. Montesi A, Pesaresi A, Cavalli ML, et al. Oropharyngeal and esophageal function in scleroderma. Dysphagia 1991; 6:219.
8. Bharadwaj S, Tandon P, Gohel T, et al. Gastrointestinal Manifestations, Malnutrition, and Role of Enteral and Parenteral Nutrition in Patients With Scleroderma. J Clin Gastroenterol 2015; 49:559.
9. Domsic RT, Nihtyanova SI, Wisniewski SR, et al. Derivation and validation of a prediction rule for two-year mortality in early diffuse cutaneous systemic sclerosis. Arthritis Rheumatol 2014; 66:1616.

10. Altman RD, Medsger TA Jr, Bloch DA, Michel BA. Predictors of survival in systemic sclerosis (scleroderma). Arthritis Rheum 1991; 34:403.
11. Ahmed F, Maclean RH, Nihtyanova SI, et al. Autoantibody predictors of gastrointestinal symptoms in systemic sclerosis. Rheumatology (Oxford) 2022; 61:781.
12. Clark KEN, Campochiaro C, Csomor E, et al. Molecular basis for clinical diversity between autoantibody subsets in diffuse cutaneous systemic sclerosis. Ann Rheum Dis 2021; 80:1584.
13. Russell ML, Friesen D, Henderson RD, Hanna WM. Ultrastructure of the esophagus in scleroderma. Arthritis Rheum 1982; 25:1117.
14. Dessein PH, Joffe BI, Metz RM, et al. Autonomic dysfunction in systemic sclerosis: sympathetic overactivity and instability. Am J Med 1992; 93:143.
15. Silver RM. Clinical aspects of systemic sclerosis (scleroderma). Ann Rheum Dis 1991; 50 Suppl 4:854.
16. Sjogren RW. Gastrointestinal motility disorders in scleroderma. Arthritis Rheum 1994; 37:1265.
17. Willerson JT, Thompson RH, Hookman P, et al. Reserpine in Raynaud's disease and phenomenon. Short-term response to intra-arterial injection. Ann Intern Med 1970; 72:17.
18. TREACY WL, BAGGENSTOSS AH, SLOCUMB CH, CODE CF. SCLERODERMA OF THE ESOPHAGUS. A CORRELATION OF HISTOLOGIC AND PHYSIOLOGIC FINDINGS. Ann Intern Med 1963; 59:351.
19. Di Trapani G, Pocchiari M, Masullo C, et al. Peripheral neuropathy in the course of progressive systemic sclerosis: light and ultrastructural study. Ital J Neurol Sci 1982; 3:341.
20. Howe S, Eaker EY, Sallustio JE, et al. Antimyenteric neuronal antibodies in scleroderma. J Clin Invest 1994; 94:761.
21. Manetti M, Neumann E, Müller A, et al. Endothelial/lymphocyte activation leads to prominent CD4+ T cell infiltration in the gastric mucosa of patients with systemic sclerosis. Arthritis Rheum 2008; 58:2866.
22. Raja J, Nihtyanova SI, Murray CD, et al. Sustained benefit from intravenous immunoglobulin therapy for gastrointestinal involvement in systemic sclerosis. Rheumatology (Oxford) 2016; 55:115.
23. Thoua NM, Derrett-Smith EC, Khan K, et al. Gut fibrosis with altered colonic contractility in a mouse model of scleroderma. Rheumatology (Oxford) 2012; 51:1989.
24. McMahan ZH, Domsic RT, Zhu L, et al. Anti-RNPC-3 (U11/U12) Antibodies in Systemic Sclerosis in Patients With Moderate-to-Severe Gastrointestinal Dysmotility. Arthritis Care

Res (Hoboken) 2019; 71:1164.

25. Tolaymat M, Sundel MH, Alizadeh M, et al. Potential Role for Combined Subtype-Selective Targeting of M1 and M3 Muscarinic Receptors in Gastrointestinal and Liver Diseases. Front Pharmacol 2021; 12:786105.
26. Suliman Y, Kafaja S, Oh SJ, et al. Anti-vinculin antibodies in scleroderma (SSc): a potential link between autoimmunity and gastrointestinal system involvement in two SSc cohorts. Clin Rheumatol 2021; 40:2277.
27. Kumar S, Singh J, Rattan S, et al. Review article: pathogenesis and clinical manifestations of gastrointestinal involvement in systemic sclerosis. Aliment Pharmacol Ther 2017; 45:883.
28. Andréasson K, Lee SM, Lagishetty V, et al. Disease Features and Gastrointestinal Microbial Composition in Patients with Systemic Sclerosis from Two Independent Cohorts. ACR Open Rheumatol 2022; 4:417.
29. Bellocchi C, Volkmann ER. Update on the Gastrointestinal Microbiome in Systemic Sclerosis. Curr Rheumatol Rep 2018; 20:49.
30. McMahan ZH, Tucker AE, Perin J, et al. Relationship Between Gastrointestinal Transit, Medsger Gastrointestinal Severity, and University of California-Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 Symptoms in Patients With Systemic Sclerosis. Arthritis Care Res (Hoboken) 2022; 74:442.
31. Kahn IJ, Jeffries GH, Sleisenger MH. Malabsorption in intestinal scleroderma. Correction by antibiotics. N Engl J Med 1966; 274:1339.
32. HORSWELL RR, HARGROVE MD Jr, PEETE WP, RUFFIN JM. Scleroderma presenting as the malabsorption syndrome. A case report. Gastroenterology 1961; 40:580.
33. Schuffler MD, Kaplan LR, Johnson L. Small-intestinal mucosa in pseudoobstruction syndromes. Am J Dig Dis 1978; 23:821.
34. Marguerie C, Kaye S, Vyse T, et al. Malabsorption caused by coeliac disease in patients who have scleroderma. Br J Rheumatol 1995; 34:858.
35. McBrien DJ, Mummery HE. Steatorrhoea in Progressive Systemic Sclerosis (Scleroderma). Br Med J 1962; 2:1653.
36. ROSSON RS, YESNER R. PERORAL DUODENAL BIOPSY IN PROGRESSIVE SYSTEMIC SCLEROSIS. N Engl J Med 1965; 272:391.
37. Stafford-Brady FJ, Kahn HJ, Ross TM, Russell ML. Advanced scleroderma bowel: complications and management. J Rheumatol 1988; 15:869.
38. D'Angelo WA, Fries JF, Masi AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. Am J

Med 1969; 46:428.

39. Rajapakse CN, Bancewicz J, Jones CJ, Jayson MI. Pharyngo-oesophageal dysphagia in systemic sclerosis. Ann Rheum Dis 1981; 40:612.
40. Almadori A, Griffin M, Ryan CM, et al. Stem cell enriched lipotransfer reverses the effects of fibrosis in systemic sclerosis. PLoS One 2019; 14:e0218068.
41. Poirier TJ, Rankin GB. Gastrointestinal manifestations of progressive systemic scleroderma based on a review of 364 cases. Am J Gastroenterol 1972; 58:30.
42. Lock G, Holstege A, Lang B, Schölmerich J. Gastrointestinal manifestations of progressive systemic sclerosis. Am J Gastroenterol 1997; 92:763.
43. Cohen S, Fisher R, Lipshutz W, et al. The pathogenesis of esophageal dysfunction in scleroderma and Raynaud's disease. J Clin Invest 1972; 51:2663.
44. Belch JJ, Land D, Park RH, et al. Decreased oesophageal blood flow in patients with Raynaud's phenomenon. Br J Rheumatol 1988; 27:426.
45. Segel MC, Campbell WL, Medsger TA Jr, Roumm AD. Systemic sclerosis (scleroderma) and esophageal adenocarcinoma: Is increased patient screening necessary? Gastroenterology 1985; 89:485.
46. Lahcene M, Oumnia N, Matougui N, et al. Esophageal involvement in scleroderma: clinical, endoscopic, and manometric features. ISRN Rheumatol 2011; 2011:325826.
47. Geirsson AJ, Akesson A, Gustafson T, et al. Cineradiography identifies esophageal candidiasis in progressive systemic sclerosis. Clin Exp Rheumatol 1989; 7:43.
48. ASGE Standards of Practice Committee, Pasha SF, Acosta RD, et al. The role of endoscopy in the evaluation and management of dysphagia. Gastrointest Endosc 2014; 79:191.
49. Katzka DA, Reynolds JC, Saul SH, et al. Barrett's metaplasia and adenocarcinoma of the esophagus in scleroderma. Am J Med 1987; 82:46.
50. Fernández-Codina A, Walker KM, Pope JE, Scleroderma Algorithm Group. Treatment Algorithms for Systemic Sclerosis According to Experts. Arthritis Rheumatol 2018; 70:1820.
51. Kirby DF, Chatterjee S. Evaluation and management of gastrointestinal manifestations in scleroderma. Curr Opin Rheumatol 2014; 26:621.
52. Parrado RH, Lemus HN, Coral-Alvarado PX, Quintana López G. Gastric Antral Vascular Ectasia in Systemic Sclerosis: Current Concepts. Int J Rheumatol 2015; 2015:762546.
53. Watson M, Hally RJ, McCue PA, et al. Gastric antral vascular ectasia (watermelon stomach) in patients with systemic sclerosis. Arthritis Rheum 1996; 39:341.

54. Maddern GJ, Horowitz M, Jamieson GG, et al. Abnormalities of esophageal and gastric emptying in progressive systemic sclerosis. Gastroenterology 1984; 87:922.
55. Blackwell JN, Hannan WJ, Adam RD, Heading RC. Radionuclide transit studies in the detection of oesophageal dysmotility. Gut 1983; 24:421.
56. Marie I, Ducrotte P, Antonietti M, et al. Watermelon stomach in systemic sclerosis: its incidence and management. Aliment Pharmacol Ther 2008; 28:412.
57. Duchini A, Sessoms SL. Gastrointestinal hemorrhage in patients with systemic sclerosis and CREST syndrome. Am J Gastroenterol 1998; 93:1453.
58. Ingraham KM, O'Brien MS, Shenin M, et al. Gastric antral vascular ectasia in systemic sclerosis: demographics and disease predictors. J Rheumatol 2010; 37:603.
59. Marie I. [Gastrointestinal involvement in systemic sclerosis]. Presse Med 2006; 35:1952.
60. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000; 43:2437.
61. REINHARDT JF, BARRY WF Jr. Scleroderma of the small bowel. Am J Roentgenol Radium Ther Nucl Med 1962; 88:687.
62. DiMarino AJ, Carlson G, Myers A, et al. Duodenal myoelectric activity in scleroderma. Abnormal responses to mechanical and hormonal stimuli. N Engl J Med 1973; 289:1220.
63. Rees WD, Leigh RJ, Christofides ND, et al. Interdigestive motor activity in patients with systemic sclerosis. Gastroenterology 1982; 83:575.
64. Greydanus MP, Camilleri M. Abnormal postcibal antral and small bowel motility due to neuropathy or myopathy in systemic sclerosis. Gastroenterology 1989; 96:110.
65. Greenberger NJ, Dobbins WO 3rd, Ruppert RD, Jesseph JE. Intestinal atony in progressive systemic sclerosis (scleroderma). Am J Med 1968; 45:301.
66. Kaye SA, Lim SG, Taylor M, et al. Small bowel bacterial overgrowth in systemic sclerosis: detection using direct and indirect methods and treatment outcome. Br J Rheumatol 1995; 34:265.
67. Wegener M, Adamek RJ, Wedmann B, et al. Gastrointestinal transit through esophagus, stomach, small and large intestine in patients with progressive systemic sclerosis. Dig Dis Sci 1994; 39:2209.
68. Horowitz AL, Meyers MA. The "hide-bound" small bowel of scleroderma: characteristic mucosal fold pattern. Am J Roentgenol Radium Ther Nucl Med 1973; 119:332.
69. Miercort RD, Merrill FG. Pneumatosis and pseudo-obstruction in scleroderma. Radiology 1969; 92:359.

70. Baron M, Hudson M, Steele R, Canadian Scleroderma Research Group. Malnutrition is common in systemic sclerosis: results from the Canadian scleroderma research group database. J Rheumatol 2009; 36:2737.

71. Caporali R, Caccialanza R, Bonino C, et al. Disease-related malnutrition in outpatients with systemic sclerosis. Clin Nutr 2012; 31:666.

72. Harrison E, Herrick AL, McLaughlin JT, Lal S. Malnutrition in systemic sclerosis. Rheumatology (Oxford) 2012; 51:1747.

73. Hansi N, Thoua N, Carulli M, et al. Consensus best practice pathway of the UK scleroderma study group: gastrointestinal manifestations of systemic sclerosis. Clin Exp Rheumatol 2014; 32:S.

74. Bae S, Allanore Y, Furst DE, et al. Associations between a scleroderma-specific gastrointestinal instrument and objective tests of upper gastrointestinal involvements in systemic sclerosis. Clin Exp Rheumatol 2013; 31:57.

75. Baron M, Bernier P, Côté LF, et al. Screening and therapy for malnutrition and related gastro-intestinal disorders in systemic sclerosis: recommendations of a North American expert panel. Clin Exp Rheumatol 2010; 28:S42.

76. Shreiner AB, Murray C, Denton C, Khanna D. Gastrointestinal Manifestations of Systemic Sclerosis. J Scleroderma Relat Disord 2016; 1:247.

77. Jayson MI, Salmon PR, Gough J, et al. Spontaneous bowel perforation in intestinal scleroderma: first report of a non-fatal case. Postgrad Med J 1972; 48:56.

78. Battle WM, McLean GK, Brooks JJ, et al. Spontaneous perforation of the small intestine due to scleroderma. Dig Dis Sci 1979; 24:80.

79. Meihoff WE, Hirschfield JS, Kern F Jr. Small intestinal scleroderma with malabsorption and pneumatosis cystoides intestinalis. Report of three cases. JAMA 1968; 204:854.

80. Hendy MS, Torrance HB, Warnes TW. Small-bowel volvulus in association with progressive systemic sclerosis. Br Med J 1979; 1:1051.

81. MESZAROS WT. The colon in systemic sclerosis (scleroderma). Am J Roentgenol Radium Ther Nucl Med 1959; 82:100.

82. Hamel-Roy J, Devroede G, Arhan P, et al. Comparative esophageal and anorectal motility in scleroderma. Gastroenterology 1985; 88:1.

83. Gyger G, Baron M. Systemic Sclerosis: Gastrointestinal Disease and Its Management. Rheum Dis Clin North Am 2015; 41:459.

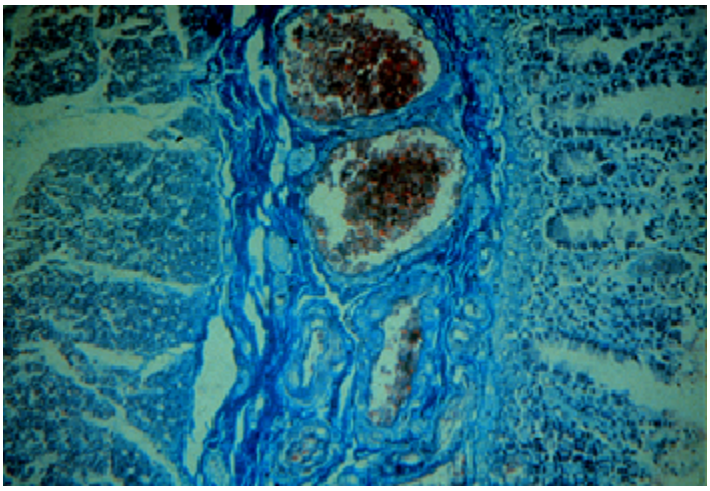
84. Cohen S. The gastrointestinal manifestations of scleroderma: pathogenesis and management. Gastroenterology 1980; 79:155.

85. Leighton JA, Valdovinos MA, Pemberton JH, et al. Anorectal dysfunction and rectal prolapse in progressive systemic sclerosis. Dis Colon Rectum 1993; 36:182.
86. Thoua NM, Abdel-Halim M, Forbes A, et al. Fecal incontinence in systemic sclerosis is secondary to neuropathy. Am J Gastroenterol 2012; 107:597.
87. Thoua NM, Schizas A, Forbes A, et al. Internal anal sphincter atrophy in patients with systemic sclerosis. Rheumatology (Oxford) 2011; 50:1596.
88. Chiou AW, Lin JK, Wang FM. Anorectal abnormalities in progressive systemic sclerosis. Dis Colon Rectum 1989; 32:417.
89. Peachey RD, Creamer B, Pierce JW. Sclerodermatous involvement of the stomach and the small and large bowel. Gut 1969; 10:285.
90. deSouza NM, Williams AD, Wilson HJ, et al. Fecal incontinence in scleroderma: assessment of the anal sphincter with thin-section endoanal MR imaging. Radiology 1998; 208:529.
91. Jacobsen S, Halberg P, Ullman S, et al. Clinical features and serum antinuclear antibodies in 230 Danish patients with systemic sclerosis. Br J Rheumatol 1998; 37:39.
92. Assassi S, Fritzler MJ, Arnett FC, et al. Primary biliary cirrhosis (PBC), PBC autoantibodies, and hepatic parameter abnormalities in a large population of systemic sclerosis patients. J Rheumatol 2009; 36:2250.
93. Reynolds TB, Denison EK, Frankl HD, et al. Primary biliary cirrhosis with scleroderma, Raynaud's phenomenon and telangiectasia. New syndrome. Am J Med 1971; 50:302.
94. Rigamonti C, Shand LM, Feudjo M, et al. Clinical features and prognosis of primary biliary cirrhosis associated with systemic sclerosis. Gut 2006; 55:388.
95. Worman HJ, Courvalin JC. Antinuclear antibodies specific for primary biliary cirrhosis. Autoimmun Rev 2003; 2:211.
96. Hu SL, Zhao FR, Hu Q, Chen WX. Meta-analysis assessment of GP210 and SP100 for the diagnosis of primary biliary cirrhosis. PLoS One 2014; 9:e101916.
97. Cobden I, Axon AT, Rowell NR. Pancreatic exocrine function in systemic sclerosis. Br J Dermatol 1981; 105:189.
98. Shawis TN, Chaloner C, Herrick AL, Jayson MI. Pancreatic function in systemic sclerosis. Br J Rheumatol 1996; 35:298.
99. Hastier P, Buckley MJ, Le Gall P, et al. First report of association of chronic pancreatitis, primary biliary cirrhosis, and systemic sclerosis. Dig Dis Sci 1998; 43:2426.

Topic 7548 Version 25.0

GRAPHICS

Duodenum in scleroderma

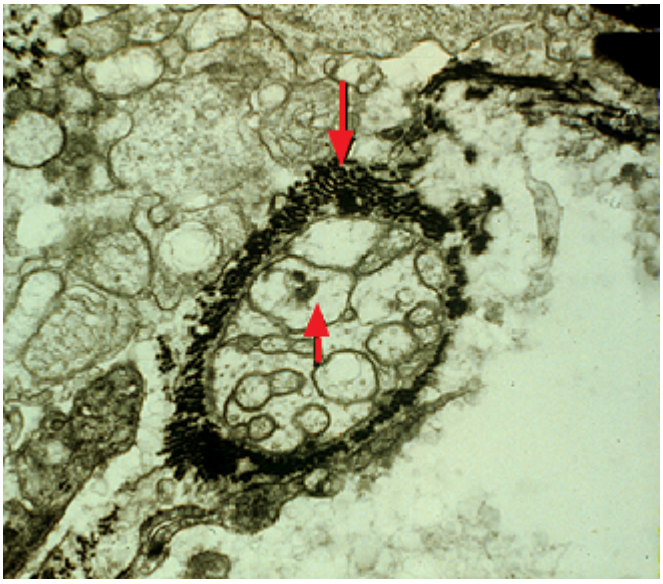


Section of duodenum from a patient with scleroderma (Masson trichrome stain). There is normal villus structure and epithelial cell morphology (right side), a mild inflammatory cell infiltrate in the lamina propria, collagen (seen in dark blue) encapsulating Brunner's glands, and fibrous replacement of the muscularis.

Courtesy of Carol M Black, MD, FRCP.

Graphic 62854 Version 1.0

Autonomic nerve in scleroderma

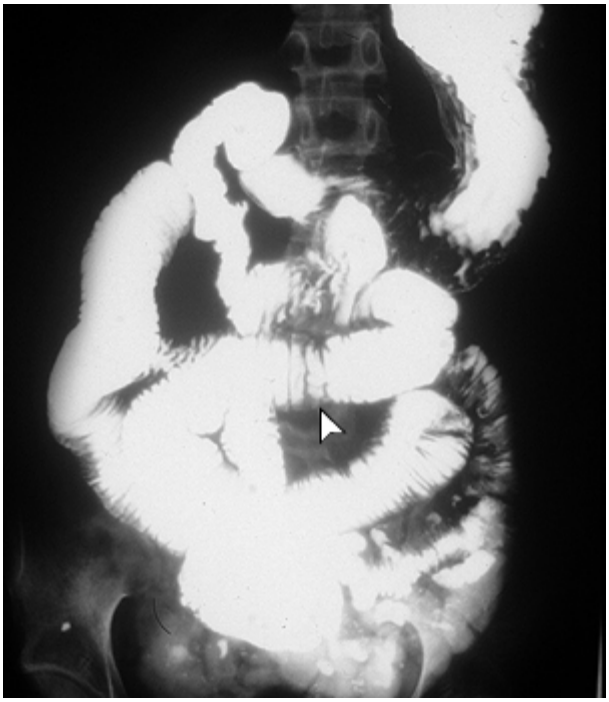


Electron micrograph of an autonomic nerve in the intestine from a patient with scleroderma. The two main changes are axonal degeneration (up arrow) and collagenous cuffing of the nerve (down arrow).

Courtesy of Carol M Black, MD, FRCP.

Graphic 54076 Version 1.0

Small bowel disease in scleroderma

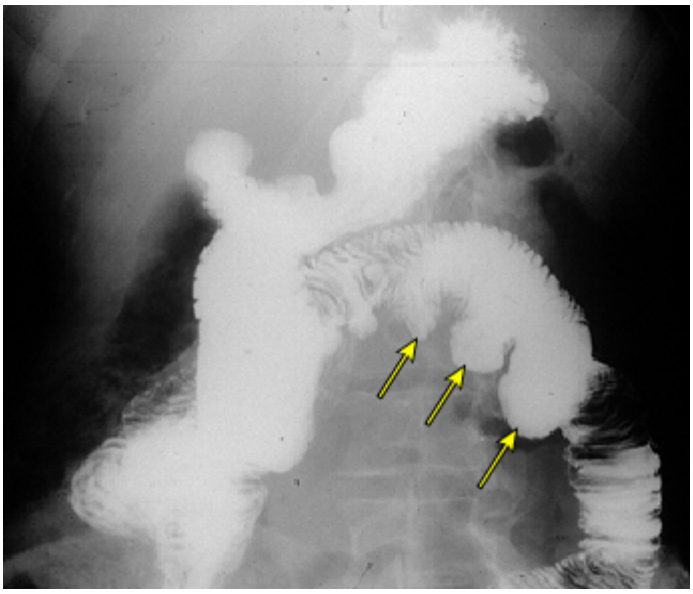


Barium follow-through examination in a patient with scleroderma shows dilated loops of small bowel, some of which have a "wire-spring" appearance due to closely packed valvulae in a dilated bowel (arrowhead).

Courtesy of Carol M Black, MD, FRCP.

Graphic 51096 Version 3.0

Upper GI barium study small bowel diverticula in scleroderma



Upper GI barium study in a patient with scleroderma shows wide-mouthed diverticula (arrows) in the proximal jejunum.

GI: gastrointestinal.

Courtesy of Carol M Black, MD, FRCP.

Graphic 81427 Version 3.0

Contributor Disclosures

Stephanie A Kaye-Barrett, MD No relevant financial relationship(s) with ineligible companies to disclose. **Christopher P Denton, MD** Grant/Research/Clinical Trial Support: Arxx Therapeutics [Scleroderma]; CSL Behring [Scleroderma, pulmonary hypertension]; GlaxoSmithKline [Scleroderma, pulmonary hypertension]; Horizon [Scleroderma]; Inventiva [Scleroderma, pulmonary hypertension]; Merck [Scleroderma, pulmonary hypertension]; Roche [Scleroderma, pulmonary hypertension]; Sanofi-Aventis [Scleroderma]; Servier [Scleroderma]. Consultant/Advisory Boards: Acceleron [Scleroderma]; Actelion [Scleroderma, pulmonary hypertension]; AstraZeneca [Scleroderma]; Bayer [Scleroderma, pulmonary hypertension]; Boehringer Ingelheim [Scleroderma]; Capella Bioscience [Scleroderma]; EMD Serono [Scleroderma]; Galapagos [Scleroderma]; GlaxoSmithKline [Scleroderma, pulmonary hypertension]; Horizon [Scleroderma]; Leadiant [Scleroderma]; Roche [Scleroderma, pulmonary hypertension]. All of the relevant financial relationships listed have been mitigated. **John S Axford, DSc, MD, FRCP, FRCPCH** No relevant financial relationship(s) with ineligible companies to disclose. **Nicholas J Talley, MD, PhD** Patent Holder: Australian Provisional Patent [Diagnostic marker for functional gastrointestinal disorders]; Biomarkers of irritable bowel syndrome [Irritable bowel syndrome]; Mayo Clinic [Dysphagia questionnaire]; Mayo Clinic [Bowel Disease questionnaire]; Nepean Dyspepsia Index [Dyspepsia]; Nestec [Irritable bowel syndrome]; Singapore Provisional Patent [BDNF Tissue Repair Pathway]. Grant/Research/Clinical Trial Support: Alimetry [Gastric mapping device research collaboration]; Allakos [Gastric eosinophilic disease]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; Intrinsic Medicine [Bowel syndrome with constipation]; NHMRC Centre for Research Excellence in Digestive Health [NHMRC Investigator grant]. Consultant/Advisory Boards: Adelphi Values [Functional dyspepsia]; Allakos [Gastric eosinophilic disease, AK002]; AstraZeneca [Eosinophilic gastritis, eosinophilic gastroenteritis]; AusEE [Eosinophilic gut diseases]; Bayer [Inflammatory bowel syndrome]; BluMaiden [Microbiome Ad Board]; Comvita Mānuka Honey [Digestive health]; Dr Falk Pharma [Eosinophilia]; GlaxoSmithKline Australia [Educational speaker eosinophilic gut disease]; Glutagen [Celiac disease]; International Foundation for Functional Gastrointestinal Disorders [Advisory board, functional GI disorders]; Intrinsic Medicine [Human milk oligosaccharide]; IsoThrive [Esophageal microbiome]; Planet Innovation [Gas capsule, inflammatory bowel syndrome]; Progenity Inc [Intestinal capsule]; Rose Pharma [IBS]; Viscera Labs [Inflammatory bowel syndrome, diarrhea]. Other Financial Interest: Elsevier textbook royalties [Medical education]. All of the relevant financial relationships listed have been mitigated. **Philip Seo, MD, MHS** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→