Chapter 10
Sjögren's Syndrome

Anna Rapti, Nikolaos Marketos, and Clio P. Mavragani

Introduction

SS is a female-dominated [1], autoimmune disorder of unknown etiology and diverse phenotypical expression. Xerostomia and keratoconjunctivitis sicca (due to lymphocytic infiltration of salivary and lacrimal glands, respectively) are considered to be the clinical hallmarks, while B-cell hyperactivity is thought to be the pathophysiological cornerstone. Genetic susceptibility and environmental triggers are combined in ways yet to be defined, leading to innate and subsequently adaptive immunity over-activation [2–5]. For most patients, the disease runs an indolent course with sicca symptoms being the main complaint, along with musculoarticular pain and potentially disabling fatigue [6, 7]. However, one third of SS patients develop extraglandular manifestations, and a small percentage of them, but considerably higher compared to the one related with other systemic autoimmune disorders, proceed to develop lymphoma. Therefore, SS provides a unique study model of malignant turn in inflammatory background, caused by an autoimmune disease [8, 9]. Early prognostic tools and better understanding of the different etiopathogenetic pathways leading to divergent disease phenotypes are challenging but also the key to development of effective treatment and improvement of quality of life for these patients.

Anna Rapti and Nikolaos Marketos contributed equally with all other contributors.

A. Rapti · N. Marketos · C. P. Mavragani (✉)
Department of Physiology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
e-mail: kmauragan@med.uoa.gr

P. Efthimiou (ed.), *Absolute Rheumatology Review*,
https://doi.org/10.1007/978-3-030-23022-7_10

Epidemiology – Definition

SS is encountered in approximately 0.5% of the general population, making it the second most common systemic autoimmune disease after rheumatoid arthritis. Women are affected at a 9:1 ratio in comparison to men, usually between the ages of 40 and 60 years [1, 10].

Primary and Secondary SS

SS has been traditionally classified into primary and secondary depending on whether it occurs alone or in the context of another systemic autoimmune disease (systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, dermatomyositis) [10]. However, it has been increasingly appreciated that this classification is rather confusing since secondary forms of the disease encompass entities with distinct genetic, clinical, and serological profiles. Therefore, the replacement of the term "secondary" by the phrase "SS-associated disease" has been proposed by several investigators [11, 12].

Etiopathogenesis

SS is a disease of so far unknown etiology. Stress, as well as environmental, genetic, and epigenetic factors, seems to interact in pathogenesis (Fig. 10.1).

Fig. 10.1 A model of potential contribution of different factors in SS pathogenesis

Higher prevalence of SS around menopause fueled the hypothesis of estrogen deficiency as a possible disease mechanism. Murine experiments have shown that estrogens inhibit the IFNγ-induced expression of adhesion molecule-1 and exhibit a protective role regarding autoimmune lesions in salivary and lacrimal glands [13]. Ovariectomy led to increase of apoptotic epithelial cells in salivary glands, associated with α-fodrin cleavage, in other murine models [14]. Moreover, increased number and impact of stressful events prior to disease onset in association with inadequate coping mechanisms, coupled with a chronically suppressed hypothalamic-pituitary-adrenal axis [15], potentially leads to defective anti-inflammatory mechanisms, thus promoting an exacerbated immune response. As in many autoimmune diseases, viruses such as Coxsackie, CMV, retroviruses, HCV, and Epstein-Barr have been previously viewed as initial triggers for SS [1, 16]. Endogenous triggers, such as long interspersed nuclear element 1 (LINE-1; L1) [17, 18], have been recently shown to be over-expressed in salivary glands of SS patients possibly as a result of defective methylation [19], leading to increased production of type I interferons and B-cell activation [3–5]. The increased familial aggregation of SS and other autoimmune diseases supports the notion that genetic background is a significant contributor in disease pathogenesis and that shared susceptibility gene variants plus common environmental stimuli are the basis for a wide range of autoimmune manifestations [20–24]. Indeed, this predisposing genetic basis seems to involve genes inside and outside the MHC locus implicated in the IFN signaling pathway, others that regulate B-cell function and antibody production, as well as the apoptotic and inflammatory genes in NF-kB pathway [4, 25] (Table 10.1). Nowadays, deregulation of epigenetic mechanisms and intestinal microbial dysbiosis attract increasing attention as potential culprits in disease onset [26–28].

The observation that lymphocytes infiltrating exocrine glands and parenchymal organs surround epithelia suggests a central role of the epithelial cell in the formation and further organization of characteristic immunopathological lesions in SS [29]. Especially, salivary gland epithelial cells have been investigated and found to

Table 10.1 Association of non-MHC class genes with SS susceptibility according to distinct pathogenetic pathways

	Type I and II IFN pathways	B-cell activation	NF-κB
Genes/ chromosomes	IRF5/Chr7	BLK-FAM167A/Chr8	TNFAIP3/chr6
	IRF5/TNPO3/Chr7	CXCR5/Chr11	TNIP1/Chr5
	STAT4/Chr2	BAFF/Chr13	LTA/LTB/TNF gene clusters
	IL12A/Chr3	GTF2I/chr7	BAFF-R/Chr22
	NCR3/NKp30/Chr6	EBF1/Chr5	

IRF5 interferon regulatory factor 5; *TNPO3* transportin 3; *STAT4* signal transducer and activator of transcription 4; *IL12A* interleukin 12A; *NCR3/NKp30* natural cytotoxicity triggering receptor 3/ natural killer protein 30; *BLK-FAM167A* B-lymphocyte kinase/family with sequence similarity 167, member A; *CXCR5* chemokine (C-X-C motif) receptor 5; *BAFF* B-cell activating factor; *GTF2I* general transcription factor 2I; *EBF1* early B-cell factor 1; *TNFAIP3* tumor necrosis factor-alpha-induced protein 3; *TNIP1* TNFAIP3-interacting protein 1; *LTA/LTB/TNF* lymphotoxin gene A, lymphotoxin gene B, tumor necrosis factor; *BAFF-R* B-cell activating factor receptor

undergo increased apoptosis [30], leading to release of autoantigens (such as Ro/SSA and La/SSB) which in turn drive the production of disease-specific autoantibodies. The immunocomplexes that are generated through this process result in type I interferon (IFN) production by plasmacytoid dendritic cells (PDCs) in individuals with genetic predisposition. Subsequently, type I IFN can reinforce epithelial activation and BAFF overexpression, as well as autoantibody production. The complex role of activated epithelia as antigen-presenting cells and cells secreting chemokines and cytokines or expressing chemotactic molecules places them at the center of the immunological process. Epithelial cells ultimately contribute to further aggregation of inflammatory cells, activation of lymphocytes (both T and B), and autoantibody production, thus closing the vicious circle of autoimmunity. This series of events can possibly culminate in extensive tissue damage and even B-cell monoclonal expansion [4, 31–35]. Therefore, the term "autoimmune epithelitis," stressing the key role and active involvement of epithelial cells, has been fairly proposed to describe SS [36].

Diagnosis and Differential Diagnosis

Thorough patient history and meticulous clinical examination of all systems are of utmost importance [10]. Family history should also be recorded, as familial clustering of cases with SS and other autoimmune conditions has been recorded [20–25]. Classification criteria are commonly used in order to establish SS diagnosis, with the latest revision having taken place in 2016 by the American/European Consensus Group (Table 10.2) [37]. Differential diagnosis is summarized schematically in Table 10.3 [37–41].

Diagnostic Tests

Laboratory Tests

Routine laboratory tests (full blood count, renal and liver function tests, serum protein electrophoresis plus immunofixation in case of hypergammaglobulinemia, erythrocyte sedimentation rate, C-reactive protein, urine analysis) and immunologic markers (rheumatoid factor, anti-nuclear antibodies, complement levels, antibodies against the cytoplasmic antigens SSA/Ro and SSB/La, cryoglobulins, anti-thyroid autoantibodies) are included in the laboratory evaluation of suspected SS [42–44]. Testing for viruses (HCV, HIV, HTLV-1) and IgG4 levels is carried out for differential diagnosis purposes, and other targeted autoantibodies or supplementary laboratory tests can be requested, according to specific clinical manifestations [38–46]. A schematic presentation of associations between specific autoantibodies detected in SS patients and disease phenotypical characteristics is shown in Table 10.4 [46–63].

Table 10.2 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary SS. The classification of pSS applies to any individual who meets the inclusion criteria (a), does not have any of the conditions listed as exclusion criteria (b), and has a score of at least 4 when the weights from the five selected criteria items are summed (c). Several changes from 2002 AECG classification criteria were made. Subjective ocular or oral symptoms are now considered a prerequisite, rather than criteria contributing to the total score as they were before. Sialography and scintigraphy have been omitted, and a higher threshold for the ocular staining score has been implemented. The list of exclusion criteria was revisited, as the newly identified IgG4-related disease was added and lymphoma was removed, while more accurate techniques are required to rule out known, confounding entities (PCR confirmation of active hepatitis C). Finally, anti-SSB/La autoantibodies positivity was concluded to have no diagnostic value in the absence of anti-SSA/Ro and was therefore withdrawn. To be noted that patients on anticholinergic drugs should be objectively evaluated for their sicca symptoms after a sufficient time of these medications has elapsed

(a) Inclusion criteria
Positive response to at least 1 of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?
4. Have you had a daily feeling of dry mouth for more than 3 months?
5. Do you frequently drink liquids to aid in swallowing dry food?
or
Suspicion of Sjögren's syndrome from the ESSDAI questionnaire (at least 1 domain with a positive item)

(b) Exclusion criteria
1. History of head and neck radiation treatment 2. Active hepatitis C infection 3. AIDS 4. Sarcoidosis 5. Amyloidosis 6. Graft-versus-host disease 7. IgG4-related disease

(c)

Criteria items	Weighted score	SS classification
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1 foci/4 mm^2	3	Score ≥ 4
Anti-Ro/SSA positivity	3	
Ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) in at least one eye	1	
Positive Schirmer's test (≤5 mm/5 min in at least one eye)	1	
Unstimulated whole saliva flow rate ≤ 0.1 ml/min	1	

Table 10.3 SS differential diagnosis. Other causes of sicca symptoms and processes infiltrating the exocrine glands need to be ruled out in order to reach the correct diagnosis. IgG4-related disease is a newly identified entity, added in the exclusion criteria list of the recently reviewed American/European Consensus SS classification criteria. It is a multi-organ, immune-mediated condition that has unified several diseases once considered to be individual. It includes Mikulicz disease (sialo/dacryo-adenitis and salivary/lacrimal gland enlargement), Küttner tumor, Riedel's thyroiditis, orbital inflammatory pseudotumor, pituitary hypophysitis, and hypertrophic pachymeningitis in the head and neck region, as well as autoimmune pancreatitis, interstitial pneumonitis, interstitial nephritis, prostatitis, retroperitoneal fibrosis, and inflammatory aortic aneurysm. Elevated serum IgG4 levels (≥135 mg/dl) and infiltration of abundant IgG4-positive plasma cells into affected organs help with differential diagnosis

Sicca symptoms (xerophthalmia and/or xerostomia)	Lymphocytic infiltration of exocrine glands	Non-lymphocytic infiltration of exocrine glands
Use of medications *Antihypertensives, antihistamines, antidepressants, isotretinoin, etc.* Previous head and neck radiation Diabetes mellitus Vitamin A deficiency Any functional or anatomical defect of the eyelid Chronic blepharitis, chronic conjunctivitis, or another chronic eye inflammation Psychogenic	Chronic viral infections *Hepatitis C, AIDS, HTLV-1* IgG4-related disease Chronic graft-versus-host disease Lymphoma	Granulomatous diseases *Sarcoidosis, tuberculosis, leprosy, syphilis* Metabolic infiltration *Hyperlipoproteinemia, diabetes mellitus, amyloidosis, hemochromatosis*

Salivary Gland Biopsy

Minor salivary gland biopsy (MSGB) (Fig. 10.2) displays a crucial role for diagnosis, prognosis, and risk stratification [64, 65]. According to American/European Consensus SS classification criteria of 2016, diagnosis cannot be established without a positive MSGB or positive anti-SSA/Ro antibodies [37]. Moreover, intense lymphocytic infiltration has been identified as an independent histopathological risk factor for NHL development [66], which is the leading cause of excess mortality in SS patients [67–69].

The presence of a lymphocytic infiltrate of ≥50 lymphocytes per 4 mm^2 of glandular parenchyma, usually located in the periductal area, is considered a positive focus score. The average number of these lymphocytic aggregates per 4 mm^2 of salivary gland tissue is the focus score (Fig. 10.3) [64]. Despite the fact that only focus score appears in the American/European consensus criteria, Tarpley score (measure of glandular architecture derangement) is also commonly used [65, 70]. Another important histopathological feature is the presence of germinal center (GC)-like structures (Fig. 10.4). The latter have been associated with higher focus score, higher frequency of extraglandular manifestations, hypergammaglobulinemia, increased RF levels, and higher prevalence of positive anti-SSA/Ro and/or anti-SSB/La autoantibodies. The presence of GC-like structures has

Table 10.4 Prevalence of specific autoantibodies in SS patients and correlation with clinical manifestations, other serological features, and disease outcomes. This table includes traditional autoantibodies for disease classification, autoantibodies identified from murine models, and autoantibodies typically associated with other autoimmune diseases. The hoped-for result of as early as possible diagnosis has recently led to the marketing of a new diagnostic kit (Sjö® test). The cumulative sensitivity of traditional (ANA, RF, anti-SSA/Ro, anti-SSB/La) and novel (anti-CA VI, anti-SP-1, anti-PSP) antibodies of Sjö® panel has been estimated to be 91.8%, whereas the sensitivities for anti-SSA/SSB alone and for the novel biomarkers alone were found to be 74.9% and 49.8%, respectively. Additionally, the cumulative specificity for the complete Sjö® panel was estimated at 79.8%. Further potential biomarkers currently under investigation are anti-kallikrein antibodies, antibodies against carbamylated proteins, and antibodies against TRIM38 proteins, among others (not shown in the table)

Type of autoantibodies	Prevalence of autoantibody positivity in pSS patients	Clinical correlation/significance
Anti-Ro/SSA Anti-La/SSB	33–74% 23–52%	Usually associated with female sex, younger age at diagnosis, more prominent lymphocytic infiltrate of the exocrine glands, and potentially a higher prevalence of extraglandular manifestations Attention needed in case of pregnancy, due to potential congenital heart block of the baby (complete heart block occurring in approximately 2% of cases)
Anti-nuclear antibodies (ANA)	59–85%	Associated with female gender, younger age at diagnosis, parotid gland enlargement, extraglandular manifestations, cytopenia, hypergammaglobulinemia, as well as increased frequency of RF, anti-Ro/SSA, anti-La/SSB, and antiphospholipid antibodies positivity
Rheumatoid factor (RF)	36–74%	Linked to earlier disease onset, female predominance, positive salivary gland biopsy, more frequent extraglandular features, and higher use of corticosteroids, among others Also, increased frequency of anti-La/SSB, anti-Ro/SSA, cryoglobulins, and ANA positivity, as well as low C3/C4 and hypergammaglobulinemia
Cryoglobulins	9–15%	One of the indisputable risk factors for non-Hodgkin's lymphoma development and SS-related death. Also, linked to earlier disease onset, higher frequency of extraglandular features (vasculitis, renal involvement, peripheral neuropathy, Raynaud's phenomenon) and cytopenia, as well as higher prevalence of parotid gland enlargement
Anti-thyroperoxidase antibodies (anti-TPO) Anti-thyroglobulin antibodies (anti-TG)	11–45% 3–100%	Autoimmune thyroid disease prevalence in SS seems to be 10–30% Furthermore, SS prevalence in already diagnosed autoimmune thyroid disease has been reported to be 3–32% (10 times higher probability of SS in autoimmune thyroid disease than in the general population) Sicca symptoms are even more frequent in the context of autoimmune thyroid disease (37% of patients develop xerostomia and 23% isolated keratoconjunctivitis sicca) Autoimmune thyroid disease-associated SS is linked to milder SS phenotype, but also to greater risk of developing further autoimmune diseases (such as autoimmune liver and inflammatory bowel diseases), requiring closer follow-up

(continued)

Table 10.4 (continued)

Type of autoantibodies	Prevalence of autoantibody positivity in pSS patients	Clinical correlation/significance
Antibodies against cyclic citrullinated peptides (anti-CCP)	3–10%	Anti-CCP-positive pSS patients do not seem to have major clinical differences from anti-CCP-negative individuals, but there is a possible association with nonerosive arthritis
Anti-mitochondrial antibodies (AMA)	1.7–27% Depending on laboratory technique for detection; indirect immunofluorescence, Western blot, or ELISA	Specific for primary biliary cirrhosis (PBC) Also, higher prevalence of Raynaud's phenomenon, peripheral neuropathy, hypergammaglobulinemia, and high ESR Valuable for separating patients with autoimmune liver involvement from those with chronic viral liver disease
Anti-smooth muscle antibodies (ASMA)	30–62%	Autoimmune hepatitis (only 1.7–4% in pSS patients)
Anti-centromere antibodies (ACA, comprising of CENP-A, CENP-B, and CENP-C)	3.7–27%	Overlapping features between SS and systemic sclerosis (SSc) Up to 40% of the ACA-positive pSS patients can progress to systemic sclerosis Associated with delayed disease onset, but increased frequency of keratoconjunctivitis sicca, Raynaud's phenomenon, peripheral neuropathy, and lymphoma Lower frequency of anti-Ro/La antibodies and higher prevalence of other coexisting autoimmune disorders, such as PBC SS patients usually recognize CENP-C alone, whereas recognition of both CENP-B and CENP-C is more frequent in SSc
Antibodies against carbonic anhydrase (anti-CA; 13 known isoenzymes)	12.5–20.8%	Anti-CA II antibodies linked to renal involvement and particularly distal renal tubular acidosis Anti-CA VI and anti-CA XIII antibodies have also been shown to correlate with urine pH and inversely with serum sodium levels (cross-reactivity between anti-CA VI and anti-CA XIII is a possible scenario, as CA VI is the only isoenzyme secreted in saliva and expressed in the parotid and submandibular glands, but not in the kidney) Anti-CA VI is considered a novel, early SS biomarker, included in commercially available Sjö® diagnostic panel. It is the most prevalent novel autoantibody of the kit among both SS and non-SS dry eye patients (52% and 43%, respectively). Anti-CA VI positivity has been linked to more severe xerophthalmia, presence of xerostomia, younger age, and negative MSGB

Type of autoantibodies	Prevalence of autoantibody positivity in pSS patients	Clinical correlation/significance
Antibodies to 21-hydroxylase (anti-21[OH])	17.50%	Anti-21[OH] positivity was not linked to overt adrenal insufficiency, but it was associated with adrenal hyporesponsiveness and evidence of more prominent B-cell activation in MSG tissue samples Decreased prevalence of subjective xerophthalmia and increased frequency of leukopenia were also noted for anti-21[OH]-positive SS individuals
Anti-muscarinic receptor antibodies	62.2–81.8%	Associated with cytopenia and higher ESSDAI scores Could partially account for the salivary gland hypofunction, the gastroesophageal symptoms, and the bladder smooth muscle hyperresponsiveness, observed in pSS patients
Antibodies against citrullinated alpha-enolase peptides (anti- CEP-1)	60% of anti-citrullinated protein antibodies (ACPA)-positive pSS patients Less than 10% of unselected pSS patients	Associated with higher urine pH levels at first evaluation (linked to distal renal tubular acidosis, nephrocalcinosis, and impaired bone health)
Antibodies against salivary protein 1 (anti-SP-1)	52% of SS patients 19% of SS patients with negative anti-Ro/anti-La	Antibodies against murine SP-1 (no known human protein analogue) seem to identify targets in human parotid glands Anti-SP-1 antibodies are considered novel, early SS biomarkers, included in commercially available Sjö® diagnostic panel Patients with lower focus scores in MSGB tend to be tested positive for anti-SP-1 more often than those with higher focus scores (who generally test positive for anti-Ro/anti-La). Especially patients expressing only anti-SP-1 antibodies (no anti-Ro/anti-La) have low or negative MSGB focus score Anti-SP-1 can also be used as a marker to separate SS-associated RA from RA not complicated with SS
Antibodies against parotid secretory protein (anti-PSP)	18%	PSP is a protein involved in the binding and clearance of infectious agents Anti-PSP is considered a novel, early SS biomarker, included in commercially available Sjö® diagnostic panel Can also be positive in non-SS dry eye disease and rarely in RA and healthy controls
Anti-α-fodrin antibodies	29% of pSS patients, but 47% of SLE patients Almost 2 times more prevalent in non-SS sicca than SS patients	Anti-α-fodrin antibodies serum concentrations have been associated with the degree of lymphocytic infiltration in salivary glands Usually found in early disease stages Most probably not useful for SS diagnostic purposes

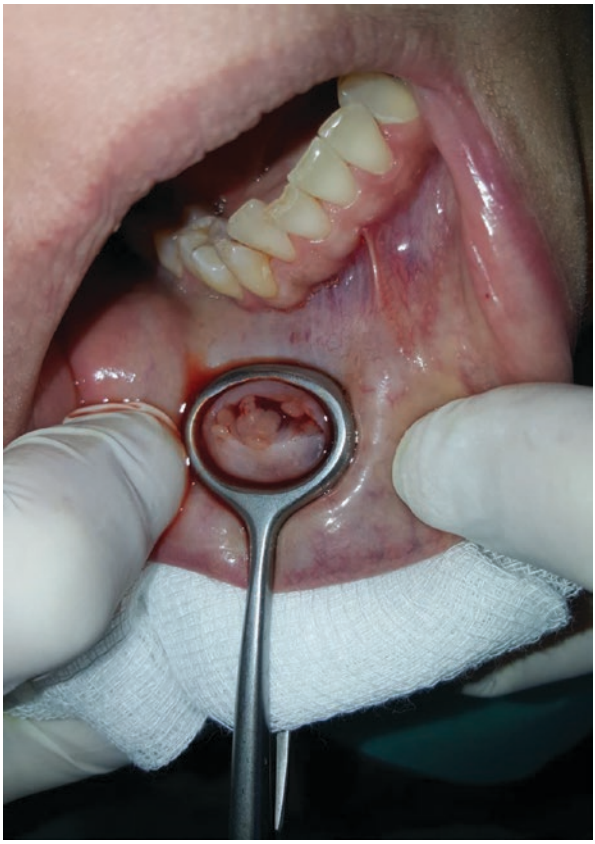

Fig. 10.2 Minor salivary gland (labial) biopsy. The procedure is simple and well-tolerated and can be done under local anesthesia on an outpatient basis. Usually 4–6 minor salivary gland lobules need to be sampled, in order for the tissue to be considered representative. Several different surgical approaches have been suggested in an effort to minimize complications. Most frequent adverse events reported in literature include temporary localized pain and bleeding, and only rarely there have been cases with persistent hypoesthesia of the lower lip (Photograph courtesy of E. Piperi, Assistant Professor in Department of Oral Pathology, School of Dentistry, UoA)

also been suggested to confer increased risk for lymphoma development. However, the contradicting results on GC-like structures significance from various studies – possibly due to poor definition on one hand and under-detection in H&E staining on the other – underline the need for uniform criteria and further research [65, 70–73].

The advantages of MSGB include easy accessibility, avoidance of skin incisions, and local anesthesia. Parotid biopsy is reserved only to rule out lymphoma in case of persistent parotid enlargement [74, 75]. MSGB sensitivity and specificity are considered to be higher than 75% and 90%, respectively [64, 76, 77].

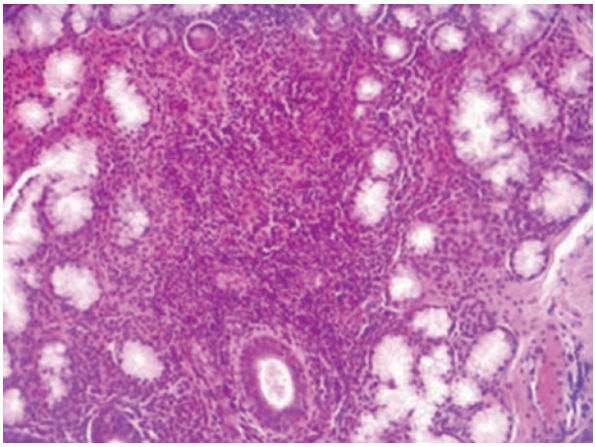

Fig. 10.3 Minor salivary gland biopsy with high focus score (Hematoxylin & Eosin staining)

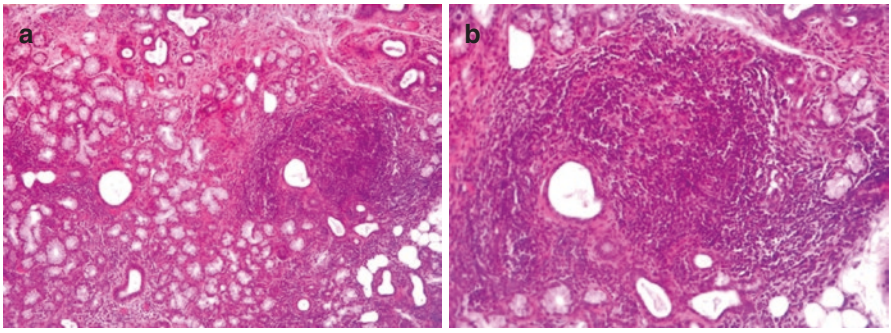

Fig. 10.4 Minor salivary gland biopsy with MALT development and germinal center-like formation in ×100 (**a**) and ×200 (**b**) magnification (Hematoxylin & Eosin staining). GC-like structures are tertiary ectopic lymphoid structures, and they are considered an advanced histopathologic lesion, previously correlated with future lymphomagenesis, extraglandular manifestations, and earlier diagnosis. However, their role in lymphomagenesis is still questioned, since more recent research has failed to demonstrate such a correlation. The prevalence of GC-like structures in SS patients is ranging from 18% to 59% according to different studies

Oral Involvement Assessment Tests

The objective evaluation of xerostomia and oral involvement in SS, except for the generally accepted MSGB, remains a challenge [75, 78]. The easiest, most common, and affordable way to assess major and minor salivary gland secretory capacity is the measurement of salivary flow or sialometry. Unstimulated whole saliva flow rate equal to or below 0.1 ml/min is considered abnormal (0.3–0.4 ml/min are expected for healthy individuals) [75].

Sialography may be used to demonstrate the morphology of the ducts, while scintigraphy can assess the salivary gland functionality. The nonspecific results of

both techniques and the involvement of radiation for the latter have led to their removal from the most recent SS classification criteria [75, 79].

Ultrasound (US), being noninvasive, inexpensive, and radiation-free, is drawing a lot of attention for the purposes of major salivary gland imaging. Multiple studies have shown good agreement and comparable results between salivary gland ultrasound and sialography and even diagnostic superiority compared to scintigraphy [80].

In addition to its value as a diagnostic tool, the prognostic value of ultrasound has also been explored. Increased parenchymal dyshomogeneity scores of major salivary glands have been found to correlate with SSA, SSB, ANA, RF, higher levels of IgG, salivary gland enlargement, cutaneous vasculitis and/or purpura, GC-like structures in salivary gland biopsy, CD4 T-cell lymphopenia, Raynaud's phenomenon, and disease activity scores. Last but not least, there is some evidence that ultrasonographic images of salivary glands change in response to treatment (rituximab versus placebo) for SS [80].

Elastography is an added feature to the classic US modality, which can increase sensitivity compared to B-mode US alone and differentiate between SS patients and sicca controls [81].

Ocular Tests

Mainly aqueous deficiency but also meibomian gland dysfunction and neuropathic pain contribute to increased tear evaporation rate, reduced tear film stability, and ocular discomfort in SS patients [82].

Keratoconjunctivitis sicca (KCS) symptoms can be quantified using patient questionnaires, like the Ocular Surface Disease Index (OSDI). The main available objective tests are Schirmer's test (Fig. 10.5), ocular surface dye staining (Fig. 10.6), and tear breakup time (TBUT) [82–84]. Among those, only the first two are included in the latest classification criteria [37].

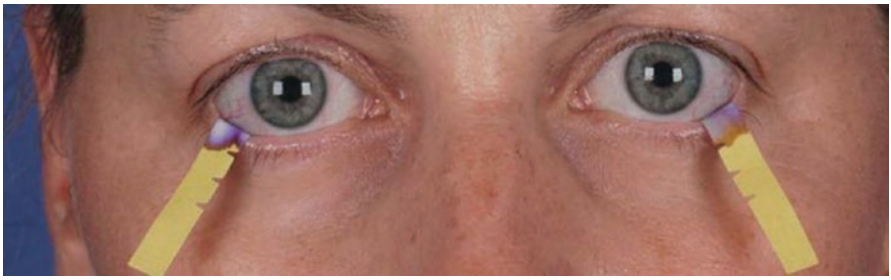

Fig. 10.5 Schirmer's test involves the measured wetting of a standardized paper strip, placed over the inferior eyelid, over a certain period of time. It is usually performed without anesthesia, and the test is considered positive when at most 5 mm of the paper are wetted in 5 min time. The cutoff point is lower (<3 mm) when the test is performed under anesthesia, as in this case we measure the basal/non-reflex tear production (Permission to re-produce kindly granted by Messmer [40])

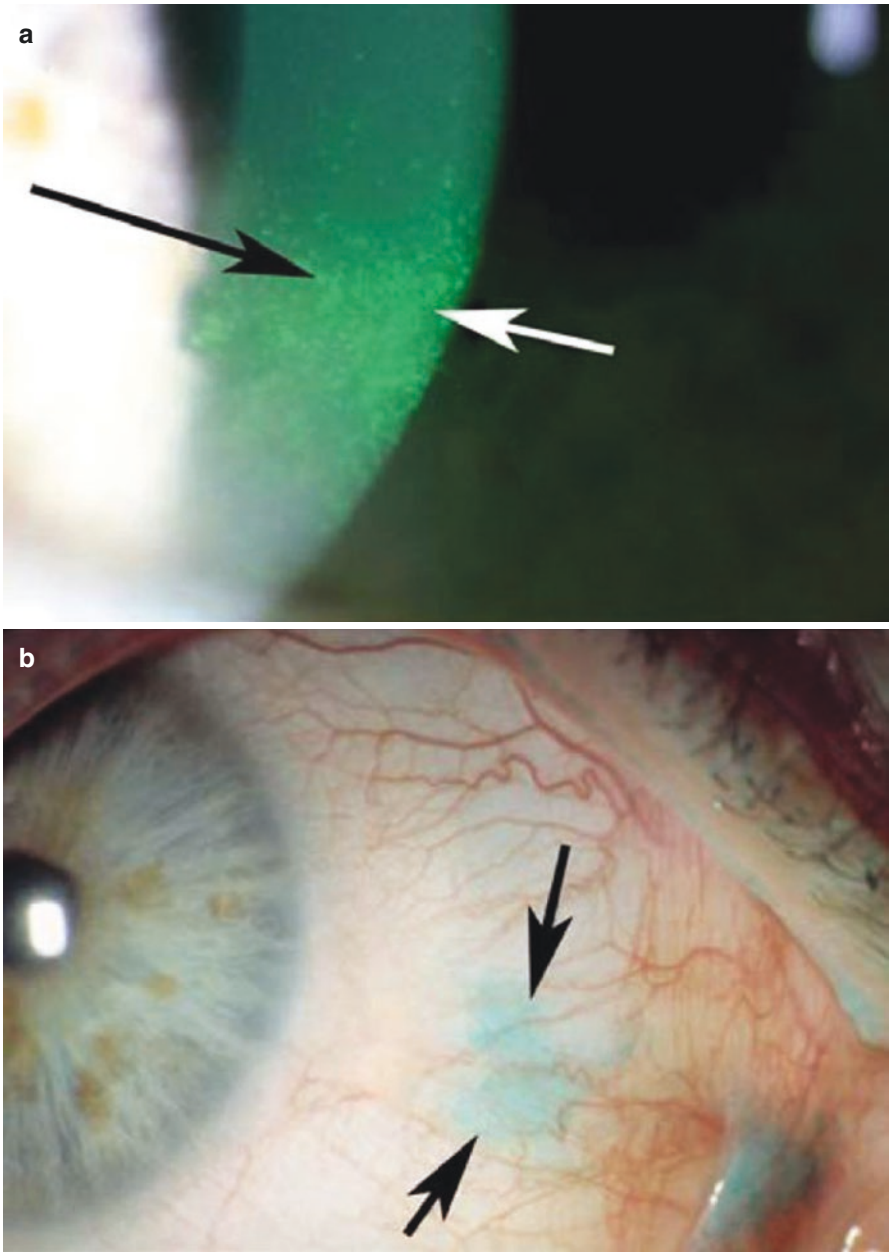

Fig. 10.6 Staining of the ocular surface in dry eye disease. Fluorescein better stains the cornea (**a**), while lissamine green (LG) is preferred for the conjunctiva (**b**). LG tends to be used nowadays instead of rose bengal (RB), due to improved toxicity and tolerance profile, given their similar staining properties. Both RB and LG bind to corneal epithelial cells that are uncoated by mucin or other proteins, and these damaged areas are easily observed under slit lamp examination. However, both dyes seem to correlate poorly to symptom severity as stated by patients in relevant questionnaires (Permission to re-produce kindly granted by Messmer [40])

Disease Activity Indexes

There are two indexes, introduced by European League Against Rheumatism (EULAR), which are used to assess SS activity from the patient's and the clinician's point of view. The first one is the EULAR Sjögren's Syndrome Patient Report Index (ESSPRI), which consists of three visual-analogue scales measuring severity of sicca symptoms, fatigue, and pain [85]. The second one is the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), which assesses the activity in 12 different domains representing organ systems. Since its introduction, ESSDAI has become the gold standard in terms of disease activity assessment because it serves as point of reference among physicians; it is widely used in randomized controlled trials as outcome measure and has been correlated with biomarkers and lymphoma development risk [42, 43].

Clinical Manifestations and Disease Management

SS can manifest with a plethora of clinical signs and symptoms, frequently vague and definitely not pathognomonic, often resulting in diagnostic delays [86]. Oral and ocular dryness, sometimes accompanied by xeroderma, upper respiratory desiccation, and vaginal dryness with subsequent dyspareunia are among the most common complaints [10]. Extraglandular manifestations (Fig. 10.7) occur in at least one third of individuals and can schematically be divided into three groups: nonspecific, periepithelial, and immune complexes mediated [6, 87–94]. The disease often runs a benign, indolent course with the exception of severe systemic complications causing excess morbidity and most importantly lymphoma, which is one of the main causes of mortality in SS [42, 67].

With regard to management, pilocarpine is usually initiated in an effort to alleviate ocular discomfort and difficulty in everyday life caused by lack of saliva, but residual lacrimal and salivary gland function is a prerequisite in order to be effective [95, 96]. SS patients must be informed on the rare side effects of pilocarpine, such as excessive sweating, nausea, diarrhea, and palpitations; for this reason, progressive dose escalation is recommended. Natural tears and lubricants for ocular use, as well as artificial saliva and oral solutions with chlorhexidine, are frequently used by patients and recommended by ophthalmologists and dentists, respectively [97]. Interestingly, in contrast to other systemic autoimmune diseases with high inflammatory load, SS-related sicca complaints do not respond to immunosuppressive treatment [98]. Mild aerobic exercise is recommended for fatigue [99], while disease-modifying antirheumatic drugs (DMARDs) are reserved for extraglandular manifestations [100–103]. The rare cases of aggressive lymphomas are managed with cytotoxic drugs [104–106]. Tables 10.5 and 10.6 display the array of clinical manifestations and the recommended treatment options in SS patients [107–120].

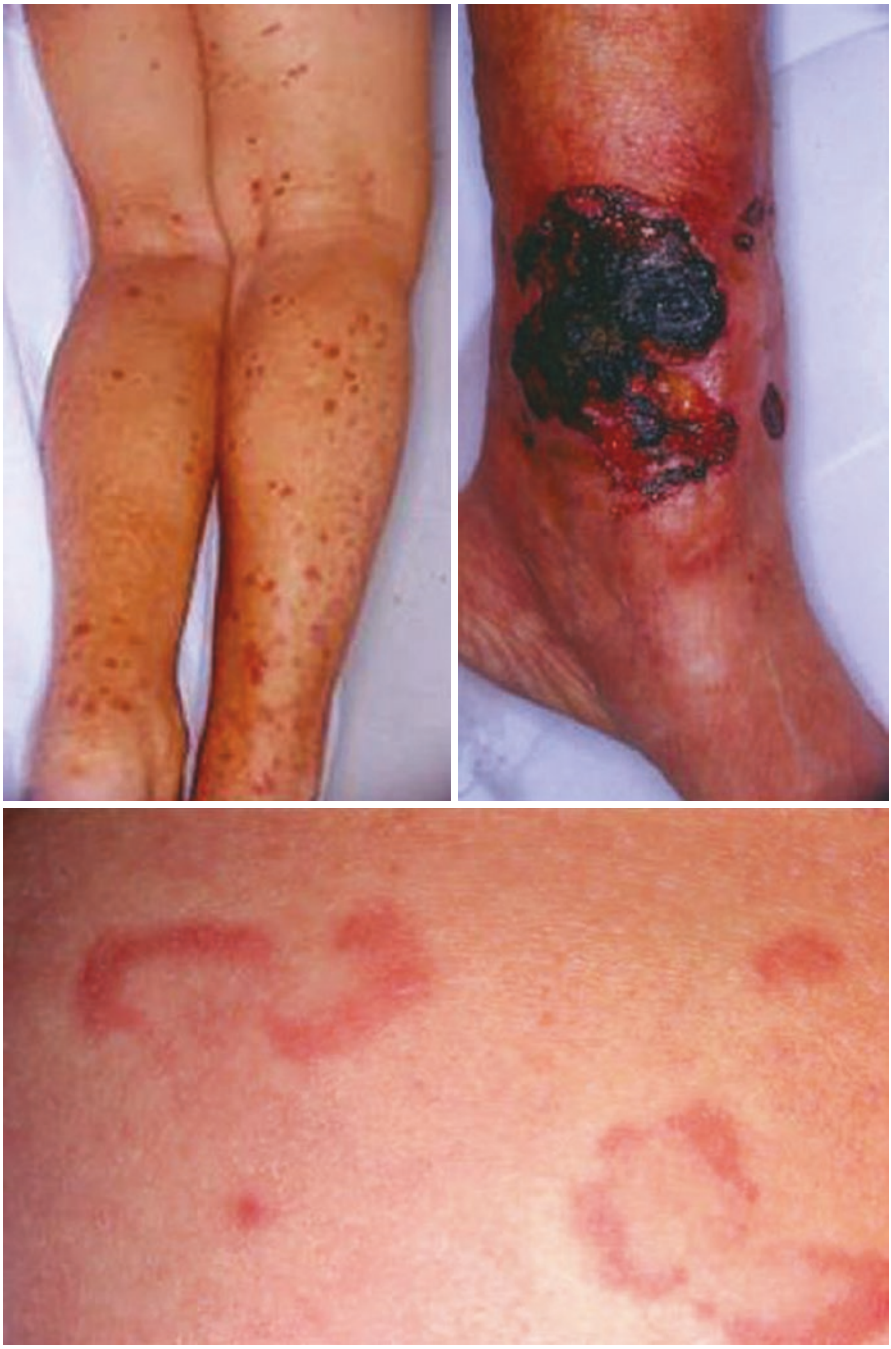

Fig. 10.7 Extraglandular features of SS. *Top left*: Palpable purpura in the lower extremities. *Top right*: Multiple necrotic cutaneous ulcers of the lower extremities in a patient with SS and cryoglobulinemia. *Bottom*: Annular urticarial lesions of the trunk (Permission to re-produce kindly granted by Hile et al. [148])

Table 10.5 Glandular manifestations and their treatment in SS patients

Organ involvement	Symptoms and signs	Therapeutic approach
Ocular	Irregularity of the corneal image, irritation, redness, photosensitivity	*No MG damage* (aqueous deficiency) Stop offending drugs, environmental changes, artificial tears, gels, ointments Ω3 suppl., CIS collyrium (0.05%) pulse steroids, punctal plugs, secretagogues, moisture chamber spectacles Topical autologous serum, contact lenses, permanent punctal occlusion Systemic anti-inflammatory medication, eyelid surgery *MG damage* (evaporative) Stop offending drugs, environment modification, lipid-rich tear substitutes, warm compress, massage CIS: 2–2.5 mg/kg/d, topical steroids, AZI, DXC, secretagogues, punctal plugs, moisture chamber spectacles Topical autologous serum, contact lenses Eyelid surgery
Oral	Dryness, caries, angular cheilitis Salivary gland enlargement	Dental fluorination, masticatory stimulation, chlorhexidine Pilocarpine hydrochloride: max 20 mg/d in divided doses Cevimeline hydrochloride: max 30 mg × 3 CS, 0.25–0.5 mg/kg/d for 10–15 d
Pancreatic	Recurrent autoimmune pancreatitis (5%)	AZA 2–3 mg/kg/d, RTX, pancreatic enzymes
Vaginal	Dyspareunia	Lubricants

MG meibomian gland, *CIS* cyclosporine, *AZI* azithromycin, *DXC* doxycycline, *CS* corticosteroids

Lymphomagenesis and Lymphoproliferation

SS is unique among autoimmune diseases as for malignant transformation risk. Those patients seem to have a 10–44-fold greater risk of developing lymphoma compared to general population, whereas systemic lupus erythematosus patients and rheumatoid arthritis patients only have a seven-fold and four-fold greater risk, respectively [67, 121]. In other words, 2.7–9.8% of SS patients are diagnosed with non-Hodgkin lymphoma (NHL) and that risk increases by 2.2% per year of age [78, 122].

Mucosa-associated lymphoid tissue (MALT) lymphomas represent 60% of cases [67]. Most common sites are the salivary glands, especially the parotid and submandibular glands, but other mucosal sites of MALT lymphoma development include the orbits, nasopharynx, stomach, thyroid, and lung [78]. Other subtypes of lymphoma found in these patients are the diffuse large B-cell lymphoma (DLBCL) and the nodal marginal zone lymphoma (NMZL), which – together with MALT – account for more than 90% of total SS-associated lymphoma cases [67].

Multiple research studies have been focusing their efforts on correlating clinical, serological, and histopathological features with risk of lymphomagenesis [66, 72, 123–126], and an attempt has also been made to formulate a predictive score for

Table 10.6 Extraglandular manifestations and their treatment in SS patients

Organ involvement	Symptoms and signs	Therapeutic approach
Nonspecific		
Musculoskeletal	Myalgias, arthralgias, Jaccoud arthropathy, rare arthritis	HCQ, MTX, or combination of both, small dose CS < 15mg qd
Raynaud's phenomenon	Cold-related color skin changes	Vasodilators, especially calcium channel blockers
Fatigue (35–50%)	Increased need for resting hours, disruption of sleep patterns	Nordic (active) walking, HCQ in some cases RTX
Periepithelial		
Bronchi (10–20%) Small airway disease (13%) ILD (17%)	Mild to moderate dyspnea and dry cough, xerotrachea	Bronchodilators AZA, RTX
Autoimmune cholangitis	LFTs abnormalities, jaundice	RTX UDCA, AZA
Renal/bladder (4–30%) Tubulo-interstitial nephritis Interstitial cystitis (0.3%)	Hypokalemic hyperchloremic distal renal tubular acidosis/ nephrocalcinosis Pollakiuria, nycturia, urinary urgency, pelvic or suprapubic pain	Urine alkalization (bicarbonate, electrolyte supplements) CS CS, CIS, surgical intervention
Immune complex-mediated disease		
Skin vasculitis Vasculitis in 5% Purpura – palpable in 5% Annular erythema	Cryoglobulinemia	CYC, AZA RTX for necrotizing vasculitis (cycles of 2gr q15 days interval/6 months)
Glomerulonephritis(rare)	Membranous or membranoproliferative	CS, RTX, CYC
Neuropathy (20%) Peripheral neuropathy CNS	Peripheral sensorimotor neuropathy or pure sensory neuropathy Motor neuropathy/ganglionopathy Mononeuritis multiplex Small fiber neuropathy MS-like	CS, 0.5–1 mg/kg, and IVIGs, RTX CS, 0.5–1 mg/kg, and CYC/ AZA, 2–3 mg/kg/d Anticholinergics, antidepressants, gabapentinoids CS, PE, RTX
Low-grade lymphoma *Disseminated lymphoma*		Wait and watch policy R-CHOP = if diffuse large B cell

HCQ hydroxychloroquine (5 mg/kg qd), *MTX* methotrexate 2.5–3 mg/15 kg qw), *CS* corticosteroids, *RTX* rituximab (cycles of 2gr q15 days interval/6 months), *AZA* azathioprine (2–3 mg/kg qd), *UDCA* ursodesoxycholic acid, *CIS* cyclosporine (2–2.5 mg/kg qd), *CYC* cyclophosphamide (750 mg–1 g/m^2), *IVIGs* intravenous immunoglobulins, *R-CHOP* rituximab-(c)yclophosphamide, (h)ydroxydaunorubicin, (o)ncovin (vincristine), (p)rednisone

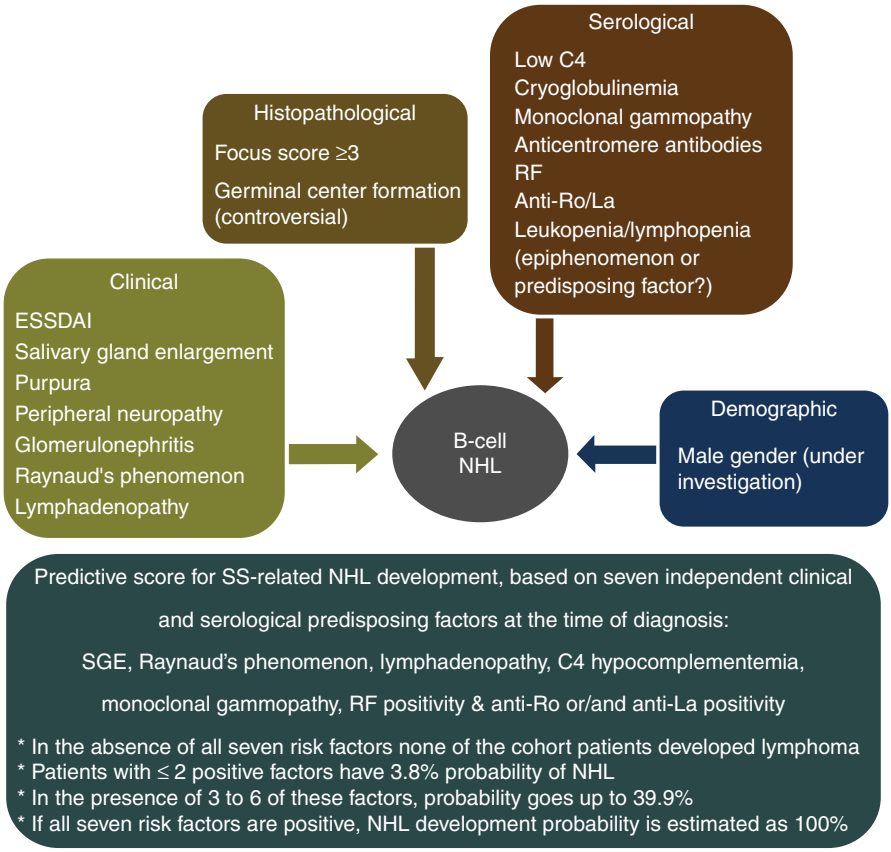

Fig. 10.8 Risk factors for lymphomagenesis in SS, as identified by various studies over the last years and a predictive score formula based on seven of them. Relevant information is gathered at the time of disease diagnosis and correlates with disease outcome, even years later, leading to the conclusion that early risk stratification is feasible for those patients. SGE salivary gland enlargement

SS-related NHL development based on data collected at the time of diagnosis [123] (Fig. 10.8). However, the molecular etiopathogenetic aspects of malignant transformation still remain largely elusive and ill-defined.

Current belief on etiopathogenesis of lymphoma focuses on four interrelated axes: chronic inflammation, B-cell activation, defective immunosurveillance, and epigenetic alterations [4, 104]. Focus score of at least 3 in MSGBs of SS patients has been identified as an independent and important predicting factor for NHL development, and the use of this threshold has a positive predictive value of 16% and a negative predictive value of 98% for that kind of malignant transformation [66]. Furthermore, the activation of P2X7 receptor-NLRP3 inflammasome complex (with subsequent increase of pro-inflammatory cytokines IL-18 and IL-1β serum levels, among others) correlates with lymphocytic infiltration severity, ESSDAI

scores, and lymphoproliferation risk. The hypothesis of inflammasome activation secondary to increased accumulation of proinflammatory nucleic acid shreds, ineffectively degraded and cleared, has recently been supported [127, 128].

Another factor promoting chronic inflammation seems to be IFNγ, as the mRNA levels in MSGBs have been associated with a higher degree of lymphocytic infiltration, shown to be a predisposing factor for lymphomagenesis [129]. Moreover, a functional variant of TNFAIP3 gene (rs2230926), encoding the A20 protein, leads to unopposed NF-κB pathway activation and is therefore involved in inflammatory process perpetuation, B-cell survival, and more aggressive disease phenotype with earlier disease onset and increased lymphoproliferation risk [130].

B-cell activating factor (BAFF), produced by various immune cells but also by the salivary epithelial cells and regulated by both type I and II IFNs, is of utmost importance for the maturation, proliferation, and survival of B cells. BAFF levels are found increased in SS patients' serum with a history of lymphoma, and high levels persist for years after treatment and remission [4, 131, 132]. Another equally important observation is the association of specific BAFF polymorphisms with SS-related lymphomagenesis and in particular the significantly different prevalence of the protective AA genotype of the rs12583006 polymorphism, as well as of the protective haplotypes TACAC and TACC and of the risk haplotype TTTC in SS patients prone to NHL development (high risk determined by the presence of adverse predictors), compared to low-risk individuals [133]. Additionally, a specific mutation (His159Tyr) of BAFF receptor (BAFF-R) is of interest, as it has been identified in more than two thirds of SS-associated MALT lymphoma. This mutation, leading to NF-kB pathway activation, was linked to earlier development of lymphoma or adverse immunological features (hypergammaglobulinemia and positive RF) [78, 134].

Finally, Fms-like tyrosine kinase 3 ligand (Flt-3 l) is a protein that acts as a cytokine and a growth factor, activating Flt-3 (or CD135) on the surface of hematopoietic progenitor cells, and therefore considered to be a mediator of B-cell survival. Higher levels of Flt-3l are strongly associated with history of lymphoma, detectable years before malignant transformation, and not affected by treatment [135].

The vicious circle of autoreactive B-cell chronic stimulation and immunocomplexes formation might finally lead to the favorable, monoclonal expansion of rheumatoid factor (RF)-reactive B cells and to the lymphomatous transformation, under defective immunosurveillance [4]. As a matter of fact, IFNα mRNA levels in MSGBs seem to strongly correlate with the expression of pro-apoptotic molecules (tumor suppressor gene p53 and auto-antigen Ro52, with the latter negatively regulating the anti-apoptotic B-cell lymphoma 2 (Bcl-2) gene) [132]. Moreover, decreased prevalence of a specific TREX1 variant (rs11797 AA genotype) in SS-related non-MALT cases was observed. This variant was shown to associate with higher mRNA IFNα levels in SS salivary gland tissues [136].

Further oncogenic mechanisms, likely to contribute to malignant turn in SS, are the over-expression of Bcl-2 due to a translocation involving chromosomes 14 and 18, leading to inhibition of apoptosis and increased B-cell survival. Apart from IFNα effect on p53 levels, specific mutations of this tumor suppressor gene were described 20 years ago in MSGBs from SS-associated NHL cases [4, 132, 137].

Epigenetic changes, involving methylating enzymes and transcription of non-coding micro-RNAs, are also implicated in lymphomagenesis [138]. MiR200b miRNAs, which regulate the expression of oncogenes and tumor suppressor genes, have been found to be downregulated in MSGBs with advanced lymphocytic infiltration and MALT lymphoma [139]. Especially miR200b-5p strongly discriminates SS patients who already have or will develop NHL from the rest of them or from sicca controls [140]. As for methylating enzymes, DNA methyltransferase (DNMT)3B and methyl-CpG-binding protein 2 (MeCP2) have been found decreased in SS-lymphoma patients [141], while methylene-tetrahydrofolate reductase (MTHFR) gene variants, leading to defective methylation and impaired stability of DNA, have lately been suggested as susceptibility factors for non-MALT lymphoma [142].

It becomes clear that the multifactorial process of lymphomagenesis is rather complicated, and the finely tuned balance between opposing forces can become deranged and lead to adverse outcomes. An example of that is the IFNγ/IFNα mRNA ratio in MSGBs, which has emerged as a histopathological biomarker for the prediction of in situ lymphoma development [132].

SS-related hematological malignancies are correlated with an eightfold higher mortality risk compared to general population [69], and one in five deaths of SS is attributable to lymphoma [68]. Follow-up every 6 months is recommended for high-risk patients. Overall, NHL 5-year survival is estimated at approximately 92%, but higher disease activity is linked to higher possibility of relapse and death [143–145]. Wait and watch strategy is suitable for MALT lymphomas localized in the salivary glands, while rituximab and chemotherapy are employed in case of disseminated or aggressive disease [106, 146, 147, 149].

Multiple-Choice Questions

1. Which of the following clinical features would set Sjögren's syndrome (SS) on top of your differential diagnosis list?

   A. A 60-year-old man with polyarthritis of the small joints of the hands, morning stiffness of >1h, and low-grade evening fever
   B. A 30-year-old woman with fatigue, hair loss, sun sensitivity of the skin, pleurisy, and oral aphthae
   C. A 50-year-old woman with ocular and oral dryness, fatigue, arthralgias of the hands and feet, and purpura
   D. A 45-year-old woman with known depression and use of relevant medication, fatigue, low-grade fever, appetite loss, and weight loss
   E. An 85-year-old woman otherwise in good health complaining for dry eyes, dry mouth, constipation, and fatigue

   Correct answer: C

Feedback:

A. Rheumatoid arthritis. Typical presentation with polyarthritis of small joints, morning stiffness.
B. Systemic lupus erythematosus presentation.
C. Sjögren's typical presentation.
D. Depression most probable; other causes must be excluded.
E. Age-related fatigue and dryness. Late onset of symptoms – autoimmune disease of lower probability.

2. Which of the following are currently believed to be implicated in disease pathogenesis?

A. UV light
B. Genes
C. Stress
D. Surgery
E. Androgens
F. All of the above
G. A + B + C + E

Correct answer: G
Feedback: All these factors except previous surgery are currently implicated.

3. Which are the main identified pathways of SS pathogenesis?

A. IFNγ
B. B-cell hyperactivity
C. NF-κB
D. All of the above
E. None of the above

Correct answer: D
Feedback: All of the above pathways are considered viable for disease pathogenesis.

4. Which of the following medications would you prescribe to a patient with ocular dryness due to pSS?
Multiple answers eligible

A. Methotrexate
B. Pilocarpine
C. Hydroxychloroquine
D. Cevimeline
E. Etanercept
F. Oral cyclosporine
G. Ocular drops of cyclosporine
H. Infliximab

Correct answer: B, D, G

Feedback:
A, C. Methotrexate and hydroxychloroquine are used for musculoskeletal manifestations, despite inadequate data.
E. TNFα inhibitors have not shown encouraging results so far.
F. Oral cyclosporine is reserved for resistant pulmonary disease, but topical treatment has been used effectively in ocular symptoms of SS.

5. Which of the following medications would worsen a patient's established SS symptoms?

   A. Artificial tears
   B. Artificial saliva
   C. Methylcellulose inserts
   D. Amitriptyline

   Correct answer: D
   Feedback: Amitriptyline is known to exacerbate oral dryness.

6. What treatment modalities would you employ to alleviate fatigue in an SS patient?
   Multiple answers eligible

   A. Corticosteroids
   B. Azathioprine
   C. Hydroxychloroquine
   D. NSAIDs
   E. Serotonin uptake inhibitors
   F. Methotrexate
   G. Pregabalin
   H. Anti-TNF agents
   I. IVIG
   J. Aerobic exercise

   Correct answer: J
   Feedback:
   A, B, C, F, H. Corticosteroids have no effect on these nonspecific symptoms nor have immunomodulatory drugs as azathioprine, hydroxychloroquine, methotrexate, or TNF inhibitors.
   J. According to guidelines only aerobic exercise is effective.

7. What treatment would you suggest to manage the same patient's oral dryness?
   Multiple answers eligible

   A. Bromhexine
   B. Pilocarpine
   C. Hydroxychloroquine
   D. Cevimeline
   E. Sugar-free fluoride-containing chewing gums
   F. Etanercept
   G. Methotrexate
   H. Infliximab

I. Regular water drinking
J. Avoidance of drying air heating systems

Correct answer: B, D, E, F, I, J
Feedback: Pilocarpine, cevimeline, chewing gums that are sugar-free, frequent water intake, and avoiding air heating may alleviate symptoms. The rest of medication on this list has no proven effect on oral dryness.

8. You prescribed pilocarpine, and 1 week later the patient is back at the office with new complaints. Which of the following could be attributable to this medication?
Multiple answers eligible

A. Constipation
B. Glaucoma
C. Acute urinary retention
D. Nausea
E. Excessive sweating
F. Diarrhea
G. Urinary infection
H. Neuropathy
I. Palpitations

Correct answer: D, E, F, I
Feedback: Constipation, glaucoma, and acute urinary retention are side effects of inhibitors of cholinergic synapses and not of agonists like pilocarpine. Urinary infection and neuropathy are not side effects of pilocarpine.

9. Which is the most likely cause of recurrent renal colic in this patient?

A. Nephrocalcinosis in the setting of distal tubular acidosis
B. Nephrocalcinosis in the setting of proximal tubular acidosis
C. Hyperparathyroidism
D. Hyperoxaluria

Correct answer: A
Feedback: Despite the fact that both hyperparathyroidism and hyperoxaluria are valid causes, nephrocalcinosis in the setting of distal and not proximal tubular acidosis seems to be the most likely cause of renal colic in the setting of SS.

10. Among the following different therapeutic strategies for SS-associated low-grade lymphoma management, which one is advised?
A. Local radiotherapy
B. Wait and watch policy
C. IV immunoglobulin
D. Combination immunochemotherapy (rituximab and CHOP)
E. Mycophenolate mofetil

Correct answer: B
Feedback: Wait and watch policy is the recommended policy. IV Ig and mycophenolate mofetil have no place on lymphoma treatment. Combination therapy

(rituximab and CHOP) is indicated in diffuse B-cell lymphomas. Current data do not support the use of radiotherapy for localized low-grade MALT lymphomas.

11. Which of the following features have been associated with increased risk for lymphoproliferation in SS?
Multiple answers eligible

A. Parotid gland enlargement
B. Positive anti-TPO/anti-TG
C. Low C4 levels
D. Distal renal tubular acidosis
E. Fibromyalgia
F. Hypergammaglobulinemia

Correct answers: A, C, F
Feedback:
B. Autoimmune thyroiditis commonly coexists with SS, and it can also be responsible for sicca symptoms without SS, but does not evoke increased risk for lymphoma.
D. Glomerulonephritis (and not distal renal tubular acidosis) confers susceptibility to lymphoma.
E. Not linked to lymphoma, but correlated with SS-associated fatigue.

12. Which of the following conditions presenting with sicca symptoms can mimic SS?
Multiple answers eligible

A. Vitamin D deficiency
B. Wilson's disease
C. Graft versus host disease
D. Hepatitis B
E. Nonsteroid anti-inflammatory medications
F. Sarcoidosis

Correct answers: C, F
Feedback:
A. Vitamin A deficiency would be the correct answer.
B. Hemochromatosis and not Wilson's disease can cause sicca symptoms.
D. Hepatitis C would be the correct answer.
E. No relevant correlation with sicca symptoms, but commonly used to alleviate joint pain.

13. A 56-year-old woman is presenting with Raynaud's phenomenon. When asked, she also admits having dry eyes over the last year and feeling tired during the last 3 months. Routine laboratory tests are nonsignificant, ANA are positive, and anti-SSA/Ro antibodies are negative. The patient was eventually classified as SS. For which of the following tests has our patient definitely been tested positive?

A. Unstimulated salivary flow rate
B. Lissamine green ocular staining

C. Minor salivary gland biopsy
D. Schirmer's test
E. Anti-SSB/La antibodies
F. Tear breakup time

Correct answer: C
Feedback: According to the new classification criteria of 2016, SS cannot be verified unless at least anti-Ro antibodies or MSGB is positive. Since anti-Ro antibodies are negative in our case, MSGB is definitely positive (focus score ≥ 1), along with at least one other positive test among unstimulated salivary flow rate, Schirmer's test, and ocular staining.

14. Which of the following patients fulfill the American/European SS classification criteria of 2016?

A. A 43-year-old woman with total unstimulated salivary flow of 1 ml/15 min, positive ANA, positive anti-TPO/anti-TG, and Schirmer's test of 4 mm in 5 min in both eyes
B. A 42-year-old woman, regular blood donor up to recently, with new-onset xerophthalmia and arthralgias, positive anti-SSA/Ro antibodies, positive anti-CCP, and focus score of 1 in MSGB
C. A 50-year-old man with tracheostomy, complaining of sicca symptoms, fatigue, and diffuse musculoarticular pain, with unstimulated salivary flow of 0.5 ml/15 min
D. A 64-year-old woman with total unstimulated salivary flow of 0.5 ml/15 min, positive anti-SSA/Ro and anti-SSB/La antibodies, positive ACA and MALT lymphoma from minor salivary gland biopsy
E. A 60-year-old man with xerophthalmia, xerostomia, chronic dry cough, abnormal objective ocular tests, intense lymphocytic infiltration in MSGB, salivary gland enlargement, subclinical jaundice, and bilateral hydronephrosis
F. A 26-year-old woman, recently treated for Chlamydia infection, presenting with sicca symptoms and fatigue, with Schirmer's test of 3 mm and 4 mm (in 5 min) in the right and left eye, respectively, and an initial assessment of the MSGB showing lymphocytic infiltration

Correct answers: B, D
Feedback:

A. Score of 2 according to criteria. Autoimmune thyroiditis could account for sicca symptoms. Further tests needed.
B. Recently tested for hepatitis and HIV since she is a blood donor. Score of 6 according to criteria. Anti-CCP presence does not exclude SS diagnosis (anti-CCP-positive SS).
C. History on previous head and neck radiation should be recorded, as suspicion of treated laryngeal cancer is raised (presence of tracheostomy). Not fulfilling criteria.

D. Score of 7 according to criteria, since MSGB with MALT is considered positive. Lymphoma is no longer an exclusion criterion, and ACA-positive SS patients are known to be at increased risk for lymphoma.
E. Suspicion of IgG4-related disease. Need more information on MSGB and serum IgG4 levels.
F. This young woman recently had a sexually transmitted disease, so HIV and HCV infection need to be ruled out before classifying her as SS. More information on the MSGB would also be helpful, as CD8+ lymphocytes are usually the ones infiltrating salivary glands in HIV infection (in contrast to predominant CD4+ lymphocytes in SS).

15. Which of the following set of features describing different female SS patients confers the highest predicted risk for NHL?

A. Distal renal tubular acidosis, positive RF, photosensitive rash, filamentary keratitis, reduced unstimulated salivary flow rate, and dental caries
B. Raynaud's phenomenon, livedo reticularis, parotid gland enlargement, lymphadenopathy, positive anti-TPO, and positive anti-TG
C. Arthralgias, fatigue, abnormal ocular staining test, reduced unstimulated salivary flow, positive anti-SSA/Ro antibodies, and positive anti-CCP
D. Monoclonal gammopathy, positive RF, positive anti-SSA/Ro, low C4 levels, lymphadenopathy, submandibular gland enlargement, and Raynaud's phenomenon
E. Monoclonal gammopathy, positive anti-SSA/Ro and anti-SSB/La antibodies, elevated γGT, C3 and C4 hypocomplementemia, positive anti-thyroid antibodies, lymphadenopathy, and Raynaud's phenomenon

Correct answer: D
Feedback: Selection of the correct answer is based on the predictive score tool for SS-associated lymphoma, as seen in Fig. 10.8.

A. One positive factor only (3.8% probability of NHL).
B. Three positive adverse features (39.9% probability of NHL).
C. One positive factor only (3.8% probability of NHL).
D. All seven identified independent predicting factors are met, which means 100% probability of developing lymphoma.
E. Five positive predisposing factors (39.9% probability of NHL).

16. Which of the following sentences are true?

A. Ultrasound of major salivary glands has replaced sialography and scintigraphy in recently revised SS classification criteria (2016).
B. Type I interferon signature is more prominent in SS-associated lymphoma cases.
C. Epithelial cells in salivary glands have an active role in SS etiopathogenesis.
D. BAFF levels in patients' serum closely follow lymphoma flares and remissions and may therefore be used for follow-up.

E. MTHFR gene variants have been found to confer increased risk for MALT lymphomas in the context of SS.
F. MALT lymphomas localized in the salivary glands should ideally be monitored closely, without need for immediate treatment.

Correct answers: C, F
Feedback:
A. Not included in criteria yet but promising results and potential future role in diagnosis.
B. IFNγ (IFN type II) is more prominent in lymphoma.
D. BAFF levels are found elevated even years after lymphoma remission.
E. MTHFR gene variants are linked to some cases of non-MALT lymphomas.

17. Which of the following diagnostic tests does not have a place in high-risk SS patients monitoring for MALT lymphoma?

A. CT chest
B. CT abdomen
C. Colonoscopy
D. Upper GI endoscopy
E. Serum protein electrophoresis and immunofixation
F. Routine laboratory panel, including LDH and β2 microglobulin

Correct answer: C
Feedback:
A, B. CTs are commonly used for diagnosis or follow-up of MALT lymphoma in patients with severe adverse predictors or relevant history.
C. MALT lymphoma is not found in the bowel; thus, colonoscopy is an unnecessary test.
D. Stomach is a common site for the development of MALT lymphoma.
E. Protein electrophoresis and immunofixation might show hypergammaglobulinemia and monoclonality, which could mean malignant transformation in some cases.
F. Routine laboratory tests are necessary in follow-up anyway and rise in LDH or β2 microglobulin could be linked to lymphoma development or reappearance after treatment.

18. Which of the following tests would you recommend as the next diagnostic step for a patient complaining about xerostomia/xerophthalmia, who is reluctant to undergo MSGB and has a positive anti-SSA/Ro result?

A. Sialography
B. Scintigraphy
C. Major salivary gland ultrasound
D. Rose bengal ocular staining
E. Unstimulated salivary flow
F. Tear breakup time

Correct answer: E

Feedback:
A, B. Sialography and scintigraphy are no longer included in SS classification criteria (2016).
C. Ultrasound is not included in SS classification criteria, despite showing promising results.
D, E. Since anti-Ro are positive (3 points), 1 more point for SS classification is required, meaning either an abnormal, objective ocular test or unstimulated salivary flow rate measurement. The latter is the easiest and cheapest way to reach diagnosis. Furthermore, lissamine green is preferred over rose bengal for ocular staining, nowadays, since it is less irritant.
F. TBUT is not included in SS classification criteria, despite being commonly used to objectify ocular dryness.

19. Which of the following etiopathogenetic events have been proven to contribute to SS-related lymphoma development?
Multiple answers eligible

A. Persistent stimulation of autoreactive B cells
B. Chromosomal translocations
C. Coxsakievirus infection
D. Epstein-Barr virus infection
E. p53 mutations
F. BAFF polymorphisms

Correct answers: A, B, E, F
Feedback:

A. True.
B. Over-expression of Bcl-2, for example, is due to a translocation involving chromosomes 14 and 18.
C, D. These viruses have been suggested as possible triggering factors for SS etiopathogenesis, but not proven to contribute to disease onset or associated lymphoma development.
E. True.
F. True.

20. Which of the following sentences is true?

A. Secondary SS is diagnosed when sicca symptoms appear in the context of hepatitis C or HIV infection.
B. Germinal center-like structures are well-defined formations in MSGBs of SS patients, associated with late disease onset.
C. Males are not affected by SS as much as women, and even if they do, they present with milder symptoms.
D. MSGBs only have a place in SS diagnosis, and if classification criteria are met anyway, patients should not undergo this invasive procedure.
E. Ocular staining score and TBUT can be used interchangeably to objectify ocular involvement in SS, according to the latest classification criteria of 2016.

F. SS classification criteria cannot be used in patients who do not experience oral and/or ocular dryness, since sicca symptoms are considered to be the disease hallmark.
G. SS is one of the most common systemic autoimmune diseases, accompanied by the highest risk for lymphoma development among them.

Correct answer: G
Feedback:

A. Active hepatitis C and HIV infection are among exclusion criteria. The term "secondary" has previously been used to describe sicca symptoms occurring in the context of another systemic autoimmune disease and tends to be replaced nowadays by the more accurate "SS-associated disease."
B. There is lack of uniform criteria for the identification of GC-like structures in MSGBs, and their documented association with more severe disease generally leads to earlier disease diagnosis.
C. Male SS patients have been suggested to present with more severe disease phenotype, despite being fewer than women.
D. MSGBs histopathological characteristics have a major prognostic value and are therefore also used in patients' risk stratification.
E. TBUT is not included in SS classification criteria of 2016.
F. Patients scoring in at least one domain of ESSDAI (having systemic involvement) are now also considered for SS diagnosis according to the latest classification criteria, even in the absence of sicca symptoms.

References

1. Mavragani CP, Moutsopoulos HM. The geoepidemiology of Sjögren's syndrome. Autoimmun Rev [Internet]. 2010;9(5):A305–10. Available from: https://doi.org/10.1016/j.autrev.2009.11.004.
2. Kiripolsky J, McCabe LG, Kramer JM. Innate immunity in Sjögren's syndrome. Clin Immunol. 2017;182:4–13.
3. Hansen A, Lipsky PE, Dörner T. B cells in Sjögren's syndrome: indications for disturbed selection and differentiation in ectopic lymphoid tissue. Arthritis Res Ther. 2007;9(4)
4. Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjögren syndrome. Nat Rev Rheumatol [Internet]. 2018;14(3):133–45. Available from: https://doi.org/10.1038/nrrheum.2018.1.
5. Mavragani CP. Mechanisms and new strategies for primary Sjögren's syndrome. Annu Rev Med [Internet]. 2017;68(1):331–43. Available from: http://www.annualreviews.org/doi/10.1146/annurev-med-043015-123313.
6. Mavragani CP. Moutsopoulos HM. Sjögren Synd Rev. 2014;186(15):579–86.
7. Cornec D, Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot J-M, Perdriger A, et al. Severe health-related quality of life impairment in active primary Sjögren's syndrome and patient-reported outcomes: data from a large therapeutic trial. Arthritis Care Res [Internet]. 2017;69(4):528–35. Available from: http://doi.wiley.com/10.1002/acr.22974.

8. Retamozo S, Brito-Zerón P, Zeher M, Sivils KL, Seror R, Mandl H, et al. Epidemiologic subsets drive a differentiated clinical and immunological presentation of primary Sjögren syndrome: analysis of 9302 patients from the big data international Sjögren cohort. Arthritis Rheumatol. 2017;69(Suppl 10):Abstract 876.
9. Fox RI. Sjögren's syndrome. Lancet (London, England) [Internet]. 2005 [cited 2018 Sep 30];366(9482):321–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16039337.
10. Mariette X, Criswell LA. Primary Sjögren's syndrome. N Engl J Med [Internet]. 2018;378(10):931–939. Available from: https://doi.org/10.1056/NEJMcp1702514
11. Mavragani CP, Moutsopoulos HM. Primary vs secondary Sjögren's syndrome: is it time these terms to be reconsidered? J Rheumatol. 2018;(In Press).
12. Rojas-Villarraga A, Amaya-Amaya J, Rodriguez-Rodriguez A, Mantilla RD, Anaya JM. Introducing polyautoimmunity: secondary autoimmune diseases no longer exist. Autoimmune Dis. 2012;1(1)
13. Tsinti M, Kassi E, Korkolopoulou P, Kapsogeorgou E, Moutsatsou P, Patsouris E, et al. Functional estrogen receptors alpha and beta are expressed in normal human salivary gland epithelium and apparently mediate immunomodulatory effects. Eur J Oral Sci. 2009;117(5):498–505.
14. Ishimaru N, Arakaki R, Watanabe M, Kobayashi M, Miyazaki K, Hayashi Y. Development of autoimmune exocrinopathy resembling Sjögren's syndrome in estrogen-deficient mice of healthy background. Am J Pathol [Internet]. 2003;163(4):1481–1490. Available from: https://doi.org/10.1016/S0002-9440(10)63505-5
15. Johnson EO, Kostandi M, Moutsopoulos HM. Hypothalamic-pituitary-adrenal axis function in Sjögren's syndrome: mechanisms of neuroendocrine and immune system homeostasis. Ann N Y Acad Sci. 2006;1088:41–51.
16. Triantafyllopoulou A, Moutsopoulos H. Persistent viral infection in primary Sjögren's syndrome: review and perspectives. Clin Rev Allergy Immunol [Internet]. 2007;32(3):210–214. Available from: https://doi.org/10.1007/s12016-007-8004-7
17. Mavragani CP, Sagalovskiy I, Guo Q, Nezos A, Kapsogeorgou EK, Lu P, et al. Expression of long interspersed nuclear element 1 retroelements and induction of type I interferon in patients with systemic autoimmune disease. Arthritis Rheumatol. 2016;68(11):2686–96.
18. Mavragani CP, Nezos A, Sagalovskiy I, Seshan S, Kirou KA, Crow MK. Defective regulation of L1 endogenous retroelements in primary Sjogren's syndrome and systemic lupus erythematosus: role of methylating enzymes. J Autoimmun [Internet]. 2018;88:75–82. Available from: https://doi.org/10.1016/j.jaut.2017.10.004.
19. Sepúlveda D, Barrera M-J, Castro I, Aguilera S, Carvajal P, Lagos C, et al. Impaired IRE1α/XBP-1 pathway associated to DNA methylation might contribute to salivary gland dysfunction in Sjögren's syndrome patients. Rheumatology [Internet]. 2018 [cited 2018 Sep 28;57(6):1021–32. Available from: https://academic.oup.com/rheumatology/article/57/6/1021/4925387.
20. Anaya JM, Tobon GJ, Vega P, Castiblanco J. Autoimmune disease aggregation in families with primary Sjögren's syndrome. J Rheumatol. 2006;33(11):2227–34.
21. Kuo CF, Grainge MJ, Valdes AM, See LC, Luo SF, Yu KH, et al. Familial risk of Sjögren's syndrome and co-aggregation of autoimmune diseases in affected families: a nationwide population study. Arthritis Rheumatol. 2015;67(7):1904–12.
22. Reveille JD, Wilson RW, Provost TT, Bias WB, Arnett FC. Primary Sjögren's syndrome and other autoimmune diseases in families. Ann Intern Med [Internet]. 1984 [cited 2018 Sep 27];101(6):748. Available from: http://annals.org/article.aspx?doi. https://doi.org/10.7326/0003-4819-101-6-748.
23. Lichtenfeld JL, Kirschner RH, Wiernik PH. Familial Sjögren's syndrome with associated primary salivary gland lymphoma. Am J Med [Internet]. 1976 [cited 2018 Sep 28];60(2):286–92. Available from: http://linkinghub.elsevier.com/retrieve/pii/0002934376904393.
24. Priori R, Medda E, Conti F, Cassarà EA, Sabbadini MG, Antonioli CM, Gerli R, Danieli MG, Giacomelli R, Pietrogrande M, Valesini GSM. Risk factors for Sjögren's syndrome: a case-control study. Clin Exp Rheumatol. 2007;25(3):378–84.

25. Nezos A, Mavragani CP. Contribution of genetic factors to Sjögren's syndrome and Sjögren's syndrome related lymphomagenesis. J Immunol Res. 2015;2015
26. Argyropoulou OD, Valentini E, Ferro F, Leone MC, Cafaro G, Bartoloni E, et al. Review One year in review 2018: Sjögren's syndrome. 2018;(17).
27. Imgenberg-Kreuz J, Sandling JK, Nordmark G. Epigenetic alterations in primary Sjögren's syndrome – an overview. Clin Immunol [Internet]. 2018;(April:0–1. Available from: https://doi.org/10.1016/j.clim.2018.04.004.
28. Mandl T, Marsal J, Olsson P, Ohlsson B, Andréasson K. Severe intestinal dysbiosis is prevalent in primary Sjögren's syndrome and is associated with systemic disease activity. Arthritis Res Ther. 2017;19(1):237.
29. Moutsopoulos HM. Sjögren's syndrome: autoimmune epithelitis. Clin Immunol Immunopathol [Internet]. 1994 [cited 2018 Sep 30];72(2):162–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8050187.
30. Polihronis M, Tapinos NI, Theocharis SE, Economou A, Kittas C, Moutsopoulos HM. Modes of epithelial cell death and repair in Sjögren's syndrome (SS). Clin Exp Immunol [Internet]. 1998;114(3):485–90. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1905140&tool=pmcentrez&rendertype=abstract.
31. Jonsson R, Vogelsang P, Volchenkov R, Espinosa A, Wahren-Herlenius M, Appel S. The complexity of Sjögren's syndrome: novel aspects on pathogenesis. Immunol Lett [Internet]. 2011;141(1):1–9. Available from: https://doi.org/10.1016/j.imlet.2011.06.007
32. Manoussakis MN, Kapsogeorgou EK. The role of intrinsic epithelial activation in the pathogenesis of Sjögren's syndrome. J Autoimmun [Internet]. 2010;35(3):219–24. Available from: https://doi.org/10.1016/j.jaut.2010.06.011.
33. Nikolov NP, Illei GG. Pathogenesis of Sjogren's syndrome. Curr Opin Rheumatol [Internet]. 2009;21(5):465–70. Available from: http://journals.lww.com/co-rheumatology/Fulltext/2009/09000/Pathogenesis_of_Sjogren_s_syndrome.5.aspx.
34. Tzioufas AG, Kapsogeorgou EK, Moutsopoulos HM. Pathogenesis of Sjögren's syndrome: what we know and what we should learn. J Autoimmun [Internet]. 2012;39(1–2):4–8. Available from: https://doi.org/10.1016/j.jaut.2012.01.002.
35. Vakaloglou KM, Mavragani CP. Activation of the type I interferon pathway in primary Sjögren's syndrome: an update. Curr Opin Rheumatol [Internet]. 2011 [cited 2018 Sep 27];23(5):459–64. Available from: https://insights.ovid.com/crossref?an=00002281-201109000-00010.
36. Mitsias DI, Kapsogeorgou EK, Moutsopoulos HM. Sjögren's syndrome: why autoimmune epithelitis? Oral Dis. 2006;12(6):523–32.
37. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European league against rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol. 2017;69(1):35–45.
38. Fujita A. Imaging of Sjögren syndrome and immunoglobulin G4-related disease of the salivary glands. Neuroimaging Clin N Am [Internet]. 2018;28(2):183–97. Available from: https://doi.org/10.1016/j.nic.2018.01.003.
39. Ramos-Casals M, Brito-Zerón P, Font J. Lessons from diseases mimicking Sjögren's syndrome. Clin Rev Allergy Immunol. 2007;32(3):275–83.
40. Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. Dtsch Arztebl Online [Internet]. 2015:71–82. Available from: https://www.aerzteblatt.de/10.3238/arztebl.2015.0071.
41. Reinertsen JL, Schaefer EJ, Bryan Brewer H, Moutsopoulos HM. Sicca-like syndrome in type V hyperlipoproteinemia. Arthritis Rheum. 1980;23(1):114–8.
42. Brito-Zerón P, Kostov B, Solans R, Fraile G, Suárez-Cuervo C, Casanovas A, et al. Systemic activity and mortality in primary Sjögren syndrome: predicting survival using the EULAR-SS disease activity index (ESSDAI) in 1045 patients. Ann Rheum Dis. 2016;75(2):348–55.
43. Seror R, Bowman SJ, Brito-Zeron P, Theander E, Bootsma H, Tzioufas A, et al. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. RMD Open. 2015;1(1):1–9.

44. Baldini C, Ferro F, Mosca M, Fallahi P, Antonelli A. The association of Sjögren syndrome and autoimmune thyroid disorders. Front Endocrinol. 2018;9(APR):1–5.
45. Terada Y, Kamoi K, Komizo T, Miyata K, Mochizuki M. Human T cell leukemia virus type 1 and eye diseases. J Ocul Pharmacol Ther [Internet]. 2017;33(4):216–23. Available from: http://online.liebertpub.com/doi/10.1089/jop.2016.0124.
46. Bournia VK, Vlachoyiannopoulos PG. Subgroups of Sjögren syndrome patients according to serological profiles. J Autoimmun. 2012;39(1–2):15–26.
47. Nezos A, Cinoku I, Mavragani CP, Moutsopoulos HM. Antibodies against citrullinated alpha enolase peptides in primary Sjogren's syndrome. Clin Immunol [Internet]. 2017;183:300–3. Available from: https://doi.org/10.1016/j.clim.2017.09.012.
48. Fayyaz A, Kurien BT, Scofield RH. Autoantibodies in Sjögren's syndrome. Rheum Dis Clin N Am. 2016;42(3):419–34.
49. Beckman KA, Luchs J, Milner MS, Ambrus JL. The potential role for early biomarker testing as part of a modern, multidisciplinary approach to Sjögren's syndrome diagnosis. Adv Ther. 2017;34(4):799–812.
50. Beckman K, Luchs J, Milner M. Making the diagnosis of Sjögren's syndrome in patients with dry eye. Clin Ophthalmol [Internet]. 2015;10:43. https://doi.org/10.2147/OPTH.580043.
51. Nordmark G, Rorsman F, Rönnblom L, Cajander S, Taussig MJ, Kämpe O, et al. Autoantibodies to α-fodrin in primary Sjögren's syndrome and SLE detected by an in vitro transcription and translation assay. p. 49–56.
52. Pertovaara M, Bootorabi F, Kuuslahti M, Pasternack A, Parkkila S. Novel carbonic anhydrase autoantibodies and renal manifestations in patients with primary Sjögren's syndrome. Rheumatology (Oxford). 2011;50(8):1453–7.
53. Shen L, Kapsogeorgou EK, Yu M, Suresh L, Malyavantham K, Tzioufas AG, et al. Evaluation of salivary gland protein 1 antibodies in patients with primary and secondary Sjögren's syndrome. Clin Immunol [Internet]. 2014;155(1):42–6. Available from: https://doi.org/10.1016/j.clim.2014.08.009.
54. Shen L, Suresh L. Autoantibodies, detection methods and panels for diagnosis of Sjögren's syndrome. Clin Immunol [Internet]. 2017;182:24–9. Available from: https://doi.org/10.1016/j.clim.2017.03.017.
55. Shen L, Suresh L, Lindemann M, Xuan J, Kowal P, Malyavantham K, et al. Novel autoantibodies in Sjögren's syndrome. Clin Immunol [Internet]. 2012;145(3):251–5. Available from: https://doi.org/10.1016/j.clim.2012.09.013.
56. Suresh L, Malyavantham K, Shen L, Ambrus JL. Investigation of novel autoantibodies in Sjogren's syndrome utilizing sera from the Sjögren's international collaborative clinical Alliance cohort – cornea and external eye diseases. BMC Ophthalmol. 2015;15(1):1–5.
57. Bergum B, Koro C, Delaleu N, Solheim M, Hellvard A, Binder V, et al. Antibodies against carbamylated proteins are present in primary Sjögren's syndrome and are associated with disease severity. Ann Rheum Dis. 2016;75(8):1494–500.
58. El Annan J, Jiang G, Wang D, Zhou J, Foulks GN, Shao H. Elevated immunoglobulin to tissue KLK11 in patients with Sjögren syndrome. Cornea. 2013;32(5):90–3.
59. Chen K-S, Jiang M-C, Liu O-K and TC-S. Discrimination between Sjögren's and non-Sjögren's Sicca syndrome by sialoscintigraphy and antibodies against α -fodrin and Ro/La autoantigens 2014;1088–1096.
60. Karakus S, Baer AN, Agrawal D, Gurakar M, Massof RW, Akpek EK. Utility of novel autoantibodies in the diagnosis of Sjögren's syndrome among patients with dry eye. Cornea. 2018;37(4):405–11.
61. Mavragani CP, Schini M, Gravani F, Kaltsas G, Moutsopoulos HM. Adrenal autoimmunity in primary Sjögren's syndrome. Arthritis Rheum. 2012;64(12):4066–71.
62. Wolska N, Rybakowska P, Rasmussen A, Brown M, Montgomery C, Klopocki A, et al. Patients with primary Sjögren's syndrome who are positive for autoantibodies to tripartite motif-containing protein 38 show greater disease severity. Arthritis Rheumatol. 2016;68(3):724–9.
63. Bunya VY, Ying G-S, Maguire MG, Kuklinski E, Lin MC, Peskin E, et al. Prevalence of novel candidate Sjogren syndrome autoantibodies in the dry eye assessment and management

(DREAM) study. Cornea [Internet]. 2018 [cited 2018 Oct 23];37(11):1425–30. Available from: http://insights.ovid.com/crossref?an=00003226-201811000-00015.
64. Wicheta S, Van der Groen T, Faquin WC, August M. Minor salivary gland biopsy—an important contributor to the diagnosis of Sjögren syndrome. J Oral Maxillofac Surg [Internet]. 2017;75(12):2573–8. Available from: https://doi.org/10.1016/j.joms.2017.05.021.
65. Carubbi F, Alunno A, Cipriani P, Di Benedetto P, Ruscitti P, Berardicurti O, et al. Is minor salivary gland biopsy more than a diagnostic tool in primary Sjögren's syndrome? Association between clinical, histopathological, and molecular features: a retrospective study. Semin Arthritis Rheum [Internet]. 2014;44(3):314–24. Available from: https://doi.org/10.1016/j.semarthrit.2014.05.015.
66. Risselada AP, Kruize AA, Goldschmeding R, Lafeber FPJG, Bijlsma JWJ, Van Roon JAG. The prognostic value of routinely performed minor salivary gland assessments in primary Sjögren's syndrome. Ann Rheum Dis. 2014;73(8):1537–40.
67. Brito-Zerón P, Kostov B, Fraile G, Caravia-Durán D, Maure B, Rascón F-J, et al. Characterization and risk estimate of cancer in patients with primary Sjögren syndrome. J Hematol Oncol [Internet]. 2017;10(1):90. Available from: http://jhoonline.biomedcentral.com/articles/10.1186/s13045-017-0464-5.
68. Ioannidis JPA, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. Arthritis Rheum. 2002;46(3):741–7.
69. Theander E, Manthorpe R, Jacobsson LTH. Mortality and causes of death in primary Sjögren's syndrome: a prospective cohort study. Arthritis Rheum [Internet]. 2004;50(4):1262–9. Available from: http://doi.wiley.com/10.1002/art.20176.
70. Navarro-Mendoza EP, Aguirre-Valencia D, Posso-Osorio I, Correa-Forero SV, Torres-Cutiva DF, Loaiza D, et al. Cytokine markers of B lymphocytes in minor salivary gland infiltrates in Sjögren's syndrome. Autoimmun Rev [Internet]. 2018;17(7):709–14. Available from: https://doi.org/10.1016/j.autrev.2018.02.003.
71. Theander E, Vasaitis L, Baecklund E, Nordmark G, Warfvinge G, Liedholm R, et al. Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. Ann Rheum Dis. 2011;70(8):1363–8.
72. Sène D, Ismael S, Forien M, Charlotte F, Kaci R, Cacoub P, et al. Ectopic germinal center-like structures in minor salivary gland biopsy tissue predict lymphoma occurrence in patients with primary Sjögren's syndrome. Arthritis Rheumatol. 2018:0–2.
73. Haacke EA, van der Vegt B, Vissink A, Spijkervet FKL, Bootsma H, Kroese FGM. Germinal centres in diagnostic biopsies of pSS patients are not a risk factor for non-Hodgkin's lymphoma but a reflection of high disease activity. Arthritis Rheumatol [Internet]. 2018;. Available from: http://doi.wiley.com/10.1002/art.40715
74. Colella G, Cannavale R, Vicidomini A, Itro A. Salivary gland biopsy: a comprehensive review of techniques and related complications. Rheumatology. 2010;49(11):2117–21.
75. Aoun G, Nasseh I, Berberi A. Evaluation of the oral component of Sjögren's syndrome: an overview. J Int Soc Prevent Commun Dent [Internet]. 2016;6(4):278–84. Available from: http://www.jispcd.org.
76. Lee YH, Song GG. SAT0431 a meta-analysis of the diagnostic value of minor salivary gland biopsy for primary Sjögren's syndrome. Ann Rheum Dis [Internet]. 2015 [cited 2018 Sep 27];74(Suppl 2):815.2–815. Available from: http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2015-eular.1209.
77. Giovelli RA, Santos MCS, Serrano ÉV, Valim V. Clinical characteristics and biopsy accuracy in suspected cases of Sjögren's syndrome referred to labial salivary gland biopsy. BMC Musculoskelet Disord. 2015;16(1):1–7.
78. Alunno A, Leone MC, Giacomelli R, Gerli R, Carubbi F. Lymphoma and lymphomagenesis in primary Sjögren's syndrome. Front Med [Internet] 2018;5(April):102. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29707540%0A http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5909032
79. Luk WH, Yeung JTH, Fung EPY, Lok CM, Ng YM. Salivary gland scintigraphy in patients with Sjögren's syndrome: a local experience with dual-tracer. Asia Oceania

J Nucl Med Biol [Internet] 2017;5(1):56–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28840140%0A http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5221687
80. Martire MV, Santiago ML, Cazenave T, Gutierrez M. Latest advances in ultrasound assessment of salivary glands in Sjögren syndrome. J Clin Rheumatol: Pract Rep Rheumatic Musculoskeletal Dis. 2018;24(4):218–23.
81. Cindil E, Oktar SO, Akkan K, Sendur HN, Mercan R, Tufan A, et al. Ultrasound elastography in assessment of salivary glands involvement in primary Sjögren's syndrome. Clin Imaging. 2018;50(April):229–34.
82. Kuklinski E, Asbell PA, Asbell PA. Sjögren's syndrome from the perspective of ophthalmology. Clin Immunol [Internet]. 2017;182:55–61. Available from: https://doi.org/10.1016/j.clim.2017.04.017.
83. Machado LM, Castro RS, Fontes BM. Staining patterns in dry eye syndrome: Rose Bengal versus Lissamine Green. Cornea [Internet]. 2009;28(7):732–4. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00003226-200908000-00004.
84. Adatia FA, Michaeli-Cohen A, Naor J, Caffery B, Bookman A, Slomovic A. Correlation between corneal sensitivity, subjective dry eye symptoms and corneal staining in Sjögren's syndrome. Can J Ophthalmol [Internet]. 2004;39(7):767–71. Available from: https://doi.org/10.1016/S0008-4182(04)80071-1.
85. Seror R, Ravaud P, Mariette X, Bootsma H, Theander E, Hansen A, et al. EULAR Sjögren's syndrome patient reported index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. Ann Rheum Dis. 2011;70(6):968–72.
86. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. Arch Intern Med. 2004;164:1275–84.
87. Pavlakis PP, Alexopoulos H, Kosmidis ML, Stamboulis E, Routsias JG, Tzartos SJ, et al. Peripheral neuropathies in Sjögren syndrome: a new reappraisal. J Neurol Neurosurg Psychiatry [Internet]. 2011;82(7):798–802. Available from: http://jnnp.bmj.com/cgi/doi/10.1136/jnnp.2010.222109.
88. Popov Y, Salomon-Escoto K. Gastrointestinal and hepatic disease in Sjogren syndrome. Rheum Dis Clin N Am [Internet]. 2018;44(1):143–51. Available from: https://doi.org/10.1016/j.rdc.2017.09.010.
89. Soliotis FC, Mavragani CP, Moutsopoulos HM. Central nervous system involvement in Sjögren's syndrome. p. 616–20.
90. Kampolis CF, Fragkioudaki S, Mavragani CP, Zormpala A, Samakovli A, Moutsopoulos HM, et al. Prevalence and spectrum of symptomatic pulmonary involvement in primary Sjögren's syndrome. Clin Exp Rheumatol. 2018;2018(10):94–101.
91. François H, Mariette X. Renal involvement in primary Sjögren syndrome. Nat Publ Group [Internet]. 2015;12(2):82–93. Available from: https://doi.org/10.1038/nrneph.2015.174.
92. Delalande S, de Seze J, Fauchais A-L, Hachulla E, Stojkovic T, Ferriby D, et al. Neurologic manifestations in primary Sjögren syndrome. Medicine [Internet]. 2004;83(5):280–91. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005792-200409000-00003.
93. Kreider M, Highland K. Pulmonary involvement in Sjögren syndrome. Semin Respir Crit Care Med. 2014;35(2):255–64.
94. Hatron PY, Tillie-Leblond I, Launay D, Hachulla E, Fauchais AL, Wallaert B. Pulmonary manifestations of Sjögren's syndrome. Presse Med. 2011;40(1 PART2):71–86.
95. Vivino FB. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren Syndrome-A randomized, placebo-controlled, fixed-dose, multicenter trial. Arch Intern Med [Internet]. 1999;159(2):174. Available from: http://archinte.jamanetwork.com/article.aspx?doi. https://doi.org/10.1001/archinte.159.2.174.
96. Dawson LJ, Caulfield VL, Stanbury JB, Field AE, Christmas SE, Smith PM. Hydroxychloroquine therapy in patients with primary Sjögren's syndrome may improve

salivary gland hypofunction by inhibition of glandular cholinesterase. Rheumatology. 2005;44(4):449–55.
97. Fife RS, Chase WF, Dore RK, Wiesenhutter CW, Lockhart PB, Tindall E, et al. Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial. Arch Int Med [Internet]. 2002;162(11):1293–300. Available from: http://sfx.scholarsportal.info/ottawa?sid=OVID:medline&id=pmid:12038948&id=doi:&issn=0003-9926&isbn=&volume=162&issue=11&spage=1293&pages=1293-300&date=2002&title=Archives+of+Internal+Medicine&atitle=Cevimeline+for+the+treatment+of+xerostomia+in+patients+.
98. Verstappen GM, van Nimwegen JF, Vissink A, Kroese FGM, Bootsma H. The value of rituximab treatment in primary Sjögren's syndrome. Clin Immunol [Internet]. 2017;182:62–71. Available from: https://doi.org/10.1016/j.clim.2017.05.002.
99. Strombeck BE, Theander E, Jacobsson LTH. Effects of exercise on aerobic capacity and fatigue in women with primary Sjögren's syndrome. Rheumatology [Internet]. 2007;46(5):868–71. Available from: https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/kem004.
100. Saraux A, Pers JO, Devauchelle-Pensec V. Treatment of primary Sjögren syndrome. Nat Rev Rheumatol [Internet]. 2016;12(8):456–71. Available from: https://doi.org/10.1038/nrrheum.2016.100.
101. Skopouli FN, Jagiello P, Tsifetaki N, Moutsopoulos HM. Methotrexate in primary Sjögren's syndrome. Clin Exp Rheumatol [Internet]. 1996 [cited 2018 Aug 27];14(5):555–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8913659.
102. Demarchi J, Papasidero S, Medina MA, Klajn D, Chaparro del Moral R, Rillo O, et al. Primary Sjögren's syndrome: Extraglandular manifestations and hydroxychloroquine therapy. Clin Rheumatol. 2017;36(11):2455–60.
103. Kruize AA, Hene RJ, Kallenberg CGM, Van Bijsterveld OP, Van Der Heide A, Kater L, et al. Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial. Ann Rheumatic Dis [Internet]. 1993;52(5):360–4. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L23165974.
104. Nocturne G, Mariette X. Sjögren syndrome-associated lymphomas: an update on pathogenesis and management. Br J Haematol. 2015;168(3):317–27.
105. Voulgarelis M, Giannouli S, Anagnostou D, Tzioufas AG. Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) for Sjögren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. Rheumatology. 2004;43(8):1050–3.
106. Voulgarelis M, Giannouli S, Tzioufas AG, Moutsopoulos HM. Long term remission of Sjögren's syndrome associated aggressive B cell non-Hodgkin's lymphomas following combined B cell depletion therapy and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Ann Rheum Dis. 2006;65(8):1033–7.
107. Rist S, Sellam J, Hachulla E, Sordet C, Puéchal X, Hatron P, et al. Experience of intravenous immunoglobulin therapy in neuropathy associated with primary Sjögren's syndrome: a national multicentric retrospective study. Arthritis Care Res [Internet]. 2011;63(9):1339–44. Available from: http://doi.wiley.com/10.1002/acr.20495.
108. Vivino FB, Carsons SE, Foulks G, Daniels TE, Parke A, Brennan MT, et al. New treatment guidelines for Sjögren's disease. Rheum Dis Clin N Am [Internet]. 2016 [cited 2018 Oct 9];42(3):531–51. Available from: https://www.sciencedirect.com/science/article/pii/S0889857X16300217?via%3Dihub.
109. Both T, Dalm VASH, Martin van Hagen P, Van Daele PLA. Reviewing primary Sjögren's syndrome: beyond the dryness – from pathophysiology to diagnosis and treatment. Int J Med Sci. 2017;14(3):191–200.
110. Brito-Zerón P, Retamozo S, Gheitasi H, Ramos-Casals M. Treating the underlying pathophysiology of primary Sjögren syndrome: recent advances and future prospects. Drugs. 2016;76(17):1601–23.
111. Cummins MJ, Papas A, Kammer GM, Fox PC. Treatment of primary Sjögren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase

III results. Arthritis Rheum [Internet]. 2003;49(4):585–93. Available from: http://doi.wiley.com/10.1002/art.11199.
112. Darrieutort-Laffite C, André V, Hayem G, Saraux A, Le Guern V, Le Jeunne C, et al. Sjögren's syndrome complicated by interstitial cystitis: a case series and literature review. Joint Bone Spine [Internet]. 2015;82(4):245–50. Available from: https://doi.org/10.1016/j.jbspin.2014.12.007.
113. Dass S, Bowman SJ, Vital EM, Ikeda K, Pease CT, Hamburger J, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis. 2008;67(11):1541–4.
114. Evans R, Zdebik A, Ciurtin C, Walsh SB. Renal involvement in primary Sjögren's syndrome. Rheumatology (United Kingdom [Internet]). 2015;54(9):1541–8. Available from: https://doi.org/10.1038/nrneph.2015.174.
115. Ferro F, Vagelli R, Bruni C, Cafaro G, Marcucci E, Bartoloni E, et al. Review one year in review 2016 : Sjögren's syndrome. Clin Exp Rheumatol. 2016;34(3):161–71.
116. Gottenberg JE, Cinquetti G, Larroche C, Combe B, Hachulla E, Meyer O, et al. Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry. Ann Rheum Dis. 2013;72(6):1026–31.
117. Karageorgas T, Fragioudaki S, Nezos A, Karaiskos D, Moutsopoulos HM, Mavragani CP. Fatigue in primary Sjögren's syndrome: clinical, laboratory, psychometric, and biologic associations. Arthritis Care Res. 2016;68(1):123–31.
118. Karaiskos D, Mavragani CP, Sinno MH, Déchelotte P, Zintzaras E, Skopouli FN, et al. Psychopathological and personality features in primary Sjögren's syndrome-associations with autoantibodies to neuropeptides. Rheumatology. 2010;49(9):1762–9.
119. Matsuda M, Hamano H, Yoshida T, Gono T, Uehara T, Kawa S, et al. Seronegative Sjögren syndrome with asymptomatic autoimmune sclerosing pancreatitis. Clin Rheumatol. 2007;26(1):117–9.
120. Meijer JM, Meiners PM, Vissink A, Spijkervet FKL, Abdulahad W, Kamminga N, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum [Internet]. 2010;62(4):960–8. Available from: http://doi.wiley.com/10.1002/art.27314.
121. Zintzaras E. The risk of lymphoma development in autoimmune diseases. Arch Intern Med [Internet]. 2005;165(20):2337. Available from: http://archinte.jamanetwork.com/article.aspx?doi. https://doi.org/10.1001/archinte.165.20.2337.
122. Chiu Y-H, Chung C-H, Lin K-T, Lin C-S, Chen J-H, Chen H-C, et al. Predictable biomarkers of developing lymphoma in patients with Sjögren syndrome: a nationwide population-based cohort study. Oncotarget [Internet]. 2017;8(30):50098–108. Available from: http://www.oncotarget.com/fulltext/15100.
123. Fragkioudaki S, Mavragani CP, Moutsopoulos HM. Predicting the risk for lymphoma development in Sjögren syndrome: an easy tool for clinical use. Medicine [Internet]. 2016;95(25):e3766. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27336863.
124. Baimpa E, Dahabreh IJ, Voulgarelis M, Moutsopoulos HM. Hematologic manifestations and predictors of lymphoma development in primary Sjögren syndrome: clinical and pathophysiologic aspects. Medicine [Internet]. 2009 [cited 2018 Sep 30];88(5):284–93. Available from: https://insights.ovid.com/crossref?an=00005792-200909000-00004.
125. Nocturne G, Virone A, Ng W-F, Le Guern V, Hachulla E, Cornec D, et al. Rheumatoid factor and disease activity are independent predictors of lymphoma in primary Sjögren's syndrome. Arthritis Rheumatol [cited 2018 Sep 30]. 2016;68(4):977–85. Available from: http://doi.wiley.com/10.1002/art.39518.
126. Tomi A-L, Belkhir R, Nocturne G, Desmoulins F, Berge E, Pavy S, et al. Monoclonal gammopathy and risk of lymphoma and multiple myeloma in patients with primary Sjögren's syndrome. Arthritis Rheumatol [Internet]. 2015;68(5):n/a–n/a. Available from: http://doi.wiley.com/10.1002/art.39534.

127. Baldini C, Santini E, Rossi C, Donati V, Solini A. The P2X7 receptor–NLRP3 inflammasome complex predicts the development of non-Hodgkin's lymphoma in Sjögren's syndrome: a prospective, observational, single-centre study. J Intern Med. 2017;282(2):175–86.
128. Vakrakou AG, Boiu S, Ziakas PD, Xingi E, Boleti H, Manoussakis MN. Systemic activation of NLRP3 inflammasome in patients with severe primary Sjögren's syndrome fueled by inflammagenic DNA accumulations. J Autoimmun [Internet]. 2018 [cited 2018 Sep 30];91:23–33. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0896841117307898.
129. Hall JC, Baer AN, Shah AA, Criswell LA, Shiboski CH, Rosen A, et al. Molecular subsetting of interferon pathways in Sjögren's syndrome. Arthritis Rheumatol. 2015;67(9):2437–46.
130. Nezos A., Gkioka E., Koutsilieris M., Voulgarelis M., Tzioufas A.G. and Mavragani C.P. TNFAIP3 F127C Coding Variation in Greek Primary Sjogren's Syndrome Patients J Immunol Res. 2018; 2018: 6923213.
131. Quartuccio L, Salvin S, Fabris M, Maset M, Pontarini E, Isola M, et al. Blys upregulation in Sjögren's syndrome associated with lymphoproliferative disorders, higher ESSDAI score and B-cell clonal expansion in the salivary glands. Rheumatology (United Kingdom). 2013;52(2):276–81.
132. Nezos A, Gravani F, Tassidou A, Kapsogeorgou EK, Voulgarelis M, Koutsilieris M, et al. Type I and II interferon signatures in Sjögren's syndrome pathogenesis: contributions in distinct clinical phenotypes and Sjogren's related lymphomagenesis. J Autoimmun [Internet]. 2015;63:47–58. Available from: https://doi.org/10.1016/j.jaut.2015.07.002.
133. Nezos A, Papageorgiou A, Fragoulis G, Ioakeimidis D, Koutsilieris M, Tzioufas AG, et al. B-cell activating factor genetic variants in lymphomagenesis associated with primary Sjögren's syndrome. J Autoimmun [Internet]. 2014;51:89–98. Available from: https://doi.org/10.1016/j.jaut.2013.04.005.
134. Papageorgiou A, Mavragani CP, Nezos A, Zintzaras E, Quartuccio L, De Vita S, et al. A BAFF receptor His159Tyr mutation in Sjögren's syndrome-related lymphoproliferation. Arthritis & Rheumatol (Hoboken, NJ). 2015;67(10):2732–41.
135. Tobón GJ, Saraux A, Gottenberg JE, Quartuccio L, Fabris M, Seror R, et al. Role of Fms-like tyrosine kinase 3 ligand as a potential biologic marker of lymphoma in primary Sjögren's syndrome. Arthritis Rheum. 2013;65(12):3218–27.
136. Nezos A, Makri P, Gandolfo S, De Vita S, Voulgarelis M, Crow MK, Mavragani CP. TREX1 variants in Sjögren's syndrome related lymphomagenesis. Cytokine. 2018;Submitted.
137. Tapinos NI, Polihronis M, Moutsopoulos HM. Lymphoma development in Sjögren's syndrome: novel p53 mutations. Arthritis Rheum [Internet]. 1999;42(7):1466–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10403275
138. Imgenberg-Kreuz J, Sandling JK, Nordmark G. Epigenetic alterations in primary Sjögren's syndrome – an overview. Clin Immunol [Internet]. 2018;(January:0–1. Available from: https://doi.org/10.1016/j.clim.2018.04.004
139. Gourzi VC, Kapsogeorgou EK, Kyriakidis NC, Tzioufas AG. Study of microRNAs (miRNAs) that are predicted to target the autoantigens Ro/SSA and La/SSB in primary Sjögren ' s syndrome. Clin Exp Immunol. 2015;182:14–22.
140. Kapsogeorgou EK, Papageorgiou A, Protogerou AD, Voulgarelis M, Tzioufas AG. Low miR200b-5p levels in minor salivary glands: a novel molecular marker predicting lymphoma development in patients with Sjögren's syndrome. Ann Rheum Dis. 2018;77(8):1201–8.
141. Mavragani CP, Nezos A, Sagalovskiy I, Seshan S, Kirou KA, Crow MK. Defective regulation of L1 endogenous retroelements in primary Sjögren's syndrome and systemic lupus erythematosus: role of methylating enzymes. J Autoimmun [Internet]. 2018;88:75–82. Available from: https://doi.org/10.1016/j.jaut.2017.10.004.
142. Fragkioudaki S, Nezos A, Souliotis VL, Chatziandreou I, Saetta AA, Drakoulis N, et al. MTHFR gene variants and non-MALT lymphoma development in primary Sjogren's syndrome. Sci Rep [Internet]. 2017;7(1):1–8. Available from: https://doi.org/10.1038/s41598-017-07347-w.

143. Voulgarelis M, Ziakas PD, Papageorgiou A, Baimpa E, Tzioufas AG, Moutsopoulos HM. Prognosis and outcome of non-Hodgkin lymphoma in primary Sjögren syndrome. Medicine. 2012;91(1):1–9.
144. Papageorgiou A, Voulgarelis M, Tzioufas AG. Clinical picture, outcome and predictive factors of lymphoma in Sjögren syndrome. Autoimmun Rev [Internet]. 2015;14(7):641–9. Available from: https://doi.org/10.1016/j.autrev.2015.03.004.
145. Papageorgiou A, Ziogas DC, Mavragani CP, Zintzaras E, Tzioufas AG, Moutsopoulos HM, et al. Predicting the outcome of Sjögren's syndrome-associated non-Hodgkin's lymphoma patients. PLoS One. 2015;10(2):1–17.
146. Pollard RPE, Pijpe J, Bootsma H, Spijkevert FKL, Kluin PM, Roodenburg JLN, et al. Treatment of mucosa-associated lymphoid tissue lymphoma in Sjögren's syndrome: a retrospective clinical study. J Rheumatol [Internet]. 2011;38(10):2198–208. Available from: http://www.jrheum.org/cgi/doi/10.3899/jrheum.110077.
147. Defrancesco I, Arcaini L. Overview on the management of non-gastric MALT lymphomas. Best Pract Res: Clin Haematol [Internet]. 2018;31(1):57–64. Available from: https://doi.org/10.1016/j.beha.2017.11.001.
148. Hile GA, et al. Cutaneous purpura of Sjögren syndrome successfully treated with hydroxychloroquine. JAAD Case Rep. 2017;3(4):326. http://creativecommons.org/licenses/by-nc-nd/4.0/. https://doi.org/10.1016/j.jdcr.2017.04.011.
149. Adrianos Nezos, Eliona Gkioka, Michael Koutsilieris, Michael Voulgarelis, Athanasios G. Tzioufas, Clio P. Mavragani, (2018) TNFAIP3 F127C Coding Variation in Greek Primary Sjogren's Syndrome Patients. Journal of Immunology Research 2018:1–8.