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From Ambiguity to Identity: A Case of IPAF Evolving into Myositis-Associated ILD

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Abstract: - *Growing insights suggest that interstitial pneumonia with autoimmune features (IPAF) and antisynthetase syndrome (ASS) may represent different stages within a single disease continuum, especially in patients who test positive for myositis-specific antibodies (MSAs). A significant proportion of MSA-positive IPAF cases eventually progress to defined connective tissue diseases, most commonly ASS, over a period of several years. Among these, anti-Jo-1 and anti-Ro52 antibodies are associated with the highest risk of progression. This clinical and immunological overlap calls into question the validity of the IPAF label for MSA-positive individuals and highlights the need for flexible classification models. Recognizing IPAF and ASS as points along a shared spectrum supports a shift toward stage-based diagnosis and more aggressive immunosuppressive treatment.*

Keywords: - *Interstitial pneumonia with autoimmune features, Anti-synthetase syndrome, rituximab, Interstitial lung disease, Anti-Jo-1*

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I. Introduction: -

Interstitial lung diseases (ILDs) are a heterogeneous group of disorders characterized by diffuse collagen deposition and architectural distortion of the pulmonary parenchyma[1]. ILD frequently complicates connective tissue diseases (CTDs), occurring in approximately 55–65% of patients with systemic sclerosis (SSc), 15–35% of those with idiopathic inflammatory myopathies (IIM), and nearly 30% of patients with rheumatoid arthritis (RA)[2]. ILD may either emerge during the course of a CTD or precede its diagnosis entirely.

A subset of ILD patients presents with clinical and/or serological autoimmune features but does not meet established CTD classification criteria. To address this diagnostic grey zone, the European Respiratory Society (ERS) and American Thoracic Society (ATS) introduced the term interstitial pneumonia with autoimmune features (IPAF) in 2015, aiming to standardize the classification of ILD patients with autoimmune traits who lack defined CTDs[3].

Despite being classified separately, up to 30–40% of IPAF patients test positive for myositis-specific antibodies (MSAs), particularly antisynthetase antibodies. These MSA-positive IPAF cases often mirror ASS in clinical outcomes, imaging patterns, and disease progression. Here we present an interesting case report of the management of a patient initially diagnosed as IPAF and then transformed into full-blown antisynthetase syndrome.

II. Case report: -

A 41-year-old non-smoker male with well-controlled hypothyroidism (on Tab Eltroxin 75 µg OD) presented with progressive SOB, which began insidiously and worsened from MMRC grade 2 to 4 over five years. It was associated with a dry cough of the same duration. There was no history of fever, rash, expectoration, chest pain, or tuberculosis. On examination, he was vitally stable except for SpO_2 of 90% on

room air. Systemic examination revealed bilateral infrascapular fine end-inspiratory crackles. Routine investigations were sent as shown in Table 1.

Table 1: Initial Investigations: -

Parameters	**Values**	**Parameters**	**Values**
HB	12.3 g/dl	ESR	39 mm in 1 hr
TLC	9900/mm3	CRP	17.5 mg/L
Platelet count	3.05L	HIV/ HbsAg/Anti-HCV	Non Reactive
Tb/Db	1.2/0.8 mg/dl	URM	NAD
AST/ALT/ALP	54/46/126 U/L	T3/T4	3.59/15.9 pmol/L
TP/SA	8.2/4.0 g/dl	TSH	1.62 uIU/L
BU/Creat	40/0.9 mg/dl	Probnp	290

Abbreviations: ESR – erythrocyte sedimentation rate; TLC – total leukocyte count; CRP – c-reactive protein; HIV – human immunodeficiency virus; HbsAg – hepatitis b surface antigen; Anti-HCV – anti-hepatitis c virus; AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alkaline phosphatase; TSH – thyroid-stimulating hormone; Probnp – b-type natriuretic peptide; TP – Total Protein; SA – Serum albumin; URM – Urine routine and microscopy

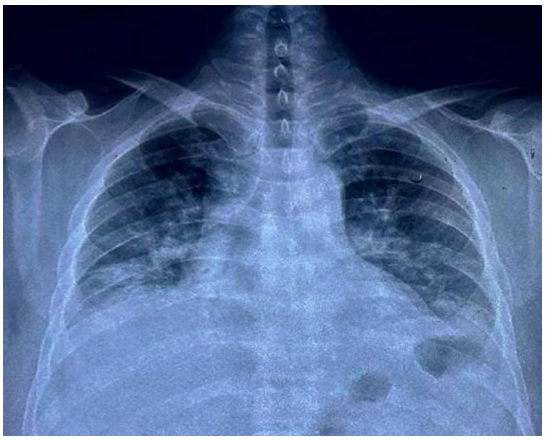

Figure 1: Chest X-ray showing bilateral lower and middle zone interstitial opacities

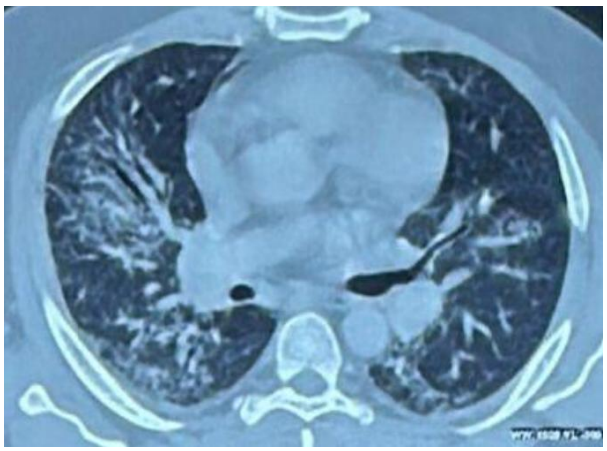

Figure 2: HRCT chest: Interstitial pneumonitis with fibrosing ILD

Table 2: Further Investigations:-

ANA	1:320 titre
ENA	Anti Ro(4+), Anti La(3+), Anti dsDNA(41 IU/ML)
ANCA	Negative
RA factor, Anti-CCP	Negative

ECG and 2D Echo	Normal study
PFT	Vital capacity is severely reduced with reduced DLCO s/o Restrictive Lung disease

Abbreviations: PFT – pulmonary function test; DLCO – diffusing capacity for carbon monoxide; ANA – antinuclear antibody; RF – rheumatoid factor; Anti CCP – anti-cyclic citrullinated peptide

Based on the above investigations, the patient was diagnosed with Interstitial Pneumonia with Autoimmune Features (IPAF). The patient was initiated on corticosteroid therapy and received six doses of intravenous cyclophosphamide. Clinical improvement was noted over a period of two months. The patient was subsequently continued on tapering doses of steroids and was discharged in stable condition.
Three years later, he presented with worsening dyspnea (MMRC grade 4) and reported B/L lower limb weakness (proximal > distal) and small joint pain associated with morning stiffness. He was investigated further, which revealed raised CPK levels and Anti Jo1 strong positivity on the myositis panel. X-ray hands revealed non-erosive arthritis.

Figure 3: MRI muscle: Post-contrast enhancement in the distal 1/3rd of the Right vastus lateralis

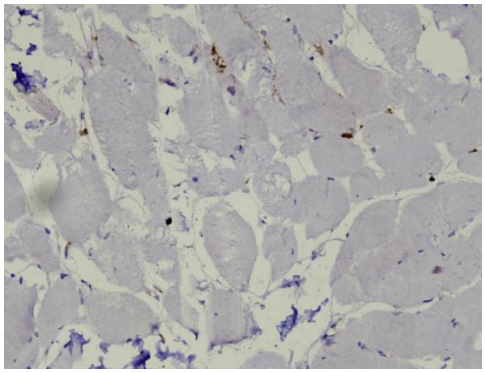

Figure 4: Muscle biopsy: Increased macrophages identified by CD68 (Early inflammatory Myopathy)

Treatment: The patient's diagnosis was revised to Anti-Synthetase Syndrome. Treatment was initiated with corticosteroids and two divided doses of rituximab, followed by a tapering course of steroids along with mycophenolate mofetil. Over the subsequent three months, the patient demonstrated significant clinical improvement, with a reduction in symptoms and improved pulmonary function test (PFT) results.

III. Discussion:

This case illustrates the dynamic clinical spectrum between interstitial pneumonia with autoimmune features (IPAF) and antisynthetase syndrome (ASS). While IPAF describes patients with interstitial lung disease (ILD) and autoimmune features that do not fulfil definitive connective tissue disease (CTD) criteria, ASS is characterized by the triad of anti-synthetase antibodies (particularly anti-Jo-1), ILD, and myositis[4]. In Inflammatory myopathy, ILD is present in 10–30% of cases at initial diagnosis and can rise to over 50% among patients with antisynthetase syndrome (ASS)[5]. In a prospective multicenter cohort of patients with interstitial pneumonia with autoimmune features (IPAF), 24.1% of the 191 enrolled individuals progressed to a defined connective tissue disease (CTD) over approximately three years. Features suggestive of idiopathic inflammatory myopathy—such as mechanic's hands and the presence of anti-PM/Scl or anti-MDA5 antibodies—were

associated with an increased likelihood of progression to myositis or a related CTD[6]. A Japanese study reported that 12.2% of patients with IPAF progressed to a definite connective tissue disease over a follow-up period of 4.5 years[7].

Distinct therapeutic approaches exist for these conditions. IPAF management typically initiates with moderate-dose corticosteroids, potentially escalating to immunosuppressants like mycophenolate mofetil (MMF) or azathioprine in progressive cases[8]. In contrast, ASS frequently necessitates high-dose corticosteroids at onset, combined with early aggressive immunosuppression (e.g., MMF, cyclophosphamide), and prompt transition to biologic therapies (e.g., rituximab, IVIG) in refractory disease[9]. Monitoring paradigms also differ substantially, with IPAF warranting a more conservative surveillance approach compared to ASS, which demands frequent assessments to track ILD progression and muscle involvement[10]. The observed progression from IPAF to ASS in this patient over three years - evidenced by seroconversion of myositis-specific antibodies (MSAs) and development of muscle involvement - aligns with emerging evidence suggesting that MSA-positive IPAF may represent a prodromal or incomplete form of ASS. This clinical scenario emphasizes several critical considerations:

1. The importance of serial antibody testing in patients with presumed IPAF
2. The need for heightened surveillance for evolving myositis in MSA-positive cases
3. The value of flexible diagnostic frameworks that accommodate disease evolution
4. The imperative for early therapeutic intensification in patients showing progression to ASS

These observations support recent proposals to refine classification systems for autoimmune-related ILD, particularly regarding the prognostic and therapeutic implications of MSA positivity in IPAF patients[11].

IV. Conclusion:

This case illustrates that MSA-positive IPAF can evolve into full-blown ASS, advocating for a dynamic, spectrum-based disease model. Early identification of high-risk features—such as anti-Jo-1 antibodies—can guide timely immunosuppression, altering disease trajectory and improving patient outcomes. Recognizing IPAF and ASS as points along a disease continuum, particularly in MSA-positive patients, allows for earlier identification of high-risk individuals, timely immunosuppressive intervention, and more personalized, stage-based treatment. This dynamic approach improves prognostication, refines classification systems, and encourages research into disease evolution and therapeutic strategies—ultimately leading to better clinical outcomes.

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