Idiopathic Bronchiolitis Obliterans With Organizing Pneumonia*

An Acute and Life-Threatening Syndrome

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Idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP) is a clinicopathologic syndrome characterized by an indolent course and favorable prognosis. This report describes five patients with a fulminating and life-threatening variant of this syndrome. Four patients presented with respiratory failure requiring respiratory assistance and positive pressure ventilation. Early recognition of the entity and prompt initiation of corticosteroid therapy in three patients was instrumental in preventing mortality. Our findings suggest that idiopathic BOOP may be the underlying pathology in a number of patients presenting with ARDS. Since corticosteroid therapy may improve survival in these patients, clinicians should heighten their index of suspicion for this entity. Early histologic diagnosis and initiation of corticosteroid therapy should be considered in patients with unexplained ARDS.

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Key words: acute respiratory failure; bronchiolitis; corticosteroids; idiopathic bronchiolitis obliterans with organizing pneumonia

Idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP), a clinicopathologic syndrome, first was described by Epler et al in 1985.1 Most of the reports describing this entity have emphasized its nonacute nature and good prognosis.1-5 Specifically, patients with this syndrome have been reported to present with a subacute illness characterized by cough, dyspnea, and constitutional symptoms. The symptoms as well as the radiologic abnormalities usually are responsive to corticosteroid therapy. However, a more acute and fulminating form of BOOP has been described lately.6 Cohen et al6 recently observed that a life-threatening form of the syndrome occurs in a subgroup of patients. The majority of the reported patients had evidence of an immunologic disorder. The occurrence of acute life-threatening respiratory failure in the setting of idiopathic BOOP has not been previously reported, although three patients described in two recent publications may have had such a presentation.7,8 Over a period of 18 months, we observed this variant of the idiopathic BOOP in 5 patients with acute, fulminating, and life-threatening symptoms presenting with severe alterations in gas exchange requiring mechanical ventilation in 4 patients and positive end-expiratory pressure (PEEP) in three.

Case Reports

Case 1

A 62-year-old woman presented to the emergency room with shortness of breath of 6 months' duration, which had worsened over the last 2 to 3 days before admission. Fever and weight loss exceeding 20 lb were also reported. The patient denied cough, orthopnea, and paroxysmal nocturnal dyspnea. Her past medical history included diabetes mellitus, hypertension, and congestive heart failure for which she was taking insulin, furosemide, and potassium supplements. She had an 80 pack-year history of cigarette smoking but no exposure to industrial or environmental agents of known pulmonary toxicity.

Physical examination on arrival revealed an obese woman in moderate respiratory distress. Her pulse was regular at 96 beats per minute. She had a regular breathing pattern at a rate of 24 breaths per minute. She was afebrile (37 C), and her blood pressure was 170/80 mm Hg. The neck veins were not engorged. Cardiac auscultation did not show any gallops or murmurs. Lung examination revealed diffuse bilateral crackles which were more marked in the basilar areas. The abdomen was soft, nontender, and without organomegaly. There was a trace of pitting edema in the lower extremities but no evidence of digital clubbing.

Laboratory studies showed normal electrolyte levels except for a slight reduction in serum bicarbonate. Complete blood cell counts revealed a WBC count of 14.3X109 with a normal differential cell count, a hematocrit value of 33.7%, and a platelet count of 597X103/mL. Arterial blood gas level analysis done with the patient breathing supplemental oxygen revealed a pH of 7.44, a PCO2 of 30.2 mm Hg, a PO2 of 136.9 mm Hg, and a hemoglobin oxygen saturation of 98%. A chest radiograph showed bilateral...

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alveolar opacities (Fig 1, A).

The patient was admitted to the hospital. Maintenance therapy with usual diuretics was continued, and cefuroxime was intravenously administered. On her second hospital day, a temperature of 39.1°C was recorded, and her oxygen supplementation requirements were increased. Erythromycin, 500 mg administered every 6 h, was added to the therapeutic regimen on the third hospital day without improvement. On the fifth hospital day, she was intubated, and mechanical ventilation was initiated. Bronchoscopy and bronchoalveolar lavage were performed on the sixth hospital day and did not disclose any malignancies or infectious agents. The patient's condition continued to deteriorate requiring higher fraction of inspired oxygen (FiO₂) and PEEP to maintain oxygenation. An open-lung biopsy was performed on the 11th hospital day and was diagnostic of BOOP (Figs 2 and 3). A detailed serum serologic evaluation of infectious causes of BOOP was conducted including measurement of titers for the organisms outlined in Table 1 (part a). In addition, the lung tissue obtained by open-lung biopsy was submitted for cultures and specialized stains to detect the organisms (Table 1 [parts b and c]). None of these serologic titers or the tissue cultures and stains were positive. Therapy was started with methylprednisolone on her 12th hospital day with gradual improvement in oxygenation. Further hospital course was complicated by Pseudomonas-caused pneumonia which responded to antibiotic therapy. Her respiratory status improved gradually, and she was weaned off mechanical ventilation on the 45th hospital day and discharged home in a stable condition on the 49th hospital day. The patient has been followed up regularly for the past 15 months. She has regained her initial body weight and has not developed any systemic symptoms, although she still requires short courses of steroids for exacerbation of respiratory problems.

Case 2

A 70-year-old woman presented to the emergency room complaining of cough associated with the expectoration of white sputum accompanied by increasing shortness of breath of several days' duration. One week prior to this admission, she had been...
seen in the same hospital with similar complaints. At that time, the diagnosis of congestive heart failure and atypical pneumonia were entertained on clinical grounds. She was discharged home. Therapy with orally administered erythromycin and diuretics was prescribed without any significant improvement.

Her past medical history was remarkable for hypertension, diabetes mellitus, hypothyroidism, and hypercholesterolemia. Her medications included thyroid hormone replacement, insulin, captopril, and lovastatin. She was an active smoker with a 45 pack-year history.

Physical examination revealed an obese female in moderate respiratory distress. Her temperature was 37.1°C. Blood pressure was 130/60 mm Hg, pulse rate was 72 beats per minute and regular, and respiratory rate was 28 breaths per minute. Neck veins were not distended. Heart examination revealed a regular rhythm with no gallops or murmurs. Examination of the chest revealed diffuse bilateral dry crackles. Extremities were moderately edematous without clubbing. Laboratory studies showed normal blood cell counts. Analysis of electrolytes revealed a sodium level of 128 mEq/L; creatinine value, 2.0 mg/dL; BUN level, 35 mg/dL. Arterial hemoglobin oxygen saturation measured by a pulse oximeter was 60% with the patient breathing room air. Arterial blood gas values done while the patient was breathing supplemental oxygen (50% FIO2) showed a pH of 7.36, Pco2 of 38 mm Hg, and Po2 of 61 mm Hg with a hemoglobin saturation of 88.7%. A chest radiograph showed bilateral interstitial reticular nodular infiltrates (Fig. 1, B). Bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy performed on the second hospital day showed interstitial fibrosis with alveolar damage and no granulomas. Prednisone therapy was started on the fourth hospital day with some improvement. An open-lung biopsy was performed on the eighth hospital day which confirmed the diagnosis of BOOP. Blood and lung tissue samples were processed for evidence of an infectious process associated with BOOP (Table 1). All titers were low and all stains were negative. Maintenance therapy with prednisone was prescribed; the patient continued to improve and was discharged home on the 14th hospital day in a stable condition.

**Case 3**

A 52-year-old man presented with a 2-week history of cough productive of white sputum. There was an associated shortness of

**FIGURE 2.** Light microscopic section of the open-lung biopsy of case 1. Features of BOOP are prominent including patchy intraluminal organization with zones of relatively unaffected lung tissue. Interstitial infiltrates are prominent. Alveolar duct walls are thickened with a mild inflammatory infiltrate (hematoxylin-eosin, original magnification ×20).

**FIGURE 3.** Higher magnification of a portion of the open-lung biopsy of case 1. A number of large intraluminal polyps with central collections of inflammatory cells are apparent (hematoxylin-eosin, original magnification ×20).
Table 1—List of Microbiologic Studies Obtained

a. Serum serology
   1. Viruses:  
      Adenovirus  
      Cytomegalovirus  
      Herpes simplex virus (types 1 and 2)  
      Influenza virus (types A and B)  
      Respiratory syncytial virus  
      Hepatitis B virus  
      Parainfluenza virus (types 1, 2 and 3)  
      HIV  
2. Bacteria:  
   Mycoplasma  
   Legionella  
3. Fungi:  
   Aspergillus  
   Blastomycosis  
   Coccioidiodomycosis  
   Histoplasmosis  
   Candida  
4. Parasites:  
   Toxoplasmosis  

b. Microbiologic cultures on lung tissue obtained by open-lung biopsy
   1. Viruses: listed above  
   2. Fungi: listed above  
   3. Bacteria: listed above plus Mycobacteria  
   4. Parasites: listed above  

c. Special stains obtained on open-lung biopsies
   1. Viruses: listed above  
   2. Fungi: listed above plus Pneumocystis  
   3. Bacteria: listed above  
   4. Parasites: listed above

breath for the previous 1 week. A 7-lb weight loss was documented in the interim. He denied fever or chest pain.

The patient had diabetes and hypertension, and his medications included metformin, furosemide, and insulin. He was a heavy smoker but had stopped smoking 10 years prior to this episode. He had no occupational, environmental exposure to known pulmonary injurious agents.

Physical examination on admission to the hospital revealed a temperature of 37.3°C, a pulse rate of 88 beats per minute, a respiratory rate of 20 breaths per minute, and a supine blood pressure of 150/90 mm Hg. No neck veins were not engorged. Heart examination revealed a regular rhythm with no gallops or murmurs. Chest examination was unremarkable. The abdomen was soft, nontender, and without organomegaly. Extremities revealed trace leg edema and no clubbing. Laboratory studies showed normal serum electrolyte values. The creatinine level was 2.1 mg/dL, and the blood glucose value was 220 mg/dL. With the patient breathing room air, arterial blood gas analysis showed a pH of 7.51, Pco₂ of 28.2 mm Hg, Po₂ of 58 mm Hg, with arterial hemoglobin oxygen saturation of 91.5%. The WBC count was 11.5X10³/mL, without a left shift. The hematocrit value was 31.5%, and the platelet count was 325X10³/mL. Chest radiograph showed right lower lobe consolidation and a right upper lobe infiltrate (Fig 1, C). Therapy was started with erythromycin given intravenously without improvement. He underwent bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy on the 10th hospital day. The results of bronchoalveolar lavage and transbronchial lung biopsy were not diagnostic, and no infectious etiology could be identified. Thoracoscopic wedge resection was done on the 16th hospital day. Histologic examination was diagnostic of BOOP. Detailed serologic evaluation was conducted as detailed in Table 1. In addition, lung tissue obtained at surgery was processed for microbiologic cultures and special stains (Table 1). The only positive findings were a slightly elevated IgG level for herpes simplex (type 1) with normal IgM levels. The IgG (but not IgM) for Toxoplasma was also elevated. All cultures and stains on lung tissue were negative. The patient died before the results of the biopsy became available, and corticosteroid therapy was not started. Postmortem examination of the lungs revealed no changes of BOOP (Fig 2). No other abnormalities in the lungs were demonstrated. Examination of other tissues revealed evidence of diffuse atherosclerosis with myocardial infarctions at various stages of acuteness involving the septum and the left papillary muscles. There was evidence of nephro sclerosis consistent with the history of hypertension.

Case 4

A 68-year-old man presented with a 5-day history of progressive shortness of breath accompanied by pleuritic chest pain. He had a mild cough with scanty white sputum that was essentially unchanged from his baseline findings. He denied fever, chills, or hemoptysis. The patient was known to have rheumatoid arthritis controlled with nonsteroidal anti-inflammatory agents alone and clinically inactive at the time of admission. He also had a history of mild hypertension not requiring any medications. He was a 50-pack-year smoker and had worked in a foundry 40 years previously for a duration of 3 years. His medications included piroxicam and omeprazole.

On arrival to the hospital, he was in moderate respiratory distress. His blood pressure was 164/92 mm Hg, pulse rate was 88 beats per minute and regular, and respiration rate was 30 breaths per minute. The neck veins were not engorged. Examination of the chest showed diffuse fine crackles in both lung fields. Heart examination showed no gallops or murmurs. Extremities had no evidence of joint deformity, digital clubbing, or pitting edema.

Arterial blood gas analysis on a nonrebreather face mask showed a pH of 7.49, a Pco₂ of 30.4 mm Hg, a Po₂ of 67.1 mm Hg, and arterial hemoglobin oxygen saturation of 91%. The WBC count was 20.6X10³/mL without a left shift. Hematocrit value was 20.6%. Electrolyte levels were all within normal limits. A chest radiograph revealed bilateral interstitial infiltrates (Fig 1, D).

Therapy was started with erythromycin, 500 mg, intravenously given every 6 h along with aerosolized bronchodilators. There was no improvement in his clinical condition. Therapy with erythromycin was stopped on the third hospital day, and an open-lung biopsy was performed which confirmed the diagnosis of BOOP. Serologic tests and lung tissue processing for histopathologic cultures and stains were not diagnostic of any concomitant infectious process except for a slightly elevated IgG titer for herpes simplex type 1 (but not IgM). Methylprednisolone, 80 mg given intravenously every 12 h, was started on the 4th hospital day. The patient required mechanical ventilation postoperatively for a total of 4 days. He was gradually weaned of oxygen and was discharged home on the 15th hospital day in a stable condition on a regimen of a daily oral dose of prednisone (60 mg) and oxygen supplementation at a rate of 3 L/min.

Case 5

A 64-year-old woman whose past medical history was unremarkable presented to the Emergency Department with a 7-day history of shortness of breath on exertion, accompanied by mild nonproductive cough. She denied any history of fever, chest pain, paroxysmal nocturnal dyspnea, or orthopnea. There was a 15-lb weight loss over a period of 1 year. The patient was taking lorazepam and furosemide. She was a 30 pack-year smoker.

On arrival to the hospital, she was in moderate respiratory distress, awake, alert, and communicative. Vital signs revealed a
regular heart rate of 120 beats per minute, a supine blood pressure of 110/60 mm Hg, a respiratory rate of 35 breaths per minute, and a temperature of 38.2°C. Her neck veins were flat. Chest examination revealed crackles in the lower two thirds of both lung fields. Heart examination revealed no gallops or murmurs. Her abdomen was soft, nontender, and without any organomegaly. Her extremities showed no clubbing or pitting edema.

Laboratory tests revealed an elevated WBC count of 14.1X10⁹/mL, hematocrit level of 39.6%, and platelet count of 211X10⁹/mL. Serum electrolyte and serum creatinine values were within normal limits. Arterial blood gas values with the patient breathing room air showed a pH of 7.54, PaCO₂ of 26.3 mm Hg, and PaO₂ of 48 mm Hg. Serologic markers for connective tissue disease were negative. A chest radiograph revealed bilateral alveolar and interstitial infiltrates (Fig 1, E). Initially, therapy was started with empiric treatment for community-acquired pneumonia—cefuroxime and erythromycin. On the third hospital day, the patient’s condition deteriorated, and mechanical ventilation and PEEP were required. Treatment was switched to ceftazidime and tobramycin without improvement. Bronchoscopy, transbronchial lung biopsy, and bronchoalveolar lavage were performed on the 4th hospital day but were nondiagnostic. The patient’s condition continued to deteriorate. An open-lung biopsy could not be performed due to the patient’s hemodynamic instability. Serologic tests and lung tissue processing for histopathologic cultures and stains were not diagnostic of any concomitant infectious process. The IgG titer for cytomegalovirus (but not IgM) was elevated. Empiric treatment with methylprednisolone was started on the 7th hospital day; however, the patient died 1 day later, and autopsy confirmed the diagnosis of BOOP. Other findings included occasional small pulmonary thromboemboli and congestive heart failure with hepatic, splenic, and gastrointestinal congestion. There was evidence of mild atherosclerotic heart disease and multiple uterine leiomyomata.

Observations

The Clinical Picture

Signs and symptoms reported by our patients were nonspecific, constitutional, and mild (Table 2). Dyspnea was the most common complaint and was exertional in one instance. Cough productive of scanty whitish sputum was reported by four patients. All diagnostic studies done on bronchial secretions were uninformative. Pleuritic chest pain was observed in one patient. There was no associated pleural effusion or pneumothorax. Different patterns of radiologic pictures emerged and included diffuse, bilateral alveolar disease, diffuse bilateral interstitial disease, and discrete consolidations as well as discrete infiltrates. The duration of symptoms before admission ranged from 3 days to 6 months.

No antecedent lung disease was reported in any of the patients. For this reason, no baseline pulmonary function tests or arterial blood gases were available. A history of systemic hypertension was reported in four patients, but none were hypertensive during the hospital stay. Similarly, diabetes mellitus was reported in three patients but appeared to be controlled in all patients. The medications regularly used by our patients represented different classes of antihypertensive drugs, none of which had been closely linked to BOOP.

Outcome

In this group of patients with BOOP, three required early mechanical ventilation and PEEP to maintain adequate oxygenation (Table 1). A fourth patient who did not require mechanical ventilation early on was difficult to wean after open-lung biopsy and required assisted ventilation for 4 days. It is interesting that of the five acutely ill patients, the two who died were those in whom corticosteroid therapy was not initiated early on during the course of the
illness. Respiratory failure was the primary cause of death in both of these patients. In contrast, the other three patients who received corticosteroid treatment (even before the diagnosis was confirmed in one instance) had a favorable outcome and were discharged home in a stable condition, although one required oxygen supplementation at home.

**DISCUSSION**

Bronchiolitis obliterans with organizing pneumonia secondary to viral infections, toxic exposures, the use of certain medications, cocaine abuse, and HIV infection has been clearly described in the literature.\(^9\)\(^-\)\(^11\) The idiopathic variety of this entity, however, was only first described in 1985 by Epler et al.\(^1\) Careful history and relevant investigations are required to differentiate the idiopathic variety of BOOP from the secondary causes of BOOP, which were just mentioned. Idiopathic BOOP, also known as cryptogenic organizing pneumonia, is a distinct clinical and pathologic disorder of unknown etiology.\(^1\)\(^-\)\(^5\) It is characterized clinically by a pneumonia-like illness with symptoms suggestive of an upper respiratory tract infection usually followed by cough, dyspnea, and crackles with or without wheezing. Radiologic presentations are variable, with bilateral patchy alveolar infiltrates being most common. Less common presentations include localized areas of consolidation, unilateral patchy alveolar infiltrates, diffuse interstitial patterns, and solitary nodular densities. Histologic features include granulation tissue plugs within lumens of small airways and granulation tissue extending into alveolar ducts and alveoli. Although the classic-idiopathic BOOP has an indolent course with good prognosis, three recently reported cases represent an acute, fulminating, and life-threatening variant of the syndrome. Bellomo et al.\(^7\) reported two acute cases in patients who developed severe respiratory insufficiency related to BOOP. Schwarz\(^8\) also reported a case of a patient who developed adult respiratory distress syndrome related to idiopathic BOOP. Cohen et al.\(^6\) recently reported a series of ten patients with rapidly progressive BOOP and poor outcome. The focus of that paper was to alert the practicing physicians to a subset of patients with BOOP who present with a fulminant course with poor prognosis and increased mortality. Careful analysis of these patients reveals that although the majority of these patients had evidence of an immunologic disorder, two may have suffered from idiopathic BOOP.

In this study, we have demonstrated that idiopathic BOOP, like secondary BOOP, may present as an acute and life-threatening illness. Three of our patients presented with ARDS requiring assisted mechanical ventilation and high levels of PEEP. It is not clear why more of the recently reported cases appear to be of the acute and fulminating variety. It is possible that there is a selection bias whereby tertiary centers like ours are receiving the more critically ill patients. Alternatively, this may be related to increased awareness of the entity by clinicians and pathologists. In the past, most reports on this entity did not seem to recognize the presence of the acute form of the syndrome. With increased awareness, increased reporting is inevitable.

What are the factors which predispose to this acute variant of the syndrome or identify patients at higher risk for this entity? Cohen et al.\(^6\) addressed this issue in their group of patients with BOOP, most of whom had the secondary variety. They observed that the presence of an immunologic disorder such as an autoimmune or a connective tissue disorder was an important predictor of the development of this entity. To determine whether this may also be an important factor in idiopathic BOOP, we analyzed our five patients as well as the other three reported cases in the literature. We could not document such an association. One patient (case 1) had fever and weight loss for 6 months prior to admission, suggesting the presence of another illness besides primary BOOP. However, this patient who has been followed up for 15 months postdischarge continues to be asymptomatic and has regained the lost weight. Another patient (case 5) had a history of prolonged weight loss, suggesting a concomitant illness. An autopsy was performed on this patient, and no pulmonary or systemic abnormalities suggestive of an entity associated with secondary BOOP were detected. Although one of our patients had a history of rheumatoid arthritis, it was inactive at the time of admission. In addition, his rheumatoid arthritis was of the mild category and had responded favorably to nonsteroidal anti-inflammatory medications. We then looked for evidence of chronic pulmonary or respiratory disease, chronic systemic illness, the use of agents and chemotherapeutic agents known to be injurious to the lung, or industrial or environmental exposures. Interestingly, none of the patients seemed to have a history of antecedent lung disease or injury, although they were all smokers. Four of our five patients and one other reported case\(^7\) had hypertension, and three had a history of diabetes mellitus. We attempted to determine the prevalence of diabetes and hypertension in reported series of idiopathic (nonacute) BOOP. However, because of the retrospective nature of these studies, that information was not available. It would be interesting to determine whether there would be a difference in the acuity of presentation of idiopathic BOOP in patients with antecedent chronic lung or systemic illnesses.

It is clear from this study that the outcome of pa-
tients with this acute variant of idiopathic BOOP depends on early initiation of corticosteroid therapy. This is also true in the acute variant of secondary BOOP. It is imperative, therefore, to have a high index of suspicion for this entity in patients presenting with acute respiratory failure and to obtain tissue diagnosis in the early phases of the illness.

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Pulmonary Alveolar Proteinosis in a Painter With Elevated Pulmonary Concentrations of Titanium*

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We present the case of a professional painter who developed pulmonary alveolar proteinosis (PAP) with severe respiratory failure. He required total bilateral pulmonary lavage on two separate occasions, 3 months apart. Quantitative analysis of particles found in lung tissues obtained by open lung biopsies demonstrated the presence of titanium (60-129 million particles of titanium per cm² of lung tissue). This report extends previous results from animal studies that demonstrated development of alveolar proteinosis in rats following exposure to titanium. It has been proposed that the overwhelming impairment of the normal clearance mechanisms of the lung by particles of titanium is one of the possible mechanisms responsible for the development of this lung disease. We suggest that a similar mechanism occurred in our patient and that titanium should be recognized as a potential cause of PAP in humans.

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Key words: alveolar proteinosis; occupational lung disease; titanium; total lung lavage

PAP is characterized by deposition of proteinaceous and lipid material within the airspaces of the lung, originally described in 1958. Associated conditions include immunocompromised states, which suggest malfunction of alveolar macrophages allowing accumulation of abnormal intra-alveolar material. Exposure to airborne dusts such as quartz, aluminum, and others in experimental animal models, as well as overwhelming concentrations of silicon dioxide in humans, have been associated with PAP. Unusual infections such as nocardiosis, aspergillosis, cryptococcosis, Pneumocystis, and others have also been associated with PAP, although it has been difficult to implicate these microorganisms as either causative or consequential.

Studies in rats exposed to titanium have been shown to develop PAP. We report a case of a subject exposed chronically, almost daily, to large amounts of paint, who developed PAP and whose lung tissues showed unusually high concentrations of inorganic particulates, predominantly titanium dioxide.

CASE REPORT

A 43-year-old man with severe shortness of breath and cough, intermittently producing large quantities of a thick yellowish material developed significant restrictive lung disease with severe hypoxemia (Table 1). His chest radiograph showed bilateral interstitial and alveolar infiltrates. His past medical history included regular use of alcohol up to 5 years prior to hospital admission. He had formerly snorted cocaine, but denied using intravenous drugs. He denied homosexual contact or contact with prostitutes. He smoked two-packs-per-day until the day of admission and had been employed as a painter for over 25 years; during the last 8 years working mainly with spray painting of buildings. Early in his career he did sandblasting for approximately 1 year. He had never used protective masks at work.

Physical examination showed acute respiratory distress. Bilateral crackles were present on auscultation. Other findings were unremarkable. His chest radiograph showed diffuse bilateral interstitial and alveolar reticular densities most evident in lower lung fields with relative sparing of the upper lobes (Fig 1). Routine laboratory tests were normal. Arterial blood gases, breathing

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