

Overview of Mixed Connective Tissue Disease in Adults

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Abstract

Introduction: Mixed connective tissue disease (MCTD) is described as a connective tissue disorder characterized by the presence of high titers of a distinctive autoantibody, now called anti-U1 ribonucleoprotein (anti-RNP). It is assumed to be an overlap syndrome that includes clinical features of major diffuse connective tissue diseases. The overlap feature often take several years to appear clear enough to be establish the confident diagnosis of MCTD. Nowadays, there is a consensus to consider MCTD as a “distinct clinical entity”.

Aim of the Work: The definition, criteria, clinical features, prognosis, and general principles of management will be presented in this review. In-depth details of management will not be presented.

Methodology: This article is a comprehensive review of medical literature regarding mixed connective tissue disease.

Conclusion: In most cases, MCTD cannot be differentiated from other classical DCTDs in the early stages as the simultaneous presence of overlap features seen in SLE, SSc, and polymyositis (PM) is rarely obvious. The overlapping features appear more evident sequentially over several years. Early symptoms are usually puffy fingers, easy fatigability, poorly defined myalgias, arthralgias, low-grade fever, and Raynaud phenomenon.

Mixed connective tissue disease has a relatively good prognosis and excellent response to glucocorticoids due to a low prevalence of serious renal disease and life-threatening neurologic problems. MCTD-associated mortality are substantial in various report, ranging from 16 to 28 percent at 10 to 12 years follow-up. The highest mortality rate is seen in patients with vascular involvement. The primary causes of death include progressive pulmonary hypertension (PAH) and its heart complications.

The management of MCTD is generally based upon the known effectiveness of specific therapies for similar diseases.

Keywords: Mixed Connective Tissue Disease; MCTD; Definition; Criteria; Prognosis; Management

Introduction

In 1972, mixed connective tissue disease (MCTD) was first described as a connective tissue disorder characterized by the presence of high titers of a distinctive autoantibody to an extractable nuclear antigens (anti-ENA) [1]. The autoantibody is now called anti-U1 ribonucleoprotein (anti-RNP). MCTD is assumed to be an overlap syndrome that includes clinical features of major diffuse connective tissue diseases (DCTD) in association with anti-U1 RNP antibodies [2]. The overlap feature often take several years to appear clear enough to be establish the confident diagnosis of MCTD [3]. Thus, MCTD is often described as an undifferentiated connective tissue disease (UCTD) early in its course.

Limited data are available regarding the epidemiology of mixed connective tissue disease (MCTD). One estimate from county on United stated found an annual incidence of 1.9 per 100,000 adults, while another study from Norway found much lower incidence, with a rate of 0.21 per 100,000 [4]. It appears that MCTD is much more common in women than in men despite the wide range in estimation [4].

The definition, criteria, clinical features, prognosis, and general principles of management will be presented in this review. In-depth details of management will not be presented.

Methods

PubMed database and Google scholar search engine were mainly used for medical literature search. On PubMed, we searched the database using Medical Subject Heading (MeSH) terms for precise identification relevant manuscripts. The search result was filtered for a time period between 2000 and 2020. However, essential old paper such as that first described mixed connective tissue disease (MCTD) are reviewed. The terms used in the search methods included mixed connective tissue disease, MCTD, criteria, definition, clinical, differential diagnosis, prognosis and management.

Definition and criteria

Diffuse connective tissue diseases (DCTD) include five major disorders: systemic lupus erythematosus (SLE); systemic sclerosis (SSc); polymyositis (PM); dermatomyositis (DM); and rheumatoid arthritis (RA). Sjögren's syndrome could commonly occur with each of these diseases. The definitive diagnosis of DCTD is based upon criteria derived from expert opinion and they are updated from time to time according to new research. Hence, none of the DCTDs can be defined as specific/distinct disease because a distinct disease requires both unique clinical features and consistent pathology by definition. Following first description of MCTD in 1972, there was controversy regarding its place as a distinctive disorder in DCTDs [2]. Nowadays, there is a consensus to consider MCTD as a "distinct clinical entity". Over long course of years, one autoimmune rheumatic disease may evolve into another; then will be considered as an overlap syndrome. The overlap syndrome occurs in approximately 25 percent of patients with one autoimmune rheumatic disease [5]. The presence of DCTD features not sufficient for diagnosis are considered to as an "undifferentiated" connective tissue disease (UCTD) [6].

Many attempts to develop and standardize the diagnostic criteria for MCTD have been made. There is a four sets of diagnostic criteria: Sharp; Alarcon-Segovia; Kasukawa; and Kahn. According to one review aimed to assess these methods, Alarcon-Segovia and Kahn criteria ae the best [7]. Alarcon-Segovia's criteria have a sensitivity and specificity of 63 and 86 percent respectively; comparable accuracy is found with Kahn's criteria [8].

Clinical features

In most cases, MTCD cannot be differentiated from other classical DCTDs in the early stages as the simultaneous presence of overlap features seen in SLE, SSc and polymyositis (PM) is rarely obvious. The overlapping features appear more evident sequentially over several years. Early symptoms are usually puffy fingers, easy fatigability, poorly defined myalgias, arthralgias, low-grade fever and Raynaud phe-

nomenon. Hence, it is common to diagnose these presentation at this point as rheumatoid arthritis (RA), SLE, SSc or UCTD [9]. The presence of swollen hands and/or puffy fingers in association with a high level of antinuclear antibody (ANA) should prompt careful follow up and observation for possible appearance of overlap features. A high titer of anti-RNP antibodies is a powerful predictor of developing MCTD in these patients [10]. Severe inflammatory myopathy, acute arthritis, aseptic meningitis, transverse myelitis, digital gangrene, high fever, acute abdomen and trigeminal neuropathy, and sensorineural hearing loss are less common early presentation [11].

MCTD can affect any organ system. MCTD over other connective tissue disorders: Raynaud phenomenon and/or swollen hands or puffy fingers [12]; no severe renal and central nervous system affection [10]; more severe arthritis than typical and the insidious onset of pulmonary hypertension (PHT) not related to lung fibrosis [11]; antibodies to ribonucleoprotein (anti-U1), especially the 68 kD protein.

As mentioned, the features are nonspecific early in MCTD course. Many patients complain of easy fatigability, myalgias, arthralgias, and of the Raynaud phenomenon leading to immature diagnosis of early stages of rheumatoid arthritis (RA), SLE, or undifferentiated connective tissue disease (UCTD). Typically, MCTD patient is a female in the second or third decades of life, not affected by sun exposure (unlike SLE). Drug-induced MCTD may occur rarely, example includes anti-tumor necrosis factor (TNF) therapy. Two incriminated environmental agents are vinyl chloride and silica.

Fever of unknown origin could be the first complaint of MCTD [2]. Tracing fever to a coexistent myositis, aseptic meningitis, serositis, lymphadenopathy, or intercurrent infection may occur. Most patients of MCTD will have early skin involvement. Usually, skin affection is the presenting feature in the form of Raynaud phenomenon in most cases [9]. Swollen digits (may be total hand) is also distinctive features [12]. Other frequently reported features include superficial vasculitis of the digits, acrosclerosis and calcinosis cutis [9]. Digit autoamputation was reported with severe Raynaud phenomenon.

Joint involvement is seen more commonly and is frequently more severe than that seen in classic DCTD. Obvious arthritis is encountered in about 60 percent of patients with MCTD, often with deformities characteristic of rheumatoid disease, such as boutonniere deformities and swan neck changes [11]. Other possible changes include small marginal erosions and a destructive arthritis, including arthritis mutilans [11]. About 70 percent of patients with MCTD show a positive rheumatoid factor (RF), and 50 percent will have a positive anticyclic citrullinated peptide (CCP) antibodies [13,14]. The term "rhupus" is used to indicate a similar overlap between SLE and RA in which a symmetric erosive polyarthritis of the small and large joints and symptoms of SLE with high titers of antibodies to double-stranded (dsDNA) and Sm as well as RF and anti-CCP antibodies are seen. Rhupus is rare with an estimated prevalence of 0.09 percent and it differs from usual MCTD in having only mild systemic involvement, and less common Raynaud phenomenon.

The presence of inflammatory myopathy (myositis) clinically and histologically identical to polymyositis (PM) is considered one of the three required overlap features for the diagnosis of MCTD [2]. Myalgia is a common, while weaknesses, electromyographic (EMG) changes, and elevation of muscle enzymes are not present in patients with the MCTD. There is a controversy whether muscular presentations are explained by a low-grade myositis, a physical deconditioning, or an associated fibromyalgia syndrome. However, a true myositis may occur in the form of acute flare against a background of general disease activity [2]. Some have reported a low-grade, insidious, and persistent inflammatory myopathy in patient with MCTD. The histologic assessment shows similar pattern seen idiopathic inflammatory myopathy with both vascular involvement of dermatomyositis and the cell-mediated changes of PM.

Approximately, three quarter of patients with MCTD show features of lungs involvement [15]. Lung involvement occurs in variable forms and wide spectrum of diseases that include pleural effusions, pleuritic pain, pulmonary hypertension (PAH), interstitial lung disease (ILD), thromboembolic and hemorrhagic disease, muscular dysfunction, and respiratory infections. Symptoms that warrant lung involvement are dry cough, dyspnea, and pleuritic chest pain. Interstitial lung disease occurs in at least 50 percent of patients with MCTD [16]. Using a combination of diethylenetriamine pentaacetate (DTPA) lung scan and high-resolution computed tomography (HRCT) raise the prevalence 67 percent [16]. The presence of Raynaud phenomenon, symptoms of dysphagia, arthritis, anti-Sm, or RF is considered a

risk factor for ILD. Pulmonary hypertension (PHT) is a complication responsible for high proportion of mortality in MCTD patients, and hence early detection is crucial. PHT is caused by bland intimal proliferation and medial hypertrophy of pulmonary arterioles. It is suspected in the presence of ≥ 4 of the following 6: exertional dyspnea; systolic pulsation at the left sternal border; an accentuated second pulmonary sound; dilation of the pulmonary artery on radiograph; right ventricular hypertrophy on electrocardiogram; right ventricular enlargement on echocardiogram [17]. The early detection of PAH is increasingly important, as there are potentially effective therapeutic options. PAH is probably underdiagnosed; its prevalence in a community rheumatology practice was 13 percent, based upon echocardiography to estimate right ventricular systolic pressure. Two-dimensional echocardiography with Doppler flow studies is the most useful screening test but a definitive diagnosis requires cardiac catheterization.

Thirty percent of MCTD patients have symptomatic cardiac involvement, and up to 40 percent have subclinical disease [18]. All three layers of the heart may be involved. Cardiac involvement alone accounts for one fifth of MCTD mortality [18]. About 20 percent of patients show abnormal electrocardiogram (ECG), most commonly hemiblock, bundle branch block, and atrioventricular block [18]. ECG is able to detect subclinical cardiac disease in up to 38 percent of patients. Pericardial effusion and mitral valve prolapse are among the most common causes of echocardiographic changes and may be seen in up to 25 percent of MCTD patients. When manifests, cardiac affection is most commonly in the form of pericarditis; being reported in up to 40 percent of patients [18]. Myocardial disease may occur, and when it does, it could be secondary to pulmonary hypertension (PAH) that is often asymptomatic in its early stages.

Sjögren's syndrome is relatively common with MCTD. According to one estimate, 32 percent of MCTD patients have Sjögren's syndrome [19]. The ocular and oral symptoms were typically moderate to severe.

The absence of severe renal disease is typical in mixed connective tissue disease [1]. It is proposed that a high titers of anti-U1 RNP antibodies may against the development of diffuse proliferative glomerulonephritis [10]. Some degree of renal involvement, however, may occur in about 25 percent of MCTD patients [12]. When renal involvement occur, it is most commonly in the form of membranous nephropathy [10]. Proteinuria in nephrotic range and hypertensive crises were reported.

The most common features that overlap with systemic sclerosis (SSc) are gastrointestinal. These feature occur in about 60 to 80 percent of patients with MCTD [15]. Motility disorder in the upper gastrointestinal tract is the most commonly seen feature. Pathological examination of lower esophageal biopsies may show severe atrophy and loss of smooth muscle cells in the muscular layer, followed by fibrosis, and with IgG and C3 deposition on immunofluorescence microscopy. Some have reported a rare occurrence of hemoperitoneum, hematemesis, duodenal bleeding, megacolon, pancreatitis, ascites, protein-losing enteropathy, primary biliary cholangitis, portal hypertension, pneumatosis intestinalis, and autoimmune hepatitis [12]. Malabsorption syndrome can occur secondary to small intestinal dilation with bacterial overgrowth. Liver involvement in chronic active hepatitis and Budd-Chiari syndrome has been identified. Pseudodiverticulae, similar to those seen in SSc, can be seen along the antimesenteric boundary of the colon. Abdominal pain in MCTD can result from hypomotility of the intestine, serositis, mesenteric vasculitis, colonic perforation, and pancreatitis.

When first described, MCTDs lack central nervous system involvement [1]. Since patients with MCTD do not develop severe CNS complications such as cerebritis, psychosis, or seizures, the initial observation remains largely correct [20]. However, about one quarter of MCTD patients may have some mild form of CNS involvement [20,21]. The most common presentation of CNS in these patient is trigeminal nerve neuropathy, and when present, it could be the presenting feature of the disease [22]. Headaches are another common CNS symptom that often vascular in origin. Less frequently, headaches can be caused by aseptic meningitis, either due to the disease itself, as a reaction to nonsteroidal anti-inflammatory drugs (NSAIDs), or by muscle tension and myofascial trigger points. Mild, unobvious sensorineural hearing loss may occur without being recognized in half of patients. Isolated cases of CNS manifestation as cerebral hemorrhage, transverse myelitis, cauda equina, retinal vasculitis, progressive multifocal encephalopathy, demyelinating neuropathy, reversible

posterior encephalopathy, and adhesive arachnoiditis have been published. Mild cognitive impairment may occur in MCTD patients and it is not associated neuropsychiatric features as seen in patients with lupus.

Patients with MCTD may show nonspecific hematologic and laboratory abnormalities. The one universal finding is a positive ANA, other common abnormalities include low-grade anemia (75 percent) [12], leukopenia mainly affecting the lymphocytes [12], hypergammaglobulinemia [2], positive rheumatoid factor (50 - 70 percent) [13], anticyclic CCP antibodies (50 percent) [14], antibodies directed against heterogeneous nuclear ribonucleoprotein, antiphospholipid antibodies that occur less frequently than in SLE, and antiendothelial cell antibodies (50 percent). Less frequent hematologic and laboratory problems include thrombocytopenia, thrombotic thrombocytopenic purpura, Coombs positive hemolytic anemia, and red cell aplasia.

Regarding vasculopathy, Raynaud phenomenon is considered typical early feature and its absence should cast doubt on the diagnosis. The characteristic vascular involvement in these patient appears as a mild intimal proliferation and medial hypertrophy affecting medium- and small-sized vessels, however, angiographic studies indicate a high prevalence of medium-sized arterial occlusions. this is also the characteristic pathology in PAH and renovascular crises [21]. Intimal proliferation and medial hypertrophy vary from those frequently seen in SLE, in which perivascular inflammatory infiltrates and necrosis are more characteristic. Elevated endostatin levels in MCTD are associated with digital ulcers and all-cause mortality. As in SSc, irregular fingernail capillaroscopy is a common encounter in MCTD. The capillary pattern is distinguished by dilation and dilation. Nailfold capillaroscopy can be performed on the bedside and it aids the prognostic stratification of those with early Raynaud phenomenon.

Prognosis

According to first description, mixed connective tissue disease has a relatively good prognosis and excellent response to glucocorticoids [1]. This is explained by the fact that these patients have a low prevalence of serious renal disease and life-threatening neurologic problems [21]. And when they occur in 25 percent of patient, renal and CNS involvements are fairly mild.

Although MCTD Patients initially appear with features similar to that of systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, or vasculitis, they are considered as a different subset of patients at risk for significant morbidity and mortality. In one follow-up analysis, 36 percent of patient required repeated courses of glucocorticoids [23]. PHT was the cause of death 6 out of 11 patients who died during the follow-up period [21]; five had IgG anticardiolipin antibodies which is considered a risk factor for severe disease.

Overall mortality is apparently lower in patients with MCTD than in patient with typical SLE. However, MCTD-associated mortality are substantial in various report, ranging from 16 to 28 percent at 10 to 12 years follow-up [23]. The highest mortality rate is seen in patients with vascular involvement. One large survival analysis reported a survival rates of 98, 96 and 88 percent at 5, 10 and 15 years following the diagnosis among 280 patients with MCTD respectively [24].

The primary causes of death include progressive pulmonary hypertension (PAH) and its heart complications [21]. Interstitial lung disease (ILD) is associated with 7.9 percent mortality at mean 4.2 years of follow-up; patients with severe lung fibrosis had a mortality of 20.8 percent [25]. Other recognized main cause of death include myocarditis, renovascular hypertension, and cerebral hemorrhage.

Principles of management

In spite of being considered as a benign and extremely responsive to glucocorticoids, mixed connective tissue disease (MCTD) was originally described as incurable. The management of MCTD is generally based upon the known effectiveness of specific therapies for similar diseases due to the lack of controlled trials comparing therapeutic approaches.

Generally, features of MCTD that also present in SLE (or overlap) such as pleurisy and pericarditis respond to prednisone at a dose of 0.25 to 1.0 mg/kg per day. On the other hand, features that overlap with systemic sclerosis (SSc) as Raynaud phenomenon and PHT are usually less responsive to therapy. Since PHT is considered the main cause of mortality in patients with MCTD, and since prompt treatment have shown some promise, early diagnosis should be ensured by routine echocardiography (ECG) for all patients. A threshold of 36 mmHg is used to establish the diagnosis of PHT as recommended by the MCTD Research Committee or the European Society of Cardiology [26]. The management of PHT in these patient include a long-acting calcium channel blocker such as nifedipine, anticoagulation, intravenous prostacyclin, prolonged immunosuppression, and angiotensin-converting enzyme inhibitors [27]. In severely progressed disease, a heart-lung transplant could be considered to achieve survival. Many of MCTD features associated with significant morbidity tend to have intermittent course and adequate response to glucocorticoids such as prednisone 0.5 to 1.0 mg/kg per day. These manifestations include aseptic meningitis, myositis, pleurisy, pericarditis, and myocarditis. By contrast, features as nephrotic syndrome, Raynaud phenomenon, deforming arthropathy, acrosclerosis, and peripheral neuropathies tend to show steroid resistant.

Gastrointestinal involvement is mostly managed according to the guidelines for similar disorders in scleroderma [28]. Esophageal involvement may response to prednisone therapy according to one longitudinal study [12]. In this study, an average dose of 25 mg/day for the treatment of esophageal dysmotility showed a significant improvement.

Rituximab could be used in patients with steroid resistant thrombocytopenia or autoimmune hemolytic anemia in a similar method of managing SLE. Sever eruptive skin involvement and steroid resistant myositis may be managed by IVIG [29]. Surgical interventions for soft tissue release and selected joint fusions could be adequate option for patients with severe hand deformities may be helped by soft tissue release operations and selected joint fusions.

Conclusion

Mixed connective tissue disease (MCTD) is described as a connective tissue disorder characterized by the presence of high titers of a distinctive autoantibody, now called anti-U1 ribonucleoprotein (anti-RNP). It is assumed to be an overlap syndrome that includes clinical features of major diffuse connective tissue diseases. The overlap feature often take several years to appear clear enough to be establish the confident diagnosis of MCTD. Nowadays, there is a consensus to consider MCTD as a “distinct clinical entity”.

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