Antisynthetase syndrome

Author: Doctor Athanasios G. Tzioufas[1]
Creation Date: November 2001

Scientific Editor: Professor Haralampos M. Moutsopoulos

[1]Consultant Rheumatologist, Department of Pathophysiology, School of Medicine, National University of Athens, 75 Mikras Asias street,11527 Athens, Greece. agtzi@med.uoa.gr

Abstract
The antisynthetase syndrome is a rare, chronic autoimmune disease of unknown etiology. The syndrome is considered as a subgroup of the idiopathic inflammatory muscle diseases. The hallmark of the disorder is the presence of serum autoantibodies which recognize the aminoacyl-tRNA synthetases, a family of intracytoplasmic enzymes which play a vital role in protein synthesis. Prevalence in the general population remains unknown. Patients with antisynthetase syndrome have a characteristic clinical picture consisting of myositis and/or interstitial lung disease and/or chronic articular involvement. Raynaud's phenomenon is frequently observed. The severity and type of pulmonary involvement determines the outcome of the disease. Prednisone usually associated with steroid sparing agents such as azathioprine or methotrexate is used for the treatment of myositis, but its efficacy has not been substantiated in double-blind trials. In the case of severe pulmonary involvement the use of cyclophosphamide given in I.V. pulses is recommended.

Keywords
autoimmune disease, aminoacyl-tRNA synthetase, myositis, interstitial lung disease, chronic articular disease, Raynaud phenomenon

Disease name and synonyms

Antisynthetase syndrome
Jo-1 syndrome

Background-definition

The inflammatory myopathies comprise a heterogenous group of chronic autoimmune disorders of unknown etiology. Polymyositis (PM) and dermatomyositis (DM) are the two major entities which constitute this group of diseases. As other systemic autoimmune disorders, PM and DM are associated with serum autoantibodies, some of which are detected almost exclusively in these diseases. Several of these autoantibodies are related to particular clinical manifestations, marking, therefore, important clinical subgroups. These clinical subgroups represent more homogenous patient cohorts, as compared to PM/DM patients, thus allowing a separate and more concise approach with relation to diagnosis and treatment.

A major subgroup in inflammatory muscle disease is the antisynthetase syndrome characterized by the presence of anti-synthetase antibodies and systemic clinical manifestations

in muscles (myositis), lungs (interstitial lung disease) and joints (chronic polyarthritis) (1).

Prevalence and epidemiology

Prevalence in the general population remains unknown. The reported annual incidence of PM/DM ranges from 2-10 new cases per million persons, and the prevalence of antisynthetase antibodies is 20-40% of the total PM/DM population. The disease affects mainly adults and the sex ratio in the reported cases is 2-3:1 female to male patients. The relative prevalence (RP) of PM/DM in Europe, exhibits a geographical latitude, increasing from North (Iceland; RP:0.08) to South (Greece; RP:0.56) (1,2).

Etiology and biological significance of antisynthetase antibodies

Etiology and the origin of antisynthetase antibodies remain unknown. These autoantibodies are directed towards aminoacyl-tRNA synthetases, a family of enzymes whose role is to catalyze the attachment of a particular amino acid to its transfer RNA (tRNA). (see table 1).

Table 1: Antisynthetase antibodies

Aminoacyl-tRNA synthetase (antigen)	Antisynthetase autoantibody
Histidyl-tRNA synthetase	Jo-1
Threonyl-tRNA	PL-7
Alanyl-tRNA	PL-12
Isoleucyl-tRNA	OJ
Glycyl-tRNA	EJ

All the synthetases are located in the cytoplasm which is the site of protein synthesis. Protein analysis after immunoprecipitation, using 35S-methionine labeled HeLa cells and monospecific anti-synthetase have shown that anti-Jo-1, anti-EJ, anti-PL-7 and anti-PL-12 antibodies give intense and discrete protein bands of 52, 75,80 and 110 Kda, respectively. Furthermore, antisynthetase antibodies precipitate the tRNAs, producing, after polyacrylamide gel electrophoresis, a pattern characteristic for each individual synthetase. Antisynthetase autoantibodies can also inhibit the autoantigen function (aminoacylation) *in vitro*. However, this property has not proved to be related with disease process so far (3).

In the Caucasians with antisynthetase syndrome, antibodies to Jo-1 are correlated with HLA DR3. HLA DR52 is even more strongly associated with the presence of these autoantibodies in patients from African and Caucasian origin. Immunogenotyping studies have shown that the alleles found at a significantly increased frequency are HLA-DRB1*0301 and DQA1*0501 (4).

Clinical picture

Patients with antisynthetase syndrome present with a similar clinical picture which includes one or more components of the triad: myositis, interstitial lung disease and joint involvement (5). Raynaud's phenomenon and fever are also frequently observed (table 2).

Myositis: Muscle inflammation is found in more than 90% of the patients and leads to major clinical features which include muscular weakness, muscle tenderness, pain and ultimately atrophy and fibrosis of the muscle. Onset is usually acute and involves proximal skeletal muscles. The patient finds it difficult to stand up from a chair or to climb stairs. The electromyogram may have several characteristic changes including small amplitude, short polyphasic potentials, spontaneous fibrillations, positive spikes at rest, irritability and high-frequency repetitive discharges. Muscle inflammation triggers elevated levels of serum creatinine kinase, aldolase, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase. Muscle biopsy is required not only to confirm the diagnosis of myositis but also to exclude other disorders which may produce a similar picture. In the case of PM, biopsy specimen discloses inflammatory infiltrates within the fascicles and necrotic muscle fibers (1).

Table 2: Clinical manifestations of antisynthetase syndrome

Clinical manifestations	Prevalence (%)
Myositis	>90
Interstitial lung disease	60
Arthritis	50
Raynaud's phenomenon	40
Fever	20
Mechanic's hands	30

Lung involvement: Interstitial lung disease (ILD) is found in more than 60% of the patients with antisynthetase syndrome and is a major cause of morbidity (5,6). ILD may overshadow myositis. Lung involvement may occur in the absence of muscular involvement. In 10 patients who had ILD without clinically overt myositis, anti-PL-12 was the most commonly found antibody (60%), followed by anti-Jo-1 and anti-OJ antibodies (20% each) (7). The clinical presentation of lung involvement in patients with antisynthetase syndrome includes a broad spectrum of symptoms and signs. Persistent

cough, chest pain, diminished exercise tolerance, dyspnea at rest or even acute respiratory failure can occur (6). Digital clubbing can be observed but not very frequently, as in idiopathic pulmonary fibrosis (8). The pulmonary function tests reveal a typical restrictive pattern and the total lung capacity varies according to the severity of the disease. Chest radiography usually reveals an interstitial pattern. High-resolution computed tomography of the lungs discloses several findings which are usually non specific. Ground glass opacities, linear opacities and irregular interfaces are more frequently seen (figure 1). Airspace consolidation, parenchymal micronodules and honeycombing are also observed. (9,10) Lung biopsy may show either bronchiolitis obliterans organizing pneumonia (BOOP), usual interstitial pneumonia and diffuse alveolar damage. Patients with BOOP usually have a more favorable prognosis as compared to patients with interstitial pneumonia or diffuse alveolar damage (11,12).

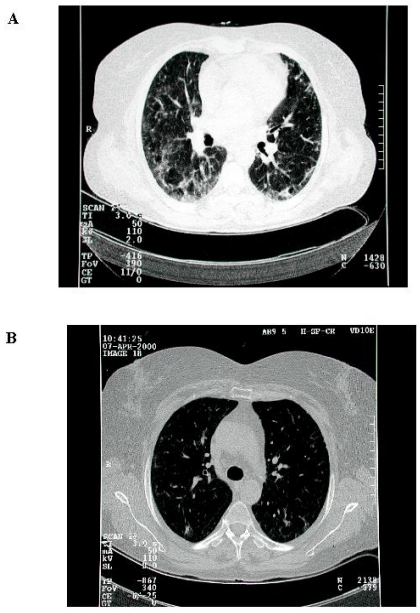

Figure 1. A 55-year-old female patient with antisynthetase syndrome.
A. High-resolution CT scan of the lungs, at diagnosis, depicts interstitial lung disease.
B. Improvement of the picture after a 6-month-treatment with intravenous immunoglobulin.

Joint manifestations: The association of arthritis with interstitial lung disease in myositis has been described several years before the description of the syndrome. Articular involvement is observed in approximately 50% of the patients and includes a broad spectrum of clinical manifestations, from arthralgia to overt synovitis and arthritis with or without bone erosions. In 21 anti-Jo-1 positive patients who have been studied for articular manifestations two distinct groups have been recognized (13). Four patients had deforming, predominantly nonerosive arthropathy with subluxations of the distal interphalangeal joints, especially the thumbs. Two patients had also associated subcutaneous calcinosis. Eight patients had non deforming arthropathy primarily affecting the small joints of the hands, wrists, shoulders, and knees. Those with deformities had a longer duration of arthritis compared with those with non deforming arthropathy (mean 14.5 years versus 3.3 years).

Other clinical features: In a systematic study of 212 adult patients with idiopathic inflammatory muscular disease, it was shown that the 47 patients with anti synthetase autoantibodies, arthritis and interstitial lung disease excepted, had also frequently, fever, and "mechanic's hands", compared to patients without these antibodies (5). Other disease manifestations include Raynaud's phenomenon, photosensitive lupus- like and dermatomyositis rashes. Small-vessel vasculitis in skin has been described in some case reports (5,14). Cardiac involvement can be observed, but its prevalence has not appeared to be different from the other PM or DM subgroups (15). Renal involvement in the form of mesangial proliferative glomerulonephritis is very rare and has good prognosis (16).

Differential diagnosis

Differential diagnosis should include diseases which cause myositis, interstitial lung disease, arthritis and Raynaud's phenomenon. Systemic scleroderma, overlap syndromes and other subgroups of PM/DM can show a similar clinical picture. When the disease is expressed only as polymyositis, other causes of muscular weakness should be considered: electrolyte disturbances; metabolic diseases; enzyme deficiencies, such as carnitine-palmitoyl transferase deficiency; neurologic diseases such as myasthenia gravis or Guillain-Barre syndrome; endocrine disorders including hypothyroidism and Cushing's syndrome; muscular dystrophies; use of drugs and toxins such as alcohol, corticosteroids, D-penicillamine, colchicine and clofibrate and infections including influenza, toxoplasmosis and human immunodeficiency virus (1).

Laboratory evaluation

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 (table 2). 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. Antibodies to Jo-1 are, by far, the most commonly detected autoantibodies (17). Antibodies to PL-7, PL-12, OJ and EJ are found but to a lesser extent (2). These autoantibodies produce a diffuse cytoplasmic pattern in indirect immunofluorescence, using as substrate Hep-2 cells. The identification of these antibodies is performed by the use of counter-immunoelectrophoresis or double immunodiffusion. Enzyme-linked immunosorbent assays (ELISA), using recombinant Jo-1 have been developed (18). This method offers high sensitivity but reduced specificity. In addition to antisynthetase antibodies, other autoantibody specificities may also be observed. 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 intracellular autoantigens and especially to Ro/SSA (17).

Prognosis and treatment

Prednisone (1mg/kg/day) remains the drug of choice for the treatment of this disorder, although a controlled trial has never been carried out to study its efficacy. Remission is achieved in 25-68% of the patients treated with high-dose corticosteroids as part of their initial therapy. Relapse rates after complete remission vary from 6 to 43% in the few studies where information is available. Late relapses after initial remission appear to be unusual (19). Cyclophosphamide administrated in monthly intraveinous pulses (1gr/body m^2), have shown to be effective, when ILD is prominent. Among the steroid-sparing agents, azathioprine (2.5 mg/kg/day), methotrexate (0.3mg/kg/week), and cyclosporine (3mg/kg/day), have been used with invariably low to moderate success. There are no results of controlled trials to indicate whether a single drug or combinations of these drugs are the treatment of choice. Intravenous immunoglobulin (IVIg), was shown in a controlled trial to be effective in steroid-resistant dermatomyositis not only in improving muscle strength and skin rash but also in resolving the underlying immunopathology. In PM, uncontrolled trials using IVIg have shown improvement in muscle strength, but the controlled clinical trial is still ongoing (20).

References

1. Medsger TA and Oddis CV. Inflammatory muscle disease. Clinical features. In: Rheumatology. Eds JH Klippel and PA Dieppe. Mosby, London UK. pp 6.12.1-6.12.14; 1994.

2. Hengstman GJD, van Venrooij WJ, Vencovsky J, Moutsopoulos HM, van Engelen BGM. The relative prevalence of dermatomyositis and polymyositis in Europe exhibits a latitudinal gradient. Ann. Rheum. Dis. 59:141-142; 2000.

3. Plotz PH, Targoff I. Myositis associated antigens. Aminoacyl-tRNA synthetases. In : Manual of Biological Markers of Disease. Eds,WJ Van venrooij and R Maini. Kluwer Academic Publications. The Netherlands. pp B6.1: 1-18; 1994.

4. Hausmanowa-Petrusewicz I, Kowalska-Oledzka E, Miller FW, Jarzabek-Chorzelska M, Targoff IN, Blaszczyk-Kostanecka M, Jablonska S. Clinical, serologic, and immunogenetic features in Polish patients with idiopathic inflammatory myopathies. Arthritis Rheum 40:1257-66; 1997.

5. Love LA, Leff RL, Fraser DD, Targoff IN, Dalakas M, Plotz PH, Miller FW. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine (Baltimore) 70:360-74; 1991.

6. Maire I, Hatron PY, Hachulla E, Wallaert B, Michon-Pasturel U, Devulder B. Pulmonary involvement in polymyositis and in dermatomyositis. J Rheumatol 25:1336-43; 1998.

7. Friedman AW, Targoff IN, Arnett FC. Interstitial lung disease with autoantibodies against aminoacyl-tRNA synthetases in the absence of clinically apparent myositis. Semin Arthritis Rheum 26:459-67; 1996.

8. Grathwohl KW, Thompson JW, Riordan KK, Roth BJ, Dillard TA. Digital clubbing associated with polymyositis and interstitial lung disease. Chest 108:1751-2; 1995.

9. Ikezoe J, Johkoh T, Kohno N, Takeuchi N, Ichikado K, Nakamura H. High-resolution CT findings of lung disease in patients with polymyositis and dermatomyositis. J Thorac Imaging 11:250-9; 1996.

10. Akira M, Hara H, Sakatani M.Interstitial lung disease in association with polymyositis-dermatomyositis: long-term follow-up CT evaluation in seven patients. Radiology 210:333-8; 1999.

11. Kalenian M, Zweiman B Inflammatory myopathy, bronchiolitis obliterans/organizing pneumonia, and anti-Jo-1 antibodies: an

interesting association. Clin Diagn Lab Immunol 4:236-40;1997.
12. Tazelaar HD, Viggiano RW, Pickersgill J, Colby TV.Interstitial lung disease in polymyositis and dermatomyositis. Clinical features and prognosis as correlated with histologic findings. Am Rev Respir Dis 141:727-33; 1990.
13. Oddis CV, Medsger TA Jr, Cooperstein LA.A subluxing arthropathy associated with the anti-Jo-1 antibody in polymyositis/dermatomyositis. Arthritis Rheum 33:1640-5; 1990.
14. Targoff IN, Arnett FC Clinical manifestations in patients with antibody to PL-12 antigen (alanyl-tRNA synthetase). Am J Med 88:241-51; 1990.
15. Poveda Gomez F, Merino JL, Mate I, Sobrino JA, Camacho J, Gamallo C Polymyositis associated with anti-Jo1 antibodies: severe cardiac involvement as initial manifestation. Am J Med 94:110-1; 1993.
16. Frost NA, Morand EF, Hall CL, Maddison PJ, Bhalla AK.Idiopathic polymyositis complicated by arthritis and mesangial proliferative glomerulonephritis: case report and review of the literature. Br J Rheumatol 32:929-31; 1993.
17. Brouwer R, Hengstman GJD, Vree Egberts W *et al.* Autoantibody profiles in the sera of European patients with myositis. Ann Rheum. Dis 60:116-123; 2001.
18. Biswas T, Miller FW, Takagaki Y, Plotz PH.An enzyme-linked immunosorbent assay for the detection and quantitation of anti-Jo-1 antibody in human serum. J Immunol Methods 98:243-8; 1987.
19. Lee W, Zimmermann B 3rd, Lally EV.Relapse of polymyositis after prolonged remission. J.Rheumatol 24:1641-4; 1997.
20. Dalakas MC. Current treatment of the inflammatory myopathies. Curr Opin Rheumatol 6:595-601; 1994.