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TANAFFOS

Evaluation of Clinical, Laboratory, and Radiologic Findings of Pulmonary and Extrapulmonary Involvement in Sarcoidosis

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Background: Sarcoidosis is a systemic disease with unknown etiology that is characterized by the presence of granuloma in various organs with diverse pulmonary and extrapulmonary manifestations. Regarding differences in the presentation of sarcoidosis in different geographical areas, the present study aimed to determine clinical, laboratory, and radiologic findings of patients with sarcoidosis in the north of Iran.

Materials and Methods: In a cross-sectional study, patients with sarcoidosis were enrolled, and demographic data in addition to disease manifestations including clinical, laboratory, and imaging findings were recorded.

Results: A total of 58 patients with sarcoidosis were enrolled in the study. The mean age and disease duration were 51.10±10.2 and 3.07±2.7 years, respectively. 62.1% of patients were female. Clinical manifestations were: cough and dyspnea (55.2%), fever and weight loss (11%), arthritis (15.5%), dermatologic presentation (15.5%), and ophthalmic involvement (17.2 %). Abnormalities in liver, renal, and calcium levels are found in approximately 1-8% of cases. The ACE level was increased in 56.9 % of patients, especially in those who presented in summer and autumn. Chest CT abnormalities were found in 94.8 % of patients, more predominantly hilar and paratracheal lymphadenopathy in 84.5% and 74.1%, respectively.

Conclusion: Although sarcoidosis presents with varying clinical, radiological, and laboratory features, knowledge of its epidemiology and the incidence of these features in different populations can aid in its diagnosis in a particular geographic area.

Keywords: Sarcoidosis; Epidemiology; Pulmonary; Extrapulmonary; Hilar adenopathy; Angiotensin-converting enzyme

INTRODUCTION

Sarcoidosis is a systemic disease with unknown etiology that primarily involves adolescents and adults, characterized by non-caseating granulomas (1). The disease most often occurs between 20-40 years of age, with women being diagnosed more frequently than men. However, in recent years sarcoidosis has tended to be seen in older people (2). The overall prevalence of sarcoidosis is between 10 and 20 per 100,000 (3). The different prevalence, clinical manifestations, and disease courses observed in different races and ethnic groups are indicators of the heterogeneous nature of the disease (1).

Clinical features and symptoms of sarcoidosis depend on which organs are involved and consist of pulmonary and extrapulmonary manifestations (1, 4). Most patients initially complain of a dry cough, shortness of breath, or

chest discomfort due to pulmonary involvement (3). Other symptoms may include constitutional symptoms, lymphadenopathy, skin rash, and involvement of the brain, eye, heart, liver, and kidney (5).

The diagnosis of sarcoidosis is based on a combination of clinical, radiographic, and histological features (3). It is important to differentiate sarcoidosis from other similar conditions since all the symptoms and laboratory results can occur in other diseases (6-8). Laboratory findings are nonspecific and cannot be used to diagnose the disease but may support the diagnosis (3). Among the long list of biochemical markers that have been suggested as aids for diagnosing and monitoring sarcoidosis, calcium in serum and urine and Angiotensin-converting enzyme (ACE) in serum are well-established diagnostic tools (9).

The diagnosis of sarcoidosis should be based on a tissue biopsy, but a patient with typical Lofgren syndrome may not require biopsy proof (10).

Regarding differences in the prevalence and symptoms of sarcoidosis in patients in different geographical areas and populations, the objective of this study was to characterize the epidemiology of sarcoidosis, with emphasis on clinical, laboratory, and imaging findings in the north of Iran.

MATERIALS AND METHODS

In a cross-sectional study, patients with sarcoidosis were enrolled in this study from September 2019 through October 2020. Patients with a diagnosis of sarcoidosis aged 20-70 years were enrolled in the study. The protocol was approved by the Ethical and Research Committee of the Mazandaran University of Medical Sciences (IR.MAZUMS.IMAMHOSPITAL.REC.1398.5762). Inclusion criteria were clinical features compatible with sarcoidosis according to laboratory findings, histopathology, and radiologic features of intrathoracic sarcoidosis. Histopathology was considered positive if they demonstrated non-caseating granuloma without evidence of acid-fast bacilli or fungi. Only patients with symmetric bilateral hilar adenopathy with or without mediastinal lymphadenopathy in the absence of symptoms or identifiable causes were considered sarcoidosis without tissue biopsy. Exclusion criteria were patients with other pulmonary diseases such as tuberculosis, and patients with other systemic disorders. The patients were evaluated by a rheumatologist, or pulmonologist, or both. All patients were referred to an ophthalmologist and cardiologist for evaluation of ocular and cardiac involvement.

Demographic data, smoking status, urban residency, the season of the year when the patient became symptomatic, the presence of symptoms related to pulmonary and extrapulmonary disease, and radiologic and laboratory findings were recorded. A chest CT scan was obtained for all of the patients and reviewed by pulmonologists. Laboratory evaluation included the measuring of ACE level, liver enzymes, serum and urine calcium, serum creatinine, and phosphorous.

Statistical analysis was done using SPSS version 19 (SPSS Inc., Chicago, IL, USA) with descriptive statistical methods for frequencies. Student's t-test and Chi-square were utilized to compare quantitative and qualitative variables, respectively. Results were considered significant at $P < 0.05$.

RESULTS

A total of 58 patients with sarcoidosis were enrolled in this study. The mean age and disease duration were 51.10± 10.21 and 3.07±2.71 years, respectively. Thirty-six (62.1%) patients were female and 22(37.9%) were male. The mean age of females was 52.80± 10.0 and in men was 48.31±9.98 years (P= 0.10). Fifty-six (96.6%) patients lived in the city. Four patients (6.8%) were current smokers. In 35(60.4%) of patients, the onset of the disease was in the summer and autumn. Demographic and basic data are shown in Table 1.

Clinical manifestations of patients are shown in Table 2. Eleven (19.0%) patients had constitutional symptoms including fever and/or weight loss, 32 (55.2%) had respiratory symptoms including cough and/or dyspnea, 23 (39.7%) had skin involvement, 9 (15.5%) had arthritis, and

10 (17.2%) had ophthalmic manifestations including anterior or posterior uveitis. None of the patients had cardiac or neurological involvement.

Table 1. Demographic and basic data in sarcoidosis patients (n=58)

Variable	Results	P value
Age (years, mean± SD)	51.10± 10.21	
Sex (number, %)		
Male	22 (37.9%)	
Female	36 (62.1%)	
Age:(year± SD)		
Male	48.31±9.98	0.105
Female	52.80± 10.0	
Disease duration (years, mean± SD)	3.07±2.71	
Residency (number, %):		
Urban	56 (96.6%)	
Rural	2 (3.4%)	
Current smoker (number, %)	4(6.9%)	
Season of presentation (number, %)*		
Spring	12 (20.7%)	
Summer	17 (29.3%)	
Autumn	18 (31.0%)	
Winter	9 (15.5%)	

*Two patients did not remember the date of onset of the disease.

Table 2. Organ involvement and clinical manifestations of patients with sarcoidosis

Symptoms		N (%)
Constitutional	Fever	7(12.1%)
	Weight loss	4 (6.9%)
Respiratory	Cough	26 (44.8%)
	Dyspnea	17(29.3%)
Dermatologic	Erythema nodosum	7 (12%)
	Maculopapular rash	12(20.7%)
	Lupus pernio	3 (5.2%)
Ophthalmologic	Anterior uveitis	6(10.3%),
	Posterior uveitis	4(6.9%)
Arthritis		9(15.5%)
Sinusitis		2(3.4%)
Mediastinal lymphadenopathy		5 (8.6%)
Extra-thoracic lymphadenopathy		5(8.6%)
Splenomegaly		1(1.7%)

Laboratory and imaging abnormalities are shown in Table 3. Fifty-five (94.8%) patients had some abnormalities in the chest CT scan including hilar lymphadenopathy, paratracheal lymphadenopathy, pulmonary nodule, perilymphatic nodules, pulmonary fibrosis, and pleural effusion. Thirty-three (56.9%) patients had elevated levels of ACE. There was no significant relationship between patients' age or disease duration with high ACE levels. Out of the 17 patients who became symptomatic in the summer, 11 of them (64.7%) had high levels of ACE. Similarly, out of the 18 patients who developed sarcoidosis in the autumn, 14 of them (77.7%) had high levels of ACE. This percentage was significantly higher than the percentage of patients with onset of the disease in winter and spring (p=0.000). No association was found between high ACE levels and other clinical or laboratory findings of patients. ACE level relation with other variables in patients is shown in Table 4.

Table 3. Laboratory and imaging abnormalities of patients with sarcoidosis

Laboratory and imaging findings		N (%)
Increasing liver enzymes		5(8.6%)
Increasing serum ALP		4(6.9%)
Increasing serum creatinine		2 (3.4%)
Hypercalcemia		3(5.2%)
Hypercalciuria		6(10.3%)
Hyperphosphatemia		1 (1.7%)
Increased level of ACE		33(56.9%)
Chest CT Scan abnormalities	Hilar lymphadenopathy	49(84.5%)
	Paratracheal lymphadenopathy	43(74.1%)
	Pulmonary nodule	13(22.4%)
	Peri-lymphatic nodules	10(17.2%)
	Pulmonary fibrosis	3(5.2%)
	Pleural effusion	1(1.7%)
	Bronchiectasis	1(1.7%)

Table 4. ACE level relation with other variables in patients with sarcoidosis

Variable	Elevated ACE level (N=33)	Normal ACE level (N=25)	P value
Age (years, mean± SD)	53± 9.2	49± 10.8	0.164
Duration (years, mean± SD)	3.5±2.7	2.4± 2.8	0.131
Season of disease onset			
Spring	3 (9%)	9(36%)	
Summer	11(33.3%)	6 (24%)	0.000
Autumn	14 ((42.4%)	4 (16%)	
Winter	4 (12.1%)	5 ((20%)	
Clinical findings			
Constitutional symptoms	7 (21.2%)	4 (16%)	0.943
Respiratory complaint	19 (57.6%)	14 (56%)	0.753
Extrapulmonary complaint	7 (21.2%)	6 (24%)	0.815
Abnormal findings in CT scan	31(93.9%)	23 (92%)	0.924
Laboratory findings			
Hypercalcemia	3 (9%)	0	0.302
Hypercalciuria	5 (15.1%)	1 (4%)	0.382
Raised creatinine	2 (6%)	0	0.456

DISCUSSION

The present study was a cross-sectional survey in 58 patients with sarcoidosis to evaluate the incidence of various clinical manifestations and laboratory and imaging findings. The most commonly involved organ was lung (55.2%). On the other hand, the most extra-thoracic manifestations were skin rash (36.2%) followed by constitutional symptoms (18.9%), ophthalmologic involvement (17.2%), and arthritis (15.5%). There was no case of cardiac or neurologic manifestation.

Many studies showed the most commonly involved organ in sarcoidosis is the lung with various manifestations. Although about half of patients are asymptomatic, others present with cough and dyspnea as common presenting symptoms. (11,12) The most typical pulmonary findings in high-resolution CT scans are perilymphatic nodules that are mainly distributed along subpleural areas, interlobular septa, and bronchial vascular bundles in addition to fibrosis (most commonly in upper lobes) in advanced cases (13,14). Moreover, bilateral hilar lymphadenopathy with or without mediastinal lymph node enlargement can be seen in about 95% of patients (13). Our rate of lung and mediastinal lymphadenopathy is almost similar to other studies.

In a cohort study during 1946–2013, most common extra-thoracic manifestations were skin rash (18%), arthralgia (12%), ophthalmologic involvement (7%), splenomegaly (4%), neurological involvement (3%), extra-thoracic lymphadenopathy (3%), exocrine gland involvement (2%), upper respiratory tract involvement (2%), and cardiac involvement (1%)(2).

In our study, forty-five (77.5%) patients had clinical or laboratory findings of extra-thoracic manifestations. The most frequent extrapulmonary manifestation was cutaneous involvement (36.2%). The skin involvement creates a good chance to have accessible tissue for biopsy and early diagnosis.

The second frequent finding in this study was constitutional symptoms (18.9%). It seems these kinds of symptoms are cytokine-mediated and may be seen in 20-35% of patients (15). Due to their nonspecific nature and tendency to occur early in the disease, diagnosing these symptoms can be challenging.

In this study, eye involvement was the third most common finding (17.2%). The eye is a frequently involved organ, affected in between 10% and 60% of patients(16). This difference may be due to the way patients are evaluated and examined, as eye involvement may be asymptomatic and can only be diagnosed by an ophthalmologist. Because of the morbidity associated with ocular involvement, ophthalmological referral for the slit-lamp exam to identify uveitis, retinal vasculitis, conjunctivitis, glaucoma, or cataract, is strongly recommended(3).

In the present study, 15.5% of patients had arthritis. It was shown that up to 25% of patients with sarcoidosis have joint involvement, which may be acute or chronic (8). In a cross-sectional study of 30 patients with sarcoidosis who had been hospitalized in the east of Iran, sarcoid arthropathy (arthritis and periarthritis) was observed in 26 patients (86.6%)(17). In another cross-sectional investigation in Guilan, Iran, presentation with Lofgren's syndrome was seen in 12.3% of patients (4). These differences can be due to the way patients are selected according to the severity or duration of the disease, the definition of joint involvement (arthritis or periarthritis), and assessment methods other than physical examination.

Acute sarcoidosis can occur with erythema nodosum and hilar lymphadenopathy, which is called Lofgren's syndrome. Another manifestation of acute sarcoidosis is Heerfordt syndrome with uveitis, fever, parotitis, and facial nerve paralysis (16). In this study, 15.5% of patients had arthritis, in combination with hilar lymphadenopathy and erythema nodosum in 8 and 3 patients, respectively. There was a patient with fever, erythema nodosum, uveitis, parotitis, facial nerve paralysis, and maculopapular rash who was diagnosed with Heerfordt syndrome.

Regarding laboratory findings, ACE level elevation may be seen in 75% of patients but it is not specific(9). In the present study, high levels of ACE were detected in

56.9% of patients. No association was found between high ACE levels and other clinical or laboratory findings. An interesting finding was the association of high levels of this marker in patients whom symptoms began in summer and autumn. Of course, this finding may be incidental, but the environmental factors that lead to developing sarcoidosis in these seasons may also play a role in increasing this enzyme.

Our study showed 5.2% of patients had hypercalcemia and 10.3% had hypercalciuria. In previous studies, 30 to 50% of patients with sarcoidosis had hypercalciuria, and 10 to 20% had hypercalcemia (18). The increased levels of 1,25-dihydroxyvitamin in pulmonary alveoli, lead to greater absorption of calcium, hypercalcemia and hypercalciuria, and nephrolithiasis. Renal involvement in sarcoidosis including nephrolithiasis and renal failure may exist in 10-20% of patients(15). We have found 9 (15.5%) patients with these manifestations.

Women seem to develop sarcoidosis at an older age(2, 19). This may be due to genetic characteristics about exposure to environmental or occupational factors. Also, the average age of patients has increased in recent years. The peak age at incidence for women shifted from 40 to 59 years in 1950 to 50 to 69 years in 2010. Similarly, the peak age at incidence for men shifted from 30 to 49 years in 1950 to 40 to 59 years in 2010(2). The mean age in our study was higher in women than men but it was not statistically significant. Patients' gender may also affect the frequency of some symptoms. As shown in one study, cutaneous involvement and uveitis were more common in women, and pulmonary symptoms were significantly more frequent among males (19). We found no clinical differences in male and female patients, probably due to the small sample size.

The small sample size was a limitation in this study, although it may be an indicator of the characteristics of the disease in this specific geographic region.

CONCLUSION

The clinical, laboratory, and imaging manifestations of sarcoidosis are diverse and may be easily confused with other diseases. In this study, we showed that the disease occurs most often in the fifth and sixth decades. Most patients can receive a diagnosis by combining their clinical and laboratory symptoms. More than 75% of patients have extra-thoracic symptoms and more than 90% of patients have abnormal chest CT scans. Knowing the epidemiology, extent, and frequency of disease symptoms in any population can help to consider and diagnose the disease. It is suggested to conduct more extensive studies with more samples in different geographical areas.

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