Review

Hematologic manifestations of primary Sjögren's syndrome

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ABSTRACT

Sjögren's syndrome (SS) is a chronic autoimmune disorder, primarily characterized by the mononuclear cell infiltration of exocrine glands exiting in parenchymal damage and secretory impairment. The spectrum of the disease extends from an autoimmune exocrinopathy to a systemic process with extraglandular manifestations. SS is defined as primary (pSS) when isolated, or secondary when associated with another autoimmune disease. Patients with pSS may present hematologic abnormalities, such as anemia, hemocytopenias, monoclonal gammopathies and lymphoprolipherative disorders, predominantly non-Hodgkin's lymphoma of B-cell origin. The increased prevalence of B-cell malignancies suggests that SS may be a boundary disease between autoimmunity and lymphoproliferation. In this paper, the hematologic manifestations of pSS are reviewed.

Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disorder, characterized by infiltration of the salivary and lacrimal glands by mononuclear cells (MNC) and damage of the parenchymal tissue, resulting in oral and ocular dryness (1). Other glandular as well as extraglandular manifestations (EGMs) may also be present. SS is defined as primary (pSS) when isolated, or secondary when associated with another autoimmune disease, most commonly rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) (1). The pathogenesis of glandular damage in SS is still poorly understood, however, the predominance among the infiltrating MNC of activated $CD4^+$ T cells (2) suggests that cell-mediated immunity plays an important role in the tissue injury. In addition to activated $CD4^+$ T cells, acinar and ductal cells may be involved in the salivary gland damage through the production of some matrix metalloproteinases responsible for the degradation of basal lamina components with subsequent detachment and degeneration of exocrine epithelial cells (3). Finally, autonomic dysfunction mainly involving the parasympathetic nervous system that controls exocrine secretion may contribute to glandular impairment reducing the saliva and tear production (4).

Patients with pSS may develop hematologic abnormalities, such as anemia, hemocytopenias, and monoclonal gammopathies. In addition, they have a high risk of developing malignant lymphoproliferative disorders, mainly non-Hodgkin's lymphoma (NHL) of B-cell origin.

In this paper, we aimed to review the hematologic manifestations of pSS.

Anemia

In a large series of patients with pSS, Ramos-Casals *et al*. (5) found anemia [defined as hemoglobin (Hb) < 11 g/L in both sexes) in 66 of 380 (20%) patients, severe in only 15 cases (4%) (Hb < 9 g/L). Seventy-one (93%) patients showed normochromic normocytic anemia, 3 (4%) microcytic anemia, and the remaining 2 (3%) macrocytic anemia (5). In 21 patients the origin of the anemia was clearly identified, whereas in the remaining 45 patients no cause other than pSS was found. Coombs' test was not performed in all patients with anemia, however no evidence of biologic hemolysis was detected. Compared with SS patients with normal hemoglobin values, those with anemia presented a significantly higher frequency of renal involvement, cutaneous vasculitis, peripheral neuropathy, antinuclear antibodies (ANA), anti-Ro/SS-A and anti-La/SS-B antibodies, rheumatoid factor (RF), cryoglobulinemia and hypocomplementemia in the univariate analysis, whereas only peripheral neuropathy and ANA were significant independent variables in the multivariate analysis.

The observed prevalence of anemia in this pSS series is comparable to that (21%) detected in previous ones totalling 805 patients (5). The most common type of anemia in pSS is normochromic normocytic, usually mild (6, 7). The pathogenesis of this type of anemia is poorly defined, since the above-mentioned study as well as previous ones did not specifically address this topic, but it is likely immune-mediated ("anemia of chronic disease"). A hallmark of the anemia of chronic disease is an alteration of iron homeostasis with increased uptake and retention of iron within cells of the reticuloendothelial system, with subsequent reduced availability of iron for erythroid progenitor cells, and iron-restricted erythropoiesis (8). Increased serum levels of some cytokines, such as interleukin (IL)-6 and IL-10 (9) that play a role in the pathogenesis of the anemia of chronic disease (8), as well as a higher number of circulating cells secreting IL-6 and IL-10 (10), have been found in pSS patients compared to healthy controls. IL-6 stimulates the hepatic expression of the acute-phase protein hepcidin, which inhibits duodenal absorption of iron, induces ferritin expression, and stimulates the storage and retention of iron within macrophages. IL-10 up-regulates transferrin receptor expression, increases transferrin-receptor-mediated uptake of transferrin-bound iron into monocytes, induces ferritin expression, and stimulates the storage and retention of iron within macrophages. These mechanisms lead to a decreased iron concentration in the circulation and thus to a limited availability of iron for erythroid cells (8). Finally, other types of anemia such as hemolytic (7, 11-14), aplastic (7, 15-17), pernicious anemia (18,19), myelodisplastic syndrome type refractory anemia with ring sideroblasts (7), and pure red cell aplasia (7,20) are rarely reported in pSS patients.

Leukopenia

Leukopenia (leukocyte count < 4 x 10^9/L) was found by Ramos-Casals *et al*. (5) in 59 of 380 (16%) patients with pSS, severe (< 2 x 10^9/L) in only 1 (0.2%). The prevalence of leukopenia in this series is similar to that (17%) reported in previous cohorts totalling 877 patients (5). Compared with those without, pSS patients with leukopenia presented a higher prevalence of peripheral neuropathy, anti-Ro/SS-A and anti-La/SS-B antibodies, RF, cryoglobulinemia, and hypocomplementemia in the univariate analysis, although only anti-Ro/SS-A antibodies and RF were significant independent variables in the multivariate analysis. The leukocyte differential count was carried out in 268 patients, and lymphopenia (< 1 x 10^9/L) was found in 23 (9%) patients, neutropenia (< 1.5 x 10^9/L) in 19 (7%), eosinophilia (> 5%) in 31 (12%), monocytosis (> 10%) in 8 (3%), and lymphocytosis (> 55%) in 2 (1%). Patients with lymphopenia showed a higher prevalence of renal involvement and anti-La/SS-B antibodies in the univariate analysis, both being significant independent variables in the multivariate analysis. Patients with eosinophilia presented a lower prevalence of cutaneous vasculitis and positive salivary gland biopsy in the univariate analysis, although only positive salivary biopsy was a significant independent variable in the multivariate analysis (5).

$CD4^+$ T-lymphocytopenia

$CD4^+$ T-lymphocytopenia, mainly due the decrease of the $CD4^+CD45RA^+$ subpopulation, is not a rare finding in pSS, being reported in about 5% of patients (21-26). It has been suggested that apoptosis may play a role in the pathogenesis of this pSS EGM (22, 24), while the role of anti-CD4 antibodies is unclear. Henriksson *et al.* (25) demonstrated the presence of anti-CD4 antibodies more frequently in pSS patients (12.6%) than in controls (0.6%). However, no correlation between the presence of anti-CD4 antibodies and $CD4^+$ T lymphocytopenia was found. In a study of 80 patients with pSS (37 anti-Ro/SS-A positive and 39 anti-Ro/SS-A negative) and 37 with sicca syndrome, absolute $CD4^+$ T-lymphocyte count was significantly lower in anti-Ro/SS-A positive than in anti-Ro/SS-A negative pSS and sicca syndrome patients (26). $CD4^+$ T-lymphocytopenia was observed in 6 of 80 (7.5%) pSS patients, and all of them were anti-Ro/SS-A positive. Therefore, $CD4^+$ T-lymphocytopenia was found in 16% (6/37) of anti-Ro/SS-A positive pSS patients, but in none of the anti-Ro/SS-A negative or sicca syndrome patients (26). Idiopathic $CD4^+$ T-lymphocytopenia (ICL) is a rare syndrome characterized by a $CD4^+$ count less than 300 cells/mm^3 in the absence of human immunodeficiency virus infection (27). Since ICL was recognized as a risk factor for NHL development (28-31) and only in pSS patients seropositive for anti-Ro/SS-A antibodies $CD4^+$ T-lymphocytopenia was found, such a subset of pSS patients may be at risk for developing NHL (26). Recently, in a report concerning a cohort of 286 patients fulfilling the American-European Consensus Criteria (AECC) for SS (32), $CD4^+$ T-lymphocytopenia was a strong risk factor for developing NHL; however, no data on the serological characteristics of the patients with lymphoma were reported (33).

Agranulocytosis

Agranulocytosis (absolute neutrophil count < 500 cells/μL) is a rare manifestation of pSS. Friedman *et al*. (34) described 2 patients with agranulocytosis and identified other 11 cases previously reported in the literature. In most cases neutropenia was a pSS presenting feature, and only in 3 patients the diagnosis of pSS preceded neutropenia (34). Coppo *et al*. (35) described 7 patients with pSS and chronic neutropenia (> 6 months) who showed non-destructive peripheral arthritis, involving small or both small and large joints. In 3 patients the pSS diagnosis preceded neutropenia from 2 to 15 years, in 1 patient neutropenia was diagnosed 9 years before pSS, and in the 3 patients neutropenia and pSS were diagnosed simultaneously. In 4 patients, neutropenia was isolated, in 2 associated with immune thrombocytopenia, and in 1 coexisted with Evan's syndrome (combination of hemolytic anemia and immune thrombocytopenia). After a mean follow-up of 34.8 months, no patient had serious infectious complications or developed a malignant lymphoid disorder (35).

The pathogenesis of agranulocytosis associated with pSS is likely immune, since both humoral and cellular mechanisms may affect the production of neutrophils in the bone marrow or cause their destruction in the peripheral circulation (34). However, Coppo *et al*. (35) did not detect autoantibodies to surface neutrophil antigens in the sera of 5 patients tested, and no influence of the patient's sera on granulocyte growth *in vitro* bone marrow cultures was found. Autoantibodies to granulocytes, as well as Coombs' test positivity and anti-platelet antibodies, have been demonstrated in a pSS patient who presented with mild asymptomatic pancytopenia (36). Interestingly, in pSS as well as in other non-organ-specific autoimmune diseases, antibodies anti-FcγRIIIb (CD16) may rescue neutrophils from apoptosis through the production of granulocyte colony-stimulating factor (CSF) and granulocyte-macrophage CSF. The delay in apoptosis is accompanied by a down-regulated expression of the proapoptotic protein Bax (37).

Thrombocytopenia

Ramos-Casals *et al*. (5) found a mild thrombocytopenia (platelet count < 150 x 10^9/L) in 48 of 380 (13%) pSS patients, a moderate thrombocytopenia (< 100 x 10^9/L) in 11 (3%), and a severe thrombocytopenia (< 50 x 10^9/L) in 3 (0.4%). When pSS patients were compared according to the presence or absence of thrombocytopenia, those with low platelet count presented a higher prevalence of renal involvement and anti-La/SS-B antibodies in the univariate analysis, being both significant independent variables in the multivariate analysis. The observed prevalence of thrombocytopenia in this series is comparable to that (11%) detected in previous ones totalling 643 patients (5). Thrombocytopenia seems to be caused by peripheral platelet destruction, due to either antiplatelet antibody or immune-complex mediation, a pathogenic mechanism similar to that described in patients with SLE (38).

Monoclonal gammopathies

Monoclonal gammopathies are characterized by the clonal proliferation of plasma cells that produce a homogenous monoclonal protein. In the absence of a malignant disorder, patients with monoclonal gammopathy are classified as having monoclonal gammopathy of undetermined significance (MGUS) (39). However, this asymptomatic disorder requires a careful follow-up, since some patients with MGUS may develop an overt hematologic neoplasia, mainly multiple myeloma (MM) (39).

Monoclonal gammopathies in pSS

In 1983, Moutsopoulos *et al*. (40), by using high-resolution gel electrophoresis combined with immunofixation and specific absorption studies, found a higher incidence of free monoclonal λ chains in the sera of patients with pSS (14 of 21 = 67%) than in those with other autoimmune diseases, such as SLE (6 of 22 = 27%), RA (4 of 29 = 14%), and systemic sclerosis (0 of 12). Monoclonal bands were detected in all the 12 patients with EGMs, in 2 of 9 (22%) with exclusive glandular involvement, and in 7 (5%) of 140 age and sex-matched normal individuals. In a following study, the Authors (AA) demonstrated in 17 pSS patients the presence of monoclonal proteins, mainly constituted by free κ or λ light chains, in 8 (47%) serum and in 13 (70%) urine samples (41). The monoclonal proteins were detected more frequently in patients with EGMs (70% in serum, 100% in urine) than in those without (14% in serum, 43% in urine). In 3 pSS patients the detection of monoclonal free light chains in the urine was followed by the development of B-cell NHL in parotid, lung or both, suggesting that free light chains could be an early diagnostic clue for the NHL development (42). Youinou *et al*. (43), by using high resolution electrophoretic technique combined with immunofixation, demonstrated monoclonal immunoglobulins (mIgs) in the serum from 10 of 20 (50%) patients with pSS, mainly in those with EGMs. This incidence was ten times higher in pSS patients than in 140 normal individuals tested as control group. Sibilia *et al*. (44) detected by immunofixation the presence of mIgs in 37 of 150 (25%) patients with pSS, correlating with immunologic features of the disease, such as RF and anti-Ro/SS-A antibodies, but not with clinical manifestations, disease duration, and corticosteroid or immunosuppressive treatments. In a series of 331 Italian pSS patients, only 2 cases of MGUS were observed (45). Brito-Zerón *et al*. (46) evaluated by immunofixation electrophoresis on agarose gels with specific antisera to IgG, IgM, IgA, and κ and λ chains the presence of circulating mIgs in 237 SS patients, 200 with pSS and 37 with hepatitis C virus (HCV)-associated SS. Of 200 pSS patients, 35 (18%) presented mIgs and the majority of them (77%) had EGMs. The monoclonal bands were IgG in 20 patients (13 κ and 7 λ), IgM in 10 (5 κ and 5 λ), IgA in 2 (both κ), and free light chains in 3 (2 λ and 1 κ). Patients with mIgs showed a significantly higher prevalence of pulmonary involvement, polyclonal hyper-γ-globulinemia, erythrocyte sedimentation rate > 50 mm/hr, and cryoglobulins than those without mIgs. Cryoprecipitate was analyzed in 3 of the 6 cryoglobulinemic patients with serum mIgs, detecting the same monoclonal band (IgMκ) found in serum. No significant association between mIgs and the main immunologic markers of pSS, such as RF, ANA, anti-Ro/SS-A and anti-La/SS-B antibodies, except for cryoglobulinemia, was found.

Monoclonal gammopathies in HCV-associated SS

In the above-mentioned study by Brito-Zerón *et al*. (46), the prevalence of mIgs in 37 patients with HCV-associated SS was higher than in 200 pSS patients, being demonstrated in 16 (43%) (10 IgMκ, 5 IgGλ, and 1 free light λ chains). The immunofixation of cryoprecipitate was performed in 6 of the 13 patients with cryoglobulins and serum mIgs: one patient had biclonal IgMκ in the cryoprecipitate, while mIgMκ was detected in serum, and the remaining 5 patients had the same monoclonal band (IgMκ) in both the cryoprecipitate and serum. In comparison with pSS patients, those with HCV-associated SS had a higher frequency of mIgs, predominantly IgMκ, and of

cryoglobulins, as well as a tendency to more frequent development of hematologic malignancies in the follow-up. Indeed, of 6 patients with mIgs who developed hematologic neoplasia, 2 had pSS, and 4 SS HCV-associated. Of the 2 pSS patients, one developed an extranodal marginal B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) involving the parotid gland, stomach and bone marrow, the other a T cell large granular lymphocyte leukemia. Of the 4 patients with HCV-associated SS and hematologic neoplasia, 1 developed a lymphoplasmacytic lymphoma, 2 MALT lymphoma, and 1 Waldenström macroglobulinemia (WM).

Thus, the presence of mIgs in SS indicates the coexistence of a B-cell monoclonal process with the polyclonal B-cell activation characteristic of the disease (41). In patients with pSS, the presence of mIgs may reflect that of cryoglobulinemia, since the monoclonal component detected in the serum is the same observed in the cryoprecipitate (46). Moreover, in patients with HCV-associated SS the presence of circulating mIgs is more indicative of cryoglobulinemia or lymphoma than of an underlying HCV infection (46). On the basis of these findings, the inclusion of serum immunofixation is recommended in the routine immunologic tests performed during the follow-up of pSS patients, with and without associated chronic HCV infection, in order to detect the possible emergence of a monoclonal B-cell subpopulation, susceptible to the development of hematologic malignancy (46).

Lymphoproliferative disorders

Epidemiology

Among autoimmune diseases, SS has the highest incidence of malignant lymphoproliferative disorders, so that SS has been considered a crossroad between the autoimmune and lymphoproliferative disorders (LPDs) (47). As a matter of fact, a recent meta-analysis of all available cohort studies linking autoimmune diseases, such as SLE (6 studies, 8700 patients), RA (9 studies, 95104 patients), and pSS (5 studies, 1300 patients), to the risk of developing NHL, demonstrated that the standardized incidence rate was higher for pSS (18.8) than for SLE (7.4) and RA (3.9) (48). The association between SS and lymphoma has been known since 1951, when Rothman *et al*. (49) described the first case of such an association. In 1964, Talal and Bunim (50) reported the first study on the incidence of lymphoma in a cohort of 58 patients with SS, followed over 4 years, and observed 3 cases of reticulosarcoma and 1 of WM. In 1978, Kassan *et al*. (51) published an epidemiological study, that attempted to estimate the risk of development of lymphoma in 136 SS patients followed at the National Institutes of Health (NIH), and found that 7 patients developed NHL from 6 months to 13 years after their first admission to NIH. This study showed that patients with SS had a higher (43.8) risk of developing lymphoma than age-matched women in the general population, seen in the same period. In 1997, Valesini *et al*. (45) demonstrated a slightly lower risk (33.3) in a series of 331 Italian pSS patients. In a recent Swedish study, the risk for NHL development in 286 patients fulfilling the AECC for SS was 16-fold increased compared with 221 non-AECC sicca patients (33). The lower risk for development of NHL in this study might reflect differences in disease severity respect to that of the previous series of pSS patients.

The occurrence of NHL is the most worrying complication of SS. The percentage of SS patients developing lymphoma varies from 1 (52) to 10% (53, 54). Differences in the criteria used for the diagnosis of SS and in the length of the follow-up might explain this variability in the incidence rate of lymphoma, as well as in the risk of developing this neoplasia. In a retrospective study of 723 patients with pSS followed for a mean of 6 years, the 10-year risk of developing LPD, most commonly B-cell NHL, was 3.9% (55). The time between the onset of SS and the diagnosis of NHL is variable. In one series of 55 patients, this time ranged from 4 to 12 years (mean 6.5 years) (56), and in another of 33 patients, the mean time was 7.5 years (57).

Etiopathogenesis

Viruses, such as Epstein-Barr virus (EBV), human herpes virus (HHV)-6 and 8, HCV and human T lymphotropic virus-1 (HTLV-1), may play a role in the development of lymphoma. A possible etiologic role of EBV in SS-associated lymphoma is suggested by the finding of a higher frequency of EBV genes or protein expression in minor salivary gland (MSG) biopsies from SS patients in comparison with controls (58,59). Moreover, EBV has been detected in lymphomatous tissue from a small number of SS patients. Indeed, Fox *et al*. (60) found EBV DNA in 2 of 5 cervical lymph nodes from SS patients with B-cell NHL. Jeffers *et al*. (61) demonstrated EBV DNA in 3 of 6 parotid gland MALT lymphoma complicating SS, but evidence for a role of EBV in tumour development was noted only in 1 high-grade lymphoma. However, EBV infection was not detected in lymphomatous tissues from 16 SS patients with NHL (62). High levels of HHV-6 DNA were observed in lymph node tissue from only 1 of 14 patients with SS-associated lymphoma (63). In a case, the role of HHV-8 in the development of a bilateral parotid MALT lymphoma associated with SS was suggested (64). In a series of 16 SS patients with NHL, no evidence for HCV or other viruses was found (62). Thus, the evidence for an etiological role of viruses in the development of SS-associated lymphoma is scanty, being documented only in a few cases.

Several chromosomal abnormalities have been described in SS-associated lymphoma. The most known is the t(14;18) chromosomal translocation, the cytogenetic hallmark of follicular lymphoma (65). This translocation juxtaposes the Bcl-2 gene with the Ig heavy chain locus, resulting in the synthesis of inappropriately highly levels of the Bcl-2 protein inhibiting B-cell apoptosis, and thus increasing both the B-cell survival and probability of neoplastic transformation (66). Pisa *et al*. (67) detected translocation of the Bcl-2 gene in 5 of 7 (71%) SS-associated NHL, but not in salivary gland biopsies from SS patients without NHL nor in the pre-lymphoma biopsies from the

same patients. However, other AA failed to demonstrate the t(14; 18) translocation in MSG biopsies with heavy chain monoclonality or in the extrasalivary lymphomas (68).

Mutations of the tumour-suppressor activity p53 gene have been detected in lymphomas, and have been associated with progression of low-grade MALT lymphoma to high-grade (69). p53 is a transcription factor, and mutations in the p53 gene are the most commonly observed genetic alterations in human cancers (70). Wild-type p53 is required for arrest in the G1 phase of the cell cycle, in response to DNA damage and/or other stress agents. Tapinos *et al*. (71) evaluated the p53 and p21 protein expression, by immunohistochemistry and Western blot analysis, in MSG specimens from 11 patients with pSS (7 with pSS alone and 4 with pSS and *in situ* NHL, defined as κ:λ ratio in MSG biopsy samples > 15:1 vs < 2:1 in those with pSS alone) and 5 controls with nonspecific sialadenitis on MSG biopsy. In addition, sequence analysis of the p53 gene was performed on DNA samples obtained from MSG biopsy specimens from all 11 pSS patients. Compared with controls, an increased p53 and p21 protein expression in MSG biopsy specimens from pSS patients was shown. In addition, sequence analysis revealed that the p53 gene was of the wild-type in patients with pSS alone, whereas not previously reported mutations in exon 5 were found in those with pSS and *in situ* NHL. All these mutations were single-base substitutions (in one patient at nucleotide 13059 of the wild-type sequence, with a G to C substitution, while the other 3 patients had a G to T substitution at nucleotide 13143 of the wild-type sequence) and appeared to be functional, since the exon 5 is included in the coding region of the p53 gene (71). The AA suggested that these mutations of the p53 gene may play a role in SS lymphomagenesis, since they might lead to a failure of the control of the cell cycle at the G1-checkpoint with subsequent uncontrolled cell proliferation (71).

The levels of the enzyme O^6-methylguanine DNA methyltransferase (MGMT) that repairs the promutagenic DNA base lesion, O^6-methylguanine, were evaluated in lymphocyte extracts from healthy controls and patients with osteoarthritis and autoimmune diseases, including pSS with and without parotid gland swelling (72). Low levels of MGMT were found only in patients with pSS and enlarged parotid glands. A deficient repair of O^6-methylguanine as a result of depressed MGMT levels might contribute to the lymphoid cell transformation into malignant phenotype in this subset of pSS patients (72). Other genetic alterations observed in pSS include trisomy 3 and trisomy 18 (62).

Apoptosis of the acinar and ductal epithelial cells of the salivary and lacrimal glands has been proposed as a possible mechanism responsible for the tissue damage in SS (73). In addition, the majority of lymphocytes infiltrating the MSG from pSS patients express the proto-oncogene product Bcl-2 (74). The expression of Bcl-2 in lymphocytes, in spite of the presence of Fas, induces resistance to apoptotic cell death ("blocked" apoptosis) (74). The expression of the apoptosis inhibitors Bcl-2 and Bcl-x_L is greater than that of the apoptosis inducer Bax. This phenomenon, allowing the survival of T- and B-lymphocytes, may increase the production of proinflammatory cytokines and autoantibodies (75), as well as enhance the ability of these immune effector cells to damage the glandular tissue (74). Moreover, the "blocked" apoptosis of the infiltrating lymphocytes may explain the increased incidence of lymphomas in patients with SS (74). Another pathway of apoptosis involves the B-cell activating factor (BAFF). A role for BAFF, a member of tumour necrosis factor (TNF) ligand family, in the development of SS associated B-cell NHL has been recently suggested. BAFF is a powerful regulator of B-cell differentiation and proliferation (76,77), and the dysregulation of its expression may be a critical element in the chain of events leading to autoimmunity (78). Indeed, the BAFF serum levels are increased in patients with SS (79,80), and strongly correlate with the titre of autoantibodies, such as RF anti-Ro/SS-A IgA and anti-Ro/SS-A IgM (80). A strong expression of BAFF was detected on infiltrating MNC and, to a lesser extent, on ductal and acinar epithelial cells in MSG biopsies from SS patients (79,81). Moreover, significantly lower levels of apoptosis among BAFF-expressing cells were detected in MSG from patients with SS compared with controls (81). The prolonged survival of autoreactive B-cells might lead to the increased production of autoantibodies and, later, to the development of B-cell NHL in SS patients (81).

Local cytokine networks are supposed to play an important role in both the development and evolution of B-cell lymphoproliferation (82). De Vita *et al.* (83) evaluated the mRNA expression of a wide panel of cytokines, such as IL-1, IL-2, IL-3, IL-4, IL-6, IL-6R, IL-10, IL-12, TNF-α, interferon-γ, and transforming growth factor-β, in SS salivary tissue from 10 patients (7 non-malignant parotid myoepithelial sialadenitis lesions with evidence of B-cell clonal expansion, and 3 B-cell NHLs), as well as from a series of 11 SS-unrelated B-cell NHLs. Overall, the pattern of cytokine expression in SS pre-lymphomatous lesions resembled that observed in both SS-related and SS-unrelated B-cell NHLs. On the other hand, IL-4 could be detected only in lymphomatous tissue (2 of 3 SS-related and 3 of 11 SS-unrelated NHLs). These findings suggest that many cytokines, in particular those strongly implicated in B-cell proliferation, such as IL-3, IL-6 and IL-10, may be involved in the progression from pre-lymphomatous to definite B-cell malignant lesions in SS, as well as in the development of SS-unrelated B-cell NHLs (83).

Predictive factors

Kassan *et al.* (51) reported that SS patients with a history of parotid swelling, splenomegaly, and lymphadenopathy had an increased risk of developing lymphoma. Splenomegaly and lymphadenopathy, but not parotid swelling, were confirmed as risk factors for the development of NHL in a series of 331 Italian pSS patients (45). A history of swollen salivary glands, lymphadenopathy and skin ulcers pre-

dicted lymphoma development in another series of 72 pSS patients (84). In the Multicenter European Study that included 765 pSS patients, lymphadenopathy, skin vasculitis, peripheral nerve involvement, low-grade fever, anemia and lymphopenia were significantly more frequent in those who developed NHL than in the general SS population (57). Monoclonal mixed cryoglobulinemia (MC) and monoclonal RF-associated cross-reactive idiotypes 17109 and G-6 (85), as well as low levels of C3 (33), C4 (12, 33), $CD4^+$ T-lymphocytopenia (33), low $CD4^+/CD8^+$ T-cell ratio ($\leq$ 0.8) (33), and hypo-γ-globulinemia (5), are predictive laboratory parameters of lymphoma development in pSS patients. Notably, Ramos-Casals *et al.* (86) found that lymphoma was associated with low C3, C4 and CH50 levels in univariate analysis, although only low C4 levels were an independent significant variable in multivariate analysis. Finally, high serum β-2 microglobulin levels, low serum IgM levels, and negativization of a previously positive RF are other biological predictors of NHL development in SS (87).

Transition from benign lymphoproliferation to malignant lymphoma

The benign lymphoepithelial lesion of SS is composed by a majority of CD4+ T cells (2) and a minority (20%) of B cells, frequently oligoclonal (88,89). Salivary glands lymphomas are thought to arise from lymphoepithelial lesion in which there are close interactions between epithelial cells, T and B cells (90). The transition from polyclonal to monoclonal lymphoproliferation, MALT lymphoma and finally high-grade malignant lymphoma is a multi-step process (90). Chronic antigenic stimulation of B cells may initially play a role, but the transition to malignant lymphoma requires additional oncogenic events, such as p53 inactivation and Bcl-2 activation. Furthermore, genetic alterations, including gene mutations and/or translocations, may facilitate the progression of low-grade lymphoma to more malignant high-grade lymphoma (90). Monotypic plasma cells, defined by a κ:λ ratio ≥ 3, have been identified by immunochemistry in MSG of 10 of 45 (22%) SS patients without evidence of systemic monoclonal LPD at the time of biopsy (91). In the follow-up, progression to systemic monoclonal LPD occurred exclusively in this subgroup of SS patients (3 of 10) (2 IgMκ monoclonal gammopathy, 1 IgMκ pulmonary immunocytoma).

Polymerase chain reaction amplification of Ig heavy chain variable-diversity-joining (V-D-J) region gene rearrangements is a more useful method for detecting monoclonality than immunochemistry and Southern blotting (92). By using this technique, Jordan *et al.* (93) identified a monoclonal gene rearrangement in 11 of 76 (14.5%) MSG biopsies from SS patients. Four of 11 (36.4%) patients with a monoclonal rearrangement, after a time variable from 1 to 23 months, developed extrasalivary MALT lymphoma. The AA suggested that the detection of monoclonality in MSG biopsies might be a valuable predictor of lymphoma. Attempting to better characterize the pre-lymphomatous stages of B-cell lymphoproliferation in SS, De Vita *et al.* (94) studied multiple tissue lesions (synchronous from different tissues and metachronous from the same tissue) from 6 patients who had an associated LPD. By molecular analyses of synchronous biopsy specimens, in only 1 patient the local overexpansion of the same B-cell clone was detected in multiple sites, suggesting the possible dissemination of the same B-cell clone. On the contrary, in the majority of SS patients with LPD in synchronous biopsy samples from different tissues, the expansion of different dominant B-cell clones was the most frequent finding. Also in metachronous biopsies, different B-cell clones predominated in the same affected tissue at different times. The AA provided conclusive evidence that B-cell clonal expansion is a frequent event in SS, but it may present different features (oligoclonal or monoclonal, smaller or larger in size, fluctuating or established, localized or disseminated) (94). Notably, these different findings may imply a variable risk of lymphoma progression, although they may all occur under the same pathologic diagnosis of lymphoproliferative lesion. On the other hand, fully benign lymphoid infiltrates appear to be either fully polyclonal or characterized by small oligoclonal B-cell expansion (94).

Histopathology

- B-cell NHLs

B-cell NHLs in SS patients occur preferentially in salivary glands and in other MALT sites (57). Various histological subtypes of NHL have been described in patients with SS, such as WM (95), immunocytoma (96), diffuse large B-cell lymphoma (DLBCL) (97), and immunoblastic lymphoma (98). However, according to the revised European-American classification of lymphoid neoplasms (65), a large number of NHLs in SS patients reported in literature can be reclassified as marginal zone lymphoma (MZL), either of low-grade or low-grade transformed into high grade lymphomas (62,99). The term "MZL" encompasses nodal and extranodal lymphomas, these latter known as MALT-type or MALT lymphoma, and indicates lymphomas that arise in the marginal B-cell compartment of lymphoid tissue outside the follicular mantle zone. MALT lymphoma was first described in 1983 by Isaacson and Wright (100) as low-grade lymphoma of the gastrointestinal tract, with features similar to the normal MALT tissue of the Peyer's patches. Later, it became evident that this lymphoma develops in the context of longstanding antigenic stimulation, such as infection with *Helicobacter pylori* (HP) or autoimmune diseases, including autoimmune thyroiditis and SS (101). The most significant clinical feature of MALT lymphomas is the clinical indolence, and they often remain localized but, when disseminate, tend preferentially to involve other sites of MALT (101). MALT lymphomas frequently show clonal chromosomal abnormalities, such as whole or partial trisomy 3, trisomy 18, and structural rearrangements of chromosome 1 with breakpoints in 1q21 or 1q34 (102). Recently, two chromosomal aberrations, t(11;18)-(q21;q21) and t(14;18)(q32;q21), mut-

ually exclusive and involving the MALT lymphoma-associated translocation gene (*MALT1),* have been reported as genetic events specific for MALT lymphoma (103,104). The t(11;18)-(q21;q21) translocation results in the synthesis of the apoptosis inhibitor-2 (*API2*)-*MALT1* fusion protein, which activates nuclear factor-κB, a transcription factor for many of survival-related genes (105). Up-regulation of these molecules promotes cellular proliferation and resistance to apoptotic signals. As a consequence, patients with gastric MALT lymphoma carrying t(11;18)-(q21;q21) are largely resistant to *HP* eradication (106, 107).

Streubel *et al.* (108) evaluated the frequency of chromosomal aberrations involving *MALT1* in 26 patients with MALT lymphoma and SS. The lymphoma was located in the parotid (in 14), orbit (in 2), and submandibular gland (in 1), whereas 9 patients had gastric MALT lymphoma confined to the mucosa and submucosa. All 9 patients with gastric MALT lymphoma had serological or histological evidence for *HP* infection. The overall frequency of *MALT1* rearrangement was lower (23.5%) in patients with extragastrointestinal MALT lymphoma than in those with gastric MALT lymphoma (78%). This finding may partially explain why gastric MALT lymphoma in patients with an autoimmune disease, such as SS, are refractory to the *HP* eradication therapy (106,107).

Royer *et al.* (62) performed a study on NHLs occurring in 16 SS patients, (15 with pSS, 1 with SS secondary to RA). These lymphomas arose in salivary glands (7 cases), as well as in other mucosal extranodal sites, such as stomach (4 cases), lung (3 cases), skin (3 cases), oral mucosa (1 case), thymus (1 case), and in nodal sites (8 cases). Low-grade MZLs were diagnosed in 12 of 16 (75%) patients, 9 of MALT-type in mucosal sites and 3 exclusively nodal. The other 4 (25%) patients presented a DLBCL, a high-grade NHL that was probably a histological transformation of an underlying low-grade MZL. Bcl-2 expression was found in 14 of 16 lymphomas tested, the t(14;18) translocation in 1 of 8, and p53 protein in 1 of 11 lymphomas, respectively. In the Multicenter European Study, 33 cases of NHLs were identified from 765 (4.3%) patients with pSS (57). The NHLs were exclusively nodal in 6 (18.2%) patients; 15 patients had both nodal and extranodal involvement (45.4%), and 12 presented an exclusively extranodal involvement (36.4%). The NHLs were classified as low-grade in 23 patients (69.7%), 12 of which were of MALT type, 8 were small lymphocytic/plasmacytoid, 1 was small lymphocytic, 1 was monocytoid B cells, and 1 was follicular, mixed small and large cells. In 10 patients, lymphomas were classified as intermediate or high-grade. Three of them had MALT type, 5 had large-cell immunoblastic, 1 had diffuse, large cells, and 1 had follicular, predominantly large cells. The salivary glands were the most common site of extranodal involvement, followed by the stomach, nasopharynx, skin, lung, lacrimal glands, liver, and bone (57). High grade life-threatening B-cell lymphomas exceptionally affect the skin (109).

- T-cell NHLs

T-cell NHLs are more rare than B-cell NHLs (110-117). The most common presentation is the cutaneous involvement, however, angiocentric T cell lymphoma of both lung (118) and central nervous system (119) has been also described. Tonami *et al.* (120) reviewed the clinical and imaging records of 27 cases of lymphoma from a total of 463 patients with SS and 2 of them were histopathologically classified as T-cell NHLs.

- Hodgkin's disease

Hodgkin's disease (HD) has been rarely described in pSS, and the prevalent histologic subtypes were lymphocytic predominance (121), lymphocytic depletion (122,123), and mixed cellularity (123,124). In a case the histologic subtype was unknown (125). In the above-mentioned study by Tonami *et al.* (120), only one of 27 patients with lymphoma had HD, subtype mixed cellularity. The relationship between HD and SS is unknown, but likely casual.

Prognosis and outcome

Despite the association between SS and NHL, the overall survival of patients with pSS is similar to that of subjects without this autoimmune disease. As a matter of fact, in the above-mentioned retrospective study of 723 patients with pSS, the standardized mortality ratio (SMR) was 1.15 for the study cohort, compared with the age- and sex-adjusted general population of Greece (55). In this study, approximately 1 of 5 deaths was caused by lymphoma, and all 7 pSS patients who developed lymphoma exiting in death during the follow-up period had either low C4 levels or palpable purpura at the first observation (55). Therefore, the presence of low C4 levels and palpable purpura at the first visit distinguished high-risk patients (~ 20%) (type I pSS) from the majority (80%) of patients with an uncomplicated disease course [type II (low-risk) pSS] (55). Similar SMR (1.17) has been reported by Theander *et al.* (126) for 265 patients fulfilling the AECC for pSS. Similarly, in this study an excess of mortality was found only for lymphoproliferative malignancy (cause-specific SMR 7.89, corresponding to 2.53 excess death per 1,000 person-years at risk). In 219 non-AECC sicca patients, the SMR was 0.71, and no excess of mortality due to any specific cause was found. Hypocomplementemia, defined as low levels of C3 and/or C4 levels at the time of diagnosis, was a significant predictor of death, mainly due to lymphoproliferative malignancy. The predictive role for an unfavourable outcome of hypocomplementemia has been confirmed in a recent study (86).

Therapy of B-NHLs

In the above-mentioned Multicenter European Study, SS patients with high or intermediate grade NHL treated with the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) had a rather poor outcome, with an estimated median overall survival of 21 months (57). The combination of rituximab, a monoclonal antibody that specifically targets CD20 surface antigen on B cells, with the CHOP regimen (R-CHOP) increased the complete response rate and prolonged event-free and overall survival

compared with CHOP alone in elderly patients with DLBCL (127). Recently, 4 SS patients with B-cell aggressive NHL were treated with such a R-CHOP regimen (128). R-CHOP was effective, since it induced in all patients a complete remission that persisted for a follow-up period ranging from 10 to 23 months (mean 15 months). In a more recent open-single case trial, 6 pSS patients with DLBCL were treated with the R-CHOP regimen and their outcome was compared with that of 9 patients included in the Multicenter European Study, treated with CHOP alone and used as historical controls (129). The difference in the overall survival between the two treatment groups was significant. Indeed, the group treated with R-CHOP showed a 100% 2-year overall survival rate, whereas historical controls showed only 37%. EGMs serving as predictors for lymphoma development, such as skin vasculitis and peripheral neuropathy, disappeared and a decrease in both circulating monoclonal MC and RF activity together with an increase in C4 levels were observed (128, 129). Rituximab alone was successful in treating parotid NHL (130-132), and ovary MALT lymphoma in a patient with SS associated with HCV infection (133). In another patient with ocular MALT lymphoma, a first course of rituximab was followed by local radiotherapy obtaining good results, but a second course of rituximab was required for inducing a complete and persistent remission (133). On the other hand, the treatment with rituximab was not successful in another pSS patient with salivary MALT lymphoma (134). Finally, remission of MALT lymphoma has been obtained with chemioterapy followed by autologous hematopoietic stem cell transplantation; interestingly, this procedure did not improve the autoimmune disease (135,136).

Other hematologic malignancies

MM is rarely associated with SS (137-139). Terpos *et al.* (140) described a patient with SS that likely pre-existed for at least 2 years prior to the appearance of MM. Ota *et al.* (141) reported a patient with SS and IgGλ MGUS, developing MM after 7 years. Extramedullary IgG and IgA plasmacytoma of the major salivary glands (142, 143), as well as a case of primary nodal plasmacytoma (144), have been also observed. Other hematologic malignancies reported in SS patients include T cell large granular lymphocyte leukemia (145), angioimmunoblastic lymphadenopathy with dysproteinaemia (146), and multicentric Castleman's disease (147).

Conclusions

Patients with pSS may present a wide variety of hematologic disorders which, sometimes, may represent the inaugural manifestation of this autoimmune disease. A mild normochromic and normocytic anemia, likely interpretable as "anemia of chronic disease", is the most common hematologic finding. Other hematologic abnormalities include cytopenias (leukopenia, $CD4^+$ T-lymphocytopenia, agranulocytosis, and thrombocytopenia), as well as monoclonal gammopathies and LPDs, mainly B-cell NHLs. Patients with SS are at risk of developing NHL, so that SS may be considered a crossroad between autoimmunity and lymphoproliferation. Hypocomplementemia is an important predictor of poor outcome (lymphoma development and death) in patients with pSS. Therefore, the clinical follow-up of pSS patients should include routine complement determination, as well as serum immunofixation in order to detect the possible emergence of a monoclonal B-cell subpopulation, susceptible to the development of a hematologic malignancy. In patients presenting predictive clinical factors of NHL development, it is advised to perform every six months both serum immunofixation and $CD4^+$ T-cell count evaluation, in order to identify those at high risk of lymphoma.

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