Acute fibrinous and organizing pneumonia associated to hematological malignancy: a case report

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ABSTRACT

Background: The acute fibrinoid and organizing pneumonia (AFOP) is an histopathological pattern, characterized by the presence of intra-alveolar fibrin and organizing pneumonia. AFOP is an entity that can be either idiopathic or associated with several clinical conditions including infectious diseases, drug interactions, and cancer. No specific treatment exists for AFOP but an excellent response to the steroid therapy has been observed.

Case Presentation: A 55-year-old man was admitted to the hospital with pneumonia diagnosis. He did not respond to antibiotics, but an excellent response to steroids was observed. Lung biopsy was done that supported the diagnosis of AFOP. After discharge, bone marrow aspiration was repeated and the diagnosis of acute myeloid leukemia with myelodysplasia-related changes was confirmed. The patient started chemotherapy but after several infections and cerebrovascular complications, the patient passed away.

Conclusion: AFOP is a rare entity associated with several diseases and often misdiagnosed as an infectious process. The diagnosis is based on histopathology and the treatment is based on steroids. Many questions still remain unanswered regarding this disease.

Keywords: Organizing pneumonia, fibrin, hematological malignancy, glucocorticoids.

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Background

The acute fibrinoid and organizing pneumonia (AFOP) is a histopathological pattern characterized by the presence of intra-alveolar fibrin and organizing pneumonia [1]. AFOP is an entity that can be either idiopathic or associated with several clinical conditions including infectious diseases, drug interactions, and cancer. It presents unspecific symptoms with respiratory and constitutional complaints, and radiographic findings with multiple distinctive patterns. No specific treatment exists for AFOP but an excellent response to steroids therapy has been observed [1–3].

AFOP is still not a well understood entity, and is defined with a distinct histological pattern that can appear together with other entities, including hematological malignancies [3].

The authors describe a case of a man admitted to hospital with pneumonia diagnosis with a previous history of myelodysplastic/myeloproliferative (MDS/MPF) neoplasm, unclassifiable. The patient was unresponsive to antibiotics but had an excellent response to steroid therapy, this leads to perform lung biopsy, in which the histological results supported the diagnosis of AFOP.

Case Presentation

We describe a case of a 55-year-old Caucasian man, with a history of arterial hypertension since 12 years, chronic kidney disease stage III of probable etiology of hypertension (patient's basal creatinine 2.7 mg/dl), ischemic cardiopathy, obstructive sleep apnea, diabetes mellitus type 2, dyslipidemia, and microangiopathic hemolytic anemia, which revealed a MDS/MPF neoplasm, unclassifiable, followed by hematological consultation and medicated with prednisolone, maximum 60 mg/day, with a progressive decrease. The patient was hospitalized with community acquired pneumonia, without complications. One month later, he was presented in the emergency department with fever, dry cough, and wheezing; since the last admission there was progressive worsening. The patient complained of 10 kg weight loss in a month. On physical examination, he was hypotensive (93/55 mmHg) with being responsive to fluid therapy, apiretic (36.3°C after acetaminophen), heart rate 73/minute, pulse oximetry 95%, and eupneic. Rhonchi was present in lung auscultation. The remaining physical examination was normal. His laboratory blood count revealed microcytic anemia with hemoglobin 7.6 g/dl (normal range 13–18 g/dl); hematocrit 26.7% (43%–55%); medium corpuscular volume 72.2 fl (87–103); medium globular hemoglobin concentration 28.5 g/dl (28–36), leukocytosis 13,810/µl (4,000–11,000/µl); platelets 256,000/µl (150,000–400,000/µl). It was described as

the presence of schistocytes and anisopoiquilocitosis in peripheral blood (described in previous laboratory count too). Other alterations were observed: renal function worsened with serum creatinine of 3.89 mg/dL (0.67–1.17) and blood urea nitrogen of 161 mg/dL (10–50); C-reactive protein 308 mg/l (<3); lactate dehydrogenase 304 U/L (135–225); and total hyperbilirubinemia 1.51 mg/dL (<1.2) the cost of direct bilirubin. In arterial gasometry, the patient presented compensatory respiratory alkalosis (pH 7.45; pCO_2 23 mmHg; pO_2 84 mmHg; HCO_3^- 15.9 mmol/l, lactates 1 mmol/l). Urinary antigen test for *Streptococcus pneumoniae and Legionella pneumophila* was negative. The chest X-ray revealed diffuse bilateral reticulonodular infiltrates (Figure 1).

The patient was admitted to hospital with sepsis due to a pulmonary infection, treated with piperacillin/tazobactam 2.25 g and IV fluid replacement therapy (2 l/24 hours). He had clinical improvement in the first 48 hours without spiking temperature. He underwent thoracic computed tomography (CT) that showed the presence of some nodes in higher number than usual of about 9 mm, the lung parenchyma with micronodular densifications in a lymphatic distribution, involving sub-pleural regions and infiltrating through bronchovascular beams; a greater nodularity located in the posterior segment of the right upper lobe of about 12 mm was observed (Figure 2). This finding indicated the presence of an atypical infectious process. Based on these results, azithromycin 500 mg/day was started. Five days after hospital admission, the patient showed clinical worsening with general malaise, dyspnea, pleuritic pain, and fever (maximum 39.5°C, with little response to acetaminophen); polypnea (40/minute), and bilateral lower thirds rales in lung auscultation. The laboratory blood count showed worsening anemia 7.4 g/dl; 10,180/µl leukocytes with 75% neutrophils and C-reactive protein 421.3 mg/l; arterial gasometry showed compensated respiratory alkalosis with hypoxia (FiO_2 36%, pH 7.412, pCO_2 28.2 mmHg; pO_2 76.8 mmHg; HCO_3^- 17.6 mmol/l; paO_2/FiO_2 213); and chest X-ray showed a worsening of diffused bilateral infiltrates. Microbiological and microbacteriological cultures in blood, urine, and sputum only grew yeast strain in sputum, without other strains. It was decided to extend antibiotherapy spectrum with vancomycin, micafungin, and imipenem and cilastatin, with prednisolone (25 mg, 8/8 hours). Twenty-four hours after the beginning of treatment, the patient showed a clear clinical and radiological improvement, with almost resolution of radiological infiltrates, in probable context of steroids (Figure 3). To clarify the situation, he realized a transthoracic CT-guided biopsy and bronchofibroscopy, which neither revealed macroscopic alterations; malignant cells on cytology or bacteriological, microbacteriological or virologic growth, highlighting only polymerase chain reaction positive for *Pneumocystis jiroveci*. In bronchoalveolar lavage (BAL), differential cell count revealed neutrophils (16.2%) and eosinophils (5%). Due to the previous history of immunosuppression by prolonged corticoid, bilaterally diffused infiltrates, dyspnea and dry cough, hypoxia, with no alternative diagnosis, it was decided to start the administration of trimethoprim/sulfamethoxazole (960 mg/day, renal dosing). Then, the pulmonary histology showed organizing pneumonia lesions and focally fibrinoid material in the alveolar spaces with negative microorganism's search (Figure 4). Thus, antibiotics were suspended and steroids were started to 1 mg/kg/day. He was discharged with a diagnosis of organizing pneumonia and acute fibrinoid likely in infectious context or hematologic malignancy.

After discharge from the hospital, the patient maintained the follow-up in Hematology–Oncology. To clarify the presence of hematological disease, the bone marrow aspiration was repeated. Now, the patient had more than 30% of blast cells in peripheral blood; the bone marrow aspirate immunophenotype revealed that 77.6% of cells were from the erythroid line, with marked changes of CD36 expression and granulocyte population with anomalous maturation. The CD34+ cells were CD13+, CD117+, and HLA-DR+. Using conventional cytogenetic analysis, 20 metaphases were studied, 10 of which were normal and the others had changes consistent with cytogenetic progression of cancer with karyotype 44, *X*, −*Y*, −5, del (7*q*), add (12*p*), −17, −22 (diagnosis karyotype 44, *X*, −*Y*, −5, del (7*q*), add (12*p*), −17, +mar [20]). Therefore, altogether this information lead to the diagnosis of acute myeloid leukemia (AML) with myelodysplasia-related changes as defined by the 2008 **World Health Organization** (WHO) classification system [4]. After this observation in clinical consultation, the patient was admitted to the hospital due to an extensive cellulitis in both periorbital areas. During this admission, it was decided to begin cytoreduction with hydroxyurea 2 g/day, which proved ineffective, requiring increased dose to 4 g/day that completed 5 days with a favorable response. After the Hematology–Oncology group consultation, it was decided to begin induction with cytarabine in standard dose (100 mg/m^2), reduction of daunorubicin dose (50 mg/m^2), and etoposide was omitted. Eight days after the beginning of induction cycle, the patient started altered level of consciousness with subsequent seizures. The patient underwent cerebral CT that revealed right parietal-occipital stroke. The patient had seizures associated with macroaspiration episode requiring orotracheal intubation. Because of comorbidities, hematological disease with poor prognosis, several infections complications during hospitalization, with many antibiotics, and worsening of AFOP, it was decided to suspend therapy keeping only support measures. The patient died after 22 days of hospitalization.

Discussion

In 2002, a new histological pattern of lung injury, characterized by the presence of intra-alveolar fibrin like balls

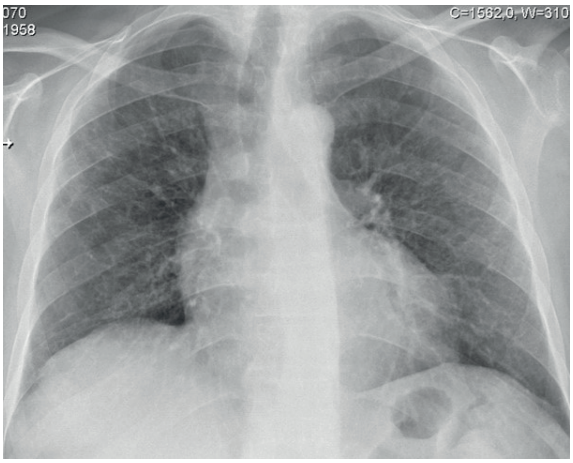

Figure 1. *Chest X-ray with bilateral diffuse reticulonodular infiltrates.*

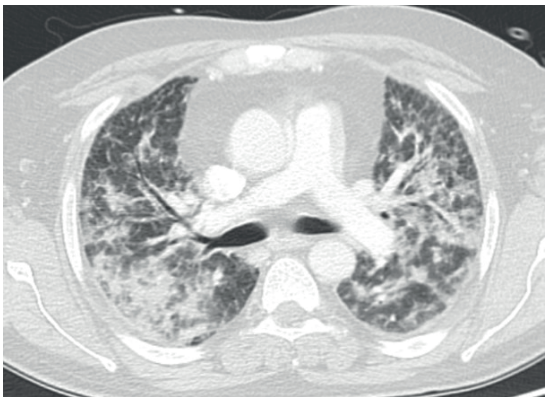

Figure 2. *Thoracic CT.*

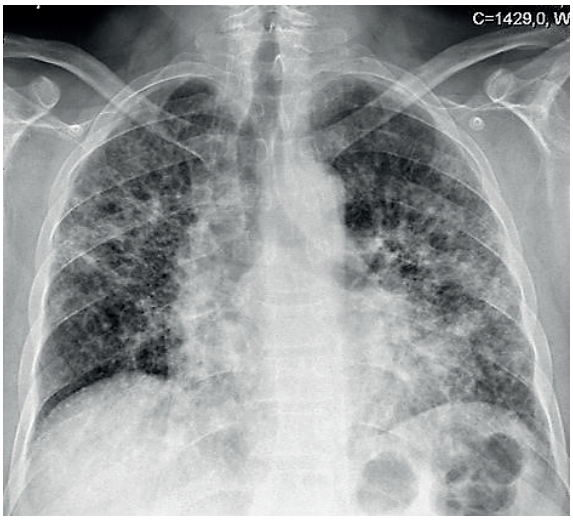

Figure 3. *Chest X-ray 24 hours after beginning of steroids.*

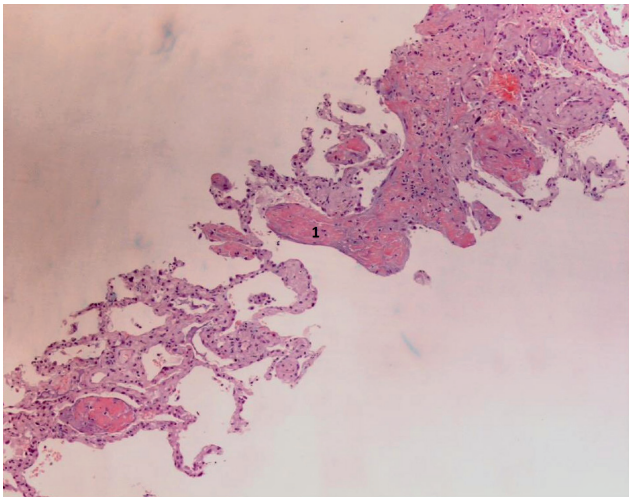

Figure 4. *Lung biopsy histology (1 - fibrinoid material and inflammatory cells in the alveolar spaces).*

and organizing pneumonia changes with diffused distribution was described [1]. This new pattern differs from more classical pattern of diffused alveolar damage by the absence of hyaline membranes, from organizing pneumonia for not presenting bodies of Masson and from eosinophilic pneumonia, because despite the AFOP can have eosinophils, it is not a dominant feature [1,3,5–7].

The AFOP is more prevalent among men, between the 5th and 6th decade of life [1,2]. It can have two different presentations: one subacute with symptoms with less than 2 months, with favorable evolution, presenting radiologically with focal or diffuse abnormalities, an indistinguishable pattern of organizing pneumonia; and the other acute, a rapidly progressive disease, with high mortality and essentially bibasilar consolidations in imaging studies, similar to diffused alveolar damage [1–3,5]. The 17 cases described by Beasley had constitutional and respiratory symptoms, being dyspnea, fever, and cough, the most common [1–3,5–12]. Also, there are cases described with pleuritic pain [1,5,11,12]. Radiologically, this is a disease that can show multiple patterns like bilateral basal, peripheral (most common), diffused distribution, or lung solitary nodule [1–3,5,9–13]. This patient presented a subacute course with cough, fever, and dyspnea with about a month and half of evolution and subsequently pleuritic pain. In the imaging studies, the chest CT showed lung parenchyma with diffused micronodules, which was almost completely reversed after steroids treatment began. The patient died in a short time after diagnosis, not for the evolution of lung disease but for multiorgan complications of his hematological disease.

The bronchofibroscopy did not show macroscopic changes and microscopy demonstrated mostly neutrophils; findings similar to other cases [5]. The BAL is not conclusive in known cases of AFOP and a biopsy for histopathology is always required. The definitive diagnosis is made by histology and the most part of authors recommended that this should be done by video-assisted thoracoscopic surgery, since the sample may otherwise be insufficient [2,7,11]. In this case, the sample was made

by CT-guided transthoracic biopsy, because the patient did not have clinical conditions for surgery and the sample was sufficient for the diagnosis.

There are no specific treatments for AFOP, so various agents are being used in several cases. Steroids and antibiotics are used in most cases [2,6,14]; but there are cases successfully treated with cyclophosphamide [1,8] and mycophenolate mofetil [8]. Up to 30% of cases require mechanical ventilation [1,5,14]. As in other similar cases; initially, this patient was treated with antibiotics, because clinical, radiological findings, and rising of acute-phase reactants were compatible with infection [2,8,9,12]. In the literature, there is a case of a patient that responded to the antibiotic treatment, which suggests a role for it in AFOP treatment [13]. In this case, after verification of the absence of microorganisms in sputum, blood, and BAL cultures, the antibiotic was discontinued, keeping steroids 1 mg/Kg/day, with good clinical response. The optimal duration of treatment has not yet been reported, but the studies indicate that the steroids should be maintained for 12–24 months, with a gradual weaning, depending on clinic and radiologic findings [5,8].

The AFOP is an entity that can be idiopathic or associated with several diseases as: drug exposure, infections, connective tissue diseases, malignant diseases, and others [1–3,5–8,12–15]. This patient had a history of MDS/MPF neoplasm, unclassifiable, however, after this acute episode, the patient had repeated marrow aspiration that showed AML. The patient showed 30% blasts in peripheral blood, the granulocyte population also had abnormal maturation, CD34+ cells were positive for CD117, CD13, and HLA-DR. The cytogenetic study also revealed cytogenetic progression of the tumor, with high genetic risk, including del (5) and del (7). According to WHO 2008 criteria, the presence of more than 20% blasts, history of MDS/MPF, the absence of prior cytotoxic treatment, and recurrent cytogenetic abnormalities fit in the diagnosis of AML with myelodysplasia-related changes. The patient prognosis belonged to the group of adverse prognosis of the European Leukemia Net, given the del (5), del (7) and the complex karyotype [16].

In the literature, cases of a patient with AML after hematopoietic stem cell transplantation [7,15]; AFOP associated to acute B-cell lymphoblastic leukemia [13] and AFOP with myelodysplastic syndrome [14] are described, and a successful treatment with corticoids and then, ventilator weaning [14] are described. This case is a patient with diagnosis of AML after MDS. So, this may be a new case in the literature, a new entity associated to AFOP: AFOP associated with acute myeloid leukemia, without previous treatment; AML with myelodysplasia-related changes.

Conclusions

Acute fibrinous and organizing pneumonia is a rare entity associated with several diseases and often misdiagnosed as an infectious process. The diagnosis is based on the histopathology and a good response to steroids is expected. Many questions remain unanswered regarding this disease; the optimal clinical management, the best treatment duration, and the related diseases. In this report, we present a case with a new association, AFOP with acute myeloid leukemia.

Acknowledgement

None.

List of abbreviations

AFOP	Acute fibrinoid and organizing pneumonia
AML	Acute Myeloid Leukemia
BAL	Bronchoalveolar lavage
CD	Cluster of Differentiation
CT	Computed tomography
FiO_2	Fraction of inspired oxygen
HLA	Human leukocyte antigen
MDS	Myelodysplastic
MPF	Myeloproliferative
pCO_2	Partial pressure of carbon dioxide
pO_2	Partial pressure of oxygen
WHO	World Health Organization

Consent for publication

Informed consent was taken from the patient, before his death, to report this case.

Ethical approval

Not applicable.

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Specialty

Internal Medicine

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Summary of the case

Patient (gender, age)	1	Caucasian man, 55 years old
Final Diagnosis	2	Acute fibrinous and organizing pneumonia associated to acute myeloid leukemia
Symptoms	3	fever, dry cough and wheezing, weight loss
Medications (generic)	4	Antibiotics, steroids
Clinical Procedure	5	Chest X-ray, thoracic computed tomography, biopsy
Specialty	6	Internal Medicine