CHEST

Original Research

HYPERSENSITIVITY PNEUMONITIS

Clinical Predictors and Histologic Appearance of Acute Exacerbations in Chronic Hypersensitivity Pneumonitis*

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Background: **Acute exacerbations (AEs) in idiopathic pulmonary fibrosis (IPF) are critical factors for its clinical course and prognosis. We have seen AEs and poor prognosis consequent to AE in patients with chronic hypersensitivity pneumonitis (HP), as has been seen in patients with IPF. The aim of this study was to evaluate the clinical features of the patients with AE in those with chronic HP.**
Methods: **We reviewed 100 consecutive patients with chronic bird fancier lung (BFL) from 1993 to 2006, and analyzed the clinical characteristics, including history, and laboratory and immunologic, imaging, BAL, and histologic findings.**
Results: **AE developed in 14 patients during this observation period (AE group), whereas 86 patients remained stable (non-AE [NAE] group). The 2-year frequency of AE among patients with chronic BFL having usual interstitial pneumonia (UIP)-like lesions seen on surgical lung specimens was 11.5%. Patients with AE were more likely to be smokers ($p = 0.003$). In pulmonary function test results, the mean total lung capacity (TLC) and diffusing capacity of the lung for carbon monoxide (DLCO) were lower in patients with AEs (TLC: AE patients, 63.0 ± 16.8%; NAE patients, 81.6 ± 20.0%; DLCO: AE patients, 41.9 ± 19.0%; NAE patients, 60.0 ± 19.4%). The mean number of lymphocytes in BAL fluid were lower (AE patients, 13.7 ± 7.5 lymphocytes; NAE patients, 37.2 ± 29.7 lymphocytes), while the number of neutrophils were greater in AE patients (AE patients, 10.7 ± 17.6 neutrophils; NAE patients, 3.6 ± 4.4 neutrophils). Histologic and/or radiologic findings revealed that all AE patients had UIP-like lesions. Diffuse alveolar damage was observed in six cases, whereas organizing pneumonia superimposed on preexistent fibrotic lesions was observed in two cases.**
Conclusions: **The present study showed several predictive factors for AE at the time of diagnosis. Low TLC and DLCO, low lymphocyte levels in BAL fluid, and a UIP-like pattern in histology at the time of diagnosis may be the risk factors for AE.** ***(CHEST 2008; 134:1265–1270)***

Key words: acute exacerbations; chronic hypersensitivity pneumonitis; diffuse alveolar damage; organizing pneumonia; risk factors

Abbreviations: AE = acute exacerbation; BFL = bird fancier lung; cNSIP = cellular nonspecific interstitial pneumonia; DAD = diffuse alveolar damage; DLCO = diffusing capacity of the lung for carbon monoxide; fNSIP = fibrotic nonspecific interstitial pneumonia; HP = hypersensitivity pneumonitis; HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; NAE = nonacute exacerbation; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; SLBx = surgical lung biopsy; TLC = total lung capacity; UIP = usual interstitial pneumonia

Recently, acute exacerbations (AEs) of idiopathic pulmonary fibrosis (IPF) are well-recognized conditions that are characterized by an acute worsening of dyspnea leading to hypoxemic respiratory failure, and accompanied by new infiltrates on radiologic images.[1,2] The histologic findings of lung biopsy specimens in IPF patients with AEs are diffuse alveolar damage (DAD) with or without hyaline membranes superimposed on usual interstitial pneumonia (UIP).[2–6] AEs have also been reported in patients with idiopathic nonspecific interstitial pneumonia (NSIP), interstitial pneumonia associated with collagen vascular diseases,[7] and in several case reports[8] of UIP-like lesions in patients with chronic hypersensitivity pneumonitis (HP).

Bird fancier lung (BFL) is an HP that is caused by the inhalation of bird-related antigens.[9] Patients can present with acute HP, but it is more likely to be a

chronic progressive disease, since exposure to birds tends to be long term with small amounts of antigens.[10] Chronic BFL is categorized into two subgroups according to the clinical features (recurrent and insidious).[11–13] Chronic BFL sometimes presents as an episode of AE, including case reports[4,14–17] of DAD superimposed on UIP-like lesions in patients with chronic HP. Little is known about the natural course of chronic BFL, especially in patients with AE.[13,18,19] In the present study, we reviewed 100 cases of patients with chronic BFL including 14 patients with AEs, and evaluated their clinical features including the frequency, predictive markers, and radiologic and pathologic characteristics.

Materials and Methods

Patients

A retrospective review of the medical records of patients with chronic BFL who were admitted to our hospital between April 1993 and November 2006 was undertaken. Most of the subjects were included in the previous article.[19] The diagnosis of chronic BFL was made based on clinical, radiologic, and histologic criteria, as was described previously.[11,13,20] We conducted inhalation provocation tests in 50 of 86 non-AE (NAE) patients and in 10 of 14 AE patients. The remaining patients for each group were positive for the reproduction of symptoms of HP by an environmental provocation or the improvement of symptoms by an avoidance of environmental antigen exposure. This study conformed to the Declaration of Helsinki and was approved by the institutional review board. Informed written consent was obtained for each subject.

Criteria of AEs

The criteria of Kondoh et al[4] were adopted to define an episode of AE. These criteria included the following: (1) aggravation of dyspnea within 1 month; (2) hypoxemia with an arterial oxygen tension/inspired oxygen tension ratio of < 225; (3) newly developing pulmonary infiltrates on chest radiographs; and (4) the absence of apparent infection or heart disease.

BAL

We performed BAL as previously described.[20] BAL was performed using three 50-mL aliquots of a sterile 0.9% saline solution. The cellular composition of the BAL fluid was determined using a cytospin smear with Wright stain by counting 200 cells. Lymphocyte phenotypes were performed by flow cytometry with monoclonal antibodies for CD4 and CD8.

Radiologic Assessment

A high-resolution CT (HRCT) scan was performed with standard technical parameters, both at the time of the initial diagnosis and the time of the AE. HRCT scans were reviewed independently by three experienced respiratory physicians. They scored ground-glass opacities for ground-glass scores and reticular opacities for fibrosis scores at the time of the initial diagnosis. The outlines of the scoring system used for the evaluation have been described previously by Kazerooni et al.[21] Each lobe of the lung was scored on a scale of 0 to 5. The scores for each lobe were averaged for all three readers for data analysis. Also HRCT scan findings during the episode of AE were classified as peripheral, multifocal, and diffuse parenchymal opacification, as previously reported by Akira et al.[5]

Pathologic Assessment

Histologic sections of surgical biopsy and/or autopsy materials were stained with hematoxylin-eosin and elastica van Gieson. Fifty-five patients underwent surgical biopsy at the time of the initial diagnosis. The histologic examinations were interpreted blindly by two pulmonary pathologist (T.A. and Y.O.). When the interpretations differed between the two pathologists, the final decision was reached by consensus. The background histologic patterns of chronic HP were classified according to the American Thoracic Society/European Respiratory Society international consensus classification as UIP-like lesions, NSIP-like lesions, and organizing pneumonia (OP)-like lesions based on the quality of fibrotic changes, including loose and dense fibrosis, and the temporal appearance. Patients with NSIP were subdivided into the following two groups: cellular NSIP (cNSIP) pattern group; and fibrotic NSIP (fNSIP) pattern group.[19,22,23] Then, we confirmed the presence of superimposed acute changes in the form of exudative DAD (with hyaline membranes), organizing DAD, or OP.[2]

Statistical Analysis

Data were analyzed using a statistical software package (StatView, version 5.0; SAS Institute, Cary, NC) and were described as the mean ± SD. The two groups were compared using the Mann-Whitney *U* test. Comparisons between groups were performed using a Fisher exact test for categoric variables. All statistical comparisons were two sided, and p values < 0.05 were considered as significant. For the frequency of AE, we evaluated the disease period for each patient at the end of November 2006, and the end point of the analysis was the time of the AE. Then, the frequency of AE was obtained from the Kaplan-Meier survival curve censoring AE, as was previously described by Park et al.[7]

Results

Clinical Features in Chronic BFL With AE

The characteristics of the 100 patients with chronic BFL are summarized in Table 1. Fourteen

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