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Subacute and chronic hypersensitivity pneumonitis: Histopathological patterns and survival

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Extrinsic allergic alveolitis;
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Summary
Background: In hypersensitivity pneumonitis (HP), survival can be predicted on the basis of the severity of fibrosis in surgical lung biopsy, but few data are available on the influence of clinical, functional, tomographic and histologic findings on prognosis.
Objectives: To describe the impact on survival of clinical data, histological patterns, and HRCT findings in subacute/chronic HP.
Methods: A retrospective analysis of 103 patients diagnosed with HP submitted to surgical lung biopsy. Chronic HP was characterized by HRCT findings indicative of fibrosis ($n = 76$).
Results: The most relevant exposures were to molds and birds. Lung biopsies revealed typical HP with granulomas in 46 patients, bronchiolocentric interstitial pneumonia in 27, and non-specific interstitial pneumonia (NSIP) in 16. By univariate analysis, several findings were predictors of mortality: older age, male sex, velcro crackles, higher FEV_1/FVC ratio, lower oxygen saturation during exercise, and absence of mosaic pattern/air trapping and presence of fibrosis on HRCT. By multivariate analysis, remained significant: age ($p = 0.007$), oxygen saturation during exercise ($p = 0.003$), and mosaic pattern/air trapping on HRCT ($p = 0.004$). Patients with NSIP had a greater survival than did those with typical histology and those with bronchiolocentric pneumonia ($p = 0.033$).

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Conclusions: A wide range of histological features are found in HP. Typical findings are seen in 45% of cases. Other common patterns are NSIP and centriacinar lesions. Survival is better in patients with NSIP and worse in those with older age, desaturation during exercise, and absence of mosaic pattern/air trapping on HRCT.

Introduction

Hypersensitivity pneumonitis (HP) is a pulmonary disease caused by inhalation of any of various antigens that trigger a diffuse inflammatory response in the small airways and pulmonary parenchyma. The classic histological HP triad includes the following:[1,2] chronic interstitial pneumonia with peribronchiolar accentuation; bronchiolitis; and non-caseating granulomas. Granulomas, however, are not present in all cases. In acute HP, granulomas are seen in 70% of cases.[3] In the subacute and chronic forms of HP, granulomas are even less common.[4,5]

Various histopathological patterns included in the classification of idiopathic interstitial pneumonias,[5–7] can result from exposure to organic antigens. In recent years, a new form of idiopathic interstitial pneumonia, with bronchiolocentric distribution of inflammation or fibrosis, in absence of granulomas and giant cells has been described.[8–11] HP can be a common cause of this form of interstitial pneumonia.[7] Due to peripheral deposition of antigens, HP can also result in a spectrum of isolated small airway diseases, including constrictive bronchiolitis.[12,13] The influence of the most common histological patterns associated with HP on survival is unknown.

In HP, the prognosis can be predicted on the basis of the severity of fibrosis observed in open lung biopsy.[14,15] However, in many cases, the diagnosis can made by non-invasive methods,[16] so clinical prognostic findings are of interest. In a recent study, univariate analysis demonstrated that evidence of fibrosis on high-resolution computed tomography (HRCT), more severe lung function abnormalities, and the presence of crackles on auscultation were predictive of reduced survival.[17]

In the present study, we describe the histopathological patterns in subacute and chronic HP, in a large sample of patients submitted to surgical lung biopsies. In addition, we sought to determine whether clinical, physiological, tomographic data and individual major histological patterns correlate with survival.

Methods

Selection of cases

The present study refers to an observational cohort of 103 adult patients with HP. The medical records of 1240 patients with interstitial lung diseases, evaluated between January of 1995 and December of 2006 at two facilities in the city of São Paulo, Brazil, were reviewed. Of those, 200 received a final diagnosis of HP. From this sample, 97 patients were excluded for the following reasons: 53 did not undergo lung biopsy (due to advanced age, clinical improvement with avoidance of further antigen exposure, very mild disease or high surgical risk); 17 were diagnosed through transbronchial biopsy; 10 presented concomitant gastroesophageal reflux; five had end-stage lung disease; six presented accompanying conditions, such as pneumoconiosis and collagen vascular diseases; three had acute HP; two presented granulomatous pneumonitis as an adverse drug effect; and one was <18 years old. Therefore, the final sample comprised 103 patients.

Clinical analysis and HRCT

A standardized protocol was applied to all patients. Data related to relevant exposure were recorded. Exposure to molds was characterized by reporting of extensive visible mold at home or in the workplace. Collagen vascular diseases, exposure to inorganic dusts, or other causes of lung fibrosis were carefully excluded by clinical and laboratorial data.

Pulmonary function tests were conducted according to the American Thoracic Society guidelines.[18] The normal values were those previously derived for the Brazilian population.[19] Peripheral oxygen saturation was evaluated at rest and after a self-paced step test exercise.[20,21]

The HRCT scans were done in all patients ($n = 103$) at the time of diagnosis. Of those, 85 were reviewed by an expert radiologist (DJ) for the presence or absence of findings associate with subacute HP and findings indicative of fibrosis. In the remaining cases ($n = 18$), the initial report, done in a systematic way by pulmonologists, was included in the final analyses. The findings on HRCT associate with subacute HP are ground-glass opacities, mosaic pattern/air trapping, and centrilobular nodules.[22–24] On HRCT scans, profuse, poorly-defined centrilobular nodules with ground-glass attenuation — or the combination of at least two or more the following findings: ground-glass opacities, poorly-defined centrilobular nodules, and a mosaic pattern and/or air trapping on expiratory HRCT — were considered highly suggestive of HP in non-smokers with relevant exposure. Chronic HP was characterized by HRCT findings indicative of fibrosis (reticular pattern, traction bronchiectasis or honeycombing), superimposed or not on findings associated with subacute HP.[25–27] Findings not compatible with HP (pleural effusion, lymphadenopathy, large nodules or masses) should be absent.

Histological findings

The histological examinations were reviewed by two pulmonary pathologists (ENAMC and RGF) by consensus. Typical HP was defined as patchy, chronic interstitial pneumonia with peribronchiolar accentuation and non-necrotizing granulomas or giant cells.[1,2] The histological patterns associated with organizing pneumonia, non-specific interstitial pneumonia (NSIP), and usual interstitial

pneumonia (UIP) were classified according to the American Thoracic Society/European Respiratory Society consensus.[28] In the absence of granulomas or giant cells, extensive areas of organizing pneumonia combined with fibrosis were seen.[29] Constrictive bronchiolitis was characterized as submucosal and peribronchiolar fibrosis with surrounding parenchyma free of involvement.[30] The bronchiolocentric interstitial pneumonia (BIP) pattern was defined according with the combination of criteria by Yousem and Dacic[9] and Churg et al.[10] as centrilobular/bronchiolocentric chronic inflammatory infiltrate associated or not with fibrosis. Sparse foci of fibromyxoid tissue and honeycombing could also be found. In many instances, there was prominent bronchiolar metaplasia overlying the fibrotic alveolar walls.

Case definition

Subacute HP was characterized as symptom duration of greater than 3 months and no fibrosis on HRCT scans. Chronic HP was characterized by HRCT findings indicative of fibrosis, irrespective duration of symptoms. The diagnosis of typical HP was based on the classic histological triad. Diagnosis of non-typical HP was done by: (1) relevant exposure preceding respiratory symptoms; (2) presence of episodic or persistent respiratory symptoms; (3) at least one of following HRCT findings consistent with HP-bilateral ground-glass, poorly defined centrilobular nodules, areas lobular air trapping or fibrotic changes considered to be atypical for UIP, that is, without subpleural fibrotic changes, lower zone predominance, and minimal to no ground-glass infiltration; (4) consistent histopathological findings as described above (organizing pneumonia, NSIP, UIP, BIP or constrictive bronchiolitis); and (5) no other identifiable cause for the lung disease. Precipitin tests and bronchoalveolar lavage (BAL) were not available in the majority of cases.

Treatment and survival

Patients were treated at discretion of assistant physicians if the avoidance of presumed antigen was not attained, or symptoms and respiratory function tests or blood gases abnormalities remained significant. Corticosteroids isolated or associated with cytotoxic agents were prescribed.

In major histopathological groups, spirometric values for forced vital capacity (FVC) obtained prior to the lung biopsy were compared to those obtained in the last visit (intervals ranged from 4 to 96 months, median 23 months).

Survival was assessed through May of 2006. Deaths were identified by follow-up contact or through telephone notification by relatives. Deaths were considered HP-related if due to respiratory failure, pneumonia, or pulmonary fibrosis. One patient was censored at the time of lung transplantation.

Statistical analysis

All data analyses were performed using the SPSS program, version 13.0.[31] Continuous data are expressed as mean $\pm$ SD, or as median and range. Continuous data with normal distribution were compared using t-tests and ANOVA. Continuous data with non-normal distribution were compared using the Kruskal–Wallis test. The chi-square test was used for comparisons of proportions. Values for FVC measured before and after treatment were compared by paired t -test. Survival time was calculated from the day of the biopsy. Cox proportional hazards regression was used to assess significant variables that influenced mortality. Variables were chosen for inclusion in the model if statistically significant by univariate analyses. The final Cox regression model was evaluated in the forward selected stepwise multivariate Cox regression analysis. Cumulative survival probabilities for histopathologic groups and desaturation status groups were estimated using the Kaplan–Meier method and log-rank tests. Two-sided p values < 0.05 were considered statistically significant.

The study design was approved by the ethics committees of the hospitals involved.

Results

Clinical findings

The study sample comprised 103 cases (64 females/39 males), 27 with subacute HP and 76 with chronic HP. Exposure to molds was reported by 36 patients, to birds by 28, and to both by 25. Exposure to isocyanates only was reported by seven patients. In the remaining six cases there was a combined exposure of isocyanates with molds in four and with birds in two. Only one patient reported no relevant exposure, but presented typical histological findings at lung biopsy. Comparison among the patients by type of exposure revealed no differences in clinical, functional, imaging, or histological findings.

The mean age was 56 ± 13 years (range, 18–78 years). Thirteen patients (13%) were smokers at the onset of symptoms. The median duration of symptoms was 18 months (range, 0–120 months). The main clinical features were dyspnea (in 88, 85%) and cough (in 80, 78%). Weight loss was reported by 30 patients (29%). Velcro crackles were heard in 63 (61%) and 'squawks' in 10 (10%). Clubbing was observed in 27 (26%). Ninety-nine patients performed acceptable spirometry tests. Mean FVC was $69 \pm 20\%$ of predicted and FEV_1/FVC ratio was $85 \pm 7\%$. Eighty-two patients completed a step test, with at least 3 min of duration. In these cases, the SpO_2 dropped from $95 \pm 3\%$ at rest to $88 \pm 7\%$ at the end of exercise.

HRCT findings

The most frequent HRCT patterns were ground-glass opacities (in 82, 80%) and findings indicative of fibrosis (in 76, 74%). Centrilobular nodules were seen in 34 (33%), mosaic pattern/air trapping in 44 (43%), and cysts in 13 (13%). In 16 (16%), we observed diffuse centrilobular nodules, which was the only finding in three cases. A highly suggestive HRCT pattern was seen in 20 (74%) of the subacute HP patients and in 40 (53%) of those with chronic HP ($\chi^2 = 3.77$, $p = 0.052$). Highly suggestive findings on HRCT scans were seen in similar proportions in the 28 patients

(61%) with typical histological findings and in the 28 (49%) presenting other histological patterns ($\chi^2 = 2.86$, $p = 0.091$).

Histological findings

In 46 patients, the histological examination of the biopsies showed classical or typical findings, with granulomas or giant cells and chronic interstitial pneumonia with peribronchiolar accentuation. Other common histological patterns included BIP ($n = 27$) and NSIP ($n = 16$, cellular pattern in four and fibrotic pattern in 12). Baseline characteristics according to histopathologic subgroup are shown in Table 1. Among the patients with NSIP, the mean age was lower and the mean duration of symptoms was shorter than among the patients with typical HP and those with BIP. Velcro crackles at auscultation and honeycombing on HRCT scans were more common among patients with BIP than among those with typical HP. Patients with typical HP presented lower FEV_1/FVC ratios and more centrilobular nodules on HRCT scans, as well as less frequently presenting honeycombing (Table 1).

In five patients, a pattern of constrictive bronchiolitis was seen, without associated interstitial findings. An organizing pneumonia pattern was seen in five patients, three of whom presented associated fibrosis.

There were four patients who had typical UIP findings at biopsy, although areas of bronchiolocentric distribution were also apparent in two. The HRCT findings were not suggestive of UIP in any of these cases.

Survival

The median post-biopsy follow-up period was 36 months. A total of 5 years after diagnosis, 27% of the patients have died. There were 17 deaths secondary to HP during the study period. By Cox univariate analysis, several findings were significant predictors of mortality by HP: older age, male sex, velcro crackles, higher FEV_1/FVC ratio, lower oxygen saturation during exercise, use of cytotoxic agents on treatment, and regarding the findings on HRCT, absence of mosaic pattern/air trapping, presence of honeycombing, and presence of fibrosis (Table 2). By multivariate analysis, mortality was associated with older age, lower oxygen saturation during exercise, and absence of mosaic pattern/air trapping on HRCT (Table 3).

Considering these three prognostic factors (older age, lower oxygen saturation during exercise, and absence of mosaic pattern/air trapping on HRCT), and changing oxygen saturation according a cutoff point of 88%, the oxygen saturation was selected as the most important predictor of

Table 1 Baseline characteristics according to histopathologic subgroup in patients with hypersensitivity pneumonitis.

Characteristic	Typical HP ($n = 46$)*	NSIP ($n = 16$)†	BIP ($n = 27$)‡	p value§
Age, year (mean ± SD)	58 ± 11	48.4 ± 15.5	57.1 ± 12	0.025
Sex, male/female	16/30	5/11	12/15	0.617
Smokers, *n* (%)	6 (13)	2 (13)	5 (19)	0.787
Duration of symptoms, in months, median (range)	17 (0—120)	9.5 (2—76)	38 (0—87)	0.023
Weight loss, *n* (%)	10 (22)	9 (56)	9 (33)	0.037
Clubbing, *n* (%)	9 (20)	3 (19)	9 (33)	0.36
Velcro crackles, *n* (%)	24 (52)	10 (63)	23 (85)	0.018
Pulmonary function				
FVC, % predicted	72.7 ± 20.5	58.5 ± 16.7	69.3 ± 19.9	0.055
FEV_1/FVC ratio, %	81.7 ± 7,1	87.2 ± 5.2	88.3 ± 6.8	<0.001
Oxygen saturation, %				
At rest (mean ± SD)	95.2 ± 1.8	92.9 ± 5,4	95.1 ± 1.8	0.333
During exercise (mean ± SD)	87.5 ± 6.8	84.4 ± 5.6	88.7 ± 5.6	0.088
HRCT findings				
Centrilobular nodules, *n* (%)	31 (67.4)	3 (18.8)	11 (40.7)	0.002
Ground-glass opacities, *n* (%)	33 (71.7)	14 (87.5)	23 (85.2)	0.254
Mosaic pattern/air trapping, *n* (%)	21 (45.7)	6 (37.5)	9 (33.3)	0.565
Honeycombing, *n* (%)	16 (45.7)	9 (64.3)	19 (79.2)	0.034
Findings of fibrosis, *n* (%)	30 (65)	12 (75)	24 (89)	0.083
Treatment				
Corticosteroids, *n* (%)	41 (89)	15 (94)	24 (89)	0.852
Cytotoxic agents, *n* (%)	18 (39)	9 (56)	9 (33)	0.323

Definition of abbreviations: HP = hypersensitivity pneumonitis; NSIP = non-specific interstitial pneumonia; BIP = bronchiolocentric interstitial pneumonia; HRCT = high-resolution computed tomography; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity.

* $n = 46$ except pulmonary function ($n = 44$) and honeycombing ($n = 35$).

† $n = 16$ except honeycombing ($n = 14$).

‡ $n = 27$ except pulmonary function ($n = 25$) and honeycombing ($n = 24$).

§ p value associated with the overall comparison across histopathologic subgroups using analysis of variance for continuous variables and χ^2 test for categorical variables. p significant at < 0.05.

Table 2 Results of univariate analysis of prognostic factors in patients with hypersensitivity pneumonitis.

Variables	Hazard ratio	95% CI	*p* value
Older age	1.05	1.00–1.09	0.049
Male sex	3.49	1.32–9.27	0.012
Duration of symptoms	1.01	0.99–1.02	0.562
Clubbing	1.02	0.33–3.13	0.978
Velcro crackles	7.15	1.63–31.45	0.009
Pulmonary function			
FVC, % predicted	0.98	0.96–1.01	0.180
FEV_1/FVC ratio, %	1.08	1.01–1.15	0.020
Higher oxygen saturation, %			
At rest	0.99	0.87–1.13	0.889
During exercise	0.92	0.86–0.99	0.025
HRCT findings			
Centrilobular nodules	1.47	0.56–3.86	0.437
Ground-glass opacities	1.66	0.58–4.71	0.343
Mosaic pattern/air trapping	0.26	0.07–0.90	0.034
Findings of fibrosis	8.14	1.08–61.61	0.042
Honeycombing	5.73	1.26–26.05	0.024
Typical HP*	1.75	0.64–4.76	0.274
Use of cytotoxic agents on treatment	3.58	1.26–10.16	0.017

Definition of abbreviations: CI = confidence interval; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; HRCT = High-resolution computed tomography; HP = hypersensitivity pneumonitis.
* Typical HP was defined as typical histological findings, including granulomas or giant cells.

mortality, by a forward stepwise analysis (hazard ratio [HR] = 16.55, 95% confidence interval [CI] = 2.17–126.15, $p = 0.007$). In patients with oxygen saturation of 88% or less at the end of exercise (desaturation), 43% had died after 5 years, compared to 4% of those with oxygen saturation above of 88% (log-rank = 13.53, $p < 0.001$) (Figure 1). Desaturation on step test remained as the main predictor of mortality after adjusting for age, sex, velcro crackles, findings of fibrosis on HRCT, and FEV_1/FVC ratio (HR = 14.96, 95% CI = 1.96–114.00, $p = 0.009$).

Table 3 Results of multivariate analysis of prognostic factors in patients with hypersensitivity pneumonitis.

Characteristic	Hazard ratio	95% CI	*p* value
Older age	1.10	1.03–1.18	0.007
Higher oxygen saturation, %			
During exercise	0.88	0.80–0.96	0.003
HRCT findings			
Presence of mosaic pattern/air trapping	0.05	0.01–0.39	0.004

Definition of abbreviations: CI = confidence interval; HRCT = high-resolution computed tomography.

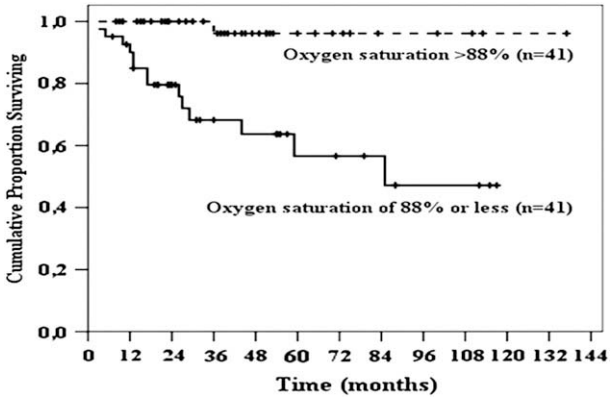

Figure 1 Kaplan–Meier survival curves for patients with hypersensitivity pneumonitis, stratified by desaturation (oxygen saturation of 88% or less) during a step test. Patients without desaturation ≤88% ($n = 41$, *dashed line*) had significantly better survival than did those with desaturation ≤88% ($n = 41$, *solid line*), (log-rank = 13.53, $p < 0.001$).

Outcomes and survival in major histologic groups

Antigen avoidance and abatement procedures were recommended in all cases. In major histologic groups ($n = 89$), a similar proportion of cases were treated with corticosteroids and cytotoxic agents (Table 1). Antigen avoidance was sufficient for disease control in six patients of these groups. Considering the three major histological patterns with functional follow-up ($n = 70$), the changes in FVC were: -0.044 ± 0.48 L in typical HP ($n = 38$); 0.262 ± 0.50 L in NSIP ($n = 13$) and -0.157 ± 0.41 L in BIP ($n = 19$), ($F = 3.23$, $p = 0.046$). A post hoc analysis showed that the NSIP group presented a significantly greater increase in FVC in comparison to BIP group ($p = 0.04$).

Mortality was similar between those with typical HP and those with BIP ($p = 0.66$). However, survival was greater in patients with NSIP ($n = 16$) than in those with typical HP and BIP groups ($n = 73$, log-rank = 4.56, $p = 0.033$; Figure 2). None of the patients with NSIP died during the study period, compared with 11 with typical HP and five with BIP ($p = 0.039$). When only patients presenting evidence of fibrosis on HRCT scans were compared, survival was still greater in the NSIP group ($n = 12$) than in the typical HP/BIP group ($n = 54$) (log-rank = 4.83, $p = 0.028$). When only patients treated with cytotoxic agents were compared, those with NSIP had a better survival (log-rank = 5.76, $p = 0.016$). When significant predictors of mortality by univariate analysis (see Table 2) were added with major histologic patterns in a multivariate analysis, the model did not converge by the small numbers of cases with NSIP and by the lack of deaths in this group.

Discussion

In the present study, we found that patients with subacute and chronic HP display a wide range of histological features. Less than half of patients disclosed classical findings of HP in surgical lung biopsy. Several findings were

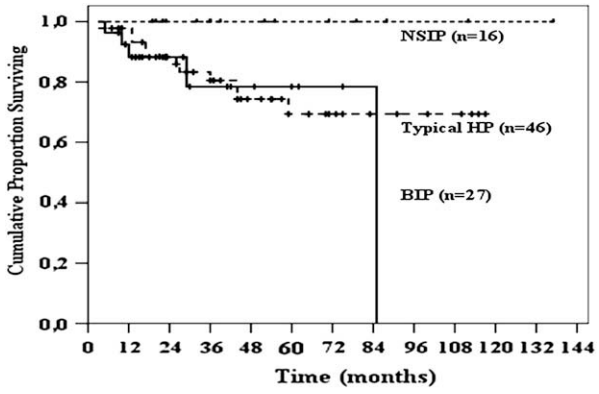

Figure 2 Kaplan—Meier survival curves for patients with nonspecific interstitial pneumonia (NSIP: $n = 16$, *dotted line*), typical hypersensitivity pneumonitis (Typical HP: $n = 46$, *dashed line*), or bronchiolocentric interstitial pneumonia (BIP: $n = 27$, *solid line*), grouped by histologic classification. There was no significant difference between those with typical HP and those with BIP (log-rank = 0.19, $p = 0.66$). Patients with NSIP had significantly better survival than did those with typical HP and those with BIP (log-rank = 4.56, $p = 0.033$).

predictive of mortality in HP, including histologic pattern and some findings on HRCT, but the best predictor seemed to be oxygen saturation during exercise.

Histological findings

In our sample, 45% of the cases presented typical histological findings, including granulomas or giant cells. In HP, the degree of bronchiolar involvement tends to be proportional to the severity of fibrosis seen in the lung parenchyma,[12] although isolated constrictive bronchiolitis can be seen.[12,13] In our sample, five patients presented a pattern consistent with constrictive bronchiolitis. In four of these cases, air trapping was the only HRCT finding. Bronchiolitis with poorly-defined granulomas or isolated giant cells on lung biopsy in patients with relevant exposure has been described.[13] Some authors have reported organizing pneumonia to be a possible HP pattern.[5,32] In three of our cases, a mixed pattern of fibrosis and extensive organizing pneumonia was found.

A distinctive picture of bronchiolocentric injury has been referred to by a variety of terms, including centrilobular fibrosis, idiopathic BIP, airway-centered interstitial fibrosis, and peribronchiolar metaplasia.[8—11] This is distinctly different from the peripheral pattern of fibrosis observed in UIP. In our patients, BIP without granulomas was seen in 27 cases: inflammation was present in all and peribronchiolar fibrosis in 25 (93%); sparse foci of intraluminal polyps in 21 (78%); and honeycombing in 12 (46%).

The NSIP pattern is now recognized as a possible expression of HP. This pattern was seen in 16 of our cases. Four cases were defined as UIP based on the biopsy, although areas of bronchiolocentric distribution were apparent in two of those cases. A typical UIP pattern can represent idiopathic pulmonary fibrosis with coincidental exposure[14] or a non-representative biopsy. In our four cases presenting UIP histological pattern, the HRCT findings were atypical for UIP in all. In cases with granulomas or giant cell are associated with any other pattern of interstitial pneumonia, a diagnosis of HP should be considered.

Patients with typical HP had greater frequency of centrilobular nodules in comparison to NSIP and BIP patterns. In the present study, the mean age was lower and the mean symptom duration was shorter in the patients with NSIP than in those with typical HP or BIP. Patients with BIP had greater frequency of velcro crackles at lung auscultation and honeycombing at HRCT, suggesting a more advanced disease in comparison to cases with typical HP and NSIP. We suggest that BIP reflects an advanced stage of HP, with fibrosis around the airways after an inflammatory phase, with disappearance of granulomas or giant cells. Our study shows that survival among HP patients varies depending on the histological pattern. No patient with NSIP died during the follow-up. Patients presenting NSIP pattern having the greatest survival.

Future attempts to classify the fibrosing interstitial lung diseases should take into account clinical and radiological manifestations, and new methods, like gene expression profile of disease, rather than relying simply on subtle histological differences as the basis for the definition of separate disease entities.[33,34]

Survival

Survival has been evaluated in a few studies involving patients with subacute or chronic HP.[14,15] In our study, total mortality in 5 years was 27%, very similar to the 29% found in a study conducted in Mexico.[14] In both studies, continuous low-grade domestic exposure to antigen was the main cause of HP. However, in our study, in only 17% of cases the death was attributed to HP.

The presence of fibrosis seen in lung biopsy is known to be the major determinant of survival in HP.[5,7,14,15] Sahin et al. concluded that HRCT findings indicative of fibrosis were not associated with a worse survival, but only 26 patients were included in their study.[27] A recent study found that the presence and extent of fibrosis in HP are associated with reduced survival.[17] In our sample, the presence of fibrosis at HRCT had influence on survival.

In our study, several variables correlated with mortality. In agreement with other studies,[17,35] patients with higher FEV_1/FVC ratio had a higher mortality. Increased FEV_1/FVC ratio is due to increased lung elastic recoil and/or decrease in resistance of airways. Both are consequence of lung fibrosis.

The absence of mosaic attenuation or air trapping on HRCT was a significant predictor of mortality. These findings on HRCT reflect small airflow obstruction due to bronchiolitis in HP. Patients with mosaic pattern had findings indicative of fibrosis on HRCT in a smaller proportion ($p = 0.013$). It can be postulated that as the disease becomes more severe, the findings indicative of air trapping tend to disappear. In the present study, clubbing did not relate to survival. Similar findings were seen in other recent study.[17]

In patients with UIP, desaturation during a 6 min walking test or at the end of a step test is strongly predictive of mortality.[21,36] During exercise, gas exchange in IPF is influenced by ventilation-perfusion mismatching, oxygen

diffusion and increased pulmonary vascular resistance.[37,38] In our study, oxygen desaturation during a step test was the better predictor of survival in patients with subacute and chronic HP. Patients with desaturation of 88% or less had a hazard of 15 fold of dying due to HP after considering other variables related to survival, but confidence interval was wide.

Limitations

There are several limitations to our study. The diagnosis of HP was largely based on clinical and radiologic findings. Relevant exposure was characterized by history. Patients with several histological patterns, including organizing pneumonia, UIP, and NSIP, without granulomas or giant cells, could have a coincident exposure. Serologic data were not available for confirmation of exposure. In patients with interstitial fibrosing lung disease, an increase in lymphocytes in BAL, in the presence of exposure and suggestive data on HRCT could obviate surgical lung biopsy, but BAL was available in a small number of cases. We do believe that bronchiolocentric interstitial pneumonia should be incorporated in the classification of interstitial pneumonias, but at present time, different criteria for this diagnosis have been proposed by different authors.[8–10] Finally, the impact of treatment on course of chronic HP must be defined by randomized clinical trials. Nevertheless, the effect of corticosteroids and cytotoxic agents seems to be small.

Conclusions

In conclusion, subacute and chronic HP can exhibit a large variety of histologic patterns. Typical findings are found in less than half of cases. Others common patterns include NSIP, and a bronchiolocentric interstitial pneumonia. Patients with NSIP are younger, have a shorter duration of symptoms, and greater survival. In contrast, patients with BIP have more advanced disease and a worse prognosis. Several factors are related to mortality, including older age, male sex, higher FEV_1/FVC ratio, velcro crackles, presence of fibrosis and absence of mosaic pattern on HRCT, and lower oxygen saturation during exercise. Irrespective other data, the best predictor of mortality seems to be a fall in oxygen saturation at exercise of 88% or less.

Conflict of interest statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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