Criteria for progressive fibrotic hypersensitivity pneumonitis in a Portuguese patient cohort

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Background. Hypersensitivity pneumonitis (HP) is a syndrome caused by sensitisation to inhaled antigens that leads to an abnormal immune response in the airways and lung parenchyma. Some patients previously diagnosed with certain types of fibrotic interstitial lung diseases (f-ILDs), including fibrotic HP (f-HP), are susceptible to develop a progressive fibrosing phenotype (PF-ILD), despite initial state-of-the-art management.

Objectives. To characterise a cohort of patients with a multidisciplinary diagnosis (MTD) of chronic f-HP, who were followed up in an ILD outpatient clinic of a hospital in Portugal, and to assess the prevalence of PF-ILD criteria in these patients.

Methods. Data were collected from all patients with a definite or provisional diagnosis of f-HP after a multidisciplinary team discussion. Patients were followed up between December 2014 and July 2019. Data included clinical characteristics, high-resolution chest tomography (HRCT) disease patterns, lung function tests, bronchoalveolar lavage and further immunological work-up, biopsy reports (conventional transbronchial lung biopsy, transbronchial lung cryobiopsy or surgical video-assisted thoracoscopic lung biopsy), all ILD multidisciplinary team records and diagnostic confidence levels. Patients were assessed according to PF-ILD criteria as defined in the INBUILD trial.

Results. We identified 83 patients with an MTD of HP, who had been followed up for at least 12 months. Of these, 63 (75.9%) were diagnosed with f-HP. Of the 63 f-HP patients, 33.3% (*n*=21) fulfilled the predefined criteria for PF-HP: 66.7% had a relative decline of ≥10% forced vital capacity (FVC); 5% a relative decline of 5 - 9% FVC, with worsening symptoms or increased fibrosis on HRCT; and 23.8% had worsening respiratory symptoms with radiological progression.

Conclusion. This single-centre cohort study demonstrated that a third of f-HP patients presented with PF-ILD, as determined by progression during initial standard-of-care treatment. A usual interstitial pneumonia (UIP)/UIP-like pattern was present in >70% of patients with f-HP, and two-thirds of these patients had an FVC decline of ≥10%. PF-HP patients were also more exacerbation prone. According to recent trial data, this segment of patients can be considered possible candidates for antifibrotic treatment, with a reasonable prospect of effectiveness. Further efforts should focus on refining knowledge of longitudinal behaviour of large multicentric cohorts of f-HP patients, establishing a consensual and uniform definition of progression for use in clinical practice, as well as developing prognostic prediction tools to better (and early) inform the disease course.

Keywords: hypersensitivity pneumonitis, pulmonary fibrosis, progressive

Afr J Thoracic Crit Care Med 2022;28(4):163-166. https://doi.org/10.7196/AJTCCM.2022.v28i4.250

Hypersensitivity pneumonitis (HP) is a syndrome caused by sensitisation to inhaled antigens that leads to an abnormal immune response in the airways and lung parenchyma. Disease susceptibility is regulated by host-related factors (genetic variations of immune response), antigen properties and exposure-related factors.[1]

A fraction of the patients previously diagnosed with certain types of fibrotic interstitial lung diseases (f-ILDs), including fibrotic HP (f-HP), are susceptible to develop a progressive fibrosing phenotype (PF-ILD), despite initial state-of-the-art management.[2-6] It is estimated that 18 - 32% of patients diagnosed with non-idiopathic pulmonary fibrosis (non-IPF) f-ILDs develop this type of disease behaviour.[7] This subgroup amalgamates different types of diseases, showing striking similarities to the clinical course seen in IPF. This is the result of similar pathogenic mechanisms, ultimately leading to ongoing collagen deposition and subsequent progressive lung function decline, worsening symptoms and health-related quality of life, treatment refractoriness and early mortality.[8-15]

There are several risk factors for progression and mortality regarding PF-ILD, such as older age, male sex, lower forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DL_{CO}) at baseline, a pathological or radiological pattern of usual interstitial pneumonia (UIP), honeycombing and traction bronchiectasis in high-resolution chest tomography (HRCT) and acute exacerbations.[15-24]

Some patients with HP may partially recover from the disease, especially those with the inflammatory/non-fibrotic form.

Nonetheless, in several previous studies, the radiological and/or histopathological evidence of f-HP has been strongly correlated with poor survival.[25,26] This subset of patients frequently experiences disease progression, particularly if the inciting antigen cannot be identified and removed.[3,27] It is estimated that only 58% of patients with f-HP are alive 7 years after diagnosis.[28] Besides antigen avoidance, the immune dysregulation component of this disease has traditionally been targeted by the use of corticosteroids and immunosuppressants, even though there are no controlled clinical trials to support their efficacy in this setting. However, there is some low-quality retrospective evidence suggesting that drugs such as mycophenolate mofetil and azathioprine can potentially reduce the need for corticosteroids and may improve the trajectory of lung function decline in some patients.[3,4,29]

The INBUILD trial included a miscellaneous group of several non-IPF f-ILD patients (26% were f-HP patients), showing previous progression with standard-of-care treatment. The study also found that antifibrotic treatment with nintedanib can significantly impact subsequent lung function decline in this population.[30]

Pirfenidone, a medication with antifibrotic properties approved for IPF, may also be useful in the management of f-HP and PF-HP,[31-33] and is currently being investigated further in clinical trials (NCT02496182; NCT02958917).

Objectives and methods

This retrospective cross-sectional study aimed to characterise a cohort of patients with a multidisciplinary diagnosis (MTD) of f-HP, followed up in an ILD outpatient clinic of a Portuguese district hospital (Centro Hospitalar do Baixo Vouga, with 450 beds, serving a population of ~300 000), and to assess the prevalence of PF-ILD criteria in the same cohort.

Data were collected from all patients with a definite or provisional diagnosis of f-HP after a multidisciplinary team discussion, including an ILD specialist, a thoracic radiologist, rheumatologist and pathologist. The patients were followed up at the designated centre between December 2014 and July 2019. The dataset included clinical characteristics, HRCT disease patterns, lung function tests, bronchoalveolar lavage and further immunological work-up, biopsy reports (relating to conventional transbronchial lung biopsy (TBLB), transbronchial lung cryobiopsy (TBLCB) or surgical video-assisted thoracoscopic lung biopsy (VATS)) and all ILD multidisciplinary team records and diagnostic confidence levels.

Patients were assessed for the presence of PF-ILD criteria, as defined in the INBUILD trial. Accordingly, a fibrosing progressive behaviour in this cohort of HP patients (PF-HP) was acknowledged if ≥1 of the following criteria were present in the previous 24 months: a relative decline in FVC of at least 10% of the predicted value; a relative FVC decline of 5 - 9% predicted, with worsening respiratory symptoms, or increased extent of fibrosis on HRCT. Patients receiving off-label antifibrotic drugs were excluded from the analysis.

Statistical analysis

Qualitative variables are expressed as absolute values and percentages, while quantitative variables are expressed as means and standard deviations (SDs) for normally distributed data, and median and interquartile range (IQR) for non-normally distributed data. The descriptive analysis was performed using SPSS version 25 (IBM Corp., USA).

Ethical approval

The study and all procedures were performed according to the ethical standards in the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. As this was a retrospective study, formal consent was not required. All data were collected anonymously.

Results

We identified 83 patients with an MTD of HP after having been followed up for at least 12 months. Of these, 63 (75.9%) were diagnosed with f-HP. This subgroup of patients had a mean age of 69.3 (SD 11.8) years and a slight female predominance (55.6%). Avian proteins (57.1%) and moulds (25.4%) were the most common recognisable inducing antigens (Table 1).

At diagnosis, 79.4% of patients had never smoked and 20.6% were previous smokers (mean of 53.0 pack-years). Regarding lung function, mean FVC at baseline was 77.6% predicted and the last mean FVC was 73.3%. The mean DL_{CO} at baseline was 51.0% and the last DL_{CO} was 50.5%. The 6-min walk distance at diagnosis was 351.8 m.

At baseline, 68.3% of patients presented with grade 1 or 2 mMRC (modified Medical Research Council) dyspnoea, 23.8% with grade 3 and 7.9% with grade 4 (Table 2).

Approximately 68.3% of the patients with f-HP complained of chronic cough and 14.3% presented with weight loss. A UIP/UIP-like pattern was present on HRCT and/or biopsy in 46.0% of patients. Regarding bronchoalveolar lavage (BAL), at diagnosis the mean total cell count was 357 000 cells/mL, with a mean lymphocyte count of 122 094 cells/µL. About two-thirds (66.7%) of f-HP patients showed elevated IgG titres for context-relevant suspicious antigens.

In 42.9% of patients a lung biopsy procedure was undertaken during the diagnostic work-up: VATS (70.4%), conventional TBLB (25.9%) and TBLCB (3.7%).

Table 1. Chronic fibrotic hypersensitivity pneumonitis and inducing antigen

Causal antigen	*n* (%)
Avian induced	36 (57.1)
Mould induced	16 (25.4)
Avian and mould induced	5 (7.9)
Isocyanate induced	3 (4.8)
Other antigens	2 (3.2)
No identifiable antigen	1 (1.6)

Table 2. Baseline dyspnoea in fibrotic hypersensitivity pneumonitis patients

Baseline dyspnoea (mMRC), grade	*n* (%)
1	8 (12.7)
2	35 (55.6)
3	15 (23.8)
4	5 (7.9)

mMRC = modified Medical Research Council.

The diagnosis of HP in these patients was based on imaging, exposure assessment, BAL lymphocytosis and histopathological findings (when available or deemed necessary), and for all patients there was a multidisciplinary discussion and a confidence level assessment. Approximately 58.7% received a definite or high-confidence provisional diagnosis, 31.7% a moderate-confidence provisional diagnosis and 9.5% a low-confidence provisional diagnosis.

Of the 63 f-HP patients, 33.3% (n=21) fulfilled the predefined criteria for PF-HP: 66.7% by a relative decline of ≥10% FVC; 9.5% by a relative decline of 5 - 9% FVC and worsening symptoms or increased extent of fibrosis on HRCT; and 23.8% through worsening respiratory symptoms with radiological progression (Fig. 1).

Compared with the non-progressive subgroup, the PF-HP patients were of a similar age at diagnosis (69.6 years and 68.8 years, respectively), with lower BAL lymphocytes (128 520 cells/µL and 109 242 cells/µL, respectively), although with a non-statistically significant difference (p=0.19). The prevalence of a UIP/UIP-like pattern on HRCT was 61.9% in the PF-HP subgroup, but only 38.1% in patients with a non-progressive phenotype (p=0.05).

During follow-up, we found that acute exacerbations occurred in 14 (22.2%) patients (26.2% of PF-HP patients and 14.3% of non-PF-HP patients), with a 30-day mortality rate of 42.9%. The global all-cause mortality rate was 31.7% and respiratory-related mortality was 60.0% (30.8% in PF-HP patients and 69.2% in non-PF-HP patients).

f-HP patients (~95.2%) were being treated with immunomodulation: 95.2% with low-dose prednisolone, 55% with mycophenolate mofetil, 20% with azathioprine and 33% with add-on hydroxychloroquine (Fig. 2). Globally, the majority of patients (71.4%) showed a relatively satisfactory antigen avoidance, with slightly higher compliance in the PF-HP subgroup (76.2%) than in the non-PF-HP subgroup (69.0%), even though a non-exposure to moulds is considered impracticable, given their ubiquitous nature. Around 38.1% of f-HP patients were started on ambulation oxygen support and 15.9% on continuous oxygen support. Globally, 27.0% were referred for respiratory rehabilitation.

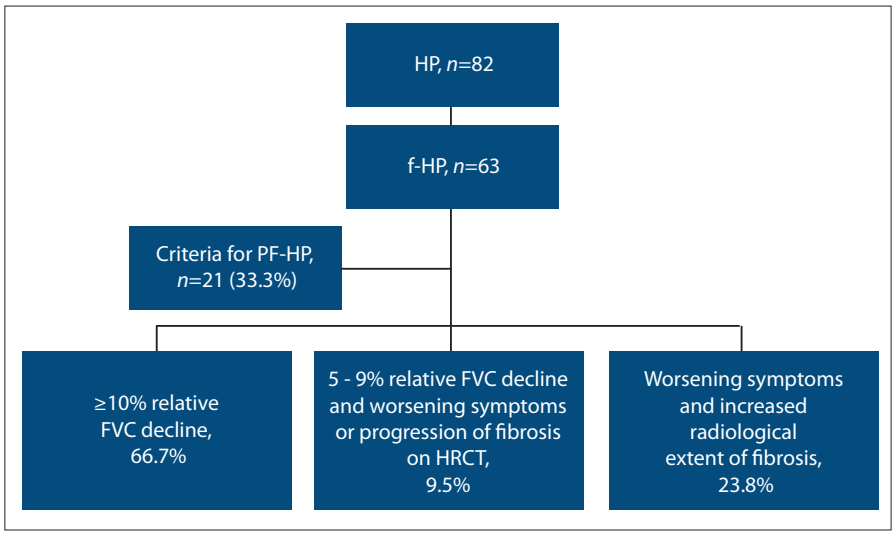

Fig. 1. Progression criteria met in the f-HP cohort. (HP = hypersensitivity pneumonitis; f-HP = fibrotic HP; PF-HP = progressive fibrotic HP; FVC = forced vital capacity; HRCT = high-resolution chest tomography.)

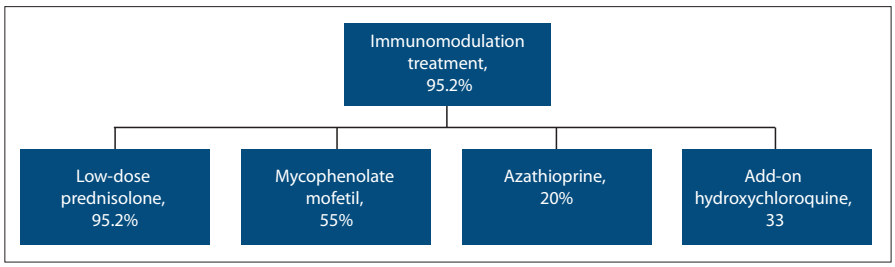

Fig. 2. Pharmacological drug regimen in the fibrotic hypersensitivity pneumonitis cohort.

Conclusion

A relevant subgroup of f-HP patients does not respond to antigen avoidance and immunosuppressive therapy, potentially assuming a progressive fibrosing phenotype. There are hardly any credible evidence-based therapies; however, this phenotypical behaviour of HP has recently gained attention in clinical trials (completed or ongoing) with antifibrotic therapy. This single-centre cohort study demonstrates that a third of f-HP patients present with a PF-ILD behaviour, as determined by effective progression with initial standard-of-care treatment. A UIP/UIP-like pattern was present in >70% of patients with PF-HP, and two-thirds of these patients progressed with an FVC decline of ≥10%. PF-HP patients were also more exacerbation prone.

According to recent trial data, this segment of patients can be considered possible candidates for antifibrotic treatment, with reasonable effectiveness. Further efforts should focus on refining knowledge regarding the longitudinal behaviour of large multicentric cohorts of patients with f-HP, establishing a consensual and uniform definition of progression for use in clinical practice, as well as developing prognostic prediction tools to better (and early) inform on disease course.

Declaration. None.

Acknowledgements. None.

Author contributions. EA was involved in the design of the study, analysis of the data, interpretation of the results, and drafting and writing of the manuscript; MF contributed to the design of the study and analysis of the data; PS, RA and IC contributed to the design of the study and analysis of the data; PGF was the senior investigator and was involved in all aspects of the study: design, analysis, interpretation of the results and supervising the writing of the manuscript.

Funding. None.

Conflicts of interest. ES has received speaking fees from Boehringer-Ingelheim and travel expenses from Menarini, Boehringer-Ingelheim,

Novartis and Mundipharma, outside the submitted work. PGF has received speaking fees and travel expenses from Boehringer-Ingelheim, Roche, Menarini, Novartis, Medinfar, Mundipharma and GSK, outside the submitted work. PGF has also participated on the advisory boards of Roche and Boehringer-Ingelheim.

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Accepted 27 September 2022.