

# New Insights into Antisynthetase Syndrome

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## ABSTRACT

*Antisynthetase syndrome (ASS) is a rare chronic autoimmune disorder (2–3 times more common in women than in men), associated with interstitial lung disease (the most important feature), dermatomyositis (DM), and polymyositis (PM). The cause of ASS is unknown. Recent developments in immunology have improved our knowledge and it is now possible to classify ASS according to the presence of myositis specific autoantibodies. The hallmark of ASS is the presence of serum autoantibodies directed against aminoacyl-tRNA synthetases (anti-ARS involved in protein synthesis). ASS is due to IgG antibodies directed against the enzyme synthase. Antisynthetase antibodies (ASAb) include: anti-histidyl- (anti-Jo-1, being the best known), anti-threonyl- (anti-PL-7), anti-alanyl (anti-PL-12), anti-isoleucyl- (anti-OJ), anti-glycyl- (anti-EJ), anti-asparaginy- (anti-KS), anti-Wa, anti-tyrosyl- (anti-YRS), anti-phenylalanyl-transfer RNA synthetase (anti-Zo), and anti-signal recognition particle (anti-SRP). Anti-Jo-1 is the most common ASAb (in ~20-30% of PM/DM patients).*

**Keywords:** antisynthetase syndrome, antisynthetase antibodies, diagnosis, prognosis

## INTRODUCTION

In recent years, antisynthetase syndrome (ASS) has been recognized as an important cause of autoimmune inflammatory myopathy in a subset of patients with dermatomyositis (DM) (1).

The inflammatory myopathies comprise a heterogeneous group of chronic autoimmune disorders of unknown etiology. Idiopathic inflammatory myopathies are characterized by muscle weakness, electromyography (EMG) histological and biochemical features of muscle inflammation (2).

The idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of rare chronic

autoimmune diseases that include polymyositis (PM) and DM. From an immunological view, PM is characterized by a cell-mediated autoimmune response directed towards myofibers, as assessed by abnormal ubiquitous MHC class I/HLA-ABC myofiber re-expression and endomysial CD8 T-cells surrounding and invading non-necrotic fibers (3). Dermatomyositis is a vasculopathic myopathy with perimysial vascular inflammation, myofiber ischemic lesions, and endomysial microangiopathy with complement activation. In most cases, these PM/DM patients with ASAb also have interstitial lung disease (ILD), the major determinant of morbidity and mortality in the ASS (4).

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Antisynthetase syndrome was first described by Marguerite and coworkers in 1990. Antisynthetase syndrome is a rare inflammatory muscle disease related to DM and PM. The cohort studies have indicated that 20-25% of patients diagnosed with PM or DM have ASAb (5). Traditionally, IIMs have been classified into three groups; PM, DM and inclusion body myositis. Antisynthetase syndrome is frequently revealed by interstitial lung disease and arthritis. Because inflammatory arthritis mimics rheumatoid arthritis (RA), ASS should be considered in atypical cases (6).

In recent years, ASS has been recognized as an important cause of autoimmune inflammatory myopathy in a subset of patients with PM and DM. It is classified as a chronic autoimmune disease. In ASS, the extent and severity of myopathy may vary considerably. The myositis is less severe than in DM and PM without ASS (7). Physicians should be familiar with its variety of clinical presentations and should include it in the differential diagnosis in patients presenting with unexplained ILD (the most important feature). Interstitial lung disease in patients with ASS and no evidence of myositis is rare and may precede other disease manifestations (8).

As a syndrome, this condition is poorly defined. Antisynthetase syndrome is 2-3 times more common in women than in men. The age at onset among adults ranges from 19 to 82 years with a mean age at onset varying from 43 to 60 yrs. Very few children and adolescents with ASS have been reported (9).

The morbidity and mortality of ASS are usually linked to the pulmonary findings. All the published studies confirm that the HLA-DRB1\*0301, DQA1\*0501 and DQB1\*0201 genes are risk factors for development of ASS with anti-Jo-1 positives (10). As represent a rather newly defined disease entity whose etiopathogenesis remains incompletely understood (11). □

### CLINICAL FEATURES

Antisynthetase syndrome is recognized as a subset of the IIMs with a relatively homogeneous clinical profile (12).

The clinical characteristics of published cases vary substantially. The main clinical features of AS are: fever, myositis (muscle inflammation), polyarthritis (inflammation in several

joints), ILD (non-specific inflammation of the lungs), "mechanic's hands" (thick, cracked skin usually on the palms and radial surfaces of the digits), Raynaud phenomenon, rash, Gottron's papules, lesions on metacarpophalangeal and interphalangeal joint areas (13). Raynaud's phenomenon is early in 2/3 of patients and can precede the myositis in years. It is more frequently found in anti-Jo-1 positive patients. At onset of disease, respiratory symptoms are present in 40-60% of patients (14). Most frequently, patients complain of shortness of breath and cough. In many patients, the symptoms of ILD such as dyspnea can be the presenting symptom. The onset of ILD preceded the onset of myositis in 33%, while myositis and ILD developed simultaneously in 60% (15). Myositis preceding ILD was observed in only 7% of the patients. Most reports indicate that the frequency of ILD in the ASS is in the range of 70-95% (16). The lung disease may present very acute, subacute or asymptomatic ILD with development of clinically apparent ILD later on. The type of onset may be classified into three groups, type I acute, type II gradual and type III asymptomatic (a classification may be important for predicting outcome and selecting optimal treatment) (17). A diagnosis of ASS should be considered even in the absence of myositis. ASS could appear as an isolated diffuse interstitial pneumonia (18).

"Mechanic's hands" are a hyperkeratosis, scaling, and fissure in fingertips and lateral aspects of the fingers, being more frequently found in the ASS and interstitial lung disease (19).

Because inflammatory arthritis mimics RA, ASS should be considered in atypical cases. Criteria for the AS have proposed recently (20). The oesophageal involvement and pulmonary hypertension could suggest overlapping systemic sclerosis (in association with anti-PL-12 antibodies) (21). Any skin sclerosis has been noticed in case of anti-PL-12 ASS. In general, approximately 14% of IIMs affect women of reproductive age, and the presence of active signs significantly increases the risk of spontaneous abortion, intrauterine death or retardation, and premature birth (22). □

### AUTOANTIBODIES

Antisynthetase syndrome is a serological subtype of IIMs characterized by the production of ASAb and the development of DM or

PM, symmetrical non-erosive arthritis or arthralgia, interstitial lung disease, mechanic's hand, fever, Raynaud's phenomenon, and photosensitivity, accompanied by some less frequent manifestations, such as cutaneous vasculitis, calcinosis cutis, periungual telangiectasia, sclerodactylia, glomerulonephritis, pulmonary hypertension, carditis and cardiomyopathy (23).

Antibodies reacting with a single synthetase are found in approximately 20-40% of the adult patients with PM and 5% of the patients with DM. Serum from an individual patient usually contains antibodies against one synthetase only, but antibodies to all the five synthetases have been described in the same serum (21). Antibodies to Jo-1 are, by far, the most commonly detected autoantibodies. Antibodies to PL-7, PL-12, OJ, and EJ are found but to a lesser extent (24). Rheumatoid factor is found in increased frequency, especially in patients with articular involvement. Sera containing anti-Jo-1 autoantibodies may also have antibodies against other intercellular autoantigens and especially to SS-A (25). Anti-Jo-1 antibodies are found in ~20% of adult patients with PM or DM. Anti-PL-12 antibodies are particularly rare (<2% of myositis) (26).

Appropriate laboratory testing with measurement of specific autoantibodies may help in the early diagnosis and treatment of ASS. In patients with myositis, the lung is commonly involved, and the presence of anti-aminoacyl-transfer RNA synthetase (anti-ARS) antibodies mark the presence or predicts the development of ILD (27). The hallmark of AS is the presence of serum autoantibodies directed against ARS. These are cellular enzymes involved in protein synthesis (28). Antisynthetase antibodies include: anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-Wa, anti-YRS, anti-Zo, and anti-SRP. Autoantibodies to eight of the ARS -the most well-recognized is anti-histidyl (Jo-1) - have all been implicated in the pathogenesis of ASS (29).

The most common antibody is "Anti-Jo-1" named after the John P, a patient with PM and ILD detected in 1980. This antibody is commonly seen in patients with pulmonary manifestations of ASS. The Jo-1 antigen was identified as histidyl-transfer RNA synthetase (30). Anti-Jo-1 antibodies are frequently present (68-87%). If 25% of the PM/DM patients have ASAb, then the prevalence of the ASAb should

be at least 3-4/100 000 (prevalence of PM/DM is around 15/100 000 (31).

The finding of ILD in 64-100% of patients possessing anti-Jo-1 autoantibodies underlines the close association between ASAb and ILD. In one study, ASS was found in 3% of DM without ILD as opposed to 63% in DM with ILD (32). The frequency of ILD appears to be highest among ASS patients who are anti-PL-12 positive, as ILD was diagnosed in 90-100% of PL-12 positives as compared to 50-75% in Jo-1 positives (33). Due to low numbers of non-Jo-1 positive ASS patients reported, it is prudent that these differences are considered and interpreted cautiously. Patients with anti-PL-7 autoantibodies may also show different clinical features when compared to Jo-1 positives (34). Anti-PL-7 autoantibodies have been associated with milder muscle weakness and almost all patients reported have had ILD. Anti-SS-A antibodies, anti-Ro52 in particular, occur in more than 50% of AS (35). They have been associated with more severe lung fibrosis. The clinicians must be aware of an isolated ILD form of anti-PL-12 syndrome and widely screen for anti-PL-12 positivity. The lack of screening for anti-PL-12 is one of the reasons why anti-PL-12 positivity is probably underestimated. The autoantibodies produced in different forms of myositis can be divided into myositis-specific and myositis-associated autoantibodies (36). A subgroup of myositis-specific autoantibodies consists of antibodies directed against ARS, i.e. the ASAb. The most commonly detected type of myositis-associated antibodies in the ASS is the anti-SS-A antibody. It has been demonstrated that the presence of ASAb is the strongest predictive factor for the development of interstitial lung disease in idiopathic inflammatory myositis, and the coexistence of anti-Jo-1 and anti-SS-A antibodies is associated with a more severe (37). Anti-Jo-1 antibodies are found in 25-30% of patients with inflammatory myopathy and other ASAb in 1-5%. It has been reported that anti-Jo-1 antibodies are closely associated with myositis, whereas patients with anti-PL-12 and anti-KS antibodies are more likely to have ILD without clinical evidence of myositis (38). More recently described anti-ARS antibodies might confer a phenotype that is distinct from that of anti-Jo-1 positive patients and is characterized by a lower incidence of myositis and a higher incidence of ILD. Anti-ARS autoantibodies have been found in pa-

tients with PM/DM. Anti-OJ antibodies are also found in PM/DM patients, although the frequency is low (in less than 2% of all patients with PM/DM). The presence of anti-PL-7 antibodies is closely associated with PM/DM- systemic sclerosis (SSc) overlap as well as ILD (39). □

## DIAGNOSIS

The clinical presentation is a clue to the diagnosis of ASS. Special investigations help to support the diagnosis. These may include the following depending on the clinical context: muscle enzymes (e.g., creatinine kinase (CK) and aldolase, these are often elevated), ASAb, electromyography (EMG), magnetic resonance imaging (MRI) of affected muscles, muscle biopsy, lung function tests, high resolution computed tomography scan (CT) of the lungs biopsy (40).

Diagnostic criteria require one or more ASAb (which target tRNA synthetase enzymes), and one or more of the following three clinical features: interstitial lung disease, inflammatory myopathy, and inflammatory polyarthritis affecting small joints. Patients presenting with ILD should be carefully evaluated for ASS (41).

In patients who present with features mimicking but atypical for RA (negative cyclic citrullinated peptide antibody status, and non-erosive arthritis), ASS should be considered (due to its potential overlap). A diagnosis of probable ASS would be met when either ILD and/or inflammatory is present in a patient with ASAb (42). Approximately 5-8% of ASS cases manifest as overlap syndromes with another connective tissue disease such as systemic lupus erythematosus, SSc and Sjögren's syndrome (43). □

## PROGNOSIS

Antisynthetase syndrome is a rare disease in the idiopathic inflammatory myopathy group and is characterised by the presence of ASAb. It has a generally poor prognosis, mainly due to irreversibly progressing pulmonary involvement. The interstitial lung damage is important because it conditions the vital prognos-

tic. The disease course is usually chronic and ASS is most likely associated with decreased survival (44).

The prognosis of ASS depends of ILD. The value of a lung biopsy in ASS cannot be over-emphasized, as it serves to describe the underlying etiology of ILD, guide therapy, and estimate prognosis (45).

Biomarkers for disease activity and disease severity have been incompletely studied in ASS. In the initial phases of disease, an acute phase response may be evident. Some case studies have reported various malignancies occurring within 6–12 months of the diagnosis of ASS. Older age at onset (>60 years), presence of malignancy, and negative anti-nuclear (ANA) antibody test confer a worse prognosis. The morbidity and mortality of the disease are usually linked to the pulmonary findings (46). The levels of anti-Jo-1 autoantibodies correlated with disease activity. The adverse clinical outcome, with relatively high morbidity and mortality rates compared with those of other forms of inflammatory myosites, is primarily due to irreversible damage of the lung parenchyma manifested as interstitial lung disease. Anti-Jo-1 myositis carries a worse prognosis in comparison with the other inflammatory myopathies (47). □

## CONCLUSION

Antisynthetase syndrome is a rare chronic autoimmune disorder of unknown cause. It includes pulmonary interstitial disease, arthritis, Raynaud's phenomenon, "mechanic's hands", and the presence of autoantibodies against ARS. It rarely presents with symmetric arthritis as the initial manifestation. ILD and myositis represent the most important clinical features of ASS. Tests for anti-Jo-1 should be obtained in patients with inflammatory muscle disease, as well as a screening for ILD. This paper illustrates the importance of having a high index of suspicion for ASS in patients with ILD. The diagnosis is important because of its prognostic and therapeutic implications.

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