Original Research Article

Longitudinal Follow up of Patients Undergoing Computed Tomography for Centrilobular Nodules at a Tertiary Care Centre

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Received: 7-05-2021 / Revised: 28-06-2021 / Accepted: 02-08-2021

Abstract

Objective : The purpose of our study was to do longitudinal follow up of patients and study evolutive patterns , signs and clinical/pathologic correlations with CT scan findings of lung nodules ,predominant centrilobular opacities or preferential centrilobular . Another aim of this study was to establish whether there is any difference in the pattern and distribution of such calcifications in tuberculosis (TB) and sarcoidosis.**Methods** :We followed up over 3 months 150 patients with lung nodules. CT scans were performed before, during, and after 3 months of anti-tuberculosis ,sarcoidosis and other treatments. Both 10-mm-thick sections and 1.5-mm-thick HRCT scans were performed. Chest HRCT scans in 150 patients with predominant centrilobular opacities or preferential centrilobular disease were retrospectively evaluated. A tentative diagnosis was made by CT scan appearance ,supported by clinicopathological analysis and final diagnosis after 3 months was confirmed by response to treatment . **Results:** 104 EBB and 105 TBLB were performed. The mean age was 47 years and 55% patients were male. Most common symptom was cough (47%) and median duration of symptoms was 3 months. Most common diagnoses were sarcoidosis and TB. 150 had final diagnosis of TB or sarcoidosis. **Conclusion:** This HRCT may be helpful to demonstrate activity in patients suspected of having tuberculosis and to assess antituberculous treatment efficiency. Combined procedures had specificity of 96.8%, PPV of 99.4% and NPV of 40.7%.Knowledge of the two centrilobular patterns in CT scan and combined with pathological tests ,is of proven worth for generating differential diagnoses and is of particular value in suggesting a likely infectious etiology in cases with tree-in-bud appearance.

Keywords: TBNA Transbronchial Needle aspiration , TBLB Transbronchial Lung Biopsy , CTBNA Conventional Transbronchial Needle aspiration ,CB NAAT Cartridge based nucleic acid amplification test ,TST Tuberculin skin test, EBB Endobronchial biopsy.

Introduction

Adequate knowledge of CT images consistent with tuberculosis and sarcoidosis is an important resource for diagnosis and treatment. The following were considered suggestive signs of tuberculosis activity: centrilobular nodules with segmented distribution,confluent micro nodules, consolidations, thick-walled cavities, nodules, masses, thickening of the bronchial walls,tree-in-bud appearance and cylindrical bronchiectasis Pulmonary tuberculosis is a chronic granulomatous disease characterized radiologically by nodules, air-space consolidation, propensity for cavitation, and calcification, and pathologically by caseating granulomas or pneumonia, and a great propensity for fibrosis and dystrophic calcification[1-3].Primary tuberculosis typically appears as air-space consolidation with hilar or mediastinal lymphadenitis. Postprimary tuberculosis appears most commonly as nodular and linear opacities at the lung apex. Atypical radiologic manifestations of tuberculosis, encountered in as many as one third of the cases of adult-onset tuberculosis, are single or multiple nodules or masses, basilar infiltrates, miliary tuberculosis with diffuse bilateral areas of ground-glass opacity, and reversible multiple cysts. Underlying histopathologic findings of typical and atypical CT findings of tuberculosis are caseating granulomas or pneumonia in the active phase and fibrosis and dystrophic calcification in the inactive phase.In this study ,we used knowledge of the patterns in CT scan and combined with clinical presentation and pathological tests ,is of proven worth for generating differential diagnoses and is of particular value in suggesting a likely infectious etiology in cases with tree-in-bud appearance. Diagnostic yield and sensitivity in various subgroups were also calculated. Separate analysis was done for patients with final diagnosis of TB and sarcoidosis where differentiating factors were analyzed. The aim of this study was to establish whether there is any difference in the pattern and distribution of such calcifications in tuberculosis (TB) and sarcoidosis[4-6].

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Materials and Methods

The study will be a prospective observational study, the patients fulfilling the inclusion criteria will be followed up for 3 months on OPD basis. Data of all patients who underwent study were collected prospectively. Clinical, demographic and radiological details were noted along with other relevant investigations.

Demographic and clinical features of study population

Out of 150 included patients, 84 were male (55.8%) and 66 (44.2%) were female. The mean age was 47 years. 57 patients (22.7%) were smokers.Cough was most common presenting symptom 88 patients (47%) followed by loss of apetite/weight, dyspnea, fever, chest pain,

hemoptysis and hoarseness of voice (3.6%). The median duration of symptoms was 3 months (IQR: 2-5 months).

Radiographic details included number, distribution, size and attenuation of mediastinal and/or hilar LNs. Parenchymal abnormalities like mass, parenchymal nodules along with other significant radiographic findings were also noted. We also noted the indication of CT, provisional clinical diagnosis, bronchoscopic findings like endobronchial granularity, lymph node size echotexture and presence or absence of coagulation necrosis sign, etc. EBB and TBLB were done whenever possible in patients with TB and sarcoidosis.

Cytological, pathological and microbiological data was recorded and diagnosis was made. Patients were then managed according to the diagnosis achieved on available clinical information and investigations and followed up till 3 months. Details of CT, treatment received and clinic-radiological response were noted and final diagnosis was made. Diagnostic accuracy of CT was determined after combining true positives and true negative. Overall sensitivity, specificity, PPV and NPV were calculated[8-10]

Consent: Written consent was obtained from the relatives of patients after explaining them the nature and purpose of the study. They were assured that confidentiality would be strictly maintained. The option to withdraw from the study was always open.

Follow up: All patients received routine care and management as per the diagnosis. They were followed up for 3 months, preferably by visit and chest imaging but patients who could not come for visit were followed up telephonically. Details were noted about further diagnostic procedures, treatment received and response (symptomatic/radiological). Based on all clinicoradiological and pathological data final diagnosis was made at 3 months.

Observation Chart

Table 1: Baseline Characterstics

Age(y ± SD)	47.0 ± 15.3
Gender -Male -Female	 84(55.8) 66 (44.2)
BMI median (range)	24 (15-47)
Socioeconomic status -Upper/middle -Lower	 94 (64.1) 56 (34.9)
Smoking	57 (22.7)

Table 2: Clinical Characteristics

Median duration (months) (Range)	3 (0-72)
Cough	88 (47)
Dyspnea	59 (31.5)
Fever	48 (31.1)
Extra pulmonary symptom	57 (34.6)
Tuberculin skin test (TST) (n=150) **-Negative** **-Positive**	 114(63.3) 36(36.6)

Table 3: Radiological Findings

CT finding	Frequency	Percent
Lung mass	48	19.1
Mediastinal mass	4	1.6
Effusion	35	14
Nodules -Perilymphatic -Centrilobular -Random	103 -50 -14 -40	41 -19.9 - 5.6 -15.9

Comparison between TB and sarcoidosis: We analyzed factors that could help in predicting whether a subject with suspected granulomatous lymphadenopathy had TB or sarcoidosis. A total of 150 patients had final diagnosis of TB or sarcoidosis (62 TB, 88 sarcoidosis).

Table 4:Comparison of baseline characteristics between TB and sarcoidosis

Parameter	TB (n=62)	Sarcoidosis (n=88)	Total (n=150)	P-value
Positive TST(≥10 mm)	48 (77.4)	4 (4.5)	52 (34.6)	<0.001
BMI (kg/m², mean±SD)	22.8 ± 4.7	26.7 ± 4.9	25.0 ± 5.1	<0.001
Fever	35 (56.5)	24 (27.3)	59 (39.3)	<0.001
Loss of weight	27 (43.5)	30 (34.1)	57 (38)	0.24
Skin and joint	4 (6.5)	13 (14.8)	17 (11.3)	0.11

Table 5: Radiographic characteristics between TB and sarcoidosis

Parameter	TB (n=62)	Sarcoidosis (n=88)	Total (n=150)	P-value
Perilymphatic nodules	6 (9.7)	38 (43.2)	44 (29.3)	<0.001
Centrilobular nodules	10 (16.1)	0	10 (6.7)	<0.001
Pleural effusion	11 (17.7)	3 (3.4)	14 (9.3)	0.003

Table 6:Pathological characteristics between TB and sarcoidosis

Parameter	TB (n=62)	Sarcoidosis (n=88)	Total (n=150)	P-value
EBB positive	7/40 (17.5)	32/83 (38.5)	39/123 (31.0)	<0.001
TBLB positive	8 /38(21)	42/76 (55.2)	50/114 (43.8)	<0.001
EBB+TBLB positive (n=123)	12/40(30)	55/83 (66.2)	67/123 (54.4)	<0.001
Both positive	47 (75.8)	79 (89.7)	126 (84)	0.02

TST in distinguishing between TB and sarcoidosis:
Out of 88 sarcoidosis patients, 4 patients had TST ≥10mm. Of these 3 patients had TST value >20. 1 of the 4 was given ATT but she didn't respond and finally started on steroids as already described above in follow up of TB patients section. 3 other patients were treated as sarcoidosis and are doing well, 2 received steroids.

Results
Pathological diagnosis was achieved in 138/150 . After 3 month follow up out of 76 reactive, 32 still remained reactive (12.7%). Combined procedures had specificity of 96.8%, PPV of 99.4% and NPV of 40.7%. 150 had final diagnosis of TB or sarcoidosis.

Statistical Analysis: Continuous variables were expressed using mean (standard deviation) and median (range). Categorical variables were expressed as frequency and percentage. Differences between continuous variables in the 2 groups were compared using the student t-test/Mann-WhitneyU test depending on pattern of distribution; differences between categorical data were compared using the chi--square test or the Fisher exact test. Characteristics helpful in differentiating between TB and sarcoidosis were analyzed using multivariate logistic regression analysis. Initially the variables were analyzed using univariate analysis to derive crude odds ratio and if found significant ($p < 0.1$) these variables were then entered in a multivariate logistic regression model to derive adjusted odds ratio and confidence limits. Level of significance was expressed as probability value (p value) and odds ratio (95% confidence interval).

Discussion
Poey C et al studied evolutive patterns and signs of activity in active tuberculosis on high resolution CT (HRCT) scans.Ground-glass pattern was noticed 26 times, 9 times after 2 month treatment and only 2 times after 6 month treatmentCentrilobular nodules (n = 17) and poorly marginated nodules (n = 21) were present only before treatment. Reticular pattern (intralobular and septal thickening), interstitial nodules, and fibrosis were seen both before and after treatment. Ground-glass pattern, poorly marginated nodules, and infiltrates as well as centrilobular nodules were related to an active infection.This HRCT may be helpful to demonstrate activity in patients suspected of having tuberculosis and to assess antituberculous treatment efficiency.[1]Okada F et al did clinical/pathologic correlation study in patients with high-resolution CT(HRCT) scan findings presenting with two patterns of centrilobular opacity.Chest HRCT scans in 553 patients with predominant centrilobular opacities or preferential centrilobular disease were retrospectively evaluated. In 141 patients who underwent biopsy, CT scan images were compared with actual specimens. Pathologically, the tree-in-bud appearance correlated well with the plugging of small airways with mucous, pus, or fluid; dilated bronchioles; and bronchiolar wall thickening. Ill-defined centrilobular nodules represented peribronchiolar inflammation or the deposition of hemorrhagic materials. [2]Murata K et al studied centrilobular lesions of the lung and demonstrated by high-resolution CT and pathologic correlation. These results suggest that the centrilobular area or the area around the terminal or respiratory bronchioles can be recognized with HRCT. In addition, the authors confirmed that centrilobular emphysema and centrilobular tuberculous nodules can be diagnosed with HRCT. Thus, HRCT can demonstrate the location of pathologic changes within a lobule and may be helpful in the differential diagnosis of diffuse pulmonary diseases.[3]

Im JG et al studied CT-pathology correlation of pulmonary tuberculosis. CT findings of early bronchogenic spread of postprimary tuberculosis are centrilobular 2- to 4-mm nodules or branching linear structure, 5- to 8-mm poorly defined nodules, lobular consolidation, cavities, and thickening of interlobular septa. Centrilobular nodules or branching linear lesions and poorly defined nodules on CT scan correspond to caseation materials filling the bronchioles, and centrilobular air-space consolidation with caseation necrosis. Poorly defined nodule or lobular consolidation usually consists of central caseation necrosis and peripheral nonspecific inflammation Withantituberculous therapy, resolution typically occurs from the peripheral portion of the poorly defined nodule or lobular consolidation and results in varying degrees of fibrous bands, bronchovascular distortion, emphysema, and bronchiectasis. [4]
Lee JY et al studied CT and pathologic correlation in pulmonary tuberculosis.Typical CT findings of active postprimary pulmonary tuberculosis include centrilobular nodules and branching linear structures (tree-in-bud appearance), lobular consolidation, cavitation, and bronchial wall thickening. The CT findings of inactive pulmonary tuberculosis include calcified nodules or consolidation, irregular linear opacity,parenchymal bands, and pericicatricial emphysema. Atypical radiologic manifestations of tuberculosis, encountered in as many as one third of the cases of adult-onset tuberculosis, are single or multiple nodules or masses, basilar infiltrates, miliary tuberculosis with diffuse bilateral areas of ground-glass opacity, and reversible multiple cysts. [5]
Differential diagnosis of centrilobular nodules was further seen in following studies.Bombarda S et al did tomographic evaluation in the active and post-treatment phases .The objective was to evaluate the structural alterations caused by tuberculosis in the pulmonary parenchyma, both during the active phase of the disease and after the end of the treatment, through computerized tomography of the thorax. Conventional tomography scans of the patients were obtained at two times: upon diagnosis and after the end of the treatment. Such signs may be useful in the diagnosis of pulmonary tuberculosis.[6]
Bendeck SE et al studied cellulose granulomatosis presenting as centrilobular nodules in CT and histologic findings.Centrilobular nodules on high-resolution CT are characterized as nodular opacities localized to the region of the bronchioloarteriolar .Although arteriolar and perivascular disease can also theoretically result in centrilobular nodules, this association is not well documented in the literature. We report a biopsy-proven case of cellulose granulom-atosis resulting in a diffuse pattern of centrilobular nodules and a tree-in-bud appearance. To our knowledge, this is the first case of an arteriolar cause of a tree-in-bud pattern to be reported with the corresponding CT and histologic findings.Szturmowicz M et al found centrilobularnodules in high resolution computed tomography of the lung in IPAH [idiopathic pulmonary arterial hypertention] patients. Such radiological changes are described either as ill-defined centrilobular nodules (CN) or as focal ground glass opacities (FGGO). [7,8]The purpose of study by Akira M et al was to analyze the high-resolution CT features of diffuse bronchioloalveolar carcinoma and determine the useful findings in differential diagnosis. High-resolution CT findings of diffuse bronchioloalveolar carcinoma included ground-glass opacity (n =29), consolidation (n = 29), nodules (n =28), centrilobular nodules (n=26), peripheral distribution (n =19), and air bronchogram (n =18). Most patients with diffuse bronchioloalveolar carcinoma had a mixture of these findings. The combination of consolidation and nodules and the coexistence of

centrilobular nodules and remote areas of ground-glass attenuation are characteristic of diffuse bronchioloalveolar carcinoma.[9]Gupta D et al studied sarcoidosis and tuberculosis. Herein the authors analyzed the relationship between sarcoidosis and tuberculosis and its implications in clinical practice.Recent molecular and immunological studies suggest mycobacterial antigens are the inciting agents in a proportion of sarcoidosis patients. Evidence is stronger from countries with high burden of tuberculosis.

Tuberculosis can manifest as a complication of treatment in sarcoidosis.

Perez RL et al studied pulmonary granulomatous inflammation and compared sarcoidosis and tuberculosis.These lesions,termed granulomas,represent an important defense mechanism against infectious organisms such as fungi and mycobacteria, but also can be elicited by noninfectious agents. If uncontrolled, granulomatous inflammation leads to excessive tissue remodeling, causing fibrosis and/or cavitation as seen in tuberculosis. [10,11]Gawne-Cain ML et al did a CT study about the pattern and distribution of calcified mediastinal lymph nodes in sarcoidosis and tuberculosis. Calcification of hilar and mediastinal lymph nodes is common and calcified nodes are frequently identified on computed tomography (CT). Lymph nodes were categorized by size and pattern of calcification.A focal pattern of calcification was commoner in sarcoidosis (58% sarcoidosis nodes, 23% TB nodes) and complete calcification in TB (62% TB nodes, 27% sarcoidosis nodes). When hilar node calcification was present it was more likely to be bilateral in sarcoidosis than in TB (65% and 8%, respectively, $P < 0.001$). CT of the mediastinum shows significant differences in distribution and pattern of calcification in lymph nodes in TB and sarcoidosis. Possible explanations for these differences include the route of lymphatic drainage of pulmonary TB and the caseating nature of tuberculous granulomas.[12]Hosoda Y et al studied epidemiological similarities and dissimilarities between sarcoidosis and tuberculosis A review of a series of studies in a Japanese work population and the general population.The work population was annually x-rayed and tuberculin tested. Hilar lymphadenopathy (HL) was observed as a common marker of the two diseases. BHL was rare in primary tuberculosis, but occurred in 95.5% of sarcoidosis subjects. In both diseases, HL resolved in a few years, though accompanying extra-pulmonary involvements delayed the resolution of sarcoidosis BHL. The grade of tuberculin sensitivity prior to sarcoidosis was not a risk factor for developing sarcoidosis Age-specific incidence curves showed a mono-modal curve in tuberculosis and a bimodal curve in sarcoidosis. Tuberculosis prevalence was higher in the South of Japan,while sarcoidosis was higher in the North.These epidemiological dissimilarities do not support a tuberculosis etiology of sarcoidosis.[13]Similar studies were done by Badar F ,Bhalla AS et al.Both catered to the dilemma of diagnosing sarcoidosis and tuberculosis.Histologically,sarcoidosis is characterized by noncase-ating granuloma which contrasts against the caseating granuloma seen in tuberculosis (TB), an infectious disease that closely mimics sarcoidosis, both clinically as well as radiologically. In TB-endemic regions, the overlapping clinico-radiological manifestations create significant diagnostic dilemma, especially since the management options are markedly different in the two entities. This review aims to summarize the clinical, laboratory, and imaging features of sarcoidosis, encompassing both typical and atypical manifestations, in an attempt to distinguish between the two disease entities.[14,15] Agrawal R et al studied tuberculosis and sarcoidosis that have similar pulmonary and extra-pulmonary manifestations. Multiple studies have found an epidemiological, molecular, and immunological link between the two. It has been suggested that mycobacterium tuberculosis could be a common patho-physiologic mechanism for tuberculosis and sarcoidosis, and that both clinical entities can trigger similar immunological response in patients. In this paper, authors suggest that tuberculosis and sarcoidosis are two ends of the same spectrum.[16]

Conclusion

Analysis of CT images based on pathologic correlation is helpful in understanding the morphology of pulmonary tuberculosis and sarcoidosis. CT study is helpful about the pattern and distribution of calcified mediastinal lymph nodes in sarcoidosis and tuberculosis. Calcification of hilar and mediastinal lymph nodes is common and calcified nodes are frequently identified on computed tomography (CT).

What this Study Add to Existing Knowledge

The aim of this study was to establish whether there is any difference in the pattern and distribution of such calcifications in tuberculosis (TB) and sarcoidosis. This study will help in early detection of disease .This study will also help you to get evidence based treatment at earliest. The data collected from our records will be useful for treating similar patients in future.

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Conflict of Interest: Nil
Source of support:Nil