Clinical manifestations of mixed connective tissue disease

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INTRODUCTION — Mixed connective tissue disease (MCTD) is defined as a generalized connective tissue disorder characterized by the presence of high titer anti-U1 ribonucleoprotein (RNP) antibodies in combination with clinical features commonly seen in systemic lupus erythematosus (SLE), scleroderma (Scl), and polymyositis (PM) \[1,2\]. It often takes several years before enough overlapping features have appeared to be confident that MCTD is the most appropriate diagnosis \[3\]. The distinctive overlap features of SLE, Scl and PM commonly appear sequentially over time. Thus, in its early stages, MCTD is often referred to as an undifferentiated connective tissue disease (UCTD) \[4,5\]. (See "Undifferentiated systemic rheumatic (connective tissue) diseases and overlap syndromes".)

This topic will review the major clinical manifestations that can occur in patients with MCTD. The pathogenesis and diagnosis of this disorder are discussed separately. (See "Definition and diagnosis of mixed connective tissue disease".)

CLINICAL MANIFESTATIONS — The early clinical features of MCTD are nonspecific and may consist of general malaise, arthralgias, myalgias, and low-grade fever \[6,7\]. A specific clue that these symptoms are caused by a connective tissue disease is the discovery of a positive antinuclear antibody (ANA) in association with the Raynaud phenomenon \[1\].

As will be described below, almost any organ system can be involved in MCTD. There are, however, four clinical features that suggest the presence of MCTD rather than another connective tissue disorder such as SLE or Scl:

- Raynaud phenomenon and swollen hands or puffy fingers \[8,9\].
- The absence of severe renal and central nervous system (CNS) disease \[10,11\]
- More severe arthritis and the insidious onset of pulmonary hypertension (not related to lung fibrosis) differentiate MCTD from both SLE and Scl \[12-14\]
- Autoantibodies whose fine specificity is anti-U1 RNP, especially antibodies to the 68 Kd protein \[15\].
General features — MCTD is much more common in women than in men (ratio of 16 to 1) [16]. Most patients present in the second or third decades of life. Unlike SLE, however, sun exposure is not a precipitating factor. Drug-induced MCTD is a rare occurrence, but may be an occasional feature of anti-TNF therapy [17,18]. Vinyl chloride [19] and silica [20] are the only environmental agents that have so far associated with MCTD.

In the early phases of the MCTD many patients complain of easy fatigability, poorly defined myalgias, arthralgias, and the Raynaud phenomenon; and diagnostic considerations include the early stages of RA, SLE or undifferentiated connective tissue disease (UCTD) [21]. Most, if not all, of the major organ systems may be involved at some time during the course of MCTD, including the skin, joints, muscles, heart, lungs, gastrointestinal tract, kidneys, central nervous system, and hematologic system [3,4]. A high titer of anti-RNP antibodies in a patient with UCTD is a powerful predictor for a later evolution into MCTD [22].

Skin — Skin involvement occurs in most patients with MCTD. The most common skin change is the Raynaud phenomenon, which usually presents early in the course of the disease [8,23]. Swollen digits and occasionally total hand edema are also distinctive features (picture 1) [13,24,25]; sclerodactyly and calcinosis cutis have been observed [26,27].

Other skin manifestations, such as discoid plaques and malar rash, are indistinguishable from SLE (picture 2A-C). (See "Mucocutaneous manifestations of systemic lupus erythematosus"). Mucous membrane involvement can include orogenital and buccal ulcerations, nasal septal perforation, and the sicca complex [13,28,29].

Fever — Fever of unknown origin may be the presenting feature of MCTD [24]. In this setting, it can usually be traced to a coexistent myositis, aseptic meningitis, serositis, lymphadenopathy, or intercurrent infection.

Arthritis — It is now apparent that joint involvement in MCTD is more common and frequently more severe than in classic SLE. 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 (picture 3) [12,25]. The radiographic appearance often resembles Jaccoud's arthropathy [30].

Other changes that can occur include small marginal erosions [31-33] (picture 4) and, in a few patients, destructive arthritis, including arthritis mutilans (picture 5 and picture 6) [12,34].

A positive rheumatoid factor is found in about 70 percent of patients with MCTD [35]. Anti-cyclic citrullinated peptide (CCP) antibodies are found in about 50 percent, especially in those MCTD patients who also fulfill the American College of Rheumatology diagnostic criteria for rheumatoid arthritis (RA) [36].

Myositis — One of the three overlap features required for the diagnosis of MCTD is an inflammatory myopathy clinically and histologically identical to PM [24,37,38]. (See "Clinical manifestations and diagnosis of adult dermatomyositis and polymyositis"). Myalgia is a common symptom in patients with the MCTD syndrome [39]. 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. Sometimes myositis occurs as an acute flare against a background of general disease activity [24]. Cases of a low grade, insidious, and persistent inflammatory myopathy have also been described. The histology of muscle involvement in MCTD is the same as idiopathic inflammatory myopathy [40,41] with features both of the vascular involvement of dermatomyositis and the cell-mediated changes of PM [42]. It is increasingly apparent that a diagnosis of "pure" PM is relatively rare, and most patients with an inflammatory myopathy turn out to have an overlap syndrome [43].

Cardiac disease — All three layers of the heart may be involved in MCTD [44]. 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 [45,46]. In some patients myocardial involvement is secondary to pulmonary hypertension (PAH); this is often asymptomatic in its early stages [47]. (See 'Pulmonary hypertension' below.)

Pulmonary involvement — The lungs are commonly affected in MCTD with involvement in about 75 percent of patients [48,49]. There is a wide spectrum of pulmonary problems that can occur in MCTD [50]:

- 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

Early symptoms that should alert one to pulmonary involvement are dry cough, dyspnea and pleuritic chest pain [50].

Interstitial lung disease — Interstitial lung disease (ILD) occurs in 30 to 50 percent of subjects [51]. A reduction in the single breath-diffusing capacity for carbon dioxide (DLCO) is commonly found on lung function testing in the early stages of ILD [50].

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 [52,53], which are similar to the findings in Scl [54]. 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 [55].

Based upon 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 [55]. Untreated ILD is usually progressive with the development of severe pulmonary fibrosis in 25 percent of subjects after four years of follow-up [51]. Esophageal dilatation has been associated with a tendency to develop interstitial lung disease in MCTD [56].

Pulmonary hypertension — A major cause of death in MCTD is pulmonary hypertension [57]. This complication is caused by a bland intimal proliferation and medial hypertrophy of pulmonary arterioles (picture 7).

The presence of pulmonary hypertension may be suspected from the history, physical findings, and laboratory tests, particularly if the patient has four or more of the following [58]:

- Exertional dyspnea
- Systolic pulsation at the left sternal border
- An accentuated second pulmonary sound
- Dilation of the pulmonary artery on x-ray (picture 8)
- Right ventricular hypertrophy on electrocardiogram
- Right ventricular enlargement on echocardiogram

The early detection of pulmonary hypertension is increasingly important, as there are now more effective therapeutic options. PAH is probably under-diagnosed, its prevalence in a community rheumatology practice was 13 percent, based on echocardiography to estimate right ventricular systolic pressure [59].

Two-dimensional echocardiography with Doppler flow studies is the most useful screening test [60], with a definitive diagnosis requiring cardiac catheterization showing a mean resting pulmonary artery pressure greater than 25mm Hg at rest [61]. 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 [62-64]. (See "Overview of pulmonary hypertension".)

Renal disease — The absence of severe renal disease is a hallmark of MCTD [1]. 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 [10,65].

However, some degree of renal involvement occurs in about 25 percent of patients [10,13,66]. Membranous nephropathy is the most common finding (picture 9A-E) [10,13,67] and nephrotic range proteinuria may occur [65]. Hypertensive crises similar to Scl kidney have also been reported [68,69]. (See "Scleroderma renal crisis".)
Gastrointestinal disease — Gastrointestinal involvement is the commonest clinical overlap feature with Scl, occurring in about 60 to 80 percent of patients [11,48]. Disordered motility in the upper gastrointestinal tract is the commonest problem [56,70,71]. There have been case reports of hemoperitoneum, hematobilia, duodenal bleeding, megacolon, pancreatitis, ascites, and protein loosing enteropathy, primary biliary cirrhosis, portal hypertension, pneumatosis intestinalis and autoimmune hepatitis [13,72-74]. Malabsorption syndrome can occur secondarily to small bowel dilation with bacterial overgrowth. Liver involvement in the form of chronic active hepatitis and Budd-Chiari syndrome has been described. Pseudodiverticulae, identical to those seen in Scl, may be seen along the anti-mesenteric border of the colon. Abdominal pain in MCTD may result from bowel hypomotility, serositis, mesenteric vasculitis, colonic perforation and pancreatitis.

Central nervous system disease — The original description of MCTD emphasized the lack of CNS involvement [1]. This observation remains largely correct since patients with MCTD do not develop severe complications such as cerebritis, psychosis, or seizures [75]. However, approximately 25 percent of patients have some, typically mild form of CNS disease [57,75].

- The most frequent CNS manifestation is a trigeminal (fifth cranial) nerve neuropathy, which may be the presenting feature of the disease [76,77]. Trigeminal neuropathy is also the most common CNS problem in patients with Scl.
- Headaches are also common. They are most often vascular in origin [78], but can be caused by aseptic meningitis [79,80], due to the disease itself or to a reaction to nonsteroidal anti-inflammatory drugs [81,82] and by muscle tension and myofascial trigger points.
- Sensorineural hearing loss is often not recognized, but is reported to occur in about 50 percent of MCTD patients [83].

Isolated cases of cerebral hemorrhage [84], transverse myelitis [85], cauda equina syndrome [86], retinal vasculitis [87], progressive multifocal encephalopathy [88,89], and demyelinating neuropathy [90] have also been reported.

Hematologic and laboratory abnormalities — Nonspecific hematologic and laboratory abnormalities are common in MCTD:

- Approximately 75 percent of patients have a low-grade anemia [13].
- As in classic SLE, leukopenia, mainly affecting the lymphocyte series, is a common finding that tends to correlate with disease activity [13,91]. (See "Hematologic manifestations of systemic lupus erythematosus in adults").
- The majority of patients have hypergammaglobulinemia [24,92].
- The rheumatoid factor is positive in 50 to 70 percent of patients [35].
- Anti-cyclic citrullinated peptide (CCP) antibodies are found in about 50 percent of patients [36].
- Many patients also make antibodies directed against hnRNP-A2, fibrillin-1, and nucleosomes, but not to RNA polymerases [93] or proteasome [94].
- Antiphospholipid antibodies occur less frequently than in SLE [95,96]. If present, they tend to correlate with thrombocytopenia and pulmonary hypertension, but not with
thrombosis and/or abortions. Anti-beta(2)-glycoprotein I antibodies are fairly uncommon in MCTD, occurring in about 10 percent of patients. Their presence is often associated with the development of pulmonary hypertension [64].

- Anti-endothelial cell antibodies occur in some 50 percent of MCTD patients [97], and appear to be reactive with a voltage-dependent anion-selective channel 1 (VDAC-1) [98]. Their occurrence tends to be associated with microvascular injury in the lung and kidneys [99].

Less common problems include thrombocytopenia, thrombotic thrombocytopenic purpura [100,101], Coombs positive hemolytic anemia [102], and red cell aplasia [103].

The one specific serological finding is that, by definition, all patients with MCTD have a positive ANA whose fine specificity is anti-U1 RNP, especially antibodies to the 68 Kd protein [104]. (See "Definition and diagnosis of mixed connective tissue disease").

Vasculopathy — The Raynaud phenomenon is a typical early feature of MCTD [23]; thus, an absence of Raynaud argues against this diagnosis. The characteristic vascular lesion of MCTD is bland intimal proliferation and medial hypertrophy affecting medium and small size vessels [105]; this is also the characteristic pathology in pulmonary hypertension and renovascular crises (picture 2A-C) [57]. This pathologic changes differs from that usually noted in SLE, in which perivascular inflammatory infiltrates and necrosis are more characteristic.

Similar to Scl, abnormal fingernail capillaroscopy is a common feature of MCTD [106,107]. The capillary pattern is characterized by dilation and drop-out (picture 10). Nailfold capillaroscopy can be performed at the bedside, a test that is useful for the prognostic stratification of those with early Raynaud phenomenon [108]. (See "Clinical manifestations and diagnosis of the Raynaud phenomenon", section on 'Nailfold capillary microscopy'.)

Angiographic studies reveal a high prevalence of medium-sized arterial occlusions (picture 11) [109].

Pregnancy — Conflicting reports describe the effects of pregnancy on the course of MCTD and the effects of MCTD on the fetus [110,111]. One study described increased fetal wastage and a 40 percent prevalence of flares during pregnancy [112]. Another report, however, did not confirm disease exacerbations associated with pregnancy or the postpartum period [24,113]. Small for gestational age infants occurred in 50 percent and 63 percent of pregnancies in one series of 20 patients [111]. 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 [114]. Furthermore, there is an association of anti-endothelial antibodies with spontaneous abortion in MCTD [115].

Patients with severe Raynaud phenomenon in general often have low birth weight infants [116], presumably due to placental ischemia. This relationship has also been described in patients with MCTD [117].
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