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Association between esophageal motor disorders and pulmonary involvement in patients affected by systemic sclerosis: a retrospective study

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Abstract

Systemic sclerosis (SSc) is a rare autoimmune disease of the connective tissue that can affect multiple organs. The esophagus is the most affected gastrointestinal tract, while interstitial lung disease (ILD) is a main feature associated with SSc. The aim of the present study was to evaluate the association and prognostic implication between motor esophageal disorders and pulmonary involvement in SSc patients. We retrospectively assessed patients with SSc who underwent both the HRM with the new Chicago Classification 4.0 and pulmonary evaluation comprehensive of function tests and high-resolution computer tomography (HrCT) with the use of Warrick score. A total score ≥ 7 was considered predictive of ILD, while a score ≥ 10 in a HrCT acquired prospectively from baseline evaluation was considered to establish significant interstitial involvement. Forty-two patients were included. We found a score ≥ 7 in 11 patients with aperistalsis, in 6 subjects with IEM and in 6 patients with a normal manometry. Otherwise, a score < 7 was observed in 3 patients with aperistalsis, and in 2 and 14 patients with IEM and with a normal contractility, respectively. Higher scores were observed in subjects with absent contractility or ineffective esophageal motility than subjects with normal motility, indeed DCI and HrCT score were inversely correlated in linear and logarithmic regression analysis. Prospectively, lower baseline LESP and greater HrCT scores at follow-up evaluation were significantly correlated. This study shows an association between motor esophageal disorder and pulmonary involvement in SSc patients: more severe is the esophageal involvement, more critical is the pulmonary disease.

Keywords Systemic sclerosis · Pulmonary fibrosis · Esophageal motility disorders

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease of the connective tissue, affecting multiple organs: skin, kidneys, gastrointestinal tract, musculoskeletal system, heart, and lungs. Two different types can be distinguished, the limited cutaneous SSc (lcSSc), in which the thickening of the skin is distal to knees, elbows and face (the trunk is spared) and the diffuse cutaneous SSc (dcSSc), in which the thickening is proximal with extension to the trunk.

Internal organs can be involved in both subtypes, but patients with dcSSc had the highest probability. The esophagus is the most affected gastrointestinal tract, with percentages ranging from 50 to 90% of the patients [1]. Aperistalsis and ineffective esophageal motility (IEM) are the main manifestations of esophageal involvement, that is characterized by a progressive extension from distal to proximal

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tract. Patients often report gastroesophageal reflux disease (GERD) symptoms, such as heartburn, regurgitation and non-cardiac chest pain or dysphagia due to motility impairment [2, 3].

On the other hand, the interstitial lung disease (ILD) is a main feature associated with SSc and is considered a diagnostic criterion of SSc [4]. Nowadays, the presence of interstitial fibrosis is one of the most important reason of morbidity and mortality in SSc and represents the third cause of death, after pulmonary hypertension and ILD-associated pulmonary hypertension, as proved by a large Spanish registry [5–7]. The ILD is identified thought pulmonary function tests (PFT) and characterized by a restrictive pattern with a reduction of Forced Vital Capacity (FVC) and alveolo-capillary CO diffusion (DLCO). The high-Resolution-CT (HrCT) is currently considered the gold standard among the non-invasive tools able to diagnose and grade ILD [8].

Several studies investigated the potential association between esophageal and pulmonary alterations, but a cause-effect relationship has not been established yet [9–11]. Moreover, most of these studies were carried out with the conventional esophageal manometry, now replaced by high resolution manometry (HRM) with its more clinically relevant new classification scheme of esophageal motility disorders, which is the Chicago Classification [12–14].

The aim of the present retrospective, but longitudinal study was to evaluate the association and prognostic implication between motor esophageal disorders at HRM according to the last Chicago Classification and pulmonary involvement in SSc patients [14].

Materials and methods

We retrospectively assessed patients with SSc who referred to the Digestive Pathophysiology Outpatient Section of the Gastroenterological Clinic of the IRCCS San Martino Polyclinic Hospital in Genoa between 2009 and 2021. Patients included underwent both the HRM and pulmonary evaluation comprehensive of PFTs and HrCT. In particular, HrCT was repeated during time and, therefore, longitudinal data have been collected so far in order to emphasize any potential association between the esophageal and pulmonary involvement.

The high-resolution manometry was performed according to Chicago protocol [14, 15]. We used the Diversatech probe, Diversatek Healthcare (Milwaukee, USA) and the normal valued recently published [16]. Manometric data were evaluated according to Chicago Classification v. 4. Contractile vigor was evaluated using the distal contractile integral (DCI). In particular, we identified patients with absent contractility in presence of 100% failed peristalsis with normal lower-esophageal sphincter relaxation behavior and with IEM when more than 70% ineffective swallows or at least 50% failed peristalsis were registered. We also collected the basal pressure of LES (LESP).

The pulmonary involvement was evaluated searching spirometric data of FVC and DLCO in the archive. FVC < 70% and DL CO < 70% of predicted values were considered abnormal. We considered as signs of interstitial pulmonary disease at HrTC the ground-glass opacity, irregular pleural margin, septal/subpleural linse, honeycombing, subpleural cysts and the broncopulmonary segments involvement. The radiologic score described by Warrick et al. was calculated giving a value to every alteration seen in HrCT [17]. The severity of the manifestation and the extension of the disease were collected and graded. A total score ≥ 7 was considered predictive of ILD, while a score > 10 indicates an interstitial involvement with a 100% of specificity.

Statistical analysis was performed using IBM SPSS Statistics 25. A Kolmogorov–Smirnov analysis was performed to test the normality of variables. The results of continuous variables were expressed as median and interquartile range. For ordinal and nominal variables, contingency tables were used for indicating frequency and percentage in the population. The associations between continuous manometric and pulmonary data were analyzed using the Mann–Whitney test. The results were significant when the p-value was less than 0.05.

The study was conducted in accordance with the research protocol and in compliance with the Declaration of Helsinki. All patients provided written informed consent to participate in the study. All the data were retrospectively evaluated, and the anonymity of the patients was preserved. The publication of the study (237REG2015) was approved by the Institutional Review Board of IRCCS Ospedale Policlinico San Martino (Genoa, Italy) and the last amendment (002) was agreed on May 28th, 2018.

Results

A raw population of 137 patients were extracted, and after we excluded patients who underwent conventional manometry ($n = 87$) and 8 patients without the results available of PFTs or HrCT, a total of 42 patients were included. Out of them, 24% were men (10/42) with a median age of 64 years (range 36–91). The median BMI was 23 kg/m^2 (range 17–31) and 39 were non-smokers. Table 1 reports medical history and antibodies status of all patients with SSc. The majority of the patients had a diffuse type SSc (28/42, 67%), while 33% had a limited cutaneous SSc (14/42).

Twenty-three patients (54.77%) had a CT-score ≥ 7, while 19 (45.23%) had a CT-score < 7. At HRM, 14 patients (33.3%) had an absent contractility, 8 (19.04%) had an IEM, while 20 (47.62%) subjects had a normal contractility.

Table 1 Demographics, clinical data and HRM, CT and PFT findings in all patients

	All patients $n=42$	Score CT < 7 $n=19$	Score CT ≥ 7 $n=23$	p-value
General characteristics				
Female gender	17 (89.5)	15 (65.2)	32 (76.2)	0.066
Age [years]	64 (61–72)	64 (62–75)	64 (56–72)	0.685
BMI [kg/m^2]	22.5 (20–25)	21 (19–26)	23 (21–25)	0.576
Alcohol intake [UA/die]	10 (0–20)	10 (0–15)	10 (0–20)	0.472
Coffee intake [*n*/die]	2 (1–2)	2 (1–2)	2 (2–2)	0.337
Smoking habits [*n*/die]	0 (0–0)	0 (0–0)	0 (0–0)	0.631
Characteristics of disease				
Type of SSc				
Limited [lcSSc]	28 (66.7)	13 (68.4)	15 (65.2)	0.823
Diffuse [dcSSc]	14 (33.3)	6 (31.6)	8 (34.8)	
Antibodies				
ANA	18 (94.7)	21 (91.3)	39 (92.9)	0.667
Anti-centromere	6 (31.6)	2 (8.7)	8 (19)	0.060
Scl-70	3 (15.8)	8 (34.8)	11 (26.2)	0.163
HRM findings				
Pressure inversion point [cm]	44 (42–46.6)	44 (42–46.5)	44 (42–47.8)	0.780
BT Liquid [%]	55 (20–90)	80 (33–90)	44.5 (18.2–70)	0.170
BT viscous [%]	60 (20–100)	70 (20–100)	60 (20–100)	0.490
Pattern HRM				
Normal	20 (47.6)	14 (73.7)	6 (26.1)	0.008
Absent contractility	14 (33.3)	3 (15.8)	11 (47.8)	
IEM	8 (19.1)	2 (10.5)	6 (26.0)	
HrCT findings				
Bronchopulmonary segments [*n*]	3 (2–6)	2 (0–3)	4 (3–6)	< 0.0001
Points according to Warrick score	1 (1–2)	1 (0–1)	2 (1–2)	< 0.0001
Subpleural cysts [Points]	0 (0–5)	0 (0–0)	5 (5–5)	< 0.0001
Septal/Subpleural lines [Points]	3 (0–3)	0 (0–3)	3 (3–3)	0.006
Ground-glass appearance [Points]	0 (0–0)	0 (0–0)	0 (0–1)	0.207
Irregular pleural margins [Points]	0 (0–2)	0 (0–2)	2 (0–2)	0.093
Honeycombing [Points]	0 (0–0)	0 (0–0)	0 (0–0)	0.107
Pulmonary function testing				
FVC [%]	99 (80–117.5)	104 (95–122)	88 (72–103)	0.014
FCV < 70%	40 (95.2)	19 (100)	21 (91.3)	0.188
DLCO [%]	78.5 (62–91)	90 (75–97)	72 (51–81)	0.017
DLCO < 70%	26 (61.9)	15 (78.9)	11 (47.8)	0.039

Continuous data are median and interquartile range and nominal data are number (% patients)

ANA Anti-nucleus antibodies, *BMI* body mass index, *BT* bolus transit, *CT* computer tomography, *dcSSc* diffuse cutaneous systemic sclerosis, *DLCO* diffusing capacity for carbon monoxide, *FVC* forced vital capacity, *HRM* high-resolution manometry, *IEM* ineffective esophageal motility, *lcSSc* limited cutaneous systemic sclerosis, *PFT*; *SSc* systemic sclerosis

Comparing manometric findings with pulmonary alterations, we found a score ≥ 7 in 11 patients with aperistalsis, in 6 subjects with IEM and in 6 patients with a normal manometry. Otherwise, a score < 7 was observed in 3 patients with aperistalsis, and in 2 and 14 patients with IEM and with a normal contractility, respectively ($p=0.0024$). Moreover, higher scores were observed in subjects with absent contractility or ineffective esophageal motility than subjects with normal esophageal motility ($p=0.008$ and $p=0.03$, respectively) (Fig. 1A). Indeed, DCI and Warrick HrCT score were inversely correlated in linear ($R^2=0.22$, $p=0.002$) and logarithmic ($R^2=0.33$, $p=0.001$) regression analysis (Fig. 1B).

Considering hypokinetic alterations together (absent contractility and IEM), we found a statistically significant correlation with greater radiologic scores (Score ≥ 7: 17/23, 73.9% patients with hypokinetic alterations and

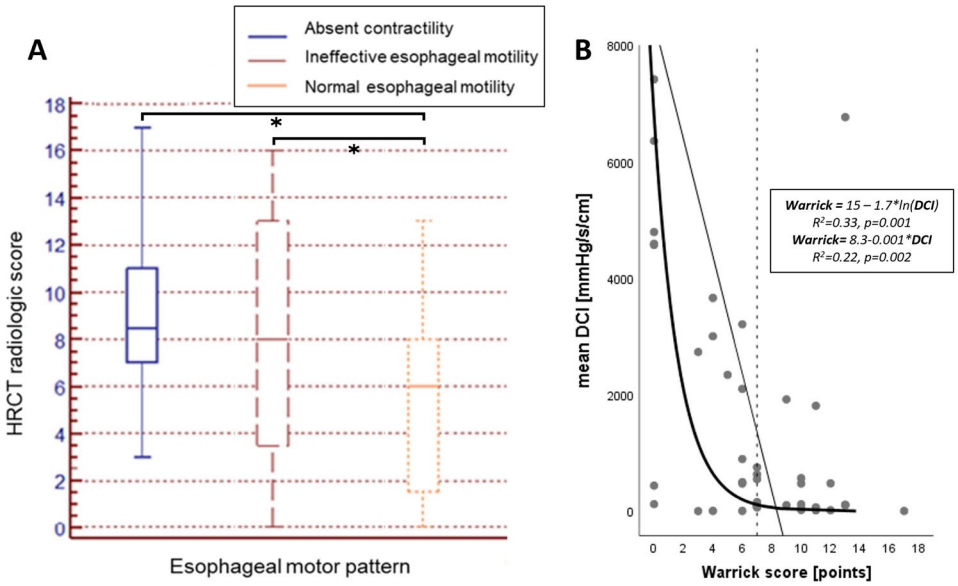

Fig. 1 Association between HrCT radiologic score and A specific esophageal motor patterns and B mean DCI. *$p < 0.01$ at non-parametric tests

Score < 7: 5/19, 26.3% patients with hypokinetic alterations, $p < 0.0001$).

On the contrary, we did not find a statistically significant association between manometric alterations and FVC and DLCO. In our population, only 2 patients showed an FVC < 70% of the predicted and 16 patients had a DLCO < 70% of the predicted. Lower values of DLCO were associated with greater CT-scores. Detailed manometric, radiologic and functional respiratory test are reported in Table 1.

Analyzing the CT scans of 34 patients taken within 3 years after the baseline evaluation, we found 20 patients (47.62%) with a CT-score > 10. There was a statistically significant association between a lower baseline LESP and greater CT scores at follow-up evaluation ($p < 0.0001$) (Fig. 2).

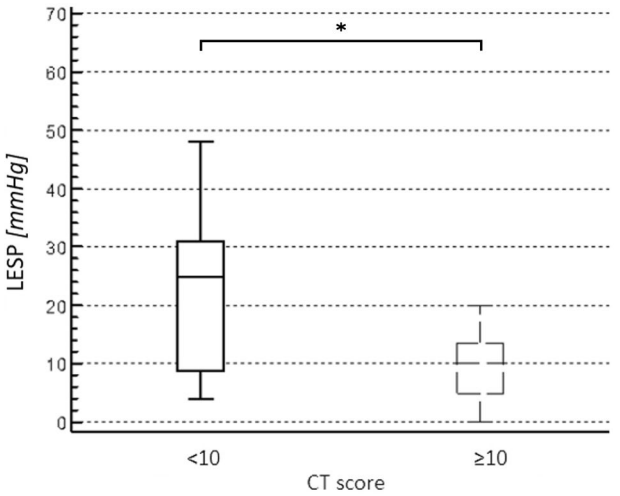

Fig. 2 Evaluation of the association between baseline LESP and CT score after 3 years. *$p < 0.01$ at Mann–Whitney U test

Discussion

Ninety percent of patients with SSc can present an esophageal involvement, and HRM may play an important role in the identification of this condition and possible association with other SSc-related manifestations. Indeed, this tool has become a valuable aid in this setting, as it has a high sensitivity even at earlier stages of the disease [18, 19]. Thus, we decided to correlate esophageal involvement by HRM with pulmonary involvement as assessed and graded by HrCT.

Studying 42 SSc patients and repeating the tests over time in 34 subjects, we found that the worse the pulmonary involvement, the worse the esophageal hypokinetic disorder with lower DCI values. Vice versa, lower LES pressures corresponded prospectively to higher pulmonary involvement at CT control after years [20]. This study underlines a potential association between hypokinetic esophageal disorders according to CC 4.0 with a severe pulmonary involvement in SSc patients, meaning a progressive concomitant damage of these tracts may be hypothesized.

Similarly, a lower LESP which is typically found in scleroderma esophagus, was associated with a worst pulmonary involvement in our patients. Hypotensive LESP was encountered in 16/42 (38.1%) of our population, while esophageal hypo- or aperistalsis affected 22/42 (52.4%) of the patients evaluated. Results consistent with literature, even if several studies included heterogeneous population [2, 13, 21]. From a pathogenetic point of view, IEM, absent contractility and

lower LESP can favor the reflux from the stomach to the esophagus, and probably to the bronchial tract, allowing the occurrence of a chronic pulmonary damage [22, 23]. This study cannot establish a causal connection between the two manifestations, that are a possible expression of the disease progression. However, their association demonstrated with the current state-of-the-art methods may have implications in the diagnostic-therapeutic process of SSc patient suggesting to perform an esophageal study when patients present a pulmonary involvement.

On the contrary, in our analysis, no association was found between esophageal disorders with FVC and DL CO. In literature, data about this association appear heterogeneous. Lock et al. found a significant correlation between distal esophageal hypo- or aperistalsis and the FVC, as well as a lower LESP and FVC, but in a retrospective study conducted according to classic manometry findings [19]. More recently, Kuchipudi et al. found a significant correlation between esophageal dysmotility and progressive DLCO impairment, with a non-significant worsening of FVC [24]. The literature is consistent with the later data as the decline of pulmonary function can be gradual over time [6, 7].

The association between lower baseline LESP and higher CT scores found at 3 years is important because may represent a red flag of a worst course of interstitial lung fibrosis. These data are in line with a study of 2001 from Marie et al. which evaluated the prognostic value of the presence of esophageal motor alterations in conventional manometry, demonstrating that severe esophageal alterations are associated with a worst course of pulmonary involvement [25]. Kimmel et al. have reported similar results, but according with HRM evaluation [13].

This study has several limitations. This is a retrospective study, with a limited sample size and full follow-up data are lacking. On the other hand, this study included SSc patients assessed both esophageal and pulmonary involvements with the state-of-the-art methods, which nowadays are HrCT and HRM with the most updated criteria available.

In conclusion, this study shows a correlation between motor esophageal disorder diagnosed with HRM and pulmonary involvement, seen in CT in patients with SSc: more serious is the esophageal involvement, more critical is the pulmonary disease, even over time. Considering the prognostic value of ILD in SSc, the correct evaluation of esophageal involvement is essential in the diagnostic work-up of this class of patients. Future prospective studies are necessary to confirm this correlation and to find tailored therapeutic strategies in order to improve clinical outcomes.

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Author contributions YMC, AP and EM: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work AND Drafting the work or revising it critically for important intellectual content AND Final approval of the version to be published AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All other authors: acquisition of data for the work AND revising it critically for important intellectual content AND Final approval of the version to be published AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have endorsed the final manuscript in its submitted form and assume responsibility for all aspects of the research.

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Data availability The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at University of Genoa.

Declarations

Conflict of interest The authors have no conflict of interests to declare.

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