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SHORT ANALYTICAL REVIEW

Immune pathogenesis of Mixed Connective Tissue Disease: A short analytical review

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Abstract Mixed Connective Tissue Disease (MCTD) was first described 35 years ago by Gordon C. Sharp and his colleagues. In the ensuing decades, a clearer understanding of the clinical and serologic features of MCTD has emerged. Classification criteria now exist to define MCTD for study purposes, the long-term outcome of the disease has been established, and novel genetic associations within the major histocompatibility complex on chromosome 6 and select regions on chromosome 3 have been identified. Studies on immune pathogenesis have made substantial progress in advancing our understanding of MCTD. In MCTD, there is a complex interaction of the innate and adaptive immune system that culminates in autoimmune disease. Antigenic structural modification occurring during apoptosis or other modifications of self antigens leads to an autoantigen driven immune process with innate immune activation, immunoglobulin G autoantibody production directed against select components of the spliceosome, B lymphocyte activation, and CD4 and CD8 T lymphocyte participation.
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Introduction

Mixed Connective Tissue Disease (MCTD) is a systemic autoimmune disease characterized immunologically by the presence of autoantibodies and T cells reactive with U1 ribonucleoprotein (U1-RNP) polypeptides of the spliceosome complex including their associated uridine-rich (U) small nuclear RNAs [1,2]. Clinically, MCTD is characterized by manifestations that overlap systemic lupus erythematosus (SLE), scleroderma, inflammatory myopathy and rheumatoid arthritis [2,3]. The initial full-length publication describing what the authors named "Mixed Connective Tissue Disease" was reported 35 years ago by Sharp, Irwin, Gould, Holman and Tan in 1972 [4]. These patients were said to represent a novel group based upon the presence of high levels of antibodies against an extractable nuclear antigen (ENA) that was RNase- and trypsin-sensitive [4].

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Subsequently, it was shown by Sharp and colleagues as well as others that ENA contained both the ribonuclease (RNase)- and trypsin-sensitive ribonucleoprotein (RNP) antigen associated with MCTD, and the RNase- and trypsin-resistant Smith (Sm) antigen associated with systemic lupus erythematosus (SLE) [5,6]. We now know that the RNP antigen consists of a complex containing a series of small nuclear ribonucleoproteins (snRNP) including three polypeptides (70kD, A and C) that are linked non-covalently with U1-RNA as part of the spliceosome complex [6–8]. The RNP antigen is now also referred to as nuclear RNP (nRNP), U1 small nuclear ribonucleoprotein (U1-snRNP) and U1-RNP [9].

The first MCTD patients in the initial report by Sharp et al. from Stanford University were described as having overlapping features of SLE, scleroderma and polymyositis [4]. These patients were felt to be both immunologically and clinically distinctive, based on the presence of antibodies to the RNase- and trypsin-sensitive RNP antigen and the absence of serious renal or central nervous system involvement, as well as their favorable initial clinical response to treatment with corticosteroids. Extensive studies on MCTD by Gordon Sharp continued at University of Missouri-Columbia with his colleagues there beginning in 1969. The history of this work on MCTD has been the subject of a recent review [10]. In the ensuing three and a half decades since the original study was reported our recognition of the disease and our understanding of the classification, clinical manifestations, long-term outcome, genetics, and pathogenesis of MCTD have all advanced substantially [1,2,11–13].

Definition of MCTD and approaches for classification of disease

Classification of disease remains a challenge in the rheumatic diseases where the precise etiology of most of the syndromes is unknown and the clinical manifestations are often overlapping; this is also true for MCTD. There are four published classification criteria for MCTD [14–19]. Three of these classification criteria have been compared in a study of 593 patients which included 80 patients with MCTD. These three sets of criteria fared similarly in their ability to capture MCTD while excluding other diagnoses [19]. The criteria published by Alarcon-Segovia and Villarreal showed a sensitivity of greater than 90% and a specificity of greater than 98% when three or more clinical criteria were included along with the presence of anti-RNP antibodies [19].

Based upon their simplicity, a number of authors prefer the use of the criteria proposed by Alarcon-Segovia and Villarreal [18]. The other published classification criteria are substantially more cumbersome to apply outside of a clinical research setting. Unfortunately, there has been no further conference addressing the topic of disease classification criteria in MCTD since the first international conference on MCTD which was held in Japan in 1986 [15]. Recent studies have used Rasch analysis for classifying patients as MCTD. Rasch is a novel approach which was originally developed for analyzing item response data, called Rasch models, that has more recently been applied to studies on the rheumatic diseases. Rasch has been applied to help define the key clinical and laboratory features that may more effectively distinguish MCTD from other similar rheumatic diseases such as SLE [20,21].

Clinical manifestations of the disease among various populations and long-term outcome

Since the initial report on MCTD, the disease has been extensively studied among patient populations from around the world. From these world-wide studies, a comprehensive description of MCTD has emerged [1,2]. The primary clinical features of MCTD are Raynaud's phenomenon, swollen fingers or diffusely swollen hands, arthralgia, with or without associated arthritis, esophageal reflux or esophageal dysmotility, acrosclerosis (i.e. sclerodactyly), mild myositis, and pulmonary involvement of a variety of forms (Table 1) [1,2,11–13,22–30]. Additional clinical features which have been commonly reported include malar rash, alopecia, anemia, leucopenia, lymphadenopathy, secondary Sjogren's syndrome and trigeminal neuralgia. The characteristic immunologic findings in MCTD are a high-titer fluorescent antinuclear antibody (FANA) with a speckled pattern and the presence of antibodies to RNP at moderate to high level in the serum; some authors require the absence of antibodies to Sm to classify patients as MCTD.

Sharp et al. recognized early in their studies that MCTD could occur in children as well as adults [28]. Early reports suggested that MCTD in children may be more severe but recent studies from the United States (US), Europe and Japan document a similar course of disease in children and adults

Table 1 Clinical features, immunologic features and genetics of Mixed Connective Tissue Disease

Clinical features
- Overlapping features of systemic lupus erythematosus, scleroderma, polymyositis and rheumatoid arthritis including:
  Raynaud's phenomenon, swollen fingers or diffusely swollen hands, arthralgia, with or without associated arthritis, esophageal reflux or dysmotility, acrosclerosis (i.e. sclerodactyly), mild myositis and pulmonary involvement including pulmonary hypertension

Immunologic features
- FANA present at high titer
- Anti-RNP antibodies and anti-70kD polypeptide antibodies
- Anti-U1-RNA antibodies

Genetics
- Major histocompatibility complex (MHC) genetic associations
  HLA-DR4 with MCTD in population-based candidate gene association studies from US, Mexico, Japan, and Europe
  Absence of HLA alleles associated with SLE (HLA-DR3) and scleroderma (DR5 and DR5 subtypes) in MCTD candidate gene studies
- Chromosome 3 regions identified in genome-wide association and linkage studies
  Ch3p23–24
  Ch3q25–26