Original Article

Pulmonary Manifestation in Systemic Sclerosis in Srinagarind Hospital

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Background: Systemic Sclerosis [SSc] can involve any organ systems, including pulmonary system which was associated with high mortality in SSc. Direct and indirect pulmonary complications can occur.

Objective: To define the radiographic differences from HRCT chest between the patients with diffuse cutaneous systemic sclerosis [dcSSc] and limited cutaneous systemic sclerosis [lcSSc]. Also, to find out the indications for HRCT chest testing and factors that may involve the patterns of pulmonary involvement.

Materials and Methods: A historical cohort study collected all adult SSc patients who were followed-up at Scleroderma Clinic in Srinagarind Hospital during 1 January 2012 until 30 November 2014 and had performed high resolution computed tomography [HRCT] of chest. Any indications of HRCT chest and clinical manifestations of patients were review.

Results: A total of 289 patients underwent HRCT chest, 229 (79.2%) were dcSSc. Median age and disease duration at time of first performing HRCT chest were 53 and 1 year, respectively. The female to male ratio was 2.2: 1. Abnormal chest radiography was the most common indication of HRCT chest (179; 61.94%), followed by abnormal chest symptoms (121; 41.87%). The most common findings in HRCT chest in both SSc subsets were septal thickening (79.9%), followed by mediastinal lymphadenopathy (59.2%). There was no statistical significance of pattern of pulmonary involvement in both dcSSc and lcSSc. Screening in asymptomatic patients for pulmonary involvement by HRCT chest was significant higher in lcSSc than in dcSSc (p<0.05). Ground glass opacity was revealed in 31.3% in asymptomatic patients who were screened HRCT.

Conclusion: There were no differences in pattern of pulmonary involvement between both SSc subsets. SSc associated interstitial lung disease and mediastinal lymphadenopathies were common findings in Thai SSc patients. One-third of the patients had ground glass opacity by HRCT chest despite of being asymptomatic.

Keywords: Systemic sclerosis, High resolution computed tomography, Pulmonary manifestation, Interstitial lung disease, Mediastinal adenopathy, Esophageal dilatation

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Systemic Sclerosis [SSc] is a sporadic connective tissue disorder. Multi-system involvements of disease processes cause the variety of clinical manifestations especially progressive clinical course. Vital organ involvement can result in morbidity and mortality. Pathophysiology included the following: autoimmune inflammation, microangiopathy and vascular fibrosis. The incidence in USA is around 9 to 19 cases per million per year. In Japan, England, Australia, the incidences appear to be lower. The incidence is higher in blacks than whites. There is a female predominance and female to male ratio is 4.6: 1 and a peak age of onset at 30 to 50 years old[(1)]. In Thailand, SSc cases are mostly found in North and Northeastern [NE] Thailand. The incidence in NE Thailand is around 1: 100,000. The onset of SSc in NE Thailand is between 40 to 50 years old, with 2: 1[(2)] female predominance.

Disease processes can involve any organ systems, including the respiratory system. The phases

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of fibrotic and vascular pulmonary manifestations of SSc include interstitial lung disease, pulmonary hypertension, and pleural involvement. In addition, indirect pulmonary complications can occur (e.g., aspiration, infection, drug toxicities, malignancy, and respiratory muscle weakness). Moreover, there are combinations of direct and indirect pulmonary manifestation and other lung diseases that are not related to SSc (lung nodules, mediastinal lymphadenopathy)[3].

Nowadays, early diagnosis of SSc-ILD is used by high-resolution computed tomography of chest before the appearance of symptom. Bronchoscopy with bronchoalveolarlarvage was not done in patients with typical HRCT of chest and didn't show severity of diease. 75% of patients with SSc developed ILD[4]. Furthermore, HRCT is a non-invasive, gold-standard for diagnosing ILD. In addition to interstitial lung disease, there are other findings in HRCT (e.g., esophageal dilatation, indirect pulmonary involvement, and other lung diseases) that are not related to SSc. European Scleroderma Trials and Research group [EUSTAR] had described that ILD was more prevalent in diffuse cutaneous group than in limited cutaneous group (53% vs. 35%)[5]. However, no data reported in the detail of ILD and the differences of pattern of lung involvement between both groups.

The present study aims to find the radiographic differences in both groups of systemic sclerosis in center of Northeastern Thailand in scleroderma clinic. Moreover, there were no previous studies about indications for HRCT testing of chest and disease duration at time of HRCT testing of chest before.

Objective

The primary objective was to define the radiographic differences between diffuse cutaneous SSc [dcSSc] and limited cutaneous SSc [lcSSc]. The secondary objective was to find indication for HRCT testing of chest and identify factors that may involve in the patterns of pulmonary involvement, as well as to examine the disease duration at time of performing HRCT of chest.

Materials and Methods

Study design

A historical cohort of adult SSc patients who were came to follow-up at Scleroderma Clinic in Srinagarind Hospital during 1 January 2012 to 30 November 2014 and had performed high resolution computed tomography [HRCT] of chest. The patients having overlap with other diseases were excluded. If the patients had received multiple HRCT results, the first HRCT which had been approved by the radiologist was used for the analysis. SSc symptoms included gastrointestinal [GI] symptoms and infra-aortic esophageal coronal diameters were reviewed. The present study was received ethical approval from The Ethics Committee in Human Research of KhonKaen University.

The present study included 289 patients who were divided into two groups of patients according to LeRoy&Medsger's classification criteria[6]. The records included the demographic data, types of systemic sclerosis, disease duration of SSc before first time performing HRCT chest, Modified Rodnan skin scores, smoking history, New York Heart Association functional classification, clinical manifestations, antibody testing, immunosuppressive drugs, indications of HRCT chest (screening, indicated symptoms, abnormal physical examination, abnormal chest radiography, and abnormal pulmonary function test), pulmonary function test, HRCT findings, infra-aortic esophageal coronal diameter, and the upper gastrointestinal symptoms. Patients who had an active infection at the time of HRCT study were not included in the pattern of lung involvement analysis.

Operation definition

SSc was defined by 2013 ACR/EULAR SSc classification criteria[7] or 1980 ACR classification criteria for systemic sclerosis[8] in case of the patients who were diagnosed as SSc before 2013.

Pulmonary involvement was defined in the patient who had any chest symptoms and/or abnormal chest radiography.

The modified Rodnan skin score [mRSS] was assessed at 17 sites as: 0 (normal), 1 (weak), 2 (intermediate) or 3 (severe) skin tightness.

Statistical analysis

Continuous variables were given as mean or median and range as appropriate. Data as median is also showed interquartile range Q1-Q3. Categorical variables were described as numbers and proportion. Analysis of the associations between each dichotomized group and categorical variables were analyzed by Chi-square test or the Fisher's exact test. T test or Mann Whitney U test were applied for analysis of the association between esophageal dilatation and upper GI symptoms. All tests were 2-tailed, and $p<0.05$

was considered significant. All data analyses were performed using Stata 11 software (version 11.0).

Results

Patient characteristics

A total 289 patients met the inclusion criteria. Of which, 229 (79.2%) were dcSSc.

The demographic data and population characteristics are shown in Table 1. Median ages at HRCT and disease duration before first time of performing HRCT chest was 53 years (interquartile range (IQR 45 to 61)) and 1 year (IQR 0.06 to 4), respectively. Female to male ratio was 2.2: 1. Median modified Rodnan skin score in patient with diffused and limited type systemic sclerosis is 12 (6 to 21) and 4 (2 to 7), respectively. For the matter of functional class, limited type systemic sclerosis is much better than the diffuse type. There were no significant differences among the 2 sub-types with respect to age, duration before first time of performing HRCT, smoking history, serology, and medication.

The common indications for HRCT chest in the studied population were due to abnormal chest radiography (179 patients; 61.9%) and abnormal symptoms (121 patients; 41.9%). Dyspnea on exertion was more frequently presented in dcSSc at time of performing HRCT chest than in lcSSc ($p<0.05$), whereas asymptomatic pulmonary involvement was more frequently revealed in lcSSc ($p<0.05$) (Table 2). Almost all of the HRCT findings had some degrees of abnormality 286 of 289 (99%). The most common finding in HRCT was septal thickening 231 patients (79.9%), followed by mediastinal lymphadenopathy 171 patients (59.2%) as shown in Table 3. However, there was no significant difference among the SSc subsets in term of pulmonary function test and radiographic findings from HRCT chest. Infra-aortic esophageal dilatation (coronal diameter at least 9 mm) was more frequently found in dcSSc (74.2%) than in lcSSc (58.3%) with $p = 0.01$ and lcSSc had less GI symptoms than dcSSc with $p<0.001$. DcSSc had dysphagia symptom more than lcSSc (39.7% vs. 23.3%, p-value = 0.02). Degree of esophageal dilatation had significant correlation with upper GI symptoms ($Z = 0.02$).

Discussion

Data on HRCT of chest patterns in different sub-types of SSc and indications for HRCT of the chest were retrospectively collected. The findings included characteristics of interstitial lung involvement, indirect pulmonary involvement, and esophageal dilatation with clinical correlation to upper GI symptom. HRCT is the

Table 1. Characteristics of SSc patients in different sub-types

Variables	Diffuse type (229)	Limited type (60)	Total (289)	p-value
Age at HRCT (median q1-q3)	53 (45 to 61)	54 (46 to 59)	53 (45 to 61)	0.90
Male (%)	80 (34.9)	10 (16.7)	90 (31.1)	<0.05
Disease duration (median q1-q3)	1 (0.06 to 3.6)	2 (0.1 to 6.055)	1 (0.06 to 4)	0.11
Skin score (median q1-q3)	12 (6 to 21)	4 (2 to 7)	9 (4 to 18)	<0.05
Smoking history				
Never (%)	185 (80.8)	55 (91.7)	240 (83)	0.13
Active smoker (%)	1 (0.4)	0 (0)	1 (0.3)	
Inactive smoker (%)	43 (18.8)	5 (8.3)	48 (16.6)	
Functional class (%)				
I	79 (34.5)	30 (50)	109 (37.7)	0.02
II	127 (55.5)	30 (50)	157 (54.3)	
III	19 (8.3)	0	19 (6.6)	
IV	4 (1.7)	0	4 (1.4)	
Serology				
Anti - Scl 70	93 (44.3)	25 (45.5)	118 (44.5)	0.87
Anti - Centromere	4 (1.9)	2 (3.6)	6 (2.3)	0.44
ANA	71 (33.8)	17 (30.9)	88 (33.2)	0.68
Medication				
None	89 (38.9)	30 (50)	119 (41.2)	0.11
Prednisolone	130 (56.8)	27 (45)	157 (54.3)	0.10
Cyclophosphamide	45 (19.7)	7 (11.7)	52 (18)	0.15
Other	10 (4.4)	4 (6.7)	14 (4.8)	0.46

Table 2. Indications for HRCT chest

Data	dcSSc n = 229 (%)	lcSSc n = 60 (%)	Total n = 289 (%)	*p*-value
Indication for performing HRCT chest				
Screening	19 (8.30)	13 (21.67)	32 (11.07)	<0.05*
Symptomatic	102 (44.54)	19 (31.67)	121 (41.87)	0.07
Dyspnea on exertion	71 (31.0)	8 (13.33)	79 (27.34)	<0.05*
Dry cough	55 (24.02)	16 (26.67)	71 (24.57)	0.67
Fatigue	12 (5.24)	1 (1.67)	13 (4.5)	0.23
Hemoptysis	2 (0.87)	0 (0)	2 (0.69)	0.46
Other	2 (0.87)	0 (0)	2 (0.69)	0.46
Abnormal chest physical examination	87 (37.99)	15 (25.00)	102 (35.29)	0.06
Abnormal chest radiography	44 (62.88)	35 (58.33)	179 (61.94)	0.51
Abnormal pulmonary function test	18 (3.49)	3 (5.00)	11 (3.81)	0.58

Table 3. The comparison of pulmonary manifestations and radiographic finding from HRCT chest between dcSSc and lcSSc

Radiographic findings from HRCT chest (%)	dcSSc n = 229 (%)	lcSSc n = 60 (%)	Total n = 289 (%)	*p*-value
Normal	3 (1.3)	0 (0)	3 (1)	0.37
Abnormal				
GGO	101 (44.1)	24 (40)	125 (43.3)	0.56
Honeycomb or bronchiectasis	127 (55.5)	34 (56.7)	161 (55.7)	0.86
Fibrosis	59 (25.8)	15 (25)	74 (25.6)	0.90
Septal thickening	187 (81.7)	44 (73.3)	231 (79.9)	0.15
Pleural thickening	25 (10.9)	7 (11.7)	32 (11.1)	0.86
Nodule	20 (8.7)	5 (8.3)	25 (8.7)	0.92
Pleural effusion	5 (2.2)	1 (1.7)	6 (2.1)	0.80
Pneumothorax	2 (0.9)	0 (0)	2 (0.7)	0.46
Lung cyst	2 (0.9)	0 (0)	2 (0.7)	0.46
Mediastinal lymphadenopathy	134 (58.5)	37 (61.7)	171 (59.2)	0.65
Pneumonia	12 (5.2)	5 (8.3)	17 (5.9)	0.36
Esophageal dilatation(mm)				
≥9 mm	170 (74.2)	35 (58.3)	205 (70.9)	0.01*
Upper GI symptoms				
Normal	92 (40.17)	37 (61.67)	129 (44.64)	<0.05*
Abnormal				
Dyspepsia	59 (25.76)	16 (26.67)	75 (25.95)	0.88
Heartburn	73 (31.88)	14 (23.33)	87 (30.10)	0.19
Dysphagia	91 (39.74)	14 (23.33)	105 (36.33)	0.02*

* Statistical significant $p<0.05$

DcSSc = diffuse cutaneous systemic sclerosis; LcSSc = limited cutaneous systemic sclerosis; HRCT = high resolution computed tomography; PFT = pulmonary function test; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; GGO = ground glass appearance; GI = gastrointestinal

non-invasive gold standard method used to evaluate interstitial lung disease. Our findings showed that most patients who came to follow-up in Scleroderma Clinic at Srinagarind Hospital had dcSSc. Female to male ratio is 2.2:1. The indications for HRCT in the present study population are due to abnormal CXR (61.94%) and abnormal symptoms (41.87%). The most significant symptom used for working up HRCT was dyspnea on exertion (79 (27.34%), especially in DcSSc group with statistical significance (*p*-value <0.05). On the other

hand, screening HRCT was more often done for the lcSSc than for the dcSSc with statistical significance (p-value <0.05). Almost all HRCT findings in the patient population had some degree of abnormality (99%). Given that the median disease duration from the presenting (non-Raynand phenomenon) symptom to the first time of HRCT chest performing was 1 year (0.06 to 4), if the data were combined, there begs a question: "Should every systemic sclerosis patient be screened for HRCT when the disease duration is more than one year?". The present study shows that HRCT chest screening was done for 32 patients, and that 10 patients had the ground glass opacity pattern (31.25%) which had to be considered for treatment with immunosuppressive drugs in order to modify the progression of fibrosis even though there was no statistical significance (p-value = 0.146). Pulmonary function tests showed that 88 of the 169 patients had FEV1/FVC ≥0.7 and FVC <80% predicted which is pulmonary or extra-pulmonary restrictive pattern e.g., thickening skin. However, pulmonary function tests were not complete, and the records showed no evidence of DLCO testing because the test is not routinely done. The most common finding in HRCT was septal thickening (79.9%). Surprisingly, the second most common finding in HRCT was mediastinal lymphadenopathy (59.2%). The nature of mediastinal lymphadenopathy was found only in 3 patients with *Mycobacterium tuberculosis* and non-*Mycobacterium tuberculosis* from sputum culture. Other patients with mediastinal lymphadenopathy had culture-negative sputum and some patients were not tested for sputum culture. Therefore, the nature of mediastinal lymphadenopathy should be identified which might be from reaction, infection or the disease itself. Comparing to study from Bhalla M et al[9] there were mediastinal adenopathy in 15 of 25 (60%) systemic sclerosis patients, while Donya F et al[10] showed only 30%. In SSc-ILD, a honeycomb appearance or bronchiectasis is more common in the lcSSc {34 of 60 (56.7%)} than dcSSc {127 of 229 (55.5%)}. There was the same result as that from Goldin et al[11], who found that honeycomb is more common in lcSSc than dcSSc. However, these results were different from that of a Thailand study by Patiwetwitoon et al[11] where fibrosis was the most common lung abnormality in HRCT chest findings. Population profiles in each study may play an important role in explaining these differences. Conversely, the ground glass opacity is more common in dcSSc {101 (44.1%)}. GGO had no significant correlation with severity of skin score (Z = 0.32). There were no significant differences of HRCT chest among the 2 subtypes in nodules, pleural effusion, pneumothorax, lung cysts, mediastinal lymphadenopathy, pneumonia, and pleural thickening.

Infra-aortic esophageal coronal diameter with ≥9 mm dilatation was found in 205 of 289. Prevalence of esophageal dilatation in SSc was about 70.9% in the present study, while other studies showed the following: 84.5% in Patiwetwitoon et al[12] 80% in the present study of Bhalla et al[9]and 62% in Vonk, et al[13] Coronal view of infra-aortic esophageal diameter ≥9 mm was defined as esophageal dilatation[14]. Esophageal dilatation ≥9 mm in 205 patients had no significant association with ground glass opacity of 94 patients (Z = 0.163). Patients with lcSSc had normal upper GI symptoms (61.67%) and dcSSc were less normal upper GI symptom (40.17%) with statistical significance (p<0.05). Infra-aortic esophageal dilatation (coronal diameter at least 9 mm) was more frequently found in dcSSc (74.2%) than in lcSSc (58.3%) with statistical significance (p-value = 0.01). More esophageal dilation in dcSSc may be associated with the degree of internal organ fibrosis. Esophageal dilatation has significant correlation with abnormal upper GI symptom (Z = 0.02). Hence, a future question is: "Can we use the degree of esophageal dilatation diameter as a marker of severity of upper GI symptom?". The objective of this study is to compare HRCT findings that include interstitial lung disease or other accidental findings from both SSc subsets. The present study shows that in the HRCT chest screening of even asymptomatic patient, abnormal HRCT chest was found at around 99%. However, clinical significance and impact on management was not studied.

The limitations of this study were as follows: Firstly, the present study was retrospective cross-sectional cohort study, and therefore, missing data and inter-observer variation should be considered. Secondly, the pulmonary function test of our center was not done with complete evaluation; diffuse capacity of the lungs for carbon monoxide [DLCO] should be evaluated for differential diagnosis between restriction from skin tightness and ILD. Thirdly, this is a single center trial, however, the number of patients who came to follow-up in Scleroderma clinic is large amount of patients. Finally, the HRCT chest findings were found, but the present study does not show the treatment significance. Further studies have been suggested and need to be multi-centered and be prospectively controlled trials. Simple systematic HRCT chest scoring should be initiated for evaluation of SSc-

ILD and should be generalized for use in general practice. Our suggestion is that the timing of HRCT chest should be scheduled in every patient with disease duration at least 1 year which may affect in the different management.

Conclusion

There were no differences in pattern of pulmonary involvement between both SSc subsets which were corresponding to our research questions. SSc interstitial lung disease and mediastinal lymphadenopathy were common findings in Thai SSc patients. Median disease duration from the presenting (non-Raynand phenomenon) symptom to the first time of HRCT chest performing was 1 year. One-third of the patients had ground glass opacity by HRCT chest despite of asymptomatic screening which may affect the treatment.

What is already known on this topic?

ILD was more prevalent in diffuse cutaneous systemic sclerosis than in limited cutaneous group. However, no data related to the differences of pattern of lung involvement between both groups.

What this study adds?

The present study showed that there were no differences of pattern of lung involvement between diffuse cutaneous and limited cutaneous group.

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Potential conflicts of interest

The authors declare no conflict of interest.

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