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Serum Specific Antibodies Do Not Seem to Have an Additional Role in the Diagnosis of Hypersensitivity Pneumonitis

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Abstract

Background: *We aimed to investigate the contribution of serum immunoglobulin G testing to the history of exposure in diagnosing fibrotic hypersensitivity pneumonitis.* **Methods:** *A single-center, retrospective, cross-sectional study recruited 63 patients diagnosed with fibrotic hypersensitivity pneumonitis in line with the guidelines of the American Thoracic Society. Descriptive statistics were presented, and Kappa statistic was performed to evaluate the compatibility between the panel and the history of exposure.* **Results:** *The median age was 63 (22-81) years, and 34 (54%) were male. Forty-six patients (73%) had a positive history of exposure. Thirty-nine patients (61.9%) had a positive HP/Avian panel. The most common exposure agent was mold (34.9%), followed by parakeet (31.7%). The antibody most frequently detected was Penicillium chrysogenum lgG (36.5%), followed by Aspergillus fumigatus (31.8%). There was no compatibility between the HP/Avian panel and history of exposure (kappa coefficient=0.18, p=0.14). When exposure was only based on the history, 9 (14.3%) patients were diagnosed with fibrotic hypersensitivity pneumonitis with moderate confidence, 11 (17.5%) with high confidence, and 43 (68.3%) with definite confidence, whereas if exposure was evaluated with history and panel, 9 (14.3%) patients were diagnosed as fibrotic hypersensitivity pneumonitis with moderate confidence, 9 (14.3%) patients with high confidence and 45 (71.4%) patients with definite confidence.* **Conclusions:** *Serum-specific precipitating antibody panel does not provide additional value to the history of exposure in diagnosing fibrotic hypersensitivity pneumonitis.*

1. Introduction

Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) characterized by type 3 and 4 inflammation caused by repeated inhalation of organic particles or reactive chemicals derived from fungal, bacterial, and animal proteins [1-3]. Although 11-65% of the patients with HP developed chronic fibrotic lung parenchymal abnormalities, identifying the antigen and removal from

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exposure may result in spontaneous resolution [4-8]. In line with this, identifying the antigen is crucial in patients with suspected HP.

Histopathological examination is the mainstay of the diagnosis. However, lung biopsies, including conventional transbronchial biopsy (TBB), transbronchial lung cryo-biopsy (TBLC), and surgical biopsy, may lead to complications such as hemorrhage, pneumothorax, and exacerbation of the disease [9, 10]. According to this, patients with typical radiological patterns, defined exposure to an antigen, and lymphocytosis in bronchoalveolar lavage (BAL) examinations have been diagnosed as HP without lung biopsy [10]. However, the history of exposure could not be identified in 60% of patients with HP, despite a detailed history-taking [5, 11, 12-15]. Serum-specific precipitating antibody panels, which have been used in a limited number of centers, may help clinicians to determine the antigen exposure more accurately compared to patient history [16]. There is little data on the prevalence of a positive serum immunoglobulin G (IgG) test among patients with HP, and it needs to be clarified how much evidence there is to support the use of a serum IgG test to screen for probable causal exposures [12].

Serum IgG testing against potential antigens associated with HP was suggested to identify potential exposures. Serum IgG testing was found to have high sensitivity (90%) and specificity (91%) for distinguishing individuals with HP from exposed individuals and unexposed individuals. In addition, serum IgG testing against potential antigens distinguished HP from other ILDs with a sensitivity and specificity of 83% and 68%, respectively [17]. In a recent paper published in Chest, Marinescu et al. pointed out that fibrotic HP could not easily distinguish from idiopathic pulmonary fibrosis with a physical exam, radiological findings, histopathological examination, and bronchoalveolar lavage findings. Instead, demographic features such as male gender, older age (>60 years), and smoking history may help physicians with the differential diagnosis. In addition, a history of exposure is critical for distinguishing these two clinical entities. At this point, serum IgG testing may also be important for differential diagnosis [18].

The American Thoracic Society (ATS) guideline suggested that a history of exposure or serum IgG testing should be considered for defining potentially causative anantigens12]. There is no clarity on the necessity of serum IgG testing usage among patients without a history of exposure. In line with this, to underline the importance of serum IgG testing, we aimed to investigate the contribution of serum IgG testing to the history of exposure in the diagnosis of fibrotic HP.

2. Methods

2.1 Study Design and Setting

We performed a single-center, retrospective, cross-sectional study at the Department of Pulmonology in chest diseases and thoracic surgery training and research hospital between June 2021 and June 2022. Our tertiary care center is a reference hospital in Turkey for patients with respiratory diseases, including interstitial lung diseases.

2.2 Study Population

Serum lgG testing has been routinely performed for patients with suspected HP in our clinic since January 2017. So, we evaluated 122 patients diagnosed with fibrotic HP between 2017 and 2022 who underwent serum IgG testing. Among them, 63 patients with a pathological diagnosis of fibrotic HP were included in the study. Patients treated with immunosuppressive agents, including corticosteroids before BAL analyses and serum lgG testing, and those with missing data were excluded from the study.

2.3 Data Collection

Demographic characteristics, comorbidities, presenting symptoms, physical findings, smoking history, history of antigen exposure, serum-specific precipitating antibody panel results, radiological, bronchoalveolar lavage, and pathological findings were collected from electronic medical records.

2.4 Definitions

2.4.1 History of Exposure

History of exposure was evaluated by an experienced occupational medicine physician with a work experience of 15 years in occupational health and

medicine using the extrinsic factor questionnaire for ILD patients developed by Vasakova et al., which includes questions about detailed occupational history and environmental exposure [19]. A physician specialist in occupational medicine evaluated the history of antigen exposure without any knowledge about serologic tests and the diagnosis of the patients.

2.4.2 Serum IgG Testing

Immunoglobulins against specific peptide components of organic antigens could be induced after exposure and measured in peripheral blood samples. The HP/Avian panel blood samples were collected and placed in a serum-gel tube for dispatch to the laboratory, where they were studied by immunodiffusion [20]. Serum IgG testing was routinely performed only once at baseline during the initial evaluation with *Alternaria tenuis/alternate, Aspergillus fumigatus, Aureobasidium pullulans, Micropolyspora fanaei, Penicillium chrysogenum, Phoma betae, Thermoactinomyces vulgaris, Trichoderma viride*, pigeon sera, pigeon DE, cockatiel, parakeet and parrot. An HP panel result was represented as a continuous parameter and considered positive if the value was above the reference. In contrast, an avian panel result was designated as a dichotomus parameter, either positive or negative (Table 1).

Table 1. Standard HP Panel list used in Turkey.

Hypersensitivity Pneumonitis Panel	Reference range (mcg/mL)
Alternaria tenuis/ alternate	<12
Aspergillus fumigatus	<46
Aureobasidium pullulans	<18
Micropolyspora faeni	<5
Penicillium Chrysogenum	<22
Phoma Betae	<8
Thermoactinomyces vulgaris	<13
Trichoderma viride	<10
Hypersensitivity Pneumonitis Avian Panel	
Pigeon Sera	Negative/Positive
Pigeon DE	Negative/Positive
Cockatiel	Negative/Positive
Parakeet	Negative/Positive
Parrot	Negative/Positive

2.4.3 Thorax High Resolution Computes Tomography HRCT

Regarding radiologic definitions, the "typical HP" pattern suggests a diagnosis of HP. It requires a) an HRCT pattern of lung fibrosis in one of the distributions and b) at least one abnormality indicative of small airway disease. The "compatible with HP" pattern exists when the HRCT pattern and distribution of lung fibrosis varies from that of the typical HP pattern; signs of small airway disease should accompany the variant fibrosis. The 'indeterminate for HP' pattern exists when the HRCT is neither suggestive nor compatible with a typical and probable HP pattern [12].

2.4.4 Bronchoalveolar Lavage

BAL protocol, including the pre-procedure preparation and BAL procedure, followed the official ATS clinical practice guideline (the clinical utility of BAL cellular analysis in ILD). Accordingly, the fiberoptic bronchoscope was wedged in the orifice of a lobar or segmental bronchus of the right middle lobe or lingula division or other appropriate location based on the findings of chest images. Diagnostic BAL was done using three 50-mL sterile isotonic sodium chloride aliquots. Sequential aliquots of normal saline of at least 100 mL (no more than 300 mL) should be instilled, and at least 30% returned for optimal sampling [21]. Cellular analysis in BAL fluid was evaluated according to ATS guidelines [12].

2.4.5 Biopsy Technique

Three or more biopsies were obtained from the involved lung parenchyma according to the HRCT scan appearance in the TBLC procedure, which was performed as recommended [22]. TBB was performed in patients unsuitable for general anesthesia, and video-assisted thoracic surgery was performed

upon the council's decision for patients who could not be diagnosed with TBB or TBLC.

2.4.6 Pathological Diagnosis

Regarding pathological definitions, the typical HP characteristics on histology were lymphocyte predominance, chronic bronchiolocentric inflammation, poorly formed non-necrotizing granulomas, giant cells, airway-centered interstitial fibrosis, and an alternative diagnosis. The probable HP pattern that differs from the typical HP pattern is the lack of poorly formed non-necrotizing granulomas. The indeterminate HP characteristics on histology were defined as selected idiopathic interstitial pneumonia patterns (cellular NSIP, organizing pneumonia, or peribronchiolar metaplasia without other features to suggest fibrotic HP) or cellular interstitial pneumonia/cellular bronchiolitis and absence of alternative diagnosis [12].

Patients were diagnosed with fibrotic HP utilizing the appropriate combination of antigen exposure, BAL results, and radiological and pathological criteria by a multidisciplinary discussion (MDD) comprising a pulmonologist, a chest surgeon, an occupational medicine physician, a rheumatologist, a radiologist, and a pathologist, in line with the ATS guidelines [12].

2.5 Data Analysis and Statistical Methods

Descriptive statistics were performed using IBM SPSS Statistics 25. Categorical variables were presented as proportions and counts. Continuous data were presented as mean and standard deviation if normally distributed, and median and interquartile range were used if not normally distributed. Kappa statistic was performed to evaluate the compatibility between the panel and the history of exposure. A p-value <0.05 was considered statistically significant.

3. Results

A total of 63 patients with fibrotic HP were included in the study. Thirty-four (54%) patients were female, and the median age was 63 years (22-81). Thirty-six (57.1%) patients were never smokers, and 35 (55.6%) had at least one comorbidity. The most common comorbidity was diabetes mellitus, hypertension, asthma, ischemic heart diseases, cardiac failure, and gastroesophageal reflux. The mean forced expiratory volume in the first second (FEV_1) (%) was 72.9±22.5, the mean forced vital capacity (FVC) (%) was 67.66±20.94, and the mean diffusing capacity for carbon monoxide (DLCO) (%) was 47.92±15.34. Fifty-one (80,9%) of 63 patients had BAL. Among them, the lymphocyte count was greater than 15% in BAL analyses of 37 patients. All patients underwent an invasive lung biopsy. Of these, 4 (6.4%) were diagnosed with TBB, 15 (23.8%) with TBLC, and 44 (69.8%) with a surgical biopsy (Table 2).

Regarding the history of exposure, forty-six patients (73%) had a positive history of exposure. The most common exposure agent was mold (34.9%), followed by parakeet (31.7%) and pigeon (17.5%). Thirty-nine patients (61.9%) had a positive HP/Avian panel. The antibody detected the most was *Penicillium chrysogenum* lgG (36.5%), followed by *Aspergillus fumigatus* (31.8%) and *Phoma betae* (22.2%). Regarding radiological findings, 24 (38.1%) patients had a typical pattern, 31 (49.2%) had a compatible pattern, and 8 (12.7%) had an indeterminate pattern. In comparison, 37 (58.7%) patients were diagnosed as typical for HP, 20 (31.7%) patients were diagnosed as probable HP, and 6 (9.5%) were diagnosed as indeterminate for HP with pathological evaluation (Table 3). Among six patients with indeterminate histopathology, one had a typical radiological pattern, and five had compatible radiological patterns in thorax HRCT. Three of these patients had a positive serological test, and three had a positive history of exposure. Regarding bronchoalveolar lavage findings, lymphocytosis was reported in all these patients. After MDD, these six patients were diagnosed with fibrotic HP.

There was no compatibility between the HP/Avian panel and history of exposure (kappa coefficient=0.18, p=0.14). If the exposure was only assessed based on the history, 9 (14.3%) patients were diagnosed as HP with moderate confidence, 11 (17.5%) patients were diagnosed with high confidence, and 43 (68.3%) patients were diagnosed with definite confidence, whereas 9 (14.3%) patients were

Table 2. Demographic, clinical characteristics, and laboratory findings of patients with fibrotic hypersensitivity pneumonitis.

PARAMETERS	ALL PATIENTS, n(%)
Age (years), median (min-max)	63 (22-81)
Female gender, n(%)	34(54)
Comorbidities, n(%)	
Any comorbidity	35(55.6)
Diabetes mellitus	14(22.2)
Hypertension	13(20.6)
Asthma	5(7.9)
Ischemic heart diseases	5(7.9)
Cardiac failure	2(3.2)
Gastroesophageal reflux	2(3.2)
Smoking Status, n(%)	
Never smoker	36(57.1)
Ever smoker	21(33.3)
Active smoker	6(9.6)
Smoking (pack/year), median (min-max)	0(0-75)
Pulmonary function test, mean±SD/median (min-max)	
FEV_1(lt)	1.94±0.74
FEV_1 (%)	72.9±22.5
FVC(lt)	2.16(0.82-5.26)
FVC(%)	67.66±20.94
FEV_1/FVC(%)	85.1(59-123)
DLCO(ml/min/mmHg)	3.7(1.3-21)
DLCO(%)	47.92±15.34
Six minutes walking test(meter), mean± SD	382.1±100.2
< 40 years of age	435.7±98
40 - 59 years of age	368.7±107.3
≥ 60 years of age	376.2±96.8
Bronchoalveolar lavage findings, mean±SD/median (min-max)	
Total cell count (cells/mm^3)	390(120-1520)
Lymphocyte count (%)	20(5-75)
Neutrophil count (%)	26.38±13.24
Diagnostic technique, n(%)	
Transbronchial biopsy	4(6.4)
Transbronchial lung cryobiopsy	15(23.8)
Surgical biopsy	44(69.8)

Abbreviations: FEV_1*: forced expiratory volume in the first second, FVC: forced vital capacity, DLCO: diffusing capacity for carbon monoxide.*

Table 3. Exposure evaluation with history and panel, radiological and pathological findings of patients with hypersensitivity pneumonitis.

History of exposure (+), n(%)	**46(73)**
History of exposure regarding HP panel, n(%)	24(38.1)
Mold exposure	22(34.9)
Farmer	8(12.7)
History of exposure regarding Avian panel, n(%)	33(52.4)
Parakeet	20(31.7)
Pigeon	11(17.5)
Cockatiel	3(4.8)
Parrot	2(3.2)
HP/Avian panel (+), n(%)	39(61.9)
HP panel (+)	33(52.4)
Alternia tenuis/alternata IgG	1(1.6)
Aspergillus fumigatus lgG	20(31.8)
Aureobasidium pullulans lgG	3(4.8)
Microplyspora faeni lgG	8(12.7)
Pencillum Chrysogenum lgG	23(36.5)
Phoma betae IgG	14(22.2)
Thermoactinomyces vulgaris lgG	8(12.7)
Trichoderma viride lgG	7(11.1)
Avian panel (+)	15(23.8)
Pigeon Sera	3(4.8)
Pigeon DE	7(11.1)
Cockatiel	7(11.1)
Parakeet	11(17.5)
Parrot	4(6.4)
Radiological diagnosis, n(%)	
Indeterminate for HP	8(12.7)
Compatible with HP	31(49.2)
Typical HP	24(38.1)
Pathological diagnosis, n(%)	
Indeterminate for HP	6(9.5%)
Probable HP	20(31.7%)
Typical HP	37(58.7%)

diagnosed with moderate confidence, 9 (14.3%) patients were diagnosed with high confidence and 45 (71.4%) patients were diagnosed with definite confidence if the exposure was evaluated with history or panel (Table 4).

Detailed evaluation of the diagnosis of patients with fibrotic HP based on the incorporation of imaging, exposure assessment, BAL lymphocytosis, and histopathological findings were depicted in Figure 1A and Figure 1B.

4. Discussion

The serum-specific precipitating antibody test is recommended for diagnosing HP in current guidelines, albeit with shallow evidence. However, serum-specific antibody panel does not seem to contribute to the diagnosis of fibrotic HP based on the results of this study.

A study conducted on 108 patients with suspected fibrosing ILD assessed the accuracy of serum antigen-specific IgG test based on history of exposure or multidisciplinary diagnosis, in addition to HRCT imaging. Independent of serum-specific antibodies, HRCT findings, history of exposure, and an interdisciplinary approach helped to diagnose 89% of the patients. While 60% of patients with positive antibodies reported no exposure, 32% of patients with negative antibody results had a history of exposure. The results of this study suggested that serum-specific antibodies could not have an important role in the diagnosis of fibrotic HP [23]. In our research, 47 (73%) of all patients evaluated by an occupational medicine physician had a history of exposure. While the panel was negative in 32.6% of the patients with a history of exposure, 47.1% of the patients with a positive panel had no history of exposure. No compatibility was found between the panel and the history of exposure (kappa coefficient=0.18, p=0.14).

In patients for whom culprit antigen cannot be identified by detailed history-taking, there is data that we can capture with serum IgG testing, so this panel has begun to be used routinely by guidelines [12]. In addition, since the same patient may have more than one antigen, the idea that a history

Table 4. Compatibility between HP/Avian panel and the history of exposure and diagnostic level of confidence combined with exposure, radiological and pathological findings.

	HP Panel		kappa coefficient	p-value
History of exposure	**(-)**	**(+)**		
(-)	22(56,4)	17(43,6)	0.180	0.140
(+)	8(33.3)	16(66.7)		
Diagnostic level of confidence combined with exposure, radiological and pathological findings				
All Patients		***n(%)***		
Exposure evaluated with only history				
Moderate confidence		9(14.3)		
High confidence		11(17.5)		
Definite confidence		43(68.3)		
Exposure evaluated with history or panel				
Moderate confidence		9(14.3)		
High confidence		9(14.3)		
Definite confidence		45(71.4)		

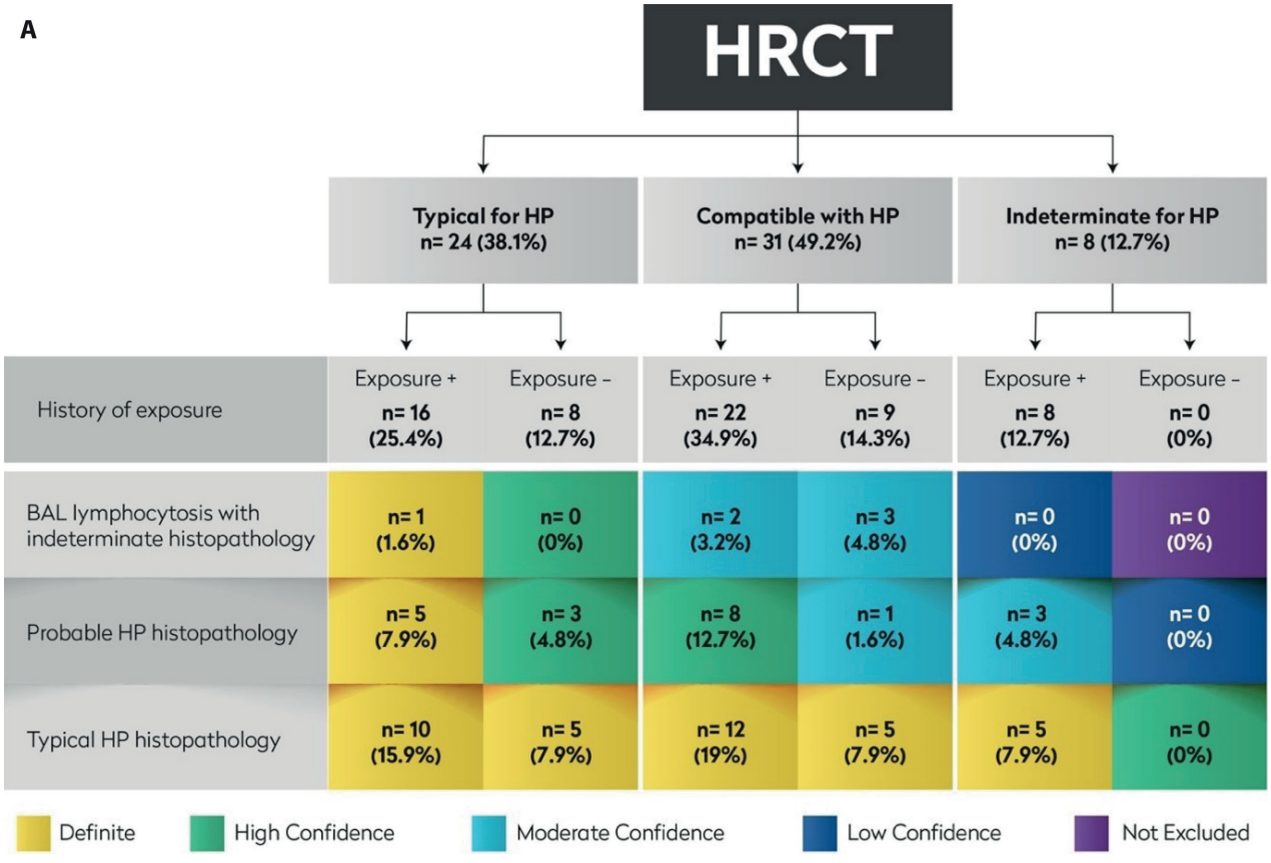

Figure 1A. Detailed evaluation of diagnosis of patients with FHP based on the incorporation of imaging, history of exposure, BAL lymphocytosis and histopathological findings.

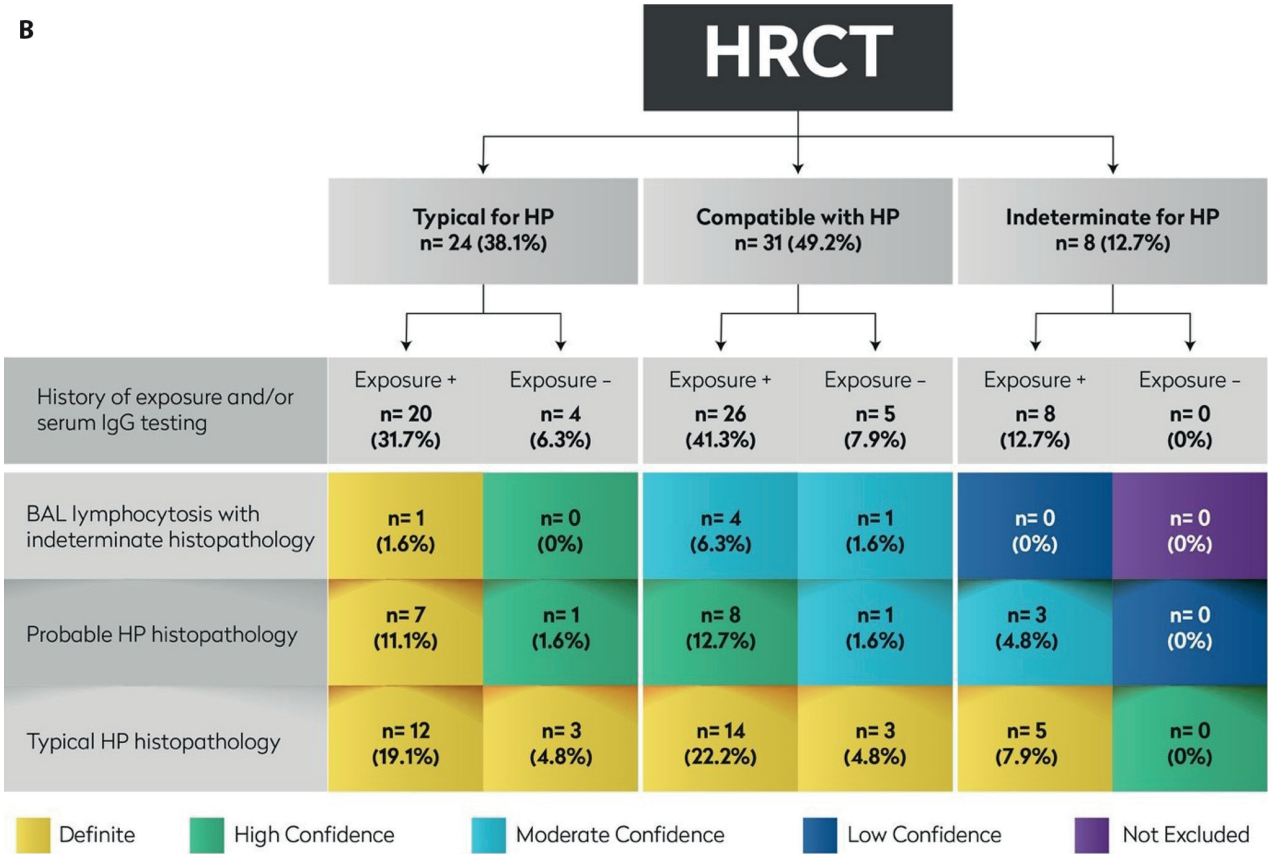

Figure 1B. Detailed evaluation of diagnosis of patients with FHP based on the incorporation of imaging, history of exposure and/or serum IgG testing, BAL lymphocytosis and histopathological findings.

of environmental exposure may be insufficient to detect a culprit antigen suggests that serum IgG testing may be advantageous [24]. However, data on the use of serum IgG are contradictory in the literature, and their sensitivity-specificity ranges are wide. The sensitivity of serum antigen-specific antibody testing in CHEST guidelines ranged from 25% to 96% and specificity from 60% to 100% [25]. One of the possible reasons for the conflicting data is the detection of antigen positivity in healthy people. Positive precipitins were found in 40-60% of exposed healthy patients, indicating the immunization state [26-28]. Another study comparing ILD and HP patients reported positive serum lgG in 7% of non-HP patients [29]. The findings of our study suggest that a detailed antigen exposure history taken by the occupational medicine physician may be sufficient for diagnosing pneumonia, with or without a serum IgG test.

Another reason for the contradictory results of serum IgG tests is that these panels need to be customized for individuals and regions. Notably, a study stating that serum IgG test may benefit clinical practice was conducted for antigens specific to an area with a high prevalence of farmer's lung [16]. Another study stated that antibody tests would contribute more to the diagnosis after being personalized depending upon the characteristics particular to the region, and an exemplary panel may include molds, bacteria, animal proteins, and chemicals [24]. Our study was strong in that respect; although Turkey does not have a personalized test, the agents detected the most in the history of exposure were also included in the serum IgG testing. However, since the most common agents were mold and bird in patients with a history of exposure, the standard test we used may be suitable for our region. On the

other hand, the algorithm leading to diagnosis by evaluating the history and the panel together did not significantly contribute to the algorithm leading to diagnosis by history alone.

Except for the exposures in the patient's history, the fact that the antigens he had never been exposed to until that day were positive in the panel was considered cross-reactivity positivity [30]. As stated earlier in our study, the antigens thought to be not the subject of exposure were positive in the panel, suggesting that they may correspond with cross-reactivity because the antigens in the standard panel were handled by an occupational medicine physician with a detailed history-taking for each patient.

There is also the presence of antigens that are not commercially available or produced in the panels, although they were detected during history-taking. Rognon et al. found *Lichtheimia corymbifera* antigen in a farmer's lung, and their study, which would be a preliminary step for kit development, was presented [31]. In Barrera's study, Saccharopolyspora rectivirgula antigen was defined as another cause of Farmer's Lung [32]. These studies show the presence of missing antigens in the standardized HP panel, which we also used, and suggest that its diagnostic value may be limited.

Another limitation of the serum lgG test is the lack of standardized antigen preparations, immunoassay techniques, and variable diagnostic thresholds for quantitative lgG tests. Nevertheless, there is a lack of data to consistently support the test as a reproducible and accurate diagnostic tool [25]. These non-standardized tests have been evaluated in various studies, and the ELISA test is thought to be more valuable [17]. In our research, the ELISA test and serum IgG test were used.

Serum lgG testing has been thought to be more significant in non-fibrotic HP studies [33-35]. Salisbury et al. did not recommend using antibody tests to diagnose fibrotic HP because antibody positivity may exist in healthy people but have a history of exposure, or antibody tests cannot detect each antigen in patients with a high diversity of antigens [36]. Our study's low serum IgG test results may be associated with the fibrotic HP diagnosis of our patients.

In the majority of these studies, the history of exposure was questioned by pulmonologists. Moreover, the decision was not taken from the diagnosis of the patients together with histopathological findings [25, 37]. Our research benefits from the comprehensive investigation with the addition of an occupational medicine physician to the MDD team [38]. The detailed evaluation of the patients, including a clear history of exposure taken by an occupational medicine physician, the pathological diagnosis of all patients, and the diagnostic decisions made in our MDD strengthen our study. Our study was limited by its retrospective nature, and it was a single-center study. As pointed out above, panels of serum IgG tests do not include all antigens. Patients may not remember especially a remote history of exposure, which can lead to a recall bias. Since only an occupational medicine physician had a history of exposure with a validated questionnaire, we could not present the possible differences between the classical history of exposure taken by clinicians and the history of exposure with a validated questionnaire taken by an occupational medicine physician.

5. Conclusions

A detailed history of antigen exposure taken by an occupational physician, and the multidisciplinary approach, improve clinicians' decisions in diagnosing patients with hypersensitivity pneumonitis with or without serum IgG testing. Considering that serum IgG tests are not easily accessible, it's thought that a detailed history-taking still maintains its place in diagnosis.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Local Institutional Ethics Committee (ethics approval number: 2006).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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

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