Editorial

Primary versus Secondary Sjögren Syndrome: Is It Time To Reconsider These Terms?

Classification of systemic autoimmune diseases on the basis of clinical, serological, and genetic characteristics has long been considered a necessary approach to determine disease prognosis and institute appropriate therapeutic strategies[1].

Has this, however, truly been pursued by the scientific community? Probably not, because similar disease-modifying agents and several immunosuppressants are implemented as baseline therapy for combating arthritis, pleurisy, or nephritis, irrespective of the character of the underlying disease. Despite our better understanding of molecular pathobiology, which eventually led to development of targeted therapies, seropositive and seronegative arthritis are still similarly treated with tumor necrosis factor inhibitors, while certain vasculitic syndromes are managed with B cell depletion therapy in the same way as rheumatoid arthritis (RA). The responses, even to those new therapies, are not uniform because these syndromes are highly polymorphic in both clinical phenotypes and underlying pathogenetic pathways.

A prototype autoimmune disorder characterized by a wide spectrum of clinical, serological, and genetic features is Sjögren syndrome (SS). It may extend from sicca symptoms and complications of mucosal dryness as a result of exocrine gland involvement, to a systemic disease or to malignant B cell lymphoproliferation in about one-fourth and one-tenth of patients, respectively. Nevertheless, sicca manifestations may also occur in several other systemic autoimmune disorders at variable frequencies ranging from 8.3% in systemic lupus erythematosus (SLE) and 20.5% in systemic sclerosis (SSc) to 31% in patients with RA[2,3].

Thirty-five years ago, taking into account clinical, serological, and genetic characteristics of patients presenting with sicca-related manifestations either alone or in the context of RA, we coined the terms *primary* and *secondary* SS, respectively[4]. More specifically, it was shown that patients with SS alone presented more frequently with recurrent parotid gland enlargement, Raynaud phenomenon, purpura, lymphadenopathy, myositis, and renal involvement compared to those with SS in an RA background (RA/SS)[5]. The latter group was also shown to be older compared to the primary SS group and to display more frequently severe arthritis, anemia, lung involvement, presence of antibodies to citrullinated antigens, and radiographic joint damage[6,7]. Additionally, patients with SS alone exhibited increased frequency of anti-Ro/SSA and La/SSB autoantibodies along with HLA-B8 and HLA-DW3 alleles compared to patients with RA and sicca manifestations in which HLA-DR4 allele prevailed[4]. It should, however, be taken into account that these observations were based on studies of a patient population from a tertiary referral center, in which disease limited to the glandular compartment was underrepresented. Immunohistochemical studies comparing the composition of lymphocytic infiltrates in labial minor salivary glands between RA patients with sicca symptoms and SS patients alone revealed milder lesions, together with increased prevalence of dendritic cells and lower prevalence of CD4+ cells in the RA-sicca subtype, further supporting the distinction into primary and secondary forms of SS[8].

Similar observations were made in patients presenting with sicca symptomatology in the context of primary biliary cirrhosis (PBC). As in patients with RA/SS, anti Ro/SSA and anti-La/SSB autoantibodies were very infrequently detected in patients with PBC-sicca and objective signs of oral or ocular dryness, such as decreased parotid flow rates or corneal ulceration, were virtually absent. These findings along with similar immunogenetic features with RA/SS lead to the assumption that SS in PBC shares characteristics of SS in the context of RA[9].

In contrast, ensuing studies of the clinical, serologic, and immunogenetic characteristics of patients with SLE presenting with sicca manifestations revealed similarities between SS and SLE/SS. More specifically, SLE/SS and primary SS were shown to have similar prevalence of oral/ocular dryness and of anti-Ro/SSA and anti-La/SSB autoantibody positivity, as well as similar range-of-focus scores in minor salivary gland biopsies. In contrast, in patients with SLE/SS, there was more prevalence of Raynaud phenomenon, arthritis, and serositis compared to the primary SS group. As opposed to RA, in which SS is rather a late sequelae, diagnosis of SS usually precedes that of SLE in almost two-thirds of patients. These observations, coupled with the comparable frequencies of the DRB1*0301 allele between these 2 groups of patients, suggested the presence of shared underlying pathogenetic pathways[10]. Moreover, studies by Drosos, *et al* and Salliot, *et al* revealed similar rates of subjective and objective sicca features, as well as comparable frequencies in anti-Ro/SSA and anti-La/SSB autoantibodies and histopathological scores in patients with SSc/SS and patients with SS[11,12].

Therefore, while the term *secondary Sjögren syndrome* was initially introduced to encompass patients with sicca symptoms in the context of RA, based on the distinctive character of the 2 entities, it was erroneously expanded to include other systemic autoimmune rheumatic diseases such

as SLE and SSc[4], in which significant similarities in both clinical and immunologic and genetic terms were observed, as highlighted above. Of interest, with no further studies, the distinction between primary and secondary forms of the syndrome was also adopted in both European and European-American classification criteria for SS[13]. Moreover, whether overlap autoimmune disorders such as SS with autoimmune thyroiditis[14], gastritis[15], autoimmune cholangitis[16], or anticentromere antibodies[17] can be classified as primary, secondary, or associated also remains unresolved.

It then becomes evident that both primary and secondary types of SS include patients from localized disease confined mainly to the exocrine glands (local SS, RA/SS, PBC/SS) to extraglandular disease (systemic SS, SS/SLE, SS/Scl) affecting virtually any organ system, and to a distinct but significant group at risk for lymphoma development[18]. Regarding the latter complication, data from the InterLymph consortium revealed an increased risk for lymphoma development in secondary compared to primary forms of disease (OR 7.92 vs 2.84 at 2 to 5 years of followup)[18].

On this basis, splitting patients into "primary" and "secondary" fails to fully reveal the wide clinical spectrum of the syndrome. Thus, in line with previous suggestions by other investigators[12,19], we propose that the terms primary and secondary SS be replaced by a more descriptive terminology: SS when the disease is expressed as an entity alone or SS associated with systemic or organ-specific autoimmune diseases, provided that in all cases, the recently published set of criteria for SS are fulfilled[20]. Indeed, in the latter, the term *secondary* no longer exists, and the presence of an underlying autoimmune disease does not exclude the classification of primary SS, once the proposed criteria are fulfilled[20].

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