УДК 616.24-002-097.1-07:612.017.3
https://doi.org/10.20538/1682-0363-2021-4-93-102

Clinical, radiologic, and morphological diagnosis of hypersensitivity pneumonitis

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ABSTRACT

Aim. To study the relationship between clinical, radiologic, and morphological features in nonfibrotic and fibrotic hypersensitivity pneumonitis.

Materials and methods. Clinical symptoms, data of high-resolution computed tomography, parameters of external respiration, and histological changes in the lung tissue obtained via open and transbronchial biopsies were studied retrospectively in 175 patients with hypersensitivity pneumonitis (HP). Statistical analysis was performed using the Statistica software.

Results. We found that the clinical error rate in the diagnosis of HP was 84.5%, among pathologists – 92%. Among all the variants of HP, the most common was fibrotic HP. It was shown that non-necrotizing granulomas and giant cells in the cavities of the alveoli, microcells, and interalveolar septa were more typical of nonfibrotic HP.

In fibrotic HP, peribronchial fibrosis, smooth muscle metaplasia in fibrotic areas, and the presence of fibroblastic foci in the walls of terminal bronchioles are signs of differential diagnosis with usual interstitial pneumonia. The classical triad of histological signs was observed in 19.2% of patients with nonfibrotic HP and in 5.6% of patients with fibrotic HP.

Conclusion. Diagnosis of HP is complex and should be based on a multidisciplinary approach involving clinicians (pulmonologists), radiologists, functional diagnostics specialists, and pathologists. In this case, it is imperative to take into account and identify factors causing development of the disease, as well as the age of patients.

Key words: nonfibrotic and fibrotic hypersensitivity pneumonitis, multidisciplinary approach, histological features.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

For citation: Cherniaev A.L., Kusraeva E.V., Samsonova M.V., Avdeev S.N., Trushenko N.V., Tumanova E.L. Clinical, radiologic, and morphological diagnosis of hypersensitivity pneumonitis. *Bulletin of Siberian Medicine.* 2021; 20 (4): 93–102. https://doi.org/10.20538/1682-0363-2021-4-93-102.

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Клинико-рентгено-морфологическая диагностика гиперчувствительного пневмонита

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РЕЗЮМЕ

Цель. Изучить взаимосвязь клинико-рентгено-морфологических признаков при нефиброзном и фиброзном вариантах гиперчувствительного пневмонита.

Материалы и методы. Ретроспективно у 175 пациентов с гиперчувствительным пневмонитом (ГП) были изучены клинические симптомы, данные компьютерной томографии высокого разрешения, показатели функции внешнего дыхания, гистологические изменения ткани легких, полученных при открытых и трансбронхиальных биопсиях. Статистический анализ осуществляли при помощи программы Statistica.

Результаты. Выявлено, что уровень ошибок в клинической практике при диагностике ГП составил 84,5%, среди патологоанатомов – 92%. Среди всех вариантов ГП наиболее часто встретился фиброзный. Показано, что ненекротические гранулемы, гигантские клетки в полостях альвеол, микросот и в межальвеолярных перегородках более характерны для нефиброзного ГП. При фиброзном ГП мозаичный перибронхиолярный фиброз, гладкомышечная метаплазия в зонах фиброза, наличие фибробластических фокусов в стенках терминальных бронхиол являются признаками дифференциальной диагностики с обычной интерстициальной пневмонией. Классическую триаду гистологических признаков наблюдали в 19,2% при нефиброзном ГП, при фиброзном – в 5,6%.

Заключение. Диагностика ГП сложна и должна быть основана на мультидисциплинарном подходе с участием клиницистов (пульмонологов), рентгенологов, специалистов по функциональной диагностике и патологоанатомов. При этом следует обязательно учитывать и выявлять факторы, вызывающие развитие заболевания и возраст пациентов.

Ключевые слова: нефиброзный и фиброзный гиперчувствительный пневмонит, мультидисциплинарная диагностика, гистологические признаки.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Для цитирования: Черняев А.Л., Кусраева Э.В., Самсонова М.В., Авдеев С.Н., Трушенко Н.В., Туманова Е.Л. Клинико-рентгено-морфологическая диагностика гиперчувствительного пневмонита. *Бюллетень сибирской медицины.* 2021; 20 (4): 93–102. https://doi.org/10.20538/1682-0363-2021-4-93-102.

INTRODUCTION

Hypersensitivity pneumonitis (HP) (extrinsic allergic alveolitis) refers to a group of immune-mediated diseases of the lung tissue and terminal and respiratory bronchioles that develop in response to antigen inhalation [1].

The most well-known types of HP are bird fancier's lung [2], farmer's lung, air-conditioner lung caused by cold air in air-conditioned rooms, chemical worker's lung, and drug-induced bagassosis [3]. According to E. Fernández Pérez et al. [4], the prevalence of HP ranges from 0.3 to 0.9 per 100,000 population. According to F. Morell et al. [5], the incidence of HP amounts to 6.2 per 100,000 population sleeping on feather pillows and 54.6 per 100,000 among poultry breeders. S. Dhooria et al. [6] demonstrated that from 2015 to 2017, 10.7% out of 803 patients with interstitial lung disease (ILD) were diagnosed with HP.

The major pathogenetic mechanisms of the disease remain unclear; however, the development of types III and IV hypersensitivities has been shown. Antigen sensitization and manifestation of clinical symptoms after repeated exposure to the antigen play a key role [7].

Historically, three HP types were distinguished: acute, subacute, and chronic. Later, acute (inflammatory, cellular) and chronic HP were distinguished, which reflected the clinical course of the disease and differed in outcomes, survival, and treatment strategy [8, 9]. In 2020, the first international guidelines on HP were created, which suggest distinguishing nonfibrotic and fibrotic HP phenotypes [1].

Symptoms of nonfibrotic (inflammatory) HP are shortness of breath, cough, chills, and fever that occur within 4–8 hours (in farmer's lung, within 12–18 hours) after exposure to the antigen and can accelerate within several hours or days [9, 10]. In fibrotic HP, patients experience shortness of breath, slightly increasing with time, dry cough, malaise, fatigue, and loss of appetite [9, 10]. In high-resolution computed tomography (HRCT) of the lungs, nonfibrotic HP is characterized by multifocal, diffuse, and centrilobular ground-glass opacities, areas of mosaic attenuation, and "air traps" during the exhalation phase [11, 12]. Among all ILDs, areas of mosaic attenuation are more common in nonfibrotic HP, which makes this sign diagnostically significant and can lead to a correct diagnosis [13]. Major signs of fibrotic HP include alteration of lung architecture, reticular changes, areas of mosaic attenuation, the head cheese sign (juxtaposition of areas with ground-glass opacities, mosaic attenuation and normal lung tissue), traction bronchiectasis, and honeycomb lung [12, 14].

The gold standard for collecting a sample is a surgical lung biopsy. A transbronchial lung biopsy provides little information due to the small amount of lung tissue. However, a transbronchial cryobiopsy is believed to be promising in diagnosing HP [15, 16].

In nonfibrotic HP, histological examination reveals bronchiolocentric interstitial pneumonia (IP), chronic cellular bronchiolitis, granulomatous inflammation, with granulomas being usually small and loose masses with indistinct margins, consisting of epithelioid and multinucleated giant cells (MGCs) commonly located in peribronchiolar regions. Additionally, scattered MGCs are observed, containing asteroid bodies, needle-shaped cholesterol crystals, and calcifications (Schaumann bodies) in the cytoplasm.

In fibrotic HP, pulmonary arterial hypertension, fibrosis, honeycombing, obliterative bronchiolitis, and MGCs in the alveolar lumina, honeycombs, and interalveolar septa prevail.

The aim of the study was to perform a retrospective analysis of the relationship between clinical, radiologic, and morphological features in nonfibrotic and fibrotic HP.

MATERIALS AND METHODS

The research included 175 patients. We studied clinical symptoms from medical histories, performed HRCT of the lungs, and obtained open (via videothoracoscopy, through a small thoracotomy incision) and transbronchial biopsy specimens. Clinically, the following signs were studied: shortness of breath on the Modified Medical Research Council (mMRC) scale, cough, sputum production, and the presence or absence of generalized weakness.

When analyzing HRCT findings, attention was paid to the localization of changes in the lung tissue, the presence of ground-glass opacities, "air traps", reticular changes, the head cheese sign, traction bronchiectasis, and disseminated focal lung disease.

When studying the respiratory function, the following was taken into account: forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), the forced expiratory volume in 1 second to forced vital capacity ratio (FEV1/FVC), total lung capacity (TLC), residual lung volume (RV), and diffusing lung capacity for carbon monoxide (DLCO).

Histological changes in the lungs were studied and then compared with the clinical referral diagnoses and pathology reports.

We conducted a histological examination of sections stained with hematoxylin and eosin and Van Gieson's stain to detect collagen and elastic fibers. The following changes were revealed: obliterative bronchiolitis; peribronchiolar fibrosis with lymphocytic infiltrates; organizing pneumonia; moderate fibrosis; smooth muscle metaplasia in fibrosis and interalveolar septa; nonspecific interstitial pneumonia (NSIP); loose non-necrotizing granulomas; honeycombing; MGCs in the alveolar lumina, interalveolar septa, and honeycombs; fibroblastic foci and their localization; bronchiolectasis; Schaumann bodies; and histological signs of secondary pulmonary arterial hypertension (SPAH).

The statistical analysis was carried out using STATISTICA 10.0 for Windows 10. The Shapiro – Wilk *W*-test was used to determine the nature of the sample and the Mann–Whitney U test was applied to determine the reliability of differences in the samples with non-normal distribution, which were considered statistically significant at $p < 0.05$. The correlations were assessed using the Spearman's rank order correlation coefficient, whereas the strength of the correlation coefficients was evaluated with the Chaddock scale.

RESULTS

HP was diagnosed only in 15.5% of all clinical referral diagnoses, i.e. clinicians misdiagnosed the disease in 84.5% of cases. Fig. 1 demonstrates the range of diagnoses.

Fig. 2 represents the range of histopathologic diagnoses. HP was diagnosed only in 8% of cases. Most often, patients were diagnosed with fibrosing lung disease (idiopathic pulmonary fibrosis). In other words, the error rate in the histological examination reached 92%. It should be noted that in 49.5% of cases, a histology report was not provided.

Fig. 3 demonstrates the frequency of the above-listed clinical symptoms in fibrotic and nonfibrotic HP. Shortness of breath, cough, and sputum production prevailed in fibrotic HP. However, the parameter of shortness of breath on the mMRC scale was not reliable.

Fig. 4 demonstrates the parameters of the pulmonary function tests. Parameters of bronchial obstruction prevailed in nonfibrotic HP; at the same time, the differences between the DLCO parameters were not significantly different in two HP types.

Fig. 5 presents data on the HRCT findings. We observed significantly more reticular changes in fibrotic HP and traction bronchiectasis was more common. Honeycombing was observed only in fibrotic HP. The differences between the remaining parameters in fibrotic and nonfibrotic HP were not statistically significant. Two HP types demonstrated diffuse changes in 42% of cases; lesions of the lower lobes prevailed in both lungs (47%). At the same time, the upper lobe lesions were detected in 11% of cases, which practically does not occur in usual interstitial pneumonia (UIP).

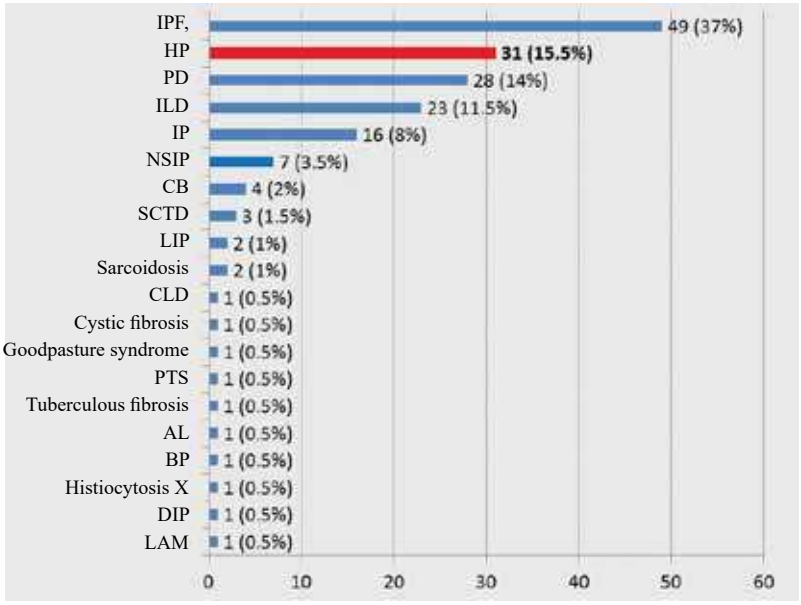


Fig. 1. Clinical referral diagnoses: IPF – idiopathic pulmonary fibrosis, HP – hypersensitivity pneumonitis, PD – pulmonary dissemination, ILD – interstitial lung disease, IP – interstitial pneumonia, NSIP – nonspecific interstitial pneumonia, CB – chronic bronchitis, SCTD – systemic connective tissue diseases, LIP – lymphoid interstitial pneumonia, CLD – cystic lung disease, PTS – post-thrombotic syndrome, AL – amiodarone lung, BP – bilateral pneumonia, DIP – desquamative interstitial pneumonia, LAM – lymphangioleiomyomatosis

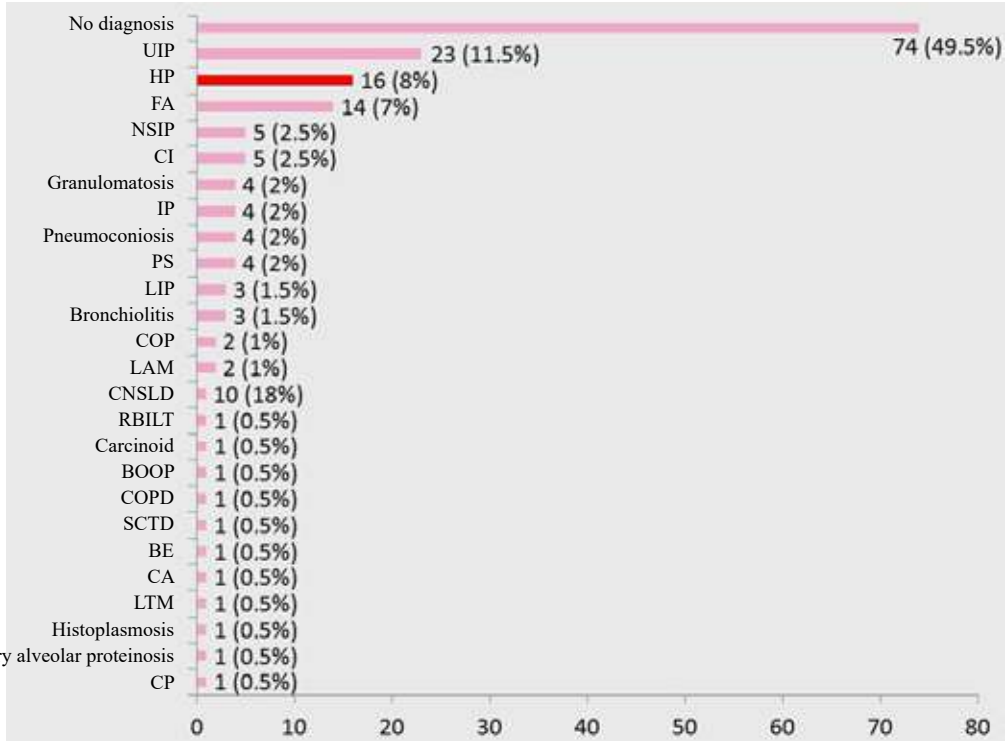


Fig. 2. Morphological referral diagnoses in HP: no diagnosis – no morphological report on the specimen from another institution was included in the medical history, FA – fibrosing alveolitis, CI – chronic inflammation, PS – pneumosclerosis, COP – cryptogenic organizing pneumonia, CNSLDs – chronic non-specific lung diseases, RBILT – respiratory bronchiolitis with another interstitial lung disease, BOOP – bronchiolitis obliterans organizing pneumonia, CA – capillary adenoma, LTM – lung tissue malformation, CP – chronic pneumonia

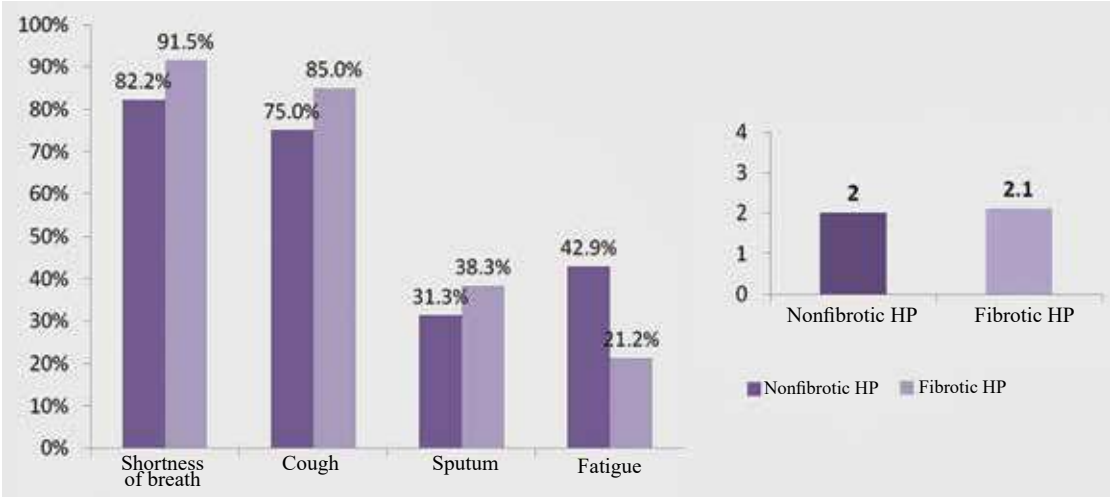


Fig. 3. The frequency of clinical symptoms in nonfibrotic and fibrotic HP

Parameter	FVC, %	FEV 1, %	FEV1/FVC	TLC, %	RV, %	DLCO, %
Nonfibrotic HP	78.37	**84.79**	**91**	76.9	103.5	53.32
Fibrotic HP	60.5	**64.22***	**88.19****	70.1	99.22	47.66

Fig. 4. Pulmonary function test parameters

Fig. 6 shows histological changes in the lung tissue in nonfibrotic HP. Obliterative bronchiolitis was the most common, granulomas and MGCs were observed to a lesser extent. NSIP, organizing pneumonia, and obliterative bronchiolitis with organizing pneumonia were detected in 96.1% of cases.

Fig. 7 demonstrates the frequency of histological signs in fibrotic HP. A microscopic examination revealed that in both fibrotic and nonfibrotic HP, obliterative bronchiolitis was mostly "string-like" (Fig. 8 *a*, *b*), and sometimes it was with fibroblastic foci in the walls of the terminal bronchioles (Fig. 8,*b*). In nonfibrotic HP, we observed MGCs in the alveolar lumina, cavities, and the interstitium (Fig. 10,*a*), non-necrotizing loose granulomas (Fig. 10,*b*), and NSIP (Fig. 11). Fibrotic HP can be also characterized by MGCs, moderately pronounced peribronchiolar interstitial fibrosis with smooth muscle metaplasia (Fig. 9), areas of bridging fibrosis (Fig. 12), peribronchiolar fibrosis with lymphocytic infiltrates, organizing pneumonia, honeycombing, Schaumann bodies, bronchiolectasis, and histological signs of SPAH (Fig. 13).

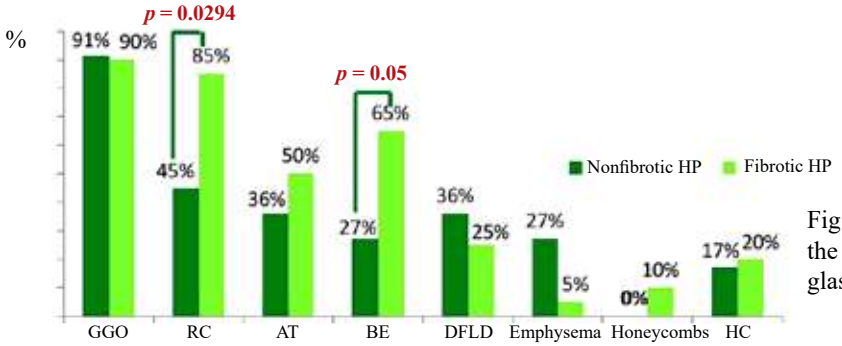


Fig. 5. Changes in the lung tissue on HRCT: HC – the head cheese sign, AT – air traps, GGO – ground-glass opacities, RC – reticular changes, DFLD disseminated focal lung disease

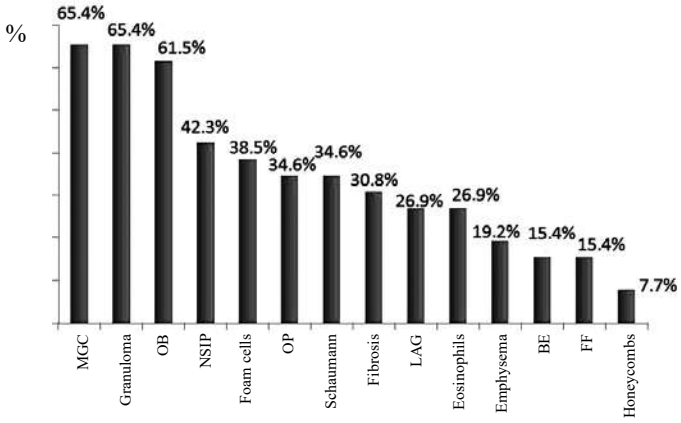


Fig. 6. The frequency of histological features in nonfibrotic HP: BE – bronchiectasis

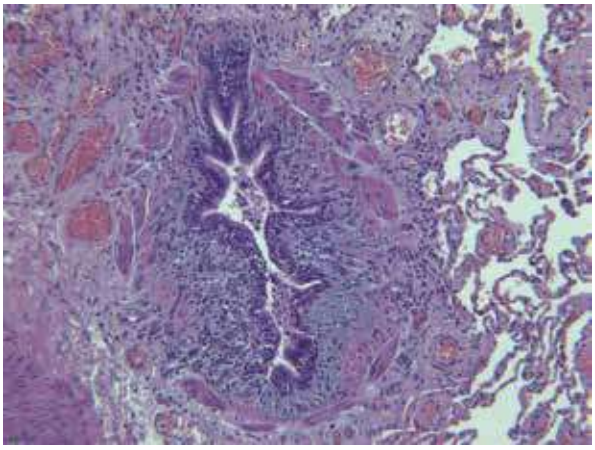
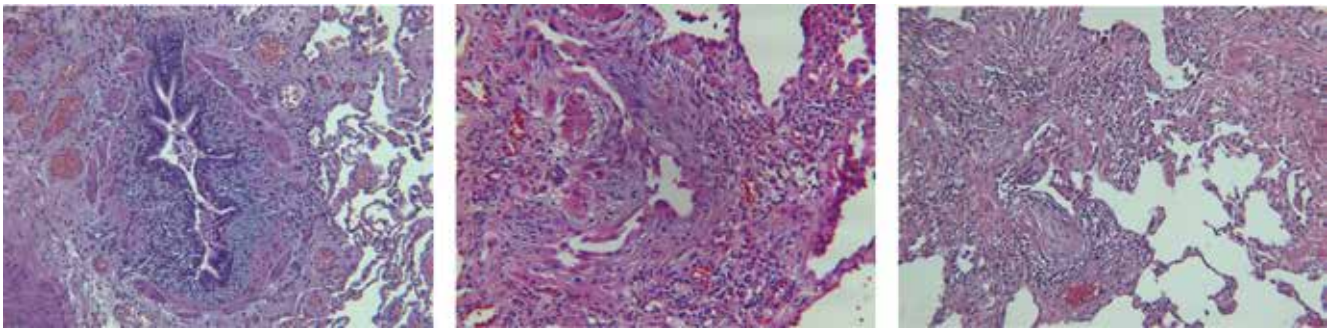
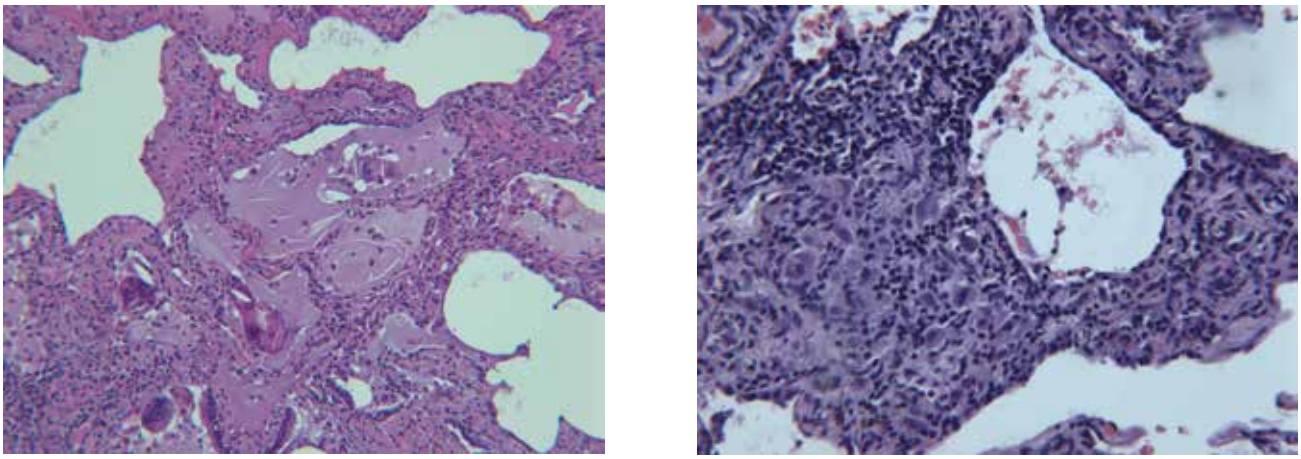


Fig. 7. The frequency of histological features in fibrotic HP



a *b* *c*

Fig. 8. Obliterative bronchiolitis in nonfibrotic and fibrotic HP: *a* – obliterative bronchiolitis, *b* – "string-like" bronchiolitis, *c* – fibroblastic foci in the wall of the terminal bronchiole with narrowing of the lumen; hematoxylin and eosin stain, ×100



a *b*

Fig. 9. Nonfibrotic HP. Giant cells and granuloma in nonfibrotic HP: *a* – MGCs in the alveolar lumina, *b* – peribronchiolar granuloma; hematoxylin and eosin stain, ×100

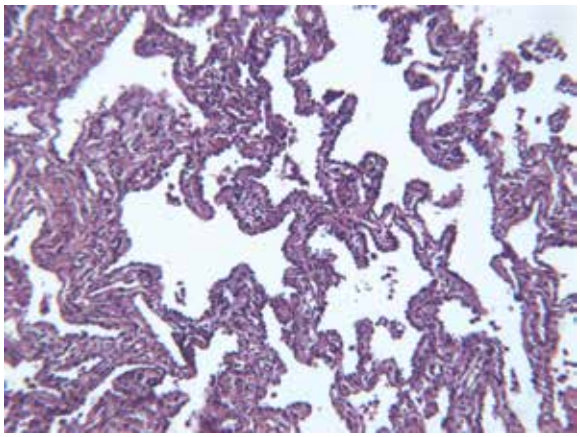


Fig. 10. Cellular NSIP in nonfibrotic HP; hematoxylin and eosin stain, ×100

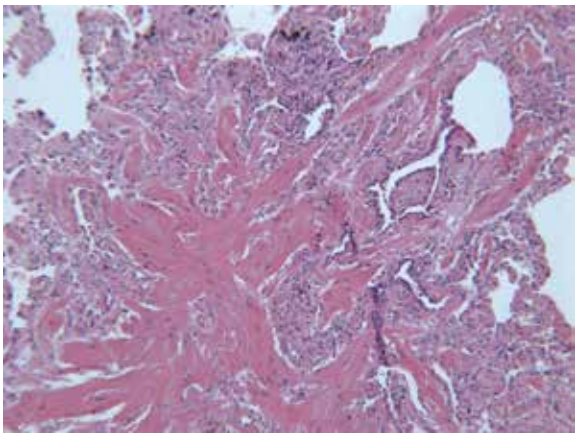


Fig. 11. Fibrotic HP. Smooth muscle metaplasia in the peribronchiolar fibrosis area; hematoxylin and eosin stain, ×100

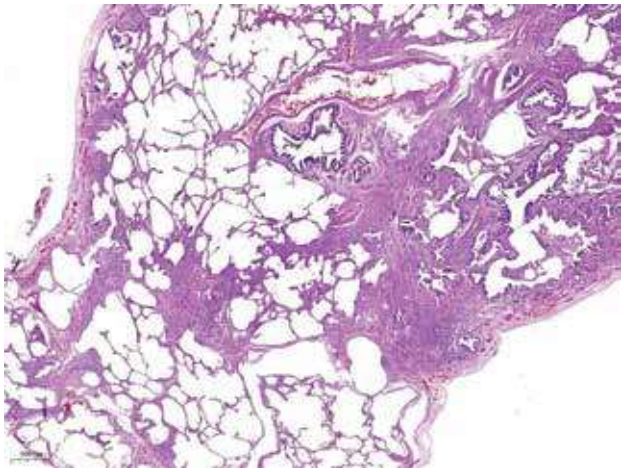


Fig. 12. Fibrotic HP. Bridging fibrosis; hematoxylin and eosin stain, ×200

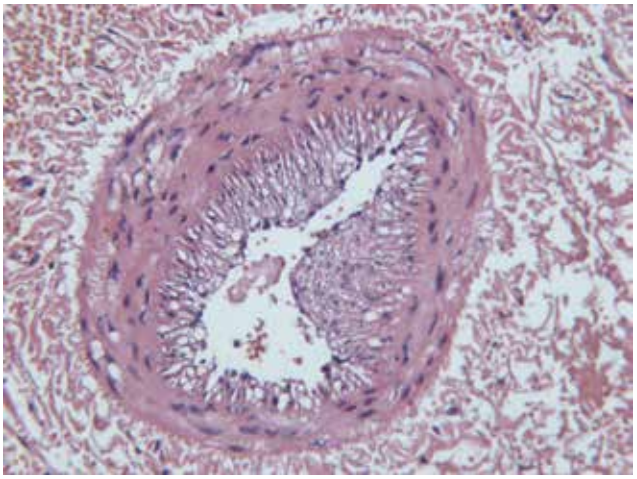


Fig. 13. SPAH in fibrotic HP. Proliferation of the intima with narrowing of the pulmonary artery branch lumen; hematoxylin and eosin stain, ×200

We compared the results of the histological analysis and lung CT findings and established that nonfibrotic HP was detected in 16% of cases, fibrotic HP – in 62% of cases, and possible HP – in 22% of cases. Pulmonary emphysema was detected only in 16 patients (9%), with one case having a combination of fibrotic HP and pulmonary alveolar proteinosis (PAP). The three key morphological HP signs that were described earlier (i.e. granulomas and/or MGCs, obliterative bronchiolitis, and NSIP) were found in 19.2% of cases in nonfibrotic HP and in 5.6% of cases in fibrotic HP.

The correlation analysis revealed a significant moderate relatioship between (1) NSIP frequency in the microscopic evaluation and the presence of honecombing in HRCT ($r = –0.34$); (2) between NSIP and the head cheese sign in HRCT ($r = 0.40$); (3) between the presence of the granuloma and reticular changes ($r = –0.34$); (4) between the presence of the granuloma and traction bronchiectasis ($r = –0.31$), (5) between honecombing and traction bronchiectasis ($r = 0.42$), and (6) between honeycombing and focal dissemination ($r = –0.32$).

DISCUSSION

Clinical HP manifestations are non-specific. The presence of shortness of breath in both HP types on the mMRC scale was not statistically significant. As in the studies by G. Raghu et al., M. Vasakova et al., M. Selman et al. [1, 9, 10], shortness of breath, cough, and sputum were 9.3, 10, and 7%, respectively, more common in fibrotic HP, but they were not statistically significant. At the same time, fatigue was observed twice as often in nonfibrotic HP. HRCT showed that, unlike UIP and lung changes in systemic connective tissue disease (SCTD), changes in the upper, middle, and lower parts of the lungs were observed in two HP types.

Consistent with the data by G. Raghu et al., B. Chong et al., and S. Kligerman et al. [1, 11, 13], pulmonary dissemination and emphysema were more often observed in nonfibrotic HP, but these changes were not statistically significant. The presence of reticular changes, “air traps”, and bronchiectasis was significantly more often observed in fibrotic HP, which did not differ from the data obtained by G. Raghu et al., L. Wang et al., and O. Dias et al. [1, 12, 14].

A microscopic evaluation of the lungs for nonfibrotic HP revealed bronchiolocentric IP, chronic cellular bronchiolitis, and granulomatous inflammation, with granulomas being usually small and loose, in the form of poorly defined clusters of epithelioid cells and MGCs, which were usually located in the peribronchiolar region. Moreover, scattered MGCs were observed in the alveolar lumina and honeycombs, terminal and respiratory bronchioles, and the interstitium. These cells often contained non-specific cytoplasmic inclusions, such as asteroid bodies and/or cholesterol crystals, and Schaumann bodies. Our data are consistent with those obtained by G. Raghu et al. and M. Kitaichi et al. [1, 17] on the fact that the described above histological signs were observed in possible nonfibrotic HP in the absence of granulomas.

Fibrotic HP is characterized by altered lung architecture due to centriacinar emphysema and bridging fibrosis; fibrous IP; the appearance of fibroblastic foci (usually in the walls of the terminal bronchioles), peribronchiolar metaplasia; and less often – by the presence of granulomas. Our data are also consistent with those of G. Raghu et al., M. Kitaichi et al., and S. Chiba et al. [1, 17, 18] in the fact that fibrosis covers both subpleural and centroacinar regions. However, as fibrosis progresses in HP, it is extremely difficult to distinguish its changes in the lungs from UIP. Moreover, the obtained data are consistent with the data of G. Raghu et al. [1] in the fact that the same histological signs are observed in possible fibrotic HP as in verified fibrotic HP, but without honeycombing and granulomas, with less pronounced peribronchiolar metaplasia and single MGCs.

In our opinion, the list of histological signs presented in the guidelines of 2020 should be supplemented with such signs as loose mosaic peribronchiolar fibrosis in fibrotic HP, smooth muscle metaplasia in the areas of fibrosis, and the presence of fibroblastic foci in the walls of terminal bronchioles, as opposed to the same foci in the walls of cells in UIP. The correlation analysis revealed significant moderate correlations between the HRCT parameters and histological changes in the lungs; however, we believe this does not allow to diagnose HP with certainty. HP is mainly diagnosed based on identifying the impact of an external factor, a CT scan of the lungs, and histopathological signs. The major problem is that no single HP sign alone is sufficient and its presence is not obligatory. This leads to possible multiple combinations of signs that contribute to correct HP diagnosis, presented in the guidelines of 2020 [1].

The age of patients with ILDs should be taken into account. Patients with different HP types are usually under 60 years of age, whereas patients with UIP are over 60.

CONCLUSIONS

1) Among clinicians, the error rate in HP diagnosis accounts for 84.5%, whereas among pathologists, it reaches 92%.

2) Among all HP types, fibrotic HP is the most common.

3) Non-necrotizing granulomas and giant cells in the alveolar lumina, honeycombs, and the interalveolar septa are more typical of nonfibrotic HP.

4) The following signs distinguish fibrotic HP from UIP: mosaic peribronchiolar fibrosis, smooth muscle metaplasia in the areas of fibrosis, and the presence of fibroblastic foci in the walls of terminal bronchioles.

4) The three key morphological HP signs were observed only in 19.2% of nonfibrotic HP cases and in 5.6% of fibrotic ones.

5) The diagnosis of HP is complex and should be based on a multidisciplinary approach involving clinicians (pulmonologists), radiologists, functional diagnostics specialists (pulmonary function technologists), and pathologists. At the same time, it is necessary to take into account and identify the factors that cause the development of the disease and the age of patients.

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Received 20.04.2021
Accepted 10.09.2021