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Morphologic diversity of chronic pigeon breeder's disease: Clinical features and survival

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Summary
Morphology in chronic HP is characterized by bronchiolocentric mononuclear inflammation, poorly formed granulomas and variable degree of fibrosis. However, recent findings suggest that this disease may present different pathologic patterns. In this study we evaluated the clinical behavior and survival of patients with pigeon breeder's disease according to the pathologic pattern. One-hundred ten biopsies were classified as "typical" ($n = 58$), non-specific interstitial pneumonia (NSIP)-pattern ($n = 22$), usual interstitial pneumonia (UIP)-like ($n = 10$), mixed pattern ($n = 9$), organizing pneumonia (OP)-pattern ($n = 3$), airway-centered interstitial fibrosis (ACIF)-pattern ($n = 3$), and non-classified ($n = 5$). Clinical features and survival were compared between patients with "typical", NSIP, and UIP patterns. There were no statistical differences between the groups in age, gender, time of symptoms, smoking, clubbing, and PaO_2. By the one-way ANOVA test we found differences in the percent of lymphocytes in bronchoalveolar lavage (BAL; $p < 0.002$) and in the forced vital capacity ($p < 0.05$) between the 3 groups. After Bonferroni correction the difference in BAL lymphocytes remained significant among the UIP-like and the typical pattern (36.1 ± 22.9 versus 64.6 ± 20.9, $p = 0.001$). UIP-like patients exhibited the worst survival rate (HR: 4.19; 95% CI: 1.66–14.47; $p < 0.004$) while NSIP-like pattern showed the best survival (HR: 0.18; 95% CI: 0.04–0.82; $p < 0.03$).

Multivariate Cox regression analysis revealed that patients with a UIP-like pattern retained a significantly worse survival (HR: 3.4 (IC 95%: 1.15–10.29; $p < 0.03$), and mortality for the NSIP group was best and approached statistical significance ($p = 0.07$). These findings demonstrate that a variety of histopathologic and imaging patterns are seen in PBD, and the presence of a UIP-like pattern confers the worst prognosis.

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Introduction

Hypersensitivity pneumonitis (HP) is a complex syndrome caused by an exaggerated immune response to the inhalation of a large variety of organic particles.[1] The most frequent antigens that cause HP in Mexico are bird-derived proteins that provoke the so-called pigeon breeders' disease (PBD).[2] The clinical behavior is heterogeneous and it is likely determined by the intensity and frequency of exposure to etiologic antigens as well as the genetic susceptibility. The disease may present as acute, subacute or chronic forms, often with overlap between these interrelated categories.[2,3]

The most frequent histopathology observed in HP consists of a granulomatous interstitial bronchiolocentric pneumonitis characterized by a prominent interstitial mononuclear infiltration, with the presence of non-necrotizing poorly formed granulomas.[4,5] Chronic cases also show variable degrees of fibrosis. However, other morphological patterns have also been described, including a relatively homogeneous interstitial inflammation and fibrosis resembling non-specific interstitial pneumonia (NSIP), and a patchy pattern of peripheral fibrosis with architectural distortion and fibroblast foci resembling usual interstitial pneumonia (UIP).[6–9] Data on the clinical correlate, including survival on these and other associated morphological expressions of HP are scanty.

In this study, we examined the histology of 110 patients with chronic PBD and then we evaluated the clinical behavior and survival rate of the most frequent morphologic patterns. We found diverse morphology including "typical" HP, NSIP pattern, UIP-like pattern, mixed pattern, organizing pneumonia (OP) pattern, airway-centered interstitial fibrosis (ACIF) pattern, and non-classified. Intriguingly no major clinical differences were found, but the survival rate was significantly reduced in patients with UIP-like pattern.

Patients and methods

We evaluated the morphological slides of a cohort of 110 PBD patients assisted at the National Institute of Respiratory Diseases (INER), México from 2000 to 2008. Diagnosis of pigeon breeder's disease was based on: (1) relevant exposure to birds preceding respiratory symptoms; (2) strong positive specific antibodies against avian antigens measured by ELISA; (3) clinical and functional features of interstitial lung disease; (4) High resolution computed tomography (HRCT) (available in 80% of the patients) showing either ground-glass attenuation with areas of lobular air trapping and/or poorly defined centrilobular nodules; (5) Presence of some poorly formed granuloma or multinucleated giant cells in lung tissue obtained in all cases through surgical open lung biopsy, independent of the predominant histologic pattern. Usually two different lung regions were sampled.

Demographic data, clinical findings, smoking status, bronchoalveolar lavage, pulmonary function tests and HRCT scans were extracted from case records. These data corresponded to the first medical visit at INER. Smoking status was characterized as "never", "former" (patients who stopped smoking at least 12 months before presentation), or "current" (patients who were either still smoking or stopped smoking less than a year before presentation). Smoking index (packs/year) was also documented.

Pulmonary function tests, including spirometry, plethysmography, and arterial blood gases and HRCT were performed as described elsewhere.[10] HRCT scans were recovered from 87 patients and evaluated by an expert blinded to clinical data. Two patterns were defined: a) Inflammatory pattern, with predominance of ground-glass opacities and centrilobular nodules and b) Fibrotic pattern defined as the presence of widespread irregular reticular opacities, honeycombing and traction bronchiectasis.[11] The scans were quantified using the method described by Kazerooni et al. modified for HP.[11,12] Specifically, HRCT were scored for ground glass attenuation and linear opacities on a scale of 0–4. According to the predominance were classified either as inflammation or fibrotic pattern. Patients were re-evaluated by a second radiologist who was blinded to the first evaluation. The interobserver agreement was $k = 0.59$ ($p < 0.01$).

Histopathologic patterns

We classified the morphological abnormalities in the following patterns: 1) Typical HP was characterized by a predominantly bronchiolocentric mononuclear cell infiltration and poorly formed non-necrotizing granulomas with variable degree of fibrosis. 2) Usual interstitial pneumonia (UIP)-like pattern was defined by dense interstitial fibrosis, often with subpleural and paraseptal distribution associated with loss of lung architecture, honeycomb changes, and fibroblastic foci. 3) Non-specific interstitial pneumonia (NSIP)-like pattern was defined by mild to moderate chronic interstitial inflammation and interstitial fibrosis showing diffuse uniform involvement of the lung tissue. 4) Organizing pneumonia (OP)-like pattern was diagnosed when the biopsy showed numerous Masson bodies. 5) Airway-centered interstitial fibrosis (ACIF)-like pattern, as previously described.[13] 6) Mixed pattern (a combination of some of the described patterns). 7) Non-classified. In addition the percent of fibrosis was determined as previously described.[14]

Bronchoalveolar lavage

BAL was performed in all patients for diagnostic purposes through flexible fiberoptic bronchoscopy as previously described.[15] Briefly, 200 ml of normal saline was instilled in 50-ml aliquots, with an average recovery of 60%–70%. The recovered BAL fluid was centrifuged at 250 g for 10 min at 4 °C. The cell pellet was resuspended in 1 ml of PBS and an aliquot was used to evaluate the total number of cells. Other aliquots were fixed in carbowax, stained with hematoxylin and eosin, and used for differential cell count. Supernatants were kept at −70 °C until use.

Statistical analysis

We compare the patients with "typical" morphology, NSIP-like and UIP-like patterns by using one way ANOVA test or Kruskall Wallis test; the comparison of pairs was

Table 1 Demographic and clinical findings of the whole cohort.

Age (yr)	45 ± 12
Female/male	99/11
Smokers/former smokers	15/4
Duration of symptoms (months)	25 ± 32
Clubbing (%)	56 (62)
FEV_1/FVC (%)	89.4 ± 12
FVC (%)	54.5 ± 17
FEV_1 (%)	57 ± 18
TLC (%)	64.8 ± 17.6
PaO_2 (mmHg)[a]	51.2 ± 9
SpO_2 at rest (%)	85.7 ± 6.7
SpO_2 (6 min walking test) (%)	72 ± 8

FVC = forced vital capacity; FEV_1 = forced expiratory volume first second; TLC = total lung capacity; PaO_2 = arterial pressure of oxygen; SpO_2 = Oxygen saturation.
[a] Normal value at the altitude of Mexico City: 67 ± 3 mmHg.

performed with Bonferroni multiple comparison procedure or Wilcoxon Rank sum test as appropriate. For categorical variables, we used the exact Fisher test. The statistical significance was set at <0.016 two sided, according with the Bonferroni correction. Survival curves of the three groups were compared with the Log Rank Tests for several groups. We calculated the hazard ratio (HR) using the Cox Regression procedure for UIP and NSIP groups and then the HR adjusted in backward Cox multivariate regression model with the following variables: age, sex, forced vital capacity (FVC), PaO_2, UIP and NSIP patterns. The proportional hazards assumption was evaluated with log—log survival curves and the scaled Schoenfeld residual goodness of fit test. All hypotheses tested in the survival analysis were two sided, with a 5 percent threshold for statistical significance. All statistical analyses were done with STATA (version 10.1).

Results

One-hundred and ten lung biopsies of PBD patients were examined; the mean age was 45 ± 12 years (range,

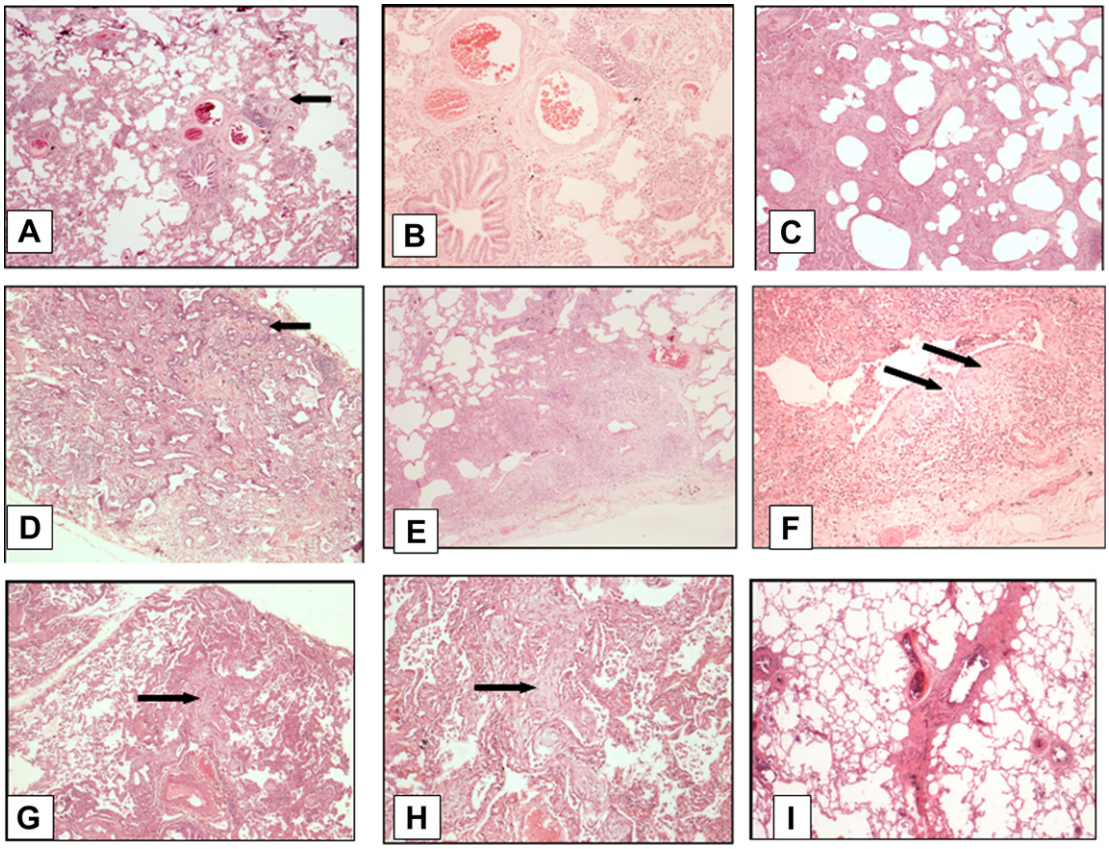

Figure 1 Histopathologic patterns in patients with chronic hypersensitivity pneumonitis. Panel A: Lung biopsy of a patient showing a "typical"-pattern. There is patchy peribronchiolar distribution of the lesions and a poorly defined granuloma (arrow; H&E 4× original magnification). Panel B: The same specimen at higher magnification (H&E, 10×). Panels C and D: Lung biopsies from two patients displaying a non-specific interstitial pneumonia (NSIP)-like pattern (H&E, 4×). Panels E and F illustrate usual interstitial pneumonia (UIP)-like pattern. There are patchy subpleural fibrotic lesions (E) and fibroblastic foci (arrows in F, H&E, 10×). Panels G and H: Lung specimen of a patient that exhibits an organizing pneumonia (OP)-like pattern (4 and 10×). It can be seen several Masson bodies occupying the alveolar spaces (arrow). Panel I: lung biopsy from a patient showing an "airways centered interstitial fibrosis (ACIF)-like pattern (H&E, 4×).

19–70 years; 99 females). As previously reported, our patients are usually women chronically exposed at home to low concentrations of avian antigens.[16,17] All patients were exposed to birds, and 13% (15 patients) were smokers at the onset of symptoms (4 former smokers). Demographic and clinical data of the whole cohort are shown in Table 1. The mean duration of symptoms was 25 ± 32 months. All patients had progressive shortness of breath and cough. Clubbing was observed in 62 patients (56%).

All patients showed a restrictive functional pattern with FVC 54.5 ± 17% of predicted, and hypoxemia at rest (85.7 ± 6.7%), that worsened with exercise (72 ± 8%).

Histological findings

Typical HP was found in 58 patients, NSIP-like pattern in 22 patients, UIP-like pattern in 10 patients, mixed pattern in 9 patients, OP-like pattern in 3 patients, ACIF-like pattern in 3 patients and non-classified lesion (unspecific pneumonitis) in 5 patients. These morphologic patterns are illustrated in Fig. 1. NSIP was usually mixed, that is, showing an interstitial inflammatory cell infiltrate with fibrosis. Fibroblastic foci were observed in the 20% of the biopsies with typical HP, 30% in those with NSIP-like pattern and in all of the cases with an UIP-like pattern. Also, patients with UIP-like pattern presented the high percent of fibrosis (49.0 ± 18.5; $p < 0.01$ compared with the typical and NSIP patterns). Changes suggestive of pulmonary arterial hypertension, including medial hypertrophy and cellular intimal proliferation and fibrosis, were more frequent in UIP-like lungs.

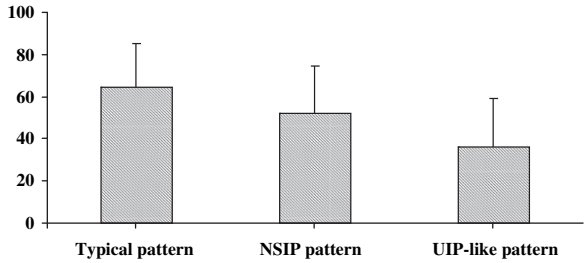

Figure 2 Percent of lymphocytes in the bronchoalveolar lavage fluids from patients with typical, NSIP and UIP-like patterns. A progressive decrease between the groups was observed; $*p = 0.001$.

Demographic, clinical and functional data of patients with typical HP, NSIP and UIP-like patterns are shown in Table 2.

There were no statistical differences between the groups in age, gender, time of symptoms before diagnosis, ever smoker, clubbing, PaO_2, and oxygen saturation at rest and on exercise.

In the one-way ANOVA test we found differences between the groups in the percent of lymphocytes in the bronchoalveolar lavage (BAL) fluid ($p < 0.002$) and in the FVC ($p < 0.05$). After the comparison of pairs the difference in BAL lymphocytes was found between the UIP group and the typical pattern (36.1 ± 22.9 versus 64.6 ± 20.9, $p = 0.001$; (Fig. 2)). The differences in FVC%, did not reach statistical significance (set at $p < 0.016$) and only a trend was observed in the comparison of the typical pattern group with the NSIP group (58.2 ± 17.2 versus 47.7 ± 13.0, $p = 0.038$).

Table 2 Demographic and clinical data of HP patients presenting typical, NSIP or UIP patterns on lung biopsy.[a]

	Typical pattern $n = 58$	NSIP pattern $n = 22$	UIP-like pattern $n = 10$	p^*
Age (yr)	44.5 ± 12.08 45(19–68)	43.7 ± 9.1 42.5 (28–61)	52 ± 14.1 54.5 (23–70)	0.15
Male gender	7/57 (12.3)	5/22 (22.7)	2/10(20)	0.46
Symptoms duration (months)	12 (1–144)	10 (2–228)	30 (7–120)	0.14
Ever smoker	7/57 (12.3)	4/22 (18)	2/10 (20)	0.60
Finger clubbing	30/56 (53)	10/21 (47.6)	8/10 (80)	0.26
BAL lymphocytes	64.6 ± 20.9	52.1 ± 22.7	36.1 ± 22.9	0.0011
BAL macrophages	33.6 ± 20.3	45.3 ± 22.8	58.9 ± 18.1	0.0028
BAL eosinophils	1 (0–9)	0 (0–13)	2 (0–13)	0.11
BAL neutrophils	0 (0–10)	1 (0–10)	1 (0–4)	0.61
FVC % predicted	58.2 ± 17.2	47.7 ± 13.0	55.8 ± 18.1	<0.05
PaO_2	53.1 ± 8.7	49.6 ± 10.0	50.0 ± 6.6	<0.40
SpO_2 rest (%)	88 (70–95)	87 (64–93)	83 (67–92)	0.18
SpO_2 exercise (%)	74 (55–86)	74 (56–84)	63 (50–76)	0.16
HRCT				
Inflammation (%)	30/40 (75)	11/16 (69)	1/7 (14)	<0.007
Fibrosis (%)	10/40 (25)	5/16 (31)	6/7 (86)	<0.007

*Data are presented as mean ± SD or median (min–max) unless otherwise indicated. All hypotheses tested were two sided, with a 5 percent threshold for statistical significance.

FVC = forced vital capacity; PaO_2 = arterial pressure of oxygen; SpO_2 = Oxygen saturation; BAL = bronchoalveolar lavage; HRCT = High resolution computed tomography.

[a] Normal value at the altitude of Mexico City: 67 ± 3 mmHg.

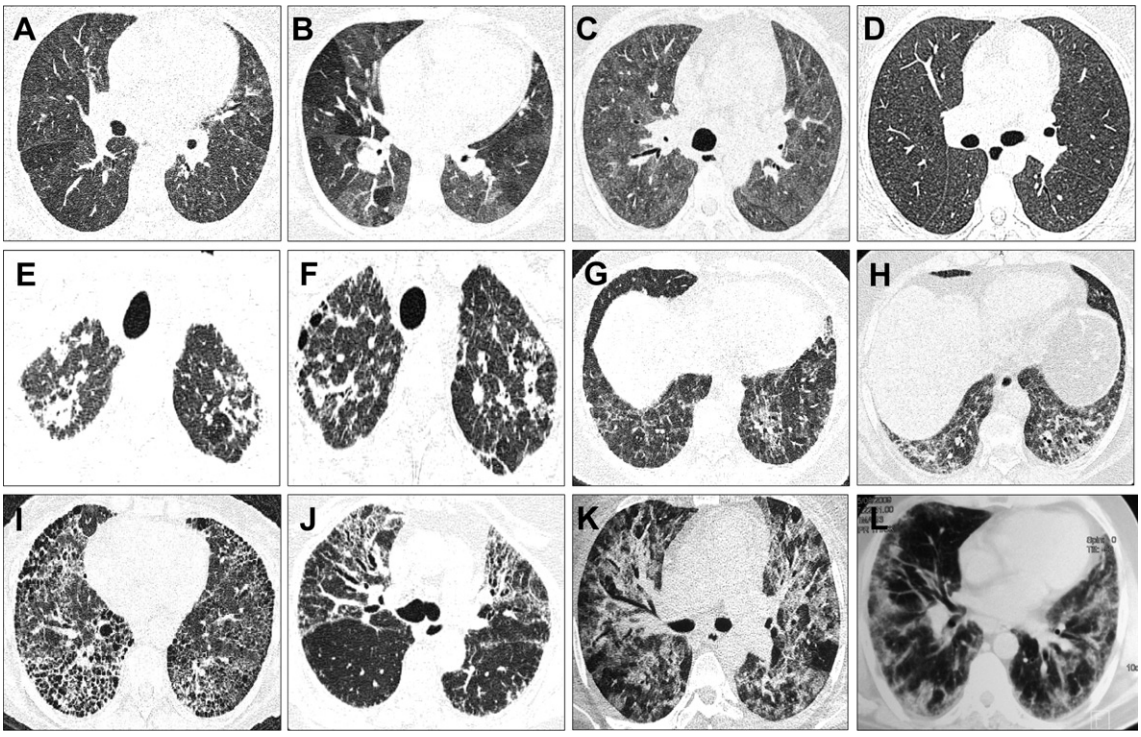

Figure 3 High resolution CT scans. Panels A and B show poorly defined micronodules and ground glass attenuation in two patients with histopathologic pattern typical of HP. Panels C and D: Ground glass attenuation, micronodules and mosaic in other two patients with typical HP-pattern. Panels E and F: peribronchovascular interstitial thickening and conglomerate fibrotic masses adjacent to central airways in two patients with ACIF-like pattern. Panels G and H: reticular and ground-glass opacities with lobar volume loss in two patients with NSIP-like pattern. Panels I and J: reticular opacities and honeycombing in two patients with UIP-like pattern. Panels K and L: Reticular and ground-glass attenuation, and peripheral parenchymal consolidations with air bronchogram in patients with OP-like pattern.

HRTC findings

HRCT findings in the different histopathologic patterns are illustrated in Fig. 3. Most patients presented mixed inflammatory and fibrotic changes. The predominance of bilateral ground-glass opacities and centrilobular nodules identified an inflammatory HRCT pattern and was seen in 30/40 (75%) patients with typical pattern, 11/16 (69%) NSIP

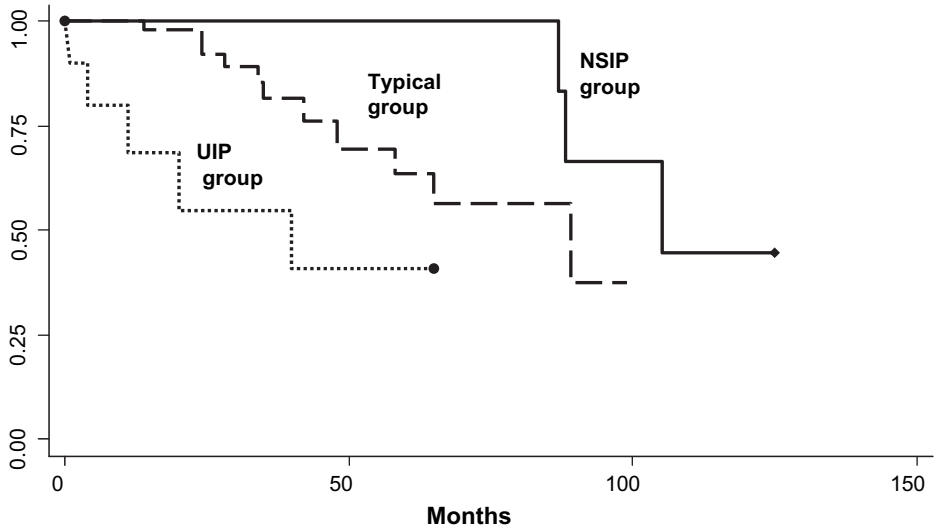

Figure 4 Survival rate in patients with HP showing "typical", NSIP, and UIP-like patterns. Patients with UIP-like pattern showed higher mortality (HR 3.4 (CI 95%: 1.15—10.29; $p < 0.03$)), compared with the "typical"-pattern group while patients with NSIP-like pattern showed a tendency to have a better survival (HR 0.23 (CI 95%: 0.05—1.09; $p < 0.07$)).

pattern and 1/7 (14%) UIP-like pattern; this difference was statistically significant (Exact Fisher test $p < 0.05$). Likewise, the trend for a lower prevalence of inflammatory pattern (UIP < NSIP < typical) was also significant ($\chi 2$ test for trend $P < 0.007$) (Table 2).

Survival analysis

The comparison of survival rate of the typical, NSIP-like and UIP-like patterns is shown in Fig. 4. In the univariate analysis, the Hazard Ratio (HR) for the UIP-like pattern group compared to the typical pattern was 4.19 (IC 95%: 1.66—14.47; $p < 0.004$). By contrast, survival rate for the NSIP-like pattern group compared with the typical pattern was 0.18 (IC 95%: 0.04—0.82; $p < 0.03$). We performed a Cox multivariate regression analysis with a backward selection procedure with the following variables: age, sex, FVC, PaO_2, UIP and NSIP patterns, and the resulting model showed that the UIP-like group has an HR of 3.4 (IC 95%: 1.15—10.29; $p < 0.03$) while the NSIP group had an HR of 0.23 (IC 95%: 0.05—1.09; $p < 0.07$). All other variables were excluded of the model. As a complementary analysis, we compared the survival rate of chronic HP displaying an UIP-like pattern with a group of 100 patients with idiopathic pulmonary fibrosis (IPF) and no differences was found (not shown).

Discussion

A growing body of evidence has shown that HP is a multifaceted disease in its clinical and morphological behavior.[2,6—9,18] Clinical forms of HP are usually divided into acute (or episodic), subacute, and chronic forms. Chronic PBD is induced by persistent and recurrent exposure to a low level of avian antigens, and importantly, these patients frequently evolve to fibrosis and eventually die from the respiratory disease. Patients with chronic disease may show various histopathological appearances. These include a typical pattern with bronchiolocentric interstitial inflammation and poorly formed granulomas or multinucleated giant cells but with interstitial fibrosis, a mixed NSIP pattern characterized by interstitial infiltration of mononuclear cells with mural incorporation fibrosis along the alveolar walls, and an UIP-like pattern that may be difficult to differentiate from the UIP found in patients with idiopathic pulmonary fibrosis. Bridging fibrosis between centrilobular and perilobular areas such as subpleural regions and areas close to the interlobular septa is often seen in chronic HP.[7]

In our study, only half of the patients with chronic PBD could be classified as typical HP; the other half showed a wide variety of morphologic patterns, the most common NSIP-like and UIP-like patterns. Few years ago, Vourlekis and colleagues reported by the first time that patients with proved HP showed non-specific interstitial pneumonia as the single histopathologic finding,[6] although previously, in their original description of NSIP, Katzenstein and Fiorelli had reported that a number of the examined samples showed lesions resembling HP.[19] In these cases, the lungs show a temporally homogeneous interstitial inflammation/fibrosis without the characteristic bronchiolocentricity of HP. In another study dealing with patients with chronic pigeon breeder's disease, it was found that half of them had morphological changes compatible with cellular or fibrotic NSIP.[9] This pattern requires a rigorous differential diagnosis with idiopathic NSIP, collagen-vascular, drug-induced or even HIV-related disease among others.

On the other hand, it has been also recently described that patients with chronic HP may present predominantly patchy peripheral fibrosis with architectural distortion and fibroblast foci resembling, microscopically, UIP.[7,20] The presence of giant cells, poorly formed granulomas, or inflammatory features of subacute HP may substantiate the diagnosis of HP. In our study, around 10% of the patients displayed an UIP pattern.

One of the interests of this study was to evaluate putative clinical differences between the different histopathological patterns. Surprisingly however, there were few clinical features that distinguish these three patterns. For example, we have previously found that digital clubbing is a frequent sign in patients with chronic PBD.[21] In the present study the high incidence of clubbing in chronic patients was corroborated but its occurrence was similar in the three morphological patterns.

Patients with UIP-like pattern showed less BAL lymphocytes and displayed more frequently irregular lineal opacities, honeycombing, and traction bronchiectasis on HRCT than the other two groups. In this context, it has been proposed that lymphocytes higher than 30% in BAL discriminate chronic HP showing UIP lesions from IPF/UIP.[22]

The most important difference between the three groups was given by the survival rate. Patients with microscopic findings compatible with usual interstitial pneumonia showed higher mortality on follow-up and interestingly, it was followed by the group of patients displaying typical HP morphology. Furthermore, no significant differences between patients with UIP-like pattern and those with confirmed idiopathic pulmonary fibrosis were found (not shown). Similar results were recently reported by Churg et al,[23] who found that 16 of the 18 patients with a UIP-like pattern died of the disease. Interestingly, BAL lymphocytosis did not show correlation with survival, since increased mortality was observed in patients with UIP-like pattern that display the lowest level of BAL lymphocytes as well as in patients with the typical pattern that showed the higher level of lymphocytes (Table 2). We have previously demonstrated that T-cell subsets distinguish subacute from chronic progressive HP.[17] However, since a small number of patients from the present study were analyzed for lymphocyte subpopulations, comparison with the diverse morphological patterns was not possible.

Intriguingly, in our study the NSIP group showed the best survival rate. Actually none of these patients died in the first 5 years of follow-up, although some of them died after 8 years of follow-up. The reason from the difference in mortality among patients with typical HP morphology and those with NSIP-like pattern is presently unknown, since the extent of the lesions and the percent of fibrosis was similar in both groups (not shown). In general, evidence of parenchymal fibrosis by HRCT or surgical biopsy has been found to be associated with decreased survival in patients with HP.[7,11] An important morphological difference between the patients with typical lesions and those with NSIP-like pattern are the prominent bronchiolocentric lesions observed in the formers. However, if the higher rate

of mortality correlates with widens damage of the small airways is presently unknown. The survival rate in HP patients showing NSIP-like pattern resulted even better than the observed in idiopathic NSIP in which although the majority of patients have a good prognosis, a 5-year mortality rate estimated is around 18%.[24]

A small group of patients showed lesions compatible with organizing pneumonia or with a recently described bronchiolar disorder named ACIF.[13] ACIF is characterized by small airway-centered interstitial fibrosis and metaplastic bronchiolar epithelium extending around and often linking fibrotic and sometimes heavily muscularized bronchioles. However, clinically and by HRCT the disease behave as an interstitial lung disease.[13]

Importantly, in 4% of the patients, the morphological lesions were not possible to properly be classified in any pattern, and the diagnosis was made by the antecedent of bird exposure, high titers of serum anti-avian specific antibodies, and more than 50% of lymphocytes in the bronchoalveolar lavage.

In summary, our results corroborate the broad variety of morphological patterns that can occur in chronic hypersensitivity pneumonitis and highlight the importance of identify environmental exposures and to integrate the clinical history, BAL, radiology and pathology findings to engage a confident diagnosis of chronic HP. It is important to emphasize that in the cases showing atypical morphological features, it is extremely important to confirm an etiological cause. Even in advances lesions, HP patients may improve or at least stabilize if further exposure to the offending antigen is avoided.

Ethical approval

This study was approved by the institutional review boards at the National Institute of Respiratory Diseases.

Competing interests

Miguel Gaxiola, Ivette Buendía-Roldán, Mayra Mejía, Guillermo Carrillo, Andrea Estrada, Mary Carmen Navarro, Jorge Rojas-Serrano have no conflict of interest to declare. Moisés Selman belongs to the Steering Committee of Boehringer for a therapeutic protocol of IPF.

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