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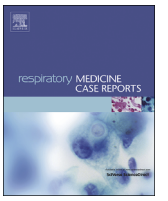

Case Report

Acute fibrinous and organizing pneumonia associated with Candida: A case report

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ABSTRACT

Background: Acute fibrinous and organizing pneumonia (AFOP) is a rare form of pneumonia, is characterized by the deposition of fibrin in alveoli, the formation of fibrin spheres, and deposition of fibrin in alveolar junctions and bronchioles adjacent to or adjacent to the alveoli, forming institutional loose connective tissue.The clinical characteristics of AFOP lack specificity. We report a special case of AFOP that may be associated with *Candida*, so as to improve our understanding and diagnosis of AFOP.

Result: In this patient who was early misdiagnosed with community-acquired pneumonia (CAP), the empirical anti-infective treatment was ineffective, and various infectious and non-infectious factors were excluded. Flexible bronchoscopy was subsequently performed, and metagenomics Next Generation Sequencing (mNGS) of Bronchoalveolar lavage fluid (BALF) showed *Candida albicans*, and further ultrasound interventional percutaneous and lung puncture biopsy was performed to diagnose AFOP according to pathology, while mNGS of lung pathological tissue also suggested *Candid.* The patient recovered well on corticosteroids.

Conclusion: The clinical manifestation, laboratory examination and imaging examination of AFOP has no specificity, lung biopsy and pathological examination should be carried out to make a clear diagnosis by comprehensively considering the clinical manifestations, auxiliary examination, pathology and other aspects of the patients. After definite diagnosis, it is still necessary to rule out various diseases and environmental exposure and further classify them as idiopathic or secondary, so as to choose monotherapy or combination therapy.

1. Background

Acute fibrinous and organizing pneumonia (AFOP) is a rare form of pneumonia, is characterized by the deposition of fibrin in alveoli, the formation of fibrin spheres, and deposition of fibrin in alveolar junctions and bronchioles adjacent to or adjacent to the alveoli, forming institutional loose connective tissue.The clinical characteristics of AFOP lack specificity. AFOP can be idiopathic or associated with known causes, In most cases, AFOP can be linked to a variety of factors, such as autoimmune diseases, lung infections, drugs, chemical or occupational exposures.In this report, we report a case of a female patient diagnosed with idiopathic AFOP who was early misdiagnosed with community-acquired pneumonia (CAP). However, the patient recovered well on corticosteroids. The patient has given informed consent for publication of the case.

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2. Case report

A 40-year-old woman, with no significant medical history, complained of cough for a 20-day history, and no fever, chills and night sweats.In addition, there was no history of poisoning, smoking or exposure to any pets and dusty environmental conditions.

The patient was admitted to the hospital on November 18, 2022, on initial examination, she was no febrile (36.8 °C).The blood pressure, heart rate and respiratory rate were 113/72 mm of mercury (mm Hg), 106 beats per minute and 21 breaths per minute, respectively.The physical examinations did not exhibit any abnormity.Laboratory testing showed the white blood cell count of 8.5×10^9/L, with neutrophil ratio of 87.6 %. The C reactive protein was elevated to 65.18mg/L.The PCT was slightly elevated (0.1ng/ml). The thoracic computerized tomography (CT) showed flaky shadows in the dorsal segment of the right lower lung, inner and posterior basal segments, ground glass nodules in the outer basal segment of the left lower lung, a little inflammation in the posterior basal segment of the left lower lung, and enlargement of mediastinal lymph nodes (Fig. 1A). Sputum cultures, and sputum acid-fast bacilli showed no organisms. Additional tests including mycoplasma chlamydia antibodies, influenza virus, cryptococcal antigen, aspergillus antigen, fungal G-test,GM-test,TB-DNA, antinuclear antibodies, anti-neutrophil cytoplasmic antibody, and tumor markers (CEA, CYFRA 211, CA 125, CA153, CA 199) were all negative. Therefore, the patient was diagnosed as hospital acquired pneumonia initially and started to take 3 g Piperacillin/Sulbactam once every 8 hours. On the 5th day of hospitalization, piperacillin sulbactam was switched to Sitafloxacin (100mg daily). However, her symptoms did not respond to above antibiotics therapy. On November 21, flexible bronchoscopy followed by bronchoalveolar lavage (BAL) in the superior segment of the right lower lung was performed and revealed no endobronchial lesion. Bronchoalveolar lavage fluid (BALF) cultures and molecular diagnostic test for tuberculosis was negative, metagenomics Next Generation Sequencing (mNGS) of the BALF demonstrated *Candida albicans* (the number of sequences is 67). At this time, pulmonary CT scan showed more flaky shadows in the dorsal segment and inner and posterior basal segments of the right lower lung (Fig. 1B). For further diagnosis, 4 lower right lung biopsy specimens were taken by the ultrasound interventional percutaneous and lung puncture biopsy on November 25, the pathology (Fig. 2) demonstrated intra-alveolar spaces containing fibrin globules, histopathocytes and organic foci; Mild chronic interstitial infiltrate and hyperplasia of type II pneumocytes were also shown; Telangiectasia, lymphocyte infiltration; The special staining was negative. The tissue changes are consistent with exudative pulmonary cellulose inflammation with organochemical foci formation. Although the pathological tissue culture were negative, mNGS of the pathological tissue demonstrated *Candida* (the number of sequences is 68).

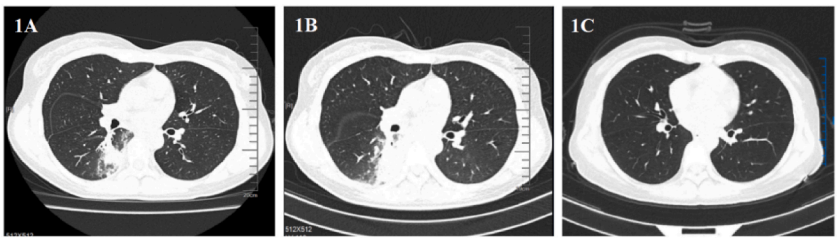

Fig. 1. The changes of chest CT during the course of the disease. A: chest CT at 2022-11-17 before admission showed patchy shadow in the dorsal-medial and posterior basal segment of the right lower lung, with a little inflammation in the posterior basal segment of the left lower lung; CT suggested that the mass shadow in the dorsal-medial and posterior basal segment of the right lower lung increased before admission, and a little inflammation in the posterior basal segment of the left lower lung; C: 2023-3-15 chest CT suggested that the focus disappeared completely after 4 months of hormone treatment.

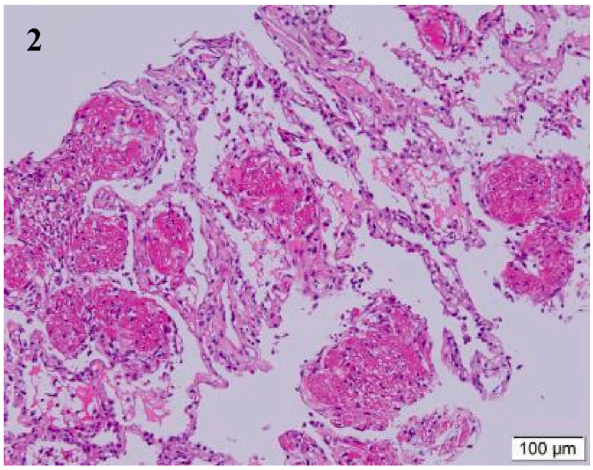

Fig. 2. Pathological examination of the right lower lung: the formation of fibrin globules, histiocytes and organized foci, septal telangiectasia, focal lymphocyte infiltration, special staining results: GMS (−), Gram (−), anti-acid (−), anti-acid fluorescence (−), fungal fluorescence (−), tissue changes were consistent with pulmonary cellulose exudative inflammation with the formation of organized foci, and no special pathogens were found. HE × 100mm.

With the diagnosis of AFOP based on pathological findings, all antibiotics were discontinued on November 30, 2022, and 40mg methylprednisolone daily was given intravenously. Four days later, cough disappeared. The white cell count and PCT decreased. Until December 5, the patient was discharged home and received 24mg of methylprednisolone orally per day, which was reduced to 16mg per day after 1 week. Repeated pulmonary CT (Fig. 1C) scan performed 10 days later after discharge showed complete absorption of the lamellar mass in the right lower lung. At follow-up, the patient was symptom-free. She tolerated the steroids well without any obvious adverse reactions.

3. Discussion

Acute fibrinous and organizing pneumonia (AFOP) is a rare lesion, acute or subacute onset. It is a new histological type of lung injury described by Beasley [1] in 2002. Different from typical diffuse alveolar damage (DAD), cryptogenic organizing pneumonia (COP) or eosinophil pneumonia (EP). The main pathological manifestation of AFOP is intraalveolar fibrin globules and organized loose connective tissue. The American Thoracic Association/European Respiratory Association classified AFOP as a rare pathological type of idiopathic interstitial pneumonia in 2003 [2]. AFOP can occur in all age groups within no gender difference [3], there is no obvious specificity of clinical manifestations, patients may come to hospital because of cough, chest tightness, shortness of breath, fever or chest pain. Laboratory tests may show an increase in inflammatory markers like CRP, WBC and IL-6 [4]. AFOP usually showed diffuse consolidation, frosted glass shadow and multifocal parenchyma abnormalities [5] which is similar to this case (Fig. 1A and B). There is no unified diagnostic standard for AFOP at home and abroad nowadays. The final diagnosis depends on the characteristic histopathological changes mainly. It is necessary to completely exclude many kinds of acute lung injury lesions such as COP, DAD and EP before AFOP can be diagnosed because AFOP is often accompanied by COP, DAD and EP in histopathology.

At present, the main diagnostic method of AFOP is histopathology, which shows that a large amount of cellulose exudate can be seen in the alveolar cavity under microscope. And the typical features are as follows: Firstly, “homogeneous eosinophilic cellulose ball" can be seen in the alveolar cavity,. In addition, there are different degrees of organized pneumonia (OP) in the cellulose spheres of AFOP which is similar to the changes of OP. The distribution of fibrin in the alveolar cavity was uneven, about 50 % of the alveolar cavity was involved, no transparent membrane was formed, no obvious aggregation of eosinophils and macrophages, no granulomatous inflammation and no obvious fibroblast activity. The secondary feature was the widening of alveolar septum and the proliferation of type II alveolar epithelial cells. Acute and chronic inflammatory cell infiltration can be seen in the alveolar septum of the involved alveoli, and the lung tissue between the lesions is basically normal [1]. The histopathological changes are similar to those in this case (Fig. 2). In addition, some studies have shown that the pathological changes of AFOP may also occur in other types of lung lesions. Feng et al. [6] reported a case of pulmonary tuberculosis and a case of poorly differentiated adenocarcinoma misdiagnosed because of typical AFOP pathological changes. Therefore, it is suggested that multi-site or mass samples should be taken for pathological examination, and other types of lesions such as pulmonary consolidation or space-occupying lesions should be excluded before the diagnosis of AFOP. At the same time, It is reported have that the biopsy pattern of lung tissue may affect the diagnosis of the disease. In two case report, the pathological diagnosis of the disease could not be confirmed by bronchoscopic biopsy for the first time, but confirmed after the next percutaneous lung biopsy [7], which is similar to our case. Therefore, percutaneous lung biopsy is recommended to confirm the diagnosis of AFOP, and the diagnostic efficiency may be improved. Although histopathology is the diagnostic standard of AFOP, it is often misdiagnosed and missed because the clinical manifestation, laboratory examination and imaging examination of AFOP has no specificity.

Imaging can not be used as a diagnostic method of AFOP because of its low specificity, but chest CT still plays an important role in judging the location and extent of lesions, and it also has guiding significance in the evaluation of therapeutic effect and prognosis of AFOP. The meta-analysis of Lee [8] et al. pointed out that patchy and patchy or mass-like consolidation were more common in the AFOP, the CT images of acute or subacute course of disease tend to be patchy and patchy or lump-like consolidation, and the survival rate of patients with patchy or lumpy-like consolidation of CT is higher than that of other CT manifestations. In addition, through the monitoring of the whole course of the disease, the comparative analysis of chest imaging before and after treatment is also helpful to the analysis of diagnosis. In this case, the chest imaging of the patient is basically absorbed (Fig. 1) after hormone treatment, which means the imaging changes are also helpful to the diagnosis.

Although hormone therapy has achieved satisfactory results in this case, there is no consensus on the treatment of AFOP. Glucocorticoid is the main therapeutic drug recommended in the guidelines [1], but there is no consensus on the dosage, timing and duration of hormone use, which needs to be adjusted according to the severity and recovery of the patient. At present, the maximum first shock dose reported is 1000mg/d [9]. If the diagnosis of secondary AFOP is considered and corticosteroid therapy alone has no obvious effect, we should consider whether to treat the primary disease at the same time according to the actual situation, adopting a combination of drugs, including mycophenolate mofetil, enalapril, immunoglobulin and cyclophosphamide [1,10–12], or adjusting the therapeutic dose of corticosteroids [13]. Surgical resection is also a feasible choice for localized lesions.

At present, the pathogenesis of AFOP is not clear, a further study is needed., Onishi [14] et al. believe that AFOP is an early histological model in the process of wound healing of lung injury. The formation of fibrin ball may be similar to the formation of hyaline membrane in diffuse alveolardamage (DAD).Under the influence of various factors, the protein serous fluid (including fibrinogen) in pulmonary capillaries infiltrates into the alveolar cavity, and fibrinogen is converted into fibrin deposition to form fibrin ball. AFOP can be idiopathic or secondary to other factors. It has been reported that a variety of factors can induce AFOP, including autoimmune diseases, drug therapy, tumor, environmental exposure and so on [7]. No correlation of these factors was found in this case. In addition, it can also be secondary to infection, such as viruses (EBV, H1N1 virus, etc.), bacteria (*Legionella*, etc.), fungi (*Pneumocystis carinii*, *Aspergillus Niger*, *Penicillium citrus*, etc.), chlamydia, etc [15–18], but the reported etiology has not been found in this case

through traditional etiological detection and mNGS detection. Interestingly, *Candida* can be detected in both bronchoalveolar lavage fluid and lung tissue through mNGS, prompting us to consider whether this case is caused by *Candida* infection.

Pulmonary candidiasis is an acute, subacute or chronic pulmonary infectious disease caused by *Candida*, which includes lung-related lesions caused by bronchial and *Candida* infection mainly, such as bronchitis, bronchopneumonia, pneumonia, lung abscess and allergic lung lesions (excluding fungal colonization), which is related to the immune status of the body closely. *Candida* is a conditional pathogen. When it is colonized, it is in the form of spores. When the human immunity decreases, it can cause invasive infection and change into pseudomycelium or fungal hyphae. According to the route of pulmonary *Candida* infection, it can be divided into primary bronchopulmonary candidiasis and secondary pulmonary candidiasis. Primary bronchopulmonary candidiasis is caused by inhalation, that is, *Candida* colonized in the oral cavity and upper respiratory tract is inhaled to the lower respiratory tract and alveoli when the body's defense mechanism is weakened, but primary pulmonary candidiasis is rarely reported and needs to be diagnosed by histopathology. There is no *Candida* invasion was found in the lung pathology in this case (Fig. 2), so primary invasive pulmonary candidiasis could not be diagnosed. Secondary pulmonary candidiasis is an invasive infection of deep tissues and organs caused by blood flow [19]. The diagnosis is mainly based on host high risk factors such as use of antibiotics, persistent granulocytopenia, solid organ or stem cell transplantation, catheter implantation, TPN, abdominal surgery, pancreatitis, glucocorticoid, use of other immunosuppressants, etc [20,21], as well as detection of *Candida* spores or hyphae in lung tissue samples, or *Candida* was cultured in lung specimens, pleural effusion or blood [22]. In addition, the detection of serum 1-3-β-D Glucan twice was higher than that of 20ng/L and combined with *Candida* culture positive and clinical manifestations, it can also be clinically diagnosed as invasive *Candida* infection (25). Because there were no high risk factors of *Candida albicans* infection in this case, in order to make a clear diagnosis, we tested the serum IgG antibody and IgM antibody of *Candida albicans* and blood fungal culture furtherly, negative results were obtained. At the same time, the pathological examination of lung tissue biopsy showed that the tissue changes were consistent with pulmonary cellulose exudative inflammation with the formation of organized foci, and there was no special pathogens were found. According to the above inspection results, he patient was eventually diagnosed with AFOP and could not be diagnosed with invasive candidiasis, We consider this to be the colonization state of *Candida*, and did not start antifungal therapy.

In this case, the diagnosis of AFOP was clear, but the deficiency was that the relationship between AFOP and *Candida* was not supported by clear clinical and laboratory data. We excluded infection, autoimmune disease, drug therapy, tumor, environmental exposure and other common factors that cause AFOP. Meanwhile, *Candida* positive was detected in mNGS of BALF and lung tissue. We have reasons to believe that the occurrence of AFOP is related to *Candida* colonization, but the specific correlation and mechanism need to be further verified in the future, More clinical and laboratory data are needed to support whether *Candida* is a risk factor for AFOP. To sum up, we report a special case of AFOP that may be associated with *Candida*, so as to improve our understanding and diagnosis of AFOP. When we find suspicious infectious lung diseases clinically and there is no obvious effect in the treatment of standardized use of antibiotics, we should be vigilant about the existence of AFOP, and further lung biopsy and pathological examination should be carried out to make a clear diagnosis by comprehensively considering the clinical manifestations, auxiliary examination, pathology and other aspects of the patients. After definite diagnosis, it is still necessary to rule out various diseases and environmental exposure and further classify them as idiopathic or secondary, so as to choose monotherapy or combination therapy.

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Zhengtu Li: Writing – review & editing. **Beini Xu:** Writing – original draft. **Jie Liu:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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