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Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disorder with multisystem involvement. The gastrointestinal (GI) tract is affected in up to 90% of patients [1–3] and gut involvement is a leading cause of morbidity. Symptoms vary based on location of involvement and degree of impairment; however, dysphagia, reflux, nausea, vomiting, pain, diarrhea, constipation, fecal incontinence, and weight loss are all commonly reported. GI involvement severely impacts quality of life and is a major cause of mortality associated with SSc [4].

While the esophagus is the most widely described site of GI involvement, SSc can affect any site within the GI tract from the mouth to the anus. This chapter will focus on foregut manifestations of SSc, ranging from the mouth to stomach with an emphasis on both motility and bleeding. Involvement of other regions of the GI tract will be detailed in other chapters.

Oropharyngeal Cavity

Oropharyngeal manifestations of scleroderma are not well studied, with estimates of involvement ranging from 20 to 80% [5–7]. Sclerosis of the oropharyngeal mucosa, muscles associated with mastication and salivary glands, can lead to difficulty in speaking, chewing, and swallowing. Reported symptoms include head and neck numbness; tongue, hard palate, and soft palate fibrosis; microstomia; oral mucosa damage; perioral skin injury; xerostomia; periodontal liga-

ment fibrous thickening; bone resorption; oral telangiectasia; trigeminal neuropathy; and significant dental caries. In addition, *sicca* symptoms are reported in up to 20% of SSc patients, and the associated decreased salivary gland production is typically associated with mild oropharyngeal dysphagia, due to lack of effective food bolus lubrication that impairs oropharyngeal transfer and esophageal transit. Significant perioral skin involvement can limit the mouth aperture and restrict food intake. Mixed connective tissue disorders that combine features of scleroderma with myositis may present with oropharyngeal dysphagia.

Therapeutic options are often limited to dietary modifications using small bolus size, soft foods, and increased use of liquid supplementation during meals. Close follow-up with a dentist or oral specialist is also recommended, as is optimal oral hygiene. To date, there are not good data to suggest that oropharyngeal manifestations of SSc respond to any specific medical therapy.

Esophagus

The esophagus is the most commonly affected organ in the GI tract in SSc, with involvement seen in over 90% of patients via both pathology [8] and symptom assessment [9]. Symptoms are related to dysmotility and commonly consist of dysphagia, heartburn, and regurgitation. The pathogenesis of dysfunction is still not clear and prior investigations have suggested several potential mechanisms. Sjogren proposed a progression of GI SSc involvement composed of three distinct steps: (1) vascular damage, (2) neurogenic impairment, and (3) replacement of normal smooth muscle by fibrosis and atrophy [10]. Under this model, there is loss of response to prokinetic therapy as fibrosis develops and progressive GI symptoms. However, to a certain extent, this theory remains speculative, as causal progression has never been demonstrated and other competing theories exist. Autoantibodies directed against enteric neurons have been identified in a subset of SSc patients [11]

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as have anti-muscarinic antibodies [12]. Responsiveness of the lower esophageal sphincter to exogenously administered methacholine but not pharmacologic administration of agents acting via cholinergic neurons supports the concept of a neurologic defect in SSc [13]. Autonomic dysfunction has also been posited as a potential mechanism [14]. In addition, there is contradictory data with regard to whether esophageal fibrosis is even present in these patients. A recent study using endoscopic ultrasound in patients with SSc revealed significant esophageal thickening as compared to unaffected controls [15]; however, in contrast, an autopsy study evaluating the esophagi of 74 patients with SSc showed significant atrophy (94% of patients) but no evidence of abnormal fibrosis [8]. It is of note that the autopsy study did not demonstrate a correlation between the histopathology and disease duration. Interestingly, although the neurons within the myenteric plexus were intact, a reduction in the interstitial cells of Cajal important in modulating nerve-muscle interactions was demonstrated. In addition, no animal model for scleroderma esophageal disease exists, although there is a mouse model for colonic fibrosis [16].

Very recently, in a novel experiment, Taroni and colleagues evaluated esophageal biopsies in patients with and without scleroderma. They performed molecular characterization of gene expression combined with detailed histological analysis and identified distinct subgroups with either an inflammatory gene expression signature or a proliferative/non-inflammatory signature – and showed that these signatures appeared to be independent of traditional clinical markers of disease progression. Interestingly, similar gene expression signatures previously identified in SSc skin biopsies were recapitulated in SSc esophageal biopsies – implying that the underlying pathogenesis in individual patients may be similar in different organ systems. This study also suggested disease heterogeneity across SSc patients. Numbers evaluated in this study were small and clinical significance remains to be elucidated, but the mechanistic implications of this work are fascinating, and potentially this could lead to the development of future tissue biomarkers and recognition of molecular phenotypes with possible clinical implications [17].

Clinical Presentation and Complications

Symptoms attributable to esophageal dysfunction occur in the vast majority of patients with SSc and include heartburn, regurgitation, and dysphagia [7, 18–21]. Gastroesophageal reflux is of particular concern due to multiple contributing mechanisms, including peristaltic dysfunction, decreased lower esophageal sphincter (LES) pressure, delayed gastric emptying, autonomic dysfunction, occasional *sicca* syndrome (seen in 20% of patients), and occasionally an associ-

ated hiatal hernia [19]. Just as important as the loss of the LES as an antireflux barrier is the loss of reflux clearance mechanisms that include secondary peristalsis and salivary bicarbonate secretion. Medications used to treat other manifestations of SSc including phosphodiesterase inhibitors and calcium channel antagonists further impair LES function and may worsen reflux. Dysphagia for solid food is related to decreased or absent esophageal peristalsis. In spite of the degree of functional impairment of esophageal motility, dysphagia is generally mild and intermittent owing to the ability of gravity to facilitate bolus transit. Furthermore, many patients, up to 40% in some series, are asymptomatic despite well-documented esophageal dysmotility [22–25]. The clinical situation, however, can be complicated if a stricture is present due to reflux, pill-induced esophagitis, *Candida*, or other etiologies. Compensatory strategies include assuming an upright posture during meals and use of liquids between swallowing of solid food.

Esophageal dysmotility and reflux in the context of SSc can be associated with significant complications. Stricture formation is particularly prevalent and believed to be related to multiple possible etiologies, including reflux, pill-induced injury, and candidal infection. Prevalence of esophageal strictures in patients with SSc has been estimated to be as high as 29% [26]. The frequent administration of proton pump inhibitor in SSc has, however, almost certainly reduced the prevalence of peptic strictures over the past two decades. A case-control study involving over 100,000 subjects evaluating risk factors for erosive esophagitis or esophageal stricture formation reported that a concurrent diagnosis of scleroderma was associated with an odds ratio of 6.1 for erosive esophagitis and 12.3 for stricture formation [27]. While reflux is believed to be the classic precipitant, candidal esophagitis is worth discussing given that patients with SSc typically have multiple risk factors, including chronic acid suppression, antibiotic administration, impaired esophageal motility, and use of immunosuppressive agents. One study reported colonization/infection rates of 15% with strictures associated with all cases [28].

The prevalence of Barrett's esophagus has been reported to be as high as 37% [29]; however, other investigators have reported significantly lower findings [26, 28], and due to this wide variation, it is not clear whether the prevalence of Barrett's esophagus in SSc patients exceeds that of the general public. Likewise, it is not clear that the risk of esophageal carcinoma is abnormal for patients with SSc [30]. It is also worth noting that most of the literature evaluating concerns for Barrett's esophagus and cancer predates widespread PPI use.

Finally, the natural history of esophageal dysmotility in SSc is not well studied; however, one recent publication evaluated patients seen over a 13-year period who had multiple esophageal scintigraphy transit studies performed. In

this publication, esophageal motility worsened in 96% of patients with diffuse SSc as compared to 59% of patients with limited SSc [31].

Relationship to Pulmonary Disease

The relationship between reflux and pulmonary disease is not well established; however, reflux may contribute to pulmonary disease through two mechanisms: (1) microaspiration leading to direct injury and (2) vagal stimulation leading to bronchoconstriction. In addition, pulmonary disease may lead to increased reflux through alteration of esophageal/gastric pressure dynamics related to enhanced inspiratory force and diminished intrathoracic pressure, use of medications that decrease lower esophageal sphincter pressure (in particular bronchodilators and sildenafil), and potentially hiatal hernia formation. Given the morbidity and mortality associated with SSc lung disease, this relationship has substantial clinical importance.

Several studies have suggested a correlation between esophageal reflux and SSc lung disease [32–36]. However, this finding has not been universal as one study did not show any association [37]. Recently, this relationship has been evaluated with pH/impedance monitoring and high-resolution computed tomography, and a strong correlation was noted between interstitial lung disease and esophageal acid exposure, acid reflux numbers, nonacid reflux numbers, and proximal reflux (all with p values <0.01) [38]. Another recent study from the Canadian Scleroderma Research Group with over 1,000 patients also showed a strong correlation between symptoms of esophageal dysmotility and worsening pulmonary function (also with p values <0.01) [39]. Given this information, the relationship between the two entities appears consistent and likely genuine; however, causality has not been established, and there is no data at present to prove that treatment of reflux in patients with SSc has any effect upon long-term pulmonary function [40].

Diagnostic Evaluation

Multiple diagnostic modalities exist to evaluate esophageal function and disease in patients with SSc. If dysphagia is present, a barium esophagram is often the initial study as it provides information related to both structure and function. Dysphagia in SSc, however, is most commonly the result of dysmotility and not a structural lesion that can be visualized radiographically. On the other hand, while manometry is often considered the gold standard for esophageal function in SSc, it does not provide structural information and would not detect an esophageal stricture. Typical radiographic features include esophageal dilatation, presence of intraesopha-

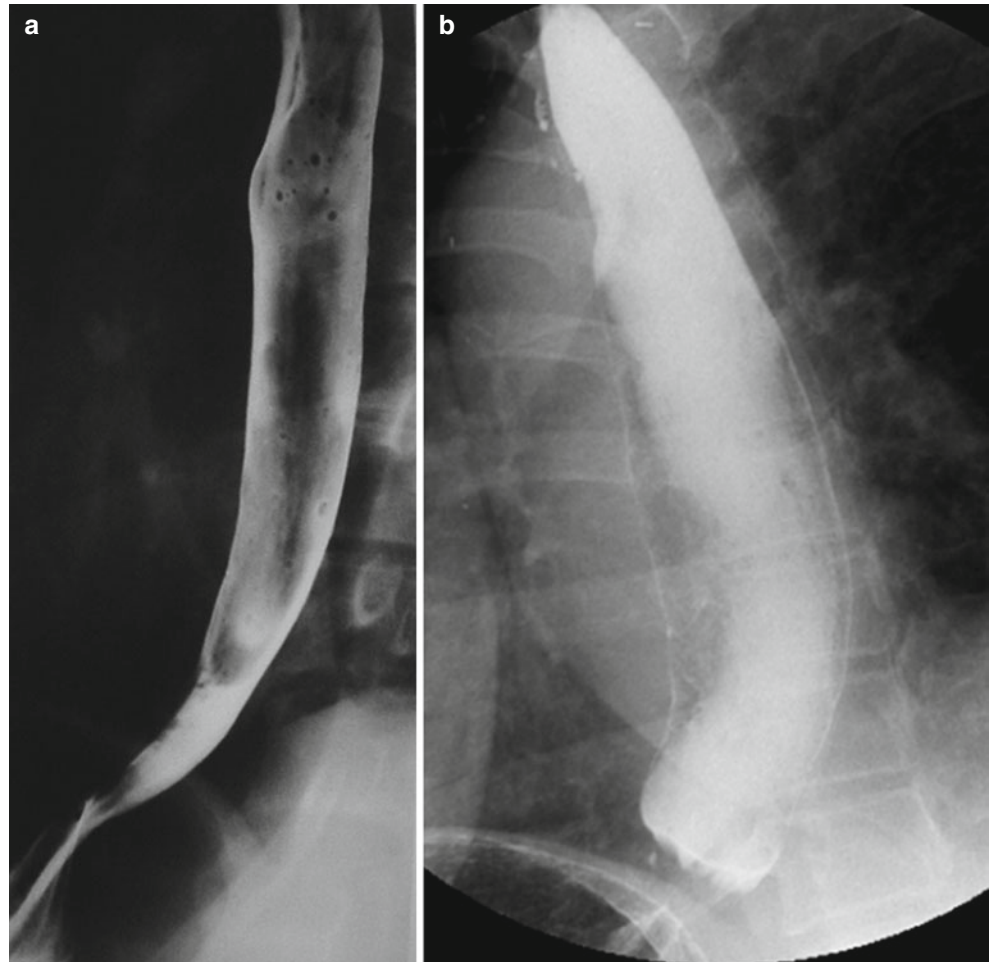
geal air, poor barium clearance, and a widely patent lower esophageal sphincter (Fig. 30.1) [41, 42]. Some authorities have recommended that a barium esophagram be the initial study for all patients with suspected scleroderma [43]; however, the sensitivity of barium studies for detection of SSc-related dysmotility has been shown to be less than manometry in several studies [43–46]. For this reason, most authorities would not recommend a barium study as the initial test for assessment of esophageal motility in the absence of significant dysphagia [19, 47].

Esophagogastroduodenoscopy (EGD) should be considered in patients presenting with esophageal symptoms related to SSc. Esophagitis has been reported in 32–77% of SSc patients undergoing endoscopy [21–23, 27, 28, 35, 43, 48–50]; however, multiple studies have shown that symptoms do not necessarily correlate with esophageal injury and that even SSc patients with no symptoms can have significant esophageal damage (Fig. 30.2) [28, 49–51]. In addition, as detailed above, *Candida* and Barrett's esophagus are clinical concerns and neither can be reliably detected without endoscopy. For these reasons, some authorities recommend early endoscopy for all patients diagnosed with SSc [49]; however, at present there are no guidelines to support that position and the decision to pursue endoscopy need to be individualized given the relative risks and benefits of the procedure. Other potential benefits of endoscopy include tissue acquisition for Barrett's esophagus to exclude dysplasia, identification of sites of upper GI hemorrhage, and ability to perform dilation of esophageal strictures.

Esophageal manometry is considered the gold standard for assessment of esophageal motility in patients with SSc [19, 47, 52]. Abnormalities are detected in up to 90% of patients, even in the absence of symptoms [53]. Typical findings on manometry include low-contraction amplitudes in the distal esophagus and, in more advanced stages, esophageal aperistalsis with decreased lower esophageal sphincter pressure (Fig. 30.3). Classically, esophageal contractile forces are maintained in the proximal esophagus, and the upper esophageal sphincter is uninvolved [54]. Defects in proximal esophageal contractile function may indicate concomitant myositis in patients with a mixed connective tissue disorder. Recently, high-resolution esophageal manometry (HRM) has entered the clinical arena, providing better quantification of peristaltic dysfunction (Fig. 30.3).

Finally, for patients with suspected reflux or continued symptoms despite medical therapy, formal reflux testing is often employed [55]. Traditional reflux testing consisted of a catheter-based pH study; however, two emerging technologies have been developed over the last decade and have changed the landscape with regard to reflux testing. Wireless pH testing eliminates the need for a catheter and records esophageal pH over a 48–96 h span. It can be combined with endoscopy, but also can be placed without endoscopic guid-

Fig. 30.1 Barium esophagram in scleroderma. Panel (a) depicts a normal esophagus with tapering at the esophagogastric junction. Panel (b) from a patient with scleroderma demonstrates pan esophageal dilatation



ance if baseline endoscopic information is known or a manometry is performed concurrently. Advantages of the wireless pH system include improve patient tolerability and prolonged recording periods that allow for increased detection of symptom-reflux correlation. The main limitation of wireless pH testing, though, is that it only looks at esophageal pH and does not allow assessment of weakly acidic or nonacidic reflux. The second emerging technology is pH impedance, which allows simultaneous measurement of bolus flow and esophageal pH, thereby allowing separation of acidic, weakly acidic, and nonacidic reflux as well as assessment of the proximal extent of reflux. While PPI therapy effectively controls esophageal acid exposure, it does not eliminate nonacid reflux which can be a major cause of morbidity in SSc patients owing to incompetency of the LES and delayed gastric emptying. Impedance technology has been studied in patients with SSc [38, 56] and does provide additional information; however, it requires an indwelling nasogastric tube for 24 h and the associated limitations therein. For clinical purposes, both modalities allow accurate assessment of reflux and can help guide clinical management in the context of ongoing reflux symptoms related to SSc [57].

Treatment

Treatment of SSc esophageal disorders can be challenging. Available therapies directed at the slowing or reversing of SSc progression including high-dose immunosuppression and stem cell transplantation have not demonstrated correction of the underlying gastrointestinal dysmotility. Nevertheless, effective therapies exist for managing the consequences of esophageal dysfunction. For those with reflux, initial treatment often consists of lifestyle modifications – including elevation of the head of the bed, avoidance of meals within 3 or more hours of lying supine, and avoidance of alcohol, caffeine, nicotine, and other known reflux exacerbants (such as tomatoes, citrus, garlic, chocolate, peppermint, onions). Care should be taken to minimize medication use that could result in esophageal inflammation or altered esophageal motility. If therapy is required for Raynaud’s syndrome, diltiazem should be employed rather than other smooth muscle relaxants as it may have less effect on lower esophageal sphincter pressure [58, 59].

Acid suppressive therapy with proton pump inhibitors (PPI) is the mainstay of therapy for reflux in patients with

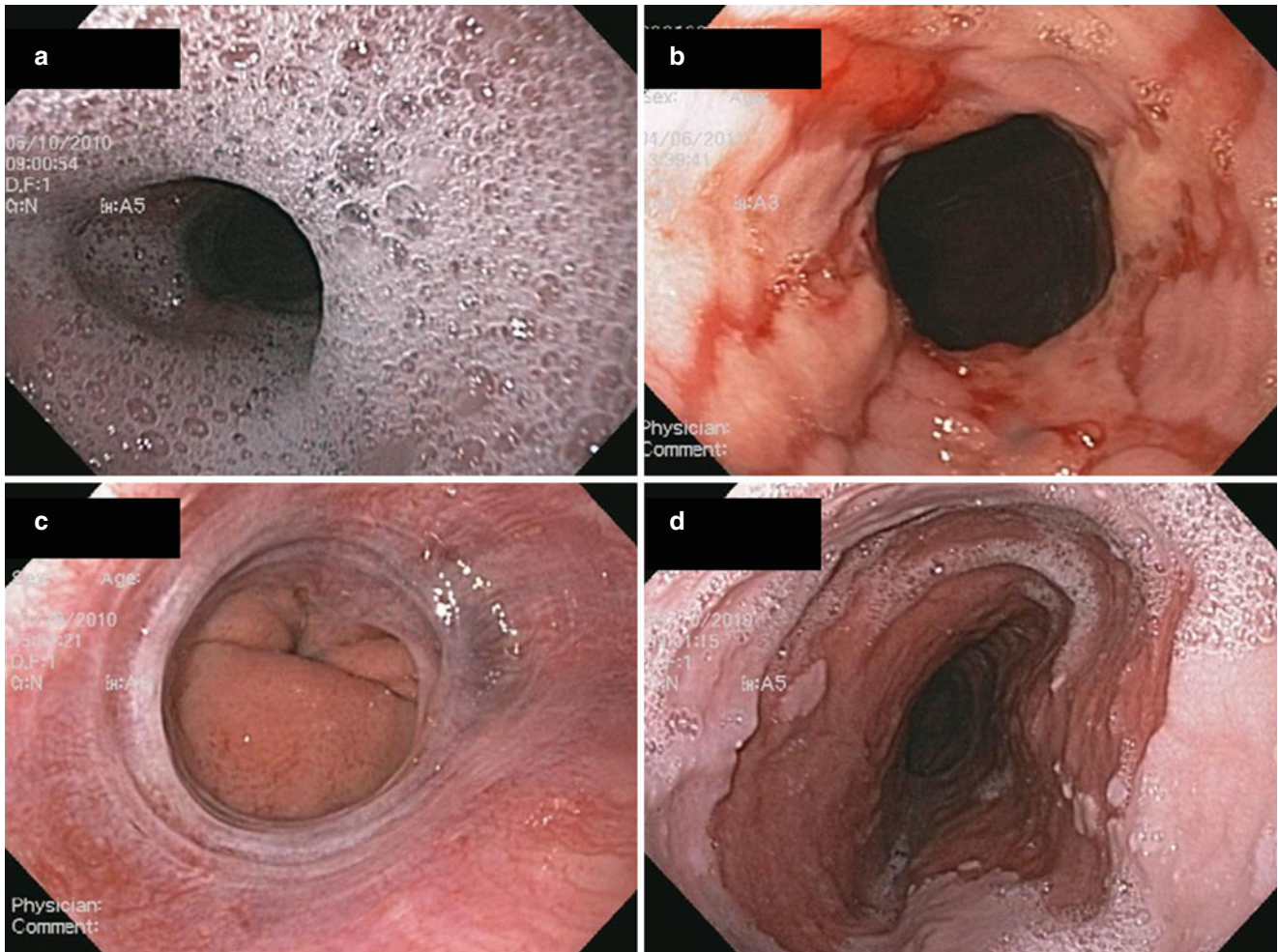


Fig. 30.2 Esophageal endoscopic findings in scleroderma. Panel (a) depicts retention of saliva within the esophagus. Panel (b) demonstrates reflux esophagitis with ulceration and stricture formation at the esogastric junction above a hiatal hernia. Panel (c) shows a peptic stricture. Panel (d) illustrates long segment Barrett's esophagus with small islands of squamous mucosa in a patient with scleroderma

gogastric junction above a hiatal hernia. Panel (c) shows a peptic stricture. Panel (d) illustrates long segment Barrett's esophagus with small islands of squamous mucosa in a patient with scleroderma

SSc. Specific randomized controlled trials showing efficacy of PPI use in patients with SSc are lacking; however, the efficacy of PPI use in the treatment of gastroesophageal reflux in the general population is well documented, and recent expert consensus (European League against Rheumatism Scleroderma Trials and Research group, UK Scleroderma Study Group) recommends PPI use for the prevention of SSc-related reflux disease, strictures, and esophageal ulcers [60, 61]. This recommendation is supported by several small studies showing improvement in either symptoms or esophagitis with prolonged PPI use [50, 62, 63]. Despite the above recommendation, it is not clear that PPI use changes the natural history of scleroderma, and there is still some debate as to whether treatment should be based on symptoms or objective measures of esophageal acid exposure [19]. There is also data to suggest that SSc patients may require higher PPI dosages than other patients with reflux symptoms [50, 64]. This is not surprising given the impairment of multiple

physiologic determinants of reflux in SSc. On the other hand, concerns exist regarding potential complications of long-term PPI therapy such as small intestinal bacterial overgrowth [65] and osteoporosis [66]. Histamine receptor blockers have also been employed with some efficacy; however, the data behind their use is less robust than with PPI use [67, 68]. One study adding ranitidine to high-dose omeprazole in SSc patients showed no change in nocturnal acid breakthrough, reflux, or quality of life [69].

If symptoms progress despite high-dose acid suppressive therapy and lifestyle change, the next step in therapy is typically the addition of a prokinetic agent. This pharmacologic category has been shown to accelerate gastric emptying and increase lower esophageal sphincter pressure. Several small randomized controlled trials demonstrated efficacy of short-term cisapride [70–74]; however, cisapride has been withdrawn from the market in the United States due to fatal, albeit rare, arrhythmias associated with long QT syndrome

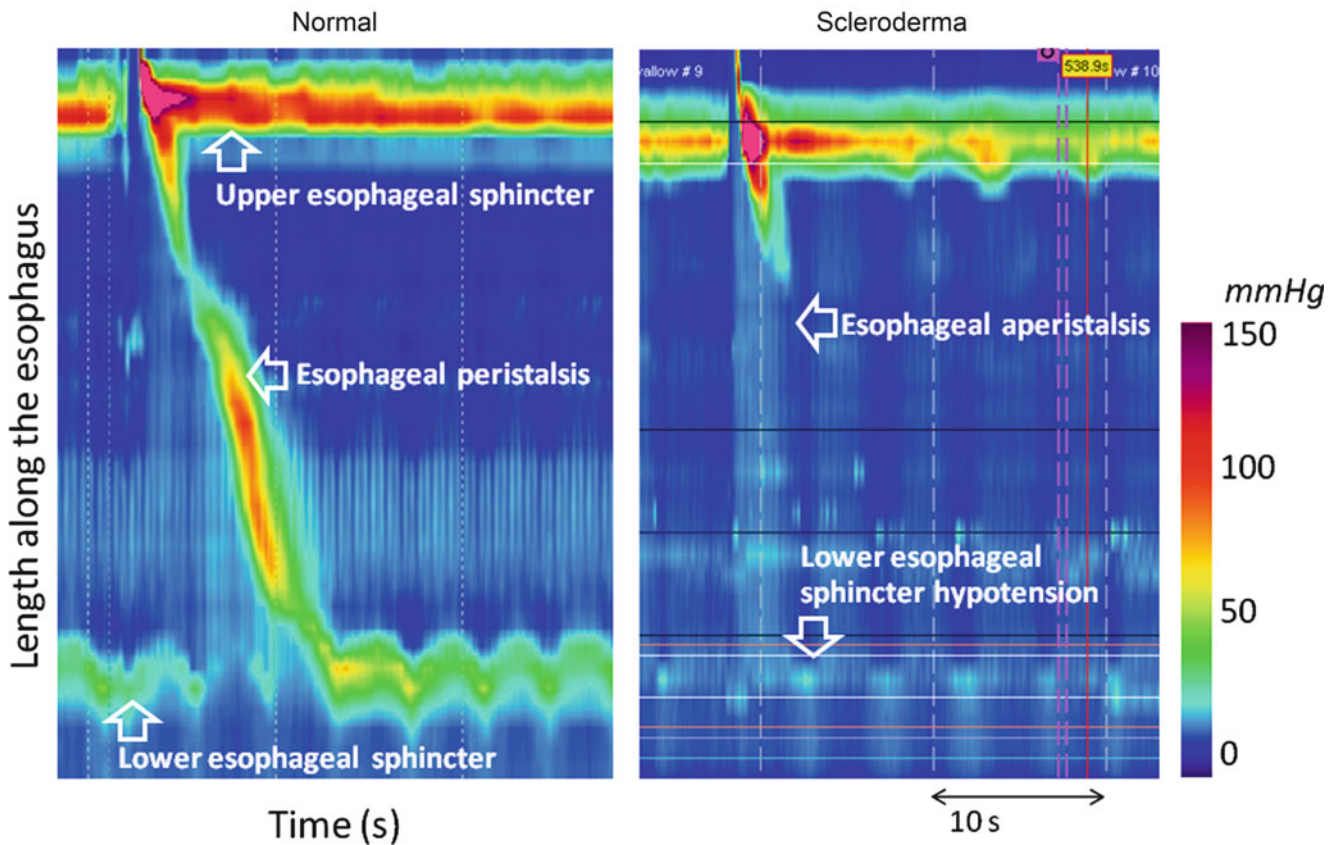


Fig. 30.3 High-resolution esophageal manometry contour plot in scleroderma. The *left* panel depicts a normal swallow with relaxation of the upper esophageal sphincter, sequential contractions in the esophageal body, and relaxation of the lower esophageal sphincter. The *right*

panel from a patient with scleroderma demonstrates intact function of the upper esophageal sphincter and proximal esophagus but complete loss of contractile activity in the esophageal body and lower esophageal sphincter

and is available only in select countries or via Janssen Pharmaceutica for compassionate use. Limited data supports the use of metoclopramide in acute use [75–78]; however, long-term data demonstrating efficacy for metoclopramide is lacking, and safety concerns exist regarding long-term metoclopramide and tardive dyskinesia [79]. Limited data exist regarding erythromycin [80, 81]; however, this agent can be associated with tachyphylaxis and nausea in a substantial subset of patients and may not be ideal for long-term use. Finally, domperidone has been suggested as possible treatment [82] with less side effects than metoclopramide; however, there is limited data regarding domperidone in SSc patients, and this drug is not FDA approved in the United States. Overall, the clinical and physiologic benefits of available prokinetic agents in SSc are, at best, modest. Nevertheless, despite the limitations detailed above, a recent expert consensus recommends consideration of prokinetic drugs for the management of SSc-related symptomatic motility disturbances, including dysphagia and reflux [60].

A recent addition to the SSc dysmotility armamentarium has been buspirone, an oral 5-HT_{1A} recent agonist which is believed to exert action on receptors in the esophagus and

fundus. It was recently found to reduce symptom severity in patients with dyspepsia, presumably due to enhanced fundic accommodation [83] – and also to improve esophageal peristalsis and enhance lower esophageal sphincter pressure in healthy volunteers [84]. Investigators from Greece evaluated 20 SSc patients with manometry before and after buspirone administration and found that buspirone enhanced lower esophageal sphincter pressure and improved peristalsis [85]. Clinical implications of this work remain uncertain; however, buspirone may be an option for patients who remain symptomatic despite further therapy, although more data are required to determine clinical efficacy and long-term safety.

In the event that gastroesophageal reflux cannot be controlled with medical therapy, surgical options do exist. Surgery is sometimes contemplated for relief of symptoms of heartburn or regurgitation that persist in spite of high-dose proton pump inhibition. The most common antireflux procedure performed today is the laparoscopic Nissen fundoplication; however, this can be associated with substantial dysphagia in SSc patients with severe dysmotility. The addition of even a minor degree of mechanical restriction at the esophagogastric junction in an SSc patient with absent

esophageal peristalsis may result in the development of secondary achalasia. Early published series report postoperative dysphagia rates ranging from 31 to 71 % [86–89]. Because of these reports, surgical intervention has typically been reserved for severe cases. Recently, a retrospective review of 23 SSc patients undergoing antireflux surgery revealed improved reflux and dysphagia postoperative rates with laparoscopic Roux-en-Y gastric bypass as compared to fundoplication [90]. Based on these studies, surgery is an option for select patients; however, the risk of postoperative dysphagia needs to be considered, and this is typically a last resort when medical therapy has been unsuccessful.

Stomach

Gastric manifestations of SSc are highly variable and stem from both dysmotility and vascular ectasia. Symptoms of gastric dysmotility (including heartburn, regurgitation, nausea, bloating, epigastric pain, early satiety, and postprandial fullness) have been reported in approximately 50 % of patients [7, 26, 52, 91, 92]. Bleeding related to gastric antral vascular ectasia is seen far less commonly and will be discussed later in this chapter [93, 94]. The pathogenesis of gastric dysmotility remains unclear but is believed to be related to both neuropathic and fibrotic changes as detailed above. Gastric involvement is associated with worsened morbidity and mortality [2, 3].

Clinical Presentation

Symptoms associated with gastric dysmotility are seen in approximately 50 % of patients and include nausea, bloating, epigastric pain, early satiety, and postprandial fullness. In addition, gastric dysfunction also contributes to gastroesophageal reflux and may manifest only as traditional reflux symptoms, such as heartburn and regurgitation. Interestingly, the presence and severity of symptoms may not correlate with gastric dysfunction as measured by scintigraphy and electrogastrography (EGG) [92, 95, 96]; however, there is data to suggest that the presence of esophageal involvement corresponds with a higher rate of gastric involvement [7].

Multiple potential mechanisms have been hypothesized and objective studies of gastric function have recorded widely divergent findings – based on patient selection and study protocol. For example, gastric emptying has been recorded to be delayed in anywhere from 10 to 75 % of SSc patients, based on studies using scintigraphy, radio-opaque markers, C¹³-labeled breath tests, and ultrasonography [51, 52, 78, 95–102]. Hypothesized mechanisms whereby SSc impairs gastric motility include alterations in gastric accommodation, motility patterns, gastric myoelectrical activity,

and gastric emptying [92]. The relative role of each of the aforementioned mechanisms is not clearly established at this time and may vary for individual patients.

Diagnostic Evaluation

There is no consensus regarding the appropriate initial study for the evaluation of gastric dysmotility in patients with SSc. Given the high prevalence of esophageal dysmotility and the nonspecific nature of the recorded symptoms, initial evaluation often consists of a barium contrast study and/or upper endoscopy. Barium contrast radiography allows a gross evaluation of gastric motility and exclusion of mechanical obstruction. Typical findings related to gastric involvement include gastric dilatation, hypomotility, and delayed transit; however, barium contrast radiography is neither sensitive nor specific and is rarely if ever performed solely for assessment of gastric SSc involvement [42]. Similarly, upper endoscopy has utility in the evaluation of SSc and allows assessment of gastritis, peptic ulcer disease, esophagitis, and a gross assessment of pyloric contractions; however, the utility of endoscopy for SSc is primarily limited to assessment of inflammation and potential bleeding etiologies, whereas the role of endoscopy in assessment of gastric motility is limited. Retained food within the stomach during routine endoscopy is generally indicative of delayed gastric emptying as patients are instructed to fast for approximately 8 h prior to the procedure. If identified in the setting of an accurate history of meal timing, retained food may obviate the need for additional testing for gastric transit.

Gastric emptying studies have been the traditional test of choice for evaluation of gastric motility. Studies employing a variety of techniques – including scintigraphy, radio-opaque markers, C¹³ breath tests, and ultrasonography – have reported abnormalities in gastric emptying in between 10 and 75 % of SSc patients, although the bulk of the studies appear to show impairment in approximately 50 % of patients [26, 52, 78, 96, 99]. As these studies were performed in tertiary care facilities, these recorded values may overestimate the true prevalence of impaired gastric emptying in SSc. In the United States, the most commonly performed modality of gastric emptying study is scintigraphy, and normative values have been well-established [103]. However, this study is not without controversy as it can be expensive, and symptoms do not always correlate with objective emptying abnormalities, both in SSc and other unrelated conditions [99, 104]. Gastric emptying has also been assessed by other modalities, including radio-opaque marker transit [96], ultrasonography [102, 105], and breath testing [52, 106].

Recently, gastric emptying has been evaluated via a wireless capsule motility system (SmartPill) that provides prolonged recording of temperature, pH, and pressure. Whole

transit is recorded over a several day period, and region transit (gastric emptying, small intestinal transit, colonic transit) can be distinguished through analysis of the pH and pressure profiles. In theory, this technology offers the ability to measure whole gut and regional transit as well as segmental motility patterns without the need for radiation exposure or catheter-based monitoring; however, data is still emerging regarding appropriate normative values and subtleties of interpretation. In addition, there is no data to date regarding the use of this technology in SSc patients. Finally, as the capsule is ingested, a theoretical risk of capsule retention does exist, and patients must be monitored to ensure the capsule has exited appropriately [107–109].

Gastric motility and myoelectrical activity can also be recorded using antroduodenal manometry (ADM) and electrogastrography (EGG). ADM consists of a manometry catheter which is passed transnasally and positioned so that pressure sensors are located in the duodenum and stomach. Prolonged pressure monitoring can be performed to allow assessment of migrating motor complex activity – in particular assessment of frequency, amplitude, and coordination of contractions. In patients with SSc, this technology can demonstrate decreased contractile amplitudes and disrupted patterns of motor activity [26, 110, 111]. EGG consists of multichannel surface recordings of gastric myoelectrical activity. The use of this technology has been largely experimental, and while abnormalities are frequently detected, it remains controversial whether EGG abnormalities correlate with either symptoms or delayed gastric emptying [99, 111, 112]. At present, both ADM and EGG are offered primarily in tertiary motility centers, and their role in routine clinical care of SSc patients remains unclear. In addition, the wireless capsule motility study has been compared directly to ADM with favorable correlation and may offer a less invasive means of obtaining similar data [107].

Treatment

Treatment of SSc-related gastric dysmotility can be challenging owing to limited treatment options. Dietary modification is typically the first line of therapy, and a gastroparesis diet, consisting of multiple, small volume, low-fat meals, is typically recommended. Liquid emptying may be preserved in certain cases, and liquid nutritional supplements and a soft diet that requires less emulsification may be of benefit, although the data behind this recommendation are limited. Enteral feeding and/or decompression via gastrostomy or jejunostomy is occasionally performed, although there are no data available regarding this approach. Similarly, limited data are available regarding the utilization of total parenteral nutrition although this is usually reserved for SSc patients with severe gastric and small bowel dysmotility.

Prokinetic agents have been the mainstay of therapy, although the data are relatively limited. Nevertheless, this approach is recommended by recent expert consensus panels [60, 61]. Metoclopramide is the only agent approved by the Food and Drug Administration in the United States for treatment of gastroparesis; however, it is associated with significant side effects including potentially irreversible tardive dyskinesia. Data regarding metoclopramide in SSc-related gastric dysmotility is largely limited to small studies evaluating short-term effects [76, 78, 110]. While short-term efficacy has been demonstrated, there is no data regarding long-term use or safety. In addition, there is a case report of one SSc patient who experienced bradycardia and cardiac arrest following metoclopramide administration [113].

Domperidone is a peripheral dopamine receptor antagonist that is believed to cross the blood-brain barrier less effectively than metoclopramide and may provide equal or superior efficacy with less side effects. There is no data regarding usage of domperidone in SSc (other than one study evaluating domperidone in esophageal dysmotility) [85]; however, there is data to support the use of domperidone in other conditions associated with impaired gastric emptying [114, 115]. At present, this medication is not approved for use in the United States; however, it can be obtained via an FDA Investigational New Drug application and is also available in at least 50 other countries. Despite the lack of data in SSc, the use of this agent can be justified based on the recent EULAR consensus recommendations [60], favorable side effect profile, and limited options available. Concern does exist for potential QT prolongation and patients must be monitored closely if this agent is employed [116].

Erythromycin is a motilin agonist and has data to support usage in both scleroderma and unrelated conditions with impaired gastric emptying. Two short-term studies demonstrated improvement in gastric emptying with erythromycin administration; one of the studies also looked at symptom response and reported improvement in early satiety, nausea, vomiting, and abdominal pain [81, 97]. A single study looked at long-term use of erythromycin (up to 48 weeks in duration) and reported benefit; however, the patients in the study were also administered octreotide concurrently, and the relative merits of each agent were not clearly elucidated [117]. Of the available agents, erythromycin has been demonstrated to have the most potent gastric prokinetic function; however, in practice it is often not as attractive as other options for several reasons. First, it is associated with tachyphylaxis. Second, side effects include cramps, nausea, diarrhea, ototoxicity, and QT interval prolongation – all limiting use [118]. Third, although erythromycin has potent prokinetic properties, a systematic review concluded that available studies do not establish efficacy of erythromycin in relieving symptoms of delayed gastric emptying [119]. For all of these reasons, erythromycin may be a less than ideal option for

long-term use – although it does have the benefit of documented short-term improvement in SSc and availability in the United States.

Cisapride is a combined 5HT₄ agonist/5HT₃ antagonist and is the most investigated prokinetic available for treatment of SSc-associated dysmotility. Small studies have demonstrated improvement in gastric emptying, antroduodenal motility, and symptoms with acute and chronic use [70, 92, 120]. However, cisapride was removed from the US market due to QT interval prolongation and numerous deaths related to cardiac arrhythmia. It is available on a limited basis for compassionate use; however, it should be used with caution, and close monitoring of the QT interval is required if this medication is initiated.

Alternative therapies have also been employed for SSc-associated gastric dysmotility and are worth considering given the imperfections of established therapies. Ginger has been shown to accelerate gastric emptying in normal individuals [121] and has been used to relieve pregnancy-associated nausea [122]. This has not been studied in SSc or gastroparesis; however, given the innocuous side effect profile, it is worth considering as an adjunct therapy.

Recently, there has also been research directed toward acupuncture and related entities as a potential remedy [123]. Acupressure to a specific GI-associated acupuncture site (PC6) was found to alter gastric myoelectrical activity (GMA) as assessed by EGG in patients with SSc in one small study. Interestingly, the alterations in GMA correlated with symptoms [124]. Based on this preliminary study, the same group evaluated the role of transcutaneous electrical nerve stimulation in symptomatic SSc patients for a 14-day trial. They reported improvement in heart rate variability, symptoms, and quality of life [125]. A further study by the same investigators showed improvement in GMA, decreased mean plasma VIP and motilin levels, increased IL-6 levels, and symptom improvement after a 14-day trial [126]. While further studies are needed, these preliminary investigations are encouraging.

Finally, endoscopic and surgical options have been posited and are worth discussing. Botulinum toxin has been investigated in impaired gastric emptying. The proposed mechanism is that botulinum toxin injected into the pylorus may relieve gastric outlet obstruction and accelerate gastric emptying. Early anecdotal experience supported this assumption; however, more recent randomized controlled trials have not shown a benefit for botulinum toxin in idiopathic or diabetic gastroparesis, and for this reason, it has largely fallen out of favor unless there is documented pyloric spasm [127]. There is no data regarding the use of botulinum toxin in patients with SSc; however, as the physiology of SSc often results in impaired contractions and lower contractile amplitudes, one could argue that SSc-associated gastric dysmotility may be even more unlikely to respond to this therapy than

patients with impaired gastric emptying related to other conditions [118]. Surgical options have also been proposed for impaired gastric emptying, including pyloric myotomy, subtotal gastrectomy, gastric bypass, and gastric electrical stimulation. There is no data to support the use of any of these procedures in SSc-associated gastric dysmotility.

Gastric Antral Vascular Ectasia

GI hemorrhage is a known consequence of SSc and can be seen in up to 15% of SSc patients in a tertiary care facility [128]. Gastric antral vascular ectasia (GAVE), also known as watermelon stomach, is the major gastric manifestation which may lead to bleeding. This is an uncommon vascular condition that was first described in 1984 [129]. While classically associated with SSc, it is not specific to rheumatologic disorders and can also be seen in atrophic gastritis, diabetes mellitus, cirrhosis, chronic renal failure, and heart disease – as well as autoimmune disorders. The true prevalence of GAVE is difficult to determine; however, this does appear to be relatively uncommon and the largest series to date to evaluate this issue reported a prevalence of 5.7% (15 cases in 274 SSc patients); however, this may be an underestimation given that many patients may be asymptomatic in early stages, and the endoscopic findings of mild GAVE can be misinterpreted as antral gastritis by even experienced endoscopists [93]. A recent publication from the European League Against Rheumatism Scleroderma Trials and Research (EUSTAR) network estimated the prevalence of GAVE to be about 1% in SSc patients [130].

The pathogenesis of GAVE remains unclear. At the moment, there are two leading hypotheses. The first theory holds that antral mucosal prolapse and abnormal gastric motility may lead to submucosal ischemia and elongation/dilatation of mucosal vessels. This theory is supported by two lines of reasoning: (1) histological evidence of both fibromuscular hyperplasia and mucosal capillary dilatation and (2) documentation of select SSc patients with high-amplitude gastric antral contractions on antroduodenal manometry [93, 129, 131, 132]. The second theory suggests that GAVE may be related to SSc-associated diffuse cutaneous telangiectasia. This theory is supported by the fact that most patients with GAVE also have telangiectasia involving other regions of the body (in particular skin) or GI tract [93]. In either case, the predilection of this vascular abnormality for the gastric antrum may be related to the distinct motility patterns that characterize the gastric antrum in distinction to other regions of the stomach.

Given the rarity of GAVE, the natural history is not well studied; however, available data suggests that the vast majority of SSc patients diagnosed with GAVE (81%) already have an established diagnosis of SSc at the time of their

endoscopic GAVE diagnosis. In an additional 8% of patients, the diagnoses of SSc and GAVE were established concurrently, whereas in the remaining 11%, the diagnosis of GAVE preceded the diagnosis of SSc. In patients known to have a diagnosis of GAVE, the median time between SSc diagnosis and GAVE onset was 18 months. Given this data, GAVE appears to be an early manifestation of SSc and the majority of cases were diagnosed within 5 years of diagnosis. The prevalence of GAVE also appears to be similar in diffuse and limited SSc, although diagnosis may be earlier in diffuse SSc as opposed to limited. It is unclear whether GAVE activity is associated with SSc activity or a more aggressive SSc phenotype. One review reported that in the majority of patients, GAVE activity does not parallel SSc activity, and GAVE can occur or progress even when disease activity was not active on other fronts; however, another recent publication reported that in the majority of patients with diffuse SSc diagnosed with early GAVE, there was also a rapid progression of cutaneous disease [93, 94]. Finally, a recent EUSTAR case-control study of 49 patients with SSc and GAVE reported that patients with GAVE were associated with a vascular phenotype, including anti-RNA polymerase III antibodies and a high risk of renal crisis [130].

The classic clinical presentation of GAVE is iron-deficiency anemia related to occult GI bleeding. Available data suggests that this is the case in approximately 90% of patients, and the mean hemoglobin at time of diagnosis has been reported to be 6.7 g/dl. Other clinical presentations include overt bleeding with melena or hematemesis; however, this is present in only a minority of patients [93]. GAVE is not specific for SSc and has been described in other autoimmune disorders, hepatic cirrhosis, chronic renal failure, cardiac disease, and bone marrow transplantation. GAVE is sometimes confused with but is distinct from portal hypertensive gastropathy with the latter entity involving the mucosa of the gastric fundus and body. Histopathology of GAVE demonstrates the presence of microvascular thrombi, vascular ectasia, spindle cell proliferation, and fibrohyalinosis.

The endoscopic appearance is classically described as erythematous streaks projecting from the pylorus in radial fashion throughout the antrum (Fig. 30.4). The term “watermelon stomach” was coined as these streaks appear similar to the outside of a watermelon [129]. Another endoscopic variant that has been described is referred to as “honeycomb stomach” and consists of diffuse angiodysplastic lesions that coalesce in the antrum [133]. Finally, a third variant has been described in which there are well-demarcated round or mushroom-shaped lesions formed by a tuft of ectatic blood vessels [134]. In addition, involvement can extend proximal to the antrum in a subset of patients [93, 94].

Treatment for GAVE remains a challenge and data is relatively limited. There are no randomized controlled trials for

non-endoscopic treatments and initial therapy is often supportive. Given that the majority of GAVE patients present with occult bleeding and iron-deficiency anemia, the first step is often iron replacement therapy, optimization of bleeding parameters (if necessary), and minimization or avoidance of medications that could either promote bleeding or injure the gastric mucosa [134, 135]. Proton pump inhibitors are also usually employed to decrease any further mucosal injury that may be potentiated by gastric acid [93]. Blood transfusions are often required given the low hemoglobin at diagnosis, other comorbidities, and slow response with the above measures – and despite conservative therapy, as many as 60–70% of patients remain transfusion dependent [134].

The number of medical therapies that have been attempted bespeaks to the inadequacies of the current options. Steroids were attempted in several early reports with moderate success. Combining those reports, 11 patients have been given steroids alone and six were reported to have complete resolution of bleeding; however, another patient had hyperglycemia and four patients had no response [134]. A case report detailed a single patient who received intravenous methylprednisolone and cyclophosphamide with complete resolution [136]. The potential benefits of steroids have to be weighed against the risks and potential caustic effect on GI mucosa.

Cyclophosphamide is also an option for refractory GAVE. In addition to the single case report detailed above using cyclophosphamide in combination with steroids, there is a recent case series describing three patients with SSc-related GAVE treated with intravenous pulse cyclophosphamide – all of whom had improvement via both clinical and endoscopic parameters [137]. However, at present this data is limited to three patients and confirmatory studies are needed.

Hormonal therapy was initially hypothesized as a treatment due to the observation that epistaxis associated with Osler-Weber-Rendu syndrome decreases during pregnancy and worsens postpartum. In an open pilot study looking at a combination of estrogen and progesterone for GAVE related to cirrhosis, four of six patients had complete cessation of bleeding; however, the endoscopic appearance was not altered, raising concern that bleeding would recur upon symptom discontinuation. In addition, the long-term risks of hormonal therapy have to be considered, and it is worth mentioning that three of the six patients treated in this study developed gynecomastia and menorrhagia [138]. A few case reports support this approach; however, data remains very limited, and this likely remains an option best suited for postmenopausal women or SSc patients judged to be too high risk for endoscopic approaches [134].

Octreotide is a third option that has been studied in cirrhotic patients with refractory vascular GI bleeding, some of whom had GAVE. However, much of this benefit may have

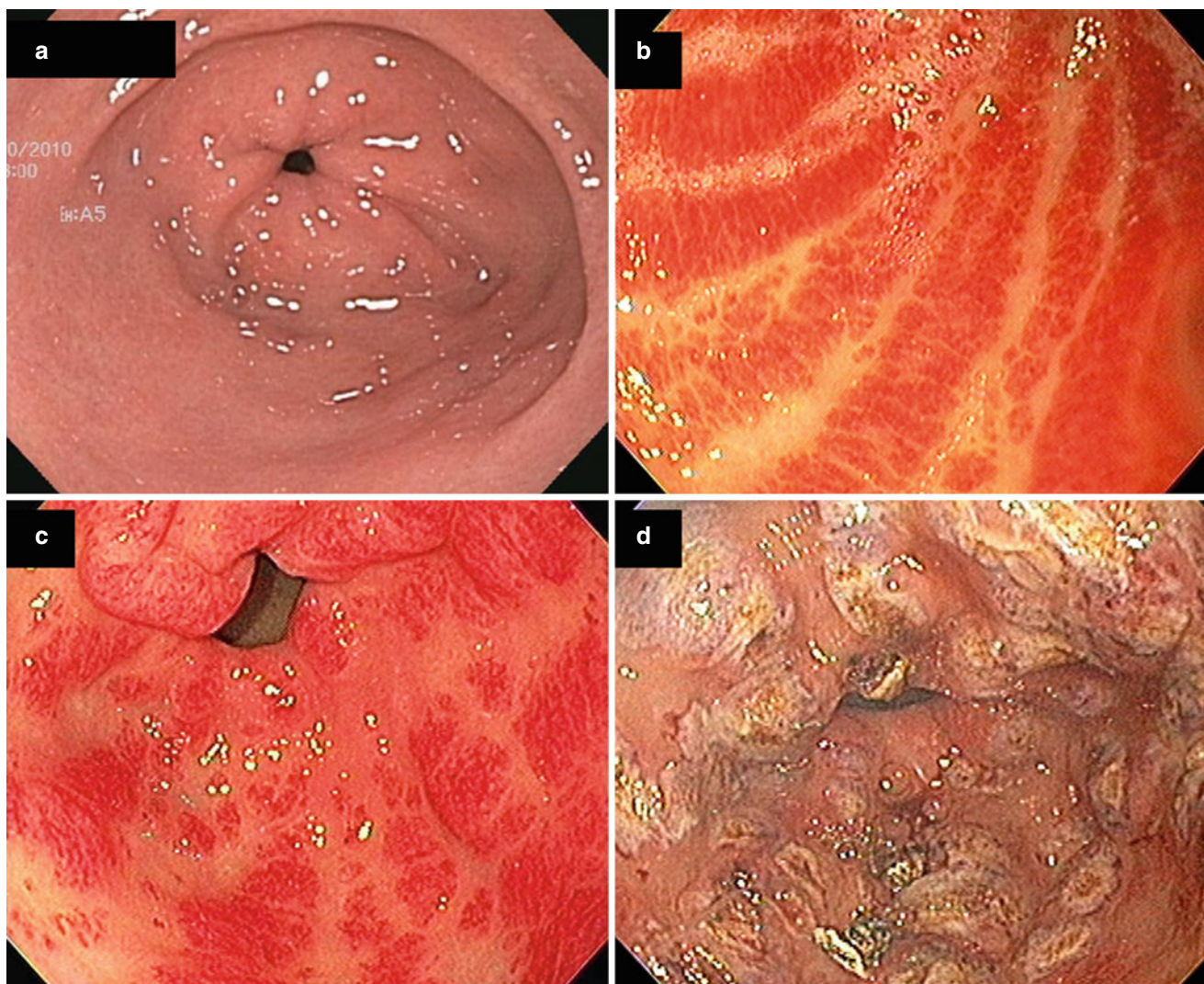


Fig. 30.4 Gastric endoscopic findings in scleroderma. Panel (a) shows the normal appearance to the gastric antrum. Panels (b, c) depict scleroderma patients with gastric antral vascular ectasia (GAVE) with erythematous, linear streaks along the long axis of the antrum. Panel (d)

shows the appearance of GAVE immediately after therapy with argon plasma coagulation. The white patches represent superficial mucosal injury created by the therapy that rapidly heal and are replaced by normal gastric mucosa

been from decreased portal pressure in the context of cirrhosis, and it is unclear if the same benefit would apply to patients with SSc. A case report describes a patient with SSc who received octreotide for GAVE without benefit [93]. Finally, there are additional case reports of other medical therapies for GAVE patients without SSc, including histamine receptor antagonists, calcitonin, tranexamic acid, interferon, serotonin antagonists, and thalidomide; however, none of these have been reported for SSc-related GAVE [93, 134].

Endoscopic therapy has become the mainstay of treatment when supportive care and medical therapy is unsuccessful. Multiple endoscopic ablative modalities have been employed, including Nd:YAG laser, argon plasma coagulation (APC), bipolar electrocautery, heater probe, and argon laser. Traditionally, the mainstay of treatment was with the

Nd:YAG laser system, and it has the largest literature to support use, with reported success rates of approximately 80% over multiple treatments; however, significant complications were reported, including hyperplastic polyps, multifocal gastric neoplasia, perforation, and death [93, 134]. APC is an electrocoagulation technique which induces superficial injury to the affected tissue through a high-frequency monopolar current conducted through ionized argon gas. As compared to Nd:YAG laser, APC offers the theoretical advantages of limited penetration depth and coagulation effect to the surrounding tissue, resulting in less complications. Published success rates for APC have been similar to those for Nd:YAG laser. Due to similar efficacy and less risk, APC has become the standard of care at present for endoscopic treatment of SSc-related GAVE [3, 93, 134].

Two new endoscopic techniques have entered the clinical arena and are worth considering: cryotherapy and radio-frequency ablation (RFA). Cryotherapy consists of the endoscopic application of either nitrous oxide or carbon dioxide (based on the system employed), resulting in a controlled thermal injury to the gastric mucosa. As opposed to Nd:YAG laser or APC, cryotherapy allows treatment of large mucosal areas relatively quickly and offers the potential of shorter procedure times and technical ease with perhaps equal efficacy. This may be especially beneficial for diffuse GAVE with large areas of involvement. The first trial evaluating cryotherapy in the human GI tract was in 2003 and included seven patients with GAVE (71.4% response) [139]. A second study employing cryotherapy specifically for 12 patients with GAVE reported a 50% complete response rate and 50% partial response rate; however, it is worth noting that eight of the 12 patients enrolled in the study had previously been treated unsuccessfully with APC [140]. Of note, it is unclear from both studies whether any of the affected patients had SSc. Nevertheless, given this information, cryotherapy is worth considering in patients with disease refractory to APC, in particular in those patients with diffuse involvement.

The second emerging endoscopic technology is RFA. This technology allows a focused radio-frequency energy delivery to gastric tissue and results in a controlled superficial injury with uniform depth of ablation. There is recent extensive data regarding this technology in Barrett's esophagus, showing both efficacy and safety [141]. Recently, this technology was employed in six patients with GAVE with no complications and improvement in five of the six treated [142]. While it is unclear if any of the patients in the study had SSc and this data is limited, this technology may be used more frequently in the future given the growing usage of RFA in Barrett's esophagus, presence in endoscopy units, and increasing technical proficiency of endoscopists.

Surgical management has been reserved as the final option for those patients who have failed endoscopic treatment options. Antrectomy has been the most common procedure performed; however, there is significant morbidity and mortality associated with this procedure, and one report suggested a mortality rate of 7.4% (in all GAVE patients, not SSc-related GAVE specifically) [93, 134, 135]. Given this, antrectomy should be reserved as a last resort for SSc patients with GAVE; however, it is an option if all else fails.

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