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Original Article

Delays in diagnosis in patients with pulmonary and extrapulmonary sarcoidosis

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Abstract

Aim: Sarcoidosis is a multisystemic disease with typical or atypical pulmonary and extra-pulmonary symptoms or frequently without symptoms. Presence of typical clinical findings and symptoms contribute to rapid diagnosis, whereas asymptomatic progression leads to delays in the diagnosis. The aim of this study was to investigate the delay in diagnosis in between patients with pulmonary and/or extra-pulmonary involvement and related symptoms and those without symptoms.

Material and Methods: Patients in the sarcoidosis clinics between 2010-2015, were retrospectively evaluated. The cases were grouped according to the presence or absence of symptoms (pulmonary and/or extra-pulmonary). The groups were compared with regard to the delay in diagnosis.

Results: Among the 300 patients, 209 (69%) were female. The mean age was 43±11.68. The disease was stage I in 67.3%, stage II in 23.7%, stage III in 5.7% and stage 0 in 3.3% of the patients. No significant difference was observed between symptomatic and asymptomatic patients with regard to total duration until diagnosis (p=0.78). A statistically significant difference was observed between patients groups with regard to physician-related delayed diagnosis(p=0.026). The mean delay in physician-related diagnosis was observed to be longer in asymptomatic cases (21.44 days) compared to patients with pulmonary symptoms (13.66 days)(p=0.036). In asymptomatic cases, the mean duration of physician-related delayed diagnosis (21.44 days) was observed to be longer in comparison with patients with extra-pulmonary symptoms (12.79 days)(p=0.016). In patient-related delayed diagnosis, no difference was observed between groups with regard to the duration until diagnosis(p=0.78).

Conclusion: Comparison of delayed diagnosis between patients with or without pulmonary and/or extra-pulmonary symptoms revealed a longer duration of delay in asymptomatic cases compared to symptomatic cases. The timing of diagnosis is very important in sarcoidosis in order to reduce morbidity and mortality; a suspicious approach to asymptomatic patients will increase the possibility of diagnosis and prevent delayed diagnosis.

Keywords: Sarcoidosis; diagnosis; delay; extrapulmonary symptoms.

INTRODUCTION

Sarcoidosis is a systemic disease of unknown cause with very diverse presentation, outcome severity and need for treatment..Some presentations of sarcoidosis may be very typical besides, for many patients presentation might be nonspesific, also associated with other diseases. This may cause significant delay in diagnosis and treatment.

Occasionally rare misleading manifestations can lead to misdiagnosis of sarcoidosis by inexperinced physicians especially in some group of patients (1,2). The presentation of sarcoidosis is associated with demographic features such as age sex and race, duration of the disease and organ involvement (3,4). In developping countries many sarcoidosis patients are misdiagnosed and treated wrong as if diagnosis is tuberculosis besides, rule out malignancies from sarcoidosis is crucial, to prevent delay in the treatment of malignancy. In Rodrigues

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et al study, in many cases they showed that even when radiologic findings are suggestive for sarcoidosis, delay in the diagnosis was occured. After all, in some cases they determined that sarcoidosis patients were diagnosed and mistreated, as they are tuberculosis patients (5).

Sarcoidosis is asymptomatic in many cases, and patients symptoms are usually nonspesific despite the fact that nearly 25% of affected patients with sarcoidosis develop chronic and progressive diseases, which causes mortality and morbidity (6). Delay in the diagnosis causes increase in health care usage, and burden of sarcoidosis (7). There are few studies about relationship between symptoms and delay in diagnosis (6,8). Pulmonary and/or extrapulmonary sarcoidosis effect on delay in the diagnosis of sarcoidosis is not adequately investigated.

In the current study, we investigated the delay in diagnosis of sarcoidosis according to patients' symptoms. The objective of the present study was to determine the frequency of delayed diagnosis in Turkey and determine the factors that could effect delayed diagnosis of sarcoidosis at specialized centers.

MATERIAL and METHODS

This retrospective cohort study was designed in a tertiary teaching hospital for chest diseases and thoracic surgery center, Sarcoidosis Outpatient Clinic, between 2010-2015. The sarcoidosis patients were grouped according to the presence of symptoms (pulmonary and / or extra pulmonary septoms) and they were compared in terms of diagnosis delay (Figure 1). The study protocol was approved by the hospitals Local Ethics Comitee (20.06.2018/041).

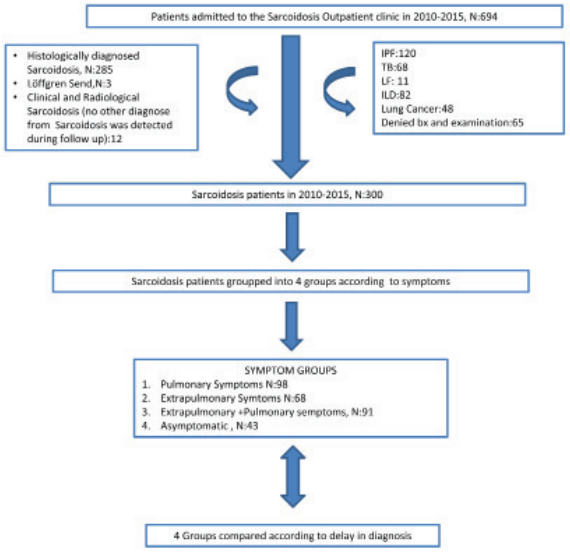

Figure 1. Flowchart of patient enrollment
Abbrevations: IPF, Idiopathic pulmonary fibrosis; ILD, Interstitial Lung Disease; TB, Tuberculosis; LF, lymphoma

Diagnosis of Sarcoidosis

Sarcoidosis was diagnosed as if clinical, radiological data are supported by the presence of non-caseating granulomas in a biopsy specimen, and alternative causes of granulomatous inflammation are ruled out (9).

Patients who did not allow biopsy for histological diagnosis and/or had Löfgren syndrome, sarcoidosis was diagnosed by clinical, radiological, laboratory compability such as Galium scintigraphy and broncho alveolar lavage (BAL) and ruling out of other diseases. Besides, during follow up absence of diseases other than sarcoidosis is also essential for the sarcoidosis diagnose.

There are five roentgenographic stages (9).
Stage 0: Normal Chest X ray.
Stage 1: Bilateral hilar lymphadenopathy.
Stage 2: Bilateral hilar lymphadenopathy together with parenchymal involvement.
Stage 3: Parenchymal involvement without Bilateral hilar lymphadenopathy.
Stage 4: Pulmonary fibrosis.

Echocardigraphy, abdominal ultrasound, ophthalmologic and dermatological examination was performed for discrimination between Pulmonary and extrapulmonary Sarcoidosis. We excluded patients who were unable to remember the time of symptom onset.

Definition and Classification of Diagnose Delay

Time intervals from the onset of symptoms to treatment have been described in literatüre (10,11).

The patient's application interval: The patient's application interval was defined as the time interval between the onset of symptoms and the first doctor visit. Health care system (doctor) interval: The health care system interval was defined as the time from the first doctor visit to the initiation of treatment.

Total interval: The total interval was defined as the time between the onset of symptoms and the time of treatment initiation. The total interval is the sum of the patient's application interval and health care system interval.

Statistical Analyses

Descriptive analysis was used to investigate patient demographics and clinical data. Statistical analysis was performed with the SPSS Statistical Package for Social Sciences version 21.0 (SPSS). Groups were compared using the Mann–Whitney U-tests for non-parametric, continuous variables, or student's t-tests for parametric continuous variables. Chi-square tests were employed for dichotomous variables. The median with interquartile range was employed for non-parametric, continuous variables, and the mean ± standard deviation was used for parametric continuous variables. Count and percentage were used when applicable statistical significance was set at $p < 0.005$.

RESULTS

Three hundred patients were included in the study. Two hundred-nine (69%) of patient were female. Mean age was 43 (±11.68) year. In study population, 67.3% was

stage I, 23.7%.stage II, 5.7% stage III and 3.3% stage 0. Sarcoidosis patients divided into four groups according to types of symptoms such as; asymptomatic, pulmonary symptoms, extra-pulmonary symptoms and pulmonary with extrapulmonary symptoms. Demografic features and ratio pulmonary and extrapulmonary symptoms were summarized in table 1.

Statistically no significant difference was determined, between the diagnosis delay and extrapulmonary and/or pulmonary symptom groups (p=0.78) (Table 2). When effect of symptoms on diagnosis delay was evalauted; delay in the diagnosis due to the physican factor was detected in asymptomatic group, with statistical significance (p=0.026) (Table 2).

Delay in the diagnosis due to physician factor in asymptomatic patients (21.44±22.11 days) was statictically longer than in patients who had pulmonary symptoms (13.66±11.61 days). (p=0.036). Delay in the diagnosis due to physician factor in asymptomatic patients (21.44±22.11days) was statictically longer than in patients who had extra-pulmonary symptoms (12.79±12.20 days, median) (p=0.016).

Statistically no significant difference was determined in four groups when the delay in the diagnosis according to patient factor was evaluated (p=0.78).

Distrubution of symptom groups according to stage of sarcoidosis was evaluated, statistically no significant difference was detected (Table 3).

Table 1. Demographic Features of Patients with Sarcoidosis

	n (%)
Gender (n, %)	
• Female	209 (69.7)
• Male	91 (30.3)
Age (mean±(SD), year)	42.55 ± 11.68
Sarcoidosis Stage (n,%)	
• Stage 0	10 (3.3)
• Stage I	202 (67.3)
• Stage II	71 (23.7)
• Stage III	17 (5.7)
Symptoms Group	
• Asymptomatic	43 (14.3)
• Pulmonary symptoms	98 (32.7)
• Extrapulmonary symptoms	68 (22.7)
• Pulmonary+ Extrapulmonary symptoms	91 (30.3)

Abbrevation: SD, standart deviation

Table 2. Comparison of Diagnosis delay according to symptom groups

		n	Mean±SD SD	p
Total Interval*	Asymptomatic group	2	10.50±4.95	0.616
	Pulmonary symptom group	97	40.72±46.64	
	Extrapulmonary symptom group	68	36.97±45.21	
	Pulmonary+Extrapulmonary symptom group	91	47.18±77.69	
Patient application Interval*	Asymptomatic group	43	21.44±22.11	0.026*
	Pulmonary symptom group	98	13.66±11.61	
	Extrapulmonary symptom group	68	12.79±12.20	
	Pulmonary+Extrapulmonary symptom group	91	15.59±18.15	
Healthcare system Interval*	Asymptomatic group	2	7.50±3.54	0.783
	Pulmonary symptom group	97	26.98±39.85	
	Extrapulmonary symptom group	68	24.18±37.23	
	Pulmonary+Extrapulmonary symptom group	91	31.58±73.29	

*p<0.05

Abbrevations: The patient's application interval; The time interval between the onset of symptoms and the first doctor visit, Health care system (doctor) interval; The time from the first doctor visit to the initiation of treatment, Total interval; The time between the onset of symptoms and the time of treatment initiation. The total interval is the sum of the patient's application interval and health care system interval; SD; Standart deviation

Table 3. Distrubution of symptom groups according to stage of Sarcoidosis

			Stage of Sarcoidosis				
			0	1	2	3	p
Symptom Groups	Asymptomatic group	n (%)	1 (10)	32 (15.8)	9 (12.7)	1 (5.9)	0.202
	Pulmonary symptom group	n (%)	1 (10)	70 (34.7)	18 (25.4)	9 (52.9)	
	Ekstrapulmonary symptom group	n (%)	5 (50)	43 (21.3)	17 (23.9)	3 (17.6)	
	Pulmonary+Ekstrapulmonary Symptom groups	n (%)	3 (30)	57 (28.2)	27 (38)	4 (23.5)	

p < 0.05

DISCUSSION

In current study, effect of symptom type on the diagnosis of sarcoidosis was evaluated, thus the diagnosis delay due to the physican factor was detected in asymptomatic patients group. The demographic data of sarcoidosis cases in our study were consistent with the literature.

In our study data about age and gender were 69% and 43 (±11.68, mean) year respectively. Regarding age and gender, our findings are similar to epidemiologic studies (12-14). In the present study it has been shown that ratio patients with stage I/II sarcoidosis was higher than the other studies eventually ratio of advance stage of (stage III/IV) sarcoidosis was low. Since the earlier stage of sarcoidosis were not referred to the specialized centers due to decreased symptoms, it might be the reason of delay in the diagnosis due to the physican factor in asymptomatic group.

In Judson et al. study, it has been reported that the presence of pulmonary symptoms or higher radiographic stages is associated with a prolonged time until diagnosis. In the same study, pulmonary symptoms and parenchymal involvement due to sarcoidosis were often regarded as manifestations of different pulmonary diseases (8). Rodrigues and collegues reval that, the diagnosis of sarcoidosis was delayed by 6 months or more nearly 60% of cases. Delayed diagnose was not affected by respiratoy/systemic symptoms gender, race, radiologic staging, individual income or type of health insurance. They also showed that delayed is associated with lower lung function at the admission. In present study, relationship between delayed diagnose and respiratory function, income, gender, and age was not evaluated. In asymptomatic group we have detected delay in the diagnosis due to physician factor.

Gerke et al study, they compared frequencies of doctor visits prescriptions, imaging was compared in sarcoidosis, and control (Asthma, Chronic obstructive pulmonary disease (COPD), pneumonia group year ago before the diagnosis was established. They determined that patients with sarcoidosis underwent a large number (an average of 14.7 visits in a year) of health care prior to diagnosis, compared to control group (7). In the current study, frequency of health care use was not evaluated.

In countries where the tuberculosis cases are frequent such as Turkey, diagnosis of tuberculosis should be ruled out when diagnose of sarcoidosis was established. Treating sarcoidosis as tuberculosis is very detrimental and vice versa. In Rodrigues et al study 17 of 100 sarcodosis patients were misdiagnosed as tuberculosis (5). In present study, study population was consisted of sarcoidosis outpatient clinic patients and whether misdiagnosed or not patients with tuberculosis were not assesed.

In the current study, diagnosis delay due to the physican factor was detected in asymptomatic patients group. In asymptomatic patient group since the diagnosis was established incidentally, delayed diagnose due to physician was an expected result. Since spontaneous regression occurs in nearly two thirds of patients, we could assume that delayed diagnose of asymptomatic patients with mild diseases were negligable. Besides approximately 25% of affected patients with sarcoidosis develop chronic or progressive disease that causes morbidity, mortality and frequent health care usage.

Our study have several limitations. Firstly, it was a retrospective, single center study. Nonetheless, it provides crucial clinical information due to the sample size and specific patient group. Secondly, due to the retrospective origin data and patients symptoms were collected from patients files thus.

The strength of this study lies in the fact that all the patients with sarcoidosis were followed-up by the same pulmonologists team, who were studied only in the sarcoidosis outpatient clinic. Secondly in our hospital,. we have ability to asses specific organ involvement and perform advanced examination techniques such as perform Fiber optic bronchoscopy, Endobronchial ultrasound (EBUS), Spirometry, diffusing capacity of the lungs for carbon monoxide, bronchoalveolar lavage.

CONCLUSION

As it is well known, rare diseases are aften associated with delayed diagnosis for different factors such as patient related, disease realted and health care related factors. Besides, even common disease like (COPD) have underdiagnosed in patients with atypic symptoms and features. In daily practice, general practioner was the first phsician that examined and consulted th patients with sarcoidosis. Under these circumstances, there is a need for improved algorithms to diagnose sarcoidosis and prevent delay in diagnosis. Further researchs and understanding of how to support and educate general practitioners in the diagnostic process of sarcoidosis is necessary. As a result,.more improved examination algorithms are needed to determine patients symptoms for clinicans espaecially for general practioners and pulmonologists.

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