"To Be or Not To Be," Ten Years After: Evidence for Mixed Connective Tissue Disease as a Distinct Entity

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Objectives: To determine if mixed connective tissue disease (MCTD) can be considered an independent clinical entity, to compare 3 different classification criteria for MCTD (Kasukawa, Alarcón-Segovia, and Sharp), and to define predictors (clinical features and autoantibodies) of potential evolution toward other connective tissue diseases (CTDs).

Methods: One hundred sixty-one MCTD patients were evaluated retrospectively at the diagnosis and in 2008. They were classified, at the diagnosis, according to the 3 classification criteria of MCTD (Sharp, Alarcón-Segovia, and Kasukawa) and reclassified in 2008 according to their evolution. Statistical analyses were performed to find out predictors (clinical features and autoantibodies) of evolution into other CTDs.

Results: After a mean of 7.9 years of disease, 57.9% of patients still satisfied MCTD classification criteria of Kasukawa; 17.3% evolved into systemic sclerosis, 9.1% into systemic lupus erythematosus,

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2.5% into rheumatoid arthritis, 11.5% was reclassified as affected by undifferentiated connective tissue disease, and 1.7% as suffering from overlap syndrome. Kasukawa's criteria were more sensitive (75%) in comparison to those of Alarcón-Segovia (73%) and Sharp (42%). The presence of anti-DNA antibodies ($P = 0.012$) was associated with evolution into systemic lupus erythematosus; hypomotility or dilation of esophagus ($P < 0.001$); and sclerodactyly ($P = 0.034$) with evolution into systemic sclerosis.

Conclusions: MCTD is a distinct clinical entity but it is evident that a subgroup of patients may evolve into another CTD during disease progression. Initial clinical features and autoantibodies can be useful to predict disease evolution.

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Keywords: *mixed connective tissue disease, systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, overlap syndrome, undifferentiated connective tissue disease, autoantibodies*

In 1972, Dr Sharp and colleagues described a new connective tissue disease, characterized by overlapping features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis/dermatomyositis (PM/DM) and by the presence of antibodies against the U1 small nuclear ribonucleoprotein autoantigen (U1 snRNP). This condition was termed mixed connective tissue disease (MCTD) and proposed as a distinct disease (1,2).

In the original publication, describing MCTD, Sharp made the 4 following claims: (1) that the syndrome was clinically identifiable by a particular group of features; (2) that the presence of high titers of antibodies to U1 snRNP was a unique (and hence diagnostic) serological feature; (3) that cerebral, pulmonary, renal involvement, and vasculitis did not occur; and (4) that the condition had a benign prognosis and responded to small doses of corticosteroids (1). Later, after observing the clinical evolution of MCTD patients, Sharp himself agreed that the original concept of MCTD had to be modified and that (1) internal organs were at risk for serious complications; (2) patients were not always steroid responsive; (3) prognosis was not always benign (3-5).

However, many clinical features, originally described, are still considered typical for MCTD, namely, frequent Raynaud's phenomenon (RP), swollen fingers, prominent arthritis, sometimes erosive, frequent peritendinous or subcutaneous nodules, increased risk of pulmonary involvement, and only rare significant renal or central nervous system disease (4).

The initial clinical presentation usually includes RP, swollen puffy hands, and polyarthritis or polyarthralgias. As the disease evolves, manifestations of SSc, SLE, PM, or rheumatoid arthritis (RA) can be observed (3,5-7).

Over the past 4 decades the distinct entity of this disease has been criticized for the following reasons: the prognosis is worse than originally described, MCTD can evolve into other connective tissue diseases (CTDs), and anti-U1 snRNP is lacking in specificity (8).

Nevertheless, many authors consider MCTD a distinct disease (6,8-11). Indeed, high-titer anti-U1 snRNP antibodies are a serologic marker for this disease and an association of HLA-DR4 haplotype has been observed both with anti-U1 snRNP and with MCTD per se (12-15).

Three sets of classification criteria for MCTD are currently used: Kasukawa, Alarcón-Segovia, and Sharp (2,16,17) (Table 1). Alarcón-Segovia's criteria are simpler compared with the others, comprising 5 clinical manifestations in addition to the serological status, while Kasukawa's criteria are better suited to analyze each sign and symptom of MCTD. The original Sharp's criteria are seen as rather complicated since they include a high number of clinical features and the titer of antiextractable nuclear antigen (8,18).

The question of whether MCTD is a distinct disease entity still remains controversial. Many authors have tried to solve this question following MCTD patients, but these attempts have still not led to a definitive answer (19-24).

For this reason, we have investigated, in a retrospective study, 161 patients with the clinical and serological features of MCTD to verify the evolution into different diseases and try to answer the question whether MCTD may remain a distinct disease.

METHODS

Patients

In this multicentric study, clinical and serological features of 161 patients with the initial diagnosis of MCTD were retrospectively analyzed.

Inclusion criterion was the diagnosis of MCTD, at disease onset, according to the expert opinion. All patients were adults and recruited by tertiary medical centers. At the diagnosis of MCTD, patients also satisfying classification criteria for a definite CTD (SSc, SLE, PM/DM) or for RA were excluded.

At the beginning of the study, the 15 centers involved collected retrospectively the data of the patients at disease onset and at the time of the last evaluation (in 2008) by reviewing medical records. In 2008, mean disease duration was 7.9 ± 5.9 years (range, 1-31 years). The female: male ratio was 11:1.

After having collected the data, every center was asked to fill the charts with classification criteria for MCTD of