Case Report

Biochemical Clues in unravelling the Puzzle of Anti- synthetase Syndrome

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Abstract

Anti-synthetase syndrome (ASSD or ASyS) is a rare, systemic autoimmune disorder characterized by the presence of anti-aminoacyl transfer RNA synthetase (anti-ARS) antibodies, most commonly anti-Jo-1. It presents with a combination of myositis, interstitial lung disease (ILD), arthritis, Raynaud's phenomenon, mechanic's hands, and constitutional symptoms, often posing significant diagnostic challenges. We report the case of a 49-year-old male carpenter who presented with persistent cough, progressive dyspnoea, proximal muscle weakness, and joint pain. High-resolution computed tomography (HRCT) of the chest revealed interstitial lung disease with bilateral basal end-inspiratory crepitations noted on physical examination. Serological testing demonstrated anti-Jo-1 antibody positivity, confirming the diagnosis of anti-synthetase syndrome. The patient was initiated on glucocorticoids, hydroxychloroquine, and steroid-sparing immunosuppressive therapy, resulting in symptomatic and functional improvement. This case underscores the importance of early recognition of anti-synthetase syndrome, particularly in patients presenting with unexplained ILD and musculoskeletal symptoms. Delayed diagnosis is often attributed to limited clinical awareness and the restricted availability of routine testing for anti-ARS antibodies, particularly anti-Jo-1, which significantly affects patient outcomes. ILD is a predominant and serious manifestation of ASyS and remains a strong predictor of disease-related morbidity and mortality. Anti-synthetase syndrome should be considered in patients with interstitial lung disease, muscle weakness, and inflammatory arthritis, especially when anti-Jo-1 antibodies are detected. Early diagnosis and immunosuppressive therapy are critical to improving prognosis and preserving lung function.

Introduction

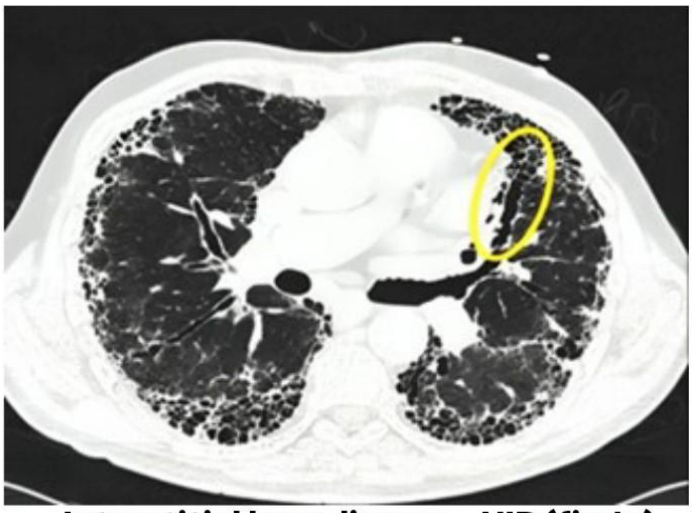
Anti-synthetase syndrome (ASS), also referred to as ASSD or ASyS, is a rare autoimmune disorder characterized by the presence of autoantibodies targeting aminoacyl-tRNA synthetases, which are essential enzymes in protein synthesis. The clinical spectrum of ASS/ASSD/ASyS typically includes proximal muscle weakness, polyarthritis, fever, Raynaud's phenomenon, interstitial lung disease (ILD), inflammatory myopathy, and hyperkeratotic changes on the fingertips [1,2]. Six specific anti-aminoacyl tRNA synthetase autoantibodies have been identified, including anti-Jo-1 (Histidyl), anti-PL7 (Threonyl), anti-PL12 (Alanyl), anti-OJ (Isoleucyl), anti-EJ (Glycyl), and anti-KS (Asparaginyl) [3]. These autoantibodies are not only central to defining the syndrome but also assist in correlating clinical phenotypes and underscore the significance of early diagnosis and individualized treatment approaches for effective ILD management [4].

Case Report

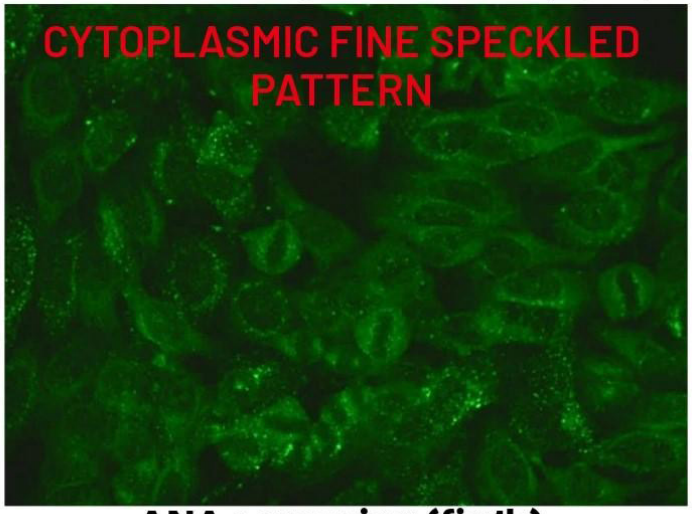
A 49-year-old male carpenter presented with a one-year history of persistent non-productive cough, progressive dyspnoea on exertion, generalized muscle weakness for four months, and multiple joint pains persisting for one year.

Clinical examination revealed synovitis of the metacarpophalangeal joints, proximal muscle weakness, and hyperkeratotic, fissured thickening along the radial aspects of the fingertips, characteristic of Mechanic's Hands. Auscultation of the chest revealed basal end-inspiratory crepitations, while vital signs remained within normal limits. Pulmonary function testing demonstrated a restrictive ventilatory defect with impaired gas transfer. High-resolution computed tomography (HRCT) of the chest confirmed interstitial lung disease (ILD) exhibiting an Usual Interstitial Pneumonia (UIP) pattern, characterized by honeycombing and traction bronchiectasis [Figure 1a]. Antinuclear antibody (ANA) screening was performed using indirect immunofluorescence (IIF) on human epithelial cells (HEp-2) and liver (Monkey) substrates (EUROIMMUN, Lübeck, Germany) at a 1:100 dilution. The fluorescence pattern observed was highly suggestive of anti-Jo-1 antibody positivity [Figure 1b]. An anti-synthetase syndrome autoantibody panel, including anti-KS, anti-EJ, anti-OJ, anti-Jo-1, anti-PL-7, and anti-PL-12, was performed using enzyme-linked immunosorbent assay (ELISA) (Bio-Rad, California, USA). The patient tested positive for both anti-Jo-1 (Histidyl) and anti-PL-12 (Alanyl) antibodies, while anti-PL-7, anti-EJ, and anti-OJ were negative. Laboratory findings demonstrated an elevated erythrocyte sedimentation rate, serum creatine kinase (CK) of 700 U/L (normal range: 40–320 U/L), and lactate dehydrogenase (LDH) of 500 U/L (normal range: 135–225 U/L), measured using AU series analysers (Beckman Coulter, USA). Based on clinical, radiological, and immunological findings, a diagnosis of Anti-Synthetase Syndrome (ASyS) was established. The patient was commenced on glucocorticoids and steroid-sparing immunosuppressants. Prednisolone was initiated at 50 mg daily and tapered by 10 mg every two weeks. Azathioprine was introduced at a dose of 100 mg per day (approximately 1.54 mg/kg/day) along with hydroxychloroquine 300 mg once daily. At the last follow-up after initiation of immunosuppressive therapy, the patient demonstrated significant clinical improvement with reduction in dyspnoea, joint pain, and proximal muscle weakness. Repeat laboratory evaluation also showed improvement in serum CK and LDH levels, supporting a favourable therapeutic response.

Figure 1 (A) and 1(B): Depicting CT scan finding revealing UIP pattern and ANA screening pattern on HEp-2 substrate reveals cytoplasmic pattern suggestive of anti Jo-1 antibodies.



Interstitial lung disease –UIP (fig 1a)



ANA screening (fig1b)

Discussion

Anti-Synthetase Syndrome (ASyS), also referred to as Anti-Synthetase Syndrome Disorder (ASSD), represents a rare and distinct subset of idiopathic inflammatory myopathies (IIMs), primarily defined by the presence of anti-aminoacyl tRNA synthetase (anti-ARS) autoantibodies along with a constellation of clinical features including interstitial lung disease (ILD), myositis, arthritis, Raynaud's phenomenon, mechanic's hands, and fever. Initially regarded as a myositis marker, the role of anti-ARS antibodies has significantly evolved over time to be recognized as a central diagnostic hallmark of ASyS, reflecting its multi-organ involvement and overlap with other connective tissue diseases [1]. Despite the growing understanding of ASyS, diagnosis and management remain complex due to the heterogeneity in clinical presentation, variability in antibody profiles, and overlapping symptoms with other autoimmune disorders. Anti-ARS antibodies are considered central to the pathogenesis and diagnosis of ASyS [2]. These insights explain the autoimmune nature of anti-ARS antibodies and their pathogenic potential in diseases like ASyS.

The patient's presentation with chronic cough, dyspnoea, arthritis, and muscle weakness prompted consideration of several differential diagnoses including rheumatoid arthritis-associated ILD, idiopathic pulmonary fibrosis, polymyositis/dermatomyositis, and systemic sclerosis-associated ILD. The UIP pattern on HRCT initially favoured fibrotic ILD, while inflammatory arthritis suggested a connective tissue disorder. However, elevated CK and LDH levels, proximal muscle weakness, and mechanic's hands pointed toward inflammatory myopathy-associated ILD. Confirmation was achieved through positive anti-Jo-1 and anti-PL-12 antibodies, establishing the diagnosis of Anti-Synthetase Syndrome.

Clinically, ASyS is notable for its diverse phenotypic spectrum. Solomon et al. highlighted cases where anti-OJ and anti-KS antibodies were predominantly associated with isolated ILD, while anti-ZO-positive patients displayed multi-systemic

involvement, including arthritis, myositis, and Raynaud's phenomenon [3]. This diversity reiterates the diagnostic challenge of ASyS, as some patients present solely with pulmonary manifestations while others experience widespread systemic disease. Our case, exhibiting anti-Jo1 and anti-PL12 co-positivity, contributes further evidence to this heterogeneity and underlines the need for clinicians to maintain a high index of suspicion even in atypical presentations. One of the most comprehensive studies on ASyS was conducted by Cavagna et al., who reported the findings from an international multicenter cohort involving 828 patients across ten countries. Their research demonstrated that anti-Jo1 antibodies were the most prevalent (72%), followed by anti-PL7, anti-PL12, anti-EJ and anti-OJ at varying frequencies [4]. Interestingly, our patient demonstrated dual positivity for anti-Jo-1 and anti-PL-12 antibodies, a rare serological finding in Anti-Synthetase Syndrome. The coexistence of both antibodies likely contributed to the prominent overlap of interstitial lung disease, inflammatory arthritis, and myositis observed in this case, highlighting the clinical heterogeneity of ASyS. ASyS patients commonly exhibit features of ILD, myositis, and arthritis, with ILD often dominating the clinical picture, particularly in anti-Jo1-positive cases. Studies have reported that up to 70% of patients with anti-Jo1 antibodies develop ILD, reinforcing its significance in disease monitoring and prognosis [5-8]. Additionally, arthralgia and arthritis in ASyS can mimic rheumatoid arthritis, especially in seronegative cases, which can mislead clinicians and delay the correct diagnosis [9].
The lung involvement in ASyS is not uniform. Although NSIP is the most frequently reported radiological pattern in Anti-Synthetase Syndrome, our patient demonstrated a UIP pattern characterized by honeycombing and traction bronchiectasis, highlighting the heterogeneity of pulmonary manifestations in ASyS [10]. Autoantibody detection has undergone significant technological advancement. Historically, anti-ARS antibodies were identified using immunoprecipitation, where they were shown to co-precipitate tRNA along with synthetases. Modern techniques now include Indirect Immunofluorescence (IIF), ELISA, Addressable Laser Bead Immunoassay (ALBIA), Fluorescent Enzyme Immunoassay (FEIA), and Chemiluminescent Immunoassay (CLIA) [11]. Among these, Line Immunoassays (LIA) have become a preferred diagnostic modality, allowing simultaneous detection of Myositis-Specific Antibodies (MSAs) and Myositis-Associated Antibodies (MAAs), enabling more efficient clinical characterization of IIMs. MSAs, including anti-Jo1, anti-Mi-2, anti-SRP, and anti-TIF1-γ, are typically specific to myositis subtypes, offering not only diagnostic but also prognostic insights. For instance, the detection of anti-Jo1 correlates strongly with ILD and guides the clinician towards early respiratory assessment. Laboratory findings significantly supported the diagnosis in our patient. Elevated CK and LDH levels indicated active muscle involvement, while the cytoplasmic ANA-IIF pattern provided an important clue toward anti-synthetase antibodies, particularly anti-Jo-1. Subsequent ELISA-based antibody profiling confirmed anti-Jo-1 and anti-PL-12 positivity. However, variations in sensitivity among different serological assays may affect antibody detection, especially in resource-limited settings. MAAs, such as anti-SSA/Ro, anti-PM-Scl, and anti-U1-RNP, while not unique to myositis, often indicate overlap syndromes with diseases like systemic lupus erythematosus (SLE) or systemic sclerosis [12-14]. ELISA-based myositis antibody profiling was useful in confirming anti-Jo-1 and anti-PL-12 positivity in our patient; however, assay-related limitations should be considered during interpretation. Variations in sensitivity and specificity among different serological platforms may influence antibody detection, and false-positive or cross-reactive results can occasionally occur, particularly in cases demonstrating dual antibody positivity. Therefore, serological findings should always be interpreted in correlation with clinical presentation, imaging findings, and other laboratory parameters. Despite the advances in serological testing, routine detection of anti-ARS antibodies apart from anti-Jo1 remains limited due to a lack of standardization, high costs, and absence of regulatory approval for many tests. This diagnostic gap is especially pronounced in resource-limited settings, reinforcing the importance of both clinical acumen and the need for improved, accessible diagnostic technologies in the future [11-14].
Additionally, Yehudina et al. described a compelling case of antisynthetase syndrome marked by ILD, Raynaud's phenomenon, digital ischemia, and severe occlusive vasculopathy. Their patient required a multi-modal treatment approach including corticosteroids, cyclophosphamide, intravenous immunoglobulin (IVIg) and rituximab to manage disease flares. Notably, the SARS-CoV-2 infection triggered ILD exacerbation, necessitating antifibrotic therapy with nintedanib, which resulted in improved lung function and clinical stability, underscoring the complex and relapsing-remitting nature of ASyS and the importance of individualized therapeutic strategies [15].

The patient described here fulfilled both the sets of criteria for the diagnosis of anti-synthetase syndrome proposed by Connors et al. and Solomon et al. Solomon et al [3], EULAR/ACR [16] and Connors et al [17] classification criteria have been included below Table 1.

Table 1: EULAR/ACR, Connors et al and Solomon et al classification criteria for Anti-synthetase syndrome.

EULAR/ACR 2017	Connors et al. (2010) Criteria	Solomon et al (2011) Criteria	Case Details
Definite IIM: score of at least 7.5 (8.7 with muscle biopsy) Probable IIM: score of at least 5.5 (6.7 with muscle biopsy)	Required: Presence of an anti-aminoacyl tRNA synthetase antibody	Required: Presence of an anti-aminoacyl tRNA synthetase antibody	Present
Anti-Jo-1 •Objective symmetrical weakness of upper and lower proximal extremities •Proximal leg muscles weaker than distal •Dysphagia or oesophageal motility disorders •Skin lesions (heliotrope rash, Gottron's papules, and Gottron's sign) •Age of onset •Typical features in muscle biopsy and elevated skeletal muscle enzymes	**PLUS, one or more of the following clinical features:** •Raynaud's phenomenon •Arthritis •Interstitial lung disease •Fever (not attributable to another cause) •Mechanic's hands (thickened and cracked skin on hands, particularly at fingertips)	**PLUS, two major or one major and two minor criteria: Major:** •Interstitial Lung Disease (not attributable to another cause) •Polymyositis or dermatomyositis by Bohan and Peter criteria **Minor:** •Arthritis •Raynaud's phenomenon •Mechanic's hands	**Findings:** •Interstitial Lung Disease (+) •Mechanic's hands (+) •Arthritis (+)

Anti-synthetase syndrome remains a diagnostically challenging entity due to its heterogeneous clinical and serological presentation. Our case highlights the rare coexistence of anti-Jo-1 and anti-PL-12 antibodies with UIP-pattern ILD, emphasizing the importance of integrating clinical, radiological, and serological findings for early diagnosis and management.

Conclusion

This case highlights the diagnostic challenge of Anti-Synthetase Syndrome in patients presenting with overlapping pulmonary and musculoskeletal manifestations. The rare coexistence of anti-Jo-1 and anti-PL-12 antibodies with UIP-pattern interstitial lung disease underscores the marked clinical and serological heterogeneity of ASyS. Recognition of elevated CK and LDH levels together with a characteristic cytoplasmic ANA-IIF pattern provided crucial biochemical clues that guided definitive serological diagnosis. Our case further emphasizes the importance of comprehensive antibody profiling and multidisciplinary evaluation for early diagnosis and timely immunosuppressive therapy, which are essential for improving clinical outcomes and preserving pulmonary function in ASyS. All authors have approved of the final draft for publication purpose and are accountable for the accuracy and integrity of the work.

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Conflict of interest

None declared.

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Ethics approval

waived off for case reports at our institute.

Supplementary data

None.

Data availability statement

All relevant data have been provided with the manuscript.

Abbreviations

Anti-synthetase syndrome (ASSD or ASyS)
anti-aminoacyl transfer RNA synthetase (anti-ARS)
interstitial lung disease (ILD)
High-resolution computed tomography (HRCT)
Usual Interstitial Pneumonia (UIP)
Antinuclear antibody (ANA)
indirect immunofluorescence (IIF)
human epithelial cells (HEp-2)
enzyme-linked immunosorbent assay (ELISA)
creatine kinase (CK)
Lactate dehydrogenase(LDH)
idiopathic inflammatory myopathies (IIMs),
Addressable Laser Bead Immunoassay (ALBIA)
Fluorescent Enzyme Immunoassay (FEIA)
Chemiluminescent Immunoassay (CLIA)
Myositis-Specific Antibodies (MSAs)
Myositis-Associated Antibodies (MAAs)
Systemic lupus erythematosus (SLE)
Intravenous immunoglobulin (IVIg)
Connective tissue diseases (CTDs)

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