Autoimmunity Reviews 9 (2010) 595–599

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Immunological profile in primary Sjögren syndrome
Clinical significance, prognosis and long-term evolution to other auto-immune disease

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ARTICLE INFO

Available online 10 May 2010

Keywords:
Primary Sjögren's syndrome
Cryoglobulinemia
Anti-SSA/SSB antibodies
Systemic sclerosis
Lupus erythematosus
Polymyositis

ABSTRACT

Objective: To study evolution of pSS immunological profile, impact on pSS activity and the long-term evolution of patients with atypical auto-antibodies in a bicentric cohort of patients with pSS ($n=445$, mean age 53.6 ± 14 years, mean follow-up 76.1 ± 51 months).
Results: 212 patients were SSA positive and 131 were both SSA and SSB positive. During follow-up, SSA antibodies disappear in 8 patients; 2 of them exhibit new systemic complications of pSS. 68 patients had cryoglobulinemia. 52 patients had other anti-nuclear antibodies (ANA) specificities: anti-RNP ($n=12$), anti-centromere ($n=14$), anti-DNA native ($n=19$), anti-Scl70 ($n=3$), anti-JO1 ($n=3$), anti-Sm ($n=3$) and anti-histone ($n=1$).
Fourteen patients developed ANA-associated auto-immune disease during the follow-up: 5 polymyositis (mean apparition delay 78 months), 6 systemic lupus erythematosus (mean occurrence delay 77 months) and 2 systemic sclerosis (mean occurrence delay 133 ± 64 months). Among these 14 patients, only three presented atypical-ANA at pSS diagnosis.
Cryoglobulinemia and anti-SSA and SSB antibodies at diagnosis were associated with new systemic involvements.
In conclusion: Cryoglobulinemia and SSA/SSB positivity are associated with systemic activity after diagnosis in pSS. Although atypical ANA are found in 12% of the cases, long-term evolution to ANA associated auto-immune diseases concerned patients with active immunological profile and extra-glandular manifestations.

Contents

1. Introduction

Primary Sjögren Syndrome (pSS) is characterized by polyclonal B cell activation leading to chronic hypergammaglobulinemia, increased

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doi:10.1016/j.autrev.2010.05.004

levels of ß2 microglobulinemia and concomitant presence of a variety of autoantibodies (Ab) both organ specific and nonspecific [1]. Among the antinuclear autoantigens targets, the ribonucleoprotein particles (Ro/SSA and La/SSB) appear to have a prominent role in pSS diagnosis and systemic activity [2–12]. RF, hypergammaglobulinemia and cryoglobulinemia, close-associated with an active systemic profile, presented also a prognosis value in pSS [2–18]. Anti-nuclear antibodies (ANA) with other specificity have been reported in large cohorts of patients with pSS [4,6,8,15,19–24]. Even so, the clinical and immunological significances of those other auto-Ab against nuclear antigens have been little studied in primary SS; furthermore long-term evolution of patients with such auto-Ab to other auto-immune disease (AID) remains unknown.

In the current study, we investigated the evolution of immunological profile of patients in a large cohort of patients with pSS and long-term follow-up. We particularly focused on patients with atypical immunological profile and/or with long-term evolution to other ANA associated AID.

2. Patients and methods

A total of 445 patients with pSS according to the 2002 revised American–European classification criteria (400 women, mean age at diagnosis 53.6 ± 14 years) from two Departments of Internal Medicine in France (Lille $n = 282$ and Limoges $n = 163$) were enrolled in the study between 1985 and 2009 [25]. In this retrospective study, patients' biographical, clinical, and laboratory data were taken from a pSS data file common to both centers [12,26]. Most of the patients had been followed at least yearly by a clinical assessment and immunological tests.

Student's T test, Wilcoxon and Chi-square tests were used to compare pSS patients with different immunological profile. A p value ≤ 0.05 was considered as statistically significant. Kaplan–Meier method was used to study the initial impact of immunological profile on the time of appearance of new systemic involvement, and the difference between curves was examined by the log-rank test.

3. Results

Systemic profile of pSS: pSS was limited to a chronic sicca syndrome in 49 patients (11%). By contrast, 396 patients (89%) presented systemic complications, which were present at time of diagnosis in 330 cases (74%). Details of clinical manifestations of pSS are described in Table 1.

3.1. Variation of immunological profile during follow-up

225 patients (51%) had hypergammaglobulinemia that was present at time of diagnosis in 201 cases (45%). During follow-up, seric gammaglobulins returned to normal levels in 21 cases only {spontaneously ($n = 12$), after corticosteroid treatment ($n = 9$)}. RF was detected in 184 patients (41%) and was present at time of pSS diagnosis in 91% of the cases ($n = 168$). ANA were positive at time of diagnosis in 316 patients (71%, mean positive dilution 1/2000) or appeared during follow-up in 31 patients (7%). On the contrary, ANA disappears in 21 cases {pSS with systemic complications ($n = 19$)}.

Table 1
Clinical and immunological characteristics {number, (percentage)}, numbers of systemic involvements (inv) associated with atypical antinuclear antibodies (ANA) and evolution to other AID in pSS.

	pSS	Atypical ANA +	Atypical ANA -	p	Evolution to AID	pSS	p
	$n = 445$	$n = 53$	$n = 392$		$n = 14$	$n = 431$	
Epidemiological data							
Male	45 (10)	4 (8)	41 (10)	0.8	2 (14)	43 (10)	0.64
Age at diagnosis (years)	53.6 ± 14	52.5 ± 13.8	53.9 ± 14.9	0.5	44.9 ± 10.7	54 ± 14.7	0.02
Focus score ≥ 1	404 (91)	49 (94)	355 (90)	0.99	14 (100)	390 (90)	0.61
Clinical manifestations							
Salivary gland enlarg.	113 (23)	19 (36)	94 (24)	0.04	3 (21)	110 (25)	0.99
Raynaud phenomenon	189 (42)	33 (63)	156 (40)	0.001	11 (78)	177 (41)	0.01
Articular involvement	222 (50)	32 (61)	190 (48)	0.07	11 (78)	209 (48)	0.05
Cutaneous vasculitis	70 (16)	9 (17)	61 (15)	0.68	4 (28)	66 (15)	0.25
Renal involvement	34 (8)	5 (9)	29 (7)	0.58	0	34 (8)	0.61
Neuropathies	70 (16)	12 (23)	58 (15)	0.09	3 (21)	67 (15)	0.44
Lymphoma	18 (4)	3 (6)	15 (4)	0.45	0	18 (4)	0.99
Pulmonary involvement	55 (12)	13 (25)	47 (12)	0.5	5 (36)	50 (12)	0.01
Muscular involvement	78 (17)	11 (21)	67 (17)	0.43	4 (28)	74 (17)	0.28
Number of systemic inv.	2.45 ± 1.35	3.1 ± 1.7	2.3 ± 1.6	0.003	3.6 ± 1	2.4 ± 1.6	0.005
pSS related death	14 (3)	0	14 (3)	0.38	0	14 (3)	0.99
Immunologic data							
Rheumatoid factor	184 (41)	22 (42)	162 (41)	0.99	7 (50)	177 (41)	0.58
ANA	347 (78)	–	–		13 (93)	334 (77)	0.3
Anti-SSA	221 (48)	25 (48)	187 (48)	0.99	10 (71)	211 (49)	0.1
Anti-SSB	139 (31)	13 (25)	126 (32)	0.34	7 (50)	132 (31)	0.14
Atypical ANA	52 (12)	–	–		3 (21)	49 (11)	0.08
Cryoglobulinemia	68 (15)	6 (11)	62 (16)	0.54	3 (21)	65 (15)	0.46
Hyperγglobulinemia	225 (50)	37 (71)	188 (48)	0.001	12 (86)	210 (49)	0.01
Lymphopenia	144 (32)	18 (35)	126 (32)	0.87	4 (28)	144 (33)	0.9
Anti-phospholipid Ab.	49 (12)	6 (11)	43 (11)	0.81	3 (21)	46 (11)	0.2
Monoclonal γpathy	36 (8)	5 (10)	31 (8)	0.59	2 (14)	34 (8)	0.31
Associated AID	101 (22)	13 (25)	88 (22)	0.72	3 (21)	98 (23)	0.9
Evolution to other AID	14 (3)	5 (10)	9 (2)	0.02	–	–	–
Treatment							
Corticosteroid	171 (38)	27 (52)	144 (37)	0.04	8 (57)	163 (38)	0.17
Hydroxychloroquine	136 (30)	20 (38)	116 (29)	0.2	10 (71)	126 (29)	0.001
Immunosuppressive drugs	83 (19)	15 (29)	68 (17)	0.05	5 (36)	78 (18)	0.07