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REVIEW

# Phases and Natural History of Sjögren's Disease: A New Model for an Old Disease?

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Sjögren's disease (SjD) is an archetypal and heterogenous autoimmune disorder that is characterized by exocrine glandular dysfunction. A proportion of patients develop severe extraglandular manifestations, such as cryoglobulinemia, and have an increased risk of lymphoma, both of which can adversely affect quality of life and occasionally mortality. As with most autoimmune disorders, the pathogenesis is poorly understood and difficult to predict, and, frustratingly, there is a lack of targeted therapies to cure this disease. We review the disease manifestations of SjD and propose a staged model for understanding the evolution of pathology. In longitudinal studies, most patients remain relatively stable in terms of their laboratory and clinical parameters. However, in the setting of various risk factors, a proportion of patients develop severe symptoms and/or lymphoma. We discuss potential underlying mechanisms for disease progression and the strengths and limitations of using a staged model to correlate the pathogenesis and spectrum of manifestations in SjD. Ultimately, understanding how and why some patients remain relatively stable, whereas others progress and develop florid systemic disease and a fraction develop lymphoma, is key to developing preventative and therapeutic treatments.

## Introduction

As a prototypic local and systemic autoimmune disease, Sjögren's disease (SjD) (also termed Sjögren's syndrome) is a debilitating disorder caused by B cell hyperreactivity, exocrine gland dysfunction, and a wide variety of systemic manifestations. Historically, SjD was divided according to whether it existed alone (primary) or secondary to another autoimmune disorder such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). More recently, there is a push to abandon these terms and describe SjD as either a standalone disorder or associated with other autoimmunity (1,2). This reflects the ambiguity that "secondary SjD" confers because some patients develop another autoimmune disease only subsequent to SjD. The focus of this review is standalone SjD, which will be referred to as "SjD." SjD is estimated to affect up to 10 people per 10,000 inhabitants in 1 study (3), making it a rare diagnosis. As with most systemic autoimmune diseases, female patients predominate over male patients (4).

Autoantibodies are some of the key pathologic and diagnostic features of SjD, consisting of autoantibodies directed against the Fc regions of immunoglobulins (rheumatoid factors [RhFs]) and the ribonucleoproteins: Ro60, Ro52/tripartite motif-containing protein 21 (TRIM21), and La. Anti-Ro60 and anti-Ro52/TRIM21 may be present in up to 70% of patients with SjD, whereas anti-La, which has higher specificity for SjD, is detected in around 40% (5,6).

SjD results in a wide spectrum of manifestations, from the characteristic sicca symptoms of the eyes and/or mouth, fatigue, and arthritis to devastating cryoglobulinemic vasculitis; however, not all patients will suffer from these complications. What causes this heterogeneous phenotype, despite seemingly being classified as the same disease? Why do some patients exhibit relatively stable glandular disease, whereas others develop florid extraglandular manifestations (EGMs)? Below, we review these different manifestations and present a model for understanding the pathogenesis and clinical spectrum of this fascinating disease.

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## Pre-disease

The notion of pre-disease is not new and refers to the evidence of autoimmunity before the onset of clinically overt symptoms, and hence, a formal diagnosis. In SjD, this often involves detection of the iconic autoantibodies and/or laboratory features (such as hypergammaglobulinemia and lymphopenia) years before diagnosis. A number of SjD-related autoantibodies predate the onset of symptoms and SjD diagnosis, including antibodies against Ro60, Ro52, La, and RhFs (7). These autoantibodies have been detected as early as 18 years before diagnosis (7). Relative to healthy controls, the presence of antecedent anti-Ro60 or anti-La increased the odds of developing SjD (8). Similarly, hypergammaglobulinemia and hypocomplementemia increased the odds of progressing to an SjD over a 2- to 3-year period (9). A pre-disease stage is not unique to SjD; in other autoimmune diseases, autoantibodies may precede the diagnosis and symptoms of disease by 5 to 9 years, as in SLE (10) and antineutrophil cytoplasmic antibody (ANCA) vasculitis (11). Furthermore, there may be other immunologic abnormalities associated with immune dysregulation occurring pre-disease that are not routinely measured in the diagnostic laboratory.

An interesting condition that allows the detection of the pre-disease stage is neonatal lupus erythematosus (NLE), in which the transplacental transfer of autoantibodies against Ro60, Ro52/TRIM21, and/or La mediate cardiac, cutaneous, hematologic, or hepatic manifestations in the neonate. NLE occurs in only 2% of seropositive mothers, with a 17% recurrence rate (12), and produces a spectrum of mild cutaneous disease to devastating congenital heart block and heart failure (13,14). Approximately 28% to 44% of mothers who give birth to babies with NLE are asymptomatic, 15% to 22% have a diagnosis of SjD (15–17), and the remaining have SLE or nondescript symptoms (18). Longitudinal studies have reported between 9% and 68% of asymptomatic mothers are diagnosed with SjD within a median of 3 years after a NLE pregnancy (15,17,18), whereas 15% to 30% remain asymptomatic, suggesting other factors in addition to autoantibodies are required for the development of SjD symptoms (18).

Approximately 16% to 17% of SjD patients may be seronegative; that is, they meet histologic and/or clinical diagnosis of SjD yet do not have the classic autoantibodies associated with the disease (anti-Ro60, anti-La, etc.) (19,20). Yet, the failure to detect these autoantibodies may be due to the relative insensitivity of assays to detect circulating autoantibodies for processes that occur at a local level. In 1 study, researchers detected anti-Ro60/Ro52 and anti-La autoantibodies in the tears of an SjD patient that were not detected in the serum (21), supporting the notion that seronegative and seropositive SjD cases are largely the same disease. In addition, SjD-associated antibody-producing B cells are concentrated in affected salivary glands and lymph nodes (and not blood) of SjD patients (22,23), suggesting that the site of origin for autoreactive B cells are in tissues. Localized production of autoantibodies may, in part, explain the failure to detect circulating antibodies in patients with seronegative SjD.

Serologically negative SjD patients tend to be a stable group, in line with autoantibody profiles remaining stable over time (24,25); however, there are rare reports of patients who develop autoantibodies after diagnosis. For example, 1 patient with anti-Ro autoantibodies and clinical evidence for SjD developed anti-La several years after diagnosis (26). It is not clear whether this case reflects an increased production of anti-La autoantibodies such that the titer reaches assay detection threshold or a spontaneous intermolecular spreading event, similar to that described in mice models (27). The tendency to produce anti-Ro and anti-La autoantibodies has been strongly linked with the risk locus human leukocyte antigen (HLA)–DQ (28) and also dictates the tendency to undergo intermolecular autoantibody spreading (29). Moreover, the HLA haplotype associates more strongly with the development of autoantibodies than SjD (30), indicating the influence of other factors on the clinical phenotype.

## Glandular manifestations of Sjögren's disease

Sicca symptoms and salivary and lacrimal gland dysfunction are the hallmarks of SjD, which may occur in the absence or presence of systemic manifestations. In longitudinal studies, sicca symptoms of the mouth and eyes are generally stable, in terms of incidence and severity, over a median period of 9 years (31). Most studies of exocrine gland dysfunction have focused on salivary glands because of the challenges of obtaining and examining lacrimal glands (32). Histologically, affected glands are characterized by lymphocytic infiltrates, possible germinal center–like structure formation, and tissue destruction, with the biopsy being instrumental in the diagnosis of SjD (33). Furthermore, duct dilation, fibrosis, and fatty infiltration may be also be seen (34). However, glandular dysfunction may occur independently of tissue destruction, which is postulated to result from dysregulated immune signaling pathways and inflammatory cytokine milieu; this is reviewed in a study by Verstappen et al (35). Moreover, functional autoantibodies that inhibit muscarinic acetylcholine receptor type 3 have been proposed to decrease salivary and lacrimal gland output in SjD (36,37). In nonobese diabetic mice that have had autoreactive T cells experimentally deleted, salivary flow rate was improved compared with untreated mice (38), indicating a role for T cells in salivary gland dysfunction in this model. Salivary gland epithelial cells may also contribute to inflammatory milieu with the secretion of inflammatory cytokines and T cell chemokines (35). Distinct gene expression profiles are seen in SjD epithelial cells with the up-regulation of genes associated with interferon and lymphomagenesis (39).

The histologic appearance of salivary glands—specifically the density of inflammatory infiltrate (focus score)—tends to

correlate with the clinical severity of sicca symptoms. Salivary gland biopsies with a focus score of > 1 are associated with antibodies against Ro60, Ro52/TRIM21, and La and objective markers of oral and conjunctival dryness, compared with focus scores of <1 or nonspecific or sclerosing chronic sialadenitis (40). Correspondingly, severe sicca is associated with the development of EGMs, serologic activity, and mortality associated with SjD (41,42). However, the mere presence of antibodies against Ro60, Ro52/TRIM21, and La was not predictive of the severity of sicca symptoms (41).

There is emerging evidence that alterations in saliva composition and salivary gland swelling without xerostomia may be detected before formal diagnosis of SjD. These findings suggest that SjD should be considered in cases of early glandular symptoms (e.g., parotidomegaly) even in the absence of dryness and raise the possibility of intervention before end-stage salivary gland dysfunction (43). A case report of a patient with sicca symptoms and abnormal labial salivary gland biopsy (LSGB) that was reversed with early introduction of glucocorticoids, supports the idea that salivary gland dysfunction could be halted with early treatment (44).

## EGMs of Sjögren's disease

The reported incidence of EGMs in SjD varies from 30% to 90%, depending on how EGMs are defined and the cohort size evaluated (45). Moreover, the incidence of each manifestation varies widely depending on the organ affected (46). The most common EGMs include lymphopenia, Raynaud's phenomenon, and arthritis/arthralgias (30). The presence of EGMs has prognostic information, with 1 cross-sectional study finding that an EGM increases the risk of cardiovascular disease, thyroid disease, and fractures, independent of age and disease duration (47). Hypocomplementemia, hypergammaglobulinemia, positive RhFs, and cryoglobulinemia were predictors of more severe EGMs (48). EGMs remain relatively stable in SjD patients in a study with a median follow-up time of 4 to 5 years (49).

The temporal relationship between glandular manifestations and EGMs of SjD is not well established. However, because most patients with EGMs have sicca symptoms or biopsy evidence for glandular dysfunction (48,50), it is likely that glandular involvement precedes or closely coincides with EGM. There are some exceptions reported in the literature in which EGMs pre-date the development of glandular manifestations. Most of these cases tend to be in patients with SjD and another autoimmune disorder. For example, a cohort of patients developed arthralgias before sicca symptoms and were subsequently diagnosed with RA and secondary SjD (now referred to as SjD with associated autoimmunity) (1,51). In another report, a young girl with juvenile idiopathic arthritis developed SjD symptoms (sicca, arthritis) and laboratory features (hypergammaglobulinemia, RhFs, and antibodies to Ro60, Ro52/TRIM21, and La) over a decade after arthritis onset (52). Other reports include the development of lymphocytic interstitial pneumonia (53) and neurologic complications (50) years before sicca symptoms and a formal SjD diagnosis. It is unclear whether these examples reflect the development of SjD subsequent to another autoimmune disorder or a true clinical prodrome.

Another potential exception of EGMs preceding glandular dysfunction is childhood-onset SjD, in which sicca symptoms appear less frequently than adult-onset SjD and may manifest after the appearance of EGMs such as renal tubular acidosis or neurologic complications (54). However, large cohort studies indicate recurrent parotitis is a consistent feature of childhood SjD and longitudinal studies are required to determine whether subclinical glandular inflammation occurs before EGMs (54).

A recent cohort study reported at least 1 EGM predating sicca symptoms in 50% of patients with SjD (55). However, it is impossible to know whether some of these patients may have had subacute glandular dysfunction or histologic evidence for SjD (without sicca symptoms) before their presentation. Moreover, there is often a dissociation between objective markers of sicca and subjective complaints in both SjD and non-SjD patients (56), indicating a selection bias in patients who attain an LSGB if they present for review of their sicca symptoms. Positive LSGB without complaints of sicca have been noted in 15% of healthy volunteers (57) and up to a quarter of SjD patients (33). Whether the former go on to develop SjD is not clear.

A major clinical challenge is predicting which SjD patients will develop more severe EGMs. Anti-Ro60, anti-Ro52/TRIM21, and anti-La autoantibodies, present in up to three-quarters of patients, are associated with a more aggressive phenotype of SjD, with more advanced glandular manifestations and EGMs (58). Yet, the relative proportions of EGMs, including laboratory features among seropositive and seronegative SjD patients, are equivalent (19,20). The identification of new biomarkers that can predict those at highest risk of severe EGMs and guide treatment decisions, particularly early intervention, is an important research area for SjD.

## Cryoglobulinemia

Cryoglobulinemia in SjD occurs in ~10% of patients and may cause devastating vasculitis and end-organ damage (59). SjD patients often present with mixed cryoglobulins consisting of a monoclonal or polyclonal RhF component, although the monoclonal RhF (type II) cryoglobulin is most commonly encountered. It is thought that mixed cryoglobulinemia exerts its pathogenicity through RhF–immunoglobulin G (IgG) immune complexes that precipitate at temperatures below 37°C (98.6F) and deposit in organs and tissues, initiating complement cascade (60). However, not all cryoglobulins manifest in clinical symptoms. In a study of SjD patients, 11% had cryoglobulins and only 7% had cryoglobulinemic vasculitis (59). This may be explained by the differences in cryoglobulin physiochemical composition that alter thermal properties and ability to stimulate complement (61) and acquisition of

immunoglobulin variable region mutations that confer pathogenicity (59,61,62).

Understanding the emergence of cryoglobulinemia rests with studying the molecular details and behavior of the RhF component (63). Analyses of evolving cryoprecipitating RhFs suggest that cryoglobulins arise from soluble RhFs (62). In one patient for whom longitudinal samples were available, a clonotypic RhF (that became a cryoglobulin) was present 2 to 3 years before the detection of cryoglobulins and symptoms of cryoglobulinemia (64). Up to three-quarters of SjD patients have a positive RhF (65), and the majority are largely unmutated (germline) (66). Singh et al demonstrated that somatic hypermutation of immunoglobulin variable regions in the RhFs increased their propensity to form insoluble aggregates and correlated with the development of cryoglobulinemia over 2 to 3 years (62).

A third of SjD patients with cryoglobulinemic vasculitis go on to develop lymphoma (59). Overexpression of stereotypic RhF clonotypes using the Ig heavy-chain variable region 1–69 and 3–7 subfamilies is associated with a higher mortality and is a strong predictor of lymphoma development (64,67–69). Advances in single-cell technologies have made it possible to identify and study the B cells responsible for producing cryoprecipitating RhFs. These analyses revealed that B cells producing cryoglobulins harbored mutations in genes recurrently mutated in B cell malignancies (62).

## Lymphoma

The lifetime risk of lymphoma in SjD patients is around 5% to 10% (70), and, compared with the age-matched general population, SjD patients are up to 48 times likely to develop lymphoma (71). Hematologic malignancies in SjD are usually of the B cell subtype and commonly include mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B cell lymphoma (71–73). Lymphoma may be extranodal in salivary glands as well. Risk factors for lymphoma development include lymphadenopathy, sialadenitis, peripheral nerve involvement, anemia, hypocomplementemia, high β2-microglobulin expression, and cryoglobulinemia (31,70). Seropositive SjD patients are more likely over seronegative patients to develop lymphoma (74), and increasing duration of SjD diagnosis increases the risk (70).

The pathogenesis of lymphoma in SjD is complex and likely reflects chronic antigenic stimulation leading to B cell hyper-reactivity, B cell proliferation, and eventually "selection" of a single B cell to undergo monoclonal B cell proliferation (75). Environmental factors, such as benzene exposure, and infectious agents are thought to be contributory to lymphomagenesis (76,77). Genetic abnormalities feature prominently in SjD patients with lymphoma. For example, polymorphisms in *TNFAIP3*, which encodes A20, a protein important in the regulation of the nuclear factor kB pathway, are found in over three-quarters of SjD patients with MALT lymphoma (78). Intriguingly, somatic mutations in *TNFAIP3* and other genes recurrently mutated in lymphomas and leukemias were also found in circulating B cells expressing a cryoprecipitating RhF in patients with SjD that had not yet progressed to lymphoma (62). Given that MALT lymphomas of the salivary gland show biased usage of stereotypic B cell receptor with RhF activities (79,80), and cryoglobulinemia is an independent risk factor for the development of lymphoma (70), it is possible that clonally expanded RhF B cells carrying lymphoma mutations may represent a premalignant state; however, longitudinal studies are required to confirm these suspicions. Nevertheless, the identification of lymphoma mutations in RhF B cells responsible for cryoglobulinemia supports the hypothesis of a shared pathogenic process in autoimmunity and lymphoid malignancy (81).

## Discussion

The pathogenesis and evolution of SjD is complex, and the factors that contribute to disease are only beginning to be unraveled. The spectrum of SjD, discussed above, can be broken down into representative stages corresponding to a pathogenic process of B cell selection, hyperactivation, mutation, and proliferation (Figure 1). At Stage 0 (pre-disease), patients demonstrate the laboratory hallmarks of the disease without overt clinical symptoms. The presence of serum autoantibodies at this stage represents the selection and activation of autoreactive B cells (82). We hypothesize that autoreactive B cells activate other lymphocytes and infiltrate exocrine glands, causing glandular inflammation. Initially, glandular involvement may be subclinical and progress to sicca and/or glandular swelling as inflammatory milieu increases (stage 1). The development of EGMs (stage 2) may occur around the onset of glandular dysfunction, although they may manifest early and predate overt glandular symptoms (55). Severe EGMs such as cryoglobulinemia are associated with the emergence of monoclonal or oligoclonal autoreactive B cells, which continue to acquire mutations over time (62). Finally, we hypothesize that as mutational burden accumulates, a single clone emerges with proliferative and survival advantage that gives rise to lymphoid malignancy, most commonly a B cell MALT lymphoma (stage 3).

A strength of our model is our attempt to harmonize clinical with pathologic features longitudinally to explain the transition from mild/stable disease to cryoglobulinemia and lymphoma. However, this model has several important limitations. SjD is undeniably a clinically heterogeneous disease; as noted above, patients may not necessarily present in a sequential or linear manner from Stage 0 or 1, and disease is not always bidirectional and progressive. Longitudinal studies (with a 5-year follow-up period) using cluster analyses reveal that SjD patients remain relatively stable in terms of their disease activity including subjective parameters (fatigue, pain) with rare progression to increased disease burden (83). Multiple factors influence where along the SjD spectrum (Figure 1) a patient exists and who progresses over time.

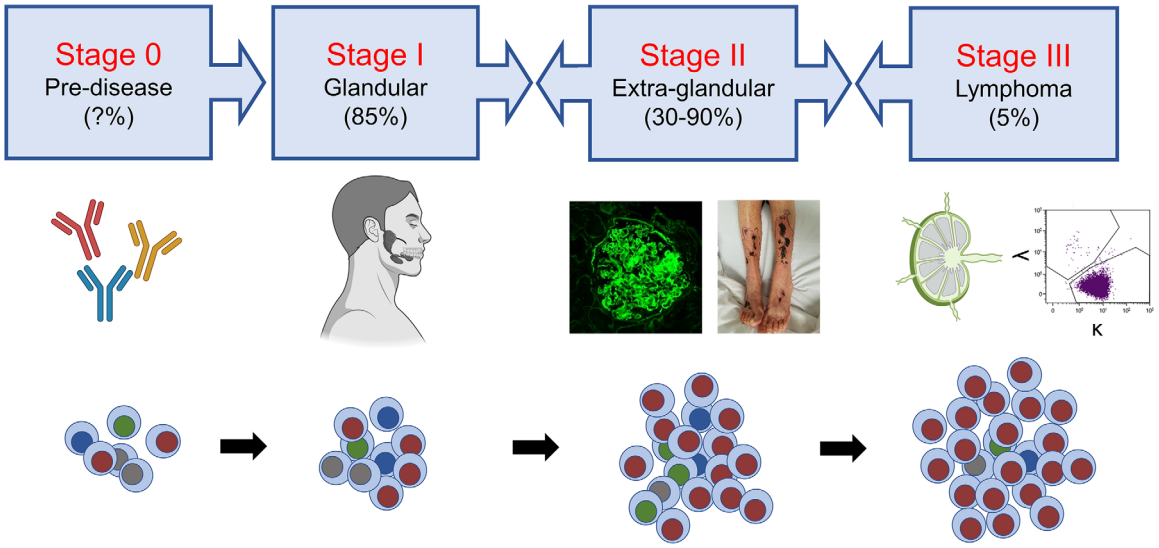


**Figure 1.** Working model for the transition of glandular SjD to cryoglobulinemia and/or lymphoma. Stages represent key clinical and pathologic features of SjD; however, they are fluid—indicated by bidirectional arrows—and patients may move within, between, and seemingly "skip" stages according to their disease activity. Patients may present at any stage, leading to an eventual SjD diagnosis. Percentages in brackets represent the approximate frequency of patients at each stage. Progressive B cell hyper-reactivity, expansion, and clonal selection drives specific complications such as cryoglobulinemia. Figure created, in part, with BioRender.com. SjD = Sjögren's disease.

Although we provide discrete stages of SjD in our model (Figure 1), it is also important to realize that SjD is a spectrum disorder, and patients' clinical symptoms do not necessarily fit in discrete categories but may span several categories, e.g., a patient with profound sicca complex and a salivary gland lymphoma without other EGMs. In addition, patients may move bidirectionally within several phases as they experience fluctuating disease courses and flares. For example, a patient who has had successful treatment of a local salivary gland MALT lymphoma may revert to a remission phase. The reasons for the variations in disease stability are still being elucidated. In stable SjD outpatients, flares occurred in 7% of patients every year and consisted of fatigue or musculoskeletal symptoms (84), suggesting that some patients probably hover on the border of glandular manifestation and EGM stages when in remission. Indeed, an unmet need in SjD research is the ability to accurately discern between stable or mild disease using current clinical indices (85).

## Conclusion

Future work is required to understand the factors that affect the progression and immunopathogenesis of SjD. In addition, studies of SjD associated with other autoimmune disorders—which is somewhat neglected in the literature—would provide insight into the development and convergence of these immunologic processes. Aiding our study, we are fortunate to be able to generate unique transcriptomic and proteomic profiles for each patient (62), so that it may be possible to develop patient-specific therapies to alleviate the burden of disease.

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## AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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