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Subacute and chronic hypersensitivity pneumonitis: Histopathological patterns and survival

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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 nonspecific 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