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Original Research Article

Usual interstitial pneumonia - secondary vs idiopathic pulmonary fibrosis

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ABSTRACT

Background: Interstitial Lung Diseases is a group of disorders where the pulmonary interstitium, alveolar structures and the small airways are affected. Identification of a specific pattern on HRCT, with a thorough clinical evaluation can help a physician in narrowing down the differential diagnosis for the underlying cause. Usual Interstitial Pneumonia (UIP) is a frequently identified pattern. Differentiating patients with definite UIP pattern, into IPF and non-IPF spectrums is important. Aim of this study is to compare UIP patients with a secondary cause vs Idiopathic Pulmonary Fibrosis.
Methods: Statistically 33 patients having UIP pattern on HRCT were evaluated based on the history of extrapulmonary symptoms, environmental exposure, drugs and subsequent serology testing. Patients were divided into two groups - IPF and UIP with a secondary cause. Both groups were compared on various clinical parameters. Inferences were drawn from the same.
Results: Total 66.6% patients were identified to have Idiopathic Pulmonary Fibrosis, 33.3% had UIP with a secondary cause. Majority of patients with a secondary cause had Connective Tissue Disorder (90.9%) and one patient of Chronic Hypersensitivity Pneumonitis (HP).
Conclusions: Absence of extrapulmonary symptoms in UIP patients need no further investigations and can be diagnosed as a case of IPF. However, presence of extrapulmonary symptoms needs further evaluation to diagnose the underlying disease and start treatment for the same.

Keywords: Connective tissue disorder, Idiopathic pulmonary fibrosis, Usual interstitial pneumonia, Usual interstitial pneumonia with a secondary cause

INTRODUCTION

Interstitial Lung Diseases is a group of disorders where the pulmonary interstitium, alveolar structures and the small airways are affected.[1] It's diagnosis is based on a clinical profile consisting of progressively increasing symptoms of dyspnea and cough, which are not resolved on antibiotics, bronchodilators or diuretics and on spirometry, give a restrictive pattern of lung dysfunction and a radiological profile consisting of an interstitial pattern, found on High Resolution Computed Tomography (HRCT). The identification of a specific pattern on HRCT, aided by other investigations and a thorough history can help a physician in narrowing down the differential diagnosis for the underlying cause. Usual Interstitial Pneumonia (UIP) is a frequently identified pattern. According to ERS/ATS guidelines on diagnosis of Idiopathic Pulmonary Fibrosis (IPF) revised in 2018, UIP pattern on HRCT is defined by the presence of subpleural and basal predominant distribution (i.e. apicobasal gradient) accompanied by honeycombing (with or without traction bronchiectasis). On

histopathology, the hallmark of UIP is dense fibrosis with architectural distortion in a predominantly subpleural or basal distribution. It was clearly stated that having a UIP pattern on HRCT does not warrant the need of surgical lung biopsy or Bronchoscopic investigations.[2]

Previously, patients with UIP pattern were considered to be synonymous to IPF. But in recent studies, it has been proven that getting a UIP pattern on HRCT is not itself diagnostic of IPF. It may represent an advanced stage of an underlying disease having an interstitial pattern. Differentiating patients with definite UIP pattern, into IPF and non-IPF spectrums, is important. As patients with IPF have poor prognosis and poor response to steroids and immunosuppressants, whereas, patients with non-IPF spectrum have a limited response to anti-fibrotics but a better response to steroids and immunosuppressants, and have a better prognosis.[3] Thus, a detailed evaluation of the patient needs to be done. This includes - a history of extra-pulmonary symptoms, history of medications or substance abuse and a history of environmental exposures at home, work, or other places the patient frequently visits. These patients should also undergo serological testing to exclude Connective Tissue Disorders (CTDs), or sarcoidosis as a potential cause. The various diseases associated with a UIP pattern include - connective tissue disorders, hypersensitivity pneumonitis, asbestosis, advanced stage of sarcoidosis and rarely drug toxicity.[4] The aim of this study was to compare UIP patients with a secondary cause vs IPF and lay down a practical tools to rule out or rule in IPF.

METHODS

A total of 33 patients diagnosed with interstitial lung disease having a definite UIP pattern on HRCT, between December 1st, 2017 and December 9th, 2019, at a tertiary care center in Bareilly (UP), were identified and included in this study. A thorough clinical history and examination for both pulmonary and extra-pulmonary symptoms was done. Extrapulmonary symptoms included skin and joint related symptoms. Old medical records were checked for any previous history of medications or comorbid conditions. A history of exposure both at home and workplace was taken. Lung functions were assessed through spirometry.[5]

Patients were divided into two groups based on the presence or absence of extrapulmonary symptoms (Figure 1). Both the groups underwent serological testing. Patients with extrapulmonary symptoms but negative serology were labelled as IPF whereas those with positive serology were labelled as UIP with a secondary cause. The second group which had no extrapulmonary symptoms but a positive serology were labelled as UIP with a secondary cause and patients with no extrapulmonary symptoms and negative serology were labelled as IPF. Serum Calcium levels, 24-hour urine calcium levels and serum ACE levels were done to look for sarcoidosis. Patients with HRCT patterns other than UIP were excluded from this study.

ILD diagnoses

Patients presenting with progressively increasing symptoms of cough and breathlessness which are not relieved on bronchodilators, antibiotics and diuretics, who have a restrictive pattern on spirometry and on HRCT, on Chest X Ray have reticular shadows with volume reduction, have an interstitial pattern of disease were diagnosed as a case of interstitial lung disease (ILD).

UIP pattern

UIP pattern on HRCT is stated when the distribution is subpleural and basal predominant with honeycombing (with or without traction bronchiectasis) and absence of features of alternate diagnosis (e.g. GGO, Cysts or nodules).[2]

Connective tissue disorder

Presence of multisystemic symptoms and diagnosis in accordance with American College of Rheumatology criteria and a positive serology for CTD.[6-8]

Hypersensitivity Pneumonitis (HP)

Respiratory symptoms with a history of environmental exposures known to cause HP, a negative serology for CTD and no symptoms/signs suggestive of CTD.[9]

IPF

Respiratory Symptoms with exclusion of other known causes of ILD (e.g. domestic and occupational environmental exposures, CTD, drug toxicity) and presence of definite UIP pattern on HRCT.[2]

Statistical analysis

Analysis was done using the relevant tools.

RESULTS

Patient populations

The mean age of patients at presentation was 52.4 years (SD, 15.8). The male to female ratio was found to be 1: 1.5. The mean duration of illness was found to be 3.15 years (SD, 1.28). The mean age of patients with Idiopathic Pulmonary Fibrosis was found to be 58.3 years (SD, 12.5). In patients having UIP pattern with a secondary cause, it was found to be 40.6 years (SD, 15.4). Dyspnea was found in 96.9% (n=32) and cough was found in 93.9% (n=31) of patients. In the extra pulmonary symptoms - the most common symptom observed was joint involvement (i.e. arthralgia

and joint stiffness) in 33.3% (n=11), followed by skin involvement (24.2%, n=8), and Raynaud's phenomenon (21.2%, n=7). A history of exposure to a significant environmental agent was observed in 3.03%(n=1) of total patients. Gastroesophageal reflux (GER) was reported in 54.5% (n=18) of patients. A positive serology for CTD was observed in 30.3% (n=10).

Various clinical parameters were compared between both the groups (Table 1). The sex distribution in IPF group was 1:1.2 as compared to the non-IPF group having the ratio of 1:2.6. Smoking was observed in 22.7% (n=5) in IPF group as compared to 9.09 (n=1) in the non-IPF group. No extrapulmonary symptoms were observed in the IPF group whereas they were present in 90.9% (n=10) in the non-IPF group.

Table 1: Comparison between Idiopathic Pulmonary Fibrosis and Secondary UIP.

Characteristics	Idiopathic Pulmonary Fibrosis N (%)	UIP with a secondary cause N (%)
Mean age (years)	58.3±12.5	40.6±15.4
Duration(years)	3.47±1.32	2.5±0.96
Male/Female	10 (45.4) /12(48)	3 (27.2) /8(72.7)
Smoking	5 (22.7)	1 (9.09)
Joint symptoms	0	7 (63.6)
Skin symptoms	0	8 (72.7)
GERD	16 (72.7)	6 (54.5)
Raynaud's Phenomenon	0	7 (63.6)
Clubbing	22 (100)	5 (45.4)
Desaturation on 6MWT	22 (100)	9 (81.8)
H/o ATT	6 (27.2)	5 (45.4)
FVC	1.77±0.73	1.91±0.82
FVC%	45.8±15.3	54.2±17.3

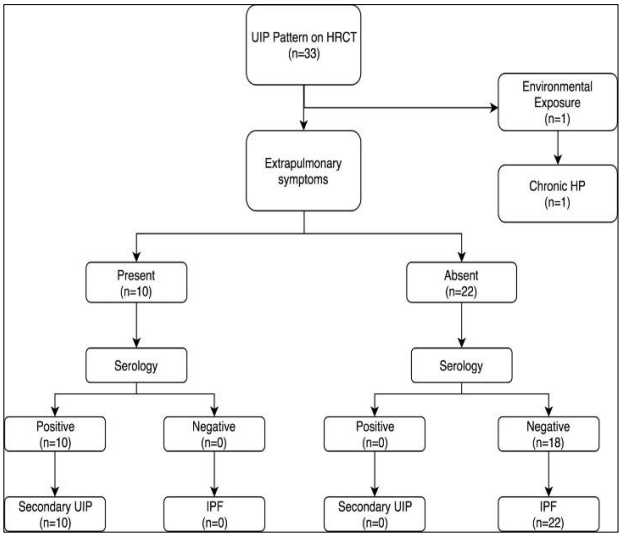

Figure 1: Study design and outcome.

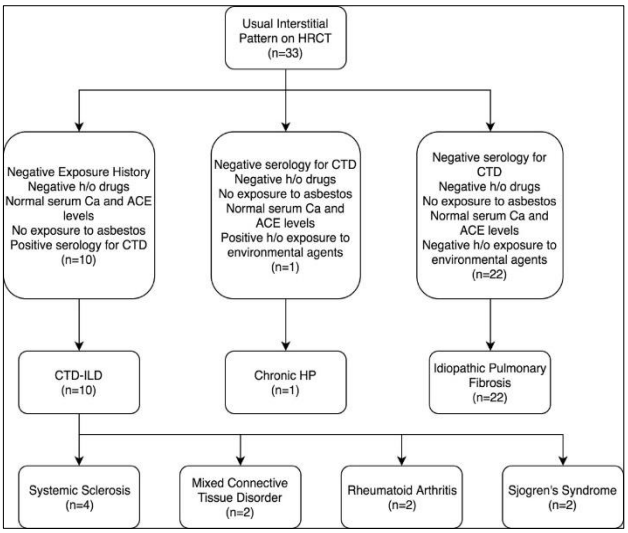

Figure 2: Outcome of the study.

After evaluation, UIP with secondary cause was found in 33.3% (n=11), and Idiopathic Pulmonary Fibrosis (IPF) in 66.6% (n=22). Majority of the UIP with secondary cause patients belonged to Connective Tissue Disorder related ILD (CTD-ILD) observed in 30.3% (n=10) and one case of chronic HP 3.03% (n=1) (Figure 1).

In the patients having a positive serology for CTD, Systemic Sclerosis was observed in four patients and two patients each of Rheumatoid Arthritis, Sjogren's and Mixed Connective Tissue Disorder (Figure 2). In the patient diagnosed with chronic HP, patient was a famer had significant exposure to grain dust.

DISCUSSION

Based on the clinical evaluation and serological testing, the patients with UIP pattern were divided into two major groups - UIP with a secondary cause and Idiopathic Pulmonary Fibrosis. The mean age of presentation was higher with patients of IPF (59 years vs 40.6 years). This was consistent with previous literature which considered age of more than 50 years as an important criterion for diagnosis of IPF.[10]

Consistent with the previous studies, incidence of smoking was found to be more in IPF group as compared to non-IPF group. Kärkkäinen et al, demonstrated that smoking influenced the course of disease in IPF.[11] And this was found to be not just common in current smokers but also in "ever-smokers". A study from United Kingdom demonstrated that the odds of developing IPF increased with increasing pack years.[12]

Sex predilection in case of our IPF patients did not contribute to the diagnosis, which was inconsistent to what was stated in the previous studies[10]. In non-IPF patients, female predilection was clearly visible as majority of our non IPF patients were associated with connective tissue disorders, which are more common in females.[13]

Extra pulmonary symptoms were only seen in patients of the non-IPF group and serology for CTD was also positive in them. In patients with no extrapulmonary symptoms, serology tests were negative. This finding suggests therefore, that in UIP patient's serology testing need not be done if extrapulmonary symptoms are absent, and these patients can be given a diagnosis of IPF. The absence of these features, thus, can to a great extent predict if the UIP pattern has a secondary cause or is purely idiopathic.[2]

GERD was found to be present exclusively in the patients with IPF. As stated in texts, relationship between gastroesophageal reflux (GER), secondary micro aspiration, and IPF remains controversial. Lee et al, in there study demonstrated that prevalence of GER is common in IPF, but they were unclear if GER is contributing to the development and/or progression of IPF.[14] Nevertheless GERD, through various studies in the past, has a higher frequency in patients with IPF.[15] In the non-IPF group GERD was observed in nearly 50% of subjects. This could be attributable to the fact that connective tissue disorders like systemic sclerosis and scleroderma have a mildly dilated oesophagus and this may lead to symptoms of GERD.[16]

On examination, clubbing was observed in nearly half of the patients of the non-IPF group as compared to the IPF group where it was present in all the patients. Various literatures have suggested that the presence of clubbing is a poor prognostic factor and indicates an advanced stage of disease.[17,18] Absence of clubbing in a patient with UIP pattern may suggest a secondary cause and thus a better prognosis.

The lung functions observed showed that despite of having nearly equal duration of illness in both the groups, the lung functions in the non-IPF group were better as compared to the IPF group.

All these parameters suggest that despite of having similar radiological profile (i.e. a definite UIP pattern) non-IPF patients i.e. patients having a UIP pattern with a secondary cause may have a better prognosis and survival as compared to the patients with IPF. One of the previous studies did a comparison of histopathological features (i.e. no. of fibroblastic foci) between patients with UIP pattern having Collagen Vascular Diseases (CVD) as an underlying cause vs patient with IPF. They found that the number of fibroblastic foci in patients with secondary UIP were significantly lower in number as compared to patients with IPF.[19] Whether the younger patients of secondary UIP had a different response to cell injury as compared to the older age groups found in patients with IPF, still needs to be validated through further studies.[20]

In conclusion we can state that, despite of having a definite UIP pattern, finding a secondary cause to it may significantly influence the treatment and thus prognosis of the patients. Furthermore, in resource limited set ups, a careful history and clinical evaluation can suffice to rule out a secondary cause in a significant number of patients with a UIP pattern on HRCT. And the absence of extrapulmonary symptoms, or absence of any environmental exposure can clinch the diagnosis of IPF without any further investigations.

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REFERENCES

1. Jay h. Ryu, Moisés Selman, Thomas V. Colby, Talmadge E. King, Jr. Idiopathic Interstitial Pneumonias; In: Murray and Nadel's Textbook of Respiratory Medicine, 5th ed. Elsevier; 2015:1118-1120.
2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respira Crit Care Med. 2018 Sep 1;198(5):e44-68.
3. Park JH, Kim DS, Park IN, Jang SJ, Kitaichi M, Nicholson AG, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease–related subtypes. Am J Respira Crit Care Med. 2007 Apr 1;175(7):705-11.
4. Singh S, Collins BF, Sharma BB, Joshi JM, Talwar D, Katiyar S, et al. Interstitial lung disease in India. Results of a prospective registry. Am J Respira Crit Care Med. 2017 Mar 15;195(6):801-13.
5. Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic interstitial pneumonias. Proceed Am Thoracic Soc. 2006 Jun;3(4):315-21.
6. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham III CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheumatism. 2010 Sep;62(9):2569-81.
7. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. Classification criteria for systemic sclerosis: an ACR-EULAR collaborative initiative. Arthritis Rheumatism. 2013 Nov;65(11):2737.
8. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary

Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol. 2017 Jan;69(1):35-45.
9. Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: perspectives in diagnosis and management. Am J Respira Crit Care medicine. 2017 Sep 15;196(6):680-9.
10. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. Am J Respir Crit Care Med. 2000;161:646-64.
11. Kärkkäinen M, Kettunen HP, Nurmi H, Selander T, Purokivi M, Kaarteenaho R. Effect of smoking and comorbidities on survival in idiopathic pulmonary fibrosis. Respiratory Res. 2017 Dec;18(1):160.
12. Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respire Crit Care Med. 1997 Jan;155(1):242-8.
13. Lahita RG. The connective tissue diseases and the overall influence of gender. Inter J Fertility Menopausal Studies. 1996;41(2):156-65.
14. Lee JS. Gastroesophageal Reflux and IPF. In Idiopathic Pulmonary Fibrosis. Humana Press: Cham; 2019:379-387
15. Tobin RW, POPE CE, Pellegrini CA, Emond MJ, Sillery JI, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. Am J Respira Crit Care Med. 1998 Dec 1;158(6):1804-8.
16. Christmann RB, Wells AU, Capelozzi VL, Silver RM. Gastroesophageal reflux incites interstitial lung disease in systemic sclerosis: clinical, radiologic, histopathologic, and treatment evidence. In: Seminars in arthritis and rheumatism. WB Saunders. 2010;40(3):241-9.
17. Spicknall KE, Zirwas MJ, English III JC. Clubbing: an update on diagnosis, differential diagnosis, pathophysiology, and clinical relevance. J Am Acad Dermatol. 2005 Jun 1;52(6):1020-8.
18. van Manen MJ, Vermeer LC, Moor CC, Vrijenhoeff R, Grutters JC, Veltkamp M, et al. Clubbing in patients with fibrotic interstitial lung diseases. Respira Med. 2017 Nov 1;132:226-31.
19. Flaherty KR, Colby TV, Travis WD, Toews GB, Mumford J, Murray S, et al. Fibroblastic foci in usual interstitial pneumonia: idiopathic versus collagen vascular disease. Am J Respira Crit Care Med. 2003 May 15;167(10):1410-5.
20. Shelton DN, Chang E, Whittier PS, Choi D, Funk WD. Microarray analysis of replicative senescence. Curr Biol. 1999 Sep 9;9(17):939-45.

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