Respir Case Rep 2024;13(3):133-140 DOI: 10.5505/respircase.2024.82856

Fibrotic Hypersensitivity Pneumonia: Three Cases Diagnosed Histopathologically

Fibrotik Hipersensitivite Pnömonisi: Histopatolojik Tanılı Üç Olgu

Coşkun Doğan, Göksel Menek

Abstract

Hypersensitivity Pneumonia is a lung disease with two forms – fibrotic and non-fibrotic – which predominantly progress with lymphocytic infiltration and granulomatous inflammation as a result of both humoral and cellular response following the exposure of susceptible individuals to any antigen. In cases with the appropriate clinical features, high-resolution lung tomography can aid the diagnosis. Coarse reticulations with irregular linear opacities/lung distortions, traction bronchiectasis and honeycombing, centrilobular nodules, ground glass densities, mosaic perfusions and air imprisonment areas can be counted among the most significant radiological features. Treatment withdrawal is the basis for corticosteroids or immunosuppressive therapies, while antifibrotic agents hold promise as new treatment options in the future. In the present study, the diagnosis, imaging and treatment characteristics of three cases with Hypersensitivity Pneumonia diagnosed using different histopathological methods are reviewed in the light of current literature.

Keywords: *Fibrosis, Hypersensitivity Pneumonia, Interstitial lung diseases.*

Öz

Hipersensitivite Pnömonisi; Duyarlı bireylerde, herhangi bir antijene maruz kaldıktan sonra meydana gelen hem humoral hem hücresel yanıt sonucunda ağırlıklı olarak lenfositik infiltrasyon ve granülomatöz inflamasyon ile seyreden fibrotik ve non fibrotik iki formu olan bir akciğer hastalığıdır. Uygun klinik özellikleri taşıyan olgularda yüksek rezolüsyonlu akciğer tomografisi tanıda çok yardımcıdır. Düzensiz lineer opasiteler/akciğer distorsiyonu ile birlikte kaba retikülasyonlar, traksiyon bronşektazisi ve bal peteği, sentrilobüler nodüller, buzlu cam dansiteleri, mozaik perfüzyon ve hava hapsi alanları önemli radyolojik özellikleri arasındadır. Tedavisinde etkenden uzaklaşma, kortikosteroidler veya immünsüpresif tedaviler temeli oluşturur iken, antifibrotik ajanlar gelecekteki yeni tedavi seçenekleri açısından umut vadetmektedir. Bu yazıda, tanısı farklı histopatolojik yöntemler ile koyulan üç Hipersensitivite Pnömonisinin tanı, görüntüleme ve tedavi özellikleri güncel literatür eşliğinde gözden geçirilmiştir.

Anahtar Kelimeler: *Fibrozis, Hipersensitivite Pnömonisi, İntertisyel akciğer hastalıkları.*

Department of Pulmonology, İstanbul Medeniyet University Faculty of Medicine, İstanbul, Türkiye

İstanbul Medeniyet Üniversitesi Tıp Fakültesi Göğüs Hastalıkları Anabilim Dalı İstanbul

Submitted (Başvuru tarihi): 08.05.2024 ***Accepted (Kabul tarihi):*** 27.08.2024

Correspondence (İletişim): Coşkun Doğan, İstanbul Medeniyet Üniversitesi Tıp Fakültesi Göğüs Hastalıkları Anabilim Dalı İstanbul

e-mail: coskund24@hotmail.com

Hypersensitivity Pneumonia (HP) is an immune-mediated inflammatory and/or fibrotic disease that affects the lung parenchyma and small airways and is caused by an antigen in susceptible individuals. It was previously referred to as extrinsic allergic alveolitis and classified as acute, subacute or chronic, but is today referred to as HP and classified as fibrotic or non-fibrotic. HP may require differential diagnosis, primarily to distinguish it from fibrotic HP (FHP) and other interstitial lung diseases (ILD). HP should be considered in the differential diagnosis of newly identified ILD cases, given its unique diagnostic approaches and treatment options when compared to other ILDs (1). Today, hundreds of organic and inorganic causes have been linked to HP (Table 1) (2).

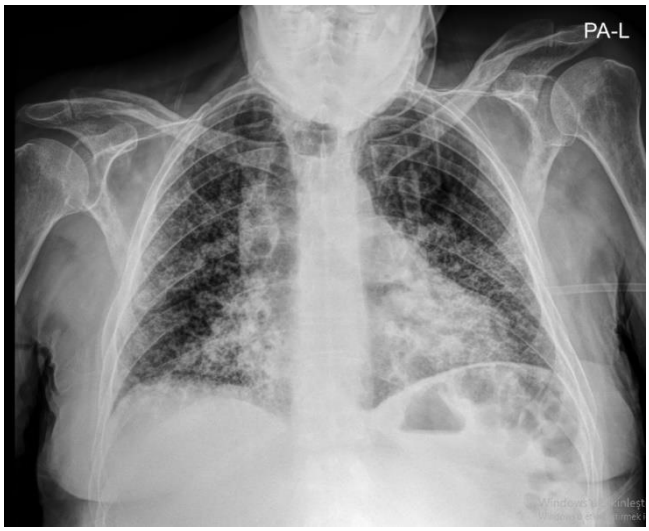

Figure 1a: Chest radiography revealing reticular-reticulonodular infiltration of the bilateral middle lower areas

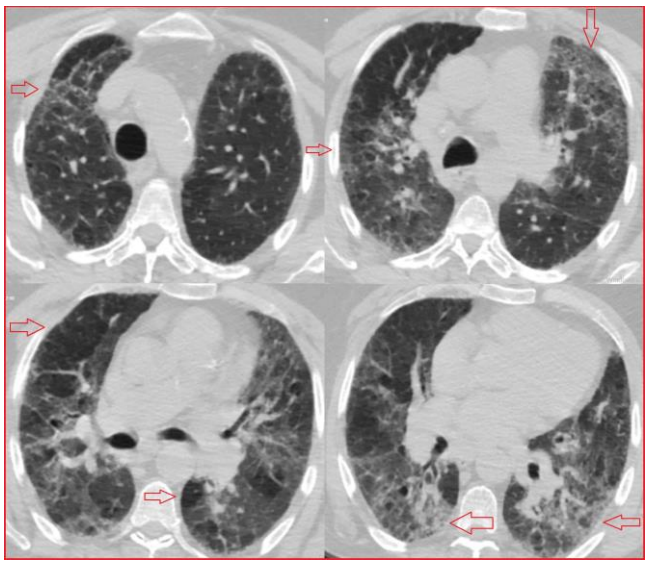

Figure 1b: HRCT revealing linear opacities in the central lung areas, increased reticular density, traction bronchiectasis, ground glass densities, mosaic perfusion and air trapping areas in places

Expected life spans have increased over time with developments in diagnostic procedures, imaging methods and treatment options, and so an increase should be expected in the number of cases with ILD and HP, which is a subheading. The diagnosis and treatment of ILD and HP usually involved multidisciplinary approach (Chest Diseases, Radiology, Pathology, Thoracic Surgery…) (3). In this article, three histopathologically diagnosed FHP cases are presented in the light of current literature to contribute to the body of literature on the diagnosis and treatment of FHP.

CASE

Case 1: A sixty-eight male farmer applied to our center complaining of dyspnea on exertion. The patient had a 20-pack-year smoking history but no significant medical or family history. Although there was no history of animal feeding in the house, he was involved in cattle care and feeding in his work. No drugs or other remarkable exposures within the home were identified. A physical examination (PE) revealed rales in the middle and lower zones of both lungs, beginning mid-inspiration and continuing through to the end. A posterior-anterior chest radiography (PACR) revealed a bilateral reticulonodular appearance (Figure 1a), and a Thorax computed tomography (CT) of the case was reported to be compatible with HP (Figure 1b). Pulmonary function and carbon monoxide diffusion tests (PFT-DLCO) produced the following results: FEV1/FVC: 69%; FEV1: 2.00 L, 72%; FVC: 2.75 L, 78%; DLCO: 3.71 L, 46%; and DLCO/VA: 0.96 L, 78%. No Broncho Alveolar Lavage (BAL) cell analysis was carried out due to the lack of facilities in our hospital, and no Fiberoptic Bronchoscopy (FOB)-BAL was performed as the patient could not have the procedure performed in a private institution. The results of an open lung biopsy of the case, decided upon by the multidisciplinary council, were found to be compatible with FHP. The patient was started on Methylprednisolone 40 mg and advised to steer clear of potentially contributing factors. The patient voluntarily discontinued the methylprenisolone treatment due to side effects in the first month of the treatment, and was followed up without medical treatment. Written informed consent from the patient for their inclusion in the study was obtained.

Case 2: A 67-year-old housewife applied to our center with complaints of dry cough and shortness of breath with effort that had increased gradually over the past year. She was a nonsmoker and had undergone an operation due to breast cancer 10 years earlier. Her father had been diagnosed with lung cancer and had worked in a medical laboratory for 10 years but had retired 22 years ago. The patient had never fed a pet, and denied any environmental or drug exposure. PE revealed clubbing of the toes

and crackles in the bilateral middle lower zones that started at the middle of inspiration and continued until the end. PACR revealed a bilateral reticulonodular appearance (Figure 2a). A Thorax CT of the case was reported as compatible with HP (Figure 2b). PFT-DLCO produced the following results: FEV1/FVC: 75%; FEV1: 1.78 L, 71%; FVC: 2.13 L, 71%; DLCO: 2.69 L, 38%; and DLCO/VA: 0.92 L, 71%. An open lung biopsy of the patient requested by the multidisciplinary council of an external center was reported to be compatible with HP, and the patient was started on Methylprednisolone 40 mg. Written informed consent from the patient for their inclusion in the study was obtained.

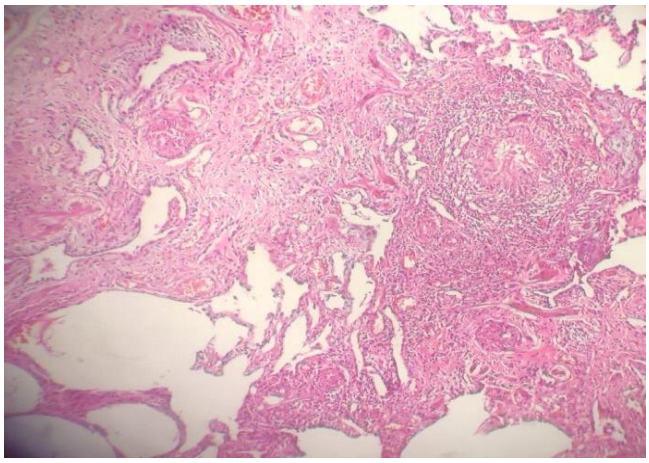

Figure 1c: *Granuloma formation and interstitial lymphocyte infiltration in a case of fibrotic hypersensitivity pneumonitis*

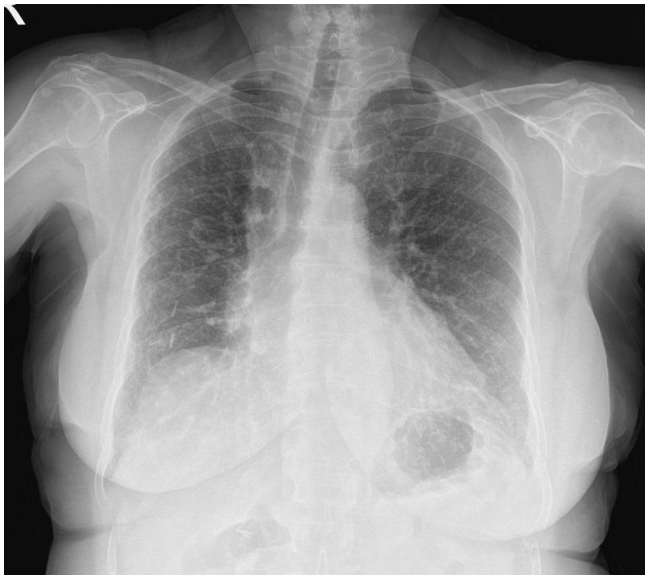

Figure 2a: *Chest radiography revealing bilateral volume loss, more prominent on the right, and reticular infiltration of the peripheral and lower areas*

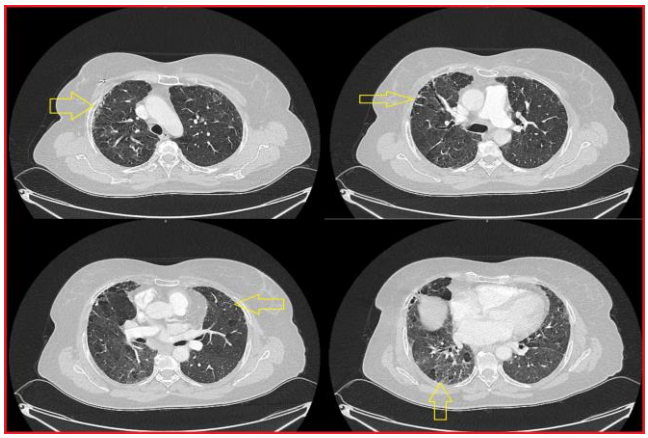

Figure 2b: *HRCT revealing peripherally located fibrotic density increases, traction bronchiectasis, ground glass densities, mosaic perfusion and air trapping areas, mostly in the central lung fields*

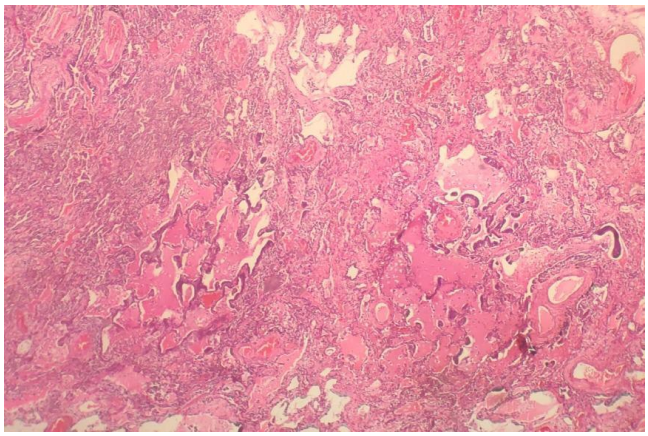

Figure 2c: *Honeycomb areas in a case with FHP*

Case 3: A 68-year-old housewife presented with exertional dyspnea and dry cough that had persisted for 3 years. She was a non-smoker, and her personal and family history were insignificant. There was no history of pet keeping, drug exposure or other notable exposure in the household. A physical examination revealed rales in the middle and lower zones of both lungs, starting mid-inspiration and continuing until the end; PACR revealed a bilateral reticulonodular appearance (Figure 3a); and a Thorax computed tomography was reported to be compatible with HP (Figure 3b). The PFT-DLCO results were as follows: FEV1/FVC: 76%; FEV1: 1.57 L, 108%; FVC: 1.93 L, 123%; DLCO: 16.4 L, 90%; and DLCO/VA: 4.47 L, 99%. A cryo-biopsy was carried out upon the request of the multidisciplinary council, and the results were reported to be compatible with HP. The patient was duly started on Methylprednisolone 40 mg. Written informed consent from the patient for their inclusion in the study was obtained.

*Table 1: Hypersensitivity Pneumonia causes**

Type of antigens	Specific antigens	
Animal protein	Bird protein, chinchilla, flour mite	
Fungi	• Trichosporon spp. • Eurotium amstelodami • Cryptococcus spp. • Absidia corymbifera • Alternaria spp. • Exophiala spp. • Bjerkandera adusta • Sphaerotheca fuliginea • Aspergillus spp. • Fusarium spp. • Candida spp. • Mucor spp. • Aureobasidium pullulans • Phoma spp. • Curvularia lunata	• Ulocladium botrytis • Penicillium spp. • Lichtheimia corymbifera • Rhizopus spp. • Scopulariopsis spp. • Cephalosporium acremonium • Rhodotorula spp. • Humicola fuscoatra • Wallemia sebi • Cladosporium spp. • Chrysonilia sitophila • Paecilomyces spp. • Neurospora crassa • Trichoderma spp. • Peziza domiciliana
Bacteria	• Thermoactinomyces spp. • Streptomyces spp. • Ochrobactrum spp. • Brevibacterium spp. • Pantoea agglomerans • Saccharopolyspora rectivirgula • Acinitobacter spp. • Staphylococcus spp. • Sphingobacterium spiritivorum	• Saccharomonospora viridis • Pseudomonas spp. • Arthrobacter spp. • Enterobacter spp. • Bacillus spp. • Stenotrophomonas spp. • Paenibacillus spp. • Rhanella spp.
Mycobacteria	• Mycobacterium avium complex • M. İmmunogenum • M. gordonae	• M. mucogenicum • M. chelonae • M. Fortuitum
Other antigens	• Mushroom spores • Cork • Sausage dust • Catechin • Hay/damp straw/silage • Metalwork fluid • Wood products • Phytase	• Isocyanates • Corn • Bacilli Calmette–Guérin • Proteolytic enzyme • Water from humidifiers • Wheat/flour • Argan • Tiger nut
Inorganic material exposure	• Wood dust • Flour mite • Proteolytic enzyme • Tiger nut • Konjak flour • Phytase • Chinchilla • Shrimp shell powder	• Sausage dust • Isocyanates • Diisocyanate • Acid anhydrides • Chloroethylenes • Acrylate compounds • Cosmetic products • Catechin phenol compounds

** Adapted from source number*

DISCUSSION

Hypersensitivity Pneumonia, especially FHP, is clinically and radiologically similar to other ILDs, although both the diagnostic and treatment characteristics are different. We report here on three histopathologically diagnosed cases who were followed for 6 years to clarify the current diagnosis, treatment and follow-up approaches to HP in the light of current literature, and to draw attention to FHP.

Table 2: *Chest HRCT Scan Features of the typical nonfibrotic/fibrotic Hypersensitivity Pneumonia**

	Scan Features of the typical nonfibrotic HP Pattern
Description	**The "typical HP" pattern is suggestive of a diagnosis of HP.** It requires *a*) at least one HRCT abnormality indicative of parenchymal infiltration and *b*) at least one HRCT abnormality indicative of small airway disease, both in a diffuse distribution
Relevant radiological findings	**HRCT abnormalities indicative of parenchymal infiltration:** • GGOs • Mosaic attenuation (Mosaic attenuation corresponding to parenchymal infiltration is created by GGOs adjacent to normal-appearing lung) **HRCT abnormalities indicative of small airway disease:** • Centrilobular nodules • Air trapping Distribution of parenchymal abnormalities: Craniocaudal: diffuse (with or without some basal sparing), Axial: diffuse
	Scan Features of the typical fibrotic HP Pattern
Description	**The "typical HP" pattern is suggestive of a diagnosis of HP.** It requires *a*) an HRCT pattern of lung fibrosis (as listed below) in one of the distributions and *b*) at least one abnormality that is indicative of small airway disease
Relevant radiological findings	HRCT abnormalities indicative of lung fibrosis are most commonly composed of irregular linear opacities/coarse reticulation with lung distortion; traction bronchiectasis and honeycombing may be present but do not predominate The distribution of fibrosis may be: • Random both axially and craniocaudally or • Mid lung zone–predominant or • Relatively spared in the lower lung zones HRCT abnormalities indicative of small airway disease: • Centrilobular nodules and/or GGOs Mosaic attenuation, three-density pattern,** and/or air trapping (often in a lobular distribution)

** Adapted from source number 1*
*** The three-density pattern was formerly called the "headcheese sign."*
Indicative of a mixed obstructive and infiltrative process:
a. The obstructive abnormality (seen in small airway disease) is manifested by areas of decreased attenuation and decreased vascularity
b. The infiltrative disorder results in GGO surrounding preserved normal lobules
Highly specific for fibrotic HP; has not been shown to be specific for nonfibrotic HP
GGO: *ground glass opacity,* **HP:** *Hypersensitivity Pneumonia,* **HRCT:** *high resolution computed tomography*

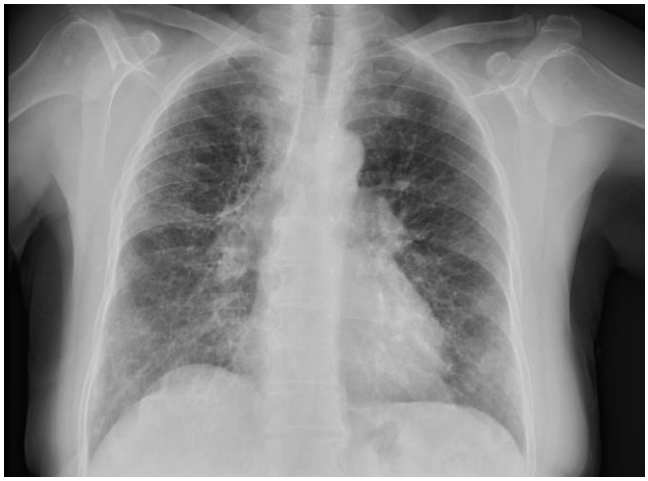

Figure 3a: *Chest radiography revealing reticular-reticulonodular infiltration in all zones, more dominant in the peripheral and middle-lower areas*

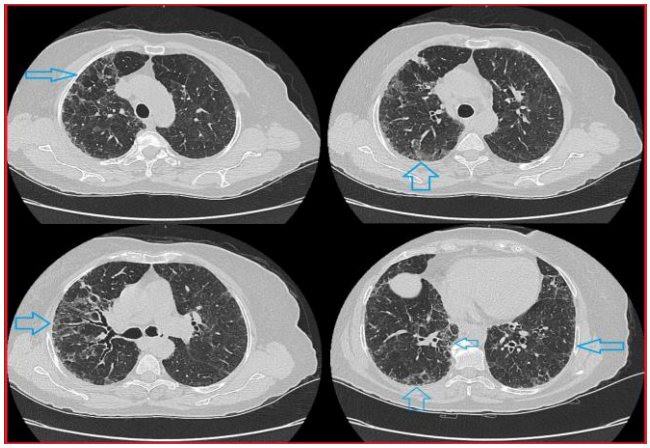

Figure 3b: *HRCT revealing ground-glass densities, traction bronchiectasis, ground-glass densities, mosaic perfusion and air trapping areas mostly in the middle lung fields*

*Table 3: Histopathological Criteria for the Diagnosis of Fibrotic Hypersensitivity Pneumonia**

Typical histopathological features of fibrotic HP; 1 or 2 and 3 in at least one biopsy site:	Both of the following features (1 or 2 from first column) in at least one biopsy site:	Either one of the following features in at least one biopsy site:
1. Chronic fibrosing interstitial pneumonia -Architectural distortion, fibroblast foci ± subpleural honeycombing -Fibrotic NSIP-like pattern 2. Airway-centered fibrosis ±Peribronchiolar metaplasia ±Bridging fibrosi 3. Poorly formed nonnecrotizing granulomas ±Cellular interstitial pneumonia ±Cellular bronchiolitis ±Organizing pneumonia pattern and Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates	1. Chronic fibrosing interstitial pneumonia -Architectural distortion, fibroblast foci ± subpleural honeycombing -Fibrotic NSIP-like pattern 2. Airway-centered fibrosis ±Peribronchiolar metaplasia ±Bridging fibrosi ±Cellular bronchiolitis ±Organizing pneumonia pattern an Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates	1. Chronic fibrosing interstitial pneumonia -Architectural distortion, fibroblast foci ± honeycombing -Fibrotic NSIP-like pattern ±Cellular interstitial pneumonia ±Cellular bronchiolitis ±Organizing pneumonia pattern and Absence of features in any biopsy site to suggest an alternative diagnosis • Plasma cells > lymphs • Extensive lymphoid hyperplasia • Extensive well-formed sarcoidal granulomas and/or necrotizing granulomas • Aspirated particulates

** Adapted from source number 1*

The American Thoracic Society, the Japanese Respiratory Society and the Asociación Latinoamericana del Tórax (ATS/JRS/ALAT), being the most up-to-date practical guidelines, recommend using the term "sensitized individuals" when referring to those with HP. In its pathogenesis, predominantly lymphocytic inflammatory patterns and granulomatous structures are observed as both humoral and cellular (antigen-specific IgG antibodies + T-helper cell type 1 (Th1) cellular immune responses) responses after exposure to any antigen in those who are susceptible (4). As a clinical feature, HP can be defined as a condition that is more common in sensitized older adults (generally in the fifth or sixth decade), in which dyspnea and cough together with mid-inspiratory squeak ral form a triad (1). Other potential symptoms include tightness in the chest, wheezing, weight loss and weakness. There is no specific laboratory value available for a firm diagnosis, although low vital capacity and diffusion capacity identified in PFT-DLCO tests, and lymphocyte dominance in bronchoalveolar lavage fluid obtained bronchoscopically are two important laboratory findings (1,5). Since surgical biopsy and Cryobiopsy were preferred for diagnostic procedures in our cases, any cellular changes in bronchoalveolar lavage fluid are unknown. That said, the clinical and laboratory changes identified supported FHP, in accordance with previous studies in literature.

While no well-defined laboratory test or auxiliary methods exist for the radiological diagnosis of HP, such methods are very useful in diagnostic studies. The currently preferred imaging approach to the diagnosis of HP is non-contrast HRCT. Although inspiratory HRCT reveals all the radiological characteristics of the disease in both FHP and nonfibrotic HP, expiratory HRCT is also recommended, due especially to its ability to reveal air trapping areas in FHP. Radiological features are classified as typical, compatible with HP and uncertain for HP, while typical HRCT findings for non-fibrotic HP (in the presence of at least one parenchyma and one airway change) are parenchyma change, ground glass opacity (GGO) and mosaic perfusion, centrilobular nodules not well defined as airway change and air trapping areas. Typical HRCT findings for FHP include (in the presence of at least one abnormal finding in both lung parenchyma and airways) parenchymal abnormalities such as fibrosis that are axially and craniocaudally randomly distributed; sparing lower lung areas are relatively; coarse reticulations with irregular linear opacities/lung distortion may be present in the middle lung areas, traction bronchiectasis and honeycombing may be present but not dominant and airway pathologies such as centrilobular nodules or GGO or mosaic perfusion, three-density pattern (Formerly head-cheese sign) or air trapping areas are not well defined airway changes. The conditions of all three patients in the present study were classified as standard inspiratory HRCTs prior to histopathological diagnosis, and all had typical HRCT findings for FHP (6,7). The chest HRCT scan results of typical nonfibrotic/fibrotic HP are presented in Table 2.

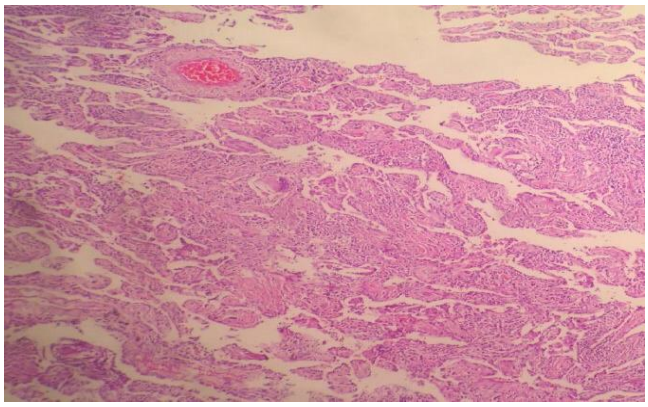

Figure 3c: Multinuclear giant cells, cholesterol clefts, alveolar septum thickening and lymphocyte infiltration in a case with FHP

In all three cases, the diagnosis was made histopathologically (2 cases surgical, 1 case cryobiopsy). Transbronchial biopsy (TBB), cryobiopsy (CB) and open lung biopsy (AAB) are the three options today for the histopathological diagnosis of HP, which can be difficult to diagnose using clinical radiological methods. Studies have reported the diagnostic efficiency of TBB to be in the range of 41–50%, CB to 82–91% and AAB to be 96–98%. As the degree of invasiveness of the method increases, so does the diagnostic efficiency rate, as expected. Today, a careful and comprehensive history is most commonly recommended, alongside radiological (HRCT) investigations and possible environmental factors/exposures. In cases identified with HP, a serum IgG antibody test is recommended against potential antigens associated with HP, along with BAL with a lymphocyte cell analysis. If a definitive diagnosis still cannot be made, TBB, CB or AAB should be taken into account (1,8,9). Fibrotic HP disease can be differentiated from all diseases with radiological interstitial involvement, especially idiopathic pulmonary fibrosis (IPF). In the differential diagnosis of HP from other ILDs, it differs from other ILDs especially with the ability to identify any exposure (exposure identification), specific HRCT findings, and histopathological/BAL cellular findings. Current guidelines related to this issue claim that in the differential diagnosis of HP, a diagnosis of HP will be definite in the presence of typical HRCT findings for HP and a typical HP histopathology in the presence of defined exposure, probable HP histopathology, lymphocytosis in BAL and indeterminate histopathology, Lymphocytosis in BAL without histopathological specimen suggests high confidence HP, indeterminate histopathology without BAL or lymphocytosis in BAL, or moderate confidence HP in the presence of only typical HRCT findings and defined exposure without histopathology (1).

The primary step in the treatment of HP should be the removal of the causative agent/cessation of exposure if the precipitating factor can be identified. Aside from this, while corticosteroids-immunosuppressive drugs can play an important role, studies of antifibrotic drugs are continuing. In non-fibrotic HP, corticosteroids are often the drug of choice, with a treatment regimen of 0.5–1 mg/kg/day prednisone for 1–2 weeks, followed by a gradual reduction to a maintenance dose of 10 mg/day. The fibrotic HP empirical starting dose is maintained for 4–8 weeks, after which it is gradually reduced to the lowest effective dose, usually 10 mg/day. The duration of treatment can be extended (months, years) based on clinical, radiological and functional data, unlike with non-fibrotic HP. There continues to be a lack of consensus on treatment durations. Mycophenolate or azathioprine can be prescribed as alternative immunosuppressive treatment options in cases that respond poorly to corticosteroids or that encounter frequent relapses. Previous studies have reported that antifibrotic treatments may be beneficial in HP cases with advanced fibrosis (10,11). The treatment of choice in all cases in the present study was methylprednisolone.

The diagnosis, imaging and treatments of three cases diagnosed with HP by histopathologic methods are presented here in the light of current literature. HP maintains its importance in routine practice related to chest diseases, due primarily to the difficulties associated with multidisciplinary diagnosis, its frequent confusion with other ILDs and the long-term treatment process.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - C.D., G.M.; Planning and Design - C.D., G.M.; Supervision - C.D., G.M.; Funding - G.M.; Materials - G.M.; Data Collection and/or Processing - G.M.; Analysis and/or Interpretation - C.D.; Literature Review - G.M.; Writing - C.D.; Critical Review - C.D.

REFERENCES

1. Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, et al. Diagnosis of hypersensitivity pneumonitis in adults. An Official ATS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2020;202:e36-e69. [CrossRef]
2. Petnak T, Moua T. Exposure assessment in hypersensitivity pneumonitis: a comprehensive review and proposed screening questionnaire. ERJ Open Res 2020; 6:00230-2020. [CrossRef]
3. Walsh SLF, Wells AU, Desai SR, Poletti V, Piciucchi S, Dubini A, et al. Multicentre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. Lancet Respir Med 2016; 4:557-65. [CrossRef]
4. Burrell R, Rylander R. A critical review of the role of precipitins in hypersensitivity pneumonitis. Eur J Respir Dis 1981; 62:332-43.

5. De Sadeleer LJ, Hermans F, De Dycker E, Yserbyt J, Verschakelen JA, Verbeken EK, et al. Effects of corticosteroid treatment and antigen avoidance in a large hypersensitivity pneumonitis cohort: a single-centre cohort study. J Clin Med 2018; 8:14. [CrossRef]

6. Salisbury ML, Gross BH, Chughtai A, Sayyouh M, Kazerooni EA, Bartholmai BJ, et al. Development and validation of a radiological diagnosis model for hypersensitivity pneumonitis. Eur Respir J 2018; 52:1800443. [CrossRef]

7. Barnett J, Molyneaux PL, Rawal B, Abdullah R, Hare SS, Vancheeswaran R, et al. Variable utility of mosaic attenuation to distinguish fibrotic hypersensitivity pneumonitis from idiopathic pulmonary fibrosis. Eur Respir J 2019; 54:1900531. [CrossRef]

8. Cascante JA, Cebollero P, Herrero S, Yagüe A, Echegoyen A, Elizalde J, et al. Transbronchial cryobiopsy in interstitial lung disease: are we on the right path? J Bronchology Interv Pulmonol 2016; 23:204-9. [CrossRef]

9. Sheth JS, Belperio JA, Fishbein MC, Kazerooni EA, Lagstein A, Murray S, et al. Utility of transbronchial vs surgical lung biopsy in the diagnosis of suspected fibrotic interstitial lung disease. Chest 2017; 151:389-99. [CrossRef]

10. Calaras D, David A, Vasarmidi E, Antoniou K, Corlateanu A. Hypersensitivity pneumonitis: challenges of a complex disease. Can Respir J 2024; 2024:4919951. [CrossRef]

11. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Yoshikazu Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019; 381:1718-27. [CrossRef]