Original Article

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Autoantibody Profile and Thorax HRCT Scan in Systemic Sclerosis with Restrictive Lung Disease

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Abstract

Objective: To identify auto-antibodies in systemic sclerosis with interstitial lung disease (ILD).

Method: This was a descriptive categorical study on auto-antibody profile in systemic sclerosis patients visiting the Rheumatology Clinic of Dr. Hasan Sadikin General Hospital, West Java, and Bandung during the period of January 2018 to December 2019 who were registered in the West Java Systemic Sclerosis Registry. Auto-antibody identification was performed using the Euroline immunoblot assays.

Results: Thirty six cases were identified during the study period with most of the cases involved women (n=35, 97.2%). The average age of patients participating in this study was 40 years, with an average duration of disease of 18 months. Diffuse cutaneous systemic sclerosis was found in 22 (61.1%) cases and limited cutaneous systemic sclerosis was observed in 14 (38.9%) cases. Specific autoantibodies were positive in 33 (91.6%) cases, with anti-topoisomerase I as the largest group, positive in 22 (52.9.3%) cases. This was followed by anti-Th/To in eight (15.7%) cases; anti-Ro52 in four (7.8%) cases; anti-centromere in three (5.9%) cases; anti-RNA polymerase in three (5.9%) cases; anti-fibrillarin in three (5.9%) cases; anti-Ku in two (3.9%) cases; and anti-PDGF in one (2.0%) case. High-resolution computed tomography of the lung showed 34 (94.4%) cases with ILD and 22 (61.1%) cases with severe lung fibrosis. Usual interstitial pneumonia was seen in 19 (52.8%) cases and non-specific interstitial pneumonia in 15 (41.7%) cases.

Conclusion: Anti-topoisomerase I, anti-Th/To, and anti-Ro52 are the most common autoantibodies observed in systemic sclerosis patients with ILD as the most prevalent feature detected with lung HRCT.

Keywords: Autoantibodies, diffuse cutaneous, lung fibrosis, restrictive lung disease, systemic sclerosis

Introduction

Interstitial lung disease is the leading cause of death among SSc patients.[1-2] Early diagnosis and assessment of the organs involved in this disease, especially the lungs, is crucial as they will lead to early treatment that will affect the morbidity, mortality, and quality of life of these patients.[1-3] Unfortunately, early diagnosis of systemic sclerosis is challenging. Many patients come to the hospital with advanced disease or visceral organ involvement. Early diagnosis of organ involvement in the early stages will have implications for more aggressive treatment.

Immunosuppressants, such as mycophenolate sodium and cyclophosphamide, given in the early stage of the disease will decrease the disease progression as seen with decreased autoantibody titer. Intravenous chemotherapy, such as cyclophosphamide, is usually given to SSc patients with interstitial lung disease and delays in this therapy will increase morbidity and mortality. Thorax HRCT scan is the gold standard for diagnosis of ILD, especially for the early-stage disease.[4,5] Due to its rapid progression, the usual interstitial pneumonia is associated with a worse prognosis. During screening, the pulmonary function test using the spirometry is usually used and it often shows a restrictive lung disease that should be viewed cautiously as extrapulmonary factors may influence the result.[6-7] The autoantibody testing has also become the gold standard for the detection of autoimmune disease and is often associated with disease progression.

Early assessment of autoantibody testing will benefit patients, especially in the early diagnosis of SSc with organ involment. Also, autoantibody testing has become the gold standard for detecting autoimmune disease and may contribute to the diagnosis of SSc and organs involved, especially the lungs.[8,9] Autoantibody titers are often associated with disease progression. A previous study has concluded that the SSc specific-autoantibody is associated with organ involvement. [9] For example, Anti-topoisomerase I, anti-U11/U12, anti-Ro52, and anti Th/To are associated with lung involvement. Anti-centromere is already proven to be associated with cardiovascular involvement (PAH). Meanwhile, anti-RNA polymerase is shown to have an association with cardiovascular (PAH) and kidney (acute renal crisis) involvement. In addition, anti-fibrillation is associated with cardiovascular involvement (PAH), as well as with musculo-skeletal injuries (myositis). An association between autoantibody subtype and clinical manifestation along with organ involvement is also observed. Severe manifestation is found in SSc with lung involvement; thus patients will seek treatment earlier. To date, there are no specific clinical markers for lung involvement. Therefore, it is expected that, in the future, the SSc specific autoantibodies testing may be used as a modality for organ involvement diagnosis, especially for detecting SSc patients with interstitial lung disease in early stages.[7,8]

Methods

This was a cross-sectional descriptive study performed on data collected from the West Java Systemic Sclerosis Registry. Diffuse and limited SSc outpatients visiting the Rheumatology Clinic of Dr. Hasan Sadikin General Hospital Bandung, Indonesia, and received treatment during the period of January 2018 to December 2019, aged over 18 years old, were included in this study. Systemic sclerosis patients with overlap syndrome with other rheumatic autoimmune diseases and incomplete medical records were excluded. Systemic sclerosis was diagnosed based on ACR/EULAR 2013 criteria.[10] Restrictive lung disease was defined based on the ATS criteria.[11] Based on the spirometry data, all participats were shown to meet the restrictive lung disease criteria. All patients underwent HRCT thorax examination as the gold standard for ILD. Interstitial lung disease was defined based on Wernick's semi-quantitative scoring system category[12] that describes the ILD progressivity by radiological patterns and lung segments involved. Statistical Product and Service Solution (SPSS) version 22 for Windows was used for data analysis. Number and percentage were used for categorical variables. Mean ± standard deviation was used for measurement data following the normal distribution while median was used for non-normal distribution measurement data. This study was approved by the ethical committee of Dr. Hasan Sadikin General Hospital Bandung, Indonesia (reference no: LB.02.01/X.6.5/24/2020). Details on patient selection is shown in Fig 1.

Results

During the study period, 4,653 outpatients visited the Rheumatology Clinic of the hospital, with 1,923 patients with all rheumatology cases, 435 with Rheumatoid Arthritis (RA), 730 with Systemic Lupus Erythematosus (SLE), and 70 with SSc. There were 36 patients in the West Java Systemic Sclerosis Registry from January 2018 to December 2019 who met the criteria for this study. Patient characteristics are shown in Table 1.

More women were affected by SSc in this study (35, 97.2%). The mean age at diagnosis was 40 ± 12 years while the median disease duration was 18 (4-58) months. The most common subtype was dcSSc (n=22, 61.6%), followed by lcSSc (n=14, 38.9%). Raynaud's phenomenon was the most common clinical manifestation found (n=34, 94.4%) followed by sclerodactyly (n=30, 83.3%), skin stiffness (n=23, 63.9%), fingertip scar (n=21, 58.3%),

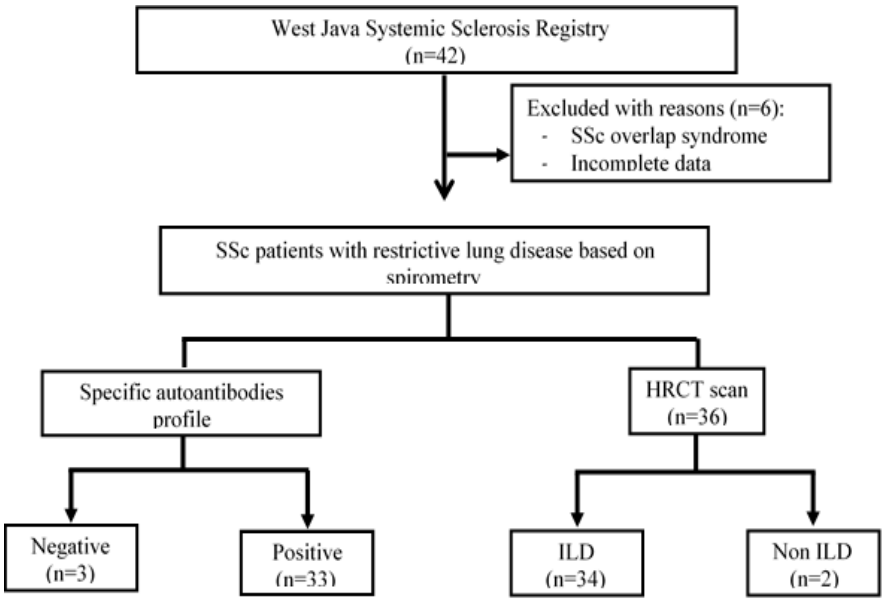

Fig 1. Patient's Selection

Table 1 Patient Baseline Characteristics

Variable	Number of Participants (n=36)
Age at Diagnosis (years)	40 ± 12
Female n (%)	35 (97.2)
Duration of disease (months) median (min-max)	18 (4–58)
Subtype, n (%)	
dcSSc	22 (61.1)
lcSSc	14 (38.9)
mRSS median (min-max)	18 (5-45)
Restrictive Lung Disease, n (%)	
Moderate to Severe	13 (36.1)
Severe	7 (19.5)
Moderate	6 (16.7)
Mild	6 (16.7)
Very Severe	4 (11.0)
Clinical Manifestation, n (%)	
Raynaud's phenomenon	34 (94.4)
Sclerodactyly	30 (83.3)
Skin stiffness	23 (63.9)
Fingertip scar	21 (58.3)
Salt and pepper appearance	20 (55.6)
Telangiectasia	18 (50.0)
Puffy fingers	5 (13.9)
Fingertip ulcer	4 (11.1)
Immunosuppressant therapy	
Methotrexate	32 (88.9)
Cyclophosphamide	4 (11.1)
Mycophenolate sodium	4 (11.1)
Azathioprine	3 (8.3)

dSSc, diffuse systemic sclerosis; HRCT, High Resolution Computed Tomography; lSSc, limited systemic sclerosis; MRSS, modified Rodnan Skin Score; ILD, interstitial lung disease. All participants meet restrictive lung disease criteria. All patients receive immunosuppressant therapy due to SSc severe manifestations

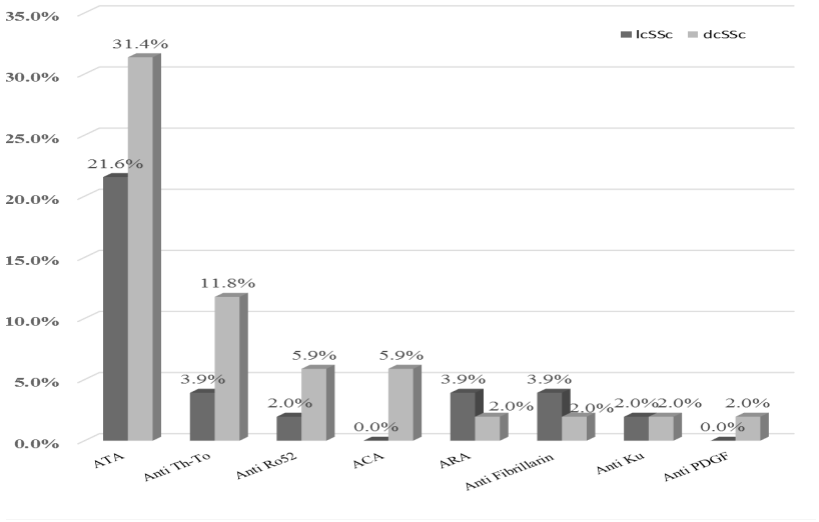

Fig 2. Overview of SSc Specific Autoantibody

salt and pepper appearance (n=20, 55.6%), telangiectasia (n=18, 50%), puffy fingers (n=5, 13.9%), and fingertip ulcer (n=4, 11.1%).

Anti-topoisomerase I was predominantly found in interstitial lung disease, both as a single and an overlap autoantibody, followed by anti-Th/To and anti-Ro52, as depicted in Fig 2. Two types of specific autoantibodies for SSc was positive in half of the patients (50%), followed by one type autoantibody (41.7%), and negative autoantibody (8.3%). The overview of the specific autoantibody is shown in Fig 2.

Almost all patients had ILD (34, 94.4%), with 22 of them had lung fibrosis 22 (61.1%) based on HRCT. Further classification using Wernick's semi-quantitative scoring system category revealedsevere ILD as the most common finding (n=22, 61.1%), followed by moderate cases (n=6, 16.7%), and mild

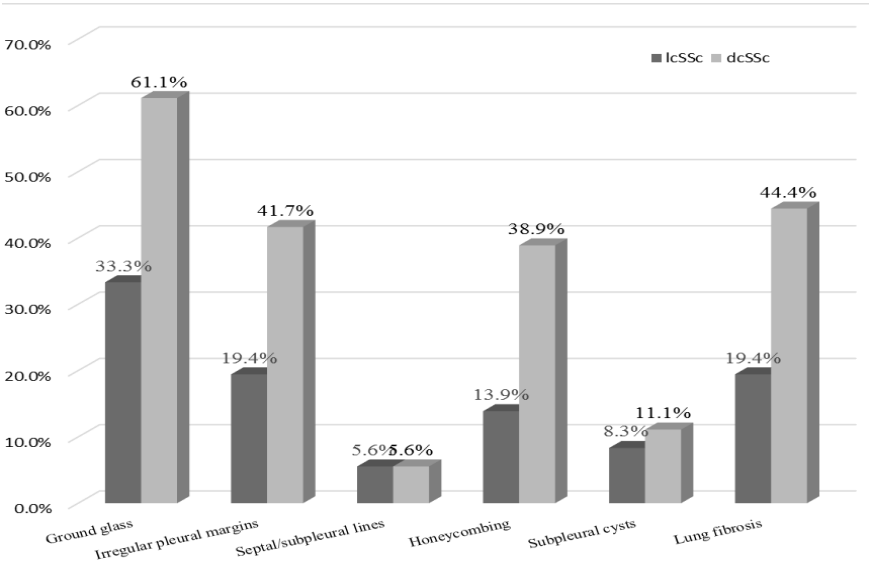

Fig 3. Interstitial Lung Disease Morphology[15]

cases (n=6, 16.7%).[12,13] Severe ILD was found in 41.7% of dcSSc and 19.4% of lcSSc. The HRCT showed usual interstitial pneumonia (UIP) in 52.8% cases, followed by non-specific interstitial pneumonia (NSIP) in 41.7% cases. The ILD morphology is presented in Fig 3.

Discussion

This study describes specific autoantibodies and thorax HRCT in SSc patients. This result differs from other studies and may suggest a difference in characteristics and disease progression of SSc patients in Indonesia. Younger age at diagnosis and shorter duration of illness was found in this study compared to other previous studies in Singapore, Malaysia, Australia, and Europe. [1,2,7,14] This reflects better early case finding in those countries. Interstitial lung disease that occurs in an early stage and younger age is usually severe and have strong relationship with a higher standardized mortality rate.[1,2,15]

Subtype SSc classification is useful for the prediction of organ involvement and disease prognosis. The dsSSc subtype is at a higher risk of death as it is associated with rapid progression and the risk of organ involvement in the early stage of the disease.[16] This study showed that the dsSSc subtype is more common and consistent, with a younger age at diagnosis and shorter duration of illness. Higher prevalence of dcSSc and ATA, when compared to Caucasians, has been reported in Han Chinese, suggesting that racial differences may contribute.[17] The environment is also a trigger factor for SSc, even though it was not fully understood. Some environmental factors that may trigger SSc, include chemical exposure of vinyl, chemical solvents, epoxy resin dan silica. Infection cytomegalovirus (CMV), parvovirus, smoking and alcohol is also play a role in triggering SSc.[16,18]

Specific autoantibodies testing has become the gold standard for the diagnosis of SSc, where it is often associated with the disease progression. An early assessment of specific autoantibodies will give benefits to the patients, especially those suffering from SSc with organs involvement. In this study, we found three dominant specific autoantibodies for SSc, i.e., anti-topoisomerase I, anti-Th/To, and anti-Ro52. Previous studies conducted by Ibrahim *et al*. in Malaysia and Ching *et al*. in Thailand have reported anti-topoisomerase, anti-Th/To, anti-Ro52, and anti-centromere as major autoantibodies in SSc.[14,19] Anti-Th/To and anti-Ro52 are not included in the ACR/EULAR 2013 for SSc diagnosis criteria, due to differences in the populations studied. Specific autoantibodies differences between Asian and European. Singapore, and Malaysia, which are multi-racial countries, have shown differences by population.[2,14] This might be due to the more diversity in human races of the two countries. HLA-DRB1*11 is found in anti-topoisomerase I, while HLA-DRB1*01 and HLA-DRB1*04 HLA-DRB1*05 are found in anti-centromere. In addition, HLA-DRB1*04 and HLA-DQB1*03 are found in Caucasian-Hispanic anti-RNA polymerase.[17,18,20] Studies on chromosomes are quite scarce. Further research is needed in Asian populations, especially in Indonesia, to determine the differences in major autoantibody and disease progression between Asian and European populations.

Specific SSc autoantibodies is associated with organ involvement and an association is observed between autoantibody subtype and clinical manifestation, along with organ involvement.[21,22] In this present study, two-type specific autoantibodies for SSc is positive in half of the participants (50%), followed by one autoantibody (41.7%), and negative autoantibody (8.3%). In several studies using the IIF, immunoprecipitation, and immunodiffusion, only a very small SSc specific autoantibodies are found to have more than one SSc-related antibody.[7,19] Anti-topoisomerase I is the dominant autoantibody found in ILD, both as single and overlap autoantibody, followed by anti-Th/To and anti-Ro52, in which this autoantibody relates to SSc-ILD. This fact is consistent with the finding of this study where anti-topoisomerase was found in 31.4% of diffuse subtype cases and 21.6% of limited subtype cases. Anti-topoisomerase I is often associated with diffuse subtype and interstitial lung disease occurrence. Other studies found anti-topoisomerase I as the most common finding in diffuse SSc with interstitial lung disease.[1,8,10,22] Anti-Th/To is found in 15.7% cases and becomes the second most dominant autoantibodies. These results are not consistent with the literature, where anti-Th/To is found to be less than other autoantibodies. A study in Japan shows only 2-5% of cases with anti-Th/To and none were found in Greece population .[20,21] In this present study, 7 of 8 positive anti-Th/To patients had interstitial lung disease. This result is similar to a previous study in Malaysia and Thailand, which reported SSc with anti-Th/To positively increases the severity and mortality rate due to lung involvement.[14,19] There are differences

in dominan autoantibody found in Japan and Greece population, compared to this study population where Anti-Ro52 was found in 5.9% of diffuse subtype cases and 2% of limited subtype cases. All patients with Anti-Ro52 positive had interstitial lung disease, which is similar to a study conducted by Ibrahim *et al*.[14] Anti-centromere was found in 5.9% of a diffuse subtype with overlapping anti-topoisomerase I autoantibody. This group showed severe interstitial lung disease. This finding is not consistent with the literature, which stated that anti-centromere has a good prognosis because it is often found in a limited subtype with rarely visceral organ involvement.[21] This may be associated with the presence of two or more autoantibodies simultaneously, especially high titer anti-topoisomerase I. Anti-RNA polymerase was found in 3.9% of diffuse subtype cases and 2% of a limited subtype with overlapping anti-topoisomerase I autoantibody. The literature states SSc with anti-RNA polymerase rarely develops into severe interstitial lung disease. This is not consistent with the results. Interstitial lung disease in this group can be associated with the presence of two concurrent autoantibodies, especially high titer anti-topoisomerase I. This study found three dominant autoantibodies, which consist of anti-topoisomerase I, anti-Th/To, and anti-Ro52. Studies conducted by Ibrahim *et al*. in Malaysia and Ching *et al*. in Thailand reported anti-topoisomerase, anti-Th/To, anti-Ro52, and anti-centromere as dominant autoantibodies.[14,19] Anti-Th/To and anti-Ro52 are not included in ACR/EULAR 2013 for the diagnosis of systemic sclerosis. This is because ACR/EULAR 2013 is based on the European and American populations, while there are differences in autoantibody dominant between Asian and European populations.[10,17,23, 24]

This study also discovered three negative cases for specific autoantibodies but with a positive ANA test. Factors that may play a role in autoantibody difference results include autoantibodies test used and autoantibodies titer.[9,22] Euroline immunoblot assay has the ability to detect 13 autoantibodies; however, there are several other autoantibodies that are linked to systemic but not included in this kit, such as anti-endothelial, anti-fibroblast, anti-matrix metalloproteinase, and anti-survivin, thus cannot be examined in this study. A high titer is associated with disease progression.

The HRCT showed that almost all patients had ILD with UIP pattern, which is different from findings of other studies conducted in Europe, in which NSIP is the common pattern.[13,25] UIP is associated with worse prognosis caused by rapid disease progression, presenting a of peripheral septal thickening craniocaudal gradient, bronchiectasis, and honeycombing.[26] Further classification using Wernick's semi quantitative scoring system found that severe ILD was the most common finding, consist with the UIP pattern.[12] ILD progression is related to morphology of lung lesion.[13,25] . This study shows that many patients seek healthcare after later stages of the disease with visceral organ involvement such as interstitial lung disease.

Risk factors for interstitial lung disease in SSc include men, older age, African-American, duration of illness, diffuse subtype, presence of ATA, decreased Forced Vital Capacity (FVC), and biomarkers.[26,27] The participants in this study are mostly women, aged between 30 – 40 years with a duration of illness less than 18 months, diffuse subtype, as well as anti-topoisomerase 1 positive with decreased FVC. Differences in gender, age, race, and duration of illness are observed in this study.

In West Java Province of Indonesia, SSc with ILD is commonly found, with diffuse cutaneous subtype as the predominant group and anti-topoisomerase I, anti-Th/To and anti-Ro52 are the most common autoantibodies observed in the area. In line with the pathogenesis, Anti-topoisomerase I triggers adhesion and activation of monocytes by binding to DNA–topoisomerase I expressed on fibroblasts.[28] This potentially lead to the amplification of the fibrogenetic cascade. Anti-Th/To and anti-Ro52 are also associated with a higher prevalence of SSc-ILD. The HRCT demonstrates predominant SSc with ILD in this population. This study identify similar autoantibodies associated with ILD among SSc patients. However, some limitations should be noted, such as the absence of data on living environment, profession, chemical exposure and previous disease history in the Registry because the registry is still in ongoing.

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