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Effectiveness of Clinical Parameters and Laboratory Values in Predicting The Clinical Course of Sarcoidosis

Sarkoidoz'un Klinik Gidişatini Öngörmede Klinik Parametreler ve Laboratuvar Değerlerinin Değerlendirilmesi - Tek Merkez Deneyimi

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ABSTRACT

Aim: The natural course of sarcoidosis is heterogeneous. There is no clear marker that can predict the course of this disease and its characteristics over months/ years. We aimed to analyze our patients' data to identify a prediction parameter at admission.

Methods: The patients with sarcoidosis and followed-up between 2015-01-01 and 2020-12-31 comprised the study group. The patients were staged by a Scadding staging system. Improvement or deterioration in at least two of the clinical-laboratory-radiological parameters indicates regression, stable disease, progression, or relapse of sarcoidosis.

Results: The study group comprised four cases (6.9%) defined as stage 0; fifteen cases (25.86%) as stage 1; 39 cases (67.24%) were defined as stage 2. The mean age at diagnosis was 40.84±13.56 in stage 0 + stage 1 group, while it was 48.05±13.36 in the stage 2 group (p=0.06). 74.1% of the cases were women. The female/male ratio was found at 2.86. 57 out of 58 cases had a pathological diagnosis (EBUS TBNA). While PFTs values and DLCO were significantly lower at advanced stages but the same statistical significance was not identified between these values and the clinical course of the disease. As a result of the multivariate analysis, it was observed that only the presence of chest pain at admission affected the progression of the disease in the follow-up period.

Conclusion: Sarcoidosis is a multi-systemic disease and there is no clear finding for predicting the poor prognosis of the disease. We conclude that chest pain symptom at admission is valuable predictive finding and can be used as a clue for the progression at follow-up.

Keywords: Sarcoidosis, prognosis, progression, EBUS TBNA

ÖZ

Amaç: Sarkoidozun doğal seyri heterojendir. Bu hastalığın seyrini ve özelliklerini aylar/yıllar içinde öngörebilecek net bir belirteç yoktur. Başvuru sırasında bir tahmin parametresi belirlemek için hastalarımızın verilerini analiz etmeyi amaçladık.

Yöntem: 01.01.2015-31.12.2020 tarihleri arasında sarkoidoz tanısıyla takipte olan hastalar çalışma grubumuzu oluşturdu. Hastaların başvuru grafileri dahil Scadding evreleme sistemi ile evrelendi. Klinik-laboratuvar-radyolojik parametrelerin en az ikisinde düzelme veya bozulma sarkoidozda gerileme, stabil hastalık, progresyon veya relaps olduğunu gösterir.

Bulgular: Çalışmaya dahil ettiğimiz 4 vaka (%6,9) evre 0, 15 olgu (%25,86) evre 1; 39 olgu (%67,24) evre 2 olarak tanımlandı. Tanı yaşı ortalaması evre 0 + evre 1 grubunda 40,84±13,56, evre 2 grubunda 48,05±13,36 idi (p=0,06). Vakaların %74,1'i kadındı. Kadın/erkek oranı 2,86 olarak bulundu. 58 olgunun 57'sinde patolojik tanı vardı. Kullanılan yöntem Endobronşial ultrasonografi eşliğinde transbronşial iğne aspirasyonu idi (EBUS TBNA). Solunum fonksiyon testleri (SFT) ve karbonmonoksit difüzyon testi (DLCO) ileri evrelerdeki hastalarda anlamlı olarak daha düşük iken, bu testlerin sonuçları ile hastalığın klinik seyri arasında aynı istatistiksel anlamlılık saptanmadı. Çok değişkenli analiz sonucunda takip döneminde sadece başvuru anında göğüs ağrısının varlığının hastalığın progresyonunu etkilediği görüldü.

Sonuç: Sarkoidoz multisistemik bir hastalıktır ve hastalığın kötü prognozunu öngörmek için net bir bulgu yoktur. Başvurudaki göğüs ağrısı semptomunun değerli bir prediktif bulgu olduğunu ve takipteki progresyon için bir ipucu olarak kullanılabileceğini düşünüyoruz.

Anahtar Kelimeler: Sarkoidoz, prognoz, progresyon, EBUS TBNA

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INTRODUCTION

Sarcoidosis is a multi-systemic granulomatous disease of unknown etiology, with initial findings and disease course that are highly heterogeneous [1]. Sarcoidosis mostly affects people between the ages of 20-60 and is observed 3 to 4 times more often in white people compared to black people. The most common symptoms of patients with sarcoidosis are cough and dyspnea followed by nonspecific symptoms such as chest pain, myalgia, joint pain and fever [2]. There is no current specific diagnostic test for sarcoidosis, but the combination of three criteria is sufficient for a sarcoidosis diagnosis: the compatible clinical radiological appearance, evidence of noncaseating granulomas, and the exclusion of other similar presentations or histopathological diseases [3]. Sarcoidosis is staged as five stages based on the Posterior Anterior Chest Radiography (CXR) [4].

The natural course of sarcoidosis is heterogeneous and spontaneous, while regression of the disease is observed in approximately one out of every three patients. But some patients have a progressive or fibrotic disease. There is no clear marker that can predict the course of this disease and its characteristics over months and years [1, 3].

We aimed to retrospectively analyze whether there is a possibility for identifying an estimation parameter between the admission and the course of the disease.

MATERIALS and METHODS

Study population

The study center is a tertiary chest diseases hospital. The patients in the study were in routine follow-up with the diagnosis of sarcoidosis between January 1st 2015 and December 31st 2020. The patients were staged by the Scadding staging based on CXR. All patients had thorax high-resolution computerized tomography (HRCT), blood count, biochemistry examinations, pulmonary function tests (PFTs) results, diffusing capacity of the lungs for carbon monoxide (DLCO), serum angiotensin-converting enzyme (ACE), urine tests, tuberculin skin tests (TST), and 24-hour urine calcium values at the time of diagnosis. An induration diameter over 5 mm in the TST test was considered positive. The study was approved by the Health Science University Keçiören Training and Research Hospital, Clinical Studies Ethic Committee (2012-KAEK-15/2395).

Diagnosis of Sarcoidosis

There is currently no specific test for the diagnosis of sarcoidosis. The diagnosis relies on the combination of three criteria, namely a compatible clinical-radiological presentation, pathological evidence of noncaseating granuloma, and exclusion of other disorders with similar presentation or histopathology [3].

Staging

The sarcoidosis cases were staged with the Scadding staging system based on CXR.

Stage 0: Normal chest radiography,

Stage 1: Bilateral hilar lymphadenopathy (BHL) and normal lung parenchyma,

Stage 2: BHL + Pulmonary interstitial infiltrates,

Stage 3: Pulmonary infiltrates without lymphadenopaty

Stage 4: Pulmonary fibrosis [4].

Clinical descriptions of response in the follow-up period

Clinical response: The total recovery or partial regression in the findings of pulmonary or extrapulmonary involvements, with or without treatment.

Laboratory response: Improvements in serum ACE level, 24-hour urine calcium level, biochemical values and decreases in sedimentation levels, improvements in forced vital capacity (FVC) (10%), and/or diffusing capacity of the lungs for carbon monoxide (DLCO) (15%).

Radiological response: Total or partial regression of findings in CXR or HRCT [5].

Complete remission: Total clinical and radiological response with or without treatment.

Relapse: After initial remission or in the tapering phase of treatment with prednisone or equivalent at doses < 20 mg/day [6].

Sarcoidosis activity

The activity of sarcoidosis is traditionally measured in two ways: using tests indicative of active granulomatous inflammation and assessing clinical deterioration in organ function [7]. Improvements in at least two of the clinical-laboratory-radiological response parameters indicate total or partial regression of sarcoidosis. Relapse, or progression in at least two of the clinical-laboratory-radiological parameters called the progression of the disease activity. The stability of the findings was defined as the stability of sarcoidosis.

Statistical analyzes

For the distribution of all continuous variables, the Kolmogorov-Smirnov or Shapiro-Wilk test, coefficient of variation value, skewness-kurtosis values, histogram, and detrended plot graphs were examined. If the data was nominal, it was shown as n /%, whereas if it was ordinal or numerical and not normally distributed, it was shown as median/ min-max; in numerical and normally distributed data, it was shown as mean±SD. Categorical data of the patient group was evaluated with the chi-square or Fisher test accordingly. As for numerical data, if there were two groups, it was evaluated with the Student T-test or the Mann Whitney U test; if there were more than two groups, it was evaluated with ANOVA or Kruskal Wallis. The Cochrane test was used for connected data with more than two groups. The SPSS version 22 was used as the statistics program and values with a p-value smaller than 0.05 were considered statistically significant.

RESULTS

All patients staging was performed by the Scadding staging system. Four cases (6.9%) were defined as stage 0; fifteen cases (25.86%) as stage 1; 39 cases (67.24%) were defined as stage 2. The mean age at diagnosis was 40.84±13.56 in stage 0 + stage 1 group, while it was 48.05±13.36 in the stage 2 group, and there was no difference between the two groups (p=0.06). 74.1% of our patients were women. The female/male ratio was found to be 2.86. Some 57 out of 58 cases had a pathological diagnosis. The main diagnostic method was endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (n=42, 72.4%). There was no statistical difference between smoking (p=0.183) and the initial Scadding stage (p=0.823) between the clinical courses. The demographic data and characteristics are shown in Table 1.

In the stage 2 sarcoidosis patients' follow-up, we observed a markedly clinical heterogeneity in terms of both regression and progression (p<0.0001). It was observed that patients who received treatment for sarcoidosis were at an advanced stage. There was no relationship between the stages and extrathoracic involvements or calcium metabolic disorder (Table 1).

The most common symptoms at admission were cough (n=44, 75.9%) followed by dyspnea (n=34, 58.6%). When the course of the disease and the symptoms at admission were examined, the presence of sputum and chest pain were statistically significant and they were associated with poor clinical prognosis (p=0.001 and p=0.002, respectively) (Table 2).

The patients' follow-up period was a minimum of 2 years and the average follow-up period was 5.24±3.97 (2-16) years. We found that a longer duration of the follow-up period was associated with an increased rate of progression (p=0.007). The difference between the stage at the diagnosis and the retrospective Scadding staging system was evaluated with the Cochran analyze and there was no significant difference (p=0.083).

In the follow-up period, 3 patients, whose initial stage was stage 2, were progressed to stage 4 (n=1) and stage 3 (n=2). We found that receiving sarcoidosis treatments were associated with having progressive diseases (p<0.0001), but the patients who received treatment were in advanced stages (p=0.006) (Table 2).

While PFTs values (Forced vital capacity (FVC), Forced Expiratory Volume in the first second (FEV1), FEV1/FVC ratio) and DLCO were significantly lower in advanced-stage patients, the same statistical significance was not identified between these values and the clinical course of the sarcoidosis (Table 2).

Forty-two patients' Transthoracic Doppler

Table 1. Demographic, clinical and diagnostic characteristics.

		Study population (n=58)	Stage 0 + Stage 1 (n=19, 32.8%)	Stage 2 (n=39, 67.2%)	p-value
Age at the diagnosis (mean±SD)		45.68±13.74	40.84±13.56	48.05±13.36	p=0.06
Gender	Male	15 (25.9%)	7 (36.8%)	8 (20.5%)	p=0.183
	Female	43(74.1%)	12 (63.2%)	31 (79.5 %)	
Smoking	Never smoked	34 (58.6%)	11 (57.9%)	23 (59%)	p=0.133
	Quitted	18 (31%)	4 (21.1%)	14 (35.9%)	
	Still smoking	6 (10.3 %)	4 (21.1%)	2 (5.1%)	
Time until diagnosis (month)		4.22±3.42	3.1±1.88	4.76±3.86	p=0.119
Duration of follow-up (year)		5.24±3.97	3.78±2.12	5.94±4.46	p=0.153
Diagnostic methods	Transbronchial parenchymal biopsy by FOB	5 (8.6%)	1 (5.3%)	4 (10.3%)	p=0.950
	EBUS TBNA for mediastinal LAP	42 (72.4%)	14 (73.7%)	28 (71.8%)	
	Mediastinoscopy	2 (3.4%)	1 (5.3%)	1 (2.6%)	
	Extrathoracic LAP biopsy	3 (5.2%)	1 (5.3%)	2 (5.1%)	
	Skin biopsy	2 (3.4%)	1 (5.3%)	1 (2.6%)	
	Clinical and radiological diagnosis	1 (1.7%)	0 (0%)	1 (2.6 %)	
	Transthoracic biopsy with Thorax CT	1 (1.7%)	0 (0%)	1 (2.6%)	
	Bronchial mucosa biopsy by FOB	2 (3.4%)	1 (5.3%)	1 (2.6%)	
Treatment	Received	24 (41.4%)	3 (15.8%)	21 (53.8%)	p=0.006
	Not received	34 (58.6%)	16 (84.2%)	18 (46.2%)	
Clinical Follow-up	Stable	32 (55.2%)	18 (94.7%)	14 (35.9%)	p<0.0001
	Regression	16 (27.6%)	1 (5.3%)	15 (38.5%)	
	Progression	10 (17.2%)	0 (0%)	10 (25.6%)	
Skin Involvement	Present	12 (20.7%)	6 (31.6%)	6 (15.4%)	p=0.153
	Not present	46 (79.3%)	16 (68.4%)	33 (84.6%)	
Ocular Involvement	Present	4 (6.9%)	0 (0%)	4 (10.3%)	p=0.148
	Not present	54 (93.1%)	19 (100%)	35 (89.7%)	
Calcium metabolism disorder	Present	7 (12.1%)	1 (5.3%)	6 (15.4%)	p=0.267
	Not present	51 (87.9%)	18 (94.7%)	33 (84.6%)	
FVC (Forced Vital Capacity)		2.84±0.76	3.29±0.84	2.62±0.62	p=0.001
FEV_1		2.40±0.73	2.88±0.77	2.17±0.59	p<0.0001
FEV_1/FVC		80.24±8.23	83.68±6.27	78.56±8.62	p=0.025
Pulmonary Function Tests results	Obstruction	10 (17.2%)	2 (10.5%)	8 (20.5%)	p=0.171
	Restriction	8 (13.8%)	2 (10.5%)	6 (15.4%)	
	Mixt	5 (8.6%)	0 (0%)	5 (12.8%)	
	Normal	35 (60.3%)	15 (79%)	20 (51.3%)	
DLCO (%)		91.50±18.69	106.73±11.13	84.07±17.10	p<0.0001
Transthoracic Doppler Echocardiography	Present	42 (72.41%)	11 (26.2%)	31 (73.8%)	p=0.033 p=0.885
	EF:	60.95±4.07	63.18±2.85	60.16±4.18	
	sPAP:	21.83±7.51	21.54±7.18	21.93±7.74	

FOB: Fiberoptic Bronchoscopy

EBUS TBNA: Endobronchial Ultrasonography Transbronchial Needle Aspiration

LAP: Lymphadenopathy

Thorax CT: Thorax Computerized Tomography

FEV1: Forced Expiratory Volume in the first second

DLCO: Diffusing capacity of the lungs for carbon monoxide

EF: Left ventricular systolic ejection fraction

sPAP: Systolic pulmonary artery pressure

Table 2. Symptoms at admission, treatment status and PFTs.

			Study population (n=58)	Stable Disease (n=32, 55.2%)	Regressed Disease (n=16, 27.6%)	Progressed disease (n=10, 17.2%)	p-value
Symptoms at admission	Shortness of breath	Present	34(58.6%)	16 (47.1%)	9 (26.5%)	9 (26.5%)	p=0.079
		Not present	24 (41.4%)	16 (66.7	7 (29.2%)	1 (4.2%)	
	Cough	Present	44 (75.9%)	23 (71.9%)	12 (75%)	9 (90%)	p=0.503
		Not present	14 (24.1%)	9 (28.1%)	4 (25%)	1 (10%)	
	Sputum	Present	8 (13.8%)	1 (3.1%)	2 (12.5%)	5 (50%)	p=0.001
		Not present	50 (86.2%)	31 (96.9%)	14 (87.5%)	5 (50%)	
	Chest Pain	Present	9 (15.5%)	4 (12.5%)	0 (0%)	5 (50%)	p=0.002
		Not present	49 (84.5%)	28 (87.5%)	16 (100%)	5 (50%)	
	Fever	Present	7 (12.1%)	4 (12.5%)	0 (0%)	3 (30%)	p=0.073
		Not present	51 (87.9%)	28 (87.5%)	16 (100%)	7 (70%)	
	Myalgia	Present	13 (22.4%)	7 (21.9%)	2 (12.5%)	4 (40%)	p=0.261
		Not present	45 (77.6%)	25 (78.1%)	14 (87.5%)	6 (60%)	
	Arthralgia	Present	9 (15.5%)	5 (15.6%)	1 (6.3%)	3 (30%)	p=0.266
		Not present	49 (84.5%)	27 (84.4%)	15 (93.8%)	7 (70%)	
Clinical follow-up status	Receiving treatment		24	4	11	9	p<0.0001
	Not receiving treatment		34	28	5	1	
PFTs findings	FVC		2.84±0.76	2.92±0.82	2.72±0.72	2.77±0.64	p=0.674
	FEV1		2.40±0.73	2.52±0.79	2.22±0.61	2.30±0.72	p=0.381
	FEV1/FVC		80.24±8.23	81.75±8.26	78.56±9.06	78.1±6.27	p=0.304
PFT results	Obstruction		10 (17.2%)	5 (15.6%)	4 (25%)	1 (10%)	p=0.307
	Restriction		8 (13.8%)	4 (12.5%)	4 (25%)	0 (0%)	
	Mixt		5 (8.6%)	3 (9.4%)	0 (0%)	2 (20%)	
	Normal		35 (60.3%)	20 (62.5%)	8 (50%)	7 (70%)	
DLCO (%)			91.50±18.69	97.34±16.78	90.5±16.14	74.4±18.96	p=0.002

FVC: Forced Vital Capacity

FEV1: Forced Expiratory Volume in the first second

PFTs: Pulmonary Function Tests

DLCO: Diffusing capacity of the lungs for carbon monoxide

Echocardiography (TTE) records were available at the time of diagnosis (n=42, 72.41%). The left ventricular systolic ejection fraction (EF) value was 60.95±4.07 and the systolic pulmonary artery pressure (sPAP) was 21.83±7.51. A negative and significant correlation was found between advanced stage and systolic EF (p=0.033) (Table 1). In follow-up, there was no relationship between the course of the disease and the initial EF and sPAP values (p=0.780 and p=0.833, respectively).

We compared laboratory test results with the clinical course. We found that presentation with high serum ACE and high 24-hour urine calcium values (hypercalciuria) were associated with progressed disease (p=0.013 and p=0.046; respectively) (Table 3).

As a result of the multivariate analysis, only the presence of chest pain at admission affected the progression of sarcoidosis in the follow-up period (odds ratio [OR]=50.94, 95% confidence interval [CI] 1.593–1628.685, p=0.026).

DISCUSSION

Sarcoidosis is more common in women aged between 20 and 60 [2, 8, 9, 10, 11]. In this study, the mean age at diagnosis was 45.68±13.74 years, and most of the patients were female (74.1%). ACCESS study female/male ratio was 1.77 [2], while in this study it was higher (2.86).

In a study by Voortmann et al., it was found that virtually all patients had organ-related or non-specific/non-organ-related symptoms. In this study, very nearly all patients had at least one symptom [12]. The most common presenting symptoms in previous studies were cough and dyspnea [5, 9, 13]. The most common symptoms

Table 3. Laboratory results at the diagnosis.

		Study population (n=58)	Stable disease (n=32, 55.2%)	Regressed disease (n=16, 27.6%)	Progressed disease (n=10, 17.2%)	p-value
White Blood Cell**		6.61 (3.08-17.46)	6.73 (4.47-17.46)	6.60 (4-13.9)	6.45 (3.08-9.6)	p=0.799
Neutrophil count **		4.11 (2.11-15.14)	4.33 (2.41-15.14)	3.79 (2.14-8.77)	3.9 (2.11-6.1)	p=0.686
Lymphocyte count **		1.56 (0.48-4.31)	1.64 (0.50-4.31)	2.73 (1.46-7.75)	1.45 (0.48-2.88)	p=0.708
Hemoglobin*		13.67±1.66	13.94±1.73	13.64±1.53	12.85±1.54	p=0.198
Anemia		5 (%8.6)	2 (%6.3)	1 (%6.3)	2 (% 20)	p=0.485
Normal		45 (%77.6)	24 (%75)	14 (%87.4)	7 (%70)	
Polycythemia		8 (%13.8)	6 (%18.7)	1 (%6.3)	1 (%10)	
Thrombocyte **		269.5 (104-700)	290.5 (172-486)	267 (159-421)	278 (104-700)	p=0.906
Blood Urea Nitrogen**		11.9 (6-27)	11.5 (6-27)	13.7 (6-17)	11.35 (8-24.9)	p=0.964
Creatinine*		0.80±0.13	0.82±0.12	0.74±0.07	0.82±0.18	p=0.083
Uric acid*		5.28±1.36	5.40±1.40	5.18±1.31	5.06±1.40	p=0.737
Albumin**		41.5 (32.9-51)	42.05 (32.9-50.9)	40.7 (35.4-46.7)	42.3 (33-51)	p=0.731
Alanine aminotransferase**		19.5 (10-70)	21.5 (12-70)	18.5 (10-48)	17.5 (10-30)	p=0.344
Aspartate aminotransferase*		22.06±6.64	22.03±6.67	22.75±6.27	21.1±7.62	p=0.831
Alkaline phosphatase*		79.31±24.05	78.43±24.34	77.37±20.27	85.2±29.85	p=0.696
Calcium (serum)**		9.5 (7.47-12.5)	9.5 (7.47-10.6)	9.45 (9-10.38)	9.40 (9-12.5)	p=0.928
C Reactive Protein**		6 (0.27-96)	5.8 (0.81-82.4)	5.6 (0.27-96)	6.85 (1.2-23)	p=0.620
Sedimentation **		22.5 (5-84)	20 (5-73)	25.5 (5-84)	23.5 (9-61)	p=0.327
Serum-angiotensin converting enzyme**		77 (18-165)	62.5 (21-165)	84 (64-161)	95 (18-136)	p=0.013
24-hour urine calcium *		167.3±108.2	145.62±65.77	164.1±125.8	241.9±158.05	p=0.046
Tuberculin Skin Test (mm) ***	Positive	4 (6.9%)	3 (9.4%)	0 (0%)	1 (10%)	p=0.440
	Negative	54 (93.1%)	29 (90.6%)	16 (100%)	9 (90%)	

* Analyzed with ANOVA and shown with mean±SD

** Analyzed by Kruskal-Wallis and shown with median (min-max)

*** Analyzed with Chi-square and represented as n (%)

in this study were cough and dyspnea too. While there was an expectation of spontaneous remission and good prognosis in cases with erythema nodosum, BHL, polyarthralgia and fever at the time of diagnosis [14], we did not find any clear information on which presenting symptoms were associated with good clinical course, remission and progression in the literature. Belhomme et al. examined the relationship between dyspnea and relapse in their studies, but they found no significant relationship [15]. Nath et al. found that only the presence of fatigue was associated with relapse [16]. In this study, we found that patients who had sputum and chest pain at the time of presenting progressed more normally in their subsequent follow-up. After multivariate analysis, we found that the initial presence of chest pain was associated with progression (odds ratio [OR]=50.94, 95% confidence interval [CI] 1.593–1628.685, p=0.026).

It is a recognized fact that patients with sarcoidosis smoke less than the general population [10]. In our study, 34 (58.6%) of our patients had never smoked and this is consistent with the literature. While smoking was not found to be associated with the stage of sarcoidosis in one study [17], it was found in another study that ex-smokers or current smokers were diagnosed at a later stage [18]. In our findings, there was no significant relationship between smoking and both the initial stage (p=0.183), and the subsequent clinical course (p=0.823).

Wirnsberger et al. found the initial symptom duration until the diagnosis of sarcoidosis was between 0 and 3 months for 25% of cases and 3 to 6 months for 17.6% of cases in their study [19]. We found a shorter initial symptom duration of 4.22±3.42 months until the diagnosis. We also examined the relationship between the duration of the initial symptoms and both the

stage of sarcoidosis and the clinical course of the disease in the follow-up. There was no significant relationship between the duration of the initial symptoms and the stage or the clinical course.

EBUS TBNA is significantly superior to the transbronchial lung biopsy as a pathological diagnosis method in pulmonary sarcoidosis [20]. While the most commonly used invasive method for the diagnosis of sarcoidosis was transbronchial biopsy with FOB, endobronchial biopsy, and conventional TBNA in previous studies [5, 16], Abakay et al. reported that they used the mediastinoscopy for diagnosis in their study [21]. The most frequently used invasive method in this study was EBUS TBNA (n=42, 72.4%).

The skin is the most common extrathoracic involvement in many studies [5, 6, 13,19]. Skin involvement [Lupus pernio (n=1) and Erythema Nodosum (n=11), Total (n=12, 20.7%)] was the most common extrathoracic involvement in our study as well.

The rate of patients who needed treatment was similar to the literature (n=24, 41.4%) [5]. In some studies, it was inferred that corticosteroid therapy is a predisposing cause of disease relapse [22,23]. In their study, Rodrigues et al. stated that patients who needed treatment at the diagnosis period and whose symptom durations were long, may be associated with relapse [6]. We found a relationship between treatment needs and progressive disease with relapses. In addition, we found that the patients with a high initial stage at the time of diagnosis had more treatment needs (p=0.006). In addition, we found that these patients were more progressed during the follow-up (p<0.0001), therefore we assume that these patients may be phenotypically inclined to the sarcoidosis that requires treatment at the diagnosis period, as stated in the study of Rodrigues, et al. [6].

The spirometric data in this study is similar to those in previous studies [6]. PFTs and DLCO test values are lower in patients with advanced stages of sarcoidosis [5]. Similar to these studies, we found that the initial PFTs and diffusion values were lower in the stage 2 group with lung involvement according to Scadding staging (for FVC, FEV1, FEV1/FVC, DLCO, respectively; p=0.001, p<0.0001, p=0.025, p<0.0001). Niksarlioglu et al. analyzed relapse and related factors, and found that patients with low DLCO values had more relapses [11]. We analyzed the initial PFTs and DLCO values and the course of the disease in the follow-up, only the patients with low initial DLCO values were progressed in the follow-up (p=0.002).

When the results of transthoracic echocardiography were examined in the literature, there was a positive relationship between low EF, high sPAP values and poor clinical prognosis [24]. In our study, we found that the initial EF value was lower in stage 2 cases (p=0.033). In clinical follow-up, we could not find a relationship between the course of the disease and the initial EF and sPAP values. Abnormal calcium metabolism was associated with acute disease and with relapse [6,25]. Similarly, Niksarlioglu et al. observed relapses more frequently in patients with hypercalciuria [11]. As a result of our study, we found that patients with hypercalciuria progressed more in clinical follow-up (p=0.046). In previous studies, a significant relationship was observed between high serum ACE level and relapse and clinical course [15]. However, Nath et al. did not find any relationship between serum ACE levels and relapse in their study [16]. We found that the patients with initial high serum ACE values progressed more frequently in follow-up (p=0.013).

Limitations

The foremost limitation of this study is its single-center and retrospective design. Additionally, it study did not comprise stage 3 and 4 patients. Although the follow-up period of our patients was comparatively long, it was heterogeneous (between 2 years and 16 years).

CONCLUSION

Sarcoidosis is a multi-systemic disease and defined as stable, regressed and progressed, according to the clinical course. There is no clear finding for predicting the poor prognosis of the disease in follow-up. We conclude that presentation with sputum and chest pain symptoms, advanced initial stage, low diffusion test values, high serum ACE and high 24-hour urine calcium values, may be associated with poor clinical prognosis. After

multivariate analyses, we conclude that chest pain symptoms at admission consist in valuable predictive findings and can be used as a clue for the progression at follow-up.

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