

The Autoimmune Tautology with a Focus on Systemic Sclerosis

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In the current issue of *IMAJ*, Rossi et al. [1] report a unique case of multiple autoimmune syndrome (MAS) characterized by the coexistence of systemic sclerosis (SSc), autoimmune liver involvement, antiphospholipid syndrome (APS) and Hashimoto's thyroiditis. MAS, first described in 1988 by two French physicians, Humbert and Dupond [2], is the best example of poly-autoimmunity, the presence of more than a well-defined autoimmune disease (AD) in a single patient [3]. To define a patient with MAS, at least three ADs should coexist [2,3].

Poly-autoimmunity represents the effect of a single genotype and similar environmental factors on diverse phenotypes. This condition, together with familial autoimmunity (i.e., co-aggregation of ADs), has

been shown to be the foundation of the autoimmune tautology hypothesis, which considers all ADs to be similar because they share several immunopathologic mechanisms [4] [Table 1]. Although the heterogeneity of ADs could be due to a collection of diverse disorders based on epidemiology, pathology or diagnostic results, the underlying etiologic mechanisms are similar.

Poly-autoimmunity is observed in about 30% of autoimmune patients, with autoimmune thyroid diseases (AITD) and Sjögren's syndrome (SS) being the most frequent diseases encountered [4-6]. Factors significantly associated with poly-autoimmunity are female gender, familial autoimmunity, Amerindian ancestry, and history of cigarette smoking [4-6].

The main difference between poly-autoimmunity and the so-called overlapping syndromes lies in the fact that the former is characterized by the presence of two or more well-defined ADs, as in the case reported by Rossi et al. in this issue of *IMAJ* [1], and the latter by the partial presence of

signs and symptoms of diverse ADs. Most of the cases of overlapping syndromes have been described in cross-sectional studies. However, evidence has shown that when poly-autoimmunity occurs there is a lag in the time interval between the first and the second AD [3]. ADs have a heterogeneous spectrum such that disease courses differ from patient to patient and, in addition, the disease goes through different phases within the same patient. Depending on the duration and activity of the disease, these subphenotypes might change. Likewise, the expression of ADs ranges from the incomplete forms or *forme frustrée* and lenient and slow evolution syndromes to the rapidly progressive and fatal forms. The imbalance between risk and protective factors (i.e., genetics, epigenetics and environmental) would explain the heterogeneity of ADs. Such is the case of mixed connective tissue disease (MCTD), the classical overlapping syndrome in which some patients will develop systemic lupus erythematosus, SSc, or rheumatoid arthritis (RA) during

Table 1. Autoimmune tautology: the commonalities of autoimmune diseases

Characteristic	Comment
Female predominance	The more frequent the autoimmune disease and the later it appears, the more women are affected
Shared subphenotypes	Autoimmune diseases share clinical signs and symptoms, even though they have a heterogeneous spectrum and course that varies from patient to patient
Poly-autoimmunity	The presence of two or more autoimmune diseases in a single patient. Clustering of autoimmune diseases is not random
Co-aggregation	Unlike familial autoimmune disease, which corresponds to the presence of one specific autoimmune disease in various members of a nuclear family, familial autoimmunity uses the term "autoimmune disease" as a trait that encompasses all accepted pathologies for which evidence suggests an autoimmune origin
Age at onset influences severity	Severity of autoimmune diseases is inversely related to the age at onset. Early-onset traits are more sensitive to genetic influence, while late-onset ones are to environmental variation
Similar pathophysiology	Induced damage by T, B cells or both, plays an important role in the pathogeny of autoimmune diseases, and although the target cells, affected organs and clinical expression differ from one another, similar immunopathological mechanisms have been established
Autoimmune ecology	Similar environmental agents may influence autoimmune diseases
Ancestry	Amerindian ancestry influences the risk of acquiring autoimmune diseases as well as its outcome, including the development of poly-autoimmunity
Common genetic factors	Combinations of common and disease-specific alleles in HLA and non-HLA genes in interaction with epigenetic and environmental factors over time will determine the final phenotype. Epistasis and pleiotropy are crucial in the understanding of the common genetic pathways of autoimmunity
Similar treatment	Similar biological, and non-biological, therapies are used to treat diverse autoimmune diseases

the course of the disease, and others will present a longstanding MCTD [7].

A primary characteristic of complex traits such as ADs is that affected individuals tend to cluster in families (i.e., familial aggregation). Familial autoimmunity is defined as the presence of diverse ADs in multiple members of a nuclear family (i.e., co-aggregation). Noteworthy, familial autoimmunity is more frequent than familial autoimmune disease [8].

SSc is an AD characterized by a complex pathogenesis, based on the interaction of injury to the vascular endothelium, exaggerated tissue regeneration and fibrosis, and extensive immune abnormalities. Following is a summary of the evidence on the autoimmune tautology focusing on SSc [Table 1]. The female preponderance in SSc has been explained by hormonal status, genetic and epigenetic differences, as well as lifestyle [9]. Patients with SSc disclose a chronic and frequently progressive course and an extensive patient-to-patient variability. One of the most prominent clinical characteristic of the disease is Raynaud's phenomenon. Nevertheless, this vasospasm may be observed in other ADs [10]. On the one hand, the classical anti-nuclear and anti-centromere antibodies are not highly specific of the disease. On the other hand, no classical SSc autoantibodies such as antiphospholipid antibodies may be observed in patients with SSc [11]. Both poly-autoimmunity and familial autoimmunity are observed in almost 40% of patients with SSc, with AITD and RA being the most frequent conditions observed [12].

Peak age at onset of SSc is between 20 and 50 years, although SSc is also described in both young and old patients. According to the work conducted by the Spanish Scleroderma Study Group, younger age at onset (age ≤ 30 years) discloses a high standardized mortality ratio [13], indicating that younger age onset is related to severity of the disease.

The mechanisms involved in its pathophysiology include the activation of autoimmune cells and hyperplasia of fibroblasts

with an increased capacity to produce collagen and diminished collagen breakdown [14]. Although fibrosis of the skin and visceral organs that results in irreversible scarring and organ failure are characteristics of the disease, SSc shares several immunogenetic mechanisms with other ADs, including an interferon (IFN) signature (increased expression and activation of IFN-regulated genes), a decreased functional capacity of circulating regulatory T cells (Tregs), and multiple genetic pathways [15-17]. Ethnicity has an important impact on the pathogenesis and clinical expression of SSc, most likely due to ancestry [18].

The influence of environmental exposure on the risk of developing ADs is paramount (i.e., the autoimmune ecology) [5]. There is growing evidence that environmental factors have an impact on epigenetic mechanisms, resulting in SSc onset and progression. Environmental factors include organic solvents, which are chemical compounds used routinely in commercial industries and have been consistently reported as risk factors for SSc and other ADs [19].

In conclusion, given what we have learned about the etiopathogenesis of ADs, which supports the view that the common features of different clinical entities outnumber their differences, we can use similar treatments for various ADs despite specific variations and regimen tailoring [14]. Identification of the common mechanisms of ADs will enhance our understanding of these complex, frequent and sometimes devastating diseases and will permit us to translate this new knowledge into clinical practice [20].

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