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ORIGINAL INVESTIGATION

Retrospective Evaluation of 100 Patients with Sarcoidosis in Gazi University, Turkey

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Abstract

OBJECTIVES: This study aimed to evaluate the diagnosis, treatment and clinical monitoring of the patients with sarcoidosis and to determine their general characteristics.

MATERIAL AND METHODS: We retrospectively examined demographic, clinical, laboratory and radiological findings of 100 patients who were followed-up with the diagnosis of sarcoidosis in Gazi University of Faculty of Medicine, Department of Chest Disease between 1994 and 2010.

RESULTS: Mean age of the patients was 44±12 years (22-82), female/male ratio was 2.8 and no difference of the age at diagnosis was found between the genders. Most commonly seen complaints included dyspnea, cough and skin disorders. It was reported that 50% of the men and 17% of the women had a history of smoking and that smokers were presented at advanced stages (Stage 2-3) (p=0.006). Three percent of our patients had familial sarcoidosis. It was seen that 96% of the patients had pulmonary tomography at the time of diagnosis. No correlation was detected between angiotensin-converting enzyme (ACE), erythrocyte sedimentation rate and serum and urine calcium levels and the disease stage. Of the patients, 34% showed impaired respiratory function test (RFT) results and 49% showed decreased diffusing capacity of carbon monoxide (DLCO) values, most commonly with restrictive pattern, at the time of diagnosis. Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC) and decreased DLCO values did not show a correlation with the stage of the disease (p<0.01). Of our patients, 16% were diagnosed with sarcoidosis based on clinical, laboratory and radiological findings, whereas other patients underwent some invasive interventions for tissue diagnosis. Most commonly used invasive methods included transbronchial biopsy (34%), punch biopsy (31%), mediastinoscopic or transbronchial mediastinal lymph node biopsy (22% and 9%, respectively). During the follow-up period, 43% of the patients received treatment. During the follow-up, 18 patients (18%) showed relapse in the period after the diagnosis. It was seen that relapse was more common in the patients with advanced stage, who have received treatment at the time of diagnosis (p<0.01 and p=0.04).

CONCLUSION: Sarcoidosis is a multisystemic disease that may have a course with several clinical findings and that should be absolutely considered in the differential diagnosis with its commonly or rarely observed findings.

KEY WORDS: Sarcoidosis, interstitial pulmonary disease, diagnosis, treatment

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INTRODUCTION

Sarcoidosis has been firstly described by Jonathan Hutchinson in 1887 in a patient with skin lesions located on the face and arms and was named as *"Mortimer's Disease"*. Sarcoidosis is a multisystemic disease characterized by non-caseating granulomatous inflammation in the affected sites and its clinical, radiological and histopathological findings has been described but its etiology has not been fully elucidated. Given the study performed by Turkish Thorax Society Clinical Problems Study Group in 2009, the incidence of sarcoidosis is estimated to be 4 per 100.000 in Turkey [1].

Sarcoidosis may be observed in an occasional pulmonary radiography or as constitutional symptoms or the symptoms of the affected organ system. In sarcoidosis, all organ systems may be involved whereas 90% of the cases may exhibit lung and intrathoracic lymph node involvement [2,3]. Therapeutic indications are among conflicting issues in the field of sarcoidosis due to several reasons such as diversity of the natural course of the disease, the lack of the data about long-term effects of the early treatment and symptomatic nature of the therapy. However, the most important trait of the disease is spontaneous remission rate equal to 60-70% and chronic disease rate equal to 10-30%. Therefore, sarcoidosis is generally considered as a benign disease with good prognosis. Mortality rate range between 1 and 5%, commonly resulting from respiratory failure, neurosarcoidosis and cardiac involvement [4].

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This study aimed to retrospectively evaluate diagnostic, therapeutic and clinical process of the patients who admitted to Gazi University, Faculty of Medicine, Outpatient Clinic of Thoracic Diseases between 1994 and 2010 and who were followed-up with the diagnosis of sarcoidosis and to determine their general characteristics.

MATERIAL AND METHODS

Study was approved by Gazi University, Clinical Research Ethic Board. In our study, we retrospectively evaluated the patients who admitted to Gazi University, Faculty of Medicine, Outpatient Clinic of Thoracic Diseases between 1994 and 2010 and who were followed-up with the diagnosis of sarcoidosis. Name of a total of 120 patients were obtained but 20 of these patients were excluded because their data were not sufficient for our study. Demographics, presenting symptoms, diagnostic methods, disease stage, family history, smoking history, laboratory results (ACE, sedimentation, blood and urine calcium levels, RFT results), tuberculin skin test (PPD) results at the time of diagnosis, extrapulmonary involvements, therapeutic response and relapse and remission status were registered in the digital database that was designed for the study.

Diagnosis

Diagnosis was made based on clinical, laboratory and radiological findings as well as by histologically demonstrating typical non-caseating epithelioid-cell granulomas and by excluding other reasons that might have led to granulomatous inflammation [5].

Biochemical Investigations

Angiotensin-converting enzyme (ACE) level was measured using kinetic method and the results ranging between 8 and 52 U/L were considered as normal. Eryhtrocyte sedimentation rate (ESR) was obtained by measuring the sedimentation rate of the erythrocytes placed into a tube within a unit of time and ESR values equal to 20 mm/h in women and to 15 mm/h in men were considered as high. Serum calcium levels were analyzed by calorimetric method in an autoanalyzer using commercially available kits (Abbott) and the results equal to or greater than 10.6 mg/dL were considered as high. 24-hour urine calcium levels were analyzed by calorimetric method in an autoanalyzer using commercially available kits (Abbott) and a result greater than 300 mg/L was considered as high.

Tuberculin Skin Test

Five units of tuberculin (0.5 mL) was intradermally injected in the anterior side of the front arm using 27-gauge needle. Induration was measured 72 hours after the injection. Those with an induration diameters ranging between 0 and 4 mm were considered as negative.

Respiratory Function Test

Respiratory function test was performed using SensorMedics Vmax 20 spirometry (SensorMedics Corp., Yorba Linda, CA, USA) in sitting position. For forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC and diffusing capacity of carbon monoxide (DLCO), the percentage values expected according to patient age, gender and height. For DLCO, the values corrected for hemoglobin were also obtained. FEV_1/FVC <70%, and vital capacity (VC) >80% were considered as obstructive pattern and FEV_1/FVC equal to 61-69% was classified as mild, FEV_1/FVC equal to 45-60% as moderate and FEV_1/FVC <45% as severe obstruction. FEV_1/FVC >70%, VC and FEV_1 <80% were considered as restrictive pattern and VC equal to 66-80% was classified as mild, 51-65% as moderate and <51% as severe restriction. FEV_1/FVC <70%, FEV_1 and VC <80% was considered as mixed pattern. An expected DLCO value below 80% was considered as a decrease of diffusion capacity. A DLCO decrease of 61-80% was classified as mild, 41-60% as moderate and <41% as severe [2,6].

Therapeutic Response Assessment

Clinical response was defined as resolution or relief of pulmonary symptoms and, if any, the symptoms related to extrapulmonary organ involvement. Laboratory response was defined as decreased blood ACE, blood and 24-hour urine calcium levels and sedimentation rates and improvements of 10% and 15% in FVC and DLCO, respectively, in RFT compared to baseline [7]. Radiological response was considered as post-treatment regression or complete recovery compared to pre-treatment pulmonary radiography or thoracic computerized tomography (CT). In our study, to have a therapeutic response, the patients were required to show improvement in at least two clinical, laboratory or radiological response parameters. Newly emergent symptoms or an increase of pre-existing symptoms, increased values of blood ACE, blood and urine calcium and sedimentation rate, defined as activity markers, decreased FVC and DLCO, newly emergent findings or increase of pre-existing findings on pulmonary radiography and/or thoracic CT were considered as relapse.

Statistical Analysis

Study data were evaluated using Statistical Package for the Social Sciences (SPSS Inc, Chicago, IL) software. Continuous variables obtained by measurement were expressed as mean and standard deviation whereas categorical variables as percentages. Categorical variables were compared using Chi-Square (X^2) test and, when necessary, Fisher's exact test. For the comparison of two groups, Student's t test was used for the variables that meet the parametric test conditions and Mann-Whitney U test for those that do not meet parametric test conditions. Comparison across three or more groups was done using Kruskal Wallis H test. In all statistical analyses, significance level was considered as $p<0.05$.

RESULTS

In our study that evaluated 100 patients diagnosed with sarcoidosis between 1994 and 2010, the number of patients diagnosed markedly increased after 2003 compared to previous years. Of 100 patients enrolled to the study, 74 (74%) were female and 26 (26%) were male. Mean age of the patients at the time of diagnosis was 44±12 (22-82). In our study, age at the time of diagnosis was similar between men and women. Smoking rate was 50% in men and 17% in women. Three patients (3%) had familial history of sarcoidosis. General characteristics of the patients are given in Table 1.

Given the complaints and clinical findings reported by our patients at the time of diagnosis, dyspnea (69%) and cough

(57%) were most commonly reported complaints and 32% of the patients showed skin findings. Clinical findings and complaints recorded at the time of diagnosis are given in Table 2 along with their incidence rates.

Of our patients, 16% (n=16) were diagnosed with sarcoidosis based on clinical, laboratory and radiological findings, whereas other patients underwent some invasive interventions for tissue diagnosis. Most commonly used invasive methods included transbronchial biopsy (34%), punch biopsy (31%), mediastinoscopic or transbronchial mediastinal lymph node biopsy (22% and 9%, respectively). Other methods utilized included peripheral lymph node biopsy (5%), open lung biopsy (3.6%) and other organ biopsies (2.3%). At the time of diagnosis, all patients underwent pulmonary radiography and 96 patients (96%) had thoracic computerized tomography (CT). Staging according to the pulmonary radiography obtained at the time of diagnosis is given in Table 1. When the patients who concomitantly had CT were staged according to their CT findings, it was found that 72% of the patients had Stage 2 and 32.2% had stage progression.

While 76.7% of ex-smokers or current smokers were diagnosed at advanced stages such as Stages 2 and 3, 55.7% of non-smokers were diagnosed at earlier stages such as stage 0 and 1. A statistically significant correlation was detected between smoking and late diagnosis (p=0.006).

Thirty eight of 64 patients (59%) who had PPD test at the time of diagnosis had negative results. When the activity markers at the time of diagnosis were examined, it was seen that 56% of the patients in whom ACE level was investigated had ACE levels above normal and mean value was 67.3±52, 3% had elevated serum calcium levels, 14% had hypercalciuria and 50% had elevated sedimentation rate. Of the patients, 34% had impaired RFT and 18.1% had mainly restrictive, 11.7% obstructive and 4.3% mixed patterns. Of the patients, 49% showed decreased DLCO values. While no significant correlation was detected between biochemical activity markers and disease stage, it was observed that RFT parameters were decreased with the progression of the disease stage and that the decreases seen in FEV_1, FVC and DLCO were statistically significant (p=0.007, 0.007 and 0.01, respectively).

Among our patients diagnosed with sarcoidosis, 98% had pulmonary involvement and 43% had extrapulmonary organ involvements, most common of which was skin involvement (32%). When extrapulmonary involvements were examined, it was seen that their incidence was higher in women (48.6%) compared to men (26.9%) but this was not statistically significant (p=0.09). Extrapulmonary involvement rates

Table 1. General characteristics of the patients

Number of patients	**100**
Gender, n (%)	
Male	26 (26)
Female	74 (74)
Age, mean±SD (range), years	**44±12 (22-82)**
Distribution by age, n (%)	
20-29 years	10 (10)
30-39 years	27 (27)
40-49 years	22 (22)
>50 years	41 (41)
Occupation, n (%)	**83 (100)**
Housewife	40 (48)
Officer	18 (22)
Teacher	11 (13)
Craftsman	7 (8)
Healthcare personnel	3 (4)
Other	4 (5)
Smoking at the time of diagnosis, n (%)	
No	70 (70)
Yes	8 (8)
Ex-smoker	22 (22)
Stage at diagnosis	
Stage 0	2 (2)
Stage 1	44 (44)
Stage 2	43 (43)
Stage 3	11 (11)

Mean±SD: mean ± standard deviation

Table 2. Clinical findings and complaints of the patients with sarcoidosis at the time of diagnosis

Clinical finding-complaint	Number of patients (%)
Dyspnea	69 (69)
Cough	57 (57)
Skin finding	32 (32)
Erythema nodosum	24 (24)
Non-erythema nodosum	8 (8)
Fatigue	22 (22)
Articular complaints	22 (22)
Chest pain	21 (21)
Ocular sign	12 (12)
Neurological complaint	11 (11)
Headache	2 (2)
Dizziness	9 (9)
Fever	9 (9)
Sputum	9 (9)
Nocturnal sweating	9 (9)
Musculoskeletal complaints	9 (9)
Myalgia	7 (7)
Bone pains	4 (4)
Weight loss	7 (7)
Hemoptysis	4 (4)

Table 3. Rate of therapy intake of the patients by stage

Stage		0 n (%)	1 n (%)	2 n (%)	3 n (%)	Total n
Therapeutic status	Yes	0 (0)	8 (18.2)	27 (62.8)	8 (72.7)	43
	No	2 (100)	36 (81.8)	16 (37.2)	3 (27.3)	57
Total		2 (100)	44 (100)	43 (100)	11 (100)	100

were significantly higher in the patients aged below 40 years (56%) compared to those aged above 40 years (33.8%) (p=0.02). Furthermore, it was found that extrapulmonary involvement rates decreased with increasing disease stage (p=0.03).

Given all follow-up periods, it was seen that 57 patients (57%) were followed-up off-treatment and 43 (43%) received therapy within various periods. Rates of therapy administration by stage are given in Table 3. Of the patient who were given treatment, 38% (n=38) were initiated on therapy at the time of diagnosis. All these patients received steroid therapy (33, methylprednisolone; 3, deflazacort; 2, fluocortolone) and 1 patient received azathioprine and 1 other received pentoxyphylline in addition to steroid therapy. It was seen that duration of the steroid therapy ranged between 1 month and 24 months and mean therapy duration was 7.8±5.5 months. Furthermore, 21 of 57 patients who were followed-up off-treatment were given inhaled corticosteroid therapy during the period of follow-up.

During the follow-up, 18 patients (18%) showed relapse after the diagnosis (1 relapse in each of 12 patients, three relapses in each of 6 patients). In the patients who were followed-up off-treatment and on-treatment at the time of diagnosis, the incidence rates for relapse were 8.1% and 34.2%, respectively (p<0.01). While no correlation was detected between the occurrence of relapse and age and gender, it was seen that the patients who were presented at later stages had a higher incidence of relapse compared to those who were presented at earlier stages (p=0.04). It was observed that 11 of 57 patients who were followed-up off-treatment did not return for the first outpatient visits and for the follow-up visits after the diagnosis and 14 of 46 patients (30%) who were followed-up off-treatment and who returned for the follow-up visits had spontaneous remission during the follow-up. Of 43 patients who were given treatment, 28 showed a therapeutic response, 7 did not respond to therapy, 6 patients were lost in follow-up and 2 patients were still receving the treatment. When 35 patients with trackable therapeutic response were examined, it was found that age, gender, disease stage and multiorgan involvement had no significant effect on therapeutic response but ACE levels at the time of diagnosis were significantly higher in the patients showed therapeutic response (88±77) compared to those who did not show (46±23) (p=0.04).

Among the patients treated, 29 (67%) experienced adverse effects with varying severities. Among all patients who received treatment, most commonly seen adverse effect was weight gain and edema with an incidence of 44.1% and this was followed by muscular weakness and endocrine and metabolic disorder (hyperglycemia, hyperprolactinemia, menstrual irregularities, increased hair development etc.) with the incidence rates of 30.2% and 20.9%, respectively. Furthermore, 13.9% reported cutaneous adverse effects and 11.9% osteopenia.

Two patients died during the follow-up. Of these two patients, one was a 82-year-old patient diagnosed with Stage 3 sarcoidosis, who had concomitant COPD, pulmonary hypertension and heart failure and the other was a 62-year-old patients diagnosed with Stage 2 sarcoidosis, who had concomitant asthma and Behcet's disease. It was reported that both patients died due to respiratory failure.

DISCUSSION

Sarcoidosis is a multisystemic disease, of which clinical, radiological and histopathological findings have been described but the etiology has not been fully elucidated. In our study that evaluated 100 patients with sarcoidosis who were followed-up in our clinic, the number of the patients diagnosed with sarcoidosis per year was markedly increased after 2003. Of the patients, 26% were male, 74% were female, 48% were housewives and 3% had familial history of sarcoidosis. It was found that 70% of the patients were non-smokers and that the smoker patients admitted at later stages. Diagnosis was put based on clinical, laboratory and radiological findings in 16% and using tissue sampling in 84% of the patients. Most commonly used diagnostic invasive method was transbronchial biopsy. Of the patients who underwent RFT, 34% showed abnormal results. Among the patients in whom diffusion measurements were done, 49% exhibited decreased DLCO values. Of the patients, 98% had pulmonary involvement and 43% had extrapulmonary involvement, most common extrapulmonary involvement being skin involvement (32%) including erythema nodosum. Fifty seven percent of the patients were followed-up off-treatment and 43% received treatment. It was observed that after the diagnosis, 18% of the patients had relapse and 30% of 46 patients who were followed-up off-treatment had spontaneous remission.

Sarcoidosis may be seen in any race and in both genders. While highest incidence rate of the disease is achieved at the age of 20-40 years, it was seen that the incidence rate showed a second peak above the age of 50 years especially in the women that reside in Scandinavian countries and in Japan [8,9]. In the study performed by Musellim et al. [1] (TTD Clinical Issues Study Group) on 293 patients with sarcoidosis in Turkey, it was concluded that the disease was more common in the women compared to men (female/male: 2.08) and that the age of women at the time of diagnosis was older by 10 years compared to men (p<0.001). In

ACCES study, female/male ratio was reported as 1.77 [10]. In the study performed by Gribbin et al. [11] in England, female/male ratio was seen to be 1.11. In our study, similarly to TTD study, 74% of the patients were women and 26% were men (female/male ratio: 2.8). However, unlike TTD study, mean age of our patients at the time of diagnosis was 44±13 (min-max: 22-82) and no difference of mean age was found between the genders (p=0.66). When our patients were grouped by their age at the time of diagnosis, it was seen that the patients were most commonly 30 to 49 years-old, whereas the largest peak was seen in the group aged above 50 years.

In many studies, the correlation of the sarcoidosis with environmental and occupational exposure was addressed. In ACCESS study, the incidence of sarcoidosis was higher among the teachers compared to control group [12]. In another study, the risk for sarcoidosis was reported to be increased among the people who are photocopying for their work [13]. In the study performed by Musellim et al. [1] in Turkey (TTD study), half of the subjects were housewives and they had no occupational interaction that could be associated with the disease. In our study, similar to TTD study, 48% of the patients were housewives. No occupational exposure was detected to establish a correlation between occupational distribution and disease.

Incidence rates of familial case of sarcoidosis was 3% in ACCESS study [14] and 5.9 in the study performed by McGrath et al. [15]. In TTD study, this rate was found to be lower (1%) compared to other studies. In our study, 3 of our patients had familial history of sarcoidosis and the incidence rate was found to be 3%, similarly to ACCES study.

It was seen that 70% of our study participants were non-smokers. Given that the incidence of smoking is 65% in men and 25% in women in the overall Turkish population, it can be concluded that the incidence of smoking is lower in our male and female patients with sarcoidosis compared to overall population. Based on literature data, it was highlighted by Douglas et al. [16] in 1987, by Harf et al. [17] in 1986 and in the study performed by TTD in 2009 in Turkey that the incidence rates of smoking among the patients with sarcoidosis were low [1,16,17]. In ACCES study, a negative correlation was reported between smoking and sarcoidosis [12]. On the other hand, in case control studies published by Gupta et al., [18] it was claimed that such a correlation did not exist.

In the patients with sarcoidosis, most commonly seen clinical findings included dyspnea, dry cough and chest pain. In the study performed by TTD, it was reported that most commonly seen complaint was cough with an incidence rate of 53.2%, which was followed by dyspnea with an incidence rate of 40.3% and chest pain an incidence rate of 22.5%, respectively [19]. In the same study, skin findings were reported in 30.7% of the patients. In our study, unlike TTD study, most commonly observed clinical finding was dyspnea (69%), which was followed by cough (57%) and skin findings (32%).

In approximately 90% of the patients with sarcoidosis, various radiological findings may be encountered at the time of diagnosis [20]. Although pulmonary radiography is sufficient for diagnosing, monitoring and staging of the pulmonary sarcoidosis, in some cases, pulmonary tomography is needed. Based on literature data and investigators' experiences, approximately 30% of the patients followed-up with the diagnosis of sarcoidosis show the conditions that require pulmonary tomography [4]. In our study, all patients had pulmonary radiography at the time of diagnosis but 96% of the patients had also concomitant pulmonary CT. While the prognostic value of the CT performed at the onset of the disease is limited, this method is known to be quite efficient in the differentiation between active inflammation and fibrosis. However, given the literature data, this rate was quite high.

When the classification of our patients by pulmonary radiography performed at the time of diagnosis was reviewed (Table 1), it was seen that 2 (2%) patients had Stage 0 and none of the patients had Stage 4 at that time. These data were similar to literature data except for the small number of patients with Stage 0 and Stage 4. When 96 patients who were evaluated using CT at the time of diagnosis were staged by CT, it was noted that the staging results changed and 72% of the patients had Stage 2. When the effect of the tomography on the staging was detailed, it was found that 35 of 95 patients (36.4%) had a different stage and that all but 4 of these patients (32.2%) exhibited a progression of stage. It was observed that CT increased the stage of the disease by at least 1 stage in 1/3 cases compared to pulmonary radiography but majority of the cases showed the results consistent with the staging based on pulmonary radiography.

In the study performed by Gupta et al. [18] in 2010 to investigate the effect of smoking on the stage in the patients with sarcoidosis, it was concluded that smoking had no effect on the stage of the disease. On the other hand, in the study performed by Douglas et al., who claimed that smoking was protective against sarcoidosis, it was demonstrated that the correlation between non-smoking and the incidence of sarcoidosis was more marked in the patients with Stage 1 disease and that this correlation was reduced with increasing stage [16]. In our study, it was found that 76.7% of ex-smokers and smokers had advanced stages such as stage 2 or 3 at the time of diagnosis ($p<0.01$). This result was statistically significant and supported the study of Douglas et al. [16]. It was thought that the diagnosis put at later stages in the smokers was due to late admission of these patients by assuming that their symptoms were due to smoking.

Changes of laboratory and SFT findings recorded in the study participants at the time of diagnosis by stages were examined and it was seen that high level of ACE in 56%, elevated serum calcium level in 1% and elevated urinary calcium level in 14% of our patients at the time of diagnosis were not correlated with the stage of the disease. The observation that increase of stage led to increased sedimentation values and lowered FEV_1/FVC values was not statistically significant. On the other hand, the decrease observed in FEV_1, FVC and DLCO values with the progression of the stage was found to be statistically significant ($p<0.01$).

Measurement of pulmonary diffusing capacity of carbon monoxide is the most sensitive SFT parameter. It was reported that in approximately 15-25 of the patients with sarcoidosis, who show normal pulmonary radiography, DLCO might be low [21]. In our study, 53% of the patients showed varying grades of DLCO decrease at the time of diagnosis. While none of the patients with Stage 0 showed low DLCO value, it was observed that severe DLCO lowering could be observed in all other groups.

Extrapulmonary involvement rates were 40.6% in TTD study and 36% in ACCESS study. In our study, the corresponding rate was 43%. In ACCESS study, no difference of extrapulmonary involvement was found across age groups, whereas it was concluded that the women were tended to be aged above 40 years and more commonly showed involvement compared to men [22]. In TTD study, no difference was found across age and gender groups and ocular involvement was reported to be more commonly seen in the age group below 40 years [19]. In our study, similarly to ACCESS study, the incidence rate of extrapulmonary involvement was higher in women (48.6%) compared to men (26.9%) (p=0.09) and affected women were presented at more advanced ages compared to affected men. Furthermore, it was found that the incidence of extrapulmonary involvement was inversely proportional with age and it was observed more commonly in the age group below 40 years compared to that above 40 years (p=0.02).

In the patients with sarcoidosis, treatment plan is generally symptom-based. In sarcoidosis, neurosarcoidosis, cardiac involvement, hypercalcemia and ocular involvement that do not respond to topical therapy, which may be potentially serious, are the absolute therapeutic indications [23]. Generally, a further indication is disease progression. Apart from these conditions, it is recommended to follow-up the asymptomatic or mild patients off-treatment due to high rates of spontaneous remission and the potential adverse effects of the therapy. Symptomatic Stage 2 and 3 patients should be considered for treatment after a follow-up period of 6 to 12 months, if clinically appropriate. On the other hand, during the follow-up or at baseline, if serious symptoms, RFT impairment, diffuse infiltration and the findings suggesting alveolitis are present, the therapy should be immediately initiated [3,23,24]. In chronic cases, there is generally a progressive disease that requires treatment. Therefore, the treatment should be immediately initiated in the patients in whom the disease has lasted for more than 2 years and who showed progressive loss of respiratory functions within the last 3 months [25].

Currently, for the treatment of sarcoidosis, the drug of choice is systemic corticosteroids [23]. In our study, while all treated patients received steroid therapy, only one patient had a steroid-free treatment plan due to the adverse effects experienced during the relapse. While majority of the patients used methylprednisolone as steroid therapy, some patients preferred to receive deflazacort or fluocortolone. Literature data suggest that, especially in the patients aged above 50 years, deflazacort may be preferred due to lower incidence of osteoporosis as an adverse effect [26,27].

In large series, the incidence rates of spontaneous remission were shown to range between 60 and 70% in the patients who were followed-up off-treatment [4]. General opinion of the investigators is that the steroids do not change the natural course of the disease and furthermore, the patients who had steroid-induced remission could have increased rates of relapse [28]. In the study performed by Gottlieb et al., [29] this insight was reinforced by the fact that 74% of the patients who had corticosteroid-induced remission experienced a recurrence of relapse. In our study, the fact that 13 of 38 (34.2%) patients in the patients who were given treatment at the time of diagnosis showed relapse compared to only 5 of 62 patients (8.1%) in the patients who were followed-up off-treatment reinforces the hypothesis that the incidence of relapse is higher in the treated patients. However, it was thought that the therapy groups should be well-randomized in order to obtain robust results about this issue.

Many studies showed that the side effects of steroids, such as weight gain, thickening of the skin, sleep disturbances, osteoporosis and neuropsychiatric disorders, could occur even at low doses and especially with long-term use, steroid therapy was also a significant risk factor for infection and steroid-related diabetes [30,31]. A specific guideline that will allow to monitor the side effects of the steroids for the patients with sarcoidosis is lacking. When the medical records of our participants were examined for side effects, it was observed that 67% of the treated patients exhibited side effects with varying grades. Most commonly seen side effects were weight gain and edema (40.1%) and, even if it was not directly attributed to steroid use, 11.6% of the patients experienced osteopenia.

It was reported that overall mortality of the disease varied between 1 and 5% in the population studies [5]. Death mostly resulted from progressive respiratory failure, neurosarcoidosis and cardiac involvement. Although the most commonly cause of death was reported to be respiratory failure, some autopsy results suggested the cardiac sarcoidosis as the main reason [28,32]. In our study, two (2%) patients died during the follow-up and, despite the presence of concomitant systemic diseases, their reason of death was reported to be progressive respiratory failure.

Retrospective design of the study and median follow-up time equal to 26 months despite the patients' follow-up time that varied between 3 months and 21 years and 13 patients who had a follow-up time less than 9 months were considered as the limitations of the study in terms of conducting some statistical analyses and obtaining robust results.

Consequently, sarcoidosis is a multisystemic disease that may have a course with several clinical findings and that should be absolutely considered in the differential diagnosis with its commonly or rarely observed findings. In this study that evaluated the data obtained in our clinic, approximately 3/4 of our patients diagnosed with sarcoidosis were women and approximately half were housewives, mean age was 44 years and there was no difference between the genders, negative correlation between smoking and disease men-

tioned in the literature was also observed in our study participants but the smoker patients were diagnosed at later stages, most common extrapulmonary involvement site was the skin, extrapulmonary involvements were more common in women, in the patients aged below 40 years and in those with lower stages and the incidence of relapse was higher in the patients who received treatment during the follow-up and in the patients with advanced stage of sarcoidosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gazi University Faculty of Medicine.

Informed Consent: Due to the retrospective design of the study, the informed consent forms were not able to be taken.

Peer-review: Externally peer-reviewed.

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