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Original Article

Clinical Study on Interstitial Lung Diseases in a Tertiary Teaching Hospital of North Kerala

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Abstract

Introduction: Interstitial lung disease (ILD) is a group of conditions affecting the lung parenchyma. The American Thoracic Society/European Respiratory Society classified the idiopathic interstitial pneumonias (IIPs) into seven specific entities and offered standardized terminology and diagnostic criteria. Review of literature shows the stress on the necessity of finding a better clinical algorithm in the diagnosis and management of IIPs.

Aim: To study the demography, risk factors, clinical features, laboratory, and radiological investigations in the diagnosis of ILDs in patients attending the tertiary teaching hospital of North Kerala.

Materials and Methods: A total of 82 patients were studied for their demography, risk factors, clinical features, laboratory, and radiological investigations in the diagnosis of ILDs in a tertiary teaching hospital. Laboratory tests, X-ray chest, high-resolution computed tomography (HRCT), pulmonary function tests, 6-min walk test, bronchiolar lavage analysis, and lung biopsy were done. Patients were categorized as autoantibody positive if they had one or more circulating autoantibody levels above the established reference values except antinuclear antibody and rheumatoid factor (RF).

Results: C-reactive protein values in 32 patients (45.07%) showed values of 1.84 ± 4.60 mg/dL. RF values in 11 patients were 102.24 ± 11.25. HRCT in 67 patients showed features of non-specific ILD in 17 and idiopathic pulmonary fibrosis (IPF) in 28. Anti ribonucleoprotein antibody test was negative in 31.37%, borderline in 52.94%, and positive in 15.68%.

Conclusions: IPF was the most common ILD in the study followed by non-specific interstitial pneumonia, desquamative interstitial pneumonia, and cryptogenic organizing pneumonia. Multidiscipline discussion and investigative approach helps in diagnosis and assessing the prognosis of ILD. The inclusion of environmental exposure factors conducted in a prospective method would go a long way to provide further insight into the etiology and diagnoses of ILD.

Key words: High-resolution computed tomography, Idiopathic pulmonary fibrosis, Interstitial lung disease, North Kerala

INTRODUCTION

Interstitial lung diseases (ILDs) are acute and chronic bilateral lung diseases with a heterogeneous group of known and unknown causes. They pose diagnostic and therapeutic challenges to the clinician. Clinicians and patients encountered with ILD are usually frustrated as there is no cause or cure for most of the ILDs. The American Thoracic Society/European Respiratory Society (ATS/ERS) classified the idiopathic interstitial pneumonias (IIPs) into seven specific entities and offered standardized terminology and diagnostic criteria. The "gold standard" need of a histological diagnosis was changed to a multidisciplinary approach.[1] The ATS/ERS update of 2013 classify the IIPs into: (1) Major IIPs: Comprising idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia, respiratory bronchiolitis-ILD (RB-ILD), desquamative interstitial pneumonia, cryptogenic organizing pneumonia, and acute interstitial pneumonias. (2) Rare IIPs: Pleuro - parenchymal fibroelastosis and lymphoid interstitial pneumonia. (3) Unclassifiable IIPs:[2] Availability of computed tomography (CT) scans of the chest has resulted in an increased awareness of ILD and the reports of the prevalence of ILD in several countries has increased since then.[3-5] In India, there are not sufficient data available related to the pattern, determinants, distribution,

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and response of treatment of ILD. According to the studies, available proportion of IPF may vary between approximately 30% and 45% of ILDs.[1] The data on diffuse parenchymal lung diseases (DPLD) published by Jindal in 1979 after 5 years of study showed 46% of patients with IPF.[6] Sharma in 1984 showed the presence of IPF in 28.6% of their patients with DPLD.[7] Maheswari *et al.* published that in their patients, females were more and the mean age was 50 years.[8] Similarly, a group of investigators from South India showed that the secondary DPLD (50.8%) was more common than IPF.[9]

Aim of the Study

The aim is to study demography, risk factors, clinical features, laboratory, and radiological investigations in the diagnosis of ILDs in patients attending a tertiary teaching hospital of North Kerala.

MATERIALS AND METHODS

A total of 82 patients attending the tertiary Teaching Hospital attached to Kannur Medical College, Anjarakandy, Kannur, Kerala, were included in this study. The study period was between February 2012 and January 2015 (3 years). The total number of outpatients attending the outpatient department of chest diseases during that period was 34928. The demographic data: Age, sex, socio-economic status, presenting complaints, smoking status, environmental/drug exposures, history of tuberculosis (TB), and connective tissue diseases were elicited. Thorough family history and physical examination of the respiratory system were done.

Inclusion Criteria

1. Patients presenting with shortness of breath and cough with bilateral basal end inspiratory crepitations
2. X-ray/CT scan abnormalities suggestive of ILD were included in this study.

Exclusion Criteria

1. Patients with malignant diseases of the lung are excluded from the study
2. Patients known to have cardiovascular diseases are excluded from the study
3. Acute pulmonary infections were excluded from the study.

The study was approved by the Institution Ethics Committee and an approved consent form was used during the entire study. Laboratory tests used in the workup of the patients were complete blood cell count (CBC), C-reactive protein (CRP), and Mantoux test; rheumatoid factor (RF), antinuclear antibodies (ANA), and anti–U1 ribonucleoprotein (A-RNP) antibodies were done. X-ray chest, high-resolution CT (HRCT) thorax, pulmonary function tests (PFTs), 6-min walk test, bronchioalveolar lavage analysis, and lung biopsy are done in patients depending on the necessity and availability. Serum CRP values above 3.0 mg/dL are taken as abnormal. Serological tests were considered as positive if the results are above the reference values except for ANA for which titers above or at 1:160 were considered positive. A-RNP value <20 U based on enzyme-linked immunosorbent assay (ELISA) was taken as negative; 20-25 U was taken as border line; a positive serology test for A-RNP is taken when the values are >26 U. The ANA values ≥1:320 and RF ≥60 IU/ml were considered positive. The HRCT findings which were looked for were ground glass opacities (GGO), septal lines, reticulations, subpleural fibrosis, traction bronchiectasis, architectural distortion, and/or honeycombing. The findings were graded as 1. Normal 2. Minimal disease: 3-4 septal lines. 3. Mild: 5 or more septal lines, reticulations, subpleural cysts and GGO. 4. Moderate disease: Grade 2 + traction bronchiectasis, peri-bronchovascular thickening, or tracheal retraction with one-third to two-thirds lung involvement. 5. Severe: Grade 2 or 3 findings with more than 2/3rd s of lung involvement.[10] The severity of the ILD on PFTs was categorized into mild: Reduced total lung capacity, reduced forced vital capacity (FVC), forced expiratory volume in first second (FEV1) <80-60% of predicted FEV1/FVC, moderate: 40-59% and severe <40% in diagnosing the severity of restrictive lung disease due to ILD. The 6 min walk test; <280 m/6 min without supplementation of oxygen is taken as positive. All the patients were followed up to 2 years. The final diagnosis was made on the basis of clinical symptoms, signs, laboratory investigations, and X-ray/HRCT findings. The collected data were analyzed using standard statistical methods.

OBSERVATIONS AND RESULTS

The total number of patients attending the Department of Chest Diseases was 34928. Among them 82 patients were included in the study that is confirmed to have been suffering from ILD. The incidence of ILD calculated for the period of 3 years among the patients attending with respiratory symptoms was 0.23. Among them, 56 were male (68.29%) and 26 were female (31.70%) with a male to female ratio of 2.15:1. The patients in the study were divided according to their age into 3 groups. 40/82 (48.78%) belonged to the age group of 42-57 years, 23/82 (28.04%) belonged to above 58 years, and 19/82 (23.17%) belonged to the age group of 26-42 years (Table 1).

Elicitation of the history and examination revealed certain risk factors among the study group. It was observed that

smoking was the most common risk factor among the patients and it was found in 59/82 patients (71.95%), working on farm fields in 27 (32.92%), and connective tissue disorders in 16 (19.51%), (Table 2).

Breathlessness was the most common symptom with which the patients presented in the study group and the symptom was found in 71/82 (86.58%), cough in 65/82 (79.26%), weight loss in 39/82 (47.56%), fever in 35/82 (42.68%), chest pain in (39.02%), and joint pains in 10 (12.19%) patients (Table 3).

Among the laboratory tests performed in the study group, complete CBC was done in all the patients. Abnormal cell counts (lymphocytosis, neutrophilia, polycythemia, and hemoglobin <10 g percentage was taken as abnormal) was observed in 44 patients (53.65%). Erythrocyte sedimentation rate (ESR) was done in all the patients. ESR ≥30 mm/first h were taken as abnormal; 57 patients had high ESR level in this study (69.51%). CRP was done in 71 patients (86.58%) and 32 (45.07%) showed abnormal values with the mean CRP values of 1.84 ± 4.60 mg/dL. Mantoux test was performed in 47/82 patients (57.31%) in those patients who gave a history of TB earlier (20), the test was positive measuring >15 mm/48 h and in 10 patients without a history of TB (21.27%). RF was done in 16 patients and 11/16 (68.75%) patients showed abnormal values with mean values of 102.24 ± 11.25. X-ray chest was done in all the 82 patients, but HRCT was done in only 67 patients. The plain chest X-ray of patients showing bilateral reticular shadows in 54 (65.85%) among the 67 HRCT scans 17 showed bilateral basal interstitial thickening and ground glass appearance which were considered positive for the diagnosis of non-specific interstitial pneumonitis (NSIP) in the study group. 28 among them HRCT showing patchy, predominantly peripheral, subpleural, bibasal reticular abnormalities, and areas of traction bronchiolectasis with limited amount of GGO were considered as IPF (Usual interstitial pneumonitis-UIP). 8 patients showed post-TB cavities. 4 patients showed only minimal reticular pattern. Bronchoalveolar lavage was performed in 29 patients and 26 (89.65%) of them showed non-specific cytology with the total cell count was 2.15×10^5 cells m^{-3}. Microbial culture results from the sputum and bronchoalveolar lavage fluid were negative. Transbronchial lung biopsy was done in 3 patients. Histopathology of specimens showed infiltration with inflammatory cells into thickened alveolar septa in 2 patients and in one the alveolitis was characterized as having chronological homogeneity. There was no granuloma formation and eosinophil infiltration. These findings were compatible with the histological pattern of non-specific ILD. The 6-min walk distance was done in 54 patients and 46 patients showed abnormal values with the mean distance was 155.6 ± 12.94 m, with 96% of minimum arterial oxygen saturation measured by pulse oxymetry. PFTs were done in 71 of the total 82 patients and the results were mild restriction in 12 (16.90%), moderate in 36 (50.70%), and severe in 23 (32.39%) of them. A-RNP antibody test was performed in 51 patients and found negative in 16 (31.37%), borderline in 27 (52.94%), and positive in 8 (15.68%). ANA was done in 68 patients and 41 (60.29%) of them had negative ANA-normal; low-level

Table 1: Age and sex

Sex	26-41 years - 19 (23.17%)	42-57 years - 40 (48.78%)	>58 years - 23 (28.04%)
Male 56 (88.29%)	13	32	11
Female 26 (31.70%)	6	8	12

Table 2: The incidence of risk factors in the study group (*n*=82)

Risk factors	26-41 years - 19 (23.17%)	42-57 years - 40 (48.78%)	>58 years - 23 (28.04%)
Smoking - 59 (71.95%)	14	28	17
Hypersensitivity to drugs- 13	2	6	5
Farmers - 27	6	10	11
Industrial toxic fumes - 8	4	3	2
Connective tissue disorders - 16	2	7	7
H/o tuberculosis - 20	5	8	7

Table 3: The symptomatology in the study group (*n*=82)

Presenting symptom	26-41 years - 19 (23.17%)	42-57 years - 40 (48.78%)	>58 years - 23 (28.04%)
Breathlessness - 71	17	37	17
Non-productive cough - 65	14	32	19
Fever - 35	7	21	7
Chest pain - 32	9	11	12
Joint pain - 10	2	4	4
Weight loss - 39	10	18	11

positivity ≥1:40 in 25 (36.76%) and ≥1:320 in 2 patients with high ANA titer (2.94%). RF was done in 16 patients with positive results in (68.75%) of the patients. The patients are categorized as autoantibody positive if they had one or more circulating autoantibody levels above the established reference values except ANA and RH factors. The positive results are alone distributed according to the age groups of the patients as shown in Table 4.

Based on the symptoms, clinical features, laboratory tests, and specific and non-specific serological tests of the patients were classified as IPF - 28 (34.14%), desquamative interstitial pneumonia - 14 (17.07%), cryptogenic organizing pneumonia - 08 (09.75%), nonspecific interstitial pneumonia - 17 (32.92%), and RB-ILD - 15 (18.29%) types of ILDs. Most of the differentiation was based on the HRCT pattern. The age group wise distribution is depicted in Table 5.

DISCUSSION

ILD basically means progressive scarring of the tissue between the air sacs and a tissue supporting them. It is present in the acute form where the symptoms increase rapidly requiring ventilator support. In chronic patients, the symptoms progress less rapidly as the scarring increases resulting in lung stiffness and hypoxia. ILD is due to known causes such as autoimmune or joint disorders, exposure to organic dust, inorganic fumes, use of medications, and exposure to radiation. Unknown causes include IIPs, such as IPF, NSIP, and sarcoidosis. This study was conducted in a Tertiary Teaching Hospital in North Kerala. Among the 82 patients, male were 56 and female were 26. More than 45% of the patients belonged to the age group of 42-57 years. The demographic data and disease burden in India related to ILD in the literature is scarce.[8-11] In the present study, more than 45% of the patients belonged to low socioeconomic group and farmers. The ILD diagnosis was made by multidisciplinary discussions and based on the new classification of IIP and the 2011 guidelines for the diagnosis of IPF using HRCT images of the chest as the main platform for diagnostic approach.[1,2,12,13] The demographic profile of Indian patients diagnosed with IPF was similar to the patients with IPF described in the patients of European and Asian descents living in the western and other eastern hemispheres of the world. Gochuico *et al.*[13]

Table 4: Investigations undertaken in the study group and their results (*n*=82)

Investigations: Positive result/actual number of test done (%)	26-41 years - 19 (23.17%)	42-57 years - 40 (48.78%)	>58 years - 23 (28.04%)
CBC - 44/82 (53.65)	15	16	13
ESR - 57/82 (69.51)	18	21	18
CRP - 32/71 (45.07)	9	12	11
RF - 11/16 (68.75)	4	05	02
ANA - 27/68 (39.70)	8	11	08
Anti RNP - 43/51 (84.31)			
Negative - 16	4	04	08
Borderline - 27	9	10	08
Positive - 8	2	04	02
X-ray chest - 54/82 (65.85)	11/19	30/40	13/23
HRCT - 55/67 (82.08)	11/19	26/28	18/20
Mantoux test - 30/47 (63.82)	7/12	16/22	7/10
PFTs - 71/71 (100)			
Mild - 12 (16.90)	2	04	06
Moderate - 36 (50.70)	7	11	18
Severe - 23 (32.39)	5	08	10
6-min walk test - 46/54 (85.18)	7	12	27
Bronchial lavage cytology - 26/29 (89.65)	10	06	10
Transbronchial lung biopsy 3/3 (100)	01	01	01

CBC: Complete blood cell count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, A-RNP: Anti-U1-ribonucleoprotein, RF: Rheumatoid factor, ANA: Antinuclear antibodies, HRCT: High-resolution computed tomography, PETs: Pulmonary function tests

Table 5: Types of ILD in the study group (*n*=82)

Type of ILD (%)	26-41 years	42-57 years	>58 years
IPF - 28 (34.14)	5	11	12
Desquamative interstitial pneumonia - 14 (17.07)	3	6	5
Cryptogenic organizing pneumonia - 08 (09.75)	2	4	2
Non-specific interstitial pneumonia - 17 (20.7)	3	11	3
RB-ILD - 15 (18.29)	4	5	6

ILD: Interstitial lung disease, IPF: Idiopathic pulmonary fibrosis, RB: Respiratory bronchiolitis

found that physical examination and PFT measurements were not sensitive methods of detecting preclinical ILD in patients with rheumatoid arthritis (RA), however, they observed that the history of smoking could be a potential risk factor for its development in the present study smoking was reported in 71.95% of the study group. PFTs showed mild in 16.90%, moderate in 50.70%, and severe in 32.39% of the patients and found to be useful in assessing the severity of the disease. The patients with RA showed positive results on X-ray chest, HRCT, and PFT in 12%, 16%, and 48%, respectively, as reported by Karazincir *et al.*[14] and they found no correlation between disease activity and HRCT findings in their patients. In the present study, X-ray and HRCT were helpful in the diagnosis of ILD in 65.85% and 82.08%, respectively. In the present study, 16 patients with connective tissue disorders were found to be presenting with symptoms of breathlessness and cough and 10 among them had joint pains; The X-ray and HRCT results among them showed positive features of reticular pattern and ground glass appearance, respectively, in 13/16 (81.25%). Baseline CRP levels are predictive of long-term ILD progression. CRP levels might aid the clinicians in identifying the patients that require more intensive management.[15] CRP levels higher than 3 mg/L had greater hospitalization and death due to chronic obstructive pulmonary disease versus <3 mg/L. The adjustment for the other variables CRP was 1.2 mg/L greater in those who were hospitalized subsequently and died. The CRP measurement predicts the status of pulmonary function volumes including FEV1 or other lung parameters.[16] In the present study, the CRP was done in 71 patients (86.58%) and 32 (45.07%) showed abnormal values with the mean CRP values of 1.84 ± 4.60 mg/dL. Bio-marker levels vary depending on the clinical status whether they are in acute state or chronic state. High bio-marker levels during an exacerbation episode correlate with the short-term prognosis and therefore, their measurement is useful in their management.[17] The patients with ILD associated with autoimmune disease, with ANA titer ≥1:1280 had improved survival, suggesting that an elevated ANA may be a marker for improved prognosis.[18] In the present study, ANA was done in 68 patients and 41 (60.29%) of them had negative ANA values normal; low level positivity ≥1:40 in 25 (36.76%) and ≥1:320 in 2 patients with high ANA titer (2.94%). RF was done in 16 patients with positive results in (68.75%) of the patients. The patients are categorized as autoantibody positive if they had one or more circulating autoantibody levels above the established reference values except ANA and RH factors. Serum antibody A-RNP estimation helps in diagnosing connective tissue disorders which may be associated with ILD. A negative anti RNP antibody result is defined as <20 U based on ELISA. Normal value excludes mixed connective tissue disorders. Sensitivity is 95-100% (if found in high titers 1: 1000000); SLE - 38- 44%, DLE - 20-30%, and RA - 10%. The degree of positivity or the titer of antibody does not indicate the severity or duration of the disease.[19] In the present study, the A-RNP titers were evaluated in 51 patients and found negative in 16 (31.37%), border line in 27 (52.94%), and positive in 8 (15.68%). The available literature shows that the diagnosis of ILD was made on clinical signs and symptoms and validated and enrolled in the ILD-India registry. Among these the hypersensitivity pneumonitis was diagnosed in 47.3% (n = 513; exposure: 48.1% air coolers), attributable to domestic environmental factors; connective tissue disease-associated ILD in 13.9% and IPF in 13.7%. In the present study, the following types of ILD could be diagnosed: IPF - 28 (34.14%), desquamative interstitial pneumonia - 14 (17.07%), cryptogenic organizing pneumonia - 08 (09.75%), nonspecific interstitial pneumonia - 17 (20.7%), and RB-ILD - 15 (18.29%) types of ILDs.

CONCLUSION

IPF was the most common ILD in the study followed by non-specific interstitial pneumonia, desquamative interstitial pneumonia, and cryptogenic organizing pneumonia. Multidiscipline investigative approach helps in diagnosis and assessing the prognosis of ILD. The diagnoses vary between investigations undertaken at referral hospitals and by ILD experts. Inclusion of environmental exposure factors conducted in a prospective method would go a long way to provide further insight into the etiology and diagnoses of ILD.

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