Original Article

Pulmonary Function and Diffusing Capacity of Carbon Monoxide in Hypersensitivity Pneumonitis: An Observational Study of 152 Patients

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Abstract

OBJECTIVE: Hypersensitivity pneumonitis (HP) is an inflammatory and/or fibrotic lung disease. The restrictive lung function with low diffusing capacity of carbon monoxide (DLCO) is common in interstitial lung diseases (ILD). There are limited data on pulmonary function test (PFT) in HP and its role for diagnosis is questionable. We analyzed the data of 152 HP patients for type of defect, lung volume, and DLCO.

MATERIAL AND METHODS: The present study is a retrospective analysis of 152 patients at one of the tertiary chest institutes in India. All diagnosed cases with at least spirometry were included. PFT findings were classified and graded as obstructive, restrictive, and mixed patterns. The correlation of PFT was calculated with disease duration and 6MWT distance.

RESULTS: The majority were female [106 (70%)], with a mean age of 47.8 ± 12.3 years. Spirometry with lung volume data were available for 97% patients. PFT was abnormal in 118 (80%) cases. Among the patterns of abnormality, the most common type was restrictive (74%) followed by mixed (15%) and obstructive (11%) with the majority in the severe to very severe grade. The mean total lung capacity (TLC) and residual volume (RV) were reduced, with the grade more severe when the pattern of abnormality was restrictive while the RV/TLC was higher suggestive of air tapping. DLCO data were available for 132 (87%) cases, with levels decreased in 67%. The severity of DLCO was highest when the pattern of abnormality was restrictive. One of the PFT parameters was abnormal in 137 (90%) cases, with isolated decreased DLCO levels seen in 16 (10%) cases. Forced vital capacity (FVC), TLC, and DLCO showed positive correlation with 6MWT distance (FVC $r = .22$, $P = .02$; TLC $r = .28$, $P = .003$; DLCO $r = .30$, $P = .002$).

CONCLUSION: The PFT abnormality is seen in >80% of HP patients. All types of abnormality were seen, with the restrictive pattern being the most common. Isolated decreased DLCO levels were seen in 10% of cases. We advised to do full PFT for diagnosis and follow-up of HP.

KEYWORDS: Hypersensitivity pneumonitis, lung volumes, spirometry, diffusion capacity, pulmonary function test

INTRODUCTION

Hypersensitivity pneumonitis (HP) is an inflammatory and/or fibrotic lung disease that typically results from an immune-mediated reaction to inhaled antigen in susceptible host.[1] The prevalence of HP varies considerably with geographic location, climatic condition with history of occupational and environmental exposures. As per published data the incidence range 0.3-0.9 per 100 000 in western world.[2,3] There is lack of prevalence study from India however available studies shown HP account for 2.4 to 10.7% of all interstitial lung disease (ILD). As per Indian ILD registry, HP was the most common type of ILD (nearly 47%).[4-7] Till recently there is lack of internationally accepted uniform diagnostic criteria for diagnosis of HP, leads to substantial varies in diagnosis over different region. Recently a Clinical Practice Guideline for diagnosis of HP has been published. The diagnosis is mainly done on basis of exposure to antigen, high-resolution computed tomography (HRCT) finding, bronchoalveolar lavage (BAL) cellular analysis, and lung biopsy findings.[1]

The pulmonary function test (PFT) is a simple, noninvasive test, primarily used to determine the physiologic abnormalities of lung. It is one of the commonly used test for diagnosis and management of ILD. There are limited data on PFT in HP. However the restrictive pattern abnormality with low diffusing capacity of carbon monoxide (DLCO) is the common type.[8-10] The role of PFT in diagnosis of HP is questionable. As the only one of the four proposed diagnostic criteria mentioned restrictive ventilator defect as one of the minor criteria of diagnosis. Similarly the decreased DLCO was also mentioned as minor diagnostic criteria in only 2 criteria.[11-14] Even recent ATS document on HP diagnosis also did not mentioned it.[1,15,16] However, Salisbury et al[16] suggested it for disease monitoring during treatment and follow-up. In the present study, we analyzed the data of PFT in 152 HP patients for type of defect, lung volume, and DLCO.

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MATERIAL AND METHODS

This study was a retrospective analysis of 152 patients, registered in 6 years (2014-2020) at one of the tertiary care chest institute in Delhi, India. The study was done after approval from human ethical committee of V.P. Chest Institute, University of Delhi (Approval No: VPCI/DIR/IHEC/2023/2 258, Date: 2023). At the time of registration, all ILD suspected patients underwent a symptom screening with examination. Investigations including routine hematology/biochemical blood tests, sputum examination, connective tissue serology, 6 minute work test (6MWT), PFT with DLCO, chest x-ray, HRCT chest, and bronchoscopy with BAL and bronchial biopsy whenever required. The detailed data of patients in standardized file were available for all the cases as per hospital protocol. The case files of all diagnosed HP patients were screened for PFT including spirometry, lung volumes, and DLCO with 6MWT findings. All diagnosed HP patients with at least spirometry were included in the analysis. Data were extracted and entered in standard research forms. The written consent was taken from all the participants. Finally we included 152 diagnosed cases of HP, who have at least baseline spirometry report with or without other PFT parameters reports for analysis in the study.

Diagnosis of Hypersensitivity Pneumonitis

The diagnosis of HP was done on the basis of a multidisciplinary approach. Diagnosis of HP was considered when the following criteria were present: (1) Exposure history to an inciting antigen, (2) Respiratory symptoms suggestive of ILD, (3) HRCT suggestive of HP, (4) rule out all other known causes of ILDs, (5) TBLB consistent with HP findings, and (6) BAL lymphocytosis (≥30%).

Exposure History

The exposure history to any inciting agent is consider positive when there is a history of exposure for a minimum of 3-6 months at patient's resident or working place. The history of exposure was considered and taken particularly for birds (pigeon, parrot), hay, molds, and occupational dust.

Pulmonary Function Test

Spirometry and lung volume were conducted on a dry, roll-seal spirometer of the Benchmark design lung function machine (P.K. Morgan, Kent, UK). Full expiratory flow volume curves have been produced as suggested by ATS. Forced expiratory volume in the first second of expiration (FEV_1)/Forced vital capacity (FVC) and total lung capacity (TLC) were taken for assessing the obstructive, restrictive, and mixed patterns. FEV_1 was taken for assessing the severity of impairment of lung function and TLC for restrictive severity. The DLCO was performed by helium dilution method with correction with hemoglobin on same machine. The percentage predicted of corrected DLCO was taken for assessing the capacity of CO diffusion. PFT was interpreted as obstructive when FEV_1/FVC was <0.80 with TLC >80% predicted; restrictive when FEV_1/FVC > 0.80 and TLC <80% predicted and mixed pattern defined as coexistence of both types. The severity of lung impairment grading was done as per standard guideline.[17-19]

Statistical Analysis

The data accrued on all the HP patients was compiled and analysed using Microsoft Office Excel software. Continuous data is presented as mean with standard deviation or median and interquartile range (due to extreme values) and categorical data is presented as number and percentages. Figures are presented as bar diagram, table, and flowchart. The correlation was calculated between PFT parameters and DLCO with duration of disease and 6MWT distance. $P <.05$ is considered as significant.

RESULTS

The majority of cases were female [106 (70%)], with a mean age of 47.8 ± 12.3 years. The most common occupation was housewife in 79 (51%). Most of patients 136 (89%) were nonsmokers. The most common presenting symptoms were breathlessness 146 (96%) and cough 143 (94%) with median duration symptoms of 18 months. The history of exposure to allergen was present in 116 (76.3%) with pigeon is the most common seen in 103 (67.7%) patients. The details of demographic parameters are given in Table 1.

We analyzed the data of 152 patients, who have at least spirometry report. The PFT including spirometry with lung volume was available for 147 (97%) patients. Out of 147 cases the PFT was normal in 29 (20%) and abnormal in 118 (80%) cases. The most common abnormality was restrictive defect in 87 (59%) followed by mixed 18 (12%) and obstructive 13 (9%) with mean FVC of 1.91 ± 0.76 L, FEV1 of 1.61 ± 0.6lts and TLC of 3.32 ± 1.06 L. In the remaining five cases only spirometry report was available. Of that five spirometry showed 2 cases of normal, 2 cases of restrictive, and 1 case of obstructive pattern. The detail of patients with different PFT and DLCO abnormalities is shown in Figure 1. The overall severity of abnormality was mild in 28 (24%), moderate in 21 (18%), moderately severe in 36 (30%), severe in 26 (22%), and very severe in 7 (6%) (Figure 2). The mean predicted TLC was 70.50 ± 18.14. Overall 132 patients able to performed diffusion capacity with mean predicted of 67.7 ± 28.7.

Out of 118 abnormal PFT, all the parameters of spirometry and lung volumes were decrease except FEV1/FVC and residual volume (RV)/TLC ratio. The most common type of abnormality is restrictive type (74%) followed by mixed (15%) and obstructive (11%). The majority of patient 69 (58%) with abnormal PFT had moderately severe to very severe grade

Main Points

- The pulmonary function test abnormality is a common finding in hypersensitivity pneumonitis subtype interstitial lung disease patients, that is, in >80% of cases.

- The commonest type lung function abnormality on spirometry was the restrictive pattern.

- The severity of abnormality grade was moderately severe to very severe in nearly 60% of cases.

- The isolated decrease in diffusing capacity of carbon monoxide (DLCO) with normal spirometry was seen in nearly 10% of cases.

- The forced vital capacity, total lung capacity, and DLCO showed significant positive correlation with 6MWT distance.

Table 1. Demographic Details of Patients at Presentation

Patients Characteristics	Patients (n, %)
Total population	152
Female	106 (70%)
Mean age (years)	47.8 ± 12.3
History of smoking	36 (11%)
Median duration of symptom (years)	18
Occupation	
Housemaker	79 (51%)
Office work	14 (9%)
Shopkeeper	11 (7%)
Symptoms	
Breathlessness	146 (96%)
Cough	143 (94%)
Fever	14 (9%)
Exposure	
Pigeon	103 (68%)
Parrot	4 (2%)
Hay	3 (2%)
Mean 6MWT (m)	324 ± 112

of abnormality. The severity of lung function impairment was highest seen in mixed type followed by restrictive and least in obstructive (Figure 1 and Table 2). The forced expiratory flow $(FEF)_{25\%-75\%}$ was reduced in overall patients with mean predicted percentage of 76.4 ± 41.89%. The impairment of $FEF_{25\%-75\%}$ was highest in mixed followed by obstructive pattern and normal in restrictive pattern (Table 2).

About lung volume values, overall the TLC was reduced with a mean predicted% of 65.69 ± 16.40. The severity of reduced lung volumes was more in restrictive than mixed type. However, it was normal in obstructive pattern with mean percentage of 96.53 ± 14.79. The RV was just below normal range with mean predicted% of 78.93 ± 32.82, it was reduced in restrictive pattern, normal in mixed and increase in obstructive. The RV/TLC was higher suggestive of air tapping with overall mean of 40.96%. It was increased in all types. It was highest in obstructive followed by mixed and least in restrictive (Table 2). The severity of restriction on basis of TLC was mild in 21 (24%) moderate in 25 (29%) and severe in 41 (47%) cases.

The DLCO value was available for 132 (87%) cases. Overall the mean predicted% was 64.66 ± 29.93 and decreased in 89/132 (67%) with normal in remaining 43/132 (33%) cases. The severity of DLCO was mild in 21%, moderate in 30% and severe in 16% cases. Out of 132 patients with DLCO report, the other PFT parameters were normal in 28 (21%) and abnormal in 104 (79%) cases. Sixteen patients with normal PFT had decreased DLCO (Figure 1). The severity of decreased DLCO was again also higher in restrictive pattern. The detail of DLCO severity in different types of spirometry pattern is shown in Figure 3. Overall 6MWT report was available in 119 (77%) patients. The mean distance on 6MWT was 324.5 ± 112.8 m with an oxygen desaturation of >4% seen in 70 (59%) patients. The oxygen desaturation was highest in restrictive pattern and the mean duration of distance was lowest in mixed pattern and highest in obstructive pattern.

One of the PFT parameter was abnormal in 137 (90%) cases of HP subtype ILD patients, i.e., either spirometry, lung volume, or diffusion capacity. Even if both spirometry and lung volume were normal, isolated DLCO was decreased in (16/29) 50% cases (Figure 1). We did the correlation of various PFT parameters and DLCO with duration of disease using Pearson's correlation. All the PFT parameters including DLCO did not showed significant correlation with disease duration. We also did the correlation of various PFT parameters and DLCO with 6MWT distance on Pearson's correlation coefficient. The FVC, TLC, and DLCO data showed statistically
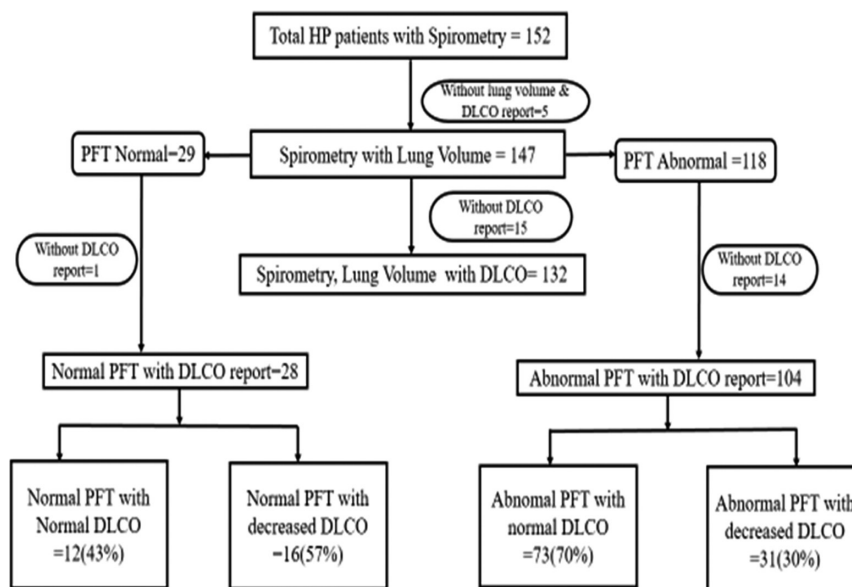

Figure 1. Overall detail flowchart of hypersensitivity pneumonitis patients with different pulmonary function test and diffusing capacity of carbon monoxide findings. HP, hypersensitivity pneumonitis; PFT, pulmonary function test; DLCO, diffusing capacity of carbon monoxide.

Table 2. The Details of Lung Functions Parameters with Various Types of Abnormality Pattern Among Abnormal PFT Patients (n = 118)

Parameter	Obstructive (n = 13)		Restrictive (n = 87)		Mixed (n = 18)		Total (n = 118)	
	Observed Value (Mean)	Pred%(Mean)	Observed Value (Mean)	Pred%(Mean)	Observed Value (Mean)	Pred%(Mean)	Observed Value (Mean)	Pred%(Mean)
FVC	2.41 ± 0.83	79.46 ± 21.20	1.65 ± 0.56	54.21 ± 13.08	1.85 ± 0.73	60.50 ± 14.40	1.76 ± o.66	57.96 ± 16.27
FEV1	1.72 ± 0.60	68.00 ± 18.04	1.47 ± 0.48	57.92 ± 14.37	1.31 ± 61	50.88 ± 16.14	1.47 ± 0.53	57.95 ± 15.56
FEV$_1$/FVC	72.00 ± 6.49		89.54 ± 4.95		69.22 ± 8.95		84.51 ± 10.30	
FEF$_{25\%-75\%}$	1.52 ± 1.17	46.61 ± 24.42	2.49 ± 0.97	90.66 ± 38.43	0.91 ± 0.59	31.33 ± 17.49	2.13 ± 1.112	76.4 ± 41.89
TLC	4.45 ± 1.10	96.53 ± 14.79	2.80 ± 0.72	60.17 ± 12.08	3.31 ± 0.69	70.11 ± 7.39	3.06 ± 0.92	65.69 ± 16.40
RV	1.97 ± 0.57	128.23 ± 29.45	3.41 ± 20.96	70.49 ± 24.42	1.35 ± 0.39	82.75 ± 25.49	2.95 ± 18.03	78.93 ± 32.82
RV/TLC	44.92 ± 10.16		39.99 ± 10.14		42.72 ± 12.38		40.96 ± 10.55	
DLCO	18.69 ± 6.40	79.08 ± 22.12	14.36 ± 6.18	61.55 ± 23.66	15.59 ± 8.99	67.83 ± 38.40	15.27 ± 6.81	64.66 ± 29.93

DLCO, diffusing capacity of carbon monoxide; FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; PFT, pulmonary function test; RV, residual volume; TLC, total lung capacity.
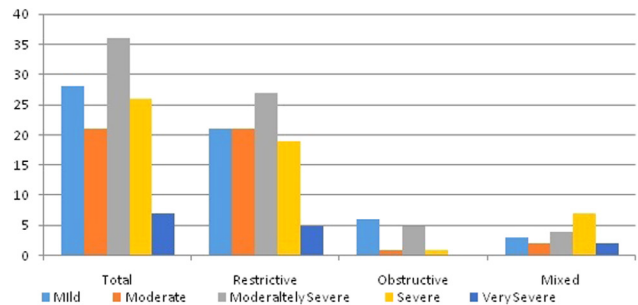

Figure 2. Severity of lung function abnormality with different pulmonary function test patterns.

significant positive correlation with 6MWT distance (FVC r = 0.22 P = .02; TLC r = 0.28 P = .003; DLCO r = 0.30 P = .002)

DISCUSSION

Hypersensitivity pneumonitis is one of the types of ILD. The restrictive type of lung function abnormality with decrease DLCO is one of the characteristics of most of the ILD. Pulmonary function test is commonly used for diagnosis, prognosis, and management follow-up of ILD. There is a lack of published data on PFT in HP subtype of ILD. So the utility of this test in HP is questionable or unclear. Even the recent ATS document on HP diagnosis and Delphi HP diagnostic criteria for chronic HP also did not mentioned it for diagnosis of HP.[1,20] Not only the recent, even all the previous proposed diagnostic criteria for HP also did not mentioned it as a major diagnostic criteria.[11-14] For definitive diagnosis of HP minimum, we need exposure history, HRCT finding with either lung biopsy finding or BAL lymphocytosis.[1,20] The history of exposure difficult to find in all HP suspected as studies had shown that the history of exposure is identified in 50%-70% cases.[16,21] So PFT with typical finding can be considered for diagnosis of HP in cases where the invasive procedure are not possible or refused by patients. Every patient with HP should undergone PFT with DLCO at the time of diagnosis for prognosis and treatment follow-up.

The most common type of lung function defect in ILD is restrictive type in most of the ILDs. In the present study we found that the lung function abnormality was seen in 80% of HP patients. Some available data on PFT in HP also showed that PFT abnormality is common and seen in 75%-90% cases (Table 3).[14,21-24] As early as in 1986 a study of farmer's lung found that the carbon monoxide transfer factor was <80%
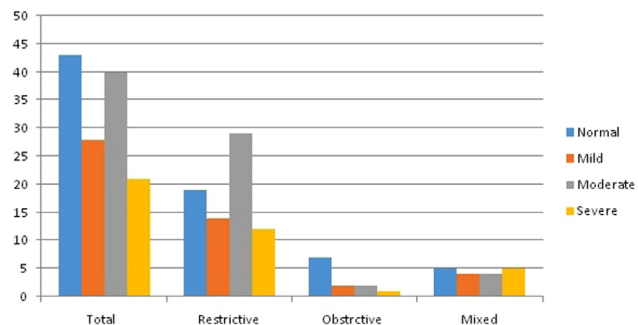

Figure 3. The detail of decreased diffusing capacity of carbon monoxide and diffusing capacity of carbon monoxide levels in different spirometry patterns.

Table 3. Various Studies of HP with PFT Findings

Author	Year	No of patients with PFT	PFT abnormality	TLC	DLCO
Cormier et al[14]	1986	92/94 (98%)	FEV1/FVC normal in all	Decreased 10/76 (13%)	Decreased 27/92 (29%)
Morais et al[22]	2004	92/113 (82%)	Normal 26%, restrictive 63%, obstructive 9%		Decreased 55%
Hanak et al[23]	2007	83/85 (98%)	Normal 8 (10%), restrictive 44 (53%), obstructive 13 (16%) & nonspecific 10 (12%)		Isolated decreased 8 (10%)
Morell et al[24]	2008	78/86 (91%)	Normal 8 (10%), restrictive 60 (77%), obstructive 7 (9%) & Mixed 3 (4%)	Decreased 19/57 (33%)	Decreased 45/53 (85%)
Kumar et al[21]	2020	101/103 (98%)	Normal 23 (23%), restrictive 69 (68%), obstructive 4 (5%) & Mixed 5 (6%)		Decreased 78/101 (77%)
Present study	2022	152 (100%)	Normal 29 (20%), restrictive 87 (59%), obstructive 13 (9%) & Mixed 18 (12%)	Decreased 105/147 (71%)	Decreased 47/132 (36%)

predicted in 27/92 (29%) and TLC was <80% predicted in 10/76 (13%) cases with normal mean FEV1/FVC. They also found that the both TLCO and TLC were negatively correlated with the radiographic score.[25] Studies had shown that the PFT can be performed in HP patients. We found that the PFT was totally normal in 20% cases. Similar to our finding, various studies had also shown that the PFT was normal in 10%-25% cases (Table 3). The present study showed that the most common type of defect was restrictive (59%) followed by mixed (12%) and obstructive (9%). Similar to our finding the most common type of abnormality in HP patients was restrictive type seen in 53%-77% cases. The obstructive and mixed types of defect were seen in 5%-15% and 4%-12% cases respectively.[21-25]

Lung volume measurement is an important part of complete lung function test. Ideally restrictive type of defect and its severity should label according to TLC rather than FVC. In the present study the overall lung volume parameters, i.e., TLC and RV were reduced and RV/TLC was increased. There is scarcity of published data on lung volume in HP. An early study of farmer's lung disease patients in 1986 found that the TLC was <80% predicted in 13% cases.[25] Morell et al[24] in a study found that the lung volume measurement was present 57 (73%) cases. They found that the TLC was <80% predicted in 19 (33%) with RV increases in 26% cases.[24] Morais et al[22] in a study of 113 HP patients found that the TLC and RV/TLC impairment were more severe in bird fancier's disease than suberosis patients. Overall the reduced TLC with maintaining of RV and increased RV/TLC is seen in HP patients suggestive of air trapping among this group of patients. However, further larger multicenter studies with all lung parameters and its correlations are needed to confirm of our findings.

The DLCO is one of the important parameters of PFT. The measurement of DLCO is important, as this identify the gas exchange abnormality and involvement of interstitium and parenchyma in the disease. The decreased DLCO is one of the characteristics finding of ILD. However again there is limited published data on HP subtype. Also the procedure is

slightly difficult than other as patient needs to hold the breath for at least 10seconds, which is difficult among ILD patients. In the present study the DLCO parameter was available in 132 (87%) cases with decreased in 67%. Various studies reported variable findings of DLCO. Studies reported the decreased DLCO varies from 29%-85% cases in HP subtype.[21,22,24,25] We found that out of 28 normal PFT finding the isolated decreased DLCO seen in 16 cases, which is nearly 10% of total patients. Similar to our finding Hank et al[23] in a study also found that the isolated decreased DLCO in 8 (10%) cases.Another study from same institute also found that the decreased DLCO with normal spirometry in 7% cases.[21] The decreased DLCO is also mentioned as minor diagnostic criteria for HP in two proposed diagnostic criteria.[13-14] The overall various findings of all PFT parameters in various published literature is summarized in Table 3. It is clear from above discussion that the decreased DLCO is common in HP patients. Even with normal lung function parameters the isolated decrease DLCO is seen in nearly 10% cases. This may be the early finding before involvement of airway. This may explained that the early involvement of interstitium with gas exchange abnormality in HP before clinical and other PFT manifestation. However there is need of prospective larger study with all parameters of PFT for further confirmation of this finding.

About strength of study, this is a large sample size study with involved HP subtype of ILD. As per best of our knowledge this is only study primary on lung function test in HP subtype ILD. Another strength of the study is that more than 85% of patients have all the parameters of PFT including lung volume and DLCO.

About the limitation, there are few limitations of this study. The study was retrospective analysis of patient's records from a single center. As the lung volume and DLCO parameters were not available in records of nearly 5%-15% cases. This might be either due to not able to perform the procedure or patient might take their report with them. The author proposed a multicenter, prospective study with follow-up for further confirmation of findings.

The PFT abnormality is common and seen in >80% of cases with the HP subtype ILD. All types of lung function abnormality are seen in HP cases, with the restrictive pattern being the most common type of defect. Isolated decreased DLCO levels are seen in nearly 10% of cases. We advised to do the full PFT in all HP patients for diagnosis and follow-up.

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