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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Hypersensitivity pneumonitis – experiences in treatment so far and opening up new possibilities

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SUMMARY

Introduction/Objective Hypersensitivity pneumonitis is a diagnostic and therapeutic challenge. It occurs due to an excessive immune response to inhaling an antigen (bacteria, fungi, or protozoa) to which the patient was previously sensitized. This study analyzes the clinical characteristics of patients during a 10-year period (2014–2023) treated at the Institute for Pulmonary Diseases of Vojvodina.

Methods A retrospective study was conducted including 74 patients. The first phase included data collection, the second phase included statistical data processing, and the third included the description of the obtained statistical parameters and discussion.

Results The average age was 57.61 ± 12.6 years; 52.7% were men, and 56.8% were non-smokers. Most patients had one or more comorbidities (70.3%). There were only 27 (36.5%) patients hospitalized more than three times. Progression and regression occurred in 14 (28%) patients each, while cessation occurred in 22 (44%). Fatal outcomes occurred in 7 (9.5%). It was determined that in patients with three or more comorbidities, ≥ 3 hospitalizations (9; 34.6%) occurred more often than < 3 hospitalizations (2; 4.2%) (Fisher's exact test = 14.46; p = 0.04). By comparing the prognosis of the disease with the number of hospitalizations, we found a statistically significant association (Fisher's exact test = 13.95; p = 0.001). The progression of the disease in patients with ≥ 3 hospitalizations (10; 62.5%) occurred more often than in patients with < 3 hospitalizations (4; 11.8%).

Conclusion To obtain adequate data on the success of therapy and its impact on slowing down the disease, further monitoring of patients who are on antifibrotic therapy is necessary.

Keywords: antifibrotic therapy; extrinsic allergic alveolitis; progressive pulmonary fibrosis

INTRODUCTION

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is one of the interstitial lung diseases (ILD). This disease occurs due to an exaggerated immune response to an antigen from the external environment, leading to symptoms that, in differential diagnosis, may resemble symptoms of acute lung infection or progressive irreversible lung damage, such as fibrosis [1, 2]. Numerous studies have assessed the prevalence of HP in various high-risk occupations. HP occurs most often among farmers and pigeon breeders. It can also occur in people employed in swimming pools, those exposed to contaminated air conditioners, employees exposed to tobacco, and others [3].

The most common symptoms are fever, myalgia, headache, cough, chest tightness, and dyspnea, usually occurring 4–12 hours after exposure to an antigen. The fibrotic form occurs due to prolonged exposure to the antigen, which initially causes inflammation and eventually leads to irreversible and often progressive interstitial fibrosis, which leads to respiratory failure [4].

According to the latest European Respiratory Association guidelines from 2022, HP is classified into fibrotic and non-fibrotic forms. A part of patients with chronic (fibrous) HP develop a progressive disease – progressive pulmonary fibrosis (PPF). For the diagnosis of PPF, at least two of the following three criteria are necessary: 1) worsening of respiratory symptoms; 2) pathophysiological criteria of disease progression (absolute decline in forced vital capacity (FVC) by ≥ 5% during one year of follow-up, or an absolute decrease in diffusing capacity of the lungs for carbon monoxide (DLCO) by ≥ 10% during one year of follow-up) and 3) radiological evidence of disease progression (one or more): increased volume of traction bronchiectasis and bronchiolectasia, increased volume of ground-glass opacity with traction bronchiectasis, new fine reticulations, increased volume or increased roughness of reticular abnormalities, new or increased volume of honeycombing, or loss of lung lobe volume [5].

Due to the lack of a diagnostic gold standard, diagnosing HP is not simple. It relies on numerous factors, such as history of exposure, clinical characteristics, antigen–antibody

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precipitation tests, radiological findings, lung function tests, and bronchological or surgical biopsies. Distinguishing HP from other ILDs can be challenging because HP's clinical, radiological, and pathohistological (PH) features are highly variable and overlap with those of other ILDs. The inflammatory disease may go unrecognized, while the fibrotic disease may be misdiagnosed as idiopathic pulmonary fibrosis [5, 6].

HP can be treated with pharmacological therapy, such as corticosteroids and immunosuppressants [mycophenolate mofetil (MMF), azathioprine, and monoclonal antibody rituximab]. Since 2022, nintedanib, a tyrosine kinase inhibitor, has been licensed in several countries to treat chronic fibrous ILD with a progressive phenotype. Another antifibrotic (pirfenidone) is still being investigated as a treatment for HP. Non-pharmacological therapy includes respiratory rehabilitation, continuous application of oxygen therapy, and lung transplantation. HP prevention includes avoiding allergens, getting regular vaccinations, avoiding smoking, and treating comorbidities [4, 7–10].

This paper aims to analyze the clinical characteristics of patients with HP treated at the Institute for Pulmonary Diseases of Vojvodina (IPDV) over a 10-year period.

METHODS

Participants and study design

The research was conducted in the form of a retrospective study, which included 74 patients with a diagnosis of HP who were treated at the Tuberculosis and Interstitial Lung Diseases Clinic of the Institute for Pulmonary Diseases of Vojvodina (IPDV) in Sremska Kamenica from January 1, 2014 to December 31, 2023. Data on patients diagnosed with HP found in the IPDV electronic database were gathered for the study's initial phase. The Integrated Health Information System (IHIS) was used to collect respondents' information. The following data were analyzed: sex, age, detection of disease (computed tomography, pathophysiology sample, multidisciplinary team decision), therapy, comorbidities, number of hospitalizations, smoking status, lung function parameter (FVC), and fatal outcome. By examining the respiratory function, the values taken for statistical processing were determined with the help of spirometry and gas analyses performed during the diagnosis and the last examination. The first finding before the therapy and the last finding where the patients used the therapy for a certain period were compared to assess the prognosis of HP according to the absolute change in FVC. During the data analyses, it was determined that a certain number of respondents lacked FVC parameters at the beginning or in the last finding, so in the final statistics, we had only 50 patients with valid FVC results. By comparing spirometric parameters, the absolute decline in FVC by ≥ 5% represented the progression of HP, while the absolute increase by ≥ 5% represented the regression of HP. If there was no decline or increase in FVC by ≥ 5%, it represented the cessation of the disease.

Analysis of data

Descriptive statistical methods, statistical hypothesis testing methods, and correlation methods were used for data analysis. With the help of descriptive statistical methods, standard statistics were performed, where the frequency was determined, measures of central tendency (arithmetic mean) were used for given parameters, and standard deviation was determined for variables where it was possible as a measure of variability, and relative numbers were used as indicators of structure. The non-parametric statistical analysis – χ^2 test and Fisher's exact test – were used to test statistical hypotheses. Using the φ correlation coefficient, the correlation between parameters was determined using Crosstabs. Hypotheses were tested at the level of statistical significance (α level) of 0.05. The results are shown in tables. Data were processed using IBM SPSS Statistics, Version 26.0 (IBM Corp., Armonk, NY, USA).

Ethics: The study was approved by the relevant ethics committee of the IPDV (No. 33-III/1), and all data were used in accordance with applicable ethical guidelines and data protection regulations.

RESULTS

The research included 74 patients diagnosed with HP, with a slight male predominance. In the study, the average age of the patients was 57.61 ± 12.6 years; the youngest was 31 years old, and the oldest was 82 years old. The most common way of establishing the HP diagnosis was with the help of PH findings in more than half (58.1%) of the patients. More than two-thirds of patients received corticosteroids (CS) as therapy. There were 10 patients (14.1%) on dual therapy and one patient (1.4%) on triple therapy. The largest number of patients had one or more comorbidities (70.3%), with arterial hypertension being the most common and present in 34 (45.9%) patients, followed by 17 (23%) patients with cardiovascular diseases (CVD), and 6 (8.1%) patients with osteoporosis and diabetes mellitus type II (DM II). Non-smokers were dominant, with 42 (56.8%) patients, while only 13 (17.6%) patients were active smokers (Table 1). The mean number of smoked cigarettes per patient was 10.14 ± 14.91. The minimum number of cigarettes consumed daily was 10, and the maximum was 80.

Regarding hospitalizations, only 27 (36.5%) patients had more than three hospitalizations (Table 1). No statistically significant association was found when comparing the number of hospitalizations with either sex (Fisher's exact test = 3.72; p = 0.09) or age (Fisher's exact test = 2.67; p = 0.14). Analysis of the relationship between smoking status and the number of hospitalizations also did not show a statistically significant association. A statistically significant moderate positive correlation (φ = 0.45; p = 0.04) was found between the number of comorbidities and hospitalizations (Fisher's exact test = 14.46; p = 0.04). With the help of the Z test, it was determined that in patients without comorbidities, ≥ 3 hospitalizations (18; 37.5%) occurred more often than < 3 hospitalizations (3; 11.5%).

Table 1. Frequency and percentage of patients with hypersensitivity pneumonitis across different variables

Variables		n (%)
Sex	Male	39 (52.7)
	Female	35 (47.3)
Detection of disease	Pathohistology	43 (58.1)
	CT	19 (25.7)
	Multidisciplinary team	12 (16.2)
Therapy	CS	50 (70.4)
	AZ	7 (9.9)
	AF	3 (4.2)
	CS + AZ	6 (8.5)
	CS + AF	3 (4.2)
	AZ + AF	1 (1.4)
	CS + AZ + AF	1 (1.4)
Comorbidities	0	22 (29.7)
	1	20 (27)
	2	21 (28.4)
	≥ 3	11 (14.9)
Smoking status	Smokers	13 (17.6)
	Ex smokers	19 (25.6)
	Non-smokers	42 (56.8)
Hospitalization	< 3	47 (63.5)
	≥ 3	27 (36.5)
Prognosis of HP	Progression	14 (28)
	Cessation	22 (44)
	Regression	14 (28)
Fatal outcome	Yes	7 (9.5)
	No	67 (90.5)

CS – corticosteroid therapy; AZ – azathioprine; AF – antifibrotic therapy; HP – hypersensitivity pneumonitis

Table 2. Number of hospitalizations and death outcomes depending on sex, age, smoking status, number of comorbidities and pronosis of hypersensitivity pneumonitis

Variables		Hospitalizations		p	Fatal outcome		p
		< 3	≥ 3		Yes	No	
Sex	Women	26 (54.2%)	8 (30.8%)	0.09	1 (14.3%)	33 (49.3%)	0.12
	Men	22 (45.8%)	18 (69.2%)		6 (85.7%)	34 (50.7%)	
Age	< 60 years	28 (58.3%)	10 (38.5%)	0.14	2 (28.6%)	36 (53.7%)	0.26
	≥ 60 years	20 (41.7%)	16 (61.5%)		5 (71.4)%	31 (46.3%)	
Smoking status	Smokers	13 (27.1%)	2 (7.7%)	0.14	2 (28.6%)	13 (19.4%)	0.72
	Non-smokers	24 (50%)	16 (61.5%)		4 (57.1%)	36 (53.7%)	
	Ex-smokers	11 (22.9%)	8 (30.8%)		1 (14.3%)	18 (26.9%)	
Comorbidities	No comorbidities	18 (37.5%)	3 (11.5%)	0.04*	1 (14.3%)	20 (29.9%)	0.08
	1	13 (27.1%)	8 (30.8%)		0 (0%)	21 (31.2%)	
	2	15 (31.3%)	6 (23.1%)		3 (42.9%)	18 (26.9%)	
	≥ 3	2 (4.2%)	9 (34.6%)		3 (42.9%)	8 (12%)	
Prognosis of HP	Progression	4 (11.8%)	10 (62.5%)	0.001*	2 (66.7%)	12 (25.5%)	0.45
	Cessation	18 (52.9%)	4 (25%)		1 (33.3%)	21 (44.7%)	
	Regression	12 (35.3%)	2 (12.5%)		0 (0%)	14 (29.8%)	

*p < 0.05

Also, in patients with three or more comorbidities, ≥ 3 hospitalizations (9; 34.6%) occurred more often than < 3 hospitalizations (2; 4.2%) (Fisher's exact test = 4.02; p = 0.14) (Table 2).

Most of the patients with HP were in cessation (22; 44%), while the same number of patients were in progression and regression (14; 28%) (Table 1). By comparing the prognosis of HP to the number of hospitalizations, we found a statistically significant association (Fisher's exact test = 13.95; p = 0.001). The correlation coefficient showed a moderate positive correlation between the prognosis of HP and the number of hospitalizations (φ = 0.53; p = 0.001). The progression of HP in patients with ≥ 3 hospitalizations (10; 62.5%) occurred more often than in patients with < 3 hospitalizations (4; 11.8%). The number of patients with cessation and regression of HP did not differ between patients with < 3 and ≥ 3 hospitalizations (Table 2).

No statistically significant association was found when comparing fatal outcome with gender (Fisher's exact test = 3.12; p = 0.12), age (Fisher's exact test = 1.62; p = 0.26), smoking status (Fisher's exact test = 0.78; p = 0.72), number of comorbidities (Fisher's exact test = 7.92; p = 0.08) (Table 2) or prognosis of HP (Fisher's exact test = 2.18; p = 0.45) (Table 2).

DISCUSSION

In this retrospective study, we analyzed data from 74 patients diagnosed with HP over a ten-year period from January 2014 to December 2023.

Our results show that the higher frequency of HP was in male patients (52.7%), and the average age was 57.61 ± 12.60 years. Nishida et al. [11] concluded that HP was also more common in men (50.41%), and the average age of the subjects was 63 years, similar to our study. Prior et al. [12] found similar data, showing that HP was more common in male patients (53.6%) and that the mean age was 63 ± 13.3 years.

Our study showed that there were 42 non-smokers (56.8%), 19 of them ended their active smoking status (ex-smokers) (25.7%), while there were 13 current smokers (17.6%). The data found in the study conducted by Prior et al. [12] indicate that 50.2% of respondents were non-smokers. In the research by Selman et al. [13], it is highlighted as an interesting aspect that HP is less common in cigarette smokers. They believe nicotine inhibits the activation of macrophages, the proliferation of lymphocytes, and their function, but this information does not apply to former smokers. They also state that if HP occurs in smokers, the clinical picture and prognosis are worse than in non-smokers. From 80% to 95% of patients with HP do not use tobacco. Creamer and Barratt [14] and Alexandre et al. [15] reported that HP is more common in non-smokers than in active smokers.

The largest number of patients from our study had no comorbidities associated with HP (29.7%); 27% had one comorbidity, 28.4% had two comorbidities, and 14.9% had three or more. The most common comorbidities were arterial hypertension (45.9%), CVD (23%), osteoporosis, and DM II (8.1%). Wälscher et al. [16] identified that the most frequent number of comorbidities in HP patients was 3.

Of 211 patients, 11% had no comorbidities, 58% had 1–3 comorbidities, and 31% had ≥ 4 comorbidities. The most common comorbidities found were cardiovascular (65%). According to the study by Prior et al. [12], the most common comorbidities were arterial hypertension (55.5%), DM II (20.4%), ischemic heart disease (17.5%), obstructive lung disease (9.5%), and pulmonary hypertension (9.5%) [12, 16].

The most diagnosed cases in our research were with the help of PH (43/74; 58.1%). In their study, Noh et al. [17] concluded that HP was diagnosed with biopsy and PH findings in significantly fewer patients (40%), and Lacasse et al. [18] concluded that HP was diagnosed based on PH findings in 37%. In the study by Casal et al. [19], 12.4% of patients, as in our case, were diagnosed based on the clinical presentation. Koyuncu et al. [20] stated that the PH diagnosis of HP was made in 43 (55.1%) patients and that the multidisciplinary team decided on the diagnosis of HP in 19 (24.7%) patients. In the study by Adams et al. [21], 85.7% of the group underwent an invasive technique (bronchoalveolar lavage, transbronchial biopsy, and/or surgical lung biopsy) to confirm the diagnosis of HP [17–21].

Improving diagnostic accuracy for HP is based on a multidisciplinary approach. This includes detailed anamnesis with environmental and occupational exposure history, high-resolution CT imaging, serological testing for antigen-specific antibodies, which is not a diagnostic standard in our country, unfortunately, and histopathology sampling when invasive diagnosis is needed. The use of diagnostic algorithms that integrate radiological, clinical, and pathological findings is essential in differentiating HP from other interstitial lung diseases, like idiopathic pulmonary fibrosis.

Impaired lung function in patients with HP plays a critical role in determining the severity of the disease. However, it does not differ from other interstitial lung diseases. Restrictive lung ventilation disorder is the most common pathological finding in these patients. In our research, in 22 (44%) patients, there was no significant change in FVC; in 14 (28%) patients there was a significant increase in FVC by ≥ 5%; and in another 14 (28%) patients there was a significant decline in FVC value by ≥ 5%. In the study conducted by Macaluso et al. [22], the initial average FVC value in the participants was 67.5%. A decline of ≥ 5% in FVC during the first year was observed in 45 patients (31%).

In recent years, MMF has been used in the treatment of HP. Casal et al. [23] conducted a study in which after a one-year treatment with MMF, FVC stabilized and DLCO improved significantly. In the study by Okuda et al. [24], the immunosuppressant-with-prednisolone group's mean change in FVC in the 12 months before therapy was substantially lower than that of the immunosuppressant-naive prednisolone group. In an analysis conducted by Kaneko et al. [25], the yearly FVC drop in the PPF group reduced from -11.5% before therapy to -4.2% in the first year following treatment ($p < 0.001$). There was no significant difference between the annual FVC change before and after therapy in the non-PPF group (1.6% *vs.* -1.7%, $p = 0.065$).

We found that the largest number of patients were treated with corticosteroids (50/74; 70.64%), followed by patients who used azathioprine (7/74; 9.9%), and in third place were patients on antifibrotic drugs (nintedanib) (3/74; 4.2%). The therapeutic indication for antifibrotic therapy for progressive forms of HP was expanded in Serbia in 2022, and due to this fact, the number of patients receiving this therapy is small. In their study, Salisbury et al. [26] noted that the most common forms of HP treatment were corticosteroids and azathioprine. Wijsenbeek et al. [27] monitored the effects of nintedanib in patients with progressive pulmonary fibrosis (PPF) using the Living with Pulmonary Fibrosis (L-PF) questionnaire. Based on the assessment of L-PF questionnaire scores, nintedanib reduced the worsening of symptoms of dyspnea, fatigue, and cough during the 52-week study in patients with PPF.

Although lung transplantation is not possible in our country, it is a treatment for patients with HP in developed countries. In the University Hospital of Munich, in the last 30 years, there were a total of 1054 lung transplantations performed, and the best five-year survival rate was observed in patients with lymphangioleiomyomatosis (LAM) and HP [28].

Our study found a statistically significant correlation between the number of comorbidities and hospitalizations. No statistically significant association was found between the death outcome and the number of comorbidities. Prior et al. [12] state that there was a statistically significant association between the number and type of comorbidities with the death outcome and increased number of hospitalizations. The highest number of deaths was in the group of patients with cardiovascular comorbidities. A combination of better patient education, earlier diagnosis, and more proactive disease care is probably needed to lower hospitalization rates among HP patients. Broader screening for environmental exposures, prompt therapy beginning after diagnosis, and multidisciplinary team participation are a few possible interventions. Additionally, improving patient access to social support services, regular follow-up, and pulmonary rehabilitation can help manage comorbidities and reduce illness exacerbations, which may minimize the frequency of hospitalizations. Wälscher et al. [16] report that deceased patients had more comorbidities than survivors. A study by Schwarzkopf et al. [29] reported that comorbidities had a clinically significant adverse effect on survival that was more pronounced in the case of untreated comorbidities. In our study, the reason for the cause-and-effect relationship between a higher number of comorbidities and a lower number of hospitalizations is not known. We can only assume that the patients received adequate therapy for associated diseases and controlled them well.

Fatal outcomes were observed in seven (9.5%) of our patients. In a study conducted by Gonnelli et al. [30], the five-year survival rate after diagnosis of HP was 66%.

The limitations of this study are: data on the pulmonary function parameter (FVC) were not available in all patients; diffusion capacity (DLCO) values were not available in most patients; therefore, the DLCO parameter was not extracted from the system in this study. The primary reason for the low number of patients in our cohort who

received antifibrotic medication is that antifibrotics were only recently authorized for use in Serbia, specifically in 2022, for progressive types of HP. As a result, only a small number of patients had access to these medications during the study period.

CONCLUSION

With the introduction of new treatment protocols for the use of antifibrotic drugs, further studies are necessary to include a more extended period and a larger number of patients on antifibrotic therapy to obtain more complete data on the success of the therapy and its effect on disease regression. Treatment will become increasingly complex, with new therapeutic options and the possibility of daily progress, taking into account pharmacological and non-pharmacological forms of therapy and a multidisciplinary approach. The future of patients with PPF is realized through the joint effort of each medical worker who treats these patients and the patients themselves.

Conflict of interest: None declared.

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Хиперсензитивни пнеумонитис – досадашња искуства у лечењу и отварање нових могућности

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САЖЕТАК

Увод/Циљ Хиперсензитивни пнеумонитис представља дијагностички и терапијски изазов. Настаје као последица претераног имунолошког одговора на удисање антигена (бактерија, гљивица или протозоа) на које је болесник претходно сензибилисан.

Циљ ове студије био је да се анализирају клиничке карактеристике болесника лечених у Институту за плућне болести Војводине током 10 година (2014–2023).

Методе Спроведена је ретроспективна студија са 74 болесника. Прва фаза истраживања обухватала је прикупљање података о болесницима, друга фаза статистичку обраду података, а трећа фаза опис добијених статистичких параметара и дискусију.

Резултати Просечна старост болесника била је 57,61 ± 12,6 година; 52,7% су били мушкарци, а 56,8% непушачи. Највише болесника имало је један или више коморбидитета (70,3%). Само 27 (36%) болесника било је хоспитализовано више од три пута. До прогресије и регресије дошло је код 14 (28%) болесника, док је стагнација потврђена код 22 (44%) болесника. Фатални исход се десио код седам (9,5%) болесника. Утврђено је да се код болесника са три или више коморбидитета чешће јављају ≥ 3 хоспитализације (9; 34,6%) него < 3 хоспитализације (2; 4,2%) (Фишеров тест = 14,46; $p = 0,04$). Упоређујући прогнозу болести са бројем хоспитализација, установљена је статистички значајна повезаност (Фишеров тест = 13,95; $p = 0,001$). Прогресија болести код болесника са ≥ 3 хоспитализације (10; 62,5%) чешћа је него код болесника са < 3 хоспитализације (4; 11,8%).

Закључак За добијање адекватних података о успешности терапије и њеном утицају на
успоравање болести неопходно је даље праћење болесника који су на антифибротској терапији.

Кључне речи: антифибротска терапија; екстринзични алергијски алвеолитис; прогресивна плућна фиброза