Original Article

Interstitial Pneumonia with Autoimmune Features – An Observational Study in a Tertiary Care Institute from South India

Ravi Charan Avala, Narendra Kumar Narahari[1], Anu Kapoor[2], Bhaskar Kakarla[1], Rajasekhar Varma[1], Paramjyothi Kruparao Gongati[1]

Department of Pulmonology, Apollo Hospitals, Vishakapatnam, Andhra Pradesh, Departments of [1]Pulmonary Medicine and [2]Radiology and Imaging, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Abstract

Background: Often, patients with idiopathic interstitial pneumonia (IIP) have certain specific clinical features to suggest an autoimmune disease but do not justify the current rheumatologic classification systems to fit into a diagnosis of connective tissue disease (CTD)-associated IIP. There is a great paucity of clinical, serological, and radiological data of these patients from India. **Aim:** The aim was to study the clinicoradiological and autoantibody profile in patients with interstitial pneumonia with autoimmune features (IPAF). **Methodology:** It was a prospective, observational study conducted in a tertiary care center between December 2015 and December 2016. A total of 30 patients who satisfied the criteria for IPAF according to the American Thoracic Society/European Respiratory Society research were included in the study. **Results:** All 30 patients satisfied IPAF criteria, but they did not meet the immunological criteria for CTD. Majority of them were female (86.67%) and nonsmokers. The mean age was 52.5 ± 14.5 years. The most common clinical symptom was inflammatory arthritis in 20 (66.67%) patients, followed by Raynaud's phenomenon in 5 (16%) patients. Nonspecific interstitial pneumonia was the most common radiological pattern seen in 20 (66.67%) patients, while antinuclear antibody (1:320) was the most common autoantibody positive in 18 (60.0%) patients, followed by rheumatoid arthritis factor in 15 (50%) patients. **Conclusions:** High female predominance along with distinct imaging, histologic and serological characteristic features are seen in patients with IPAF as compared to those with IIP. Further studies in patients with IPAF are needed to understand the natural history and its management.

Keywords: Autoantibody profile, autoimmune features, connective tissue disease, interstitial pneumonia, nonspecific interstitial pneumonia

Introduction

The idiopathic interstitial pneumonias (IIP) are a group of nonneoplastic disorders characterized by varying patterns of inflammation and fibrosis of the lung parenchyma with distinct clinical, radiologic, and histopathologic features.[1] They include the entities of idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia, acute interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease (ILD), desquamative interstitial pneumonia, and lymphocytic interstitial pneumonia (LIP). The diagnosis of IIP requires the exclusion of known causes of interstitial pneumonia, such as environmental or occupational exposures, connective tissue disease (CTD), and drug- or radiation-induced lung injury.[2] Identifying an underlying etiology in IIPs is clinically relevant in terms of long-term prognosis and management.[2]

As a high prevalence of CTD (30%) in seen in patients with newly diagnosed ILD, current guidelines recommend excluding CTD to diagnose an IIP.[2,3] This is because CTD-ILD has a more favorable prognosis, and the available therapeutic options differ significantly.[4] Often, patients with IIP have

Access this article online	
Quick Response Code:	**Website:** www.ijrconline.org
	DOI: 10.4103/ijrc.ijrc_13_20

Address for correspondence: Dr. Narendra Kumar Narahari, Department of Pulmonary Medicine, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad - 500 082, Telangana, India.
E-mail: drnarendrajipmer@gmail.com

How to cite this article: Avala RC, Narahari NK, Kapoor A, Kakarla B, Varma R, Gongati PK. Interstitial pneumonia with autoimmune features – An observational study in a tertiary care institute from South India. Indian J Respir Care 2020;9:209-15.

Received: 21-02-2020 **Revised:** 03-06-2020
Accepted: 11-06-2020 **Published:** 07-07-2020

certain specific clinical features to suggest an autoimmune disease but do not fit into a diagnosis of CTD-associated IIP according to the current rheumatologic classification systems.[5] Confusing terms such as undifferentiated CTD-associated ILD, lung-dominant CTD, and autoimmune-featured ILD[1] were given to these patients.

The American Thoracic Society (ATS) and European Respiratory Society (ERS) supported an international working group to generate a consensus for patients with IIP with features of autoimmunity. They proposed the term "interstitial pneumonia with autoimmune features" (IPAF) and developed consensus-derived classification criteria.[1] This new classification system is given in Table 1. It consists of three domains, the clinical, serological, and morphological domains. The clinical domain consists of certain extrathoracic features that are suggestive but not diagnostic of an underlying CTD. The specific autoantibodies that are strongly associated with CTD constitute serologic domain. The morphologic domain consists of certain radiographic patterns, histopathological features, and multicompartment features. A morphological criterion is satisfied if any one of the items from the three subdomains is present. To fulfill the criteria of IPAF, at least one feature from at least two of the domains is required as per consensus.[1]

Interstitial pneumonia may arise during the course of an established CTD, but sometimes, it occurs as an early and exclusive manifestation of an otherwise occult CTD.[1] It was observed in the literature that the survival of the IPAF cohort was slightly better than IPF but not so favorable when compared to CTD-ILD.[6] There is a great paucity of clinical, serological, and radiological data in IPAF patients from India. No study on IPAF has been reported from India so far. Recent advances in diagnostic modalities have provided new hope for precise diagnosis, prognosis, and better management of the disease. The present study is an initial attempt, which aimed to study the clinicoradiological and autoantibody profile in patients with IPAF.

Methodology

The study was carried out in the department of pulmonary medicine at a tertiary care hospital for both Telangana and Andhra Pradesh states. It was a prospective, observational study conducted between December 2015 and December 2016. Institutional ethics committee approval was obtained. All patients presenting with signs, symptoms, and imaging suggestive of interstitial pneumonia were analyzed. The diagnosis of ILD was made by a multidisciplinary team including a pulmonologist, radiologist, and pathologist with a specific interest in ILD at our institution. A total of 30 adult patients who fulfilled the criteria for IPAF according to ATS/ERS research criteria [Table 1] were included as the study population.

The data obtained included demographic information (age, race/ethnicity, and sex) and medical/surgical history, including

Table 1: Classification criteria for "interstitial pneumonia with autoimmune features"

Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and
Exclusion of alternative etiologies and
Does not meet criteria of a defined connective tissue disease and
At least one feature from at least two of these domains:
Clinical domain
Serologic domain
Morphologic domain
Clinical domain
Distal digital fissuring (i.e., "mechanic hands")
Distal digital tip ulceration
Inflammatory arthritis or polyarticular morning joint stiffness ⩾60 min
Palmar telangiectasia
Raynaud's phenomenon
Unexplained digital edema
Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)
Serologic domain
ANA ≥1:320 titer, diffuse, speckled, homogeneous patterns or
ANA nucleolar pattern (any titre) or
ANA centromere pattern (any titre)
Rheumatoid factor ≥2× upper limit of normal
Anti-CCP
Anti-dsDNA
Anti-Ro (SS-A)
Anti-La (SS-B)
Anti-ribonucleoprotein
Anti-Smith
Anti-topoisomerase (Scl-70)
Anti-tRNA synthetase (e.g. Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS)
Anti-PM-Scl
Anti-MDA-5
Morphologic domain
Suggestive radiology patterns by HRCT:
NSIP
OP
NSIP with OP overlap
LIP
Histopathology patterns or features by surgical lung biopsy:
NSIP
OP
NSIP with OP overlap
LIP
Interstitial lymphoid aggregates with germinal centers
Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)
Multicompartment involvement (in addition to interstitial pneumonia)
Unexplained pleural effusion or thickening
Unexplained pericardial effusion or thickening
Unexplained intrinsic airways disease (by PFT, imaging or pathology)

Contd....

Table 1: Contd...

Unexplained pulmonary vasculopathy

Adapted from Fischer *et al*.[1] Reproduced with permission of the © ERS 2020: European Respiratory Journal 46 (4) 976-987; DOI: 10.1183/13993003.00150-2015 Published 30 September 2015. ANA: Antinuclear antibody, Anti-CCP: Anti-cyclic citrullinated peptide antibody, Anti-dsDNA: Anti-double-stranded DNA antibody, Anti-LA (SS-B): Anti-Sjogren syndrome B antigen antibody, Anti-MDA-5: Anti-melanoma differentiation-associated gene 5 antibody, Anti-PM-Scl: Anti-polymyositis-scleroderma antibody, Anti-ribonucleoprotein: Anti-ribonucleoprotein antibody, Anti-Ro (SS-A): Anti-Sjogren syndrome A antigen antibody, Anti-Smith: Anti-Smith antibody, Anti-topoisomerase(Scl-70): Anti-DNA topoisomerase antibody, Anti-tRNA synthetase: anti-tRNA synthetase antibodies, HRCT: High-resolution computed tomography, LIP: Lymphoid interstitial pneumonia, NSIP: Nonspecific interstitial pneumonia, OP: Organizing pneumonia, PFT: Pulmonary function tests

hypothyroidism, gastroesophageal reflux (GER), diabetes mellitus, coronary artery disease (CAD), and tobacco use. Information regarding drug usage such as immunosuppressant drugs and anticancer drugs, and history regarding environmental and occupational exposure were recorded. Physical signs such as clubbing and crackles and autoimmune features such as rash and joint pains, Raynaud's phenomenon, telangiectasia, and Gottron's patches were recorded in the clinical domain of IPAF classification. Serologic autoantibody testing was performed for all the patients.

Laboratory studies included antinuclear antibody (ANA) with immunofluorescence pattern and titers, rheumatoid factors (RF) (considered significant if titers ≥ 2 × upper limit of normal), cyclic citrullinated protein antibody, myositis-specific antibodies, anti-Ro/anti-Sjögren's-syndrome-related antigen A antibody, anti-La/SSB antibody, anti-ribonucleoprotein antibody, anti-Smith antibody, and anti-Scl-70 antibody. All the serological studies were reviewed with the expert microbiologist. Any value above the upper limit of normal was considered a positive serology for all the serologic antibodies other than ANA and RF.

For the morphologic domain, chest computed tomography (CT) images were reviewed by an expert thoracic radiologist and defined by patterns (NSIP, usual interstitial pneumonia [UIP], organizing pneumonia [OP], NSIP/OP, LIP, and others), as per the international recommendations. High-resolution CT (HRCT) findings such as bilateral basal reticulation with traction bronchiectasis, peribronchovascular pattern with subpleural sparing, and associated ground-glass attenuation are defined as NSIP. HRCT findings suggestive of OP are defined as bilateral, basal, and subpleural areas of patchy peribronchovascular consolidation. NSIP with OP is characterized as bilateral basal predominant consolidation, often peridiaphragmatic, associated with features of fibrosis (e.g. traction bronchiectasis, reticular abnormality, or lower lobe volume loss). Predominant peribronchovascular cysts, with or without ground-glass opacities, or reticular abnormalities are suggestive of LIP. Thus, to be diagnosed as IPAF, a patient with a UIP pattern on HRCT would need to have at least one feature from the other two domains (a clinical feature or a serologic feature) or another morphologic feature.[1]

Pulmonary function tests (PFT) were performed routinely in the evaluation of ILD. While assessing morphologic domain, intrinsic airway disease was noted when FEV1/forced vital capacity (FVC) was <70% or when mosaic attenuation was seen on HRCT. Pulmonary vasculopathy was determined by findings of pulmonary arterial hypertension on two-dimensional echocardiography.

Pericardial disease was determined by either echocardiographic or HRCT findings, and pleural disease was based on HRCT findings of pleural inflammation, thickening, or effusion.[1] Those who fulfilled diagnostic criteria of IPAF among all patients with ILD were included in the present study. In this study, we excluded patients with environmental exposure and other known cause of ILD such as sarcoidosis, hypersensitive pneumonitis, drug-induced ILD, and CTD-ILD. The demographic data, pulmonary and extrapulmonary manifestations, common radiological patterns in HRCT chest, and common autoantibodies associated with them were analyzed using SPSS software (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp).

Results

The 30 patients who fulfilled classification criteria for IPAF are described in Table 2. All presented to our center for evaluation of their underlying ILD. Majority were females and nonsmokers who presented in their sixth decade. Of the 30 patients, 26 (86.67%) were females (female-to-male ratio of 6.5:1). The mean age of patients in the study was 52.5 ± 14.5 years, with the youngest patient being 18 years and the oldest being 75 years. In the present study, all male patients were smokers and none had occupational exposures.

The most common comorbidities observed were hypertension, diabetes, and hypothyroidism seen in nine patients each. In the present study, the most common clinical presentation was arthritis with morning stiffness which accounts for 20 (66.67%), followed by Raynaud's phenomenon in 5 (16.67%). Digital edema was the least common presenting feature accounting for 1 (3.33%) [Table 3].

Among the serological domain, ANA (1:320) positivity was the most common serological finding followed by immunoglobulin M RF (≥2 times) [Figure 1]. Among ANA-positive patients, the most common patterns identified were homogeneous accounting for 9 (50%), followed by a speckled pattern in 6 (33.3%). Cytoplasmic, nucleolar, homogeneous, and speckled patterns were seen in 5.55% each. NSIP pattern was the most common morphological pattern on HRCT accounting for 20 (66.67%), followed by organizing pneumonia 5 (16.67%) [Figure 2].

Among three domains, serological domain was seen in 26 (86.6%), followed by clinical domain in 25 (83.34%) and morphological domain in 27 (90%) patients. Fourteen patients (14 [46.6%]) satisfied all three domains in our study.

Table 2: The clinical and autoantibody profile and radiological imaging patterns of all 30 patients with "interstitial pneumonia with autoimmune features" in our study

Classification criteria	IPAF patient's, *n* (%)
Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) and	30 (100)
Exclusion of alternative etiologies and	30 (100)
Does not meet criteria of a defined CTD and	30 (100)
At least one (1) feature from at least two (2) of these domains:	30 (100)
Clinical domain (each 1 point)	
Distal digital fissuring (i.e. 'mechanic hands')	4 (13.33)
Distal digital tip ulceration	5 (16.67)
Inflammatory arthritis or polyarticular morning joint stiffness > 60 min	20 (66.67)
Palmar telangiectasia	0 (0)
Raynaud's phenomenon	5 (16.67)
Unexplained digital edema	1 (3.33)
Unexplained fixed rash on the digital extensor surfaces (i.e., "Gottron's sign")	5 (16.67)
Serologic domain (each 1 point)	
ANA, either diffuse, speckled, or homogeneous patterns at >1:320 titer or ANA nucleolar pattern or centromere pattern at any titer	18 (60)
RF >2 X upper limit of normal	15 (50)
Anti-CCP	1 (3.33)
Anti-dsDNA	1 (3.33)
Anti-Ro (SS-A)	2 (6.66)
Anti-La (SS-B)	0 (0)
Anti Jo-1	1 (3.33)
Anti-ribonucleoprotein (Sm RNP)	1 (3.33)
Anti-topoisomerase (Scl-70)	2 (6.66)
Anti PL 7, 12, PM Scl, MDA 5	0 (0)
Morphologic domain	
Suggestive radiology patterns by HRCT	
NSIP	20 (66.67)
OP	5 (16.67)
NSIP with OP overlap	0 (0)
LIP	1 (3.33)
Histopathology patterns or features by surgical lung biopsy	ND
Unexplained multi-compartment involvement	
Pleural effusion or thickening	0 (0)
Pericardial effusion or thickening	0 (0)
Intrinsic airways disease	0 (0)
Pulmonary vasculopathy	14 (46.60)

ANA: Antinuclear antibody, Anti-CCP: Anti-cyclic citrullinated peptide antibody, Anti dsDNA: Anti–double-stranded DNA antibody, Anti-LA (SS-B): Anti–Sjogren syndrome B antigen antibody, Anti–MDA-5: Anti–melanoma differentiation-associated gene 5 antibody, Anti–PM-Scl: Anti–polymyositis-scleroderma antibody, Anti-ribonucleoprotein: Anti-ribonucleoprotein antibody, Anti-Ro (SS-A): Anti-Sjogren syndrome A antigen antibody, Anti-Smith: Anti-Smith antibody, Anti-topoisomerase(Scl-70): Anti-DNA topoisomerase antibody, Anti–tRNA synthetase: Anti-tRNA synthetase antibodies, HRCT: High-resolution computed tomography, LIP: Lymphoid interstitial pneumonia, NSIP: Nonspecific interstitial pneumonia, OP: Organizing pneumonia, PFT: Pulmonary function testing, ND: Not done, CTD: Connective tissue disease

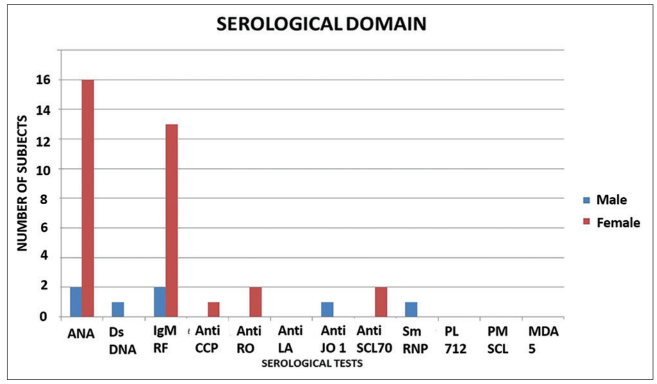

Figure 1: Autoantibody profile, gender distribution and frequency

Serological and morphological domain was satisfied in 7 (23.3%) patients, followed by clinical and morphological domain in 5 (16.6%) patients and 4 (13.3%) patients satisfied both clinical and serological domains. Of the 30 IPAF patients, 14 (46.6%) patients had PAH. Almost all patients had restrictive ventilatory abnormality on lung function testing. Average forced vital capacity in the study population was 68.9%.

Discussion

The present study reports our clinical experience of a cohort of patients with IPAF. This study was conducted with the aim to fill in the gaps in the knowledge regarding clinical features, radiological patterns, and autoantibodies associated with patients with IPAF in the Indian population. Most patients had clinical and/or serologic features suggestive of underlying CTD, but none met classification criteria for any of the defined CTDs. None of the patients in our cohort did evolve into a well-defined CTD, during the period of 2 years.

The important observations made from our study were that majority of our patients were female, emphasizing that IPAF is more common in female patients. It is very important to rule out an autoimmune cause of ILD in all ILD patients, even if it is not associated with clearly defined CTD. Most of the patients were diagnosed as obstructive airway disease, IPF, or pulmonary tuberculosis before presenting to our center. It showed limited awareness about the disease among community and treating physicians. The most common clinical symptom among clinical domain was arthritis with morning stiffness. Most of our patients had NSIP pattern with significant ground-glass haziness on HRCT chest, indicating ongoing inflammation. Fibrotic NSIP or UIP pattern seen may represent long-standing disease. The most common autoimmune profile was ANA, which was positive in 60%, followed by rheumatoid arthritis factor in 50% of the patients. Studies of IPAF with their respective main findings are described in Table 4.

Nearly 91% had shortness of breath, while cough was present in nearly all patients (96.4%). Anemia and clubbing were the most common general physical examination findings. General symptoms suggestive of rheumatological flavor such as joint pains, myalgias, gastroesophageal reflux disease, and fever were also commonly reported. Most of the patients in our study group had NSIP (67%) as a major pattern in HRCT chest among the morphological domain. All patients (100%) had received some treatments prior to evaluation at our center, majority being given inhalational therapy (77.8%).

Table 3: Clinical domain, gender distribution, and frequency

Most common clinical domain				
Cinical presentation	Male	Female	Total	Percentage
Digital fissure (mechanic hands)	0	4	4	13.33
Digital tip ulcer	0	5	5	16.66
Arthritis	3	17	20	66.67
Telangiectasia	0	0	0	0.00
Raynaud's phenomenon	0	5	5	16.67
Digital edema	1	0	1	3.33
Rash (Gottron's sign)	0	5	5	16.67
Others*	0	8	8	26.67

*General symptoms suggestive of rheumatological flavor like myalgias, dryness of mouth, GERD, fever, constitutional symptoms in 26% of study population.

When coming to the overall distribution of domains in our study, morphological domain was seen in 27 patients, serological in 26, and clinical domain in 25 patients. For satisfying IPAF criteria according to ATS/ERS, in our study, 14 (46.6%) patients fulfilled all the three domains, 7 (23.3%) fulfilled serological and morphological domains, 5 (16.6%) fulfilled clinical and morphological domains, and 4 (13.3%) fulfilled clinical and serological domains. Oldham *et al*.[6] in their series observed that 21 (14.6%) patients met IPAF criteria through a combination of clinical and serological domains, 12 (8.3%) by clinical and morphological domains,

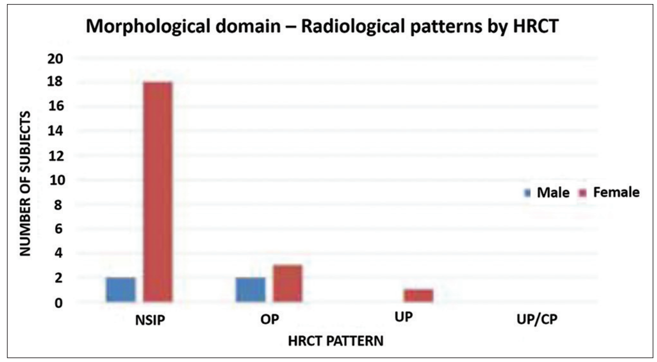

Figure 2: Morphological domain, gender distribution and frequency

Table 4: Studies of interstitial pneumonia with autoimmune features with their respective main findings

Authors/year of publication	Number of subjects (*n*)	Mean age (years)	Sex, *n* (%)	Clinical domain (%)	Serologic domain (%)	Morphologic domain
Oldham *et al*, 2016[6]	144	63.2±11	Female, 75 (52)	Raynaud phenomenon (27.8) followed by inflammatory arthritis(17.4) and mechanic hands (10.4)	ANA (77.6), anti RO (16.6), RF (13.0)	UIP (54.6% on HRCT and 73.5% by SLB), NSIP (31.9% on HRCT and 22.9% by SLB)
Chartrand *et al*, 2016[7]	56	54.6±10.3	Female, 40 (71.4)	Raynaud phenomenon (39), mechanic hands (28.6)	ANA (48), Anti RO (42.9), Anti-tRNA synthetase (35.7)	NSIP (57.1% on HRCT and 23% by SLB), Interstitial lymphoid aggregates with germinal centres (23% by SLB)
Ferri *et al*, 2016[8]	35	63±12	Female, 24 (69)	Raynaud phenomenon (66.7), arthralgias (66.7)	ANA (81.3), RF (14.3)	NA
Sharma *et al*, 2016[9]	28	56.9±12.2	Female, (86)	Joint pains (46%), Dry eyes/mouth (32%)	ANA and RF (40.0), anti Ro (21.2%)	UIP (35.7% on HRCT), NSIP (32% on HRCT, 66% by SLB)
Collins *et al*, 2017[10]	15	54.6±11.8	Male, 8 (53)	NA	NA	HRCT/histopathology: UIP (33%), NSIP (27%) and unclassifiable fibrosis/other pattern (40%)
Ahmad *et al*, 2017[11]	57	64.4±14	Male, 29 (50.9)	Raynaud phenomenon (74.1), inflammatory arthritis (48)	ANA (82.4), Anti-tRNA synthetase (17) Anti RO (9.4)	NSIP (42.1% on HRCT and 8.8% by SLB), NSIP with OP overlap (15.8% on HRCT)
Lim *et al*, 2019[12]	54	67.9±10.5	Female, 35(64)	Inflammatory arthritis (76.5), Raynaud phenomenon and Unexplained digital edema (17.6)	ANA (63.3), RF (28.6)	NSIP (87.2 % on HRCT), Interstitial lymphoid aggregates with germinal centres (41.7% by SLB), OP (33.3% by SLB)
Present study	30	52.5±14.5	Female, 26 (86.6)	Inflammatory arthritis (66.7), raynaud phenomenon and Digital ulcers (16.67)	ANA (60.0) RF (50)	NSIP (66.7% on HRCT) OP (16.67% on HRCT) UIP (10% on HRCT)

ANA: Antinuclear antibody, RF: Rheumatoid factor, Anti-Ro (SS-A): Anti-Sjogren syndrome A antigen antibody, HRCT: High-resolution computed tomography, NSIP: Nonspecific interstitial pneumonia, SLB: Surgical lung biopsy, UIP: Usual interstitial pneumonia, OP: Organizing pneumonia, NA: Not available

73 (50.7%) by serological and morphological domains, and 38 (26.4%) by all three domains which is in agreement with our study. A study done by Chartrand *et al*.[7] showed that 29 (52%) patients had at least one feature in each of the three IPAF domains, 21 (37.5%) had at least one feature in both serologic and morphologic domains, 5 (9%) had at least one feature in both clinical and morphologic domains, and 1 (2%) had at least one feature in both clinical and serologic domains.

In our study, pulmonary hypertension is observed in 14 (46%) patients, whereas Ahmad *et al*.[11] observed the same in 22% among 57 IPAF patients in their retrospective study. We did not observe any multicompartment involvement such as unexplained pleural effusions, pericardial effusions, and intrinsic airway disease. Chartrand *et al*.[7] observed pleural effusions in 6 (10.7%) patients, pericardial effusions, intrinsic airway disease, and vasculopathy in 1 (1.8%), 7 (12.5%), and 17 (30.4%), respectively. Ahmad *et al*.[11] also observed multicompartment involvement in the form of pleural effusions, pericardial effusions, intrinsic airway disease, and vasculopathy in 1 (1.8%), 1 (1.8%), 5 (8.8%), and 10 (17.5%), respectively, in their study population.

Pulmonary function tests (PFTs), in our study, revealed a total of 24 (80%) patients having restriction at the time of diagnosis. Normal PFT was observed in 5 (16.66%) patients. Average FVC in our study population was 68.9. Oldham *et al*.[6] observed mean FVC 61 ± 18.3 in their study population. Ahmad *et al*.[11] identified average FVC of 80.2% in their study population.

Diagnosing autoimmune features in a patient with ILD is clinically relevant in terms of long-term prognosis and management.[12,13] Most of the studies in the literature showed that IPAF had a better survival than IPF cohorts, and when compared to CTD-ILD, the survival is not so favorable.[6,14] There seems to be a constructive criticism about IPAF classification that it does not address the limitations of current rheumatologic criteria of CTD. Lack of clarity regarding morphological domain assessment and inclusion of several autoantibodies such as anti-amino-acyl tRNA synthetase which are highly specific for inflammatory myopathy (antisynthetase syndrome) are the most common concerns.[14,15] Inclusion of the lung as the target organ in the current classification of CTD might obviate the need for IPAF, as ILD is often the initial manifestation of CTD.[14] Furthermore, there is little evidence in current literature about what exact proportion of IPAF patients convert into well-established CTD. Two single-center studies suggested that 10% of patients with UIP and 17% of patients with NSIP on surgical lung biopsy ultimately developed CTD.[16,17] However, in a study by Chartrand *et al*.,[7] none of the patients in their IPAF cohort developed CTD during a 5-year follow-up period.

The clinical features of IPAF are varied and a lot of heterogeneities are seen due to potential selection bias in the studies.[15] In a recent systematic review and meta-analysis by Kamiya and Panlaqui,[18] age, male gender, smoking, UIP pattern (radiological/pathological), FVC%, and percentage of predicted diffusing capacity of the lung for carbon monoxide were identified as prognostic indicators for all-cause mortality of IPAF. However, in multivariate analysis, the age was associated with worse all-cause mortality of IPAF.[18]

A study by Lim *et al*.[12] showed that the IPAF group had better overall survival with less exacerbations and a longer time to first exacerbations when compared to the IPF group. A study by Yoshimura *et al*.[19] also confirmed the same. However, studies by Ahmad *et al*.[11] and Oldham and Danoff[14] revealed that there was no statistically significant difference in the all-cause mortality between the two entities. It was observed that the larger number of cases with UIP pattern on HRCT (29.6% and 54.6%) was included in their studies. The prognosis of IPAF when compared to IPF/CTD-ILD seemed to be dependent on the proportion of cases of UIP pattern (radiological/pathological) included in the studies.[18] It was observed that the prognosis of IPAF was better when a small proportion of UIP pattern was present. As the UIP pattern is associated with worse clinical outcomes, it was presumed to influence the long-term prognosis of IPAF.[18]

In our study, morphological domain was satisfied in 27 patients (90%) followed by serological (86%) and clinical domains (83%). A study by Yoshimura *et al*.[19] also showed the same, whereas studies by Oldham and Danoff,[14] Ahmad *et al*.,[11] and Chartrand *et al*.[7] showed a high prevalence of clinical and serological domains. While the presence of multicompartment features was associated with poor outcome, clinical and serological domains were associated with decreased mortality risk.[20]

The treatment strategy in the IPAF population is still unclear, as most of the proposed strategies are extrapolated from CTD-ILD studies.[15] Should we treat IPAF, similar to IPF with pirfenidone or with immunosuppressive drugs used in CTD? The question still remains unclear. Randomized controlled studies are needed to explore the treatment strategies, whether antifibrotics or immunosuppressive agents and their combination are efficacious. Recently, nintedanib, a tyrosine kinase inhibitor with antifibrotic properties, and pirfenidone, another antifibrotic drug used in IPF, were included in the clinical trials and the results are awaited.[20] Hence, it is imperative to identify the clinical, autoimmune, and imaging phenotypes to predict the outcomes and to plan treatment. Further research is still needed to clarify whether IPAF is a distinct clinical entity with lung involvement as a primary manifestation or a clinical entity which can evolve into a well-defined CTD-ILD.[15]

The major limitation of this study was a small sample size and also referral bias. Cases referred to our center are probably more chronic, and there was a significant delay in presenting to us. Histopathological data were not obtained, as the patients did not give consent for a surgical lung biopsy. The primary clinicians and radiologists were confident of the patterns observed clinically and radiologically, and there was no clinicoradiological discordance or atypical HRCT patterns. No deaths were observed during the study period, and there was no conversion to established CTD. Limited follow-up data available in our patients at the time of the analysis hindered our conclusions on the ultimate long-term prognosis of IPAF.

Conclusions

A high female predominance along with distinct imaging and histologic and serological characteristic features are seen in patients with IPAF which differ from those with IIP. Subtle extrathoracic signs and symptoms suggestive of CTD are often seen in patients with a diagnosis of ILD. These features should be systematically evaluated to study the natural history and prognosis of IPAF. More prospective randomized control trials in the near future will address the controversies and limitations of the IPAF cohort. Long-term follow-up of these patients will help us to identify whether or how often they can fully evolve into a given CTD or autoimmune disorder so that a targeted therapeutic strategy can be planned at an early stage in the near future. A multidisciplinary approach involving departments of pulmonology, rheumatology, radiology, and pathology will contribute to better diagnosis and management of these patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, *et al*. An official European Respiratory Society/American Thoracic Society research statement: Interstitial pneumonia with autoimmune features. Eur Respir J 2015;46:976-87.
2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al*. American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis: an Official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018;198: e44-68.
3. Lee CT, Oldham JM. Interstitial pneumonia with autoimmune features: Overview of proposed criteria and recent cohort characterization. Clin Pulm Med 2017;24:191-6.
4. Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. Lancet 2012;380:689-98.
5. Fischer A, West SG, Swigris JJ, Brown KK, du Bois RM. Connective tissue disease-associated interstitial lung disease: A call for clarification. Chest 2010;138:251-6.
6. Oldham JM, Adegunsoye A, Valenzi E, Lee C, Witt L, Chen L, *et al.* Characterization of patients with interstitial pneumonia with autoimmune features, Eur Respir J 2016;47:1622-4.
7. Chartrand S, Lee JS, Swigris JJ, Stanchev L, Fischer A. Clinical characteristics and natural history of autoimmune forms of interstitial lung disease: A single-center experience. Lung 2019;197:709-13.
8. Ferri C, Manfredi A, Sebastiani M, Colaci M, Giuggioli D, Vacchi C, *et al*. Interstitial pneumonia with autoimmune features and undifferentiated connective tissue disease: Our interdisciplinary rheumatology-pneumology experience, and review of the literature. Autoimmun Rev 2016;15:61-70.
9. Sharma R, Talwar D, Tuteja M. Clinico-radiological and autoimmune profile correlation in patients with autoimmune featured interstitial lung disease (AIFILD): An observational study in Indian scenario. Chest 2016;149:A456.
10. Collins BF, Spiekerman CF, Shaw MA, Ho LA, Hayes J, Spada CA, *et al*. Idiopathic interstitial pneumonia associated with autoantibodies: A large case series followed over 1 Year. Chest 2017;152:103-12.
11. Ahmad K, Barba T, Gamondes D, Ginoux M, Khouatra C, Spagnolo P, *et al*. Interstitial pneumonia with autoimmune features: Clinical, radiologic, and histological characteristics and outcome in a series of 57 patients. Respir Med 2017;123:56-62.
12. Lim JU, Gil BM, Kang HS, Oh J, Kim YH, Kwon SS. Interstitial pneumonia with autoimmune features show better survival and less exacerbations compared to idiopathic pulmonary fibrosis. BMC Pulm Med 2019;19:120.
13. Hu Y, Wang LS, Wei YR, Du SS, Du YK, He X, *et al*. Clinical characteristics of connective tissue disease-associated interstitial lung disease in 1,044 Chinese patients. Chest 2016;149:201-8.
14. Oldham JM, Danoff SK. COUNTERPOINT: Does interstitial pneumonia with autoimmune features represent a distinct class of patients with idiopathic interstitial pneumonia? No. Chest 2019;155:260-3.
15. Graney BA, Fischer A. Interstitial pneumonia with autoimmune features. Ann Am Thorac Soc 2019;16:525-33.
16. Kono M, Nakamura Y, Enomoto N, Hashimoto D, Fujisawa T, Inui N, *et al*. Usual interstitial pneumonia preceding collagen vascular disease: A retrospective case control study of patients initially diagnosed with idiopathic pulmonary fibrosis. PLoS One 2014;9:e94775.
17. Kono M, Nakamura Y, Yoshimura K, Enomoto Y, Oyama Y, Hozumi H, *et al*. Nonspecific interstitial pneumonia preceding diagnosis of collagen vascular disease. Respir Med 2016;117:40-7.
18. Kamiya H, Panlaqui OM. Systematic review and meta-analysis of the prognosis and prognostic factors of interstitial pneumonia with autoimmune features. BMJ Open 2019;9:e031444.
19. Yoshimura K, Kono M, Enomoto Y, Nishimoto K, Oyama Y, Yasui H, *et al*. Distinctive characteristics and prognostic significance of interstitial pneumonia with autoimmune features in patients with chronic fibrosing interstitial pneumonia. Respir Med 2018;137:167-75.
20. Fernandes L, Nasser M, Ahmad K, Cottin V. Interstitial pneumonia with autoimmune features (IPAF). Front Med (Lausanne) 2019;6:209.