Chapter 16
Gastroesophageal Reflux

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Clinical Vignette

Case 1: A 35-year old woman with a 5-year history of Raynaud phenomenon and 6 months of puffy hands that prohibits her from wearing rings presents to the emergency department with complaints of substernal chest pain and inability to catch her breath. The patient endorses smoking cigarettes (10 cigarettes per day for 20 years). She takes no medications. Her family history is significant for a maternal cousin with systemic lupus erythematosus. On exam, the skin on her fingers bilaterally appears shiny and tight. Digital pitting is noted on the finger pulps. ECG abnormalities and elevated troponins are not noted. Chest computed tomography for pulmonary emboli reveals no evidence for emboli, but ground glass opacities especially in the right middle lobe and at the lung bases bilaterally are noted. She is discharged

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home on daily omeprazole daily and told to follow-up with her primary care physician for gastroesophageal reflux.

Case 2: A 45-year old woman with diffuse cutaneous systemic sclerosis (dcSSc) for 1 year complicated by polymyositis presents with severe epigastric pain. She was initially prescribed prednisone 60 mg PO QD with steroid taper and weekly oral alendronate pills to prevent steroid-induced osteoporosis along with calcium, vitamin D and weight-bearing exercise. She notes midline pain just inferior to the xiphoid process. She presents to a rheumatologist who urges her to stop taking weekly alendronate and refers the patient to a gastroenterologist who performs an upper endoscopy (EGD). During the EGD, a large white tablet, likely alendronate, is extracted from the upper esophageal 1/3 and proton pump inhibition is prescribed. Three weeks later the patient endorses complete resolution of pain.

Epidemiology

Reflux of gastric contents into the esophagus resulting in symptoms or esophageal damage is referred to as gastroesophageal reflux disease (GERD). Gastroesophageal reflux disease is highly prevalent in patients with systemic sclerosis (SSc/scleroderma) and can be associated with impairments in health-related quality of life especially sleep [1, 2]. Abnormal esophageal motility on diagnostic testing is reported in 75–90% of patients with SSc, highlighting an additional pathophysiologic component [3]. The prevalence of SSc-GERD depends upon the detection modality that includes barium swallow, high-resolution manometry, pH reflux and impedance testing and upper endoscopy/ esophagogastroduodenoscopy (EGD). SSc subtype (limited versus diffuse cutaneous), age, race and sex do not appear to strongly influence SSc-GERD development, but longer SSc duration and the presence of interstitial lung disease have been associated with more manometric esophageal abnormalities [4, 5].

Pathogenesis

Gastroesophageal reflux (GER) is a physiologic process whereby gastric contents flow retrograde into the esophagus [6]. Patients with SSc can experience acid and/or non-acid GER (discussed below). In the postprandial period, gastric acid floats atop undigested food forming what is called the gastric acid pocket that functions as a gastric acid reservoir [6]. The higher the location of the gastric acid pocket relative to the crural diaphragm, the more acidic the refluxate [6]. Additionally, impairment of normal esophageal peristalsis in SSc also contributes to GERD development. Abnormal esophageal function in SSc has been attributed to a four-stage process that mirrors SSc skin changes: (1) an early vasculopathy that manifests as mild changes in intestinal permeability, transport, and absorption, (2) neural dysfunction, (3) smooth muscle atrophy, and (4) end-stage fibrosis [7]. Autopsy studies demonstrate that the major pathology is likely smooth muscle atrophy as opposed to fibrosis [8–11]. Additionally, antimyenteric autoantibodies have been described in SSc patients that may contribute to neural dysfunction [12]. The end result is a flaccid esophagus and lower esophageal sphincter (LES) that permit GER.

Clinical Presentation

Patients with SSc-GERD may spontaneously report typical reflux symptoms including the sensation of intermittent regurgitation of stomach contents into the chest, throat or mouth especially following meals, or during forward flexion or recumbency. In most cases, patients will only endorse typical GERD symptoms during a detailed review of systems. Atypical GERD symptoms include atypical chest pain (Case 1), hoarseness, pharyngitis, halitosis, dental and periodontal issues, and nasopharyngeal complaints (ear and sinus fullness). In these instances, a high index of suspicion is required for accurate diagnosis. The presence of extraesophageal

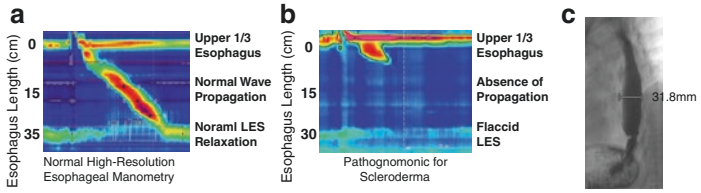

Figure 16.1 High-resolution esophageal manometry. (**a**) Image from a normal exam showing the initiation of a swallow and normal esophageal peristalsis and lower esophageal sphincter relaxation. (**b**) Image from an abnormal exam from a patient with SSc showing absent esophageal peristalsis and lack of lower esophageal sphincter relaxation. (**c**) Esophagram or barium swallow exam that demonstrates esophageal dilation as well as peptic stricture formation, a consequence of uncontrolled gastroesophageal reflux disease

symptoms such as cough, throat irritation, hoarseness, laryngitis or pharyngitis should prompt consideration of additional diagnostic testing including esophageal reflux testing and manometry (Fig. 16.1a and b) or barium swallow (Fig. 16.1c). Long standing, uncontrolled GERD commonly results in peptic stricture formation with resultant dysphagia.

Diagnostic Evaluation

Twenty-four-hour ambulatory pH testing with multichannel intraluminal impedance (MII) is the current state-of-the-art GERD assessment tool (Fig. 16.2). Patients record timing of meals, medications and sleep and note reflux symptoms by depressing a button on an event recorder worn around the waist or over the shoulder. The nose is anesthetized prior to placement of the catheter that is swallowed into the stomach, and no sedation is provided to enable patient participation. The catheter consists of impedance recording channels intermittently spaced as well as pH electrodes placed at different points in the esophagus. The impedance recording channels detect liquid, semisolid, or gas GER episodes based on elec-

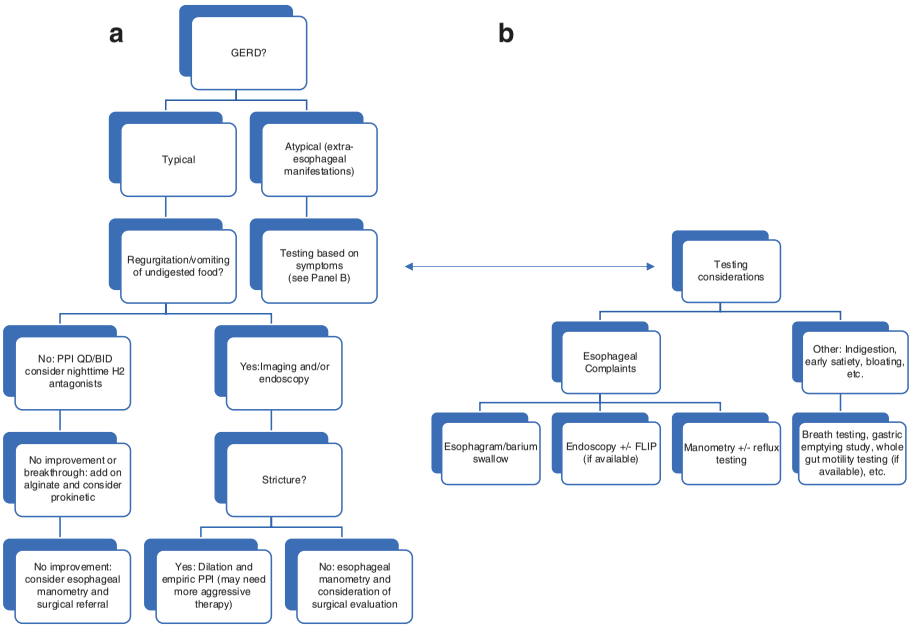

FIGURE 16.2 Approach to the SSc patient with gastroesophageal reflux disease (GERD). (**a**) SSc patient with typical GERD symptoms. (**b**) SSc patient with atypical GERD symptoms. *FLIP* Functional Lumen Imaging Probe

trical resistance changes (measured in ohms), to electrical current flow, between adjacent electrodes along the length of the MII probe [13]. Reflux events by impedance are defined as a ≥ 50% reduction in impedance values. Refluxate is considered acidic, mildly acidic and nonacidic with pH ≤4, 4–<7 and ≥7 respectively. Acid exposure time (AET) is defined as the total time that the esophageal mucosa is exposed to a refluxate with pH < 4. A total AET ≥ 4.5% during a 24 period is considered abnormal. The proportion of the time spent with acid exposure in supine and upright positions is also determined. The Demeester score is also calculated with any score greater than 14.72 signifying abnormal esophageal acid exposure. The score is calculated using six variables including the percent of total time with pH <4, supine and upright time with pH <4, number of episodes lasting at least 5 min, longest episodes (minutes), and total number of episodes with pH <4. Impedance testing enables measurement of the proximal height of the refluxate that may be associated with concomitant SSc-interstitial lung disease (ILD) [14].

Esophageal manometry evaluates the form and vigor of esophageal contractions in response to a swallow. Expected abnormalities in SSc include weak contractions, ineffective esophageal motility, and absent peristalsis (Fig. 16.1). Resting LES pressure is also expected to be low, particularly in advanced disease (Fig. 16.1). The impedance portion of the exam evaluates for clearance of the saline bolus used to initiate the swallow. Of note, absent peristalsis is not specific for SSc and can be found in patients with overlap syndromes, systemic lupus erythematosus, polymyositis, etc. [15].

At some institutions the multiple rapid swallow (MRS) test, performed during esophageal manometry, is used to evaluate peristaltic reserve. The patient repetitively swallows sips of saline spaced several seconds apart in the supine position. The normal response in a person with intact esophageal neural mechanisms and muscular integrity is an initial diminution and subsequent augmentation of esophageal body and LES contractions [16]. Patients with SSc, regardless of manometric motility diagnosis, demonstrated impaired esophageal

peristalsis and LES contractions compared to healthy controls [16]. These data suggest that abnormal response to MRS may be the most common esophageal manometric abnormality in patients with SSc.

A barium swallow, another out-patient procedure that provides a simple assessment of esophageal structure and diameter, can be performed prior to consideration of esophageal endoscopy or manometry. Some institutions favor endoscopy with manometry in all patients with SSc and avoid barium swallow exams. This is due to the concern that concomitant gastric and intestinal hypomotility can lead to barium retention that may extravasate into the peritoneum in patients with pneumatosis cystoides intestinalis. The risk is very low and the decision to perform esophageal manometry versus barium swallow is best made in close consultation between the treating rheumatologist and gastroenterologist.

Esophagogastroduodenoscopy (EGD) is an essential tool to evaluate for esophagitis and esophageal strictures that can complicate uncontrolled GER. It is also useful for assessing for candida esophagitis and other forms of infectious esophagitis, ulcer formation and esophageal metaplasia (Barrett's esophagus).

Treatment

The management of SSc-related GERD starts with aggressive lifestyle modifications including smoking cessation, head of bed elevation, attainment and maintenance of ideal body weight. Dietary modification is essential and involves avoidance of food and drink before periods of recumbency, avoidance of excess alcohol consumption, and eating small frequent, as opposed to large infrequent, meals. Pharmacologic treatments include agents that reduce gastric acid secretion, such as proton pump inhibitors (PPI) (best taken 30 min prior to the largest meal), histamine H2 receptor antagonists, antacids, physical LES barriers (alginic acid formulations) and prokinetic agents (Table 16.1 and Fig. 16.2). Compared with

Table 16.1 GERD pharmacologic treatments

Histamine H2 antagonists	
Cimetidine	
Famotidine	
Loxtidine	
Lamitidine	
Proton pump inhibitors (in order of increasing potency)	**Relative potency**
Pantoprazole	0.23
Lansoprazole	0.90
Dexlansoprazole	Not studied
Omeprazole	1.00
Esomeprazole	1.60
Rabeprazole	1.82
Antacids	
Calcium carbonate	
Magnesium trisilicate	
Aluminum hydroxide	
Alginic acid formulations	
Sodium alginate and potassium bicarbonate	
Promotility agents	
Domperidone	
Metoclopramide	
Macrolide antibiotics Azithromycin [6] Erythromycin	

Based on the mean 24-h gastric pH, the relative potencies of the five PPIs compared to omeprazole [17].

healthy volunteers, patients with GERD need a 1.9-fold higher PPI dose to achieve a given increase in mean 24-h intragastric pH [17]. Prior to increasing PPI dose or frequency, physicians should counsel patients regarding proper PPI administration (30 min before meals) and/or consider trialing a different PPI (e.g. higher potency PPI) (Table 16.1). Lifestyle modifications, in addition to once or twice daily PPIs, can be insufficient for symptom control [18]. Recent results of a 4-week randomized trial of alginic acid (n = 37) versus domperidone (n = 38) in SSc patients with partial response to twice daily omeprazole failed to discern which of these add-on therapies is superior [18].

Invasive interventions including laparoscopic fundoplication, and Roux-en-Y gastric bypass (gastrojejunostomy) are performed in select patients with SSc, but only after a comprehensive multidisciplinary evaluation including esophageal manometry and nutritional status assessment [19]. Esophageal dysmotility on manometry consisting of ineffective, weak or absent peristalsis increases the risk for post-operative dysphagia. However, study results have shown that the degree of pre-operative esophageal dysmotility manometry parameters does not adequately predict post-operative dysphagia [19].

Gastroesophageal reflux complicating lung transplantation is a concern in patients with SSc [20, 21]. Thus, transplantation centers have developed protocols for addressing this potential complication including aggressive PPI, head of bed elevation to 45° and anti-reflux surgical interventions such as fundoplication. Peri-transplant anti-reflux surgery has been shown to improve 1- and 3-year survival in lung transplant recipients, though this has not been specifically studied in SSc patients. Analysis of the United Network for Organ Sharing (UNOS) data from 229 adults with SSc, 201 with pulmonary arterial hypertension (PAH), and 3333 with ILD who underwent lung transplantation in the US between May 4, 2005 and September 14, 2012 demonstrated no difference in 30-day post-transplant survival between patients with SSc and those with ILD (HR 0.65[95% CI 0.27–1.58]) [22]. Moreover, in the patients who survived 1-year, the 3-year survival among SSc

patients exceeded PAH survival rates suggesting that lung transplantation should not be refused to SSc patients out of concern for GERD [22].

Incomplete Response to Proton Pump Inhibition in SSc Patients

The results of a recent retrospective case-control study of 38 non-SSc patients and 38 SSc patients who were taking PPI BID and underwent 24-hour ambulatory impedance pH testing found that 58% of SSc patients had manometric findings of the "scleroderma esophagus" defined as hypotensive esophagogastric junction tone and absent contractility (Fig. 16.1b) [23]. Additionally, SSc patients had significantly higher total acid exposure time (AET) 6.8% (2.4–18.7) compared to 1.8% (0.5–3.8) in non-SSc controls ($p < .001$). 72% of SSc patients had absent esophageal contractility compared to none of the controls ($p < .001$). Moreover, SSc patients had substantially reduced mean nocturnal baseline impedance 492 ohms (257–915) compared to 2783 ohms (1050–3275) in controls ($p < .001$), suggestive of more liquid reflux and potentially impaired esophageal clearance. Thus, patients with SSc may experience more GERD symptoms due to delayed esophageal content and refluxate clearance.

Exacerbating Factors

The high prevalence of asymptomatic GERD warrants caution, and, if possible, the avoidance of pharmacotherapies that are often associated with pill esophagitis whereby pills lodge in the upper or mid 1/3 of the esophagus and can cause erosions. Oral bisphosphonates (as described in Case 2), some antibiotics such as doxycycline, oral iron or potassium and some NSAIDs are common culprits [24, 25]. When possible, liquid, intramuscular or parenteral formulations should be prescribed. Noncompliance with lifestyle modifications, listed above, may also worsen GERD symptoms.

Summary

Gastroesophageal reflux disease is common in patients with SSc. Lifestyle and medication modifications coupled with newer diagnostic and treatment modalities help inform medical decision-making and improve health-related quality of life.

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References

1. Yang H, Xu D, Li MT, Yao Y, Jin M, Zeng XF, et al. Gastrointestinal manifestations on impaired quality of life in systemic sclerosis. J Dig Dis. 2019;20(5):256–61.
2. Horsley-Silva JL, Umar SB, Vela MF, Griffing WL, Parish JM, DiBaise JK, et al. The impact of gastroesophageal reflux disease symptoms in scleroderma: effects on sleep quality. Dis Esophagus. 2019;32(5)
3. Gyger G, Baron M. Systemic sclerosis: gastrointestinal disease and its management. Rheum Dis Clin N Am. 2015;41(3):459–73.
4. Ntoumazios SK, Voulgari PV, Potsis K, Koutis E, Tsifetaki N, Assimakopoulos DA. Esophageal involvement in scleroderma: gastroesophageal reflux, the common problem. Semin Arthritis Rheum. 2006;36(3):173–81.
5. Crowell MD, Umar SB, Griffing WL, DiBaise JK, Lacy BE, Vela MF. Esophageal motor abnormalities in patients with scleroderma: heterogeneity, risk factors, and effects on quality of life. Clin Gastroenterol Hepatol. 2017;15(2):207–13. e1
6. Rohof WO, Bennink RJ, de Ruigh AA, Hirsch DP, Zwinderman AH, Boeckxstaens GE. Effect of azithromycin on acid reflux, hiatus hernia and proximal acid pocket in the postprandial period. Gut. 2012;61(12):1670–7.
7. Gyger G, Baron M. Gastrointestinal manifestations of scleroderma: recent Progress in evaluation, pathogenesis, and management. Curr Rheumatol Rep. 2012;14(1):22–9.
8. Treacy WL, Baggenstoss AH, Slocumb CH, Code CF. Scleroderma of the esophagus. A correlation of histologic and physiologic findings. Ann Intern Med. 1963;59:351–6.
9. 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(3):428–40.
10. Roberts CG, Hummers LK, Ravich WJ, Wigley FM, Hutchins GM. A case-control study of the pathology of oesophageal disease in systemic sclerosis (scleroderma). Gut. 2006;55(12):1697–703.
11. Ebert EC. Esophageal disease in scleroderma. J Clin Gastroenterol. 2006;40(9):769–75.
12. Howe S, Eaker EY, Sallustio JE, Peebles C, Tan EM, Williams RC Jr. Antimyenteric neuronal antibodies in scleroderma. J Clin Invest. 1994;94(2):761–70.
13. Mousa HM, Rosen R, Woodley FW, Orsi M, Armas D, Faure C, et al. Esophageal impedance monitoring for gastroesophageal reflux. J Pediatr Gastroenterol Nutr. 2011;52(2):129–39.
14. Savarino E, Bazzica M, Zentilin P, Pohl D, Parodi A, Cittadini G, et al. Gastroesophageal reflux and pulmonary fibrosis in scleroderma: a study using pH-impedance monitoring. Am J Respir Crit Care Med. 2009;179(5):408–13.
15. Kimmel JN, Carlson DA, Hinchcliff M, Carns MA, Aren KA, Lee J, et al. The association between systemic sclerosis disease manifestations and esophageal high-resolution manometry parameters. Neurogastroenterol Motil. 2016;28(8):1157–65.
16. Carlson DA, Crowell MD, Kimmel JN, Patel A, Gyawali CP, Hinchcliff M, et al. Loss of peristaltic reserve, determined by multiple rapid swallows, is the Most frequent esophageal motility abnormality in patients with systemic sclerosis. Clin Gastroenterol Hepatol. 2016;14(10):1502–6.
17. Kirchheiner J, Glatt S, Fuhr U, Klotz U, Meineke I, Seufferlein T, et al. Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. Eur J Clin Pharmacol. 2009;65(1):19–31.
18. Foocharoen C, Chunlertrith K, Mairiang P, Mahakkanukrauh A, Suwannaroj S, Namvijit S, et al. Effectiveness of add-on therapy with domperidone vs alginic acid in proton pump inhibitor partial response gastro-oesophageal reflux disease in systemic sclerosis: randomized placebo-controlled trial. Rheumatology (Oxford). 2017;56(2):214–22.
19. Bakhos CT, Petrov RV, Parkman HP, Malik Z, Abbas AE. Role and safety of fundoplication in esophageal disease and dysmotility syndromes. J Thorac Dis. 2019;11(Suppl 12):S1610–s7.
20. Perez Rivera CJ, Kadamani Abiyomaa A, Gonzalez-Orozco A, Ocampo MA, Caicedo I, Mosquera MS. Total gastrectomy in systemic scleroderma when anti-reflux surgery is not viable: a case report. Int J Surg Case Rep. 2019;62:103–7.

21. Panchabhai TS, Abdelrazek HA, Bremner RM. Lung transplant in patients with connective tissue diseases. Clin Chest Med. 2019;40(3):637–54.
22. Bernstein EJ, Peterson ER, Sell JL, D'Ovidio F, Arcasoy SM, Bathon JM, et al. Survival of adults with systemic sclerosis following lung transplantation: a nationwide cohort study. Arthritis Rheumatol. 2015;67(5):1314–22.
23. Stern EK, Carlson DA, Falmagne S, Hoffmann AD, Carns M, Pandolfino JE, et al. Abnormal esophageal acid exposure on high-dose proton pump inhibitor therapy is common in systemic sclerosis patients. Neurogastroenterol Motil. 2018;30(2):e13247.
24. Kikendall JW, Friedman AC, Oyewole MA, Fleischer D, Johnson LF. Pill-induced esophageal injury. Case reports and review of the medical literature. Dig Dis Sci. 1983;28(2):174–82.
25. Kikendall J. Pill-induced esophageal injury. In: Castell DORJ, editor. The esophagus. Third ed. Philadelphia: Lippincott Williams & Wilkins; 1999. p. 527–37.