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The Antisynthetase Syndrome

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1. Introduction

The antisynthetase syndrome (ASS) was first described by Marguerie and coworkers in 1990 as a triad of polymyositis, diffuse interstitial lung disease (ILD) and serum autoantibodies to aminoacyl transfer RNA synthetases (anti-ARS) (1). Later, cohort studies have indicated that 20-25 % of patients diagnosed with polymyositis (PM) or dermatomyositis (DM) have anti-ARS antibodies (2-4). In most cases, these anti-ARS+ PM/DM patients also have ILD. The ILD is, in fact, the major determinant of morbidity and mortality in the ASS.

The most common of the anti-ARS, anti-Jo-1, was first described in 1980. Three years later, the Jo-1 antigen was identified as histidyl-tRNA synthetase (5;6). In recent case series, the anti-Jo-1 antibody accounts for 68-87% of the anti-ARS observed in ASS (7-9). The seven other anti-ARS identified (Table 1) are all rare, but their relative frequencies have not been extensively studied (7;8). With very few exceptions, each patient has only one anti-ARS antibody (10). More than half of the anti-ARS+ patients also possess anti-SSA autoantibodies (8;9;11) and then most frequently anti-Ro52 (11).

2. Disease definition

At present, there is no internationally accepted definition of ASS and no classification criteria have been established. Consequently, the clinical characteristics of published ASS cases vary substantially. Some studies have included all patients with anti-ARS, regardless of clinical manifestations, while others have selected patients according to predefined clinical features.

As it is generally agreed upon that ILD is the clinical hallmark of ASS, this clinical feature is regarded mandatory for the diagnosis of ASS by most workers. The finding of ILD in 64-100 % of patients possessing anti-Jo-1 autoantibodies underlines the close association between anti-ARS and ILD (3;9;12-17). In one study (3), anti-ARS were found in 3% of DM without ILD as opposed to 63% in DM with ILD, further emphazising the importance of pulmonary disease in ASS. Thus, ILD is an important but not a compulsory feature of ASS diagnosis.

In ASS, the extent and severity of myopathy may vary considerably (18). Usually, the myositis is less severe than in DM and PM without anti-ARS. Some cases develop clinically overt myositis, others present with hypomyopathic or even amyopathic disease. Thus, a diagnosis of ASS should be considered even in the absence of myositis.

Criteria for the ASS have been proposed recently (19). These criteria suggest that a diagnosis of ASS could be made in the presence of positive serologic testing for an anti-ARS plus one

of the following; myositis, ILD, arthritis, fever, Raynaud`s phenomenon or Mechanic`s hands. We feel, however, that ILD and myositis represent the most important clinical features of ASS, hence at least one of them should be included in such classification criteria. It is thus tentatively suggested that a diagnosis of definite ASS should require anti-ARS and either ILD and/or inflammatory myopathy plus at least one other clinical criterion commonly found in this syndrome (Table 2). A diagnosis of probable ASS would be met when either ILD and/or inflammatory is present in a patient with anti-ARS.

3. Epidemiology

ASS is a rare disease, but its frequency in the general population is not known. In most studies, the estimated population prevalence of PM/DM is around 15/100 000 (refs). If 25% of the PM/DM patients have anti-ARS, then the prevalence of the anti-ARS should be least 3-4/100 000. ASS has been reported in both Caucasian, Asian and Afro-American patients, but it is known if the prevalence of the disease differs between ethnic groups.

The age at onset among adults ranges from 19 to 82 years with a mean age at onset varying from 43 to 60 yrs (2;3;9;12;20). Very few children and adolescents with ASS have been reported. A female dominance, with about twice as many females as men affected, has been found in most series (3;9;12).

4. Pathology

Muscle. The results of histological examination of muscle tissue are somewhat conflicting. In one early study (21), the authors demonstrated prominent perimysial inflammation with fragmentation and perifascicular myopathic changes whereas endomysial inflammation was uncommon. Consequently, these findings suggested a dermatomyositis pattern in ASS rather than polymyositis. In subsequent reports, the picture has become less clear as a polymyositis pattern has been more commonly observed than a dermatomyositis pattern (13;22). Some studies have, however, concluded with similar frequencies of polymyositis and dermatomyositis in ASS (8;23). In our own experience, the majority of cases exhibit changes compatible with a diagnosis of dermatomyositis. The frequent occurrence of dermatological lesions to some extent supports a closer relationship to dermatomyositis than to polymyositis. Moreover, the frequent findings of vasculopathic changes at nail fold capillaroscopy may also favor a vasculopathic genesis rather than a myopathic one. Further studies of muscle and vessel pathology in ASS are clearly warranted.

Lung. Limited pathologic case series have shown that the ILD in ASS encompasses various histologic subtypes and both non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), cryptogenic organizing pneumonia (COP) and diffuse alveolar damage (DAD) may be diagnosed (20;24;25).

5. Genetics

Most works on the genetics of ASS have been confined to candidate genes in the very polymorphic Human Leukocyte Antigen (HLA) region. All the published studies confirm that the HLA-DRB1*0301, DQA1*0501 and DQB1*0201genes are risk factors for the development of anti-Jo-1+ ASS (7).

6. Disease mechanisms

Already in the 1980's it was speculated that the *in vivo* formation of anti-histidyl tRNA synthetase antibodies was driven by viral infections, possibly through molecular mimicry between viral proteins and histidyl tRNA synthetase (HRS) (26). The basic idea was that the cross-reactive anti-HRS (anti-Jo-1) caused damage through its ability to inhibit HRS and/or through formation of immune complexes . Although never backed by experimental evidence, the viral hypothesis is still highlighted in many reviews on ASS.

More recent studies have focused more on auto-antigenic properties of the HRS molecule per se. A very interesting finding in this respect, was that soluble HRS acted as a chemokine and attracted CD4+ T cells (27). In inflamed tissues marked by cell destruction and high concentrations of free HRS this mechanism could contribute to the breaking of tolerance (27). Another observation has been that HRS expression is upregulated in regenerating muscle cells. Areas with active myositis should thus have very high expression of HRS. Together, these studies indicate that muscle inflammation *per se* may increase the levels of HRS and the likelihood of initiating immune responses to HRS, at least in genetically susceptible individuals. Whether similar mechanisms are operative in the lung is not known, but it has been suggested that HRS adopts a more immunogenic conformation in the lung than in blood cells (28). Previously, it was shown that T cells from the blood of both ASS patients and healthy individuals often recognized HRS (29). No data on T cell or B cell reactivities to HRS in inflamed muscle or lung exist, but CD4+ T cells from the bronchoalveolar lavage fluid of two anti-Jo-1+ ASS patients have been shown to contain the same T cell receptor gene family (30).

7. Clinical features

Disease onset. At onset of disease, respiratory symptoms are present in 40-60 % of patients. In one case series (3), the onset of ILD preceded the onset of myositis in 33%, while myositis and ILD developed simultaneously in 60%. Myositis preceding ILD was observed in only 7% of the patients. At onset of disease, patients may also present with constitutional symptoms such as fever (seen in 35-90% of the patients), loss of appetite and weight loss (2;3;31;32). Other features seen at onset of ASS are joint pain, arthritis, tenosynovitis, and Raynaud`s phenomenon.

Respiratory symptoms. The reported frequency of ILD in ASS varies, depending on patient selection and the sensitivity of the tests applied to detect ILD (18). Most reports indicate that the frequency of ILD in the ASS is in the range of 70-95 % (3;9;12-14;16;31), but some few case series have found lower frequencies (2;33). The frequency of ILD appears to be highest among ASS patients who are anti-PL12 positive, as ILD was diagnosed in 90-100% of PL-12 positives as compared to 50-75% in Jo-1 positives (20;34).

Most frequently, patients complain of shortness of breath and cough. The lung disease may present very acute, subacute or asymptomatic ILD with development of clinically apparent ILD later on. Consequently, the type of onset may be classified into three groups, type I acute, type II gradual and type III asymptomatic. Such a classification may be important for predicting outcome and selecting optimal treatment.

Muscle weakness is reported at onset of disease in 20-50 % of patients. Most commonly, it involves the proximal and axial muscles (31;33). Patients may also report muscular stiffness and pain. The muscular component is thus indistinguishable from that seen in PM and DM.

However, muscle involvement is less frequent and usually milder than in non-ASS patients (18). The reported accumulated incidence of myositis ranges from 40-94% (3).

The tendency to milder myositis among cases with PL-12 was further supported by the findings of a frequency of 60% PL-12 among patients without clinically evident myositis (35). ASS may also present with a hypo- or even amyopathic dermatomyositis pattern.

Skin symptoms. Dermatological features are frequently encountered in ASS, being observed in 7-70% of the various reports (3;9;12;14;32;33). Mechanic`s hands appear as fissuring and scaling of the lateral and distal aspects of the hand, and is rarely seen in conditions other than ASS. In ASS, this clinical feature is seen in 0-32% of cases (3;9;12;31-33). Histological examinations of biopsy specimens of Mechanic`s hands have displayed mononuclear cell infiltrates around the blood vessels and mucin deposition in the dermis (36). As in DM, heliotrophic rash is seen in 7-38% (3;14;31;36). Gottron`s lesions appearing on bony prominences such as finger knuckles are observed in 9-69% of patients (3;31;33;36). Microvascular changes presenting as periungual erythema may also be seen (1). Although infrequently reported, V-sign and Shawl-sign may also develop in ASS.

Joint pain or swelling. Arthritis is a frequent clinical manifestation of ASS, being seen in 42-82% of reported cases (2;3;9;12;14;36). Although rare, a subluxating arthropathy involving the distal joints of the fingers (37) is a rather characteristic feature of ASS. ASS may also present as a symmetric inflammatory polyarthritis initially indistinguishable from that of rheumatoid arthritis (38). Tenosynovitis has also been reported. Joint pain without signs of inflammation also occur frequently in ASS (66-89%) (2;32).

Gastrointestinal symptoms. Involvement of the gastrointestinal canal is usually restricted to the distal parts of the oesophagus. The incidence of distal oesophageal dysmotility evidently depends on the tests used to identify the abnormality, but is diagnosed in 5-52% of the reports (9;12;31-33). Oesophageal disease is an important clinical feature of ASS as dysphagia leading to aspiration may further damage the already compromised pulmonal function. In patients with end stage interstitial lung disease, this manifestation may restrict patients`possibilitis of being accepted for lung transplantation. Routine examinations using barium enema x-ray is therefore recommended to diagnose oesophageal dysmotility which should be treated vigorously.

Vascular symptoms. Clinical signs of vasculopathy may appear. Raynaud`s phenomenon accompanies ASS in 30-50 % of cases (2;3;9;12;14;20;32). Skin necrosis and ischemic ulcera have also been observed in ASS (39). Pulmonary arterial hypertension has not been subjected to studies aimed at detecting its true incidence that is using echocardiography to screen all cases. It is, however, infrequently observed in DM and PM, and in one study (43) PAH was diagnosed by echocardiography in 16 of 198 consecutive cases (0,8%). It was thus concluded that mild to severe PAH is a rare complication of IIM (43). In ASS, cases with fatal (40) and acute (41-43) PAH have been observed. In our patient cohort of 67 cases of ASS, PAH diagnosed by right heart catherization was observed in nine cases and represented a frequent cause of death in this syndrome.

Other clinical features seen rather commonly in ASS include, sicca symptoms (8-54%) (2;9;31;32), sclerodactyli (12) and subcutaneous calcinosis (44). Glomerulonephritis may be seen (45).

Clinical features stratified by anti-aaRS. In general, the similarities of the clinical features among patients possessing different ASS are rather impressive. Some differences have, however, been suggested. Due to low numbers of non-Jo-1 positive ASS patients reported, it is prudent that these differences are considered preliminary and interpreted cautiously.

Among PL-12 positive ASS, the histological features of ILD is predominantly of the NSIP pattern (20), while myositis is mostly mild (34). In one study (20), CK levels increased to up to twice the normal level in only two individuals. Interestingly, two of these cases were diagnosed with PAH.

Patients with anti-PL7 autoantibodies may also show different clinical features when compared to Jo-1 positives. Anti-PL-7 autoantibodies have been associated with milder muscle weakness (46) and almost all patients reported have had ILD (46;47). Seven patients with anti-OJ autoantibodies were described by Sato et al (48) of whom all had ILD, and four presented muscle weakness and polyarthritis. None had Raynaud`s phenomenon or sclerodactyli. In a study of eight patients with anti-KS autoantibodies, 88% had ILD 25% (49).

Other clinical associations. Anti-SSA antibodies, anti-Ro52 in particular, occur in more than 50% of ASS (8;11) and have been associated with more severe lung fibrosis (13). In one study (50) patients without anti SSA autoantibodies more often lacked fibrosis on the initial CT scans compared to patients possessing these autoantibodies. In another study (33), patients with such autoantibodies seemed to be predisposed to the development of a more severe ILD as assessed by both HRCT and lung function tests.

8. Disease associations

Cancer. The increased risk of cancer in DM is well documented. In one study of 103 patients with DM, 15 patients had concomitant malignancy (51) and the risk of cancer was highest among those without myositis-specific autoantibodies. Thus, ASS was suspected to provide some protection against the development of cancer. However, subsequent case reports of concurrent ASS and cancer appeared (52;53), clearly showing that ASS does not provide total protection against development of malignant disease. Whether or not the risk of cancer is less in ASS compared to other IIM remains to be studied. However, in a recent study from Japan , 4.8 % of patients with DM and concomitant cancer possessed anti-Jo-1 antibody as opposed to 15.9 % in DM patients without malignant disease (54). Although these findings may indicate some protective effect of anti-ARS against development of malignancy, further studies are warranted to corroborate such an association.

Other immune-mediated disorders. Approximately 5-8 % of anti-ARS cases manifest as overlap syndromes with another connective tissue disease such as systemic lupus erythematosus, systemic sclerosis and Sjøgren`s syndrome (55).

9. Evaluation and diagnosis

Assessment of the respiratory system. The diagnosis of ASS associated ILD is based on HRCT of lungs. Ground glass opacities, subpleural fibrosis and bronchiectasies, all due to compromise of the alveolar-capillary interface, may be observed early in the disease course. In some cases, the progression of ILD is severe, culminating in end stage pulmonal disease (honeycombing) after a rather short disease duration. In other cases, more limited abnormalities on HRCT are seen with little impact on lung function.

Lung function tests typically reveals a restrictive pattern with FVC or total lung capacity less than 80% of the predicted value for age and height and a decrease in the diffusing capacity for carbon monoxide. As lung function tests are readily reproducible and minimally invasive, such tests are recommended both for uncovering occult ILD and for

monitoring disease severity and disease progression. Lung biopsy offers unclear prognostic value (19), and is not recommended as a routine procedure in the evaluation of ASS.

Assessment of the musculoskeletal system. Evaluation of muscular involvement reveals in the majority of cases significant elevations of creatin kinase (CK). Compared to PM, the elevations of CK are often modest, in the majority of cases not exceeding 5000 IU/ml (2;3;9). In a few cases, however, the myositis is severe, exhibiting CK levels of several thousands and causing severe muscular weakness. MRI will in cases of clinically overt disease show oedema initially, and by time development of fibrosis, fatty deposits and atrophy. In hypomyopathic patients, MRI and CK levels may be normal in spite of muscular weakness. In other cases of hypomyopathic ASS, there are no muscle complaints while CK levels may be elevated or MRI may show signs of inflammation. Amyopathic ASS denotes a condition in which neither clinical symptoms nor laboratory abnormalities are present.

10. Assessment of other organ systems

Further evaluation of patients with ASS should include barium oesophageal x-ray which in more than 25 % of cases will reveal distal oesophageal dysmotility. Diagnosis and proper treatment of oesophageal dysmotility is important to avoid further damage to the lungs by aspiration. Another important disease complication is represented by pulmonary hypertension, either pre- or post capillary. Echocardiography should therefore be considered in the work-up of ASS. If PAH is suggested by echocardiography, the diagnosis should be verified by right heart catherization. Capillaroscopy may show reduced capillary density (56), and in two studies nailfold capillary changes were detected in 31 and 89%, respectively (3;9). Whether or not the occurrence of such vasculopathic changes differ between those with a histologic pattern of dematomyositis as oppsoded to polymyositis remains to be studied.

11. Evaluation of disease activity and disease severity

Biomarkers for disease activity and disease severity have been incompletely studied in ASS. Whether or not traditional markers for acute phase responses such as SR and CRP correlate with the actual activity and progression of disease remains to be seen. In the initial phases of disease, an acute phase response may be evident. One study suggested that levels of anti-Jo-1 autoantibodies correlated with disease activity (12), but these findings await confirmation. Thus, further research of ASS biomarkers for disease activity and disease severity should be strongly encouraged.

12. Treatment

Treatment of ASS is a challenge as no controlled trials have been performed and recommendations are based on single case reports and small patient series.

Standard treatment regimes include corticosteroids in addition to immunosuppressives. The role of corticosteroids in ASS associated ILD and their potential impact on disease course and patient survival is, however, unclear. Corticosteroids have little prospective evidence supporting their use (19), but their well documented intense anti-inflammatory efficacy suggests that they may be an essential part of initial therapeutic regimen. Moreover, the efficacy of corticosteroids in suppressing myositis is well documented. Thus, most

clinicians regard corticosteroids as a basic part of the therapeutic regimen of ASS. In acute or subacute pulmonary disease, high doses of oral glucocorticosteroids are usually administered (1 mg/kg/day). At some centers, intravenous methylprednisolon in doses of 500-1000 mg/day for 2-3 consecutive days are used as initial treatment. It should be noted, however, that there are no studies that clearly show the superiority of intravenous to oral corticosteroid treatment. In gradually developing ILD (type II) moderate doses of corticosteroids (0.5 mg/day initially) are most often preferred.

There is unfortunately no general consensus to what immunosuppressives that should be preferred in addition to corticosteroids in ASS. Although placebo-controlled trials are lacking, favorable experiences with cyclophosphamide in other connective tissue diseases have led many clinicians to prefer this drug as an adjunct to steroids. The choice of immunosuppressive treatment, however, clearly depends on the severity and extent of disease. In moderate to mild cases, a combination of oral glucocorticosteroids and either cyclophosphamide, azathioprine or methotrexate may be recommended. However, in our experience this regimen is insufficient in cases with acute and rapidly progressing ILD. Although based on retrospective case series, we recommend a combination of oral corticosteroids, cyclophosphamide and the anti-CD-20 monoclonal antibody rituximab as induction therapy in type I ASS (57). The efficacy of rituximab has also been reported in several case reports (58;59).

Others have experienced favorable effect of calcineurin inhibitors such as cyclosporin A (60) and tacrolimus (23). Another therapeutic option is mycophenolate mofetil and for myositis methotrexate may be valuable as an adjunct to corticosteroids. Clearly, multicenter randomised controlled studies of the efficacy of immunosuppressive therapy in ASS is highly warranted.

In end stage pulmonary disease, lung transplantation appears the only therapeutic option, but is rarely accepted due to oesophageal dysmotility. The dermatological manifestations may be favorable treated by hydroxychloroquine.

13. Disease outcome

The final outcome of ASS largely depends on the type and progression of ILD. Myositis have usually limited impact on outcome. The majority of patients run a chronic disease course (24) and will require immunosuppressive therapy for several years. Unfortunately, no follow-up study including a large number of patients have been performed to display the impact of ASS on functional outcome and quality of life. In one study of 12 patients followed for 5.5 years, muscle function improved in all and pulmonary function normalized in 1/3 (32).

In a study of 32 patients (61), patients with acute onset and respiratory insufficiency were compared to those with a gradual onset of ILD. The percentage of patients in whom the ILD improved at three months was significantly higher among those with acute onset. However, most patients with ILD progression after 12 months were among those with acute onset. Other studies have also shown an association between acute and subacute onset and poor prognosis (62).

Whether or not the pattern of HRCT findings is indicative of final outcome is a matter of debate. Ground glass opacities, initially thought to represent reversible inflammation have been associated with a better response to therapy (63), hence a more favorable outcome. However, ground glass opacities may also represent fine reticular fibrosis, and some studies have suggested a poor prognosis in patients demonstrating such changes (64). Finally, mortality appears to have little relationship to biopsy subtype (19).

Mortality and causes of death in ASS have been rarely subjected to investigation. After an average of 5.5 years, only one of 12 patients succumed ((32) and mortality was estimated to 8%. Others have found a cumulative mortality of 14% (9). At present, the overal annual mortality of ASS cannot be exactly assessed, but it can be concluded that ASS is associated with excess mortality.

In general, the mortality in IIM has improved during the last decades, from a 5-year survival of 65% in the 1960ies compared to 75-96% in the last decade (65). If modern therapy and more aggressive therapy have had the same impact on ASS remains to be seen.

14. Future perspectives

ASS represent a rather newly defined disease entity whose etiopathogenesis remains incompletely understood. The disease course is usually chronic and ASS is most likely associated with decreased survival. Due to its low incidence large scale prospective investigations are few. Knowledge about the clinical aspects of ASS has accumulated, while outcome, prognostic markers, biomarkers for disease activity, treatment, mortality and risk of cancer have been insufficiently investigated.

Anti-Jo-1	histidyl
Anti-PL-12	alanyl
Anti-PL-7	threonyl
Anti-EJ	glycyl
Anti-OJ	isoleucyl
Anti-KS	asparaginyl
Anti-Zo	phenylalanyl
Anti-Ha	tyrosyl

Table 1. Antisynthetase autoantibodies.

Antisynthetase autoantibody demonstrated on two separate occasions	Plus at least one of the following
Plus	Arthritis/arthralgia
Either Interstitial lung disease	Raynaud`s phenomenon
And/or Inflammatory muscle disease	Gottron`s paples or sign
	Mechanic`s hands
	D

Table 2. Suggested classification criteria for ASS.

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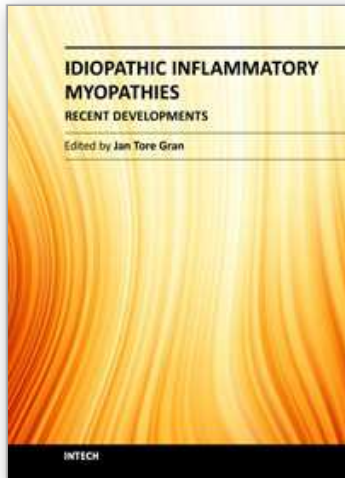
Idiopathic Inflammatory Myopathies - Recent Developments

Edited by Prof. Jan Tore Gran

The term "myositis" covers a variety of disorders often designated "idiopathic inflammatory myopathies". Although they are rather rare compared to other rheumatic diseases, they often cause severe disability and not infrequently increased mortality. The additional involvement of important internal organs such as the heart and lungs, is not uncommon. Thus, there is a great need for a better understanding of the etiopathogenesis of myositis, which may lead to improved treatment and care for these patients. Major advances regarding research and medical treatment have been made during recent years. Of particular importance is the discovery of the Myositis specific autoantibodies, linking immunological and pathological profiles to distinct clinical disease entities. A wide range of aspects of myopathies is covered in the book presented by highly qualified authors, all internationally known for their expertice on inflammatory muscle diseases. The book covers diagnostic, pathological, immunological and therapeutic aspects of myositis.

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