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Severe Gastrointestinal Involvement in Systemic Sclerosis: Report of Five Cases and Review of the Literature

Kanyakorn Jaovisidha, MD,* M. E. Csuka, MD,† Urias A. Almagro, MD,‡ and Konrad H. Soergel, MD§

OBJECTIVE To review current literature on the gastrointestinal tract (GIT) manifestations of systemic sclerosis (SSc) and to report on 5 patients with severe gastrointestinal SSc.
MATERIALS AND METHODS The clinical course and histopathology of 5 patients are described. A review of the medical literature registered in MedLine and PreMedLine databases from 1996 through mid-2004 was performed using the keywords systemic sclerosis and scleroderma and combining them with text words such as gastric, gastrointestinal, anorectal, colonic, and hepatic.
RESULTS All 5 patients had severe GIT involvement: 4 with diffuse cutaneous SSc (dcSSc) and 1 with limited cutaneous SSc (lcSSc). Autopsy results of 2 patients who died from severe malnutrition and aspiration pneumonia are presented. Literature review includes involvement from oral cavity to anus with varying degrees of severity. Most GIT manifestations result from dysmotility secondary to infiltration of the gastrointestinal wall with fibrous tissue and can cause life-threatening malabsorption and malnutrition. Diagnostic tests, pathology, and treatments of GIT SSc are reviewed.
CONCLUSIONS GIT involvement in SSc can be severely debilitating and even life-threatening. Although morbidity is inevitable, appropriate supportive treatment can prolong survival.
RELEVANCE GI complications of SSc cause significant morbidity and mortality.

KEYWORDS systemic sclerosis, scleroderma, gastrointestinal motility, gastrointestinal diseases

Systemic sclerosis (SSc), a connective tissue disease, is characterized by vascular damage and fibrosis of the skin and internal organs, notably the gastrointestinal tract (GIT), lung, heart, and kidney (1). Two subsets of SSc are distinguished by the extent of skin involvement: diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) (2). The GIT is the most common organ system to be involved in both subsets of SSc. Although esophageal dysmotility is eventually present in 80% of patients (1), involvement of the entire GIT, including liver and pancreas, is described. Mortality from GIT complications of SSc is reported to be low with only 1 GIT death in 100 Swedish SSc patients followed for a mean of 7.7 years (3). The cause of death was peritonitis from perforation of a viscus.

Severe organ involvement in SSc was reported by Steen and Medsger using the Pittsburgh Scleroderma Databank (4). Considering only severe organ involvement, the GIT was the least frequent with only 8% of 953 patients assessed in contrast to 24% with severe skin thickening, 15% with severe heart disease, and 16% with pulmonary fibrosis. However, only 15% of patients with severe GIT involvement were living 9 years after onset of symptoms with the majority of deaths occurring within 3 years. Morbidity associated with small and large intestinal involvement can be severely debilitating

*Clinical instructor, Division of Rheumatology, Department of Medicine, Chulalongkorn University, Bangkok, Thailand 10110.
†Associate Professor of Medicine, Division of Rheumatology, Medical College of Wisconsin, Milwaukee, WI 53202.
‡Professor of Pathology, Department of Pathology, Medical College of Wisconsin, Milwaukee, WI 53202.
§Professor Emeritus, Division of Gastroenterology and Hepatology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI 53202.
Disclaimer: This work is not supported by any pharmaceutical company.
Address reprints requests to M. E. Csuka, MD, Associate Professor of Medicine, Division of Rheumatology, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI 53226. E-mail: mecsuka@mcw.edu

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but has not been studied systematically. Medsger and coworkers in 1999 proposed a disease severity scale for several organ systems (5). For the GIT, a scale of 0 is normal; 1 (mild) is for distal esophageal hypoperistalsis or abnormal small bowel series; 2 (moderate) is for distal esophageal aperistalsis or antibiotics required for bacterial overgrowth; 3 (severe) is for malabsorption syndrome or episodes of pseudoobstruction; and 4 (end stage) is for need for parenteral hyperalimentation.

Over the past 2 decades, treatment with angiotensin converting enzyme (ACE) inhibitors has improved the prognosis in acute renal hypertensive crisis of SSc. Research directed at understanding the pulmonary complications of SSc has led to clinical trials evaluating therapies that may retard the progression of pulmonary fibrosis. Treatment of pulmonary hypertension with prostaglandins and endothelin receptor antagonists have offered hope that SSc may be more responsive to therapy (6). To date, the management of GIT SSc remains empirical and symptom driven. The protean GIT manifestations in SSc are a significant challenge to developing treatment protocols for this aspect of SSc.

Materials and Methods

Case Selection

The death of 2 women from GIT SSc prompted an informal review of serious GIT involvement in SSc patients evaluated and treated at the Froedtert and Medical College of Wisconsin Rheumatology Clinic. Between 1995 and 2003 an additional 3 living cases were identified based on serious GIT involvement beyond the esophagus requiring diagnostic and therapeutic interventions for management. SSc patients with end-stage GIT involvement requiring total parental nutrition (TPN) were not included. These 5 women with SSc (4 dcSSc and 1 lcSSc) were selected to illustrate the spectrum of severe GIT involvement in patients with SSc (Table 1). Four of the cases satisfied the American College of Rheumatology classification for SSc based on the presence of skin thickening proximal to the metacarpophalangeal joints (7). The fifth woman had limited disease with sclerodactyly, Raynaud's phenomenon, telangiectasias, and positive anticentromere antibody (8). Two died from complications of GIT involvement: aspiration pneumonia and severe malnutrition.

Case 1

This 61-year-old female experienced a rapid progression of disease beginning with refractory myositis confirmed by muscle biopsy in 1995 to death from aspiration pneumonia caused by severe GIT dysmotility 2 years later. Early mortality from GIT SSc with such short disease duration has only recently been appreciated in the literature (4). Initial laboratory findings were ANA 1:1280 with a speckled pattern and negative antibodies against centromere, Jo-1, ribonucleoprotein (RNP), Smith, Scl-70, double-stranded DNA, and SSA. Despite treatment with azathaprine and prednisone, her proximal muscle weakness progressed.

One year after presenting with proximal muscle weakness, she complained of mouth dryness, dysphagia, gastroesophageal reflux disease (GERD) symptoms, and constipation as well as Raynaud's phenomenon, diffuse skin thickening, and weight loss of 25 to 30 pounds. Diagnostic studies including barium esophagogram, upper gastrointestinal (UGI) study, and small-bowel-follow-through (SBFT) confirmed distal esophageal dysmotility, hiatal hernia, GERD, and mild dilation of the proximal to mid small bowel. Cisapride was not helpful. Subsequent evaluation of worsening abdominal pain and distension included a computerized tomography (CT) scan and exploratory laparotomy, which showed mesenteric ischemia without infarction or ruptured viscus, pneumatosis cystoides intestinalis (PCI), and pneumoperitoneum. PCI was treated with 7 days of high flow oxygen; however, poor motility in the distal esophagus, acute duodenitis, and absent motility in stomach and duodenum persisted as confirmed by esophagogastroduodenoscopy (EGD). The patient was discharged home on lansoprazole, metoclopramide, erythromycin, and metronidazole administered through a nasogastric (NG) tube and weekly intravenous methotrexate for treatment of SSc-associated myositis. Three weeks later, she died from complications of aspiration pneumonia, septic shock, and UGI bleeding.

At autopsy, there was extensive PCI without evidence of intestinal infarction or perforation (Fig. 1). Multiple esophageal ulcerations with intervening normal mucosa, extending for 6 cm proximal from the gastroesophageal junction, were present without evidence of fungi or cytomegalovirus. A 1-cm duodenal ulcer was identified. Microscopically, changes in esophagus, stomach, small intestine, and colon included smooth muscle atrophy and replacement by connective tissue, more severely affecting the inner circular layer of the muscularis propria. Her SSc severity scale of GIT involvement by Medsger and coworkers was 3 (5).

Case 2

A 51-year-old woman was diagnosed with SSc at age 29 when she presented with calcinosis, Raynaud's phenomenon, GERD, sclerodactyly, telangiectasia, multiple fingertip ulcers, and progressive skin thickening of the chest, upper arms, and thighs. After living for 27 years with SSc and surviving significant morbidities including hand deformity, pulmonary fibrosis, renal hypertensive crisis with cardiomyopathy, and chronic leg ulcers, it was severe colon dysmotility that ultimately caused her death. Treatment with D-penicillamine (500 mg per day) was associated with regression of generalized skin thickening to near normal without effect on progressive distal phalangeal resorption, multiple finger flexion contractures or sclerodactyly. This therapy was discontinued after 26 years when nephrotic syndrome was diagnosed. Three months later, hypertensive renal crisis, congestive heart failure, and symptomatic pericarditis required hospitalization. Renal function stabilized with an ACE inhibitor (enalapril 10 mg twice a day), proteinuria resolved, and anemia of chronic disease improved with erythropoietin and iron.

Meanwhile, the first episode of severe GIT SSC involve-