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DEMOGRAPHIC AND CLINICAL FEATURES OF PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME IN ANTALYA

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ABSTRACT

Background: Primary Sjögren's syndrome (SS) is an autoimmune disease display symptoms of ocular and oral dryness, salivary glands enlargement systemic manifestations such as, muscle-joints and gastrointestinal symptoms, hematological, neurological and pulmonary involvements. This study was conducted to determine demographic, characteristics and clinical features of primary SS patients in Turkey.

Methods: In this study were included the patients with primary SS (pSS) diagnosed between 2004-2014 years at the Akdeniz University Hospital, Antalya, Turkey. The clinical and laboratory features were retrospectively obtained from medical charts.

Results: We had 718 patients with suspected pSS at 10 years. 372 patients were classified as pSS according to 2012 American Collage of Rheumatology Classification Criteria for Sjögren's Syndrome. pSS was more frequent among women and ratio women/men was 11/1. The mean age at the time of pSS diagnosis was 50.3±11.81 years. In men, pSS was diagnosed at an older age, and lung involvement was common than women. Joint involvement is the most common extraglandular involvement. Anemia is present in 21.1 % of the patients. Malignancy was diagnosed in 14 patients (3.8%) and 18 patients died (4.8%) during follow-up. Hydroxychloroquine is the most preferred drug as a therapeutic agent

Conclusions: This study suggested that the characteristics of Turkish pSS patients are similar to the other studies, but we observed lung involvement higher male than female pSS.

1. Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease with unknown etiology and involves mainly salivary and lacrimal glands [1]. The symptoms are nonspecific at the onset of disease, however, pSS is a chronic disease and it needs long follow-up time, treatment and supportive care [2]. Despite all therapeutic approaches, malignancies, lypmhomas in particular, and serious organ involvements develop and pSS related mortality increases [3].

Several studies has shown that pSS mortality is related to systemic involvement and lymphoma[4-6]. pSS cohort studies show that mortality rates decreased in recent years, while mortality in 1970s was 48%, in 2000s was 5-15% [7-12]. In a recently published report [13] adjusted standardized mortality ratio was 4.66 (95% CI 3.85-5.60), survival rates at 5, 10, 20 and 30 years were calculated as 96%, 90%, 81% and 60%, respectively. It is suggested that male gender, criyoglobulinemia, low C4, constitutional symptoms, pulmonary involvement and biologic domains of EULAR SS Disease Activity Index (ESSDAI) were related to high risk of mortality.

The incidence, severity, and outcome of the disease show variability between different ethnical-origin groups. This variability is related to the socioeconomic genetic and/or environmental factors (14). In our country, there is limited data about incidence, clinical course, extra-articular

symptoms, and outcomes of pSS patients. The aim of this study was to evaluate the demographic and clinical features of Turkish pSS patients followed-up in a single tertiary referral hospital in Antalya.

2. Material and Methods

Patients

We reviewed retrospectively clinical and laboratory findings of preliminary diagnosis of 718 pSS patients who applied Medical Faculty Rheumatology Department from 2004 to 2014. Only 660 patient's charts and electronic data were available. 271 patients were not fulfilled criteria of ACR 2012 criteria for pSS[15]. Of 17 patients who have not enough data were excluded from the study. Demografic data, clinical, laboratory findings and treatment informations of pSS diagnosed 372 patients were collected.

Each patient's data reviewed and collected from hospital files and electronical records. In any time of follow-up, all of symptoms, clinical findings and organ involvement related to disease were noted. Autoantibodies, including anti-nuclear antibodies (ANA), rheumatoid factor (RF), Anti-Ro and Anti-La, results also were noted.

A positive labial salivary gland biopsy (LSGB) was described a focus score>1 per 4 mm 2 tissue sample. A focus was determined to be a collection of mononuclear cells with more than 50 lymphocytes/plasma cells and macrophages [16].

The duration of disease was defined as the time from diagnosis to study or the date of death. To detect patients death and malignancies hospital records were reviewed. The causes of death were investigated in the medical records if the patient had died in our hospital. If the patient had been lost to follow-up, the patient or his/her first degree relatives were contacted by phone and also the patient's situation alive or dead was noted. We also reviewed whether or not any of patients died from National Insurance Registry System.

The study was approved by the local ethic committee and conducted in the basis of World Medical Association Helsinki Declaration.

Statistical analysis

Windows SPSS 18 program (SPSS Inc., Chicago, USA) was used for statistical analysis. Demographic characteristics were analyzed with descriptive statistics. Chi-quare test were used to compare categorical data. Group distributions were assessed with kolmogorow-smirnov test. When comparing continuous data, as the distribution was normal, the Student-T test was used and results were expressed as mean ±SD (standard deviation). The parameters do not meet the normal distribution were compared with Mann Whitney U test.

3. Results

In this study, we analysed the data of 372 patients who diagnosed pSS between 2004 – 2014 in a tertiary referral hospital. Mean age is 55.6±11.9 years, mean diagnosis age is 50.3±11.8 years and mean duration follow-up is 5.25±3.44 years. The percentage of female is 91.7%. ANA, Anti-Ro, Anti-La and RF are positive 58.8%, 37.0%, 15.8%, 24.1% in patients, respectively. Labial salivary gland biopsy was performed in 337 patients (90%) and the percentage of patients with focus score ≥1 is 69.7% (Table 1).

The frequency of anaemia is 21.1%, leukopenia 11.1% and thrombocytopenia 0.8 % during follow-up. Joint complaints are the most frequent systemic symptoms (71.4% of patients), 6.1% of patients had cutaneous rash and 18% Reynaud phenomenon. Gastrointestinal symptoms had 21.9% and elevated liver function tests were detected in 17.9 % of patients. Lung involvement was 12.6% and neurological findings were seen in 6.5% of patients (Table 1).

The most commonly (90.9%) used agent for the

treatment was hydroxychloroquine sulphate. The percentage of corticosteroids use was 32.7%, metotrexate was 16.0% and azatiopurine was 10.2%. The frequency of pilocarpine hydrochloride for sicca symptoms was very low (11.6%) (Table 1).

Female pSS patients are younger than male patients (mean age; 49.9±11.7 vs 54.6±12.3, p=0.036). But there is no difference in disease duration between female and male patients (p=0.616). ANA positivity rates are higher in females than in males (41.9% vs 60.4%, p=0.046). Anemia and joint involvements are significantly higher in women (p<0.001), however lung involvement rate is significantly higher in men (p <0.001) (Table 2).

There are 14 patients diagnosed malignancy. The incidence of malignancy is 3.8% in the 10-year follow-up period. Median age of the malignancy diagnosis is 62.5 years (Min- Max; 43-85). Characteristics of patients with malignancy were shown on Table 3.

Mortality rate is 4.8% and significantly higher in male (n:5, 16.1%) than in female (n:13, 3.8%) (p=0.003) in 10-years period. Median age of death is 68-years (Min-Max=48-85) and the median time

Table 1: The demographic features of the study group (n=372)

Age (Mean±SD)(y)	55.6±11.9	
Age of Diagnosis(Mean±SD)(y)	50.3±11.8	
Duration of Disease (Mean±SD)(y)	5.25±3.44	
	(%)	**(n/total case)**
Sex(Female)	91.7	(341/372)
Death	4.8	(18/372)
LSG focus score >1	69.7	(235/337)
Laboratory features		
ANA (+)	58.8	(152/217)
RF (+)	24.1	(85/268)
Anti-Ro(+)	37.0	(122/208)
Anti-La(+)	15.8	(52/278)
ANCA(+)	14.5	(9 /53)
Anemia	21.1	(77/288)
Leucopenia	11.1	(41/330)
Thrombocytopenia	0.8	(3/363)
Hypergammaglobulinemia	33.7	(34/101)
Hypocomplementemia	8.7	(19/217)
Clinical features		
Skin Eruptions	6.1	(14/217)
Raynaud phenomenon	18.0	(54/246)
Arthritis or arthralgia	71.4	(266/372)
Hepatic involvement	17.9	(31/142)
Gastrointestinal involvement	21.9	(39/139)
Arterial hypertension	35.8	(133/372)
Lung involvement	12.6	(47/372)
Neurologic involvement	6.5	(24/372)
Malignancy	3.8	(14/372)
Treatment Usage		
Anti-malarial	90.9	
Corticosteroid	32.7	
Azathiopurine	10.2	
Methotrexate	16.0	
Sulfasalazine	7.3	
Pilocarpine	11.6	
Others(Cyclophosphamide,anti-TNF...)	4.4	

LSG=Labial salivary gland, ANA=Antinuclear antibody, RF=Rheumatoid arthritis, ANCA=Anti-neutrophil cytoplasmic antibody, TNF=Tumor necrosis factor

from diagnosis to death is 6.5 years (Min-Max=1-10). The frequency of death is higher in patients with lung manifestations. The other causes of death are malignant, heart failure, fournier gangrene and surgical complications.

4. Discussion

Our study provided detailed information of about 372 pSS patients various parameters such as demographic and clinical features, laboratory findings. The female/male ratio was 11/1 and this

Table 2. Clinical and serological characteristics in female and male patients with pSS

	Female (n=341)	Male (n=31)	p
Age (Mean±SD)(y)	55.1±11.7	60.1±12.3	0.026
Age of Diagnosis(Mean±SD)(y)	49.9±11.7	54.6±12.3	0.036
Duration of Disease (Mean±SD)(y)	5.22±3.4	5.54±2.9	0.616
Death	%3.8	%16.1	0.003
ANA	%60.4	%41.9	0.046
RF	%23.7	%28.6	0.562
Anti-Ro	%36.9	%37.5	0.955
Anti-La	%16.0	%12.5	0.649
Anemia	%22.5	%6.5	0.037
Leucopenia	%11.2	%9.7	0.799
Thrombocytopenia	%0.9	%0.0	0.597
Skin Eruptions	%6.1	%5.9	0.974
Raynaud phenomenon	%19.3	%4.0	0.057
Joint symptoms	%74.0	%42.9	<0.001
Hepatic involvement	%17.5	%23.1	0.614
Gastrointestinal involvement	%21.2	%30.8	0.423
Arterial hypertension	%36.2	%31.6	0.690
Lung involvement	%9.4	%48.4	<0.001

ANA=Antinuclear antibody, RF=Rheumatoid arthritis

Table 3. Clinical features of patients with malignancy

No	Age	Gender	Duration of disease (y)	Treatment	Malignancy
1	60	F	7	HQ	Skin small cell
2	74	F	3	CS, HQ, AZA	Endometrium
3	70	F	5	CS, HQ, AZA, CyC	Endometrium
4	43	F	3	unknown	Marginal Zone lymphoma
5	62	F	6	CS, HQ, AZA, CyC	Myelodysplastic syndromes Lymphoma
6	43	F	6	HQ	Breast
7	54	F	7	HQ	Breast
8	54	F	3	HQ	Overium
9	60	F	10	HQ	Overium
10	67	M	8	CS, HQ	Pancreatic
11	62	F	7	CS, HQ	Thyroid papillary
12	65	F	8	unknown	Pancreatic
13	84	F	7	HQ	Colon
14	63	F	10	unknown	Lung (non-small cell)

F=Female, M=Male, CS= Corticosteroid, HQ= Hydroxychloroquine sulphate, AZA=Azathiopurine, CyC=Cyclophosphamide

rate was similar to other studies (female/male: 9-20/1) in the literature [17-20]. Both hospital and community-based studies suggest that women more prominent in pSS [21-22]. The mean age of diagnosis in our center was similar with literature [23-25]. Furthermore, the diagnosis age is older in male patients.

In the literature, it is reported that the frequency of anemia was 17.1-20%, leucopenia was 16-19.9% and thrombocytopenia was 8.1-13% in pSS patients [26-28]. However, we revealed that anemia rate was 21.1%, leukopenia 11.1% and thrombocytopenia 0.8% in pSS patients of this study.

Our study showed that the frequency of joint symptoms were 71.4%, Reynaud's Phenomenon 18.0%, gastrointestinal symptoms 21.9%, abnormal liver function tests 17.9% and skin rash 6.1%. The recent studies are reported to frequency of Reynaud's Phenomenon was %14-21 and that is similar to our study [21,29-30]. There were 24 patients with periferal and central neurologic involvements (6.5%). The frequency of neurologic involvement is similar to literature studies [28-29,31-33].

Lung involvement was 12.6% of patients in this study. In our previously reports, lung involvement rate was 12% and 11.4% in pSS patients [23-28,31-34]. In the literature, some studies reported that 3-28% of pSS patients had lung involvements [10, 12, 28, 35-36]. Although pulmonary parenchymal changes can been detected up to 65% of pSS patients with high resolution imaging, only a small portion of them have clinical symptoms [37-41]. The lung involvement rates are highly variable between studies in the literature because the definition of lung involvement and screening imaging methods are different. In this study, pulmonary involvement defined as having clinically symptoms, restricted pulmonary function tests (FVC <%80) and infiltrations in high-resolution computed tomography according to the classiffication of CT patterns described in the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias [42].

There were 18 death events (4.8% of all patients) in 10-year follow-up period. Eight of deaths were associated with pulmonary manifestations, three of them were from solid organ malignancies. However, interestingly none of them was from lymphoma. In another study, it was reported that 20 of 100 pSS patients died during 10-year follow-up period [8]. In that study, 7 deaths were related to malignancy, 5 deaths were related to cerebrovascular events and of 4 deaths were related to cardiac events. In another report including 723 pSS patients [11], mortality rate was 5.3% (39 deaths) and the most common cause of death was related to malignancy (7 lymphoma, 10 non-lymphoma). Petrovaara et al.[10] found 17 deaths in a period of 15 years follow-up in their study including 110 patients; 6 deaths were from cardiac pathology, 4 malignancies, 3 cerebrovascular events, 3 infections and 1 drug toxicity. There is a study compared the cause of deaths in pSS and secondary SS [43].

The relationship between systemic autoimmune diseases, including pSS, and cancer have been known for a long time [22,44]. pSS is known to increase the risk of lymphoma[45]. This study revealed that 3.8% (n:14) of patients developed malignancies. Lymphoma was diagnosed only two patients. In a study [46], malignancy in pSS were found in 33 of 286 patients (11.5%) during 18-year follow-up in Sweden. Eleven of these 33 patients were non-Hodgkin lymphoma (NHL). It also was found the risk factor for the development of lymphoproliferative malignancies related to the decreasing rate of CD4 + / CD8 + T lymphocytes. In the another study including 1320 pSS patients [47] malignancy were 2.2% in a period of 15-year follow-up in China population. Lymphoma was diagnosed only 8 patients. In the other studies in literature, the frequency of lymphoma was reported 2.7-9.8% [10,

44-45, 48]. Lymphoma rate was 5% in 22-year period [48], and 3% in 25-year [45]. In our study, mean duration of the disease is lower than the other studies. We assume that low rate of lymphoma and lymphoma related mortality are associated with short disease duration and follow-up.

There are some limitations in this study. Certain clinical data such as smoking were not enough due to retrospective design. Sufficient information was not noted in patients without symptoms or findings of organ involvements. Serum immunoglobulins and complement levels were not performed in all patients. Besides, tests of ANA, RF and Anti-Ro/La were not performed concurrently and in the same technics.

In conclusion, pSS may exhibit different clinical presentation in different populations. Since our trial includes data from pSS patients followed-up by a single center, it cannot be representative of the whole Turkish pSS patients but this study provide detailed information about the clinical and demographic data and also survival in pSS patients in Antalya, Turkey.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local ethic committee at 12.10.2014 (Number:531)

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