The spectrum between antiphospholipid syndrome and systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) and the antiphospholipid syndrome (APS) are interconnected autoimmune diseases. APS was primarily described by Graham Hughes in a group of patients with SLE who suffered from obstetric morbidity and/or recurrent thromboses [1]. Along the years, it was noted that patients may exhibit APS manifestations with no characteristic of SLE classified as primary APS, whereas APS presenting concomitantly with SLE was termed secondary APS. Unlike SLE, APS was not considered to be a systemic disease. However, in the course of time, APS was found to be associated with damage to various organs and systems and to evolve into SLE in about 10 % of patients. Moreover, the expression lupus-like APS was coined to define APS patients displaying systemic “SLE features” although SLE criteria cannot be fulfilled [2, 3].

For years, clinicians and scientist have tried to better discriminate between these conditions. Certain manifestations of SLE such as the presence of antinuclear antibodies, complement activation, or immune mediated kidney disease were accepted as markers to distinguish this disease from primary APS. However, in the last decades, the presence of antinuclear antibodies, hypocomplementemia, non-thrombotic kidney disease, and renal failure were all documented in patients diagnosed with primary APS and the activation of complement was found to be related with APS in experimental models [2]. Last but not the least, the antiphospholipid antibodies serve as criteria for both syndromes and are present in 100 % of APS patients and in up to 40 % of SLE patients, of which many will eventually develop overt APS [2–4]. Hence,

the great heterogeneity and overlap between these autoimmune diseases raised the debate: Are they a single condition with varied phenotypes, or different diseases with diverse pathogenic mechanisms sharing phenotypes? [5–7].

In the current issue, Freire PV et al. [8] retrospectively analyzed a cohort of 80 patients with primary APS of which 14 (17.5 %) progressed within 5.2 ± 4 years to SLE-APS. The latter was significantly younger at diagnosis and their disease duration was longer. In addition, the presence of autoantibodies and particularly antinuclear ones were noted in 100 % of patients finally diagnosed with concomitant APS-SLE compared to 51 % of patients that remained with the diagnosis of primary APS ($P=0.0005$). Moreover, specific autoantibodies (i.e., anti-dsDNA, anti-ribosomal P, anti-Ro/SS-A, anti-La/SS-B, and anti-U1RNP) were exclusively found among patients ultimately diagnosed with concomitant SLE, supporting the notion that primary APS may differ from APS associated with SLE.

The role of autoantibodies as markers and players in the mosaic of autoimmunity is well established [9, 10]. For instance, antinuclear antibodies alongside a wide array of related specific autoantibodies are key markers and servers as criteria for diagnoses of some autoimmune diseases [9]. Furthermore, several specific antibodies were linked with clinical manifestations of different diseases further supporting their plausible pathogenic role [11, 12]. But perhaps the most substantial evidence is a series of studies demonstrating that specific autoantibodies can be detected years before the development of an overt disease. Indeed, Arbuckle et al. [13] found that 88 % of SLE patients were antibody positive up to 30 years prior to diagnosis and a stepwise accumulation of these antibodies was a marker of the preclinical stage of SLE. Similarly, the presence of anti-mitochondrial antibodies (AMA) in primary biliary cirrhosis (PBC), anti-*Saccharomyces cerevisiae* antibodies in Chron’s disease, and anti-neutrophil cytoplasmic antibodies (ANCA) both in ulcerative colitis and in ANCA-

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associated vasculitis were documented years before diseases were overt [14–16]. Noteworthy, antiphospholipid antibodies presence may precede the diagnosis of APS in patients diagnosed both with primary or secondary APS.

Autoimmune diseases are chronic conditions initiated by the loss of tolerance to self-antigens, followed by a preclinical stage, usually marked by autoantibodies production. The appearance of full blown disease, namely the clinical stage, is strongly linked with the individual genetic susceptibility and exposure to diverse environmental factors [17, 18]. Notably, the presence of specific autoantibodies may predict the disease phenotype and the production of these autoantibodies is also determined by genetics and the environment [19]. Both human leukocyte antigen (HLA) and non-HLA genes are linked with autoantibodies production, suggesting that the genetic predisposition to the development of a specific autoantibody clues to a precise clinical portrait [17]. Regarding SLE and APS, distinct polymorphisms of common genetic factors have been associated with both conditions suggesting that these entities are variants within a continuum of disease [2].

The role of environmental factors in induction of autoantibodies production and disease phenotypes has been extensively studied, and it seems that a wide array of such factors contribute to autoimmunity. Numerous infectious agents have been related to autoimmunity and production of autoantibodies [20–22] as well as with evident diseases such as SLE and APS [23–27]. Additional factors such as hormones [28, 29], vitamins such as vitamin D [30–32], sun exposure, etc. were also allied the pathogenesis of both SLE and APS [33].

Reflecting on the question, are APS and SLE distinct diseases or not? It seems that the truth is halfway. Thus, the notion that these autoimmune conditions represent a spectrum ranging from primary APS through concomitant diseases to isolated SLE had been accepted by many auto-immunologists and is supported by clinical, genetic, and environmental studies [2]. In this issue, the study of Freire PV et al. [8] supported, on the one hand, the concept of a continuum between primary APS and concomitant SLE-APS. On the other hand, Freire PV et al. [8] were able to identify predictive factors of progression along this spectrum, namely early age of onset and the presence of specific autoantibodies as markers of a change from primary APS to APS-SLE. This stands in agreement with the perception that in the near future, we may be able to predict the risk of an individual to develop autoimmunity or to evolve from one autoimmune disease to another [34, 35]. The ability to analyze and define genetic factors has made genetic analysis common and in certain cases part of routine evolution. Current determination of serological markers (i.e., autoantibodies, vitamin levels, hormone levels, etc.) has changed dramatically in recent years as the usage of automated multivariant platforms became feasible, and the era of immune array and chips which enable detections of tens and hundreds of these markers is at our door [36].

Disclosures None.

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