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CASE REPORT

Anti-Ro52 Antibodies – Independent Risk Factors for the Development of Interstitial Lung Disease in Systemic Sclerosis

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Abstract

Introduction: Systemic sclerosis (SSc) is a multisystem autoimmune disease in which interstitial lung disease (ILD) is a leading cause of morbidity and mortality. Anti-Ro52 antibodies have been associated with a higher prevalence of ILD, greater fibrosis burden, and poorer outcomes, yet their role as isolated biomarkers in SSc remains under investigation.

Case Report: We present a 64-year-old female with hypothyroidism who initially presented with polyarthralgia of the small joints without overt synovitis. Six months later, she developed Raynaud's phenomenon, puffy hands, and exertional dyspnea. Capillaroscopy showed an active scleroderma pattern, and serology revealed isolated anti-Ro52 antibody positivity. High-resolution computed tomography demonstrated nonspecific interstitial pneumonia (NSIP) with 25–30% pulmonary involvement, preserved diffusion capacity, and early pulmonary arterial hypertension. Limited cutaneous SSc with ILD was diagnosed, and treatment with mycophenolate mofetil, low-dose methylprednisolone, and vasodilators was initiated. Over two years of follow-up, HRCT showed a reduction in ILD extent to 10%, with stable DLCO (77–83%).

Conclusions: This case highlights isolated anti-Ro52 positivity as a potential biomarker for ILD in SSc. Extended autoantibody testing may enable earlier identification of high-risk patients. Prompt immunosuppressive therapy initiation can stabilize or improve lung involvement, potentially preventing irreversible pulmonary damage.

Keywords: systemic sclerosis, anti-Ro52 antibodies, interstitial lung disease.

Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disorder in which progressive fibrosis affects the skin and a range of internal organs. Among rheumatic diseases, it is associated with the highest cause-specific mortality [1]. Interstitial lung disease (SSc-ILD) develops in roughly one-third to one-half of patients, contributing substantially to morbidity, impairing health-related quality of life, and representing the leading cause of disease-related death. Its clinical course is highly variable: some individuals show little or no functional decline for years, even without therapy, whereas others progress to end-stage respiratory failure despite treatment [2, 3].

Immunosuppressive agents such as cyclophosphamide and mycophenolate mofetil are frequently prescribed in specialized centers, with evidence suggesting that they can slow the rate of pulmonary deterioration. More recently, biologics including rituximab and tocilizumab, as well as the tyrosine kinase inhibitor nintedanib, have demonstrated disease-modifying potential in this setting. These interventions, however, carry risks of adverse effects; therefore, therapeutic strategies must be individualized. Identifying patients at an early stage who are likely to develop progressive pulmonary fibrosis may enable earlier use of targeted therapy to prevent irreversible lung injury [4, 5].

Autoantibody profiles in SSc correlate with distinct clinical manifestations, including the occurrence and trajectory of ILD. Anti-topoisomerase I (anti-Scl-70) is strongly associated with progressive fibrotic lung disease, while anti-Ro52 reactivity is linked both to SSc-ILD and to increased mortality. Ro52, also referred to as tripartite motif-containing protein 21 (TRIM21), is an E3 ubiquitin ligase thought to regulate immune activity by ubiquitinating inflammatory mediators, thereby influencing autoimmune process [6].

Case Report

We present the case of a 64-year-old female patient with a known history of hypothyroidism, undergoing hormonal replacement therapy, who was admitted to the Rheumatology Department of Emergency Clinical County Hospital of Craiova in September 2022, presenting polyarthralgia, mainly of the small joints of

the hands, with no signs of clinical inflammation.

An initial evaluation of the patient revealed tenderness on palpation of the small joints of the hands, without clinically visible swelling and without the presence of local inflammatory signs (calor, rubor, tumor, dolor). Paraclinical assessment showed an elevated ESR of 53 mm/h (normal value <12 mm/h), a slightly elevated CRP of 6.14 mg/dl, seronegativity for rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA), and no other abnormalities in the laboratory tests. Ultrasonographic evaluation demonstrated grade 2 synovial proliferation in the radiocarpal and intercarpal joints bilaterally, mild joint effusion in the second metacarpophalangeal joints bilaterally, contour irregularities of the bone cortex with a "step-up" appearance consistent with osteophytes in the second to fifth distal interphalangeal joints bilaterally and in both first carpometacarpal joints, without sonographically detectable erosions. The diagnosis of seronegative rheumatoid arthritis was established at that time, and treatment with hydroxychloroquine 200 mg/day was initiated. An extended ANA blot profile was recommended in the outpatient setting to rule out a potential connective tissue disorder.

Six months later, the patient was re-admitted to the Rheumatology Department, reporting new-onset vasospastic discoloration of the upper extremity digits following exposure to cold temperatures, accompanied by exertional dyspnea.

Upon reassessment, the patient exhibited puffy hands with mild cutaneous induration involving the distal and middle phalanges, tenderness of the small joints of the hands, and vasospastic discoloration of the upper extremity digits. We performed a Schirmer's test which was negative. The cold immersion test yielded a positive result, consistent with Raynaud's phenomenon. The six-minute walk test demonstrated a baseline oxygen saturation of 98%, with a decline to 94% following a distance of 433 meters.

Laboratory investigations revealed an ESR of 34 mm/h and positivity for anti-Ro52 antibodies on the extended ANA blot profile, with no other significant abnormalities. Abdominal ultrasonographic evaluation demonstrated no pathological findings, while cardiac assessment identified a pulmonary artery pressure of 35 mmHg and mild mitral regurgitation, leading to the subsequent diagnosis of probable pulmonary arterial hypertension.

Ultrasonographic evaluation of the parotid glands revealed no pathological changes. Hand ultrasonography demonstrated grade 2 synovial proliferation in the radiocarpal and left intercarpal joints, without detectable Power Doppler signal, exudative tenosynovitis of the flexor tendons of digits II–V bilaterally, and exudative tenosynovitis of the first extensor compartment on the right. Nailfold capillaroscopy showed reduced cutaneous transparency with poorly visualized capillary loops, rare avascular areas, frequent dilated capillaries and megacapillaries, occasional isolated hemorrhages, consistent with an active scleroderma pattern. Barium swallow and upper gastrointestinal series revealed a normal esophagus; hypotonic, elongated stomach with parallel mucosal folds; spontaneously patent pylorus with homogeneous opacification; and a normally unfolded duodenal loop.

Also, in January 2023, prior to the hospital admission, a high resolution computed tomography (HRCT) was performed which revealed reduced pulmonary volume, predominantly in the lower lobes bilaterally, pulmonary architectural distortions, characterized by reticular thickening of the interlobular and subpleural septa, associated with traction bronchiectasis and minimal interstitial and alveolar infiltrates with a "ground-glass" appearance, involving both lungs, with a peripheral distribution. The changes were more prominent in the basal segments of the lower lobes bilaterally, the lateral and medial segments of the middle lobe, the superior and inferior lingular segments, and the upper lobe of the left lung. The pattern was compatible with nonspecific interstitial pneumonia (NSIP) with pulmonary involvement estimated at 25-30% (Figure 1). Alveolar–capillary diffusion capacity (DLCO) was preserved at 80% of predicted.

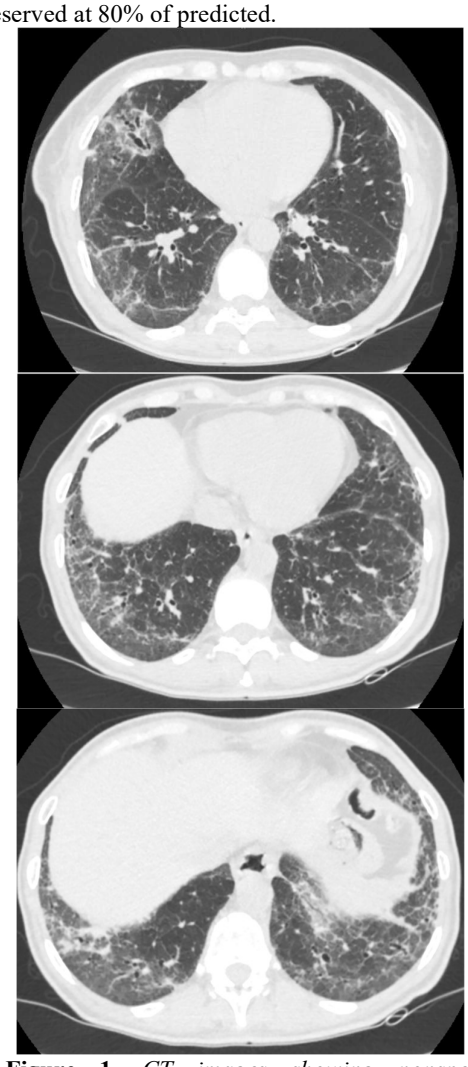

Figure 1. *CT images showing nonspecific interstitial pneumonia pattern.*

Based on these findings, the diagnosis of systemic sclerosis, limited cutaneous subtype was established. Immunosuppressive therapy was initiated with Mycophenolate Mofetil 2 g/day and also a low dose of methylprednisolone of 4 mg daily was administered. Calcium channel blockers (nifedipine 20 mg daily) and vasodilators such as pentoxifylline were prescribed for Raynaud's phenomenon.

The patient was evaluated every 6 months through laboratory tests, HRCT, and DLCO. The HRCT appearance remained unchanged at the first two re-evaluations, later with a reduction in the percentage of pulmonary involvement from 25–30% to 15–20% in June 2024. Currently, the degree of pulmonary involvement is 10% with an NSIP pattern, with lung parenchyma showing architectural distortions characterized by reticular thickening of the interlobular and subpleural septa associated with traction bronchiectasis, minimal interstitial and alveolar infiltrates with a ground-glass appearance involving both lung fields, with a peripheral distribution, more evident in the basal segments of the lower lobes bilaterally, the lateral and medial segments of the middle lobe, the superior and inferior lingular segments, the upper lobe of the left lung, with an appearance of air trapping on expiratory phase. DLCO showed a fluctuating course with values between 77–83%, but within normal ranges.

The patient is still receiving immunosuppressive therapy with 2 g of Mycophenolate Mofetil daily and treatment for Raynaud's phenomenon, while corticosteroids were discontinued.

Discussions

This case illustrates the potential role of anti-Ro52 antibodies as a biomarker for pulmonary involvement in systemic sclerosis. Although the patient's initial presentation suggested a seronegative rheumatoid arthritis, the subsequent emergence of Raynaud's phenomenon, scleroderma-pattern capillaroscopic changes, and high-resolution CT findings of nonspecific interstitial pneumonia (NSIP) confirmed limited cutaneous SSc with ILD. Anti-Ro52 positivity—reported in multiple connective tissue diseases—has been associated in SSc with higher ILD prevalence, greater extent of lung fibrosis, and increased mortality.

In this patient, early detection of ILD and prompt initiation of mycophenolate mofetil correlated with radiologic improvement and stable diffusing capacity over two years, underscoring the benefit of early intervention. The case supports the utility of extended autoantibody testing in SSc, as anti-Ro52 may identify patients at heightened risk for progressive pulmonary fibrosis, even in the absence of other SSc-specific antibodies. Targeted screening could enable closer surveillance and earlier therapy, potentially improving long-term respiratory outcomes.

Interstitial lung disease frequently complicates a range of autoimmune disorders, notably idiopathic inflammatory myopathies (IIM), systemic sclerosis, and systemic lupus erythematosus (SLE). The clinical trajectory and prognosis of ILD are shaped by both the underlying autoimmune condition and the radiologic–histopathologic pattern of lung injury. Across these variables, ILD remains a major contributor to patient morbidity and mortality. Although its clinical impact is well established, the molecular drivers, prognostic markers, and risk factors underlying ILD onset and progression are still incompletely characterized [7].

Among emerging biomarkers, antibodies targeting Ro52—a protein encoded by TRIM21, functioning as an intracellular E3 ubiquitin ligase in antiviral immunity—have gained attention in autoimmune disease–related ILD. The breakdown of immune tolerance is thought to initiate their production. Anti-Ro52 reactivity is increasingly identified in SSc and IIM, and unlike anti-Ro60, with which it was historically grouped under the anti-SSA/Ro label, anti-Ro52 demonstrates a stronger link to ILD occurrence and poorer pulmonary outcomes [8].

An investigation by Hamberg et al (2023) examined the presence and significance of autoantibodies in both bronchoalveolar lavage (BAL) fluid and serum from patients with newly diagnosed SSc-associated ILD. Fifteen patients underwent bronchoscopy with BAL collection, followed by autoantibody profiling via addressable laser bead immunoassay. A separate longitudinal cohort of 43 early SSc-ILD patients had baseline serum antibody assessment and serial lung function testing over at least two visits spanning two or more years. Associations between specific autoantibodies and lung function decline were evaluated using linear mixed-effects models. Immunohistochemistry of lung tissue from healthy controls and SSc patients assessed Ro52 antigen localization. The results revealed a marked enrichment of anti-Ro52 antibodies in the pulmonary compartment of patients with recent-onset SSc-ILD, suggesting potential local pathogenicity. The alignment of serologic, BAL, and tissue-level findings reinforces the view that anti-Ro52 could serve as a valuable marker for identifying individuals at heightened risk for progressive fibrotic lung disease in SSc [9].

A study by Yin et al (2025) evaluated the individual and combined clinical implications of antibodies against Ro52/TRIM21 and Ro60/SSA in systemic sclerosis (SSc). Data were obtained from the Renji Scleroderma Longitudinal Cohort, comprising 379 patients with a minimum follow-up of one year. Participants were stratified into four serological categories: negative for both antibodies, positive for anti-Ro52 alone, positive for anti-Ro60 alone, and positive for both. Multivariable logistic regression and survival modeling were applied to examine associations with organ involvement and disease course. Of the total cohort, 12.7% (48 patients) demonstrated dual antibody positivity. Co-expression was frequent, with 43.6% of anti-Ro52–positive individuals also harboring anti-Ro60 reactivity, and 62.3% of those positive for anti-Ro60 likewise exhibiting anti-Ro52 antibodies. The double-positive

group displayed markedly higher frequencies of interstitial lung disease (79.2%), pulmonary arterial hypertension (25.0%), digital ulceration (41.7%), and gastrointestinal manifestations (79.2%). These findings delineate a clinically distinct subset of SSc patients in whom concurrent anti-Ro52 and anti-Ro60 reactivity portends severe multi-organ involvement and a more aggressive disease trajectory, particularly affecting pulmonary outcomes. Incorporating combined antibody testing into routine assessment may improve risk stratification and guide closer surveillance of patients most likely to experience rapid progression [10]

A study by Wodkowski et al (2015) sought to determine the phenotype and survival outcomes associated with monospecific anti-Ro52/TRIM21 positivity, defined as the presence of these antibodies in the absence of any other SSc-related autoantibodies. A combined cohort from Canada, Australia, and the United States comprising 1574 individuals with SSc was analyzed. Clinical and demographic data were harmonized, and all serum samples underwent testing using an identical immunodiagnostic platform. Statistical modeling was applied to examine associations between monospecific anti-Ro52/TRIM21 reactivity and key outcomes, including interstitial lung disease (ILD) and mortality. Of the study population, 103 patients (6.5%) demonstrated monospecific anti-Ro52/TRIM21 antibodies, 324 (20.6%) had overlapping reactivity with other SSc-specific antibodies, and 1147 (72.9%) were negative. ILD emerged as the only clinical feature significantly linked to monospecific status. Furthermore, monospecific anti-Ro52/TRIM21 positivity was associated with a higher risk of death. Findings from this large multinational dataset provide compelling evidence that monospecific anti-Ro52/TRIM21 antibodies are independently associated with ILD and reduced survival in SSc, reinforcing their potential as a prognostic biomarker with predictive clinical value [11].

As a final point, numerous studies have demonstrated that anti-Ro52 antibodies are strongly associated with progressive interstitial lung disease in systemic sclerosis, supporting their role as valuable biomarkers for disease progression and risk stratification. As a result, while several ILD subtypes are well defined, a proportion of patients exhibit progressive disease, characterized by declining lung function, worsening symptoms, and reduced quality of life. With antifibrotic therapies now approved for both idiopathic pulmonary fibrosis (IPF) and other progressive fibrotic ILDs, early identification of progression risk factors has become essential for guiding therapeutic decisions and improving outcomes [12].

Conclusions

This case highlights the potential role of anti-Ro52 antibodies as a prognostic biomarker for interstitial lung disease in systemic sclerosis. Early identification of anti-Ro52 positivity in patients with SSc-ILD may facilitate timely initiation of targeted immunosuppressive therapy, which in this case was associated with radiologic improvement and preservation of pulmonary function over a two-year follow-up period.

Evidence from multiple large cohorts indicate that anti-Ro52 antibodies—whether monospecific or coexisting with anti-Ro60—are independently linked to higher ILD prevalence, more severe multi-organ involvement, and increased mortality. These observations support the incorporation of anti-Ro52 testing into routine systemic sclerosis assessment to improve risk stratification, guide surveillance strategies, and inform early therapeutic interventions. In the context of emerging antifibrotic and immunomodulatory treatments, recognizing patients at greatest risk for progressive pulmonary fibrosis remains essential for optimizing long-term outcomes.

Conflicts of Interest: The authors declare no conflicts of interest.

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