Mortality in Sjögren's syndrome

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ABSTRACT

Sjögren's syndrome (SS) is a chronic autoimmune disease that involves primarily the exocrine glands and results in their functional impairment. The disease may occur alone (primary SS, pSS) or in association with other autoimmune diseases, such as rheumatoid arthritis (secondary SS, sSS). Although the clinical manifestations of pSS patients are mainly those of an autoimmune exocrinopathy, 40% to 50% of patients develop extraglandular disease, which may be manifested either by epithelial lymphocytic invasion of lung, liver, or kidney (resulting in interstitial nephritis) or by skin vasculitis, peripheral neuropathy, glomerulonephritis, and low C4 levels, conditions which represent an immune-complex mediated disease. Patients belonging to the latter category, inferring a high risk for development of non-Hodgkin's lymphoma, by default have a worse prognosis with higher mortality rates. In this review, the role of several factors involved in mortality of pSS, as well as markers predictive for lymphoma development are discussed.

Introduction

Sjögren's syndrome (SS) is a chronic inflammatory process that primarily involves the exocrine glands. SS is characterized pathologically by infiltration of the functional glandular epithelium by autoreactive lymphocytes, occurring either independently (primary SS) or in association with other autoimmune rheumatic diseases (secondary SS) (1). Affecting 0.5% of the general population, primary SS (pSS) appears to be a common systemic autoimmune disorder, with prevalence similar to that of rheumatoid arthritis (RA) (2). Mounting clinical and laboratory evidence highlighting the central role of the epithelial cell in disease pathogenesis and evolution prompted introduction of the term 'autoimmune epithelitis' as the etiological name of this disorder (3).

SS could, in general, be characterized as a chronic benign autoimmune condition displaying slow progression and low morbidity and mortality rates; therefore studies on survivorship in pSS provided standardized mortality ratios (SMR) indicating mortality risk only slightly higher than that of the general population (4, 5). However, lymphoma development, a serious complication of pSS with an estimated prevalence of 4.3%, significantly increases the risk of premature mortality (6, 7). In this review, we identify and discuss the published data concerning mortality in patients with pSS and explore cause-specific mortality as well as predictor variables for death, with an emphasis on mortality etiologically-associated with lymphoid malignancies.

Clinical expression and outcome of pSS

It is widely accepted that pSS primarily affects females during the fourth and fifth decades of life (8). The syndrome runs a slow and temperate course, as full development can take approximately 6 to10 years, and, given the nonspecific nature of its initial manifestations, the incipient diagnosis can be obscure, necessitating the use of clinical tests for the evaluation of the salivary and ocular involvement (9). Parotid or major salivary gland enlargement occurs in 60% of the patients. Loss of exocrine function predominantly affects lacrimal and salivary flow, leading to kerato-conjunctivitis sicca (KCS) and xerostomia, two of the most typical symptoms of the disease. These symptoms are attributable to corneal and conjuctival epithelium destruction and chronic salivary gland inflammation respectively. The symptoms are usually not severe and in part subjective, usually cause local irritation and discomfort, decreased visual acuity, and increased incidence of dental and periodontal disease. Less typical but more serious complications may include

corneal ulceration and perforation and acute bacterial sialadenitis. Additional xeroses also contribute to a wide spectrum of nonspecific clinical manifestations, including recurrent bronchitis and pneumonitis, hypochlorhydria, mild chronic pancreatitis and, vaginal atrophy in postmenopausal women.

The periepithelial lymphocytic infiltration of organs beyond the exocrine glands also is an early feature of the disease process, producing varied extraglandular symptomatology such as interstitial nephritis, nonimmune liver disease and obstructive bronchiolitis (10-12). These systemic manifestations are generally mild, even subclinical, as opposed to the prominent sicca features. It is of paramount clinical and prognostic importance that the benign conditions mentioned above be distiguished from extraepithelial manifestations stemming from immune-complex deposition at extraglandular sites, mainly small or medium-sized vessels, renal glomeruli, and peripheral nerve microvessels (13-15). First brought to light with observations of an ongoing B-cell hyperactivity in SS, numerous studies have since confirmed the increased incidence of lymphoid malignancies in certain pSS patients manifesting palpable purpura (a sign of vasculitis), glomerulonephritis, and peripheral neuropathy (6, 7, 16). The occurrence of these serious immune-complex-mediated complications, usually late in the disease process, appears to define a distinct 'high risk' type of SS, with excess mortality due to lymphoproliferative hematologic malignancies (6, 16, 17).

Factors associated with increased mortality in pSS

Several longitudinal studies investigating aspects of outcome in pSS including mortality provided evidence on the overall benign prognosis of pSS. These studies concluded that, apart from a significantly increased incidence of malignant lymphomas in these patients, the disease is characterized over time by modest or clinically-insignificant deterioration in specific organ-related symptomatology and function. This fact, along with the well-documented low frequency of severe organ involvement, justifies the virtually unaffected mortality rates reported in pSS (4,5), in contrast to other rheumatic connective tissue diseases such as RA, scleroderma, and systemic lupus erythematosus (SLE), all of which have been associated with increased mortality rates, especially cardiovascular death (18-20).

Survivorship studies on pSS have been limited in several respects, the sample size being the most significant (Table I). In a disease affecting primarily middle-aged females, a population with low death rates, mortality studies require a large number of person-years if they are to include a meaningful number of deaths (Table II). Kruize *et al*. were the first to attempt an assessment of the long-term outcome of pSS, following-up 31 pSS patients for 10 to 12 years after their initial diagnosis (21). They reported 3 deaths, all due to malignant lymphoma. Another study, conducted by Martens *et al*., included 50 pSS patients diagnosed between 1976 and 1992 in Minnesota, USA, and reported survival comparable to that of the healthy population (4). Similarly, a longitudinal cohort study in Finland reported the SMR in 110 patients with pSS diagnosed from 1977 to 1992 as 1.2 (confidence interval or *p*-value not provided), only slightly increased compared with that of the general population (5).

Skopouli *et al*. studied the clinical and laboratory evolution of the disease, as well as its impact on overall survival, in a prospective cohort study of 261 Greek patients with pSS followed for a 10-year period (6). After comparing the results with those of the general Greek population and adjusting for sex and age, the authors found an SMR of 2.07 (95% confidence interval [95% CI] 1.03-3.71). Interestingly, the overall

Table I. Recent mortality studies in Sjögren's syndrome.

Study [Last name of first author]	Reference number	Year	Location	Number of patients	SMR (CI)
Skopouli	6	2000	Greece	261	2.07 (95%CI 1.03-3.71)
Petrovaara	5	2001	Finland	110	1.2 (95%CI not reported)
Ioannidis	17	2002	Greece	723	1.15 (95%CI 0.86-1.73)
Theander	22	2004	Sweden	484	1.17 (95%CI 0.81-1.63)
Brito-Zeron	24	2007	Spain	266	1.22 (95%CI not reported)
Alamanos	23	2006	Greece	422	1.02 (95%CI 0.4-2.0)

SMR: standardized mortality ratio; CI: confidence interval.

Table II. Acute causes of death.

	Number of deaths in each study attributable to each acute cause					
	Skopouli (6)	Petrovaara (5)	Ioannidis (17)	Theander (22)	Brito-Zeron (24)	Alamanos (22)
Vascular causes	**4**	**9**	**12**	**11**	**9**	NR
Cardiovascular	2	6	5	11	9	–
Cerebrovascular	2	3	7	0	0	–
Malignancy	**4**	**4**	**17**	**6**	**5**	NR
Lymphoma	3	2	7	6	2	3
Infection	**–**	**3**	**3**	**–**	**8**	NR
Renal	**–**	–	–	–	–	–
Pulmonary	**2**	**–**	**2**	**–**	–	–
Drug toxicity	**–**	**1**	**–**	–	–	–
Other causes	**1**	**–**	**5**	**17**	**3**	**–**
Total no. deaths	**11**	**17**	**39**	**34**	**25**	**47**

NR: not reported.

mortality of patients with pSS was increased only in patients with specific clinical and laboratory features, namely the presence of purpura, decreased C4 complement levels (≤0.2g/l), or mixed monoclonal cryoglobulinemia at the time of pSS diagnosis. These features were identified as adverse prognostic factors, predicting serious evolving sequelae such as glomerulonephritis, lymphoma development, and death. This study was the first to document specific long-term risk factors for mortality in patients with pSS. Lymphoproliferative malignancy was the key determinant of the increased mortality.

The most systematic study to date on long-term risk of mortality in pSS has been reported by Ioannidis *et al.* (17). The authors analyzed, albeit retrospectively, data covering approximately 4,500 person-years of follow up and reported an SMR of 1.15 (95% CI 0.86-1.73) compared with the general population. Approximately 1 in 5 deaths were attributed to lymphoma, which may account for the small increase in the mortality risk compared with the general population. However, the 10-year risk of developing a lymphoproliferative disease stood at only 4%. The presence of palpable purpura, with a hazard ratio (HR) of 4.16, 95% CI 1.65-10.5, and low C4 levels, with a HR of 2.4, 95% CI 0.99-5.83, at diagnosis distinguished the small, yet important and distinct group of these high-risk patients.

Based on these data, our department suggested a predictive classification model which divides pSS patients into two distinct groups, carrying two different levels of risk of unfavourable outcome (lymphoma development and death). Patients with low C4 levels and/or palpable purpura are classified as high risk (type I SS), while those without are classified as low risk (type II SS). Propitiously, 80% of all pSS patients are type II SS.

Cause-specific SMRs were estimated in a Swedish prospective cohort study of 484 pSS patients followed up for a median 7 years (22). The SMR for these patients was 1.17 (95% CI 0.81-1.63) compared to a 7.89 (95% CI 2.89-17.18) lymphoproliferative disease cause-specific SMR. In this study, the risk of dying of hematologic malignancy was increased nearly 8-fold in pSS patients (2.53 cases per 1,000 patient-years). pSS patients with low C4 levels had an increased cause-specific SMR due to the presence of lymphoproliferative disease and an increased HR for death compared to patients with normal C4 levels. The primary findings of these two studies (17, 22), namely the insignificantly altered life span of the general pSS population and the increased number of deaths attributable to lymphoma, have been recently confirmed by an epidemiological study of pSS from northwestern Greece (23).

Hypocomplementemia has been extensively evaluated as a potential predictor of a more severe disease course in pSS. A study of 266 Spanish pSS patients clearly demonstrated a significant association of mortality with low C4 levels ≤0.11g/l (HR 5.47, 95% CI 1.43-20.86), systemic involvement (HR 4.51, 95% CI 1.25-16.31), vasculitis (HR 4.58, 95% CI 1.06-19.87), and cryoglobulinemia (HR 4.58, 95% CI 1.06-19.87). Low C3 levels ≤0.82g/l (HR 7.54, 95% CI 1.46-39.01) were linked with development of non-Hodgkin's lymphoma (24). Patients with at least two of these variables experienced lower survival rates in comparison to those without two variables, with SMR of 6.71 (confidence interval or *p*-value not provided). This study reconfirmed the prognostic value of low C4 levels and cryoglobulinemia at diagnosis, first proposed by Skopouli *et al.*, suggesting a pathogenetic association between hypocomplementemia and cryoglobulinemic vasculitis. In another study, the same authors reported that low C3, C4, or CH50 levels at protocol entry were closely associated with systemic expression and adverse outcomes such as lymphoma development and death (25).

The aforementioned studies demonstrate that low levels of C4, C3, CH50, as well as cryoglobulinemic vasculitis, constitute significant predictors of increased mortality in pSS. Although in our department all these parameters are routinely evaluated at diagnosis, C4 levels appear to carry the greatest prognostic value since several large studies have identified them as independent risk factors for increased mortality using multivariable modeling (6, 17, 24). These studies underscore the prognostic significance of systemic manifestations along with complement levels at diagnosis. It further emerges that the link between these predictors and increased mortality rates is development of lymphoma.

Clinical and serological risk factors of lymphoma development in SS patients

Among autoimmune diseases, pSS displays the highest incidence of malignant lymphoproliferative disorders (26). This association was first highlighted in a pioneering study conducted at the National Institutes of Health that reported a 44.4-fold increase in the relative risk of lymphoma development in pSS (27). This extreme estimate of the relative risk may be attributable to referral bias or patient selection that can be expected for a specialized academic research center. Subsequent studies in pSS estimated the lifetime risk of lymphoma development at around 5-10% (7, 28-31). A recent meta-analysis assessed the risk of malignant lymphoproliferation to include a random effects standardized incidence rate (SIR) for pSS of 18.9 [95% CI (9.4-37.9)], for SLE SIR=7.52 [95% CI (3.3-17.3)], and for RA SIR=3.25 [95% CI (2.05-5.16)] (32).

Malignant lymphoma apparently is the only recognized cause of death for which patients with pSS are at increased risk. However, as only 5% of pSS patients will ultimately manifest lymphoma, it constitutes a complication rather than a usual occurrence. With that in mind, the question that arises is whether such factors as the clinical and serological profile of the disease or antibody pattern can predict disease expression and identify the patients at risk (Table III).

In 1971, Anderson *et al.* showed that a decrease of serum immunoglobulins levels and disappearance of the rheumatoid factor (RF) heralded a progression to lymphoma (28). According to Kassan *et al.*, SS patients who have lymphadenopathy, splenomegaly, and

Table III. Possible risk factors for lymphoma development.

Risk Factors (relevant references)
Parotid gland enlargement (17, 27)
Purpura (6, 17)
X-ray (27)
Low C3 (25, 31)
Low C4 (6, 17, 25, 31)
Low CH50 (25)
Cryoglobulinemia (6, 16)
Monoclonal paraproteinemia (33)
Increased β-2 microglobulin (29, 34)
Lymphocytopenia (31)
Hypoglobulinemia (28)
Lymphadenopathy/ spleenomegaly (27)

parotid gland enlargement or who have been exposed to low-dose radiation or chemotherapy showed an increased risk of lymphoma development (27). Our department found that the presence and the amount of mixed monoclonal cryoglobulinemia at diagnosis constituted the most significant serologic factors for predicting the risk of lymphoma development in PSS patients, confirming an older report that suggested monoclonal paraproteinemia and urinary free light-chains as indicators of subsequent lymphoma development (16, 33).

Palpable purpura, low C4, and mixed monoclonal cryoglobulinemia were proposed by Skopouli *et al*. as simple but reliable markers of an increased risk of lymphoproliferation at diagnosis (6). Expanding on these data, Ioannidis et al, demonstrated that lymphoproliferative disease was independently predicted by parotid gland enlargement, palpable purpura, and low C4 levels. Patients presenting at least one of these 3 features at diagnosis had a 9.08-fold higher risk of developing lymphoma than those not displaying any of these features, who were found to be at negligible risk of developing lymphoma during follow-up (17).

In a univariate analysis, Ramos-Casals *et al*. demonstrated that lymphoma was associated with low C3, C4, and CH50 levels, with low C4 levels alone being an independent significant variable in multivariate analysis (25). Finally, sporadic reports on specific associations between other biological and clinical parameters and lymphoma risk in pSS identified CD4+ T-lymphocytopenia, high β-2 microglobulin, and low serum IgM serum levels, as well as vasculitic ulcers and prior use of immunosuppressive treatment as possible predictors of lymphoma evolution (29, 31, 34, 35).

One study showed that pSS patients who developed lymphomas were at greater risk of developing a second malignancy (34). This observation, which requires further investigation, could be explained either by common pathogenetic links between lymphoma and subsequent additional cancers or by therapy-related toxicity, rather than by pSS itself. In any case, it is possible that non-lymphoid cancers may account for a higher mortality in pSS patients.

Clinical aspects of lymphoproliferation in SS

Non-Hodgkin's lymphoma has a 4.3% prevalence in pSS patients, with the median age at lymphoma diagnosis being around 58 years and the median time from pSS diagnosis to lymphoma diagnosis 7.5 years (7, 27). Various histologic subtypes of non-Hodgkin's lymphoma have been described in pSS patients, including follicular, lymphoplasmacytoid, and diffuse large B-cell lymphoma (DLBCL), with mucosa-associated lymphoid tissue (MALT) lymphomas, a subtype of marginal zone B-cell lymphoma, being by far the most common (7, 27, 32, 36-42). In a series of 33 parotid MALT lymphoma cases, almost half of the patients had a history of pSS (43). Another case-control study showed a 28-fold increased risk of developing a marginal zone lymphoma (including MALT lymphomas) and an 11-fold increased risk of DLBCL in pSS (44). Although two more recent, population-based Scandinavian studies indicated a lower proportion of marginal zone B-cell lymphomas among pSS-related non-Hodgkin's lymphoma, they also reconfirmed the close association between marginal zone lymphomas and pSS (31, 44).

Extranodal marginal zone B-cell lymphoma of MALT type is the third most common non-Hodgkin's lymphoma, with an incidence rising steadily over the last two decades (45, 46). As a rule, MALT lymphomas are indolent lymphoproliferative diseases, frequently located in mucosal and nonmucosal extranodal sites, mostly epithelial, a fact suggesting that lymphomatous cells home to epithelia rather than mucosa (47, 48). The overall survival of patients with MALT lymphoma is 85% to 95% at 5 years, showing slight variances according the site affected (49-51). Nongastric MALT lymphomas in non-pSS populations generally appear to have good outcomes, unaffected by the multi-focal nature of this lymphoma, displaying a 5-year overall survival rate between 86% and 100% (50, 52). Regardless of our expanding understanding of the bio-pathologic nature of MALT lymphomas, treatment-data still remain limited. Furthermore, none of the conventional oncologic approaches appear to influence survival and outcome of these patients (51).

In one retrospective analysis, Ambrosetti *et al*. reported no significant differences in outcomes among pSS patients with salivary MALT lymphomas undergoing a variety of treatment modalities, including surgery, radiotherapy, and chemotherapy (43). Similarly, as we previously demonstrated, pSS patients with indolent salivary MALT lymphomas usually display an uncomplicated clinical course with a median overall survival of 6.4 years, as treated and untreated patients with MALT lymphomas showed the same overall survival over a median follow-up of 6 years (7). Interestingly, none of the deaths recorded in this group of patients was directly related to lymphoma or the chemotherapy administered. It is important to remember that some patients with persistent disease may be managed expectantly without any therapeutic interference, and they may go on to live a normal lifespan.

Prognosis in MALT lymphoma has been reported to be influenced by several variables, including poor performance status (PS), bulky tumor (≥7 cm), high levels of serum LDH and β2-microglobulin, and low serum albumin level (53, 54). Unequivocally, the presence of a large-cell component at diagnosis is associated with a poorer outcome (53, 54). Although systemic dissemination at diagnosis has been associated significantly with dismal prognosis in certain

studies, its actual impact on survival remains controversial (51, 55). In another study, lymph node involvement, among other factors, predicted poorer outcomes (53).

Lymphomas in pSS patients tend to evolve toward a less-differentiated histological subtype (DLBCL) in 10% of cases (7). Histologically, the transformation of a benign MALT lymphoma to a DLBCL is heralded by the emergence of an increased number of transformed blasts forming sheets or clusters, finally composing a confluence effacing the preceding MALT lymphoma. Most high-grade lymphomas located in salivary glands are DLBCLs. Precisely how many of the DLBCLs do arise from pre-existing MALT or follicular low grade lymphoma is unknown, but numerous immunohistochemical, karyotypic, and genotypic studies have provided convincing proof that the supervening large-cell lymphomas arise from the same clone as the low-grade lymphomas. Thus the majority of the high-grade lymphomas in pSS patients truly represent blastic-variances of either marginal zone B-cell or follicular lymphomas (56). This histologic transformation to a higher-grade lymphoproliferation always connotes a poorer prognosis. Therefore, the identification of de novo or secondary DLBCLs in pSS patients is prognostically significant, since the median overall survival of these patients has been estimated to be only 1.8 years in both cases (10).

Conclusion

pSS is a chronic benign autoimmune disorder with mortality rates only slightly increased compared with that of the general population. However, lymphoma development, a rare yet serious complication of pSS, has been associated with an excess in the overall disease mortality. The increasing awareness of this fact prompted the investigation of clinical and serological parameters that could serve as markers of an aggravated disease course, possibly leading to lymphoma development and death. Severe involvement of the exocrine glands, vasculitis, hypocomplementemia, and cryoglobulinemia at diagnosis are features that identify a 'high-risk' pSS population with a specific need for closer monitoring as well as tailored and probably more robust therapeutic management. These patients bare a strong predisposition for the development of malignant lymphoma, mainly of extranodal MALT type. The occasional transformation of a previous MALT lymphoma to DLBCL is characterized by poorer outcome.

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