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# Polyautoimmunity in Sjögren Syndrome

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**KEYWORDS**

• Sjögren syndrome • Polyautoimmunity • Autoimmune tautology

**KEY POINTS**

- Polyautoimmunity corresponds to the presence of more than one well-defined autoimmune disease in a single patient.
- Sjögren syndrome has been described in association with a large variety of both organ-specific and systemic autoimmune diseases.
- The most frequent polyautoimmunity in Sjögren syndrome is autoimmune thyroid disease.
- Main factors associated with polyautoimmunity are tobacco smoking and some genetic variants.
- The study of polyautoimmunity provides important clues for elucidating the common mechanisms of autoimmune diseases (ie, the autoimmune tautology).

## INTRODUCTION

Autoimmune diseases (ADs) are chronic conditions initiated by the loss of immunologic tolerance to self-antigens due to the interaction of hereditary (ie, genetics and epigenetics) and environmental factors over time.[1] Sjögren syndrome (SS) is an AD characterized by a progressive lymphocytic and plasma cell infiltration of the salivary and lachrymal glands. It is accompanied by the production of autoantibodies leading to xerostomia and keratoconjunctivitis sicca (sicca symptoms).[2] The spectrum of the disease extends from an organ-specific autoimmune disorder (autoimmune exocrinopathy) to a systemic process involving the musculoskeletal, pulmonary, gastrointestinal,

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hematologic, vascular, dermatologic, renal, and nervous systems (Fig. 1). Because the target tissue involved in the autoimmune histopathologic lesions of SS is the epithelium, the term "autoimmune epithelitis" is currently used to describe the disorder.[3]

The diagnosis of SS is based on the combination of symptoms and the presence of the autoimmune characteristics: activation of T cells (ie, positive salivary gland biopsy) or B cells (ie, presence of autoantibodies). However, not all the individuals presenting sicca symptoms have SS. The main differential diagnosis of this disorder includes the use of medications with anticholinergic effects and endocrine diseases (eg, hypothyroidism, diabetes, and hypoandrogenism). No single test of oral or ocular involvement is sufficiently sensitive and specific to form a standard diagnosis of SS. Only the simultaneous positivity of various tests with the presence of subjective symptoms and serologic abnormalities (eg, anti-Ro and anti-La antibodies) and the presence of a score that is more than a "focus score" on the minor salivary gland biopsy (ie, at least 50 cells present in 4 $mm^2$ of gland surface unit) allow sufficient accuracy to diagnose this condition. The classification criteria for SS are those of the American-European Consensus Group (AECG), which require either salivary gland abnormality showing

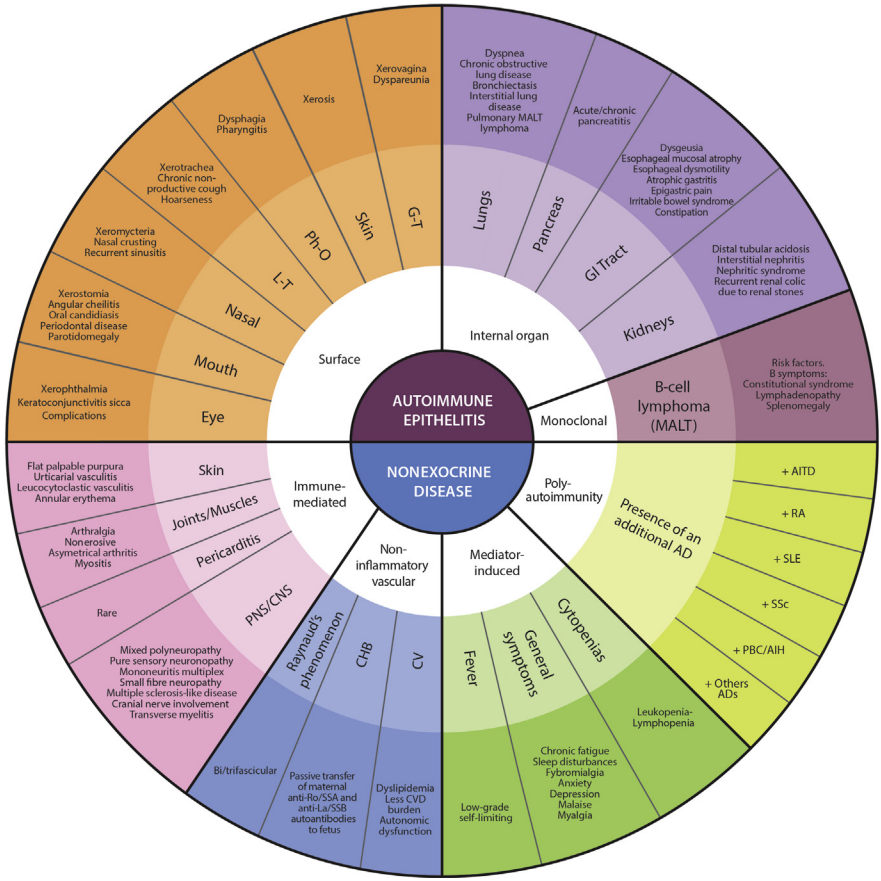



**Fig. 1.** Clinical spectrum of SS. AT, atherosclerosis; CHB, congenital heart block; CNS, central nervous system; CV, cardiovascular; CVD, cardiovascular disease; GI, gastrointestinal; GMN, glomerulonephritis; G-T, genital tract; L-T, laryngotracheal; MALT, mucosal-associated lymphoid tissue; Ph-O, pharyngo-esophageal; PNS, peripheral nervous system.

foci of lymphocytic infiltration or positive serology in the form of anti-Ro or anti-La antibodies.[4] Recently, new classification criteria have been proposed[5] and compared with the AECG criteria.[6]

There is compelling evidence showing that ADs share several physiopathologic mechanisms that are reflected in the clinical similarities they exhibit and in the multiple combination of ADs observed in a single patient and in their families (ie, the autoimmune tautology) (**Fig. 2**).[7] Polyautoimmunity and the multiple autoimmune syndrome (MAS) are terms used to describe the presence of more than one AD in the same patient. Polyautoimmunity refers to ADs co-occurring within patients, while MAS is a term used when a patient develops 3 or more ADs.[8,9]

### *Historical Perspective*

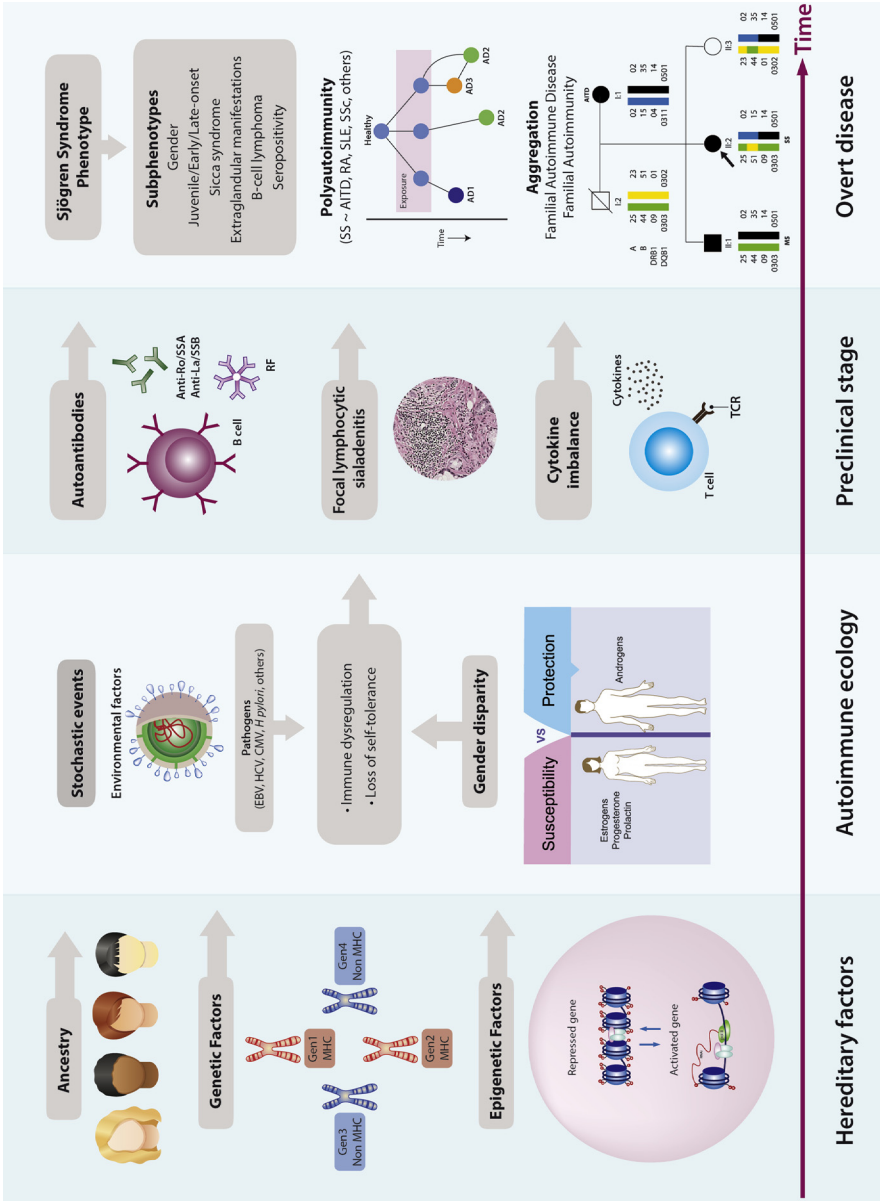
Since the first description by Henrik Sjögren in 1933, it has been well known that most of the patients with this syndrome present with polyautoimmunity. In fact, of the 19 patients he originally described, 13 (68.4%) also had rheumatoid arthritis (RA).[10]

In the classical description of 62 patients with SS by Bloch and colleagues[11] in 1965, most of them had an additional AD, including RA, systemic sclerosis (SSc), or polymyositis. Moreover, Bloch and Bunim[12] were the first to suggest a shared immunopathologic mechanism for SS, systemic lupus erythematosus (SLE), SSc, and autoimmune thyroid disease (AITD) as well as a possible familial aggregation of these diseases in patients with SS. In 1979, Moutsopoulos and colleagues[13] clarified the distinction between primary and secondary SS and recommended that the disease be termed primary when it occurs alone and secondary when it is associated with another AD. Since then, the term secondary SS has been used to describe the coexistence of SS with mainly RA or SLE. However, and as is shown herein, SS may coexist with all the systemic ADs and with most of the organ-specific ADs. In this case, the authors have proposed the term polyautoimmunity,[14] which groups all the taxonomy terms referring to coexistence of well-defined ADs in a single individual because some of the terms previously used are confusing and exclude various associations. This view has been also adopted by an expert consensus, which stated that regardless of any concurrent organ-specific or multiorgan AD, SS should be diagnosed for all who fulfill the criteria they proposed without distinguishing between primary or secondary.[5]

### *Polyautoimmunity or Overlap Syndrome?*

Polyautoimmunity was used by Sheenan and Stanton-King[15] for the first time while describing a patient with idiopathic thrombocytopenic purpura (ITP), pernicious anemia (PA), AITD, SSc, pancreatic exocrine insufficiency, and celiac disease before dying of vasculitic complications. The case they depicted corresponds to a typical MAS, which is already included in the term polyautoimmunity.

Polyautoimmunity has been referred to as overlap syndrome; some of these are frequent enough to have been given names like rhupus and sclerodermatomyositis.[14] The main difference between polyautoimmunity and the overlapping syndromes lies in the fact that the former is the presence of 2 or more well-defined autoimmune conditions fulfilling validated classification criteria, whereas the latter is the partial presence of signs and symptoms of diverse ADs. Most of the cases of overlapping syndromes have been described in cross-sectional studies. As has been shown, there is a lag in the time interval between the first and the second AD.[16] For example, in the mixed connective tissue disease (MCTD), the classical overlap syndrome, some patients will develop SLE, SSc, or RA during the course of the disease, and some will present with a longstanding MCTD.[17] Long-term studies have shown that MCTD remains an


Sjögren Syndrome Phenotype
Subphenotypes
Gender
Juvenile/Early/Late-onset
Sicca syndrome
Extraglandular manifestations
B-cell lymphoma
Seropositivity
Polyautoimmunity
(SS ~ AITD, RA, SLE, SSc, others)
Healthy
Exposure
Time
AD1
AD3
AD2
Aggregation
Familial Autoimmune Disease
Familial Autoimmunity
AITD
Autoantibodies
Anti-Ro/SSA
Anti-La/SSB
RF
B cell
Focal lymphocytic sialadenitis
Cytokine imbalance
Cytokines
TCR
T cell
Stochastic events
Environmental factors
Pathogens
(EBV, HCV, CMV, H.pylori, others)
• Immune dysregulation
• Loss of self-tolerance
Gender disparity
Susceptibility
vs
Protection
Androgens
Estrogens
Progesterone
Prolactin
Ancestry
Genetic Factors
Gen1 MHC
Gen2 MHC
Gen3 Non MHC
Gen4 Non MHC
Epigenetic Factors
Repressed gene
Activated gene
Time
Hereditary factors
Autoimmune ecology
Preclinical stage
Overt disease

overlap syndrome in about 60% of the patients. The remaining 40% progress to SSc, SLE, or RA,[18] highlighting the fact that ADs are a spectrum ranging from the incomplete forms or "forme frustre" and lenient and slow evolution syndromes to the rapidly progressive and fatal forms (see **Fig. 1**). The imbalance between permissive and protective factors (ie, hereditary and environmental) interacting over time may explain this spectrum[1] and the fact that "there are no diseases but rather patients."

## POLYAUTOIMMUNITY IN SJÖGREN SYNDROME

SS has been described in association with a large variety of ADs including AITD, RA, SLE, SSc, autoimmune hepatitis (AIH), and primary biliary cirrhosis (PBC), and the like[19–21] (**Table 1**). Lockshin and colleagues[22] reported a prevalence of polyautoimmunity in 52% of their patients with SS (defined by ophthalmologist-prescribed artificial tears or punctal plugs, salivary gland hypertrophy, and/or cryoglobulinemia). Patients with polyautoimmunity differed from those with "pure" SS regarding race (ie, "non-white").

Amador-Patarroyo and colleagues[21] assessed a cohort of 410 patients with SS and observed a prevalence of polyautoimmunity in 32.6% of them. The most frequent and closely coexistent diseases were AITD (21.5%), RA (8.3%), SLE (7.6%), and inflammatory bowel disease (0.7%), which together constituted a cluster group. There were 35 (8.5%) patients with MAS. Similar results were reported by Lazarus and Isenberg.[23] As a corollary, patients with SS should be monitored on a regular basis for polyautoimmunity.

### *Sjögren Syndrome and Autoimmune Hepatitis*

Endocrine symptoms documented in SS patients are mainly due to concomitant thyroid dysfunction.[24] Between 15% and 30% of patients with SS develop AITD, primarily Hashimoto thyroiditis (HT).[25] Patients with SS seropositive for antithyroid peroxidase and antithyroglobulin antibodies are at risk of future thyroid disease.[25]

The prevalence of SS is 10 times higher in patients with autoimmune thyroiditis.[26] It is advisable that patients with SS be screened periodically for thyroid function.[26] The association of HT in patients suffering from SS defines a subset of patients with milder disease and normal C4 levels.[27] The histologic picture of HT per se is highly similar to that of SS.[28] HT may evolve to lymphoma in 0.5% of patients.[29] One-third of the patients with AITD have SS features, and one of 10 antinuclear antibody (ANA) -positive AITD patients shares the diagnosis of SS.[28]

**Fig. 2.** Fourth-stage model for the pathophysiology of ADs (eg, SS). Each stage shows the known phenomena that, when it has accumulated, will be the causative scenario for the onset of ADs. First, heritable factors have an impact over the life of the individuals. They converge and interact to increase or decrease the risk an individual would have of developing the disease. Second, the autoimmune ecology corresponds to the effect of environmental factors, which, acting stochastically, will also influence the risk and course of disease. Once the autoimmune tolerance is lost by the interaction of heritable and environmental factors, a preclinical stage characterized by B- and T-cell dysregulation arises. This third phase may take years before the phenotype becomes clinically evident. The clinical stage has a broad spectrum of subphenotypes that can influence outcomes, treatment, and mortality. Note that familial autoimmunity corresponds to the presence of different ADs in a nuclear family. AOD, age at onset of disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; MHC, major histocompatibility complex; RF, rheumatoid factor; TCR, T-cell receptor.

**Table 1**
**Sjögren syndrome and polyautoimmunity**

| | Phenotype | | | | |
|---|---|---|---|---|---|
| | | SS | | | |
| **Variable** | **SS** | **+AITD[b]** | **+RA** | **+SLE** | **+SSc** |
| Prevalence | 0.1%–4.8% | 15%–30% | 4%–31% | 9%–19% | 14% |
| Autoimmune profile | Anti-Ro/SSA (33%–74%)<br>Anti-La/SSB (23%–52%)<br>RF (36%–74%)<br>ACPA (3%–10%)<br>ANA (59%–85%)[a] | Anti-TPO<br>Anti-Tg<br>ANA | ACPA (71.4%)<br>Anti-Ro/SSA and anti-La/SSB (12%) | Higher RF, anti-Ro/SSA, and anti-La/SSB<br>Anti-La/SSB as serologic marker | ACA (37%)<br>Anti-SCL70 (13%)<br>Anti-Ro/SSA (39%)<br>Anti-La/SSB (22%)<br>Anti-RNA Pol (2%) |
| Physiopathology | Focal lymphocytic sialadenitis (minor salivary glands), with a focus score $\geq$1<br>SS may be associated with organ damage due to several mechanisms | Infiltrate consists of primarily $CD4^+$ T lymphocytes<br>The thyroid epithelial cells express HLA class II molecules and adhesion molecules | Differences in genetic and immunologic pathways | Sharing many immunogenetic features | Lymphocytic infiltration of salivary glands leading to oral dryness is one of the main features in SS as well as salivary gland fibrosis |

| | | | | | |
|---|---|---|---|---|---|
| Subphenotype characteristics | SS has a wide clinical spectrum that extends from benign local exocrinopathy to systemic disorder that affects several organs | Milder disease and normal C4 levels | Articular involvement and RA activity are independent of SS | Milder SLE-related features and a predominance of SS-related features | Limited SSc predominantly associated |
| Prognosis | Lymphoma (5%–10%) | Progress to B-cell MALT lymphoma is probable<br>Lymphoma (0.5%) | Doubled standardized incidence ratio for NHL | Lower risk of developing glomerulonephritis | SS may be protective against SSc-associated pulmonary fibrosis |
| Treatment approach | Immunosuppressant agents (eg, CsA, AZA, MTX, MMF, and LEF are all used empirically in SS with extraglandular manifestations) | No immunosuppressant agents required | Corticosteroids and immunosuppressants (eg, methotrexate)<br>Rituximab may be considered in refractory cases | HCQS, corticosteroids, and in more severe cases immunosuppressants have been effectively used, including Rituximab | In refractory or severe cases, immunosuppressants, such as AZA, MMF, or CYC, have to be considered<br>High-dose IVIg can be an effective option |

*Abbreviations:* ACA, anticentromere antibodies; anti-Tg, antithyroglobulin antibodies; anti-TPO, antithyroid peroxidase antibodies; AZA, azathioprine; CsA, cyclosporine A; CYC, cyclophosphamide; HCQS, hydroxychloroquine; IVIg, intravenous immunoglobulin; LEF, leflunomide; MALT, mucosal-associated lymphoid tissue; MMF, mycophenolate mofetil; MTX, methotrexate; RF, rheumatoid factor; SSA, Anti SS related antigen A antibodies (Ro/SSA antibodies); SSB, Anti-SS related antigen B antibodies (La/SSB antibodies); TNF, tumor necrosis factor.

[a] Other autoantibodies described in SS patients: ACA (3.7%–27%), anti-SCL70 (<5%), AMA (1.7%–13%), and ASMA (30%–62%).

[b] Mainly HT. Prevalence of SS corresponds to the general population. Prevalence of AITD, RA, SLE, and SSc corresponds to that observed associated with SS.

*Adapted from* Iaccarino L, Gatto M, Bettio S, et al. Overlap connective tissue disease syndromes. Autoimmun Rev 2013;12(3):363–73.

### *Sjögren Syndrome and Rheumatoid Arthritis*

RA is frequently associated with both sicca symptoms and true SS. Patients with RA may show evidence of dry eye regardless of the coexistence of SS or other concomitant disease.[30] The prevalence of sicca symptoms in patients with RA ranges from 30% to 50%,[31,32] and the percentage of RA patients who fulfill SS classification criteria ranges from 4% to 31%.[31–33] Arthralgia arthritis, in turn, is reported in 70% of SS patients. Many investigators consider SS an extra-articular manifestation of RA, although differences in genetic and immunologic pathways involved in the disease process have been documented.[31]

Prevalence of anticitrullinated protein antibodies (ACPA) has been reported in 7.2% of patients with SS who are RF negative and without arthritis.[34] Median-term follow-up of ACPA-positive patients with SS showed that almost half of them developed RA, particularly in the presence of elevated acute phase reactants.[35] In the authors' series, ACPA were observed in 9% of SS patients, of whom 80% were RF positive.[36] This prevalence was higher (67%) in SS-RA patients.[36] Iwamoto and colleagues[37] detected ACPA in 21% of SS patients with arthritis and in none of those without arthritis. Notably, ACPA were found in 71.4% of patients classified as having SS-RA and in 6% of SS patients with arthritis but without RA. RF is not helpful for differentiating patients with SS from those with SS-RA polyautoimmunity. SS-RA patients are less frequently anti-Ro and anti-La antibody positive than patients with SS (12% vs 82%).[38]

The number of joints involved and the activity of RA are independent of the presence of SS.[39] A 17% cumulative prevalence of SS was described in a Spanish cohort of RA patients.[40] Similar results were observed in an Austrian cohort.[41] In Finland, a doubling of the standardized incidence ratio for non-Hodgkin lymphoma (NHL) in RA patients with polyautoimmunity when compared with RA patients without SS was described.[42]

### *Sjögren Syndrome and Systemic Lupus Erythematosus*

SLE is probably the AD most closely related to SS due to the significant overlap in their clinical and immunologic expression. The prevalence of sicca syndrome in SLE ranges between 18% and 34%.[20] Recent studies have described a prevalence of associated SS in SLE patients ranging between 9% and 19%.[31,43,44] In a large prospective series, skin involvement, such as photosensitivity or malar rash, oral ulcers, arthritis, Raynaud phenomenon, and psychosis, were reported more frequently in the SS-SLE group.[45] SS-SLE patients are older with a lower risk of developing glomerulonephritis compared with SLE patients.[45] Other investigators reported a higher frequency of fatigue and thrombocytopenia in SS-SLE patients.[43] A meta-analysis disclosed a 17.8% prevalence of SS.[46] SS-SLE patients constitute a subphenotype characterized by milder SLE-related features and a predominance of SS-related features.[31,43] One study found patients with SS-SLE were also more likely to have AITD compared with those with only SLE.[47] In summary, the polyautoimmunity SS-SLE seems to be characterized by less organ involvement, a more specific autoantibody profile, and a favorable clinical outcome.

Among families identified by the presence of SLE, both "primary" and "secondary" SS tend to occur within the same families.[48] Aggarwal and colleagues mentioned in their article "These results highlight the commonalities between these two forms of SS, which in fact correspond to the same disease."[48]

### *Sjögren Syndrome and Systemic Sclerosis*

Sicca symptoms are common in SSc because they are observed in 68% to 83% of the cases. However, only 14% of SSc-sicca patients fulfill the criteria for SS.[49] SS-SSc is

more often complicated by peripheral neuropathy and additional ADs or autoantibodies not typical for either SS or SSc alone.[19,49]

Digital ulcers were reported in 11.8% of the cases and pulmonary hypertension in 23.6%. In SS-SSc, skin involvement seems to be less severe than in SSc patients and the incidence of digital ulcers lower.[50] SS may be protective against SSc-associated pulmonary fibrosis. Limited SSc was predominantly associated with SS in these studies.[47]

### *Sjögren Syndrome and Hepatic Autoimmune Diseases*

Liver involvement was one of the first systemic manifestations reported in SS.[51] After eliminating hepatotoxic drugs and fatty liver disease, the 2 main causes of liver disease in SS are chronic viral infections and autoimmune liver diseases, which require different therapeutic approaches and have different prognoses.[52] With respect to viral infections, chronic HCV infection is the main cause of liver involvement in SS patients from the Mediterranean area, whereas chronic HBV infection may be the main cause of liver involvement in SS patients from Asian countries.[52]

After eliminating viral hepatitis, PBC should be considered the main cause of liver disease in SS.[52] PBC-SS patients may have a broad spectrum of abnormalities of the liver. In fact, the comparison of liver histology between the PBC with SS patient group and the PBC without SS patient group showed that the incidence of lymphoid nonsuppurative cholangitis was higher in PBC-SS patients.[53] SS has been shown to be the most common AD complicating concomitant SLE and PBC.[54] Serologically, the diagnostic hallmark of PBC is the presence of significant titers of antimitochondrial antibodies (AMA), which is possibly the most specific autoantibody in clinical immunology.[52]

AIH is diagnosed in 1.7% to 4% of patients with SS.[55] AIH is the second most frequently observed autoimmune liver disease in SS (all reported cases are type I), and nearly 10% of these patients may have AIH-PBC.[56] Only 10% of SS-related type I AIH patients may have positive AMA (AIH-PBC); therefore, AMA could discriminate between PBC and AIH.[52] In an evaluation of polyautoimmunity in AIH, SS was the most frequent (15.2%).[57] When the prevalence of concurrent extrahepatic AD in patients with AIH/PBC polyautoimmunity was assessed, SS was observed in 8.4%, which corresponds to the MAS phenotype.[58]

## SEVERITY OF POLYAUTOIMMUNITY

Polyautoimmunity may impact the outcome of ADs. In the case of SS-SLE and SS-SSc patients, several investigators suggest a more benign course of SLE and SSc, respectively, and therefore, a better prognosis.

SS-SLE patients have a lower risk of developing glomerulonephritis compared with SLE patients. The coexistence of SS in patients with SLE does not affect the severity of SLE.[59] Rather, it seems to be a protective factor against the development of lupus nephritis.[43,45] In terms of treatment, the efficacy and safety of rituximab therapy in patients with refractory ITP and SLE and/or SS were evaluated. All patients with SS had a complete response to treatment.[60]

Patients with NHL associated with SLE had sicca symptoms, salivary gland swelling, and anti-Ro and anti-La antibodies significantly more often than patients with SLE alone.[61] SS disease severity has been shown to be the strongest predictor of swallowing disorders, but these disorders did not differ on the basis of SS polyautoimmunity or SS alone.[62] A more frequent lung involvement (25% vs 8.1%; $P = .05$) has been found in patients with SS and ACPA positivity.[35]

As mentioned, skin involvement in limited SSc seems to be less severe when it appears in SSc-SS, and the incidence of digital ulcers is lower than that reported in SSc patients.[50] Furthermore, SS may be protective against SSc-associated pulmonary fibrosis.[63] The explanation for these phenomena requires further analysis in order to understand the physiopathogenic pathways underlying this apparent protective effect.

## FACTORS ASSOCIATED WITH POLYAUTOIMMUNITY IN SJÖGREN SYNDROME

Besides duration of disease, both genetics and environmental factors have been reported to be associated with polyautoimmunity in SS.[21,64]

In a study in which patients with SS and polyautoimmunity were evaluated by whole exome sequencing, novel and rare mutations were identified.[64] Among them, those harbored by the *LRP1/STAT6* locus were considered the strongest causative factors for polyautoimmunity. *LRP1/STAT6* mutation is involved in extracellular and intracellular anti-inflammatory pathways that play key roles in maintaining the homeostasis of the immune system. A lack of influence of Th17 polymorphisms on the susceptibility and severity of SS-RA polyautoimmunity was recently reported.[65]

Smoking per se is considered a risk factor for both the development of ADs, such as RA, SLE, and AITD, and the positivity of autoantibodies.[66] Pathophysiologic mechanisms have been described including influence on lymphocytic and plasma cell functions, apoptosis and effects on cytokines, and hormonal imbalances. A controversial effect of habitual smoking on the spectrum of the disease has been reported in SS. Manthorpe and colleagues[67] showed that SS patients who smoked had anti-Ro and anti-La antibodies less frequently and a lower focus score than those who did not smoke. They explain that smoking may lower the focus score by reducing the lymphocyte infiltration in salivary glands, thus reducing the production of anti-Ro and anti-La antibodies. Karabulut and colleagues[68] showed an association between SS, ANA titers, and habitual smoking. In addition, positive smoking status was associated with polyautoimmunity in SS patients.[21]

The association between polyautoimmunity and low socioeconomic status in SS patients has been highlighted.[69] This finding is in concordance with the influence of socioeconomic status on chronic diseases in which low socioeconomic status is associated with morbidity and mortality.[70]

The influence of infection on polyautoimmunity has been evaluated in some studies. Vasculitis in SS patients was associated with the presence of immunoglobulin G *Saccharomyces cerevisiae* antibodies.[71] These results may be related to the fact that microbe-activating specific innate immune responses are critical, whereas antigenic cross-reactivity may perpetuate immune responses leading to chronic autoinflammatory disease.[72] There are numerous case reports or case series showing the association with an infectious agent (varicella zoster, Epstein-Barr virus, *Helicobacter pylori* infection, hepatitis C virus) and polyautoimmunity in SS.[73]

## AUTOIMMUNE TAUTOLOGY AND SJÖGREN SYNDROME

Polyautoimmunity is one of the major arguments supporting the autoimmune tautology (ie, the common mechanisms of ADs) due to the fact that in an individual with 2 or more diseases, the same genetic background, and the same environment influence the appearance of different phenotypes. Ten characteristics supporting this logically valid propositional theory applied to SS are shown in **Table 2**.

**Table 2**
**Sjögren syndrome in light of the autoimmune tautology**

| Characteristic | Description |
|---|---|
| Female preponderance | Female-to-male ratio as high as 10:1. Some studies have found differences with respect to immunologic, clinical, and severity features (including lymphoma risk) in men with SS. |
| Shared subphenotypes | Sicca symptoms are nonspecific. Another AD (eg, RA, SSc) could manifest with dry mouth and eyes. Several systemic manifestations of SS are present in other autoimmune conditions. Autoantibodies (ie, ANA, anti-Ro, anti-La, rheumatoid factor) are not specific to SS and may be present in other ADs. |
| Polyautoimmunity | SS has been described in association with a large variety of ADs, both organ-specific (eg, AITD, multiple sclerosis, PBC, AIH) and systemic (eg, RA, SLE, SSc). |
| Familial autoimmunity | Familial coaggregation of ADs has been reported in up to 38% of patients with SS with AITD, SLE, and RA being the most frequent. |
| Similar pathophysiology | Damage induced by T or B cells, or both, plays a major pathogenic role in ADs. Although the autoimmune phenotype varies depending on the target cell and the affected organ, the local mechanisms for tissue injury are similar (eg, activation of the type I interferon pathway, decreased T- and B-regulatory functions). Focal lymphocytic aggregates are the histopathologic hallmark of SS, but they are similar to the inflammatory infiltrate seen in organ-specific ADs (eg, type 1 diabetes, AITD). |
| Autoimmune ecology | Environmental factors, including infectious agents (eg, EBV, CMV), vitamin D deficiency, and smoking are associated with SS and other ADs. |
| Influence of age of onset | Although SS is a late-onset disease, clinical manifestations of juvenile SS may vary more than those seen in adult patients (eg, lower frequency of sicca syndrome, higher rates of parotid enlargement, higher prevalence of immunologic markers). |
| Influence of ancestry | The highest rates of SS are documented in northern Europe, while the rates in North America and mainland Europe seem to be comparable, and the lowest rates are observed in some parts of Asia. Note that nothing is published on detailed series of SS cases in African descendents. |
| Common genetic factors | The genetic risk factors for ADs consist of 2 forms, those common to many conditions and those specific to a given disorder. SS shares genetic factors at the MHC and non-MHC loci with several other ADs. |
| Similar treatment | In addition to sicca treatment, patients with SS (mainly those with systemic manifestations) may benefit from immunosuppressive treatment (eg, corticosteroids, cyclophosphamide, methotrexate) and antimalarials. In refractory cases, B-cell depletion therapy may be considered. |

*Abbreviations:* CMV, cytomegalovirus; EBV, Epstein-Barr virus; MHC, major histocompatibility complex.

## FUTURE CONSIDERATIONS

Based on polyautoimmunity and depending on severity, ADs may be categorized as major and minor conditions. In this sense, how polyautoimmunity affects major ADs warrants further investigation. In turn, the identification of commonalities among ADs may provide insights about salient mechanisms that are necessary and perhaps sufficient for autoimmunity to occur (see Fig. 2). Last, polyautoimmunity, as an

extreme phenotype of autoimmunity, would be critical for dissecting genes of major effect conferring susceptibility to autoimmunity. Assessment and clustering of polyautoimmunity in SS and other ADs will help to define plausible approaches to studying the autoimmune tautology.

## SUMMARY

Polyautoimmunity is a frequent condition in SS and follows a grouping pattern. The most frequent ADs observed in SS are AITD, RA, and SLE. Genetic and environmental factors influence the development of polyautoimmunity.

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