Original Article

Concomitant Presence of Allergic Rhinitis (AR) in Chronic/Fibrotic Hypersensitivity Pneumonitis (C/F-Hp) Patients: Significant Correlation!

Salman Ayyaz,[1] Shakeel Ahmad Khan,[2] Mudassar Rasool,[3] Sumbal Ayyaz,[4] Muhammad Atif[5]

[1]Department of Pulmonology & Critical Care Medicine, SIMS/ Services Hospital, Lahore; [2-5]Department of Pulmonology & Critical Care Medicine Bakhtawar Amin Medical College & Trust Hospital, Multan, Pakistan

Abstract

Background: Chronic/Fibrotic Hypersensitivity Pneumonitis (C/F-HP), inspite of its high prevalence, is often under-diagnosed due to the complexity of its diagnostic process, which typically involves lung biopsies. These invasive procedures carry significant risks, especially for patients who are severely ill. This study explores the potential of Allergic Rhinitis as a non-invasive clinical indicator for diagnosing C/F-HP, aiming to simplify the diagnostic approach and reduce the need for biopsies.

Objective: The objective of this study was to assess the occurrence of AR in patients with C/F-HP and evaluate its utility as a clinical marker for non-invasive diagnosis.

Method: This cross-sectional descriptive study was conducted at BAM&DC between July 2021 and December 2022. A total of 107 patients diagnosed with C/F-HP, aged 18 to 60, were enrolled using a consecutive sampling technique. The exclusion criteria included patients with known causes of Interstitial Lung Disease and comorbid conditions. Allergic Rhinitis was diagnosed based on clinical history and serum IgE levels, following AAFP guidelines.

Results: The study comprised 107 C/F-HP patients, with a mean age of 46.73 ± 9.36 years. Male patients accounted for 59.8% of the cohort. AR was diagnosed in 99 out of 107 patients (92.5%), with an average serum IgE level of 542.65 ± 182.93. A small percentage (3.7%) of AR patients had normal IgE levels, possibly due to prior corticosteroid use. Among AR-positive patients, males outnumbered females (62:37), reflecting a similar ratio in the overall C/F-HP population.

Conclusion: This study highlights a significant correlation between AR and C/F-HP, suggesting that AR could serve as a reliable clinical indicator for C/F-HP diagnosis, potentially reducing the need for invasive lung biopsies. It seems that our Hypothesis "in an uncertain ILD patient, if AR is concomitantly present, C/F-HP should be sought out", stands validated. Further research is recommended to solidify these findings.

Received: 30-06-2024 | **1st Revision:** 04-11-2024 | **2nd Revision:** 22-02-2025 | **Accepted:** 26-07-2025

Corresponding Author | Prof. Salman Ayyaz, Professor & Head, Department of Pulmonology & Critical Care Medicine, SIMS/ Services Hospital, Lahore **Email** : ayyazsalman@gmail.com

Keywords | Chronic/Fibrotic Hypersensitivity Pneumonitis, Allergic Rhinitis, Lung Biopsy, Serum IgE Levels, Occupation

How to cite: Ayyaz S, Khan SA, Rasool M, Ayyaz S, Atif M. Concomitant Presence of Allergic Rhinitis (AR) in Chronic/Fibrotic Hypersensitivity Pneumonitis (C/F-Hp) Patients: Significant Correlation!Ann King Edw Med Univ.2025;31(4):

Production and Hosting by KEMU

https://doi.org/10.21649/akemu.v31i4.5758

2079-7192/

Introduction

Hypersensitivity pneumonitis is an immune-mediated lung disease with high prevalence that develops in genetically susceptible individuals after repeated inhalation of organic antigens including fungal, bacterial,

insects, plants and animal proteins as well as inorganic antigens like isocyanates, tri-metallic anhydride, contaminated fertilizer, etc.[1] HP is classified conventionally into acute, sub-acute and chronic HP,[2,3] depending on the nature of inciting antigen, intensity, and duration of exposure, host factors, and radiological findings. Patients with HP develop dyspnea, cough and mid inspiratory squeaks.[4]

Similarly, allergic rhinitis is an inflammation of the nasal mucosa, mediated by immunoglobulin E (IgE). It results from exposure to different allergens[1] i.e house dust mites, pollen, certain molds, occupational allergens, and animal danders. In the USA, allergic rhinitis is considered as the first most common chronic disease in children and fifth most common chronic disease in the adults.[5,6] It is thought to be the most common type of chronic disease affecting upto 30 to 40 percent of population. Both entitites may share the same antigens to trigger the hypersensitivity immune responses (Type 1 hypersensitivity reaction in case of allergic rhinitis and type 3 and 4 in case of chronic / fibrotic HP).

To reach the diagnosis of HP is usually a difficult task despite recent advances in medical sciences. Hypersensitivity pneumonitis is not a uniform disease but it behaves like a dynamic clinical syndrome due to diverse clinical features and radiological patterns.[7] HP is classified into fibrotic and non-fibrotic phenotypes with definite ATS diagnostic criteria.[8]Whenever BAL was done for lymphocytosis, 40% lymphocytosis was considered to be diagnostic in favor of hypersensitivity pneumonitis[8]. Most of the time, due to late presentation, fibrotic/chronic HP patients are usually deemed as high risk for any sort of lung biopsy i.e trans-bronchial biopsy, cryo-biopsy or surgical lung biopsy because of poor cardiorespiratory reserves as well as patient's poor performance status. Though ATS criteria for the high confidence diagnosis of HP may avoid the lung biopsy as well as its associated cumbersome complications especially in fibrotic HP, still unavailability of definitive exposure history, bronchoalveolar lavage facilities as well as the diverse/ nonspecific pattern of HRCT chest makes the diagnosis of HP burdensome and difficult.

Previously, recognition of definite UIP pattern on HRCT, in the presence of proper medical history was considered a great breakthrough in terms of its reliability as well as feasibility for the diagnosis of IPF.[9] Similarly, our proposed association of allergic rhinitis with chronic HP can create a great ease for clinicians to arrive at a plausible diagnosis. It's utility as one of the clinical indicator for the non-invasive diagnosis of C/F-HP may obviate the need for lung biopsy.

Methods

The cross-sectional descriptive study was conducted in the Pulmonology Department of Bakhtawar Amin Medical College & Trust Hospital, Multan Pakistan from July 1, 2021 to December 31, 2022.

The study was conducted with sample size of 107 patients. This sample size was calculated assuming 50% prevalence of allergic rhinitis, 95% confidence interval and 9% margin of error. Patients of age between 18 years to 60 years were studied, after taking informed consent by consecutive sampling technique. The study was conducted after the approval from Ethical Board.

An inclusion criteria of the study was all the patients between 18 and 60 years of age having chronic/ fibrotic HP (as per ATS criteria) with specific exposure history of more than 6 months and without any comorbidities. Patients having ILDs with known causes other than HP and comorbidities like DM, HTN, CKD, CLD and CCF were excluded. Similarly, patients with connective tissue diseases, severe pulmonary hypertension, respiratory failure and BMI <18 and >30 were also excluded. Consecutive 107 patients were included in this study that fulfilled the inclusion criteria after informed consent. Out of 107 patients, 55 were pigeon/parrots breeders, 31 were power loom workers and 21 were painters. Once registered, the Allergic Rhinitis was diagnosed / determined by the History (considered most relevant) and serum IgE levels as per AAFP criteria[5,6] and its frequency was calculated in the CH/F-HP patients.

The data was analyzed through SPSS version 23. Age and IgE levels are presented as mean and standard deviation (SD). Gender, occupation and allergic rhinitis are presented as frequency and percentages. Chi-square test (Fischer's exact test) is used for comparison in cross tabulation. P-value < 0.05 is taken as significant.

Result

107 patients of C/F-HP patients were divided into 2 age groups viz, group A 18-40 years old, group B 40-70. Mean age +/- SD was 46.73 +/- 9.363. Group A comprised of 29/107 (27.10%) patients, and group B 78/107 (72.90%) patients. Male patients were 64/107 (59.8%) and female patients were 43/107 (40.2%). Paint factory workers were 21/107 (19.6%), pigeon/parrot breeders were 55/107 (51.4%), and power loom workers were 31/107 (29.0%).

Allergic Rhinitis was diagnosed in 99/107 (92.5%) chronic / fibrotic - HP patients. The mean +/- SD of total serum IgE level in 95/99 of these AR patients was 542.65 +/- 182.930 IU/ml. Of these 99/107 AR patients,

4 had normal serum IgE level but with clinical features of AR (considered most relevant diagnostically). On careful inquiry, it was found that they were taking high dose oral and inhaled steroids. It was keenly observed that 99/107 patients (92.5%) had allergic rhinitis. In group A 28/29 patients, and in group B 71/78 patients fulfilled AAFP criteria for the diagnosis of AR. In the patients with positive diagnosis of AR male patients were 62/64, and female patients 37/43. Whereas C/F-HP patients displayed male:female ratio of 64:43, and in these patients, AR was elicited in 99 patients with male:female ratio of 62:37. Of the 8/107 C/F-HP patients who were negative for AR, 1/20 patients were paint factory worker, 4/51 pigeon/parrot breeders, 3/28 power loom workers.

Table 1: *Demographic characteristics of patients with chronic hypersensitivity pneumonitis (N=107)*

Age (year),	**Mean 46.73**	**± SD ± 9.369**
Gender	N	%
Male	64	59.8%
Female	43	40.2%
Occupation	**N**	**%**
Paint factory	21	19.6%
Pigeon breeder	55	51.4%
Power loom	31	29.0%
Serum IgE level (IU/ml) mean ± SD	**Mean** 542.65	**± SD** ± 182.930
Allergic Rhinitis	N	%
Yes	99	92.5%
No	08	7.5%

Table 2: *Relationship of demographic factors with Allergic Rhinitis in patients with chronic hypersensitivity pneumonitis (N=107)*

Factors		**Allergic Rhinitis**		**p-value***
		Yes	**No**	
Age	Up to 40 years	28	1	0.443
	> 40 years	71	7	
Gender	Male	62	2	0.058
	Female	37	6	
Occupation	Paint Worker	20	1	0.794
	Pigeon Breeder	51	4	
	Power Loom	28	3	

** Chi-Square Test(Fischer's exact test where cell count < 5)*

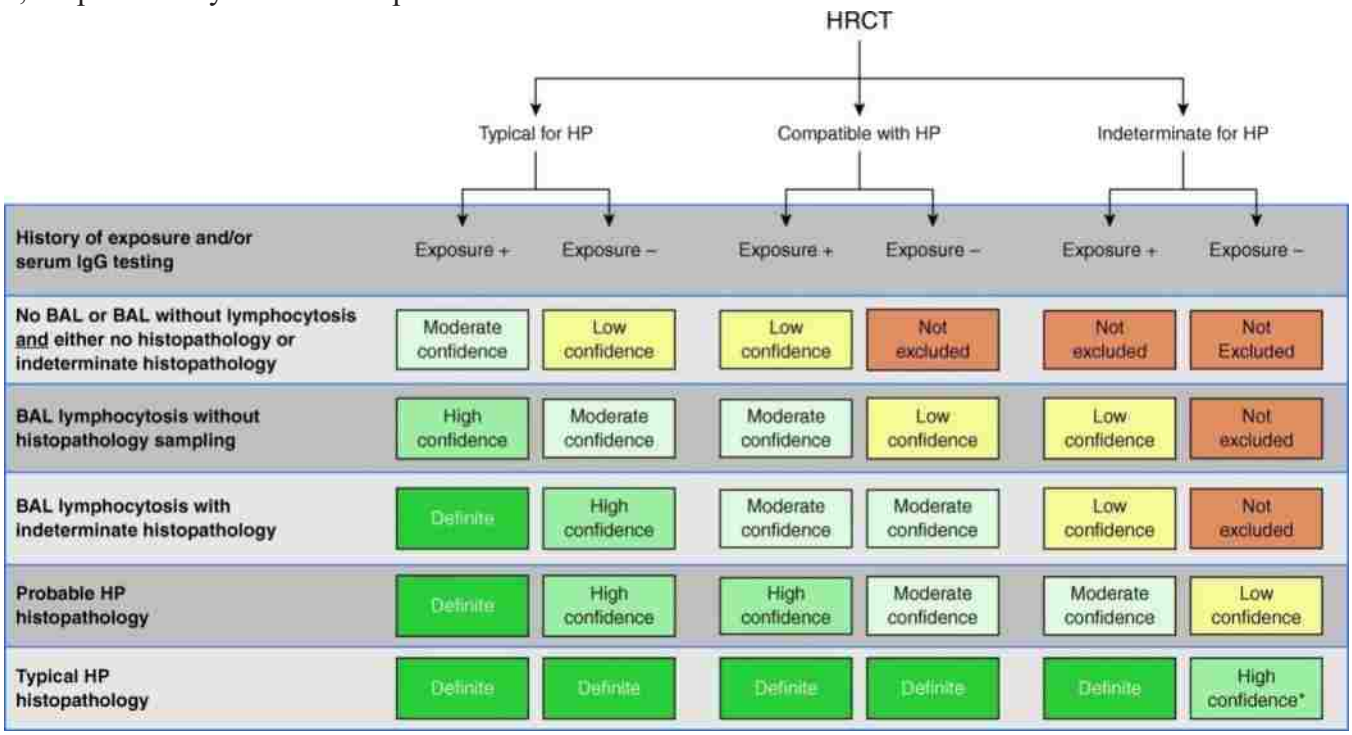
Discussion:

Prevalence of HP varies with regional disparities in race, climate, and occupational exposures. Available studies estimate an incidence between 0.3 and 0.9 per 100000 individuals,[10] although an incidence of 54.6 per 100000 bird breeders has also been reported. Patients of acute HP may experience, flue like illness (chills, low grade fever, malaise), wheezing as well as physical findings of rales and cyanosis. C/F-HP develops in genetically susceptible individuals, as a result of hypersensitivity type 3/4 reactions, after repeated exposure to one or more inciting antigens / allergens i.e fungal, bacterial, animal, insect proteins, decayed wood, and inorganic antigens like isocyanates, tri-metallic anhydride, contaminated fertilizer etc.[11,1] Several potential inciting agents and hundreds of sources of such agents have been reported. These inciting agents are diverse, vary by geographic region, and are usually protein antigens derived from micro-organisms fungi, or animals e.g avian antigens). They may also be polysaccharides or low molecular weight non-proteins chemicals (e.g isocyanates, tri-metallic anhydride). The location of exposure can be occupational, household related or recreational[11]. Hypersensitivity pneumonitis is a common entity but underdiagnosed due to lack of clinical expertise and complex diagnostic work with its associated complications[12]. Allergic rhinitis is the most common chronic disease in children in the United States and is the fifth most common chronic disease in the United States overall. AR is estimated to affect one in every six American and consequently adds health expenditures.[13] Diagnosis of all types of rhinitis including allergic rhinitis, seasonal allergic rhinitis, perennial allergic rhinitis, intermittent allergic rhinitis and episodic allergic rhinitis requires comprehensive history (most relevant), skin prick and/or IgE levels. Measurement of IgE levels 384+154 IU/ml can confirm the high confidence diagnosis of allergic rhinitis and can be used as a prognostic marker to determine treatment outcome. Both entities may share same antigens / allergens to trigger the hypersensitivity immune responses (Type 1 hypersensitivity reaction in case of allergic rhinitis and type 3 and 4 in case of chronic / fibrotic HP).[14,15]

In this study, 107 Chronic/Fibrotic-HP patients meeting inclusion criteria were studied including 64 males and 43 females. Our data showed a gender distribution of 59.8% male patients and 40.2% female patients as shown in the table. In our studied data, 55 patients were pigeon / parrot breeders, 31 of them were power loom worker and 21 were employees of paint factories.[16] All of them had allergen exposure for more than 6 months with chronic / fibrotic type HP. Patients having diverse

comorbid, acute respiratory failure, severe pulmonary hypertension, BMI> 30 or less than 18, primary pulmonary hypertension, ILD with other etiologies and connective tissue diseases were excluded from the study. CTD is a common etiology of HP pattern[17,18]. So, we particularly ensured that patients did not have any clinical or laboratory evidence of any common or uncommon connective tissue disorder.

High confidence diagnosis of chronic / fibrotic hypersensitivity pneumonitis was made without biopsy using ATS criteria[8]. This criteria emphasize the diagnosis of



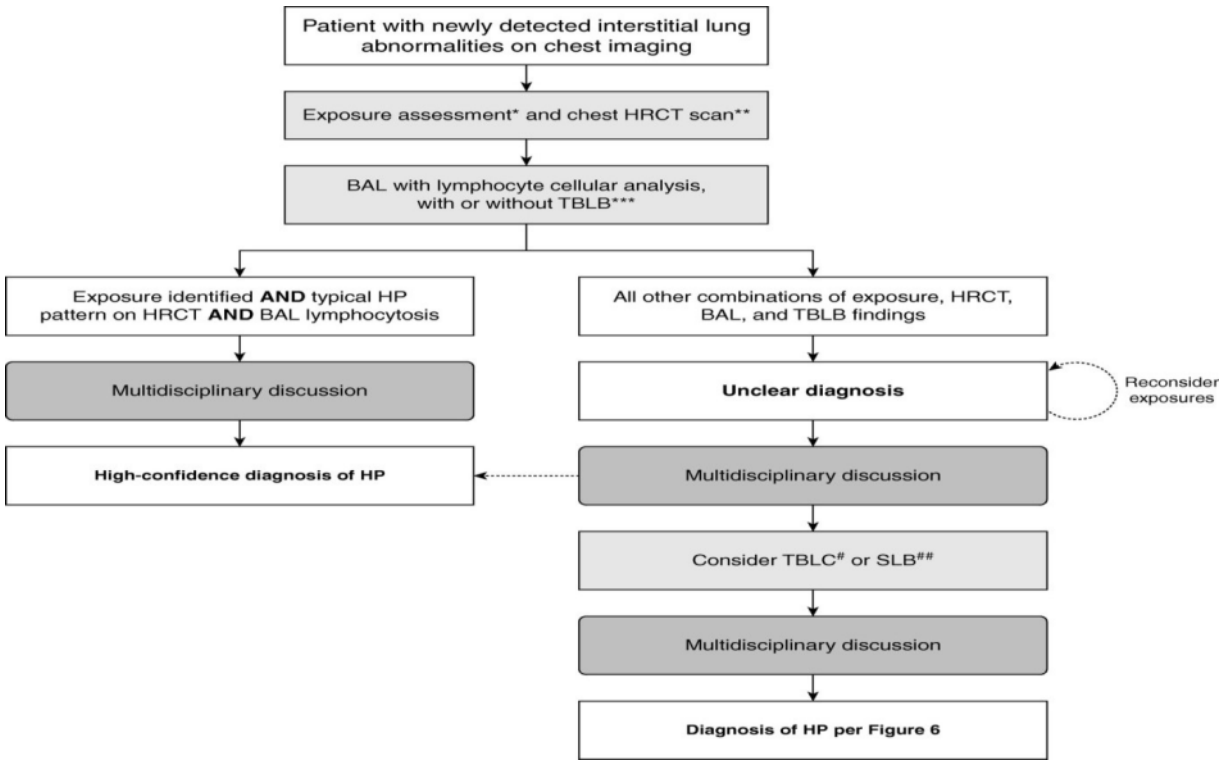


Figure-1: *ATS Diagnostic Criteria for C/F HP*

chronic hypersensitivity pneumonitis based on triad of typical exposure to specific antigen (avian proteins, proteins derived from fungal and bacteria etc), typical radiological findings consistent with hypersensitivity pneumonitis and lymphocytosis (>40%) seen on bronchoalveolar lavage.[12] After fulfilling these criteria, a multidisciplinary discussion was necessary to give a conclusion in favor of C/F-HP.[19]

Chronic HP is associated with marked diversity of radiological patterns on HRCT chest and almost any pattern related with ILDs is possible i.e patchy or diffuse ground glass opacities, centrilobular nodules, patchy or random reticulations, cysts, emphysema, traction bronchiectasis, bronchiolectasis, head cheese sign (triple density sign) and sometimes bilateral/ bibasal honeycombing pattern as in UIP. So, it is to be noted that diversity in radiological patterns is of a wide spectrum as it can give almost any pattern associated with ILDs.[19,7] Therefore, we can't rely on the radiological pattern alone and it should be interpreted in relevance with the clinical history, exposure and BAL lymphocytosis as per ATS criteria. Patients with fibrotic HP have low vital capacity, diffusion capacity but high percentage of lymphocytosis in their BAL fluid.[19,13] ATS criteria demands "several features for both groups (Fibrotic HP and Non fibrotic HP) including thorough history and validated questionnaire to identify potential exposure to particular antigen. History of definitive exposure and/or Serum IgG testing against potential antigens associated with HP is suggested to identify potential exposures. For patients with nonfibrotic HP, recommendations were made in favor of obtaining BAL for lymphocytic cellular analysis, and suggestions for transbronchial, cryo and/or surgical lung biopsy. In order to make the diagnosis of chronic / fibrotic HP as per ATS recommendations we rely on at least three evidences (HRCT pattern, Typical exposure and BAL lymphocytosis) followed by consensus given by multidisciplinary committee. However, in the presence of poor cardiorespiratory reserves, we avoided proceeding with lung biopsies in order to avoid their associated cumbersome complications. Following table and flow sheet show the algorithm needed to make diagnosis of C/F-HP with high confidence avoiding lung biopsy as per ATS criteria[8] (Figure-1).

In our studied data, 55 patients were pigeon / parrot breeders, 31 of them were power loom workers and 21 were employees of paint factories. All of them had allergen exposure for more than six months with fibrotic type HP. Ninety-five patients out of 107 were found to have symptoms of allergic rhinitis with elevated IgE levels meeting its diagnostic criteria. While four patients had typical symptoms of allergic rhinitis but normal IgE levels (due to high dose corticosteroid use). On careful inquiry, it was found that they were taking oral and / or inhaled steroids.

It was keenly observed that 99 out of 107 patients had allergic rhinitis. Both entities may share same antigens in most of the cases and trigger the hypersensitivity immune responses (Type1 hypersensitivity reaction in case of allergic rhinitis and type 3 and 4 hypersensitivity reactions in case of chronic / fibrotic HP). Any associated genetics linkage may be sought out in future with more advance studies.

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Allergic Rhinitis was diagnosed in 99/107 (92.5%) patients with C/F-HP patients. Mean +/- SD of total SERUM IgE in these AR patients was 542.65 +/- 182.930. Of these 99/107 AR patients, 4 had normal serum IgE level but with clinical features of AR (most relevant diagnostically). In group A 28/29 patients, and in group B 71/78 patients fulfilled AAFP criteria for the diagnosis of AR. In the patients with positive diagnosis of AR male patients were 62/64, and female patients 37/43. Whereas C/F-HP patients displayed male: female ratio of 64:43, and in these patients AR was elicited in 99 patients with male: female ratio of 62:37. Of the 8/107 C/F-HP patients who were negative for AR, 1/20 patients was paint factory worker, 4/51 pigeon/parrot breeders, 3/28 power loom workers.

This data showed strong association of allergic rhinitis with chronic HP. Based on this observation, we formulated a hypothesis that "in an uncertain ILD, if allergic rhinitis is concomitantly present, chronic / fibrotic HP should be sought out". It can help to overcome dilemma of invasive work up which is not possible in most of the cases due to poor cardiopulmonary reserves as well as unavailability of definitive exposure history and diagnostic resources (esp BAL facilities). This hypothesis may offer a great breakthrough in diagnosis of hypersensitivity pneumonitis and can decrease the cost, time and the availability of trained human resource needed to follow the current diagnostic algorithm. It is to be noted that complexity of diagnostic work up often leads

to underestimation of chronic HP cases.[19]

A study conducted by Pieter Bogaert et al, depicted that although pathophysiologically diverse clinical entities, HP is considered as an immune counterpart of bronchial asthma.[14] Review of clinical studies as well as data from animal models reveal significant overlap between both important airway diseases. In genetically susceptible individuals allergen driven signaling elicits hypersensitivity type-III/IV inflammatory reactions driven by Th cells and IgG causing lung fibrosis in its chronic form.[20,14]

In another important study by Yosri Akl et al, 87.5% of Hypersensitivity Pneumonitis patients had chronic inflammation of the nasal mucosa and 77.5% of the patients had a high burden of sino-nasal symptoms depicted by sino-nasal outcome test-22 (SNOT-22).[21,15] In the past, diagnosis of Idiopathic Pulmonary Fibrosis was a challenging task, but its association with definite UIP pattern on HRCT chest was of great help in reducing further investigations.[22] So, this association of allergic rhinitis and chronic/fibrotic HP shown by our data can give similar benefits and complexity of the diagnostic algorithm for C/F-HP will be reduced to a great extent.

Limitation:

Cross sectional design of the study limits the hypothesis testing. We would recommend cohort study to test the hypothesis generated from our research protocol.

Strengths:

Comprehensive Diagnostic Criteria: The study followed ATS criteria for diagnosing chronic/fibrotic HP, including typical exposure, radiological findings, and BAL lymphocytosis. This robust methodology enhances diagnostic confidence in the absence of biopsy.

Large Sample Size for Niche Conditions: With 107 chronic/fibrotic HP patients, the study offers valuable insights into a relatively underdiagnosed condition, contributing to the understanding of its significant clinical presentation and impact.

Strong Association between Allergic Rhinitis and HP: The study presents a novel hypothesis linking allergic rhinitis to chronic/fibrotic HP, potentially simplifying the diagnostic process in uncertain cases and reducing the need for invasive procedures.

Gender and Age Data: The study provides detailed gender and age breakdowns of patients, offering useful demographic insights that can inform future research and clinical management strategies for HP.

Multidisciplinary Approach: The involvement of a multidisciplinary discussion to finalize the diagnosis is a strength, as it ensures a comprehensive and collective evaluation of complex cases.

Conclusion

This study illuminates the so far unearthed coincidence/correlation of AR in C/F-HP patients and lays premium upon AR to be employed as one of the clinical indicator for the diagnosis of C/F-HP , as very high frequency of AR was noted in C/F-HP patients. It seems that our Hypothesis "in an uncertain ILD patient, if AR is concomitantly present, C/F-HP should be sought out", stands validated. This study holds the potential to obviate the need of lung biopsy for the diagnosis of C/F-HP. To firmly establish it, more rigorous studies are warranted in this regard.

Declaration: This abstract presentation of this article has been submitted in Longdom Conferences applauds, Paris, France in November 2023.

Ethical Approval: The Ethical Review Committee of Bakhtawar Amin Medical & Dental College, Multan approved this study vide letter No. 0603-21/ EC/ BAM & DC.

Conflict of Interest: The authors declare no conflict of interest.

Funding Source: None

Author's Contribution

SA: Conception & design, acquisition of data, drafting of article, critically revised it for important intellectual content, final approval of the version to be published

SAK: Analysis & interpretation of data

MR: Acquisition of data

SA: Analysis & interpretation of data

MA: Acquisition of data

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