Severe oesophageal disease and its associations with systemic sclerosis

G.P. Karamanolis[1], K. Denaxas[1], S. Panopoulos[2], K.-V. Bournia[2], A. Zorbala[2], D. Kamberoglou[1], D. Schizas[1], S.D. Ladas[1], P.P. Sfikakis[2]

[1]Academic Department of Gastroenterology, National and Kapodistrian University of Athens, Medical School, "Laiko" Hospital, Athens; [2]Joint Academic Rheumatology Program, National and Kapodistrian University of Athens, Medical School, Athens, Greece.

George P. Karamanolis, MD, PhD
Konstantinos Denaxas, MD
Stylianos Panopoulos, MD, PhD
Kalliopi-Vasiliki Bournia, MD
Alexandra Zorbala, MD
Dimitrios Kamberoglou, MD
Dimitrios Schizas, MD, PhD
Spiros D. Ladas, MD, PhD
Petros P. Sfikakis, MD, PhD

Please address correspondence to:
Dr George P. Karamanolis,
Academic Department of Gastroenterology,
"LAIKON" General Hospital,
Agiou Thoma 17,
Athens11527, Greece.
E-mail: georgekaramanolis@yahoo.co.uk

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ABSTRACT

Objective. *Severe oesophageal disease in patients with systemic sclerosis (SSc), referred as scleroderma oesophagus, is characterised by ineffective or absent peristalsis along with hypotensive oesophagogastric junction (hEGJ). The associations between scleroderma oesophagus and different clinical and laboratory manifestations of SSc is still controversial. In this study we aimed to assess associations between scleroderma oesophagus, diagnosed by high resolution manometry (HRM), and other manifestations of disease.*

Methods. *Fifty-four consecutive SSc patients (49 women, mean age 50.6±11.6) with oesophageal symptoms underwent clinical interview, medical records review and HRM. HRMs were analysed according to the Chicago Classification in order to provide oesophageal motility diagnosis; EGJ <9 mmHg was considered hypotensive. Demographic characteristics, patient-reported symptoms, SSc subtypes, pulmonary fibrosis, cutaneous ulcers, and anti-Scl-70 positivity were compared between SSc patients with or without scleroderma oesophagus. Comparison was also performed in computed tomography (CT) findings of oesophageal lumen in 26 patients with available data. Oesophageal dilatation was deemed present when the diameter was >9 mm.*

Results. *Absent contractility was present in 37 (68.5%) patients; among these patients hEGJP was found in 32, thus 32/54 (59.2%) patients had classic scleroderma oesophagus. There were no associations with gender, age, oesophageal symptoms, skin involvement extent, anti-Scl-70, pulmonary fibrosis and cutaneous ulcers. Notably, oesophageal dilation on chest CT was more frequent in patients with scleroderma oesophagus compared to those without (77% vs. 7%, p=0.04, respectively).*

Conclusion. *Scleroderma oesophagus diagnosed by HRM was present in less than 2/3 of symptomatic patients with SSc and associated only with oesophageal dilation in CT. Although further studies are needed, oesophageal dilation on chest CT may be a non-invasive alternative for evaluation of SSc patients with oesophageal symptoms.*

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune fibrotic disease affecting the skin and other organs including the gastrointestinal tract. Oesophagus is commonly affected in SSc and oesophageal function is compromised in up to 90% of patients (1-4). The pathogenesis of oesophageal involvement in SSc is still not fully understood; vascular damage with hypoperfusion and ischaemia followed by neurogenic involvement from microvascular changes and nerve compression by collagen deposition and inflammation seems to play a key role. As a result, smooth muscle atrophy occurs, following by weak muscle contractions (6-7).

Patients with SSc and oesophageal involvement usually report two types of symptoms: due to gastro-oesophageal reflux disease (GERD), such as heartburn and regurgitation and/or due to oesophageal dysmotility, such as dysphagia and chest pain. (5, 8). Manometry is considered the gold standard method for the assessment of oesophageal dysmotility in patients with SSc. The main manometric findings include the presence of ineffective or absent distal oesophageal peristalsis and decreased lower oesophageal sphincter (LES) pressure (8-9). Combination of distal aperistalsis and hypotensive LES is called as classic scleroderma oesophagus. Although progression of SSc seems to affect oesophageal motor involvement, it is unclear whether classic

scleroderma oesophagus is present in all SSc patients or whether associated with different disease's manifestations. Previous studies have shown inconsistent associations between oesophageal dysfunction and SSc laboratory and clinical manifestations (10-19). The majority of these studies have used different diagnostic criteria for oesophageal motility in patients with SSc and conventional manometry (10-17). We thought that implementation of oesophageal high-resolution manometry (HRM) in order to characterise oesophageal motility could allow a better assessment of classic oesophageal scleroderma over conventional manometry (20-21). Moreover, the use of the 2013 American College of Rheumatology SSc criteria could provide a unique opportunity to improve sensitivity and specificity for SSc diagnosis (22). Thus, our objectives were: 1) to quantify classic oesophageal scleroderma by using HRM in patients with SSc; and 2) to evaluate the associations between classic oesophageal scleroderma and various SSc manifestations.

Methods

Study population

This was a single centre retrospective study of prospectively evaluated SSc patients, who fulfilled the updated 2013 American College of Rheumatology (ACR) criteria for SSc (22) and underwent a HRM. All patients were referred from the Rheumatology Unit of our hospital in a 1-year time period for the evaluation of oesophageal symptoms. Only patients with technical limitations of HRM were excluded. None of our patients had a history of oesophageal dilation for stricture. The study protocol was approved by the ethics committee of 'Laikon' General Hospital and informed consent was obtained from all patients involved.

High-resolution manometry

Oesophageal manometry was performed with a water-perfused assembly with 22 pressure sensors (Solar GI HRM, MMS, Enschede, The Netherlands). The administration of proton pump inhibitors and prokinetics were interrupted 48 hours before HRM proceeding. All patients were fasted and were studied in the supine position. The HRM catheter was passed transnasally and positioned to record from the hypopharynx to the stomach. The catheter was fixed in place by taping it to the nose. The manometric examination included a 30-sec period to assess basal LES pressure and 10 swallows of 5 mL water. Double swallows were discarded and these were repeated. The integrated relaxation pressure (IRP), distal contractile integral (DCI) and distal latency (DL) were measured and the Chicago Classification (CC) was applied to provide oesophageal motility diagnoses (23). Resting oesophago-gastric junction pressure (EGJP) was measured during baseline recording period by using isobaric contour at end-expiration; EGJP <9 mmHg was considered hypotensive (hEGJP). Classic scleroderma oesophagus was defined as absent peristalsis along with hEGJP.

Clinical and laboratory SSc characteristics

Before proceeding to HRM studies, all patients filled out a self-reported symptom questionnaire in order to assess the presence of oesophageal symptoms, such as dysphagia, heartburn, regurgitation and chest pain. Demographic data and phenotypic characteristics of the disease were collected from the clinical charts. Moreover, in 26 patients supra- and infra-aortic coronal diameters of oesophagus were measured in high resolution chest computing tomography (CT) performed within the previous 3 months. Oesophageal dilatation was deemed present when either of the diameters were ≥9 mm (24).

Classic scleroderma oesophagus and SSc-related manifestations

Association between classic scleroderma oesophagus and the following SSc-related manifestations was studied: i) presence of patients-reported upper gastrointestinal symptoms i) SSc ii) subtype (diffused-limited type) as defined using the LeRoy criteria (25), ii) presence of cutaneous ulcers defined as a denuded area of tissue with well-demarcated borders involving loss of both the dermis and epidermis, iii) presence of pulmonary fibrosis (PF) was established if pulmonary interstitial pattern was evidenced by high-resolution CT, iv) positive serologic tests such as anti- Scl-70 autoantibodies and v) oesophageal thoracic-CT findings.

Statistical methods

Values were expressed as mean ± SD. The student t-test and chi-squared were used to comparisons when appropriate. A p value <0.05 was considered significant.

Results

Fifty-four patients (49 women, mean age 50.6±11.7 years) were finally included. A technically limited HRM was present in 4 patients, who were excluded. Table I summarises demographic characteristics, SSc manifestations, CT findings, and presence of oesophageal symptoms.

Absent contractility using CC was present in 37 (68.5%) patients; among those patients with absent contractility, hEGJP was found in 32, thus 32/54 (59.2%) patients had classic scleroderma oesophagus. Ten patients had ineffective oesophageal motility, whereas 7 patients had normal oesophageal motility.

Association of classic scleroderma oesophagus and SSc-related manifestations

Patients with and without classic scleroderma oesophagus did not differ in terms of age and gender. There was no difference in proportion of diffused SSc, cutaneous ulcers, PF, presence of positive anti-Scl 70 antibodies and presence of oesophageal symptoms between patients with and without classic scleroderma oesophagus.

High resolution CT scans were available in 13 SSc patients with and in 13 without scleroderma oesophagus. Oesophageal dilation on chest CT was significantly more frequent in patients with scleroderma oesophagus compared to those without (77% *vs*. 7%, p=0.04, respectively). Table II summarises the associations between scleroderma oesophagus and various SS-related manifestations.

Table I. Demographic characteristics, disease characteristics, symptoms, and manometric findings in study population.

	n=54
Age (yrs)	52. 5 ± 11.9
Sex (F/M)	49/5
Duration of disease (yrs)	8.7 ± 6.7
Diffuse SSc (n, %)	26 (48)
Pulmonary fibrosis	41 (75.9)
Cutaneous ulcers	31 (57.4)
Anti-Scl 70 (%)	9 (41)
C/T coronal diameters > 9 cm (%)	18 (69.2%)*
Presence of symptoms (%)	
-dysphagia	31 (57.4)
-heartburn	46 (85.2)
-regurgitation	47 (87.0)
-chest pain	20 (37.0)

*Data available in 26 SSc patients.

Table II. Associations between scleroderma oesophagus and various SS-c manifestations.

	scleroderma oesophagus (n=32)	no scleroderma oesophagus (n=22)	*p*
Age (yrs)	52. 5 ± 11.9	52. 5 ± 11.9	
Sex (F, %)	28 (87.5)	21 (98.4)	0.362
Duration of disease (yrs)	9.1 ± 6.2	8.4 ± 6.1	0.663
Diffuse SSc (n, %)	12 (55.5)	14 (43.8)	0.646
Pulmonary fibrosis (n,%)	25 (78.1)	15 (68.1)	0.750
Cutaneous ulcers (n, %)	19 (59.4)	12 (54.5)	0.854
Anti-Scl 70 (n,%)	23 (71.9)	12 (54.5)	0.540
CT coronal diameters > 9 cm (n, %)*	10 (76.9)	1 (7.7%)	0.045
Presence of symptoms (%)			
-dysphagia	18 (56.3)	13 (39.1)	0.914
-heartburn	25 (78.1)	21 (95.4)	0.620
-regurgitation	28 (87.5)	19 (86.4)	0.126
-chest pain	13 (56.3)	7 (31.8)	0.653

*Data available in 26 SSc patients (13 with and 13 without scleroderma oesophagus).

Discussion

Our data showed that classic scleroderma oesophagus, diagnosed by HRM, is common in SSc patients with oesophageal symptoms affecting almost 60% of them. However, we were unable to identify any association between scleroderma oesophagus and various SSc manifestations, except of a significant association between oesophageal dilation on thoracic C/T.

Classic scleroderma oesophagus motor pattern, consisting of absent distal contractility and hEGJ, has been suggested as the typical pattern of oesophageal involvement in SSc patients. Indeed, Roman *et al*. showed that scleroderma oesophagus was found in 55% of SSc patients using the 1980 ARC criteria (13, 26). However, recent studies have challenged this hypothesis showing that this pattern was present in only one-third of SSc patients (18-19). Our findings contrast with those results; in our cohort the motor pattern of classic scleroderma oesophagus was the predominant one. Our study share similarities with the two ones cited above, as we used the update ACR criteria for SSc and CC for HRM. Thus, a putative explanation of discrepancy could be the fact that our patients referred for HRM for evaluation of oesophageal symptoms, whereas in other studies HRM was performed at the discretion of patients' treatment physician. Moreover, Crowell *et al*. used a higher resting EGJ pressure cut-off to characterise EGJ as hypotensive (19).

Although an association of oesophageal dysmotility and diffused type of scleroderma has been reported (13), recent data found no significant difference in CC diagnoses between patients with diffused and limited SSc (18-19). Our results did not confirm any associations between scleroderma oesophagus and type of SSc. Moreover, in accordance with recent studies, our data showed that scleroderma oesophagus had no relationship with age, gender, and serological markers, such as ant-Scl 70 (18-19). Similar to previous studies, we did not observe an association between scleroderma oesophagus and symptoms (13, 18), although a recent study reported more severe oesophageal symptoms in SSc patients with compromised oesophageal motility (19). Someone could argue that even in healthy subjects there is no agreement between objective measurements of oesophageal function and perception of oesophageal symptoms, suggesting a role of hypersensitivity, presence of which is still under investigation in SSc (27-28).

Presence of organ involvement has been considered as part of a severe SSc form and it is supposed to be associated with severe motor oesophageal abnormalities in patients with SSc. Previous studies have reported various associations between absent contractility and other organ involvement. There is a controversy regarding association between skin involvement and oesophageal dysmotility (13, 18-19), whereas a more definite association between worse pulmonary function and aperistalsis has been observed (13, 18-19). In contrast, we were unable to establish any association between scleroderma oesophagus and organ involvement in our cohort. Different pulmonary involvement assessment and use of different subtypes of contractility abnormalities could explain the discrepancy among the studies.

We observed a significant association between scleroderma oesophagus and oesophageal dilation on CT scan. This is an important aspect of our study, as patients with SSc undergo routine chest CT as a screening test for lung fibrosis. Keeping in mind that HRM is an invasive and not routinely performed in everyday practice diagnostic test, measurement of oesophageal diameter on chest CT could be used as a radiological marker of the functional oesophageal status in SSc patients (29). Chest CT is a non-invasive, easily repeatable, widely available and with little need of patient cooperation. Our findings are in accordance with reports showing a strong correlation between oesophageal dilation on CT and oesophageal dysmotility measured by transit scintigraphy or barium swallow (24, 30). Moreover, our results validated the importance of the ≥9mm threshold for oesophageal dilation, which Pitzer *et al*. showed that it had a great sensitivity and specificity (24).

Our study was strengthened by a well-characterised cohort of patients with SSc and the use of most current CC diagnostic criteria. In addition, time between HRM and high resolution chest CT was at maximum 3 months. A methodology weakness of current study is the retrospective design, even though HRMs were performed in a prospective way. Moreover, we included only SSc patients with symptomatic oesophageal involvement, thus it is possible that our results over-estimated the prevalence of classic scleroderma oesophagus. Owing to relatively small number of subjects with available chest CT, further studies are needed to confirm the association between presence of scleroderma oesophagus in HRM and oesophageal dilation on CT.

In conclusion, we observed that classic scleroderma oesophagus was the most prevalent contractility pattern in SSc patients with oesophageal symptoms, even though it was present in less than 2/3 of symptomatic patients. We also found that classic scleroderma oesophagus significantly correlated with presence of dilated oesophagus on high resolution chest CT. Thus, oesophageal dilation on CT scan, performed routinely as a screening tool in SSc patients, could be an alternative to evaluate oesophageal dysfunction. The ≥ 9mm threshold should be used for the definition of oesophageal dilation on chest CT.

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