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Acute Fibrinous and Organizing Pneumonia: A Case Report and Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

EF 1,2 **Daniel Arnaud**
EF 1,3 **Zoya Surani**
E 4 **Abhay Vakil**
EF 5,6 **Joseph Varon**
EF 4,7 **Salim Surani**

1 Department of Research, Dorrington Medical Associates, Houston, TX, U.S.A.
2 Autonomous University of Tamaulipas, Victoria, Tamaulipas, Mexico
3 Veterans Memorial High School, Corpus Christi, TX, U.S.A.
4 Department of Medicine, University of North Texas, Denton, TX, U.S.A.
5 Critical Care Services, United Memorial Medical Center, Houston, TX, U.S.A.
6 Acute and Continuing Care, The University of Texas Health Science Center at Houston, Houston, TX, U.S.A.
7 Department of Medicine, Texas A&M University, Corpus Christi, TX, U.S.A.

Corresponding Author: Salim Surani, e-mail: srsurani@hotmail.com
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Patient: Female, 35
Final Diagnosis: Acute fibrinous and organizing pneumonia
Symptoms: Shortness of breath
Medication: —
Clinical Procedure: Video assisted thoracoscopic lung biopsy
Specialty: Pulmonology

Objective: Unknown etiology

Background: Acute fibrinous organizing pneumonia (AFOP) is a rare condition of the lung that is associated with acute lung injury, and has a poor prognosis. AFOP is characterized histologically by intra-alveolar fibrin. AFOP has been described to be associated with lung infections, connective tissue disorders, drugs, toxic environmental exposure, and in lung transplantation. However, most cases of AFOP remain idiopathic, and because the condition can present with a wide variety of clinical manifestations, open lung biopsy or video-assisted thoracoscopic (VAT) lung biopsy is necessary for the diagnosis. Currently, treatments for AFOP remain under investigation.

Case Report: A 35-year-old woman presented with a cough and dyspnea, and was initially diagnosed to have pneumonia. Due to the progression of her symptoms and increasing respiratory failure she underwent video-assisted thoracoscopic (VAT) biopsy and was diagnosed with AFOP, 19 days following hospital admission. She was treated with mechanical ventilation, intravenous steroids, and cyclophosphamide. She required tracheostomy after 14 days of mechanical ventilation and died two weeks later.

Conclusions: AFOP is an uncommon clinical condition, with a poor prognosis, which often has a delay in diagnosis. Some patients benefit from steroids and immunosuppressive therapy. Currently, new treatments for AFOP are under investigation.

MeSH Keywords: Acute Lung Injury • Bronchopneumonia • Thoracoscopy

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Background

Acute fibrinous organizing pneumonia (AFOP) is a rare condition of the lung that is associated with acute lung injury, has a poor prognosis, and is characterized histologically by intra-alveolar fibrin. [1]. A wide variety of signs, symptoms, and radiographic findings make AFOP difficult to diagnose clinically, and a lung biopsy is required for the diagnosis [2]. We report a case of a young woman who presented with respiratory distress, and who was diagnosed with AFOP on lung biopsy. A review of the recent and relevant literature on AFOP is included.

Case Report

A 35-year-old woman presented to the emergency department (ED) with a two-week history of a cough and dyspnea. She was provisionally diagnosed with pneumonia, following chest X-ray and clinical work up at an outlying hospital facility. The patient was a poor historian, but she acknowledged a cough, shortness of breath, and sore throat, and she denied any recent travel, exposure to any chemicals, or any pets. Her past medical history was significant for schizoaffective disorder, hypothyroidism, hypertension, and obesity. The patient had no history of substance abuse.

Because of her worsening clinical condition, she was admitted to the intensive care unit (ICU). Her blood pressure was 142/75 mmHg, heart rate 112 beats/min, respiratory rate of 24 breaths/min, temperature 98.6°F and oxygen saturation of 94% on oxygen supplementation with a nasal cannula that delivered oxygen at a rate of 6 L/min. She was sitting up in bed, oriented only to person, and was in moderate respiratory distress. Cardiac examination was unremarkable except for her tachycardia. Lung examination showed reduced air entry and crackles in both lung bases.

Initial laboratory data included a white blood cell count (WBC) of $5.9 \times 10^3/\mu\text{L}$, hemoglobin (Hb) 15.4 g/dL, hematocrit (HCT) 50.1%, platelets (PLT) $90 \times 10^3/\mu\text{L}$, sodium (Na^+) 133 mEq/L, potassium (K^+) 4 mEq/L, serum chloride (Cl) 89 mEq/L, serum bicarbonate (HCO_3^-) 31 mEq/L, blood urea nitrogen (BUN) 13 mg/dL, serum creatinine 1 mg/dL glucose 107 mg/dL, lactic acid 3.3 mmol/L, and serum calcium of 9.2 mg/dL. Arterial blood pH was 7.40, arterial blood gases (ABGs) were pH 7.40, pCO_2 51.2 mmHg, pO_2 of 72.4 mmHg, and calculated HCO_3^- of 30.2 mEq/L, while breathing oxygen at 6 liters/min. Rapid serum testing for influenza A and B antibodies were negative. On chest X-ray, bilateral pulmonary infiltrates were seen, predominantly in the left lower lobe (Figure 1). A computed tomography (CT) scan of the chest showed left lower lobe consolidation, patchy infiltrates, and a 'ground-glass' appearance in the right and left lower lobes (Figure 2).

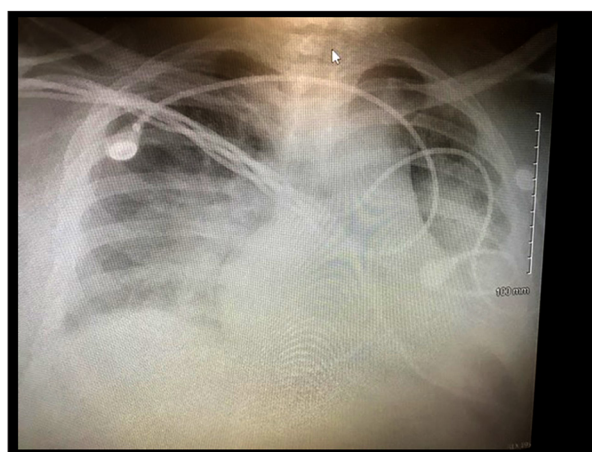


Figure 1. Chest X-radiograph in a case of acute fibrinous organizing pneumonia (AFOP). Chest radiograph shows bilateral parenchymal infiltrates, predominantly in the left lower lobe.

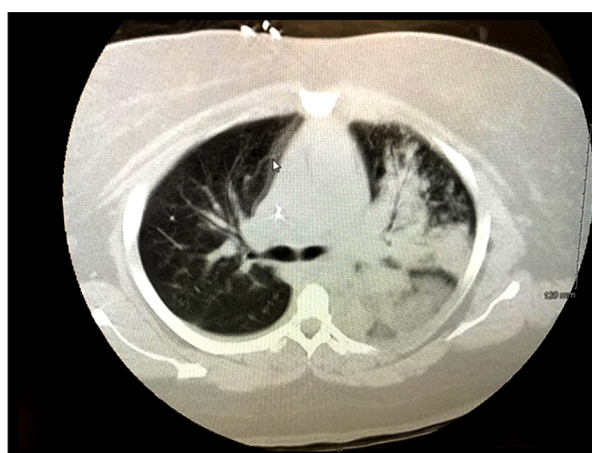


Figure 2. Non contrast-enhanced chest computed tomography (CT) in a case of acute fibrinous organizing pneumonia (AFOP). Non contrast-enhanced chest computed tomography (CT) shows consolidation of the left lower lobe with an air bronchogram.

Treatment commenced with non-invasive mechanical ventilation with bi-level positive airway pressure (BiPAP) therapy. Her inspiratory positive airway pressure (IPAP) was 16 cm H_2O and her expiratory positive airway pressure (EPAP) was 8 cm H_2O , with a fraction of inspired oxygen (FiO_2) of 50%. She was initially treated empirically with moxifloxacin 400 mg IV every 24 hours; piperacillin/tazobactam at 3.375 grams intravenous (IV) every 6 hours; and solumedrol 40 mg IV every 8 hourly. Despite these therapeutic interventions, her pulmonary function deteriorated, necessitating emergency intubation with assisted mechanical ventilation. A two-dimensional (2D) echocardiogram was done to assess left ventricular systolic dysfunction, and to rule out any possibility of congestive heart failure complicating her pulmonary status, which showed a normal aortic root,

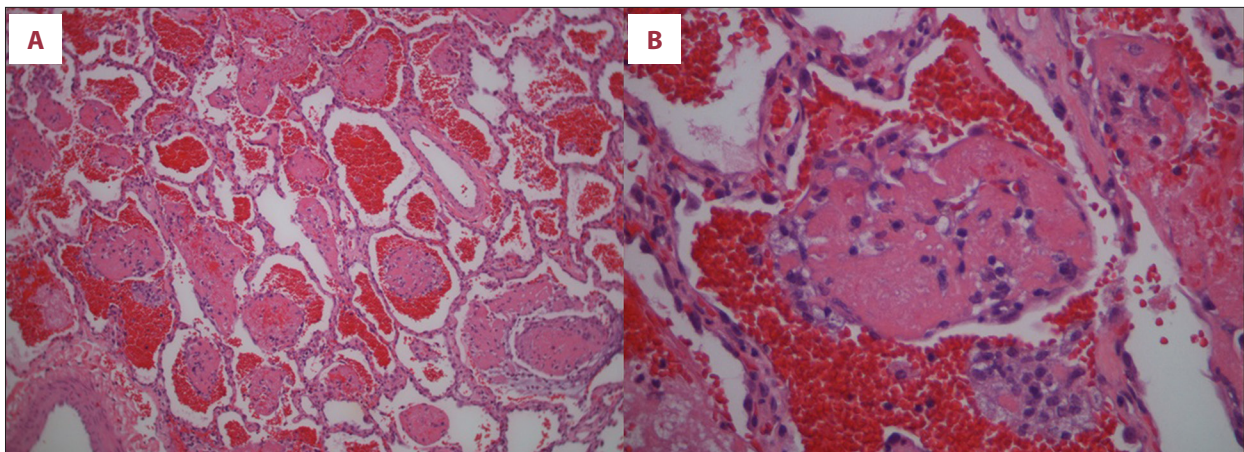


Figure 3. Photomicrographs of the histology of the appearance of acute fibrinous organizing pneumonia (AFOP) on lung biopsy. (A) (Low power) and (B) (high power) photomicrographs of the histopathology of a lung biopsy from this case, showing the typical appearances of acute fibrinous organizing pneumonia (AFOP). The alveolar spaces are dilated, and some are filled with intact red cells (arrow head), and others are filled with eosinophilic (pink) fibrin (arrows), but there are no hyaline membranes. Hematoxylin and eosin (H&E) stain.

a left atrium that was normal in size and function, a normal left ventricular cavity dimension, with an estimated ejection fraction of 55–60% with no pericardial effusion.

The patient underwent serological testing for HIV infection, including a respiratory viral panel of tests, and for *Mycoplasma pneumoniae* antibody. Molecular diagnostic testing was undertaken using a *Chlamydia* DNA probe, *N. gonorrhoeae* DNA probe, the rapid plasma regain (RPR) test for syphilis, and a hepatitis panel, which were all negative. The patient underwent video-bronchoscopy, which showed mild secretion in the left lower lobe. Broncho-alveolar culture, performed after several days in hospital, grew *Serratia marcescens*. A single blood culture grew *S. epidermidis*, which was felt to be contaminant as repeat cultures were negative. Urine culture grew *Candida albicans*.

Because of the persistent pulmonary infiltrates and worsening respiratory function, the patient underwent video-assisted thoracoscopic (VAT) lung biopsy with wedge resections of both the left upper lobe and left lower lobe. Histopathology, using standard hematoxylin and eosin (H&E) staining, reported a multifocal but patchy lung abnormality, with areas of relatively normal and areas of lung showing numerous intra-alveolar macrophages containing brown intracytoplasmic pigment. Dilated alveolar spaces were present, some filled with intact red cells, and others contained large amounts of eosinophilic (pink) fibrin, with no hyaline membranes. The histopathology appearances were typical for a diagnosis of acute fibrinous organizing pneumonia (AFOP) (Figure 3A, 3B). In some peripheral lung, there was myxomatous fibrous organization, but no vasculitis or capillaritis were seen, very few polymorphonuclear leukocytes (neutrophils) or eosinophils and no granulomas or necrosis were seen.

After 19 days following hospital admission, based on the histopathological findings, the patient was diagnosed with AFOP and was treated with intravenous steroids and cyclophosphamide. The patient initially showed some clinical response but remained on mechanical ventilation. She also required tracheostomy after 14 days of mechanical ventilation and was transferred to a long-term care hospital. Two weeks later, she developed worsening respiratory failure and oxygenation status and died.

Discussion

Acute fibrinous organizing pneumonia (AFOP) is an uncommon form of response to acute lung injury that is characterized by the distinctive histological feature of intra-alveolar fibrin and the presence of organizing pneumonia, found in a patchy distribution in the lung parenchyma, usually affecting the lower lobes [3]. Associated histopathological findings that have been described include type II pneumocyte hyperplasia, alveolar wall inflammation, and myxomatous degeneration of the alveolar septa [3].

First reported in 2002 in a 17-patient case series by Beasley et al., AFOP was described histologically as a condition that should be distinguished from diffuse alveolar damage (DAD), bronchiolitis obliterans with organizing pneumonia (BOOP), and eosinophilic pneumonia (EP) in the setting of acute lung injury [3–5]. More than 100 cases of AFOP have been reported in the literature [4]. Men are affected by AFOP slightly more commonly than women [2,6,7]. AFOP has been diagnosed in all age groups, but it is most commonly reported in patients between 50 and 70 years of age (average, 62 years). In our case report, the patient was much younger than

Table 1. The clinical associations with acute fibrinous organizing pneumonia (AFOP).

Autoimmune diseases	Ankylosing spondylitis Anti-phospholipid syndrome Anti-synthetase syndrome Dermatomyositis Sjogren's syndrome Systemic lupus erythematosus (SLE) Polymyositis Primary biliary cirrhosis (PBC)
Drugs	Abacavir Amiodarone Bleomycin Decitabine Everolimus Sirolimus Zacytidine
Environmental causes	Aerosols Asbestos Coal Dusts
Infections	Acinetobacter baumannii Aspergillus fumigatus Chlamydia pneumoniae Cytomegalovirus H1N1 Influenza Haemophilus influenzae Histoplasmosis Human immunodeficiency virus (HIV) Pneumocystis jirovecii
Transplantation	Allogenic hematopoietic stem cell transplant (HSCT) Lung transplant

the average reported age for AFOP, being a 35-year-old woman. Only five cases of AFOP have been reported in children [2,6]

The etiopathogenesis of AFOP remains elusive and has been associated with multiple possible causes, such as infections, connective tissue disorders, drugs, environmental exposure, and organ transplantation (Table 1) [7,8]. AFOP has been reported in the post-transplant period with features similar to acute rejection, primary graft dysfunction or infections, such as cytomegalovirus (CMV) [8]. In our case report, there was no evidence of connective tissue disorder, environmental toxins or chemical exposure or any infection, and it is possible that this case, as in many cases was an idiopathic case of AFOP [2,3,6,9,10].

Clinically, there are two different clinical patterns of AFOP; one is characterized by an acute onset of the disease with a fast progression to death due to respiratory failure and multi-organ dysfunction, with the average time from onset to death of 29 days [5,6]. The case we have presented represented the more

rapidly fatal pattern of AFOP. The second clinical pattern of AFOP has a less aggressive nature with slower progression [3–5,7].

The most commonly reported presenting symptoms of AFOP include dyspnea, cough, fever, and progressive respiratory failure [3]. Less commonly, hemoptysis may be present [6,8]. In some cases of AFOP, patients have presented with pleural effusions and, very rarely, with pneumothorax [9]. The symptoms of AFOP can mimic those of community acquired pneumonia [6]. These nonspecific symptoms result in a delay in the diagnosis of AFOP. Beasley and collaborators described a mean time from onset of symptoms to diagnosis of 19 days, and Gomes and coworkers reported a mean time of 43.9 days [1,5].

AFOP also has nonspecific and variable radiographic appearances. The most common imaging finding is bilateral patchy infiltrates at the lung bases with ground-glass appearance and inter-lobar septal thickening [3]. Other radiographic findings reported include diffuse bilateral miliary infiltrates, as well as generalized nodules with lobar consolidation [3,6].

Lung biopsy, either open lung biopsy, CT-guided lung biopsy, or video-assisted thoracoscopic (VAT) lung biopsy, is the preferred method for diagnosis of AFOP [2]. Bronchoscopy with bronchoalveolar lavage usually provides nonspecific findings and does not provide a definitive diagnosis [6].

The case we have presented of AFOP highlights the nonspecific symptoms and signs on presentation, including the imaging findings, and has highlighted the importance of lung biopsy diagnosis. In this case, the patient was not typical for patients with AFOP previously reported in the literature, being relatively young age and a female patient. There was no history of a cause for AFOP in this case, with no environmental toxin exposure, chemical exposure, pets or recent travel. The finding of the broncho-alveolar culture of *Serratia marsecens* may have been a healthcare-associated infection (HAI) following hospital admission. Because the patient showed a waxing and waning pattern of symptoms, we believe that this contributed to the delay in video-assisted thoracoscopic (VATS) lung biopsy.

Meanwhile, the prognosis for AFOP remains poor, and the best treatment for this condition is still under investigation. There are several cases where patients with AFOP have had a modest benefit with steroids and immunosuppressive therapy [3]. Patients with an underlying connective tissue disorder or other autoimmune diseases may benefit the most from immunosuppressive therapy [2]. Mycophenolate mofetil and cyclophosphamide have been suggested by some authors as treatment options for these cases [2].

However, most patients with the fulminant pattern of the disease will die, despite corticosteroid therapy, mechanical

ventilation, and/or extracorporeal life support [8]. The mortality in these cases has been reported to exceed 90% [5,8]. When both patterns of the disease are included, the reported mortality is close to 50% [8]. The need for mechanical ventilation has been associated with mortality in almost 100% of the cases [5].

Treatments for AFOP that are currently being investigated include the use of tumor necrosis factor (TNF) inhibitors. Hara and coauthors have demonstrated that heme oxygenase-1 (HO-1) is overexpressed in the intra-alveolar fibrin found in AFOP [11]. A known inducer of HO-1 is TNF- α [12]. Etanercept, a TNF inhibitor, has been reported as an effective treatment for acute lung injury and in a case of AFOP [11,13]. A TNF inhibitor was not initially used in our patient as the patient showed an initial response to steroids and cyclophosphamide. However, her course was later complicated after an initial recovery with a very rapid and progressive deterioration and death.

Because there is currently no ideal treatment for AFOP, the treatment of choice and therapy duration should be made on the basis of the medical course and etiology, with some patients being dependent on steroids, immunosuppressants, and oxygen. Recently an association of anti-EJ autoantibodies with necrotizing myopathy and AFOP was reported with very good response to intravenous (IV) methylprednisolone and immunoglobulin [14]. Antibiotic therapy has recently been shown to have a possible positive effect on the course of AFOP [15]

Surgical resection of localized areas of pulmonary AFOP has been suggested to be curative [16]. Renaud-Picard et al. have reported a patient who developed AFOP after lung transplantation

for cystic fibrosis, who was successfully 'rescued' by an emergency bilateral lung re-transplantation [2,16]. However, there is insufficient data at present to determine whether a transplanted lung will undergo recurrence of AFOP.

This case presents an important learning point for the clinicians who should be aware of the unusual clinical condition of AFOP, which can affect patients who are at a younger age. Tissue diagnosis via VATS lung biopsy should be considered at the earliest stage possible, as mortality approaches 100% once the patient requires mechanical ventilation for respiratory failure.

Conclusions

Acute fibrinous and organizing pneumonia (AFOP) is an under-diagnosed clinicopathological condition that has a variable presentation, which means that it might be more common than previously thought. There is often a delay in the diagnosis of AFOP, as in our case. Furthermore, there is no consensus as to the most effective drug treatment for AFOP, and mortality remains very high. The clinician should be aware of the existence of this fatal condition, that it can occur at a younger age than described in the literature, and that early histological diagnosis and aggressive therapy with steroids and immunosuppressive agents are required before the patient progresses to fatal respiratory failure.

Conflicts of interest

None.

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