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LONG-TERM FOLLOWUP OF PATIENTS WITH SJÖGREN'S SYNDROME

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Objective. **To assess long-term outcome in patients with isolated keratoconjunctivitis sicca (KCS), primary Sjögren's syndrome (SS), and secondary SS.**

Methods. **In 112 patients referred because of dry eyes, an ophthalmologic diagnosis of KCS was made based on results of the Schirmer I test, the tear fluid lysozyme concentration, and rose bengal staining. Subsequent assessments, including sublabial salivary gland biopsy, were performed. Followup assessments were performed 10–12 years after initial diagnosis.**

Results. **Six patients were excluded because no biopsy specimen was available. Seventy-three percent of the remaining 106 patients were female, with a mean age of 53.5 years and a mean symptom duration of 3.9 years. Application of the 1987 classification criteria of Daniels and Talal revealed a diagnosis of isolated KCS in 56 patients, primary SS in 31, and secondary SS in 19. At baseline, 2 of 56 patients with isolated KCS and 8 of 31 with primary SS exhibited mild features of organ-specific autoimmune disease. At followup, 2 of 38 patients with isolated KCS and 4 of 21 with primary SS had developed new features related to autoimmune disease, not necessitating treatment with corticosteroids; none of the patients developed major glandular complications. Three of 30 patients with primary SS died of malignant lymphoma. In 1 of these patients, the possibility could not be excluded that sicca symptoms and infiltrates seen on sublabial salivary gland biopsy had occurred concomitantly with early stages of lymphoma. Malignant lymphoma did not develop in any of the patients with isolated KCS or secondary SS.**

Conclusion. **Primary Sjögren's syndrome is characterized by a stable and rather mild course of glandular and extraglandular manifestations, in marked contrast to the increased risk for development of malignant lymphoma in these patients. Since patients with isolated KCS do not have an increased risk for development of malignant lymphoma, a presumptive diagnosis of primary SS should be confirmed in patients with sicca syndrome.**

Sjögren's syndrome (SS) is an autoimmune exocrinopathy characterized by lymphoid infiltration and functional deterioration of exocrine glands, especially of lacrimal and salivary glands. SS mainly results in keratoconjunctivitis sicca (KCS) and xerostomia, but extraglandular involvement may occur. SS may develop in the absence (primary SS) or in the presence (secondary SS) of another systemic autoimmune disease (1–6). The course of primary SS may be complicated by the development of extraglandular involvement and organ-specific autoimmune disease; discrepancies in reported frequencies of these complications possibly result from the different criteria used for the diagnosis of SS (1–6). Since the first report of an increased incidence of malignant lymphoma in patients with SS (7), multiple examples of this association have been described, and primary SS is often considered to be a link between autoimmune and lymphoproliferative disease (4–8). Based on an epidemiologic study, the risk of malignant lymphoma in patients with SS has been estimated to be ~6.4 cases per 1,000 per year (8).

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In the present study we investigated outcome in patients with isolated KCS, patients with primary SS, and patients with secondary SS, 10–12 years after the initial diagnosis. We studied the development and complications of glandular disease and extraglandular manifestations, as well as the occurrence of lymphoproliferative disease in patients with primary SS and secondary SS. In patients with initial primary SS, we investigated for the development of rheumatoid arthritis or other systemic autoimmune diseases.

PATIENTS AND METHODS

From 1976 through 1980, an ophthalmologic diagnosis of KCS was made in 112 patients who had been referred because of dry eyes. The diagnosis was based on results of the Schirmer I test, the tear fluid lysozyme concentration, and corneal and conjunctival staining with rose bengal dye (evaluated by slit lamp, and with estimation of the van Bijsterveld score) (9). Subsequent assessments included medical history and physical examination, as well as biochemical and immunoserologic investigations. Sublabial salivary gland biopsies were performed according to the method of Greenspan (summarized in ref. 4). For long-term evaluation, we applied the criteria proposed in 1987 by Daniels and Talal (4,10,11) to the available data. SS-related KCS was thus defined by an abnormal rose bengal test result and reduced tear meniscus and break-up time, or an unanesthetized Schirmer test result <5 mm/5 minutes.

Followup assessments were performed 10–12 years after initial diagnosis. Patients who were not regularly seen at our outpatient department were traced with the help of their general practitioner or the Municipal Registry office. Medical history, physical examination, tear gland function tests, and biochemical and immunoserologic (antinuclear antibodies, anti–double-stranded DNA, and rheumatoid factor) investigations were repeated. A second sublabial salivary gland biopsy was not obtained because of its invasive character. In order to determine the lymphocytic focus score, sublabial salivary gland biopsy specimens obtained at initial diagnosis were reviewed by 2 of the authors (CB and PCMdeW) (4,10). The more specific and sensitive quantitative immunohistologic criteria to confirm the diagnosis of SS, based on percentages of IgA- and IgG-containing plasma cells, could not be used in this study: all sublabial salivary gland biopsy specimens had been fixed in buffered formol solution, thus making quantitative immunohistochemical investigation unreliable (12,13).

Six patients were excluded from the study because their sublabial salivary gland biopsy specimens were not available for review at followup. In 31 patients without another systemic autoimmune disease, review of the lip biopsy specimen revealed a focus score >1, i.e., more than 1 focus of at least 50 lymphocytes/4 mm^2, compatible with a diagnosis of primary SS. In 56 patients without another systemic autoimmune disease, review of the sublabial salivary gland biopsy revealed a focus score <1; thus, the initial ophthalmologic diagnosis of KCS was maintained. In 19 patients with a focus score >1, a diagnosis of secondary SS was made because of the presence of another connective tissue disease: rheumatoid arthritis in 11 patients, dermatomyositis in 2, systemic sclerosis in 4, and systemic lupus erythematosus in 2. At followup, additional tests were performed, including testing for antibodies against extractable nuclear antigens (anti-RNP, anti-Sm, anti–Ro/SS-A, and anti–La/SS-B antibodies) determined by counterimmunoelectrophoresis, and anti-RNP, anti-Sm, anticentromere, anti–Scl-70, and anti–La/SS-B antibodies by HeLa cell immunoblotting.

Statistical analysis. To determine the statistical significance of differences between the groups of patients with isolated KCS, primary SS, and secondary SS at study entry and at follow up, the chi-square test and the Kruskal-Wallis test were used for dichotomous and continuous variables, respectively. To determine the significance of differences between the groups with isolated KCS and primary SS and between the groups with primary SS and secondary SS at study entry, the chi-square test and the Mann-Whitney test were used for dichotomous and continuous variables, respectively. The statistical significance of differences within patient groups at followup versus study entry was determined with the McNemar test and the Wilcoxon signed rank test for dichotomous and continuous variables, respectively.

RESULTS

Baseline findings. Baseline characteristics of the patients by group are shown in Table 1. In contrast to the 2 other patient groups, the primary SS group was almost exclusively female (93%, versus 58% in the secondary SS group and 66% in the isolated KCS group). Although the patients in the 3 groups reported dryness of the eyes with equal frequency, patients with secondary SS less often reported a sandy feeling in the eyes ($P < 0.05$). Swelling of the parotid glands was noted particularly in patients with primary SS and secondary SS ($P < 0.01$), whereas myalgia and arthralgia were predominantly seen in patients with secondary SS ($P < 0.05$). Arthritis was observed only in patients with secondary SS and rheumatoid arthritis ($P < 0.001$). Raynaud's phenomenon was reported in all 3 patient groups. A statistically significant difference in the results of tear gland function tests was noted between the 3 patient groups: in patients with primary SS, tear fluid lysozyme concentration, Schirmer I test, and the rose bengal test showed a significantly higher degree of deterioration than in patients with isolated KCS or secondary SS.

Statistically significant differences in terms of laboratory parameters were also seen: increased erythrocyte sedimentation rate (ESR) in patients with primary SS and secondary SS ($P < 0.001$) and decreased serum hemoglobin levels in patients with primary SS and secondary SS ($P < 0.001$) as compared

Table 1. Baseline characteristics of the patients, by group*

	Isolated KCS (n = 56)	Primary SS (n = 31)	Secondary SS (n = 19)	*P*
Females	37 (66)†	29 (93)	11 (58)†	$0.001 < P < 0.01$
Mean ± SD age, years	50.7 ± 16.0	55.8 ± 13.2	58.2 ± 13.2	
Mean ± SD disease, years	3.4 ± 3.6	5.4 ± 5.1	3.0 ± 2.6	
Dry eyes	51 (91)	28 (90)	15 (79)	
Sandy feeling in eyes	47 (84)	25 (81)	10 (53)†	$0.01 < P < 0.05$
Inflammatory reaction in eyes	16 (29)	12 (39)	2 (10)	
Oral dryness	39 (70)	28 (90)	16 (84)	
Oral infection	2 (4)	2 (6)	1 (5)	
Subjective parotid swelling	0 (0)†	14 (45)	5 (26)	$0.001 < P < 0.01$
Fatigue	18 (32)†	15 (48)	6 (32)	
Myalgia	19 (34)	14 (45)	13 (68)	$0.01 < P < 0.05$
Arthralgia	18 (32)	12 (39)	13 (68)	$0.01 < P < 0.05$
Arthritis	0 (0)	0 (0)	11 (58)†	<0.001
Raynaud's phenomenon	9 (16)	4 (13)	4 (21)	
Objective parotid swelling	3 (5)	6 (19)	4 (21)	
Lymphadenopathy	0 (0)	1 (3)	0 (0)	
Hepatomegaly	0 (0)	1 (3)	0 (0)	
Splenomegaly	0 (0)	0 (0)	0 (0)	
Neuropathy	0 (0)	1 (3)	0 (0)	
Malignant lymphoma	0 (0)	0 (0)	0 (0)	
Extraglandular disease	2 (4)†	8 (26)	8 (42)	<0.001
Antinuclear antibodies	1 (2)†	13 (42)	5 (26)	<0.001
Rheumatoid factor	3 (5)†	15 (48)	5 (26)	<0.001
Antithyroid antibodies	3 (5)	3 (10)	2 (10)	
Antiparietal antibodies	0 (0)	1 (3)	0 (0)	
Anti–smooth muscle antibodies	0 (0)	1 (3)	1 (5)	
Antimitochondrial antibodies	0 (0)	0 (0)	1 (5)	
Anti–salivary gland antibodies	0 (0)	2 (6)	1 (5)	
Mean ± SD tear lysozyme concentration, μg/ml	1,061 ± 727†	511 ± 308	1,066 ± 770†	<0.001
Mean ± SD Schirmer test result, mm/5 minutes	9.9 ± 8.7†	4.5 ± 3.3	6.6 ± 5.0	$0.001 < P < 0.01$
Mean ± SD rose bengal test	3.4 ± 2.0†	4.6 ± 1.7	3.0 ± 1.7†	$0.001 < P < 0.01$
Mean ± SD ESR (Westergren), mm/hour	11.8 ± 13.1†	38.5 ± 27.6	40.3 ± 27.6	<0.001
Mean ± SD serum hemoglobin, gm/dl	14.5 ± 1.1†	13.2 ± 1.5	12.9 ± 2.3	<0.001
Mean ± SD IgG, gm/liter	12.2 ± 3.3†	19.9 ± 8.7	15.8 ± 6.2	<0.001
Mean ± SD IgM, gm/liter	1.5 ± 0.9	2.2 ± 2.8	3.0 ± 4.7	
Mean ± SD IgA, gm/liter	1.9 ± 0.7†	3.4 ± 1.9	3.0 ± 2.3	<0.001

* Except where otherwise indicated, values are the number (%). Normal values are are follows: tear lysozyme concentration ≥1,400 μg/ml; Schirmer test >5 mm/5 minutes; rose bengal test <3; erythrocyte sedimentation rate (ESR) 2–12 mm/hour; serum hemoglobin 11.9–17.2 gm/dl; serum IgG 6.83–11.17 gm/liter; serum IgM 0.86–1.78 gm/liter; serum IgA 0.89–1.99 gm/liter. KCS = keratoconjunctivitis sicca; SS = Sjögren's syndrome.

† $P = 0.05$ versus primary SS group.

with KCS, whereas in patients with primary SS, serum IgG and IgA levels were significantly increased ($P < 0.001$). Antinuclear antibodies and rheumatoid factor were predominantly seen in patients with primary SS or secondary SS ($P < 0.001$).

At study entry, 8 of 31 patients with primary SS exhibited extraglandular manifestations or organ-specific autoimmune disease (patients 57–64, Table 2). One of these patients (patient 57) had lymphadenopathy and hepatomegaly, but no cause was found despite extensive examination including laparotomy, and the findings proved to be transient. Of the patients with isolated KCS, 1 exhibited vitiligo and primary autoimmune hypothyroidism and 1 had hyperthyroidism (patients 1 and 2, Table 2). Among the patients with secondary SS, organ-specific autoimmune disease was seen in 1 (patient 89, Table 2), whereas several patients expressed extraglandular manifestations which could be attributed in part to the underlying systemic autoimmune disease (Table 2).

Findings at followup. In the primary SS group, 1 patient was unwilling to cooperate and 1 was lost to followup. Eight of 30 patients with primary SS had died at the time of the followup investigation; lymphoid malignancy was the cause of death in 3 (Table 2). Of these 3 patients, 1 had developed a rapidly progressive swelling of the left submandibular gland and enlarged lymph nodes in the neck region within 2

Table 2. Extraglandular and organ-specific autoimmune disease in patients with KCS, primary SS, and secondary SS at study entry and at followup, and overall mortality and mortality related to lymphoma at followup*

Group, patient no.	Findings at study entry	Findings at followup†
Isolated KCS (n = 56, 38)		
Patient 1	Vitiligo, primary autoimmune hypothyroidism	NC
Patient 2	Hyperthyroidism	NC
Patient 3	–	IgA nephropathy
Patient 4	–	Antithyroid antibodies, euthyroidism
Patient 5	–	Primary hypothyroidism, no antithyroid antibodies
Primary SS (n = 31, 21)		
Patient 57	Hepatomegaly,‡ lymphadenopathy‡	Death due to infection
Patient 58	Primary biliary cirrhosis	NC
Patient 59	Primary autoimmune hypothyroidism	NC
Patient 60	Primary autoimmune hypothyroidism	RA
Patient 61	Vitiligo	NC
Patient 62	Hyperviscosity syndrome‡	IgMκ paraproteinemia, peripheral neuropathy
Patient 63	Renal tubular acidosis, leukocytoclastic vasculitis (skin on legs)	NC
Patient 64	Mild renal dysfunction, pericarditis‡	NC
Patient 65	–	Sclerodactyly, no anti-centromere or anti–SC1-70 antibodies, pernicious anemia, antiparietal antibodies
Patient 66	–	Raynaud's phenomenon
Patient 67	–	Death due to lymphoma§
Patient 68	–	Death due to lymphoma
Patient 69	–	Death due to lymphoma
Secondary SS (n = 19, 12)		
Secondary SS/RA (n = 11, 6)		
Patient 87	Systemic vasculitis‡	–
Patient 88	Pericarditis‡	Cardiovascular disease
Patient 89	Primary autoimmune hypothyroidism	Death due to cardiovascular disease
Patient 90	Cardiomyopathy	Death due to cardiovascular disease
Secondary SS/DM (n = 2, 2)		
Patient 98	Interstitial nephritis	NC
Secondary SS/SSc (n = 4, 3)		
Patient 100	IgA nephropathy	NC
Patient 101	–	Primary autoimmune hyperthyroidism
Secondary SS/SLE (n = 2, 1)		
Patient 105	Bone marrow hypoplasia	Cerebrovascular accident
Patient 106	Mixed type III cryoglobulinemia	Death due to cardiovascular disease

* n values represent the totals at study entry and at followup, respectively. KCS = keratoconjunctivitis sicca; SS = Sjögren's syndrome; NC = not changed; RA = rheumatoid arthritis; DM = dermatomyositis; SSc = systemic sclerosis.
† Mortality related to lymphoma was 0/53, and overall mortality was 10/53, in the group with isolated KCS. Mortality related to lymphoma was 3/30 and overall mortality was 8/30 in the group with primary SS. Mortality related to lymphoma was 0/18 and overall mortality was 6/18 in the group with secondary SS.
‡ Transient.
§ Lymphoma developed within 2 months of diagnosis (see Results).

months after primary SS was diagnosed; biopsy of the submandibular gland revealed a centroblastic/centrocytic malignant lymphoma. Sicca symptoms had started 6–12 months before the diagnosis of primary SS was made. Her death may (arbitrarily) be considered not SS related because in retrospect, the possibility cannot be excluded that the sicca symptoms as well as the infiltrates seen on sublabial salivay gland biopsy were due to early stages of lymphoma.

The second patient developed extreme fatigue and dizziness 3 years after study entry; further investigation revealed malignant lymphoma, i.e., immunoblastic sarcoma located in the abdomen, bone, and cerebrum. In spite of treatment with cytostatic drugs, the patient died 2 years after the diagnosis of malignant lymphoma.

The third patient was admitted to the hospital 3 years after study entry because of confluent hemorrhage of the skin of the abdomen, arms, and legs. Within 3 days she went into coma, a clinical diagnosis of intracerebral hemorrhage was made, and she subsequently died. Autopsy revealed polymorphic

Table 3. Differences in patient groups between baseline and followup*

	Isolated KCS (n = 38)		Primary SS (n = 21)		Secondary SS (n = 12)	
	Baseline	Followup	Baseline	Followup	Baseline	Followup
Dry eyes	33 (87)	30 (79)	19 (90)	19 (90)	9 (75)	9 (75)
Sandy feeling in eyes	34 (89)	26 (68)†	19 (90)	15 (71)	7 (58)	4 (33)
Inflammatory reaction in eyes	13 (34)	1 (3)‡	9 (43)	2 (9)	2 (17)	0 (0)
Oral dryness	27 (71)	26 (68)	18 (86)	16 (76)	10 (83)	7 (58)
Oral infection	1 (3)	1 (3)	0 (0)	0 (0)	1 (8)	0 (0)
Subjective parotid swelling	4 (10)	1 (3)	7 (33)	4 (19)	5 (42)	2 (17)
Fatigue	15 (39)	14 (37)	8 (38)	9 (43)	4 (33)	7 (58)
Myalgia	14 (37)	17 (45)	10 (48)	12 (57)	9 (75)	5 (42)
Arthralgia	12 (32)	17 (45)	8 (38)	9 (43)	7 (58)	6 (50)
Arthritis	0 (0)	0 (0)	0 (0)	1 (1)	6 (50)	6 (50)
Raynaud's phenomenon	7 (18)	4 (10)	3 (14)	4 (19)	2 (17)	2 (17)
Objective parotid swelling	2 (5)	1 (3)	4 (19)	2 (9)	4 (33)	2 (17)
Lymphadenopathy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hepatomegaly	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Splenomegaly	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Neuropathy	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Lymphoma	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Antinuclear antibodies	0 (0)	5 (13)	11 (52)	12 (57)	3 (25)	3 (25)
Anti–doubled-stranded DNA	0 (0)	1 (3)	0 (0)	3 (14)	1 (8)	1 (8)
Rheumatoid factor	2 (5)	5 (13)	11 (52)	11 (52)	2 (17)	4 (33)
Antithyroid antibodies	2 (5)	5 (13)	3 (14)	4 (19)	1 (8)	1 (8)
Antiparietal antibodies	0 (0)	1 (3)	1 (5)	1 (5)	0 (0)	0 (0)
Anti–smooth muscle antibodies	0 (0)	2 (5)	0 (0)	2 (10)	0 (0)	0 (0)
Antimitochondrial antibodies	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)
Anti–salivary gland antibodies	0 (0)	0 (0)	1 (5)	2 (10)	1 (8)	1 (8)
Counterimmunoelectrophoresis						
Anti-RNP antibodies	–	0 (0)	–	0 (0)	–	0 (0)
Anti-Sm antibodies	–	0 (0)	–	0 (0)	–	0 (0)
Anti–SS-A antibodies	–	0 (0)	–	13 (62)	–	1 (8)
Anti–SS-B antibodies	–	0 (0)	–	11 (52)	–	0 (0)
HeLa cell immunoblotting						
Anti-RNP antibodies	–	1 (3)	–	0 (0)	–	0 (0)
Anti-Sm antibodies	–	1 (3)	–	0 (0)	–	0 (0)
Anticentromere antibodies	–	1 (3)	–	0 (0)	–	1 (8)
Anti–Sc1-70 antibodies	–	1 (3)	–	0 (0)	–	1 (8)
Anti–SS-B antibodies	–	6 (16)	–	9 (43)	–	2 (17)
Mean ± SD (Westergren), mm/hour	8.3 ± 5.7	11.5 ± 9.7†	37.8 ± 29.7	44.6 ± 37.8	31.1 ± 27.2	26.9 ± 18.9
Mean ± SD serum hemoglobin, gm/dl	14.5 ± 1.0	14.3 ± 1.0	13.4 ± 1.5	13.2 ± 1.5	12.9 ± 2.3	13.7 ± 2.3
Mean ± SD IgG, gm/liter	12.1 ± 3.4	11.6 ± 3.5	19.9 ± 8.1	16.9 ± 6.1†	16.0 ± 6.6	14.6 ± 5.1
Mean ± SD IgM, gm/liter	1.5 ± 0.9	1.5 ± 0.9	2.5 ± 3.4	2.7 ± 4.1	2.2 ± 3.0	1.4 ± 0.6
Mean ± SD IgA, gm/liter	2.0 ± 0.7	2.2 ± 0.9†	3.6 ± 2.2	3.5 ± 1.6	2.4 ± 1.4	2.6 ± 1.7

* Except where otherwise indicated, values are the number (%). See Table 1 for definitions and for normal values.
† $0.01 < P < 0.05$, versus baseline.
‡ $P < 0.001$ versus baseline.

immunocytoma in the liver, spleen, and abdominal lymph nodes; furthermore, extensive hemorrhagic diathesis and diffuse intravascular coagulation were noted.

Among the remaining 21 patients with primary SS who were available at the time of followup, 4 had developed new features of autoimmune disease (patients 60, 62, 65, and 66; Table 2). Within the primary SS patient group, no statistically significant differences in symptoms and signs between baseline and followup were noted, apart from the observation that patients with primary SS did not experience as much inflammatory reaction of the eyes at followup ($P < 0.05$) (Table 3). No statistically significant differences in laboratory parameters were noted except for a decrease in the mean serum IgG level ($P < 0.05$) (Table 3).

Six of the patients with secondary SS had died at followup, but none of the deaths was due to lymphoid malignancy; 1 patient in the secondary SS group was unwilling to cooperate. Among the remaining 12 patients available at followup, 1 patient with second-

ary SS and systemic sclerosis had developed primary autoimmune hyperthyroidism (patient 101, Table 2). No statistically significant differences in symptoms and signs or in laboratory parameters between study entry and followup were noted in this group (Table 3).

In the KCS group, 3 patients were lost to followup and 5 were unwilling to cooperate. Ten of 53 patients with KCS had died; none had died of malignant lymphoma. Among the 38 patients with KCS available at followup, 2 had developed features possibly related to autoimmune disease (patients 4 and 5, Table 2). At followup, the proportion of KCS patients who experienced a sandy feeling in the eyes ($P < 0.05$) or an inflammatory reaction of the eyes ($P < 0.001$) was lower than at baseline (Table 3). No further differences in symptoms and signs between study entry and followup were noticed.

Regarding differences in laboratory parameters in the 3 patient groups at followup, anti–Ro/SS-A and anti–La/SS-B antibodies (by counterimmunoelectrophoresis) were present predominantly in patients with primary SS and were absent in patients with KCS ($P < 0.001$); anti–La/SS-B antibodies determined by HeLa cell immunoblotting were present in all 3 patient groups ($P > 0.05$) (Table 3). Statistically significant differences between the 3 patient groups at followup were noted for the ESR ($P < 0.001$) and for serum hemoglobin ($P < 0.05$), IgG ($P < 0.01$), and IgA ($P < 0.05$) levels.

DISCUSSION

In this report we have described the long-term course in a group of 112 patients initially referred to our ophthalmology department because of KCS. Based on application of the classification criteria as proposed by Daniels and Talal, 50 of these patients appeared to have SS. When applying the proposed European Economic Community criteria (14) to the data available at followup, 2 of 38 KCS patients without positive lip biopsy results and all primary SS and secondary SS patients would fulfill these criteria (results not shown). At baseline, 2 of 56 patients with isolated KCS (4%) had features possibly related to autoimmune disease, while 8 of 31 patients with primary SS (26%) and 8 of 19 patients with secondary SS (42%) had extraglandular or organ-specific autoimmune disease ($P < 0.001$) (Table 2), not necessitating treatment with corticosteroids in any of the patients. This rather mild character of SS at the time of inclusion in the study is comparable with that reported in previous studies (1–3,15), despite differences in the selection of patients and in the classification criteria used.

At followup, 4 of 21 patients with primary SS (19%) had developed new features of autoimmune disease, including benign paraproteinemia, peripheral neuropathy, sclerodactyly, and Raynaud's phenomenon (Table 2). Since the prevalence of RA approaches 1.0% in most reported series of Caucasian subjects (16), it can be questioned whether the development of RA meeting the American College of Rheumatology (formerly, the American Rheumatism Association) criteria (17) in 1 patient with primary SS should be considered remarkable. No distinctive predictive value of any laboratory parameter assessed at study entry, with regard to prediction of the development of extraglandular manifestations, could be determined, possibly because of the stable course of the disease. Apart from the development of new extraglandular manifestations in 4 patients, the absence of major differences within the primary SS patient group between study entry and followup is consistent with our clinical observation of absence of major exacerbations and remissions of disease activity in primary SS. In contrast to the demonstration in previous studies of severe extraglandular features of autoimmune disease necessitating corticosteroid treatment (4–6), the extraglandular manifestations in our population with primary SS can be considered mild.

The observation that none of the patients with isolated KCS or secondary SS had developed lymphoproliferative disease confirms the suggestion that it is primary SS in particular which gives rise to an increased risk for the development of lymphoproliferative disorders. At followup, 3 of 30 patients with primary SS had died of malignant lymphoma. In 1 patient, the possiblility that sicca symptoms as well as infiltrates seen on sublabial salivary gland biopsy were due to early stages of lymphoma cannot be excluded. One other patient had developed benign IgMκ paraproteinemia. Covering a total of ~480 person-years from the start of symptoms as recorded in the medical history (310 person-years from the time of diagnosis of primary SS) in the primary SS patient group, these findings are broadly compatible with those reported in a study by Kassan and coworkers (8).

The patients with primary SS and secondary SS in our series may represent a subgroup of SS patients, since all initially had been referred to an ophthalmol-

ogy department because of dry eyes. Apart from the marked risk for development of malignant lymphoma, necessitating clinical followup of the individual patient on a regular basis, our findings show that primary SS is characterized by a stable and relatively mild course. Since patients with isolated KCS do not have an increased risk for development of malignant lymphoma, a presumptive diagnosis of primary SS should be confirmed in order to determine the necessity of long-term medical monitoring.

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