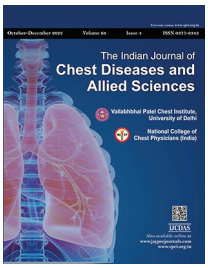
ORIGINAL ARTICLE

Effect on the Prevalence of Various Diffuse Parenchymal Lung Diseases due to Paradigm Change in the Guidelines



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Abstract

Background: Diffuse parenchymal lung diseases (DPLDs) have gone through various changes in nomenclature and classification since they were first described in 1868. Increasing knowledge about their etiopathogenesis has since led to several reclassifications and changes in the nomenclature. This has had a major impact on the prevalence of each interstitial lung disease (ILD) reported by the different registries worldwide. In this study, we attempted to describe the distribution of the different DPLDs in our population and reported changes in prevalence due to changing diagnostic criteria for the disease.

Materials and methods: We analyzed retrospective data of 434 patients. For the initial 75 patients, ATS/ERS guidelines published in 2002 were followed in the diagnosis of the ILD (group I). In the later part of the study (359 patients), the diagnosis was based on the computed tomography (CT) patterns defined by ATS/ERS/JPS/ALAT statement on diagnosis of idiopathic pulmonary fibrosis (IPF) and updated 2013 ATS/ERS guidelines (group II).

Results: Of the 75 patients in group I, IPF was the most common diagnosis (52%) made at that time, followed by sarcoidosis and connective tissue-related ILD (CTD-ILD) with 12% each. Group II had 359 patients, with IPF again being the most commonly diagnosed ILD with 21.3%. This was followed by CTD-ILD (18.6%), sarcoid (14.7%), and idiopathic nonspecific interstitial pneumonitis (iNSIP; 13.3%). The changing guidelines have an impact on reporting of different DPLD by our multidisciplinary teamover a period of time. Though IPF was the most commonest DPLD reported among both the groups, the diagnosis of IPF had fallen by more than half in the second group. It was paralleled by an increase in the diagnosis of iNSIP and chronic hypersensitivity pneumonitis. These reported changes in the prevalence of DPLDs may reflect the better-defined criteria in the latest guidelines and a better understanding of the fibrotic ILDs other than IPF by the multidisciplinary team.

Conclusions: The frequency of diagnosis of the different DPLDs has changed, following the publication of several guidelines in the last decade. It has recognized newer entities with greater clarity, such as idiopathic NSIP and interstitial pneumonia with autoimmune features.

Keywords: Diffuse parenchymal lung diseases, Interstitial lung disease, Idiopathic pulmonary fibrosis, Interstitial pneumonitis, Multidisciplinary team.

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Abbreviations used in this Article

DPLDs = Diffuse parenchymal lung diseases; ILD = Interstitial lung diseases; IPF = Idiopathic pulmonary fibrosis; CTD-ILD = Connective tissue-related ILD; iNSIP = Idiopathic nonspecific interstitial pneumonitis; IGRA = Interferon Gamma Release Assay; MDT = Multidisciplinary team; IPAF = Interstitial pneumonia with autoimmune feature; CT = Computed tomography.

Introduction

The interstitial lung diseases, also termed as DPLDs have gone through various changes in nomenclature and classification since they were first described in 1868.[1] Terms like desquamative interstitial pneumonia,[2] Cirrhosis cystica pulmonum,[3] and lymphangitis reticularis pulmonum[4] were used till Liebow and Carrington grouped these disorders under ILDs or DPLDs in 1969.[5] Increasing knowledge about their etiopathogenesis has since led to several reclassifications and changes in the nomenclature. Reclassification has also involved redefining the diagnostic criteria.

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The major definitions of diagnostic criteria were in 2002 and 2011, with updates in 2013, 2015, and 2018.[6–9] Not unexpectedly, this has had a major impact on the prevalence of each ILD reported by the different registries worldwide. In this study, we attempted to describe the distribution of different DPLDs in our population at a tertiary care center in South India, and to understand the reported changes in prevalence due to changing diagnostic criteria for the disease.

Materials and Methods

Data of 434 patients were collected retrospectively in two phases over a period of 10 years (January 2010–March 2020) at our tertiary care center. The was approved by the Institutional Review Board and Ethics Committee of Narayana Hrudayalaya, Bengaluru. A standardized clinical proforma was used for the data collection, which included details of symptoms and signs, tobacco use, family history, and exposure to known causes of DPLD including occupational agents, drugs, and organic dusts including animals and plants.

Spirometry and the 6-minute walk test were done on all who could perform the tests, and diffusion studies in a few cases. Connective tissue workup was done to rule out autoimmunity. Serum angiotensin-converting enzyme levels, Mantoux test, and/or an Interferon Gamma Release Assay (IGRA) were done when there was a suspicion of sarcoidosis and/or to rule out tuberculosis. Chest X-ray and high-resolution computed tomography were done in all patients.

Each case was discussed in a multidisciplinary team (MDT) meeting before they were offered any intervention, either diagnostic or therapeutic. The MDT consisted of at least one pulmonologist and one radiologist, though there were usually at least 2 radiologists and 4–6 pulmonologists. A rheumatologist formed part of the MDT during the discussion of suspected CTD-ILD and a pathologist when a biopsy had been obtained. A thoracic surgeon was invited when a surgical/VATS lung biopsy was needed. The team of pulmonary physicians included at least one lung transplant specialist.

For the diagnosis of ILD in the initial 74 cases (group I; January 2010 to December 2012), ATS/ERS guidelines published in 2002 were followed. The later 359 cases (group II; January 2016 and March 2020), the diagnosis of IPF was based on the CT patterns defined by ATS/ERS/JPS/ALAT statement on diagnosis of IPF,[7] which was included in the subsequent guidelines by ATS/ERS in 2013.[8] Unfortunately, we did not have the complete data of the patients between January 2013 and December 2015, hence no patients were included in the study during this time period for the analysis.

A diagnosis of sarcoidosis was confirmed by histopathology or cytopathology, with transbronchial needle aspiration of mediastinal nodes (conventional TBNA earlier, EBUS TBNA later) with or without transbronchial lung biopsy in most of the cases. If endobronchial irregularity or nodularity was seen during the bronchoscopic procedure, then bronchial mucosal biopsy was also done.

Connective tissue diseases-associated ILDs were diagnosed based on a defined CTD (based on clinical history and findings, with a positive autoimmune profile) and associated CT findings of ILD. The diagnosis of interstitial pneumonia with autoimmune features (IPAF) was added in group II based on the ATS/ERS definition in 2015.[10]

The pre- and post-biopsy MDT concordance in our study was defined as the percentage of histopathological diagnoses which truly correlated with the pre-biopsy clinico-radiological MDT diagnosis.

Table 1: Proportion of different patterns of diffuse parenchymal lung diseases (DPLD) in both the groups

ILD diagnosis	*Group I n (%)*	*Group II n (%)*
IPF	39 (52%)	77 (21.4%)
CT-ILD	12 (16%)	67 (18.6%)
Sarcoid	12 (16%)	53 (14.7%)
HP	5 (7%)	44 (12.2%)
iNSIP	3 (4%)	48 (13.3%)
COP	2 (2.6%)	21 (5.8%)
CPFE	0	18 (5.0%)
Unclassifiable	0	14 (3.8%)
Others	2 (2.6%)	17 (4.7%)
Total	75	359

COP, cryptogenic organizing pneumonia; CPFE, combined pulmonary fibrosis and emphysema; CT-ILD, connective tissue disease-related; HP, hypersensitivity pneumonitis; iNSIP, idiopathic nonspecific interstitial pneumonitis; IPF, idiopathic pulmonary fibrosis

Results

A total of 434 patients were studied. The median age of this population was 53 years (mean 56.6 ± 13.6 years). Of them, 130 patients were in the age group of 50–59 years, and 116 patients were aged between 60 and 69 years. More than half of the population (56.6%) in our study belonged to the age group between 50 and 69 years. The distribution of age (58.4 ± 12.2 vs 57.4 ± 13.6 years; $p = 0.556$) and gender (male/female, 38/37 vs 190/169; $p = 0.799$) were comparable between group I ($n = 75$) and group II ($n = 359$).

Based on the clinical and radiological picture, the diagnosis of the type of ILD was reached by consensus at the MDT meeting (Table 1). Of the 75 patients, in group I, IPF was the most common diagnosis (52%) made at that time, followed by sarcoidosis and CTD-ILD with 12% each. Biopsy was done in 16 patients (21.3%) as histopathological confirmation was felt necessary only in these 21.3% patients. The yield was positive in 14 patients. Two samples were inadequate for any diagnosis. The diagnosis was concordant with the MDT diagnosis in 12 patients. In two cases, the biopsy result was different from the earlier MDT diagnosis. Hence the concordance of diagnosis was seen in 75% (12 out of 16) of the patients. Treatment decision was changed by the biopsy in only 2 cases (2.6%). Group II had 359 patients, with IPF again being the most commonly diagnosed ILD with 21.4%. This was followed by CTD-ILD (18.6%), sarcoid (14.7%), and iNSIP (13.3%).

A unanimous MDT diagnosis by consensus was achieved in 273 (76%) patients. Histopathological confirmation was advised only in 86 (24%) patients. A definite histopathological diagnosis was reached in 76 patients (88.3%; 76 out of 86). Ten samples were considered inadequate for diagnosis. The tissue diagnosis was concordant with the prior MDT diagnosis in 70 out of 76 patients, 6 patients had a change in the prior MDT diagnosis after biopsy. Hence the MDT decision was changed in the diagnosis for only 6 (1.6%) cases. When the MDT recommended for histopathological

Table 2: Types of sampling methods used in the groups

Sampling method	*Group I (n = 16)*	*Group II (n = 86)*
Conventional TBLB	5	2
Conventional TBNA	8	28
Surgical lung biopsy	1	4
Cryobiopsy	0	42
Combined TBNA + Cryobiopsy	2	10

TBLB, transbronchial lung biopsy; TBNA, transbronchial needle aspiration

Table 3: Number of samplings in each pattern and their concordance with MDT

	Group I		*Group II*	
ILD type	*Samplings (n)*	*Concordance n (%)*	*Samplings (n)*	*Concordance (%)*
Sarcoid	8	7 (87.5)	49	43 (87.7)
IPF	4	2 (50)	0	0
NSIP	2	1 (50)	13	7 (53.8)
HP	1	1 (100)	9	7 (77.8)
COP	1	1 (100)	3	2 (66.7)
CTD-ILD	0	0	8	7 (87.5)
Others	0	0	4	4 (100)
Total	16	12 (75)	86	70 (81.4)

MDT, multidisciplinary team; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; HP, hypersensitivity pneumonitis; CTD-ILD, connective tissue disease-related ILD; COP, cryptogenic organizing pneumonia; NSIP, nonspecific interstitial pneumonitis

confirmation, it was subsequently concordant with the biopsy in 70 of 86 patients biopsied (81.4%) (Table 2). The overall concordance for group I was 75%, with sarcoid having the best concordance and IPF having the least concordance (Table 3). The overall concordance for group II was 81.4% with the highest for sarcoid and least for iNSIP.

When we combined the groups, histopathological confirmation was felt necessary in only 23.5% (102 out of 434) of the cases, with the remaining 332 (76.5%) patients, diagnosis was achieved unanimously by the MDT. The yield of the biopsy was 88.2% (90 out of 102) and overall concordance with the MDT diagnosis was 80.4% (70 out of 86). Effectively a biopsy changed the diagnosis in only 1.8% (8 out of 434) overall in the entire cohort.

Discussion

The increasing clarity and objectivity in the clinico-radiological criteria for the diagnosis of the various DPLDs have guided the MDTs in reaching the diagnosis with greater accuracy.[7] The changing guidelines have an impact on reporting of different DPLDs by our MDT over a period of time. Though IPF was the commonest DPLD reported among both the groups (52% in group I and 21.4% in group II), the diagnosis of IPF had fallen by more than half in the second group.

A similar observation was seen in the Italian registries, where IPF was reported as the most common ILD initially with 43.2% and later the percentage of IPF was reported to fall significantly to 27.4%.[11,12] Schweisfurth from Germany also reported that IPF with 39.2% was the leading cause for ILD in their country initially, later the percentage of IPF was reported to decrease marginally.[13,14]

Table 4: Comparison of previously published studies from the Indian subcontinent on diffuse parenchymal lung diseases with our study

Author	*Year*	*Study population*	*Percentage of IPF*
Present study	2020	434 patients with DPLD	26.7%
Dhooria et al.[21]	2018	803 patients with ILD	21.2%
Singh et al.[22]	2017	1082 patients with ILD	13.7%
Kumar et al.[23]	2014	289 patients with DPLD	27.7%
Kundu et al.[24]	2014	92 patients with DPLD	38%
Sen and Udwadia[25]	2010	274 patients with DPLD	43%
Jindal et al.[26]	1997	61 patients with DPLD	46%

IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; DPLD, diffuse parenchymal lung diseases

Studies published in the subcontinent initially showed a high prevalence of IPF. Whereas the trend was similar to other registries in the later studies, which reported a significant decline in the prevalence of IPF (Table 4).

The decrease in IPF diagnoses in our population was paralleled by an increase in the diagnosis of the non-IPF fibrotic ILDs between the two phases of the study. Idiopathic NSIP diagnosis increased from 4% to 13.3%, chronic hypersensitivity pneumonitis from 7% to 12.2%, and cryptogenic organizing pneumonia from 2% to 5.8%. Idiopathic NSIP was made a "distinct entity" in 2013 guidelines which was considered provisional in earlier guidelines.[8] Since then, radiologists and clinicians have been made more aware of this entity and hence a greater number of iNSIPs were confidently diagnosed. Guidelines also incorporated the criteria for chronic hypersensitivity pneumonitis in 2013 with definite clinical, radiological, and histopathological patterns.[8] Hence this could have affected the sharp increase in the rate of the diagnosis of HP in our study. Conditions like sarcoidosis which always had a fairly clear diagnostic CT appearance were reported with nearly the same frequency (16% in group I and 14.7% of patients in group II).

Connective tissue diseases-associated ILD which has definite clinical features and immunological tests to confirm the diagnosis also did not differ between the two groups significantly. However, inclusion of IPAF under the umbrella of CTD-ILD[10] led to marginal increase in the reporting of CTD-ILD in group II (16% in group I and 18.6% in group II). These reported changes in the prevalence of DPLDs may reflect the better-defined criteria in the latest guidelines and a better understanding of the fibrotic ILDs other than IPF by the MDT.

The advances were seen even on the histopathological front, in terms of better biopsy techniques as well as a better understanding of various patterns. Cryobiopsy which is shown to have a better yield, with a larger, representative sample and similar safety outcomes compared to forceps biopsy[15,16] was incorporated into our practice in the later group of patients. In spite the addition of cryobiopsy, the requirement of histological confirmation did not change between the two groups in our patients. In our cohort, we noticed that the biopsy was advised only in 23.9% of patients in group II and 21.3% of patients in group I. Also, cryobiopsy changed the diagnosis only in 1.6% of patients in group II, which was not

significantly different from group I (2.6%) where flexible forceps biopsy was done.

The results from our study suggests that strict adherence to the changing guidelines by MDT has changed the trend of diagnosis of DPLD more than just the change in the intervention techniques. Worldwide, MDT diagnoses have been shown to have high reliability.[17–19] It is increasingly being accepted that a biopsy should only be considered in patients with probable or indeterminate radiological patterns for UIP. Histological evaluation, due to its limited reliability and intrinsic risks particularly in elderly or highly comorbid patients is being replaced by the MDT discussion.[20]

Our study had obvious limitations. The MDT diagnosis with unanimity was accepted as the correct diagnosis. Only when an unanimity in diagnosis could not be reached, a biopsy was advised.

Conclusions

The frequency of diagnosis of the different DPLDs has changed, following the publication of several guidelines in the last decade. It has offered more objectivity in the diagnostic criteria, as well as recognized newer entities with greater clarity such as idiopathic NSIP and IPAF. This has implications for: (i) citing the findings of older registries, (ii) the interpretation of studies prior to these new guidelines and for management decisions based on older studies, and (iii) planning for the use of resources based on older data. The MDT discussion reaches the right diagnosis in more than three-quarters of cases and avoids the need for biopsy in the majority of patients with DPLD. Where a biopsy is performed, the diagnosis changes in only a small minority of cases, a finding of importance given the potential risks in the elderly, those with more advanced diseases and patients with multiple comorbidities.

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