Chronic dyspnea with Raynaud's phenomenon and elevated ANA: A diagnosis of systemic sclerosis sine scleroderma

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ABSTRACT

Systemic sclerosis (SSc) should be considered in all patients initially diagnosed with idiopathic interstitial lung disease (ILD), even in the absence of classical scleroderma cutaneous features. Systemic sclerosis sine scleroderma (ssSSc) is a rare subtype of SSc, and the diagnosis requires the absence of characteristic skin thickening but the presence of the three following criteria: (A) Raynaud's phenomenon or the equivalent of abnormal nail fold capillaries, (B) positive antinuclear antibody (ANA), typically with nucleolar or speckled immunofluorescence pattern, and (C) at least one internal organ involvement of ILD, renal dysfunction, esophageal/bowel dysmotility or pulmonary arterial hypertension; in the absence of an alternative rheumatological diagnosis. The radiological and histopathological features of systemic sclerosis sine scleroderma-associated interstitial lung disease (ssSSc-ILD) are commonly those of non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) that cannot help distinguish between idiopathic interstitial pneumonia, different types of connective tissue diseases, or even different subsets of SSc. Therefore, other than chest imaging, the use of nail fold capillaroscopy, positive serum ANA antibody, echocardiogram, and esophagram are essential, in conjunction with the clinical presentation for facilitating the diagnosis of ssSSc. We present a case of a 58-year-old woman presenting with chronic dyspnea, a positive review of systems for Raynaud's phenomenon, and found to have elevated nucleolar immunofluorescence pattern of ANA with chest imaging consistent with the diagnosis of ssSSc-ILD. The uniqueness of this case is that despite symptomatic alleviation with oral mycophenolate therapy, our patient's restrictive lung disease on pulmonary function tests continued to decline, requiring initiation of oral nintedanib therapy leading to stability and improvement. However, due to the rarity of ssSSc, the use of oral nintedanib for systemic sclerosis-associated ILD has only been formally assessed on patients with diffuse cutaneous systemic sclerosis and limited cutaneous systemic sclerosis.

Key Indexing Terms: Systemic sclerosis; Systemic sclerosis-associated with interstitial lung disease; Systemic sclerosis sine scleroderma; Systemic sclerosis sine scleroderma-associated with interstitial lung disease. **[Am J Med Sci 2023;365(2):198–204.]**

INTRODUCTION

Patients with interstitial lung disease (ILD) generally seek medical attention due to respiratory symptoms of dyspnea, cough, or abnormal chest imaging performed for an alternative reason. ILD commonly presents in the context of an established connective tissue disease (CTD) but can be the first or only manifestation of an occult CTD. ILD can even occur in patients with features suggestive of a CTD but not meeting any diagnostic criteria for a specific CTD known as interstitial pneumonia with autoimmune features (IPAF).[1–3] Therefore, a comprehensive history and clinical examination, as well as ancillary investigations involving autoantibodies, pulmonary function test (PFT), and high-resolution computed tomography (CT) chest, are essential. It is estimated that around 15-19% of patients who presents clinically with ILD have, or will develop, a specific CTD which is indistinguishable from those with idiopathic ILD.[1,2,4] Systemic sclerosis (SSc) is a systemic inflammatory connective tissue disorder characterized by abnormal fibrosis of the skin, microvasculature, and visceral organs.[1,5,6] SSc can be divided into diffuse cutaneous systemic sclerosis (dcSSc) with widespread skin thickening, limited cutaneous systemic sclerosis (lcSSc) with skin thickening limited to distal extremities/face, and systemic sclerosis sine scleroderma (ssSSc).[1,7] The diagnosis of ssSSc requires the absence of classical skin thickening and the presence of (A) Raynaud's phenomenon or the equivalent of abnormal nail fold capillaries; (B) positive antinuclear antibody (ANA), typically with nucleolar or speckled immunofluorescence pattern; and (C) at least one internal organ involvement of ILD, renal dysfunction, esophageal/bowel dysmotility or pulmonary arterial hypertension (PAH); in the absence of an alternative CTD diagnosis (Table 1).[6-8] SSc affects females more than males by a ratio of three to one.[1,5,9] We

Table 1. Proposed diagnostic criteria for systemic sclerosis sine scleroderma (ssSSc).[6–8]

Systemic Sclerosis Sine Scleroderma Diagnostic Criteria (ssSSc)
1) Raynaud's phenomenon or corresponding peripheral vascular hallmarks (digital tip pitting scars or ulcers; gangrene, abnormal nailfold capillaries).
2) Positive ANA, typically nucleolar or speckled immunofluorescence pattern.
3) At least one of the following: A) Interstitial lung disease (ILD), B) Primary pulmonary artery hypertension without ILD, C) Esophageal dysmotility, D) Cardiac involvement, E) Renal failure consistent with scleroderma renal crisis.
4) No other defined connective tissue disease or other disorder as a cause for above.

present a case of a 58-year-old woman presenting with chronic dyspnea, a positive review of systems for Raynaud's phenomenon, and found to have elevated nucleolar immunofluorescence pattern of ANA with chest imaging consistent with the diagnosis of ssSSc-associated interstitial lung disease (ssSSc-ILD).

CASE PRESENTATION

A 58-year-old woman with a past medical history of Raynaud's phenomenon presented with a three-month history of dyspnea. She denied any cough, fever, angina, dyspepsia, arthralgia, skin rash, or myalgia. Her Raynaud's phenomenon was diagnosed two years ago after she reported a change in her fingertips color during exposure to a cold surface. She did not have any workup for her Raynaud's phenomenon. She had no family history of lung or rheumatological diseases. She was a lifelong non-smoker and worked as a teacher for most of her life. Her age-related cancer screenings were up to date. She had no exposure to livestock nor occupational exposure to asbestos, coal dust, beryllium, silica dust, or dust from hard metal objects, such as cobalt. Vital signs were unremarkable, with oxygen saturation of 94% in room air. Her oral mucosa was moist without any parotid gland tenderness or swelling. No cervical lymphadenopathy was appreciated. Lung examination revealed velcro-like inspiratory crackles most pronounced at the base of her lungs. No murmurs were heard on auscultation of her heart. She had a good range of motions of her joints without any swelling. She had normal muscle tone and strength in all her extremities without any muscle tenderness. No rash, ulcer, skin thickening, or hair loss was appreciated on dermatological examination. Her initial chest radiograph revealed bilateral diffuse reticulations concerning for ILD. Therefore, a CT chest (Figure 1) was pursued that showed diffuse, bilateral, ground-glass opacification (GGO) predominantly in the peripheries with reticulations and traction bronchiectasis. Laboratory values demonstrated normal complete blood count (CBC) and comprehensive metabolic panel. However,

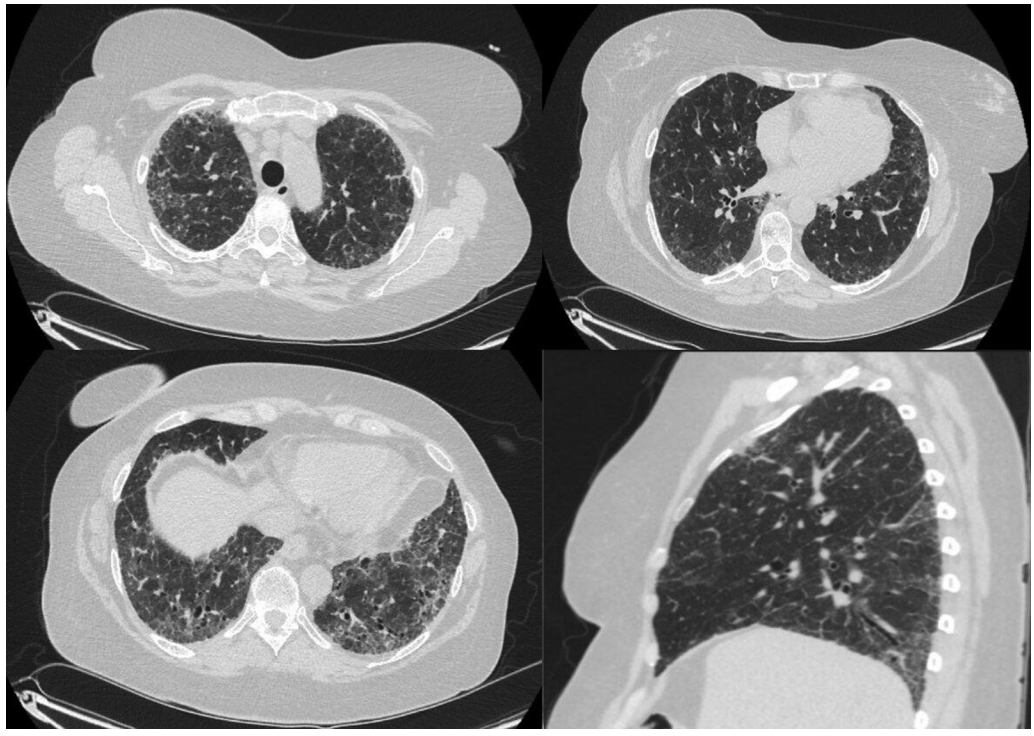

FIGURE 1. Chest computed tomography (axial and sagittal view) demonstrating diffuse, bilateral, ground-glass opacification (GGO) predominantly in the peripheries with reticulations and traction bronchiectasis.

Table 2. Pertinent laboratory results.

	Value on Presentation	Reference Range
Inflammatory Markers		
Erythrocyte Sedimentation Rate, mm/hr	65	0 – 25
C-Reactive Protein, mg/L	55	<8
Serologies		
Antinuclear Ab (ANA), IU/mL	2600	<160
Cytoplasmic Anca (C-ANCA), AU/mL	<20	<20
Perinuclear Anca (P-ANCA), AU/mL	<20	<20
Anti-Centromere Ab, Unit	<160	<160
Anti-dsDNA Ab, IU/mL	<30	<30
Anti-Scl-70 Ab, U/mL	<50	<50
Anti-Th/To Ab, U/mL	<1	<1
Anti-Histone Ab, U/mL	<1	<1
Anti-U1 RNP Ab, U/mL	<1	<1
Anti-Smith Ab, U/mL	<1	<1
Anti-Sjogren A Ab, U/mL	<1	<1
Anti-Sjogren B Ab, U/mL	<1	<1
Anti-RNA Polymerase III Ab, U/mL	<20	<20
Complement Levels		
C3, mg/dL	130	85 – 200
C4, mg/dL	30	20 – 50
Myositis Panel		
Anti-Jo-1 Ab, U/mL	<1	<1
Anti-PL-7 Ab, U/mL	<1	<1
Anti-PL-12 Ab, U/mL	<1	<1
Anti-OJ Antibody, U/mL	<1	<1
Anti-EJ Antibody, U/mL	<1	<1
Anti-KS Antibody, U/mL	<1	<1
Anti-Zo Antibody, U/mL	<1	<1
Anti-Mi 2 Antibody, U/mL	<1	<1
Anti-SRP Antibody, U/mL	<1	<1
Anti-MDA-5 Antibody, U/mL	<1	<1
Rheumatoid Arthritis Panel		
Rheumatoid factor, IU/ML	<14	<14
Anti-Cyclic Citrullinated Peptide Ab, U/mL	<20	<20

Ab = antibody, ANA = antinuclear antibody, ANCA = Antineutrophil-cytoplasmic antibody, Anti-dsDNA = Anti-Double Stranded DNA, Anti-U1 RNP = Anti-U1 Ribonucleoprotein, Anti-CCP = Anti-Cyclic Citrullinated Peptide.

her inflammatory markers were elevated, involving erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) of 65 mm/hr and 55 mg/L, respectively (Table 2). Her ANA returned positive at 2600 IU/L with a nucleolar immunofluorescence pattern. However, autoantibodies suggestive of CTDs of rheumatoid arthritis, polymyositis, Sjogren syndrome, and systemic lupus erythematosus returned negative. An echocardiogram revealed a normal left ventricular ejection fraction of 55% without any evidence of pulmonary hypertension, pericardial effusion, or valvular heart disease. Barium swallow demonstrated no evidence of esophageal dysmotility. Her nail fold capillaroscopy showed dilated loops and bushy capillaries, neo-vascularization, and microhemorrhages.

The diagnosis of systemic sclerosis sine scleroderma-associated interstitial lung disease (ssSSc-ILD) was made. Her initial PFT revealed severe restriction with forced vital capacity (FVC) of 40% (1.48 Liters), forced expiratory volume over 1 second (FEV-1) of 48% (1.30 Liters), total lung capacity (TLC) of 45% (2.03 Liters), FEV-1/FVC ratio 88%, diffusion capacity of carbon monoxide (DLCO) of 45%, and DLCO corrected for alveolar volume (DLCO/VA) of 52% (Table 3). She was started on oral immunosuppressive therapy of mycophenolate at 500 mg twice daily with the intention of titrating up to 1500 mg twice daily over a one-month period. She reported improvement in her clinical symptoms with reduced frequency of her Raynaud's phenomenon. However, repeat PFT three months later showed worsening restriction with FVC 33% (1.22 L), FEV-1 40% (1.08 L), TLC 40% (1.80 L), DLCO 41%, and DLCO/VA 50%. The decision was made to begin combination therapy with the addition of oral nintedanib therapy to mycophenolate that eventually showed stability and improvement on her serial PFTs, shown in Table 3. She continued her follow-up in the clinic every three months with repeat PFTs, where she experienced no drug-related side effects from combination therapy.

Table 3. Pulmonary function test (PFT) from initial evaluation and months after initiation of therapy with mycophenolate and combination therapy of mycophenolate and nintedanib.

Timeline	FVC L (%)	FEV-1 L (%)	FEV-1/FVC ratio	TLC L (%)	DLCO	DLCO/VA
Initial Evaluation	1.48 (40%)	1.30 (48%)	88%	2.03 (45%)	45%	52%
3 Months After Mycophenolate	1.22 (33%)	1.08 (40%)	89%	1.80 (40%)	41%	50%
3 Months After Combination Therapy	1.37 (37%)	1.19 (44%)	87%	2.02 (45%)	45%	52%
6 Months After Combination Therapy	1.45 (39%)	1.24 (46%)	86%	2.08 (46%)	46%	53%
9 Months After Combination Therapy	1.53 (41%)	1.33 (49%)	87%	2.18 (48%)	50%	55%

FEV-1 = forced expiratory volume over 1 second, FVC = forced vital capacity, TLC = total lung capacity, DLCO = diffusion capacity of carbon monoxide, DLCO/VA = diffusion capacity of carbon monoxide corrected for alveolar volume.

DISCUSSION

The diagnosis of ssSSc-ILD was made based on the absence of skin thickening and presence of: (A) Raynaud's phenomenon, (B) positive ANA with nucleolar immunofluorescence pattern, (C) pulmonary involvement of ssSSc-ILD, and (D) lack of alternative CTD to explain these clinical findings (Table 1).[6–8] ssSSc-ILD is a type of CTD-ILD that may present as the predominant or sole clinical manifestation, and even precede other systemic features of ssSSc disease.[1,6,8] Although only 2-8% of people with SSc fall into the ssSSc group compared to 53-62% in lcSSc and 33-40% in dcSSc, around 26-80% of ssSSc patients will be diagnosed with ssSSc-ILD.[1,5–7,10–12] The frequency of other internal organ involvements such as gastrointestinal (esophageal/bowel), cardiac/pulmonary hypertension, and renal are 56-80%, 9-23%, and 4-22%, respectively.[5,7,10–12] The mean age of ssSSc-ILD diagnosis is around 51 to 58-years of age, but the onset of ssSSc symptoms, such as dyspnea or Raynaud's phenomenon, is suspected to be as early as 5 to 15-years prior to ILD onset due to the insidious ssSSc presentation, which lacks the characteristic skin thickening.[1,5–7,9–14]

It is not uncommon for 27 to 60% of patients initially diagnosed with ssSSc to be reclassified as having lcSSc with the development of sclerodactyly during a follow-up period of 2 to 4-years.[7,8,10–12] It has even been proposed that the accurate diagnosis of ssSSc can be made with the agreement of two board-certified rheumatologists after more than five years of ssSSc symptoms onset.[12,14] Therefore, even in the setting of multiple large observational studies performed in SSc patients, the true prevalence of ssSSc is likely to be underestimated due to the ongoing diagnostic difficulty by the absence of classical skin thickness seen in other types of SSc. Another differential diagnosis considered, had our patient not met the diagnosis of ssSSc based on the insidious clinical presentation, isolated positive ANA, and evidence of ILD on chest imaging, was IPAF. IPAF, unlike CTD-ILD, is an ILD with clinical, serological, and morphological features that suggest an underlying autoimmune process but does not meet any established criteria for a specific CTD.[15] These clinical manifestations consist of specific musculoskeletal findings; in contrast, the serological domain consists of positive autoantibodies, and morphological features comprised of chest imaging, histopathological, or pulmonary physiologic results indicative of ILD.

In any patient with ILD, a meticulous evaluation with specific laboratory testing tailored to clinical impression is essential in identifying an occult CTD such as ssSSc, as autoantibodies alone are not sensitive or specific. However, there is no consensus on which serological testing is required during the initial evaluation.[2] Moreover, the type of autoantibody obtained during follow-up or whether serial monitoring of autoantibody levels is necessary to monitor disease progression remains uncertain.[16] The American Thoracic Society/European Respiratory Society/Japanese Respiratory Society and Latin American Thoracic Association (ATS/ERS/JRS/ALAT) recommend considering testing for ANA, anti-cyclic citrullinated peptide (anti-CCP), and rheumatoid factor (RF) in all patients with suspected ILD, even without overt features of a CTD.[2,17] This is done in conjunction with routine laboratory workup involving complete blood count, renal panel, urinalysis, ESR, CRP, and muscle enzymes.[1] ANA test is useful in the initial screening process and provides essential information about other autoantibodies that need to be screened for. However, the ANA test has limitations that may lead to erroneous conclusions and interpretations. This finding is further complicated by variations in titer cutoffs and patterns between different laboratories. In addition to clinical findings, interpretation of positive ANA results needs to consider the patient's age together with false-positive from infections, drug therapy, and other non-rheumatological inflammatory diseases.[16,18,19] In general, a high ANA titer (1:160 and above) is more likely to be associated with CTD and has been shown to have a sensitivity and specificity of 87% and 95% in diagnosing SSc.[1,2,16,18,19] Other specific antibody tests such as extractable nuclear antigen (ENA) antibodies panel for anti-Scl70, anti-SSA/Ro, anti-SSB/La, anti-Smith, anti-U1 RNP, and anti-Jo-1 are recommended if clinical suspicion for CTD is high based on clinical findings or supplant a positive ANA test.[1,2,17]

ANA antibodies (ab) are found in more than 94% of those with ssSSc, with the most frequent type being non-SSc-associated autoantibodies (44-50%) followed by anticentromere ab (29-50%), anti-Scl-70 ab (6-28%); anti-RNA polymerase III ab and anti-Th/To ab at 6%, respectively.[1,5–7,10,20] Anti-Scl-70 ab has been associated with ssSSc-ILD and a more significant decline in PFT, whereas anticentromere ab may be considered protective against ILD but associated with an increased incidence of pulmonary arterial hypertension (PAH).[2,3,11,20,21] Anti-Th/To antibodies are almost exclusively seen in ssSSc and lcSSc with a reported prevalence of 6% and 11%.[20–22] Up to 9% of patients diagnosed with idiopathic pulmonary fibrosis (IPF) have positive ANA with or without concurrent positive anti-Th/To antibody, which could be the earliest or only diagnostic clue to support the diagnosis of underlying occult ssSSc.[23] These autoantibodies have emerged as a useful screening marker that favors the diagnosis of underlying ssSSc-ILD and PAH, even in the absence of overt symptoms.[2,20–23] Furthermore, anti-Th/To ab if present has been associated with poor survival in ssSSc patients likely from the increasing prevalence of fibrotic ILD with severe restrictive physiology and concomitant PAH.[2,21–23]

Moreover, ssSSc-ILD will demonstrate restrictive lung physiology on PFT with a decrease in FEV-1, FVC, TLC, DLCO, and DLCO/VA.[1,3,5] During the initial evaluation of patients with ssSSc-ILD, 31-35% and 60-84% will have FVC and DLCO less than 70% predicted, respectively.[7,9–12] Multiple large observational studies demonstrated that the incidence of ILD, the severity of restriction at the time of diagnosis, and disease progression based on the degree of FVC decline were more significant in patients with dcSSc than in patients lcSSc and ssSSc.[11] However, the reduction in DLCO was more significant in ssSSc versus other groups of SSc, which was likely due to loss of pulmonary capillary blood volume in the setting of increased PAH incidence as opposed to the extent of ssSSc-ILD.[3,11]

In ssSSc-ILD, the radiological and histopathological features are commonly non-specific interstitial pneumonia (NSIP) followed by usual interstitial pneumonia (UIP).[1–3,5,6] Surgical lung biopsies are rarely performed as chest imaging, and autoantibodies in the proper clinical context are often sufficient to support CTD-ILD diagnosis and distinguished it from other ILDs, altering the management and prognosis. However, in cases where surgical lung biopsies are performed, histopathological findings of NSIP are often identified and should raise suspicions of underlying CTD.[1,2] Other histopathological findings seen in CTD-ILD include organizing pneumonia, lymphocytic interstitial pneumonia, follicular bronchiolitis, diffuse alveolar damage, and abundance of germinal centers/lymphoid follicles.[1–3] Radiological features that favor ssSSc-ILD over idiopathic ILD and IPF are the presence of hilar/mediastinal lymphadenopathy, pleural/pericardial effusion, pleural thickening, esophageal thickening/dilation, and the lack of apicobasal distribution of lung involvement, especially when there is an absence of apparent clinical manifestations of SSc such as skin thickening that occur in the setting of ssSSc in which Raynaud's phenomenon may be the only clue of the diagnosis.[2,3,6,24] The presence of pericardial effusion on chest imaging or echocardiography has been observed to be a useful marker to suggest the diagnosis of underlying PAH.[6] It is not uncommon for ssSSc-ILD to be misclassified as IPF even in the correct clinical setting with the surgical lung biopsy-proven usual interstitial pneumonia (UIP) pattern that is universally found in IPF.[23,25]

With the advancement of therapies and increasing recognition of SSc-related complications, the main cause of death has shifted from scleroderma renal crisis to respiratory failure primarily from progression of ILD followed closely by PAH, gastrointestinal, and cardiac-related deaths, and lastly, the former (scleroderma renal crisis).[3,5,13,26] Furthermore, the increased incidence of SSc-related complications of ILD and PAH could be possibly due to improved life expectancy as a result of better treatment response with fewer patients diagnosed with SSc succumbing to underlying scleroderma renal crisis that often occurs within few years of diagnosis onset.[11,26] The treatment regimen for ssSSc-ILD (a type of CTD-ILD) differs from IPF, where immunosuppressive therapy will be the option of choice, whereas, in IPF, it is anti-fibrotic therapy.[2,25] Even though CTD-ILD has often been described to confer a better prognosis than idiopathic ILD and IPF, the prognosis of patients with ssSSc-ILD has been observed to be similar, especially when non-responsive to immunosuppressive therapy.[3,23,25] Multiple observational studies have reported that the incidence of ILD, degree of lung restriction at the time of diagnosis, rate of PFT decline, and survival rate between ssSSc and lcSSc were similar despite an increased incidence of PAH in ssSSc.[5,7] However, compared to patients with dcSSc, these cohorts of SSc patients had better survival rates, which could be explained by the higher incidence of ILD, increased severity, and progressive decline in restrictive lung physiology, PAH, and renal involvement in dcSSC patients. Therefore, poor prognostic markers for ssSSc patients are the presence of ssSSc-ILD, age of ssSSc-ILD diagnosis, the interval between symptoms onset to ssSSc-ILD diagnosis, severity and rate of decline in restrictive lung disease (FVC/DLCO), degree of GGO and reticular pattern on chest CT, concurrent renal dysfunction or PAH, positive anti-Th/To and anti-Scl-70 ab, respectively.[2,3,6,11,21–23]

Immunosuppressive therapies for systemic sclerosis-associated ILD (SSc-ILD) have advanced tremendously over the past decade with reduced dependence on corticosteroids. The role of corticosteroids is limited in SSc-ILD patients due to the four-fold increased risk of developing renal crisis associated with high-dose (15 mg/day <) prednisone use.[26] The Scleroderma Lung Study-1 (SLS-1) trial was one of the pioneer randomized controlled trials

that included SSc-ILD patients with moderate restriction (mean FVC and TLC of 68% and 70%) to 12-month therapy of oral cyclophosphamide versus placebo.[27] An improvement in restrictive lung physiology (FVC and TLC), dyspnea, quality of life, and skin involvement were noted in the cyclophosphamide group despite increased leukopenia/neutropenia and hematuria incidence after one year of therapy. However, a 2-year follow-up to SLS-1 demonstrated that despite the sustained improvement in dyspnea, the rate of decline in lung restriction and the difference in skin involvement was no longer apparent after cessation of oral cyclophosphamide a year later.[28] Another double-blinded trial called SLS-2 randomized SSc-ILD patients with moderate restriction (mean FVC and TLC of 66% and 67%) receiving either 24-month oral mycophenolate versus 12-month of oral cyclophosphamide therapy.[29] There were no significant differences in the decline of lung physiology, degree of dyspnea, or skin involvement over the 24-month study period but less incidence of adverse events involving leukopenia and thrombocytopenia in the mycophenolate group. Based on these previous trials, a double-blinded placebo-controlled trial termed SENSCIS randomized SSc-ILD patients (mean FVC 72%) to receive oral anti-fibrotic agent of nintedanib.[30] Around 48% of patients in this study were on mycophenolate therapy, and nintedanib was shown to decrease the decline in lung restriction, particularly FVC, over a 1-year period. However, there was no change in the quality of life or degree of dyspnea in both groups. Nevertheless, the increased adverse events involving diarrhea and hepatitis in the nintedanib group lead to a higher incidence of therapy discontinuation at a ratio of 2:1 compared to placebo. Lastly, the therapy of choice for ssSSc-ILD remains unclear as current clinical evidence was extrapolated from randomized controlled trials involving SSc-ILD patients with lcSSc (40-48%) and dcSSc (52-60%).[27,29,30] The optimal duration of therapy remained unknown, as many randomized controlled trials limit the course of treatment to 1 to 2-year with clinical follow-up of 2 to 3-year due to the hypothesis that 1 to 2-year treatment might induce SSc remission, preventing further disease progression and reducing therapy-related side effects.

CONCLUSIONS

In a patient presenting with chronic dyspnea due to ILD with the clinical finding of Raynaud's phenomenon and isolated elevation of serum ANA with nucleolar immunofluorescence pattern, the diagnosis of ssSSc and IPAF should be considered. A diagnosis of ssSSc-ILD requires the absence of classical skin thickening of systemic sclerosis with the presence of (A) Raynaud's phenomenon, (B) positive ANA, typically with nucleolar or speckled immunofluorescence pattern, (C) ILD, and (D) lack of alternative CTD to explain these clinical findings. Up to 27-60% of patients initially diagnosed with ssSSc will be reclassified as having lcSSc with the development of sclerodactyly during a follow-up period of 2 to 4-years. Oral nintedanib has emerged as an effective add-on therapy to immunosuppression in improving the restrictive lung physiology in SSc-ILD patients. However, its effectiveness in patients with ssSSc-ILD remains unclear due to the lack of ssSSc patients enrolled in multiple randomized controlled trials.

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DECLARATION OF COMPETING INTEREST

No author has a conflict of interest to disclose.

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