Gastrointestinal complications: the most frequent internal complications of systemic sclerosis

A. Forbes and I. Marie

Manifestations of SSc in the gastrointestinal (GI) tract are common, occurring in 50–90% of patients. They typically result from the fibrosis that characterizes this disease. Manifestations of SSc can affect many sites within the GI tract, and patients may experience substantial dysfunction in the processes of motility, digestion, absorption and excretion. Oesophageal dysfunction is the most common GI manifestation, but patients may also experience dysfunction of the stomach, small intestine, colon and rectum, each of which can be responsible for severe and distressing symptoms. At present, few specific therapeutic options are available for the treatment of these patients, but relief of symptoms is often possible with appropriate knowledge and support. It is therefore particularly important to identify, monitor and manage these patients carefully, with a view to minimizing further degeneration and maximizing quality of life.

KEY WORDS: Gastrointestinal tract, Oesophagus, Stomach, Small intestine, Large intestine, Rectum, Anus, Systemic sclerosis.

Introduction

The gastrointestinal (GI) tract is primarily responsible for the processes of digestion and excretion, and is frequently affected by manifestations of SSc [1]. The excessive fibrosis, inflammation and vascular dysfunction characteristic of SSc is seen also in the GI tract, and it is thought that GI impairment in affected patients results from progressive histological lesions similar to those found in other organs. Sjögren proposed a progression of scleroderma-tous GI involvement: vascular damage (grade 0), neurogenic impairment (grade 1) and myogenic dysfunction (grade 2) with the replacement of normal smooth muscle by collagenous fibrosis and atrophy [2]. It is the fibrotic aspect of this disease that is mainly reported to underlie GI manifestations in SSc patients [3].

The GI tract is possibly the second most common site of SSc organ damage, and can affect patients with lcSSc and dcSSc [1]. Manifestations of SSc can impair the function of many parts of the GI tract, affecting motility, digestion, absorption and excretion. GI manifestations of SSc can be severe, causing patients to experience symptoms including pain, dysphagia, vomiting, diarrhea, constipation, faecal incontinence and substantial weight loss. GI manifestations of SSc impact severely on prognosis and quality of life (QoL), and are associated with reduced survival. The mortality rate attributable to GI involvement is reported to be 6–12% [4–9].

Any site within the GI tract can be affected by SSc. Although the oesophagus is most frequently implicated, it is disease at other sites that is responsible for the more serious morbidity and death [10–12]. In this article, we discuss the individual implications of oesophageal, gastric, intestinal and rectal manifestations of SSc and current diagnostic and treatment strategies.

Oesophageal manifestations

Normal oesophageal function is estimated to be affected in 70–90% of patients with GI manifestations of SSc [1, 2, 13, 14]. Symptoms of oesophageal dysfunction typically include dysphagia, poor eating, heartburn and nausea or vomiting, which can lead to severe weight loss. For reasons that are not well understood, oesophageal manifestations of SSc may not always be symptomatic, but early diagnosis remains important as delay increases the risk of complications. Moreover, the incidence of severe oesophageal motor impairment may correlate with that of interstitial lung disease (ILD), one of the leading causes of death in SSc patients [10, 15, 16].

Gastro-oesophageal reflux

Oesophageal dysfunction in SSc typically manifests within the lower two-thirds of the oesophagus as a weakened lower oesophageal sphincter and with profound loss of peristaltic action [11, 17]. Patients may also experience uncoordinated oesophageal motility or complete oesophageal paralysis, leading to high morbidity [18]. Such dysfunction permits pathological reflux of acidic gastric contents into the oesophagus, which is more damaging still because of the poor antegrade motility leading to it being improperly cleared [2, 17]. Oesophageal damage resulting from gastro reflux may initially manifest as simple peptic oesophagitis progressing to erosive oesophagitis, bleeding and frank ulceration. If untreated, peptic stricture formation, fistulae and an achalasia-like syndrome may occur. It is probable that these features lead the affected SSc patient to a high risk of Barrett’s oesophagus [2].

The routine screening of SSc patients for oesophageal abnormalities during initial evaluation is therefore recommended. The presence and severity of oesophageal involvement can be determined from the combination of upper GI endoscopy, ambulatory pH studies and oesophageal manometry, which together facilitate decision-making in treatment and management. In order to manage gastro-oesophageal reflux in SSc patients, behavioural modifications (such as smoking cessation, elevation of the head of the bed, avoiding eating in the hours before retiring) are generally recommended, in addition to long-term, high-dose proton pump inhibition (PPI) to reduce gastric acid secretion from the parietal cells [10].

Barrett’s oesophagus and oesophageal adenocarcinoma

Chronic gastro-oesophageal reflux in SSc patients can be complicated by Barrett’s oesophagus. Barrett’s oesophagus is a disorder in which the normal stratified squamous epithelial lining of the distal oesophagus undergoes metaplasia, with normal epithelial cells being replaced by an abnormal columnar epithelium including goblet cells (Fig. 1) [10, 11, 17–21]. Barrett’s oesophagus is thought to be relatively common in patients with oesophageal manifestations of SSc, with an estimated incidence of 6.8–12.7% compared with the population risk of <1% [10, 11, 17].
Gastric manifestations

The gastric manifestations of SSc include severe bleeding from vascular ectasia, and, more commonly, an electromechanical dysfunction that leads mainly to delayed gastric emptying, contributing in turn to gastro-oesophageal reflux [12, 28, 29]. Gastric pathology is associated with increased morbidity and mortality [10–12].

Delayed gastric emptying

Gastric involvement in SSc can lead to significant delay in emptying, particularly of solids, and this is most likely in patients with abnormal oesophageal motility and in those with deSSc [29–31]. Delayed gastric emptying can result in complete food intolerance and increased severity of gastro-oesophageal reflux [29–31]. Delayed gastric emptying can usually be diagnosed by electrogastrographic recordings or else from scintigraphic evaluation following a radiolabelled meal [29–31]. Current therapeutic strategies are usually based on pro-motility agents such as metoclopramide and domperidone, which can increase the tone and amplitude of gastric contractions, and relax the pyloric sphincter [30]. Beneficial effects of low-dose erythromycin have also been demonstrated in SSc patients with prokinetic-resistant, severely delayed gastric emptying, an effect that comes from its motilin-like properties and are independent of any anti-microbial action [31]. In severely affected patients it can be useful to place a wide-calibre percutaneous gastrostomy tube to permit intermittent drainage, and thereby avoid or diminish the tendency to vomiting. It is not inevitably the case that such a patient will require artificial nutritional support at this stage, but there is clearly a major overlap with those entering a phase of established intestinal failure (see below), and in the relatively early stages during which gastrostomy may be used either for feeding or for drainage according to the clinical priorities of a given day.

Gastric antral vascular ectasia

Some SSc patients with gastric manifestations may experience frank haemorrhage or iron-deficiency anaemia from gastric antral vascular ectasia (GAVE). GAVE, also known as ‘watermelon stomach’, has a unique endoscopic appearance that is characterized by multiple, parallel longitudinal columns of red vessels within the gastric antrum radiating to the pylorus, resembling the stripes on a watermelon (Fig. 2) [32, 33]. GAVE is a key cause of chronic, GI bleeding in SSc patients, and in some cases may be an early manifestation; its aetiology remains unclear [11, 29, 34, 35]. For SSc patients with GAVE, therapeutic strategies have usually included blood transfusion, iron supplementation and, occasionally, antrectomy [36, 37]. More recent reports have suggested that endoscopic laser ablation can be effective in as many as 75% of cases [38–40]. The simpler and safer laser technique of argon plasma coagulation (APC) offers an additional option, although experience of this technique is still limited [33].

Intestinal manifestations

SSc can also affect the small and large intestine, including the rectum and the anus. Involvement of the small intestine causes malabsorption, sometimes in conjunction with pseudo-obstructions, and can lead to severe malnutrition [12, 28]. Reduced blood flow within the small intestine may also contribute to impaired nutrient absorption [41]. Colonic manifestations can include diarrhoea, faecal incontinence and haemorrhage.

Small intestinal manifestations

Malabsorption syndrome typically occurs in SSc as a result of bacterial overgrowth, which is in turn usually the consequence of impaired motility. Following diagnosis (from endoscopic sampling or from hydrogen breath test) it will often initially respond

FIG. 1. Endoscopic appearance of long-segment Barrett’s oesophagus. The metaplastic columnar epithelium contrasts with the normal, pale appearance of the squamous lining. Image reproduced with permission from the BMJ Publishing group [21].

The abnormal epithelium in Barrett’s oesophagus typically exhibits DNA damage, and when the histological characteristics have intestinal (rather than gastric) features there is evidence that there is an increased risk of subsequent oesophageal adenocarcinoma [22, 23]. Although this increased incidence is now established in the general population, there are few data specific to SSc and conclusions must be more guarded. The prevalence of oesophageal adenocarcinoma in SSc patients with GI manifestation has been estimated by three groups to be low. There are many differences, however, between SSc patients with Barrett’s oesophagus and those in the general population, not least the high risk of premature death from other manifestations of SSc, given that Barrett’s cancers are rare in those under the age of 50 yrs [10, 17, 24]. Conversely, one retrospective analysis suggested that SSc patients with severe symptoms of Barrett’s oesophagus may be at greater risk of oesophageal adenocarcinoma [25]. Another study compared the incidence of cancer in SSc patients with the Surveillance Epidemiology and End Results cancer registries, concluding that SSc patients were at significantly greater risk of oesophageal cancer (not specifically Barrett’s oesophagus) and oropharyngeal cancers than the general population [26].

Cautious management of SSc patients with Barrett’s oesophagus is therefore recommended, and will be based mainly on treatments for the underlying gastro-oesophageal reflux [21]. The American College of Gastroenterology recommends that patients with Barrett’s oesophagus undergo regular surveillance endoscopies, and in SSc patients who develop Barrett’s oesophagus, screening by endoscopy every 2–3 yrs is recommended if no dysplasia is present [21, 27]. If low-grade dysplasia is present, endoscopic screening should be performed at least annually. In those with high-grade dysplasia serious attention should be given to non-operative therapies in patients who (because of other elements of their SSc) are unsuited to oesophageal resection [10, 27]. Photodynamic therapies and other endoscopically delivered options are increasingly validated in the non-SSc patient with high grade dysplasia, and may be effective even when frank malignancy has supervened and the tumour is inoperable.
well to antibiotics. Unfortunately the response is rarely prolonged and subsequent courses are rarely as effective as the first. The small intestinal hypomotility may provoke luminal dilatation and overt pseudo-obstructions. It is probable that this is the result of abnormal collagen deposition as in the oesophagus but there are fewer histological data. The net result is pain and food intolerance, together with abdominal distension, and leads to diarrhoea, and the risk of profound malnutrition [2, 28, 42].

The therapeutic options are essentially supportive, but simple agents acting on motility can make huge differences initially [12]. For patients who experience repeated intestinal pseudo-obstruction, octreotide therapy (50 µg/day, subcutaneously) may offer a relevant option, although experience of this treatment is still limited. Indeed, such octreotide regimens have been reported to induce Phase III-like migrating motor complexes, the normal electrophysiological phenomena by which the peristaltic wave is conducted in a co-ordinated fashion along the small intestine [11, 28, 42]. Previous authors have suggested that small bowel manometry should be performed to assist in the selection of symptomatic SSc patients with intestinal pseudo-obstruction who may benefit from octreotide therapy. These data may result in improvement of patients’ management and reduction of medical costs (as octreotide is an expensive therapy) [28, 42]. The use of small bowel manometry has also been proposed as a means to avoid unnecessary initiation of octreotide therapy. Although octreotide therapy is considered as a safe medication, it may be responsible for severe adverse effects, such as intestinal perforation due to octreotide-associated increased small bowel intraluminal pressure [28, 42]. Octreotide should accordingly be used with caution in SSc.

Patients with severe small intestinal manifestations losing their response to antibiotics are often helped by overnight tube feeding. In most cases it will be more convenient and acceptable for the patient if a percutaneous gastrostomy device is placed, but some patients prefer to self-intubate with a fine-bore nasogastric tube each evening. The latter is a very safe technique if (once in the posterior pharynx) the tube is actively swallowed without the use of a guidewire, which could permit its steered passage towards the respiratory tract.

Sadly, the progressive nature of SSc may ultimately lead to advanced intestinal failure. For these patients, intravenous nutrition (IVN) is often required, administered using fairly standard regimens but with relatively low volume and low sodium, usually for 4 or 5 days/week. The short-term outcome in patients treated with IVN can be good, but the advent of intestinal failure appears to be a marker of poor long-term outcome, most such patients succumbing within 2 yrs from the more directly fatal consequences of SSc affecting other body systems.

**Colonic scleroderma**

The early phases of colonic SSc are associated with constipation from delayed intestinal transit. However, it is unusual for this to persist, as parallel small intestinal hypomotility and luminal dilatation leads to bacterial overgrowth and diarrhoea. Colonic telangiectasias are common in SSc and may bleed overtly or be responsible for anaemia. Pseudodiverticula are common but probably incidental, and patients may experience troublesome rectal prolapse in a context in which surgical repair is relatively contraindicated. Apart from the concerns in respect of major co-morbidity in SSc, reconstructive GI surgery has a strong tendency for slow and generally poor healing, which may be linked to abnormalities of the supportive connective tissues.

Standard, bulk-forming, laxatives are helpful in the early constipated phases [40], and may also help in control of incontinence. Collagen deposition in the rectum can lead to reduced rectal compliance for some patients, and thus to anismus which can appear to the patient as diarrhoea [40]. Urgency can be so profound as to lead to incontinence that is only partially responsive to opioids such as loperamide. ‘Watermelon rectum’ is also described in SSc (with GAVE in one published case [43]). Rectal haemorrhage can then be managed with endoscopic therapy using laser ablation or APC [43].

**Anal scleroderma**

Faecal incontinence reportedly affects 38% of SSc patients and in many of these the principal pathology lies in the anal canal [40]. Connective tissue deposition and loss of the internal anal sphincter are usually implicated; this can be detected at anal endosonography [44]. For these patients, sphincter muscle training can be beneficial, but when this is insufficient sacral nerve stimulation may prove a much more acceptable solution than creation of a defunctioning stoma [45]. Pilot studies suggest that this technique may induce beneficial clinical effects, and can abolish incontinence in some patients [45].

**Conclusion**

GI manifestations of SSc are common and widespread. Their effects on prognosis, morbidity, mortality and QoL can be substantial. While a number of therapeutic strategies exist, their limitations and the progressive nature of the disease can mean that their impact is both incomplete and short term.

The management of patients with SSc should therefore follow a multidisciplinary approach, and include regular monitoring for the development or progression of GI manifestations. It is probable that earlier detection and treatment of GI disease will reduce the risk of further complications, such as Barrett’s oesophagus and malnutrition. There are clear needs for further research into both pathogenesis and future therapeutic options.

**Rheumatology key messages**

- SSc commonly affects many parts of the GI tract.
- GI manifestations result from the characteristic fibrosis of SSc and can impair motility, digestion, nutrient absorption and excretion.
Acknowledgements

The authors received editorial assistance from Elements Communications, supported by an educational grant from Actelion Pharmaceuticals Limited (Allschwil, Switzerland). A.F. is supported by the Comprehensive Biomedical Research Centre of University College Hospital and University College London.

Supplement: This paper forms part of the supplement entitled ‘Ten years of partnership: translating ideas into progress in systemic sclerosis’. This supplement was supported by an unrestricted grant from Actelion Pharmaceuticals Ltd.

Disclosure statement: The authors have declared no conflicts of interest.

References


Gastrointestinal manifestations in SSc