Pathogenetic Aspects of Sjögren's Syndrome: Relationships with Cryoglobulinemia and Lymphoproliferation of MALT

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27.1 Introduction

Sjögren's syndrome (SS) is defined both as an autoimmune and a lymphoproliferative disease [1, 2]: in fact, B cells are overexpanded since the onset of the disease. SS is a disorder of mucosa-associated lymphoid tissue (MALT). Autoimmune epithelitis is also a crucial event [3].

The risk of B-cell lymphoma evolution is markedly increased in SS [4] (about 5 % of patients), and B-cell overexpansion represents a predisposing factor for non-Hodgkin's lymphoma (NHL), usually involving MALT tissue. Of note, patients may progress from a fully benign lymphoproliferation to an overt B-cell NHL through intermediate stages [5].

This wide spectrum of manifestations offers the opportunity to analyze in detail the etiopathogenetic events involved in the process of B-cell lymphomagenesis, by using SS as a model.

Cryoglobulinemia, with or without a concomitant cryoglobulinemic vasculitis (CV), and the persistent swelling of the major salivary glands (usually the parotids) represent the two main risk factors for B-cell NHL evolution in SS.

Understanding the mechanisms involved in the transition from B-cell overexpansion to lymphoproliferation might lead to the development of more effective and targeted treatments still currently lacking in SS.

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27.2 The Classification of SS-Related Lymphoproliferation of MALT

The diagnosis of B-cell malignancy is based on tissue biopsy, and the B-cell malignancy in SS is classified according to the current standards [6]. The integration of clinical, pathologic, and molecular results is crucial in difficult cases. The proposed classification, discussed at international levels [7], distinguishes between fully benign lymphoproliferation (a feature of SS) and nonmalignant lymphoproliferative disorder (a more advanced stage toward B-cell malignancy). These processes may involve different MALT sites, the lymph nodes, and more rarely the bone marrow, and may be associated with hypergammaglobulinemia, positive M-component, and/or cryoglobulinemia (polyclonal, oligoclonal, or monoclonal).

Fully benign lymphoproliferation is usually represented either by infiltrates without histological sign of malignancy in MALT sites or reactive lymphadenopathy in the absence of serum M-component [7].

In lymphoepithelial or myoepithelial sialadenitis (MESA) with benign lymphoid infiltrates, the lobular architecture of the gland is preserved. Lymphoepithelial lesions are characterized by monocytoid and marginal zone B cells (centrocyte-like). Reactive follicles without expansion of the mantle or marginal zones are also present, and small lymphocytes and plasma cells (usually not in broad sheets) are prominent in the interfollicular regions.

Several MALT sites may be involved, including gastric MALT lesions up to a grade 2 [8, 9].

The nonmalignant lymphoproliferative disorder includes the cases of "lymphoproliferative lesion" in MALT sites, nodal atypical lymphoproliferative disorder [10], and monoclonal cryoglobulinemia or M-component in biologic fluids [7].

In MESA with "lymphoproliferative lesions," the process is diffuse or multifocal within the gland. Islands of acini are often preserved, while aggregates of centrocyte-like cells may be present within a diffuse lymphoid infiltrate. Nonconfluent centrocyte-like cell "halos" surrounding the lymphoepithelial lesions are often observed. Lymphoepithelial aggressiveness may be pronounced. Areas of immunoglobulin light-chain restriction may be also present.

Conversely, in **low-grade MALT-type marginal zone B-cell lymphomas**, a dense lymphoid infiltrate diffusely involving the gland is usually observed. It can occur as a localized mass, with obliteration of acini. Lymphoid cells and plasma cells present monotypic immunoglobulin expression. Plasmacytic differentiation may occur. A large cell component may be detected. Reactive lymphoid follicles and lymphoepithelial lesions are usually prominent as observed in MESA. However, in contrast with MESA, centrocyte-like cells form broad interconnecting strands between lymphoepithelial lesions (key feature) and broad "halos" around the epithelial cell nests.

Gastric MALT lesions of grades 3 and 4 according to Wotherspoon and Isaacson [8] and lymphoproliferative lesions not presenting definite malignant features are considered SS-related nonmalignant lymphoproliferative disorders [9].

An accurate pathologic evaluation is critical in distinguishing between nonmalignant and low-grade malignant lymphoproliferation of MALT. B-cell monoclonality alone is not a criterion to establish B-cell malignancy [7]. Different patterns of tissue B-cell expansion can be identified by molecular analyses in SS-related MALT lesions by studying synchronous and metachronous tissue lesions, implying a different risk of lymphoma progression: polyclonal, oligoclonal or monoclonal expansion without clonal persistence, monoclonal expansion with clonal persistence, and monoclonal expansion with dissemination. Then, molecular analyses of B-cell clonal expansion proved to be of major value for prognosis, rather than for diagnosis [7].

27.3 The Pathogenesis of SS-Related Lymphomas of MALT: Lessons from Infection-Related Lymphomas

Gastric B-cell NHL of MALT, associated with *H. pylori* infection, is the most important model of infection-related acquisition of lymphoid tissue and B lymphomagenesis [8]. Other infection-related B-cell NHLs include those related to hepatitis C virus (HCV), *Chlamydia psittaci* (ocular adnexa), *Borrelia burgdorferi* (skin), and *Campylobacter jejuni* (small intestine) [11]. These associations support the role of an infectious trigger in boosting the expansion of a B-cell clone. However, subsequent stochastic oncogenetic events are necessary to make the clone proliferation in part or fully independent from the initial infectious trigger. Thus, the observation that infection-related NHLs may often respond to the eradication of the infectious trigger, though the expanded B-cell clone persists in tissues (as detected by molecular studies), is not surprising. In addition, the malignant B-cell clone is not directed toward the infectious agent, supporting the concept that autoreactivity is implicated in infection-related B-cell lymphomagenesis [11].

Overall, one can speculate that mechanisms occurring in MALT lesions of SS share some similar pathogenic events in infection-related lymphomagenesis.

27.4 Rheumatoid Factor Specificity of SS-Related Lymphomas

SS-related lymphomas and also a fraction of B-cell lymphomas related to infection (see above) appear to derive from B cells involving immunoglobulin genes associated with autoantibody production [12, 13].

The expansion of anti-SSA/SSB and rheumatoid factor (RF)-positive clones in SS salivary glands is frequently observed also in the absence of a frank lymphoproliferation. In MESA and in B-cell lymphomas in SS, the expanded clones often show a biased VH and Vk gene usage (e.g., VH1-69, VH3-7, VH4-59, Kv325, and Kv328), particularly VDJ combinations (e.g., VH1-69/DP10-D-JH4, VH3/DP54-DH21/9-JH3, VH4/DP71-D2-JH2), and similarity with RF database sequences [13–19].

Interestingly, these sequences are similar to those detected in HCV-related lymphomas [20]. Martin and coworkers documented the B-cell NHLs in SS produced RFs [17]. Overall, malignant B-cell lymphoproliferation in SS does not appear to involve the B-cell clones producing anti-SSA/SSB antibodies, but, rather, the RF autoantibodies.

27.5 B-Cell Expansion in MALT Sites in SS

The development of ectopic lymphoid structures (ELSs) in labial salivary gland biopsies of patients with SS has been well described [21–24]. The definition of ELS is based on the presence of periductal lymphomonocytic cell clusters characterized by T and B lymphocytes and the differentiation of CD21+ follicular dendritic cell (FDC) networks. The hypothesis that the lymphoneogenetic process is controlled by reactivation of pathways physiologically involved in secondary lymphoid organ development is supported by the observation of increased levels of lymphoid chemokines CXCL13 and CCL21 in salivary glands (SGs) of patients with SS with lymphoid features.

The identification of lymphoid chemokines in the SG of SS suggests that alternative cell types may express lymphoid chemokines during chronic inflammation. Importantly, both resident, nonlymphoid cells and infiltrating immune cells have been shown to produce lymphoid chemokines in the target organ. Ductal epithelial cells, together with infiltrating mononuclear cells, were the main source of lymphoid chemokines, supporting the notion that the periductal organization of the lymphoid aggregates in SS might be dependent on chemokine gradients displayed by epithelial cells [25–27]. Thus, growing levels of evidence support that subsets of stromal cells and infiltrating immune cells are critical in the development of ELS in the SG of SS.

Lymphomas are the main cause of increased mortality in SS. Evidences that MALT-NHL development is the result of an antigen-driven immune response comes from the observation that in gastric MALT-NHL malignant marginal zone B-cell proliferation is dependent on *H. pylori*-specific T cells [28, 29], and eradication of *H. pylori* may result in tumor regression [30]. Similarly, in SS, the evidence that a common clonal lineage exists between the polyclonal and later monoclonal B-cell population with progression from lymphoepithelial lesions toward SG and extraglandular MALT-NHLs [14, 15, 31] strongly suggests that SS-MALT-NHL is a multistep antigen-driven process. SS-related MESA and MALT-NHLs of the parotids often display IgVH-CDR3 with RF homology [13, 17, 32], suggesting a cross talk between autoimmunity and lymphomagenesis, potentially supported by a chronic antigenic stimulation.

A study analyzing labial SG biopsies obtained at the time of diagnosis of SS patients who later developed parotid MALT-NHL showed that ELSs were present in over 75 % of these patients several years before malignant transformation [33]. These data were confirmed in a large cohort of SS patients, where the presence of ELS in labial SG at diagnosis conferred a 15-fold increased risk of B-cell lymphoma compared to SS patients with a positive biopsy but without features of ELS [34].

Thus, severe lymphoproliferation of salivary MALT is associated with a higher risk of NHL in SS. This might be detectable in labial salivary gland biopsies at the time of diagnosis by routine light microscopy of H&E sections. The assessment of lymphoid features of labial salivary glands should be routinely performed in SS.

The early identification of lymphoproliferation features would also allow the recognition of a subset of SS patients with a more severe disease phenotype, which would potentially benefit from a more intensive follow-up and treatment [35, 36].

27.6 Cryoglobulinemia Developing: Lessons from HCV-Related Cryoglobulinemia

In HCV-related cryoglobulinemic vasculitis, HCV infection triggers the expansion of RF-positive clones. Why this preferentially occurs in the course of HCV infection, when compared to other chronic infections, is still controversial. A study demonstrated that RFs in HCV-related cryoglobulins also recognize the HCV epitope NS3 and reported that NS3 HCV peptide can induce the production of an anti-HCV antibody with RF capacity [37]. These observations support a possible mechanism for infections in triggering autoimmunity, i.e., a double antibody reactivity or a mechanism of molecular mimicry.

Cryoglobulinemia detection is a red flag for lymphoma. Indeed, nearly a half of SS patients with lymphoma present with circulating cryoglobulins, also in the absence of HCV infection. The identification of other triggers in SS deserves additional study.

27.7 The Clinical Picture of Cryoglobulinemic Vasculitis in SS

New classification criteria for cryoglobulinemic vasculitis (CV) have been recently published [38] and validated [39] (Table 27.1). The presence of serum mixed cryoglobulinemia, i.e., serum positivity of cryoglobulins, occurs in about 10–15 % patients with SS [38], while a frank clinical CV is less frequent, though it greatly affects the SS-related morbidity [40].

The biologic and, to some extent, the clinical characteristics of HCV-unrelated CV may be different from HCV-related CV. A sub-analysis of the sensitivity and the specificity of the CV classification criteria was performed in 55 SS patients carrying serum cryoglobulins with or without the clinical picture of CV (CwV) [41]. This sub-analysis demonstrated that sensitivity and specificity of the classification criteria for the CV in SS patients were high: 88.9 % and 91.3 %, respectively [41]. No statistical differences between SS-CV and SS-CwV patients were observed as regard to clinical features of lymphoproliferation, including lymphadenopathy, splenomegaly, salivary gland swelling, lacrimal gland swelling, and B symptoms, while the prevalence of a lymphoproliferative disorder per se was more frequent in CV than in CwV (nonmalignant lymphoproliferative disorder in 13/29 in CV vs.

Table 27.1 Classification criteria for cryoglobulinemic vasculitis

(i) *Questionnaire item*: at least 2 out of the following:	
Do you remember one or more episodes of small red spots on your skin, particularly involving the lower limbs?	
Have you ever had red spots on your lower extremities, which leave a brownish color after their disappearance?	
Has a doctor ever told you that you have viral hepatitis?	
(ii) *Clinical item*: at least 3 out of the following 4 (present or past):	
Constitutional symptoms	Fatigue
	Low-grade fever (37–37.9 °C, >10 days, no other cause)
	Fever (>38 °C, no other cause)
	Fibromyalgia
Articular involvement	Arthralgias
	Arthritis
Vascular involvement	Purpura
	Skin ulcers
	Necrotizing vasculitis
	Hyperviscosity syndrome
	Raynaud's phenomenon
Neurologic involvement	Peripheral neuropathy
	Cranial nerve involvement
	Vasculitic CNS involvement
(iii) *Laboratory item*: at least 2 out of the following 3 (present)[a]:	
Low serum C4	
Presence of serum rheumatoid factor	
Presence of serum monoclonal component	

Satisfied if at least two out of three items (questionnaire, clinical, laboratory) are positive. The patient must be positive for serum cryoglobulins in at least two determinations at ≥12-week interval

CNS central nervous system

[a]The fulfillment of the laboratory item in a patient satisfying the criteria highlights the possible presence of cryoglobulinemic vasculitis even in the absence of serum cryoglobulins by initial testing

4/26 in CwV, malignant lymphoma in 10/29 CV vs. 3/26 CwV). Furthermore, as compared to SS-CwV, SS-CV was more frequently characterized by the presence of type II cryoglobulinemia and NHL [42].

Skin vasculitis in the course of SS was deeply investigated by a recent Italian collaborative network of rheumatologic centers [43]. A total of 652 SS patients were examined, and cryoglobulinemic purpura was well differentiated from hypergammaglobulinemic purpura. Peripheral neuropathy, low C4, leukopenia, serum monoclonal component, and the presence of anti-SSB/La antibodies characterized CV, whereas RF, leukopenia, serum monoclonal component, and anti-SSA/Ro antibodies were significantly associated with hypergammaglobulinemic purpura. A lymphoma was associated only with CV. While hypergammaglobulinemic purpura in SS seems to be related to a benign B-cell proliferation, CV seems to be a systemic

immune complex-mediated vasculitis with complement activation and a high risk of lymphoma. CV, but not hypergammaglobulinemic purpura, can be envisaged in SS as a prelymphomatous condition [43].

27.8 Relationship between SS-Associated Cryoglobulinemia and MALT Lymphoproliferation

B-cell NHL is a well-described complication in a subset of patients with CV secondary to HCV infection [44]. However, CV may also occur in HCV-negative patients, including subjects with SS. Of note, HCV-related CV and SS-associated HCV-unrelated CV are both associated with mixed cryoglobulinemia and predispose to B-cell NHL.

While lymphomas complicating the course of HCV-related CV usually involve the bone marrow [44, 45], B-cell NHL complicating the course of SS usually involves the MALT sites [1, 7, 31, 46].

Cryoglobulinemia appears to be linked to MALT lymphoproliferation in SS and shows a different biologic background when compared to HCV-associated cryoglobulinemia.

Recently, our group further elucidated this aspect [47]. First, molecular analyses of bone marrow B-cell clonal expansion were performed in consecutive SS cases with mixed HCV-unrelated cryoglobulinemia and compared with classical HCV-associated CV patients without SS. A polyclonal pattern was more frequently observed in SS patients with type II or type III mixed cryoglobulinemia, while a B-cell oligo-/monoclonal expansion was more frequently detected in HCV-related CV. Furthermore, the bone marrow was rarely involved in SS-related lymphomas supporting the crucial role of chronic inflammation and lymphoproliferation of salivary MALT in predisposing to lymphoma [34, 47]. Lastly, in the patient with SS, CV, and parotid B-cell NHL of MALT, bilateral parotidectomy results in a decrease in serum RF and cryoglobulins, implying a critical role of salivary MALT for the production of cryoglobulins [47].

27.9 Upregulation of B-Lymphocyte Stimulator and Lymphoproliferation

The B-lymphocyte stimulator (BLyS), also called B-cell activating factor (BAFF), was identified in 1999. Transgenic mice overexpressing BLyS developed critical lymphoid proliferation in blood and in the marginal zones of lymph nodes and high titers of immunoglobulins and autoantibodies, such as RF, anti-DNA antibodies, and sometimes cryoglobulins. As these mice aged, they also developed a lupus-like glomerulonephritis or a Sjögren's-like syndrome (with salivary gland inflammatory infiltration) and eventually a B-cell lymphoma [48–50].

Consonant with these observations, high levels of BLyS in the serum and/or in the affected tissue have been detected in SS and in CV [51–53]. Furthermore, a

strong BLyS upregulation has been in SS associated with lymphoproliferation, either nonmalignant or malignant [54]. In addition, anti-BLyS therapy with belimumab proved to be effective in a preliminary open study in 30 patients with primary SS, all anti-SSA or anti-SSB positive [55, 56]. These observations strongly support pathogenetic implication of BLyS in SS.

Of note, anti-CD20 therapy with rituximab may not deplete the B-cell infiltrate in the SS salivary tissue [57]. Indeed, the local expression of BLyS in the MALT tissue is crucial for tissue resistance to B-cell depletion as shown in a murine model [58].

Rituximab or belimumab alone is ineffective in inducing a regression of low-grade parotid lymphoma of MALT. However, we recently reported that only a sequential use of rituximab preceded by belimumab resulted in a regression of low-grade parotid lymphoma of MALT [59]. One can speculate that, being effective on MALT, the sequential or combined use of anti-BlyS and anti-CD20 therapy might be effective not only in severe SS but also on sicca manifestations in this disease [59].

Conclusions

In SS, the local MALT microenvironment sustains the local expansion of B cells. A first pathogenic trigger, such as an infection, may lead to local inflammation, which in turn stirs up an autoimmune process.

The chronic stimulation of RF-positive B cells in the MALT microenvironment causes their preferential expansion in SS, leading to an increased risk for B-cell lymphoma. Lymphoma transformation may occur when stochastic oncogenetic events occur. The RF produced by the B-cell clones, either nonneoplastic or neoplastic, may behave as a cryoglobulin and possibly lead to a concomitant vasculitis.

SS can be then considered both an autoimmune and a lymphoproliferative disorder.

Future studies focusing on SS-related B-cell lymphoproliferation may contribute to identify the key pathogenetic events and to develop new therapeutic strategies in SS.

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