Respiratory Medicine 114 (2016) 53–60

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Predictors of survival in coexistent hypersensitivity pneumonitis with autoimmune features

Ayodeji Adegunsoye [a, *], Justin M. Oldham [a, 1], Carley Demchuk [b], Steven Montner [c], Rekha Vij [a], Mary E. Strek [a]

[a] Department of Medicine, Section of Pulmonary and Critical Care Medicine, The University of Chicago, 5841 S. Maryland Avenue, Chicago IL 60637, USA
[b] Department of Medicine, The University of Chicago, 5841 S. Maryland Avenue, Chicago IL 60637, USA
[c] Department of Radiology, The University of Chicago, 5841 S. Maryland Avenue, Chicago IL 60637, USA

ARTICLE INFO

Article history:
Received 9 December 2015
Received in revised form
22 February 2016
Accepted 18 March 2016
Available online 21 March 2016

Keywords:
Autoimmunity
Connective tissue disease
Hypersensitivity pneumonitis
Interstitial lung disease
Pulmonary fibrosis
Immunosuppressive therapy

ABSTRACT

Background: Hypersensitivity pneumonitis (HP), an immune-mediated inflammatory interstitial lung disease (ILD), can result from exposure to several well-recognized antigens. Despite antigen avoidance, progressive pulmonary fibrosis and death can occur, suggesting that additional factors may contribute to disease activity. We hypothesized that the presence of autoimmunity might impact clinical course in patients with HP. In this study, we examined an HP cohort to identify those with HP and autoimmune features (HPAF), and determine its prevalence and outcomes.

Methods: The University of Chicago ILD registry was screened to identify patients with HP. Patients were characterized as HPAF if they had an autoimmune disease or features of autoimmunity, defined as the presence of specific connective tissue disease (CTD) symptoms and serologies. Demographics, clinical characteristics, and outcomes were compared between groups. Survival analysis was performed using Cox regression to identify predictors of transplant-free survival in this cohort.

Results: One hundred twenty patients with chronic, fibrotic HP were identified. Of these, 18/120 (15%) were characterized as HPAF. Compared to those without evidence of autoimmunity, patients with HPAF had a higher proportion of females (54% vs. 83%, respectively; $p = 0.02$) but were otherwise similar with regard to clinical characteristics. The presence of autoimmunity was an independent predictor of increased mortality (HR 4.45; 95% CI 1.43–13.88; $p = 0.01$) after multivariable adjustment.

Conclusions: Fifteen percent of patients with chronic, fibrotic HP displayed evidence of a concurrent defined autoimmune disease or autoimmune features suggestive of CTD. The presence of autoimmunity in patients with chronic, fibrotic HP may portend a poorer prognosis. Future studies are needed to validate these findings and determine the impact of immunosuppressive treatment.

Interstitial lung disease (ILD) encompasses a heterogeneous group of diffuse parenchymal lung diseases often characterized by inflammation and scarring of the pulmonary parenchyma, resulting in significant morbidity and mortality [1]. While it is well-recognized that ILD can develop secondary to connective tissue disease (CTD), there is increasing awareness that features of autoimmunity are common among patients characterized as having idiopathic interstitial pneumonia (IIP) [2], and that systematic evaluation of patients with IIP can reveal a previously unrecognized autoimmune process [3–6] The clinical implications of autoimmune features in those with IIP who fail to meet established rheumatologic criteria remain unclear, but some studies suggest an improved prognosis [7,8].

Hypersensitivity pneumonitis (HP) is an ILD caused by a wide variety of small organic particles. These antigens include fungi, proteins from animals and insects and some chemical compounds [9]. As these antigens are ubiquitous, it remains unclear why only a small fraction of exposed individuals develop HP. One explanation may lie with abnormal T cell function, as individuals with HP do not suppress T-cell proliferation after exposure to known antigen when compared to healthy controls [10]. T cell dysregulation is also

* Corresponding author. The University of Chicago, Section of Pulmonary and Critical Medicine, 5841 South Maryland MC 6076, Chicago, IL 60637, USA.
E-mail address: deji@uchicago.edu (A. Adegunsoye).
[1] Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, The University of California at Davis, 4150 V Street, Suite 3400, Sacramento, CA 95817, USA.

http://dx.doi.org/10.1016/j.rmed.2016.03.012

Abbreviation list

aCCP	anti-citrullinated protein antibody
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
BMI	body mass index
CAD	coronary artery disease
CI	Confidence Interval
C-reactive protein	CRP
CTD	connective tissue disease
DLCO	diffusion capacity of the lung for carbon monoxide
FVC	forced vital capacity
GER	gastroesophageal reflux
HLA	human leukocyte antigen
HP	Hypersensitivity pneumonitis
HR	hazard ratio
HRCT	high-resolution computed tomagraphy
IIP	idiopathic interstitial pneumonia
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
OR	odds ratio
PFT	pulmonary function testing
RA	rheumatoid arthritis
RF	rheumatoid factor
SD	standard deviation
SLB	surgical lung biopsy
SLE	systemic lupus erythematosus
TLC	total lung capacity
UCTD	undifferentiated connective tissue disease
UIP	usual interstitial pneumonia

common among individuals with several CTDs [11–13], and raises the question of whether autoimmune disease is more likely to be present among patients with HP.

In this study, we systematically assessed an HP cohort to identify patients with autoimmune features (HPAF), defined as the presence of documented autoimmune disease or contemporaneous autoimmune serologies and clinical features suggestive of an undifferentiated connective tissue disease (UCTD) [7]. We then characterized clinical features and outcomes among patients with HPAF and compared them to those HP patients without evidence of autoimmunity.

1. Materials and methods

1.1. Study population

This retrospective analysis was conducted at the University of Chicago with approval of our Institutional Review Board (IRB #14163A) and all patients provided informed consent. We identified consecutive patients aged ≥18 years who enrolled in the University of Chicago ILD registry, were diagnosed with HP based on multidisciplinary evaluation, and were seen in the ILD clinic between January 1, 2006 and February 28, 2015. (Fig. 1). Data was extracted using the electronic medical record. Variables collected included demographic data (age, race/ethnicity, gender), symptoms, co-morbid conditions (autoimmune disease, coronary artery disease, gastroesophageal reflux), history of tobacco use, use of chronic corticosteroid and immunosuppressive therapy, physical examination findings such as body mass index (BMI), crackles and clubbing, assessment of environmental antigen exposures (avian, mold, hot tub, unknown), laboratory data including serologies and C-reactive protein (CRP), serial PFTs including percent predicted total lung capacity (TLC), forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO), six minute walk test and histopathologic findings. An experienced pulmonary pathologist with expertise in ILD previously reviewed all surgical lung biopsies. Outcomes assessed included all-cause mortality, lung transplantation and ≥10% decline in FVC. Outcomes were ascertained by review of medical records, telephone interviews and the Social Security Death Index.

1.2. Enrollment criteria

All patients in the University of Chicago ILD registry are assessed for exposure to antigens commonly associated with HP, regardless of referring diagnosis. A diagnosis of HP was based on multidisciplinary evaluation of patients' clinical features, HRCT findings and surgical lung biopsy results by physicians with expertise in ILD. Patients were diagnosed with HP and were included in the current study if they met the following criteria:

(1) HRCT features compatible with HP: mosaic attenuation/air trapping, centrilobular nodules, reticulation, traction bronchiectasis, and honeycombing. (2) Surgical lung biopsy specimens, when obtained, demonstrated presence of a histologic pattern consistent with HP. This included lymphocytic predominant interstitial infiltrates, with/without poorly formed granulomas, distributed in a bronchiolocentric pattern. Histologic fibrosis was also noted when present. (3) Exclusion of an alternative etiology for these findings. The presence of antibodies to serum precipitins supported the diagnosis, but was not a requirement.

1.3. HRCT review and scoring

Features suggesting HP and pulmonary fibrosis, as defined by reticulation, traction bronchiectasis or honeycombing pattern, were recorded. All HRCTs were systematically reviewed and scored by a senior chest radiologist (S.M.) who was blinded to clinical phenotype. The mean extent of these morphological features was scored to the nearest 5% in all three zones of each lung as previously described [14,15] resulting in a semi-quantitative HRCT fibrosis score. These findings were graded on a scale of 1–4: 1 – normal attenuation; 2 – reticular abnormality; 3 – traction bronchiectasis; and 4 – honeycombing. Independent assessment was made for each of these four HRCT findings in three (upper, middle and lower) zones of each lung. The score for each zone was determined by multiplying the grading scale score by the percentage involvement for each zone. The average score of all six zones was calculated as the total score for each patient. Using this method, the highest score was 203 points and the lowest score was 100 points.

1.4. Autoimmune features

Patients were classified as HPAF if they had a documented diagnosis of autoimmune disease [16–19] including scleroderma, Sjogren's disease, idiopathic inflammatory myopathy (IIM), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and ulcerative colitis. Patients were also classified as HPAF if at least one specific CTD symptom and one serologic test suggestive of autoimmune disease were present, as previously proposed by Corte et al. [7]. Specific CTD symptoms included Raynaud's phenomenon,