Original Article

Clinical and Radiological Profile of Acute Fibrinous and Organizing Pneumonia: A Retrospective Study

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Abstract

Background: Acute fibrinous and organizing pneumonia (AFOP) is a unique pathological entity with intra-alveolar fibrin in the form of "fibrin balls" and organizing pneumonia. It was divided into rare idiopathic interstitial pneumonia according to the classification notified by American Thoracic Society/European Respiratory Society in 2013. As a rare pathological entity, it is still not well known and recognized by clinicians. We reviewed the clinical features of 20 patients with AFOP diagnosed in a teaching hospital.

Methods: The medical records of 20 patients with biopsy-proven diagnosis of AFOP were retrospectively reviewed. The patients' symptoms, duration of the disease, comorbidities, clinical laboratory data, pulmonary function testing, radiographic studies, and the response to treatment were extracted and analyzed.

Results: Fever was the most common symptom and was manifested in 90% of AFOP patients. For clinical laboratory findings, systematic inflammatory indicators, including C-reactive protein and erythrocyte sedimentation rate, were significantly higher than normal in AFOP patients. In accordance with this increased indicators, injured liver functions were common in AFOP patients. Inversely, AFOP patients had worse clinical conditions including anemia and hypoalbuminemia. For pulmonary function testing, AFOP patients showed the pattern of restrictive mixed with obstructive ventilation dysfunction. For high-resolution computerized tomography (HRCT) findings, the most common pattern for AFOP patients was lobar consolidation which was very similar to pneumonia. However, unlike pneumonia, AFOP patients responded well to glucocorticoids.

Conclusion: Patients with AFOP manifest as acute inflammatory-like clinical laboratory parameters and lobar consolidation on HRCT, but respond well to steroid.

Key words: Acute Fibrinous and Organizing Pneumonia; Clinical Features; High-resolution Computerized Tomography; Inflammatory Indicators

Introduction

Acute fibrinous and organizing pneumonia (AFOP) was firstly described by Beasley *et al*. in 2002.[1] This newly described pathological entity has a unique pattern which is different from others, and exhibited as a typical "fibrin balls" filling within the intra-alveolar space without the formation of hyaline membrane. Moreover, mild acute and/or chronic inflammation, type 2 pneumocyte hyperplasia, and alveolar extension are also seen in the slide.[1,2] So far, a total of 21 English articles introduced us with this newly discovered disease, and 67 patients with AFOP were reported or mentioned in their articles.[3-8] Most of the literatures were case reports and there was no further systematic information regarding clinical parameters related to this rare and unique pathological entity.

According to the update of the International Multidisciplinary Classification of Idiopathic Interstitial Pneumonia,[9] AFOP is defined as a rare pathological pattern related to certain

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conditions including infections, connective tissue diseases, exposure to some drugs, hematological diseases, and following lung transplantation.[10] Beasley *et al*. proposed that AFOP may represent a variant histologic pattern of diffuse alveolar damage,[1] or it may reflect a tissue sampling issue since the small sampling method may lead to misdiagnosis.[11] However, due to a relatively higher level of injury, open lung biopsy is not the regular sampling method for helping diagnosis, while transthoracic needle biopsy (TNB) and/or transbronchial lung biopsy (TBLB) are still the most useful tool for obtaining tissue samples during regular clinical course. How we get useful information helping diagnosis using these regular and relatively smaller sampling methods are still under consideration. In 2013, Paraskeva *et al.* reported that AFOP was the second common phenotype of chronic lung allograft dysfunction (CLAD) in patients after lung transplantation.[8] In their reports, all the AFOP patients developed respiratory failure and died during the investigation. Hence, patients in their report were categorized into fulminant form according to Beasley's criteria. However, there is no report regarding the clinical course of AFOP for nontransplantation patient. Here, we conducted a retrospective study to describe the clinical parameters including the clinical presentation, etiology, radiological manifestation, diagnostic evaluation, and response to treatment manifested by nontransplantation patients with pathologically diagnosed AFOP.

Methods

All the patients with AFOP in the Affiliated Drum Tower Hospital of Nanjing University Medical School from January 2007 to June 2013 were reviewed. The study was approved by the Institutional Review Boards of our institutions. AFOP is characterized by a pattern of organizing pneumonia where the predominant histological finding is the presence of intra-alveolar fibrin balls (involving above 30% of the alveolar spaces within a specimen) and type 2 pneumocyte hyperplasia, thus resembling an acute lung injury pattern, but lacking hyaline membrane formation.[1] The final diagnosis of all the patients was made by a multidisciplinary approach of experienced clinician, radiologist, and pathologist. We reviewed patients' symptoms, duration of the disease, comorbidities, laboratory data, pulmonary function testing, radiographic studies, and the response to treatment.

Statistical analysis

Data are presented as means ± standard error of the mean. Continuous variables were compared using the unpaired *t*-test or the Mann–Whitney *U*-test. Categorical variables were compared using the Chi-square test or Fisher's exact test. $P < 0.05$ was considered statistically significant. GraphPad Prism, version 5 software (GraphPad software Inc,. La Jolla, USA) was used for statistical analysis.

Results

Characterization of patients

Twenty patients were identified with a biopsy-proven diagnosis of AFOP, 9 men and 11 women. Sixteen patients were pathologically diagnosed by computerized tomography (CT)-guided TNB and other 4 patients were diagnosed by TBLB. Among these, 4 patients received TBLB and percutaneous lung biopsy successively, and these 4 patients were confirmed AFOP despite the different sampling methods [Figure 1]. The mean age of AFOP patients was 58.8 ± 1.9 years. Comorbidities of the patients were listed in Table 1, one patient was diagnosed with acute leukemia, and one was multiple myeloma. Two patients were diagnosed with

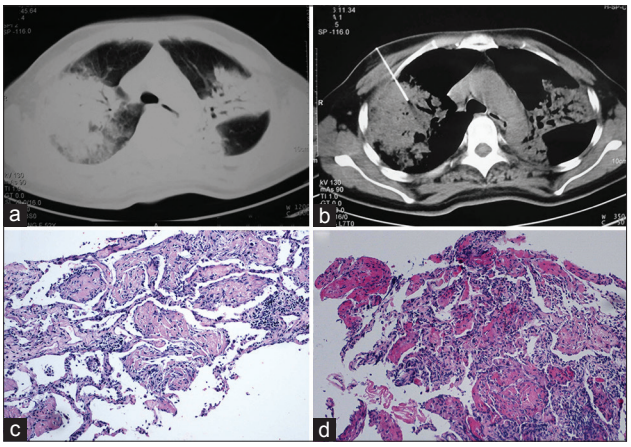

Figure 1: Patient 1, female, 52 years old. Cough, sputum, and fever for more than 20 days. Computerized tomography scan showed bilateral lobar consolidation; (a) Lung window; (b) Mediastinal window; (c) The patient was confirmed to have acute fibrinous and organizing pneumonia by using transthoracic needle biopsy; (d) Three days later, the same patient was confirmed to have the same pathological diagnosis of acute fibrinous and organizing pneumonia using transbronchial lung biopsy.

Table 1: Characterization of the patients in our study

Characterizations of patients	Values
Numbers	20
Males, *n*	9
Active smokers, *n*	4
Previous smokers, *n*	1
Age, years*	58.8 ± 1.9
The duration of symptoms before diagnosis, days*	32.4 ± 4.8
Symptoms, *n*	
Fever	19
Cough	18
Sputum	17
Dyspnea	10
Physical examination	
Crackles	7
Duration of fever, days*	25.5 ± 4.3
Duration of hospital stay, days*	16.7 ± 2.2
Comorbidity	
Chronic lung diseases	2
Hematologic diseases	2
Chronic heart diseases	4
Diabetes	4
Chronic renal diseases	1
Solid malignant tumors	1

AFOP: Acute fibrinous and organizing pneumonia. *Data are presented as means ± standard error of the mean.

asthma. Four patients with diabetes, one patient with chronic renal disease, and other four patients with hypertension were recorded. The mean duration of symptoms before diagnosis was 32.4 ± 4.8 days for AFOP. Four AFOP patients were active smokers and one AFOP patient was previous smokers. The most common symptom in AFOP patients were fever (19/20), having a mean duration of 25.5 ± 4.3 days and median temperature at 39.1°C (38.1–41.2°C), and then followed by cough (18/20) and sputum (17/20). And, dyspnea was also a common symptom and appeared in half of the AFOP patients (10/20). Crackles were presented in 7 of 20 AFOP patients. In addition, the mean durations of hospital stay for AFOP patients were 16.7 ± 2.2 days.

Laboratory parameters

Six AFOP patients presented with leukocytosis, and three patients with leukopenia. The mean hemoglobin for patients with AFOP was 105.2 ± 4.5 g/L which was lower than the normal value. Fifteen of 20 patients in AFOP group were shown with anemia [Table 2].

Table 2: Laboratory parameters and pulmonary function test of AFOP patients

Clinical parameters	Values
Routine blood test	
WBCs, $\times 10^9$	8.9 ± 1.0
Neutrophil, $\times 10^9$	6.7 ± 1.0
Hemoglobin, g/L	105.2 ± 4.5
CRP, mg/L	70.8 ± 9.9
ESR, mm/h	82.7 ± 7.5
Liver function test	
ALT, U/L	46.2 ± 9.3
AST, U/L	35.5 ± 6.8
ALP, U/L	140.0 ± 20.8
γ-GT, U/L	110.0 ± 22.6
LDH, U/L	204.7 ± 16.6
ALB, g/L	32.7 ± 0.7
Renal function test	
Serum creatinine, μmol/L	51.0 ± 2.0
BUN, mmol/L	4.3 ± 0.5
Oxygenation index (P/F)	341.7 ± 20.6
Pulmonary function	
Actual TLC, L	4.6 ± 0.5
Percentage of predicted TLC, %	77.2 ± 14.4
Actual FEV_1, L	2.1 ± 0.2
Percentage of predicted FEV_1, %	78.6 ± 13.3
Actual FVC, L	2.8 ± 0.2
Percentage of predicted FVC, %	76.6 ± 14.6
FEV_1/FVC, %	78.0 ± 10.5
Actual DLco, $ml \cdot min^{-1} \cdot mmHg^{-1}$	6.5 ± 2.0
Percentage of predicted DLco, $ml \cdot min^{-1} \cdot mmHg^{-1}$	9.8 ± 1.0

WBCs: White blood cells; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ALT: Alanine aminotransferase; AST: Aspartate transaminase; ALP: Alkaline phosphatase; γ-GT: Gamma glutamyl transferase; LDH: Lactic dehydrogenase; ALB: Albumin; TLC: Total lung capacity; FEV_1: Forced expiratory volume in the first second; FVC: Forced vital capacity; DLco: Diffusion capacity for carbon monoxide; AFOP: Acute fibrinous and organizing pneumonia; BUN: Blood urea nitrogen; P/F: PaO2/FiO2 ratio. Data are presented as means ± standard error of the mean.

We then extracted the parameters indicating systemic inflammation and systemic organ injury. The values of C-reactive protein (CRP) in AFOP patients were remarkably higher than the normal value and presented as a mean value of 70.8 ± 9.9 mg/L. In accordance with CRP, erythrocyte sedimentation rate (ESR) was also significantly increased above normal value in patients with AFOP (a mean value of 82.7 ± 7.5 mm/h) [Table 2].

For liver function tests, seven AFOP patients showed elevated alanine aminotransferase (ALT) and/or aspartate transaminase (AST) levels. Similar to ALT/AST, alkaline phosphatase had higher value in AFOP patients than normal (140.0 ± 20.8 U/L), five patients had higher values above normal. Eleven AFOP patients showed elevated serum gamma glutamyl transferase (γ-GT) concentration, and the mean value of γ-GT was 110.0 ± 22.6 U/L. And taken together, it seemed that there was a trend of liver injury in AFOP patients. As a supportive evidence for elevated systemic inflammation and worse situation, hypoalbuminemia was found in fifteen AFOP patients with a mean value of 32.7 ± 0.7 g/L which was lower than normal. All patients showed normal with renal function testing. Five AFOP patients developed respiratory failure, and the mean value of oxygenation index PaO_2/FiO_2 ratio for all AFOP patients was 341.7 ± 20.6. Results are shown in Table 2.

Elevated rheumatoid factor (RF) titer was found in two AFOP patients. And, there were no positive findings for RF, anti-nuclear antibody (ANA), anti-Sjogren's syndrome antibody, p-anti-neutrophil cytoplasmic antibody (ANCA), and c-ANCA in the remaining AFOP patients.

Eight AFOP patients had blood culture available, and there was no positive result. Fifteen AFOP patients had withdrawn sputum for bacterial cultures. A patient with AFOP had positive sputum culture for *Pseudomonas putida* and *Staphylococcus xylosus*. And, another one patient with AFOP was positive for *Pseudomonas aeruginosa*. For fungal culture or examination, only three AFOP patients had performed G test and GM test; 16 patients were sampled for sputum cultures. Two AFOP patients had positive G test and other four AFOP patients had positive result of sputum culture. Six AFOP were examined for virus infection of cytomegalovirus (CMV) and Epstein–Barr (EB), and there was no positive finding.

Pulmonary function testing

Pulmonary function testing was available for nine AFOP patients. Three patients were normal with pulmonary function testing, one patient was with obstructive ventilation dysfunction due to having asthma for more than 20 years, the other two patients exhibited a restrictive ventilation dysfunction, and the remaining three patients showed a mixed ventilation dysfunction. Six patients had mild to moderate degree of decrease in pulmonary diffusion function. The mean value of percentage of predicted forced expiratory volume in the first second (FEV_1), FEV_1/forced vital capacity, and percentage of predicted total lung

capacity, diffusion capacity for carbon monoxide (DLco), and percentage of predicted DLco was 78.6 ± 13.3%, 78.0 ± 10.5%, 77.2 ± 14.4%, 6.5 ± 2.0 ml·min^{-1}·mmHg^{-1}, and 67.1 ± 17.9%, respectively. Based on the above mean values, mixed ventilation dysfunction was the most common type in AFOP patients. Results are shown in Table 2.

Findings on high-resolution computerized tomography

For AFOP patients, the most common patterns of lung abnormality on the initial scans were lobar consolidation (13/20), ground glass opacity (GGO, 9/20), and patchy consolidation (7/20). These images were distributed along with the bronchovascular bundles and/or subpleural lungs in 13 of 20 patients. Seventy-five percent of patients showed bilateral lung abnormality. Pleural effusion was detected in five patients, and solitary nodule was detected in two patients. Band-like consolidation was observed in four patients. The most common composite images appeared in eight patients, and were lobar consolidation accompanying with GGO. Fifteen patients showed bilateral lung abnormality. One AFOP patient showed reverse-halo sign. Taken together, lobar consolidation was the most common pattern shown in AFOP patients. Results are shown in Table 3.

Treatment response and prognosis

All the patients received antibiotic therapy before they got a diagnosis of AFOP. However, no patient was in remission using antibiotic alone. No patient received mechanical ventilation during the therapy after the diagnosis. Except for two patients, all the other AFOP patients received glucocorticoid intravenously or orally. The dose varied from 30 to 40 mg prednisone per day. The mean duration for relieving from the symptom after receiving steroid administration was 4.3 ± 2.4 days. Two deaths were reported among AFOP patients 3 months later after initial treatment due to the primary disease of multiple myeloma and acute leukemia, respectively. All other patients were clinical remission within 1–3 months after glucocorticoid therapy [Figure 2]. And, one patient relapsed with lung infiltration and symptom again 5 months after using steroids and received increased dose of steroid therapy after that.

Table 3: Characterization of the HRCT findings of AFOP patients

HRCT patterns	AFOP patients, *n*
Lobar consolidation	13
Ground glass opacity	9
Patchy consolidation	7
Solitary nodule	2
Reticular pattern	0
Pleural effusion	5
Reverse-halo sign	1
Band-like consolidation	4
Bilateral lung abnormality	15
Bronchovascular bundles distribution	6
Subpleural lungs distribution	8

HRCT: High-resolution computerized tomography; AFOP: Acute fibrinous and organizing pneumonia.

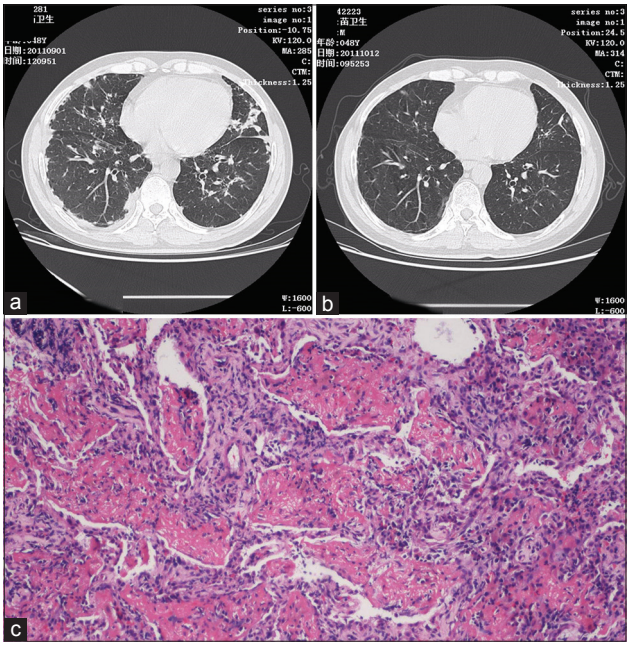

Figure 2: Patient 2, male, 48 years old. Fever, cough, and dyspnea for 2 months. (a) High-resolution computerized tomography scan showed bilateral patchy consolidation; (b) The shadows were disappeared after 1 month of glucocorticoid treatment; (c) The patient was diagnosed with transbronchial lung biopsy and the pathological result showed "fibrin balls" filling within the alveolar.

Discussion

Here, we conducted a retrospective study on paralleling the clinical parameters and radiological findings of AFOP. Patients with AFOP: (1) Exhibit severe systematic inflammations and elevated serum inflammatory indicators such as CRP and ESR; (2) Have increased abnormality in liver function, impaired ability of albumin synthesis; (3) Have worse physical condition such as anemia; (4) Display lobar consolidation more commonly on high-resolution CT (HRCT) scan. AFOP patients in our reports were all pathologically diagnosed using TNB and TBLB and no patients received open-lung biopsy; however, four of these patients underwent TBLB and TNB successively, and results were exhibited stably as AFOP despite different sampling biopsy methods [Figure 1]. Although, open-lung biopsy remains the standard for the diagnosis, but a good specimen obtained via transbronchial lung biopsy and TNB may be sufficient for making a diagnosis.[12] Hence, we considered that the diagnosis for patients with AFOP included in our study is reliable.

According to the previous reports, most of the patients with AFOP had known secondary causes, including lung transplantation, infections including H1N1 virus, Chlamydia pneumonia, HIV, malignant hematological diseases, and connective tissue diseases.[7,13-16] However, as shown in Beasley's report, most of their patients were diagnosed with AFOP without any secondary cause. Beasley's report was a retrospective study which was similar to the present study

and had a limitation on exploring the secondary causes. Also, subjects in the previous studies were not limit to the specific populations such as patients with lung transplantation and HIV. Hence, it is reasonable that patients in the present study had low rate for defining a secondary cause related to AFOP. In the current report, one AFOP patient had myelodysplastic syndrome, one had acute leukemia, one had elevated RF titer, and the other one had both positive RF and ANA. Moreover, the AFOP patients in our study seemed to be more sensitive to opportunistic infections since four patients were positive for sputum fungal culture, one patient had positive blood culture for fungi and one had positive G test, and two patients were positive for *Psuedomonas* spp. in sputum. This could partly explain why the patients in the current study had higher level of CRP, ESR, and worse physical conditions of hypoalbuminemia and anemia. Also, we noticed that no patient in our study had a positive result for virus infection which was obviously different from Paraskeva *et al.*'s study,[8] and this might be due to that only CMV- and EB-DNA titer detection were included in the current study and not all patients underwent the detection.

Because patients in Paraskeva's study were after lung transplantation and were diagnosed with CLAD, the pulmonary function testing in their report was not fit for the usual situation of the nontransplantation populations. As shown in our study, AFOP patient showed a mixed ventilation dysfunction. Although there is no systemic information of pulmonary function for AFOP patient and cryptogenic organizing pneumonia (COP) patients, which share some common pathological features with AFOP were confirmed to have restrictive pattern mixed with obstructive pattern on pulmonary function which was similar to the present study.[17,18] This study observed pulmonary function for AFOP among nontransplantation patients.

Unlike to the previous description of the radiological findings for COP patients that patchy consolidation ranked the most common pattern on HRCT findings, AFOP showed a lobar consolidation on HRCT scanning. The predominant changes on CT scan in Paraskeva *et al.*'s study were GGO which was obviously different from our report.[8] However, the heterogeneity of the patients was also obvious, and most of the patients in their study were suspected with a viral infection and this may partly explain the CT scan difference between our patients and theirs. Also, the most common radiographic pattern in Beasley's description was bilateral basilar infiltrates based on chest X-ray examination which was not that comparable to our study that was based on HRCT scanning. This article describes the HRCT findings with a relatively large-scale population on nontransplantation AFOP patients.

As Beasley suggested that there were two forms of AFOP, a fulminant form leading to rapid deterioration and death which was shown in Paraskeva's patients, while our patients more likely exhibited as subacute form resembling COP from which most individuals recovered by using steroids. Hence, as a distinct entity which might be secondary to a definite disease, its prognosis might be dependent on the severity of the primary disease. According to the above findings, we suggest that you should be aware of AFOP diagnosis when you face a patient with acute inflammatory reactions, such as fever with elevated CRP, ESR, and having lobar consolidation, but they do not respond well to antibiotics use.

In conclusion, patients with AFOP have acute and severe manifestations such as long duration of fever, elevated serum CRP and ESR, abnormality in liver function, and worse physical condition of anemia and hypoalbuminemia. With distribution of lobar consolidation on HRCT which is very similar to pneumonia, AFOP patients only respond well to steroid but not antibiotic use.

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Conflicts of interest

There are no conflicts of interest.

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