Autoimmune rheumatic disorders constitute a diverse group of illnesses with significant clinical and immunological variability. Their clinical presentation and course vary, ranging from subclinical and mild to severe and life-threatening, and from slow and indolent to acute and catastrophic. Some of these disorders can be manifested simultaneously in the same individual or, alternatively, one nosological entity may evolve into another. For instance, Sjögren’s syndrome (SS) frequently co-exists with various other rheumatic conditions, whereas a patient with an organ-specific disease (e.g. myasthenia gravis or thyroiditis) can progress to a systemic autoimmune disorder, such as systemic lupus erythematosus (SLE) or SS. A multi-faceted activation of the immune system occurs in these disorders, as illustrated by the presence of autoantibodies directed against one or multiple autoantigens and/or mononuclear inflammatory infiltrates in the affected tissues. The interplay of genetic factor(s) and environmental agent(s) is thought to account for the development and clinical course of these diseases. The nature of such factors, however, remains obscure, whereas the implication of microorganisms has been speculative.

In an effort to establish an avenue of communication among clinical investigators, diagnostic/classification criteria have been established for a number of autoimmune rheumatic disorders [2, 3]. Nevertheless, grouping individuals with diverse clinical and immunological manifestations into a disorder carries the risk of masking certain important or differentiating features.

Recent advances in the clinical, immunological and immunogenetic profile of one of these disorders, namely SS, can serve as a paradigm to illustrate the problem and offer some solutions. This autoimmune disorder is common and affects primarily females at the fourth to fifth decade of life. It presents with a diverse clinical spectrum ranging from disease confined in the exocrine glands to systemic disorder, whereas in a considerable number of patients lymphoid neoplasia ensues. The lungs, kidneys, liver and thyroid gland are frequently affected, and several lines of evidence suggest that epithelial cells are the main targets of destruction [4]. SS can be found alone or in association with almost all autoimmune rheumatic disorders. The diagnosis is based on the criteria put forward by a European multicentre study [3]. Accordingly, all conditions (metabolic, infectious, degenerative, inflammatory, neoplastic and drug side-effects) that mimic the clinical and histopathological features of SS should be excluded.

In the late 1970s, comparison of the clinical, serological and immunogenetic profiles of patients with SS without evidence for another autoimmune disorder and those of patients with rheumatoid arthritis (RA) and SS has shown similarities and differences. Consequently, the terms ‘primary’ and ‘secondary’ SS were proposed for the former and the latter groups of patients. Compared to patients with secondary SS, patients with primary SS present significantly more often parotid gland enlargement and systemic manifestations, such as Raynaud’s phenomenon, lymphadenopathy, splenomegaly, purpura and renal tubular acidosis. In addition, primary SS, but not secondary SS, is characterized by the occurrence of serum autoantibodies against Ro(SSA) (in 60%) and La(SSB) (in 40%) ribonucleoproteins, and is associated with distinct HLA haplotypes [5, 6]. Although the incidence, clinical expression and serology of SS in various autoimmune diseases have been evaluated [7], comparative studies of well-defined groups of patients with SS co-expressed with autoimmune rheumatic diseases other than RA have never been performed. Despite this fact, during the present decade, the term ‘secondary SS’ has been arbitrarily granted to SS occurring in patients with any autoimmune disorder [3].

Today, 20 yr after the original classification, clinical, histopathological and serological evidence implies the existence of at least two additional SS groups.

1. Primary SS overlapping with other autoimmune disorders. This group includes individuals who clinically express SS and suffer from another defined rheumatic disease. These patients express autoantibodies to Ro(SSA) and La(SSB) proteins as frequently as patients with the ‘primary’ disorder. Immunogenetic studies have revealed that the immune response to Ro(SSA) and La(SSB) autoantigens is associated with distinct major histocompatibility complex (MHC) class II alleles, regardless of the clinical entity where they occur [8, 9]. Patients with autoimmune disorders who present features of SS and express anti-Ro(SSA) and anti-La(SSB) responses could qualify for this group [10]. Careful evaluation of the clinical and immunogenetic profile of this group, and in comparison to that of primary or secondary SS groups, should be performed.

2. SS with other autoantibody specificities. The patients of this group are seemingly indistinguishable from primary SS. On closer scrutiny, however, these patients reveal characteristic clinical and serological features. Their autoantibody profile consists of reactivities compatible with other autoimmune disorders (namely, autoantibodies to mitochondria, thyroid peroxidase or centromere) [11, 12]. Most often, these individuals do not express the overt clinical picture of the corresponding disorder (i.e. primary biliary cirrhosis, thyroiditis or limited scleroderma). However, the histopathological evaluation of liver or thyroid tissues in SS
patients displaying anti-mitochondrial or anti-thyroid peroxidase antibodies reveals an early lesion of biliary cirrhosis or thyroiditis, respectively. Nail-fold capillaroscopy of SS patients with anti-centromere antibodies has revealed vascular lesions comparable to those encountered in scleroderma (paper submitted for publication).

On the basis of their immune response, SS patients can be subdivided into three major subgroups: those with anti-Ro(SSA) and anti-La(SSB) response; those without specific autoantibody response; and those with autoantibodies against certain autoantigens, such as thyroid peroxidase, mitochondria and centromere. Furthermore, the detailed analysis of the initial pathological lesions in the exocrine glands may be also instructive for the subclassification of patients with SS. Studies have suggested that in patients with ‘primary’ SS and in those with ‘secondary’ SS associated with RA or primary biliary cirrhosis, the lesion starts in close proximity to exocrine glandular ducts, whereas in patients with sicca manifestations occurring in the context of SLE or infection by the human immunodeficiency virus (HIV) the initial lesion is perivascular [13, 14]. In contrast, in patients with chronic graft-versus-host disease who develop an SS-like syndrome, the lesion is diffuse rather than focal [15]. Histopathological studies involving multicentre collaboration could also be extended to comparisons with the SS-like tissue-infiltrating lesions found during infection by HIV or by the hepatitis C virus. Finally, SS patients can also be subdivided into groups according to their MHC class II associations. It will be very interesting to evaluate the clinical similarities and differences of these groups, as well as their clinical course and disease evolution.

Splitting patients into subgroups on the basis of more global assessment may provide more homogeneous populations of patients for study and allow more precise evaluation of disease parameters. This is likely to become particularly productive if careful studies of groups are designed and performed. Are these studies feasible? In order to collect a reasonable number of individuals with SS from the various patient subgroups, multicentre multinational studies involving several disciplines (i.e. rheumatology, ophthalmology, dentistry, pathology and immunology) should be initiated. The acquisition of appropriate funding for the elaboration of these studies appears a daunting task. Such an orchestrated effort is mandatory and granting agents should be convinced.

It can be anticipated that the SS subgroups described above represent a common spectrum of the disorder. Ultimately, splitting SS patients in subgroups may lead to such a realization. However, this may well pre-date identification of the factor(s) that are responsible for the disease, whose discovery remains imperative.

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