



## Pathophysiology of acute fibrinous and organizing pneumonia – Clinical and morphological spectra



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### ABSTRACT

Acute Fibrinous and Organizing Pneumonitis (AFOP) is a disease with histopathological pattern characterized by the presence of intra-alveolar fibrin in the form of fibrin “balls” and organizing pneumonia represented by inflammatory myofibroblastic polyps. Symptoms of this rare interstitial pulmonary disease can be either acute or sub-acute and it can rapidly progress to death. Diagnosis should be considered in the Intensive Care Unit (ICU) if patients' symptomatology and radiology correlates with non-responding or progressive pneumonia and when morphology, on biopsies, encompasses criteria of diffuse alveolar damage (DAD) and organizing pneumonia (OP) balancing in between.

Three clinical cases of patients presenting severe lung disease requiring mechanical ventilation and prolonged intensive care fitted on the variable spectra of AFOP histopathology and had poor outcome: a 23 year-old woman had AFOP in the context of antiphospholipid syndrome pulmonary compromise; a 35 year-old man developed a lethal intensive care pneumonia with AFOP pattern registered in post-mortem biopsy; and a 79 year-old man died 21 days after intensive care unit treatment of a sub-pleural organizing pneumonia with intra-alveolar fibrin, seen in post-mortem biopsy.

The predominance of acute fibrin alveolar deposition pattern is helpful in raising AFOP differential diagnosis while organizing pneumonia pattern establishes a wider range of diagnosis that can go till solitary pulmonary nodule, remaining indefinite to suggest diagnosis. The performance time of biopsy in a larger number of clinical cases may be helpful in establishing the evolutionary morphological pattern, taking in mind the poor outcome of the disease, deserving rapid diagnosis to define treatment.

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### 1. Introduction

Acute Fibrinous and Organizing Pneumonitis (AFOP), described by Travis [1] in 2002, is a rare histological pattern of interstitial pneumonitis characterized by the deposit of intra-alveolar fibrin and diffuse organizing pneumonia within the alveolar ducts and bronchioles, with large etiological spectra. There is radiological overlap with other recognized histopathological patterns of acute pulmonary lesion, namely diffuse alveolar damage (DAD), organizing pneumonia (OP) and eosinophilic pneumonia (EP).

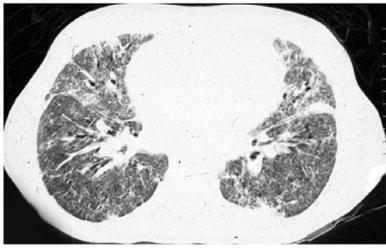
AFOP can be idiopathic or associated with known causes of underlying diseases like connective tissue disorders [1,2] (polymyositis and ankylosing spondylitis), drugs (amiodarone), occupation exposure (zoologist, coal miner, construction worker, hairspray) [1], immune system disorders (long-term steroids, poorly controlled diabetes, alcoholism, lymphoma) [1,3] and infections (*Haemophilus influenzae*, *Acinetobacter baumannii*) [1], requiring a prompt clinical evaluation.

Clinical presentation can be acute or sub-acute with dyspnea, fever and cough. These two different clinical subsets of disease may have progression described as fulminant illness with rapid progression to death (from 6 to 36 days after presentation), and there are cases that run under a sub-acute clinical evolution with recovery.

Since the first description of the disease, there have been few reports of this entity in the literature, showing both its rarity and difficult recognition. Mechanical ventilation (MV) was needed at

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**Fig. 1.** High-resolution chest CT presented diffuse ground glass opacities, intra-lobular reticulation and small cysts in the upper lobes, middle lobe and lingula, suggesting pulmonary fibrosis.

least in four of the clinical described cases [4–7], enhancing the importance of being aware of the large morphological spectra that can be present, in order to identify the disease and therefore understand different patterns of clinical evolution.

## 2. Materials and methods

### 2.1. Patient 1

A 23-year-old woman, non-smoker, complained of dry cough and nasal congestion over 2 weeks and after a few days, presented progressive stomach pain, loss of appetite, nausea, vomiting, abdominal distention and fever. She had a past medical history of thrombocytopenia of unknown etiology.

On physical examination she was pale, febrile (38.8 °C), with high respiration rate (RR), heart rate (HR) and blood pressure (BP). Pulmonary examination showed bilateral crackles. The abdomen was distended and painful.

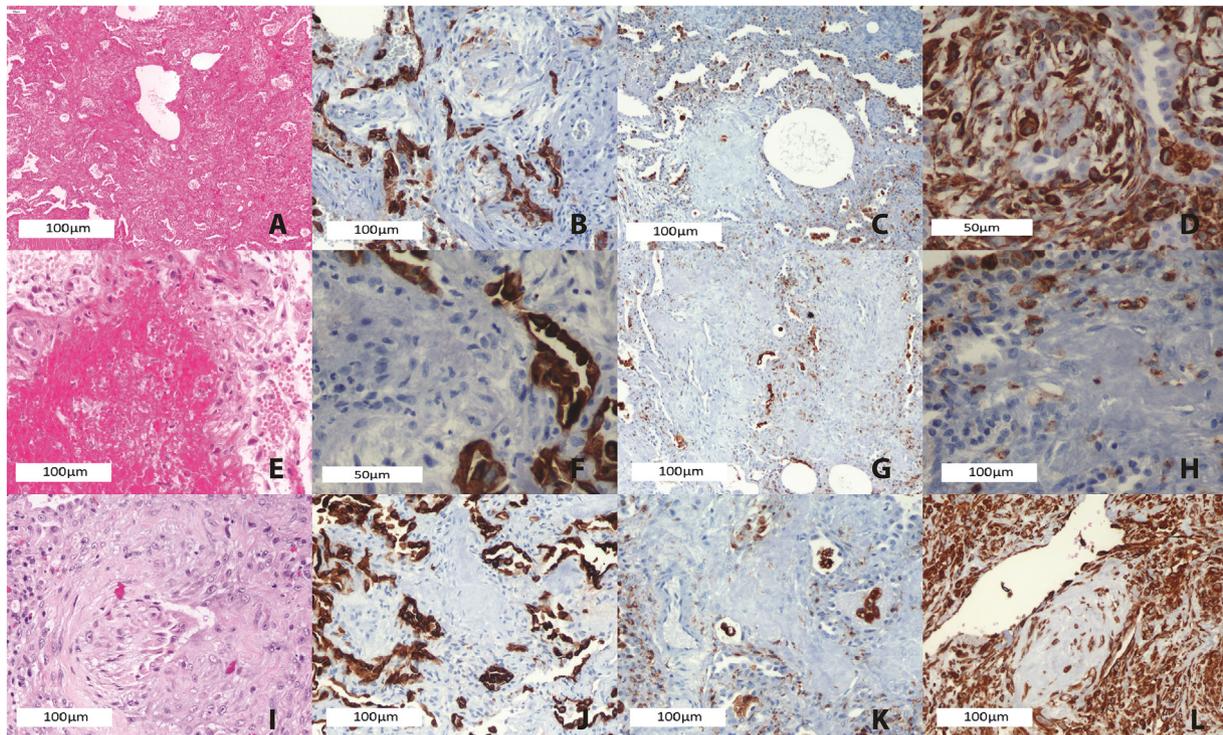
Arterial blood gases analysis showed severe partial respiratory insufficiency ( $\text{PaO}_2/\text{FiO}_2$  183 mmHg). She had normochromic normocytic anemia, thrombocytopenia, leukocytosis, altered coagulation, elevated C-Reactive Protein (CRP), liver enzymes and serum creatinin. Chest X-ray presented bilateral interstitial infiltrates with exsudation.

The patient was admitted to the Intensive Care Unit (ICU) with Community Acquired Pneumonia (CAP) and severe respiratory failure – Acute Physiology and Chronic Health Evaluation (APACHE) II of XVI and needed mechanical ventilation (MV). Infectious agents' culture exams were negative.

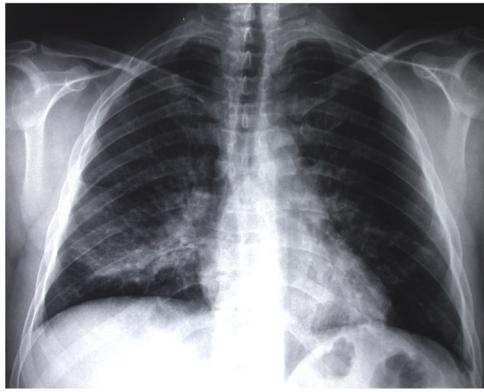
At day 20, she developed bilateral pleural effusion and bilateral pneumothorax, complicated with bronchopleural fistula that required surgery. High-resolution chest computer tomography (HRCT) presented diffuse ground glass opacities, intra-lobular reticulation and small cysts in the upper lobes, middle lobe and lingula, suggesting pulmonary fibrosis (Fig. 1).

Surgical lung biopsy performed during surgical intervention revealed a lobular architectural disarrangement, with both recognized patterns of DAD and OP, showing up as intra-alveolar hyaline fibrin with focal hemorrhage, associated with terminal airways alveolar myofibroblastic inflammatory polyps (young fibroblastic proliferation in myxoid matrix) and focal peripheral collagen scars – AFOP with a balanced approach, valuing equally both the interpretation of acute fibrin deposition and OP with scarce macrophages (Fig. 2 A and B). At this point, the patient started steroid therapy.

The patient presented then thrombosis, positive lupic anti-coagulant with elevated kaolin-cephalin time and persistent thrombocytopenia, leading to the diagnosis of antiphospholipid syndrome supported by positivity of anticardiolipin antibodies and B2 glycoprotein I. Low molecular weight heparin and antiplatelet agent along with steroids was prescribed.



**Fig. 2.** A – D: Patient 1. A – HE X 100; alveoli full of fibrin and peripheral fibroblasts. B – CK7 X 100; alveoli distortion by foci of young fibroblasts proliferation intermingled with fibrin matrix. C – CD68 X 100; macrophages surrounding fibrin balls. D – Vimentin X 200; inflammatory intra-alveolar myofibroblastic polyp. E – H: Patient 2. E – HE X 100; intra-alveolar hyaline membrane balls. F – CK7 X 200; hyaline membranes and inflammatory cells occupying alveolar spaces together with pneumocytes II hyperplasia. G – CD68 X 100; scarce number of macrophages surrounding hyaline balls. H – Vimentin X 100; reduced number of fibroblasts around a hyaline ball. I – L: Patient 3. I – HE X 100; fibroblasts proliferation and collagen deposition intermingled with fibrin membranes in alveolar spaces. J – CK7 X 100; homogeneous alveolar occupation by both fibroblasts and fibrin. K – CD68 X 100; macrophages clusters in alveolar spaces. L – Vimentin X 100; fibroblasts around a remnant of a fibrin ball.



**Fig. 3.** Chest X-ray. Heterogeneous consolidation in right pulmonary field.

The patient was in the ICU for 7 months and then transferred to a Medicine ward where she died 10 months after the emergency room admission.

### 2.2. Patient 2

A 35-year-old man, non-smoker, was admitted to the emergency room complaining of sore throat, fever and cough with muco-purulent sputum over the previous 3 days, progressively worsening. Past medical history included head trauma, partial amputation of the left foot 14 years before and psychiatric follow-up.

On physical examination, the patient had fever (38 °C), high RR and HR and oxygen saturation of 90% at room air. A purulent exudate covering the tongue, tonsils, uvula and palate, as well as purulent nasal secretions and painless cervical lymph nodes were observed, without changes on pulmonary auscultation.

White blood cell (WBC) count, CRP, serum creatinine and blood urea nitrogen (BUN) were elevated. ABG showed hypoxemia with hypocapnia (PaO<sub>2</sub>/FiO<sub>2</sub> 272 mmHg). Chest X-ray showed heterogeneous consolidation with imprecise limits in the lower third of the right pulmonary field (Fig. 3).

The patient was admitted to the ICU on the same day with CAP, partial respiratory insufficiency, acute renal failure and sepsis (APACHE II of IX). He required mechanic ventilation, antibiotic therapy and hemodialysis.

On the 4<sup>th</sup> day, PaO<sub>2</sub>/FiO<sub>2</sub> ratio was 80 mmHg and steroids were prescribed on the 10<sup>th</sup> day.

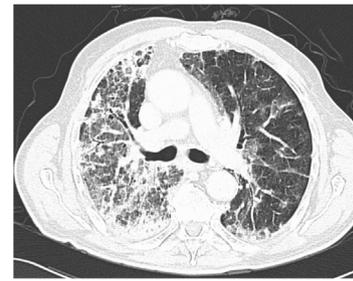
Cultural exams were negative: bronchoalveolar lavage (BAL) showed neutrophils predominance (75%) and a CD4/CD8 ratio at 1.30. Autoimmune, bacterial and viral serologies were persistently negative.

The patient's condition kept worsening despite all efforts and died on day 20 with multiple organ failure.

A small *post-mortem* lung tissue biopsy showed organized miofibroblastic proliferation foci with macrophages, embedded in a myxoid matrix in bronchioles and alveolar ducts lumina with a predominant pattern of fibrin balls occupying surrounding alveoli, without relevant inflammation corresponding to AFOP with relevance for the DAD pattern (Fig. 2 C and D).

### 2.3. Patient 3

A 79-year-old-man, former smoker (6 units' pack-year) complained of moderate effort dyspnea, productive cough with mucous sputum, fatigue, anorexia and weight loss (5 Kg in the previous week). There was a medical background of myocardial infarction a year earlier with atrial fibrillation. Regular medication included



**Fig. 4.** Chest CT. Bilateral consolidation areas and scattered centimetric bullae. Densification ground glass areas in the right upper lobe, traction bronchiectasis, interlobular septa thickening and subpleural cystic lesions.

furosemide, warfarin, amiodarone, perindopril, carvedilol and atorvastatin.

On physical examination, body temperature was 36.8 °C, RR was 20 cycles/min, HR was 98/min, BP was 150/90 mmHg and oxygen saturation was 95% at room air. Lung auscultation revealed bibasilar inspiratory crackles.

Laboratory exams exhibited elevated creatinine, CRP and leucocytes. ABG showed hypoxemia (PaO<sub>2</sub>/FiO<sub>2</sub> 248 mmHg) and in chest X-ray, there were bilateral consolidation areas resembling nodular opacities.

HRCT revealed mediastinal enlarged lymph nodes, bilateral consolidation areas and scattered centimetric bullae. In the right upper lobe, there were ground glass densification areas, traction bronchiectasis, interlobular septa thickening and subpleural cystic lesions (Fig. 4).

Additional evaluation showed elevated tumoral marker Cyfra 21.1 (10 ng/mL; normal <3.3) and negative autoimmunity exams. The erythrocyte sedimentation rate was 50 mm/h, serum angiotensin converting enzyme level was normal as well as immunoglobulins electrophoresis.

On day 10 there was clinical worsening, with respiratory failure (PaO<sub>2</sub>/FiO<sub>2</sub> 86 mmHg) and MV was needed (APACHE II of 24). The patient started antibiotherapy.

On the 6<sup>th</sup> day in the ICU steroids were added to treatment, and on the 12<sup>th</sup> day a Carlens' Mediastinoscopy was performed and the enlarged lymph nodes presented the normal morphology with high number of pigmented macrophages.

There was progressive clinical, analytical and radiological deterioration and the patient died 21 days after admission in the ICU.

*Post-mortem* lung tissue biopsy showed pulmonary parenchyma morphological distortion with subpleural scars with miofibroblasts and collagen deposition, without remnant epithelial cells; well organized miofibroblastic inflammatory polyps filling bronchioles and alveolar spaces together with macrophage desquamation; small fibrin plugs within alveolar lumina completed an AFOP morphological pattern with dominant histopathological features of organizing pneumonia (Fig. 2 E and F).

## 3. Discussion

AFOP is a rare histological pattern of interstitial pneumonitis with acute or sub-acute clinical presentation, with clinical and histopathological features that overlap with DAD, OP and EP, but with a different outcome and well-established morphological criteria that make it a distinct entity. The AFOP pattern differs from DAD by the absence of the classic hyaline membrane formation on the latter and instead presents a patchy distribution of alveolar fibrin "balls". Patients with DAD pattern have a clinical presentation of Acute Respiratory Distress Syndrome (ARDS) with acute respiratory failure usually requiring MV. The mortality rate is high, between 50 and 60%. Although both diseases show similar clinical evolution,

which led Travis to think that the AFOP pattern could represent a fibrinous variant of DAD, almost all patients with DAD require ventilation support whereas only 30% (5 patients) of first series of AFOP patients described needed it. However, all of those five patients died in the course of the disease. AFOP seems to represent a distinctive and underreported pattern of lung injury [1].

OP pattern is characterized by the presence of fibroblastic Masson bodies within the bronchioles, alveolar ducts and alveoli, as seen in OP/Bronchiolitis Obliterans Organizing Pneumonia/Cryptogenic Organizing Pneumonia with different amount of fibroblastic collagen matrix deposition as seen in the three presented cases. AFOP differs from the histological pattern of EP through the lack of tissue and peripheral eosinophils.

In the reported cases, the dominant symptoms were dyspnea, cough (3 patients) and fever (2 patients). Hemoptysis and constitutional symptoms were not significant.

In the first patient biopsy, intra-alveolar fibrin and OP morphology were present; although without recognized occupational exposure, an autoimmune disease was established. The second patient had no medical or environmental factors to be associated with the development of AFOP and the biopsy showed a DAD pattern over imposing on OP. In the third case, however, the patient had an amiodarone intake of 200 mg id for about one year, like that described by Travis in one of the patients of his series [1], and presented AFOP with OP predominance.

In patients with SARS (Severe Acute Respiratory Syndrome) Hwang et al. [8] described in Toronto epidemic surgical biopsies with DAD pattern with hyaline membranes and interstitial thickening or predominantly composite AFOP pattern. Once again, this study suggests that AFOP could represent a histological variant of DAD, which may explain the few cases reported and be included on this category, or difficulties in morphology interpretation and in histological description might be assumed, as emphasized by Travis [1].

Cincotta et al. [4] published a retrospective study of lung biopsies of children with ARDS. In this study, it was suggested that AFOP might be a feature of the later phases of acute lung injury where DAD might have been predominating in the initial phases. The fact that AFOP is a late feature explains why this entity has only been recognized in recent years: more patients are surviving the initial stages of lung injury.

In this small series of three cases where sampling error has to be emphasized, there were CT patterns that can be correlated with the temporal evolution of disease, validated through the predominant pattern or both of DAD followed by OP scarring.

In the first and second cases, there was a good correlation between radiology and microscopic findings: on the first one the chest X-ray was consistent with pneumonia, with fibrin occupying alveolar spaces and beyond ground glass pattern. The second patient chest X-ray showed bilateral cotton-like opacities well supported by DAD pattern predominance in the biopsy. In the third patient, however, bilateral consolidation areas were first considered metastatic disease rather than pneumonia, raising the common difficulties when organization is relevant. Kobayashi et al. [10] described a clinical case of AFOP whose radiographic presentation was that of a solitary pulmonary nodule, corresponding to a dominance pattern of OP in AFOP and corroborating the organizing predominance of OP in AFOP.

Based on these simple data it might be possible to define a characteristic radiographic pattern that would help to overcome different surgical sampling raising difficulties to integrate the variable morphology in the clinical parameters. However, in these three cases, there was not a common pattern of presentation or microscopy-CT correlation, making the task difficult, but supporting a possible spectral evolution of the disease to be researched in future cases.

Treatment modalities applied included antibiotic and steroids, alone or combined, diuretics and MV, the last one required in 5 patients (30%). However, no treatment was yet identified as the most advantageous [1]. Some reported cases of AFOP in which steroids and immunosuppressive agents (cyclophosphamide, mycophenolate) [7,11] were used, with good clinical outcome.

In Beasley cohort, 9 of the 17 patients died of the disease. The follow-up ranged from 6 days to 5 years with two distinct patterns of disease progression: rapid progression to death and sub-acute course with recovery [1].

The three patients reported in this paper started antibiotic therapy and steroids were added latter. In two cases, the patients had fulminating illness, with progression to death in about 20 days. The first patient was submitted to prolonged MV with only a short period of spontaneous ventilation and despite all therapeutic efforts, thrombotic recurrent complications led to death in the 10<sup>th</sup> month of hospital stay. It is relevant to mention that these two patients had DAD pattern in the biopsies superimposed over the OP pattern that predominated in the biopsy of the third patient, showing that DAD pattern dominance is a bad prognostic indicator.

Diagnosis of AFOP should be considered in the ICU when patients are non-responding or have progressive pneumonia pattern. In fact, a cause for non-resolving pneumonia is the non-infectious etiology of pulmonary infiltrates that can mimic infectious pneumonia [12]. Numerous disorders like OP, EP, acute interstitial pneumonia, pulmonary alveolar proteinosis, sarcoidosis and more recently AFOP, may mimic infectious pneumonia, and the latest diffuse lung consensus advises the approach to the correct diagnosis when a surgical biopsy has to be considered. As stated by Gomes et al, AFOP is a non-specific reaction to several agents, and the clinical presentation is heterogeneous with clinical course defined by the severity of the fundamental disease [13].

In patients with progressive organ, failure there is an urgent need for a definitive diagnosis. Trans-bronchial lung biopsy can be performed with a reasonable diagnostic yield and an acceptable risk in mechanically ventilated patients. Open-lung biopsy in critically ill patients requiring MV usually is performed outside of the ICU but sometimes at the bedside [14].

Patients with lung disease of unknown etiology unresponsive to empirical treatment demand an accurate histological diagnosis for specific treatment prescription, since the clinical course seems influenced by the severity of the underlying disorder [15]. AFOP is uncommon, and the diagnosis may not be present in the clinician differential hypothesis; the delay in diagnosis may be fatal, so histological diagnosis is of pivotal importance, with some patients benefiting of therapy with steroids and immunosuppressive agents [16].

When all measures and diagnostic procedures fail to provide a definitive diagnosis with a fatal outcome, *post mortem* lung tissue study provides an important tool for the understanding of the underlying pathologic process in order to improve, in future cases, diagnosis and treatment [17,18].

Reporting these three clinical cases had the purpose to highlight the acute presentation of AFOP as a particular lung disease more recently described, initially confused with pneumonia, running with severe respiratory failure and immediate need for mechanic ventilation, with no response to antibiotics or steroids. More clinical and radiographical data are needed to characterize this controversial entity and to understand how it can be dealt with to improve patients' management, supported by the apparent correlation of both diagnostic images of CT and histopathology. These studies would emphasize guidelines to establish the surgical biopsy timing and correspondent morphological interpretation.

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