Mixed connective tissue disease, overlap syndromes, and eosinophilic fasciitis

P J Maddison

While the cause of connective tissue diseases (CTDs) remains unknown the classification of individual patients will continue to depend on identifying certain patterns of clinical and laboratory features. This is the basis of the various classification criteria for systemic sclerosis,1 systemic lupus erythematosus (SLE),2 and other connective tissue diseases. As many as 25% of patients with CTD, however, present with overlapping clinical features. The term ‘overlap syndrome’ is applied to what appears to be a very heterogeneous group of disorders, though features associated with systemic sclerosis are often a major component. Frequently, patients have a mild CTD characterised by Raynaud’s phenomenon, oedema of the hands, and, possibly, acro sclerosis and arthritis, which has been termed ‘undifferentiated CTD’.3 Other patients present manifestations of more than one definite CTD and commonest among these are disorders with features of systemic sclerosis combined with those of SLE4 or polymyositis,5 or both, with features of systemic sclerosis or SLE and rheumatoid arthritis,6,7 and features of Sjögren’s syndrome in association with any of the other CTDs. Overlapping features may occur concurrently, but more commonly over time one syndrome takes on the features of another. It is still contentious whether or not overlap syndromes represent the coexistence of separate diseases, the broad clinical expression of one of the rheumatic diseases, or distinct clinical entities with distinctive aetiology and pathogenesis.

In some cases overlap syndromes are associated with a particular serological marker (table 1). Antibodies to the RNA binding proteins Ro (SSA) and La (SSB) are associated with Sjögren’s syndrome developing in association with other CTDs, such as systemic sclerosis or SLE. Recent reviews suggest that Sjögren’s syndrome in this context resembles primary Sjögren’s syndrome and differs significantly from secondary Sjögren’s syndrome accompanying rheumatoid arthritis.8 Severe xerophthalmia, xerostomia, and parotid gland enlargement are often prominent, resembling primary Sjögren’s syndrome, in which these features are common. This contrasts with secondary Sjögren’s syndrome accompanying rheumatoid arthritis, in which they are uncommon.

Antibodies to PM-Scl (PM-1), a nucleolar antigen,9 and Ku, a DNA binding nuclear protein complex composed of two polypeptides of 86 and 70 kD,10 identify patients with overlap features of polymyositis and systemic sclerosis. Antibodies to histidyl t-RNA synthetase identify patients with polymyositis who develop interstitial pulmonary disease.11

Possibly, CTDs represent a genetically determined host response to a number of environmental triggers. A number of studies, for example, have shown that the presence of certain HLA class II genes is associated with specific immune responses to autoantigens such as Ro and La,12 13 U1RNP,13 Ku,14 and Jo-1.15

Mixed connective tissue disease

Mixed connective tissue disease (MCTD) was initially described in 1972 by Sharp and coworkers16 as a unique syndrome with features of SLE, systemic sclerosis, and myositis associated with antibodies to a nuclear ribonucleoprotein, U1RNP. Subsequently, the serological specificity was defined to epitopes on the 70 kD phosphoprotein uniquely associated with the ribonucleoprotein particle containing U1RNP.17 The original claims for MCTD have subsequently become points of contention. These include the clinical distinctiveness, based on the presence of a particular group of features—notably, Raynaud’s phenomenon, arthralgias and arthritis, puffy hands, abnormal oesophageal motility, myositis, and lymphadenopathy and by the absence of cerebral and renal disease and vasculitis, a benign prognosis, responsiveness to corticosteroids, and the presence of high titres of anti-U1RNP.

Since 1972 our concepts of this condition have evolved and the original claims require considerable modification. Organ involvement is often extensive and there is a tendency to evolve away from a ‘mixed’ clinical picture so that many patients eventually develop the unequivocal picture of a classical CTD, most often systemic sclerosis. The problem remains as to whether or not MCTD, being essentially serologically defined, warrants the status of an independent disease.

The lack of consensus as to whether MCTD is a specific entity is due to a lack of criteria for its diagnosis. Recently, at a meeting in Japan, three different sets of criteria were described18

Table 1  Serological markers of overlap syndromes

<table>
<thead>
<tr>
<th>Overlap syndrome</th>
<th>Antibody specificity</th>
<th>HLA class II antigen association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren’s syndrome/systemic lupus erythematosus or systemic sclerosis</td>
<td>Ro, Ro-La</td>
<td>DQw5, DQw6 DR3</td>
</tr>
<tr>
<td>Systemic sclerosis/polymyositis</td>
<td>PM-Scl (PM-1)</td>
<td>DQw1/DQw2</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>Ku</td>
<td>U1RNP</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>U1RNP</td>
<td>DQw7, 8, 9</td>
</tr>
<tr>
<td>Polymyositis/interstitial disease</td>
<td>Jo-1</td>
<td>DRw52</td>
</tr>
</tbody>
</table>
The basic premise is that the presence of high titres of antibodies to U1RNP modifies the expression of a CTD in ways that are relevant to prognosis and treatment. To avoid a circular argument there is a need to include patients in studies with overlap features irrespective of serological findings. There are only a few reports analysing overlap syndromes defined by clinical criteria alone, and in these, antibodies to U1RNP fail to identify a distinctive clinical group. Lazo and Morteo, for example, evaluated the influence of anti-U1RNP in a group of 27 patients with overlap features and concluded that the range of clinical manifestations was unrelated to the presence or absence of these antibodies. Antibodies to U1RNP have been known to disappear during the course of the disease, however, and prospective clinical studies are now required.

The cause of MCTD is unknown. The transient appearance of antibodies to U1RNP has been reported during treatment with procaainamide, but drugs have not been associated with the clinical syndrome. Interestingly, Khan et al reported four patients with MCTD and antibodies to U1RNP who were exposed during the course of their occupation to vinyl chloride. The clinical picture in these cases contrasts with 'vinyl chloride disease', which is characterised by Raynaud's phenomenon, striking acroosteolysis and, sometimes, scleroderma-like skin changes. In this disorder specific autoantibodies have not been detected.

The association with toxic exposure in these cases of MCTD might be merely coincidental. As three cases of MCTD have previously been reported after breast augmentation surgery, however, the question is raised whether or not a variety of environmental insults can induce clinical and serological features of MCTD in a patient with a particular genetic background.

There are familial cases of MCTD but, until recently, no haplotype association has been described. Black and coworkers showed an increased incidence of HLA-DR4 in patients with MCTD compared with controls (table 3). The association, however, was only significant in patients with polyarthritis, some of whom had erosive disease, though there was no association with rheumatoid factor. The association, therefore, is related to a particular pattern of disease expression rather than to MCTD per se. On the other hand, there was a significant alteration in the Gm allotype frequencies in patients with MCTD. This Gm association may be particularly important because Gm associations are not well defined for rheumatoid arthritis, SLE, or systemic sclerosis. More recently, the presence of autoantibodies to U1RNP both in association with MCTD and SLE has been strongly linked to the DQβ gene associated with DQw7, 8, and 9.

The prevalence of MCTD is not known precisely but it is generally considered to be more common than systemic sclerosis and polymyositis but less common than SLE. There is a marked female preponderance (about 8:1:1) and apparently no ethnic group is particularly susceptible. Cases are recognised in children. It has been suggested that MCTD produces more morbidity in children with a higher prevalence of features such as significant myocarditis, glomerulonephritis, thrombocytopenia, seizures, and aseptic meningitis. These observations, however, may be the result of a selection bias.

The initial presentation is rarely distinctive and often comprises Raynaud's phenomenon, swollen puffy hands, polyarthritides, and rash. As the disease evolves, overlapping features tend to

Table 2. Concordance of three sets of criteria with clinical diagnosis of mixed connective tissue disease (MCTD) in 593 patients with connective tissue disease. (After Alarcon-Segovia and Cardiel, 1989)

<table>
<thead>
<tr>
<th>Behaviour (n)</th>
<th>Criteria</th>
<th>% Concordance with clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alarcon-Segovia Sharp et al</td>
<td>Confirming MCTD (80) 100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Ruling out MCTD in:</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>0 (99) 90</td>
<td>87.5</td>
</tr>
<tr>
<td>Sclerodema</td>
<td>(80) 100</td>
<td>55</td>
</tr>
<tr>
<td>RA*</td>
<td>(100) 100</td>
<td>100</td>
</tr>
<tr>
<td>DQw7*</td>
<td>Gm (11) 100</td>
<td>84</td>
</tr>
<tr>
<td>Sjögren's</td>
<td>(80) 99</td>
<td>96</td>
</tr>
</tbody>
</table>

*SLE=systemic lupus erythematosus; RA=rheumatoid arthritis; DM/Pm=dermatomyositis/polymyositis; t57-5% as definite, 42-5% as probable.
occur sequentially. A broad spectrum of manifestations is seen (table 4). Features reported to be particularly characteristic of MCTD, occurring more commonly there than in other CTDs, include an erosive arthritis, multiple subcutaneous nodules in the peritendinous regions of the forearms and hands, juxta-articular calcinosis, and pulmonary hypertension.

Polyarthritis is a prominent feature and is somewhat more severe than in typical SLE. There is a tendency to develop deformities of the hands and feet as a result of periarticular involvement leading to ligamentous and capsular laxity. Sometimes erosions are seen radiologically and can be extensive, mainly affecting the interphalangeal and first carpometacarpal joints (fig 1). In MCTD an association has been noted between arthritis and the presence of HLA-DR4. Rheumatoid factor is detected in about 50% of cases, and 40% have small, often multiple, subcutaneous nodules over the flexor tendons of the forearms, extensor tendons of the hands close to the metacarpophalangeal and proximal interphalangeal joints, extensor tendons on the dorsum of the foot, and over the Achilles tendon. Histologically they show non-specific inflammation and not the typical morphology of rheumatoid nodules.

The most common neurological complication is trigeminal neuropathy. Interestingly, this is also a neurological manifestation of systemic sclerosis but is uncommon in more typical cases of SLE. Vascular headaches, often with features of migraine are common, but other neurological complications are rarely seen. Similarly, clinically significant glomerulonephritis is uncommon, though cases of membranous nephropathy have been seen.

Abnormal lung function tests, especially the single breath diffusing capacity, are abnormal in most patients, but only a minority are symptomatic. Pulmonary hypertension, however, is an increasingly recognised complication. Sometimes this is secondary to interstitial pulmonary fibrosis but more commonly is a primary event associated with intimal proliferation of pulmonary arterioles. Those affected often have a poor prognosis and right ventricular failure can progress rapidly.

Involvement of the pulmonary arterioles is part of a generalised vasculopathy which characterises MCTD and dominates the clinical picture in a minority of patients. There are a few descriptions, for example, of intimal proliferation of renal vessels, resembling that seen in systemic sclerosis, resulting in hypertensive crisis and renal failure. At least 50% have nailfold capillary changes similar to those found in systemic sclerosis. Angiography has been used to show organic obstruction of digital vessels in a large proportion of patients with MCTD, emphasising the propensity of these patients to develop vasculopathy of both small and medium sized vessels.

Proteins complexed in small nuclear ribonucleoprotein particles (snRNPs) to uridylic acid (U) enriched snRNAs are important targets for autoimmunity in CTDs. As summarised in table 5 these snRNPs have at least seven core

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**Table 4** Cumulative clinical manifestations in mixed connective tissue disease

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Prevalence (%)</th>
</tr>
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<tbody>
<tr>
<td>Skin and mucous membranes</td>
<td></td>
</tr>
<tr>
<td>Swollen hands</td>
<td>60</td>
</tr>
<tr>
<td>Rash</td>
<td>50</td>
</tr>
<tr>
<td>Mucosal ulceration</td>
<td>45</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>40</td>
</tr>
<tr>
<td>Gottron's papules</td>
<td>40</td>
</tr>
<tr>
<td>Heliotrope</td>
<td>30</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>80</td>
</tr>
<tr>
<td>Myalgia</td>
<td>70</td>
</tr>
<tr>
<td>Nodules</td>
<td>50</td>
</tr>
<tr>
<td>Jaccoud's arthropathy</td>
<td>35</td>
</tr>
<tr>
<td>Myositis</td>
<td>25</td>
</tr>
<tr>
<td>Erosions</td>
<td>20</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>Reduced oesophageal motility</td>
<td>75</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Rare</td>
</tr>
<tr>
<td>Pseudodiverticula</td>
<td>Rare</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Raynaud's phenomenon</td>
<td>95</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>40</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>40</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Rare</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Reduced CO transfer</td>
<td>75</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>50</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td></td>
</tr>
<tr>
<td>Trigeminal neuropathy</td>
<td>15</td>
</tr>
<tr>
<td>Aseptic meningitis</td>
<td>5</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>10</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
proteins in common and a varying number of particle specific proteins. Antibodies to U1RNP recognise three polypeptides, termed 70 kD, A, and C, found uniquely in association with U1RNP (reviewed in ref 37). The great majority of serum samples containing anti-U1RNP react with 70 kD and A with fewer reacting with the C polypeptide. About 60% of serum samples react with BB'. cDNA clones coding for these proteins have been cloned, and assays based on recombinant antigens have been developed by some laboratories to identify antibodies to U1RNP of particular specificity. Another method for doing this, which is currently more accessible, is the Western technique of immunoblotting. It has been suggested that the reaction of antibodies with the 70 kD polypeptide of U1RNP is an important serological marker for MCTD, whereas antibodies to U1RNP in MCTD associated with SLE are directed to epitopes on other polypeptides, particularly BB'. This, however, has not been our experience, and during the course of a 10 year prospective clinical study of anti-U1RNP positive patients we found anti-70 kD with equal prevalence in patients satisfying the criteria for MCTD and SLE. Long term follow up of large numbers of patients is required to resolve this.

In most patients the antibody profile to U1RNP is detected at the initial presentation with clinical disease and remains constant during the course. Occasionally, the antibody profile evolves after the disease has presented or, alternatively, the antibodies subsequently disappear. Antibody titres sometimes fluctuate but do not accurately reflect clinical disease activity. Antibodies to single stranded DNA, histones, and cardiolipin occur with a prevalence seen in SLE. Antibodies to double stranded DNA are uncommon, however, as are antibodies to other ribonucleoprotein antigens, such as Sm, Ro, and La.

Mixed connective tissue disease in many patients has a benign course, but a follow up by Nimelset et al of the original 25 patients described by Sharp in 1972 showed that the prognosis is not invariably favourable. Although clinically significant glomerulonephritis and neuropsychiatric disease is uncommon, some patients develop life threatening complications, such as pulmonary hypertension.

Eosinophilic fasciitis

Eosinophilic fasciitis is generally recognised by the often rapid appearance of tender swelling of the arms and legs that evolves over days to weeks into brawny induration, which may closely resemble systemic sclerosis. This is associated with blood eosinophilia and a characteristic histological picture of inflammation and sclerosis primarily affecting the deep fascia and subcutis.

The first published report was by Shulman in 1975. Since then more than 200 cases have been reported and the full extent of the clinical spectrum is becoming known. Some consider eosinophilic fasciitis to be part of the spectrum of systemic sclerosis as after one or two years a large proportion of patients develop chronic fibrotic and atrophic cutaneous features and some develop systemic manifestations of systemic sclerosis. There are significant differences that seem to set eosinophilic fasciitis apart from systemic sclerosis, however. These include the relative absence of Raynaud’s phenomenon, normal nailfold capillaries, sparing of the epidermis and dermis, infrequent visceral involvement, absence of the serological features which characterise systemic sclerosis, and the development of haematological complications, such as aplastic anaemia and thrombocytopenia, which are extremely rare in typical systemic sclerosis.

The cause is unknown. Multiple cases within a family with sharing of HLA genes has been reported, suggesting that genetic factors may be involved. An interesting feature is the association of many cases with strenuous exertion, especially in men. There has been speculation that there is a hypersensitivity reaction to muscle tissue following exercise induced damage, but there may be multiple aetiological triggers. A temporal association has been reported with cancer, and the administration of drugs such as those used in antituberculous treatment and phenytoin. Although exposure to toxic agents has been suggested in the pathogenesis of eosinophilic fasciitis, there is no evidence for this in most cases. Recently, there have been increasing reports, particularly from the USA, of L-tryptophan induced ‘eosinophilia-myalgia syndrome’, some cases of which closely resemble eosinophilic fasciitis. Consumption of L-tryptophan has been implicated, which is sold over the counter for a variety of neuropsychiatric disorders, insomnia, and various musculoskeletal complaints. Features of the syndrome include marked peripheral eosinophilia, intense myalgias, and sensory symptoms, which can progress to a severe neuromuscular disorder with axonal degeneration and myopathy, constitutional symptoms with fever and pulmonary manifestations, resembling Löfgren’s syndrome. About one third of patients develop oedema and cutaneous induration, mainly affecting the extremities, similar to eosinophilic fasciitis. Interestingly, abnormal tryptophan metabolism has been postulated in both idiopathic sclerodema and eosinophilic fasciitis. Raised basal urine and plasma concentrations of kynurenine have been reported as well as higher concentrations after L-tryptophan loading. The possibility of a toxic contaminant of L-tryptophan in cases of eosinophilia-myalgia syndrome has not been excluded, however.

In contrast with systemic sclerosis, the female to male ratio in eosinophilic fasciitis is about equal. In a recent review of 52 patients seen at the Mayo Clinic the mean age of onset was 47 years (range 11-72) and in 24 (46%) it was related to strenuous exertion. A case has been reported to occur during pregnancy. Cutaneous manifestations are the presenting feature in most cases and evolve through three stages: pitting oedema, which is frequently present at onset, peau d’orange or dimpling, and induration. These stages are often present
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simultaneously in different areas of the body and virtually any part of the body can be involved, but the face is not usually affected. The arms and legs are most commonly affected (fig 2) and, in contrast with previously held views, simultaneous involvement of hands and feet is not uncommon. Not previously emphasised is the fact that localised morphoea may occur. Joint contractures, particularly of the elbows, ankles, and knees, are common, resulting from induration and sclerosis of subcutaneous tissue. Carpal tunnel syndrome is commonly described and occurs in about 25% of patients, sometimes preceding the skin manifestations.

Systemic involvement is more common than previously thought. There have been isolated cases of oesophageal, pulmonary, or cardiac involvement, but in contrast with systemic sclerosis there is relative sparing of the viscera. On the other hand, synovitis is common and may be the presenting feature. Sometimes there is a symmetrical polyarthritis which resembles rheumatoid arthritis, and joint erosions can occur. When synovial fluid has been examined it has been found to be inflammatory with a mononuclear cell infiltrate consisting mainly of lymphocytes, most of which carry the phenotype of activated suppressor/cytotoxic T cells. A low grade myositis is commonplace. Lakhampal et al reported abnormal electromyograms in 11 of 15 patients tested. Although only one had a raised serum creatine kinase level, four had low grade myositis on biopsy.

Associated haematological disease is commonly reported. This includes aplastic anaemia, attributed in some cases to a serum inhibitor of erythroid stem cells, and thrombocytopenia associated in some cases with antibodies to platelets. Malignant transformation is also seen.

Blood eosinophilia, often impressive, is the most striking laboratory abnormality. Eosinophilia greater than 7% of the differential count occurs in over 60% of cases. Peripheral eosinophilia can be transient, however, even in the absence of corticosteroid treatment, and the diagnosis of eosinophilic fasciitis should not be dismissed because of a normal laboratory finding. Similarly, tissue eosinophilia seen on histological examination of the fascia correlates with the presence or absence of a peripheral eosinophilia. Antinuclear antibodies, which characterise systemic sclerosis, are not found in eosinophilic fasciitis.

A deep biopsy, which must include tissue from the epidermis to skeletal muscle including the deep fascia, confirms the diagnosis (fig 3). Changes range from inflammation with minimal connective tissue change or connective tissue alteration to severe sclerosis. The deep fascia and septa of the subdermal fat are most extensively affected, whereas the epidermis is normal or only slightly atrophic. Some studies emphasise that there is overlap of histological features with systemic sclerosis. Tissue eosinophilia, for example, is also a feature of about 20% of patients with systemic sclerosis.

Initial reports suggest that eosinophilic fasciitis is a condition responsive to corticosteroids with a benign course. This, however, is not borne out in all cases described, and effects of therapeutic intervention must be judged against...
the background of spontaneous resolution, which occurs within three to five years of onset in a large proportion of cases. Relapses, although unusual, do occur. A clinical response to high dose prednisolone is expected in about 70% (remission in 15%, partial improvement in the rest) irrespective of when in the course the drug is given. The erythrocyte sedimentation rate and eosinophilia nearly always respond, but in some cases the disease progresses despite normal laboratory values. Various other agents have been used, and reports suggest that a response to hydroxychloroquine is more consistently seen than to colchicine or penicillamine. Due patient with carcinoma of the breast showed marked improvement after mastectomy.\textsuperscript{51}

Appendix: Proposed criteria for MCTD\textsuperscript{a}

\textbf{Sharp et al}\textsuperscript{a}

Major criteria
1 Myositis, severe
2 Pulmonary disease
   (a) CO diffusing capacity <70% normal lung or
   (b) Pulmonary hypertension
   (c) Proliferative vascular lesions on lung biopsy
3 Raynaud’s phenomenon or oesophageal hypomotility
4 Swollen hands or sclerodactyly
5 Highest noted anti-extraction nuclear antigen titre ≥1/10 000 and anti-U1RNP positive and anti-Sm negative

Definite diagnosis = 4 major criteria.

\textbf{Alarcon-Segovia et al}\textsuperscript{a}

1 Serological
   Positive anti-RNP at a haemagglutination titre of 1/1600 or higher
2 Clinical (at least three)
   Oedema of hands
   Synovitis
   Myositis (proved by laboratory findings or biopsy)
   Raynaud’s phenomenon (two or three colour phase)
   Acrosclerosis (with or without proximal scleroderma)
3 The association of oedema of the hands, Raynaud’s phenomenon, and acrosclerosis requires the addition of at least one of the other two criteria.

\textbf{Kasahara et al}\textsuperscript{a}

I Common symptoms
1 Raynaud’s phenomenon
2 Swollen fingers or hands
II Anti-nRNP antibody
III Mixed findings
   (A) SLE-like findings
   1 Polyarthritis
   2 Lymphadenopathy
   3 Facial erythema
   4 Pericarditis or pleuritis
   5 Leucocytopenia (<4×10\textsuperscript{9} cells/L) or
   6 Thrombocytopenia (<100×10\textsuperscript{9} platelets/L)
   (B) Progressive systemic sclerosis-like findings
   1 Sclerodactyly
   2 Pulmonary fibrosis, restrictive change of lung (vital capacity less than 80%) or reduced diffusion capacity (T\textsubscript{1}co less than 70%)
   3 Hypomotility or dilatation of the oesophagus
   4 Polymyositis like findings
   1 Muscle weakness
   2 Increased serum level of myogenic enzymes (creatine kinase)
   3 Myogenic pattern in electromyograph

Diagnosis
1 Positive in either of one of two common symptoms
2 Positive anti-RNP antibody
3 Positive in one or more findings in two or three disease categories of hands, B, and C

Diagnosis for MCTD is positive when diagnosis points 1, 2, and 3 are all fulfilled.

\textsuperscript{a}Adapted from the Proceedings of the international symposium on mixed connective tissue disease and anti-nuclear antibodies Tokyo, 29-30 August 1986.\textsuperscript{14}

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