Histopathologic Features and Outcome of Patients With Acute Exacerbation of Idiopathic Pulmonary Fibrosis Undergoing Surgical Lung Biopsy*

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Study objectives: To define the clinicopathologic features and outcome of acute exacerbation in patients with idiopathic pulmonary fibrosis (IPF) undergoing surgical lung biopsy.

Design: Retrospective, single-center study.

Setting: Tertiary care, referral medical center.

Patients: Seven patients with acute exacerbation of IPF who underwent surgical lung biopsy.

Results: The median age of these seven patients was 70 years (range, 59 to 74 years); two were women. Five patients had a smoking history and included two current smokers. All patients were experiencing an exacerbation of dyspnea for a median duration of 14 days (range, 7 to 28 days) prior to presentation. In three of these patients, the acute deterioration was the presenting feature of IPF, while in the remaining four patients the diagnosis of IPF had previously been established. Chest radiography demonstrated bilateral mixed alveolar-interstitial infiltrates in all of them. CT revealed ground-glass opacities and consolidation bilaterally in all patients with associated peripheral honeycombing in six of them. Echocardiography was performed in six patients and demonstrated pulmonary hypertension in all. BAL fluid was obtained in five patients and revealed neutrophilia in all. Surgical lung biopsy showed diffuse alveolar damage (DAD) in five patients with associated collagen fibrosis and honeycomb changes typical of usual interstitial pneumonia (UIP). One biopsy showed a combination of UIP and organizing pneumonia, while one biopsy showed only DAD. Despite treatment with lung-protective ventilation strategies and high-dose systemic corticosteroids, six patients (86%) died during their hospitalization.

Conclusions: Although IPF is typically associated with an insidious, slowly progressive clinical course, acute exacerbations occur and may be the presenting manifestation in some patients. In either situation, current management strategies including high-dose corticosteroid therapy appear to be relatively ineffective for these patients with acute exacerbation undergoing surgical lung biopsy.

Key words: interstitial pneumonia; pulmonary fibrosis; respiratory failure

Abbreviations: AIP = acute interstitial pneumonia; DAD = diffuse alveolar damage; DLco = diffusing capacity of the lung for carbon monoxide; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia
or cardiac failure. In this study, we describe the clinical presentation, radiologic features, histopathologic findings, response to therapy, and clinical outcomes of seven patients with acute exacerbation of IPF, including three patients in whom this was the initial presentation.

**Materials and Methods**

We conducted a computer-assisted search of the Mayo Clinic database to identify patients with IPF who underwent surgical lung biopsy and were seen at our institution during a 7-year period from January 1, 1996, through December 31, 2002. Of 58 patients confirmed to have IPF by surgical lung biopsy, 7 patients (12%) underwent lung biopsy during an episode of acute exacerbation. None of these patients had an identifiable cause for their clinical deterioration other than an identifiable lung disease, IPF. In addition, none of these patients had an associated connective tissue disease or a known cause for diffuse pulmonary fibrosis such as occupational dust exposure, radiation therapy to the chest, fibrogenic drug therapy, or aspiration pneumonia. The remaining 51 patients presented with chronic respiratory symptoms consisting of exertional dyspnea and/or cough. All 51 patients had UIP on surgical lung biopsy. Three of these 51 patients were inpatients at the time of the surgical consultation for lung biopsy: 2 patients had been hospitalized for evaluation and management of newly diagnosed hypoxemia, and 1 other patient was admitted for management of a spontaneous pneumothorax. Two of these 51 patients (3.9%) required prolonged mechanical ventilation after surgical lung biopsy and eventually died during their hospitalization from respiratory failure.

Acute exacerbation was defined using the following criteria proposed by Kondoh et al\(^5\) and Akira et al\(^6\): (1) acute worsening of dyspnea within 1 month of presentation, (2) new pulmonary infiltrates on chest radiography or CT, (3) deterioration in pulmonary function measurements or gas exchange, and (4) absence of an identifiable cause including infections or cardiovascular disease. Documentation of new infiltrates or precipitous decline in lung function was not required in patients without a prior diagnosis of IPF since baseline results were not available. All patients without an established diagnosis of IPF prior to presentation with acute respiratory failure had evidence of UIP on either surgical lung biopsy or CT scan performed within 2 weeks of presentation. All patients met the criteria for definite or presumptive IPF as outlined in the 2000 American Thoracic Society/European Respiratory Society consensus statement.\(^2\) All lung biopsy specimens and autopsy slides were reviewed by one of us (J.L.M.). Special stains for fungi and Pneumocystis (Gomori methenamine silver) were performed in all surgical lung biopsies, and stains for acid-fast bacilli (auramine rhodamine) were performed in six of them. Medical records were examined in detail to gather clinical, laboratory, radiologic, and pulmonary function data at presentation. Follow-up data were also extracted.

Spirometry and measurements of lung volumes and diffusing capacity of the lung for carbon monoxide (DLCO) were performed in our laboratory using standard techniques.\(^9\) Pulmonary function data included plethysmographically determined total lung capacity, FVC, FEV\(_1\), ratio of FEV\(_1\) to FVC, and DLCO. Data are reported as mean ± SD unless otherwise stated. This study was approved by the Mayo Foundation institutional review board. Patients who did not authorize the use of their medical records for research were excluded from this study.

**Results**

**Demographic and Clinical Features**

We identified seven patients with an acute exacerbation of IPF. The median age of these seven patients was 70 years (range, 59 to 74 years); two patients (29%) were women (Table 1). Five patients (71%) had a smoking history and included two current smokers. Four patients (57%) had the diagnosis of IPF established previously with a median interval of 15 months (range, 6 to 25 months) prior to presentation; three patients did not.

Four patients with previously diagnosed IPF had pulmonary function tests performed 6 to 17 months (median, 9 months) prior to the current presentation. Pulmonary function results were abnormal in all four patients with a restrictive defect and a

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**Table 1—Clinical Summary of Seven Patients With Acute Exacerbation of IPF**

<table>
<thead>
<tr>
<th>Age, Sex</th>
<th>Smoking</th>
<th>Known IPF</th>
<th>Presentation</th>
<th>Physical Findings</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>69, female</td>
<td>Previous, 30 pack-yr</td>
<td>Yes</td>
<td>Worsening dyspnea, cough, fever</td>
<td>Inspiratory crackles, digital clubbing</td>
<td>Corticosteroids</td>
<td>Died</td>
</tr>
<tr>
<td>70, male</td>
<td>Previous, 20 pack-yr</td>
<td>Yes</td>
<td>Worsening dyspnea, flu-like symptoms, fever</td>
<td>Inspiratory crackles</td>
<td>Corticosteroids</td>
<td>Survived</td>
</tr>
<tr>
<td>59, male</td>
<td>Previous, 45 pack-yr</td>
<td>Yes</td>
<td>Worsening dyspnea, cough, flu-like symptoms</td>
<td>Inspiratory crackles, digital clubbing</td>
<td>Corticosteroids</td>
<td>Died</td>
</tr>
<tr>
<td>64, male</td>
<td>Never</td>
<td>Yes</td>
<td>Worsening dyspnea, cough, fever</td>
<td>Inspiratory crackles, digital clubbing</td>
<td>Corticosteroids, cyclophosphamide</td>
<td>Died</td>
</tr>
<tr>
<td>74, male</td>
<td>Current, 25 pack-yr</td>
<td>No</td>
<td>Worsening dyspnea, flu-like symptoms</td>
<td>Inspiratory crackles</td>
<td>Corticosteroids, cyclophosphamide</td>
<td>Died</td>
</tr>
<tr>
<td>73, female</td>
<td>Current, 34 pack-yr</td>
<td>No</td>
<td>Worsening dyspnea, cough</td>
<td>Inspiratory crackles, digital clubbing</td>
<td>Corticosteroids</td>
<td>Died</td>
</tr>
<tr>
<td>74, male</td>
<td>Never</td>
<td>No</td>
<td>Worsening dyspnea, cough, flu-like symptoms</td>
<td>Inspiratory crackles, digital clubbing</td>
<td>Corticosteroids</td>
<td>Died</td>
</tr>
</tbody>
</table>
reduced single-breath DLCO. Mean total lung capacity was 67 ± 13% of predicted, FVC was 69 ± 11% of predicted, and DLCO was 46 ± 7% of predicted.

Two patients were receiving colchicine (0.6 mg/d), and another patient was receiving prednisone (20 mg/d) for IPF at the time of acute exacerbation. Four patients were not receiving any pharmacologic therapy for IPF. One patient with previously diagnosed IPF had been receiving supplemental oxygen therapy (via nasal cannula at 2 L/min) for 3 months prior to the current presentation.

The symptoms and signs noted at presentation are summarized in Table 1. All patients presented with an acute onset of dyspnea or acute worsening of chronic dyspnea over a median of 14 days, (range, 7 to 28 days). Additional symptoms included cough in five patients (71%), flu-like syndrome in four patients (57%), and fever in three patients (43%). On physical examination, all patients manifested inspiratory crackles, and digital clubbing was noted in five patients (71%), including two patients without a previously established diagnosis of IPF.

All patients were hospitalized for evaluation and management of worsening dyspnea and hypoxemia. Invasive mechanical ventilation was needed for all seven patients. The median interval between admission to the hospital and the institution of invasive mechanical ventilation was 3 days (range, 0 to 6 days). Three patients (43%) were initially managed with noninvasive bilevel positive airway pressure ventilation for a median duration of 6 h (range, 1 to 10 h) prior to the institution of invasive mechanical ventilation.

Surgical lung biopsy was performed after a median interval of 10 days (range, 4 to 16 days) following hospital admission; all patients were supported by invasive mechanical ventilation at the time of this biopsy. Biopsy specimens were obtained by limited thoracotomy in six patients (86%) and by video-assisted thoracoscopic surgery in one patient (14%). Postsurgical complications occurred in three patients (43%) and consisted of a prolonged air leak in all three patients. They were all treated conservatively with eventual resolution of the air leak.

**Arterial Blood Gas and BAL Results**

By the time of the surgical lung biopsy, all seven patients had been supported with invasive mechanical ventilation for a median interval of 8 days (range, 4 to 14 days) using lung-protective ventilation strategies. On the day of surgical lung biopsy, the mean ratio of PaO2 to the fractional concentration of inspired oxygen was 114.1 ± 32.7 (range, 98 to 165). The mean arterial pH was 7.38 ± 0.07, and the mean PaCO2 was 54.1 ± 8.6 mm Hg. The mean positive end-expiratory pressure employed was 15.5 ± 5.4 cm H2O, and two patients (29%) received inhaled nitric oxide therapy.

BAL was performed prior to surgical lung biopsy in five patients (71%) after a median interval of 3 days (range, 0 to 5 days) following initial presentation. Neutrophils were the predominant cell type identified in the BAL fluid, with a mean percentage of 65.1 ± 18.9. Macrophages, lymphocytes, and eosinophils accounted for 24.3 ± 13.6%, 11.2 ± 10.5%, and 2.1 ± 2.7% of cells recovered by BAL, respectively. Bronchoscopic lung biopsy was performed in two patients and revealed nonspecific inflammatory and fibrotic changes. Microbiologic studies including cultures and immunoassays to identify potential infectious pathogens were performed on the BAL fluid as well as blood, sputum, and tracheal secretions; all results were negative.

**Chest Radiography and CT of the Chest**

The predominant findings on chest radiography and CT are summarized in Table 2. Bilateral alveolar-interstitial infiltrates were seen on chest radiographs of all patients. Four patients (57%) had evidence of cardiomegaly. Pleural effusions were seen in three patients (43%) and were bilateral but small in size.

CT of the chest was performed on all seven patients after a median of 5 days (range, 3 to 9 days) following initial presentation. All patients had ground-glass opacities bilaterally along with patchy areas of consolidation involving predominantly the dependent zones of the lungs (Fig 1). Peripheral honeycombing was seen in six patients (86%). Six patients (86%) had CT angiography performed, and all results were negative for pulmonary embolism.

**Echocardiography**

Six patients had transthoracic echocardiograms performed within 4 days of initial presentation. Left ventricular systolic function including ejection frac-
tion was normal in all patients, as was morphologic assessment of the mitral and aortic valves. Right ventricular enlargement and hypertrophy was present in all six patients, and right ventricular systolic function was impaired in five of these patients (83%). The mean calculated right ventricular systolic pressure was 65.2 ± 13.4 mm Hg, (range, 39 to 75 mm Hg). Aside from annular dilatation, morphologic findings of the tricuspid and pulmonary valves were normal in all patients. Two patients (33%) had small pericardial effusions without evidence of cardiac tamponade.

Surgical Lung Biopsy and Autopsies

A combination of UIP and diffuse alveolar damage (DAD) was present in five lung biopsies. UIP was characterized by patchy collagen fibrosis with associated scarring distributed in a peripheral, subpleural fashion with associated honeycomb change. Evidence of superimposed DAD comprised areas of diffuse alveolar septal expansion and distortion by fibroblasts and myofibroblasts within a pale staining matrix. DAD was present extensively in three cases but was a focal finding in two cases. A biopsy from a patient with digital clubbing and bibasilar honeycombing on CT scan showed DAD without features diagnostic of underlying UIP. Additional features of acute lung injury in the six cases showing DAD included hyaline membranes (five cases), squamous metaplasia of bronchiolar epithelium (four cases), and fibrin thrombi (one case). One biopsy showed features typical of UIP with patchy zones of associated organizing pneumonia but without histlogic features of DAD (Fig 2).

Autopsies were performed in two patients who died during their hospitalization, including the patient who had only DAD on surgical lung biopsy. Sections from both were similar in showing underlying fibrotic lung disease with peripheral honeycomb change typical of UIP and superimposed organizing DAD.

Treatment

Systemic corticosteroid therapy was administered to all seven patients; in four of these patients, corticosteroid therapy had been initiated empirically 6 to 13 days before surgical lung biopsy. Four patients (57%) received an IV bolus of methylprednisolone, 500 to 1,000 mg, once a day for 3 days.
followed by 1 to 2 mg/kg/d administered in divided doses; the remaining three patients (43%) were initiated on 1 to 2 mg/kg/d of IV methylprednisolone administered in divided doses without an initial bolus. This was tapered gradually over a median duration of 6 weeks (range, 3 to 8 weeks). Two patients (29%) also received an IV dose of 600 to 750 mg/m² of cyclophosphamide after lung biopsy. All patients received empiric broad-spectrum antibiotic therapy until the results of the lung biopsy and microbiologic studies were available, resulting in discontinuation of these agents in five patients (71%).

Outcome

Six patients (86%) died during their hospitalization. Mechanical ventilation was withdrawn in these six patients after a median duration of 29 days (range, 20 to 57 days) based on the wishes of the patients or immediate family members. One patient (14%) survived to hospital discharge. This 70-year-old man had been treated with IV methylprednisolone, 500 mg, once a day for 3 days and was eventually dismissed receiving prednisone, 40 mg/d, after a hospitalization of 25 days. His prednisone treatment was continued at varying doses until his death 30 months after the surgical lung biopsy. The cause of death was acute respiratory failure attributed to another episode of acute exacerbation of IPF.

Discussion

A subset of patients with IPF experience acute exacerbation without an identifiable cause. To date, this variation on the natural history of IPF has been described only in patients with previously established diagnoses. In nearly half of our patients, this was instead the presenting manifestation of their previously unrecognized chronic interstitial lung disease. In most patients, IPF is a slowly but relentlessly progressive disease associated with a median survival of 2 to 3 years after diagnosis.1–3 The most common causes of death are respiratory failure and cor pulmonale generally resulting from advanced fibrotic lung disease.10–16 IPF patients may also suffer acute respiratory deterioration related to complications such as pneumonia, pulmonary embolism, pneumothorax, myocardial infarction, and congestive heart failure.10,11,15

Acute exacerbation of IPF was initially described by Kondoh and colleagues5 and represents an abrupt and unexpected worsening of the underlying lung disease. It is also referred to as the accelerated phase of IPF. These episodes are characterized by an acute worsening of dyspnea over a course of <1 month, accompanied by new pulmonary infiltrates on chest radiographs, worsening hypoxemia that rapidly progresses to respiratory failure, and the absence of other identifiable causes for the exacerbation.5 CT scans commonly reveal peripheral ground-glass opacities and consolidation in association with peripheral honeycombing.5–8

The pathogenesis of acute exacerbation of IPF remains unclear. Examination of BAL fluid from patients experiencing this event has consistently revealed neutrophilia, which probably relates to the underlying histopathologic pattern of injury, DAD.7,12,14 Echocardiography has demonstrated evidence of pulmonary hypertension that likely reflects the severity of the underlying lung disease.14,15 The cause of these episodes does not appear to be related to infections or to oxygen toxicity.5

Several studies7,12,14–16 have evaluated the short- and long-term prognoses among patients with IPF admitted to the ICU. As expected, acute respiratory failure was the most common cause for ICU admission for these patients. In approximately one half of patients, no specific cause was found for the acute respiratory decompensation.12,15,16 A combination of UIP and DAD is the most common finding in surgical lung biopsies in this setting.15 Given the poor prognosis of these patients, some authors12–14 have questioned the usefulness of initiating mechanical ventilation in patients with IPF.

DAD was the most common finding in surgical lung biopsies from our patients and was superimposed on features typical of UIP in all but one of these. This combination of findings has been reported most commonly by others as well.5–8,15 The fact that all of our patients were in respiratory failure with new opacities on imaging studies prior to biopsy supports the argument that DAD was the underlying lesion for the acute exacerbation rather than a consequence of therapy, ie, ventilator-induced lung injury. DAD was the only finding in one of our patients who had clinical, radiologic, and autopsy support for a diagnosis of IPF, indicating that in occasional patients histologic evidence of underlying UIP may be lacking. Acute interstitial pneumonia (AIP), also termed Hamman-Rich syndrome, was the most common differential diagnosis in our patients. AIP is an uncommon form of rapidly progressive, diffuse interstitial lung disease characterized by DAD on lung biopsy.17,18 Distinguishing accelerated IPF from AIP hinges on recognition of underlying UIP in the former. Evidence of underlying UIP may take the form of an established history, clubbing, and/or supportive radiologic or histologic findings.

Despite lung-protective mechanical ventilation strategies and high-dose corticosteroid therapy, the prognosis associated with acute exacerbations of IPF...
is poor. Although Kondoh and colleagues\textsuperscript{5} reported improvement following corticosteroid therapy in all three of their patients, we were unable to confirm their observation. Only one of our seven patients survived hospitalization and was discharged home with a new prescription of supplemental oxygen, which he continued until his eventual death 30 months later.

The incidence and clinical implications of acute exacerbations in patients with IPF are relatively unknown. Although the number of cases described to date is relatively limited, Rice and colleagues\textsuperscript{8} conclude in a review of autopsy findings that acute exacerbation associated with a histopathologic pattern of DAD may be a common terminal event. Unfortunately all relevant studies, including our own, are retrospective in design with associated limitations. In addition, the poor prognosis associated with acute exacerbation may partly relate to case ascertainment bias in bringing those patients who are more severely affected to medical attention. It is possible that these acute episodes of lung injury vary in severity and may be relatively common in the clinical course of patients with IPF. If so, optimal management of patients with IPF would require a better understanding of the true incidence, pathogenetic mechanisms, and clinical effects of these acute episodes.

In summary, we have described clinical, radiologic, and histopathologic findings associated with acute exacerbation in IPF and demonstrated that this acute exacerbation can occasionally be the initial clinical presentation in some patients with IPF. Acute exacerbation of IPF in patients undergoing surgical lung biopsy is associated with a poor prognosis and does not appear to respond to high-dose corticosteroid therapy, contrary to a previous report.\textsuperscript{5} In order to formulate a more effective management strategy, we need a better understanding of the pathogenesis of these acute exacerbations that severely impact the survival of patients with IPF.

REFERENCES
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