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Other CTD: Inflammatory Myopathies and Sjogren's (P Basharat and JFL Albayda, Section Editors)

Lymphoma in Sjögren's Syndrome: Predictors and Therapeutic Options

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Abstract

Purpose of review Sjögren's syndrome (SS) is a chronic systemic disorder of autoimmune origin characterized by impaired secretory function of the exocrine glands and a high susceptibility for non-Hodgkin's lymphoma development. The aim of the present review is to summarize the main clinical and molecular contributors of lymphoma development in the setting of SS and discuss current therapeutic options.

Recent findings Male sex, earlier SS onset, systemic features including salivary gland enlargement, purpura, lymphadenopathy, Raynaud's phenomenon, tongue atrophy, autoantibody production, depressed C4 complement levels, monoclonal gammopathy, and cryoglobulinemia are the main features denoting a high-risk SS phenotype for the practicing clinician. Additional molecular markers involving innate immune pathways, B cell activation, and epigenetic alterations have been recently revealed. For the treatment of SS-related lymphoma, the basic principles for treatment of lymphomas in general are applied.

Summary Identification of predictors for lymphoma development in the setting of SS is of crucial importance for a prompt diagnosis and early therapeutic intervention. Moreover, discovery of novel genetic and epigenetic contributors through international collaborative efforts will allow a better understanding of underlying molecular pathways and establishment of tailored treatment approaches for these patients.

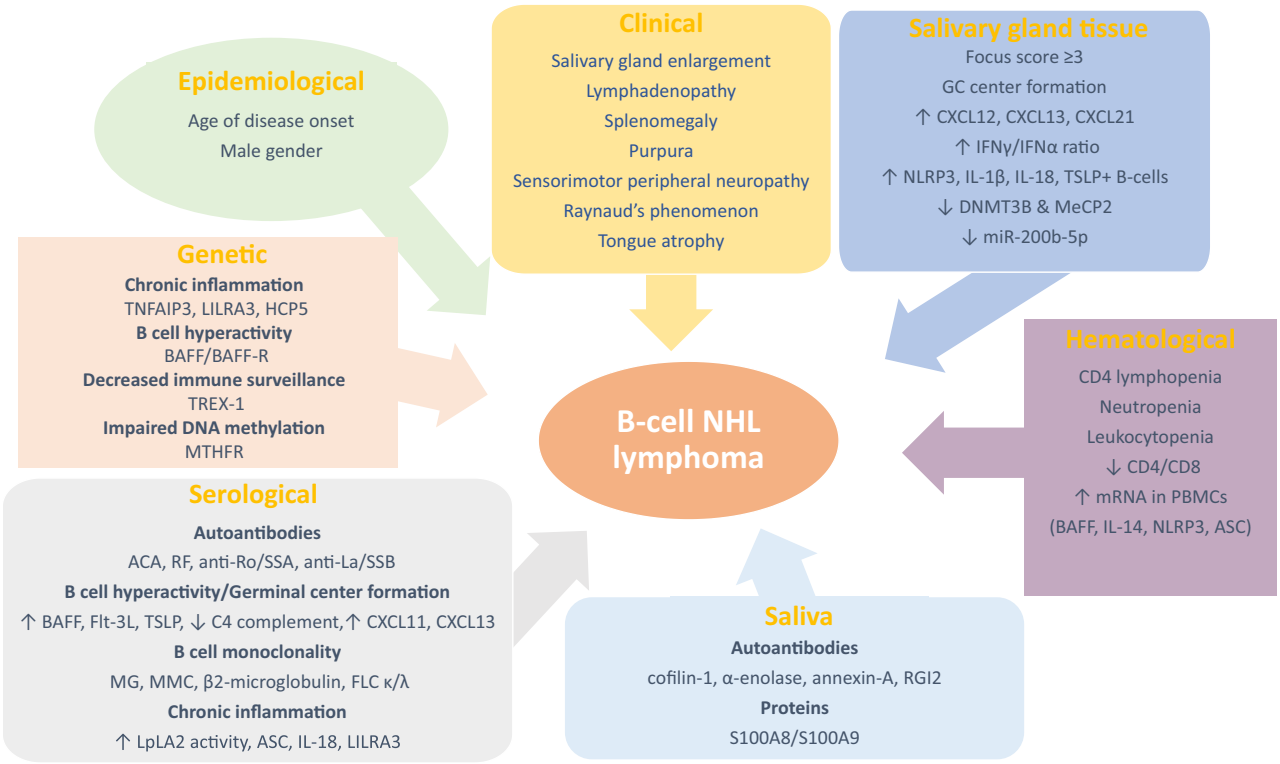

Fig. 1. An overview of clinical and molecular contributors of lymphoma development in primary Sjögren's syndrome. ↑: increased; ↓: reduced; rheumatoid factor: RF; tumor necrosis factor-alpha induced protein 3: TNFAIP3; B cell activating factor: BAFF; B cell activating factor receptor: BAFF-R; Interferon α/γ: IFNα/γ; three prime repair exonuclease 1: TREX-1; leukocyte immunoglobulin-like receptor subfamily A member 3: LILRA3; Major histocompatibility complex P5 gene: HCP5; methylene tetrahydrofolate reductase: MTHFR; DNA methyltransferase 3B: DNMT3B; methyl CpG binding protein 2: MeCP2; peripheral blood mononuclear cells: PBMCs; Rho GDP-dissociation inhibitor 2: RGI2; Extracellular lipoprotein-associated phospholipase A2: Lp-PLA2; free light chains κ/λ: FLCκ/λ; Fms-like tyrosine kinase 3 ligand: Flt-3 L; chemokine (C-X-C motif) ligand 11/12/13/21: CXCL11/12/13/21 NOD-like receptors containing pyrin domain 3: NLRP3; apoptosis-associated speck-like protein containing C-terminal caspase recruitment domain [CARD]:ASC; Thymic stromal lymphopoietin: TSLP; monoclonal gammopathy: MG; mixed monoclonal cryoglobulinemia: MMC; anti-centromere antibodies: ACA

Introduction

Sjögren's syndrome (SS) is a chronic systemic autoimmune disorder, with a prevalence of about 0.5% in the general population affecting primarily perimenopausal women (at a ratio of women to men of 9: 1) [1, 2]. SS can occur alone in the absence of a concomitant autoimmune disorder (primary SS) or can be associated with other autoimmune diseases [3]. As a result of lymphocytic infiltration and inflammation in exocrine glands, mucosal dryness ensues, mainly manifested by dry mouth and dry eyes [1]. Beyond sicca and musculoskeletal complaints, other systemic manifestations arising from lung, liver, kidney and nervous system involvement can be also present [4]. B cell hyperactivity expressed as hypergammaglobulinemia along with the presence of specific serum autoantibodies (against ribonucleoproteins) represents a disease hallmark [1]. The most severe complication of SS is the development of mainly B cell-driven, Non-Hodgkin lymphoma (NHL)

[4], estimated to occur in 5–10% of SS patients, conferring the highest susceptibility among all autoimmune disorders [5].

Local immunocomplexes formation at level of ectopic germinal-like centers (EGCs) in salivary glands has been proposed to stimulate polyclonal B cells to secrete rheumatoid factor (RF), ultimately leading to monoclonal and malignant transformation possibly aided by amplifying growth factors [6•]. The most common type of NHL in the context of SS is extra nodal marginal zone (MZ) mucosa-associated lymphoid tissue (MALT) lymphoma affecting approximately 65% of the whole SS population affected by lymphoma [7]. Other marginal and non-marginal zone lymphomas have been also described including splenic and nodal MZ, as well as lympho-plasmacytoid and diffuse large B cell (DLBC) lymphomas [8, 9]. SS-related MALT lymphomas affect mainly parotid and sub-mandibular salivary glands (SGs) – the major disease target organs – and follow an indolent course in the majority of cases; however, nasopharynx, pulmonary and gastrointestinal involvement needs to be excluded [6•]. Though the traditional view considers lymphoma development as the end result of a long-lasting inflammatory process in the SS salivary glands, a growing body of evidence supports an adverse profile present early in disease course. Thus, over the last decades, it has been well appreciated that young disease onset along with specific clinical and serological features are strong predictors for aggressive disease phenotypes, characterized by systemic involvement and profound B cell hyperactivity [10, 11]. These findings imply that inherent genetic contributors might play a key role in lymphomagenic events observed in the setting of SS and fueled international research efforts to identify gene variations with functional implications in chronic inflammation and B cell activation. The aim of the present review is to summarize the main epidemiological, clinical, serological, histological, and genetic biomarkers which have been proposed as potential predictors for lymphoma development in the setting of SS (Fig. 1) [12••].

Epidemiological Markers

An increasing body of evidence supports an association between younger disease onset (age < 35 years) with systemic features and presence of autoantibodies [11, 13–15], which have been previously shown to be adverse predictors for lymphoma development [15, 16•, 17]. However, direct evidence of association between age of SS onset and lymphoma development remains to be established [19–22]. Male gender has been also shown to be a strong risk factor for lymphomagenesis [23–29], an observation confirmed in a recent study involving 1300 patients fulfilling the American-European Consensus Group (AECG) 2002 criteria for SS in which the standardized incidence ratio (SIR) for NHL was higher in men than women (18 vs 5). This observation was also confirmed for the rest of hematological cancers (multiple myeloma: 43 vs 36 and Hodgkin lymphoma: 59 vs 16) [30].

Clinical Markers

Salivary gland enlargement, especially parotid enlargement [8, 16, 18, 23, 29, 31–34] is consistently reported as a main predictive factor leading to lymphoma development, firstly reported in 1978 by Kassan SS et al. [35]. Of interest, a recent multicenter study revealed that isolated salivary gland swelling without the presence of certain serological biomarkers (cryoglobulins, leukopenia, positive anti-La/SSB antibodies) was not

associated with lymphoma development [36]. Diffuse lymph nodes swelling along with splenomegaly are also well-known systemic manifestations linked to increased risk for non-MZ lymphomas, while regional localization is mainly associated with MALT type [37]. Palpable purpura, the most common form of cutaneous vasculitis seen in SS [38], usually manifested as a non-blanching purpuric rash is among the identified predictors for increased morbidity [16•, 17–19] and lymphoma-related mortality [39] in SS patients. Both sensorimotor and sensory axonal neuropathies have been previously shown to be related to markers of polyclonal B cell hyperactivity such as autoantibodies and hypergammaglobulinemia [40, 41]. Of interest, the majority of sensorimotor neuropathies have been associated with features denoting monoclonal B cell hyperactivity such as mixed cryoglobulinemia, monoclonal gammopathy, and abnormal κ/λ-free light chain ratio together with extra-glandular manifestations [33, 40, 41]. Raynaud's phenomenon as well as excessive atrophy and tongue fissuring have been also recently recognized as independent risk factors for lymphoma development [16•, 42, 43, 44•]. Finally, SS disease activity as assessed by the EULAR SS disease activity index (ESSDAI) tool has been viewed as a determinant for increased mortality in the setting of SS [7, 45]. In order to formulate an easy predicting tool for use in clinical practice, an algorithm based on 7 independent clinical and serological predictors present at disease diagnosis was constructed and included salivary gland enlargement (SGE), lymphadenopathy, Raynaud's phenomenon, anti-Ro/SSA or/and anti-La/SSB antibodies, RF positivity, monoclonal gammopathy, and C4 hypocomplementemia. Thus, patients presenting with less than 2 of above predictive markers had a probability for NHL development of 3.8%, those with 3 to 6 risk factors 39.9%, while those with all 7 markers reached 100% risk [16•].

Salivary Gland tissue Markers

The main histopathological finding in SS patients is periductal aggregation of lymphocytes in target tissues such as salivary or lacrimal glands. Focus score (FS) is the principal histological criterion used to diagnose SS, defined by the presence of an aggregation of at least 50 lymphocytes per 4mm^2 [46]. Recent data indicate that the extent of lymphocytic infiltration in SGs is a strong independent risk factor for lymphoma development [47–49], with FS ≥ 3 increasing the risk by almost 15 times [48]. Another important histopathological feature of MALT lymphoma is the presence of lymphoepithelial tissue lesions surrounded by malignant high proliferative B cells expressing the immunoreceptor Fc receptor-like protein 4 (FcRL4 or IRTA1) [50]. Increased number of intraepithelial FcRL4+ B cells – especially in parotid glands – along with higher immunohistochemical and mRNA expression of FcRL4 was observed in salivary gland tissues derived from SS and SS MALT patients, respectively, compared to sicca controls [51]. Since FcRL4 expression has been previously linked to MZL development [52] and rheumatoid arthritis (RA) [53], the presence of FcRLA4+ B cells in SS SGs could be predictive for the development of MALT, especially in parotid glands.

In targeted organs, lymphocyte infiltrations form secondary structures resembling EGCs, previously linked to higher disease activity, autoantibody production, and increased probability for lymphoma development [54–56], though the latter association has been debated in recent reports [57, 58]. Of interest, chemokines CXCL12, CXCL13, CCL21, or activation-induced cytidine deaminase (AID) have been shown to be upregulated in SGs characterized by EGC formation [59, 60], or lymphoma development [61]. Further support for a role of chronic inflammation in SS-related lymphomagenesis comes from several salivary gland tissue studies revealing an upregulation of inflammatory molecules [62, 63, 64••] as well as dampened A20 expression (a negative regulator of chronic inflammation) in SS complicated by lymphoma compared to those without [65]. Moreover, the number of interleukin-18 (IL-18) expressing macrophages and inflammasome components transcripts [purinoreceptor 7 (P2X7R), Nod-like receptor family protein 3 (NLRP3), Il-1β and IL-18] were found to be increased in SS NHL patients in association with features previously linked to lymphoma development, such as salivary gland enlargement and low C4 levels [63, 64••, 66]. Heightened salivary gland tissue interferon-γ (IFNγ) [62] and IFNγ inducible apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G (APOBEC3G) [61], but low IFNα transcripts, were also found in these patients implying that an imbalance between IFNγ-mediated chronic inflammatory responses and IFNα-related immune surveillant functions could contribute to malignant transformation at the level of salivary gland tissue. Upregulation of proapoptotic molecules p53 and NF-related apoptosis-inducing ligand (TRAIL) by IFNα could potentially account for the immune surveillant IFNα properties at the level of SS salivary gland tissue [62]. On this basis, IFNγ/IFNα mRNA ratio in SS MSG tissues could serve as histopathologic predictor for lymphoma development, with high discriminative ability between SS-lymphoma and SS non-lymphoma patients (AUC = 0.88, 95%CI: 0.7–1.0, *p* value: 0.001) [62]. Another remarkable molecule with a role in chronic inflammation, autoimmunity, and malignancy is thymic stromal lymphopoietin (TSLP), a pleiotropic cytokine primarily expressed by activated lung and intestinal epithelial cells, as well as by immune cells [67]. MSG tissues of SS-lymphoma patients reduced immunohistochemical TSLP expression, but increased number of TSLP+ B cells was demonstrated compared to non-lymphoma and healthy controls (HC), implying a possible role of TSLP to SS-related lymphoproliferation [68].

Epigenetic and transcriptional alterations have been increasingly recognized as potential contributors for lymphoid malignancies [69]. In MSG tissues from patients with SS complicated by lymphoma decreased mRNA expression of enzymes involved in methylation machinery such as DNA methyltransferase 3B, and methyl CpG-binding protein 2 and DNA methyltransferase 1 were detected compared to SS without lymphoma [70]. Finally, miR-200b-5p – a microRNA previously implicated in solid tumors oncogenesis [71, 72] – has been also shown to be downregulated in high-risk or SS-lymphoma patients [73••].

Peripheral Blood Markers

Among hematologic abnormalities, $CD4^+$ lymphopenia and low $CD4^+/CD8^+$ ratio have been detected in patients with lymphoproliferative

disorder [19], while neutropenia and lymphocytopenia have been associated to MZBCL and non-MZBCL development, respectively, at the time of diagnosis [74]. Gene expression studies in peripheral mononuclear cells revealed higher mRNA levels of BAFF [62], IL-14 [75], NLRP3, and apoptosis-associated speck-like protein (ASC) [64••].

Serological Markers

Since B cell hyperactivity has been shown to be a cardinal feature for SS lymphomagenesis, autoantibodies including anti-Ro/SSA and/or anti-La/SSB [11, 16•, 32, 76], RF [16•, 18, 36] anti-centromere antibodies (ACA) [77] have been all associated with lymphoma development in the context of SS. C4 hypocomplementemia, possibly as a result of excessive immune complex formation and activation of the classical complement pathway, has been consistently shown to influence both lymphoma risk and SS-related mortality [17, 19, 32, 39, 45, 78]. Cytokines involved in B cell growth and survival including B cell-activating factor (BAFF), Fms-like tyrosine kinase 3 ligand (Flt-3 L), and TSLP have been shown to be increased in serum derived from SS-lymphoma patients compared either to SS patients without lymphoma and/or HC [62, 79, 80••, 81, 82, 83••] or autoimmune disease controls [81]. Moreover, serum chemokine levels previously shown to contribute to EGCs formation such as CXCL13 and to a lesser degree CXCL11 were also found to be elevated in SS patients with lymphoma compared to those without [84]. Serum B cell monoclonality indicators such as monoclonal gammopathy [16•, 85, 86], mixed monoclonal cryoglobulinemia (MMC) [87], increased β2-microglobulin levels [88] along with increased free light chain κ/λ ratio [85] were also found to be strong predictors for lymphomagenesis among SS patients.

Given that uncontrolled inflammation has been associated with SS-related lymphoma, identification of soluble inflammatory biomarkers attracted particular interest. Thus, increased serum activity of the lipoprotein-associated phospholipase A2 (Lp-PLA2) [89] mainly produced by macrophages – previously shown to prevail in SS severe histopathological lesions [63] – was found in SS patients complicated by lymphoma compared to both uncomplicated SS and HC. Similarly, serum inflammasome components such as ASC and IL-18 were found to be increased in SS patients at high-risk for lymphoma development or complicated by lymphoma compared to low-risk SS and HC [64••]. Leukocyte immunoglobulin-like receptor subfamily A member 3 (LILRA3) is another inflammatory mediator recently found to be increased in serum of young onset SS-lymphoma patients [90]. LILRA3 is a soluble immunoreceptor, secreted by monocytes and B-cells inducing NK and CD8+ cells production stimulating inflammatory responses [91, 92].

Salivary markers

Salivary glands are the major site of lymphomagenesis in SS setting, and changes in protein saliva content could be indicative for the disease pathogenesis. Over the last years, several efforts have been made aiming at identification of saliva proteins with a potentially predictive role in

malignant transformation [93, 94]. Of interest, a novel panel of saliva autoantibodies was found to be able to distinguish the SS MALT subset from SS and HC [95]. These autoantibodies are directed against cofilin-1, an action-binding protein, dissembling actin filaments, alpha-enolase (glycolytic enzyme implicated in carcinogenesis), annexin-A2 (a protein related to cellular growth and signal transduction pathways), and Rho GDP-dissociation inhibitor 2 (RGI2) (a negative regulator of the proliferating enzyme Rho GTPase in hemopoietic cells). Moreover, proteomic analysis of whole unstimulated saliva revealed that the molecules of alarmin family S100A8 (calgranulin A) and S100A9 (calgranulin B) were significantly higher in SS-MALT subgroup, in comparison to SS and HC, supporting a potentially discriminatory role for malignant transformation [96].

Genetic Markers

The presence of aggressive disease phenotypes with a high predilection to lymphoma development early in the disease course implies that inherent factors such as a distinct genetic background are a key contributor in SS-related lymphoma development. Since molecular pathways leading to chronic inflammation, B cell activation, defective immunosurveillance or DNA methylation are involved in lymphomagenesis in general [97], variations in genes involved in these pathways attracted particular attention over the last years (Table 1).

Among the first genes studied was *tumor necrosis factor-alpha-induced protein 3* (*TNFAIP3*) with potential implication in both autoimmune [88, 98, 99] and neoplastic disorders [100]. Several variants of this gene have been shown to result in impaired function of the encoded A20 protein [101], a negative feedback regulator of NF-kB pathway [102], leading to uncontrolled inflammatory states. In SS, the rs2230926G minor allele of the *TNFAIP3* gene had a prevalence ranging from 12.05% in French, 7.14% in the UK, to 8.8% in the Greek population increasing lymphoma susceptibility in the setting of SS by 2.23, 3.12, and 2.6, respectively [103, 104]. Of interest, the corresponding prevalence in SS lymphoma patients of Greek origin with SS-onset ≤ 40 years was 18.2% [105], supporting a greater impact of genetic influences in the early onset disease groups.

Similarly, the wild-type variant of the *LILRA3* gene was also found to be highly prevalent (100%) in the younger onset SS group of Greek origin complicated by lymphoma compared to 81.8% in SS non-lymphoma and 83.2% in HC, respectively [90]. Previous studies reported that a deleted variation of *LILRA3* was identified as a risk factor for both lymphomagenesis [91] and SS development [106] in Caucasians, while the functional *LILRA3* variant (non-deleted/ wild type) was shown to increase susceptibility for RA [107], systemic lupus erythematosus (SLE), and SS [108] in Chinese population. Given that functional *LILRA3* gene has been linked to increased LILRA3 protein serum levels and inflammatory states among RA patients [107, 109], we postulate that involvement in inflammatory pathways lie behind the association of *LILRA3* and related lymphoma in the young onset SS patients.

Recently, the rs3099844 variant of the major histocompatibility complex P5 (*HCP5*) gene has been found to increase lymphoma susceptibility

among Italian SS patients by 7.2-fold [110]. This gene encodes an endogenous retroelement, primarily expressed in thymus, spleen, and lymphoid lineage cells, acting as an inflammatory regulator [111]. *HCP5* variants have been previously linked to both psoriasis/psoriatic arthritis and SLE in association with anti-Ro antibodies [112, 113]. In SS patients, a significantly higher frequency of the rs3099844 *HCP5* variant was detected compared to HC, especially in patient subgroups characterized by the presence of autoantibodies, hypergammaglobulinemia leucopenia, and increased focus scores [110].

In view of the cardinal role of B cell activation in SS-related lymphomagenesis as mentioned earlier, genetic variants of both the *BAFF* gene and the receptor of BAFF on B cells have been shown to increase lymphoma risk among SS patients. Previous studies linked the *BAFF* gene polymorphisms – rs9514828/rs12583006 – with enhanced neoplastic risk [114–116], and with autoimmune susceptibility related to rs9514828 variant [117, 118]. In the context of SS, increased frequency of the minor T allele of the rs9514828 variant was detected in the high-risk group; in contrast, the minor A allele of the rs12583006 was prevalent in the low-risk group [119]. In haplotype terms, the high-risk SS group displayed lower frequencies of the TACAC and TACC haplotypes and higher frequency of the TTTC haplotype in comparison to the low-risk SS, but not the HC group. In a subsequent report, increased frequency of the His159Tyr mutation of the BAFF receptor (BAFF-R) has been shown in SS patients complicated by MALT lymphoma compared to both non-lymphoma and HC groups [120], with a frequency in the SS MALT group with age of disease onset between 31 and 40 years reaching 70%. The presence of this mutation was found to be associated with upregulation of the alternative NF-kB pathway in B cells derived from SS-lymphoma patients, implying enhanced B cell signaling as potential contributor to SS-related lymphomagenesis [120].

Recently, Nezos et al. revealed a lower prevalence of the rs11797 A minor allele of the *Three-prime repair exonuclease 1 (TREX-1)* gene in SS patients with lymphoma of non-MALT type compared to HC [121]. TREX-1 is an exonuclease involved in both endogenous nucleic acid clearance [122, 123] and prevention of genomic instability [124, 125]. The potentially protective role of the rs11797 A minor allele could be attributed to suppressed type I IFN production and defective immunosurveillance properties, as already suggested [61]; SS patients carrying the rs11797 AA genotype were shown to display increased mRNA expression of type I IFN-related genes in MSG tissues. Of note, *TREX-1* gene variants have been previously associated with Aicardi-Goutieres syndrome [126, 127], SLE [128, 129], systemic sclerosis [130], and disorders characterized by activation of type I IFN pathway, while new studies link TREX-1 function with regulation of antitumor immunity [131].

As mentioned above, epigenetic mechanisms, involving mainly methylation pathways, have been proposed as major contributors for lymphoma evolution. Recently, in the SS context, an increased frequency of *methylene-tetrahydrofolate reductase (MTHFR)* c. 677C > T (rs1801133) related to impaired DNA methylation and a reduced frequency of *MTHFR* c. 1298A > C (rs1801131) – leading to increased DNA double-strand breaks levels – were observed in SS non-MALT compared to non-lymphoma SS patients and HC [132], implying that defective suppression of oncogenes [133] and increased genomic instability are potential tumorigenic mechanisms in these patients.

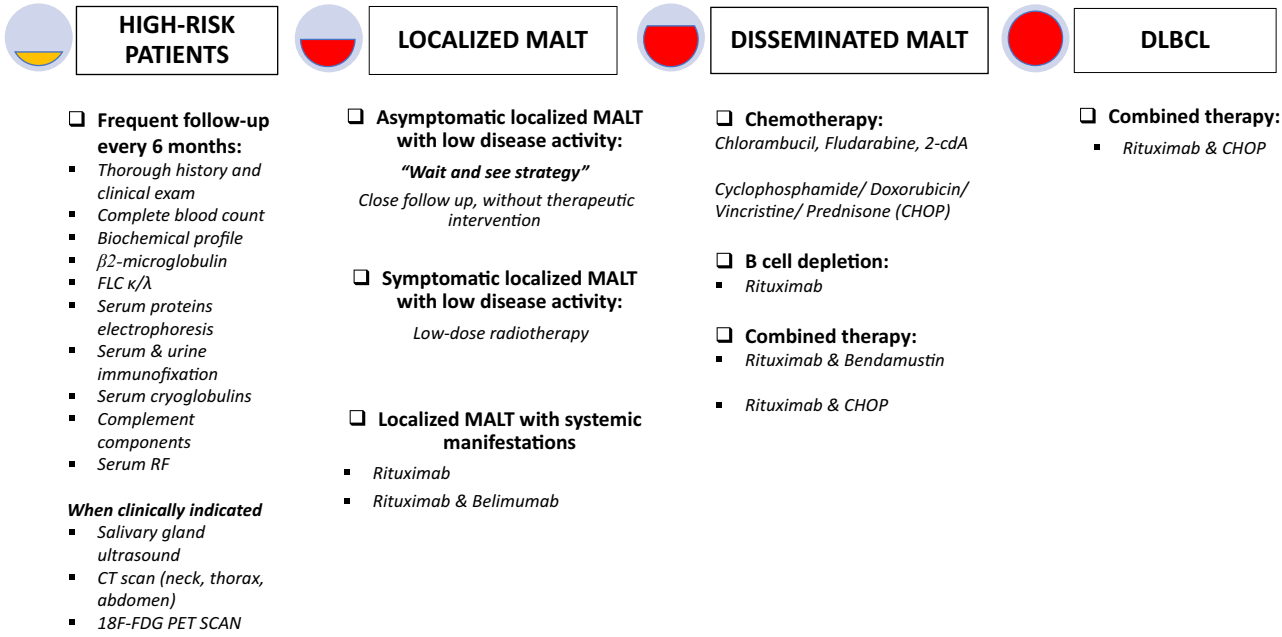

Fig. 2. An overview of diagnostic and therapeutic approach for high-risk and lymphoma SS patients. Free light chains κ/λ: FLCκ/λ; Diffuse large B cell lymphoma: DLBCL; Cyclophosphamide/ Doxorubicin/ Vincristine/ Prednisone: CHOP; cladribine: 2-cdA.

Pharmacological Management of lymphoma

Despite the identification of several molecular contributors in SS-lymphomagenesis and distinct clinical phenotypes, treatment options and predictors of clinical responsiveness remain limited. In a multicenter international study including 242 patients with MALT lymphoma of the salivary glands, initial treatment included local therapy either with surgery, radiation, or both in about 60% of patients, while the rest were treated with systemic therapy, including 54% with localized and 46% with stage IV-disseminated disease. While the therapeutic approaches applied were diverse, in the majority of cases, an alkylating agent either as monotherapy or in combination with rituximab were most commonly implemented.

According to the recent EULAR, Sjögren's task force recommendations, after lymphoma diagnosis, a personalized therapeutic approach should be followed considering the histological lymphoma subtype and stage as well as SS activity [134]. Since the presence of SS has been found to be independently associated with better overall survival together with the observation that patients with stage I or stage II disease were not benefited by local or systemic therapy [135], a "wait and see" approach is preferable for SS patients with localized MALT lymphoma confined in salivary glands and low disease activity [37, 136]. However, for SS patients with symptomatic, disabling parotid swelling, low-dose involved-field radiotherapy could be a sufficient treatment [136]. For SS localized-MALT patients with extraglandular manifestations, administration of

rituximab (anti-CD20 monoclonal antibody) could be an option [37]. Given the key role of BAFF in B cell clonal expansion and lymphoma development [79], it was suggested that targeting simultaneously BAFF and CD20 through belimumab/rituximab co-administration could represent another prominent therapeutic approach for SS-related MALT treatment with systemic manifestations [137]. For patients with disseminated MALT (characterized by multiple rather than regional lymph node involvement, splenomegaly and/or bone marrow infiltration, and multiple extranodal site involvement), a personalized treatment (depending from individual clinical characteristics and disease stage) should be considered, applying B cell depletion strategy in association or not with chemotherapy [37, 136]. The latter include alkylating agents such as cyclophosphamide, doxorubicin, vincristine plus prednisone (R-CHOP) [37], chlorambucil [138], the purine analogue cladribine (2-cdA) [139], or the antimetabolite fludarabine [140, 141]. Recently, given the beneficial effects of rituximab co-administration with the alkylating agent bendamustine (R-Benda) in previously untreated mantle-cell lymphoma [142] and MALT [143], the safety and efficacy of R-Benda was tested by a retrospective study including 13 SS-MALT patients mostly with disseminated disease resulting in complete regression of lymphoma and improvement in ESSDAI score [144]. Finally, for SS patients complicated by DLBC lymphoma, association of rituximab with polychemotherapy such as CHOP is preferred than rituximab monotherapy showing significant survival benefit [37, 145] (Fig. 2).

The availability of prognostic markers for pharmacotherapy response is also restricted, highlighting the need for the identification of predictors of therapeutic response. Higher baseline serum levels and salivary gland overexpression of BAFF have been associated with shorter duration of B cell depletion [146], poor treatment response [147], and persistence of focal lymphocytic sialadenitis [148] in rituximab-treated SS patients. In addition, SS-lymphoma patients with higher ESSDAI score were shown to be poor responders to pharmacological therapy compared to those with lower disease activity [7, 136]. Heightened blood and salivary NK cell numbers and elevated type I IFN activity at baseline have been shown to predict response to belimumab with the first being associated with worse outcomes [149], while the second with decreased IgG, IgM, and RF serum levels [150, 151].

Practical Advices for SS Patients in High-Risk for Lymphoma Development

The identification of several clinical and molecular risk factors for the SS-related lymphomagenesis allowed the stratification of patients in low- and high-risk subsets. Nevertheless, the accurate prediction of lymphoma onset remains challenging. According to expert opinion, SS patients recognized as high-risk group for lymphoma development are recommended to be followed-up every 6 months, monitoring the complete blood count, biochemical profile, β2-microglobulin [88] and FLC k/λ serum levels [85], serum protein electrophoresis, serum and urine immunofixation, serum cryoglobulins, complement components, and RF levels [152]. Given that disease activity has been shown to be strongly related to lymphoma development [18] and overall survival [7], thorough assessment of systemic organ involvement is mandatory. Salivary gland

ultrasound with Doppler [153], and potentially a follow up salivary gland biopsy [154] should be also considered, given their valuable role in predicting [153] and detecting in situ lymphoma development [154], respectively. 18F-FDG positron emission tomography seems to have a potential role in detecting SS-related lymphoma, particularly an SUVmax in the parotid glands of ≥ 4.7 and/or the presence of focal pulmonary lesions. However, no differences in the number of sites, uptake pattern, or mean SUVmax. in lymph nodes were detected between SS patients with or without lymphoma [155] (Fig. 2).

Conclusions

Predicting with accuracy lymphoma development at the time of SS diagnosis has been a major challenge over the last decades. Significant research efforts led to identification of several clinical, hematological, serological, and histopathological risk features for lymphoproliferation. Moreover, documentation of novel genetic and epigenetic associations through international collaborative efforts will enhance our ability for a better understanding of underlying molecular pathways and ultimately for the discovery of tailored therapies for these patients.

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Compliance with Ethics Guidelines

Conflict of Interest
The other authors declare that they have no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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