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Occult Fibrosing Interstitial Lung Disease Revealing Anti-PL-12 Antisynthetase Syndrome in a Patient with Autoimmune Overlap

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Abstract

Antisynthetase syndrome (ASS) is an autoimmune condition characterised by antibodies directed against aminoacyl-transfer RNA synthetases and is frequently associated with interstitial lung disease (ILD). Pulmonary manifestations commonly present with dyspnoea and cough; however, clinically occult or minimally symptomatic ILD may delay recognition and diagnosis. We report the case of a 67-year-old woman with a background of rheumatoid arthritis, Sjögren's syndrome, and CREST syndrome who presented following multiple falls without significant respiratory symptoms. Autoimmune evaluation demonstrated high-titre antinuclear antibodies with anti-PL-12 and Ro52 positivity. High-resolution computed tomography (HRCT) of the chest demonstrated fibrosing interstitial lung disease with a non-specific interstitial pneumonia (NSIP) pattern. Pulmonary function testing revealed a restrictive defect with reduced diffusion capacity (DLCO 57% predicted). The constellation of lung-dominant ILD, anti-PL-12 positivity, and connective tissue disease overlap supported a diagnosis of antisynthetase syndrome. Despite radiologically significant pulmonary involvement and impaired gas transfer, the patient remained minimally symptomatic from a respiratory perspective. Immunosuppressive therapy with mycophenolate mofetil and a tapering course of prednisolone was initiated following multidisciplinary assessment. This case highlights the potential for clinically occult but radiologically and functionally significant ILD in antisynthetase syndrome, particularly in patients with autoimmune overlap. Early recognition requires careful integration of serological, radiological, and functional findings, even in the absence of overt respiratory symptoms.

Keywords: Antisynthetase syndrome; Interstitial lung disease; Pulmonary manifestations

Introduction

Antisynthetase syndrome (ASS) is a subset of idiopathic inflammatory myopathy characterised by autoantibodies directed against aminoacyl-transfer RNA synthetases [1]. The syndrome encompasses a heterogeneous clinical spectrum including interstitial lung disease, inflammatory myopathy, arthritis, Raynaud's phenomenon, fever, and mechanic's hands [1-6]. Among these manifestations, ILD represents a major determinant of morbidity and mortality [1,4]. Anti-Jo-1 antibodies are the most frequently identified antisynthetase antibodies; however, non-Jo-1 antibodies such as anti-PL-12 are increasingly recognised as important markers of lung-dominant disease [2,3]. Patients with anti-PL-12 antibodies may demonstrate severe pulmonary involvement with minimal or absent myositis, complicating timely diagnosis [2,3]. Interstitial lung disease associated with antisynthetase syndrome most commonly demonstrates non-specific interstitial pneumonia (NSIP) or organising pneumonia patterns on HRCT imaging [5]. Importantly, the severity of radiological abnormalities may not correlate with symptom burden, and some patients remain minimally symptomatic despite significant fibrotic disease and impaired gas exchange [5]. The diagnosis may be particularly challenging in patients with established autoimmune overlap

syndromes, where pulmonary abnormalities may initially be attributed to pre-existing connective tissue disease rather than antisynthetase syndrome specifically. We report a case of occult fibrosing ILD with an NSIP pattern revealing anti-PL-12 antisynthetase syndrome in a patient with rheumatoid arthritis, Sjögren's syndrome, and CREST overlap disease.

Case Presentation

A 67-year-old woman was admitted following multiple falls over several days. Her medical history was significant for rheumatoid arthritis, Sjögren's syndrome, CREST syndrome, peripheral neuropathy, narcolepsy, and previous meningioma requiring craniotomy with residual acquired brain injury. At presentation, the patient denied significant respiratory symptoms, including exertional dyspnoea, productive cough, pleuritic chest pain, or haemoptysis. She reported being able to walk up one flight of stairs without stopping, but had not pushed herself to greater exertion. There was no acute respiratory distress, and initial clinical assessment was focused primarily on the neurological and rehabilitation aspects of her presentation. Computed tomography imaging of the brain and neck demonstrated no acute intracranial pathology or large vessel occlusion. Stable left frontotemporal encephalomalacia related to previous neurosurgical intervention was noted. During admission, the patient underwent further autoimmune evaluation because of her established connective tissue disease background and elevated inflammatory markers. Serological testing demonstrated positive antinuclear antibodies with a speckled pattern at a titre of 1:640, anti-SSA/Ro60 positivity, Ro52 positivity, and anti-PL-12 positivity on myositis immunoassay. Despite the absence of significant respiratory symptoms, HRCT of the chest was performed to evaluate possible connective tissue disease-associated pulmonary involvement.

Investigations

Laboratory investigations demonstrated elevated inflammatory markers: C-reactive protein 24 mg/L (normal <5), erythrocyte sedimentation rate 42 mm/hr (normal <20). Mild abnormalities in liver function tests (ALT 58 U/L, AST 45 U/L) and renal function (creatinine 1.1 mg/dL, eGFR 55 mL/min/1.73m²) were also present during admission.

Autoimmune testing demonstrated:

- Positive ANA (speckled pattern, titre 1:640)
- Positive anti-SSA/Ro60 antibodies
- Positive Ro52 antibodies
- Positive anti-PL-12 antibodies

Other myositis-associated antibodies, including anti-Jo-1, anti-PL-7, anti-MDA5, and anti-Mi-2 antibodies, were negative. There was no clinically overt proximal muscle weakness during admission. Formal neuromuscular assessment and longitudinal biochemical monitoring (creatine kinase, aldolase) were planned as outpatient investigations and subsequently showed normal results. HRCT of the chest demonstrated fibrosing interstitial lung disease with an NSIP pattern characterised by bilateral lower-zone predominant ground-glass opacification, reticulation, traction bronchiectasis, and fibrotic change without definite honeycombing (Figure 1).

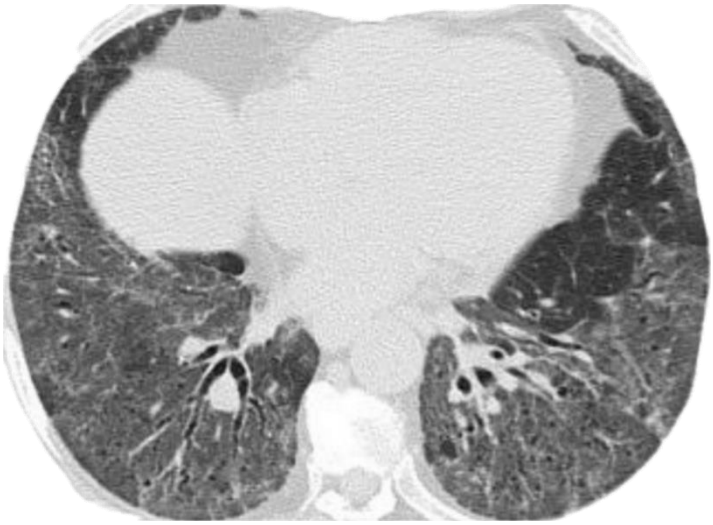


Figure 1: *High-Resolution CT Chest.*

Description: *Axial HRCT image (lung window) at the level of the lower lobes showing bilateral, symmetrical ground-glass opacification, fine reticulation, and mild traction bronchiectasis with lower-zone predominance. No definite honeycombing is present. These findings are consistent with a fibrosing non-specific interstitial pneumonia (NSIP) pattern.*

Pulmonary function tests (performed as an outpatient two weeks after discharge) demonstrated a restrictive ventilatory defect with reduced diffusion capacity for carbon monoxide (DLCO), consistent with fibrosing interstitial lung disease. Spirometry showed a reduced forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) with a preserved FEV_1/FVC ratio. Lung volumes confirmed restriction, and gas transfer was moderately impaired. Detailed results are presented in Table 1. A sleep study was performed and excluded significant nocturnal hypoxia or obstructive sleep apnoea (apnoea-hypopnoea index 4.2 events/hour, mean overnight SpO_2 93%).

Summary of Key Laboratory Findings

- Parameter Finding
- CRP 24 mg/L (elevated)
- ESR 42 mm/hr (elevated)
- ANA Positive (1:640 speckled)
- Anti-SSA/Ro60 Positive
- Ro52 Positive
- Anti-PL-12 Positive

- ALT/AST Mildly elevated
- Creatinine/eGFR Mild impairment

Pulmonary Function Test Results

Parameter Predicted Observed % Predicted
FVC (L) 2.45 1.82 74%
FEV_1 (L) 1.92 1.48 77%
FEV_1/FVC (%) 78 81 104%
Total lung capacity (L) 4.10 2.95 72%
DLCO (mmol/min/kPa) 6.8 3.9 57%
DLCO/VA (mmol/min/kPa/L) 1.65 1.32 80%

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Interpretation: Mild to moderate restrictive defect with moderately reduced DLCO (57% predicted), suggestive of fibrotic interstitial lung disease with impaired gas transfer.

***Table 1**: Pulmonary Function Test Results.*

Parameter	Predicted	Observed	% Predicted
FVC (L)	2.45	1.82	74%
FEV_1 (L)	1.92	1.48	77%
FEV_1/FVC (%)	78	81	104%
Total Lung Capacity (L)	4.10	2.95	72%
DLCO (mmol/min/kPa)	6.8	3.9	57%
DLCO/VA (mmol/min/kPa/L)	1.65	1.32	80%

Differential Diagnosis

The differential diagnosis included connective tissue disease-associated interstitial lung disease related to rheumatoid arthritis, Sjögren's syndrome, or systemic sclerosis spectrum disease [5]. Drug-induced interstitial lung disease (e.g., from methotrexate, which the patient was not taking) and infective causes were also considered and excluded by appropriate cultures and serology. However, the presence of anti-PL-12 antibodies in combination with fibrosing NSIP-pattern ILD and Ro52 positivity strongly supported antisynthetase syndrome with lung-dominant disease [2,3]. The absence of significant myositis did not exclude this diagnosis, as non-Jo-1 antisynthetase antibodies are recognised to present with isolated or predominant pulmonary involvement [2,3].

Diagnostic Considerations

The diagnosis of antisynthetase syndrome was based on the presence of anti-PL-12 antibodies and characteristic interstitial lung disease, consistent with recognised diagnostic frameworks [1,6]. The patient did not meet full criteria for any single connective tissue disease but had features of an overlap syndrome. This case demonstrates the diagnostic complexity of autoimmune overlap syndromes, where pulmonary abnormalities may initially be attributed to previously established connective tissue disease. The coexistence of rheumatoid arthritis, Sjögren's syndrome, and CREST syndrome complicated diagnostic attribution and may have contributed to delayed recognition of antisynthetase syndrome specifically. Ro52 positivity was considered clinically significant because previous studies have associated Ro52 antibodies with more severe and progressive ILD phenotypes in antisynthetase syndrome, particularly in patients with non-Jo-1 antibodies [2,4].

Treatment

Immunosuppressive therapy was initiated following multidisciplinary review (respiratory and rheumatology) in the outpatient setting, given the presence of progressive fibrosing ILD on HRCT, reduced DLCO (57% predicted), and positive anti-PL-12 antibodies. The patient was commenced on mycophenolate mofetil at an initial dose of 500 mg twice daily, titrated after two weeks to 1 g twice daily as tolerated. In addition, a short course of oral prednisolone was prescribed (25 mg daily for two weeks, then tapered by 5 mg every week to 5 mg daily, with a plan to discontinue after two months). Intravenous cyclophosphamide or rituximab was not required at this stage. The patient tolerated mycophenolate mofetil without significant gastrointestinal adverse effects. Baseline and follow-up full blood counts and liver function tests were arranged. Influenza and pneumococcal vaccinations were administered prior to commencing immunosuppression.

A plan was made for:

- Repeat pulmonary function tests in 3 months
- Repeat HRCT chest in 6–12 months or earlier if clinical deterioration
- Rheumatology reviews every 3 months
- Respiratory outpatient review at 4 weeks, 12 weeks, and then 6-monthly
- Monitoring of mycophenolate levels (as indicated) and periodic surveillance for opportunistic infection (e.g.,

Pneumocystis jirovecii prophylaxis considered if prolonged high-dose steroids needed)

Outcome and follow-up

The patient remained clinically stable throughout admission and did not develop respiratory deterioration. She was discharged with outpatient follow-up arrangements. At three-month follow-up, the patient reported no worsening of dyspnoea (modified Medical Research Council dyspnoea score remained 1). There were no new muscle weakness, arthralgia, or sicca symptoms. Repeat pulmonary function testing showed stable FVC (1.79 L, 73% predicted) and DLCO (4.0 mmol/min/kPa, 59% predicted). Mycophenolate mofetil was continued without dose reduction, and prednisolone was successfully tapered to 5 mg daily with plans to discontinue after two months. A follow-up HRCT is planned at six months to assess for progression of fibrosis. The patient has been advised to present immediately for any new dyspnoea, cough, or fever, and to undergo regular vaccination updates. Long-term surveillance for pulmonary hypertension (given CREST overlap) will be performed annually with echocardiography.

Discussion

Antisynthetase syndrome is a heterogeneous autoimmune condition with variable clinical manifestations that frequently complicate timely diagnosis [1,6]. While ILD is a common manifestation, the extent of pulmonary involvement may not correlate with respiratory symptom burden [5]. Anti-PL-12 antibodies are strongly associated with lung-dominant disease and may present without overt inflammatory myopathy [2,3]. In contrast to anti-Jo-1-associated disease, patients with anti-PL-12 antibodies often demonstrate severe or progressive pulmonary involvement despite minimal muscular manifestations [2,3]. This case illustrates several diagnostically important features. First, significant fibrosing NSIP-pattern ILD was identified despite minimal respiratory symptoms. Second, the coexistence of rheumatoid arthritis, Sjögren's syndrome, and CREST syndrome complicated diagnostic attribution and risked obscuring the diagnosis of antisynthetase syndrome. Ro52 positivity was an additional clinically important finding. Ro52 antibodies have been associated with more severe ILD phenotypes, progressive fibrosis, and poorer pulmonary outcomes in inflammatory myopathy-associated ILD [4]. The combination of anti-PL-12 and Ro52 positivity therefore raises concern for progressive pulmonary disease despite initial clinical stability. Another important aspect of this case is the recognition that clinically occult ILD may exist despite extensive radiological abnormalities and significant gas transfer impairment. In our patient, the baseline DLCO was reduced to 57% predicted despite minimal dyspnoea, highlighting the value of routine pulmonary function testing even in asymptomatic patients with autoimmune overlap. The decision to initiate mycophenolate mofetil was guided by the combination of anti-PL-12 serology, fibrosing NSIP pattern, and impaired gas transfer, consistent with recent recommendations for early treatment to prevent progression [1,4]. Because ILD is a major determinant of prognosis in antisynthetase syndrome, delayed recognition may have significant implications for long-term pulmonary outcomes [1,4]. Early integration of serological, radiological, and functional findings is therefore essential.

Conclusion

Antisynthetase syndrome may present with clinically occult but radiologically and functionally significant interstitial lung disease, particularly in patients with anti-PL-12 antibodies and autoimmune overlap syndromes. Lung-dominant disease may occur in the absence of overt myositis or significant respiratory symptoms, potentially delaying diagnosis. This case highlights the importance of maintaining a high index of suspicion for antisynthetase syndrome in patients with connective tissue disease overlap and unexplained interstitial lung abnormalities. Early recognition, pulmonary function testing, and multidisciplinary assessment are essential to guide monitoring and management, including timely initiation of immunosuppressive therapy.

Learning points

- Antisynthetase syndrome may present with clinically occult interstitial lung disease despite minimal respiratory symptoms.
- Anti-PL-12 antibodies are strongly associated with lung-dominant disease and may occur without overt myositis.
- Ro52 positivity may indicate increased risk of progressive interstitial lung disease.
- Autoimmune overlap syndromes may obscure recognition of antisynthetase syndrome.
- Radiological severity of ILD may not correlate with symptom burden; pulmonary function testing (especially DLCO) can identify clinically important gas transfer impairment.
- Early multidisciplinary evaluation and immunosuppressive therapy (e.g., mycophenolate mofetil) should be considered to prevent disease progression.

Ethical Statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying clinical images. A copy of the consent form is available for review by the journal editor.

Conflict of Interest

The authors declare no conflict of interest.

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