The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Myositis overlap syndromes

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1 Introduction

Some patients with myositis may also have clinical or laboratory signs and symptoms of another, defined, connective tissue disease, such as systemic lupus erythematosus (SLE), scleroderma, rheumatoid arthritis, mixed connective tissue disease (MCTD) or Sjögren's syndrome. The term "overlap syndrome" is then used for such patients to recognise the differences in clinical course, prognosis and management. Classification into overlap syndromes is facilitated by detection of autoantibodies associated with each of these syndromes. The main overlap syndromes, with myositis as one of the important features, include mixed connective tissue disease (MCTD, Sharp's syndrome), antisynthetase syndrome (ASS), polymyositis/scleroderma overlap (PM/Scl) associated with anti-PM/Scl antibody and scleroderma/polymyositis Scl/PM associated with anti-Ku antibody (Tables 1, 2) [1].

The prevalence of overlap syndromes is unknown — for MCTD it is probably around 10/100 000. ASS constitutes about 30 % of polymyositis and dermatomyositis cases. In MCTD the female:male ratio is about 9 : 1, in ASS 2.7 : 1.

2 Diagnostic measurements for experts

The MCTD is characterised clinically by Raynaud's phenomenon, so called puffy hands, sclerodactyly, arthritis, oesophageal dysmotility and myositis. A prerequisite for diagnosis of MCTD is the presence of high titre of anti-U1-RNP autoantibodies. This was defined originally in haemagglutination assay, which is no longer employed by most laboratories. Therefore this criterion is not currently associated with a specified titre and requires a statement of clearly positive, high levels of anti-U1-RNP instead. U1-RNP contains A, C and p68 antigens, and in contrast to SLE, MCTD is associated particularly with antibodies against the latter antigen. Occasionally, high levels of anti-p68 are also found in SLE and these patients often have some clinical features of MCTD such as myositis, fibrosing alveolitis, Raynaud's phenomenon and sclerodactyly. The presence of anti-Sm or anti-dsDNA antibodies indicates that SLE — with a much higher prevalence of nephritis and of SLE

Table 1. Signs and symptoms of MCTD, ASS and PM+Scl overlaps [1, 4, 5].

Clinical features		% of patients
MCTD	Arthritis/arthralgia	95
	Raynaud's phenomenon	85
	Decreased oesophageal motility	67
	Impaired pulmonary diffusing capacity	67
	Swollen hands	66
	Myositis	63
	Lymphadenopathy	39
	Skin rash	38
	Sclerodermatous changes	33
	Fever	33
	Serositis	27
	Splenomegaly	19
	Hepatomegaly	15
	Neurologic abnormalities	10
	Renal disease	10
ASS	Myositis	> 85
	Interstitial lung disease	89
	Arthritis	94
	Raynaud's phenomenon	67
	Fevers	87
	Mechanic's hands	71
PM/Scl (Anti-PM/Scl)	Raynaud's phenomenon	100
	Arthritis/arthralgia	97
	Myositis	88
	Lung fibrosis	78
	Sclerodactyly	97
	Sjögren's syndrome	34
	Dermatomyositis rash	38
	Dysphagia	78
	Calcinosis	47
Scl/PM (Anti-Ku)	Raynaud's phenomenon	86
	Limited scleroderma	84
	Diffuse systemic scleroderma	16
	Myositis	40

MCTD, mixed connective tissue disease, **ASS**, antisynthetase syndrome, **PM/Scl**, polymyositis/scleroderma overlap syndrome.

typical skin reactions — could be diagnosed. In order to diagnose myositis, muscle weakness should be demonstrated by manual muscle testing, and evidence of elevation of muscle enzymes, electromyographic myogenic changes and inflammation in muscle biopsy should be provided. The major cause of morbidity and mortality in patients with MCTD is pulmonary hypertension, which should be suspected in patients with dyspnoea and should indicate tests for pulmonary arterial pressure.

The antisynthetase syndrome (Table 1) is associated with one of the currently known antisynthetase autoantibodies (see chapter polymyositis and dermatomyositis). The clinical features are characterised by interstitial lung disease, myositis, Raynaud's phenomenon, fevers, non-erosive arthritis and a skin rash on the hands (so called mechanic's hands, Fig. 1). As interstitial lung disease is highly associated with anti-synthetase antibodies and is important for prognosis, all these patients should be evaluated for possible pulmonary involvement. Lung function tests, including diffusing capacity of the lung for carbon monoxide (DLCO), and high resolution computer tomography (HRCT) should be performed. HRCT will show inflammatory alveolitis or advanced changes including fibrosis. In some cases, interstitial lung disease is the presenting symptom and precedes manifestation of muscle disease by several months.

In patients presenting overlap features between scleroderma and myositis, particular attention should be paid to detection of anti-PM/Scl and anti-Ku antibodies.

Table 2. Diagnostic criteria for MCTD [3].

Clinical criteria
• Oedema of the hands
• Synovitis
• Myositis
• Raynaud's phenomenon
• Acrosclerosis
Laboratory criteria
• Positive anti-nRNP at a high concentration*

Requirements for the diagnosis: Serologic criterion + at least 3 clinical
(In the case that oedema, Raynaud's phenomenon and acrosclerosis are combined, then 4 clinical criteria are required).
*Original text stated: Positive anti-nRNP at a haemagglutination titre of 1:1600 or higher.

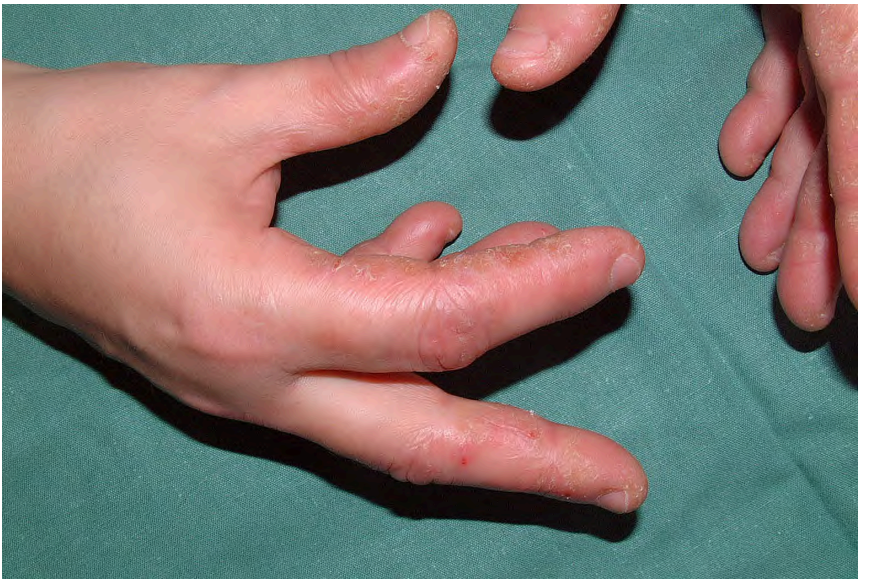


Figure 1. Mechanic's hands in a patient with antisynthetase syndrome.

3 Requirements for family practitioners

Frequency of individual clinical symptoms in MCTD varies (Table 1) and they are usually not present at the same time, but appear sequentially [2]. The earliest signs are swollen hands with puffy fingers, arthritis, Raynaud's phenomenon, myositis and sclerodactyly. Arthritis is very common and may be quite severe leading to deformities. It is usually non-erosive, but occasionally marginal erosions or even large destructions may develop. MCTD was originally described as a relatively benign disease, but this has changed during the last 20 years, and it is known that some patients have renal, cerebral, pulmonary and cardiac involvement. Particularly significant is pulmonary hypertension, because it is the most frequent cause of death in these patients. Trigeminal neuropathy may also be present. The fact that several different diagnostic criteria sets were proposed for the disease [3] reflects the heterogeneity of the patients and also some controversies about the real existence of the syndrome. The latter fact arises from longitudinal observations showing development of clearly defined rheumatoid arthritis, systemic lupus erythematosus or scleroderma in some patients. However, most of the patients fulfilling the criteria for MCTD have a distinct syndrome.

ASS usually presents acutely, with myositis, fever, dyspnoea, arthritis, mechanic's hands (Table 1) [4]. Interstitial lung disease is sometimes the leading symptom with myositis being found only when specifically looked for or not

present at all. But in many cases myositis is quite severe. Patients usually have symmetrical polyarthritis of hands and wrists, which resembles rheumatoid arthritis, however feet are usually spared and there are no X-ray erosions. The disease has moderate response to therapy and tends to flare after tapering. ASS patients do not usually have renal and CNS disease. Serositis is also rare in ASS.

Patients with anti-PM/Scl antibodies have myositis or scleroderma, mostly with limited cutaneous involvement, or both diseases. Pulmonary involvement is less severe than in ASS and patients usually have a good prognosis [5].

Anti-Ku antibodies may be detected in scleroderma-polymyositis overlap syndrome and these patients represent a group characterized by Raynaud's phenomenon, sclerodermatous skin changes restricted to the extremities, inflammatory myopathy responsive to glucocorticoids, occasional extramuscular inflammation, and good prognosis.

When initial signs and symptoms hinting at a myositis overlap syndrome (muscular weakness, general weakness or fatigue, fever, CK elevation, articular swelling or effusion, Raynaud's phenomenon, dyspnea, skin changes typical for SLE, dermatomyositis or scleroderma, cytopenia, or combinations of these symptoms, particularly when together with antinuclear antibodies) are detected, the patient should be referred to a specialist for further diagnostic steps. Depending on which symptoms are prominent, this preferentially should be a rheumatologist, a neurologist, or a dermatologist.

4 Follow up

Clinical observations

In MCTD the overlapping features develop sequentially and patients should be investigated for their presence. Particular attention should be given to pulmonary hypertension, which may develop in the absence of interstitial lung disease and may progress rapidly. Other organs may be affected as the disease progresses and occasionally patients may develop symptoms and signs compatible with another defined rheumatic disease entity and therefore renal, cardiac, CNS, and gastrointestinal status should be checked periodically.

In ASS the follow up is similar to PM/DM patients with particular attention to interstitial lung disease.

Expectations

For many MCTD cases the prognosis is favourable and patients usually respond to glucocorticoid treatment. Some patients develop pulmonary hypertension, which may lead to death rapidly. More rarely myocarditis, renovascular hypertension, and cerebral haemorrhage appear. Articular disease can sometimes cause significant

deformities. In most cases the disease goes into a remission over time with low inflammatory disease activity and the anti-RNP antibodies may disappear.

Patients with ASS often have relapsing myositis and arthritis. Interstitial lung disease may stabilise with treatment; however, in some patients it may be progressive and the prognosis is somewhat worse than in MCTD.

Blood tests

Complete blood count is used to look for leucopenia or thrombocytopenia. Urine is checked for proteinuria. Serum levels of "muscle enzymes" are measured in order to assess muscle involvement.

Patients with MCTD usually have extremely high levels of gammaglobulins and IgG, which may decrease during treatment and increase with flare. Acute phase proteins may be abnormal, particularly when arthritis is present, but frequently there is only mild elevation. Complement levels are usually normal. Rheumatoid factors are found in about 70 % of MCTD patients.

The autoantibodies typical for the overlap syndromes usually persist during disease course, and their specificity doesn't change much. Although anti-Jo-1 has been shown to fluctuate in correlation with disease activity in longitudinal measurements, frequent re-measurements of the myositis overlap typical autoantibodies in general are of no value in the long term management of the patient.

5 Management

Treatment of MCTD follows the approaches used in systemic lupus erythematosus, polymyositis, scleroderma, and rheumatoid arthritis and is dependent on the presenting symptoms or pattern of organ involvement. In some patients nonsteroidal antirheumatic drugs may suffice, but in the majority, various doses of glucocorticoids are necessary. When used in appropriate doses the treatment is usually successful. Immunosuppressive drugs may have to be used, such as cyclophosphamide, azathioprine, methotrexate, and hydroxychloroquine depending on the organ involvement and degree of reversibility of the symptoms. Raynaud's phenomenon is difficult to treat; calcium channel blocker nifedipine, angiotensin-II receptor blocker losartan or intravenous prostacyclins may be effective. In pulmonary hypertension endothelin receptor antagonists bosentan or sitaxentan may be used. Some patients benefit from the use of phosphodiesterase-5 inhibitor sildenafil. Long-term anticoagulation is recommended. The tyrosine kinase inhibitor imatinib mesylate has recently been shown to improve pulmonary fibrosis in MCTD.

Treatment of ASS is the same as described in the polymyositis and dermatomyositis chapter.

6 Diagnostic tests

There is no single diagnostic test in overlap syndromes and diagnosis in these conditions is dependent on a number of clinical variables and blood tests from which autoantibodies are particularly helpful.

Anti-U1-RNP antibodies produce a speckled nuclear pattern (Fig. 2) in indirect immunofluorescence on HEp-2 cells (IIF) or other substrates and are detected in high titres of around 1 : 1000 or more. They were originally described as antibodies reactive with ribonuclease-sensitive extractable nuclear antigen (ENA), which distinguished them from anti-Sm antibodies that reacted with ENA even after ribonuclease treatment. Anti-U1-RNP may be detected by immunodiffusion or counterelectrophoresis using ENA, by Elisa or LIA assay with purified or recombinant antigens, immunoblotting or immunoprecipitation with ^{32}P labelled extracts. Line immunoassays usually detect anti-U1-RNP reliably. U1-RNP contains C, A and p68 antigens and MCTD is particularly characterised by anti-p68. Anti-p68 very often is accompanied by antibodies to BB' which should not be interpreted as anti-Sm activity unless a concomitant reaction with anti-Sm-D is observed. The levels of anti-U1 RNP antibodies do not seem to correlate with disease activity, but may decrease or disappear after long disease duration.

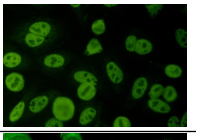
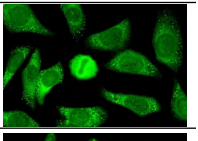
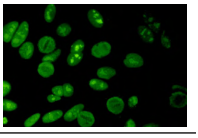
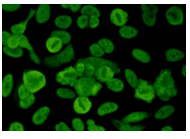
Autoantibody	Immunofluorescence on HEp-2 cells	
U1-RNP	speckled, or coarse granular; no staining of nucleoli and metaphase chromosomes; high titer	
Jo-1	granular cytoplasmic; no nuclear staining (unless other ANA are simultaneously present)	
PM-Scl	nucleolar, plus fine granular staining of nucleoplasm, no staining of metaphase chromosomes; often low titer	
Ku	fine granular, no staining of metaphase chromosomes; mostly high titer	

Figure 2. Immunofluorescence findings on HEp-2 cells typical for autoantibodies in myositis overlap syndromes.

Antisynthetase antibodies found in ASS produce a fine speckled cytoplasmic pattern in IIF (Fig. 2). There are 8 autoantibodies currently recognised, from which anti-Jo-1 is by far the most frequent (see polymyositis and dermatomyositis chapter). Serum levels of anti-Jo-1 tend to correlate with the activity of the disease.

Anti-PM/Scl produce a homogeneous nucleolar pattern on IIF (Fig. 2). They can be detected by immunodiffusion or immunoprecipitation, but are nowadays detected mostly by line or enzyme immunoassays with native or recombinant antigens or peptides. Autoantibodies are directed predominantly against two molecules of 100 kDa (100 %) and 75 kDa (60 %).

Anti-Ku antibodies produce a speckled nuclear pattern sparing nucleoli on IIF (Fig. 2). Some laboratories use counterimmunolectrophoresis, but line immunoassay is available.

7 Testing methods

Benefits

For detection of antibodies to U1-RNP, Jo-1, PM/Scl and Ku, commercial assays are available. Indirect immunofluorescence can suggest the type of autoantibody. Anti-U1-RNP and anti-Jo-1 can be measured quantitatively by Elisa.

Limitations

For anti-U1-RNP and anti-Jo-1 many assays with usually good reliability are available. There are fewer opportunities to detect anti-PM/Scl and particularly anti-Ku. These assays must be validated in each laboratory with known antibody specificities to ensure reliable performance.

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