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Sarcoidosis, a report from guilan (an iranian northen province) (2001-09)

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Abstract. *Background:* Sarcoidosis is a chronic multiorgan autoimmune disorder that affects all racial and ethnic groups and occurs at all ages. *Objective:* The aim of this study was to assess the clinical and epidemiological features of sarcoidosis patients in a referral clinic of pulmonary disease in city of Rasht (Guilan-Iran). *Method:* This retrospective study was done by reviewing sarcoidosis patient's records containing demographic, sign and symptom and clinical data in a pulmonary clinic in Rasht from 2001-09. All statistical analyses were achieved using SPSS. *Results:* most common signs and symptoms were respiratory, systemic and musculoskeletal complaints. According to Chest X-Ray, 61.3% had bilateral hilar lymphadenopathy (BHL) alone (stage 1), and 24.2% had BHL plus parenchymal involvment (stage 2). The most common abnormal finding in spirometry was small airway disease. The follow-up data showed that 178 patients (45.2%) had significant improvement clinically, radiologically or both. *Conclusion:* It seems many clinical and radiological aspects of sarcoidosis in our patients are similar to other series. However, presentation with Lofgren's syndrome is a common feature and skin (n=48, 12.3%) and eye (n=19, 4.8%) involvement are less frequent. There is significant difference between west and east of Guilan in relation to referred patients (12.9% vs 78.5% respectively). Of course this may be due to referral issues of patients and medical teamwork connections *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 282-288)*

Key words: Sarcoidosis, Epidemiology, Guilan

Introduction

Sarcoidosis is a chronic multiorgan granulomatous inflammatory disorder of unknown etiology, characterized by non-caseating granulomas, primarily affects the lungs and the lymphatics (1, 2).

Sarcoidosis affects people of all racial and ethnic groups and occurs at all ages, although it usually develops before the age of 50 years, with the peak incidence at 20 to 39 years (3). There are numerous reports of familial clustering of sarcoidosis (4).It typically presents with BHL, pulmonary intrestitial opacities, and skin, joint or eye lesions. Respiratory system is the most common organ involved, which is followed by skin and lymph nodes (4).Lofgren's syndrome, an acute presentation of disease consisting of arthritis, erythema nodosum (EN), and BHL, occurs in 9 to 34% of the patients (3). Sarcoidosis is one of the few pulmonary diseases with a higher prevalence in non-smokers (5).

The diagnosis of sarcoidosis is established on the basis of compatible clinical and radiologic findings, supported by histologic evidence in one or more organs of non-caseating epithelioid-cell granulomas in the absence of organisms or particles and rule out similar disease. The diagnosis of sarcoidosis is reasonably confirmed without biopsy in patients who present with Lofgren's syndrome. In all other cases, a biopsy specimen should be obtained from the involved organ (4).

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The majority of patients recover spontaneously (4, 6).Some features of sarcoidosis such as lupus pernio, neurologic involvement, bone cysts, and pulmonary fibrosis predict a more chronic course, with a low rate of remission. Approximately one third of patients suffer a more persistent and progressive disease requiring prolonged treatment with corticosteroids and occasionally with one or more second-line drugs such as azathioprine (6).

There are few studies on sarcoidosis in Iran. Thus, we undertook this study to further increase the knowledge about the disease in Guilan (a northern province of Iran).The aim of the study was to assess the epidemiological and clinical features of sarcoidosis in the patients from a referral pulmonary clinic in Rasht.

Materials and methods

This is a retrospective study which was done by reviewing of sarcoidosis patient's records in a pulmonary clinic in Rasht from 2001-09. Two groups of patients were entered:

Cases with definitive diagnosis of sarcoidosis;

Patients with Lofgren's syndrome (sudden onset of ankles arthritis, fever, and BHL, with or without EN)

Patients who by clinical and radiographic considerations were biopsied (usually from the lungs, but some from the skin and lymph nodes) and non-caseating granuloma compatible with sarcoidosis was confirmed by the pathologist. In these patients, other similar diseases [usually tuberculosis (TB) and lymphoma] has been rejected based on clinical manifestations and laboratory data.

Cases as highly suggestive for diagnosis of sarcoidosis; Patients who based on clinical and radiographic findings of pulmonary sarcoidosis have been considered as a possible case (they did not consent to biopsy or because their critical clinical conditions biopsy was not possible) and in the course of the disease the differential diagnosis of sarcoidosis have been rejected.

Patients included in two groups: those who directly visited due to respiratory problems, and those who referred for consultation, because of other specific organ involvement such as arthritis or ocular involvement from relevant experts around the province. Patient's data was collected by reviewing the records and completing the checklist prepared for demographic characteristics (age, sex, duration of symptoms, living area, and employment status), patient's sign and symptom and paraclinic finding (laboratory data, radiographic findings and Pulmonary Function Test. All statistical analyses were achieved using SPSS software (SPSS version 18, USA).

Results

There were 392 cases during 8 years. The mean age was 42.8 ± 9.8 with the range of 15-81 yrs. The predominant sex was female (n=249, 63.5 %) and the most patients were in the age group of 40-50 years. Seasonal distribution showed that the most common referred season was autumn with the frequency of 103 cases (26.3%). According to patient's Body Mass Index, 182 (46.5%) were overweight.

Geographical distribution showed that 12.9% of cases were settled in the east and 78.5% in the west of Sepidrood River which divided Guilan to two part (Figure 1). Others (8.6%) were referred from the neighborhood of Guilan.

The most common signs and symptoms were related to respiratory complaints (248 cases; 63.3%) including dyspnea and cough, systemic problems (127 cases; 32.4%) such as weight loss and fever, musculoskeletal complaints (80 cases; 20.4%) including of limb and/ or joint swelling, arthritis, and arthralgia, upper respiratory tract symptoms (65 cases; 16.6%) such as post nasal discharge, and cardiovascular problems including chest pain and palpitation (55 cases; 14%). There were 28 patients (14.7%)

Fig. 1. Distribution of patients according to the region in Guilan (%)

with EN and three patients (0.8%) had been suffering from uveitis (Table 1). Some interesting patients presentations observed in the study were association with breast granulomatosis, psoriatic arthritis, paracardiac mass with invasion to pericardium, biopsied granulomatous lymphadenitis during CABG surgery, endobronchial mass, palpitation in a patient with pacemaker, cirrhosis, systemic sclerosis, sjogren's syndrome, splenomegaly with hypo-proliferative anemia, and quadriplegia (spinal cord involvement).

The most important comorbidities were rheumatoid arthritis (n=11, 2.8%), chemical warfare injuries (n=10, 2.5%) and asthma (n=9, 2.3%).There were 2 cases (0.05%) with history of TB.

The most abundant familial history of disease in our study was asthma with the frequency of 23 cases (5.9%). TB and Sarcoidosis was reported in the first degree relatives of 4 and 7 patients, respectively.

History of patients' drug consumption revealed that NSAIDs and β-blockers (15.3%, 3.3%, respectively) were the most prevalent drugs and 182 cases (46.4%) had no any drug consumption history, at the referral time.

Regarding to smoking history, 362 cases (92.3%) were nonsmoker. There were 15 smokers (3.8%) and 6 passive smokers (1.5%). Nine patients (2.3%) had stopped smoking at the diagnosis time.

The most common pulmonary abnormalities in physical examination were wheezing and crackle. In 256 patients (65.3%) there were normal findings in the respiratory system.

According to CXR which was done for 194 cases at the first referral time, 119 cases (61.3%) had BHL alone (stage 1), 47 (24.2%) had BHL and parenchymal involving (stage 2), 4.6% and 2.7% of patients were in stage 3 and stage 4, respectively.

Based on chest CT scan which was requested for 258 (65.8%), 162 (62.8%) had both BHL and parenchymal involving (stage 2) and 59 (22.9%) had BHL alone (stage 1). The most prevalent of chest CT scan findings was lymphadenopathy and interstitial lung involvement (table 2).

Spirometry was performed for 300 patients. In 163(54.4%) spirometry was normal, 95(31.6%) had obstructive and 42 patients (14%) had restrictive pattern. Overall, the most common abnormal findings in spirometry was small airway disease pattern (only MMEF25-75 <65%) which was seen in 61 patients (20.3%).

Serum angiotensin converting enzyme (ACE) level was requested for 195 patients. Range of ACE

Table 1. Frequency of patient's signs & symptoms

Clinical presentations	Number (%)
Respiratory	248 (63.3%)
Dyspnea	61.7%
Dry cough	58%
Wheezing	31%
Productive cough	19.3%
Hemoptysis	1%
Systemic	127 (32.4%)
Weight lost	50%
Fever	42.5%
Fatigue	5%
Musculoskeletal	80 (20.4%)
Limb & Joint swelling	48.7%
Myalgia	18.7%
Arthritis & Arthralgia	16.2%
Bone pain	11.2%
UpperRespiratoryTract (PND, …)	65 (16.6%)
Cardiovascular (Chest Pain, Tachycardia)	55 (14%)
Skin	48 (12.2%)
Erythematous	58%
Dermatitis	35%
Nodule	4%
Erythema Plaque	3%
Gastrointestinal (Abdominal pain, nausea &vomiting ,...)	43 (11%)
Eye (redness, itching, uveitis)	19 (4.8%)
Neurologic (dizziness, Vertigo, pares thesis)	13 (3.3%)

Table 2. Frequency of Chest CT scan findings

Chest CT findings	Number (percent)
LAP	183 (46.7)
Interstitial involvement	112 (28.6)
Alveolar involvement	20 (5.1)
Pleural involvement	20 (5.1)
Fibrosis	19 (4.9)
Hypodence area	10 (2.6)
Bronchiectasis	5 (1.3)
Pulmonary HTN	3 (0.8)
Cardiomegaly	3 (0.8)
Mass	2 (0.5)

level was 11-396 U/L and mean level was 64.6 ± 46 U/L. In 151 (77.4%) patients ACE level was higher than normal. Serum calcium (Ca) level was evaluated in 142 cases. Range of serum Ca level was 8-11 mg/dl (mean: 9.2 ± 0.6) and hypercalcemia was seen in four patients (2.8%). Urinary Ca level was measured in 84 patients (range: 18-795 mg/24h mean: 188.8 ± 110.4 mg/ 24h) and hypercalciuria was seen in 15 patients (17.8%).

PPD test was performed for 144 patients and was positive (>15 mm) in 8 cases (5.5%).

Sputum smears examination for acid fast bacteria (AFB) was performed for 54 patients which in all of them the result was negative. In bronchoalveolar lavage (BAL) 17 (58.6%) out of 29 cases showed preference of PMN to lymphocytes.

Diagnostic biopsy was done in 123 patients. The most biopsied organs were lung (by fiberoptic bronchoscopy) and skin (60; 48.8%, 29; 23.6%), respectively (Table 3).

Diagnosis of sarcoidosis was confirmed in 293 patients; 33 previously known cases of sarcoidosis were referred for pulmonary evaluation, 147 cases were diagnosed as Lofgren's syndrome, and 113 patients which diagnosis of sarcoidosis was confirmed by biopsy in them (included a case of Heerfordt's syndrome by triad of uveitis, parotiditis, and facial nerve palsy). We had 99 patients (25.3%) in the highly suspected group.

With respect to therapy 186 patients (47.4%) were indicated to treat by steroids. The treatment period varied according to response, mostly for 6-12 months. Starting dose of the steroid in most of them was in the range of 25 to 50 mg per day. In some cases, oral non steroidal anti-inflammatory drugs were administered for the control of joints pain.

Table 3. Distribution frequency of organs biopsied

Organ Biopsied	Number (%)
Lung parenchymal (TBLB, Bronchoscopy)	60 (48.4)
Skin	29 (23.6)
Bronchus	18 (14.6)
Thoracic LN	4 (3.3)
Inguinal LN	2 (1.6)
Hilar LN	2 (1.6)
Supraclavicular LN	1 (0.8)
Cervical LN	1 (0.8)
Parotid	1 (0.8)

All patients, including those who had no indication for treatment, were planned to follow up for 2-3 years. The follow-up data was available for 275 cases; 117 patients (29.8%) had only one visit and some patients (98; 35.7%) had follow up period less than 1 year. In 178 patients (45.2%) we observed significant improvement in clinical feature, CXR or both. Sixty three cases (16.1%) showed recurrence over the follow up period with good response by restarting therapy. There was only one refractory case (0.3%) with clinical and CXR deterioration who was controlled by adding methotrexate. The remaining 33 patients (8.6%) had unchanged and non-progressive condition.

Discussion

Our findings suggested that the age of patients and most common signs and symptoms prevalence of sarcoidosis in Guilan province are somewhat similar to other studies in this field (Table 4).

The ratio of sarcoidosis prevalence in women to men in our study was 3.3/1 which was somewhat higher than similar studies (Table 4).

Despite other studies the ratio of smoker to non-smoker people in our study was very low; 1 to 15 (Table 4).

Similar to other studies, the most common signs and symptoms was related to respiratory and systemic issues. A Saudia Arabia study on 33 patients in 2011 showed that after respiratory symptoms (%48) and shortness of breath (%21), systemic symptoms like fever (%21) and weight loss (%18) were the most prevalent symptoms gained from patients (7). In Amoli's study, the similar results were observed; the most common complaints were cough (%59.6), shortness of breath (%37.4) and fever (%28.7) (8).

Although, cardiovascular symptoms were seen in %14 of patients in the present study, in Saudia Arabia study, no patients had such symptoms (7). In Amoli's survey, chest pain was the only complaint with the frequency of %18.3 (8).

Overall, skin involvement was reported in 25 to 35 percent of patients; but this organ involvement was %12.2 in the present study. In Saudia Arabia study, skin involvement was not observed in any patients (7). Erythema nodosum (EN) was seen in %7.1 of our patients similar to other studies (%10).

Table 4. Comparison with other studies

Study / Variable	Current study	Amoli (8)	Saudi Arabia (7)	Turkey (12)	Zagreb, Croatia (13)	Berliner AR, et al. (9)	Baughman RP, et al. (10)
Age (Y)	42.8± 9.8	42	-	40.3	-	-	-
Female/Male	3.3	1.28	-	-	-	-	-
Smoking/ Nonsmoking	1/15	1/3	-	-	1/3.3	-	-
Signs & Symptoms	Cough (77.3%) Dyspnea (61.7) Systemic *(32.4%) Skin (12.2%) Erythem nodosom (7.1%) Cardiac **(14%) Eye Involvement (4.8%)	Cough (59.6%) Dyspnea (37.4%) Systemic (28.7%) Cardiac** (18.3%)	Cough (48%) Dyspnea (21%) Systemic (39%) Cardiac/Skin (0%)	-	-	-	-
Lab Data	Hypercalcemia (2.8%) hypercalciuria (17.8%) ↑AST (45.8%) ↑ALT (47.8%) ↑ALP (39.4%) ↑ACE (77.4%)	↑ACE (83%)	↑Blood Ca (6%) ↑ACE (46.8%)	-	-	↑Blood Ca (11%) ↑Urinary Ca (45%) Renal stone (10%)	↑AST, ALT, ALP (>10%)
PPD test (positive: >15mm)	5.5%	9%	-	-	-	-	-

** systemic: Weight loos, Fever, Fatigue,...*

***Cardiac: Chest pain, Palpitation,...*

Normal range of Blood Total Ca: 8.5-10.5, Urinary Ca: urinary excertion of more than 250-300 mg of Ca per day. Normal range of AST: 8-40, ALT: 8-56, ALP: 42-128, Normal ACE: less than 40 mg/lit 15

Eye involvement frequency was considered as %25 to %80 (2), but our result was %4.8. The most prevalent type of eye involvement in our study was uveitis which was similar to other reports.

In our survey hypercalcemia and hypercalciuria were seen in %2.8 and %17.8 of subjects, respectively, which were significantly lower than Barlinar and colleagues study results (9) (Table 4).

In a case-control study done by Baughman RP and colleagues in 2001, increased serum levels of liver enzymes including alkaline phosphatase and aminotransferase were seen in more than %10 of patients (10). The increased serum levels of liver enzymes were conformed to the result of present study in increasing AST and ALT and Alkaline phosphatase (%45.8, %47.8 and %39.4 of patients, respectively). In our study 77.4% of subjects had serum ACE level higher than normal which was more than Saudi Arabia study (46.8%) and similar to Amolis study (83%).

In more than half of patients in the present study (%65.3), normal respiratory function test was gained. This finding was in contrast with the result of Shorr AF and colleagues study in 2001 (11) which showed that %65 of patients had airflow limitation and also revealed that at least %50 of patients had COPD and a reduction in the ratio of FEV1 to FVC. However, obstructive pattern was seen in %32 of subjects, and %14.5 had restrictive pattern in our study. The higher ratio of obstructive to restrictive pattern was seen in Saudia Arabia's study; %38 obstructive, 26% restrictive and one of the patients had a mixed pattern (n=33), but in the Amoli study, the prevalence of obstructive pattern was lower than restrictive pattern.

The results of CXR stages in the present study were consistent with prevalence of stage 1 (61%) of disease in our patients which was more prevalent than other studies (Table 5).

In the present study, PPD was performed on 144 patients, 8 of whom (%5.5) had positive test results (more than 15mm). In Amoli's study, also, PPD was done on 243 patients who were negative in 222 patients(%91). The severity of response in 8 patients was

Table 5. The results of CXR findings in relation to other studies

Study Variable	Current study	Amoli (8)	Saudi Arabia (7)	Zagreb, Croatia (13)	Finland & Hokkaido (14)
CXR staging	I (61%) II (24.2%) NL (7.2%)	I > II	I (39.4%) II (45%)	I (48.6%) II (39.7%)	Finland: I (38%) II (39%) NL (1%) Hokkaido: I (57%) II (29%) NL (19%)

Stage I: Bihilar Lymphadenopathy, Stage II: BHL and reticulonodular infiltrates, Stage III: Bilateral pulmonary infiltrates, Stage IV: fibrocystic sarcoidosis typically with upward hilar retraction, cystic, and bullous changes 2

17 to 23 but they did not have active TB. In addition, for 13 patients (%5.3) positive test results were reported which was consistent with our finding.

In our study, the most prevalent location for diagnostic biopsy was lung by trans-bronchial biopsy (TBB) with the frequency of %48.4; however, in the study done in Saudia Arabia, the most prevalent biopsy location was through mediastinoscopy with the frequency of %39.4. In our study, 152 patients underwent biopsy, which the result was non diagnostic in 29 of them. However in %81 of patients, non-caseating granuloma was reported by pathologist.

In 184 (%47.4) cases oral corticosteroids were prescribed and in some patients, non-steroidal anti-inflammatory drugs were used to control the pain. In Amoli's study, Treatment with prednisolone (usually starting with 30 mg per day and then tapering) was used in 185 patients (%59.6) and chloroquine was used in 4 patients.

In Saudia Arabia's study, %75 of patients got significant recovery both clinically and radiographically and the rate of recurrence was %10. In Amoli's study, overall after 20 years of follow up, in 55 cases(%31.2) the sickness persisted actively. Furthermore, in 79 cases(%44.9) the sickness stopped, and mortality was observed in 9 cases.

In our study clinical and/or radiographic recovery was seen in 46.2% and recurrence was occurred in 16.1%. Chronic persistent disease was seen in 8.6% of patients and %29.8 of cases did not have any follow up (Table 6).

Conclusion

It seems that sarcoidosis is more prevalent in Guilan, especially in west part, and probably in northern area than any other part of Iran. The significant difference in geographic distribution of disease in Iran should be evaluated in future genetic and epidemiologic multicenter studies.

We propose a close medical teamwork connection for better and more efficient patient's evaluation and management. Preparing a website for Iran sarcoidosis information is a good idea.

Sometimes the diagnosis of sarcoidosis is delayed or even missed due to systemic and nonspecific manifestations. So, it is necessary for physicians to be familiar with epidemiologic features of sarcoidosis for the best approach and management of these patients.

Table 6. Follow up results

Study Variable	Current study	Amoli (8)	Saudi Arabia (7)
Treatment	Steroid therapy (47.4%) Just follow up ± NSAID (52.6%)	Prednisolone in 185 patients (%59.6) Chloroquine in 4 patients	-
Follow-up results	recovery (clinical or/and radiography) (45.2%) recurrence rate (16.1%) persisted actively: (8.6%) out of the Follow-up: (29.8%)	persisted actively: (31.2%) stopped: (44.9%) mortality: 9 cases (n=176) out of the Follow-up: (42.2%)	recovery (clinical & radiography), (75%) recurrence rate (10%)

References

1. Hills SE, Parkes SA, Baker SB. Epidemiology of sarcoidosis in the Isle of Man-2: evidence for space-time clustering. Thorax 1987; 42:427-30
2. Newman LS, Rose cs, Maier LA. Sarcoidosis. N Eng J Med 1997; 3361224-34
3. Michael C, lannuzzi, M.D., Benjamin A. Rybicki, Ph.D., and Alvin S.Teirstein, M.D. Sarcoidosis, A medical progress, N Engl J Med 2007;357:2153-65
4. Siltbach LE, James DG, Neville E, et al. Course and prognosis of sarcoidosis around the world. Am J Med 1974; 57:847- 52
5. Sam, Amir H, James T, H. Teo (2010). Rapid Medicine/ Edition 2. ISBN 1405183233
6. Baughman RP, Lower EE, Roland M du bois. Sarcoidosis. The LANCET 2003; 361:1111-18
7. Thamer H Al-Kaouzaie, Jaffar A Al-Tawfiq, Faisal M Al Subhi. Sarcoidosis in the eastern region of Saudi Saudia Arabia. Annals of thoracic medicine, Vol 6, Issue 1, January-March 2011
8. Amoli K. Sarcoidosis: a report from 310 patients with sarcoidosis in Iran. Teymoorzade Tabib Publication, ISBN 978-964-420-867-6
9. Berliner AR, Haas M, Choi MJ. Sarcoidosis: the nephrologist's perspective. Am J Kidney Dis 2006;48:856-70.
10. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, et al; Case Control Etiologic Study of Sarcoidosis (ACCESS) researchgroup. Clinical characteristics of patients in a case control study of sarcoidosis. Am J RespirCrit Care Med 2001;164:1885-9.
11. Andrew F. Shorr, MPH; K. G. Torrington; O. W. Hnatiuk. Endobronchial Involvement and Airway Hyperreactivity in Patients with Sarcoidosis. Chest. 2001; 120(3): 881-886. doi: 10.1378/chest. 120.3.881
12. Uygun S, Yanardag H, Karter Y, Demirci S. Course and prognosis of sarcoidosis in referral setting in Turkey; analysis of 166 patients. Department of Internal Medicine, Istanbul University, CerrahpaşaMedical Faculty, Istanbul, Turkey. Acta Medica (Hradec Kralove). 2006;49(1):51-7
13. AlilovicM, Peroš-Golubicic T, Tekavec-Trkanjec J, et al. Epidemiological Characteristics of Sarcoidosis Patients Hospitalized in the University Hospital for Lung Diseases "Jordanovac" (Zagreb, Croatia) in the period 1997- 2002. Collegium Antropologicum, 2006:30(3);513-517.
14. PietinalhoA,Lahtela L, Palikhe A, et al. The prognosis of pulmonary sarcoidosis in Finland and Hokkaido, Japan. 2000 Jun;17(2):158-66, Japan.
15. References range list from Upsala University Hospital ("Laborationoslista"). Artnr 40284 sj74a. Issued on April 22, 2008