

**SARCOIDOSIS- A CLINICORADIOLOGICAL PROFILE OF 30 PATIENTS**

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**ABSTRACT****BACKGROUND**

Sarcoidosis is an inflammatory multisystem granulomatous disease of unknown aetiology and predominantly affects the lungs, followed by eye, skin, peripheral lymph node, liver, spleen, heart, central nervous system, musculoskeletal system and salivary glands.

Aim- To find out the clinical profile of sarcoidosis patients prospectively admitted to a respiratory unit.

**MATERIALS AND METHODS**

The study was conducted on 30 patients of sarcoidosis, who were admitted for various respiratory complaints, in the Department of Pulmonary Medicine, GSVM Medical College, Kanpur & Govt. Medical College, Kannauj. A thorough respiratory evaluation was done including clinical evaluation for signs and symptoms, chest x-ray PA view, HRCT Thorax, Spirometry, sputum for AFB, PPD, serum ACE, serum Calcium, 24-hour urinary calcium, BAL Fluid analysis, CD4 to CD8 of BAL fluid.

**RESULTS**

30 patients of sarcoidosis were evaluated. Of the total patients, male & female were 11 and 19 respectively and ratio was 1:1.7. The mean age of study group was 34.8 years (Range 27-51). Dyspnoea was present in all the patients followed by dry cough (93.3%). Bilateral hilar lymphadenopathy plus pulmonary opacity was the most common radiological presentation of sarcoidosis in 14/30 (46.7%). Pleural effusion was noted in a single case. Extrapulmonary manifestations like subcutaneous nodules were seen in only one case while uveitis also observed in single case only. Sputum for AFB was negative in 2 cases, while others did not raise sputum. PPD testing showed no induration among all, except one where it showed mild induration (6 mm). Serum ACE was elevated in 24/30 patients (86.6%). Serum Calcium was elevated in 10/30 patients (28.6%). 24-hour urinary calcium was elevated in 8/30 patients (26.6%). Spirometry showed a restrictive pattern in 71.4% (i.e. 20/28) and was normal in 17.9% cases while the other three patients did not cooperate. The CD4 to CD8 of BAL fluid levels were raised in all cases of sarcoidosis (range 2.9- 4.4).

**CONCLUSION**

Bilateral hilar lymphadenopathy plus pulmonary opacity was the most common radiological presentation of sarcoidosis and BAL fluid CD4 to CD8 counts are easy to perform and helpful in supporting diagnosis of sarcoidosis along with clinical and radiological features.

**KEYWORDS**

Sarcoidosis, Hilar Lymphadenopathy, Serum ACE, BAL fluid.

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**BACKGROUND**

Sarcoidosis is a multisystem, inflammatory disorder of unknown aetiology that affects individuals worldwide. This disease shows a consistent predilection for adults less than 40 years of age with slightly higher disease rate for women.<sup>1</sup>

Sarcoidosis involves the bronchi or lung in more than 90 percent of patients and intrathoracic manifestations are protean, ranging from asymptomatic bilateral hilar lymphadenopathy to chronic, progressive, (ultimately fatal), respiratory insufficiency. In sarcoidosis, diagnosis is established on the basis of clinicoradiological features supported by histopathological evidence of non-caseating granulomas after exclusion of known causes (tuberculosis, leprosy, fungal infection).<sup>1-2</sup>

The true burden of sarcoidosis in India is not clearly known as reliable epidemiological data are not available. In India, the first reported biopsy proven case of sarcoidosis was reported from Calcutta in 1956.<sup>3-4</sup> Another study from India reported 190 biopsy proven cases of sarcoidosis from 1972 to 1998 and another 206 cases have been discovered, while searching through the existing literature in this

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country.<sup>5</sup> Due to high prevalence of TB in India and also the resemblance in clinicoradiological features, sarcoidosis in India frequently gets treated as TB.<sup>6</sup>

The aim of present study was to determine the clinicoradiological profile of pulmonary sarcoidosis in the Indian context.

## MATERIALS AND METHODS

The present case series consisted of 30 consecutive patients who attended the outpatient and inpatient section, at the Department of Tuberculosis and Respiratory Diseases and Department of Internal Medicine, G.S.V.M. Medical College, Kanpur (India) from September 2009 to August 2016.

A detailed clinical history and physical examination was carried out in all the patients. This was followed by haemogram, chest radiography, sputum smear examination for acid-fast bacilli (AFB) on two consecutive days, Mantoux test, spirometry, serum angiotensin converting enzyme (ACE) levels, serum calcium, PPD, Urinary calcium and high resolution computed tomography of thorax (HRCT).

Chest radiographs were classified by Scadding stages:

0- normal chest radiographic findings; I- bilateral hilar adenopathy with normal lung parenchyma; II- bilateral hilar adenopathy with pulmonary infiltrates; III- pulmonary infiltrates without hilar adenopathy; IV- pulmonary fibrosis/fibrocystic parenchymal changes.<sup>7</sup>

The diagnosis of sarcoidosis was based upon compatible clinical, radiological, laboratory and/or histologic demonstration of noncaseating granulomas, and exclusion of other diseases capable of producing a similar histologic or clinical picture (ATS/ERS/WASOG).<sup>1</sup>

In the presence of a compatible clinical picture, the first step is to choose the site for a proper biopsy. Transbronchial lung biopsy (TBLB) is the recommended procedure in most cases and its diagnostic yield depends largely on the experience of the operator, ranging from 40% to more than 90%.<sup>8</sup> When bronchial or transbronchial biopsies are nondiagnostic, and no other accessible sites for biopsy are identified, surgical lung biopsy may be indicated. The finding of mediastinal adenopathy on the conventional CT scan should prompt biopsy by mediastinoscopy before video-assisted thoracoscopic lung biopsy (VTLB) or open lung biopsy. The diagnostic yield of all of these procedures are reported to be more than 90%.<sup>9-10</sup>

The diagnosis of sarcoidosis in patients without histology is usually based upon clinical and/or radiological features. The clinical and/or radiological features alone may be diagnostic for patients with Stage I (reliability of 98%) or Stage II (89%) disease, but are less accurate for patients with Stage III (52%) or Stage 0 (23%) disease.<sup>11</sup> In some instances, bronchoalveolar lavage (BAL) and studies on lymphocyte subpopulations are helpful. According to Costabel, a BAL fluid CD4/CD8 ratio greater than 3.5 has a sensitivity of 53%, a specificity of 94%, a positive predictive value of 76% and a negative predictive value of 85%.<sup>12</sup> In other words, a BAL fluid CD4/CD8 ratio > 3.5 provides a diagnosis of sarcoidosis with a specificity of 94% even if the TLB has not been diagnostic.

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.

## RESULTS

Of the 30 patients, with sarcoidosis, 11 were males while 19 were females (Ratio M: F; 1:1.7). The mean age of study group were 34.8 years (Range 27-51). Mean duration of respiratory complaints was 8.7 months (Range 2-14 months). Dyspnoea was present in all the patients followed by dry cough (93.3 %). Sputum for AFB was negative in all patients. 31.5% cases of sarcoidosis, misdiagnosed as pulmonary tuberculosis and had a history of anti-tubercular treatment. This might be due to radiological similarities between sarcoidosis and pulmonary tuberculosis and a lack of awareness and paucity of diagnostic facilities.

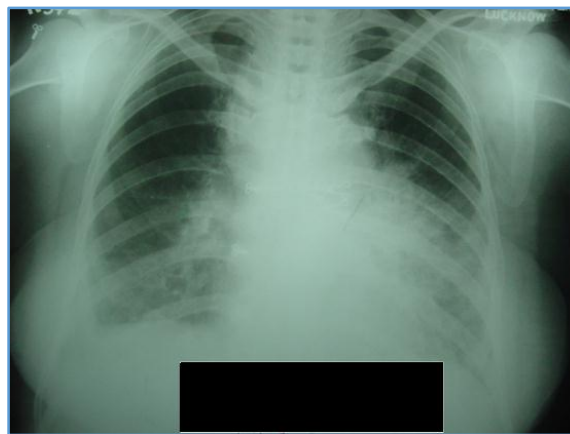
Bilateral hilar lymphadenopathy plus pulmonary opacity (Stage II) was the most common radiological presentation of sarcoidosis in 14/ 30 (46.6 %). HRCT thorax revealed enlarged intrathoracic lymph nodes in 25 (92.3 %) cases, GGO in 15 (53.8 %) cases, Inter septal thickening in 8 (30.7 %) cases, honey combing in 4 (15.4 %) cases and Pleural effusion in 1 (12.5 %) case. Extrapulmonary manifestation of sarcoidosis was observed in two cases, one had erythema nodosum and another had uveitis. Spirometry showed restrictive pattern in 80 % cases (Mean FEV1/FVC 86 % and Mean FVC 1.16 Litre), while 3 (20 %) patients did not cooperate. (Table 1: Shows patient's characteristics of study group). PPD was negative in 93.3 % cases. Serum ACE (> 40 U/L) was elevated in 24 cases (86.6 %). Hypercalcaemia (serum calcium > 10.5 mg/dL) was observed in 10 (33.3 %) cases. Hypercalciuria (24-hour urinary calcium > 300 mg/dL) was seen in 8 (26.6 %) patients. Bronchoscopic findings of nodules and erythema were observed in 6 and 4 % cases respectively.

FOB, were performed in all the patients and bronchial aspirate was negative for AFB in all the patients. BAL Fluid CD4 to CD8 ratio was elevated in all cases of sarcoidosis (Mean: 3.6, Range- 2.9-4.4). Others system were within normal limits. TBLB was performed only among 11 patients who underwent bronchoscopy (n=30); histopathological examination revealed non-caseating granulomas in 8 (72.7%). In 22 patients diagnosis of sarcoidosis was made on the basis of compatible symptoms and signs and/or raised serum ACE levels, negative Mantoux test, suggestive chest radiograph, HRCT thorax findings and raised BAL fluid CD4/CD8 ratio and this was further confirmed on follow-up by clinical and radiological response to corticosteroids.

In present case series, of the 12 patients (40 %) with type -I sarcoidosis, 10 were treated and 2 were initially observed but later treated. Eleven (36.6 %) of these were cured and one (3.3 %) declared to have arrested disease. All the 14 patients with type-II sarcoidosis and 2 patients with type-III sarcoidosis and 2 patients with type-IV sarcoidosis were treated & declared to have arrested disease. The one patient with extrathoracic sarcoidosis was declared cured after treatment. The mean duration of treatment were 13.8 months (range: 8-16 months)



**Figure 1. Showing Subcutaneous Nodular Lesions over the Back of Chest**



**Figure 2. Chest X-ray of a 45-year-old Female reveals Right Paratracheal and Hilar Lymphadenopathy**

Sl. No.	Parameter		Total Number	%
1	Age	20-29 years	2	6.7
		30-39 years	9	30
		40-49 years	14	46.7
		50-59 years	4	13.3
		>60 Years	1	3.3
2	Sex	Females	19	63.3
		Males	11	36.7
3	Radiographic staging	Stage I	12	40
		Stage II	14	46.7
		Stage III	2	6.7
		Stage IV	2	6.7
4	History of smoking	Females	None	-
		Males	8 (Mean Pack Years =10.3, Range: 7-14)	26.7
5	Past H/O of ATT		14	46.7
6	Symptoms	Cough	28	93.3
		Breathlessness	30	100
		Chest pain	5	16.7
7	Extrapulmonary manifestations	Uveitis	1	3.3
		Subcutaneous nodule	1	3.3

**Table 1. The Characteristics of Study Population (n=30)**

Sl. No.	Name of Authors	Country	Year of Publication	No. of Patients	Radiographic Stage of Sarcoidosis (%)				
					0	I	II	III	IV
1	Vishwanathan R	India	1959	1	Records Incomplete				
2	De MS et al	India	1968	1	Records Incomplete				
3	Guleria JR	India	1971	4	Records Incomplete				
4	Gupta Samir	India	1977	7	Records Incomplete				
5	Chakravarty SC	India	1978	24	Records Incomplete				
6	Bambery p	India	1987	40	2	53	30	15	ND
7	Kashyap	India	1997	29	3	45	34	18	ND
8	Rosha	India	2000	60	1	62	30	7	ND
9	Sharma SK	India	2001	106	0	24	63	13	ND
10	R. Kumar	India	2012	146	2.8	51.4	37.1	5.7	2.8
11	Present study	India	2017	30	-	40	46.6	6.6	6.6

**Table 2. Published Cases of Sarcoidosis in India**

Sl. No.	Name of Authors	Country	Year of Publication	No. of Patients	Radiographic Stage of Sarcoidosis (%)				
					0	I	II	III	IV
1	Siltzbach LE	USA	1967	244	0	45	39	16	ND
2	Romer FK	Denmark	1982	243	0.4	55	40	4.5	ND
3	Hillerdal G	Sweden	1984	505	3	61	25	10	1
4	Gupta SK	British Isles	1985	818	14	56	18	11	ND
5	Hunninghake GW	USA	1994	98	20	18	27	10	25
6	Gottlieb	USA	1997	337	8	45	29	17	ND
7	Chappel AG	British Isles	2000	212	9	51	20	15	5
8	Pietinalho A	Finland	2000	437	0	44	43	13	0.4
9	Pietinalho A	Japan	2000	457	0	67	27	5	0
10	Baughman RP	USA	2001	736	8	40	37	10	5
11	Kitter G	Turkey	2011	293	4.8	51.9	31.7	5.1	0.7
12	Fatih Ors	Turkey	2013	45		48.9	31.1	8.9	4.4
13	Carrillo-Perez DL	Mexico	2014	21	42.9	29	9.5	9.5	9.5

Table 3

## DISCUSSION

Sarcoidosis today is being more frequently recognised than earlier and is now seen as an important emerging disease in India. The true burden of sarcoidosis in India is not clearly known due to underreporting caused by its resemblance to TB. In the present study, 46.7% cases have been misdiagnosed as tuberculosis and had taken ATT before coming to our hospital.

The ATS/ERS/WASOG statement states that sarcoidosis consistently shows a predilection for adults under age 40; peaking in those aged 20-29 years.<sup>1</sup> However, studies done in Scandinavian countries and Japan report a second peak in incidence in women aged over 50 years.<sup>13-14</sup> Other studies from western countries also report more than 70% patients of sarcoidosis to be of less than 40 years of age.<sup>15</sup> A study done from India among sarcoidosis patients revealed the average age of 46 years (range) and 70% of them were in 4<sup>th</sup>/5<sup>th</sup> decades.<sup>16</sup> Rajkumar et al reported average age of 43 years (range 22-70) in sarcoidosis patients and majority were aged more than 40 years.<sup>6</sup> Another study from India reported average age of 40 years in sarcoidosis patients.<sup>17</sup> In present study, the mean age of study population was 34.8 years (range: 27-61 years) and majority were in between 30-49 years.

Studies done globally report slightly higher disease rate for women in sarcoidosis.<sup>1,18</sup> In the only population-based incidence study of sarcoidosis in the United States, rates were 5.9 per 100,000 person-years for men and 6.3 per 100,000 person-years for women.<sup>19</sup> Various studies from India reported male predominance.<sup>20-21</sup> Similar observations have been found in present case series also.

Till date the most accepted proposed pathogenic hypothesis is that various antigens could promote sarcoidosis in genetically susceptible individuals.<sup>1,22</sup> It appears to occur more frequently in non-smokers. This inverse relationship between smoking and sarcoidosis has been observed in various other studies.<sup>23-24</sup> In our study also, majority (73.3 %) of patients were non-smokers.

Cough, dyspnoea, dry cough and chest pain have been reported in one-third to one-half of the patients and haemoptysis rarely occurred.<sup>1,18,25</sup> In the present study, pulmonary symptoms were the most common complaints with the predominance of dyspnoea (100%) which was

followed by cough (93.3%) and chest pain in 16.6% of the sarcoidosis patients.

A negative Mantoux test has a high sensitivity value for the diagnosis of sarcoidosis. Even the Bacillus Calmette-Guerin vaccination administered during childhood has been found to have no correlation with a negative Mantoux reaction.<sup>26</sup> 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.<sup>27</sup> In our study also, we found that Mantoux test was negative in 93.3% patients.

Certain laboratory tests such as serum angiotensin converting enzyme (ACE) level, while often helpful in corroborating the diagnosis, did not make the diagnosis of sarcoidosis definitive.<sup>28</sup> 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.<sup>29</sup> In previous Indian studies, elevated serum ACE levels were documented in 70.5% patients.<sup>30-31</sup> In the present study, elevated levels of serum ACE were observed in 86.6% of cases.

Hypercalcaemia occurs in about 10% of the patients with sarcoidosis and hypercalciuria is about three times more frequent and are due to dysregulated production of 1,25-(OH) 2-D3 (calcitriol) by activated macrophages trapped in pulmonary alveoli and granulomatous inflammation.<sup>32-33</sup> In present study, the hypercalcaemia and hypercalciuria were observed in 33.3% and 26.6% cases of sarcoidosis respectively.

Most series have found that stage I is the most common radiographic stage, but significant variability exists.<sup>1</sup> Similarly, radiographic stages I and II have been reported to be the predominant stages in most studies from Scandinavia.<sup>34</sup> In contrast to this, some studies from the United States and British Isles cite a disproportionate representation of radiographic stage III and IV disease.<sup>35-36</sup> Previous studies from India<sup>6,8</sup> report that most of the radiographic abnormalities belonged to stage I and II,<sup>21,37</sup> but another study<sup>26</sup> found that stage II and III were more common.<sup>38</sup> In present study, the most common stage of sarcoidosis on presentation was found to be stage II (46.6 %) followed by stage I (40%). (The details of different radiographic stages of sarcoidosis patients in various

Indian<sup>6,16-17,21,37,39-43</sup> & international<sup>18,34,36,38,44-51</sup> studies are summarised in table 2 and table 3).

The classic radiographic feature of sarcoidosis is bilateral hilar lymphadenopathy and is reported to be present in nearly three quarters of patients.<sup>1</sup> Previous studies have found that right paratracheal lymph nodes may be also be involved concomitantly.<sup>29,34</sup> Computed tomography (CT) may reveal the enlargement of left paratracheal, paraaortic, and subcarinal lymph node groups also.<sup>52</sup> In present study, we found hilar/mediastinal lymphadenopathy on CT (n=27) in 92.6% patients. Unilateral hilar lymph node enlargement has been reported as being uncommon (seen in <10%) in the West.<sup>28</sup> In our series, it was not seen in any of the patients.

In sarcoidosis, cutaneous involvement occurs in about 25% of patients.<sup>53</sup> Two clinically important and easily recognisable skin lesions are erythema nodosum and lupus pernio. Erythema nodosum is the hallmark of acute sarcoidosis and the lesion consists of raised, red, tender bumps or nodules on the anterior aspects of the legs. Lupus pernio represents chronic sarcoidosis and consists of indurated plaques associated with discolouration of the nose, cheeks, lips, and ears. Other skin lesions in chronic sarcoidosis include plaques, maculopapular eruptions, subcutaneous nodules, changes in old scars, alopecia, and hypo- and hyperpigmented areas. In present case series, one patient had multiple subcutaneous nodules (Figure: 1). ACCESS study group found prevalence of skin involvement (excluding erythema nodosum) in United States of America to be 15.9% and erythema nodosum was observed in 8.3%.<sup>18</sup> Yanardag H et al retrospectively evaluated the clinical features of patients diagnosed as sarcoidosis and who had skin involvement.<sup>54</sup> They had observed cutaneous involvement in 170 patients (136 females, 34 males) and the most frequent skin lesion was erythema nodosum (20.5%), followed by subcutaneous nodules (4.3%), maculopapular eruptions (3.7%), scar lesions (2.9%), lupus pernio (LP) (2.7%) and psoriasiform plaques (0.9%).

Joint pains occur in 25 to 39% of patients with sarcoidosis and deforming arthritis is rare.<sup>29</sup> The joints most commonly affected are knees, ankles, elbows, wrists, and small joints of the hands and feet. In present case series, 23.3% patients had symptoms of joint pain.

Ocular involvement may occur in 11 to 83% of patients with sarcoidosis.<sup>55</sup> Any part of the eye or orbit may be affected; uveitis is the most common of all sarcoid eye lesions. In present case series, one patient had symptoms of chronic uveitis.

In patients of suspected pulmonary sarcoidosis, the initial diagnostic procedure of choice is flexible fibreoptic bronchoscopy (FOB) with transbronchial lung biopsy (TBLB).<sup>8,29</sup> The bronchial mucosa in sarcoidosis may appear normal, erythematous, miliary or large nodules, yellowish nodules with a cobblestone appearance and occasionally, endobronchial granulomas form a mass-like lesion that can obstruct the bronchial lumen.<sup>56-58</sup>

The prevalence of abnormal bronchial mucosa in sarcoidosis has been reported to vary from 33% to 70% in different studies.<sup>57,59</sup> Torrington et al reported that both black and white patients with sarcoidosis had abnormal mucosa in approximately half of the patients.<sup>60</sup> In present study, we found bronchial mucosa involvement in the form of erythema in 6.1%, plaques in 3.8% and nodules in 12.2 percent.

Fibreoptic bronchoscopy is a safe and minimal invasive procedure, available to make the diagnosis, including needle aspiration, BAL, transbronchial biopsy, open-lung biopsy, and mediastinoscopy.<sup>25</sup> Each of these techniques has advantages and disadvantages. BAL is safe, minimally invasive, and provides useful information for the diagnosis of sarcoidosis. The characteristic findings in BAL for sarcoidosis are normal or only mildly elevated total cell count with a predominance of lymphocytes, usually a normal percentage of eosinophils and neutrophils, and an absence of plasma cells and foamy alveolar macrophages.<sup>61</sup> Drent M et al reported that no single cell type present in bronchoalveolar lavage (BAL) fluid appears to be predictive for sarcoidosis. They also highlighted that in sarcoidosis the majority of cases have an increased number of lymphocytes and a normal number of eosinophils/neutrophils and in severe cases the number of neutrophils can be increased as well.<sup>62</sup> The cell discrimination findings of BALF in the present study were revealed the predominance of lymphocytic plus neutrophilic and lone lymphocytic alveolitis.

Bronchoalveolar lavage CD4/CD8 ratios may be of diagnostic value in sarcoidosis, obviating the need of biopsy in 40–60% of patients and it may depend on the individual facilities, knowledge and skill of the investigators involved in the various diagnostic techniques.<sup>1</sup> Costabel et al reported that a BAL fluid CD4/CD8 ratio of 3.5 or greater had a sensitivity of 52% and specificity of 94% in 117 consecutive patients with biopsy-proven sarcoidosis.<sup>12</sup> Winterbauer et al described that a ratio of 4.0 or greater distinguished<sup>27</sup> patients with sarcoidosis from 28 patients with other interstitial lung diseases with a sensitivity of 59% and a specificity of 96%.<sup>63</sup> Thomeer and Demedts compared<sup>42</sup> patients with sarcoidosis and 90 patients with other forms of diffuse lung disease and found that a CD4/CD8 ratio of greater than 4.0 had a sensitivity of 55% and a specificity of 94%.<sup>64</sup> These three studies reached similar conclusions: in patients with a clinical picture typical of sarcoidosis, an elevated CD4/CD8 ratio in BAL may prove diagnostic of sarcoidosis and obviate the need for confirmation by additional biopsy. It is important to note that in the study of Winterbauer et al, transbronchial biopsy had a specificity of 89% for the distinction between sarcoidosis and other forms of diffuse lung disease and was thus not better than the CD4/CD8 ratio in this respect.<sup>63</sup> SP Kantrow et al reported that in pulmonary sarcoidosis BAL fluid CD4/CD8 ratio is highly variable and these authors found that only 42% in a population of 86 patients with biopsy-proven sarcoidosis had a ratio greater than 4.0, and that 12% had an inverted ratio below 1.0.<sup>65</sup>

Danila E et al prospectively evaluated diagnostic role of BALF CD4/CD8 ratio in pulmonary sarcoidosis manifested in different radiographic and clinical forms and they found Normal BALF cell counts in 7% of sarcoid patients. They also found that optimal cut-off points for CD4/CD8 ratio are 3.5 and 4.0 for asymptomatic and symptomatic patients, respectively.<sup>66</sup> In the present study, TBLB was performed in 36.6% of the patients (i.e. 11/30) and more than half of them were diagnostic (i.e.8/11).

## CONCLUSION

Sarcoidosis is a chronic granulomatous inflammatory disorder of unknown origin with heterogeneous outcome and not uncommon in India. The clinical and radiological features

of sarcoidosis closely resemble tuberculosis and in countries with high prevalence of TB, like India, it is often misdiagnosed. In present study, bilateral hilar lymphadenopathy plus pulmonary opacity was the most common radiological presentation of sarcoidosis. In present study, TBLB was performed in 11 patients only (i.e. 11/30); histopathological examination revealed non-caseating granulomas in 8 (72.7%) patients. The present study also highlighted that the CD4 to CD8 of BAL fluid levels were raised in all cases of sarcoidosis and are easy to perform and helpful in supporting diagnosis of sarcoidosis along with clinical and radiological features.

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