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-beta2 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 sub-phenotype 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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References

Capsule

Continuous requirement for the TCR in regulatory T cell function

Foxp3+ regulatory T cells (Treg cells) maintain immunological tolerance, and their deficiency results in fatal multi-organ autoimmunity. Although heightened signaling via the T cell antigen receptor (TCR) is critical for the differentiation of Treg cells, the role of TCR signaling in Treg cell function remains largely unknown. Levine et al. demonstrated that inducible ablation of the TCR resulted in Treg Cell dysfunction that could not be attributed to impaired expression of the transcription factor Foxp3, decreased expression of Treg cell signature genes or altered ability to sense and consume interleukin 2 (IL-2). Instead, TCR signaling was required for maintaining the expression of a limited subset of genes comprising 25% of the activated Treg cell transcriptional signature. These results reveal a critical role for the TCR in the suppressor capacity of Treg cells.

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Eitan Israeli

Induction of the nuclear receptor PPAR-γ by the cytokine GM-CSF is critical for the differentiation of fetal monocytes into alveolar macrophages

Tissue-resident macrophages constitute heterogeneous populations with unique functions and distinct gene-expression signatures. While it has been established that they originate mostly from embryonic progenitor cells, the signals that induce a characteristic tissue-specific differentiation program remain unknown. Schneider and team found that the nuclear receptor PPAR-γ determined the perinatal differentiation and identity of alveolar macrophages (AMs). In contrast, PPAR-γ was dispensable for the development of macrophages located in the peritoneum, liver, brain, heart, kidneys, intestine and fat. Transcriptome analysis of the precursors of AMs from newborn mice showed that PPAR-γ conferred a unique signature, including several transcription factors and genes associated with the differentiation and function of AMs. Expression of PPAR-γ in fetal lung monocytes was dependent on the cytokine GM-CSF. Therefore, GM-CSF has a lung-specific role in the perinatal development of AMs through the induction of PPAR-γ in fetal monocytes.

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