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Mixed Connective Tissue Disease

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Abstract Mixed connective tissue disease (MCTD) is a condition characterized by the overlap of features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and polydermatomyositis (PM/DM) in association with high titers of antibodies against a ribonuclear protein (RNP). Clinical manifestations of MCTD are extremely variable and disease onset may be undifferentiated.

Raynaud phenomenon, swollen fingers, arthritis, myositis, esophageal dysfunction and pulmonary hypertension represent the most frequent clinical manifestations. In the original description, MCTD was described as benign conditions characterized by the absence of renal and neurological manifestations and a good response to corticosteroid therapy. This observation has not been confirmed by studies that have shown that one-third of MCTD patients have a severe disease and require corticosteroid and immunosuppressive therapy. The major cause of death in these patients is pulmonary hypertension, followed by infections.

A debate is still open on whether MCTD represent a distinct clinical entity or rather an overall between different established connective tissue diseases (CTDs). The answer to this question might become clear as more data on disease pathogenesis will be known.

Keywords Mixed connective tissue disease · classification criteria · anti-U1RNP antibodies

Introduction

Mixed connective tissue disease (MCTD) was first described by Sharp in 1972 as a condition characterized by the overlap of features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and polydermatomyositis (PM/DM) in association with high titers of antibodies against a ribonuclear protein (RNP) (1). A debate is still open on whether MCTD constitutes a distinct clinical entity or rather represents the overlap of well-defined conditions or a "bridge" between different connective tissue diseases (CTDs) within the spectrum of systemic autoimmunity (2, 3).

Clinical Manifestations

The clinical manifestations of MCTD at onset and during the follow-up are reported in Table 8.1. The onset of MCTD is variable and is often characterized by the presence of Raynaud phenomenon or arthritis (4, 5, 6, 7).

Raynaud phenomenon is observed in up to 90% of patients and is included in all the different classification criteria. Half of the patients have nailfold capillary changes similar to those found in SSc (8).

Joint involvement is common and is characterized by symmetric arthritis of hands and wrists. In 20% of the patients, an erosive arthritis as well as a tendency to develop Jaccoud arthritis has been observed (4, 5).

Infrequent at disease onset, myositis is observed in up to 70% of the patients during the follow-up. Muscle involvement in MCTD seems less severe than that of PM/DM and more responsive to therapy. Histologically, myositis in MCTD resembles DM more closely. Many patients present with diffuse myalgias, which should be distinguished form myositis (4, 5, 6, 9).

Pulmonary involvement is primarily represented by pulmonary hypertension, which is the primary cause of death in these patients (10, 11, 12). Pulmonary hypertension appears to be correlated with the presence of vasculopathy of pulmonary arteries rather than interstitial lung disease. Interstitial lung disease may also be observed; in a recent study of 144 MCTD patients, chest X rays were abnormal in 91% of patients, of whom 66.6% had active interstitial lung disease detected by high-resolution computed tomography (HRCT) (11).

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TABLE 8.1. Clinical manifestations of mixed connective tissue disease (MCTD) patients at onset and during the disease course.

	At onset (%)	Cumulative (%)
Raynaud's phenomenon	74	90–96
Arthritis/arthralgias	68	95–96; erosions 20
Esophageal dysfunction	9	66–80
Pulmonary dysfunction	0	66–75
Swollen hands	45	66–75
Sclerodactily	11	40–50
Myositis	2	25–51
Skin rash	13	50–53
Leukopenia	9	53
Pleuritis/pericarditis	19	30–43
Pulmonary hypertension	0	23–30
Diffuse sclerosis	0	19
Nervous system disease	2	15–17
Renal disease	0	10–11

Two-thirds of MCTD patients develop swollen hands with sausage fingers, and some patients develop sclerodactily; however, an extensive skin sclerosis seems rare. Other cutaneous manifestations are represented by skin rashes similar to subacute or discoid cutaneous lupus or DM (Gottron papules and heliotrope rash). Some patients may also present livedo reticularis and telangectasias (4, 5, 6).

Esophageal dysfunction has been observed in up to 75% of patients, but may be asymptomatic. Dysphagia has been reported in average 38% of patients (4, 5, 6).

The most frequent form of cardiac involvement is pericarditis, which usually does not cause tamponade. In a study of 16 MCTD patients, noninvasive assessment showed evidence of cardiac abnormalities in 38% of patients and evidence of pericarditis in 25% of patients (13).

Renal involvement is not frequent; renal manifestations include glomerulonephritis, nephrotic syndrome and scleroderma renal crisis. Mesangial and membranoproliferative lesions have been observed. Neurological involvement is rare and is represented by trigeminal nevralgia and vascular headache. Hematological manifestations are represented by cytopenias, particularly leukopenia and thrombocytopenia (4, 5, 6).

Histologically, MCTD is characterized by a widespread vasculopathy that may involve small- and medium-sized vessels. This vasculopathy differs from that observed in SSc as it is less associated with fibrosis and presents immunoglobulin and complement deposits in the vessel walls (4).

Laboratory Abnormalities

MCTD is associated with the presence of high titers of anti-U1RNP antibodies specifically directed against the proteins A, C or 70 K complexed with U1RNA (1, 3, 5, 7, 14). Anti-RNP antibodies, however, are not specific for MCTD as they are observed in other CTDs also such as SLE, rheumatoid arthritis (RA) and SSc. Although anti-U1RNP antibodies are crucial for the classification of MCTD, their pathogenetic role in the development of the disease has not been established yet.

Anti-Ro, anti-La and anti-phospholipid antibodies have also been described in MCTD patients with lower frequency.

HLA Type and MCTD

Different studies have shown an association between MCTD and the specific HLA haplotype HLA DR4 (3, 15, 16). In a study comparing MCTD patients, SLE patients and healthy controls, HLA DRw4 was observed in 45% of MCTD patients, 14 of SLE patients and 18% of controls (15). Some authors have suggested the presence of an association between HLA DR4 and the occurrence of erosive arthritis in MCTD patients.

Prognosis

In the original description by Sharp and colleagues, MCTD was described as a rather benign condition characterized by a good response to corticosteroid therapy (1). However, further follow-up of the originally described patients and long-term data on other cohorts of patients have not confirmed this description (4, 5, 17, 18). In a study assessing the long-term outcome of 47 MCTD patients, 38% had continued active disease requiring corticosteroid or immunosuppresive therapy or had died (4). It has been estimated that about one-third of MCTD patients have a favorable outcome, one-third have a more aggressive disease, and the remaining have a good outcome but require continuous therapy with either corticosteroids or immunsuppressive drugs.

The main causes of death in MCTD patients are represented by pulmonary hypertension, respiratory insufficiency, heart failure and infections.

Diagnostic Criteria

Three different sets of classification criteria for MCTD have been validated and are used in the literature (Table 8.2) (1, 19, 20). The original Sharp criteria have been found to have a high sensitivity, but a low specificity. The sensitivity of Alarcon-Segovia criteria varies between 62 and 96% with a high specificity (86–96%), similarto Kasukawa criteria (88% sensitivity and 65.5–87% specificity). Alarcon-Segovia criteria appear the best classification criteria for MCTD (21, 22).

TABLE 8.2. Three different sets of classification criteria for mixed connective tissue disease (MCTD).

Sharp et al. 1972	Alarcon-Segovia et al.	Kasukawa et al.
Major	Serologic	Common symptoms
Myositis, severe	Anti-U1 RNP hemagglutination titer $\geq$ 1:1600	Raynaud's phenomenon
Pulmonary involvement	Clinical	Swollen fingers or hands
Raynaud's phenomenon	Edema of the hands	Anti-RNP antibodies
Swollen hands or sclerodactily	Synovitis	Mixed symptoms
Anti-ENA $\geq$1:10,000 and anti-U1RNP positive and anti-Sm negative	Myositis	1. SLE-like features
Minor	Raynaud's phenomenon	polyarthritis
Alopecia	acrosclerosis	lymphadenopathy
Leukopenia		facial erythema
Anemia		pericarditis or pleuritis
Pleuritis		leuko-thrombocytopenia
Pericarditis		2. SSc-like symptoms
Arthritis		sclerodactily
Trigeminal neuropathy		pulmonary fibrosis, restrictive changes of lung, reduced diffusion capacity
Malar rash		hypomotility or dilatation capacity
Thrombocytopenia		3. PM-like findings
Mild myositis		muscle weakness
History of swollen hands		elevated serum levels of muscle enzymes
		Myogenic alterations on EMG
Anti-U1RNP antibodies titer $\geq$1:4000 AND at least 4 major criteria or anti-U1RNP antibodies titer $\geq$ 1:1000 AND 2 major criteria among 1,2, 3 AND 2 minor criteria	Serological criteria AND at least 3 clinical criteria, including myositis or synovitis	Anti-U1-RNP AND 1 of the 2 common symptoms AND 1 or more of the mixed symptoms in at least 2 categories

Is MCTD a Distinct Clinical Entity?

Since its description debate still exists on whether MCTD represents a distinct clinical entity or the overlap between other CTDs. Some authors have proposed to consider MCTD as an undifferentiated condition waiting to evolve to more definite CTD (2, 3).

The criticisms to the concept of MCTD are the following: (a) MCTD is not the benign condition initially described, (b) patients may be diagnosed as having other CTD or will develop other CTD during the follow-up, (c) anti-U1RNP antibodies can be observed in other CTD also, (4) the clinical picture of MCTD has been observed in the absence of anti-U1RNP antibodies also, and (5) there are no data suggesting a pathogenetic role for anti-U1RNP antibodies.

Nevertheless, it is certain that MCTDs have peculiar clinical, serological, histological and genetic features. Whether these are sufficient to constitute a distinct clinical entity is difficult to define and probably only a better understanding of pathogenesis and etiology of autoimmune diseases might help in solving this issue (6).

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