CHEST Selected Reports

# Acute Exacerbations of Fibrotic Hypersensitivity Pneumonitis*

## A Case Series

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***Background:*** **It is now recognized that a significant portion of patients with idiopathic pulmonary fibrosis (IPF) can have sudden and rapid deteriorations in disease course that cannot be explained by infection, heart failure, or thromboembolic disease. These events are often fatal and have been termed *acute exacerbations* (AEs) of underlying disease. While best described in patients with IPF, they have also been reported in patients with other forms of interstitial lung disease. We sought to determine if this same phenomenon occurs in patients with hypersensitivity pneumonitis (HP).**

***Methods:*** **We retrospectively reviewed our clinical experience at National Jewish Medical and Research Center for patients with surgical lung biopsy-proven fibrotic HP who had an acute decline in respiratory status and met criteria similar to those proposed for the diagnosis of an AE of IPF.**

***Results:*** **Over a 2-year period, we identified four patients with an AE of fibrotic HP. All patients had a clinical course similar to that most frequently described in AEs of IPF: respiratory failure requiring assisted ventilation, lack of clinical response to high-dose corticosteroid therapy, and a poor prognosis (all cases resulted in death or emergent lung transplantation). Lung biopsy at the time of the AE, explant, or autopsy revealed organizing diffuse alveolar damage superimposed on fibrotic lung disease.**

***Conclusions:*** **Fibrotic HP, like other forms of fibrotic lung disease, can be associated with AEs of disease. Further investigation into similarities and pathways common in AEs of various fibrotic lung diseases may yield additional insight into this recently recognized syndrome.** ***(CHEST 2008; 134:844–850)***

**Key words:** acute exacerbation; diffuse alveolar damage; diffuse alveolar hemorrhage; fibrosis; hypersensitivity pneumonitis; idiopathic pulmonary fibrosis

**Abbreviations:** AE = acute exacerbation; AE-IPF = acute exacerbation of idiopathic pulmonary fibrosis; CTA = CT angiogram; DAD = diffuse alveolar damage; DAH = diffuse alveolar hemorrhage; DLCO = diffusing capacity of the lung for carbon monoxide; GERD = gastroesophageal reflux disease; HP = hypersensitivity pneumonitis; HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia

Classically, the clinical course of idiopathic pulmonary fibrosis (IPF) has been described as gradually declining function, with death resulting from progressive chronic respiratory failure or, less commonly, a superimposed pulmonary infection.[1,2] Data[3–5] suggest that patients with IPF can have an acute, idiopathic deterioration in respiratory status without a clear decline in pulmonary function prior to the event. This rapid deterioration in respiratory status has been termed an *acute exacerbation* (AE) of IPF (AE-IPF) and is increasingly recognized as a common event in patients with IPF, appears to be unpredictable, and often results in respiratory failure and death.[3–6]

Although much of the literature on AEs describes patients with IPF, AEs have been described in other fibrotic lung diseases, including connective tissue disease-associated nonspecific interstitial pneumonia (NSIP)[7,8] and idiopathic NSIP.[8,9] While only a small number of cases of AEs in these conditions have been reported, survival appears better in patients with idiopathic NSIP than in connective tissue disease-associated NSIP and IPF.[8,9]

Hypersensitivity pneumonitis (HP) results from an acquired immunologic response to the repeated inhalation of organic antigens or simple chemicals.[10] In the subacute or chronic form of disease, fibrosis on surgical lung biopsy is present in as many as 64% of cases.[11] Fibrosis in HP has been shown to predict a worse outcome with a median survival of 7.1 years, compared to a median survival of at least 20.9 years in patients without fibrosis.[11] Although a reduced survival has been noted, the clinical course preceding death in patients with fibrotic HP has not been well defined. Herein, we describe the clinical course of

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four patients with a known diagnosis of fibrotic HP who had an AE of disease resulting in death or requiring emergent lung transplantation. These cases suggest that the underlying cause of death in some patients with fibrotic HP is the result of an AE.

## Materials and Methods

We retrospectively reviewed the clinical files of patients undergoing consultation, evaluation, or treatment over a 2-year period (January 1, 2005, through January 1, 2007) at the Interstitial Lung Disease Program, National Jewish Medical and Research Center (Denver, CO). The Institutional Review Board approved this retrospective case series.

We sought out subjects with a clinico-radiographic-pathologic (via surgical lung biopsy) diagnosis of fibrotic HP,[12,13] a recent clinical course consistent with an acute decline in respiratory status, and surgical lung biopsy, explant, or autopsy tissue at the time of the decline. To define an acute decline in respiratory status, we modified proposed criteria from the recent consensus statement of the National Heart, Lung, and Blood Institute-sponsored IPF Network on AEs in IPF (Table 1).[6]

We identified four subjects who met this case definition of an AE of fibrotic HP. Clinical data were abstracted from the medical record, radiographic data were reviewed by at least one of the expert faculty members of the Interstitial Lung Disease Program, and the pathologic material from the initial diagnosis of fibrotic HP was reviewed by an expert pulmonary pathologist at our institution; these cases are described below.

## Results

### *Case 1*

A 59-year-old woman with a 9-year history of biopsy-proven fibrotic HP secondary to mold exposure in her home environment was admitted to the hospital after 1 to 2 months of increasing dyspnea associated with a nonproductive cough. At the time of the initial diagnosis of fibrotic HP, she had moved out of her home, had the mold abated, and returned back to her home several months prior to the onset of the current symptoms. At the onset of symptoms, she was found to have new ground-glass opacities and progressive linear and reticular opacities on high-resolution CT (HRCT) of the thorax. She was treated with methylprednisolone, 20 mg/d, for a presumed HP exacerbation. Despite therapy, her symptoms worsened and she was admitted for further evaluation. She was afebrile but required 6 L of supplemental oxygen to maintain oxygen saturations > 90%. Laboratory studies were unrevealing. An admission CT angiogram (CTA) of the chest was negative for pulmonary embolism but demonstrated increased diffuse ground-glass opacities overlying the previously noted linear and reticular opacities. An echocardiogram showed normal left ventricular function. Treatment with broad-spectrum antibiotics and high-dose methylprednisolone was initiated. Bronchoscopy revealed a neutrophil-predominant lavage with negative microbiologic studies. Two days after admission, the patient required mechanical ventilation for progressive respiratory failure. Surgical lung biopsy was performed on hospital day 6 and revealed acute and organizing diffuse alveolar damage (DAD) superimposed on fibrotic HP with no features of active HP. No organisms were seen, and all culture results were negative. Despite treatment with pulse-dose steroids, her respiratory status continued to deteriorate. She died approximately 1 month after admission.

**Table 1—*Case Definition for the AE of Fibrotic HP***

1. A consensus diagnosis of fibrotic HP based on clinical, radiographic, and pathologic criteria[12,13] prior to the onset of the AE
2. Unexplained worsening or development of dyspnea within 2 months
3. New bilateral radiographic opacities
4. Absence of detectable clinical infection (including negative routine bacterial, viral, fungal, and mycobacterial culture results and negative *Pneumocystis jiroveci* immunofluorescent staining of secretions from the respiratory tract)
5. Absence of identifiable etiology for the clinical symptoms and radiographic findings (including normal evaluation of cardiac function and negative evaluation for pulmonary embolism)

### *Case 2*

A 66-year-old man with fibrotic HP diagnosed by surgical lung biopsy 4 months prior was admitted with 4 to 6 weeks of increasing dyspnea. An inciting antigen was not identified at the time of diagnosis, and the patient remained in his home environment. He was treated with prednisone, 40 mg/d, with significant improvement in his dyspnea. Four to 6 weeks prior to hospitalization, as the corticosteroids were being tapered, he began to have increasing dyspnea. Despite increasing the prednisone dose and initiating azathioprine therapy, the dyspnea continued to worsen. He was subsequently admitted for further evaluation, where he was found to be afebrile but had a new oxygen requirement of 3 L to maintain oxygen saturations > 90%. HRCT of the thorax revealed new bilateral ground-glass opacities, but echocardiogram, CTA of the chest, and infectious evaluation were unrevealing. He was treated with high-dose corticosteroids and broad-spectrum antimicrobials; however, he continued to deteriorate and required mechanical ventilation. A surgical lung biopsy revealed organizing DAD without evidence of infection or active HP. Despite aggressive care, he died 78 days after hospital admission.

### *Case 3*

A 66-year-old man with known fibrotic HP diagnosed by surgical lung biopsy 6 years prior was admitted after 8 weeks of worsening dyspnea. Although no inciting antigen was identified, the exposure was presumed to be in the home environment, and he moved out of the home at the time of initial diagnosis. At the onset of his worsening dyspnea, he complained of subjective fevers and chills. His corticosteroid dose was increased, but his symptoms worsened. He was hospitalized for an AE, at which time he required 10 L of oxygen to maintain saturation > 90% at rest. HRCT showed bilateral ground-glass opacities, and no alternative etiology for his deterioration was identified. He was treated with high-dose corticosteroids and broad-spectrum antibiotics with no appreciable improvement,