

Sarcoidosis at the Pulmonary Medicine Department of a tertiary care hospital in Mumbai. Our experience and The New Modified Criteria Clinical Radiological Physiological (TNMC CRP) score for sarcoidosis: A novel proposition to assess the functional status

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Abstract

Sarcoidosis is a multisystemic granulomatous disease most commonly involving the pulmonary system and having a myriad of manifestations. However literature is scanty pertaining to the profile and scoring system in sarcoidosis. This study was undertaken

to understand the profile of sarcoidosis and an endeavor to assess the functional status with a simplified scoring system. This was an observational study undertaken in the department of Pulmonary Medicine at a tertiary care. The profile of these patients was studied in terms of clinical features, radiological findings, the New Modified Criteria Clinical Radiological Physiological (TNMC CRP) score, six-minute walk distance (6MWD), spirometry, arterial blood gas parameters, serum angiotensin converting enzyme (ACE) levels and tissue biopsy histopathology. The 68 patients included 41 women and 27 men with a mean age of 42.7 years. They comprised of 18 (27%), 39 (57%), 4 (6%), 7 (10%) cases of stage 1, 2, 3, 4 sarcoidosis respectively. Most common presenting symptom and sign was progressive dyspnea 49 (72%), and peripheral lymphadenopathy 15 (22%). Serum ACE was elevated in 57 (83%). The average 6MWD was 360 meters. Most common high resolution computed tomography (HRCT) finding was mediastinal lymphadenopathy and peri-bronchovascular nodules. Spirometry was restrictive abnormality in 48 (96%) patients. Evidence of pulmonary hypertension (PH) was present in 32 (47%) patients. Tissue diagnosis revealed granulomatous inflammation in 51 biopsies with a transbronchial lung biopsy (TBLB) yield of 62%. The average TNMC CRP score was 5. There was a positive correlation between this score and 6MWD which was statistically significant. The score correlated with the functional status. Diagnosis of sarcoidosis warrants a comprehensive and multimodality approach. HRCT and tissue biopsy are the most important diagnostic armamentariums. Modified simplified scores help assess the functional status of the disease.

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Introduction

Sarcoidosis belongs to a large family of disorders that share granuloma formation as common denominator [1]. Sarcoidal granulomas can involve any organ. Clinical sarcoidosis is manifested as intrathoracic lymph node enlargement, pulmonary involvement, skin or ocular signs and symptoms, or some combination of these findings in most cases [2]. Diagnosis is established by a multidisciplinary approach by a combination of clinico-radiological features supported by histopathological evidence of non-caseating granulomas after exclusion of other known causes. Sarcoidosis is reported less commonly in India and this has been attributed to factors such as its resemblance to tuberculosis [3], lack of screening programs and lack of awareness amongst physicians and pathologists regarding the disease. However, sarcoidosis is not a rare disease in India as initially thought. This is highlight-

ed in various studies [4]. About 90% of patients have pulmonary lesions and 60% of them have respiratory complaints. Extra pulmonary manifestations of sarcoidosis include involvement of skin, eye, heart, nervous system, endocrine and exocrine glands, gastrointestinal, genitourinary, hematological and immunological systems, bones, muscle and joints. There is significant heterogeneity in the onset, clinical course, prognosis and complications of the disease. Also there is scarcity of simplified scores that can serve as surrogate markers of disease severity and aid prognostication. Hence, we conducted this study to understand the spectrum of clinico-radiological manifestations of sarcoidosis and to propose a simple score (a modification of the existing CRP score) to assess the functional status.

Materials and Methods

This was a retrospective study undertaken with Institutional Ethics Committee permission at the Pulmonary Medicine Department of a tertiary care hospital in Mumbai. We included 68 consecutive cases of sarcoidosis over a three-year period. Diagnosis of sarcoidosis was established on the basis of clinico-radiological features supported by histopathological evidence of non-caseating granulomas after exclusion of other known causes. Demography details were noted. Symptoms including cough, dyspnea, fever, chest pain, and skin, ocular and joint complaints were noted. Detailed general and systemic examination was performed. Post exercise desaturation, 6-min walk test distance (6MWD), and arterial blood gas analysis (ABG) were noted. Baseline hematological and biochemical tests and Mantoux test were performed. Radiological tests in form of chest X-ray (CXR) and high resolution computerized tomography (HRCT) of thorax were done. Spirometry was done to assess the forced expiratory volume in first second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio. Serum Angiotensin converting enzyme (ACE) level and wherever possible 18 fluoro-deoxy glucose positron emission tomography (FDG PET) and gallium scan reports were noted. Histopathological diagnoses were obtained by biopsy or fine needle aspiration cytology of the organ system involved. The various sites biopsied were transbronchial lung biopsy (TBLB), peripheral lymph nodes, mediastinal lymph nodes, skin, thyroid and Mantoux site. Clinical radiological physiological (CRP) score is a scoring system that can be used in patients with sarcoidosis to assess the functional status. This score incorporates parameters like clinical symptoms, radiographic stage and physiological tests. CRP score is calculated as the sum of all the scores. Score of 1 is assigned for individual symptoms such as cough, dyspnea and weight loss. Radiological staging is scored as 0, 1, 2, 3, 4 points for stage 0, 1, 2, 3 and 4, respectively. Score of 1 each is assigned for the presence of obstructive, restrictive or mixed defects in spirometry, reduced diffusing capacity of the lungs for carbon monoxide (DLCO) and partial pressure of oxygen (PaO₂) <70 mmHg [5]. Though of salient utility this score may have certain shortcomings. One of it involves the need to perform a sophisticated lung function assessment with DLCO which may be a hindrance in resource limited settings. Hence in an attempt to overcome this obstacle, we formulated a new score, TNMC CRP Score replacing DLCO test with ACE level. The rationale behind this was that DLCO is difficult to perform test and may not be readily available in resource limited settings. On the other hand, serum ACE levels are comparatively easier to perform and available in most standardized laboratories. The New Modified Criteria Clinical Radiological

Physiological (TNMC CRP) score replaced the parameter "reduced DLCO values" with "elevated S.ACE levels". The abbreviation denoted the purpose of the test and the abbreviation of our institute, too. The data was analyzed and was presented in the form of percentage and frequency.

Results

Sixty-eight patients were included in the study. They comprised of 18 (27%), 39 (57%), 4 (6%), 7 (10%) cases of stage 1, 2, 3, 4 sarcoidosis respectively. Most of the patients (40) belonged to the age bracket of 31-50 years. Mean age was 42.7 years. Our study included 41 women and 27 men suggesting a female preponderance. Most common symptoms were progressive dyspnea in 49(72%) followed by dry cough in 50 (74%), productive cough in 24 (36%), fever in 21 (32%), chest pain in 8 (12%) and hemoptysis in 4 (5.88%). Five patients were asymptomatic cases of type 1 sarcoidosis picked up incidentally on routine examination. Most common extra pulmonary symptoms observed were ophthalmic in nature in 10 (16%). The complaints of red eye, blurred vision and reduced vision were predominantly reported. Miscellaneous other extrapulmonary symptoms were hoarseness of voice, skin rash, dysphagia, joint pain, altered bowel habits, generalized weakness, myalgia and menstrual abnormalities in 1 patient each respectively. On general examination, the most common finding was the presence of peripheral lymphadenopathy in 15 (22%). There were 6, 4, 1 patients of cervical, axillary and dual inguinal with axillary lymphadenopathy, respectively. Second most common finding was presence of clubbing seen in 13 (20%) cases. In 39 (58%) patients, the general examination was normal. The findings of systemic examination were unremarkable in 43 (64%). Twenty-one (32%) showed presence of bibasilar crackles, 2 (4%) had bronchial breath sounds and 4 (6%) had reduced breath sounds on the right side. All 4 patients with reduced breath sounds had hydropneumothoraxes. Serum ACE levels were elevated in 36(72%). Highest level of ACE level was 310 u/l. Lowest level encountered was 15 u/l. The average ACE level encountered in the study was 91.6 u/l. The Mantoux test was done in all patients. It was negative in 44 and positive in 6 patients. 6MWD and ABG were done in all except type 1 sarcoidosis. The average 6MWD was 360 m.

Chest radiograph findings suggested type I disease in 19 (28%), type 2 in 28 (41%) and type 3 in 21 (31%). Miscellaneous CXR findings were hydropneumothoraxes (3), collapse (1), fibrosis (2), fissural thickening (1), pneumothorax (1) and pleural plaques (1). HRCT thorax was done in all patients. After incorporating the findings of HRCT thorax, the frequency of various types of sarcoidosis in the study changed to 18 (27%), 39 (57%), 4 (6%), 7 (10%) for type 1, 2, 3, 4, respectively. Thus, HRCT thorax played a very important role in diagnosis and also staging of sarcoidosis. Most common HRCT finding was mediastinal lymphadenopathy (64/68), peri-fissural nodules (50/68), peri-lymphatic nodules (50/68) and peri-bronchovascular nodules (50/68). Other frequent findings included air trapping, consolidation and ground glass attenuation. Fluorodeoxyglucose positron emission tomography (FDG PET) scan reports were available in 32 patients. In 8, the only FDG avid structures were the mediastinal lymph nodes (all 7 of type 1 sarcoidosis). Twenty-four patients had both lung and mediastinal lymph nodal FDG uptake (21 of type 2 sarcoidosis and 2 of type 4 sarcoidosis). One patient of type 3 sarcoidosis had isolated FDG uptake in the lung. Gallium scan reports were available in 7 patients. In 4 cases, the structure with intense gallium uptake

was mediastinal lymph nodes. Two had uptake in lung and one patient had no uptake on gallium scan. Spirometry was done in all patients. It was found to be restrictive in 48 (70%), obstructive in 2(3%) and normal in 18 (27%). ECG was normal in 44, however ECG abnormalities were detected in 6 patients. Most commonly encountered ECG finding was right bundle branch block. Two-dimensional echocardiography (2D ECHO) showed that 23 (34%), 2(3%), 7(10%) patients had mild, moderate and severe pulmonary hypertension (PH), respectively.

Tissue diagnosis was done in all patients. Therefore, the total number of biopsies done in this study was 68 (Table 1). Granulomatous inflammation was seen in 51 biopsies (Table 2). In the rest, the diagnosis was established with clinico-radiological and serology correlation. The different tissue biopsy sites were TBLB (26), peripheral lymphnode (10), mediastinal lymph node (9), skin (3), Mantoux site (2), thyroid (1) (Table 1). Out of the 42 TBLBs performed, 26 (62%) showed the evidence of granuloma on histopathological examination. Distribution of granulomas diagnosis was 17/18, 28/39, 2/4 4/7 for type 1, 2, 3 and 4 sarcoidosis, respectively. Thirty-eight patients enrolled in this study had concomitant presence of other comorbidities. The most common comorbidities found amongst this study population were gastroesophageal reflux disease (GERD) (21), hypertension (14), osteoporosis (14), OSAS (11), diabetes mellitus (11) and psychiatric illness in the form of anxiety or depression (6). Extrapulmonary involvement was seen in 12 patients. These included 2 cases with thyroid involvement, 10 cases with uveitis and one patient with renal calculi.

TNMC CRP score was calculated in all patients. In view of the unavailability of DLCO gas mixtures at times, the DLCO measurement was difficult at our centre. To overcome this problem, we replaced "DLCO reduction" scoring parameter with "elevated Serum ACE levels". The average TNMC CRP score was 5. The functional parameters in these patients were correlated with TNMC CRPS score. The 6MWD correlated with TNMC CRP score and the

correlation was found to be statistically significant with a P value <0.0001 based on Pearson r coefficient with r value -0.691 and 95% confidence interval -0.798 to -0.542. 6MWD had positive correlation with forced vital capacity (FVC) when calculated with Pearson coefficient with P value <0.0001 and r value 0.4993. Thus, indirectly correlating with the TNMC-CRP score. Pulmonary hypertension (PH) had positive correlation with modified TNMC CRP score with p value of <0.0001 and r value 0.5724. The TNMC CRP score thus correlated well with the functional status.

Discussion

This was a retrospective observational study. It enrolled 68 patients of sarcoidosis. The patient group showed a slight female preponderance. As with many inflammatory diseases, sarcoidosis affected women more than men [6]. Most of the patients enrolled in this study belonged to the age group of 31 yrs to 50 yrs. Sarcoidosis usually develops before the age of 50 years, with the incidence peaking at 20 to 39 years. In a north Indian study, the average age at presentation was 43 years [6]. Studies from western countries report that more than 70% patients with sarcoidosis were of less than 40 years of age. Similar observations had been made in other Indian studies [7,8]. Dry cough was the commonest symptom in our study followed by progressive dyspnea. Similar findings were reported in an Indian study done by Sharma *et al.*, in which the frequency of dry cough (83%) was more than dyspnea (61%) [8]. Fever was found in 32% of our patients. On the contrary, the incidence of fever documented in a study done in Indian population was higher 56% [9]. The most common non respiratory complaint that the patients had was ophthalmic in 10 (16%) patients. This was consistent with one of the review articles suggesting eye involvement in 10-25% cases [10]. Most common general examination finding in our study population was peripheral lymphadenopathy (22%), commonest involved were cervical lymph nodes. Yanardag *et al.* reported an incidence of 14.5% for peripheral lymphadenopathy in sarcoidosis and the most commonly encountered lymphadenopathies were cervical and supraclavicular [11]. Clubbing was encountered in 13 (20%) of our cases. Clubbing was a rare finding and usually seen in advanced fibrotic stage [12]. Respiratory system examination was unremarkable in around 64% of our study population and bilateral basal crackles were heard in 32% of patients. In a study done by Kumar *et al.* crackles were appreciated in 49.3% of patients [6]. In our study the serum ACE levels were elevated in 83%. In a case control study done to assess the effectiveness of ACE levels in diagnosis and regulating therapy in sarcoidosis, they were elevated in about 15 of 17 patients [13].

CXR classified the patients as per the Scadding classification as 28% to stage 1, 41% stage 2, and 31% stage 3. The ACCESS study [14] found that the 8% of the patients had stage 0, 40% stage 1, 36% stage 2, 10% stage 3, and 5% stage 4. CXR helped to diagnose certain complications like pneumothorax. After incorporating the HRCT thorax in diagnosis, the frequency of various types of sarcoidosis in our study changed. Thus it played a very important role in diagnosis and was more accurate as compared with CXR. Fatih and co-workers encountered a similar finding [15]. Mediastinal lymphadenopathy was the most common finding with or without lung involvement. Mediastinal lymph nodes were found in 94% of the study population. As per a review article on imaging features of sarcoidosis, 80% of sarcoidosis cases had mediastinal lymphadenopathy [16]. Most common group of mediastinal lymph

Table 1. Various biopsy sites.

Site of biopsy	Total	Granuloma obtained
Transbronchial lung biopsy	42	26
Peripheral lymph nodes	10	10
Mediastinal lymph nodes	10	9
Skin	3	3
Thyroid	1	1
Mantoux site biopsy	2	2
Total	68	51

Table 2. Table showing the distribution of biopsied patients with granulomatous inflammation.

Sarcoidosis	Total patients	Total number of biopsies with granulomatous inflammation
I	18	17
II	39	28
III	4	2
IV	7	4
Total		51

nodes to be encountered in our study was hilar lymph node involvement. In most instances except in 3 cases, hilar lymphadenopathy was bilateral. The next most common finding on HRCT was the presence of peri-bronchovascular nodules (73%) and peri-fissural nodules (73%). In an HRCT based study of 18 biopsy proven cases of sarcoidosis, fourteen patients had predominant nodular opacities [17]. A study on FDG PET in sarcoidosis concurred with our finding of mediastinal lymph nodes being the commonest FDG avid structure [18]. The most common abnormality on spirometry was restrictive lung functions seen in 70% of the patients. A retrospective study from Brazil reported restrictive abnormality in 23% of the study population. This difference could be attributed to a larger proportion of type 2 and 3 Sarcoidosis cases in our study compared to the Brazilian study [19]. ECG abnormalities were seen in 8.9%. In a Caucasian study on pulmonary sarcoidosis, an abnormal ECG was recorded in 16.3% patients [20]. In our study most of the patients had mild PH. In a retrospective evaluation of 106 patients with sarcoidosis, Sulica *et al.* found that 51% of the patients with a pre-existing clinical indication for performing echocardiography had evidence of PH by transthoracic echocardiography [21].

We pursued for tissue diagnosis in all patients as histopathological demonstration is the most convincing and definitive mode of diagnosis [22]. Granulomatous inflammation was found in 51 biopsies (75%). In rest the diagnosis was established with clinicoradiological and serology correlation. Most common method of tissue diagnosis was TBLB. Out of the 42 TBLBs performed, 26 (62%) showed the evidence of granuloma on histopathological examination. Thus TBLB served as an extremely useful tool for the definitive diagnosis and could avoid the need for more invasive tissue diagnosis like a thorascopic or an open lung biopsy. Thirty-five of our patients had concomitant presence of other comorbidities with GERD being the most common. A study done to assess the prevalence of GERD in interstitial lung diseases reported 70% of the patients with sarcoidosis to have GERD [23]. In a study for comorbid illnesses and chest radiographic severity in African American sarcoidosis patients, around 15% of the patients had GERD [24]. Another comorbidity associated with sarcoidosis was systemic hypertension. In a large cohort patient analysis, the incidence of systemic hypertension was 22.4% [25]. Eleven of our patients (16%) had obstructive sleep apnea. In a study done by Turner and co-workers on sleep apnea in sarcoidosis, 14/83 where sleep apneic [26]. Contrary to our study, others have shown a higher percentage of extrapulmonary involvement. In a study, done in Turkey the percentage of extrapulmonary involvement was seen in 40% of the patients [27]. Ophthalmological evaluation was done in all patients and was normal in all except 10 patients. In a Chinese study, 60 patients with biopsy-proven sarcoidosis had uveitis [28]. The ATS sarcoidosis guidelines also recommend a baseline eye evaluation irrespective of symptoms [29]. They also recommend baseline serum creatinine, serum alkaline phosphatase, serum calcium and electrocardiogram to rule out extrathoracic manifestations of sarcoidosis [29].

A chronic lung disease with extrapulmonary manifestations like sarcoidosis needs a multifaceted assessment involving clinical, radiological and physiological assessment. This plays a vital role in the disease severity staging and prognostication. CRP score is a scoring system that was firstly used in IPF to predict the severity of the pathologic process and functional impairment. It was later employed in sarcoidosis to assess the functional status. This score incorporates parameters like clinical symptoms, radiographic stage and physiological tests. CRP score is calculated as the sum of all the scores. Score of 1 each is assigned for individual symptoms,

such as cough, dyspnea, and weight loss. Radiological staging is scored as 0, 1, 2, 3, 4 points for stage 0, 1, 2, 3, and 4, respectively. Score of 1 each assigned for the presence of obstructive, restrictive, or mixed defects in spirometry, reduced DLCO and partial pressure of oxygen (PaO_2) <70 mmHg⁵. In a retrospective study on 26 patients diagnosed with pulmonary sarcoidosis the 6MWD inversely correlated with the CRP score ($\rho = -0.364$, $p = 0.047$) and positively correlated with forced vital capacity (FVC) % ($\rho = 0.407$, $p = 0.039$)⁵. Though of salient utility this score may have certain shortcomings. One of it involves the need to perform a sophisticated lung function assessment with DLCO which may be a hindrance in resource limited settings. Hence in an attempt to overcome this obstacle, we formulated a new score, TNMC CRP Score replacing DLCO test with ACE level. The rationale behind this was that DLCO is difficult to perform test and may not be readily available in resource limited settings. On the other hand, serum ACE levels are comparatively easier to perform and available in most standardized laboratories. The role of CRP was to assess the functional status. In diseases like Sarcoidosis serological markers like Serum ACE levels correlated and reflected well upon the functional status of the disease. The TNMC CRP was thus assessed with functional parameters. The 6MWD correlated inversely with TNMC CRP score with a statistically significant correlation with a P value <0.0001 based on Pearson r coefficient with r value -0.691 and 95% (confidence interval -0.798 to -0.542). 6MWD also had positive correlation with FVC when calculated with Pearson coefficient with p value <0.0001 and r value 0.4993 similar to the study done by Esam *et al.* [5]. Thus, indirectly correlating with FVC. The TNMC CRP score correlated well with the functional status of the disease. Hence, we propose that the TNMC CRP score may be considered as a possible alternative to assess the functional status of Sarcoidosis particularly in resource limited settings where facilities for DLCO measurement may not be available. However studies with larger sample size are required to endorse our results.

Our study thus stands noteworthy from various aspects. It is a comprehensive assessment of profile of Sarcoidosis involving a good sample size on a background of very limited data available on this disease which shows a good response to therapy. Our study also endeavors to assess the functional status in these patients with the aid of a novel scoring system which can be employed in resource limited settings, too.

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