Mixed Connective Tissue Diseases: New Aspects of Clinical Picture, Prognosis and Pathogenesis

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The term "mixed connective tissue disease" (MCTD) was coined in 1972 by Sharp et al. [1-6] to refer to a distinct systemic autoimmune disease characterized by overlapping features of systemic lupus erythematosus, systemic sclerosis, polymyositis/dermatomyositis and rheumatoid arthritis, in association with antibodies against the U1 small nuclear ribonucleoprotein autoantigen (U1snRNP) as a serological hallmark. The initial belief that MCTD represents a relatively benign condition with a good response to corticosteroid therapy was subsequently challenged by a number of observations. In fact, the lengthy follow-up of the originally described patients and long-term data on other cohorts of patients have shown that about one-third of MCTD patients have a favorable outcome, one-third have a good outcome but require continuous therapy with either corticosteroids or immunosuppressive drugs, and the remaining third have a more aggressive disease [5,7-10].

Recent studies have confirmed that polyarthritis, Raynaud's phenomenon, puffy fingers and sclerodactyly are the most common presenting symptoms. However, long-term follow-up has shown that patients accrue new symptoms – such as esophageal hypomotility, nervous system manifestations, pulmonary arterial hypertension and interstitial lung disease. In many studies, pulmonary involvement – either pulmonary fibrosis or pulmonary hypertension – has emerged as an important prognostic factor in MCTD [11-15].

In 2005, Bodolay and co-authors [13] reported a 66.6% prevalence of active interstitial lung disease in consecutive patients with MCTD. In a recent study, Gunnarsson et al. [14] reported at least one abnormality compatible with lung fibrosis in 52% of MCTD patients, with severe lung fibrosis observed in 19% assessed with high resolution computed tomography. Importantly, severe lung fibrosis was associated with increased mortality [14]. On the other hand, Gunnarsson et al. [15] recently re-evaluated an unselected cohort of MCTD patients and found that the prevalence of pulmonary arterial hypertension was only 3.4%. Interestingly, the presence of anti-beta-2 glycoprotein I antibodies was associated with pulmonary arterial hypertension in a small cohort of MCTD patients [16].

Recent data have suggested that anti-U1RNP autoantibodies may play a central role in the disease pathogenesis. In fact, anti-U1RNP autoantibodies were found to interact with lung tissue, contributing significantly to disease manifestations [17]. Although the presence of anti-U1RNP autoantibodies is mandatory for the diagnosis, the coexistence of other autoantibody specificities is a common finding in MCTD patients, with a significant influence on disease expression. Szodoray and collaborators [18] described three different clinical and serological sub-phenotypes of disease; the first subgroup appears to be characterized by patients with anti-endothelial cells and antiphospholipid antibodies in association with pulmonary arterial hypertension, Raynaud's phenomenon, livedo reticularis and vascular thrombosis. The second subgroup is mainly characterized by the presence of lung involvement (interstitial lung disease), esophageal dysmotility and myositis. The third subphenotype is characterized by a higher prevalence of anti-CCP antibodies and erosive arthritis [18,19].

In this issue of *IMAJ* [20] the same authors describe the association between MCTD with pulmonary fibrosis and autoimmune liver involvement, and suggest that a common pathogenetic mechanism may explain this association. Importantly, a good response to immunosuppressive therapy with azathioprine was noted. This observation suggests the presence of an additional clinical sub-phenotype of MCTD. Future cohort studies aimed at investigating the prevalence of this association may add important information about MCTD – both clinical and prognostic – that may enable the treating physician to establish a personalized treatment and follow-up.

CONCLUSIONS

Over the last decade, several advances in our knowledge of the disease course and pathogenesis of MCTD have been made. The concept of MCTD appears clinically useful, as it identifies a group of patients in whom severe and life-threatening organ involvement can occur, especially during follow-up. Increased surveillance for specific manifestations and prognostic stratification according to different clinical and serological features could improve patients' survival and quality of care.

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MCTD = mixed connective tissue disease

References

1. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease: an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am J Med* 1972; 52: 148-59.
2. Sharp GC, Diagnostic criteria for classification of MCTD. In: Kasukawa R, Sharp GC, eds. Mixed Connective Tissue Diseases and Anti-Nuclear Antibodies. Amsterdam: Elsevier, 1987: 23-32.
3. Kasukawa R, Too T, Miyawaki S, et al. Preliminary diagnostic criteria for classification of mixed connective tissue disease. In: Kasukawa R, Sharp GC, eds. Mixed Connective Tissue Diseases and Anti-Nuclear Antibodies. Amsterdam: Elsevier, 1987: 41-7.
4. Alarcon-Segovia D, Villareal M. Classification and diagnostic criteria for mixed connective tissue disease. In: Kasukawa R, Sharp GC, eds. Mixed Connective Tissue Diseases and Anti-Nuclear Antibodies. Amsterdam: Elsevier, 1987: 33-40.
5. Cappelli S, Bellando Randone S, et al. "To be or not to be," ten years after: evidence for mixed connective tissue disease as a distinct entity. *Semin Arthritis Rheum* 2012; 41: 589-98.
6. Habets WJ, de Rooij DJ, Salden MH, et al. Antibodies against distinct nuclear matrix proteins are characteristic for mixed connective tissue disease. *Clin Exp Immunol* 1983; 54: 265-76.
7. Nimelstein SH, Brody ST, McShane D, Holman HR. Mixed connective tissue disease: a subsequent evaluation of the original 25 patients. *Medicine* 1980; 59: 239-48.
8. Burdt MA, Hoffman RW, Deutscher SL, Wang GS, Johnson JC, Sharp GC. Long-term outcome in mixed connective tissue disease. *Arthritis Rheum* 1999; 42: 899-909.
9. Hajas A, Szodoray P, Nakken B, et al. Clinical course, prognosis, and causes of death in mixed connective tissue diseases. *J Rheumatol* 2013; 40: 1134-42.
10. Tani C, Carli L, Vagnani S, et al. The diagnosis and classification of mixed connective tissue disease. *J Autoimmun* 2014; 48-49: 46-9.
11. Vegh J, Szodoray P, Kappelmayer J, et al. Clinical and immunoserological characteristics of mixed connective tissue disease (MCTD) associated with pulmonary arterial hypertension (PAH). *Scand J Immunol* 2006; 64: 69-76.
12. Fagundes MN, Caleiro MTC, Navarro-Rodriguez T, et al. Esophageal involvement and interstitial lung disease in mixed connective tissue disease. *Respir Med* 2009; 103: 854-60.
13. Bodolay E, Szekanecz Z, Dévényi K, et al. Evaluation of interstitial lung disease in mixed connective tissue disease (MCTD). *Rheumatology* 2005; 44: 656-61.
14. Gunnarsson R, Aaløkken TM, Molberg Ø, et al. Prevalence and severity of interstitial lung disease in mixed connective tissue disease: a nationwide, cross-sectional study. *Ann Rheum Dis* 2012; 71: 1966-72.
15. Gunnarsson R, Andreassen AK, Molberg Ø, et al. Prevalence of pulmonary hypertension in an unselected, mixed connective tissue disease cohort: results of a nationwide, Norwegian cross-sectional multicentre study and review of current literature. *Rheumatology* 2013; 52: 1208-13.
16. Hasegawa EM, Caleiro MT, Fuller R, Carvalho JF. The frequency of anti-beta 2-glycoprotein I antibodies is low and these antibodies are associated with pulmonary hypertension in mixed connective tissue disease. *Lupus* 2009; 18: 618-21.
17. Hof D, Cheung K, de Rooij DJ, et al. Autoantibodies specific for apoptotic U1-70K are superior serological markers for mixed connective tissue disease. *Arthritis Res Ther* 2005; 7: R302-9.
18. Szodoray P, Hajas A, Kardos L, et al. Distinct phenotypes in mixed connective tissue disease: subgroups and survival. *Lupus* 2012; 21: 1412-22.
19. Takasaki Y, Yamanaka K, Takasaki C, et al. Anti-cyclic citrullinated peptide antibodies in patients in mixed connective tissue disease. *Mod Rheumatol* 2004; 14: 367-75.
20. Zold E, Bodolay E, Deszo B, Soos G, Nakken B, Szodoray P. Mixed connective tissue disease associated with autoimmune hepatitis and pulmonary fibrosis. *IMAJ* 2014; 16: 733-4.