A retrospective study of long-term outcomes in 152 patients with primary Sjögren's syndrome: 25-year experience

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ABSTRACT

The objective of this study was to evaluate the 25-year outcome of patients with primary Sjögren's syndrome (pSS). One hundred and fifty-two patients diagnosed with pSS (American–European classification criteria) were retrospectively and descriptively analysed (1986–2011). Of all 152 patients, 55.9% were alive, 18.4% had died and 25.7% discontinued follow-up (mostly due to old age). Malignancy affected 28.3% and non-Hodgkin's lymphoma (NHL) affected 10.5%. The adjusted risk for development of NHL was an odds ratio (OR) of 10.5 (95% confidence interval [CI]: 3.05–36.42) in patients with vasculitis ($p<0.001$), and OR 3.4 (95% CI 1.05–11.2) in the presence of glandular complications (parotid swelling, lymphadenopathy) ($p=0.041$). Seventy-five patients (49.3%) developed other autoimmune diseases (autoimmune thyroid disease [15.8%], pulmonary fibrosis [7.2%] and vasculitis [10.5%]). Although the course of pSS is relatively benign, over 25 years patients experience more clinical complications than previously described. In addition, vasculitis and glandular manifestations were significant predictors for NHL.

KEYWORDS: Sjögren's syndrome, long-term follow-up, autoimmune diseases, non-Hodgkin's lymphoma, neoplasia

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune epithelitis.[1] It affects approximately 0.5% of the general population,[2,3] making it one of the most prevalent systemic autoimmune diseases, second only to rheumatoid arthritis.[4] One of the most well-described risks to patients with SS is the development of non-Hodgkin's lymphoma (NHL), the lifetime probability of which has been reported to be between 5% and 15%,[5] or 20-fold higher than in the general population.[3] In primary Sjögren's syndrome (pSS), there are a number of other less well-established clinical complications that add to the burden of disease. These include other types of malignancies, other autoimmune diseases,[6] vasculitis[7] and haematological disorders.[8,9] Sinister complications such as the malignancies are typically late events whereas other complications accumulate over time.[10]

The aim of this study was to analyse the demographic, serological, immunological and phenotypic characteristics of 152 patients followed up in the Centre for Rheumatology, University College Hospital, London, over a long-term follow-up.

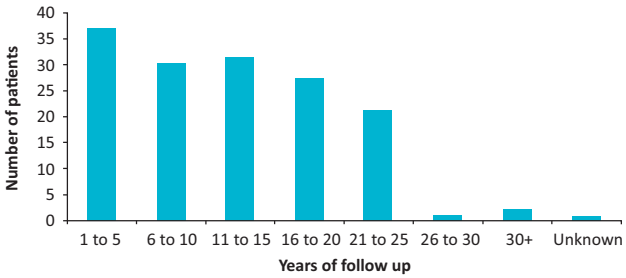

Fig 1. Summary of years of follow-up for the study

Patients and methods

Patients

Between January 1986 and December 2011, 152 patients had been diagnosed with pSS at the authors' unit. All patients met the revised American–European classification criteria (2002) for pSS.[11] Patients with secondary SS were excluded. The authors retrospectively reviewed case notes, computer records and primary health-care databases on an audit basis. They analysed demographic (age at diagnosis, sex, race [white, African–Caribbean, Asian, other], years of follow-up and outcome [alive, dead, lost to follow-up]), serological (antinuclear antibody [ANA], rheumatoid factor, anti-Ro/SSA, anti-La/SSB, anti-ribonucleoprotein [RNP]), histological (minor salivary gland lip biopsy) and clinical features. Clinical features were divided arbitrarily into glandular manifestations (parotid swelling, lymphadenopathy) and extraglandular manifestations (non-erosive arthritis, Raynaud's phenomenon, central and peripheral nervous system [CNS and PNS] disease, and other autoimmune diseases). It is important to note that this distinction is arbitrary,

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and that other groups may have classified differently.

The autoimmune diseases considered included thyroid (hypo- and hyperthyroidism, autoimmune thyroiditis), dermatological (cutaneous lupus, psoriasis, vitiligo), gastrointestinal (autoimmune hepatitis, primary biliary cirrhosis, coeliac disease, pernicious anaemia, ulcerative colitis), renal (renal tubular acidosis, glomerulonephritis) and pulmonary autoimmune diseases (fibrosis, interstitial disease), as well as vasculitis, systemic lupus erythematosus, scleroderma, myositis, sarcoidosis, anti-phospholipid syndrome, rheumatoid arthritis, uveitis, polymyalgia rheumatica and autoimmune cytopenias. All aforementioned autoimmune diseases were diagnosed at least

Table 1. General characteristics of the cohort studied (n=152).

	n (%)
1 Age at diagnosis (mean)	**54.4 (SD 13.5)**
2 Female:male	**139:13 (91.4:8.6)**
3 Race	
> Caucasian	132 (86.8)
> Asian	13 (8.6)
> Afro-Caribbean	5 (3.3)
> Others	2
4 Years of follow up	**12.4 (SD 7.4)**
5 Outcome	
> Alive	85 (55.9)
> Deceased	28 (8.6)
> Lost to follow up	39 (25.7)
6 Positive lip biopsy	**136 (89.5)**
7 Immunological features	
> ANA	115 (75.7)
> anti Ro/SSA	85 (55.9)
> anti La/SSB	54 (35.5)
> RF	83 (54.6)
> anti RNP	7 (4.6)
8 Haematological alterations	**78 (51.3)**
> Hypergammaglobulinaemia	56 (36.8)
> Hypogammaglobulinaemia	7 (4.6)
> MGUS	15 (9.9)
9 Glandular manifestation	**31 (20.4)**
> Lymphadenopaty	14 (9.2)
> Parotid swelling	21 (13.8)
10 Extraglandular manifestation	**108 (71.1)**
> Arthritis	30 (19.7)
> Raynaud	47 (30.9)
> Central nervous system	14 (9.2)
– Stroke	4 (2.6)
– Parkinson	2 (1.3)
– Others	8 (5.3)
> Peripheral nerve system	24 (15.8)
– Carpal tunnel syndrome	9 (5.9)
– Neuropathy	13 (8.6)
– Both	2 (1.3)
> Others autoimmune diseases	75 (49.3)
– Dermatological	16 (10.5)
• Cutaneus lupus	4 (2.6)
• Psoriasis	2 (1.3)
• Vitiligo	2 (1.3)
– Thyroid	24 (15.8)
– Mesenteric	16 (10.5)
• Hepatitis	4 (2.6)
• Primary biliar cirrhosis	6 (3.9)
• Coeliac	3 (2.0)
• Pernicious aneamia	2 (1.3)
• Ulcerative colitis	1 (0.7)
– Renal	10 (6.6)
• Renal tubular acidosis	6 (3.9)
• Glomerulonephritis	4 (2.6)
– Lung (interstitial/fibrosis)	11 (7.2)
– Systemic erythematosus lupus	2 (1.3)
– Scleroderma	6 (3.9)
– Miositys	3 (2.0)
– Sarcoidosis	1 (0.7)
– Antiphospholipid	2 (1.3)
– Reumatoid arthritis	3 (2.0)
– Uveitis	2 (1.3)
– Reumatoid polimialgia	1 (0.7)
– Autoinmune citopenias	4 (2.6)
– Vasculitis	16 (10.5)
> Patients with 1 AD	46 (30.3)
> Patients with 2 AD	24 (15.8)
> Patients with 3 AD	4 (2.6)
> Patients with 4 AD	1 (0.7)
11 Lymphoma	**16 (10.5)**
12 Others cancers	**30 (19.7)**

AD = autoimmune disease; ANA = antinuclear antibody; IQR = interquartile range; MGUS = monoclonal gammopathy of unknown significance; NHL = non-Hodgkin's lymphoma; RNP = ribonucleoprotein; SD = standard deviation.

1 year after pSS was diagnosed. Major haematological disorders were also noted, including hyper- and hypogammaglobulinaemia, monoclonal gammopathy of unknown significance (MGUS) and autoimmune cytopenias. Minor haematological alterations such as anaemia or non-autoimmune cytopenias were not noted. Finally, we considered the onset of solid and haematological malignancies, with particular attention to NHL.

Statistical analysis

Epidemiological, serological and clinical features were descriptively analysed. Frequencies and percentages were used for categorical variables, and mean (standard deviation [SD]) or median (interquartile range [IQR]) was used for continuous variables. A univariant analysis (χ^2 and Fisher's tests) was used to compare the four most prevalent and/or relevant clinical findings, which were as follows:

- haematological disorders
- all malignancies (including NHL)
- NHL
- other autoimmune diseases.

A multivariant analysis was used for statistically significant features. Logistic regression and bivariant analysis was also performed to avoid the presence of confounding variables and calculate the adjusted OR (odds ratio) and 95% confidence interval (95% CI). A two-tailed value of $p<0.05$ indicates statistical significance. The statistical analysis was performed using the IBM SPSS Statistic 19.0 (SPSS, Chicago, IL, USA).

Results

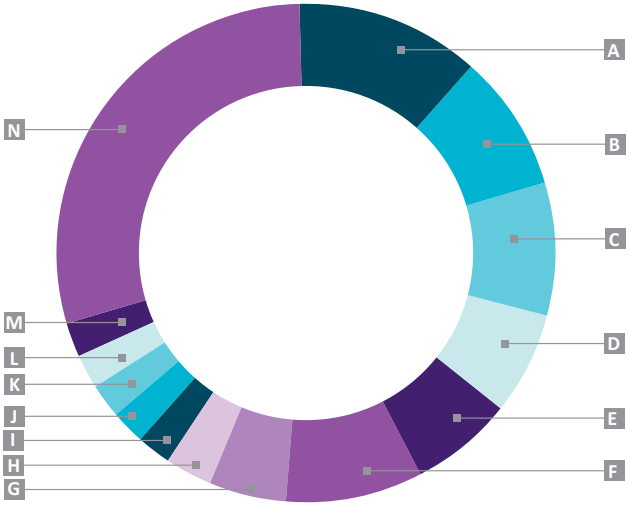
General characteristics

Our cohort was predominately white European (86.8%) and female (91.4%). The mean age of diagnosis was 54.4 years (SD=13.5 years). The number of years of follow-up since a diagnosis was made ranged from 1 year to 47 years (median=11; IQR 6–19) and are summarised in Fig 1; 39 patients (25.6%) discontinued follow-up at some point during the study period, mainly due to being too elderly to travel to the clinic easily. For these patients, the authors included clinical complications until the final follow-up appointment. Of the remaining 113 patients, 28 (18.5%) died at some point during the study period. The mean age of death was 72.1 years (SD=12.3 years).

Serologically, the presence of ANAs was the most frequent finding (75.7%) followed by anti-Ro/SSA antibodies and rheumatoid factor in just under 55%. Extraglandular manifestations were 3.4-fold more common than glandular manifestations (108 [71.1%] vs 31 [20.4%]). Of glandular manifestations, parotid swelling was the most common (n=21; 13.8%), and of extraglandular manifestations, additional autoimmune diseases were the most common (n=75; 49.3%).

Additional autoimmune diseases

Additional autoimmune diseases were the most common extraglandular manifestation in our cohort, with a total of 75 patients (49.3%) developing at least one (see Table 1 for autoimmune diseases included). Autoimmune thyroid disease was the most frequent of these (n=24, 15.8%; 32.0% of autoimmune diseases), followed by vasculitis, dermatological and gastrointestinal autoimmune diseases, which occurred in 16 patients each (21.3% of global autoimmune diseases each). Of dermatological autoimmune diseases, cutaneous lupus was the most common (n=4; 2.6%) and of gastrointestinal diseases, primary biliary cirrhosis was the most frequent (n=6; 3.9%). Autoimmune lung and renal diseases were present in 11 (7.2%) and 10 (6.5%) patients, respectively. Twenty-nine patients (38.7%) developed more than one additional autoimmune disease, up to a maximum of four in one patient (0.7%). Table 2 compares those with and those without additional autoimmune diseases; a significantly higher incidence was found in females (72 [96.0%] vs 67 [87.0%]; p<0.01), those with positive anti-Ro/SSA (48 [64.0%] vs 37 [48.1%]; p<0.05), positive anti-La/SSB (33 [44.0%] vs 21 [27.3%]; p<0.03) and those who also had haematological disorders (46 [61.3%] vs 35 [45.5%]; p<0.05). There was no significant difference in years of follow-up in those who developed additional autoimmune diseases. Multivariant analysis was unable to demonstrate risk factors for the development of additional autoimmune diseases.



A	Gynaecological cancer (ovarian, cervical)
B	Bladder cancer
C	Skin cancer
D	Breast cancer
E	Lung cancer
F	Oropharyngeal cancer
G	Brain cancer
H	Hepatocellular carcinoma
I	Multiple myeloma
J	Pancreatic cancer
K	Bowel cancer
L	Thyroid cancer
M	Prostate cancer
N	Lymphoma

Fig 2. Summary of all the malignancies that the patients developed.

Table 2. Primary Sjögren's syndrome with and without autoimmune diseases

	Primary SS with ADs n (%)	Primary SS without ADs n (%)	p
Total	**75**	**77**	
Age >50 years old	49 (65.3)	47 (61)	0.583
Sex: female	72 (96)	67 (87)	0.017
Race: white European	63 (84)	69 (89.6)	0.641
Years of follow up >12	40 (53.3)	38 (49.3)	0.623
ANA	57 (76)	58 (75.3)	0.923
Anti-Ro/SSA	**48 (64)**	**37 (48.1)**	**0.048**
Anti-La/SSB	**33 (44)**	**21 (27.3)**	**0.031**
Rheumatoid factor	46 (65.7)	37 (55.2)	0.209
RNP	6 (8)	1 (1.3)	0.062
Haematological disorders	**46 (61.3)**	**35 (45.5)**	**0.05**
Osteoarthritis	17 (22.7)	13 (16.9)	0.327
Raynaud's	24 (32)	23 (29.9)	0.776
CNS	9 (12)	5 (6.5)	0.241
PNS	**18 (24)**	**6 (7.8)**	**0.006**
Glandular manifestations	11 (14.7)	20 (26)	0.084
Lymphadenopathy	**3 (4)**	**11 (14.3)**	**0.028**
Parotid swelling	9 (12)	12 (15.6)	0.522
NHL	9 (12)	7 (9.1)	0.599
Other malignancies	19 (25.3)	11 (14.3)	0.087
Death	16 (21.3)	12 (15.6)	0.361

ANA = antinuclear antibody; CNS = central nervous disease; HDs = haematological diseases; NHL = non-Hodgkin's lymphoma; PNS = peripheral nervous system; RNP = ribonucleoprotein; SS = Sjögren's syndrome.

Haematological disorders

Seventy-eight patients (51.3%) developed haematological derangements. Under the arbitrary classification outlined in the methods, hypergammaglobulinaemia was the most common (n=56; 36.8%), followed by MGUS (n=15; 9.9%) and hypogammaglobulinaemia (n=7; 4.6%). Table 3 compares those with and those without haematological disorders; a significantly higher incidence was found in patients who had a longer follow-up (≥12 years), and those with positive anti-Ro/SSA (60 [77.0%] vs 25 [33.8%]; p<0.001) and positive anti-La/SSB (39 [50.0%] vs 15 [21.1%]; p<0.001). Significantly fewer patients had Raynaud's phenomenon (10 [24.4%] vs 28 [37.8%]; p<0.011). The adjusted risk of developing haematological disorders was and OR of 0.3 (95% CI 0.1–0.8 in patients with Raynaud's phenomenon (p=0.01), OR 1.1 (95% CI 1.01–1.2) in patients with a longer follow-up (p=0.001), OR 0.7 (95% CI 0.2–1.9) in patients with positive anti-La/SSB (p=0.478), and OR 0.2 (95% CI 0.1–0.5) in those with positive anti-Ro/SSA (p=0.001).

Malignancy

A total of 43 (28.3%) patients developed malignancy; 13 developed NHL alone, 3 developed NHL and a second cancer (melanoma in 2 cases, ovarian cancer in 1), and 27 developed haematological and solid malignancies besides NHL. This brought the total incidence of non-lymphoma cancers to 19.7% (n=30) and total incidence of NHL to 10.5% (n=16).

Non-Hodgkin's lymphoma

Patients diagnosed with NHL were compared with all other patients (Table 4). The parameters of sex, age, race, duration of disease, and haematological and immunological characteristics did not show any statistically significant differences. However, the incidence of glandular manifestations was significantly higher in the lymphoma group (7 [43.8%] vs 24 [17.6%]; p<0.05), as was the incidence of vasculitis (7 [43.8%] vs 7 [6.6%]; p<0.001). The incidence of other cancers and mortality were not significantly different between the two groups. In the multivariant analysis the adjusted risk for development of NHL was OR of 10.5 (95% CI 3.05–36.42) in patients with vasculitis (p<0.001), and OR 3.4 (95% CI 1.05–11.2) in the presence of glandular manifestations (p=0.041).

All malignancies

Other malignancies that the patients developed included: gynaecological (n=5: 3 ovarian, 2 cervical), bladder cancer

Table 3. Primary Sjögren's syndrome with and without haematological diseases

	Primary SS with HDs n (%)	Primary SS without HDs n (%)	p
Total	**78**	**74**	
Age >50 years old	46 (56.8)	50 (70.4)	0.082
Sex: female	75 (92.6)	64 (90.1)	0.59
Race: white European	69 (85.2)	63 (88.7)	0.718
Years of follow up (≤12)	**34 (43.5)**	**44 (59.4)**	**0.050**
ANA	61 (75.3)	54 (76.1)	0.915
Anti-Ro/SSA	60 (74.1)	25 (35.2)	<0.001
Anti-La/SSB	**39 (48.1)**	**15 (21.1)**	**<0.001**
Rheumatoid factor	47 (63.5)	36 (57.1)	0.447
RNP	4 (4.9)	3 (4.2)	1
Extraglandular manifestations	56 (69.1)	52 (73.2)	0.578
Other autoimmune diseases	12 (14.8)	6 (8.5)	0.226
Dermatological	10 (12.3)	6 (8.5)	0.435
Vasculitis	10 (12.3)	6 (8.5)	0.435
Lung	4 (4.9)	7 (9.9)	0.243
Renal	5 (6.2)	5 (7)	1
Thyroid	13 (16)	11 (15.5)	0.925
Mesenteric	9 (11.1)	6 (8.5)	0.583
2 Raynaud's phenomenon	**19 (23.5)**	**28 (39.4)**	**0.011**
3 CNS	7 (8.6)	7 (9.9)	0.796
4 PNS	16 (9.8)	8 (11.3)	0.152
5 Osteoarthritis	15 (18.5)	15 (21.1)	0.565
Glandular manifestations	19 (23.5)	12 (16.9)	0.317
Lymphadenopathy	7 (8.6)	7 (9.9)	0.796
Parotid swelling	15 (18.5)	6 (8.5)	0.073
NHL	9 (11.1)	7 (9.9)	0.802
Other malignancies	15 (18.5)	15 (21.1)	0.687
Death	11 (13.6)	17 (23.9)	0.116

ANA = antinuclear antibody; CNS = central nervous disease; HDs = haematological diseases; NHL = non-Hodgkin's lymphoma; PNS = peripheral nervous system; RNP = ribonucleoprotein; SS = Sjögren's syndrome.

(n=4), skin (n=4: 3 melanomas, 1 basal cell carcinoma), lung (n=3, including 1 mesothelioma), breast (n=3), oropharyngeal (n=3), CNS (n=2: 1 cavernoma, 1 meningioma), and single cases of each of the following: hepatocarcinoma, multiple myeloma, pancreatic cancer, bowel cancer, thyroid cancer and prostate cancer. These are summarised in Fig 2. Table 5 compares the features of all patients who developed solid and haematological malignancies versus those who did not. The malignancy group was significantly older (>50 years: 28 [93.3%] vs 68 [55.7%]; p<0.001), significantly fewer were anti-Ro/SSA positive (12 [40.0%] vs 73 [59.8%]; p<0.05] and significantly more were RNP positive (4 [13.3%] vs 3 [2.5%]; p<0.02). There was no statistically significant difference in any other clinical feature. In the multivariant analysis the adjusted risk for the development of malignancies was OR of 9.6 (95% CI 2.1–42.9) in patients aged >50 years (p=0.003), OR 0.6 (95% CI 0.3–1.4) for anti-Ro/SSA-positive patients (p=0.609) and OR 4.9 (95% CI 0.9–25.6) in RNP-positive patients (p=0.06).

Discussion

Primary Sjögren's syndrome is not generally thought to be associated with life-expectancy-shortening complications, especially when it is compared with systemic lupus erythematosus and rheumatoid arthritis.[12] However, trends in the development of more ominous complications of pSS appear to be latent.[10] Despite new studies of outcome in pSS with large sample sizes, classification is hotly debated and few studies boast an average follow-up of >10 years.[7,10,12–16] The current report demonstrates a retrospective analysis of 152 patients with pSS followed carefully over 25 years, with an average duration of follow-up of 12.5 years (SD=7.4 years). This is the largest and longest study of pSS patients

Table 4. Primary Sjögren's syndrome with and without non-Hodgkin's lymphoma (NHL)

	Primary SS with NHL n (%)	Primary SS without NHL n (%)	p
Total	**16**	**136**	
Age >50 years old	8 (50)	88 (67.4)	0.249
Sex: female	13 (81.3)	126 (92.6)	0.142
Race: white European	16 (100)	116 (85.3)	0.853
Years of follow-up (≤12)	8 (50)	70 (51.4)	0.911
ANA	15 (93.8)	100 (73.5)	0.120
Anti-Ro/SSA	10 (62.5)	75 (55.1)	0.575
Ant-La/SSB	6 (37.5)	48 (35.3)	0.862
Rheumatoid factor	9 (75)	74 (59.2)	0.364
RNP	2 (12.5)	5 (3.7)	0.160
Haematological disorders	9 (56.3)	72 (52.9)	0.802
Extraglandular manifestations	13 (81.3)	95 (69.9)	0.401
> **Other autoimmune diseases**	9 (56.3)	66 (48.5)	0.695
– Lung	2 (12.5)	9 (6.6)	0.326
– Thyroid	3 (18.8)	21 (15.4)	0.720
– Renal	2 (12.5)	8 (5.9)	0.284
– Mesenteric	1 (6.3)	14 (10.3)	1.00
– Dermatological	0.00	16 (11.8)	0.221
– Vasculitis	7 (43.8)	9 (6.6)	<0.001
> **Raynaud's phenomenon**	7 (43.8)	40 (29.4)	0.261
> **CNS**	0.00	14 (10.3)	0.364
> **PNS**	2 (12.5)	22 (16.2)	1.00
> **Osteoarthritis**	4 (25)	26 (19.1)	0.284
Glandular manifestations	7 (43.8)	24 (17.6)	0.022
> Lymphadenopathy	4 (25)	10 (7.4)	0.043
> Parotid swelling	6 (37.5)	15 (11)	0.011
Other malignancies	3 (18.8)	27 (19.9)	1.00
Death	6 (37.5)	22 (16.2)	0.80

ANA = antinuclear antibody; CNS = central nervous disease; NHL = non-Hodgkin's lymphoma; PNS = peripheral nervous system; RNP = ribonucleoprotein; SS = Sjögren's syndrome.

from the UK.[10] The demographic and serological features of our population were similar to those previously described in the literature.[10,14,16–21]

The development of additional autoimmune diseases was found in just under half of the cohort (49.3%), which is more than others report.[22] The most common of these was autoimmune thyroid disease, as demonstrated by previous studies.[6,18,23,24] Importantly, 19.0% of patients developed more than one additional autoimmune disease, up to a maximum of four in one patient. This is consistent with the phenomenon of 'polyautoimmunity' as previously described.[6] Relevant characteristics ($p<0.05$) of those who develop additional autoimmune diseases in our cohort were: female anti-Ro/SSa and anti-La/SSb positive, and haematological disorders. These results are supported by previous findings.[10]

The total malignancy rate in our cohort was higher than in any other study that the authors could identify,[5,25] with over a quarter (28.3%) developing cancer, mostly due to an increased incidence of lymphoma. The relative prevalence of solid and haematological malignancies besides NHL was significantly related to older age ($p<0.001$). These observations argue against pSS being a direct risk factor for the development of systemic malignant transformation. Evidence for such a relationship is much firmer in the case of NHL. However, with only two other studies to compare,[5,25] there is a lack of data to corroborate this finding due to a shortage of extended follow-up studies. Nevertheless, it has long been known that systemic autoimmune diseases can potentiate dysplastic changes. This in turn is related to the aforementioned breakdown of immune tolerance, supported by the fact that RNP-positive patients had a 4.9-fold

Table 5. Primary Sjögren's syndrome with and without other malignancies

	Primary SS with other malignancies n (%)	Primary SS without other malignancies n (%)	p
Total	**30**	**122**	
Age >50 years old	**28 (93.3)**	**68 (55.7)**	**<0.001**
Sex: female	27 (90)	112 (91.8)	0.721
Race: white European	25 (83.3)	107 (87.7)	0.682
Years of follow-up (≤12)	13 (43.3)	65 (53.2)	0.328
ANA	20 (66.7)	95 (77.9)	0.201
Anti-Ro/SSA	12 (40)	73 (59.8)	<0.053
Anti-La/SSB	9 (30)	45 (36.9)	0.48
Rheumatoid factor	18 (60)	65 (60.7)	0.941
RNP	4 (13.3)	3 (2.5)	<0.023
Haematological disorders	15 (50)	66 (54.1)	0.687
Extraglandular manifestations	25 (83.3)	83 (68)	0.098
> **Other autoimmune diseases**	5 (16.7)	13 (10.7)	0.354
– Dermatological	1 (3.3)	15 (12.3)	0.198
– Vasculitis	4 (13.3)	12 (9.8)	0.522
– Lung	1 (3.3)	10 (8.2)	0.693
– Renal	3 (10)	7 (5.7)	0.415
– Thyroid	8 (26.7)	16 (13.1)	0.092
– Mesenteric	5 (16.7)	10 (8.2)	0.177
> **Raynaud's phenomenon**	8 (26.7)	39 (32)	0.574
> **CNS**	2 (6.7)	12 (9.8)	0.738
> **PNS**	8 (26.7)	16 (13.1)	0.092
> **Osteoarthritis**	8 (26.7)	22 (28)	0.275
Glandular manifestations	3 (10)	28 (23)	0.115
Lymphadenopathy	1 (3.3)	13 (10.7)	0.305
Parotid swelling	2 (6.7)	19 (15.6)	0.253
NHL	3 (10)	13 (10.7)	1
Death	13 (43.3)	15 (12.3)	0.187

ANA = antinuclear antibody; CNS = central nervous disease; NHL = non-Hodgkin's lymphoma; PNS = peripheral nervous system; RNP = ribonucleoprotein; SS = Sjögren's syndrome.

increased adjusted risk of any kind of malignancy (95% CI 0.9–25.6; p<0.06) in the multivariant analysis, and those who developed non-lymphoma malignancies were less likely to be anti-Ro/SSA positive (p<0.053) in the univariant analysis.

NHL is the only malignancy with a proven link to pSS.[5] Occurring in 10.5% of patients, NHL was the single most common subtype of malignancy in this cohort. This is higher than national statistics[22] and previous data,[7,12,13,15,18,25–27] but similar to the rates found by Kruize *et al*[14] (10.0%) and others. This is probably due to chronic local inflammation[28] coupled with intrinsic abnormalities in B cells and B-cell activating factors,[1] as explained in depth by Youinou *et al*.[28,29]

There are wide ranges of suggested predictors for the development of NHL in pSS. However, in the authors' cohort only patients with vasculitis and glandular manifestations demonstrated a 10.5-fold and 3.42-fold increased adjusted risk for developing NHL, respectively (vasculitis: 95% CI 3.05–36.42; p<0.001; glandular manifestations: 95% CI 1.05–11.2; p=0.041). As supported by Sutcliffe *et al*,[27] no serological mediators are implicated as risk factors. Serological markers that were not tested should be analysed prospectively in the future to confirm this. It was surprising that there was no relationship between NHL and the duration of follow up, as previously shown.[15] This is possibly due to the technical limitations of this retrospective study and the need for a higher sample size.

Importantly, this study found that 18.8% of patients with NHL had a second cancer. This is supported by a previous study.[27] Here it is possible that defective DNA-repair mechanisms and

cytotoxic therapies contribute. However, the latter are unlikely because very few of the patients in this study received cytotoxic therapy, but they could form the basis of further study. Although NHL does not significantly decrease life expectancy,[13] this second malignancy is often a source of mortality.

Haematological disorders affected more than 50% of the cohort. Hypergammaglobulinaemia (36.8%) and MGUS (8.6%) were most common. These findings were significantly related to years of follow-up and, although they were more common in those with positive anti-Ro/SSA ($p<0.001$) and positive anti-La/SSb ($p<0.001$), this could not be confirmed by the multivariant analysis. These findings implicate both a temporal and an immunological relationship for haematological disorders in pSS. Interestingly, haematological disorders were inversely correlated to those with Raynaud's phenomenon ($p<0.01$; OR <1). However, the incidence of Raynaud's phenomenon is difficult to interpret. A recent study has suggested that MGUS is associated with a poor prognosis in pSS.[9] However, this study does not show significant differences in glandular manifestations, lymphoma, other cancers, other extraglandular manifestations or mortality in the haematological disorders group.

Other complications in this study's cohort were common and variable: almost half the patients displayed Raynaud's phenomenon; and non-erosive arthritis rates were high, related to the high mean age of the cohort. Just over a quarter of patients developed CNS and PNS disturbances, reflecting most of the previous studies.[10,20] However, neuropsychiatric complications should be interpreted with caution because they are difficult to document reliably and extremely heterogeneous in the literature. The most common nervous manifestation in this cohort was peripheral neuropathy.

To conclude, the present study summarises a single centre's 25-year experience of 152 patients with pSS, followed for a mean of 12.4 years. Globally, these data demonstrate that patients with pSS experience an increased rate of malignancy (mainly NHL), and additional autoimmune and haematological disorders. The findings indicate that shorter outcome studies are at risk of underestimating the burden of pSS and a universal thread has been the importance of a holistic and vigilant approach to follow up. ■

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