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Case Report

The unseen threat: anti-PL7 anti-synthetase mediated interstitial lung disease

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ABSTRACT

Anti-synthetase syndrome (ASS) is a rare autoimmune disorder within the spectrum of idiopathic inflammatory myopathies, defined by the presence of anti-aminoacyl-tRNA synthetase antibodies, most commonly anti-Jo1. Less frequent antibodies, such as anti-PL7, are associated with predominant pulmonary involvement and minimal muscle symptoms. Interstitial lung disease (ILD) is the most serious complication and may be the initial or sole presenting feature. Due to its rarity and atypical manifestations, anti-PL7-associated ASS can be underdiagnosed, especially in elderly patients presenting with unexplained ILD. Herein this case reports the case of a 74-year-old woman who presented with exertional dyspnea and a persistent dry cough for three months. Examination revealed Raynaud's phenomenon, hyperkeratotic skin changes on the hands (mechanic's hands), and digital ulceration. Imaging confirmed bilateral ground-glass opacities consistent with ILD. Autoimmune serology showed a positive ANA (1:320, speckled pattern) and anti-PL7 antibody, with no evidence of myositis. Based on Connors et al's criteria, a diagnosis of anti-synthetase syndrome was made. The patient received high-dose intravenous corticosteroids and cyclophosphamide, with limited clinical improvement. She was discharged on request on long-term oxygen support and oral steroids for outpatient follow-up. This case highlights the diagnostic challenge of ASS, especially when classical myositis features are absent. Anti-PL7-positive patients often present with isolated ILD, carrying a poorer prognosis compared to anti-Jo1-positive patients, and may not respond to standard immunosuppression. Early recognition of dermatologic signs and prompt antibody testing are essential for diagnosis. Aggressive initial therapy may be required, and biologic agents should be considered for refractory cases.

Keywords: Antisynthetase syndrome, Autoimmune disorder, Anti-PL7, Interstitial lung disease, Idiopathic inflammatory myopathy

INTRODUCTION

Anti-synthetase syndrome (ASS) is a rare autoimmune syndrome, often considered as a part of a wider spectrum of disorders called 'idiopathic inflammatory myopathies'.[1] It is characterized by the presence of antibodies against amino-acyl transfer RNA synthetase (ARSA), the most common antibody being anti-Jo1, seen in approximately 73% of the patients.[2] Less commonly, other antibodies like anti-PL7 (anti-threonyl), anti-PL12 (anti-alanyl), anti-OJ (anti-glycyl), anti-KS (anti-asparaginyl), anti-ZO (anti-phenylalanyl), and anti-tyrosyl tRS antibodies may be seen.[2,3] ASS usually presents with myositis, non-erosive arthritis, and interstitial lung disease (ILD). Other less common manifestations include fever, mechanic's hands, and Raynaud's phenomenon. ASS is an uncommon condition, with an estimated incidence of 0.56 cases per 100,000 people and a prevalence of 9.21 per 100,000 individuals.[4] It is 2-3 times more common in females, and the mean age of onset varies between 43 and 60 years.[5] The

presence of anti-Jo1 antibody has been well linked to the development of ILD in patients with ASS.[3] However, the manifestations in patients with anti-PL7 antibodies have not been extensively studied, possibly because these antibodies are often rare (present in 3-4% cases).[6] Herein, we describe a rare case of a 74-year-old female with anti-PL7-positive ASS presenting with interstitial lung disease. This case report highlights the need to consider ASS in unexplained ILD, given its therapeutic and prognostic significance. The outcomes often vary by antibody type, with anti-PL7 ASS linked to a poorer prognosis than anti-Jo1, requiring more aggressive management and subsequent follow-up.[1,2]

CASE REPORT

A 74-year-old female presented to the emergency department with complaints of dyspnoea on exertion and a persistent dry cough for 3 months, which had become progressively worse over a week. There was no history of fever, chest pain, or hemoptysis. Past medical history was significant for multiple hospitalizations for pneumonia managed with antibiotics. There was no significant family or social history. On arrival, vitals were: blood pressure: 130/70 mmHg, pulse: 100/min, respiratory rate: 22/min, SpO_2: 75% on room air. Auscultation revealed normal S1-S2 and bilateral basal inspiratory crackles. Skin examination showed peeling and hyperkeratosis of hands (Figure 1), Raynaud's phenomenon, with trophic skin changes showing ulceration and gangrene of digits (Figure 2). Examination of other organ systems was unremarkable. The patient was immediately put on oxygen support and was thoroughly investigated. Initial labs revealed normal complete blood count (CBC), normal renal and liver function tests. Chest X-ray showed bilateral basal infiltrates. Computed tomography (CT) chest showed bilateral ground-glass opacities suggesting interstitial lung disease (Figure 3).

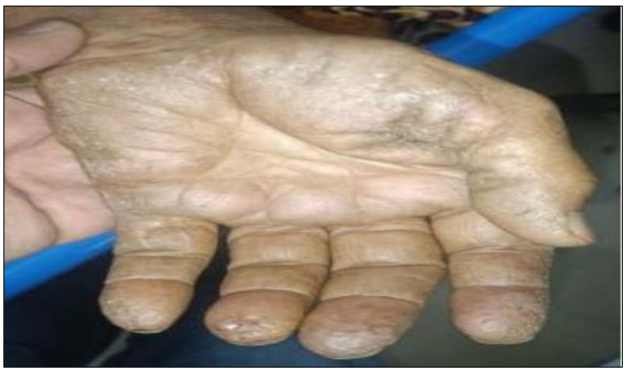

Figure 1: Peeling and hyperkeratosis of the hand.

The 2D echo was normal. The presence of dermatological findings, Raynaud's phenomenon, and pulmonary symptoms raised the suspicion of autoimmune pathology. Surprisingly, ANA titres came out to be 1:320 (speckled pattern), and the anti-PL7 antibody was positive. Anti-Scl-70, ANCA, and other autoimmune antibody tests were negative. There were no clinical or laboratory features of myositis (normal muscle enzymes), arthritis, or systemic lupus erythematosus. Based on Connors et al's criteria, the diagnosis of ASS was established. The patient received intravenous methylprednisolone (0.5 g/day for 3 days), followed by a single dose of IV cyclophosphamide (1 g). Despite initial management, there was limited clinical improvement. Given the guarded prognosis and patient's preference, she was discharged on long-term oxygen support and oral steroids, with planned outpatient follow-up.

Figure 2: Ulceration and gangrene of digits.

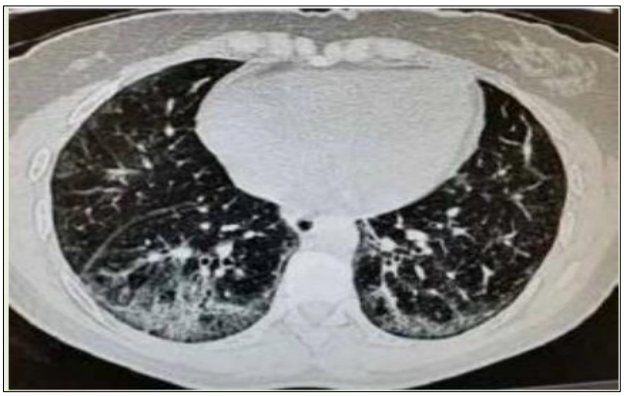

Figure 3: Bilateral ground-glass opacities on HRCT chest.

DISCUSSION

ASS is an autoimmune disorder characterized by the formation of autoantibodies against aminoacyl transfer RNA synthetases, which are a group of cytoplasmic and mitochondrial enzymes necessary for RNA transcription and protein synthesis.[1] Although not completely understood, the etiopathogenesis is believed to involve a breakdown in immune tolerance and increased self-reactivity of the immune system, particularly in genetically predisposed individuals when exposed to certain environmental triggers.[7] Despite being considered a part of idiopathic inflammatory myopathies, patients with ASS may not have classical symptoms of myopathy at the time of presentation; however, muscle involvement

(predominantly proximal muscles) can be seen at later stages of the disease.[8]

The most common extramuscular manifestation is ILD, seen in approximately 67-100% of the cases.[1,5] Other clinical features include fever, arthritis, Raynaud's phenomenon, digital ischemia, and dermatological findings of mechanic's hands and hiker's feet (scaly, fissured, hyperkeratotic plaques). The diagnosis of ASS can be made using the diagnostic criteria proposed by Connors et al and Solomon et al (Tables 1 and 2).[9,10]

Table 1: Connors et al criteria for the diagnosis of ASS.

Definitive criteria	Presence of an anti-aminoacyl tRNA synthetase antibody
PLUS	
One or more of the following	Raynaud's phenomenon, arthritis, interstitial lung disease, fever (not attributable to another cause), and mechanic's hands (thickened and cracked skin on hands, particularly at fingertips)

In the case described, a 74-year-old female with a history of recurrent pneumonia presented with progressive dyspnoea and dry cough. Further examination revealed classical features such as mechanic's hands and Raynaud's phenomenon, with additional evaluation confirming ILD on imaging and a strongly positive anti-PL7 antibody. The diagnosis of anti-synthetase syndrome was made using the criteria proposed by Connors et al. Notably, anti-PL7-associated ASS is often associated with a predominantly pulmonary phenotype and carries a worse prognosis than Jo-1-associated disease.[1,2] Interestingly, despite the severity of the lung disease, the patient did not exhibit overt muscle weakness or elevated muscle enzymes, consistent with the findings seen especially in anti-Jo1 negative patients, and may delay diagnosis due to the absence of classical myositis.

ILD can present as chronic dyspnoea, dry cough, fine inspiratory crackles on auscultation (often in later stages), and a restrictive pattern on pulmonary function tests. Radiologically, ASS associated ILD can be confirmed on HRCT chest, depicting classical findings of reticular or ground glass opacities, predominantly involving the basilar zones of the lungs, that hug or 'pancake' the diaphragm.[3] Traction bronchiectasis with/without consolidation might be present. Broncho-alveolar lavage or lung biopsies are not routinely required. Our patient exhibited bilateral basal infiltrates with ground-glass opacities, consistent with nonspecific interstitial pneumonia (NSIP) or organizing pneumonia (OP) patterns, which are commonly observed in ASS-associated ILD.[1] Pulmonary hypertension can also be seen primarily due to the autoimmune nature of the disease, or secondary to ILD, however, the echo in our patient was normal.[1]

Table 2: Solomon et al criteria for the diagnosis of ASS.

Definitive criteria	Presence of anti-aminoacyl tRNA synthetase antibody
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

Anti-PL7-mediated ASS is closely associated with the overlap with other autoimmune diseases like polymyositis, dermatomyositis, and systemic sclerosis.[5,6] Features of arthritis may resemble the symmetrical polyarthritis seen in rheumatoid arthritis (RA), and ASS should be considered as a differential diagnosis in atypical cases of suspected RA.[5] The link between ASS and the development of malignancy remains uncertain. While some studies, including a large cohort analysis, have found no significant increase in cancer incidence among ASS patients compared to the general population, other case series and individual reports have documented the occurrence of various malignancies (breast, cervix, stomach, nasopharynx) at different intervals following the diagnosis of ASS.[7] Overall, age-appropriate cancer screening is necessary for all patients of ASS. Therapeutically, immunosuppressants remain the mainstay of initial treatment in ASS. High-dose corticosteroids are often used adjunctively with cyclophosphamide, azathioprine, or mycophenolate mofetil for disease modification.[8]

In our case, the patient received IV methylprednisolone pulses followed by cyclophosphamide. However, the lack of clinical improvement correlates with the refractory nature of PL7-positive ILD. There is growing interest in the use of biologics such as rituximab for steroid-resistant cases, supported by data suggesting improved pulmonary function and disease control.[8]

CONCLUSION

This case reinforces the importance of considering ASS in the differential diagnosis of unexplained ILD, particularly in the elderly population, were non-infectious, autoimmune causes may be under-recognized. The recognition of systemic signs such as mechanic's hands and Raynaud's phenomenon can aid early diagnosis. Furthermore, the detection of anti-PL7 antibodies necessitates close pulmonary monitoring and early initiation of aggressive immunosuppression due to the progressive course and refractory nature towards standard treatments. Given the rare nature and severity of the disease, further research is required to develop evidence-based guidelines for optimal management and to improve the overall prognosis in patients with ASS.

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