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Clinical features of sarcoidosis in Oman: a report from the Middle East region

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Abstract. *Background:* Though clinical features of sarcoidosis follow a similar pattern, some heterogeneity is seen in different ethnic and racial groups. *Objectives:* To describe for the first time the clinical characteristics of sarcoidosis patients in the Sultanate of Oman. *Methods:* The data on all cases of sarcoidosis followed up in the two tertiary hospitals in Oman were retrieved retrospectively. *Results:* Of the 92 patients, for representing the ethnic data only Omani patients (n=83) were included. The mean age was 52.90±12.35 years. Majority were females (72.3%, n=60). Cough (n=44, 53.0%), dyspnea (n=39, 47%), arthralgia (n=26, 31.3%) and fatigue (30.1%) were the major symptoms. Arthralgia was reported by 41.7% of the females and 4.3% of the males (p= 0.001). Uveitis was present in 16 (19.3%), erythema nodosum in 8 (9.6%) and hypercalcemia in 13 (15.7%). The radiological stage at presentation was stage 0, 18.7%; I, 28%; II, 17.3%; III, 24% and IV, 12%. Majority (61.4%) of the patients had tissue diagnosis; intra-thoracic site 70.6%. Pulmonary function showed abnormal diffusion in 75%. Sixty eight received treatment, 81.9% took prednisolone. Based on radiograph good outcome (Resolving) was noted in 20.9%, intermediate (Stable) in 73.1% and poor (Progressive) in 6%. Lung function wise, resolving, stable and progressive disease was seen in 31.4%, 40.0% and 28.6% respectively. *Conclusion:* The clinical picture of the patients with sarcoidosis from Oman was similar to that reported from the rest of the world. Region wise, our patients were older and arthralgia and hypercalcemia were more common. The management of sarcoidosis needs a more organized approach in the country with clear guidelines on monitoring and treatment *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 201-208)*

Key words: sarcoidosis, Oman, arabs, Middle East

Introduction

Sarcoidosis is a systemic granulomatous disorder of unknown cause characterized by frequent pulmonary involvement and is seen all over the world and affects both sexes, all races and all ages (1,2). Last decade saw many advances in the area of etiology, genetics, diagnostic methods and treatment (3,4). The lungs are involved in most cases and are affected without other organ disease in approximately 50% of patients; the skin, liver and eyes being the most frequent extra pulmonary sites (5). Sarcoidosis can affect the entire length of the respiratory tract, from the nose to the terminal bronchioles, leading to a wide range of lung dysfunction (6). Sarcoidosis may consist of several overlapping clinical syndromes and can be categorized into different clinical phenotypes (7). Though the clinical features generally follow a

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similar pattern, significant heterogeneity in clinical characteristics and severity of the disease among patients from different ethnic and racial groups have been described (8,9).

In general, incidence peaks between the ages of 20 and 50 years, with a second smaller peak after the age of 60 (5). The incidence of sarcoidosis appears to be higher in Scandinavian countries and in Afro-Caribbean people, and also marginally higher in women (5,8-12). A Case Control Etiologic Study of Sarcoidosis (ACCESS) which examined 736 patients at ten centers within the USA found that the blacks tend to have a more severe disease while whites presented with a milder form (5). In a recent report on 1774 patients form the US, blacks showed more advanced radiographic stages of sarcoidosis, more organ involvement, and required anti-sarcoidosis medication more frequently when compared to the whites (13).

Sarcoidosis has been reported with a slight clinical variation from the Middle East countries (14-20). In a study from Kuwait, Behbehani et al (16), noted that the respiratory symptoms and the skin manifestations were more common among the Arabs whereas constitutional and eye symptoms were more frequent among Asians residing in the same country. Whereas in native Saudis the disease was found to present with severe constitutional symptoms, relatively frequent eye involvement and stage II disease at presentation (18).

There is no data on the clinical features of sarcoidosis in Oman. The aim of this study is to describe the clinical presentation, the mode of diagnosis, the treatment approach and the prognosis in patients with sarcoidosis in the Sultanate of Oman.

Material and Methods

Oman is a country in the southeast coast of Arabian Peninsula, at the confluence of the Persian Gulf and Arabian Sea. The sultanate has a total land area of 309,500 square kilometers and diverse climatic conditions with humid coastal areas, a hot and dry desert interior and regions with seasonal heavy rains

All cases of sarcoidosis seen and followed up in the two tertiary hospitals in Oman, Sultan Qaboos University Hospital (SQUH) and Royal Hospital (RH) were included. The study was approved by the ethical committees of both hospitals independently. The cases were retrieved from the hospital information system and the needed data were collected retrospectively. A diagnosis of sarcoidosis was accepted either by tissue diagnosis or convincing clinico-radiological presentation in each case. Three criteria were used for diagnosis; compatible clinical and radiological presentation, evidence of non-caseating granulomas in tissue biopsy, and no evidence of other diseases capable of producing a similar histological or clinical picture (1).

The clinical details were gathered using a structured data collection sheet. The age, duration of symptoms, symptoms at presentation, clinical signs, basic investigation results, the chest radiographic and computed tomography (CT) scan findings, pulmonary function test (PFT) values, the results of immunological work up and the details of treatment were collected. The method of diagnosis either clinio-radiological or biopsy proven were clearly recorded. The extra pulmonary involvement when present was documented. The response to treatment and the details of follow up radiographs and PFT values were also collected. The region of residence, occupation and history of exposure to environmental, occupational or toxic substances were recorded if documented in the clinical notes. Modified Scadding criteria was used for staging: stage 0, no lung involvement; stage I, hilar enlargement alone; stage II, hilar enlargement plus parenchymal lesions; stage III, parenchymal lesion alone; and stage IV, lung fibrosis (21).

The outcome was judged by the radiological or pulmonary function variation as noted in the most recent radiograph and the pulmonary function data. We used the following terms for classifying the outcome. Resolving, when a definite radiological improvement was documented; Stable, when the lesions remained stationary; and progressive, when it worsened. Similarly PFT wise; Resolving, when the FVC or TLC improved by 15% or if the DLCO improved by 10%; Stable, when these values remained more or less the same; and Progressive if the FVC or TLC worsened by 15% or if the DLCO came down by 10% (22).

These data were then entered in the SPSS data sheet and analyzed. Descriptive statistics and when needed cross tabulation to look for gender, race or age related differences were done.

Results

There were 92 patients; 9 were expatriates. For representing the ethnic data we included only Omani patients (n=83) in the subsequent analysis. Forty six (55.4%) patients were seen and treated in RH and 37 (44.6%) in SQUH. Majority of the patients were females (72.3%, n=60). The mean age of the study group was 52.90±12.35 years (Males 52.78±13.66 and Females 52.95±11.94 years). More than half (56.8%) of the patients were in the 40 to 60 years age group (Table 1). Family history of sarcoidosis was obtained in 3 (3.6%) patients.

Cough (n=44, 53.0%) was the predominant symptom, followed by dyspnea (n=39, 47%) and arthralgia (n=26, 31.3%). Fatigue was reported by 30.1% of the patients. (Tables 2, 3). Though all the symptoms were more frequent in the females, a significant difference was seen only in the presence of arthralgia. Arthralgia was reported by 41.7% of the females and 4.3% of the males (p= 0.001). Uveitis was present in 16 (19.3%), erythema nodosum in 8

Table 1. Showing demographic and clinical features of patients with sarcoidosis in Oman

Characteristics		N.	%
Age groups (n=81)	20-29	9	11.1
	30-39	14	17.3
	40-49	25	30.9
	50-59	21	25.9
	>60	12	14.8
Place of diagnosis	RH	40	48.2
	SQUH	31	37.3
	Private Sector	3	3.6
	Abroad	9	10.8
Method of diagnosis	Clinico radiological	32	38.6
	Histology	51	61.4
Histology	Lung	21	41.2
	Mediastinal Lymph node	15	29.4
	Peripheral lymph Node	7	13.7
	Liver	6	11.8
	Skin	2	3.9
SACE level (n=64)	High	33	51.6
	Normal	31	48.4
Stage	0	14	18.7
	I	21	28.0
	II	13	17.3
	III	18	24.0
	IV	9	12.0
Pulmonary function (n=55)	Normal	10	18.2
	Obstructive	9	16.4
	Restrictive	24	43.7
	Isolated diffusion defect	12	21.9
Medications	Prednisolone	68	81.9
	Azathioprine	11	13.3
	Inhaled steroids	8	9.6
	NSAID's	4	4.8
	Infliximab	1	1.2
Duration of treatment (n=67)	Up to 1 year	28	41.8
	1.1 to 3	20	29.9
	1.1 to 5	8	11.9
	>5 years	11	16.4

Table 2. Clinical characteristics (Symptoms) of total population at presentation and distribution among genders with statistical significance

Characteristics	Total N=83	%	Females N=60	%	Males N=23	%	P
Cough	44	53%	34	56.7%	10	43.5%	0.281
Dyspnea	39	47%	29	48.3%	10	43.5%	0.692
Chest pain	20	24.1%	16	26.7%	4	17.4%	0.377
Fever	17	20.5%	14	23.3%	3	13%	0.298
Arthralgia	26	31.3%	25	41.7%	1	4.3%	0.001
Weight loss	9	10.8%	7	11.7%	2	8.7%	0.697
Fatigue	25	30.1%	19	31.7%	6	26.1%	0.620

Table 3. Clinical characteristics (Signs) of total population at presentation and distribution among genders with statistical significance

Characteristics	Total N=83	%	Females N=60	%	Males N=23	%	P
Uveitis	16	19.3%	14	23.3%	2	8.7%	0.130
Erythema nodosum	8	9.6%	8	13.3%	0	0%	0.065
Skin nodules	10	12%	8	13.3%	2	8.7%	0.561
Lymph nodes	10	12%	8	13.3%	2	8.7%	0.561
Hypercalcemia	13	15.7%	9	15%	4	17.4%	0.788

(9.6%) and hypercalcemia in 13 (15.7%). Erythema nodosum was seen only in the females while hypercalcemia was more common in the males, though these differences were not statistically significant (Tables 2, 3)

Chest radiograph was done in 75 (90.4%) and CT in 76 (91.6%) patients. Chest radiograph was normal in 14 (18.7%) patients. It showed isolated hilar prominence in 21 (28.0%), hilar adenopathy and pulmonary opacities in 13 (17.3%), only pulmonary opacities in 19 (24.0%) and fibrotic changes in 9 (12.0%). CT chest was normal in 8 (10.5%), showed hilar lymphadenopathy in 5 (6.6%), hilar and mediastinal adenopathy in 9 (11.8%), lymph node and parenchymal in 47 (61.8%) and only parenchymal involvement in 11(14.5%) (Figure 1).

Majority (61.4%) of the patients had a tissue diagnosis, 70.6% from an intra-thoracic site (Table 1). The stage of the disease at presentation was almost evenly distributed, though more patients were in stage I and stage III (Table 1).

Pulmonary function tests were done in 55 (66.3%) patients. Restrictive defect was seen 43.7% of the patients, obstructive defect in 16.4% and isolated diffusion defect in 21.9%. The diffusion was abnormal in 30 out of 40 (75%) tests where diffusion was done. The mean FVC and FEV1 were 2.39±0.78 liters and 1.87±0.55 liters respectively. The median total lung capacity (TLC) was 95.5% and the diffusion (DLCO) 67.0%. Serum angiotensin converting enzyme (SACE) and Mantoux testing were done only in 64 and 36 patients respectively. SACE level was high in 33 (51.6%) patients, while Mantoux test was negative in 88.9%

Only one patient (1.2%) had a cardiac involvement while central nervous system involvement was seen in 2 (2.4%) and gastrointestinal involvement in 9 (10.8%) patients. Six patients had a liver biopsy to confirm the diagnosis. Aspartate aminotransferase (AST) level was recorded only in 45 patients, out of which 6 (13.3%) had an elevated level. But, alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were done in nearly all patients and were elevated in 13.3% and 12.2% respectively. The levels were not very high and the highest value ranged between 1.5 to 2.2 times the normal values.

Sixty eight patients were put on treatment while 15 did not receive any form of treatment. Most of the patients (71.6%) received treatment for three years or less while 16.4% patients were continuing treatment for 5 years or more. Majority (81.9%) of the patients were on Prednisolone (Table 1). Fifty six patients are currently on regular follow up and were seen at least once in the last 2 years.

Only 35 out of the 55 (63.6%) patients who did an initial pulmonary function had a follow up test

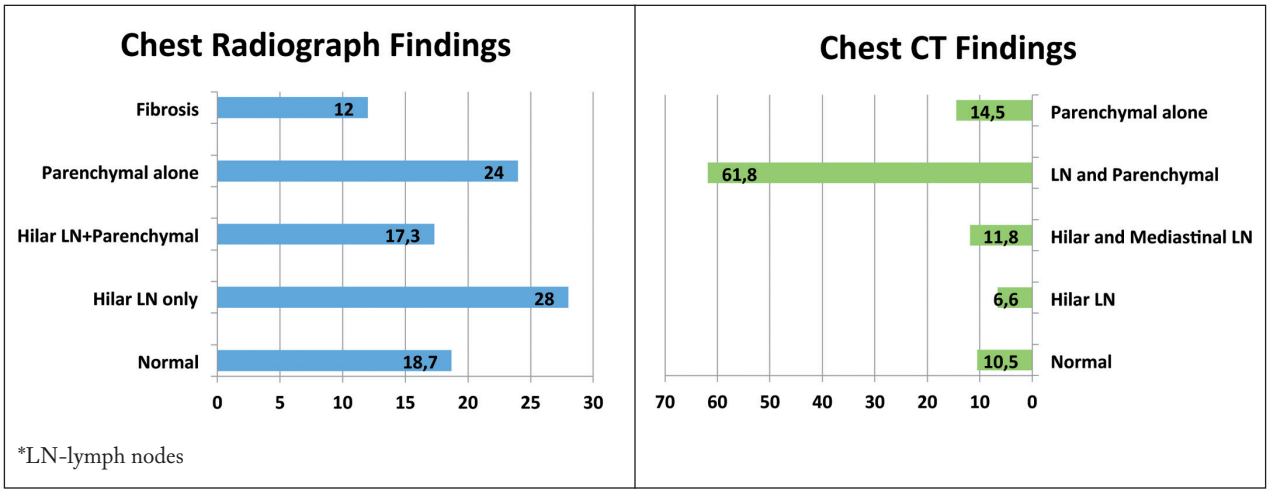

Fig. 1. Showing the Chest radiographic and CT scan findings in patients with sarcoidosis in Oman

while 67 out of the 75 (89.3%) patients had follow up chest radiographs. When assessing the outcome based on most recent chest radiograph, good outcome (Resolving) was noted in 20.9%, intermediate (Stable) in 73.1% and poor (Progressive) in 6%. In contrast, lung function wise, resolving, stable and progressive disease was seen in 31.4%, 40.0% and 28.6% respectively.

Discussion

This is the first report on sarcoidosis from the Sultanate of Oman. The clinical characteristics of these patients were not much different from that reported from the rest of the world. When compared to the patients from this region our patients were older and had arthralgia and hypercalcemia more commonly on presentation. CT was more useful in identifying the disease involvement and pulmonary function tests were more objective when assessing prognosis. Most of our patients were on oral prednisolone and a good majority was treated for 3 years or less.

Our patients with a mean age of around 53years were generally older than the patients from the other Middle East countries. Arab patients are reported to be generally younger (15,16). The results from Kuwait showed a peak of sarcoidosis among Arab males at 30-39 years and Arab females at 40-59 years (16).

Cough was the predominant symptom, followed by dyspnea and arthralgia. Fatigue was reported by 30% of the patients. All the symptoms were more frequent in the females. A significant difference was seen only in the presence of arthralgia, with 41.7% of the females reporting it. In a study comparing the two major races residing in Kuwait, Behbehani et al (16), noted that the respiratory symptoms and the skin manifestations were more common among the Arabs whereas constitutional and eye symptoms were more frequent among Asians. But, Khan and colleagues reported that in native Saudis the disease was characterized by severe constitutional symptoms, relatively frequent eye involvement and stage II disease at presentation (18). Another retrospective study on 104 Arabic patients reports that the main symptoms were dyspnea (76%), cough (72%) and weight loss (33%) (15). Similarly the most common presentations from the eastern region of Saudi Arabia were cough (48%), dyspnea (21%), joint pain (18%), splenomegaly (12%), hepatomegaly (9%), and lymphadenopathy (5%) (14). Erythema nodosum was seen in 8.3% and skin manifestations in 15.9% of patients in ACCESS study while 9.6% of our patients had erythema nodosum and 12% had skin nodules. Interestingly, erythema nodosum was seen only in the females in our group. Erythema nodosum was a notable feature in Turkey (23). When compared to the patients from this region, the frequency of the presenting symptoms were the more or less the same. Arthralgia and hypercalcemia were probably more in our patients.

Though most patients with sarcoidosis present with stages I-III, chest radiographic findings appear to vary worldwide. Patients from Japan had stage I disease whereas Europeans and Americans present with a higher radiographic staging (24,25). The stage of the disease at presentation in our group was almost evenly distributed, though more patients were in stage I and stage III, a different pattern when compared to the reports from the region (15,16) CT was normal only in 10.5% of patients while chest radiograph was normal in 18.7% indicating that CT chest picked up more abnormalities when compared to the chest radiograph alone. Moreover, 80.3% of the patients showed lymph node and 76.3% showed parenchymal involvement in the CT. Currently, CT represents the reference standard for the assessment of both mediastinal lymph nodes and pulmonary findings (26). In the appropriate clinical setting, a combination of characteristic mediastinal and parenchymal abnormalities on CT are virtually diagnostic of sarcoidosis. CT is essential for resolving diagnostic uncertainties, assessing disease extent, detection of complications and identifying irreversible lung involvement though its role in disease monitoring and prediction of outcome is not well documented (27).

The main pulmonary function abnormality was a diffusion defect seen in two thirds of our patients. Restrictive defect was seen in 43.7%. It is known that decreased diffusion capacity is the most common abnormality found on pulmonary function testing and is often accompanied by restrictive ventilatory dysfunction (3). Mantoux test was negative in 89% of the patients tested while SACE level was high in only 51.6%. It is known that SACE levels even after correction for a genetic polymorphism is not accurate in the diagnosis of sarcoidosis (4). Sarcoidosis is known to produce tuberculin anergy, which is not affected by high prevalence of tuberculosis infection. So a negative TST result is likely to support the diagnosis of sarcoidosis in the appropriate clinical settings (28).

There is no definite cure for sarcoidosis, and treatment only changes the granulomatous process and its clinical consequences. No clear guidelines exist and it is not really known whether treatment can change the outcome (4). The toxicities of the medications may more than offset their benefit in patients with negligible to mild disease. Systemic corticosteroids remain the standard treatment. Judson et al reports that the patients who received 500 mg of prednisone equivalent in the previous year had an improved quality of life compared to patients receiving >500 mg (29). Challenges to optimal outcome are the phenotypic variation, heterogeneity of organ response, or a lack of uniform response to treatment (30). Majority of our patients were on oral prednisolone and nearly 72% were treated for 3 years or less. More than two third of the patients are currently on regular follow up at this point. Eighteen percent were not on any form of treatment.

The clinical course for sarcoidosis varies with the disease resolving spontaneously within 2 years in half of the patients and in many other cases within 5 years (4). But some patients progress to chronic and progressive disease which may lead to life-threatening conditions (31). Refractory sarcoidosis refers to patients progressing despite treatment Prognosis in sarcoidosis depends mainly on the mode of onset, host factors, initial clinical course, and extent of disease. Follow up on a cohort of 215 sarcoidosis patients from the ACCESS study showed that sarcoidosis tends to improve or remain stable in the majority of patients after two years (32). Erythema nodosum is more common among certain racial groups and is known to portend a good prognosis. African – American patients tend to have a worse long term prognosis and higher rates of relapses (1,33). By contrast, no racial difference in the prognosis was noticed in another report from Kuwait. In that study, better initial lung function values, presence of arthralgia and early stage of the disease were the most important predictors of good prognosis while sex, age, ethnicity, fever, weight loss or erythema nodosum did not influence the outcome (34). A good outcome, resolving or stable disease was noted in 71.4% of our patients when measured using pulmonary function values and in 94% when radiologic data was used. The plausible explanation for the difference could be that there is no direct relation between the radiological and the functional improvements. The significance of this observation need to be judged carefully as only 42% of the total patients had the pulmonary function repeated during follow up. Clinical improvement was difficult to measure as the progress notes were often incomplete and did not mention specifically the changes in symptoms.

Genetic and host factors play a role in the pathogenesis of sarcoidosis. Familial clustering of

sarcoidosis has been reported with a five times more chance of having another member developing the disease (35,36). It is interesting to note that with a high prevalence of consanguinity and the existence of genetic disorders in this region, the presence of sarcoidosis in another family member was documented in only 3.6% of our patients. The accuracy of this information need to be verified in prospective studies as this might just be a reflection of poor documentation. It is also worthwhile to note the relatively less cardiac and neurological involvement.

There are many limitations for this study. The first and foremost is the retrospective nature of report with a lot of information on the clinical presentation and the investigations being incomplete. Secondly, this study was undertaken at the tertiary hospitals in the capital governorate which could have influenced the referral pattern based on the severity and also the distance. Third limitation is probably a selection bias as most of the patients were from the adult pulmonology clinics

In conclusion, the clinical picture of the patients with sarcoidosis from Oman was similar to that reported from the rest of the world. Region wise, our patients were older with arthralgia and hypercalcemia being more common. Moreover, the management of sarcoidosis needs a more organized approach in the country with clear guidelines on the frequency of follow up imaging and pulmonary function tests as well as the choice of drugs and the duration of treatment.

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