ORIGINAL ARTICLE

Gastrointestinal involvement in patients with systemic sclerosis

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KEY WORDS

antinuclear antibodies, esophagus, gastrointestinal involvement, pulmonary involvement, systemic sclerosis

ABSTRACT

INTRODUCTION Gastrointestinal (GI) involvement is a serious complication of systemic sclerosis (SSc).

OBJECTIVES The aim of the study was to determine the incidence of GI manifestations in SSc.

PATIENTS AND METHODS We studied 73 patients with SSc (60 women and 13 men). Diffuse cutaneous SSc (dcSSc) was diagnosed in 30 patients and limited cutaneous SSc (lcSSc) in 43 patients. Upper GI involvement was assessed based on clinical symptoms such as dysphagia and gastroesophageal reflux-related complications. The majority of patients underwent radiographic examination including a barium swallow. Lower GI involvement was evaluated on the basis of such clinical symptoms as constipation and diarrhea.

RESULTS GI symptoms were observed in 54 (74%) SSc patients. Upper GI symptoms were observed in 54 (74%) patients and lower GI symptoms in 22 (30%) patients. The presence of anticentromere antibodies is associated with a lower risk of GI involvement. There are no significant differences in the incidence of pulmonary involvement between SSc patients with and without GI symptoms.

CONCLUSIONS GI involvement is observed in the majority of SSc patients. Clinical symptoms of GI involvement are significantly more common in patients with dcSSc. The incidence of upper GI symptoms is significantly higher than that of lower GI symptoms.

INTRODUCTION Systemic sclerosis (SSc) is a multiple-system autoimmune disease characterized by the coexistence of microvascular involvement, autoimmune response, and fibroblast activation that lead to fibrosis in the skin and multiple organs, e.g., the lungs, kidneys, heart, and gastrointestinal (GI) tract.[1-3] There are 2 different subtypes of SSc, i.e., limited cutaneous SSc (lcSSc) with dominant vascular manifestations and diffuse cutaneous SSc (dcSSc) with dominant collagen accumulation. GI involvement occurs in both subtypes of SSc.[4]

In about 10% of SSc patients, GI disease develops before cutaneous manifestations occur.[4] The esophagus is most frequently affected,[4-7] followed by the anorectum, stomach, small bowel, and colon.[8-10] The most common symptoms of upper GI tract involvement are regurgitation, bloating, heartburn, retrosternal pain including gastroesophageal reflux disease (GERD), and dysphagia associated with impaired peristalsis of the lower ⅔ of the esophagus.[7,11] Gastric involvement may lead to gastroparesis with epigastric discomfort. Gastric antral venous ectasia may result in GI hemorrhage.[12] Symptoms of small and large bowel involvement include bloating, diarrhea, and chronic constipation. Pseudo-obstruction and bacterial overgrowth may result in abdominal pain, malabsorption, and weight loss.[5,13,14] Unlike cardiopulmonary and renal involvement, GI manifestations of SSc rarely result in lethal complications. However, they may significantly affect the quality of life of SSc patients. The aim of the present study was to determine the prevalence of different clinical GI manifestations in patients with dcSSc and lcSSc.

PATIENTS AND METHODS The study included 73 SSc patients (60 women and 13 men) hospitalized consecutively in the Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Poland, between

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January 2005 and October 2008. Patients fulfilled the American College of Rheumatology classification criteria for SSc. They were categorized according to the criteria of Le Roy et al.[15] as having lcSSc (n = 43) or dcSSc (n = 30). The mean age was 53.6 ±13.5 years. The mean disease duration was 8.2 ±7.2 years (TABLE 1). All patients were treated with proton-pump inhibitors. Prokinetic drugs were used only in symptomatic patients.

Upper GI involvement was assessed according to clinical symptoms such as dysphagia, gastroesophageal reflux-related complications including heartburn, bloating, retrosternal pain, and epigastric discomfort such as gastroparesis. The majority of patients underwent radiographic examinations including a barium swallow. A number of patients underwent gastroscopy. Lower GI involvement was evaluated based on clinical manifestations such as constipation or diarrhea. In addition, evaluation of antinuclear antibodies (ANA), anticentromere (ACA), and antitopoisomerase I (Scl-70) antibodies was performed in each patient. Lung involvement was evaluated using high resolution computed tomography.

All calculations were performed with Statistica 6.0. Data were analyzed using the following nonparametric tests: the Fisher exact test and χ^2 test for comparison between groups. A P-value <0.05 was considered statistically significant.

RESULTS Fifty-four (74%) SSc patients developed clinical symptoms of the GI tract involvement. Moreover, the prevalence of GI complications was statistically significantly higher in patients with dcSSc than in those with lcSSc (P <0.0001, TABLE 2). Furthermore, upper GI complaints were reported in 54 (74%) SSc patients. Lower GI tract symptoms were observed in 22 (30%) SSc patients (TABLE 3). There were no statistically significant differences in upper and lower GI complications between the subgroups of SSc patients (TABLE 4). We performed 67 X-ray barium swallows and found typical SSc abnormalities such as esophagus dilatation, mucosal smoothing, and decreased peristalsis in 44 (66%) SSc patients. Hiatus hernias occurred in 12 (18%) patients. We observed no pathological changes in 16 (24%) patients. Gastroscopy was performed in 18 patients. Mucosal inflammation of the esophagus, stomach, and duodenum was observed in 8 patients; 1 patient had duodenal ulcer, 3 had hiatus hernia, 2 had gastroesophageal reflux, 2 had bowel motility disorders characteristic of SSc, and 1 had gastric cancer. In 4 cases, gastroscopy did not show any lesions.

ANA were detected in 68 (93%) patients with SSc, ACA in 19 (26%), and Scl-70 antibodies in 25 (34%). Among patients with GI involvement, ANA were observed in 52 (96%), ACA in 10 (19%), and Scl-70 in 21 (40%) subjects. Among the patients without GI manifestations, ANA were detected in 16 (84%), ACA in 9 (47%), and Scl-70 in 4 (21%) cases. We did not observe statistically significant differences in the prevalence of ANA between the groups of SSc patients with and without GI involvement. The prevalence of ACA was statistically significantly higher in SSc patients without GI complications than in those with GI involvement (P <0.004). There were no statistically significant differences in the prevalence of Scl-70 antibodies between the groups of SSc patients with or without GI symptoms (TABLE 5). Interstitial lung disease was observed in 36 (67%) patients with GI and in 7 (37%) patients without GI symptoms. No statistically significant differences were observed in the occurrence of lung complications between the groups with and without GI involvement (χ^2 test, P <0.06).

TABLE 1 Characteristics of the study group

clinical data	SSc group
number of patients	73
women	60
men	13
type of SSc (number of patients)	dcSSc (30) lcSSc (43)
mean age (years)	53.58 ±13.52
mean disease duration (years)	8.2 ±7.2

Abbreviations: SSc – systemic sclerosis, dcSSc – diffuse cutaneous SSc, lcSSc – limited cutaneous SSc

TABLE 2 Gastrointestinal involvement in patients with diffuse cutaneous SSc and limited cutaneous SSc

Subtype of disease (n)	GI involvement, n (%)
lcSSc (43)	25 (58)
dcSSc (30)	29 (97)
Fisher exact test	P = 0.0001

Abbreviations: GI – gastrointestinal, others – see TABLE 1

TABLE 3 Upper and lower gastrointestinal involvement in patients with SSc

GI involvement, n (%)	54 (74)
upper GI involvement, n (%)	54 (74)
lower GI involvement, n (%)	22 (30)

Abbreviations: see TABLES 1 and 2

TABLE 4 Upper and lower GI involvement in patients with dcSSc and lcSSc

subtype of disease	lcSSc	dcSSc	P
upper GI involvement, n (%)	21 (62)	23 (77)	NS
lower GI involvement, n (%)	5 (15)	13 (43)	NS

Abbreviations: NS – nonsignificant, others – see TABLES 1 and 2

DISCUSSION GI abnormalities in SSc involve motility dysfunction and mucosal damage in different segments of the alimentary tract. Myogenic

TABLE 5 The prevalence of antinuclear (ANA), anticentromere (ACA) and antitopoizomerase I (Scl-70) antibodies in patients with SSc

	ANA	ACA	Scl-70
all patients with SSc, n = 73 (%)	68 (93)	19 (26)	25 (34)
patients with GI involvement, n = 54 (%)	52 (96)	10 (19)	21 (40)
patients without GI involvement, n = 19 (%)	16 (84)	9 (47)	4 (21)
P	NS	<0.004	NS

P value – χ^2 test

Abbreviations: see TABLES 2 and 4

and neurogenic factors are involved in the pathogenesis of these abnormalities.[12,16] The myogenic manifestations are associated with smooth muscle cell damage due to progressive fibrosis, while the neurogenic ones result from autonomic nervous system dysfunction.[17,18] Moreover, anti-M3R antibodies are implicated in the pathogenesis of gastrointestinal motor dysfunction.[17,18] The available data demonstrate that patients with severe GI complications have significantly higher titers of anti-M3R antibodies compared with those with mild disorders.[19] Other causes include increased expression of profibrotic factors, such as transforming growth factor β, connective tissue growth factor or endothelin 1, which contribute to progressive fibrosis and damage to the walls of the GI tract.[20,21]

The available data demonstrate that GI manifestations are found in 75% to 90% of SSc patients.[4-6] In our study, 74% of patients had signs and symptoms of GI involvement. Esophageal involvement is reported in about 90% of SSc patients.[4,6] We observed upper esophageal symptoms in 74% of our patients. Abnormalities of esophageal motility decrease the tone of lower esophageal sphincter, which favors gastroesophageal reflux and prolonged exposure of the mucosa to gastric contents. Such a condition may result in erosive esophagitis, Barrett's esophagus or even esophageal adenocarcinoma. Barrett's esophagus is a consequence of long-term gastroesophageal reflux and increases the risk of esophageal adenocarcinoma by 0.5% annually (depending on the extent of dysfunction).[14] Current evidence shows that about 30% of patients with esophageal dysfunction suffer from GERD or mucosal ulceration.[5] Other characteristic lesions within the esophageal mucosa in SSc patients are teleangiectasias, which may contribute to GI tract hemorrhages.[12,17,22] About 2% of patients may develop esophageal stenosis.[5,23] Esophageal lesions in SSc are most commonly assessed using barium swallow examinations, which visualize long-term retention of a contrast medium due to esophageal dilatation and decreased peristalsis. During contrast examinations of the GI tract, the type of contrast should be considered due to the risk of aspiration complications typical of SSc. In some cases, the upper GI tract disorders are diagnosed using manometry, pH-metry, and endoscopy. Endoscopy is useful in detecting cardia leakage, teleangiectasias, which may contribute to GI bleeding or reflux esophagitis rather than Barrett's esophagus.[24]

In the current study the assessment was retrospective and it is difficult to track the patients' records especially the results of endoscopy. The study was based mainly on radiographic examinations, including barium swallow as a noninvasive screening test. Radiographic examinations were better tolerated by patients. Gastroscopy was performed only in patients with clinical indications.

According to the literature, gastric involvement is observed in 10% to 75% of SSc patients.[5,17] The main symptoms include early satiety and epigastric pain related to gastroparesis caused by gastric motor dysfunction leading to emptying problems.[5,17,18] In many cases, it is difficult to differentiate such symptoms from those of GERD. In our study, abdominal discomfort was observed in 54 SSc patients. In the majority of cases, its symptoms were accompanied by typical GERD symptoms. In 1 patient, gastric adenocarcinoma was diagnosed based on endoscopic findings. In SSc patients, the lower alimentary tract is less frequently affected than the upper part. According to the data, the small intestine is affected in about 30% of SSc patients, while lesions in the large intestine are detected in about 10% to 15% of patients.[5,17] We observed that the incidence of lower alimentary tract symptoms was significantly lower than that in the upper part – about 30%. In the population studied, morphological and functional abnormalities of the upper and lower alimentary tract were statistically significantly more common in dcSSc compared with lcSSc. Our findings are in line with other studies.

The incidence of clinical symptoms related to alimentary involvement is higher in patients with dsSSc.[5,6,25] Nishimagi et al.[25] reported that alimentary involvement was more common in dsSSc with rapid progression of skin lesions. Moreover, in patients with severe GI tract symptoms, the incidence of interstitial lung disease was found to be lower compared with patients without such complaints.[24,25] We observed that the incidence of pulmonary lesions in patients with or without alimentary involvement was comparable. Furthermore, we assessed the presence of ANA, ACA, and Scl-70 antibodies in patients with GI involvement. ANA, ACA, and Scl-70 were equally common in

patients with GI involvement and in all patients with SSc. It has been reported that ANA occur in about 95% of SSc patients.[26] We detected ANA in over 90% of SSc patients and almost all patients with GI involvement. Nishimagi et al.[25] showed that nucleolar fluorescence ANA were more common in patients with GI involvement. Moreover, they demonstrated the presence of a-U1RNP, a-U3RNP, and a-Ku antibodies in 57% of patients with GI symptoms.[25] ACA occur in 22% to 36% of SSc patients.[27] We found ACA in 26% of SSc patients. Furthermore, the occurrence of ACA was statistically significantly higher in SSc patients without GI involvement compared with those with GI symptoms. Thus, the presence of ACA could be associated with a lower risk of GI tract disorders. Similar results were reported by Savas et al.[28] who observed a higher incidence of ANA and Scl-70 antibodies than that of ACA in patients with GI symptoms.

We did not observe statistically significant differences in the incidence of Scl-70 antibodies in SSc patients with and without GI involvement. However, Scl-70 antibodies were found in 34% of the entire SSc group, which is in line with the published data (22%–40%).[27]

Histological and functional abnormalities in the GI tract are common complications of SSc. We found them in 54 (74%) SSc patients. Our results showed that GI clinical symptoms were significantly more common in patients with dcSSc. Upper GI symptoms were more frequent than lower GI ones. The presence of ACA was related to a lower risk of GI involvement. Pulmonary involvement in SSc patients with and without GI symptoms was comparable.

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ARTYKUŁ ORYGINALNY

Zajęcie przewodu pokarmowego u chorych na twardzinę układową

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przeciwciała przeciwjądrowe, przełyk, twardzina układowa, zajęcie płuc, zajęcie przewodu pokarmowego

STRESZCZENIE

WPROWADZENIE Zajęcie przewodu pokarmowego to jedno z najgroźniejszych powikłań w przebiegu twardziny układowej (TU).

CELE Celem pracy była ocena częstości występowania objawów ze strony przewodu pokarmowego u chorych na TU.

PACJENCI I METODY Badano 73 chorych na TU (60 kobiet i 13 mężczyzn). U 30 pacjentów rozpoznano uogólnioną postać TU, a u 43 ograniczoną postać TU. Zajęcie górnego odcinka układu pokarmowego oceniano na podstawie objawów klinicznych takich jak dysfagia oraz objawy refluksu żołądkowo-przełykowego. U większości pacjentów wykonano zdjęcie z kontrastem barytowym. Dolny odcinek przewodu pokarmowego oceniano na podstawie takich objawów klinicznych, jak biegunka i zaparcia.

WYNIKI Zajęcie układu pokarmowego stwierdzono u 54 chorych (74%) na TU. Objawy ze strony górnego odcinka przewodu pokarmowego występowały u 54 chorych (74%) na TU, a ze strony dolnego odcinka przewodu pokarmowego u 22 chorych (30%). Obecność przeciwciał antycentromerowych wiąże się z mniejszym ryzykiem występowania zmian w przewodzie pokarmowym. Nie obserwuje się różnic w częstości występowania zmian płucnych u chorych z zajęciem i u chorych bez zajęcia przewodu pokarmowego.

WNIOSKI Zajęcie przewodu pokarmowego stwierdza się u większości chorych na TU. Istotnie częściej objawy kliniczne związane z zajęciem układu pokarmowego występują u chorych na uogólnioną postać TU. Zmiany dotyczą częściej górnego odcinka przewodu pokarmowego.

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