Original Article

Sarcoidosis in North Indian Population: A Retrospective Study

Raj Kumar[1], Nitin Goel[1] and S.N. Gaur[2]

Departments of Respiratory Allergy and Applied Immunology[1] and Respiratory Medicine[2], Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India

ABSTRACT

Background. Sarcoidosis is a systemic granulomatous disease of unknown origin most commonly involving the lungs. Sarcoidosis is frequently misdiagnosed due to its clinico-radiological resemblance to tuberculosis (TB). Hence, the present study was undertaken with the aim of studying the clinico-radiological profile of sarcoidosis in the Indian context.

Methods. We retrospectively studied 146 patients diagnosed to have sarcoidosis during the period 2001-2010 at one of the respiratory units at Vallabhbhai Patel Chest Institute.

Results. Majority of them (70%) were more than 40 years of age; females comprised 58.2% of the patients. Before coming to our clinic, 30% patients had been misdiagnosed to have TB. Cough (89.7%) was the most common presenting symptom; joint symptoms (28.8%) and end inspiratory crepitations at lung bases (49.3%) were other salient manifestations. Cutaneous involvement and digital clubbing were rarely seen. Pulmonary function testing showed restriction with impaired diffusion in 72.7% patients. The most common radiological feature was bilaterally symmetrical hilar lymphadenopathy. Transbronchial lung biopsy (TBLB) had a very high diagnostic yield (90.8%).

Conclusions. Sarcoidosis is often misdiagnosed as TB in India. Transbronchial lung biopsy has high diagnostic yield in sarcoidosis. **[Indian J Chest Dis Allied Sci 2012;54:99-104]**

Key words: Sarcoidosis, Transbronchial lung biopsy, Tuberculosis, Mantoux test, Pulmonary function test.

INTRODUCTION

Sarcoidosis is a multi-system granulomatous disorder of unknown aetiology.[1,2] Multiple phenotypes are observed according to involved organs.[2] But, sarcoidosis primarily affects the lungs and lymphatic system.[1,2] Sarcoidosis has been reported from almost all parts of the world with variable epidemiologic observations in different studies.[1] In the United States of America, incidence rate of sarcoidosis was 5.9/100,000 person years for men and 6.3/100,000 person years for women.[1] But sarcoidosis has been under reported, especially from developing countries due to its resemblance to tuberculosis (TB)[1-3] and lack of facilities to perform invasive diagnostic tests. Because of these reasons sarcoidosis still is an under-diagnosed disease, although with increasing awareness physicians are more vigilant for it.

The true burden of sarcoidosis in India is not clearly known as reliable epidemiological data are not available. From India, the initial reports of sarcoidosis were published from Calcutta in the East, particularly in relation to the *Marwari* community.[3] But later the disease has been reported from other regions as well.[4-6] Due to high prevalence of TB in India and also the resemblance in clinico-radiological features, sarcoidosis in India frequently gets treated as TB. This study was, therefore, undertaken with the aim to study the clinico-radiological profile of pulmonary sarcoidosis in the Indian context.

MATERIAL AND METHODS

This study includes 146 patients diagnosed to have sarcoidosis during the period 2001-2010 at one of the respiratory units at Vallabhbhai Patel Chest Institute, Delhi. The diagnosis of sarcoidosis was based upon compatible clinical, radiological, laboratory and/or histopathological features as per the joint statement of the American Thoracic Society, the European Respiratory Society and the World Association of Sarcoidosis and Other Granulomatous Disorders (ATS/ERS/WASOG)[1] and also exclusion of any other causes of the same.

A detailed history was recorded and physical examination was performed in all the patients at the

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Correspondence and reprint requests: Dr Raj Kumar, Professor and Head, Department of Respiratory Allergy and Applied Immunology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110 007, India; Phone: 91-11-9810146835; Fax: 91-11-27666549; E-mail: rajkumarvpci@gmail.com

time of initial presentation. Laboratory investigations included haemogram, chest radiograph, and sputum smear examination for acid-fast bacilli (AFB), Mantoux test, pulmonary function testing (PFT), electrocardiogram, laboratory tests like serum calcium, serum angiotensin converting enzyme (ACE) levels and 24-hour urinary calcium. Chest radiograph and high resolution computed tomography (HRCT) were performed in most of the patients. Fibreoptic bronchoscopy (FOB) and transbronchial lung biopsy (TBLB) was performed in patient willing for the procedure and if they were physiologically fit [forced vital capacity (FVC) > 1L, arterial oxygen tension (PaO_2) > 60mm Hg on room air]. In patients who were either not fit to undergo FOB or refused to undergo the same, the diagnosis was made on the basis of clinical, laboratory and radiological features and response to corticosteroid treatment. Corticosteroid treatment was given as: prednisolone 20-40 mg per day for eight weeks, followed by alternate day for four weeks and then tapering by 5mg every four weeks till a dose of 5-10mg alternate days was reached. This maintenance dose was continued till a minimum duration of 12 months of total steroid therapy. The dose and duration of therapy was individualised in each patient.

RESULTS

The average age at presentation was 43 years (range 22 to 70 years); majority (n=89, 70%) were aged more than 40 years. There were 85 (58.2%) females; most of them (55, 64.7%) were housewives. The average duration of illness was 20.5 months. Majority of the patients (129; 88.4%) were non-smokers. Family history of sarcoidosis was present in one patient. Forty-three (29.5%) patients had taken anti-tuberculosis treatment (ATT) due to misdiagnosis as TB before being diagnosed as sarcoidosis. The most common presenting symptom was found to be cough being present in 131 (89.7%) followed by exertional dyspnoea in 102 (69.9%), fever in 37 (25.4%), arthralgia/arthritis in 42 (28.8%) and skin lesions in 15 (10.3%). On examination, 17 (11.6%) patients had digital clubbing and chest crepitations were present in 72 (49.3%) patients. All patients were sputum smear-negative. Mantoux test was found to be negative in all patients.

Radiographic evidence of bilateral hilar lymphadenopathy was noted in 130 (89%) patients. Parenchymal infiltrates were seen in 68 (46.6%) patients with or without lymphadenopathy. The patterns observed were reticular, reticulonodular, nodular (miliary in 14) and alveolar opacities. On radiological staging, maximum number of subjects (51.4%) had stage I disease followed by stage II (37.1%), stage III (5.7%), stage IV (2.8%). A normal chest radiograph was observed in 3% of patients.

HRCT (n=143) revealed enlarged intrathoracic lymph nodes in 139 (97.2%) and parenchymal involvement in 104 (72.7%) patients. Honey-combing was present in 14 (9.8%) and pleural involvement was seen in 7 (4.9%) patients.

Spirometry was performed in all the patients; complete PFT was performed in 143 patients. Restrictive pattern was found in 86 (58.9%), obstructive pattern in 26 (17.8%), mixed pattern was documented in 21 (14.4%) patients; spirometry was normal in 13 (8.9%) patients. Diffusion impairment was present in 104 (72.7%) of patients. Hypercalcaemia (serum calcium >10.5 mg/dL) was seen in 31 (21.2%) patients. Hypercalciuria (24-hour urinary calcium >300mg/dL) was seen in 83 (56.8%) patients. High serum ACE levels (>40 U/L) were observed in 84 (57.5%) patients. Skin lesions were present in 14 (9.6%) patients. Skin biopsy performed from these sites was consistent with sarcoidosis in five patients.

One hundred and thirty-one patients gave consent for undergoing FOB. Bronchoscopic findings of nodules, plaques and erythema were noted in 16 (12.2%), 5 (3.8%) and 8 (6.1%) patients, respectively. TBLB was performed in all these patients who underwent bronchoscopy (n=131); histopathological examination revealed non-caseating granulomas in 119 (90.8%). Bronchial aspirate was negative for AFB in all the patients. There were 27 patients who either did not give consent for bronchoscopy (n=15) or in whom diagnosis could not be confirmed even after bronchoscopic biopsy (n=12). In these 27 patients diagnosis of sarcoidosis was made on the basis of compatible symptoms and signs and/or raised serum ACE levels, negative Mantoux test and suggestive chest radiograph and HRCT findings as per ATS/ERS/WASOG statement[1] and this was further confirmed on follow-up by clinical and radiological response to corticosteroids.

Comparison of observations documented in the present study with other published studies is shown in the table.[4,6,8,9,22,24,26,38-47]

DISCUSSION

The true burden of sarcoidosis in India is not clearly known due to under reporting caused by its resemblance to TB. In our study, 29.5% patients had been misdiagnosed as TB and had taken ATT before coming to our clinic. The ATS/ERS/WASOG statement[1] states that sarcoidosis consistently shows a predilection for adults under age 40; peaking in those aged 20-29 years. However, studies[1,2] done in Scandinavian countries and Japan report a second peak in incidence in women aged over 50 years. Other studies from western countries also report more than 70% patients of sarcoidosis to be of less than 40 years of age.[1,2] In contrast to this, our study revealed that

Table. Prevalence of radiographic stage of sarcoidosis at the time of initial presentation in various published studies

Country, Year of Publication[ref]	No. of Patients	Radiographic Stage of Sarcoidosis (%)				
		0	I	II	III	IV*
Sweden, 1984[39]	n=505	3	61	25	10	1
Denmark, 1982[22]	n=243	0.4	55	40	4.5	ND
British Isles, 1983[26]	n=818	14	56	18	11	ND
British Isles, 2000[40]	n=212	9	51	20	15	5
Finland, 2000[41]	n=437	0	44	43	13	0.4
Japan, 2000[41]	n=457	0	67	27	5	0
USA, 1967[42]	n=244	0	45	39	16	ND
USA, 1985[43]	n=86	10	49	21	20	ND
USA, 1994[38]	n=98	20	18	27	10	25
USA, 1997[24]	n=337	8	45	29	17	ND
USA, 2001[9]	n= 736	8	40	37	10	5
India, 1979[44]	n=24	0	33.3	25	41.7	ND
India, 1987[6]	n=40	2	53	30	15	ND
India, 1997[45]	n=29	3	45	34	18	ND
India, 2000[46]	n=60	1	62	30	7	ND
India, 2002[4,8†]	n= 194†	1	33	57	09	ND
India, 2012 (Present study)	n=146	2.8	51.4	37.1	5.7	2.8

*Stage IV not universally adopted ND: Not described
† Data published in reference 8 appended in reference 4
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70% of the sarcoidosis patients were more than 40 years of age. Similar observations have been made in other Indian studies.[7,8]

Studies done globally[1,9] report a slight female preponderance in sarcoidosis, whereas, a male preponderance is reported in Indian reports.[7,8] But in our study we found a slight female preponderance (58.2%). Till date the most accepted proposed pathogenic hypothesis is that various antigens could promote sarcoidosis in genetically susceptible individuals.[1,2] It appears to occur more frequently in non-smokers. This inverse relationship between smoking and sarcoidosis has been observed in various other studies.[10,11] In our study also, majority (88.4%) of patients were non-smokers. Familial sarcoidosis has also been described.[12,13] In the current series, familial involvement was observed in one patient.

In other studies, dyspnoea, dry cough, and chest pain has been found to occur in one-third to one-half of all patients.[1] We found cough to be the most common symptom (89.7%) followed by exertional dyspnoea (69.9%). Clubbing (11.6%) was rare, which was in accordance with western studies.[1,14] Lung crepitations were present in fewer than 20% of patients with sarcoidosis in most studies in western countries,[1,14] whereas in our study we found 49.3% of patients to have crepitations.

Presentations in the form of "Lofgren Syndrome" (erythema nodosum, bilateral hilar lymph-adenopathy and fever) and "Heerfordt Syndrome" (fever, enlarged parotid glands, anterior uveitis and facial nerve palsy) were not seen in any of the patients, strengthening the observation made earlier that such presentations are uncommon in India.[9] Involvement of parotid glands in sarcoidosis is uncommon and reported occurrence is about six percent.[15] In the present study none of the patients had parotid gland involvement.

In sarcoidosis skin involvement has been reported to be affected by race, e.g., skin involvement in the form of erythema nodosum is more common in patients of northern European descent.[16] Cutaneous involvement has been reported to occur in 25% of patients in western countries.[1] Similarly, ACCESS study group[9] found prevalence of skin involvement (excluding erythema nodosum) in United States of America to be 15.9%; erythema nodosum was observed in 8.3%.[9] In our study, cutaneous involvement was seen in 10.3% patients and none of the patients had erythema nodosum. Joint symptoms were seen in 28.8% patients. Arthralgias were more common than arthritis in our patients. Joint symptoms have been reported to occur in 25%-39% patients from the West.[14]

A negative Mantoux test has a high sensitivity value for the diagnosis of sarcoidosis. Even the bacilli Calmette-Guerin vaccination administered during childhood has been found to have no correlation with a negative Mantoux reaction.[17] This study[17] has also concluded that tuberculin anergy in sarcoidosis is not influenced by the rate of Mantoux positivity in the general population. A positive Mantoux test (irrespective of the size of reaction) in a suspected case of sarcoidosis should arouse strong suspicion of an alternate or an additional diagnosis of TB.[18] In our study also, we found that Mantoux test was negative in all the patients.

Hypocalcaemia and hypercalciuria are reported to occur at a significant rate in Europeans and Americans of Caucasian descent[19] and rare in one study of mostly black patients.[20] The ACCESS study group[9] also found that abnormalities of calcium metabolism were more common in Caucasians. In our study, hypocalcaemia was present in 21.2% patients and hypercalciuria was noted in 56.8% of patients.

Serum ACE levels are increased in 30%-80% of patients with sarcoidosis and may be a surrogate marker of total granuloma burden as noted by studies from western countries.[14] In previous Indian studies,[21,22] elevated serum ACE levels were documented in 70.5% patients. Elevated levels of serum ACE were observed in 57.5% of our patients.

According to various studies geographic regions, ethnicity and referral bias play an important role in determining the incidence of different radiographic stages of sarcoidosis. Most series have found that stage I is the most common radiographic stage, but significant variability exists. Similarly, radiographic stages I and II have been reported to be the predominant stages in most studies from Scandinavia.[23] In contrast to this, some studies from the United States and British Isles[24,25] cite a disproportionate representation of radiographic stage III and IV disease. Previous studies from India[6,8] report that most of the radiographic abnormalities belonged to stage I and II but another study[26] found that stage II and III were more common. In our study, the chest radiograph was abnormal in more than 95% patients. The most common stage of sarcoidosis on presentation was found to be stage I (51.4%) followed by stage II (37.1%), stage III (5.7%) and stage IV (2.8%) in that order.

The classic radiographic feature of sarcoidosis is bilateral hilar lymphadenopathy and is reported to be present in nearly three quarters of patients.[1] Previous studies[14,23] have found that right paratracheal lymph nodes may be also be involved con-comitantly. Computed tomography (CT) may reveal the enlargement of left para-tracheal, para-aortic, and subcarinal lymph node groups also.[27] We found hilar/mediastinal lymphadenopathy on CT (n=143) in 97.2% patients. Bilaterally symmetrical hilar lymphadenopathy was seen in the majority. Unilateral hilar lymph node enlargement has been reported as being uncommon (seen in <10%) in the West.[28] In our series it was not seen in any of the patients.

The most common parenchymal abnormality seen on CT was ground-glass pattern, although the most classic finding that has been observed in previous descriptions is widespread small nodules with a bronchovascular and subpleural distribution and thickened interlobular septae.[29] Miliary pattern was present in 14 (9.6%) of our patients, although it has been described as a rare finding in sarcoidosis.[30]

On analysis of pulmonary function tests in sarcoidosis, a restrictive defect with reduced lung volumes, i.e., vital capacity (VC) and total lung capacity (TLC)] is characteristic. The typical lung function abnormalities of sarcoidosis are decreased lung volumes and diffusing capacity.[14] The diffusing capacity for carbon monoxide (DLCO) is the most sensitive of the PFT parameters.[31] Even when chest radiographs are normal, forced vital capacity (FVC) or DLCO is reduced in 15%-25% and 25%-50% of patients, respectively. We found impaired diffusion in 72.7% patients tested. Airflow obstruction [e.g., reduced forced expiratory volume in one second (FEV_1) and expiratory flow rates] occurs in 30%-50% of patients with pulmonary sarcoidosis.[31] In our study, low FEV_1/FVC was encountered in 32.2% patients (17.8% pure obstructive and 14.4% mixed pattern).

In patients of suspected pulmonary sarcoidosis the initial diagnostic procedure of choice is flexible FOB with TBLB.[14] Bronchoscopic appearances in sarcoidosis include erythema, nodules, plaques and cobblestoning of bronchial mucosa. The prevalence of abnormal bronchial mucosa in sarcoidosis has been reported to vary from 33%[32] to 70%[33] in different studies. Torrington *et al*[34] found that both black and white patients with sarcoidosis had abnormal mucosa in approximately half of the patients. In our study, we found bronchial mucosa involvement in the form of erythema in 6.1%, plaques in 3.8% and nodules in 12.2 percent. Depending mainly on the experience of the clinician, the diagnostic yield of TBLB ranges from 40% to more than 90%.[35] Gupta *et al*[34] reported the diagnostic yield of TBLB to be 76% whereas Shorr *et al*[33] reported the same to be 59 percent. Such a high sensitivity of TBLB could be explained by the perilymphatic distribution of the granulomas. In our study, the diagnostic yield of TBLB was found to be 90.8 percent.

In the present study, in 27 patients, the diagnosis of sarcoidosis was based on suggestive clinical, radiological and laboratory features and response to corticosteroid treatment. In a study,[36] it was concluded that these features may be diagnostic,

especially for stage I (reliability 98%) and stage II (89%) sarcoidosis. In an asymptomatic individual, the presence of bilateral hilar and right paratracheal lymphadenopathy has been found to be specific for sarcoidosis by Winterbauer *et al*.[37] In case of an asymptomatic individual this approach has proved correct in more than 95% of cases and remains a cost-effective method especially in developing countries with limited resources.[38]

CONCLUSIONS

Sarcoidosis has clinical, radiological and serological manifestations which vary according to race. The clinical and radiological features of sarcoidosis closely resemble TB. In countries with high prevalence of TB, like India, sarcoidosis is often misdiagnosed as TB. Hence, patients having bilateral hilar lymphadenopathy with or without infiltrates should be investigated for sarcoidosis.

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