Serologic features of primary Sjögren's syndrome: clinical and prognostic correlation

Sjögren's syndrome (SS) is a chronic inflammatory systemic autoimmune disease. The disease spectrum extends from sicca syndrome to systemic involvement and extraglandular manifestations, and SS may be associated with malignancies, especially non-Hodgkin's lymphoma. Patients with SS present a broad spectrum of serologic features. Certain serological findings are highly correlated with specific clinical features, and can be used as prognostic markers.

KEYWORDS: clinical features ▪ hematologic abnormalities ▪ lymphoma ▪ prognosis ▪ serologic findings ▪ Sjögren's syndrome

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Sjögren's syndrome (SS) is a chronic inflammatory systemic autoimmune disease characterized by diminished lachrymal and salivary gland function due to lymphocytic infiltration of these glands, leading to progressive destruction.

In the absence of associated systemic autoimmune diseases, patients are classified as having primary SS (pSS). In pSS, decreased exocrine gland function leads to the 'sicca complex', a combination of dry eyes (xerophthalmia) and dry mouth (xerostomia). Secondary SS (sSS) is associated with other rheumatic conditions, of which the most common is rheumatoid arthritis [1–3].

Epidemiology

The epidemiological information has been changing, in 2002 the classification criteria of the American-European Consensus Group (AECG) proposed the presence of the autoantibodies: anti-SSA (Ro)/anti-SSB (La) for the diagnosis of pSS, consequently a large number of patients with other immunological markers and severe sicca symptoms, but without autoantibodies, were excluded from the pSS diagnosis. According to the AECG classification criteria, the prevalence of pSS is approximately 0.4% in the adult population, with a yearly incidence of four out of 100,000 in the general population, far lower than previously assumed. In addition, the repeatedly reported male/female ratio of 1:9 seems to be more in the range of 1:20. Approximately 60% have the disease secondary to rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis [4,5].

Up to 40% of pSS patients develop extraglandular disease, but only 5–10% of pSS patients suffer from severe extraglandular manifestations. In particular, palpable purpura, hypocomplementemia, cryoglobulinemia and non-Hodgkin's lymphoma are associated with increased mortality [6–8].

Recently, after the SICCA study, in 2012 new criteria for SS was proposed. The criteria are based on an expert opinion group and analyses of data from the Sjögren's International Collaborative Clinical Alliance, criteria validation included comparisons with classifications based on AECG criteria. The new criteria requires at least two of the following three:

- Positive serum anti-SSA/anti-SSB or positive rheumatoid factor (RF) and antinuclear antibody titer ≥1:320;
- Keratoconjunctivitis sicca with ocular staining score ≥3;
- Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm² [9].

These criteria are thought to be stricter than those previously applied, and so the prevalence might decline.

Etiopathogenesis

The etiological term 'autoimmune epithelitis' has been suggested, owing to the essential role of the epithelium in the immune response and the histopathological lesions of SS [10]. Environmental, genetic and hormonal contributors seem to be involved in the pathogenesis of the disease [11].

Genetic risk factors such as *STAT-4*, *IL-T6*, haplotype *HLA DRw52-DR2-DR3-B8*, the heterozygosity of the *HLA-DQ* genetic locus [12] and, more recently, *IRF5*, have been identified [13]. The association between HLA and SS is restricted to patients with anti-Ro/or anti-La antibodies [14,15].

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Environmental risk factors, possibly including chronic viral infections such as the Epstein–Barr virus, cytomegalovirus, hepatitis C virus, human herpes virus 6, coxsackie virus and several retroviruses suggest molecular mimicry, particularly autoantibodies against Ro and La nuclear antigens. In addition, the mechanisms that control or perpetuate reactivation cycles of viral replication and inflammatory responses, such as the production of interferons (IFNs), are likely to be important in SS [16–18].

In terms of the pathophysiology, the infiltrating cells (T, B and dendritic cells) in glandular elements leads to the secretion of cytokines and activation of pathways of IFN-1 and -2. The production of autoantibodies interferes with muscarine receptors and promotes destruction. The secretion of metalloproteinases (MMPs) impedes the interaction of the glandular cell with its extracellular matrix; these MMPs are correlated with disease severity [19]. A genetic alteration of the distribution or expression of aquaporin water channels that may contribute to sicca symptoms in primary SS has also been described [20].

Clinical manifestations of Sjögren's syndrome

Sicca complex occurs in all patients, but is the only disease manifestation in 31%. In addition to the exocrine glands, many other organs can be involved in SS. Clinically relevant extraglandular manifestations occur in more than 20% of patients with pSS. The development of malignant B-cell lymphoma is the most important complication, affecting approximately 5% of pSS patients [21].

Severe involvement in parotid sialoscintigraphy has been used as a prognostic factor for an adverse outcome in SS patients [22]. However, recently the ultrasonography of major salivary glands has demonstrated more sensibility than sialoscintigraphy in the detection of pSS onset. Therefore, ultrasonography of major salivary glands can be used as an alternative tool to sialoscintigraphy as predictive for adverse outcome [23].

On the other hand, it is important to use indices to measure the symptoms and the activity of the disease, such as the EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI), an index designed to measure patients' symptoms in pSS, and EULAR Sjogren's syndrome disease activity index (ESSDAI), which measures disease activity in patients with pSS. These tools can be used to evaluate disease progression [24,25].

Serologic findings

Patients with SS present a broad spectrum of serologic features (cytopenias, hypergammaglobulinemia, high erythrocyte sedimentation rate, autoantibodies, cryoglobulins and other key biomarkers). Certain serological findings are highly correlated with specific clinical features and can be used as prognostic markers.

The identification of biomarkers for SS in peripheral blood offers a very practical alternative to current approaches for diagnosis and classification of SS cases [21].

Autoantibodies

Anti-SSA/Ro and Anti-SSB/La are the hallmark antibodies in pSS, and are present in 40–80% of patients. Patients with anti-Ro/La antibodies have the highest prevalence of most systemic, hematologic and immunologic alterations [3].

In immunological studies, antinuclear antibodies (ANA) are the most frequently detected, but anti-Ro/SSA is the most specific [14]. In addition anti-SSA/Ro and anti-SSB/La autoantibodies might be present in serum far before SS is clinically present [26].

HLA class II markers confer genetic susceptibility to SS. The association with *HLA-DRB1*03* suggests that HLA alleles predispose to autoantibody secretion, without being associated with clinical outcomes. *HLA-DR15* favors anti-SSA production, whereas *HLA-DR3* is associated with both anti-SSA and anti-SSB production [15].

Garcia-Carrasco *et al.* in a cohort of 400 patients with pSS demonstrated that antinuclear antibodies, anti-Ro/SSA antibodies, RF and anti-La/SSB antibodies are the most common immunologic patterns (**Table 1**) [27].

IgM-RF, anti-Ro/SSA and anti-La/SSB have been associated with an earlier disease onset, glandular dysfunction, complete atrioventricular block, extraglandular manifestations (EGM) and other markers of B-cell activation: these patients also seem to have a higher risk of developing hypergammaglobulinemia, hypocomplementemia and lymphadenopathy. Anti-Ro/SSA is the strongest predictor of the presence of EGM (**Table 2**) [14,28]. They are useful in the diagnosis of pSS and help to identify more 'active' patients; however, their association with response to treatment is unclear.

The presence of IgA-RF is closely associated with the presence of Ro/SSA, anti-La/SSB autoantibodies and also is associated with renal disease (**Table 2**) [29].

Although the congenital AV block is related to the presence of autoantibodies anti-Ro/SSA and anti-La/SSB; after reviewing the literature, the authors have not found that the clinical manifestation of congenital AV block has any relationship to the development of lymphoma in patients diagnosed with pSS. Therefore, although this has not been included as a predictor of the evolution of the disease, this clinical manifestation may change the prognosis.

Atypical autoantibodies

Antiphospholipid antibodies

Some study results suggest that gene interaction between DR2 and DR3 may play a part in the production of antiphospholipid antibodies in patients with SS [12].

Antiphospholipid antibodies are found in approximately 20–30% of patients with pSS, a lower percentage than patients with sSS. Reports suggest that anticardiolipin antibodies (aCL) are the most common, followed by lupus anticoagulant (LA) and anti-β2GP1 antibodies. The presence of antiphospholipid antibodies in patients with pSS is related to immunological diseases such as thyroiditis, primary biliary cirrhosis and a higher prevalence of hypergammaglobulinemia (especially aCL), but not with antiphospholipid syndrome (TABLE 2) [30–32].

Cryoglobulins

Cryoglobulins are single or mixed immunoglobulins that undergo reversible precipitation at low temperatures. Types II and III, known as mixed cryoglobulinemia, are associated with chronic inflammatory states such as SS, with a prevalence of approximately 20%, and viral infections (particularly HCV). In these disorders, the IgG fraction is always polyclonal with either monoclonal (type II) or polyclonal (type III) IgM (rarely IgA or IgG) with RF activity. According to European studies, mixed cryoglobulinemia type II (IgG polyclonal plus IgM κ) is the most frequent type in pSS and the monoclonal components (IgA and IgG) are prevalent in Eastern countries [33].

Primary SS patients with cryoglobulinemia have a higher prevalence of cutaneous vasculitis, hypocomplementemia and leucopenia, and HCV infection compared to patients without cryoglobulinemia. Cryoglobulinemia has also been associated with an increased presence of extraglandular manifestations and the development of lymphoma. Therefore, the presence of cryoglobulinemia is a risk factor for the development of lymphoproliferative processes.

Table 1. Common immunologic patterns.

Immunologic test	Frequency (%)
Antinuclear antibodies	74
Anti-Ro/SSA antibodies	40
Rheumatoid factor	38
Anti-smooth muscle antibodies	35
Anti-La/SSB antibodies	26
Anti-parietal cell gastric antibodies	20
Antiperoxidase antibodies	18
Antithyroglobulin antibodies	13
Low CH50	12
Cryoglobulinemia	9
Low C4	8

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Cryoglobulinemia at diagnosis is significantly associated with an increased risk of lymphoma (TABLE 2) [34,35].

Other autoantibodies

Anti-DNA, anti-Sm, anti-RNP, anti-topoisomerase1/Scl70, anticentromere (ACA) and anti-Jo1 are considered as atypical autoantibodies and have been studied in pSS. Their presence is not considered to be significant because they are not strictly related to sicca symptoms or EGM, although approximately 15% of patients develop another autoimmune disease [36]. Gulati *et al.* reported an increased risk of EGM (most common Raynaud's phenomen) and lymphoma in pSS patients with ACA (TABLE 2) [37,38].

Henrikkson *et al.*, in a study of 214 patients with pSS, found anti-CD4 antibodies in 12.6%, similar to the 13% found in HIV-1 patients. However, there was no correlation between anti-CD4 antibodies and the $CD4^+$ T count [39].

In another study, Tsuboi *et al.* reported that some patients with SS present inhibitory autoantibodies against the M3 muscarinic acetylcholine receptor (M3R). Anti-M3R can be detected by immunofluorescent analysis using lacrimal glands [40].

Complement

While autoantibodies are important in diagnosing SS, complement is considered as a marker of the prognosis. Patients who present constantly low levels of complement components C3 and/or C4 have more unfavorable outcomes, including lymphoma, severe disease manifestations and

premature death. Low complement levels in pSS may not only be due to genetically-determined low production, but also to increased consumption (TABLE 2) [41].

Zadura *et al.* investigated how the C4b-binding protein (C4BP), a major complement inhibitor in the fluid-phase, can influence C4 and C3 levels; they found that C4BP levels were increased in plasma in the acute phase, with a decrease in C3 and C4 levels, probably due to consumption, and they also identified C4BP as an acute phase marker, together with IL-6 and C-reactive protein (CRP). On the other hand, C4BP levels were inversely related to IgG levels, the extent of autoantibody production and global disease activity. C4BP levels were decreased in parallel with C3, C4 and $CD4^+$ T-cell counts only in severe cases with intensive ongoing autoantibody production and systemic extraglandular disease manifestations, suggesting that disturbed complement regulation may contribute to pathogenicity in pSS [41].

Hypocomplementemia has been associated with a higher frequency of vasculitis and lymphoma [3]. Hypocomplementemia, cryoglobulinemia and lymphocytopenia at pSS diagnosis are the strongest predictors. Survival is clearly reduced in patients with hypocomplementemia (TABLE 2) [42].

Immune system cells & interleukins in pSS

The innate immune cell system and the regulatory T-cell system are responsible for the maintenance of tolerance. In pSS, the suppressor function of the regulatory system is dysfunctional.

Reports have shown disproportionate levels of immune cell types in pSS patients compared to healthy individuals, due to a dysfunction of immune cells and components with regulatory capability. Szodoray *et al.* suggest that elevated levels of natural killer, natural killer T and T-regulatory type 1 (Tr-1) cells in pSS could be part of an increased counterregulatory reaction, presumably to compensate autoimmune responses. These cells, predominantly Tr-1, are increased in proinflammatory processes such as EGM [43]. IL-10, known as a human cytokine synthesis inhibitory factor, is not elevated in pSS owing to the dysfunction of Tregs, despite the elevated levels of these cells. Presumably, in inflammatory processes, the elevation and action of IL-6 and TNF-α on T cells may affect their function, and may also produce autoreactive T cells and resistance to Tregs.

$CD4^+$ and $CD25^+$ Tregs increase as a feedback process, attempting to compensate the progression of disproportional immune responses [43,44]. In addition, Foxp3 is important in the

Table 2. Autoantibodies and complement.

Serologic finding	Clinical correlation
Anti-SSA/Ro, Anti-SSB/La	Earlier disease onset, presence of EGMs
IgM-RF	Risk of hypergammaglobulinemia, hypocomplementemia and lymphadenopathy
IgA-RF	Associated with renal disease
Antiphospholipid antibodies (particularly aCL)	Immunological diseases such as thyroiditis and primary biliary cirrhosis Higher prevalence of hypergammaglobulinemia
Antineutrophil cytoplasmic antibodies	Risk of EGMs and lymphoma
Cryoglobulins (types II, IgG polyclonal plus IgM κ)	Higher prevalence of cutaneous vacuities, hypocomplementemia and leucopenia Increased presence of EGMs and development of lymphoma
Anti-DNA, anti-Sm, anti-RNP, anti-topoisomerase1/Scl70, anticentromere, anti-CD4 antibodies and anti-Jo1	Are not related to EGMs or sicca symptoms. However, patients could develop another autoimmune disease
Complement (C3/C4)	Low levels have been related to lymphoma, severe disease manifestations and premature death
C4BP	Increased in acute phase In severe cases are decreased in parallel with C3, C4 and $CD4^+$ T cells

aCL: Anticardiolipin antibodies; EGM: Extraglandular manifestation; pSS: Primary Sjögren's syndrome.

Table 3. Immune cells and cytokines in primary Sjögren's syndrome patients.

Immune cells and cytokines	Serologic finding/clinical correlation
Peripheral natural killer, natural killer T cells Tr-1 cells	Increased Strongly increased, mainly in patients with EGMs
Peripheral $CD4^+$, $CD25^+$ Treg cells Peripheral $CD27^+$ memory B cells	Decreased
Circulating cytokines	Strongly increased TNF-α, IL-6 IFN-γ, IL4 normal IL-10 decreased
Correlation between regulatory cell populations and soluble cytokines	Negative correlation between IL-10 and Tr-1 cells Positive correlation between IFN-γ and Tr-1 cells
Association between autoantibodies with peripheral regulatory cells	No association between the presence of autoantibodies and percentages of any type
Foxp3	Decreased Related to the development of hypocomplementemia and enlarged salivary glands
Chemokines: CXCL13, CCL21 and CXCL12	Expressed in salivary glands of pSS patients and in MALT lymphoma
FLT3-ligand	Levels are elevated May explain the clinical evolution of pSS to B-cell lymphoma

EGM: Extraglandular manifestation; MALT: Mucosa-associated lymphoid tissue; pSS: Primary Sjögren's syndrome; Tr-1: T-regulatory type 1.

development and function of Treg cells in salivary gland biopsies, and peripheral blood is decreased in comparison with healthy individuals. Moreover, reduced Foxp3 levels correlate with adverse predictors for lymphoma development, such as the presence of C4, hypocomplementemia and enlarged salivary glands (TABLE 3) [43–46].

In addition, a reduction in peripheral memory B cells ($CD27^+IgM^+$) may be involved in the pathogenesis of pSS and its malignant complication, B-cell lymphoma, owing to a lack of appropriate censoring mechanisms and incomplete differentiation processes within the ectopic lymphoid tissues in pSS [47].

On the other hand it has been reported that abnormal B-cell distribution in the blood (Bm2 + Bm2′)/(eBm5 + Bm5) could be a diagnostic marker for SS [48].

Recently, two molecules have been detected: FLT3-ligand and CXCL13 (TABLE 3).

The chemokines CXCL13, CCL21 and CXCL12 are known to play differential roles in the organization of the lymphoid tissues and the development of lymphoid malignancies. CXCL13, CCL21 and CXCL12 are expressed in the salivary glands of patients with Sjogren's syndrome and mucosa-associated lymphoid tissue lymphoma. And FLT3-ligand levels are elevated in patients with primary SS and correlate with abnormal B-cell distribution. Serum levels of FLT-3L might explain the clinical evolution of pSS to B-cell lymphoma that is observed in some patients, thus opening the possibility of new avenues for therapy [49].

Hematologic abnormalities

Abnormalities are frequent and may be the first sign of latent SS. Anemia of chronic disease and hypergammaglobulinemia are common hematologic manifestations at diagnosis and during the course of pSS. Patients with anti-Ro antibodies have the highest frequencies of hematological abnormalities and altered immunological markers.

Anemia

Between 16 and 50% of patients with pSS have anemia, with normocytic-microcytic anemia being the most common type. Hemolytic anemia has been described but is not common, even though the Coombs test is positive in 22–47% of patients. In most cases, the cause of hemolysis is not identified.

Patients with anemia have a higher prevalence of renal involvement, cutaneous vasculitis, peripheral neuropathy, ANA, RF, cryoglobulinemia and hypocomplementemia (TABLE 4) [50].

Pure red cell aplasia is a very rare complication of pSS and may be the first manifestation of lymphocytic or lymphoblastic leukemia, or lymphoma (non-Hodgkin's or Hodgkin's), and

Table 4. Hematologic findings and proteins.

Hematologic findings	Clinical correlation
Normocytic–microcytic anemia	Prevalence of renal involvement, cutaneous vasculitis, peripheral neuropathy Presence of ANA, RF, cryoglobulinemia and hypocomplementemia
Lymphopenia	Significantly associated at diagnosis with an increased risk of lymphoma
Monoclonal gammopathy	Associated with EGMs and risk of lymphoproliferative disease
Polyclonal hypergammaglobulinemia	Higher prevalence of extraglandular manifestations and B-cell lymphoma
Hypogammaglobulinemia	Associated with lymphoproliferative syndromes, humoral immunodeficiency
Erythrocyte sedimentation rate (>50 mm/h)	Thyroiditis, renal disease, peripheral neuropathy, cutaneous vasculitis Anti-SSB/La, RF, cryoglobulinemia and hypocomplementemia
B2 microglobulin	Useful method for estimating the degree of lymphocytic infiltration Possible evolution marker of lymphoproliferation
Soluble receptor IL-2	Possible evolution marker for lymphoma

ANA: Antinuclear antibodies; EGM: Extraglandular manifestation; RF: Rheumatoid factor.

therefore strict monitoring of patients with SS and pure red cell aplasia is mandatory [51].

Monoclonal gammopathy

Monoclonal gammopathy is common in patients with SS, and is normally monoclonal gammopathy of undetermined significance not associated with lymphoma. The presence of monoclonal light chains in serum and urine is normal and is found in greater percentages in patients with EGM and in much smaller percentages in patients with sicca syndrome. Monoclonal gammopathy has been associated with pulmonary disease, cryoglobulinemia and an increased risk of lymphoproliferative disease [50].

Recently, it has been described that monoclonal gammopathy was detected in 22% of patients with pSS fulfilling the 2002 criteria, with mIgGκ being the most frequent type of band detected. In HCV-associated SS patients, the prevalence was higher (52%), with IgMκ being the most prevalent band detected. Monoclonal gammopathy was associated with a higher prevalence of parotid enlargement, EGM, hypergammaglobulinemia, cryoglobulinemia and related markers (RF and hypocomplementemia), and with a poor prognosis (development of neoplasia and death) (Table 4) [52].

Polyclonal hypergammaglobulinemia

Polyclonal hypergammaglobulinemia is one of the most characteristic analytical findings in SS, and reflects the lymphocyte hyperactivity characteristic of the disease. There are reports of hypergammaglobulinemia. A very high level of hypergammaglobulinemia has been observed just before the onset of lymphoma in patients with SS, whereas clinical disorders due to elevated gammaglobulins, such as thrombosis due to hyperviscosity, are exceptional. Hypergammaglobulinemia, the presence of antibodies (ANA, anti-Ro/SS-A, anti-La/SS-B, and RF) and elevated erythrocyte sedimentation rate lead to a higher prevalence of EGM and B-cell lymphoma (Table 4) [14,50,51,53].

Erythrocyte sedimentation rate

Patients with erythrocyte sedimentation rate >50 mm/h normally have a higher prevalence of EGM [50]. It is a useful biological marker in pSS to identify patients with increased polyclonal B-cell hyperactivity (Table 4) [51].

Proteins

CRP has not been clearly shown to be a diagnostic or prognostic marker. B2 microglobulin is increased in patients with SS and is a predictor of progression of sicca syndrome, levels of b2 microglobulin in glands are related to lymphocytic infiltration. In addition, it is a useful method for estimating the degree of active lymphocytic infiltration and could be used to evaluate a possible evolution of lymphoproliferative disorders. B2 microglobulin, together with soluble receptor IL-2, is a marker of possible evolution to lymphoma [50].

Prognosis

Most pSS patients will not develop extraglandular manifestations neither malignances; however, the prognosis and mortality are more closely related to the presence of potentials

complications, including lymphoma. In pSS patients, the risk of developing lymphoma is 15–20-times higher than in people without pSS. The possibility of developing lymphoma in pSS patients is 7.5% [3,32]. The median time from diagnosis of SS to development of lymphoma is approximately 10 years. The most common types of lymphomas in SS are low grade B-cell lymphomas, marginal zone B-cell lymphomas, mucosa-associated lymphoid tissue lymphoma and extranodal locations (parotid, GI tract and lung). They are the cause of death in 20% of patients with SS [2,21,34,54].

Conclusion & future perspective

Early diagnosis of SS can be difficult, especially in patients with unspecific serological tests or unspecific clinical manifestations, therefore the diagnosis could require a lot of time. However, the presence of some serological findings help us to identify pSS at an early stage and also help us to predict a decline in function in pSS patients, measure the activity disease or prevent the initial presence of complications such as B-cell lymphomas [55]; consequently, those serological findings offer a very practical alternative to current approaches for diagnosis and treatment of pSS cases.

In addition, recent genomic and proteomic developments are unlocking the mystery of the disease process, as well as contributing to our ability to define, diagnose and develop new treatment modalities for patients with this complex disorder. Therefore, the need to explore new laboratory techniques and treatments is becoming an important issue to overcome this disease [49,56,57].

Executive summary

Background

- Sjögren's syndrome (SS) is a chronic inflammatory systemic autoimmune disease characterized by diminished lachrymal and salivary gland function due to lymphocytic infiltration of these glands, leading to progressive destruction.

Epidemiology

- The prevalence of primary SS (pSS) is approximately 0.4% in the adult population, with a yearly incidence of four out of 100,000 in the general population.
- The disease spectrum extends from sicca syndrome to systemic involvement and extraglandular manifestations, and SS may be associated with malignancies, especially non-Hodgkin's lymphoma.
- Sicca complex occurs in all patients, but is the only disease manifestation in 31%. Clinically relevant extraglandular manifestations occur in more than 20% of patients with pSS.

Etiopathogenesis

- Environmental, genetic and hormonal contributors seem to be involved in the pathogenesis of the disease.
- Environmental risk factors, possibly including chronic viral infections such as the Epstein–Barr virus, cytomegalovirus, hepatitis C virus, human herpes virus 6, coxsackie virus and several retroviruses suggest molecular mimicry, particularly autoantibodies against Ro and La nuclear antigens.

Serological findings

- Patients with SS present a broad spectrum of serologic features. Certain serological findings are highly correlated with specific clinical features and can be used as prognostic markers.
- Anti-SSA/Ro and Anti-SSB/La are the hallmark antibodies in pSS, being present in 40–80% of patients.
- Complement is considered as a marker of the prognosis. Hypocomplementemia has been associated with a higher frequency of vasculitis and lymphoma.

Immune system cells

- In pSS, the suppressor function of the regulatory system is dysfunctional.

Lymphoma

- The possibility of developing lymphoma in pSS patients is 7.5%. The median time from diagnosis of SS to development of lymphoma is approximately 10 years.
- Mucosa-associated lymphoid tissue lymphomas are the type of lymphoma most often observed in SS subjects.

Hematologic abnormalities

- Anemia of chronic disease and hypergammaglobulinemia are common hematologic manifestations at diagnosis and during the course of pSS.
- SS carries a generally good prognosis; however, the prognosis and mortality are more closely related to the presence of other autoimmune diseases and the potential complications.
- Serological findings offer a very practical alternative to current approaches for diagnosis and treatment of pSS cases.

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▪▪ **Analytical features have a significant impact on the clinical presentation of primary Sjögren's syndrome, influencing the prevalence and diversity of extraglandular manifestation involvement.**

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