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# CLINICORADIOLOGICAL SPECTRUM OF SARCOIDOSIS PRESENTING TO A TERTIARY CARE CENTRE IN TUBERCULOSIS ENDEMIC AREA

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## ABSTRACT

**Background:** Sarcoidosis is a multisystem, inflammatory disorder in which lung and intrathoracic lymph node are commonly involved. In a patient with consistent clinico-radiological features, the diagnosis is established by histological or cytological demonstration of non-caseating epithelioid-cell granuloma in tissues. The true incidence of sarcoidosis is difficult to discern in tuberculosis endemic areas as both disease conditions have outstanding resemblance. In case of thoracic involvement flexible bronchoscopy remains the procedure of choice owing to good sensitivity and low complication rates. **Material and Methods:** This was a retrospective study done on 62 patients confirmed to have sarcoidosis based on clinic-radiological and bronchoscopy data. Clinical history, laboratory, spirometry and bronchoscopy data were extracted from medical records of the patients and analysed. **Results:** Out of the 62 patients, 48 (77%) had histological evidence of granuloma in one of the bronchoscopy samples. In the remaining 14 patients the diagnosis was confirmed after response to treatment at the end of 6 months. The distribution of study population was: Stage I - 24 (39%), Stage II - 31 (50%) and Stage III - 7 (11%) disease. Dry cough, dyspnoea, fever and weight loss were the most common symptoms. The mean serum ACE levels was 84 (±37) U/L. Mantoux test was negative (induration < 5 mm) in all patients. Spirometry revealed an abnormality in 18 (29%) patients. EBUS-TBNA had the highest diagnostic yield as it was positive in 26 out of 32 (81%) patients, followed by TBLB which was positive in 26 out of 44 (59%) patients. Conventional TBNA yielded the diagnosis in 9/24 (38%) and EBB in 9/37 (24%) patients. **Conclusion:** Sarcoidosis is common in tuberculosis endemic area and differentiation from tuberculosis is important for treatment purpose. EBUS has the highest yield in detection of granuloma from bronchoscopy samples followed by bronchoscopic lung biopsy.

**KEYWORDS:** Sarcoidosis, transbronchial needle aspiration, endobronchial ultrasound, bronchoscopic lung biopsy.

## INTRODUCTION

Sarcoidosis is a multisystem, inflammatory disorder of unknown etiology which occurs at all ages, race and ethnicity with a peak incidence at 20 to 39 years.[1] Lung and the intrathoracic lymph node are the most common sites of involvement and occurs in more than 90% cases.[2,3] Cough, dyspnoea and constitutional symptoms are the most common manifestations. Supportive laboratory features include a raised erythrocyte sedimentation rate (ESR), negative mantoux reaction, raised serum angiotensin converting enzyme (ACE) levels, hypercalcemia and hypercalciuria.

The true incidence of sarcoidosis is difficult to discern in tuberculosis endemic areas as both disease conditions have outstanding resemblance. Many patients with sarcoidosis receive anti-tuberculous therapy without histological confirmation and it still remains an under-reported entity. The diagnosis of sarcoidosis is established by clinico-radiological findings and histological or cytological evidence of non-caseating epithelioid-cell granuloma at the site of affliction i.e. the lymph nodes, lung or bronchial mucosa or the extrathoracic sites.[4] In case of thoracic involvement sampling the mediastinal nodes, lung parenchyma or the bronchial mucosa is preferred and flexible bronchoscopy remains the procedure of choice owing to good sensitivity and low complication rates.[5–7]

## MATERIAL AND METHODS

This retrospective study was conducted in the Department of Pulmonary Medicine and Sleep Disorders, AIIMS, New Delhi, between June 2014 and July 2015. Medical records of all patients suspected to have Stage I to III sarcoidosis were reviewed.

***Inclusion Criteria***

1. Age > 18 years and
2. Suspected Stage I (mediastinal or hilar lymphadenopathy) or Stage II (lymphadenopathy and parenchymal abnormalities) or Stage III (parenchymal infiltrates) sarcoidosis

***Exclusion Criteria***

1. Incomplete data
2. Patient on antitubercular therapy
3. Suspected Stage IV sarcoidosis in the absence of histological evidence for sarcoidosis
4. Presence of AFB or culture of mycobacteria in sputum or any samples (transbronchial needle aspiration (TBNA), bronchoalveolar lavage fluid (BALF), bronchoscopic lung biopsy (TBLB) or endobronchial biopsy (EBB)
5. Presence of granuloma with necrosis in any of the histological samples obtained by TBNA, TBLB or EBB.
6. Lack of response or worsening during systemic therapy for sarcoidosis if histological evidence of granulomatous inflammation is absent.

The following sets of data were extracted from patient records:

1. Detailed history and clinical examination of the patient for the presence of lymphadenopathy, ocular or joint involvement.
2. Laboratory: Hemogram, Erythrocyte sedimentation rate, Liver Function Tests, Serum Calcium, 24 hour Urine Calcium, Serum ACE levels, Mantoux test.
3. Radiology: A Chest X-ray and CT Chest (CECT+HRCT)
4. Spirometry: Forced vital capacity (FVC), Forced Expiratory volume in 1 sec (FEV1) and FEV1/FVC ratio. Diffusion capacity of carbon monoxide (DLCO) if available
5. Bronchoscopy: results of TBNA, TBLB and EBB.

***Diagnosis of Sarcoidosis***

A diagnosis of sarcoidosis was made if the following criteria were fulfilled:

1. Supportive clinical profile and radiological features, and
2. Cytology or biopsy (TBNA/EBUS-TBNA sample or EBB or TBLB) consistent with Sarcoidosis i.e. presence of non-caseating granulomas and
3. Exclusion of similar presenting disease (Fungal infection, malignancy or TB).

For those patients in whom the initial bronchoscopy was negative, the final diagnosis was made after a follow up period of 6 months of management based on clinic-radiological picture and response to treatment.

***Statistical Analysis***

Primary data analysis was done in Stata 11.2 and presented as mean ± SD / Median (Min-Max) and frequency (percentage) with 95% confidence interval.

**RESULTS**

A total of 62 patients were confirmed to have sarcoidosis during the study period. Out of the 62 patients, 48 (77%) had histological evidence of granuloma in one of the bronchoscopy samples. In the remaining 14 patients without granuloma in any of the histological samples, the diagnosis was confirmed by response to treatment after 6 months of diagnosis. The mean age was 39.7 (± 10.2) years. Majority (n=39, 63%) were males and belonged to an urban background (n=48, 77%). Twenty-four (39%) had presence of mediastinal lymphadenopathy without lung infiltrates i.e. stage I disease. Similarly, 31 (50%) had both mediastinal lymphadenopathy and lung nodules i.e. stage II disease and remaining 7 (11%) had stage III disease characterized by presence of lung nodules only. The flow of the patient included in the study is given is figure 1.

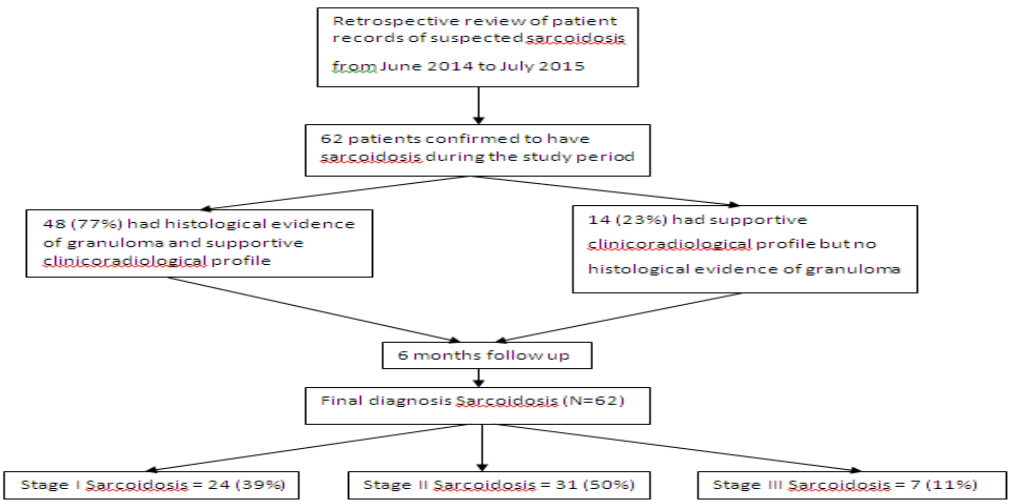


**Figure1: Flow of the patients enrolled into the study**

Dry cough was the most common symptom present in 44 (71%) patients. Dyspnoea and fever was present in 32 (52%) and 21 (34%) patients respectively. Other constitutional symptoms such as weight loss and fatigue

were present in 37 (46%) patient. Joint pain and visual symptoms occurred in 14 (23%) and 12 (19%) patients respectively. Wrist, knee and finger joints were the most commonly involved. Uveitis was documented after ophthalmological evaluation in 5 (8%) patients, while in the remaining 7, past history of eye redness, pain and watering was present. Atypical central chest pain was present in 9 (15%) patients.

Nineteen (31%) patients had prior history of ATT intake on clinico-radiological basis despite having negative sputum examination for AFB. None had clinical improvement while on ATT. Hypertension was present in 9 (15%) and diabetes was present in 7 (11%) patients. History suggestive of atopic manifestations was present in 8 (13%) patients. Five (8%) patients had palpable cervical lymph node enlargement. However, the aspiration and biopsy showed reactive lymph node tissue and no granuloma was detected. Chest auscultation revealed abnormality (crepitations and/or wheeze) in 12 (19%) patients. The clinical characteristic of the study population is tabulated in table 1.

**Table 1. Clinical characteristics of the study population**

| | N (Frequency) | Percentage |
|---|---|---|
| **Total Patients** | 62 | 100% |
| **Symptoms** | | |
| Dry Cough | 44 | 71% |
| Dyspnoea | 32 | 52% |
| Weight Loss and fatigue | 37 | 46% |
| Fever | 21 | 34% |
| Joint Pain | 14 | 23% |
| Uveitis | 12 | 19% |
| **Past history** | | |
| ATT intake | 19 | 31% |
| Hypertension | 9 | 15% |
| Diabetes | 7 | 11% |

The mean hemoglobin level was 12.9 (± 1.3) gm/dl and the mean ESR was 37 (± 18) mm in the 1$^{st}$ hour. The mean serum calcium level was 9.8 (±1) mg/ dl. Nine (15%) patients had hypercalcemia i.e. corrected serum calcium of more than 10.2 mg/dl. No patient had renal dysfunction, whereas 17 (27%) had deranged liver function tests, raised alkaline phosphatase levels was the most common abnormality present in 16 (26%) patients. Hypercalciuria i.e. 24 hour urinary calcium more than 300 mg was present in 10 (16%) patients. The mean serum ACE levels was 84 (±37) U/L. Raised serum ACE levels of more than 40U/L was present in 43 (69%) patients and the highest ACE level recorded was 195 U/L. Mantoux test was negative (induration < 5 mm) in all the patients.

Spirometry revealed an abnormality in 18 (29%) patients, 15 (24%) having restriction and 3 (5%) having mixed pattern. No patient had isolated obstruction on spirometry. Reduced DLCO was documented in 9 (15%) patients. The mean lymph node size in patients with stage I and II sarcoidosis was 21.2 (±6.4) mm. The mean paratracheal and subcarinal lymph node size were 21 (±4.4) mm and 26.4 (±7.5) mm respectively. The mean hilar node size on CT scan was 18.4 (±3.8) mm. Nodules in the lung parenchyma was noted in the CT scan of 40 (65%) patients whereas 4 (6%) had alveolar opacities in the lung parenchyma. Laboratory and radiological features of the study population is shown in table 2.

**Table 2. Laboratory and radiological features of the study population**

| | |
|---|---|
| **Laboratory** | |
| Hemoglobin* | 12.9 (± 1.3) gm/dl |
| Serum Calcium* | 9.8 (±1.0) mg/dl |
| Serum ACE* | 84 (±37) U/L |
| Raised Alkaline phosphatase** | 16 (26%) |
| 24-hour Urine Calcium>300mg/day** | 10 (16%) |
| Raised serum ACE >40U/L** | 43 (69%) |
| Negative Mantoux (<5mm)** | 62 (100%) |
| **PFT** | |
| Abnormal Spirometry** | 18 (29%) |
| Restriction** | 15 (24%) |
| Obstruction** | 0 (0%) |
| Mixed** | 3 (5%) |
| Reduced DLCO** | 9 (15%) |
| **CT Scan** | |

| | |
|---|---|
| Lymph Node size* | 21.2 (±6.4) mm |
| Right paratracheal* | 21 (±4.4) mm |
| Subcarinal* | 26.4 (±7.5) mm |
| Hilar* | 18.4 (±3.8) mm |
| Lung Nodule** | 40 (65%) |

** data presented as mean (± SD) ** data presented as frequency (percentage).*

Thirty (48%) underwent bronchoscopy for histological diagnosis whereas 32 (52%) underwent an EBUS procedure. TBNA was performed in 56 (90%) patients, TBLB in 44 (71%) and EBB in 37 (60%) patients. In 14 (23%) patients who had stage II disease on radiology, EBUS procedure was followed by bronchoscopy with TBLB and EBB in the same sitting. Right paratracheal and sub carinal lymph node stations were the most frequently sampled stations. A median of 4 TBLB samples were taken during bronchoscopy. Overall, EBUS-TBNA had the highest diagnostic yield as it was positive in 26 out of 32 (81%) patients, followed by TBLB which was positive in 26 out of 44 (59%) patients. Conventional TBNA yielded the diagnosis in 9/24 (38%) and EBB in 9/37 (24%) patients respectively. The details of bronchoscopy procedures and the diagnostic yield are shown in table 3.

**Table 3. Details of bronchoscopy procedures and the diagnostic yield in the study population.**

| | N/Total | Percentage |
|---|---|---|
| **Procedures** | | |
| Bronchoscopy | 30/62 | 48% |
| EBUS | 32/62 | 52% |
| Bronchoscopy + EBUS | 14/62 | 23% |
| **Diagnosis** | | |
| Granuloma on TBNA (Total) | 35/56 | 63% |
| Conventional TBNA | 9/24 | 38% |
| EBUS-TBNA | 26/32 | 81% |
| Granuloma on TBLB | 26/44 | 59% |
| Granuloma on EBB | 9/37 | 24% |

## DISCUSSION

The true incidence of sarcoidosis in the tuberculosis endemic areas is not known as epidemiological studies are lacking. A few studies from India in the past have reported sarcoidosis to be common among those visiting respiratory clinics.[8,9] We report the clinicoradiological profile of 62 patients presenting to our centre during 1 year of study period. All confirmed cases of sarcoidosis with consistent clinic-radiological and histological features were included. One of the strengths of the study is that the 6 months follow up data of all the patients were available at the time of diagnosis and any alternate diagnosis made within this period were excluded.

The mean age was 39.7 (± 10.2) years and the majority were males and belonged to an urban background, which is similar to the findings in the study by Gupta et al. done from the same region. Dry cough, dyspnoea, fever and weight loss were the most common symptoms. Raised serum ACE levels and a negative mantoux reaction was a common occurrence as reported by previous studies.[9,10] Only 5 patients had cervical lymphadenopathy, no patients had renal insufficiency and very few had deranged liver function tests. Extrapulmonary manifestations were few because the patients were recruited only from respiratory clinic and there may have been a selection bias.

Differentiating sarcoidosis from tuberculosis still remains a great challenge to the clinicians in our part of the world. In our study, 19 (31%) patients had prior history of ATT intake on clinico-radiological basis despite having negative sputum examination for AFB. Due to close resemblance of the two disease conditions, many patients receive ATT prior to the diagnosis, in tuberculosis endemic areas. Hence, it is imperative to achieve histological and microbiological diagnosis in patients who present with mediastinal lymphadenopathy and lung nodules in appropriate clinical setting. Differentiating the two is important as, on the one hand cotricosteriods used for the treatment of sarcoidosis worsens tubercular infection and on the other, unnecessary ATT exposes the patient to adverse effects and increased cost of therapy.

In the absence of easily accessible biopsy sites (skin or superficial lymph nodes), flexible bronchoscopic procedures are the preferred modality for diagnosis.[5–7,11] In our study, endobronchial ultrasound (EBUS) had the highest yield (81%) in the diagnosis of sarcoidosis compared to other bronchoscope procedures. EBUS is considered superior in the diagnosis of sarcoidosis compared to conventional TBNA and bronchoscopic lung biopsy.[5,7] However if TBLB is combined with TBNA, the yields may approach to that of EBUS, as reported in previous studies by Gupta et al and Li et al.[12,13] In our study, 14 patients with stage II sarcoidosis who underwent EBUS-TBNA also underwent TBLB in the same sitting, which may further help to increase the yield of EBUS centered approach. The yield of TBLB,

TBNA and EBB was similar in our study as compared to previous studies.[5,7,12,14]

One of the limitations of our study is that we did not evaluate the findings of bronchoalveolar lavage (BAL) fluid in our cohort. We routinely do not perform CD4:CD8 ratio in the BAL fluid as previous studies have shown that BAL lymphocytosis and lymphocyte subset determination is highly variable in biopsy-proven sarcoidosis.[15]

## CONCLUSIONS

Sarcoidosis is common in tuberculosis endemic area and differentiation from tuberculosis is important for treatment purpose. EBUS has the highest yield in detection of granuloma from bronchoscopy samples followed by bronchoscopic lung biopsy.

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