

MIXED CONNECTIVE TISSUE DISORDERS (MCTD)

INTRODUCTION

Connective tissue diseases (auto immune rheumatic diseases) are a group of disorders of unknown etiology. Their classification depends upon identifying clusters of clinical and laboratory features. Five major diffuse connective tissue diseases (DCTD) exist according to current classification schema: systemic lupus erythematosus ; scleroderma ; polymyositis ; dermatomyositis ; and rheumatoid arthritis . A sixth disorder, Sjögren's syndrome, is commonly associated with each of these diseases, but is called primary Sjögren's syndrome when it occurs alone.

There are problems to classify individual patient into one of the defined autoimmune rheumatic disease because (1) Most of the clinical and laboratory features are not exclusive to one disease (2) Many of the symptoms and signs do not occur concurrently (3) Some of the patients present typical features of overlap syndrome of more than one disease. However, identification of specific disease is valuable for treatment, prognosis and research. The term Undifferentiated connective tissue diseases, Overlap syndrome, Mixed connective tissue disease have been used on patient who are not placed comfortably with any one of the defined autoimmune and rheumatic diseases. These terms are not interchangeable but unfortunately often used.

Undifferentiated connective tissue diseases (UDCTD): The diagnosis of UDCTD is used to those patients with features strongly suggestive of autoimmune rheumatic diseases but who do not fulfill the criteria of any one of the disorders. Ex: Raynaud's phenomenon, polyarthritis, rash, myalgias. This entity may evolve into a specific disease or may persists unchanged over years or may even disappear.

Overlap syndrome: The term has been used when two or more autoimmune diseases occur in the same individual simultaneously. Example: Systemic lupus erythematosus, rheumatoid arthritis, scleroderma, dermatomyositis, polymyositis in various combinations.

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DEFINITION: MCTD was first described by Sharp et al (1971-72) as a distinct syndrome in which the combination of features similar to those of systemic lupus erythematosus (SLE), systemic

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sclerosis (SSC), dermatomyositis/polymyositis and rheumatoid arthritis (RA). The disease was considered unique as it was associated with autoantibodies to a Ribonuclease – sensitive component of extractable nuclear antigen (ENA) now known as U₁RNP.

EPIDEMIOLOGY: MCTD is now recognized to occur throughout the world. It is predominantly a disease of females, with female to male ratio of 16:1. (1) The disease is seen among all age groups range from 4 – 80 years; the mean age of onset in adult is 35 years and 10 years in children. The incidence was low when compared with other collagen disease like systemic lupus erythematosus, dermatomyositis/polymyositis, rheumatoid arthritis and Scleroderma.

A study from Japan showed 2.7 per 1, 00,000, (SLE - 20.9 per 1, 00,000, scleroderma - 5.7 per 1, 00,000, PM/DM - 4.9 per 1, 00,000). The various studies have shown genetic association between HLA D4 and DR2.

Vinyl chloride and silica are the only environmental agents that have so far associated with MCTD. (2)

HISTO & IMMUNOPATHOLOGY: There is both T-cell & B cell response with less immune complex formation. The characteristic lesions in the involved organs are intensive obliterative, proliferative vascular lesions in large, medium and small vessels with less inflammatory infiltrates. There is increased synthesis of type III collagen result in abnormal type I – Type III ratio, whereas in scleroderma the ratio is maintained.

IS MCTD A SPECIFIC DISEASE?

A patient with swollen hands and/or puffy fingers in association with a high titer speckled ANA should be carefully followed for the evolution of overlap features. A high titer of anti-RNP antibodies in such a patient is a powerful predictor of a later evolution into MCTD (3)

The major reason to consider MCTD a distinct clinical entity is that the presence of high titers of anti-UI RNP antibodies

is associated with several distinctive clinical characteristics; for example:

- Patients with UI RNP antibodies seldom develop diffuse proliferative glomerulonephritis, psychosis, or seizures; these abnormalities are a major source of morbidity and mortality in SLE (4)
- Patients with UI RNP antibodies nearly always have an early development of Raynaud phenomenon and a nail fold capillary pattern that is the same as in Scl but different from classical SLE (5)
- The Raynaud phenomenon only occurs in about 25 percent of patients with classical SLE.
- Patients with UI RNP antibodies are more likely to develop pulmonary hypertension than patients with classical SLE or Scl. Pulmonary hypertension is the major cause of death in MCTD (6)
- Patients with UI RNP antibodies are more likely than SLE patients to be rheumatoid factor positive and develop an erosive arthritis (7)

Thus, the concept of MCTD is useful in defining a subgroup of patients with unique clinical features, treatment profile, and prognosis. Whether MCTD is a unique subset of SLE or Scl or is a distinct clinical entity is not clinically so important.

CLINICAL FEATURES

In the early phases of the MCTD many patients complain of easy fatigability poorly defined myalgias, arthralgias and Raynaud's phenomenon; and diagnostic considerations include the early stages of RA, SLE or undifferentiated connective tissue disease (UCTD). (8) Most, if not all, of the major organ systems may be involved at some time during the course of MCTD. (9) A high titer of anti-RNP antibodies in a patient with UCTD is a powerful predictor for a later evolution into MCTD. (10)

Skin and mucus membrane: The most common skin change is the Raynaud's phenomenon, which usually presents early in the course of the disease (11). Skin manifestations may present as a malar rash, generalized erythematous rash, pigmentation / depigmentation, chronic discoid lesions (similar to SLE, DM / PM, Scleroderma). It is characteristically associated with swelling of the hands particularly fingers (sausage appearance) and the skin may be taut, thick with occasional telangiectasia. Mucous membrane involvement can include orogenital and buccal ulcerations, nasal septal perforation, and the sicca complex.

Fever: Fever of unknown origin may be the presenting feature of MCTD (12). In this setting, it can usually be traced to a coexistent myositis, aseptic meningitis, serositis, lymphadenopathy, or intercurrent infection.

Vascular involvement: Raynaud's phenomenon is one of the commonest symptoms seen in 75%-100% of patients. It may be the first presenting symptom and its absence argues against this

diagnosis. It may be associated with ischemic necrosis, ulceration of finger tips (rare) and nail fold capillary scope may show dilated branched 'bushy' capillaries, which is useful for the prognostic stratification of those with early Raynaud's phenomenon. Angiographic studies revealed a high prevalence of medium-sized arterial occlusions (13)

Joints: Approximately 60 percent of patients with MCTD develop an obvious arthritis, often with deformities characteristic of rheumatoid disease, such as boutonniere deformities and swan neck changes. The radiographic appearance often resembles Jaccoud's arthropathy. A positive rheumatoid factor is found in about 70 percent of patients with MCTD (14)

Muscles: Myalgias and myositis can be seen in 30%-50% of patients. The features may be similar to dermatomyositis and polymyositis. It usually have favorable prognosis requiring less dose of corticosteroids. In most patients there is no demonstrable weakness, EMG abnormalities or elevation of muscle enzymes. It is often unclear whether the symptom represents a low-grade myositis, physical deconditioning or an associated fibromyalgia syndrome. The histology of muscle involvement in MCTD is the same as idiopathic inflammatory myopathy with features both of the vascular involvement of dermatomyositis and the cell-mediated changes of PM.

Gastrointestinal System: The symptoms may range from heartburn, dysphagia, diarrhea and symptoms of malabsorption. Disordered motility in the upper gastrointestinal tract is the commonest problem (15). It may present as vasculitis with complications like bowel ischemia, intestinal perforation and pancreatitis.

Neurological involvement: The original description of MCTD emphasized the lack of CNS involvement. Neurological manifestations are seen in 20-30% patients presenting as aseptic meningitis, trigeminal neuralgia, demyelination, transverse myelitis and peripheral neuropathy. The most frequent manifestation is a trigeminal (fifth cranial) nerve neuropathy.

Heart: All three layers of the heart may be involved in MCTD (16). An abnormal electrocardiogram is noted in about 20 percent of patients. The most common EKG changes are : right ventricular hypertrophy, right atrial enlargement, and inter-ventricular conduction defects. Pericarditis is the commonest clinical manifestation of cardiac involvement being reported in 10 to 30 percent of patients; pericardial tamponade is rare. Involvement of the myocardium is increasingly recognized (17). In some patients myocardial involvement is secondary to pulmonary hypertension (PHA); this is often asymptomatic in its early stages.

Lungs: There is a wide spectrum of pulmonary problems that can occur in MCTD (18):

- Pleural effusions
- Pleuritic pain
- Pulmonary hypertension

- Interstitial lung disease
- Thromboembolic disease
- Alveolar hemorrhage
- Diaphragmatic dysfunction
- Aspiration pneumonitis/pneumonia
- Obstructive airways disease
- Pulmonary infections
- Pulmonary vasculitis

Pleuropulmonary involvement is common, it may be asymptomatic or the patient may present with pleurisy and effusion, interstitial lung disease, pulmonary arterial hypertension (PAH). A major cause of death in MCTD is pulmonary hypertension. This complication is caused by a bland intimal proliferation and medial hypertrophy of pulmonary arterioles (19). The development of pulmonary hypertension has been correlated with a nail-fold capillary pattern similar to that seen in Scl, anti-endothelial cell antibodies and anticardiolipin antibodies (20). The early detection of pulmonary hypertension is increasingly important, as there are now more effective therapeutic options. Pulmonary function abnormalities may be due to the changes in the small vessels, smaller airways or respiratory muscle involvement.

High resolution computed tomography (HRCT) is a sensitive test to determine the presence of ILD. The commonest HRCT findings are septal thickening, ground-glass opacities, nonseptal linear opacities and peripheral / lower lobe predominance (21), which are similar to the findings in Scl. Rapid clearance of technetium labeled diethylenetriamine pentaacetate (DTPA lung scan) is closely correlated with CT evidence of interstitial lung disease and with a decreased DLCO (22). Based on a combination of high resolution CT (HRCT) and DTPA scans, the prevalence of interstitial lung disease in MCTD was found to be 66.6 percent. Untreated ILD is usually progressive with the development of severe pulmonary fibrosis in 25 percent of subjects after four years of follow-up (23).

Kidney: The absence of severe renal disease is a hallmark of MCTD; It is possible that high titers of anti-U1 RNP antibodies, which are characteristic of MCTD, may protect against the development of diffuse proliferative glomerulonephritis, independent of whether these antibodies occur in MCTD or classic SLE. It may be associated with membranous nephropathy, nephrotic syndrome, and renal crisis with accelerated hypertension akin to scleroderma.

Pregnancy: Conflicting reports describe the effects of pregnancy on the course of MCTD and the effects of MCTD on the fetus. One study described increased fetal wastage and a 40 percent prevalence of flares during pregnancy (24). The mechanism for pregnancy complications is probably an autoimmune reaction against placental tissues, as immunostaining studies show deposits of fibrinogen, IgG, IgM, IgA, and complement 3 (C3) localized to the trophoblast basement membrane (25). Furthermore, there

is an association of anti-endothelial antibodies with spontaneous abortion in MCTD (26).

Patients with severe Raynaud's phenomenon in general often have low birth weight infants (27).

LABORATORY FINDINGS: The laboratory manifestation includes Anemia, leucopenia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia (100%), positive coombs test, and Rheumatoid factor positive in 50 to 70% of patients. Antinuclear antibody positivity is seen in 100% of patients in high titre with coarse speckled pattern. Anti U₁RNP antibodies by haemagglutination test is highly characteristic feature of MCTD. Many patients also make antibodies directed against hnRNP-A2, fibrillin-1, and nucleosomes, but not to RNA polymerases (28). The absence of anti-Sm antibodies and anti-DNA antibodies in a sero positive for anti UIRNP is an important discriminating finding for MCTD from SLE. Antiphospholipid antibodies occur, but are less common than in those with SLE

DISTINCTIVE CLINICAL IMMUNOLOGICAL GENETIC FEATURES OF MCTD

Clinical - constellation of arthritis, swollen hands, Raynaud's phenomenon, abnormal esophageal motility, sclerodactyly, myositis, PAH

B cell response - High titer anti UIRNP particularly 70KDa, in the absence of other antibodies.

T cell response - SnRNP - 70KDa-reactive T cells found in the peripheral blood of the patients

Genetic - Association with HLADR4, DR2

Immune complexes - Low level of immune complexes found in the circulation than in the SLE

Histopathology - Proliferative vasculopathy in the absence of fibrosis and lymphocytic and plasmacytic infiltrates

Diagnostic criteria : Several attempts have been made to standardize the diagnostic criteria for MCTD. One study reviewed four sets of diagnostic criteria: Sharp, Alarcon-Segovia, Kasukawa, and Kahn, and concluded that those of Alarcon-Segovia and Kahn were "best" (29). The criteria utilized by Alarcon-Segovia had a sensitivity and specificity of 63 and 86 percent and is the most widely used (30).

CRITERIA DEFINED BY SEGOVIA -VILLARRE ET.AL

- A. Serological criteria: Anti UIRNP – at hemagglutination 1:1600
 - B. Clinical Criteria: (1) Swollen hands (2) Synovitis (3) Myositis (4) Raynaud's phenomenon (5) Acrosclerosis
- MCTD is present if A is associated with three or more clinical criteria one of which must be Synovitis / Myositis.

TREATMENT — No controlled trials have been performed to

guide therapy. Instead, the management of patients with MCTD generally rests upon the known effectiveness of specific therapies for similar problems seen in SLE, scleroderma, or polymyositis.

In general, those features of MCTD also observed among patients with systemic lupus erythematosus (eg, pleurisy, pericarditis) respond to prednisone at a dose of 0.25 to 1.0 mg/kg per day. By comparison, scleroderma-like features (eg, Raynaud phenomenon, pulmonary hypertension) are usually less responsive to therapy.

Pulmonary hypertension is the main cause of death among patients with MCTD; early consideration should be given to the administration of therapies which have shown some promise in this disorder. These therapies include a calcium channel blocker (usually long-acting nifedipine), anticoagulation, intravenous prostacyclin, prolonged immunosuppression (beginning with steroids and combining with cyclophosphamide if necessary), and angiotensin converting enzyme inhibitors (31)(32)(33)(34)(35) Advances in the treatment of pulmonary hypertension have led to reduced morbidity and mortality. Long-term treatment with intravenous epoprostenol or prostacyclin improves exercise capacity, hemodynamics and survival in most patients. Bosentan, an oral endothelin-1 antagonist and phosphodiesterase inhibitors such as sildenafil are proving useful in the management of this complication.

Many of the clinical manifestations of MCTD associated with significant morbidity tend to be intermittent and responsive to corticosteroids (prednisone 0.5 to 1.0 mg/kg per day); these disorders include aseptic meningitis, myositis, pleurisy, pericarditis, and myocarditis. By comparison, nephrotic syndrome, Raynaud phenomenon, deforming arthropathy, acrosclerosis, and peripheral neuropathies are usually steroid resistant.

Many gastrointestinal problems can be managed according to the treatment guidelines established for similar disorders in scleroderma. Prednisone, may be effective in the treatment of esophageal involvement (36).

Intravenous immune globulin (IVIG) may also have a role in the treatment of severe, eruptive skin disease (37), and of steroid resistant myositis.

Patients with severe hand deformities may be helped by soft tissue release operations and selected joint fusions.

PROGNOSIS: MCTD has relatively good prognosis in view of low prevalence of serious renal disease and life-threatening neurologic problems. Mortality associated with MCTD ranges, in different studies, from 16 to 28 percent at 10 to 12 years. (38). Those patients with more features of scleroderma and polymyositis had a worse prognosis. The major causes of death include progressive pulmonary hypertension and its cardiac complications, myocarditis, renovascular hypertension and cerebral hemorrhage. Morbidity is quite high in patients with MCTD due to multiple factors including recurrent musculoskeletal pain, fibromyalgia, gastroesophageal acid reflux, ischemic ulcers and even outright gangrene with autoamputation of digits, deforming

arthritis, consequences of extended corticosteroid use and the stress of living with a potentially fatal condition.

TREATMENT OF MCTD

Type of disease activity	Recommendations
1. Mild UTCD (Raynaud's Phenomenon, arthritis, fever)	NSAIDs, antimalarials, low dose steroids, calcium channel blockers(CCB), avoid cold exposure
2. Disease activity like RA	NSAIDs, antimalarials, low dose steroids, Methotrexate, or other immunosuppressive drugs.
3. Mild to moderate SLE like involvement (rash, anemia, leucopenia lymphadenopathy)	Avoid exposure to sun, topical steroids Antimalarials, low dose steroids
4. SLE like major organ involvement (myocarditis, myositis, glomerulonephritis and severe esophageal Involvement)	Moderate to high dose steroids, cyclophosphamide or other immuno-Suppressive drugs.
5. Esophageal involvement without upper sphincter involvement	Raise head end of the bed, avoid coffee & smoking, proton pump inhibitors, prokinetics.
6. Asymptomatic pulmonary arterial hypertension (PAH)	CCB, ACE inhibitors, vasodilators
7. Severe PAH	CCB, ACE inhibitors, corticosteroids, immunosuppressive drugs

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